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Computerized Intelligence and Mathematical Models for COVID-19 Diagnosis: A Review

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Background: The COVID-19 infection, with its unknown aspects, has posed numerous challenges to public health systems worldwide, rapidly disseminating across borders. In the context of diagnosis, researchers are endeavoring to enhance diagnosis accuracy through improved decision-making processes. The present study aimed to conduct a comprehensive review of the benefits of using computerized intelligence and mathematical models for diagnosing COVID-19 infections.
Methods: We searched for relevant references on the PubMed and Google Scholar databases, with inclusion criteria and search strategies utilized to identify full-text articles in English. A narrative report of our findings was presented based on the synthesis of our data.
Result: The advantageous application of computerized intelligence has been approved in various medical domains, including prevention, diagnosis, and risk assessment.
Conclusion: Collaborative efforts are anticipated to enhance pandemic control with increased precision and reduced costs.

1. Introduction

In December 2019, a new strain of coronavirus was identified Wuhan, China, and subsequently disseminated worldwide, leading the World Health Organization (WHO) to declare a pandemic outbreak in March 2020 [1]. The pandemic infection develops a severe viral acute respiratory syndrome called SARS-COV2. This disease commonly induces respiratory symptoms, ranging from mild to severe respiratory failure, as well as other less common complications. The COVID-19 outbreak has created a global health emergency [2], imposing a significant economic burden and mobility restrictions in the world [3]. Compared to other types of SARS-CoV infections, COVID-19 exhibits a higher transmission rate and can be transmitted in various ways among different populations, including pregnant, immunocompromised, and addicted individuals [4]. Therefore, prompt diagnosis and early isolation of infected

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patients are crucial in breaking the chain of transmission. Real-time reverse transcription-polymerase chain reaction (RT-PCR) testing of nasopharynx specimens is currently considered the gold standard for diagnosing COVID-19. However, a reliable diagnosis also requires a physician`s clinical judgment, imaging findings, and laboratory tests [5]. Given the significant rate of false-negative results associated with RT-PCR testing for SARS-CoV2, performing high-resolution computed tomography (HRCT) of the lungs and assessing a patient′s clinical presentation and epidemiologic history are crucial. Rapid IgM and IgG tests based on immunoassay technology are also available, providing results within 10-15 min [6]. While these tests are efficient for screening purposes, the World Health Organization (WHO) has not recommended their use in patient management and follow-up [6]. Research has indicated that patients with comorbidities, such as diabetes or cardiovascular disease, are at a higher risk of experiencing complicated illnesses associated with COVID-19 [7]. Reports suggest that the virus can invade different organs functions, leading to serious complications in the heart, liver, lung, kidney, brain, and coagulation system [8, 9]. Among these complications, cardiomyopathy, myocarditis, ventricular arrhythmias, thromboembolic events, and hemodynamic instability are considered the most life-threatening [10]. According to the high burden of the disease on the economy of different countries and the mobility of people worldwide, early diagnosis and treatment are crucial in managing this disease. Indeed, the widespread transmission of COVID-19 has resulted in serious challenges to both the economy and public health worldwide [11]. According to Vinaytosh Mishra [12] in 2020, the more people become accustomed to social distancing protocols, the more they get attracted to telemedicine during the pandemic. Telemedicine has been recognized as a valuable method for connecting patients with physicians while maintaining self-quarantine. It not only provides safe management for patients, their families, and society but also helps healthcare providers estimate the risk and outcomes of infections. Despite limitations, such as the lack of physical examination, the new generation of computerized intelligence has improved telemedicine during the pandemic [13]. This study conducts a comprehensive review of relevant literature, with a focus on the critical role of telemedicine in diagnosing patients with COVID-19.

2. Materials and Methods

We reviewed the literature to identify studies emphasizing the key role of computerized intelligence in diagnosing COVID-19 infections. All full-text articles in English, published between February 2019 and August 2021, in Pubmed and Google Scholar databases, were included with the following keywords used in our search strategy: "diagnosis", "computerized intelligence", "COVID-19", "mathematical model", and "SARS-CoV-2". Relevant studies were selected to provide a comprehensive review of the widespread use of technology during the pandemic. Initially over 720 articles were identified from the scientific databases. After removing repeated articles, review articles, articles without the full text in English, and articles published in unaccredited journals (exclusion criteria), a total of 110 articles were obtained. Two researchers (Elham Sabouri and Ehsan Saburi) independently examined all abstracts, resulting in the inclusion of 26 articles related to the topic of our study.

3. Results and Discussion

The incubation period of COVID-19, which refers to the time between exposure to the virus and the onset of the symptoms, is estimated to be approximately eight days [14]. During this phase, individuals infected with the virus who do not display symptoms, known as asymptomatic carriers, can spread the virus. Some asymptomatic carriers may remain asymptomatic through the course of their infection. The sooner we can detect this group and isolate them, the better we will control the pandemic and reduce the rate of transmission. The clinical presentations of COVID-19 vary greatly ranging from asymptomatic cases to flu-like symptoms, up to life-threatening respiratory failure in severe cases. However, the clinical presentation of SARS-CPV-2 infection includes a variety of atypical symptoms and signs, such as cough, dyspnea, fever, respiratory symptoms, viral Pneumonia, and gastrointestinal discomfort; additionally, the infection may rarely manifest with diabetic ketoacidosis (DKA) [15, 16]. Therefore, ancillary examinations are needed to make an exact diagnosis of COVID-19, as well as the epidemiological history [17]. Currently, laboratory tests used to identify SARS-CoV-2 consist of RT-PCR, rapid IgG, and IgM tests, viral culture, and NAAT tests. The gold-standard test for SARS-CoV-2 identification is the real-time quantification RT-PCR (qRT-PCR), which is recommended as the routine confirmation test by the WHO [18]. There are some susceptibilities about the RT-PCR tests, as though it is not always considered an appropriate test in the case of point-of-care diagnosis. Preanalytical concerns such as issues with patient identification, improper specimen collection procedures, suboptimal swab characteristics and transportation, specimen contamination, and manual errors can lead to inaccurate results [19]. Moreover, the high cost of equipment and the need for biosafety conditions may make the test challenging to provide to large populations in many societies. On the other hand, taking the test after receiving antiretroviral therapy results in more false negative reports [20]. Although culture-based virus detection has provided valuable data about the pathogenesis of the virus for researchers, it cannot be used as a routine diagnostic tool in societies due to the long duration of the culture cycle [21]. In patients with COVID-19, certain laboratory abnormalities are frequently observed, including high serum C-reactive protein, increased lactate dehydrogenase, elevated alanine aminotransferase, aspartate aminotransferase, lymphopenia, modest prolongation of prothrombin times, mild thrombocytopenia, and elevated D-dimer values, etc.

However, these abnormalities are not specific to COVID-19 infection and may also be present in other chronic inflammatory diseases and cases of Pneumonia caused by other microorganisms [10, 22]. Point-of-care tests can be performed in clinical laboratories and patient care facilities, such as physicians' offices or emergency departments, providing a significant advantage by bringing the diagnostic test for SARS-CoV-2 closer to the patient [17]. Rapid IgM/IgG tests in immunoassay technology provide results in 10-15 min [6], making them appropriate for screening and early detection of patients. However, these tests have a lower sensitivity and positive predictive value compared to RT-PCR tests [23]. Lung CT scan is a standard diagnostic test for COVID-19 and presents unique features of respiratory involvement, such as diffuse, peripheral ground-glass opacities, and the rings of Saturn appearance [24, 25]. However, there are also some shortcomings associated with CT imaging, and the lack of evidence-based data about various features, as new features may be presented every day [26]. While the nucleic acid amplification test (NAAT) for SARS-CoV-2 is subject to false-negative results and has limitations in detection, chest CT is a simple and efficient method of detecting lung lesions and providing early-stage diagnoses [27]. However, reports show that chest CT findings are only expected in around 15% of patients [10]. Thus, a combination of epidemiological history, clinical manifestations, laboratory data, and imaging findings must be used to clinically diagnose the COVID-19 infection. A broad spectrum of laboratory tests can be used, including nucleic acid detection, immune identification technology such as Point-of-care Testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA), and blood culture [20], which can complicate the diagnostic process due to various variables. However, the diagnostic methods mentioned above do not provide specific and reliable diagnostic features to distinguish COVID-19 from other viral infections or pneumonia. The lack of an appropriate diagnostic test poses significant obstacles in gathering results for diagnosis. Further, the absence of an integrated and inclusive recording data system about the clinical status of patients in different stages of the disease results in an enormous amount of needed data being missed, which can lead to a delay in the time of diagnosis.

3.1 Factors influencing the diagnosis and possible delayed diagnosis

Breaking the chain of transmission is crucial to end the COVID-19 pandemic. While vaccination has reduced the number of severe infections, only a small portion of the global population has been vaccinated. Thus, early diagnosis and timely remain critical to breaking the transmission chain. However, there are considerable challenges in making accurate diagnoses of COVID-19, and diagnostic errors can negatively impact individual patient health and the effectiveness of public health policies and emergency plans authorized by national and international organizations [28]. COVID-19 shares similar symptoms with other respiratory illnesses, such as seasonal CoV, adenovirus, influenza, bocavirus, para-influenza, human metapneumovirus, Bordetella pertussis, respiratory syncytial virus rhinovirus, Mycoplasma pneumonia, Legionella pneumophila, and even the mosquito-borne dengue virus [29]. Therefore, early screening is essential for making the correct diagnosis at the right time, as the diversity of initial manifestations and subclinical symptoms can delay the diagnosis [30, 31]. The safety and quality of laboratory tests, such as RT-PCR testing, can be affected by numerous factors, including patient and/or sample misidentification, insufficient and inappropriate collection of material (for quality or volume), transportation and storage issues(e.g., prolonged transportation time, injury exposure, and defective cold chain), and the presence of interrupting substances (e.g., the release of cellular components interfering with the assay due to whole-blood freezing, use of inappropriate additives). Procedural points, such as pipetting errors during manual sample preparation or aliquoting, cross-contamination, and sample mismatch can also impact the quality of RT-PCR testing. Sample contamination, even in the presence of trace amounts of external DNA, and performing the test for patients with a history of antiretroviral therapy are major concerns that can lead to false-negative results [32, 33]. An alternative to the widely used RT-PCR diagnostic method for detecting SARS-COv-2 is the development of antigen detection tests, which directly detect viral particles in nasopharynx specimens [34]. However, the availability of these tests is limited in many regions of the world. The improvement of in-time diagnosis cannot eliminate the virus and stop the pandemic. Numerical simulations and sensitivity indicate that such improvements can lead to positive outcomes, including a reduction in the primary reproduction number, a decrease in the risk of transmission, and prevention of a COVID-19 endemic. For instance, the effort to shorten the peak time and reduce the peak value of new confirmed cases and new infections can lead to a decrease in the cumulative number of confirmed cases and total infections. However, to effectively control the spread of the virus, stricter prevention strategies, in addition to improved diagnostic plans, are needed. Such strategies include early isolation of patients following the first clinical manifestation, isolating and quarantining suspected cases similarly to confirmed ones, implementing an inclusive data system, increasing essential equipment such as the number of beds in hospitals, and providing close follow-up for patients using an organized tracking system. These measures are expected to break the transmission chain [35]. The person-to-person transmission of SARS-COv-2 highlights the critical role of diagnostic delay in disseminating the virus [36]. Asymptomatic carriers and symptomatic patients who do not accept isolation and quarantine due to mild or moderate symptoms can transmit the infection to healthy individuals and their family members, resulting in an increased risk of spatial transmission and potential infection of COVID-19. Patient identification is, therefore, of great importance to public health, as it allows for the confirmation of infection, treatment, and tracking of the patients. However, various challenges, as mentioned earlier, can delay

the diagnosis, leading to an increase in infections, economic loss, and other problems in different aspects of people's lives [37].

3.2 Challenges against old and new diagnostic methods

The diagnosis of SARS-CoV-2 can be achieved through two strategies, namely the detection of viral RNA detection or the detection of antibodies produced following exposure to the virus. Polymerase chain reaction (PCR) or nucleic acid hybridization are commonly used techniques for detecting the SARS-CoV-2 viral RNA. Serological and immunological assay techniques, such as ELISA, are also employed to detect the antigens or antibodies of the virus. It should be considered that both detection categories are critical and complementary to each other. Viral RNA detection is useful for diagnosing active infection. On the contrary, serological assays are essential in identifying individuals who have developed an immune response to the virus, subsequently releasing antibodies to remove the infection [38]. Recently, RT-PCR and immunological assays are the preferred diagnostic methods used globally These diagnostic techniques can be used during the acute phase of infection, after the infection, and following vaccination to monitor innate immune system response [39]. However, laboratory staff must be well-trained to perform the tests appropriately. Furthermore, while PCR results can be obtained within a few days, immunological assays require the complex production of antibodies and recombinant proteins. It is evident that investigating novel diagnostic methods with higher sensitivity and lower costs for the detection of SARS-CoC-2 is an important research priority for a growing number of researchers worldwide. In the context of the diagnosis of SARS-CoV-2, it is expected that biosensors will eventually replace real-time detection and routine measurements. Biosensors represent a class of bioanalytical devices that integrate the selectivity features of a biomolecule with the sensitivity of a physicochemical transducer. Various types of biosensors have previously been developed and applied in the diagnosis of COVID-19 [40]. Sheikhzadeh et al. [40] reviewed various serological and molecular methods currently used for detecting SARS-CoV-2. While RT-PCR is capable of detecting viral DNA in respiratory samples, blood, saliva, urine, and stool, it is not widely used due to the high cost of essential thermocyclers and the need for experts to perform the assay and interpret the findings. Additionally, standard control is necessary to mitigate errors that may lead to false-negative results. LAMP methods are considered reliable alternatives for RT-PCR, associated with acceptable sensitivity and specificity. However, certain kits have shown lower sensitivity. LAMP assays typically require about 30 min to perform and allow for the use of crude samples, enabling their possible integration into point-of-care (POC) tests. CRISPR represents another method developed for detecting SARS CoV-2, offering high sensitivity and specificity and capable of being performed in one hour. Furthermore, CRISPR can be coupled with lateral flow assays. An advantage of LAMP and CRISPR is that they do not require an expensive thermocycler. Another method performed by non-professional staff, using blood or serum samples, is called Lateral flow. The test takes only 15 minutes to obtain the results. Although they have the disadvantage of prolonged time of antibody production, they are minimally affected by problems associated with storage, transport, and sample collection. ELISA is another alternative that is easily performed, however, neither ELISA nor lateral flow assays are likely to have benefits in early detection. However, research suggests the benefits of using it to investigate herd immunity and check the immunity of healthcare providers [40].

3.3 The role of computational intelligence in radiological diagnosis

In patients infected with COVID-19, imaging methods are used to assess pulmonary involvement and respiratory conditions. Several research studies have demonstrated the advantages of using lung CT scans as the most suitable imaging modality for evaluating pulmonary involvement during the infection. Given the varied patterns of lung involvement observed in the findings of lung CT scans, mathematical models that appraise imaging characteristics may be beneficial for risk stratification not only in the case of diagnosis but also for prognosis prediction [41]. The first step towards determining specific radiologic involvement patterns in patients with COVID-19 is through computational intelligence. These radiologic patterns can then be matched with their accompanying clinical signs and symptoms to define which radiologic features are most commonly associated with severe clinical conditions and which ones are mostly correlated with a mild presentation [42]. Intelligent computational analysis of radiologic patterns, coupled with concurrently recorded laboratory test results, can identify possible correlations between radiologic features and laboratory data. Moreover, the co-presentation of imaging features and laboratory findings remarks may also indicate the possibility of severe respiratory failure, followed by a poor prognosis. Through computational intelligence, radiologic features and different outcomes of COVID-19 can be analyzed together, providing mathematical models of significant relationships between radiologic findings and patient prognosis. This pattern determination represents a form of risk stratification based on radiologic patterns that can aid physicians and health care providers in deciding whether to admit the patient to the intensive care unit with intensive monitoring, admit them inward, or determine that hospitalization is unnecessary [43]. In addition, using computational analysis to identify radiologic patterns can help determine the prognosis of COVID-19 patients with different patterns of lung involvement. This approach as it enables healthcare providers to identify patients with poor prognoses based on their radiologic features, potentially saving lives and improving patient outcomes.

3.4 The role of computational intelligence in laboratory diagnosis

The recent increase in the number of COVID-19 cases across the world has encouraged a global effort to develop point-of-care platforms for rapid diagnosing of SARS-CoV-2 [44]. At present, two common laboratory tests, PCR and rapid tests, are utilized for diagnosing COVID-19 infection. However, PCR tests have limited sensitivity and specificity. These tests are also time-consuming, taking approximately 24 h to provide results. Furthermore, patients awaiting their test results may continue to spread the infection. In contrast, rapid tests are readily available and inexpensive, producing immediate results, making them suitable for early patient detection. Rapid tests offer a significant advantage in disease control by providing early detection of patients, which is crucial in breaking the transmission cycle. Moreover, the affordability and accessibility of these tests make them a feasible diagnostic option for all healthcare clinics, laboratories, hospitals, and screening centers, without any budget waste. Equipped laboratory centers, screening offices, or other healthcare clinics and hospitals can use these rapid tests to detect patients early [45]. Subsequently, these organizations and offices must log the test results in an inclusive record system to provide data for analysis by computational intelligence. By evaluating the accuracy and effectiveness of screening protocols and the spread of the disease in different areas, governmental organizations and healthcare providers can make informed decisions, such as implementing lockdowns in specific areas rather than state-wide, reducing the economic burden of the pandemic disease.

3.5 The role of computational intelligence in clinical diagnosis

In order to reduce the pressure on healthcare systems, it is imperative to improve diagnostic and preventive strategies while providing proper management for infected patients. Therefore, there is an urgent need for models that can estimate the risk of infection and predict the poor outcomes following infection by using a combination of several characteristics and variables. These models can assist healthcare staff in triaging patients, particularly in situations limited resources [46, 47]. The main goal of these prediction models is to support healthcare providers, physicians, and health system managers in decision-making process [48]. The accuracy of diagnosing SARS-CoV-2 infections can be improved by developing more integrated point-of-care molecular devices. These short-turnaround-time (STAT) tests are crucial for real-time patient management and infection control strategies. They can differentiate COVID infection from less aggressive infectious respiratory disorders with lower attack rates. In addition to being secure, simple, and swift, these tests can be performed in local hospitals and clinics with essential equipment and well-trained staff [49]. Computational intelligence plays a vital role in controlling pandemic diseases by providing mathematical models of clinical, laboratory, and radiologic features [50]. These findings may help all healthcare providers in making decisions regarding a definite diagnosis of the disease. These models include those that indicate the risk of developing COVID-19 or being admitted to a hospital with a severe clinical condition, those that predict the presence of covid-19 in patients with suspected infection, and those that predict the prognosis or course of infection in patients with COVID-19 [48]. Through computational analysis of clinical symptoms and signs, we can investigate the more common clinical manifestations of the disease and identify significant relationships between clinical presentations and severe or mild infection and prognosis. These prediction models can be classified into three categories: models for the general population to predict the risk of having COVID-19 infection based on contact history and clinical presentations, models for healthcare providers to diagnose the disease, assess the risk of severe disease, and perform essential diagnostic modalities such as imaging or laboratory tests, and models for health system managers and governmental organizations to assess the prognosis of patients and the epidemiological pattern of spreading the pandemic disease [51]. The data resulting from computational analysis provides doctors and healthcare workers with a risk-based approach to suspected patients [52]. This enables them to decide what kinds of tests should be performed, such as rapid tests or imaging [53]. Furthermore, patients are expected to perform diagnostic tests themselves using telemedicine. Although telemedicine-guided PCR-based self-collection approaches have appeared to be less sensitive, they are thought to be beneficial in minimizing the exposure of healthcare staff to affected patients [54]. Computational analysis has identified several patient conditions that are strongly associated with poor prognosis, including severe dyspnea, oxygen saturation below 90%, and altered mental status. Based on these findings, it is crucial to establish clear criteria or protocols for hospital admission to ensure prompt and appropriate treatment [24]. Using these models, a comprehensive step-by-step protocol can be established to determine the needed approaches for patients with known exposure, suspected exposure, or no known contact [55]. To prevent the further spread of COVID-19 through delayed detection, two critical steps must be taken. First, a primary patient detection system must be designed. This involves dedicating specific health centers to screening suspected patients, including those with known contact or clinical manifestations. The second step involves establishing an effective patient tracking system to monitor and manage diagnosed patients, including a comprehensive record of their contacts and movements to facilitate contact tracing. The location and admission criteria for these centers should be announced through the media. It is crucial to inform the public that individuals with known or suspected contact with patients with COVID-19 or those who have visited high-risk areas such as crowded places or presented with typical symptoms should seek admission to these centers [56]. In addition, to enable early patient detection, these centers should be

equipped with primary and necessary facilities, including knowledgeable staff, electronic devices for recording patient information in the risk stratification system, and kits for rapid tests [57]. Also, medical equipment for physical examination, such as a thermometer, pulse oximeter, and blood pressure monitor is required to assess pantient's clinical presentation accurately. At these screening centers, healthcare workers should document all signs and symptoms of patients and assess physical examinations using the risk stratification system designed by computational intelligence [58]. Additionally, the healthcare providers should record patint's history of contact with known or suspected patients in the last two weeks. By capturing this information, healthcare providers can estimate the risk of infection in a patient through the aforementioned models. Based on their risk assessment, the healthcare providers can decide whether the patient requires a rapid test, CT scan, hospital admission, or no further action [59]. Patients who are asymptomatic or have no known or suspected contact, and are at low risk of infection, need no further action. However, healthcare workers should warn these patients of potential red flags, including dyspnea and severe weakness, and recommend that they seek medical attention if they experience any of these symptoms. Asymptomatic patients with a known history of contact with infected patients are considered a moderate risk and should undergo rapid testing. If the test result is negative, they can be managed as low-risk patients. However, if the test result is positive, they will be considered infected and should undertake further steps (Fig.1). High-risk groups for COVID-19 infection include patients with a positive history of known contact with infected patients and typical clinical manifestations. These patients should undertake rapid tests besides a thorough assessment of the severity of their disease and clinical manifestations. If hospitalization is indicated based on the test results and patient evaluation, they should be admitted to the hospital for further management. Otherwise, they should be quarantined at home. All patients with moderate to high risk of COVID-19 infection should be entered into the patient tracking system. Upon entering the system, healthcare providers should conduct a comprehensive history of the patient's commutes and contacts over the last two weeks. All the places the patient was admitted to or all people they had contact with should be recorded in the tracking system. Using the collected data, an automatic alarm system should be designed to notify all the places the patients visited, such as banks, organizations, and offices to perform screening and early detection protocols for all individuals who had contact with the patient. According to the history taken in the patient tracking system, all individuals who had contact with a COVID-19 patient in the last two weeks should be notified of the possible infection and admitted to screening centers for further evaluation and testing. In cases where patients cannot provide a reliable due to altered mental status or dementia, government personnel should track the patient's admissions and contacts history. As described above, we can use the models in the case of risk stratification, diagnostic strategy selection, and potential prevention. Moreover, the use of the models regarding disease management and recovery has been approved through the studies [60]. However, researchers all around the world are investing their efforts into developing more advanced and high-quality models to enhance the accuracy of diagnosis and choosing the appropriate treatment strategies. Collaborative efforts between computer engineers and medical researchers are anticipated to lead to the development of novel methods for controlling the pandemic. Furthermore, the integration of technology and mathematical models can equip the healthcare system with more accurate and cost-effective diagnostic and prognostic tools [61, 62]. However, the careful monitoring of computerized organizations is essential to improve safety and sensitivity within the standard level.

4. Conclusion

Despite the unfortunate health-related burden caused by the COVID-19 pandemic, it has provided an opportunity to foster collaboration between technology and medicine. The crucial role of computerized intelligence in various medical fields has been well-established through numerous research studies. Telemedicine, for instance, has emerged as a promising tool that not only facilitates doctor-patient interactions while adhering to social distancing rules but also empowers physicians to enhance their decision-making capabilities in the diagnosis and treatment of COVID-19 infection. However, while diagnostic and prognostic models are widely used among physicians, it is crucial to investigate the most accurate models with the least diagnostic bias through rigorous research studies. Efficient evaluation and monitoring of these models are essential to improve their sensitivity and specificity within the standard level. By doing so, healthcare providers can leverage the benefits of computational models while mitigating potential risks, improving patient outcomes, and ultimately controlling the spread of the pandemic.

Authors' Contributions

Elham Sabouri, Amin Saburi, Ehsan Saburi: search strategy and drafting; supervising the project; editing the manuscript. Reza Gerami, Tina Zeraati, Mostafa Ghanei: search strategy and drafting.

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Conflicts of Interest

The authors declare no conflicts of interest.

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