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Research Paper

Hyponatremia at Admission in Hospitalized Patients With COVID-19: Risk Factors and Impact on Prognosis

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ABSTRACT

Background: Electrolyte disorders, particularly hyponatremia, have been reported in a considerable number of patients with Coronavirus Disease 2019 (COVID-19).

Objective: The current study aims to evaluate the risk factors, symptoms, and prognosis of hyponatremia in hospitalized patients with COVID-19.

Methods: In this retrospective cohort study, 467 patients with COVID-19 were divided into 4 groups based on the sodium level at the time of admission: normal, mild hyponatremia, moderate hyponatremia, and severe hyponatremia. Symptoms, laboratory findings, and prognosis were compared among these groups. The risk factors for the occurrence of moderate/severe hyponatremia and the association of hyponatremia with in-hospital mortality were investigated using logistic regression analysis.

Findings: Hyponatremia was diagnosed in 60% of the patients. The prevalence of mild, moderate, and severe hyponatremia was 80.7%, 15.1%, and 4.2%, respectively. The severity of the clinical symptoms and level of hypoxia showed no significant difference between the groups. White blood cells count was significantly higher and lymphocyte percentage was significantly lower in hyponatremia groups compared to the normal group. The history of chronic kidney disease was an independent risk factor for the moderate/severe hyponatremia (Adjusted OR=5.11, 95%CI: 1.72-15.2, P=0.003). After adjustment of different risk factors, moderate/severe hyponatremia remained a significant independent risk factor for in-hospital mortality (OR=2.58, 95%CI: 1.13-5.88, P=0.024).

Conclusion: Hyponatremia is prevalent in COVID-19 patients. However, it is not definitely associated with severity of COVID-19 at the time of admission. Moderate/severe hyponatremia is associated with higher in-hospital mortality rate despite the similarity of disease severity between the sodium groups.

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1. Introduction

Hyponatremia is one of the most common electrolyte disorders in hospitalized patients [1]. Evidence show that about 30% of patients with pneumonia suffer from different levels of hyponatremia [2]. In these cases, different forms of hyponatremia (hypervolemic, euvolemic, or hypovolemic) with a variety of pathophysiological mechanisms may be involved [3]. The most frequent etiology of hyponatremia is the increased secretion of antidiuretic hormone (ADH) caused by various stimulants such as cytokines, hypoxia, nausea, drugs, and hypovolemia occurs due to fluid loss mostly because of fever, vomiting, and diarrhea [4, 5]. According to previous studies, hyponatremia occurs in approximately one-third of patients with Coronavirus Disease 2019 (COVID-19), and severe cases of this disorder are independently associated with about 40% of in-hospital deaths [6]. The patients with moderate or severe hyponatremia are 80% more likely to require invasive mechanical ventilation [6]. Hyponatremia is associated with more severe COVID-19 or Community-Acquired Pneumonia (CAP) clinical symptoms and laboratory findings [7-11]. Hence, higher mortality in patients with hyponatremia may be attributed to COVID-19 disease severity.

Investigating the independent role of hyponatremia in increasing mortality is important. Risk factors in developing hyponatremia in patients with COVID-19 have been less evaluated. Age, male gender, history of diabetes or ischemic heart disease, and disease severity have been reported as risk factors for hyponatremia in CAP or COVID-19 diseases [6-9]. Regarding the limited information about the independent role of hyponatremia in increasing mortality, this study was conducted to evaluate the risk factors, symptoms, and prognosis of hyponatremia in patients with COVID-19.

2. Materials and Methods

The is a retrospective cohort study was conducted on 475 patients aged ≥18 years with COVID-19 admitted to Velayat Hospital in Qazvin, Iran, from September to November 2020. Polymerase Chain Reaction (PCR) method was used to confirm COVID-19 disease in participants. Hypernatremia cases were excluded from the study. Patients were divided into separate groups based on the serum sodium levels at the time of admission as following: normal (135 mmo/l≤Na≤145 mmol/L), mild hyponatremia (130.1 mmol/l≤Na≤135 mmol/L), moderate hyponatremia (125.1 mmol/L≤Na≤130 mmol/L), and severe hyponatremia (Na≤125 mmol/L). As the risk of mortality due to hyponatremia is high when Na≤125 mmol/L, the cutoff level of 125 was described as severe [12]. The information was collected through designed questionnaires before admission. The considered surveyed data included clinical complaints, underlying diseases (hypertension, ischemic heart disease, diabetes, chronic respiratory disease, hepatic encephalopathy, and chronic kidney diseases), smoking, laboratory findings at the time of admission, and in-hospital mortality.

The Kolmogorov-Smirnov test was used for examining the normality of quantitative data distribution. The comparison of quantitative data and categorical data between the study groups were conducted using Kruskal-Wallis test (all quantitative variables had non-normal distributions) and Chi-square test, respectively. Multivariable logistic regression analysis was performed to investigate the predictors of moderate/severe hyponatremia (Na≤130 mEQ/L). The independent variables were age, gender, underlying diseases (hypertension, ischemic heart disease, diabetes, chronic respiratory disease, and chronic kidney diseases), smoking, blood sugar, creatinine, corticosteroid use, respiratory rate, and O_2 saturation without oxygen supply. Multivariable logistic regression was also used for examining the association of moderate/severe hyponatremia with mortality. Two models were used; in model 1, adjustment was performed for age, gender, moderate/severe hyponatremia, smoking, and underlying diseases. In model 2, adjustment was performed for the variables in model 1 in addition to blood sugar, creatinine, and clinical indicators of COVID-19 severity (respiratory rate, O_2 saturation without oxygen supply, and systolic blood pressure). The analyses were performed in SPSS software, version 20 and $P<0.05$ was statistically significant.

3. Results

Totally, 475 patients participated in the study. Hypernatremia was diagnosed in 8 patients (1.7%); therefore, they were excluded from the study. Hyponatremia was diagnosed in 285 (61.0%) patients. The mild, moderate, and severe cases of hyponatremia were found in 230 (80.7%), 43 (15.1%), and 12(4.2%) patients with hyponatremia, respectively.

Clinical findings

The results showed no significant difference between the groups in terms of age, gender, and clinical complaints. On the first day of hospitalization, the systolic blood pressure in severe and moderate hyponatremia groups (114.0±16.3 mmHg and 118.3±19.8 mmHg, respectively) were significantly lower than in mild hyponatremia and normal sodium groups (126.4±19.2 mmHg and 126.6±22.5, mmHg, respectively) (P=0.031). In other vital signs such as pulse rate, respiratory rate, and body temperature, the results showed no significant difference between the groups (Table 1).

Laboratory findings

The White Blood Cells (WBC) count in the severe hyponatremia group was significantly higher than in other groups (12.500±4.500 vs. 7600±5.700 in normal, 7.300±3.400 in mild, and 7.700±3.600 in moderate hyponatremia groups, P<0.001). All the three hyponatremia groups had higher percentage of neutrophils and lower percentage of lymphocytes compared to the normal group. The blood sugar level in mild, moderate, and sever hyponatremia groups was significantly higher than in normal group (153.2±85.0mg/dL in mild, 155.9 ±90.3 mg/dL in moderate, and 148.3±109.9 mg/dL in severe hyponatremia groups vs. 126.5±46.8 mg/dL in normal group, P=0.048). The serum creatinine level was higher in the severe hyponatremia group compared to other groups (2.2±1.3 mg/dL vs. 1.3±1.4 mg/dL in moderate, 1.4±1.4 mg/dL in mild, and 1.3±0.7 mg/dL in normal groups, P=0.013) (Table 1).

Underlying diseases and risk factors

The history of chronic lung disease was significantly different between sodium groups; 7 patients (16.3%) in the moderate hyponatremia group, one patient in the severe hyponatremia group (8.3%) and 5 patients (2.7%) in the normal sodium group had a history of chronic lung disease (P=0.001) (Table 1). The history of diabetes was also significantly different between the groups; 4 patients (33.3%) in severe, 11 patients (25.6%) in moderate, and 59 patients (25.7%) in mild hyponatremia groups had a history of diabetes. On the other hand, 25 patients (13.7%) in the normal group had a history of diabetes (P=0.016). Regarding the history of ischemic heart disease, hypertension, chronic renal diseases, and smoking, there was no significant difference between the hyponatremia groups (Table 1). The history of corticosteroid use was significantly different between sodium groups. No patient was received corticosteroid in the severe hyponatremia group, while the percentage of corticosteroid use in other groups were between 5.5% to 13.0% (P=0.043)

Table 2 shows the results of finding risk factors of moderate/severe hyponatremia. There was a strong association between history of chronic lung disease and moderate/severe hyponatremia. The risk of moderate/severe hyponatremia in the patients with a history of chronic lung disease was 5.11 times higher (P=0.003, 95% CI: 1.72-15.20), while in the patients with history of diabetes, its risk was 2.35 times higher (P=0.014); however, after adjustments, the association of diabetes with moderate/severe hyponatremia was not significant (Table 2).

Clinical course

The rate of admission to the intensive care unit was higher in hyponatremia groups compared to the normal sodium group, but it was not significance (P=0.071). The mortality rate was significantly higher in moderate and severe hyponatremia groups than in mild hyponatremia and normal groups (50% and 25.6% vs. 13.5% and 14.3%, respectively, P=0.002) (Table 3). Predictors of mortality are shown in Table 4. In different models of adjustment, the risk of mortality in moderate/severe hyponatremia groups were 2.20-2.58 times higher (Table 4). Age, history of chronic respiratory disease, and smoking were other risk factors of mortality.

4. Discussion

In this study, more than half of the hospitalized patients with COVID-19 had hyponatremia. Most of them had mild hyponatremia and only about 20% of hyponatremic patients had moderate/severe hyponatremia. The indicators of the severity of COVID-19 demonstrated no significant difference between the hyponatremia groups and normal group. The history of chronic kidney disease was associated a five-time increase in moderate/severe hyponatremia. With regard to this impact on prognosis, moderate/severe hyponatremia was associated with about a 2.5-time increase in mortality. This higher risk of mortality was independent of age, O_2 saturation, and underlying diseases.

Since the outbreak of COVID-19, some studies have reported high incidence of electrolyte disorders, especially hyponatremia. Hyponatremia is the most common electrolyte disorder in hospitalized patients with COVID-19 with a prevalence of about 30%-50% [6, 13, 14] or lower (about 20%) [14]. There is limited evidence about the risk factors of hyponatremia in COVID-19. The present study revealed that the history of chronic kidney disease was a strong risk factor for hyponatremia in COVID-19 patients. The history of long-term use of inhaled corticosteroids was not surveyed in our study.

Table 1. Characteristics of patients in the first hours of admission for different study groups

	Characteristics	Mean±SD / No. (%)				P
		Normal (n=182)	Mild Hyponatremia (n=230)	Moderate Hyponatremia (n=43)	Severe Hyponatremia (n=12)	
	Age (y)	60.7±18.1	61.8±15.6	66.0±12.7	61.2±14.8	0.368
	Gender (male)	100(54.9)	144(62.6)	28(65.1)	7(58.3)	0.383
Complaints	Dyspnea	130(71.4)	142(61.7)	30(69.8)	9(75.0)	0.177
	Cough	132(62.1)	140(60.9)	25(58.1)	8(66.7)	0.942
	Chest pain	14(7.7)	12(5.2)	0	1(8.3)	0.247
	Diarrhea	14(7.7)	14(6.1)	1(2.3)	0(0)	0.457
	Nausea/Vomiting	38(20.9)	57(24.8)	10(23.3)	5(41.7)	0.376
	Malaise	57(31.3)	68(29.6)	15(34.9)	3(25)	0.871
	Myalgia	60(33)	49(21.3)	10(23.3)	3(25)	0.161
Vital signs	T (centigrade)	36.9±0.8	36.8±0.8	36.9±0.7	36.4±0.9	0.412
	RR (minute)	18.9±2.6	19.3±3.3	19.1±4.0	18.8±1.3	0.434
	PR (minute)	91.3±14.9	89.7±17.3	88.2±15.8	93.5±22.3	0.826
	SBP (mmHg)	126.6±22.5	126.4±19.2	118.3±19.8	114±16.3	0.031
	DBP (mmHg)	79.1±14.1	78.9±12.7	73.1±15.2	74±10.3	0.059
History	Hypertension	25(30.2)	74(32.2)	18(41.9)	4(33.3)	0.539
	Ischemic heart disease	31(17)	32(13.9)	9(20.9)	5(41.7)	0.063
	Smoking	12(6.6)	15(6.5)	3(7.0)	2(16.7)	0.6
	Chronic respiratory disease	5(2.7)	8(3.5)	7(16.3)	1(8.3)	0.001
	Diabetes	25(13.7)	59(25.7)	11(25.6)	4(33.3)	0.016
	Chronic kidney disease	4(2.2)	6(2.6)	1(2.3)	0(0)	0.946
	Corticosteroid use	10(5.5)	30(13.0)	5(11.6)	0(0)	0.043
Laboratory findings	WBC (mL)	7.6±5.7	7.3±3.4	7.7±3.6	12.5±4.5	<0.001
	Lymphocytes (%)	21.7±13.2	18.4±1	15.4±8.1	10.5±3.9	<0.001
	Neutrophils (%)	74.3±11.6	77.0±10.6	79.4±11.9	85.5±4.4	<0.001
	Blood sugar (mg/dL)	126.5±46.8	153.2±85	155.9±90.3	148.3±109.9	0.048
	Blood urea nitrogen (mg/dL)	22.1±17.8	24.6±28.6	20.5±11.6	37.8±33.7	0.051
	Creatinine (mg/dl)	1.3±0.7	1.4±1.4	1.3±1.4	2.2±1.3	0.013
	O_2 saturation (%)	86.7±4.5	85.8±5.4	86.1±4.0	89.0±2.3	0.074

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SD: Standard Deviation; T: Temperature; RR: Respiratory Rate; PR: Pulse Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WBC: The White Blood Cells

Table 2. Predictors of moderate/severe hyponatremia

Variables	Crude OR (95%CI)	P	Adjusted OR (95%CI)	P
Age (y)	1.01 (0.99-1.01)	0.103	1.01 (0.99-1.03)	0.260
Gender (male)	1.43 (0.77-2.67)	0.271	1.32 (0.72-2.41)	0.364
History of hypertension	1.53 (0.82-2.87)	0.158	1.18 (0.56-2.47)	0.648
History of ischemic heart disease	1.66 (0.81-3.41)	0.139	1.42 (0.62-3.26)	0.399
History of diabetes	2.35 (1.13-4.87)	0.014	1.14 (0.48-2.69)	0.762
History of chronic respiratory disease	6.02 (1.88-19.27)	0.001	5.11 (1.72-15.20)	0.003
History of chronic kidney disease	0.93 (0.10-8.18)	0.953	0.81(0.08-7.51)	0.856
History of smoking	1.41 (0.47-4.21)	0.638	1.32 (0.38-4.61)	0.658
RR	1.02 (0.92-1.12)	0.708	1.09 (0.98-1.21)	0.102
O_2 saturation	1.00 (0.97-1.07)	0.908	1.03 (0.96-1.11)	0.314
Blood sugar	1.00 (1.00-1.02)	0.065	1.00(0.99-1.00)	0.230
Creatinine	1.29 (0.98-1.69)	0.069	1.44 (0.98-2.11)	0.059
Corticosteroid use	0.58(0.19-1.78)	0.342	0.77(0.22-2.69)	0.681

OR: Odds Ratio; RR= Respiratory Rate

However, according to the routine practice in Iran, inhaled corticosteroids are commonly prescribed for the patients with chronic kidney disease. In the study by Woods et al., a considerable number of patients (20%) who had taken inhaled corticosteroids had various ranges of renal failure [15]. Patients with renal insufficiency are susceptible to hyponatremia, mainly due to the disturbance of free water clearance and lower threshold for vasopressin secretion. Therefore, the five-time increase of hyponatremia in COVID-19 patients with a history of chronic kidney disease may be attributed to previous medications, especially inhaled corticosteroids.

Traditionally, hyponatremia is classified into hypovolemic, isovolemic, and hypervolemic [3]. Above-mentioned risk factor of hyponatremia (history of chronic kidney disease) can be related to isovolemic hyponatremia. Other isovolemic hyponatremia, i.e., the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH), is the most common cause of hyponatremia in pneumonia patients [4] due to various mechanisms. Hypoxia stimulates baroreceptors by vasoconstriction and reduction of atrial filling pressure. Increased stimulation of osmoreceptors because of high interleukin-6 level, nausea, vomiting, and pain is another mechanism of SIADH [4, 16, 17]. Hypovolemia is another common

Table 3. Clinical course of patients in different study groups

Variables	Mean±SD / No. (%)				P
	Normal	Mild Hyponatremia	Moderate Hyponatremia	Severe Hyponatremia	
Admission to ICU	14(7.7)	26(11.3)	8(18.6)	3(25.0)	0.0.071
Duration of hospitalization in survived patients (days)	5.7±5.4	6.6±7.7	7.2±6.2	3.6±1.9	0.376
Days to death in expired patients (days)	5.0±4.0	8.0±8.5	7.4±10.2	5.3±4.3	0.423
Death rate	26(14.3)	31(13.5)	11(25.6)	6(50.0)	0.002

Table 4. Predictors of mortality in hospitalized patients with COVID-19 disease

Variables	Crude OR (95%CI)	P	Model 1 (95%CI)	P	Model 2 (95%CI)	P
Age (y)	1.04(1.02-1.06)	<001	1.06(1.03-1.08)	<0.001	1.06 (1.03-1.08)	<0.001
Gender (male)	1.32(0.79-2.22)	0.279	1.60(0.79-3.22)	0.186	1.43 (0.68-3.01)	0.340
Moderate/severe hyponatremia	2.68(1.32-5.44)	0.006	2.20(1.05-4.59)	0.036	2.58(1.13-5.88)	0.024
History of ischemic heart disease	1.21(0.64-2.30)	0.546	1.12(0.55-2.24)	0.611	2.06(0.80-5.28)	0.133
History of hypertension	1.22(0.73-2.04)	0.442	0.93(0.38-1.69)	0.571	0.77(0.35-1.70)	0.530
History of diabetes	0.79(0.41-1.50)	0.479	0.78(0.32-1.90)	0.589	0.89(0.33-2.41)	0.832
History of chronic respiratory disease	5.66(2.31-13.87)	<0.001	6.14(1.99-18.93)	0.002	4.68(1.43-15.31)	0.011
History of chronic kidney disease	1.23(0.26-5.85)	0.787	1.45(0.65-2.48)	0.231	1.41(0.65-2.89)	0.368
Smoking	3.58(1.68-7.64)	0.001	4.88(1.670 14.27)	0.004	4.89(1.55-15.380	0.007
O_2 saturation	0.94(0.90-0.98)	0.014	-	-	0.95(0.89-1.02)	0.212
RR	1.03(0.96-1.10)	0.398	-	-	1.01(0.89-1.12)	0.977
SBP	0.46(0.99-1.00)	0.466	-	-	0.99(0.98-1.01)	0.908
Creatinine	1.14(0.97-1.33)	0.097	-	-	1.38(0.91-2.10)	0.122
Blood sugar	0.99(0.99-1.00)	0.600	-	-	1.00(0.99-1.00)	0.842

SD: Standard Deviation; OR:Odds Ratio; RR: Respiratory Rate; SBP: Systolic Blood Pressure

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etiology of hyponatremia. Hypovolemia can stimulate antidiuretic hormone secretion by stimulating baroreceptors [18]. Cuesta et al. investigated the etiology of hyponatremia in patients with CAP and showed that the SIADH and hypovolemia were the etiologies of hyponatremia in 46% and 42% of cases, respectively [5]. The hypovolemia in pneumonia increases insensible loss due to fever, tachypnea, anorexia, and vomiting [19]. In our study, the frequency of fever and gastrointestinal symptoms (diarrhea and vomiting) was no significant different between the hyponatremia and isonatremic dehydration groups. Hence, hypovolemia is less likely to be the main etiology of hyponatremia in COVID-19 patients. Hypervolemia is the third and least common cause of hyponatremia [4]. In a study, there was no significant difference between patients with hyponatremia and normal sodium levels regarding the history of heart failure and cirrhosis or receiving hypotonic serum [4].

Association of hyponatremia with poor prognosis in CAP has been evaluated previously. In a retrospective study by Zilberberg et al. on 7965 hospitalized patients with CAP, the in-hospital death rate was higher in hyponatremia group (OR=1.3, 95% CI: 0.90-1.87) [9]. In a study carried out by Nair et al., hyponatremia at the time of admission was associated with 7% increase in death [2]. In Hirsch et al.'s study conducted on more than 10.000 patients, there was a u-shaped association between serum sodium level and mortality. Both hyponatremia or hypernatremia were associated with significantly higher odds of mortality [20]. In the studies by Frontera et al. and Tezcan et al. on COVID-19 patients, hyponatremia was an independent risk factor of in-hospital mortality (caused increase by 43% and 10.3 times, respectively) [6, 13]. In Tzoulis et al.'s study, morbidity (needing mechanical ventilation) was higher in the hyponatremia group. However, hyponatremia was not the risk factor of in-hospital mortality, except for the subgroup of patients with hypovolemic hyponatremia [21].

There are also some studies with controversy results about the independent role of hyponatremia in the increase of in-hospital mortality rate. Hyponatremia may be an indicator of disease severity and higher death rate in hospitalized patients with hyponatremia, or may be attributed to more severe underlying systemic diseases. In De Carvalho et al.'s study on the patients with COVID-19, hyponatremia group had more severe disease and more extensive pulmonary lesions in the CT-scan [22]. In the study by Chawla et al., [12], the association of hyponatremia with in-hospital mortality was evaluated based on the medical records of about 45.000 hospitalized patients. Among hyponatremic patients, mortality was increased by 10% as serum sodium dropped from 134 to 120 mEQ/L; the serum sodium level of 120-124 mEQ/L was associated with the highest rate of mortality. However, in the patients with serum sodium <120 mEQ/L, the death rate was reduced compared to the patients with serum sodium level of 120-124 mEQ/L. More than two-third of dying patients with serum sodium of <120 mEQ/L had at least two severe systemic diseases. Most of the survived patients with very severe hyponatremia (serum sodium <110 mEQ/L) had hyponatremia due to the use of drugs. Researchers concluded that the higher mortality rate in hospitalized patients with hyponatremia was related to underlying diseases, rather than degree of hyponatremia. However, they compared two groups of completely different patients: survived patients with severe hyponatremia without underlying diseases and critically-ill patients with less severe hyponatremia. In most studies, hyponatremia is associated with more severe CAP or COVID-19 [6, 9, 13]. In our study, hyponatremia was not associated with more severe COVID-19 by assessing respiratory rate and O_2 saturation. In all the above studies, hyponatremia was independently associated with increased mortality rate after adjusting the disease severity and other factors.

Our study had some limitations. Its design was retrospective, but gathering data was performed prospectively based on a specific questionnaire designed for hospitalized patients with COVID-19. In this regard, we could not determine the exact rate of death in hyponatremic patients. The second limitation was the lack of information about medication history before hospitalization, especially the history of diuretics use, which could be one of additional risk factors for hyponatremia. The novelty of this study was first related to reporting the occurrence of different degrees of hyponatremia independent of COVID-19 severity. The second novel finding was the strong predicting power of the history of chronic kidney disease as a risk factor for moderate/severe hyponatremia. The third novelty was the higher mortality rate of moderate/severe hyponatremia group despite the similar degrees of COVID-19 between different serum sodium level groups.

5. Conclusion

There is high prevalence of hyponatremia in hospitalized COVID-19 patients. Patients with hyponatremia have no severe COVID-19 disease at the time of admission. The history of chronic kidney disease is a strong risk factor for hyponatremia. There is a 2.5-fold increased risk of mortality in COVID-19 patients with serum sodium level ≤130 mEQ/L, regardless of disease severity and history of underlying chronic diseases.

Ethical Considerations

Compliance with ethical guidelines

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Authors' contributions

Conceptualization and Supervision: Negar Sheikhdavoodi and Sima Hashemipour; Methodology: Sima Hashemipour; Investigation, Writing-original draft, and Writing-review & editing: All authors; Data collection: Maryam Gheraati, Sima Hashemipour, and Milad Badri; Data analysis: Sima Hashemipour; Funding acquisition and Resources: Maryam Gheraati.

Conflict of interest

The authors declared no conflict of interest.

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