VIEWPOINT

Serological (Antibody-Based) Tests for COVID-19: A Pathologist's Perspective

Muhammad Usman Shams[1], Raees Abbas Lail[2], Sobia Khalid[3]

ABSTRACT

The essential and critical role of laboratory medicine in the current Coronavirus disease of 2019 (COVID-19) outbreak regarding diagnosis, therapeutics and prognostics cannot be overruled. No laboratory test is perfect and there is always a dilemma especially for respiratory diseases as in case of tuberculosis. Sensitivity, specificity, PPV and NPV are not always perfect for any one test. In case of COVID-19, we need to step ahead of PCR and also start supplementary serology testing. It will provide wide range of information, important for future thinking, planning and actions against COVID-19.

KEYWORDS: COVID-19, Antibody-based tests, Screening, World Health Organization.

How to Cite This:

Shams MU, Lail RA, Khalid S. Serological (antibody – based) test for COVID-19 – a pathologist's perspective. Biomedica. 2020; 36 (COVID19-S2): 43-6.

INTRODUCTION

There is an essential and critical role of laboratory medicine in the current Coronavirus disease of 2019 (COVID-19) outbreak regarding diagnosis, therapeutics and prognostics. The proposed model of laboratory testing as well as guidance to the patients at different levels in COVID-19 is shown in Fig.1.

Currently, the laboratory role is confined to the diagnosis of suspected cases which is confirmed by viral RNA-based tests using real-time reverse transcription polymerase chain reaction (rRT-PCR) or Next-Generation Sequencing (NGS) methods.

1. Dr. Muhammad Usman Shams
Research Director, Mughal Diagnostics & Research Labs, a project of Mughal Eye Hospital Trust Johar Town, Lahore-Pakistan.
2. Dr. Raees Abbas Lail
Associate Professor, Head Department of Pathology
Sahiwal Medical College, Sahiwal-Pakistan.
3. Dr. Sobia Khalid
Lecturer, Department of Morbid Anatomy & Histopathology
University of Health Sciences, Lahore-Pakistan.

Correspondence to:
Dr. Raees Abbas Lail
Associate Professor
Head, Department of Pathology
Sahiwal Medical College, Sahiwal
Email: raeisabbas@gmail.com

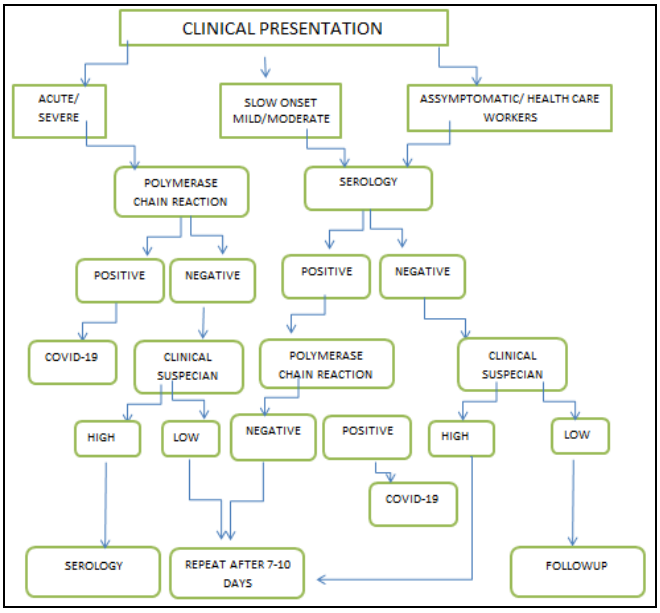

Fig.1: Laboratory Testing Role in COVID-19.

The underlying principle is that viral RNA can be detected from the nasal and pharyngeal swab, bronchoalveolar lavage, and blood plasma using detection techniques targeting some specific genes of the virus.[1]

As the active debate right now is to detect virus, RT-PCR has become a priority and serologic tests

have become under-utilized in COVID-19 pandemic. In fact, to find a path out forthis pandemic, serologic testing will become essential in near future and the sooner serologic tests are started, the better it is.

Serologic Tests or Antibody Detection

Serologic tests are based on the principle of detecting specific antibodies (a type of blood proteins) against the virus in the blood of COVID-19 patients. There are two types of antibodies that are potential targets in serologic testing: Immunoglobulin M (IgM) is the first antibody that the body makes in response to a foreign substance and can usually appear a couple of days after any infection. Regarding COVID-19, median duration of IgM antibody detection is reported to be 5 days [interquartile range (IQR): 3 – 6]. Immunoglobulin G (IgG) is produced later on in any infection, but quite specific. Positive result means either a person is currently infected or was recently infected. It is a potential measurement of immunity status as well. Regarding COVID-19, IgG antibody can be detected at the end of 2 weeks and remains detectable for weeks to months.[2,3] The details of antibody titers related to clinical features (Fig.2).

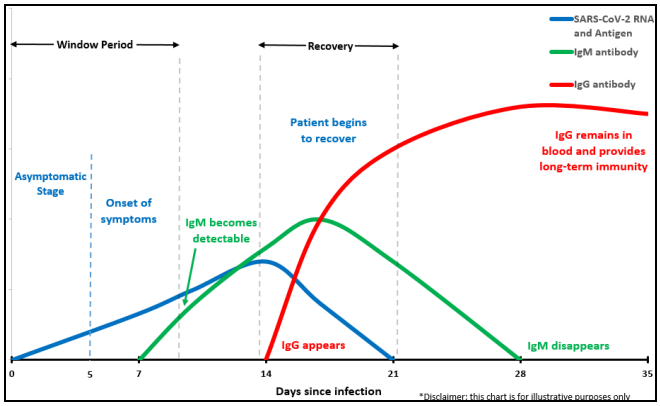

Fig.2: Antibody titers related to clinical features in COVID-19[4]

Serologic Techniques for COVID-19 Detection

The following laboratory testing methods/kits are available for detection of COVID-19 antibodies: Rapid Diagnostic Tests (immuno-chromatography or colloidal gold method) and ELISA.[5] Several assays for serologic testing are available in the market, but their use alone for diagnosis of COVID-19 is NOT recommended.

Need for Antibody Detection Methods for COVID-19

A. Limitations of RT-PCR testing as 'Screening Method'

As with serologic testing, negative PCR may also give a false sense of hope. As PCR has only diagnostic value and it does not offer any additional information regarding prognostication and treatment. Only symptomatic or active or string positive contact/travel history patients are offered PCR. Asymptomatic patients or patients with mild disease most likely escape any type of screening currently. PCR is an expensive, sophisticated test available in limited laboratory setups.[5,6]

B. Potential Benefits of Serologic Testing

Serologic testing can possibly detect viral RNA-negative individuals presenting late in their illness, even for patients with mild symptoms, immunocompromisedand asymptomatic patients. Serologic testing can give us diagnostic, prognostic and therapeutic information at the same time. For instance; the epidemiologic surveillance can be done. It means defining hotspots allowing government to precisely target their tactics.Herd immunity development can be assessed based on IgG levels. It can tell us who can go back to work first or safe to travel. In fact, in some countries like Germany are considering using serologic tests to issue immunity certificates to people who have survived COVID-19. Contact tracing can be made more cost-effective. Donors can be screened for utilization as a source for (currently experimental) therapeutic or prophylactic antibodies regimens. True span of COVID-19 pandemic can be determined as all types of patients may be detected. Increased IgM levels in COVID-19 patients have been suggested to be a marker of poor outcome.In supplement with molecular testing, valuable information will become available for future research and planning. One such prospective is that serologic testing has more sensitivity than PCR testing. Recently China-based studies with promising results have shared the benefits of serological testing over PCR.[3,5,6] Serologic testing is

less risky, more convenient and cost effective (1/3rd to 1/5th cost of PCR). Mass testing with ease will be possible.[4]

Test results			Clinical Significance
PCR	IgM	IgG	
+	–	–	Patient may be in the window period of infection.
+	+	–	Patient may be in the early stage of infection.
+	+	+	Patient is in the active phase of infection.
+	–	+	Patient may be in the late or recurrent stage of infection.
–	+	–	Patient may be in the early stage of infection. PCR result may be false-negative.
–	–	+	Patient may have had a past infection, and has recovered.
–	+	+	Patient may be in the recovery stage of an infection, or the PCR result may be false-negative.

Fig.3: PCR and Antibody Titers Related to Clinical Features in COVID-19.[4]

C. Serologic Testing Kits Availability

On April 2, FDA granted first EUA (emergency, transit approval) to a serological (rapid diagnostic) test for COVID-19. The language used is cautious but promising like 'FDA does not intend to object' and 'the known and potential benefits of your product when used for diagnosing COVID-19 outweigh the known and potential risks of your product. A handful of CE-IVD marked serologic testing assays, both ELISA and Rapid Test kits for COVID-19 have become available. A few of these companies are already operational in Pakistan. WHO does not 'deny' serology testing role in COVID-19 in its Laboratory Testing Guidance (19 March, 2020). It only emphasizes 'once validated serology tests are available'.[1,2]

D. Utilization of Serologic Testing for COVID-19

Screening: An Inclusion criterion is symptomatic patients, preferably if onset of symptoms is more than 3 days. If serology is positive, go for confirmation of active disease by PCR (same principle as prevalent with Hepatitis screening). If serology is positive & PCR is negative, repeat serology after 10 – 14 days and/or quarantine only in high clinical suspicion cases. If serology is negative, repeat serology after 10-14 days and/or quarantine only in high clinical suspicion cases. Patients with severe, acute respiratory symptoms are exempted and should go directly for PCR.IgM positivity is active or recent infection, while IgG positivity is late/recovering or recurrent or recovered infection.[7]

Utility of the screening programme is that PCR testing burden will be reduced. It can be offered to all asymptomatic or mild cases& healthcare workers. A mobile laboratory can be setup at airports/dry ports to more effectively screen 'travellers' in just few hours.[7,8]

Beyond screening: n inclusion criterion is all COVID-19 positive cases. It has to be done at baseline and then periodically monitor IgM and IgG levels.

Utility of the beyond screening programme is that immune status of every patient will be determined. Poor outcome or immune deficiency may be highlighted. Safe IgG level for discharge of patient may be determined and validated. 'An immune' individual may be labeled for safe work and/or travel purposes. Potential plasma donor can be filtered.

CONCLUSION

No laboratory test is perfect and there is always a dilemma especially for respiratory diseases as in case of tuberculosis. Sensitivity, specificity, PPV and NPV are not always perfect for any one test. In case of COVID-19, we need to step ahead of PCR and also start supplementary serology testing. It will provide wide range of information, important for future thinking, planning and actions against COVID-19.

CONFLICT OF INTEREST

None to declare.

FINANCIAL DISCLOSURE

None to disclose.

REFERENCES

1. World Health Organization. Laboratory testing for Coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2020. World Health Organization. Available online at: https://apps.who.int/iris/handle/10665/331329. [Last accessed on April 29, 2020].
2. Policy for Coronavirus disease-2019 tests during the public health emergency. (Revised) Immediately in effect guidance for clinical laboratories, commercial

manufacturers, and food and drug administration staff. Available online at: https://www.fda.gov/media/135659/download. [Last accessed on May10, 2020].
3. Jia X, Zhang P, Tian Y, Wang J, Zeng H, Wang J, et al. Clinical significance of IgM and IgG test for diagnosis of highly suspected COVID-19 infection. medRxiv. 2020. Available online at: https://doi.org/10.1101/2020.02.28.20029025. [Last accessed on March12, 2020].
4. COVID-19 Rapid Test. Available online at: https://www.biopanda.co.uk/php/products/rapid/infectious_diseases/COVID19.php. [Last accessed on May 15, 2020].
5. Liu R, Liu X, Han H, Shereen MA, Niu Z, Li D, et al. The comparative superiority of IgM-IgG antibody test to real-time reverse transcriptase PCR detection for SARS-CoV-2 infection diagnosis. medRxiv. Available online at: https://www.medrxiv.org/content/10.1101/2020.03.28.20045765v1. [Last accessed on March12h, 2020].
6. Wang Z, Li H, Li J, Yang C, Guo X, Hu Z, et al. Elevated serum IgM levels indicate poor outcome in Patients with Coronavirus disease 2019 pneumonia: a retrospective case-control study. Available online at:https://ssrn.com/abstract=3557987. [Last accessed on May12th, 2020].
7. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling early humoral response to diagnose novel Coronavirus disease (COVID-19). Clin Infect Dis. 2020: ciaa310.
8. Xiao SY, Wu Y, Liu H. Evolving status of the 2019 novel Coronavirus infection: proposal of conventional serologic assays for disease diagnosis and infection monitoring. J Med Virol. 2020; 92 (5): 464-7.
9. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human Coronavirus infections – the state of the art. Emerg Microbes Infect. 2020; 9 (1): 747-56.
10. Lippi G, Plebani M. The critical role of laboratory medicine during Coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020. Available online at: https://www.degruyter.com/view/journals/cclm/ahead-of-print/article-10.1515-cclm-2020-0240/article-10.1515-cclm-2020-0240.xml [Last accessed on February 15h, 2020].

Author's Contribution

MUS: Conception and design of published data.
RAL: Conception, design and acquisition of published data.
SK: Drafting the manuscript, critical review for intellectual content.
RA: Drafting of manuscript.

Dr. Muhammad Usman Shams (MBBS, M. Phil., FCPS), is working as Research Director at Mughal Diagnostics & Research Labs, a project of Mughal Eye Hospital Trust (Johar Town) Lahore. He researchinterests include dermatopathology, cancer pathobiology, and molecular pathology. Presently Mughal Diagnostic Laboratory is testing Coronavirus on RT-PCR under his supervision. He has more than 15 peer reviewed national and international research publications.