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Is there any association between plasma lipid profile and severity of COVID-19?

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SUMMARY

Background: COVID-19 is an infectious disease which caused a pandemic with many diseases and fatalities. This new variant of coronavirus called SARS-CoV-2 and is primarily characterized by respiratory symptoms. There are some data indicating that LDL-cholesterol (LDL-C) as well as HDL-cholesterol (HDL-C) levels are inversely correlated to disease severity and could act as a predictor for disease progression and unfavorable prognosis. However, the results of some other studies do not confirm this. This current study aimed to provide an answer to this question.

Methods: This prospective, single-center study analyzed 367 confirmed COVID-19 patients to find whether there are any differences in plasma lipoproteins between survivors and non-survivors patients or between the patients with a “duration of < 10 days intensive unit care (ICU) stay” and patients with a “duration of > 10 days ICU stay”.

Results: No association between any lipid/lipoprotein parameter and the severity of COVID-19 could be found but survivors and non-survivors patients did differ concerning total cholesterol and LDL-C levels.

Conclusion: Multivariate cox regression analysis could not prove any association between lipids/lipoproteins and severe events in COVID-19 patients. Significantly less non-survivors with COVID-19 were taking atorvastatin than survivors which is consistent with the majority of previous findings.

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1. Introduction

CoRonaVirus Disease 2019 (COVID-19) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2), a new variant of coronavirus, leading to an infectious disease which was declared a pandemic by the WHO was first originated at Wuhan, in Hubei province, in early December 2019 [1]. The disease is primarily characterized by respiratory symptoms ranging from mild to severe. The significant clinical features of COVID-19 such as fever, cough, fatigue, and dyspnea can progress to acute respiratory distress syndrome (ARDS) and respiratory failure, necessitating mechanical ventilation and extracorporeal membrane oxygenation (ECMO) [2]. Other medical complications associated with COVID-19 include cardiovascular diseases, sepsis, multiorgan failure, and thromboembolic events [3].
severe respiratory distress syndrome. Until now almost 120 millions of people have got this disease in the world and more than 2.6 millions died.

It is well known that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor [2]. However, despite initial concerns about the use of ACE inhibitors and a number of papers discussing this issue [3], European Society of Cardiology (ESC) and American College of Cardiology (ACC) as well as American Heart Association (AHA) and Heart Failure Society of America (HFSA) [4] have recommended not to begin but neither to discontinue ACE inhibitors or angiotensin–II receptor blockers in COVID-19 patients. However, hemodynamic status and clinical findings of patients should be considered to make an optimal decision [5].

It has been shown that SARS-CoV-2 can cause an increased thrombus formation and embolic events either by direct action on platelets leading to endothelial damage or by indirect effects causing inflammation and coagulopathy [6]. Therefore, low-dose aspirin, P2Y purinoceptor (P2Y12) inhibitors as well as complements of platelets have recommended not to begin but neither to discontinue ACE inhibitors or angiotensin-II receptor blockers in COVID-19 patients. However, hemodynamic status and clinical findings of patients should be considered to make an optimal decision [5].

Concerning plasma lipids and lipoproteins in COVID-19 patients it is indicated that LDL-cholesterol (LDL-C) as well as HDL-cholesterol (HDL-C) levels are inversely correlated to disease severity and could predict disease progression and poor prognosis [7]. This could be partially explained by some older data suggesting that both LDL-C and HDL-C are decreased in critically ill patients because of impairment of lecithin-cholesterol acyltransferase, mainly in sepsis. Thus, regarding that lipid profile may be a predictor of survival, non-survivors have a lower LDL-C and HDL-C level than survivors [8]. It is also well known for many decades that total cholesterol (TC), LDL-C and HDL-C levels are lower in many terminal diseases, such as lung cancers [9]. However, patients with different viral infections such as those with chronic hepatitis B and dengue virus also have decreased TC, LDL-C and HDL-C while patients with human immunodeficiency virus (HIV) infection have decreased HDL-C and increased LDL-C levels [10–12].

Since there is no consistency in published data on association between plasma lipoproteins and severity of COVID-19, particularly concerning survivors and non-survivors, this study was performed.

2. Methods

2.1. Participants and study design

This prospective, single-center study was made in Sina Hospital in Hamadan, Iran. COVID-19 pneumonia patients admitted between May 10, 2020 and October 10, 2020 at hospital because of were included consecutively and prospectively. Included COVID-19 patients were participated in accordance with World Health Organization (WHO) interim guidance [13]. Diagnosis of COVID-19 pneumonia was made according to physical examination, chest computed tomographic (CT) scan confirmed with positive results of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) obtained from nasopharyngeal swab specimens. Incomplete medical records or follow-up data, less than 18 years of age or 80 years above, pregnancy or chronic medical conditions, including fatal acute organ injury (i.e., acute stroke, acute coronary syndrome, and severe acute pancreatitis) were considered as exclusion criteria. All patients were monitored until definite outcomes. These outcomes included: complete recovery and/or discharge, partial recovery (patients who were discharged from the hospital using respiratory aids such as nasal catheters or masks and continued to receive respiratory care at home) or death. Longer stay in the hospital (which is mostly a sign of deterioration in those patients) was another outcome since the length of stay in hospital could be used as an indicator of severity of the disease [14]. The study was approved by the Research Ethics Committee of the Hamadan University of Medical Sciences, Hamadan, Iran, with code (IR.UMSHA.REC.1400.289) and written informed consent of participants was obtained.

2.2. Data collection

Patients demographic characteristic (age, gender, history concerning drug treatment and surgery), comorbidities (diabetes, hypertension, coronary heart disease, chronic renal disease, chronic pulmonary disease, chronic liver disorders, and malignancy), vital signs at the beginning of hospitalization (Apache II score, blood pressure, pulse rate, respiratory rate, temperature and percutaneous oxygen saturation (SPO2)), CT scan findings (consolidation, ground-glass, and bilateral pulmonary) were collected. The patients were treated with anti-viral and antibiotic treatment as single drug therapy (antiviral drug lopinavir/ritonavir or hydroxychloroquine), double treatment (an antiviral drug lopinavir/ritonavir or hydroxychloroquine and a cephalosporin or glycopeptide antibiotics such as vancomycin) and triple drug therapy (an antiviral drug such as lopinavir/ritonavir or hydroxychloroquine and two cephalosporins or a cephalosporin and a glycopeptide drug – vancomycin) and some were treated with statins and antihypertensives as well. Laboratory measurements were performed for following parameter: white blood cells count (WBC), lymphocytes count, neutrophil count, platelets count, hemoglobin (HB), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CPK), C-reactive protein (CRP), international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PITT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and lipid profile including total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and non-HDL-C. Data concerning mortality, length of stay in the intensive care unit (ICU) and in the hospital and treatment procedures including respiratory support (extracorporeal membrane oxygenation (ECMO)), treatment with hyper immune plasma, hemoperfusion and mechanical ventilation (MV) were collected.

2.3. Definitions

In the present study, patients who were admitted to ICU were considered as severe cases. The presence of one of the following criteria was considered for ICU admission: invasive mechanical ventilation due to presence of respiratory distress; cardiovascular shock; acute extrapulmonary organ failure in newly diagnosed patients who required organ support treatment; other critical conditions based on expert specialists’ decision for ICU management in accordance with patients’ situation.

Cardiovascular disease was defined as experiencing ischemic heart disease, cardiomyopathy, myocardial infarction, serious arrhythmia as well as heart valve disease resulting in myocardial injury and/or cardiac dysfunction. Chronic respiratory disease referred to as respiratory system dysfunction leading to disorder of pulmonary ventilation problems, such as chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, lung cancer, interstitial lung disease, and bronchial asthma. Acute respiratory distress syndrome (ARDS) was categorized as Berlin definition [15]. Chronic kidney disease was determined as impairment structure or function of kidneys, such as chronic glomerulonephritis, uraemia, interstitial nephritis, polycystic kidney disease, diabetic nephropathy, and hypertensive nephropathy. Acute kidney injury was characterized based on the Kidney Disease Improving Global
Outcomes (KDIGO) definition [16]. Also, chronic liver disease was defined as liver dysfunction, such as chronic viral hepatitis, liver cirrhosis, autoimmune hepatitis, and liver cancer.

TC, TG, HDL-C and LDL-C concentration were assessed at admission in ICU and then every day in the Biochemistry Laboratory of Sina Hospital in Hamedan, Iran. TC, LDL-C, HDL-C and TG concentrations were measured using routine enzymatic assays (CHOL, HDL-C, LDL-C and TRIG methods, Dimension VISTA1 System, Siemens Healthineers). LDL-C < 1.40 mmol/L; TC < 5.2 mmol/L; and TG < 1.7 mmol/L were considered as reference values. According to the French National Authority for Health (HAS) in 2017 and the ESC/EAS Guidelines for the Management of Dyslipidaemias, LDL-C concentration target values have been recommended as LDL-C <3.0 mmol/L in low to moderate cardiovascular risk patients, and LDL-C <2.6 mmol/L in high risk patients [17].

2.4. Statistical analysis

Mean ± standard deviation (SD) was applied for continuous variables and frequency (percentage) was considered for categorical variables. Since the median of hospitalization was 10 days, we proposed less and more than 10 days as a measure of severity, comparing between non-severe (duration of ≤ 10 days ICU stay) and severe (duration of >10 days ICU stay) patients. Also and non-survivors vs. survivors were analyzed using Independent sample t-test or Mann–Whitney U-test (this test was used to analyze all continuous variables because data was not normally distributed). Chi-square test or Fisher exact test (in case of small samples) were used to compare the distribution of categorical data. Finally, univariate and multivariate analyses were performed to check the associations between the laboratory parameters and disease severity. Effects of laboratory variables on the risk of severe events were estimated using the Cox regression model. IBM SPSS version 16 software was used for all statistical analyses. Significance level of 0.05 was used.

3. Results

A total of 367 confirmed COVID-19 patients were recruited in current study. Table 1 shows the demographic and baseline clinical data of patients with COVID-19. No sex and comorbidity differences were identified between the survivors and non-survivor patients neither between the patients with a “duration of ≤10 days ICU stay” nor patients with a “duration of >10 days ICU stay”. No vital signs including Apache II score, SPO2, WBC, number of days between symptoms onset and ICU admission and days of hospitalization before ICU admission were significantly associated with severity or mortality. Non-survivor patients were significantly older than survivors (p = 0.01). Atorvastatin was administered in 81 patients (before and during admission) and among them 75 patients (91.5%) received 40 mg while the others were treated with a lower dose. There was a significant negative association between atorvastatin treatment and mortality. Mortality was significantly lower in patients who were treated with atorvastatin (p = 0.036). However after adjusting for age and sex as the potential confounders for both treatment with statins and mortality in a logistic regression, no statistical significance between statins and mortality could be proven (p = 0.213). Also, 129 patients were treated with antihypertensive drugs (before and during admission). There was no association between antihypertensive drugs and severity of the disease or mortality. A total of 48 patients were treated with captopril as an angiotensin-converting enzyme (ACE) inhibitor, 60 patients used losartan as an angiotensin II receptor blocker (ARB) and 21 patients used other antihypertensive drugs including metoprolol and amiodipine. No association was found between the type of antihypertensive drugs and severity of the disease or mortality (Table 1).

As shown in Table 2, there were no statistically differences in laboratory parameters between patients with a “duration of ≤10 days ICU stay” and patients with a “duration of >10 days ICU stay”. Only total cholesterol, LDL-C, TG/HDL-C, and monocytes/HDL-C

| Parameter | Total (n = 367) | Duration ≤10 days (n = 160) | Duration >10 days (n = 185) | p-value | Mortality Survivor (n = 206) Non-Survivor (n = 161) | p-value |
|-----------|----------------|-----------------------------|-----------------------------|---------|-----------------------------------------------|---------|
| Age, years<sup>a</sup> | 66.33 (15.96) | 66.54 (16.05) | 66.30 (15.89) | 0.889 | 63.37 (16.17) | 70.12 (14.91) | 0.001 |
| Male | 205 (56%) | 86 (54%) | 105 (57%) | 0.59 | 111 (54%) | 94 (58%) | 0.40 |
| Comorbidity | | | | | | |
| Hypertension | 161 (44%) | 73 (46%) | 79 (43%) | 0.30 | 89 (43%) | 72 (45%) | 0.29 |
| Diabetes | 96 (26%) | 43 (27%) | 47 (25%) | 0.81 | 48 (30%) | 48 (30%) | 0.15 |
| CVD | 98 (27%) | 43 (27%) | 46 (26%) | 1.00 | 48 (30%) | 50 (31%) | 0.07 |
| CRD | 13 (3.5%) | 7 (4.4%) | 5 (2.7%) | 0.557 | 7 (3.1%) | 6 (3.7%) | 0.78 |
| CKD | 6 (1.6%) | 5 (3.1%) | 1 (0.54%) | 0.103 | 3 (1.5%) | 3 (1.5%) | 0.70 |
| Apache II score<sup>b</sup> | 15.47 (2.45) | 15.59 (2.42) | 15.31 (2.46) | 0.29 | 15.51 (2.28) | 15.39 (2.28) | 0.66 |
| Oxygen saturation<sup>b</sup> | 79.9 (11.54) | 81.0 (11.9) | 80.9 (10.8) | 0.093 | 80.6 (10.8) | 78.9 (12.4) | 0.19 |
| White blood cell count<sup>b</sup> | 9.98 (8.52) | 10.05 (6.42) | 9.9 (10.2) | 0.092 | 9.5 (7.15) | 10.6 (10.01) | 0.24 |
| Days between symptoms onset and ICU admission<sup>c</sup> | 6 (2) | 6 (2) | 6 (2) | 0.31 | 6 (2) | 6 (3) | 0.27 |
| Days of hospitalization before ICU admission<sup>c</sup> | 4 (3) | 4 (3) | 4 (3) | 0.19 | 4 (3) | 4 (3) | 0.92 |
| Atorvastatin | 81 (22.2%) | 36 (22.5%) | 41 (22.2%) | 0.940 | 44 (27.3%) | 37 (18.1%) | 0.016 |
| Antihypertensives | 129 (35.3%) | 64 (40%) | 59 (31.9%) | 0.117 | 65 (31.9%) | 64 (39.8%) | 0.118 |
| ACE inhibitor (captopril) | 48 (37.2%) | 24 (37.5%) | 24 (40.7%) | 0.935 | 25 (38.5%) | 23 (35.9%) | 0.680 |
| ARB (losartan) | 60 (45.6%) | 30 (46.9%) | 24 (46.1%) | 0.32 | 28 (43.1%) | 32 (50.5%) | 0.26 |
| Others | 21 (16.3%) | 10 (15.6%) | 9 (15.3%) | 0.12 | 12 (18.5%) | 9 (14.1%) | 0.50 |

ACE: Angiotensin-converting enzyme (ACE) inhibitors; ARB: Angiotensin II Receptor Blockers; CRD: Chronic respiratory disease, CVD: Cardiovascular disease, CKD: Chronic kidney disease; ICU: intensive care unit.

Significant p-values are marked in bold.

<sup>a</sup> Mean ± standard deviation (SD).

<sup>b</sup> Median (IQR).

<sup>c</sup> Mean (sd).
showed significant differences between the survivors and non-survivors. Cox regression analysis was made to analyze the association between the lipids/lipoproteins levels and the “risk of developing severe events” in COVID-19 patients. Table 3 shows multivariate cox regression analysis for severe events in COVID-19 patients. Our results indicated that only mean platelet volume (MPV) and age were associated with lower and higher risk of severe events, respectively (Tables 3 and 4).

4. Discussion

We could find no association between any lipid/lipoprotein parameter and the severity of COVID-19 but there survivors and non-survivors did differ concerning TC and LDL-C concentrations. However, multivariate cox regression analysis could not prove any association between lipids/lipoproteins and severe events in COVID-19 patients.

The results of current study differ from the results of some other studies. Hu et al. were among the first who describe that TC, LDL-C and particularly HDL-C were decreased in COVID-19 patients when compared with the controls and that HDL-C was associated with the severity of COVID-19. They have also noted that in patients with severe disease, in the early stage serum cholesterol level significantly decreased and in the recovery period it tended to be normal [18]. Wang et al. in an observational study showed that HDL-C was lower in COVID-19 patients compared with healthy participants, and that low HDL-C in COVID-19 patients was inversely correlated with developing severe events [19].

Results of some other studies differ from some previously mentioned. Some of them indicated low LDL-C and HDL-C concentrations in ICU admitted patients in severe COVID-19 pneumonia without any association with poor outcomes [20]. Nevertheless, in a retrospective study on 248 patients, severe COVID-19 pneumonia cases (n = 74) had higher TG and HDL-C but lower LDL-C levels while TC and LDL-C levels at admission were negatively correlated with length of hospital stay [21]. In Huang et al. recently published cross-sectional retrospective study on 86 severe COVID-19 patients, 132 non-severe COVID-19 patients and 76 healthy individuals. HDL-C was significantly lower in COVID-19 group than in control group and even more significantly lower in severe COVID-19 group than in non-severe COVID-19 group [22]. These results might suggest that HDL-C levels in patients with COVID-19 could reflect the severity of the disease and might have a

Table 2
Baseline laboratory results of patients infected with COVID-19.

| Parameter                  | Severity Duration ≤10 days (n = 160) | Severity Duration >10 days (n = 185) | p-value | Mortality Survivor (n = 206) | p-value |
|---------------------------|-------------------------------------|-------------------------------------|---------|-----------------------------|---------|
| Total cholesterol, mg/dL  | 126.58 (38.420)                     | 130.21 (36.170)                    | 0.446a  | 128.99 (38.98)              | 0.652a  |
| Triglycerides, mg/dL      | 154.20 (89.44)                      | 159.66 (90.64)                     | 0.594b  | 145.16 (72.14)              | 0.019b  |
| HDL-C, mg/dL              | 29.21 (13.14)                       | 30.43 (13.63)                      | 0.404b  | 30.85 (12.83)               | 0.125b  |
| LDL-C, mg/dL              | 77.39 (35.93)                       | 79.96 (34.36)                      | 0.515b  | 82.09 (31.89)               | 0.017b  |
| Non-HDL-C mg/dL           | 98.28 (35.97)                       | 98.55 (52.12)                      | 0.594b  | 97.61 (48.4)                | 0.927b  |
| TG/HDL-C                  | 8.03 (10.91)                        | 7.47 (11.98)                       | 0.660b  | 6.25 (6.19)                 | 0.023b  |
| LDL-C/HDL-C               | 3.23 (2.23)                         | 3.20 (2.05)                        | 0.878b  | 3.19 (1.99)                 | 0.860b  |
| Monocytes/HDL-C           | 0.13 (0.14)                         | 0.11 (0.12)                        | 0.227b  | 0.11 (0.12)                 | 0.041b  |
| Neutrophils/Lymphocytes   | 6.49 (5.37)                         | 7.11 (7.07)                        | 0.375b  | 6.35 (5.85)                 | 0.096b  |
| Monocyte/HDL-C ratio      | 1.010                               | 0.959                               | 0.028   | 1.012                       | 0.002   |
| Platelets/Lymphocytes     | 17.21 (18.31)                       | 17.71 (20.01)                      | 0.816b  | 17.31 (18.61)               | 0.305b  |
| MPV, f                    | 9.21 (3.03)                         | 9.05 (3.91)                        | 0.672b  | 9.28 (3.51)                 | 0.243b  |
| Monocytes, (×10^9/L)      | 2.81 (1.78)                         | 2.58 (1.44)                        | 0.185b  | 2.63 (1.63)                 | 0.453b  |

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; MPV: Mean platelets volume.
Significant p-values are marked in bold.

Table 3
Multivariate Cox regression analysis for severe events in COVID-19 patients.

| Parameter                  | Hazard ratio | 95% CI       | p-value |
|---------------------------|--------------|--------------|---------|
| Age (year)                | 1.022        | 1.010 - 1.035| 0.001   |
| Gender                    | 0.967        | 0.670 - 1.397| 0.860   |
| LDL-C, mg/dL              | 0.995        | 0.984 - 1.007| 0.439   |
| Triglycerides, mg/dL      | 1.002        | 0.999 - 1.005| 0.111   |
| LDL-C/HDL-C ratio         | 1.080        | 0.885 - 1.319| 0.448   |
| HDL-C, mg/dL              | 1.009        | 0.984 - 1.034| 0.496   |
| Monocyte/HDL-C ratio      | 1.194        | 0.946 - 1.438| 0.194   |
| TG/HDL-C                  | 0.998        | 0.974 - 1.023| 0.880   |
| Total cholesterol, mg/dL  | 0.995        | 0.984 - 1.005| 0.306   |
| Non-HDL-C mg/dL           | 1.003        | 0.994 - 1.011| 0.530   |
| MPV, f                    | 0.943        | 0.895 - 0.994| 0.028   |
| Monocytes, (×10^9/L)      | 1.027        | 0.840 - 1.254| 0.797   |
| Neutrophils/Lymphocytes   | 1.010        | 0.995 - 1.063| 0.713   |
| Platelets/Lymphocytes     | 0.999        | 0.980 - 1.018| 0.913   |
| Lymphocytes/Lymphocytes   | 0.983        | 0.966 - 1.016| 0.455   |

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; MPV: Mean platelets volume.
Significant p-values are marked in bold.
significant impact on the prognosis. The only retrospective study on severe COVID-19 infected patients with confirmed outcomes (survivors or non-survivors) showed an increasing trend of TC, LDL-C and HDL-C in survivors but HDL-C levels were dramatically decreased in non-survivors [23].

In our study survivors were more likely to receive atorvastatin than non-survivors. It is well known that statins are LDL-lowering drugs with many pleiotropic effects, such as anti-inflammatory activity [24–32]. Although there were some ideas that statins might increase mortality risk in COVID-19 patients, we were among the first groups to suggest using a molecular docking study that statins are potential SARS-CoV-2 main protease inhibitors which can directly affect the virus particle [33]. Afterwards it has been shown that there was an association between antecedent statin use in admitted COVID-19 patients and lower inpatient mortality [34] shown that there was an association between antecedent statin use and decreased in-hospital mortality in COVID-19 [36]. In two meta-analyses recently published in-hospital use of statins was associated with a lower mortality rate in patients with COVID-19 [37–39]. However, some other authors based upon a study including 7780 patients could not prove that statin therapy might have an effect on hospital mortality of COVID-19 patients although odds of developing COVID-19 were 35% lower in the statin therapy group than in the control group [40]. Another study on 4842 patients with COVID-19 could also not prove any association between recent statin exposure and risk of all-cause mortality or severity of the disease [41]. Therefore, it seems that there are still many open questions concerning the role of statins in COVID-19 patients. However, the results of this study indicating that survivors were more likely to receive atorvastatin than non-survivors are consistent with the most of the published studies.

Concerning the limitations of this study, although the number of participants was not small, a larger number would give a more reliable result. Only one in five of our patients did take a statin, and all of them were treated only with atorvastatin. Therefore, the results concerning the effects of statins on COVID-19 are difficult to interpret. Finally, in the present study lipid/lipoprotein levels were assessed at admission to ICU and not at admission to the hospital. This might be a limitation when comparing the results of this study with some other studies investigating similar issues [20,42–44].

5. Conclusion

There was no association between lipid/lipoprotein parameters and the severity of COVID-19 but there was a significant difference between survivors and non-survivors concerning TC and LDL-C. However, multivariate cox regression analysis could not confirm any association between lipids/lipoproteins and severe events in COVID-19 patients. Non-survivors were less likely to receive atorvastatin than survivors but due to a small number of patients this result has to be reconsidered based upon a much larger number of patients.

Author contribution

Conception: AV, AS; Design: AV, AS, FR; Statistical analysis: MAP; Data collection: LS, ASh, GM; Writing the initial draft: AV, LS, ASh, ZR, MAP, GM; Writing and reviewing: FR, TJ, AS; Approval of the final version: all authors.

Grants and funding

None.

Declaration of competing interest

None.

Acknowledgments

Thanks to support and advice from the “Sina (Farshchian) hospital”, Hamadan University of medical sciences. Moreover, thanks to advice and support from the “Clinical Research Development Unit of Baqiyatallah Hospital”.

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