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Original Article

Vitamin D deficiency and its impact on outcomes in myocardial infarction patients: a prospective observational study

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Abstract

Objectives: Vitamin D deficiency has been linked to cardiovascular diseases, but its impact on outcomes in myocardial infarction (MI) patients remains unclear. This study investigated the relationship between serum vitamin D levels and short-term and medium-term outcomes in patients with myocardial infarction. Ischemic heart diseases (IHD) are the most common cause of death in the world. Identifying risk factors and predictors can play a critical role in identifying high-risk people in screenings, identifying high-risk patients during admission to the hospital, and adjusting these risk factors in patients to improve prognosis.

Methods: This prospective observational study was conducted on 212 patients diagnosed with myocardial infarction at Seyed al-Shohada Hospital in Urmia, Iran. Having been admitted, the patients had their serum vitamin D levels measured using the same blood sample for routine tests. Levels of vitamin D were categorized as normal (>30 ng/ml), insufficient (21-29 ng/ml), or deficient (<20 ng/ml). The patient's files provided the demographic, clinical, and biomedical information, echocardiography, and angiography data. The patients were followed for at least six months post-MI, with a maximum follow-up of 11 months. Follow-up occurred through monthly phone calls and outpatient clinic visits as needed. Primary outcomes included in-hospital complications (such as death, significant bleeding, acute pulmonary edema, cardiogenic shock, and arrhythmias), cardiac readmissions, and mortality. Logistic regression and Cox regression analyses were used to examine the connection between outcome variables and vitamin D levels, adjusting for potential confounders including age, gender, blood pressure, diabetes, blood lipids, creatinine, disease severity (SYNTAX score*), and left ventricular ejection fraction. The mean serum level of vitamin D in patients on admission was 33. 62 ng/dL. The average number of hospitalization days was 4.8 days, and the rate of re-hospitalization was 26.6% in the six-month follow-up and 30.3% in the 9-month follow-up. The hospital mortality rate was equal to 1.4%, and the mortality rate at the end of the follow-up period was equal to 8.3%. The most common complication during hospitalization among the patients was ventricular tachycardia. However, in follow-up, re-hospitalization due to previous issues was the most common complication.

Results: The mean serum vitamin D level was 33. 62 ng/ml,with 52.8% of patients having insufficient or deficient levels. The most common in-hospital complication was ventricular tachycardia (11.5%). Vitamin D deficiency was not significantly associated with in-hospital complications. However, during the follow-up period, vitamin D deficiency was significantly related to increased risk of readmission to hospital (HR: 6.984, 95% CI: 3.500-13.936, p<0.001). The 6-month readmission rate was 26.6%, increasing to 30.3% at 9 months. Vitamin D deficiency was also associated with increased cardiac mortality (HR: 12.936, 95% CI: 1.494-112.016, p=0.020) during follow-up. The 9-month mortality rate was 8.3%. Other factors contributing to cardiac mortality included disease severity (SYNTAX score) and female gender.

Conclusions: While vitamin D deficiency did not impact short-term complications, it was associated with increased risk of hospitalreadmission and mortality in MI patients during medium-term follow-up. These findings suggest that vitamin D status can significantly impact long-term outcomes for MI patients.

Keywords: Vitamin D Deficiency / adverse effects, supplements, Myocardial Infarction / mortalit y, Coronary Disease / mortality, Myocardial Infarction/prognosis

* **The SYNTAX score:** An angiographic tool to determine the complexity of coronary artery disease. The score is the sum of the points assigned to each lesion identified in the coronary tree with >50% diameter narrowing in vessels >1.5mm diameter.

Introduction

Cardiovascular diseases, as reported by the World Health Organization, are the leading cause of mortality worldwide, claiming an estimated 17.9 million lives annually. This group of disorders encompasses a range of conditions, including ischemic heart disease, coronary artery disease, rheumatic disease, heart failure, among others. Ischemic heart disease, in particular, is one of the most prevalent cardiovascular diseases. It can lead to a reduction in heart function and, in severe casesdeathdue to factors such as increased blood lipids, decreased coronary blood flow, and other heart vessel disorders. In 2016 alone, over 7.4 million people died worldwide of ischemic heart disease globally. (1) Vitamin D, a fat-soluble steroid, plays various roles in the human body. In recent years, vitamin D deficiency has emerged as a global health concern. The deficiency is most prevalent in regions like the Middle East and southern Africa, with risk factors including older age, particularly in women, higher latitudes, winter season, limited sunlight exposure, skin pigmentation, and low vitamin D content in consumed foods. (2) The prevalence of vitamin D deficiency in adults in the United States is approximately 10%, and this figure rises to 29% in obese children. (3) It is estimated that the prevalence of vitamin D deficiency in the general population is between 30-50 percent. (4)Recently, Tabrizi et al. in a study showed a high prevalence of vitamin D deficiency in Iran, which was reported in 45.64%, 61.90%, and 60.45% in men, women, and pregnant women, respectively (5). Although the main function of vitamin D is in bone metabolism and calcium homeostasis, recent studies have shown that this vitamin can play an important role in other body systems, including the cardiovascular system. In the pathophysiological justification of this connection, we can mention the connection of vitamin D with the improvement of vascular dilation (6, 7).the connection with the coagulation system (8), the renin-angiotensin-aldosterone system, and hypertrophy of myocardial cells and blood volume homeostasis (9-11). On the other hand, there are connections between vitamin D deficiency and other diseases such as diabetes and high blood pressure, which are known risk factors for heart diseases. (12, 13) Vitamin D deficiency is associated with hypertension, diabetes, metabolic syndrome, cardiac hypertrophy, and chronic kidney disease, predisposing factors for cardiovascular diseases (4, 12, 14-17). In addition to the relationship between vitamin D and coronary heart disease, many studies have been reviewed (18, 19). In a study in the United States, about 95% of patients admitted to the hospital with acute coronary syndrome had low vitamin D levels (20). In a long-term study, low vitamin D levels were associated with an increased risk of ischemic heart disease, myocardial infarction, and early death during hospitalization (21). However, the results of using vitamin D supplements in preventing cardiovascular diseases or improving its outcomes are varied. Some studies have shown improved survival in heart failure patients and patients with end-stage renal disease treated with vitamin D supplementation. (22) Also, the survival of patients with end-stage renal disease (ESRD) treated with vitamin D supplementation is improved, which was originally related to the reduction of mortality from cardiovascular diseases (23). However, the results of a clinical trial on 5108 people aged 50-84 years with a high monthly dose of vitamin D showed that vitamin D did not prevent cardiovascular disease compared to a placebo (24). Another clinical trial also found no reduction in attenuation in patients with advanced heart failure who received 4000 IU of vitamin D daily (25). Given the high prevalence of vitamin D deficiency and the limited number of studies examining the short-term and long-term effects of vitamin D in heart patients, this study aims to investigate the effect of vitamin D serum levels during hospitalization in patients with myocardial infarction and the results six months later.

Materials and Methods

In a previous study at Seyed al-Shohda Hospital, the one-year mortality rate of patients was 7.9%. In the ongoing study, with a follow-up period of six months, the mortality rate for patients at the six-month mark is expected to be lower than the previously mentioned rate. Based on a 4% mortality rate over six months and an odds ratio of 2.5 for vitamin D deficiency, along with a correlation coefficient of 0.2 between confounding variables the sample size required for this study was estimated to be about 214 people according to Hsieh et al.'s article. (26) The study was launched with the participation of 247 patients diagnosed with myocardial infarction. Patients whose follow-up was impossible for 6 months were excluded. A total of 212 patients with myocardial infarction were finally included. This study was a prospective observational study conducted at Seyed al-Shohada Hospital in Urmia. As part of the study, all patients underwent a vitamin D test using the same blood sample for routine tests upon admission. For enrolled patients, relevant demographic, clinical, and biomedical information, as well as echocardiography and angiography data, were recorded from their patient files. After hospital discharge, patients were followed up for a minimum of six months post-myocardial infarction. Follow-up occurred through monthly phone calls and doctor’s visits as needed.

Study Objective

The study aimed to investigate the association between serum vitamin D levels and short- and medium-term outcomes in patients diagnosed with myocardial infarction. In this study, the primary outcome was six-month mortality. The minimum and maximum follow-up time in the examined patients was zero and 11 months. We also investigated major side effects experienced during hospitalization, such as death, significant bleeding requiring blood transfusion, acute pulmonary edema (with or without mechanical ventilation), cardiogenic shock, clinically important tachyarrhythmias (including ventricular fibrillation, sustained ventricular tachycardia, and atrial fibrillation), bradyarrhythmias requiring a pacemaker, and acute kidney injury. Additionally, the study monitored readmissions related to acute coronary syndrome, acute decompensated heart failure (ADHF), and other relevant clinical events,

including stroke, major bleeding, life-threatening tachyarrhythmias, and death during the follow-up period. Since specific therapeutic interventions other than the routine treatment plan were not offered to the patients, no special funding was allocated to this research. Certainly! Here's a more clear and polished version of the text:

Data Analysis Method (Statistical Analysis and Data Processing)

Quantitative variables were presented as mean and standard deviation. If the data did not follow a normal distribution, median and interquartile range were used. Categorical data were represented as ratios and percentages. Vitamin D levels were categorized as follows:

1-Normal: values greater than 30 ng/ml

2- Vitamin D insufficiency: values between 21 and 29 ng/ml

3-Vitamin D deficiency: values less than 20 ng/ml

The study used logistic regression and Cox regression to examine the connection between the outcome variables and vitamin D levels. A significance level of less than 0.05 was used in the analyses, and all the statistical analyses were conducted using SPSS version 20 software.

Exclusion Criteria

Patients who underwent dialysis, had known malignancies, liver failure, valvular diseases, or were taking medications affecting calcium and vitamin D metabolism were excluded. Additionally, patients with a history of myocardial infarction or heart bypass surgery were not part of the study.

Intervention

Patients received standard medical or interventional treatment prescribed by consultant cardiologists.

Informed Consent

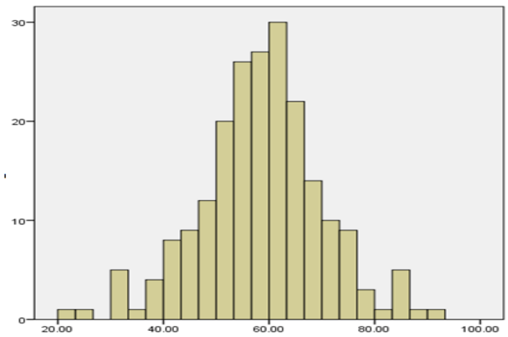
Patients provided informed consent before participating in the study.

Results

In the study, the average age of patients was approximately 58.6 years, with most falling between 45 and 65 years old. A significant majority (80.2%) of the patients were male. However, educational attainment was generally low, with only 9.4% having a university education. The mean body mass index (BMI) was 27.27, and 68.6% of patients were obese or overweight**.**

Table1. Demographic data of participants

gender	Frequency	Percentage	
Female	42	19.8	
Male	170	80.2	
Total	212	100	
Age			
20-44	23	11.0	
45-54	50	23.8	
55-64	80	38.1	
65-74	40	19.0	
75-90	17	8.1	
Total	210	100	
BMI			
Underweight	2	1.0	
Normal	59	30.4	
Overweight	83	42.8	
Obesity	50	25.8	
Vitamin D level			
Normal	100	47.2	
Insufficiency	45	21.2	
Deficiency	67	31.6	
Type of Myocardial Infarction	STEMI	157	75.8
	Non-STEMI	50	24.2



Finger1. The histogram of the age distribution of myocardial infarction patients admitted to Seyed al-Shohada Hospital in Urmia in 2019.

Events that happened during hospitalization in heart attack patients the distribution of events during hospitalization in the heart attack patients studied is shown in Figure 2. The most frequent events observed during hospitalization were ventricular tachycardia, ventricular fibrillation, and cardiogenic shock, with 24, 10, and 9 cases, respectively.

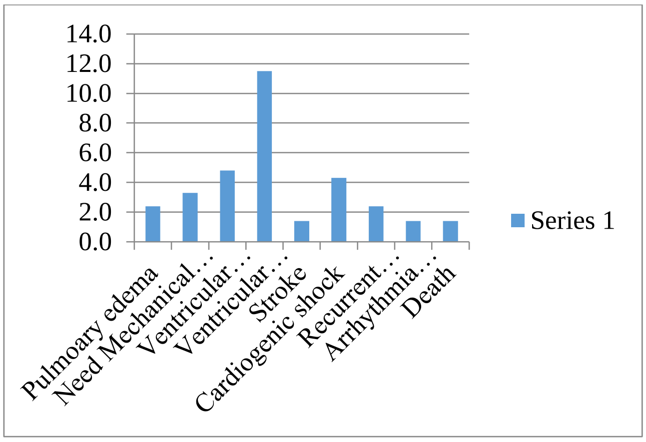


Figure2. Frequency of events during hospitalization in heart attack patients

Follow-up of the patients and outcomes during the follow-up period **a**fter hospital discharge. Patients were monitored for events such as re-hospitalization, recurrent heart attacks, and mortality. The follow-up duration ranged from zero to 11.04 months, with the date of death serving as the endpoint for deceased patients. The mean and standard deviation of the follow-up period was 8.23 ± 1.77 months and the median follow-up period was 8.48 months. Figure 3 shows the distribution of events occurring during the follow-up period. The highest frequency of events related to re-hospitalization due to cardiac causes (60 cases), repeated myocardial infarction (20 cases), and death from all causes (15 cases). One person died due to covid infection.

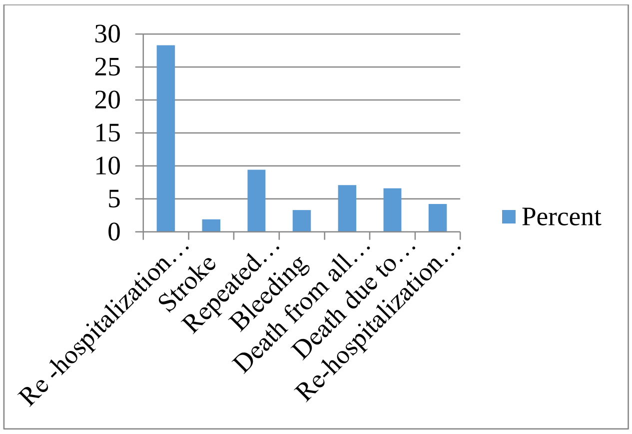


Figure3. Frequency of outcomes of myocardial infarction patients admitted to Seyed al-Shohdai Hospital in Urmia in 2019 during the follow-up period from the time of hospitalization.

The relationship between hospital events and serum vitamin D levels. Among hospital events in myocardial infarction patients in Table 2, the number of occurrences of most events was low. The most commonly observed event was ventricular tachycardia. Its relationship to vitamin D serum levels was analyzed using logistic regression with the forward method after adjusting for these variables (including age, gender, blood pressure, diabetes, blood lipids, creatinine, total cholesterol level, triglyceride level, the severity of the disease using the Syntax score and left ventricular ejection fraction). The model was determined so that the serum level of Vitamin D must be included. The study examined several variables of ventricular tachycardia. Among these variables, disease intensity and patient age showed significant associations; so the chance of ventricular tachycardia decreased by 6% with each one-year increase in patient age, and for each increase in the SYNTAX score, the chance of ventricular tachycardia increased by 10%. However, there was no significant relationship between vitamin D serum levels and the incidence of ventricular tachycardia Table 2.

Table2. Illustrates the result of logistic regression analysis to determine the relationship between the serum level of vitamin D and the occurrence of ventricular tachycardia in myocardial infarction patients admitted to Seyed al-Shohada Hospital in Urmia in 2019

	Beta coefficient	Standard error	P Value	odds ratio	95% confidence interval of the odds ratio
Age	- 0.059	0.026	0.025	0.943	0.896 – 0.993
SYNTAX score	0.096	0.029	0.001	1.101	1.040 – 1.165
Normal vitamin D			0.696	1	
Vitamin D insufficiency	-0.705	0.831	0.396	0.494	0.097 – 2.521
Vitamin D deficiency	-0.077	0.613	0.900	0.926	0.279 – 3.078

The relationship between cardiac readmission and vitamin D serum level

The study used Cox regression analysis to investigate the relationship between cardiac readmission and vitamin D serum level with adjustment after adjusting for these variables (age, gender, hypertension, diabetes mellitus, hyperlipidemia, serum creatinine, total cholesterol, and triglycerides, SYNTAX score for disease severity and left ventricular ejection fraction). Among the variables, two variables, SYNTAX score, and vitamin D deficiency, showed a significant relationship with re-hospitalization for cardiac causes in patients.So, with every one-point increase in SYNTAX score, the risk ratio for re-hospitalization increases by 1.035 (with a 95% confidence interval of 1.004-1.066). Furthermore, the risk ratio for readmission in patients with vitamin D deficiency was found to be 6.984 (with a 95% confidence interval of 3.500-13.6).

Table3. Shows the result of the Cox regression analysis to determine the relationship between vitamin D serum level and cardiac re-hospitalization in myocardial infarction patients admitted to Seyed al-Shohadai Hospital in Urmia in 2019 during 11 months of follow-up

	Beta coefficient	Standard error	P Value	odds ratio	95% confidence interval of the odds ratio
SYNTAX score	0.034	0.015	0.026	1.035	1.004 – 1.066
Normal vitamin D				1	
Vitamin D insufficiency	0.514	0.515	0.318	1.672	0.610 – 4.585
Vitamin D deficiency	1.944	0.353	<0.001	6.984	3.500 – 13.936

The relationship between cardiac mortality and vitamin D serum level

The relationship between cardiac mortality during hospitalization and one month later could not be investigated due to the small number of deaths. However, over the six-month follow-up period, 14 deaths from cardiac causes occurred. The relationship between vitamin D serum levels and these deaths was determined using Cox regression analysis, with adjustment for the variables of age, gender, hypertension, diabetes, hyperlipidemia, serum creatinine level, Total cholesterol and triglycerides, SYNTAX score for disease severity and left ventricular ejection fraction. Among the variables, three variables showed a significant relationship with cardiac mortality during the study period: gender, SYNTAX score, and vitamin D deficiency. The hazard ratio for women versus men was 7.448 (with a

95% confidence interval of 1.492-37.188), for SYNTAX score, was 1.148 (with a 95% confidence interval of 1.040-1.268), and for vitamin D deficiency was 12.936(with a 95% confidence interval of 1.494-112.016).The wide confidence interval is due to the low number of events during the follow-up period in the patients under investigation, and the small number of patients under investigation.

Table4. Illustrates the result of the Cox regression analysis to determine the relationship between the serum level of vitamin D and cardiac mortality in myocardial infarction patients admitted to Seyed al-Shohadai Hospital in Urmia in 2019 during 11 months of follow-up

	Beta coefficient	Standard error	P Value	odds ratio	95% confidence interval of the odds ratio
Female	2.008	0.820	0.014	7.448	1.492 – 37.188
SYNTAX score	0.138	0.051	0.006	1.148	1.040 – 1.268
Normal vitamin D				1	
Vitamin D insufficiency	2.043	1.477	0.167	7.715	0.427 – 139.443
Vitamin D deficiency	2.560	1.101	0.020	12.936	1.494 – 112.016

Discussion

Many epidemiological studies have shown that the male gender is a serious risk factor for ischemic heart disease (27, 28), and the occurrence of ischemic heart disease in men occurs at a younger age (29, 30). The present study also found a higher occurrence of this disease in men, especially in younger age groups. Furthermore, previous observational studies have reported a connection between weight gain, obesity, and cardiovascular diseases has been established. Hence, a high prevalence of obesity and overweight among the patients, found in this study was expected. (31-33). It was also noted that education level and socioeconomic status have a significant impact on the occurrence and societal burden of ischemic heart disease. Consequently, the low educational level observed among the patients was predictable. The mean serum vitamin D level among the hospitalized patients in the study was 33.62 ng/ml. However, more than half of the patients (52.8%) had insufficient or low vitamin D levels. In a 2016 study by Aleksova et al., it was found that patients with cardiac ischemia had a median serum vitamin D level of 17.25ng/ml, suggesting a potential association between vitamin D levels and long-term mortality.Notably, more than 90% of these patients had vitamin D levels below30 ng/ml. In a study by De Metrio et al. in 2015(36), which investigated the relationship between vitamin D levels and complications and mortality in ischemic heart disease, only 11% of patients had levels higher than 10 ng/ml. In the same line, in another study in 2012 by Correia et al. (37). which explored the correlation between severe vitamin D deficiency and acute coronary syndrome hospital mortality, the mean serum vitamin D level in patients was 19.5 Ng/ml, with 10% having levels less than 10 ng/ml. Interestingly,the present study observed higher serum level of vitamin D compared to other studies, and a smaller percentage of patients in this study had levels below 30 Ng/ml. This difference can be due to regional differences. In the current study, the increased proportion of male participants and variations in indicators like body mass, compared to similar research, may impact the average and distribution of vitamin D deficiency classification. Typically, these factors influence serum vitamin D levels (38, 39).Moerover, considering that disease detection and sampling occurred during the warm seasons (May to September) in this study, it is reasonable to anticipate elevated vitamin D levels. Leong et al.study also reported a similar pattern (35). Among hospitalized patients, ventricular tachycardia was the most common complication, with a prevalence of 11.5%. , followed by ventricular fibrillation, cardiogenic shock, and the need for mechanical ventilation. Notably, there was no significant correlation between vitamin D levels and the occurrence of these complications, and age and disease severity emerged as the primary factors influencing complications. De Metrio et al. (36) reported that the most common hospital complications among patients were acute kidney injury, atrial fibrillation, acute pulmonary edema, ventricular fibrillation, and tachycardia. In contrast to our study, De Metrio et al. found an association between vitamin D levels and certain hospital complications. The discrepancy may stem from the higher complication rates observed in this study compared to ours. The present study reported a very low incidence of hospital complications overall. The hospital mortality rate among the patients was 1.4%. There was no significant relationship between vitamin D serum levels and hospital mortality. However, contrasting our findings, a study by De Metrio et al. (36) reported a hospital mortality rate of 2.6%, with a clear association between vitamin D levels and mortality. Similarly, Correia et al. (37) found a higher hospital mortality rate of 6.8%, especially in individuals with low vitamin D levels (24 vs. 4.9%).The discrepancy between our results and these studies could be attributed to differences in the average serum vitamin D levels and the distribution of vitamin D deficiency among the study populations. The present study discovered that the 9-month mortality rate among patients was 8.3%. Factors contributing to mortality from cardiac causes included disease severity, vitamin D deficiency, and female gender. However, re-hospitalization rates at six and nine months were 26.6% and 30.3%, respectively. Consistent with our findings, a study by Correia et al. (37) revealed that long-term cardiac mortality and overall mortality were significantly higher in patients with deficient vitamin D levels (29% vs. 8.6%). In the same line, Demetrio et al. (36) reported a one-year mortality rate of 6.2% and a re-hospitalization rate of 5.5%, emphasizing the role of vitamin D as a determinant factor in long-term mortality and readmission of patients. The study's limitations include its single-center design and the relatively short follow-up period. Additionally, the wide confidence intervals for some risk estimates, particularly for mortality, indicate a need for larger sample sizes in future studies to increase precision.

Conclusion

To sum up, the findings from this study provide valuable insights into the impact of vitamin D deficiency on patients with myocardial infarction. Short-term complications during hospitalization were not significantly influenced by serum vitamin D levels. However, several factors emerged during the follow-up period. Age and disease severity were identified as significant factors influencing complications. Serum vitamin D levels did not directly impact hospital complications; however, this does not discount the potential role of vitamin D in other aspects of patient health. Ventricular tachycardia was identified as the most common complication during hospitalization. During the follow-up period, re-hospitalization due to heart problems was the prevailing issue. Patients with low vitamin D levels are more likely to be re-hospitalized. These findings suggest that addressing vitamin D deficiency may be crucial in preventing recurrent heart-related issues. Furthermore, vitamin D deficiency was also linked to mortality, highlighting its significance in long-term outcomes. These results underscore the need for effective management strategies to reduce the risk of readmission in this patient population. In summary, this study contributes to the growing body of evidence indicating that vitamin D deficiency may be a crucial factor in long-term outcomes and overall well-being for patients with myocardial infarction. Future research should focus on larger, multi-center studies with longer follow-up periods to further understand these relationships and explore potential interventions.

Ethical Statements

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Ethical code: IR.UMSU.REC.1398.402.

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Funding acquisition, resources, supervision, project administration: Mirhossein Seyed-mohammadzad

Conflicts of Interest

The authors declare that they have no conflicts of interest concerning this article. The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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