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Original Article (Pages: 18649-18658)

Lactate Dehydrogenase as a New Prognostic Factor for Mortality in Multisystem Inflammatory Syndrome in Children

Seyed Hesamedin Nabavizadeh [1, 2], Mina Esmailli [3], Hossein Esmaeilzadeh [1, 2], Soheila Alyasin [1, 2], * Aida Askarisarvestani [1]

[1] Division of Allergy and Clinical Immunology, Department of Pediatrics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.

[2] Allergy Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.

[3] Clinical Pediatrician, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Background: Multisystem Inflammatory Syndrome in Children (MIS-C) is a rather newly described entity that can potentially end in multisystem failure in children following COVID-19 infection. The prognosis of patients with MIS-C is multifactorial; consequently, many risk factors increase the risk of mortality and severity of this disease. In this study we aimed to evaluate the prognostic effect of various parameters in mortality and intensive care unit admission of patients with MIS-C.

Methods: in this cross-sectional study, the information of patients with MIS-C were extracted in a tertiary pediatric center during a one-year period. The relationship between mortality and ICU admission of the patients with demographic information and lab data were assessed.

Results: a total of 88 male-predominant (56.8% vs. 43.2%, P=0.135) entered the study. Seven patients had expired and 71 patients were discharged from the hospital. In our study, demographic information of the patients and their lab data were not associated with mortality except for Lactate Dehydrogenase (LDH) level. All of the expired patients had elevated LDH, while only 53.1% of the discharged patients showed increased LDH (P=0.016); on the other hand, LDH did not differ between patients who were managed in ICUs and the ones who were managed in wards.

Conclusion: LDH can be counted as a prognostic tool for mortality in MIS-C and might be regarded as a part of evaluation for ICU admission in this disease.

Key Words: COVID-19, Lactate Dehydrogenase (LDH), Multisystem Inflammatory Syndrome in Children (MIS-C).

* Please cite this article as: Nabavizadeh SH, Esmailli M, Esmaeilzadeh H, Alyasin S, Askarisarvestani A. Lactate Dehydrogenase as a New Prognostic Factor for Mortality in Multisystem Inflammatory Syndrome in Children. Int J Pediatr 2024; 12 (03):18649-18658. DOI: **10.22038/ijp.2024.80040.5455**

Corresponding Author:

Aida Askarisarvestani, Division of Allergy and Clinical Immunology, Department of Pediatrics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. Email: askariaida@gmail.com

Received date: Jan.19,2024; Accepted date: Mar.05,2024

1- INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was found to be responsible for pneumonia cases first encountered in December 2019 in China (1). Acute COVID-19 primarily affects the respiratory system and is mostly asymptomatic or mild in the pediatric population (2). In severe cases of COVID-19, the pathogenesis is mostly based on immune dysregulation and the cytokine storm followed by inappropriate immune system activation (3). Such a pathogenic base is postulated to be responsible for long-term COVID-19 complications such as multisystem inflammatory syndrome in children (MIS-C) (4).

MIS-C is defined by World Health Organization and United States Center for Disease Control and prevention as long-lasting fever, with paraclinical evidence of apparent inflammation, with involvement of at least two organ systems, with evidence of current or recent COVID-19 infection and no other explanatory inflammatory or infectious process (5, 6).

Patients mostly present with fever and gastrointestinal and cardiovascular symptoms such as abdominal pain, vomiting, and tachycardia, myocarditis, decreased left ventricular ejection fraction, and hypotension (4).

Patients with MIS-C might follow a severe course of the disease requiring intensive care unit admission. Approximately 2% of the patients with MIS-C have been reported to have expired in their course of hospitalization. Such patients were more likely to be older and were shown to have gastrointestinal and cardiovascular symptoms (7, 8).

In this study, we aimed to evaluate the risk factors for MIS-C mortality and find a new criterion for PICU admission in MIS-C patients.

2- METHODS AND MATERIALS

2-1. Design and participants

This study followed a cross-sectional protocol. Participants of the study included patients afflicted with MIS-C who were admitted to Namazee hospital, the referral tertiary center of Pediatrics in Southern Iran, affiliated to Shiraz University of Medical Sciences. In this study, the contact information of the patients who were admitted to PICU and pediatric wards of our center were extracted. After reaching out to the patients and/or their legal guardians, interview sessions were planned. After obtaining a written consent form, the patients and/or their legal guardians were asked about the course of their disease and the presented symptoms of MIS-C as well as their demographic information. The cases were selected from among the patients and further clinical data of the patients in regards to their course of hospitalization were evaluated.

2-1-1. Inclusion and Exclusion Criteria

The inclusion criteria of our study encompassed all of the patients younger than 18 years old, who were admitted to our center from March 2020 to March 2021 with a diagnosis of MIS-C based on CDC criteria, i.e. a persistent fever for more than a day, along with evidence of organ involvement as well as evidence of current or previous COVID-19 infection. The exclusion criteria of our study were age ranges older than 18 years old, inability to access the clinical data or inability to contact the patients' legal guardians, and unwillingness of the patients and/or their legal guardians to participate in the study. A census method was used for sampling.

2-2. Data collection

The diagnosis of MIS-C was made based on the American Center for Disease Control, and Prevention criteria was as follows: patients younger than 21 years old

with fever more than 38 Celsius degrees for more than 24 hours, in conjunction with involvement of more than two organ systems including gastrointestinal, mucocutaneous, hematologic, cardiac, renal, respiratory, or neurological systems with elevated inflammatory markers and positive SARS-CoV-2 RT-PCR or serologic testing or a positive history of exposure to confirmed COVID-19 cases (9).

The information of the patients were extracted using a checklist containing the demographic data, presenting symptoms of the disease, the total course of hospitalization, PICU admission, final outcome, and the paraclinical data such as laboratory data on admission, echocardiography findings, imaging studies, and SARS-CoV-2 RT-PCR or serologic tests, as well as treatment strategies used for the patients.

2-3. Data analysis

The data was categorized into categorical qualitative variables. The data was then entered into IBM SPSS version 26.0 and reported as frequency and percentages. The associations between outcome and PICU admission with other variables were evaluated using chi-squared test or Fischer's exact test as appropriate.

3- RESULTS

A total of 88 patients with a diagnosis of MIS-C entered the study. The highest proportion of patients (34 patients or 38.6%) were 2-5 years old. Fifty patients (56.8%) were male and 38 (43.2%) were female. Seven patients (8.0%) expired in their hospitalization course while 81 patients (92.0%) survived the disease. Among the studied population, 40 patients (45.5%) were not admitted to PICU, when 48 patients (54.5%) had PICU admission. **Table 1** summarizes the demographic information of the patients.

The associations between various demographic information, MIS-C presentations, and lab data with outcome were evaluated using Chi-squared test or Fischer's exact test. In these analyses only abnormal Lactate Dehydrogenase (LDH) was associated with the worst outcome. Consumption of intravenous immunoglobulins was associated with better outcomes in MIS-C patients.

We then examined the association between PICU admission with the demographic information, MIS-C presentation, and paraclinical findings of the patients. Older patients were more likely to be admitted to PICU; moreover, patients with hypotension, abnormal echocardiography, electrolyte imbalance, elevated troponin, procalcitonin, and D-dimer were more in prone of ICU admission. However, LDH was not a discriminating factor in decision making with regards to ICU admission in MIS-C patients.

4- DISCUSSION

In this study, 88 patients with MIS-C were evaluated, seven of whom (7.95%) died due to this disease. In this study, we found that patients with higher lactate dehydrogenase levels were more likely to expire. Furthermore, treatment with IVIG was associated with a better outcome in these patients. Patients with older age, hypotension, abnormal echocardiographic findings, electrolyte imbalance, high procalcitonin, D-dimer, and troponin were more likely to be admitted to PICU. However, LDH level was not different between patients with and without PICU admission.

In two systematic reviews by Santos et al. and Jiang et al., it was reported that the total mortality rate for MIS-C was about 2%. However in our study, about 8% of the patients expired due to MIS-C. Such difference might be attributed to various factors such as the national COVID-19 vaccination program for the pediatric

population, health seeking behaviors of the studied populations, PICU beds and their equipment, and the demographic differences among the studied populations (7, 8).

In our study, apart from long-lasting fever, the most common presenting sign and symptom of MIS-C was dermatologic rash followed by gastroenteritis and tachycardia. In a systematic review by Santos et al., the authors found that the most common symptoms of MIS-C were fever, gastrointestinal symptoms, abdominal pain, and rash. Even though our findings are relatively similar, the small difference between the results might have been due to the retrospective nature of our study compared to other studies (7).

Table-1: Demographic and clinical information of the patients

Variable		Frequency	Percentage
Age	0-1 year	6	6.8%
	2-5 years	34	38.6%
	6-10 years	30	34.1%
	11-14 years	13	14.8%
	15-18 years	5	5.7%
Sex	Male	50	56.8%
	Female	38	43.2%
Weight	Underweight	21	23.9%
	Normal	56	63.6%
	Overweight	11	12.5%
History of prematurity	Positive	5	5.7%
	Negative	83	94.3%
Passive smoking	Positive	15	17.0%
	Negative	73	83.0%
Breast milk consumption	Yes	75	85.2%
	No	13	14.8%
Hospitalization duration	≤7 days	35	39.8%
	>7 days	53	60.2%
PICU admission	No	40	45.5%
	<3 days	25	28.4%
	≥3 days	23	26.1%
outcome	Expiration	7	8.0%
	Survival	81	92.0%

In a study by Cetin et al., by evaluating 63 patients with MIS-C in Turkey, they found that brain natriuretic peptide, serum total protein, and troponin levels could be used in a model to predict mortality in MIS_C.; they also found that a D-dimer level of 2890 had a sensitivity of 91.2% for mortality, and a BNP level of 8332 had an 86.4% specificity for mortality in MIS-C patients. However, in their study, LDH was not associated with mortality (10). In order to shed light on the reasons behind the difference between their findings and ours, further studies with larger sample sizes are needed.

In another study by Angurana et al., conducted on 40 children from northern India, two patients (5%) died due to MIS-C.; they found that both patients who died in their course of hospitalization

experienced refractory shock. They also found that leukocytosis and decreased ejection fraction in echocardiography were prognostic factors of shock and consequently, mortality in children with MIS-C. However, due to the small number of patients, and unknown pathophysiology of shock in those patients, this conclusion might be oversimplified. They did not find any other difference between the patients with and without shock regarding their laboratory findings (11).

In a research study performed by Alkan et al. on 36 children with MIS-C from Turkey, they divided the patients into three subcategories of mild, moderate, and severe MIS-C., finding that patients with severe MIS-C were more likely to have lymphopenia, higher procalcitonin, higher interleukin 6, higher troponin, higher pro-BNP, D-dimer, and ferritin. In their study, although the mean LDH level of patients with severe MIS-C was higher than mild and moderate MIS-C, this difference was not statistically significant. The apparent contrast in the studies might be due to the fact that the severity of MIS-C was defined by the authors rather than by an objective finding, such as death (12).

Table-2: Evaluation of the effects of demographic and clinical information of the patients on MIS-C mortality

Variable			Expiration (n=7)	Survival (n=81)	P-value
Demographic information	Age	0-1 year	0 (0.0%)	6 (7.4%)	0.806
		2-5 years	3 (42.9%)	31 (38.3%)	
		6-10 years	2 (28.6%)	28 (34.6%)	
		11-14 years	1 (14.3%)	12 (14.8%)	
		15-18 years	1 (14.3%)	4 (4.9%)	
	Sex	Male	6 (85.7%)	44 (54.3%)	0.135
		Female	1 (14.3%)	37 (45.7%)	
	Weight	Underweight	2 (28.6%)	19 (23.5%)	0.579
		Normal	5 (71.4%)	51 (63.0%)	
		Overweight	0 (0.0%)	11 (13.6%)	
	History of prematurity	Positive	0 (0.0%)	5 (6.2%)	0.654
		Negative	7 (100%)	76 (93.8%)	
	Passive smoking	Positive	0 (0.0%)	15 (18.5%)	0.598
		Negative	7 (100%)	66 (81.5%)	
	Breast milk consumption	Yes	7 (100%)	68 (84.0%)	0.313
		No	0 (0.0%)	13 (16.0%)	
	Hospitalization duration	≤7 days	4 (57.1%)	31 (38.3%)	0.278
		>7 days	3 (42.9%)	50 (61.7%)	
	PICU admission	No	1 (14.3%)	39 (48.1%)	0.017
		<3 days	1 (14.3%)	24 (29.6%)	
		≥3 days	5 (71.4%)	18 (22.2%)	
MIS-C presentations	Fever duration > 24 hours	Yes	5 (71.4%)	56 (69.1%)	0.634
		No	2 (28.6%)	25 (10.9%)	
	Cough	Yes	0 (0.0%)	11 (13.6%)	0.379
		No	7 (100%)	70 (86.4%)	
	Rash	Yes	4 (57.1%)	45 (55.6%)	0.627
		No	3 (42.9%)	36 (44.4%)	

Variable			Expiration (n=7)	Survival (n=81)	P-value
	Conjunctivitis	Yes	2 (28.6%)	25 (30.9%)	0.634
		No	5 (71.4%)	56 (69.1%)	
	Gastroenteritis	Yes	4 (57.1%)	42 (51.9%)	0.551
		No	3 (42.9%)	39 (48.1%)	
	Tachypnea	Yes	2 (28.6%)	16 (19.8%)	0.439
		No	5 (71.4%)	65 (80.2%)	
	Tachycardia	Yes	4 (57.1%)	30 (37.0%)	0.256
		No	3 (42.9%)	51 (63.0%)	
	Hypotension	Yes	4 (57.1%)	26 (32.1%)	0.176
		No	3 (42.9%)	55 (67.9%)	
	Abdominal pain	Yes	2 (28.6%)	30 (37.0%)	0.499
		No	5 (71.4%)	51 (63.0%)	
Paraclinical studies	COVID-19 RT-PCR	Negative	2 (28.6%)	14 (18.5%)	0.380
		Positive	5 (71.4%)	66 (81.5%)	
	COVID-19 serology	Negative	7 (100%)	60 (74.1%)	0.137
		Positive	0 (0.0%)	21 (25.9%)	
	echocardiography	Normal	4 (57.1%)	30 (37.0%)	0.256
		In favor of MIS-C	3 (42.9%)	51 (63.0%)	
	WBC	Normal	1 (14.3%)	18 (22.2%)	0.529
		Abnormal	6 (85.7%)	63 (77.8%)	
	BUN and Creatinine	Normal	5 (71.4%)	73 (90.1%)	0.179
		Abnormal	2 (28.6%)	8 (9.9%)	
	Serum Sodium and Potassium	Normal	6 (85.7%)	73 (90.1%)	0.543
		Abnormal	1 (14.3%)	8 (9.9%)	
	ESR and CRP	Normal	1 (14.3%)	6 (7.4%)	0.452
		Abnormal	5 (71.4%)	75 (92.6%)	
	procalcitonin	Normal	2 (28.6%)	18 (22.2%)	0.502
		Abnormal	5 (71.4%)	63 (77.8%)	
	D-Dimer	Normal	1 (14.3%)	13 (16.0%)	0.692
		Abnormal	6 (85.7%)	68 (84.0%)	
	Liver transaminases	Normal	4 (57.1%)	69 (85.2%)	0.093
		Abnormal	3 (42.9%)	12 (14.8%)	
	Albumin	Normal	5 (71.4%)	63 (77.8%)	0.502
		Abnormal	2 (28.6%)	18 (22.2%)	
	Ferritin	Normal	1 (14.3%)	10 (12.3%)	0.621
		Abnormal	6 (85.7%)	71 (87.7%)	
	Troponin	Normal	1 (14.3%)	29 (35.8%)	0.239
		Abnormal	6 (85.7%)	52 (64.2%)	
	LDH	Normal	0 (0.0%)	38 (46.9%)	0.016
		Abnormal	7 (100%)	43 (53.1%)	
Therapeutic agents	IVIG	Received	2 (28.6%)	53 (65.4%)	0.001
		Did not receive	5 (71.4%)	28 (34.6%)	
	Aspirin	Received	2 (28.6%)	55 (67.9%)	0.050
		Did not receive	5 (71.4%)	26 (32.1%)	
	Enoxaparin	Received	1 (14.3%)	43 (53.1%)	0.055

Variable			Expiration (n=7)	Survival (n=81)	P-value
		Did not receive	6 (85.7%)	38 (46.9%)	
	Corticosteroid	Received	5 (71.4%)	69 (85.2%)	0.308
		Did not receive	2 (28.6%)	12 (14.8%)	
	Dopamine	Received	4 (57.1%)	22 (27.2%)	0.111
		Did not receive	3 (42.9%)	59 (72.8%)	

Table-3: Evaluation of the effects of demographic and clinical information of the MIS-C patients on PICU admission

Variable		No picu admission (n=40)	Picu <3 days (n=25)	Picu ≥3 days (n=23)	P-value
Demographic information					
Age	0-1 year	5 (12.5%)	0 (0.0%)	1 (4.3%)	0.049
	2-5 years	18 (45.0%)	10 (40.0%)	6 (26.1%)	
	6-10 years	10 (25.0%)	13 (52.0%)	7 (30.4%)	
	11-14 years	6 (15.0%)	1 (4.0%)	6 (26.1%)	
	15-18 years	1 (2.5%)	1 (4.0%)	3 (13.0%)	
Sex	Male	20 (50.0%)	16 (64.0%)	14 (60.9%)	0.487
	Female	20 (50.0%)	9 (36.0%)	9 (39.1%)	
Weight	Underweight	10 (25.0%)	5 (20.0%)	6 (26.1%)	0.756
	Normal	26 (65.0%)	15 (60.0%)	15 (65.2%)	
	Overweight	4 (10.0%)	5 (20.0%)	2 (34.8%)	
History of prematurity	Positive	4 (10.0%)	0 (0.0%)	1 (4.3%)	0.226
	Negative	36 (90.0%)	25 (75.0%)	22 (95.7%)	
Passive smoking	Positive	10 (25.0%)	3 (12.0%)	2 (8.7%)	0.185
	Negative	30 (75.0%)	22 (88.0%)	21 (91.3%)	
Breast milk consumption	Yes	31 (77.5%)	24 (96.0%)	20 (87.0%)	0.119
	No	9 (22.5%)	1 (4.0%)	3 (13.0%)	
MIS-C presentations					
Fever duration > 24 hours	Yes	29 (72.5%)	15 (60.0%)	17 (73.9%)	0.487
	No	11 (27.5%)	10 (40.0%)	6 (26.1%)	
Cough	Yes	7 (17.5%)	3 (12.0%)	1 (4.3%)	0.314
	No	33 (82.5%)	22 (88.0%)	22 (95.7%)	
Rash	Yes	22 (55.0%)	17 (68.0%)	10 (43.5%)	0.231
	No	18 (45.0%)	8 (32.0%)	13 (56.5%)	
Conjunctivitis	Yes	13 (32.5%)	8 (32.0%)	6 (26.1%)	0.856
	No	27 (67.5%)	17 (68.0%)	17 (73.9%)	
Gastroenteritis	Yes	16 (40.0%)	16 (64.0%)	14 (60.9%)	0.107
	No	24 (60.0%)	9 (36.0%)	9 (39.1%)	
Tachypnea	Yes	8 (20.0%)	7 (28.0%)	3 (13.0%)	0.437
	No	32 (80.0%)	18 (72.0%)	20 (87.0%)	
Tachycardia	Yes	11 (27.5%)	11 (44.0%)	12 (52.2%)	0.124
	No	29 (72.5%)	14 (56.0%)	11 (47.8%)	
Hypotension	Yes	3 (7.5%)	15 (60.0%)	12 (52.2%)	<0.001

Variable		No picu admission (n=40)	Picu <3 days (n=25)	Picu ≥3 days (n=23)	P-value
	No	37 (92.5%)	10 (40.0%)	11 (47.8%)	
Abdominal pain	Yes	13 (32.5%)	9 (36.0%)	10 (43.5%)	0.683
	No	27 (67.5%)	16 (64.0%)	13 (56.5%)	
Paraclinical studies					
COVID-19 RT-PCR	Negative	4 (10.0%)	5 (20.0%)	7 (30.4%)	0.102
	Positive	36 (90.0%)	20 (80.0%)	15 (65.2%)	
COVID-19 serology	Negative	30 (75.0%)	18 (72.0%)	19 (82.6%)	0.672
	Positive	10 (25.0%)	7 (28.0%)	4 (17.4%)	
echocardiography	Normal	5 (12.5%)	18 (72.0%)	11 (47.8%)	<0.001
	In favor of MIS-C	35 (78.5%)	7 (28.0%)	12 (52.2%)	
WBC	Normal	13 (32.5%)	4 (16.0%)	2 (8.7%)	0.063
	Abnormal	27 (67.5%)	21 (84.0%)	21 (91.3%)	
BUN and Creatinine	Normal	37 (92.5%)	22 (88.0%)	19 (82.6%)	0.489
	Abnormal	3 (7.5%)	3 (12.0%)	4 (17.4%)	
Serum Sodium and Potassium	Normal	39 (97.5%)	19 (76.0%)	21 (91.3%)	0.020
	Abnormal	1 (2.5%)	6 (24.0%)	2 (8.7%)	
ESR and CRP	Normal	3 (7.5%)	2 (8.0%)	2 (8.7%)	0.986
	Abnormal	37 (92.5%)	23 (92.0%)	21 (91.3%)	
procalcitonin	Normal	15 (37.5%)	2 (8.0%)	3 (13.0%)	0.010
	Abnormal	25 (62.5%)	23 (92.0%)	20 (87.0%)	
D-Dimer	Normal	12 (30.0%)	2 (8.0%)	0 (0.0%)	0.003
	Abnormal	28 (70.0%)	23 (92.0%)	23 (100%)	
Liver transaminases	Normal	37 (92.5%)	19 (76.0%)	17 (73.9%)	0.092
	Abnormal	3 (7.5%)	6 (24.0%)	6 (26.1%)	
Albumin	Normal	34 (85.0%)	15 (60.0%)	19 (82.6%)	0.050
	Abnormal	6 (15.0%)	10 (40.0%)	4 (17.4%)	
Ferritin	Normal	7 (17.5%)	1 (4.0%)	3 (13.0%)	0.276
	Abnormal	33 (82.5%)	24 (96.0%)	20 (87.0%)	
Troponin	Normal	23 (57.5%)	4 (16.0%)	3 (13.0%)	<0.001
	Abnormal	17 (42.5%)	21 (84.0%)	20 (87.0%)	
LDH	Normal	20 (50.0%)	12 (48.0%)	6 (26.1%)	0.155
	Abnormal	20 (50.0%)	13 (52.0%)	17 (73.9%)	
Therapeutic agents					
IVIG	Received	28 (70.0%)	16 (64.0%)	11 (47.8%)	0.261
	Did not receive	12 (30.0%)	9 (36.0%)	12 (52.2%)	
Aspirin	Received	29 (72.5%)	17 (68.0%)	11 (47.8%)	0.132
	Did not receive	11 (27.5%)	8 (32.0%)	12 (52.2%)	
Enoxaparin	Received	15 (37.5%)	17 (68.0%)	12 (52.2%)	0.055
	Did not receive	25 (62.5%)	8 (32.0%)	11 (47.8%)	
Corticosteroid	Received	33 (82.5%)	23 (92.0%)	18 (78.3%)	0.401
	Did not receive	7 (17.5%)	2 (8.0%)	5 (21.7%)	
Dopamine	Received	4 (10.0%)	15 (60.0%)	7 (30.4%)	<0.001
	Did not receive	36 (90.0%)	10 (40.0%)	16 (69.6%)	

5- CONCLUSION

At the end, it is worth noting that MIS-C patients with higher LDH were more likely to experience mortality. And, LDH was not associated with higher ICU admissions. Then, we conclude that elevated lactate dehydrogenase level in patients with MIS-C is associated with higher risk of mortality consequently, this laboratory finding can be integrated in the criteria of assessing patients for PICU admission.

6- ETHICAL CONSIDERATIONS

This study was approved by the Committee of Ethics in Biomedical Research of Shiraz University of Medical Sciences by the code IR.SUMS.MED.REC.1400.176.

7- FUNDING

This article is derived from the dissertation of ME for the degree of specialty in pediatrics. The authors received a grant for this matter from Shiraz University of Medical Sciences under the code 22529.

8- CONFLICTS OF INTEREST

None.

9- ACKNOWLEDGMENTS

The authors would like to thank the Deputy of Research and Technology in Shiraz University of Medical Sciences for their support.

10- AUTHOR CONTRIBUTION

SHN and AA designed the study. ME, SA, and HE gathered the data. AA was responsible for data analysis. ME and AA wrote the first draft of the manuscript. All of the authors read the manuscript and revised it. The final form of the manuscript is accepted by all of the authors.

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