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Electrolyte imbalance in patients with COVID-19 pneumonia

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ABSTRACT

Introduction: Electrolyte abnormalities are among the most common complications among the patients admitted with coronavirus disease 2019 (COVID 19) pneumonia and maybe contributed to its course of disease and severity.
Objectives: The current study aims to assess the prevalence and association of electrolyte imbalance among patients with COVID 19 pneumonia.
Patients and Methods: The current observational study has been conducted on 323 patients with COVID 19 pneumonia. On-admission blood samples were taken to assess electrolytes (sodium, potassium, calcium, and magnesium), complete blood count and differentiation (CBC with diff), and other biomarkers. Further measurements of electrolytes were conducted during the period of hospitalization if needed. The frequency and association of electrolyte imbalance with diverse demographic, clinical, laboratory, and in-hospital characteristics was assessed.
Results: Hypo/hypernatremia, hypo/hyperkalemia, hypo/hypermagnesemia and hypo/hypercalcemia were presented in 14.5%/9.4%, 3.8%/10.3%, 7.9%/9.3%, and 10.9%/10.8%, respectively. Time to discharge was remarkably higher among the patients with hypernatremia ($P=0.031$). The patients with hypermagnesemia were significantly younger than the other cases ($P=0.016$). The C-reactive protein (CRP) level was statistically less among the patients with hypercalcemia ($P=0.025$). There was no associative outcome between potassium abnormalities and patients' characteristics.
Conclusion: The present study showed that electrolyte imbalances are common laboratory abnormalities during COVID-19. However, we found no associative role, since ions balance plays a crucial prognostic role for COVID-19.

Implication for health policy/practice/research/medical education:
In the study on 323 patients with COVID 19 pneumonia, we found that electrolyte imbalances are common laboratory abnormalities during COVID-19. However, we found no associative role.
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Original

Introduction

Coronavirus disease 2019 (COVID-19) is an unrelenting emerged pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This pandemic led to millions of infections and deaths worldwide, affecting society, healthcare systems, and governmental policies (1-4). Patients with COVID-19 exhibit mild to severe presentations, among which approximately 15% of the patients experience severe pneumonia, and less than 5% of them develop acute respiratory distress syndrome and multiple organ failure (5).

The exact mechanism of COVID-19 infection is partially elucidated, but to date, it has been suggested that SARS-CoV-2 invades human cells through binding of its spikes to angiotensin I converting enzyme 2 (ACE2) on the cell membrane (6). This enzyme is generally expressed on the cell surface of different tissues, particularly in the lungs.

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Physiologically, ACE2 has a crucial role in the renin-angiotensin system (RAS), controlling blood pressure and electrolyte balance. In patients with COVID-19, SARS-CoV-2 binds ACE2 and induces degradation of ACE2, which leads to reabsorption of sodium and water, the elevation of blood pressure, and potassium excretion. An emerging body of evidence represents other electrolyte imbalances in patients with COVID-19 (7,8).

Sodium, calcium, potassium, chloride, phosphate, and magnesium are the common electrolytes involved in many metabolic and homeostatic functions such as enzymatic and biochemical reactions, neurotransmission, and hormone function. Electrolytes have to be balanced for the management of many clinical conditions (9). Electrolyte imbalance is generally defined as an abnormality in fluids and electrolytes concentration. Various mechanisms such as impaired absorption and distribution, excessive or inadequate administration, hormonal changes, altered excretion via gastrointestinal and renal losses are responsible for electrolyte imbalance (10). Recent studies have presented that, patients with more severe COVID-19 exhibit a higher proportion of electrolyte imbalance, hypokalemia in particular (11). Besides, sodium metabolism imbalance was a prognostic factor in patients with COVID-19 pneumonia. In this regard, hypo and hypernatremia were found in 20.5% and 3.7% of COVID-19 patients, respectively (12).

Objectives

The current study aims to assess electrolyte imbalance in hospitalized patients due to COVID 19 in Isfahan, the center of Iran.

Patients and Methods

Study design

The present observational study was conducted on patients with COVID-19 admitted at Amin, and Al-Zahra hospitals, affiliated at Isfahan university of medical sciences, from May to June 2020.

The study protocol was explained to the patients or their legal guardians; they were reassured about the confidentiality of personal information and signed written consent.

All over 18 years old patients admitted to the mentioned centers with a documented diagnosis of COVID-19 pneumonia according to signs/symptoms, high resolution computed tomography of the chest, and positive polymerase chain reaction (PCR) were included in the study.

Data collection

The study checklist consisted of three sections was completed by an internal medicine specialist.

The first section assesses the demographic characteristics (age and gender) and on-admission presentations of the patients, including pulse rate (per minute), respiratory rate (per minute), oxygen saturation (O_2 sat), systolic blood pressure (SBP), and diastolic blood pressure (DBP) (mm Hg), and sublingual body temperature (°C).

Blood samples were taken from the antecubital vein of the patients and sent to a reference laboratory to evaluate complete blood count and differentiation (CBC with diff), C-reactive protein (CRP), lactate dehydrogenase (LDH), albumin, and electrolytes (sodium, potassium, magnesium and calcium).

The COVID-19 infection treatment and electrolyte imbalance correction were conducted according to the national and World Health Organization (WHO) guidelines. Based on the treating physician's opinion, the electrolytes were rechecked during the hospitalization, if necessary.

Electrolyte imbalance was classified as, hyponatremia (Na < 135 mEq/L)/ hypernatremia (Na > 145 mEq/L), hypokalemia (K < 3.5 mEq/L)/ hyperkalemia (K > 5.5 mEq/L), hypomagnesemia (Mg < 1.7 mg/dL)/ hypermagnesemia (Mg > 2.4 mg/dL) and hypocalcemia (Ca < 8.5 mg/dL)/ hypercalcemia (Ca > 10.5 mg/dL).

The serum level of sodium was corrected according to plasma glucose. In this term, by any 100 mg/dL serum glucose level above 400 mg/dL, the sodium level was 1.6 mEq reduced.

Besides, the calcium level was corrected based on albumin concentration according to the formula:

Corrected calcium (mg/dL) = Serum calcium (mg/dL) +0.8 (4-serum albumin (g/dL))

The third section of the study assessed the way of oxygenation (non-invasive ventilation or orotracheal intubation), intensive care unit (ICU) admission requirement duration of hospital stay, and in-hospital outcomes (discharge or death).

Statistical analysis

The mean and standard deviation of all statistical indicators were used to describe the quantitative frequency of data. The one-way analysis of variance (ANOVA) statistical test was administered to examine the significance of the quantitative variables in different residency fields. The χ^2 test was applied to examine the qualitative variables in different fields. Data were analyzed using SPSS software version 20 (SPSS, Inc., Chicago, IL, USA). The *P* value of less than 0.05 was considered statistically significant.

Results

In the present study, 323 patients with COVID-19 pneumonia were enrolled for the analysis. The studied population was predominantly males (184 patients, 57%) and had the mean age of 60.02 ± 17.18. In terms of past medical history, 12 (3.8%) patients had chronic obstructive pulmonary disease, 21 (6.6%) end-stage renal disease, 15 (4.7%) malignancies, 20 (6.3%%) cerebrovascular accidents, 5 (1.6%) pulmonary thromboembolism, 71 (2.3%) diabetes mellitus and 61 (19.1%) ones had ischemic heart disease.

According to Table 1, hypo/hypernatremia, hypo/hyperkalemia, hypo/hypermagnesemia and hypo/hypercalcemia were presented in 14.5%/9.4%, 3.8%/10.3%, 7.9%/9.3%, and 19.9%/10.8%, respectively.

Table 1. The frequency of electrolytes imbalance in patients with COVID-19

	No.	%
Sodium		
Hyponatremia	46	14.5
Normal	242	76.1
Hypernatremia	30	9.4
Potassium		
Hypokalemia	12	3.8
Normal	275	85.9
Hyperkalemia	33	10.3
Magnesium		
Hypomagnesemia	23	7.9
Normal	240	82.8
Hypermagnesemia	27	9.3
Calcium		
Hypocalcemia	57	19.9
Normal	198	69.2
Hypercalcemia	31	10.8

SBP ($P=0.035$) and time to discharge ($P=0.031$) were statistically different parameters in the patients with sodium ion balance disturbances. Other demographic, clinical, laboratory tests and in-hospital outcomes were not affected by serum sodium level differences (Table 2).

Based on the findings of Table 3, on-admission potassium level was not associated with any of the manifestations of the patients. Detailed information is shown in this table.

Magnesium imbalance was not associated with any of the demographic, clinical, laboratory, and in-hospital outcomes of the patients, except for oxygen saturation in which those with hypermagnesemia had better saturations than the other two groups ($P=0.037$; Table 4).

The levels of CRP ($P=0.25$) and ICU-admission ($P=0.018$) were remarkably fewer in hypercalcemic patients. The other variables did not differ, as demonstrated in Table 5.

Discussion

In the current investigation, the balance of the most significant body electrolytes, including sodium, potassium, magnesium, and calcium, were assessed to figure out the potential role of their imbalance on the outcomes of the patients with COVID-19 pneumonia. Our findings showed that approximately 25% of the patients had

Table 2. The characteristics of the COVID-19 pneumonia patients with sodium imbalance

		Hyponatremia	Normal	Hypernatremia	*P* value
Demographic characteristics					
Age (years)		58.17 ± 20.17	60.47 ± 17.7	58.2 ± 19.85	0.64
Gender (male)		25 (54.3)	140 (57.9)	16 (53.3)	0.832
Clinical manifestations					
Pulse rate (per minute)		94.20 ± 19.13	92.46 ± 18.74	94.73 ± 21.81	0.881
Systolic blood pressure (mm Hg)		121.28 ± 17.78	123.90 ± 20.53	133.20 ± 23.27	0.035
Diastolic blood pressure (mm Hg)		74.39 ± 10.62	79.27 ± 42.74	80.97 ± 12.77	0.167
Respiratory rate (per minute)		23.07 ± 6.52	24.08 ± 6.60	22.70 ± 5.07	0.316
O_2 saturation,	<90%	90 (43.5)	157 (64.9)	18 (60)	0.109
	90% ≤O_2 sat < 93%	14 (30.4)	46 (19)	6 (20)	
	≥93%	12 (26.1)	39 (16.1)	6 (20)	
Temperature (°C)		37.42 ± 1.04	37.32 ± 0.79	37.10 ± 0.68	0.470
Laboratory tests					
C-reactive protein (mg/L)		58.93 ± 45.06	72.88 ± 46.37	75.34 ± 37.23	0.135
Lactate dehydrogenase (U/L)		908.32 ± 526.03	1074.09 ± 982.50	965.37 ± 544.15	0.810
Absolute lymphocyte count (10^3 cells/µL)		1081.06 ± 822.56	1283.72 ± 1023.63	1277.84 ± 726.35	0.362
In-hospital outcomes					
ICU admission		28 (60.9)	126 (52.1)	18 (60)	0.433
Orotracheal intubation/non-invasive ventilation		15 (32.6)/31 (67.4)	51 (21.1)/191 (78.9)	22 (73.3)/8 (26.7)	0.213
Death, n (%)		12 (26.1)	48 (19.8)	7 (23.3)	0.603
Time to ICU admission (days)		2 ± 2	4 ± 7	2 ± 4	0.088
Time to discharge (days		13 ± 16	13 ± 9	18 ± 15	0.031
Time to death (days)		14 ± 8	14 ± 9	12 ± 16	0.348

Data are expressed as mean ± SD or No. (%).

Table 3. The characteristics of the COVID-19 pneumonia patients with potassium imbalance

		Hyponatremia	Normal	Hypernatremia	*P* value
Demographic characteristics					
Age (years)		55.42 ± 16.10	60.34 ± 18.45	59.18 ± 17.54	0.63
Gender (male)		5 (41.7)	156 (56.7)	21 (63.6)	0.417
Clinical manifestations					
Pulse rate (per minute)		94.17 ± 2.41	92.95 ± 18.51	92.12 ± 22.99	0.859
Systolic blood pressure (mm Hg)		124.00 ± 22.55	124.54 ± 20.25	124.73 ± 25.94	0.961
Diastolic blood pressure (mm Hg)		77.08 ± 14.13	78.82 ± 39.81	78.79 ± 22.07	0.962
Respiratory rate (per minute)		24.67 ± 8.47	23.77 ± 5.74	23.91 ± 10.39	0.491
O_2 saturation,	<90%	6 (50)	173 (62.9)	17 (51.5)	0.198
	90% ≤O_2 sat < 93%	2 (33.33)	58 (21.1)	6 (18.2)	
	≥93%	4 (66.67)	44 (16)	10 (30.3)	
Temperature (°C)		37.60 ± 1.18	37.31 ± 0.82	37.25 ± 0.73	0.775
Laboratory tests					
C-reactive protein (mg/L)		70.36 ± 43.09	72.58 ± 45.84	58.63 ± 44.77	0.308
Lactate dehydrogenase (U/L)		1483.70 ± 2372.19	960.25 ± 915.92	886.03 ± 641.36	0.329
Absolute lymphocyte count (10^3 cells/µL)		1086.92 ± 536.20	1272.37 ± 994.28	1293.33 ± 1044.83	0.981
In-hospital outcomes					
ICU admission		8 (66.7)	145 (52.7)	20 (60.6)	0.464
Orotracheal intubation/non-invasive ventilation		4 (33.33)/ 8 (66.67)	62 (22.5)/ 213 (77.5)	9 (27.3)/ 24 (72.7)	0.592
Death, n (%)		2 (16.7)	60 (21.8)	6 (18.2)	0.823
Time to ICU admission (days)		5 ± 4	3 ± 5	6 ± 13	0.557
Time to discharge (days		15 ± 9	13 ± 10	15 ± 4	0.138
Time to death (days)		26 ± 12	13 ± 10	15 ± 4	0.557

Data are expressed as mean ± SD or No. (%).

Table 4. The characteristics of the COVID-19 pneumonia patients with magnesium imbalance

		Hyponatremia	Normal	Hypernatremia	*P* value
Demographic characteristics					
Age (years)		62.96 ± 17.81	60.97 ± 17.85	50.67 ± 20.76	0.016
Gender (male)		16 (69.6)	143 (59.6)	12 (44.4)	0.177
Clinical manifestations					
Pulse rate (per minute)		94.61 ± 22.05	93.36 ± 18.49	90.93 ± 23.48	0.393
Systolic blood pressure (mm Hg)		126.04 ± 15.03	124.58 ± 21.38	121.26 ± 18.16	0.593
Diastolic blood pressure (mm Hg)		75.74 ± 10.58	79.25 ± 49.63	77.30 ± 13.44	0.853
Respiratory rate (per minute)		23.61 ± 6.44	23.85 ± 6.51	23.11 ± 5.52	0.876
O_2 saturation,	<90%	14 (60.9)	154 (64.2)	10 (37)	0.037
	90% ≤O_2 sat < 93%	7 (30.4)	45 (18.8)	8 (29.6)	
	≥93%	2 (8.7)	41 (17.1)	9 (33.3)	
Temperature (°C)		37.44 ± 0.99	37.36 ± 0.86	37.09 ± 0.55	0.484
Laboratory tests					
C-reactive protein (mg/L)		57.86 ± 46.45	74.49 ± 46.26	64.71 ± 36.59	0.204
Lactate dehydrogenase (U/L)		979.25 ± 421.93	1072.80 ± 983.94	894.80 ± 600.90	0.396
Absolute lymphocyte count (10^3 cells/µL)		1218.13 ± 1047.73	1252.26 ± 976.62	1483.04 ± 117.13	0.473
In-hospital outcomes					
ICU admission		11 (47.8)	128 (53.3)	15 (55.6)	0.849
Orotracheal intubation/non-invasive ventilation		7 (30.4)/ 16 (69.6)	52 (21.7)/ 188 (78.3)	8 (29.6)/ 19 (70.4)	0.444
Death, n (%)		5 (21.7)	47 (19.6)	8 (29.6)	0.470
Time to ICU admission (days)		3 ± 4	4 ± 7	2 ± 4	0.231
Time to discharge (days		15 ± 9	13 ± 10	15 ± 4	0.138
Time to death (days)		26 ± 12	13 ± 10	15 ± 4	0.557

Data are expressed as mean ± SD or No. (%).

serum sodium imbalances. Systolic blood pressure was remarkably higher among the cases with hypernatremia.

Similarly, Hu et al showed that hyponatremia is a common condition among hospitalized patients with COVID-19, in general. They also presented that hyponatremia was associated with older age, more severe symptoms, course of the disease, and lung involvement. The comparison of hypernatremic patients with normonatremic ones revealed more length of stay and mortality (13). Sterns et al and Reynolds et al separately presented that gastrointestinal source of fluid loss and renal insufficiency is the underlying conditions associated with sodium imbalance. Therefore, it seems that more severe COVID-19, which leads to multi-organ failure, is responsible for sodium imbalance (14,15).

However, we found no associative outcome between sodium imbalance and the clinical, laboratory, and in-hospital outcomes; it has been emphasized on the role of hyponatremia on clinical outcomes of the patients and its association with heart failure (16). In confirmation, the higher fatality of hyponatremic patients may be attributed to the high expression of ACE2 on myocytes. Therefore, more severe COVID-19 infections can concurrently affect sodium ion balance in the kidneys and myocardium ion-dependent channels (17).

Potassium on-admission imbalance was noted in 14.1% of the patients, including 3.8% and 10.3% with hypokalemia and hyperkalemia, respectively. Eleven out of 31 hyperkalemic patients (35.48%) had end-stage renal disease. We found no role for potassium ion imbalance and the clinical outcomes of the patients. Nevertheless, potassium is one of the most important ions in body fluids, and its imbalance may lead to a significant increase in the in-hospital and outpatient fatality of COVID-19 patients (7,18). Tongyoo et al have presented a significantly higher mortality rate among the critically ill patients admitted at ICU with abnormal potassium level (19). In addition, a cohort study has even presented hyperkalemia as a prognostic factor for acquired pneumonia-infected patients admitted to ICU (20). The significance of potassium ion balance is to the extent that another study has stated potassium level above 4.5 mEq/L, which is in the normal range as a predictor of mortality (21).

The mechanisms by which, potassium affects the outcomes of the patients are not well elucidated; however, numerous theories have been presented. Primarily, potassium is modifying the electrophysiological properties of the resting membrane potential in the myocardium and may be contributed to the incidence of arrhythmia. In addition, hyperkalemia leads to a decrease in ventricular

Table 5. The characteristics of the COVID-19 pneumonia patients with calcium imbalance

		Hyponatremia	Normal	Hypernatremia	*P* value
Demographic characteristics					
Age (years)		61.93 ± 18.06	59.67 ± 18.59	55.71 ± 18.66	0.32
Gender (male)		30 (52.6)	121 (61.1)	15 (48.4)	0.267
Clinical manifestations					
Pulse rate (per minute)		90.32 ± 19.38	93.07 ± 19.63	97.29 ± 17.87	0.641
Systolic blood pressure (mm Hg)		122.26 ± 19.26	124.91 ± 20.35	123.19 ± 20.68	0.483
Diastolic blood pressure (mm Hg)		75.12 ± 11.61	80.44 ± 46.12	74.81 ± 9.94	0.258
Respiratory rate (per minute)		25.58 ± 7.80	23.30 ± 6.10	23.03 ± 5.72	0.108
O_2 saturation,	<90%	39 (68.4)	123 (62.1)	17 (54.8)	0.551
	90% ≤O_2 sat < 93%	8 (14)	42 (21.2)	6 (19.4)	
	≥93%	10 (17.5)	33 (16.7)	8 (25.8)	
Temperature (°C)		37.17 ± 0.87	37.36 ± 0.85	37.23 ± 0.76	0.082
Laboratory tests					
C-reactive protein (mg/L)		78.06 ± 48.08	73.05 ± 44.93	50.39 ± 40.70	0.025
Lactate dehydrogenase (U/L)		871.74 ± 478.78	961.82 ± 763.89	2336.69 ± 1321.04	0.821
Absolute lymphocyte count (10^3 cells/µL)		1272.97 ± 944.06	1261.59 ± 1044.80	1278.87 ± 811.90	0.777
In-hospital outcomes					
ICU admission		24 (42.1)	117 (59.1)	12 (38.7)	0.017
Orotracheal intubation/non-invasive ventilation		11 (19.3)/ 46 (80.7)	52 (26.3)/ 146 (73.3)	4 (12.9)/ 27 (87.1)	0.188
Death, n (%)		8 (14)	41 (20.7)	9 (29)	0.239
Time to ICU admission (days)		4 ± 4	3 ± 7	4 ± 4	0.142
Time to discharge (days		13 ± 12	14 ± 11	11 ± 7	0.676
Time to death (days)		18 ± 16	13 ± 8	10 ± 10	0.495

Data are expressed as mean ± SD or No. (%).

excitability and precipitates complete heart block and sinus arrest (22). Accordingly, multi-organ failure is the outcome of severe COVID-19, affecting kidney function and potassium imbalance, which deteriorates the condition. It is noteworthy that hyperkalemia represents acid-base balance disorders and can be considered a manifestation of more severe respiratory distress (23).

The other side of potassium imbalance is hypokalemia that has not been presented as perilous as hyperkalemia but is common, particularly in patients under diuretics. As most critically ill COVID-19 patients are in adulthood, hypokalemia should be considered; however, no association with ICU admission requirement or mortality was noted (24).

In addition, 7.9% of patients suffered from hypomagnesemia, and 9.3% had hypermagnesemia. Our finding also uncovered that O_2 saturation is significantly related to magnesium imbalances; however, we found no logic for that. Magnesium is an ion associated with immune function, and impressive numbers of studies tried to make an association between magnesium supplemental therapy and COVID-19 infection outcomes (25). Hypomagnesemia has been presented as a risk factor of increased mortality due to COVID-19, which may be attributed to the negative effect of hypomagnesemia on potassium balance on a hand elongation of QT-interval on ECG (26). The other study stated a surprising hypothesis that, hypomagnesemia was more common among the COVID-19 patients requiring hospital admission, but the critically ill ones mainly presented hypermagnesemia (27). Nevertheless, magnesium imbalance has not been well elucidated in COVID-19.

Moreover, the present study showed that 19.9% of patients were hypocalcemic, and 10.8% were hypercalcemia. Although this high rate of calcium ion imbalance seems surprising, numerous other studies have notified this finding. In this regard, recent studies have raised hypothesis regarding intestinal absorption, imbalance in regulatory mechanism involving parathyroid hormone and vitamin D, or a direct effect caused by SARS-CoV-2 (28,29). It should be noted that, viruses require calcium ion for their structure formation, entry, gene expression, virion maturation and release (30), nevertheless, the mechanism by which calcium ion imbalance occurs has not been well detected. This type of electrolyte imbalance was significantly related to ICU admission and CRP level. Surfing the literature has shown that hypocalcemia is a common electrolyte imbalance in viral infections (31). The exact mechanism of hypocalcemia during COVID-19 is not precise; however, some evidence showed that patients with COVID-19 commonly suffer from chronic malnutrition leading to vitamin D deficiency and low intestinal absorption of calcium. Besides, calcium is predominantly bound to albumin in the plasma and a decrease in serum albumin will cause hypocalcemia (32-34). To determine the prognostic value of calcium imbalance, Liu et al showed that serum calcium levels were negatively associated with leukocytes, CRP, procalcitonin, IL-6 and D-dimer, nevertheless positively correlated with lymphocytes and albumin. They also showed that patients with hypocalcemia presented poor outcomes more commonly (35).

Conclusion

The present study showed that electrolyte imbalances are common laboratory abnormalities during COVID-19. However, we found no associative role, but ions balance plays a crucial prognostic role for COVID-19.

Limitations of the study

Along with the strength, this study has some limitations. The study has been conducted on the patients with COVID-19 pneumonia, nevertheless not both in-patients and outpatients. However, logically electrolyte disturbances are more prominent among admitted ones. Moreover, the study of outpatients could provide a better vision for supplementation in the course of the disease. Furthermore, the authors could assess the patients in separated groups of ICU admitted and general wards to make a better vision of electrolytes imbalance. Further studies with larger sample populations can help better generalizability of the outcomes.

Authors' contribution

SS, EK and EN contributed to the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. ZN and SP contributed to the conception of the work, conducting the study, revising the draft.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (IR.MUI.MED.REC.1399.495). Accordingly, written informed consent was taken from all participants before any intervention. Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no competing interests.

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