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Short Communication

Immune Response in COVID-19: Sero-Diagnostic Evidence for Clinical use and Research

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Abstract

Serological markers have remained the mainstay of infectious disease diagnosis and treatment monitoring for last so many decades. The comfort associated with serology testing has emerged from end user understanding, availability of "Rapid Point of Care testing (POCT)" formats and most importantly decreased turnaround times (TAT). In recent times, COVID-19 has burdened the healthcare systems across the globe. Rapid and accurate diagnosis is imperative to contain this contagion in the context of case detection, contact tracing, quarantine, admissions, therapeutic assessment for convalescent sera administration and epidemiological surveys for herd immunity. Nucleic Acid Tests (NAT) evolved as an accurate and early diagnostic modality and is currently considered as the standard in SARS-CoV-2 diagnosis. Though sensitive enough to pick up early disease, NAT testing is limited by false negative results in later half of the infection cycle along issues like higher cost, need for sophisticated equipment, skilled laboratory workers and oversight by pathologist thus hindering use on mass-scale. Serological diagnostic strategies, if used rationally may be a potentially cost-effective option for resource limited settings along with additional benefits for defining immune status and epidemiological surveys. This mini-review attempts to discuss and consolidate data on available and candidate serological markers including various antibodies (IgM, IgG and IgA), and antigen tests to guide clinical practitioners and researchers.

Background

The new normal for today is COVID-19; a reality with magnitudes of sorrow and losses and with humanity just taken aback despite the unmatchable list of scientific achievements and medical breakthroughs. It was in "Wuhan", the initial epicenter of this terrifying happening which further metamorphosed into a global pandemic. Puzzled with the extensive communicability and varying mortality of this virus, mankind also started to witness the socio-economic implications [1]. The disease "COVID-19" has undeniably emerged as the most discussed disease from the known times. Being new to mankind in many ways, certain characteristics of the disease need more research and science has yet to solve some basic queries for developing diagnostics and therapeutics.

An important caveat in diagnostic science remains the optimal and timely provision of results for managing care delivery pathways, which makes these test results central to the overall healthcare management. While Reverse Transcriptase- Polymerase Chain Reaction (RT-PCR) has a higher sensitivity and positive predictive value, key challenges include reliance on the time of testing during illness, higher cost, longer turnaround times (TAT) and need of skilled human resource [2]. In the wake of aforementioned limitations a window of need and opportunity arises where immune based diagnostics can fit in. We already appreciate the early derangements in terms of cellular immunity in patients with COVID-19 like leukopenia and lymphopenia [3]. Specific IgM and IgG immune responses have a time-tested evidence from multiple viral infections including dengue and hepatitis [4]. COVID-19 serological diagnosis is also available but current opinion about the use of IgM and IgG in the clinical setting is not well-established [5]. However, some researchers have shown some contrary evidence

with more sensitivity and efficiency in diagnosing COVID-19 infections albeit in differing ways. Xie [6] and Li [7] have observed better performance of IgM-IgG combined kits than use of IgM alone in the diagnosis of COVID-19 [6,7]. The available COVID-19 serodiagnostics provide an argument based upon data variability, which varies between two extremes of opportunity in terms of a feasible conduct of reliable COVID-19 testing and inaccurate data leading to compromise in contact tracing. However, the authors are of the view that serological evidence provides us with opportunity for contact tracing and epidemiological studies apart from possible diagnostic utility in resource-limited medical facilities.

We therefore planned a review to analyze existing data on antibody and antigen testing for COVID-19. The objective was to provide an updated viewpoint on IgG, IgM and IgA antibody time kinetics and diagnostic performance along with evidence available on antigen tests for SARS-CoV-2.

Review Methodology

We used initially PubMed with search words "antibody tests in COVID 19". Further search was made on Google Scholars and Google in general to find more articles. We excluded following categories from our search: Articles not having free access (n=12), case histories (n=7), studies not dealing with diagnostic performance (n=9), most commentaries and perspectives (n=7), studies dealing solely with convalescent plasma (n=5), studies dealing only with pathophysiology or for clinical usage (n=19), studies dealing with antigen extraction methodologies and monoclonal Ab preparation (n=16). We could only find many articles specifically dealing with the use of IgA in COVID-19 so we expanded a general search on Google to include few more articles. Finally, data on using antigen was minimal and we attempted to incorporate some very preliminary diagnostic test evaluation data. The search was concluded in June-2020.

We shortlisted our research area into following categories to help address immune response and serological diagnosis in COVID-19 as: A- Time kinetics of SARS-CoV-2 antibodies, B-Diagnostic performance of IgM and IgG, C- Diagnostic performance of IgA antibody and D-Diagnostic performance of SARS-CoV-2 antigens

Results

We were able to consolidate data about various aspects of serological diagnosis in COVID-19. Firstly, the viral structure as depicted in Figure 1 guides us about the selection of various antigens and antibody response against these antigens. The interactions between different antigens and antibodies assessed through various techniques results in the response which is presented to clinics for interpretation. In any infectious disease various factors including time of testing during incubation period, underlying immune status and effect of associated disease like some autoimmune disorder finally determine the diagnosis potential of serological techniques. Therefore, we first attempted to evaluate the time kinetics of the antibodies with regards to infection onset and further course as presented in Table 1. Further on we discuss the diagnostic performance of IgM, IgG and IgA for diagnosing COVID-19 infection as shown in Table 2 and Table 3 respectively. Figure 2 shows the suggested pattern various serological markers along with viral RNA based upon our reviewed data.

Table 1: Literature review representing time kinetics and sero-conversion of antibodies after SARS-CoV-2 exposure.

	Methods	N	Outcome measure	Diagnostic comment	Technical comment	Ref
1	Chemiluminesence (ELISA)	P=173	Sero-conversion & time kinetics for SARS-CoV-2	NA	Combinations of RNA PCR with Abs, IgM and IgG be used for diagnosis Sero-conversion for Abs, IgM and IgG was on day 11, 12, 14	[8]
2	ELISA (Gold Immunochromatography (Innovita Co China)	P=82 C=58	Time kinetics of IgM, IgA & IgG sero-conversion	Sensitivity (qPCR)= 51.1% qPCR +IgM=98.1%	Median IQR for IgM & IgA appearance was 5d Median IQR for IgG appearance was 14d Combined use of IgM & qPCR suggested	[9]
3	Gold Immunochromatography (Innovita Co China)	P=21	Sero-conversion of IgG & IgM response for S & N protein	NA	Ab sero-conversion predicts negative results in NAT Sero-conversion varied between less severe cases to severe cases by 10 day to 6 weeks Asymptomatic cases sometimes show no sero-conversion Increase Ab titers predicted severe disease	
4	Rapid method using "Colloidal Gold Antibody Test (GICA)" for IgM and IgG	P=38	Comparison between RNA test & Ab performance	Overall sero-conversion rate was 50% for IgM and 92% for IgG	Low positive rates for IgM (23%) & IgG(54%) during early infection IgM (50%) & IgG (88%) detection improved over RNA testing from day-8 of infection RNA test sensitivity was lower in later half of disease (13%) than IgM (52%) and IgG (91%) Combined Ab+RNA testing suggested	[11]

5	Magnetic Chemiluminesce enzyme assay [MGCLIA]	P=285 FU cohort (YCH)=63 FU of 52 RT-PCR neg	Evaluating sero-conversion & IgM and IgG sensitivity	Overall Sensitivity for IgG=83%	Median sero-conversion time was 13d for both IgG and IgM, with inconsistent results for IgM Sero-conversion of IgG with > 4 fold IgG increase in sequential testing has diagnostic sensitivity of 83% Combined RT-PCR with Ab testing approach recommended	[12]
6	ELISA[(Livzon Diagnostics Inc.,) Zhuhai, CHINA]	P=67	Evaluation of host serological and viral time kinetics	IgM rise > IgG IgG fall later than IgM	IgM rise by day 10 post infection and decline by day 30 IgG start rising by day 20 and remain elevated	[13]
7	A Cochrane review from 54 studies	16000	Week wise appearance of Abs in SARS-CoV-2 infection	Week-1: 30% Week-2: 72% Week-3: 94%	Correct testing timings have to be used for better diagnostic yield	[14]

Table 2: Literature review showing diagnostic performance of IgM and IgG for SARS-CoV-2.

	Methods	N	Outcome measure	Sensitivity/ Specificity	Technical comment	Ref
1	Chemiluminesence	P=43 C=33	Diagnostic performance of IgM and IgG	Sensitivity: IgM=48%, IgG=89% and Specificity IgM=100%, IgG=91%	IgG sensitivity > IgM	[15]
2	ELISA	P=3	Evaluation of SARS-CoV-2 IgA and IgG	S1 specific IgG specificity more than IgA	Recommended IgG & IgA against S1-protein (SARS-CoV-2)	[16]
3	ELISA	P=66 C=24	IgG/IgM performance against N-antigen	Sensitivity, specificity, PPV, NPV for IgM was 77%,100%, 100%&80% while IgG was 81%, 97%, 85% & 89%. specificity=97%	Sero-conversion by day 4 Ab provides help in diagnosis Combined use of Ab test and NAT recommended	[17]
4	Lateral Flow Immunoassay	P=397 C=128	Evaluation IgM-IgG combined assay	Sensitivity=87% Specificity=91%	Combined IgM/IgG provides better sensitivity & specificity	[18]
5	Rapid kits with different methods	NA	Meta-analysis comparing available tests	1-IgM sensitivity=82% 2-IgG sensitivity=97% specificity=98%	Antibody analysis help in emergency setting IgM has very low sensitivity in early disease (10-44%)	[19]
6	CLIA (iFlash1800)	P=61 C=64	Role of serological diagnostics in COVID-19	ROC analysis showed AUC IgM=0.918 AUC IgG=0.980	Recommended using IgM/ IgG for diagnosis	[20]
7	Comparison of different methods	NA	Review	IgM sensitivity (50-81%), IgG sensitivity (81-100%)	Variables affecting Ab test includes antigen selection, cross-reactivity, test day of incubation cycle and patient's co-morbid	[21]
8	ELISA	P=38	Comparing IgM-IgG with RT-PCR	NA	Combined use of RT-PCR and IgM-IgG is suggested	[22]
9	Rapid method [GCCOV-402a, "Zhejiang Orient Gene Biotech Co Ltd"(China)]	P=29 C=124	Evaluation of IgM-IgG rapid method against RT-PCR	Sensitivity IgM =69%, Ig G = 93% Specificity IgM =100%, IgG = 99%	High negative predictive value to rule out COVID-19 Indicates past infection & possible immune status	[23]
9	ELISA	P=214	Comparative assessment of Abs to N and S protein against NAT	N-Protein sensitivity IgM=68%, IgG=70% S-protein sensitivity IgM=77%, IgG=74%	Ab was less sensitive in initial phase of disease but increased in later half of disease Supplementary use advised	[24]

10	Colloidal Gold Labeled Immuno Chromatography	NA	Review of IgM & IgG diagnostic performance	Sensitivity: IgM=73%, IgG=100%, Specificity: IgM=99%, IgG=100%	More data needed to authenticate due to variability in findings	[25]
11	Review of 53 studies	-	Evaluation of sensitivity & specificity	Varying results	Only combined use of antibody testing and RT-PCR was suggested	[26]
12	Comparison of LFIA, ELISA and CLIA	293	Comparison of given methods with RT-PCR results	All method's sensitivity=100% IgG specificity with LFIA and CLIA>ELISA	Sensitivity by all three methods was 100% LFIA & CLIA are more specific than ELISA	[27]

Table 3: Reviewed data on SARS-CoV-2 IgA as serological biomarker.

	Methods	N	Outcome measure	Sensitivity/ Specificity	Advantages	Ref
1	ELISA	P=82 C=58	Time kinetics of IgM, IgA & IgG sero-conversion	Sensitivity (qPCR)= 51.1%qPCR +IgM=98.1%qPCR +IgM=98.1%	Median IQR for IgM & IgA appearance was 5d Median IQR for IgG appearance was 14d Combined use of IgM & qPCR suggested	[9]
2	ELISA	NA	NA	NA (Full text NA)	IgA spike appears earlier by 4d than IgM (6d) and remains higher, long-lasting and has a persistent performance	[28]
3	ELISA	NA	Diagnostic evaluation of SARS-CoV-2 antigens, IgA and IgG	S1 specific IgA demonstrated higher sensitivity for SARS-CoV-2 but S1 specific IgG showed higher specificity than IgA	Recommended IgG & IgA against S1 protein of SARS-CoV-2	[16]
4	Review	NA	Evaluation of natural history of IgA, IgM and IgG	NA	IgA show response in early phase followed by IgM and mainly IgG in later half of disease	[29]
5	CLIA method for measuring N-antigen and RBD	P=87	Comparison between N-antigen and RBD-antigen based Abs including IgA, IgM and IgG	Abs sensitivity against RBD antigen were: IgA=98.6%, IgM=96.8%, IgG=96.8%	Higher diagnostic performance with RBD than N-antigen	[30]
		C=483		Abs specificity against RBD antigen were: IgA=98.1%, IgM=92.3%, IgG=99.8%	IgA adds to improve sensitivity & early detection IgA correlates with COVID-19 severity	
6	Proteome-peptide Microarrays for Abs Flow cytometer for B-cell derived cells	NA	Comparative analysis of V-derived cells and Abs in COVID-19	NA	IgA showed early response As a prognostic marker higher IgA levels are associated with bad prognosis	[31]

Table 4: Review of data on SARS-CoV-2 infection diagnosis utilizing antigen test.

	Methods	N	Outcome measure	Sensitivity/ Specificity	Advantages	Ref.
1	Field Effect Transistor Biosensing Device	NA	Detection of SARS-CoV-2 in culture media	Limit of detection very low	Need proof of concept evaluation in real-time clinical practice	[36]
2	ICT method	328	Evaluation of N-antigen detection against qRT-PCR	Sensitivity =58% Specificity = 99.5% Accuracy of 83% against a ct qRT-PCR threshold of <22	Promising results against conventional gold standard qRT-PCR	[37]
3	ICT method	774	Antigen test evaluation against qRT-PCR	Median positive % agreement = 24% with up to a very high false positive rate (76%)	The diagnostic performance of this technique was demonstrated to be poor even with a very low selected ct values of qRT-PCR	[38]
4	ICT method	148	Evaluation of N-antigen detection against qRT-PCR	Sensitivity = 30% Specificity = 100% Overall accuracy = 50% against a ct threshold of qRT-PCR of 26	N-antigen test for SARS-CoV-2 has high NPV and specificity Not good for screening	[39]

5	ICT method	127	Evaluation of N-antigen detection against qRT-PCR	Sensitivity = 94% Specificity =100% Accuracy = 96& Kappa co-efficient=0.9	The test has high sensitivity and specificity Can be used for screening	[40]

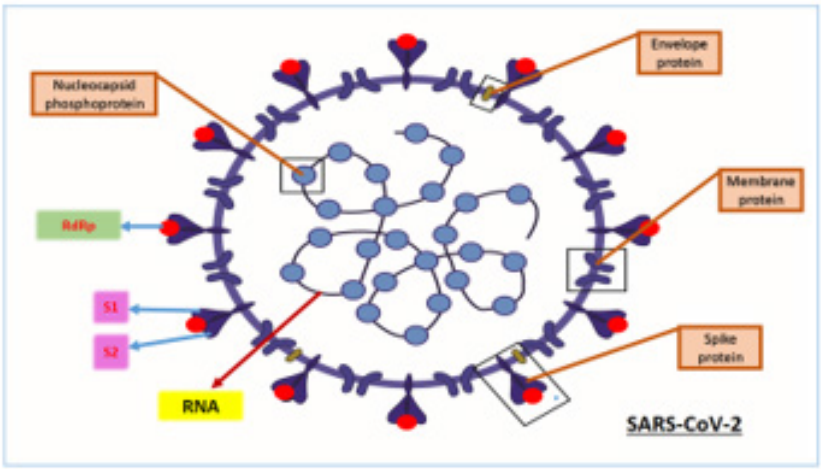

Figure 1: Schematic showing SARS-CoV-2 virus with various protein and RNA.

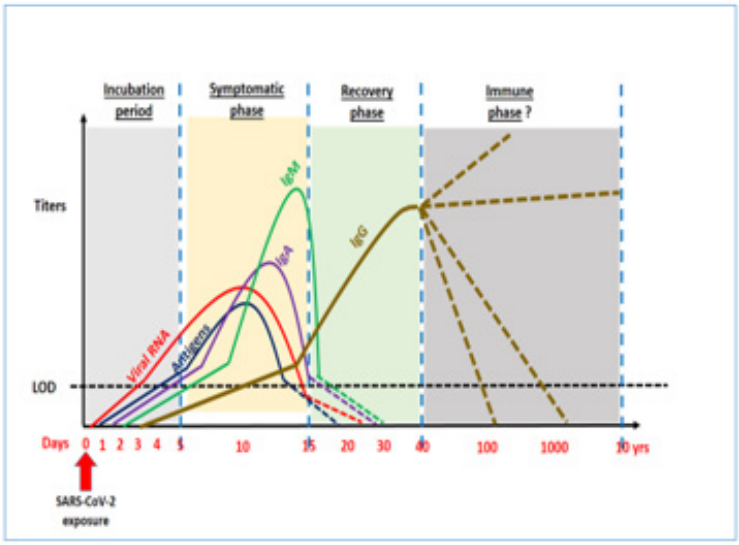

Figure 2: Schematic showing Time kinetics of COVID-19 and rise and fall of Antigens, viral loads, various antibodies.

Another rapid testing methodology on the horizon is SARS-CoV-2 antigen detection. Currently, not much data exists with regards to availability and most importantly performance evaluation of antigen detection for this virus. However, the concept has been validated in the past for other viruses like Dengue by immunoassay for "Dengue NS-1 antigen" and SARS-CoV [32,33]. In lieu past research, the clinical market is taking on the flight to develop antigen-based assays. The usual targets considered for antigens include detection include S1, S2, Whole spike, Nucleocapsid, S1 STD and S1 RBD [34]. The assumed benefit of using COVID-19 antigen tests remains in the increased sensitivity to detect the infection without any need for the requirement of highly sophisticated instruments, skilled expertise and cost [35]. The antigen test though promising has limited data to support as shown in Table 4. While the PCR technique has limitations as explained above and diagnostic Antibody testing may not be useful for early detection, antigen detection may be a possibility in our fight towards early detection of COVID-19 especially at primary care medical set up and more so in community and resource limited settings.

Discussion

Though we are in the initial phase of COVID -19 sero-diagnosis, the authors believe the need of the hour is to develop validated immunologic assays not only for COVID-19 case identification but also for contact tracing, epidemiological evaluation of immunity and probable utility in therapeutic slogan associated with convalescent sera donations. In the long-term disease management utilizing serological testing will probably be need more often. The specific Ab-tests for COVID-19 are currently focused towards Spike protein or its sub-units and nucleocapsid with an earliest detectable rise after 5-8 days (IgM) /5-15 days (IgG) with maximum titers around 10-20 days (IgM) /10-30 days (IgG) and troughs reaching around 20-30 days (IgM) with less clarity on IgG with enormous data variability [8-12]. However, most studies in this regard show a consensus that Ab-test including IgM may not have the requisite diagnostic sensitivity in the earliest phase of COVID-19 diagnosis [8,9,11,13]. Studies designed to assess the diagnostic performance show variable data, which probably resulted due to factors inherent to antibody targets, incubation time-frame of testing, cross-reactants and patient symptomatology. Our reviewed data, still suggests a very high diagnostic sensitivity and specificity for IgG in comparison to IgM which could be related to the timings of analysis during COVID 19 infection [15-27]. However, multiple authors have suggested to combine the use of IgM, IgG and NAT test to gain higher diagnostic efficiency [17,20,24,18]. Another important aspect related to above discussion is the fact that almost all studies have demonstrated low sensitivity for IgM in earlier disease phase ranging as low as 48% to highest being 82% [15,19].

Another aspect worth appreciating is minimal focus on IgA antibody which is notoriously high in secretions including nasopharyngeal specimens in respiratory tract infections. We reviewed this area and found IgA to be sensitive in the early phase of the disease from 4d to 6d which closely overlaps with the timeframe of PCR positivity [2,9,29-31]. The sensitivity seems to increase by more than 98% by using IgA against the RPD antigen than N-antigen as demonstrated by Ma [16,30]. We as authors feel IgA being secretory antibody in respiratory epithelia could be an ideal serological biomarker marker for detecting early disease. More quality trials are warranted to tap its complete potential as early disease biomarker.

Antigen testing is one more area where early detection of disease is possible as has been employed in various infectious threats including the previous SARS-CoV outbreak [32-33]. Recently the research though preliminary and to some extent contrasting with our hopes, still allowed some valuable data on use of candidate antigens on spike and nucleocapsid proteins [34-40]. We feel that assessing antigen rather than antibody can provide higher diagnostic sensitivity for early detection in coming days.

Certain limitations to this review need to be emphasized: COVID-19 is a rapidly evolving healthcare research theme and ongoing research may provide better insight to various aspects of serological diagnostics. Secondly, the authors feel that most authors cited in this research have shared their shortcomings, which may be taken into considerations while deciphering clinical applications. Thirdly, some research work still needs to publicized and final shape of preprints may emerge differently. Lastly, the data related to COVID-19 is increasing by every day and every research suffers with the half-life issue. The current data only attempts to consolidate data as per the submission dates.

Amidst research limitations, rapidly growing data on the subject and expanding bio-technological innovations the study has been able to define some unchartered domains revolving serology diagnostic areas in a consolidated manner for future users. More significant to highlight here is the pivotal work pertaining to the use of IgA antibodies and potential of SARS-CoV-2 associated antigens in research, which may revolutionize in futuristic "plug and play" diagnostics at the bed site. We also feel the feasibility of serological COVID-19 diagnostics will finally lead the main battle front in fight against the pandemic by providing timely diagnostics, ruling out disease in NAT negative suspects, defining the end of active disease by PCR negativity and disappearance of IgM antibody, appearance of protective IgG and/or neutralizing antibody, measuring herd immunity in community and finally paving way for possible convalescent sera use in COVID-19 therapeutics by deploying IgG titers and neutralizing antibodies.

Conclusion

IgM and IgG are not useful in isolation to provide early diagnosis during COVID-19 infection. However, both can have a role in supplementing PCR test results for diagnosing COVID-19. IgG as a marker of past infection along with neutralizing antibodies can help in defining immunity from SARS-CoV-2 infection, measuring herd immunity status and therapeutic use in assessing compatibility for convalescent sera. IgA has the potential to develop as an early disease marker along with various candidate SARS-CoV-2 antigen tests. Further research is needed to finalize time kinetics of rise and fall of various antibodies, antigen characterization and validation for clinical use.

Declarations

a) We the authors of this review titled: "Immune response in COVID-19: Sero-diagnostic evidence for clinical use and research" declare no conflict of interest.

b) The authors declare no competing interests.

c) There were no sponsors or funding sources available for this study

Contribution- SHK

(Correspondence) Study plan, data review, manuscript writing, referencing. SKZ: Manuscript writing, data review and finalization. Both authors approved the final version of manuscript.

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