ANALYSIS OF THE RESULTS OF THE IMMUNOENZYME STUDY FOR COVID-19 (LITERATURE REVIEW)

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The literature review considers methods for detecting coronavirus infection, the sensitivity and specificity of laboratory tests, the determination of antigens or antibodies, their advantages and disadvantages. Laboratory tests reflect the state of immunity, the development of the disease, damage to organs and systems, and the quality of treatment. The correct appointment and interpretation of the test result is important for obtaining additional information in the diagnosis, for choosing the right treatment for the disease and predicting its development. In general, laboratory diagnostic methods aimed at identifying nucleic acids, antigens or antibodies are of great importance.

Keywords: *coronavirus infection, immunoenzyme assay, sensitivity, specificity, IgG, IgM.*

CORONAVIRUS INFECTION (COVID-19) has rapidly spread worldwide over a short period of time. Despite strict quarantine measures, disease management has become a global problem [1, 5, 18, 25]. In December 2019, a case of pneumonia of unknown etiology was registered in China. Health experts determined that the new pathogen of the infection is a severe acute respiratory syndrome, which is genetically 80% similar to SARS-CoV-1 and was named SARS-CoV-2 or COVID-19 [48, 50]. Starting with respiratory failure symptoms, the disease manifests as pneumonia and, in some cases, resembles the flu [2, 14]. However, the mortality rate from COVID-19 is significantly higher than from the flu or other common respiratory infections [32, 39, 41].

The virus was first detected in the Hubei province of China and quickly spread from person to person over a short period of time. Contact with an infected person or airborne transmission is a way of transmitting the virus [22, 54]. According to the World Health Organization (WHO), as of 31.03.2021, the number of registered cases of the new coronavirus infection worldwide was 127,877,462 people, of which 2,796,561 cases had a fatal outcome [35].

The virus that causes severe acute respiratory syndrome (SARS-CoV-2) belongs to the beta-coronavirus group, and it is believed that their source may be bats or pangolins. The etiological agent of COVID-19 is SARS-CoV-2, which causes diseases associated with mild or severe acute respiratory distress syndrome and multi-organ failure [16, 21, 23].

Viruses belonging to the coronavirus family (CoV) were first isolated from humans in 1962. Initially, coronaviruses were considered the cause of mild respiratory and gastrointestinal diseases in humans and animals. In 2002-2003, an epidemic of severe acute respiratory syndrome caused by coronavirus 1 (SARS-CoV-1) occurred in China, and in 2012, the "Middle East respiratory syndrome coronavirus" (MERS-CoV) outbreak occurred in Latin America and particularly in Saudi Arabia. It has been proven that both of these viruses are transmitted from animals to humans and from person to person [43].

Individuals aged 60 and over often have underlying comorbidities and weakened immune systems, making them more vulnerable to COVID-19 infection [3, 8, 20]. This group also experiences a more severe course of the disease [49]. The virus primarily develops in the upper and lower respiratory tract and quickly spreads to other organs. SARS-CoV-2 causes acute respiratory distress syndrome and multiple systemic changes in the form of a "cytokine storm," leading to impaired immune function [25].

Cytokines are formed from small molecular peptides, mainly glycoproteins. They are synthesized by various cells, including macrophages, lymphocytes, neutrophils, and reticuloendothelial cells. Most patients infected with the virus show significant changes in the concentration of lactate dehydrogenase, ferritin, D-dimer, interleukin-6, and C-reactive protein [7, 19]. Observations during the pandemic show that multiorgan damage, acute respiratory distress syndrome, and mortality in COVID-19 patients are directly related to the so-called "cytokine storm." Recognition and control of the "cytokine storm," as well as the use of cytokine antagonists to treat patients with this virus, may increase treatment efficacy and reduce mortality rates [4].

Like other infectious diseases, obtaining the necessary material to detect infection is the main stage of COVID-19 laboratory diagnosis [6, 15]. COVID-19 samples are most commonly obtained from upper and lower respiratory secretions, as well as blood and pleural fluid [55].

Using special reagents, it is now possible to determine the amount of IgG, IgM, and IgA antibodies produced in the human body, which indicate ongoing infection. IgM antibodies are produced 5-7 days after infection with the SARS-CoV-2 virus and are the main indicator of laboratory diagnosis during the initial period of infection. IgG antibodies are produced 10-15 days after infection and can persist for several months. IgA antibodies are an important component of mucosal immunity and may be detected in mucosal secretions after 6-8 days, but their role in the diagnosis of coronavirus infection has not yet been determined [30, 45].

Currently, serological analyses are used to monitor the development of diseases, which allow the detection of disease biomarkers in blood or other biological fluids [9, 37]. Various types of serological tests, such as enzyme-linked immunosorbent assays (ELISA), are used to detect antibodies produced by the body in response to infection [26, 40].

Diagnostic laboratory tests are an important tool in the fight against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogens and other infections. To understand these tests, it is important to know their sensitivity and specificity. Sensitivity of testing lies in correctly identifying individuals who are truly positive for the disease, as well as reducing the number of false negative results [11, 12]. Specificity, or the uniqueness of testing, lies in the ability to correctly identify those who are truly negative (true negative results) and reducing the number of false positive results. False results can be classified as analysis errors. The consequences of analysis errors can be assessed through false positive or false negative results [13]. False positive results may lead to the need for repeat testing of patients, while false negative results may lead to the spread of infections as patients and medical workers may assume that the patient is not infected. Therefore, it is important to understand how sensitivity and specificity of tests affect disease identification. The sensitivity and specificity of diagnostic tests also affect the production and use of experts. The higher the sensitivity and specificity of testing (both at 100%), the more accurate the results will be in diagnosing the disease [47].

ELISA is a universal enzyme-linked immunosorbent assay system widely used in laboratories of all sizes [17]. During blood analysis to detect SARS-CoV-2, special anti-IgM, anti-IgG, and anti-IgA antibodies are added to the test system, which bind to the virus antigen and attach to specific enzymes. Substrates linked to the enzymes react and change color, which can be measured spectrophotometrically to determine the quantity or quality of antibodies. Currently, various ELISA test systems are available for the general detection of antibodies against SARS-CoV-2, which have been developed with an accuracy of 97.5% and 96.7% [33].

There are ELISA kits that can detect antibodies produced in response to COVID-19 antigens or virus antigens. They are used to detect specific antibodies that are formed in response to the virus [10]. If there are antibodies to the virus in the microtube, it means that virus antigens can be detected. First, the patient's biomaterial containing SARS-CoV-2 virus antigens is placed in the microtube, then an enzyme is added that can measure the presence of antibodies. Finally, a substrate is added to the plate that allows measuring the accumulation of antigen-antibody [51].

To detect total antibodies, Bio-Rad Labs and Mount Sinai laboratory have developed the following ELISA test systems, which have shown accuracy from 99.6% to 100% for specificity. However, sensitivity remains relatively low, from 92.2% to 92.5% [31].

COVID-19 and other diseases continue to threaten people's health worldwide, so diagnostic tests that accurately determine viral diseases such as SARS-CoV-2 and distinguish them from others are needed now [38]. Such tests allow detecting the presence of the virus in the patient's body at early stages of the disease, using coronavirus antigens or nucleic acids. Tests that detect antigens allow checking the

presence of virus surface proteins, and their detection can help quickly determine the presence of SARS-CoV-2 infection [35].

SARS-CoV-2 consists of four main proteins: nucleocapsid protein (N), envelope protein (M), conversion protein (E), and surface protein (S). Such tests help quickly classify and diagnose COVID-19, reduce analysis time and patient testing costs [28].

Niko and other authors investigated the effectiveness of recombinant IgG against COVID-19 at different stages of coronavirus infection. After confirming the presence of COVID-19 using PCR analysis in ELISA tests, sensitivity to recombinant N was detected in 70.6%, and recombinant S - in 58.8% during the period from 5-9 days of illness. During the next 10-18 days, an increase in sensitivity to recombinant N up to 100% and to recombinant S up to 93.8% was observed. To study the effectiveness of the ELISA test for detecting IgG and IgM antibodies against SARS-CoV-2 using S and N proteins, Liu and colleagues conducted an analysis that showed that if a test for S protein is used, sensitivity to IgG antibodies will be less than 60% after 6-10 days, but after 16 days, it will increase to over 90%. In Finland, COVID-19 was initially detected by immunofluorescence analysis of IgM and IgG antibodies against SARS-CoV-2 in erythrocytes. For this, patient plasma is constantly filtered through a buffer, and then incubated for 30 minutes for IgG and 2 hours for IgM. If antibodies were not detected after 4 days from the onset of infection, after 9 days, the level of IgM and IgG titers was 1:80, after 20 days - 1:32 and 1:128. When plasma samples of the control group were diluted more than 1:20, no specific binding was observed [27].

The efficacy of immunofluorescent and neutralizing assays has been investigated at various stages of SARSCoV-2 infection. The sensitivity of immunofluorescent and neutralizing assays was evaluated through PCR tests. According to the results, the accuracy of detection was 76.5% within 5-9 days and 100% within 10-18 days. Although immunofluorescent assays are preferred for early diagnosis, the possibility of obtaining false results when using this assay is also very high. Therefore, additional sensitivity checks of this method are required [36].

Diagnosis of asymptomatic COVID-19 can be difficult in the early stages of the disease. For this reason, enzyme-linked immunosorbent assays, based on the detection of antibodies against SARS-CoV-2, allow for the detection of IgG even after the disease has been contracted and during recovery. This can help determine the fact of infection, conduct epidemiological studies, and evaluate vaccine efficacy [52].

Understanding the essence of special antigens and antibodies that allow for the assessment of disease severity and immunity duration is crucial for detecting COVID-19. Some studies show that the average seroconversion time for IgM is about 7 days after symptom onset, and it can be detected in some patients within 10-12 days. IgG usually appears later than IgM. The average seroconversion time for IgG is approximately 14 days, and it reaches its highest level after 3 weeks, remaining at a high level for about 6 weeks. This indicator is almost 100% positive, remaining at a

high level for 4-5 weeks, after which it begins to gradually decrease over the next few weeks [44].

Currently, enzyme-linked immunosorbent methods based on various diagnostic methods are fast, reliable, accessible, widely available, highly automated, and have other safety and many advantages. Although some people have difficulty diagnosing the disease quickly and accurately due to the incubation period in the initial stage of COVID-19, antibody detection can prevent false negative results. In addition, checking the dynamics of antibodies is of great importance for determining the disease in people in direct contact with patients. The use of vaccines also strengthens the requirements for antibody testing. However, interaction between some reagents may affect test accuracy and reliability, so it is extremely important to control the quality of reagents [28].

Despite their convenience and comfort, the principle of operation of antigen tests varies greatly. Eighty-seven samples of nasopharyngeal and oropharyngeal secretions were studied with four different tests to detect four different SARS-CoV-2 antigens. Three of these tests correctly identified objects with high viral titers, where more than 80% of viral patients are positive. However, one of the tests gave poor clinical results [53].

The use of antigen tests as the sole basis for COVID-19 diagnosis is impossible due to low sensitivity during the first week of infection, when high viral titers are observed in naso- and oropharyngeal samples. However, the widespread use of enzyme-linked immunosorbent analysis is due to its availability and rapid results, as well as the possibility of using it as a screening tool to detect suspicious patients, high-risk groups, and monitor immune status, especially in epidemic conditions when disease outbreaks occur [34].

Laboratory studies help to choose the correct treatment methods, study the dynamics of treatment, and determine possible complications. Recent studies show that relative lymphocyte counts are of great importance for disease prognosis and therapeutic tactics [24]. Monitoring the dynamics of relative and absolute T-lymphocyte counts in clinical practice helps to understand the increase in immune function, choose treatment methods, and control immune responses. Additionally, many COVID-19 patients may develop acute respiratory failure, which can manifest with symptoms of liver, kidney, heart, neurological symptoms, and manifestations of impaired function of many organs [42].

Therefore, monitoring heart function, hepatorenal indices, and other biochemical parameters is important for choosing appropriate treatment methods and improving clinical outcomes in coronavirus infection. Additionally, some medications, such as antiviral drugs, fever-reducing and pain-relieving medications, may have hepatorenal toxic effects [46].

Bruzzone and his colleagues found the effectiveness of 7 different rapid diagnostic tests compared to PCR and showed that the overall sensitivity and

specificity of antigen tests are 78.7% and 100%, respectively. The antigen detection test is usually highly specific but not as sensitive as the nucleic acid detection test [29]. It should be noted that under certain conditions, immunoassay methods have several significant advantages. Further research should focus on expanding testing capabilities, simplifying the testing process, and presenting results in a user-friendly format [56].

To determine sensitivity, it is necessary to calculate the virus titer with a probability of a positive test result of no less than 95%. The lower limit of accuracy indicates greater sensitivity of test results when samples with low virus content are taken to obtain a positive test result. Although test samples have high sensitivity and specificity (about 100%), the prevalence of the disease, variations in viral genes, and sample type can affect test accuracy [47].

Literature review showed that laboratory analyses can reflect immune status, disease progression, organ damage, and treatment quality. Their rational use is important to provide broader data for diagnosis, choose the correct treatment methods for the disease, and predict its development. In general, methods of laboratory diagnosis aimed at detecting nucleic acids, antigens, or antibodies are of great importance.

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