Neurology Asia 2024; 29(1) : 105 – 113

Clinical profile and prognosis of COVID-19 patients with neurological manifestations: A city-wide cross-sectional study in Iran

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Abstract

Background & Objective: In this study, we aimed to evaluate past medical and social history, initial symptoms, laboratory values, clinical course, and outcome of COVID-19 patients with neurological manifestations in Shahroud, Iran. *Methods:* In this cross-sectional study, data from all registered COVID-19 patients in Shahroud during March 2020 to July 2021 (n=30,228) were initially reviewed in terms of the prevalence of neurological symptoms. Additionally, the data of COVID-19 patients admitted to Shahroud's hospital (n=8,412) was evaluated in details according to the clinical profile, socio-demographic characteristics, laboratory findings, and in-hospital outcomes. Data were compared between COVID-19 patients with and without neurological manifestations. Predictive factors of ICU admission and mortality in COVID-19 patients with neurological manifestations were also evaluated. *Results:* Fever, chills, anorexia, myalgia, arthralgia, nausea, vomiting, cough, dyspnea, diarrhea and abdominal pain were significantly more common among COVID-19 patients with neurological symptoms compared to COVID-19 patients without such symptoms. Furthermore, smoking, drug abuse and history of underlying diseases were significantly more prevalent among the former group. Patients with neurological symptoms were more likely to be admitted to the hospital and ICU and had higher mortality rates. In terms of laboratory findings, hemoglobin, hematocrit, platelet count, and albumin levels were significantly lower in the patients with neurological symptoms. Age ≥ 50 years and history of underlying diseases were associated with increased ICU admission in COVID-19 patients with neurological manifestations.
Conclusions: The following strategies could prove beneficial for COVID-19 patients: (i.) reduction of smoking and substance abuse, (ii.) close monitoring of more symptomatic patients and patients with a history of underlying diseases for neurological manifestations, (iii.) providing appropriate intensive care for older patients and those with underlying diseases who have neurological manifestations and (iv.) early detection of anemia, thrombocytopenia, and hypoalbuminemia.

Keywords: COVID-19, neurological manifestations, clinical course, outcome

INTRODUCTION

In late December 2019, a new type of coronavirus broke out in Wuhan, China. The new virus was called SARS-COV-2 which resulted in a global pandemic. In the beginning of the pandemic, the most common symptoms of coronavirus disease-2019 (COVID-19) included fever, cough, dyspnea, myalgia, and fatigue.[1] Gradually, several studies have reported different neurological manifestations of COVID-19 involving the central and peripheral nervous systems. These

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Date of Submission: 21 April 2023; Date of Acceptance: 6 November 2023

https://doi.org/10.54029/2024etk

manifestations included headache, impaired consciousness, seizures, dizziness, ataxia, smell and taste dysfunction, and neuropsychiatric symptoms, and according to studies, at least one neurological symptom has been observed in more than 90% of patients with COVID-19.[2-5] Besides its common neurological manifestations, SARS-COV-2 can also cause significant neurologic complications, including meningoencephalitis, ischemic and hemorrhagic stroke, peripheral and cranial neuropathies, and Guillain-Barre syndrome.[3,4,6] It has been found that critical neurologic events, especially manifestations such as acute cerebrovascular disease, loss of consciousness, and skeletal muscle damage, are more common among patients with severe COVID-19 infection.[3,7] It has also been seen in some cases that neurological manifestations can be the sole presenting symptoms of COVID-19.[7]

Although several pathophysiological pathways have been proposed for the progression of COVID-19, the cellular angiotensin-converting enzyme 2 (ACE2) receptor has been proposed as a main site of entry for SARS-CoV-2. ACE2 receptors have been detected over neurons and glial cells.[4] The proposed neurotropic mechanisms for SARS-COV-2 include direct or indirect viral entry via the hematogenous route or neuronal retrograde dissemination.[7] The virus can infect endothelial cells of the blood-brain barrier to gain access or infect leukocytes for dissemination into the central nervous system (CNS), as the hyperemic brain tissue and edema as well as degenerated neurons have been observed in the autopsy results of some patients.[8] SARS-CoV-2 can also affect the nervous system indirectly by inducing neuroinflammation through cytokine storms and immune-mediated mechanisms. Moreover, COVID-19-induced coagulopathy and hypoxia can predispose patients to cerebrovascular accidents.[9]

Overall, COVID-19 has become a great challenge for neurologists. This necessitates extensive research to determine the characteristics and underlying mechanisms of COVID-19's neurological manifestations in order to timely diagnosis and make efficient treatment. Although various studies have been performed on this topic, data regarding clinical course and outcome of COVID-19 patients with neurological involvement is still lacking. In this study, we aim to evaluate past medical and social history, initial symptoms, laboratory values, clinical course, and final outcome of COVID-19 patients with neurological manifestations in Shahroud, Iran.

METHODS

Study design

In this cross-sectional study performed under the supervision of Shahroud University of Medical Science in Iran, all COVID-19 patients in Shahroud from March 2020 to July 2021 were included. Eligible COVID-19 patients were identified by a positive SARS-COV-2 nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR) test. Exclusion criteria included lack of patient consent or cooperation and incomplete patient records. Patient death was defined as Glasgow Coma Scale <3 and undetectable vital signs.

Data collection

Data were collected by interviewing outpatients and reviewing inpatients' hospital charts. Clinical symptoms including (i.) general symptoms such as fever, chills, sore throat, rhinorrhea, epistaxis, nausea, vomiting, diarrhea, abdominal pain, cough, dyspnea, anorexia, myalgia, and arthralgia, and (ii.) neurological symptoms such as headache, dizziness, vertigo, altered mental status, ataxia and seizures in all confirmed COVID-19 cases were recorded. The rest of the data were evaluated in COVID-19 patients that presented to Shahroud's hospitals (regardless of their admission status). These data included demographic characteristics, including age, gender, history of smoking or substance abuse, and underlying diseases, such as pulmonary disease, cardiovascular disease, diabetes, and chronic kidney disease (CKD). The laboratory values including complete blood count, renal and liver function test, electrolytes, inflammatory markers, lipid profile, LDH and CPK were documented. Moreover, hospital and intensive care unit (ICU) admission status, length of hospital stay, and the outcome of the patients were also recorded.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0. SPSS, Inc., Chicago, IL, USA). Demographic characteristics and other categorical variables were reported as frequencies and percentages. Continuous variables were reported as means and standard deviations. Chi-Square Test and the Independent Samples T-test were used for the comparison between COVID-19 patients with and without neurological manifestations. Multivariate regression analysis with 95% confidence intervals (95% C.I.) was used to

determine the factors affecting ICU admission and mortality in COVID-19 patients with neurological manifestations. P-value ≤ 0.05 was considered statistically significant.

Ethics

All data were used to evaluate the study-related objectives, taking into consideration the confidential principles of patients' information. Informed consent was obtained from all outpatients based on the Declaration of Helsinki, and the research has been approved by the Ethics Committee of Shahroud University of Medical Sciences, Shahroud, Iran (Ethics Committee code: IR.SHMU.REC.1398.160).

RESULTS

The total number of confirmed COVID-19 cases in the study period was 30,228. A total of 475 patients were identified of having neurological symptoms (mean age 56.4 ± 19.4). According to Table 1, fever, chills, anorexia, myalgia, arthralgia, nausea, vomiting, cough, dyspnea ($p < 0.001$), diarrhea ($p = 0.004$) and abdominal pain ($p = 0.008$) were more common among COVID-19 patients with neurological symptoms compared to COVID-19 patients without such symptoms.

Of the total COVID-19 cases, 8,412 patients had been admitted to Shahroud's hospitals, among whom 213 had documented neurological symptoms (mean age 59.4 ± 18.9). There was no difference in gender distribution among COVID-19 patients with neurological symptoms ($p = 0.784$), however, Smoking ($p = 0.001$), drug abuse, and history of underlying diseases ($p < 0.001$) were more common among COVID-19 patients with neurological symptoms compared to COVID-19 patients without such symptoms. The former group was also more likely to be admitted to hospital and ICU and had higher mortality rates ($p < 0.001$). Length of hospital stay was similar in the two groups ($p = 0.360$) (Table 2).

Investigation of the laboratory findings demonstrated that hemoglobin ($p = 0.013$), hematocrit ($P = 0.004$), platelet count ($p = 0.030$) and albumin ($p = 0.012$) levels were significantly lower in COVID-19 patients with neurological symptoms compared to COVID-19 patients without such symptoms. No significant difference was found in other laboratory values between the two groups ($p > 0.05$) (Table 3).

Multivariate regression analysis demonstrated that age ≥ 50 years ($p = 0.013$) and history of underlying diseases ($p = 0.006$) were significantly associated with increased ICU admission in COVID-19 patients with neurological manifestations. No significant interaction was observed between the predictive factors. Moreover, none of the measured variables had a significant relationship with mortality in these patients ($p > 0.05$) (Table 4).

Table 1: Initial clinical symptoms of COVID-19 patients by their neurological symptoms status

	Presence of neurological symptoms		
n (%)	**No**	**Yes**	**P value**
Fever	5,912 (19)	181 (38)	**<0.001**
Chills	4,567 (15)	130 (27)	**<0.001**
Anorexia	3,879 (13)	154 (32)	**<0.001**
Sore throat	4,394 (14)	85 (17)	0.057
Rhinorrhea	2,423 (8)	29 (6)	0.131
Epistaxis	57 (0.1)	1 (0.2)	0.601
Myalgia	7,563 (31)	156 (32)	**<0.001**
Arthralgia	5,296 (17)	125 (26)	**<0.001**
Nausea	2,610 (8)	83 (17)	**<0.001**
Vomiting	1,114 (3)	41 (8)	**<0.001**
Diarrhea	1,736 (5)	43 (9)	**0.004**
Abdominal pain	1,447 (4)	42 (14)	**0.008**
Dyspnea	4,096 (13)	176 (37)	**<0.001**
Cough	7,099 (23)	177 (37)	**<0.001**

Table 2: Past medical and social history, admission status and outcome of COVID-19 patients by their neurological symptoms status

	Presence of Neurological Symptoms		
n (%)	**No**	**Yes**	**P value**
Smoking	429 (5)	24 (11)	**0.001**
Drug abuse	222 (3)	16 (10)	**<0.001**
Other underlying diseases	2,111 (25)	100 (46)	**<0.001**
Hospital admission	2,906 (35)	148 (69)	**<0.001**
ICU admission	461 (5)	50 (23)	**<0.001**
Mortality	261 (8)	34 (21)	**<0.001**
Length of hospital stay (mean ± SD)	8.6 ± 12.7	9.6 ± 13.8	0.360

ICU: intensive care unit, SD: standard deviation.

Table 3: Laboratory values of COVID-19 patients by their neurological symptoms status

	Presence of Neurological Symptoms		
Mean ± SD	**No**	**Yes**	**P value**
WBC × 10^3	6.2 ± 2.4	5.9 ± 2.3	0.552
Neutr%	69.7 ± 12.9	71.1 ± 13.7	0.182
Lymph%	25.1 ± 12.3	23.8 ± 13.1	0.223
Mono%	2.8 ± 1.1	2.7 ± 1.2	0.425
Hb	13.2 ± 1.9	12.7 ± 1.8	**0.013**
Hct	39.9 ± 5	38.8 ± 5.4	**0.004**
Plt × 10^3	209.8 ± 78.4	202.3 ± 72	**0.030**
Urea	36.9 ± 24.6	38.1 ± 23.9	0.552
Cr	1.1 ± 0.7	1.1 ± 0.6	0.661
Na	136.1 ± 4.1	136 ± 4.9	0.746
Mg	2.2 ± 5.1	2.1 ± 0.3	0.803
Chol	132.3 ± 38	139.9 ± 41.7	0.112
BS	134.2 ± 72.8	147.7 ± 88.2	0.074
TG	108.4 ± 100.6	117.3 ± 56.8	0.456
HDL	34.1 ± 18.7	30.8 ± 16.3	0.628
LDL	74.5 ± 23	76.9 ± 24.2	0.387
AST	41.5 ± 72	39.8 ± 37.6	0.784
ALT	37.8 ± 66.9	28.2 ± 28.3	0.094
ALK-P	190.2 ± 130.3	205.3 ± 104.9	0.186
Ferritin	343.3 ± 323	399.2 ± 352.3	0.449
LDH	509.3 ± 298.7	549.2 ± 285.4	0.194
Alb	3.5 ± 0.6	3.2 ± 0.6	**0.012**
ESR	37.1 ± 27.2	41 ± 30	0.130

WBC: white blood cells, neutr: neutrophils, lymph: lymphocytes, mono: monocytes, Hb: hemoglobin, Hct: hematocrit, Plt: platelets, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Cr: creatinine, FBS: fasting blood sugar, BS: blood sugar, Chol: total cholesterol, TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALK-P: alkaline phosphatase, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, SD: standard deviation.

Table 4: Multivariate regression analysis of variables affecting ICU admission and mortality in COVID-19 patients with neurological manifestations

	ICU Admission			Mortality		
Variable	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age ≥ 50 years	2.28	1.18, 4.40	**0.013**	2.09	0.74, 5.86	0.161
Male gender	0.99	0.59, 1.67	0.992	1.53	0.78, 2.99	0.212
Smoking	1.54	0.80, 2.96	0.197	0.56	0.21, 1.48	0.251
Underlying diseases	2.11	1.23, 3.62	**0.006**	1.74	0.85, 3.57	0.126

ICU: intensive care unit, CI: confidence interval, OR: odds ratio.
Underlying diseases: diabetes, cardiovascular disease, respiratory disease, liver disease, cancer.

DISCUSSION

In this cross-sectional study, we comprehensively evaluated the clinical and paraclinical profile, as well as the clinical outcomes of a large cohort of patients with COVID-19 in Shahroud, Iran. Overall, our findings demonstrated that several study variables are associated with the incidence of neurological symptoms in COVID-19 patients. Accordingly, age ≥ 50 years and a history of underlying diseases were significantly associated with increased ICU admission in COVID-19 patients with neurological manifestations.

The significance of demographic characteristics in the prognosis of COVID-19 patients has been extensively investigated in previous studies. Consistent with our findings, the fact that increasing age causes more adverse outcomes in COVID-19 patients has been confirmed in a study conducted in Italy.[10] In another study, age over 70 years has been introduced as a factor for poorer outcome.[11] Additionally, while we found that gender was not an influential factor in the development of neurological manifestations in COVID-19 patients, Severo *et al*.[4] reported that there was a male predominance in the incidence of acute vascular neurological manifestations and a female predominance in the incidence of acute inflammatory neurological manifestations in COVID-19 patients, suggesting that gender might contribute to the pattern of neurological manifestations in COVID-19.

Our findings demonstrated that the history of smoking and substance abuse were more common among COVID-19 patients who presented to the hospital with neurological symptoms compared to COVID-19 patients without neurological symptoms. In line with our findings, different studies have demonstrated the association between tobacco smoke and cerebrovascular-neurological dysfunction. The mechanisms behind the toxic effects of smoking include inflammation, oxidative stress, atherosclerosis, disruption of the blood-brain barrier (BBB), and hyperactive immune response. Smokers are more vulnerable to bacterial and viral inflammatory neuropathologies compared to non-smokers.[12] Brake *et al*. showed that smoking can upregulate the ACE2 receptor which acts as a binding site for the S protein of SARS-CoV-2.[13] ACE2 receptors have been detected in neurons and glial cells.[4] Substance use disorder has been frequently reported to increase the risk of infectious diseases, which might be due to inhalation of contaminated smoke or sharing contaminated injection equipment.[14] Substance use disorder is also associated with various neurologic complications such as seizures, stroke, altered mental status, and ataxia.[15] These findings could explain the association found between smoking and substance abuse and the incidence of neurological symptoms in COVID-19 patients in our study. Considering the rise in smoking and substance abuse due to COVID-19-related depression and anxiety[16], it is important to effectively address this problem through psychosocial strategies to prevent its' detrimental effects on mental and physical health during the COVID-19 pandemic.

The findings of the present study also revealed that COVID-19 patients with a history of underlying diseases were more likely to develop neurological symptoms. History of underlying diseases was also associated with increased ICU admission in COVID-19 patients with neurological manifestations. Previous studies have shown that comorbidities such as chronic obstructive pulmonary disease (COPD), cardiovascular and cerebrovascular diseases, diabetes, hypertension, and CKD were associated with more severe infection and poorer outcomes in COVID-19 patients.[17,18] Siow *et al*. also showed that patients with comorbidities are more likely to suffer from

stroke as a complication of COVID-19 and have higher ICU admission and mortality rates.[19] The study conducted by Frontera *et al*. also showed that comorbidities such as hypertension, diabetes, hyperlipidemia, venous thrombosis, and atrial fibrillation were more common in patients with neurological symptoms than in patients without neurological symptoms.[20] The possible underlying mechanisms for these findings include vascular endothelial injury, dysfunctional hemostatic system, and pro-inflammatory state or chronic inflammation associated with these comorbidities. Up-regulation of ACE2 is probably to blame for the severity of disease in diabetic and hypertensive patients.[18]

We further demonstrated that age ≥ 50 years was significantly associated with increased ICU admission in COVID-19 patients with neurological manifestations. This is in line with previous studies that have reported that increased age is associated with adverse outcomes and high mortality in COVID-19 patients.[21,22] Furthermore, in our study, COVID-19 patients who developed neurological symptoms were more likely to be admitted to the hospital and the ICU and had higher mortality rates compared to COVID-19 patients without neurological symptoms ($p = 0.000$). This is in agreement with a previous study that showed that patients with COVID-19 encephalitis had an increased need for ICU admission and higher mortality rates compared to the general population of COVID-19 patients.[6] Espiritu *et al*.[23] also found out that new-onset neurological symptoms were associated with higher rates of ICU admission and mortality in hospitalized COVID-19 patients. However, in another study, it has been reported that the presence of neurological symptoms, despite the effect of the severity of the disease, did not affect the mortality in patients with these symptoms.[24] Moreover, no association was found between the length of hospital stay and neurological symptoms in the mentioned study, which is similar to the findings in our study. This issue can be related to the fact that the SARS-CoV-2 virus can penetrate into the cardiorespiratory centers of the patient's brain stem through transsynaptic transmission and cause a disturbance in them, thus causing the deterioration of the patients' respiratory condition and increasing their needs to be ventilated.[25] Moreover, the increase in ICU admission and mortality rates can be due to COVID-19-related neurological complications such as meningoencephalitis, ischemic stroke, and cerebral hemorrhage[2,3], though this association needs to be confirmed with further research. These findings emphasize the need for vigilant monitoring of COVID-19 patients with neurological symptoms to properly identify and treat neurological complications and prevent possible long-term morbidities.

Considering the pattern of symptoms accompanying neurological manifestations, our study showed that fever (38%), dyspnea (37%), and cough (37%) were the most common clinical symptoms among COVID-19 patients who had neurological manifestations, which were followed by anorexia (32%) and myalgia (32%). On the other hand, myalgia (31%) and cough (23%) were the most common clinical symptoms among COVID-19 patients without neurological manifestations, with the other symptoms being less prevalent. Our findings further showed that fever, chills, anorexia, myalgia, arthralgia, nausea, vomiting, cough, dyspnea, diarrhea and abdominal pain were significantly more common among COVID-19 patients with neurological symptoms. In the study conducted by Flores-Silva *et al*., dyspnea is known to be associated with neurological symptoms in patients with COVID-19 and it was also seen that a very high percentage of COVID-19 patients with neurologic manifestations suffer from symptoms such as cough and fever.[24] In other words, these patients were more symptomatic at presentation. Furthermore, neurological complications such as encephalitis and acute cerebrovascular events occur more commonly in patients with severe COVID-19 infection.[2,6,7] Therefore, it may be beneficial for physicians to monitor more symptomatic COVID-19 patients closely for possible neurological manifestations.

Evaluation of the laboratory values in our study, demonstrated that hemoglobin, hematocrit, and platelet count were significantly lower in COVID-19 patients with neurological symptoms compared to those without such symptoms. According to Bergamaschi *et al*., anemia is a common and persistent finding in COVID-19 during hospitalization, presumably through different mechanisms, including chronic inflammation, thrombotic microangiopathy, and autoimmune hemolysis.[26] Anemia has been identified as an independent risk factor for severe and critical COVID-19. For instance, COVID-19 patients with anemia are more likely to have increased IL-6, indicating a severe inflammatory reaction. Moreover, insufficient hemoglobin impairs the oxygenation capability of blood and exacerbates anoxia in multiple organs and

tissues.[27] On the other hand, COVID-19 depletes platelets through various mechanisms, including (i.) infection of bone marrow stem cells, (ii.) autoimmune platelet destruction, and (iii.) increased platelet consumption (microangiopathy). Various studies have reported platelet count as a valuable prognostic marker in COVID-19 patients. Thrombocytopenia has been found to be associated with COVID-19 progression and increased mortality in these studies.[28] Prevention and early treatment of anemia and thrombocytopenia in COVID-19 patients should be prioritized to prevent COVID-19 progression and possible neurological complications. The level of ferritin in the study conducted by Eskandar *et al*.[29], has been associated with neurological symptoms in COVID-19 patients, but such a result was not found in our study ($p = 0.449$). Moreover, In a study conducted by Mao *et al*.[7], the number of lymphocytes was found to be lower in patients with neurological symptoms than in patients without these symptoms. This result was also observed in our study, and this could be the result of immunosuppression in patients with neurological symptoms.

Our findings also demonstrated that COVID-19 patients with neurological symptoms also had lower albumin levels compared to COVID-19 patients without such symptoms ($p = 0.012$). Low serum albumin may be correlated with increased physiologic stress in inflammation. In a previous study, low albumin was found to be a strong predictor of mortality in hospitalized patients with COVID-19. In pro-inflammatory states, cytokines increase capillary permeability which allows nutrients, including albumin, to escape into the interstitium. Therefore, the reduced serum albumin levels in inflammatory states may reflect the increased escape of albumin from the vascular space and uptake by cells rather than a decrease in synthesis.[30] In light of this, monitoring albumin levels in COVID-19 patients could prove beneficial for predicting the clinical course and outcome of these patients.

In conclusion, our study underscores the significance of several factors associated with the incidence and prognosis of neurological manifestations in COVID-19. Smoking and substance abuse are possible predisposing factors to neurological symptoms in COVID-19 patients. Implementing appropriate psychosocial strategies for the reduction of smoking and substance abuse during the COVID-19 pandemic may prove beneficial for the prevention of neurological complications. Close monitoring of patients that are more symptomatic at presentation might be of benefit for the early detection of neurological symptoms. Prevention and early treatment of anemia and thrombocytopenia should be prioritized in COVID-19 patients with neurological manifestations. Monitoring albumin levels may have a prognostic value in these patients which is yet to be confirmed. Vigilant monitoring of COVID-19 patients with neurological symptoms, especially the older patients and those with underlying diseases, and providing appropriate intensive care are crucial to properly identify and treat neurological complications and prevent possible long-term morbidities and mortality. We recommend further research on the history, clinical course, and outcome of patients with different COVID-19-related neurological complications to better identify the predisposing and prognostic factors for each of them. These studies can help provide healthcare workers with a better understanding of COVID-19 which ultimately leads to better care for the patients.

This study had several limitations. Most of the clinical symptoms were patients' subjective descriptions. The reported neurological manifestations could be caused by certain underlying diseases or medication side effects. We could not distinguish whether patients' neurological manifestations were caused directly by the virus or indirectly through hypoxia or damage to other organs. The facilities and policies of different hospitals in Shahroud vary and this difference can play a role in a patient's clinical course and outcome. It was not possible to use further diagnostic modalities such as brain computerized tomography (CT) scan and magnetic resonance imaging (MRI) for all patients because of the pandemic restrictions. Genetic diversity of individuals in the distribution of ACE2 receptors in different parts of the body including the nervous system and differences in virus strains were not considered in this study.

ACKNOWLEDGEMENTS

The authors offer their heartfelt thanks to Yasin Naeemi, who assisted in conduction of this study, but did not live long to see it published. May his soul be at peace.

DISCLOSURE

Financial support: This study was financially supported by Shahroud University of Medical Sciences.

Conflict of interests: None

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