ABSTRACT

In December 2019 in the city of Wuhan, in China, the first cases of infection caused by the new SARS-CoV-2 virus appeared, and later on, the disease caused by this virus was named COVID-19. Shortly after this, on March 11th, 2020, the WHO characterized COVID-19 as a global pandemic. The symptoms of COVID-19 and acute cardiovascular disorders (e.g., heart failure, pulmonary embolism or myocardial ischemia) frequently overlap, which poses a challenge for the establishing of a differential diagnosis in clinical practice. Rapid serological tests, which detect IgM and IgG classes of antibodies for SARS-CoV-2, have been developed with the primary purpose of screening the population’s immunological response to the SARS-CoV-2 virus. However, rapid serological tests are often used outside their original purpose, i.e., for triage of possibly infected, non-vaccinated individuals, because they offer quick results, which may be particularly relevant in emergency settings. If serological testing is used to guide the admission of non-vaccinated patients with acute cardiovascular disorders to either an isolation unit for suspected COVID-19 positive individuals, or to hospital facilities for non-infected patients, it is important to recognize its limitations, in order to reduce the risk of false-positive or false-negative results. Hence, appropriate patient selection and cautious test interpretation is necessary to avoid misdiagnosis. The aim of this paper is to illustrate how serological testing may be used as a screening tool to inform the management of non-vaccinated patients with acute cardiovascular disorders requiring urgent hospital admission. As an illustration, we describe two clinical situations, in which serological testing produced meaningful results.

Key words: COVID-19, triage, false-positive, false-negative, misdiagnosis

SAŽETAK

U decembru 2019. godine, u gradu Vuhanu, u Kini, registrovani su prvi slučajevi infekcije izazvane novim SARS-KoV-2 virusom. U daljem toku je bolest izazvana ovim virusom nazvana KOVID-19. Ubrzo nakon toga, 11. marta 2020. godine, Svetska zdravstvena organizacija proglasila je pandemiju KOVID-19 infekcije. KOVID-19 i akutna kardiološka stanja (npr. srčana insuficijencija, embolija pluća ili ishemija miokarda) često imaju sličnu kliničku prezentaciju, što predstavlja izazov u postavljanju adekvatne dijagnoze u kliničkoj praksi. Osnovna namena brzih seroloških testova za detekciju IgM i IgG antitela na SARS-KoV-2 je procena imunološkog odgovora na ovaj virus. Međutim, brzi serološki testovi se često upotrebljavaju van okvira osnovne namene, za trijažu potencijalno inficiranih, nevakcinisanih pacijenata, zbog brzog dobijanja rezultata, što je naročito važno u urgentnim stanjima. Ukoliko se serološko testiranje koristi za trijažu nevakcinisanih pacijenata, u smislu prijema u izolacionu jedinicu za suspektne KOVID-19 pozitive bolesnike ili na odeljenja gde su smetleni KOVID-19 negativni bolesnici, potrebno je poznati njihova ograničenja da bi se redukovao rizik lažno pozitivnih i lažno negativnih rezultata. Neophodna je adekvatna selekcija pacijenata i obavljena interpretacija rezultata kako bi se izbegla pogrešna dijagnoza. cilj ovog rada je da opiše kako se serološki testovi mogu upotrebiti za trijažu kardioloških pacijenata, navakcinisanih protiv SARS-KoV-2 virusa, koji zahtevaju urgentnu hospitalizaciju. Radi ilustracije, prikazuju dva bolesnika kod kojih je primenom ovih testova dala sveshodne rezultate.

Ključne reči: KOVID-19, trijaža, lažno pozitivni, lažno negativni, pogrešna dijagnoza

OGRANIČENJA PRIMENE BRZIH SEROLOŠKIH TESTOVA NA SARS-KOV-2 KOD NEVAKCINISANIH PACIJENATA U URGENTNIM KARDIOŠKIM STANJIMA

LIMITATIONS OF RAPID SEROLOGICAL TESTING FOR SARS-COV-2 IN NON-VACCINATED PATIENTS IN ACUTE CARDIAC CARE

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In December 2019 in the city of Wuhan, in China, the first cases of infection caused by the new SARS-CoV-2 virus were registered, and later on, the disease caused by this virus was named COVID-19 [1]. Shortly after this, on March 11th, 2020, the WHO characterized COVID-19 as a global pandemic. The typical clinical presentation includes bilateral interstitial pneumonia; however, many patients also develop acute respiratory distress syndrome (ARDS) or multiorgan involvement. In particular, individuals with cardiovascular diseases have a twice to threefold higher risk of adverse outcomes, as compared to patients without comorbidities [2].

The symptoms of COVID-19 and acute cardiovascular disorders (e.g., heart failure, pulmonary embolism or myocardial ischemia) frequently overlap, which poses a challenge for the establishment of a differential diagnosis in clinical practice, especially in emergency settings. The confirmation of COVID-19 infection requires a positive antigen test or a positive reverse transcriptase polymerase chain reaction (RT-PCR) test of nasopharyngeal secretions, as standard diagnostic methods [3]. Rapid antigen testing was not available in most healthcare settings during the best part of 2020. With regard to RT-PCR testing, it may take a considerable amount of time to obtain the results. Occasionally, patients with a negative test result may be SARS-CoV-2 carriers, with delayed development of viral shedding (false-negative test), thus posing a threat for the spreading of the virus. Rapid serological tests, which detect IgM and IgG classes of antibodies for SARS-CoV-2, have been developed with the main purpose of screening the population for immunological response to SARS-CoV-2 [4]. However, rapid serological tests have often been used during 2020 outside their original purpose, for the triage of possibly infected individuals, because they offer quick results, which may be particularly relevant in emergency settings. The aim of this paper is to illustrate how serological testing may be used as a screening tool to inform the management of non-vaccinated patients with acute cardiovascular disorders requiring urgent hospital admission.

As an illustration, we describe two clinical situations, in which serological testing produced meaningful results.

The first case is a 76-year-old male presenting with high fever (38.6 °C) and dyspnea for 10 days before admission. The patient had a history of cardiomyopathy and signs of heart failure (S3 gallop, bilateral lung rales, hepatomegaly, lower extremity edema), but also, he had been in contact with a COVID-19 positive family member 12 days before admission, and he had not been vaccinated for SARS-CoV 2. Although he was
protiv virusa SARS-CoV-2. Iako je pacijentu dijagnostiko-
Kovana dekompenzovana srčana insuficijencija, pozitiv-
tivan test na IgM antitela za SARS-CoV-2 indikovao je
maje u izolacionu jedinicu, a KOVID-19 je potom po-
tvrđen pozitivnim RT-PCR testom.

Drugi je slučaj sedamdesetdevetogodišnjeg muš-
karca sa disnejom, subfebrilnom temperaturom (37,4
°C), oštrim bolovima u grudima, u trajanju od tri dana
pre prijema, i negativnim epidemiološkim upitnikom na
KOVID-19, koji je takođe bio nevakcinisan. Dijagnostiko-
vana mu je plučna embolija, ali je nalaz kompjuterizato-
pane tomografije (CT) takođe otkrio i ekstenzivne ob-
strane promene denziteta „mlečnog stakla”, suspektne
na KOVID-19 pneumoniju. Test ovog pacijenta na SARS-
CoV-2 IgM antitela bio je negativan, ali je on ipak pri-
mlijen u izolacionu jedinicu, s obzirom na to da je bio vi-
soko klinički suspektan na KOVID-19 oboljenje, koje mu
je u daljem toku potvrđeno pozitivnim RT-PCR testom.

DISKUSIJA

Ukoliko se serološko testiranje primenjuje (kada brzi an-
tigenski test nije dostupan) kako bi se donela odluka o
tome da li da se osobe nevakcinisane protiv KOVID-19
infekcije sa akutnim kardiovaskularnim oboljenjima pri-
me u jedinicu za izolaciju pacijenata za koje postoji sum-
ja da su pozitivni na KOVID-19 ili u kapacitete bolnice
za neinficirane pacijente, važno je razumeti ograničenja
ovog testa u pogledu smanjenja rizika od lažno pozitiv-
nih ili lažno negativnih rezultata. Stoga, u ovu svrhu, tre-
ba primenjivati samo testove sa visokom senzitivnošću
i specifičnošću. Test koji se koristi u našoj inštituciji ima
prijavljenu senzitivnost od 87% i specifičnost od 100%
za detektovanje IgM klase antitela, dok je senzitivnost
za otkrivanje IgG klase antitela 96%, a specifičnost 98%.

PREVENCIJA LAŽNO NEGATIVNIH REZULTATA

Test koji se koristi u našoj inštituciji ima
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PREVENTING FALSE-NEGATIVE TEST RESULTS

Priority should be given to non-vaccinated patients with high pretest probability, i.e., high likelihood of having the COVID-19 infection and of producing a detectable number of antibodies, which takes approximately one to three weeks from infection [5]. This point is well illustrated by the first clinical situation described above, where the epidemiological data were compelling, and sufficient time had elapsed to allow antibody detection.

For patients with low pretest probability, as in the second case described above (i.e., presenting within the first 7-10 days after symptom onset, with unclear exposure data), serological testing may be futile, yielding false-negative results. In this situation, an orthogonal testing algorithm should be employed. This implies the sequential use of two independent tests (SARS-CoV-2 antigen detection in nasopharyngeal secretions or RT-PCR testing) to validate serological findings. In our case, the patient was admitted to an isolation unit
Based on clinical suspicion, and orthogonal testing with the use of RT-PCR to confirm COVID-19 was employed. It is of note that this approach allowed both appropriate clinical management and the prevention of in-hospital spread of the SARS-CoV-2 infection.

**PREVENTING FALSE-POSITIVE TEST RESULTS**

Although serological tests are considered to have high sensitivity and specificity for SARS-CoV-2, exceptionally, false-positive results in non-vaccinated patients may occur. Available data are scarce, but the data that does exist suggest that, in patients with a moderate to high titer of the rheumatoid factor, IgM antibodies for SARS-CoV-2 can test false-positive, presumably due to antibody cross-reactivity [6]. In the same way, cases of cross-reactivity with serological tests for dengue fever and Kawasaki disease have been described [7,8]. These rare, but clinically relevant situations, need to be considered when interpreting test results.

**CONCLUSION**

In conclusion, the diagnostic validity of serological tests in non-vaccinated patients depends on the pre-test probability and the likelihood of producing a detectable number of antibodies. Hence, if serological testing is used to guide hospital admission, appropriate patient selection and cautious test interpretation is necessary to avoid misdiagnosis. Furthermore, RT-PCR remains the gold standard for confirming COVID-19.

**Conflict of interest:** None declared.