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The role of lovastatin in the attenuation of COVID-19

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ABSTRACT

The mounting evidence regarding the pathogenesis of COVID-19 indicated that the cytokine storm has an axial role in the severity of this disease, which may lead to thrombotic complications, acute respiratory distress syndrome (ARDS), and myocardial damage, among other consequences. It has recently been demonstrated that statins are known to have anti-viral, anti-inflammatory, anti-thrombotic, and immunomodulatory features; however, their advantage has not been evaluated in COVID-19. This study aimed to investigate the protective effects of lovastatin in intensive care unit (ICU) patients with COVID-19. The case-control study consists of 284 ICU patients, which classified into three groups as follows: 1) the patients who no received lovastatin as a control (92 patients), 2) patients received 20 mg per day lovastatin (99 patients), and 3) patients received 40 mg per day lovastatin (93 patients). Each group's demographic and clinical parameters, along with CRP, interleukin (IL)-6, IL-8 levels, and mortality rate, were studied in three-time points. The results showed that there was no statistically significant difference between our study groups in terms of age and sex. ($P > 0.05$). Besides, in patients, receiving lovastatin the CRP, IL-6, IL-8 levels were significantly decreased from T1 to T3 than to the control group. Our results also showed that the use of lovastatin in COVID-19 patients significantly reduced the length of hospitalization in the ICU compared with the control group. In addition, our results showed that the mortality rate in patients receiving lovastatin was lower when compared to the control group; however, this difference was not statistically significant. Since the cytokine storm is a significant factor in the pathology of SARS-CoV-2, our findings highlighted the potential use of lovastatin to mitigate the inflammatory response induced by SARS-CoV-2 infection.

1. Introduction

In December 2019, the novel pathogen was called SARS-CoV-2, the etiologic agent of COVID-19, which emerged in Wuhan, China, representing a pandemic warning to global health [1–5]. This pandemic can overcome national healthcare policies and significantly influence the world economy if SARS-CoV-2 extension and virulence are not included, or efficient medications are not generated [6–8]. The cellular receptor involving in entering the SARS-CoV-2 to the host cells is angiotensin-converting enzyme 2 [9,10]. The renin-angiotensin-aldosterone system (RAAS) is dysregulated after interaction between SARS-CoV-2 and ACE-2, which might ac as a possible mechanism contributing to this

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pathogen's virulence [10]. The blend of direct and indirect pathogenic effects of the SAES-CoV-2, such as uncontrolled inflammation and thrombosis, and impaired regulation of RAAS may underlie the severe form of COVID-19, which can emerge with ARDS, myocardial injury, and thrombotic results [11]. According to the available evidence of many anti-inflammatory agents, anti-thrombosis and immunomodulatory drugs can be promising in treating COVID-19 patients [12]; among these drugs, statins are one of the drug classes with anti-inflammatory effects, anti-thrombotic, immunomodulatory, and antiviral properties.

Statins act as an inhibitor of the key enzyme in cholesterol biosynthesis called hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase [13]. Statins have pleiotropic effects via targeted HMG-CoA reductase, an enzyme that limits the pathway of mevalonate and cholesterol [14]. Recently, it has been appreciated that statins (including lovastatin) have an anti-viral [15–17], antithrombotic and anti-inflammatory features address them as an engaging class of medications in the context of COVID-19 [18,19]. Moreover, statins can influence viral transmission and infectivity in cellular membranes through the effect on lipid rafts [19–22]. Statins appear to potentially alleviate the influence of myocardial damage and thrombotic effects correlated with critical COVID-19 manifestations [13].

In this case-control investigation, we evaluated the impacts of lovastatin on the dynamic changes in the levels of selected inflammatory markers, including CRP, IL-6, and IL-8, and the outcome of COVID-19 patients, including mortality rate.

2. Material and methods

2.1. Subjects

This case-control study aimed to evaluate lovastatin's protective effect in ICU patients with COVID-19 via assessing the inflammatory factors, duration time of hospitalization, and mortality rate. For this goal, a total number of 284 cases with COVID-19 admitted to the Firouzgar Hospital, Iran University of Medical Sciences were selected in this examination and categorized within three groups as regards: the first group contained 92 ICU cases with COVID-19 who no received lovastatin, the second group consisted of 99 ICU cases with COVID-19 who received lovastatin 20 mg per day for one week, the third group consisted of 93 ICU cases with COVID-19 who received lovastatin 40 mg per day for one week. For understanding the protective role of lovastatin on dynamic change in inflammatory markers, including CRP, IL-6, and IL-8, we took blood samples from COVID-19 cases admitted to the ICU in three times points, as follows:

- the first time on the day of hospitalization (time point 1 or T1)
- the second time three days after hospitalization (time point 2 or T2)
- the third time six days after hospitalization (time point 3 or T3)

Of note, after each sampling, we separated the serum and immediately placed it at −80°C until the time of the test. Additionally, this investigation was approved by the ethics board of the Iran University of Medical Sciences (IUMS) (ECIUMS; IR.IUMS.REC.1399.185).

2.2. Laboratory validation and assessment

The study was performed at three-time points (T1-T3). At each time point, 5 ml peripheral blood was collected from each patient and quickly following sample gathering, the serum was isolated by centrifugation and put at − 70 ° C up to use. The serum's routine biochemical parameters from confirmed COVID-19 patients were done on the day of admission by standard automated methods in a Technicon Dax autoanalyzer (Technicon Instruments, CO, USA).

2.3. The enzyme-linked immunosorbent assay (ELISA) for inflammatory markers

According to the manufacturer's structure, CRP levels were assayed using BOSTER BIOLOGICAL TECHNOLOGY (Boster Biological Technology, Wuhan, China, # EK7040). IL-6 and IL-8 levels were assayed by R & D Systems ELISA kit (IL-6; R & D Systems, Minneapolis, MN, USA, # D6050, IL-8; R & D Systems, Minneapolis, MN, USA, # Q8000B) according to the manufacturer's structure.

2.4. Statistical methods

Continuous and categorical variables were summarized as median (IQR) and n (%), respectively. To examine differences among independent groups, we used the Wilcoxon rank-sum test, χ^2 test, or Fisher's exact test where appropriate. The correlation between laboratory tests was analyzed using the Pearson correlation coefficient. A two-sided α of less than 0·05 was considered statistically significant. Statistical analyses were done using R version 4.1.1 (2021-08-10).

3. Result

3.1. Demographic characteristics, laboratory findings in COVID-19 patients

Table 1 summarized the demographics and laboratory findings in COVID-19 patients. Our findings pointed that there were no statically significant regarding sex and age in all groups of COVID-19 patients ($P > 0.05$). Besides, our result demonstrated that there were no statically significant regarding mean cell hemoglobin (MCH), lactate dehydrogenase (LDH), glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), smoking in, kidney failure, lung disease, heart disease, and death rate among the different group of COVID-19 cases ($P > 0.05$). Also, in order to determine the role of gender in the clinical outcome of patients with COVID-19, we analyzed patients treated with lovastatin by sex (Table 2). As shown in Table 2, the statistically significantly different factors between men and women include age and IL-6 (T1) levels; more details are displayed in Table 2

3.2. The effect of lovastatin on the dynamic changes of inflammatory cytokine in patients with COVID-19

As presented in Table 1 and Fig. 1, the CRP levels were significantly higher in cases who will receive 20 mg/day lovastatin than other groups on the day of admission ($P < 0.05$). Also, the levels of IL-8 were significantly higher in the control group when compared with other study groups ($P < 0.05$). After receiving lovastatin, inflammatory cytokine including CRP, IL-6, and IL-8 were significantly reduced in cases receiving lovastatin than in the control group ($P < 0.05$). CRP levels were gradually decreased; in a way, in the groups receiving 20 and 40 mg/day of lovastatin, CRP levels were significantly reduced when compared to the control group ($P < 0.05$). There was no statistically significant difference in serum levels of IL-6 on the day of hospitalization between the three groups. However, after receiving lovastatin, the IL-6 levels significantly declined in patients receiving lovastatin than the control group ($P < 0.05$). The reduction in IL-6 was dose-dependent manner; in this way, the 40 of IL-6 was reduced more significantly than the 20 mg dose. In the same way, administration of lovastatin leads to a significant decline in IL-8 levels in cases receiving lovastatin than the control group ($P < 0.05$), like the effect of lovastatin on IL-6 in this case, the dose-dependent manner reduced the decrease in serum IL-8.

3.3. The effect of lovastatin on the time of hospitalization and mortality rate in patients with COVID-19

As shown in Table 1 and Table 3, in patients receiving lovastatin, the

Table 1
Demographic and laboratory, and dynamic change in inflammatory markers of different groups of patients with COVID-19.

Variable	N	Overall, N = 284[1]	Group			p-value[2]
			Control, N = 92[1]	Treatment 1, N = 99[1]	Treatment 2, N = 93[1]	
Sex	284					0.6
Female		145 (51%)	47 (51%)	47 (47%)	51 (55%)	
Male		139 (49%)	45 (49%)	52 (53%)	42 (45%)	
Age	284	45 (36, 54)	42 (36, 51)	45 (37, 55)	44 (36, 54)	0.2
LDH	284	512 (457, 564)	504 (448, 563)	517 (459, 569)	517 (457, 564)	0.5
SGPT	284	43 (34, 45)	43 (35, 45)	39 (34, 45)	43 (34, 46)	0.7
SGOT	284	43 (34, 46)	40 (34, 45)	43 (34, 46)	43 (35, 49)	0.094
Cigarette	284					>0.9
Negative		280 (99%)	91 (99%)	97 (98%)	92 (99%)	
Positive		4 (1.4%)	1 (1.1%)	2 (2.0%)	1 (1.1%)	
Kidney.failure	284					0.8
Negative		282 (99%)	91 (99%)	98 (99%)	93 (100%)	
Positive		2 (0.7%)	1 (1.1%)	1 (1.0%)	0 (0%)	
Lung.disease	284					0.5
Negative		281 (99%)	92 (100%)	98 (99%)	91 (98%)	
Positive		3 (1.1%)	0 (0%)	1 (1.0%)	2 (2.2%)	
Cardiovascular.disease	284					0.7
Hypertension + CAD		3 (1.1%)	2 (2.2%)	1 (1.0%)	0 (0%)	
Hypertension		37 (13%)	10 (11%)	15 (15%)	12 (13%)	
Negative		244 (86%)	80 (87%)	83 (84%)	81 (87%)	
Cardiovascular.Drug.regimen	284					0.4
Carvedilol		33 (12%)	10 (11%)	13 (13%)	10 (11%)	
Carvedilol + Aspirin		2 (0.7%)	0 (0%)	0 (0%)	2 (2.2%)	
Metoral		2 (0.7%)	0 (0%)	2 (2.0%)	0 (0%)	
Metoral + Aspirin		3 (1.1%)	2 (2.2%)	1 (1.0%)	0 (0%)	
None		244 (86%)	80 (87%)	83 (84%)	81 (87%)	
Discharge	284	6 (5, 7)	7 (6, 8)	6 (5, 7)	6 (5, 7)	<0.001
Follow	284					0.068
Death		6 (2.1%)	4 (4.3%)	0 (0%)	2 (2.2%)	
Discharge		278 (98%)	88 (96%)	99 (100%)	91 (98%)	
CRP_T1	284	70 (55, 89)	67 (55, 80)	78 (60, 94)	65 (51, 86)	0.002
CRP_T2	284	21 (15, 30)	24 (20, 32)	21 (15, 30)	18 (13, 27)	<0.001
CRP_T3	284	10 (7, 13)	12 (10, 16)	10 (8, 13)	7 (5, 11)	<0.001
IL6_T1	284	43 (35, 47)	41 (34, 48)	45 (37, 48)	43 (35, 47)	0.2
IL6_T2	284	65 (50, 85)	86 (65, 96)	65 (47, 80)	56 (46, 65)	<0.001
IL6_T3	284	9 (7, 13)	12 (8, 16)	9 (7, 12)	8 (6, 9)	<0.001
IL8_T1	284	30 (24, 34)	32 (26, 40)	30 (24, 34)	29 (23, 34)	0.035
IL8_T2	284	50 (43, 59)	56 (48, 75)	49 (45, 58)	43 (39, 54)	<0.001
IL8_T3	284	9 (8, 13)	12 (9, 15)	10 (8, 12)	8 (7, 11)	<0.001
delta_CRP	284	−58 (-75, −44)	−53 (-65, −42)	−65 (-82, −50)	−56 (-75, −43)	<0.001
delta_IL6	284	−32 (-39, −25)	−28 (-36, −20)	−34 (-40, −27)	−34 (-39, −26)	<0.001
delta_IL8	284	−20 (-25, −14)	−20 (-29, −12)	−19 (-25, −14)	−20 (-25, −16)	0.9

Abbreviations: LDH; Lactate dehydrogenase, SGPT: Serum glutamate-pyruvate transaminase, SGOT; Serum glutamic-oxaloacetic transaminase, CAD; Coronary Artery Disease, CRP; C-reactive protein, IL-6; Interleukin 6, IL-8; Interleukin 8.

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Kruskal-Wallis rank-sum test; Fisher's exact test

length of hospitalization was significantly diminished than in the control group ($P < 0.05$). As illustrated in Table 3, the factors involved in death include heart disease and IL-6, which were statistically significant compared to survivors ($P < 0.05$). Our results also showed that the mortality rate in patients receiving lovastatin was reduced than in the control group, but this reduction was not statistically meaningful ($P > 0.05$).

4. Discussion

To date, our understanding regarding the pathogenicity of SARS-CoV-2 remains incomplete. However, the rapid expansion of our finding regarding SARS-CoV-2 pathogenesis indicated that critical mechanisms that may contribute to the pathophysiology of multi-organ damage to infection with SARS-CoV-2 hold endothelial cell damage and thrombosis, inflammation, dysregulation of the immune response, and dysregulation of the RAAS [23]. Since many anti-inflammatory, immunomodulatory, and anti-thrombotic drugs may hold a potential role in treating and preventing COVID-19 [12], statins with these properties are among the available potential drugs to prevent or treat COVID-19 patients.

Previous reports demonstrated that the use of statins such as lovastatin (inhibitor of HMG-CoA reductase) could inhibit replication of respiratory viral infections such as RSV [24,25] and influenza [26]. In this case-control investigation, we evaluated the efficacy of lovastatin in alleviating inflammation, duration time of hospitalization, and mortality incidence in ICU cases with COVID-19.

Our study results indicated that lovastatin might have a beneficial function in cases with COVID-19, which agrees with the previous investigations that indicated that receiving statin might have a beneficial effect in COVID-19 patients [27–31]. The vast majority of the investigation indicated that the excess inflammatory response or cytokine storm has an axial determinant in the pathogenesis of SARS-CoV-2 [32–35]. The study result showed that the administration of lovastatin could attenuate the inflammatory response due to SARS-CoV-2 infection. The study results are under previous studies, indicating that CRP levels were raised in cases with COVID-19 [8,36,37]. Our result agrees with the previous study, which indicated that statins could decrease CRP [35,38,39]. The previous investigation indicated that after interaction between SARS-CoV-2 and its receptor ACE2, CRP is produced [40–42], which is a marker of the acute phase of inflammation and has been correlated to prognosis mortality and severity of COVID-19 [42–44].

Table 2
The role of gender on the laboratory findings and dynamic change in inflammatory markers of COVID-19 patients treated with lovastatin.

Variable	N	Overall, N = 284[1]	Sex		p-value[2]
			Female, N = 145[1]	Male, N = 139[1]	
Group	284				0.6
Control		92 (32%)	47 (32%)	45 (32%)	
Treatment 1		99 (35%)	47 (32%)	52 (37%)	
Treatment 2		93 (33%)	51 (35%)	42 (30%)	
Age	284	45 (36, 54)	45 (37, 56)	44 (35, 52)	0.005
LDH	284	512 (457, 564)	512 (459, 564)	509 (455, 564)	0.7
SGPT	284	43 (34, 45)	43 (35, 45)	40 (34, 46)	>0.9
SGOT	284	43 (34, 46)	43 (34, 48)	42 (34, 46)	0.8
Cigarette	284				0.056
Negative		280 (99%)	145 (100%)	135 (97%)	
Positive		4 (1.4%)	0 (0%)	4 (2.9%)	
Kidney. Failure	284				0.2
Negative		282 (99%)	145 (100%)	137 (99%)	
Positive		2 (0.7%)	0 (0%)	2 (1.4%)	
Lung. Disease	284				>0.9
Negative		281 (99%)	143 (99%)	138 (99%)	
Positive		3 (1.1%)	2 (1.4%)	1 (0.7%)	
Cardiovascular. Disease	284				0.3
Hypertension + CAD		3 (1.1%)	3 (2.1%)	0 (0%)	
Hypertension		37 (13%)	19 (13%)	18 (13%)	
Negative		244 (86%)	123 (85%)	121 (87%)	
Cardiovascular. Drug.regimen	284				0.6
Carvedilol		33 (12%)	17 (12%)	16 (12%)	
Carvedilol + Aspirin		2 (0.7%)	1 (0.7%)	1 (0.7%)	
Metoral		2 (0.7%)	1 (0.7%)	1 (0.7%)	
Metoral + Aspirin		3 (1.1%)	3 (2.1%)	0 (0%)	
None		244 (86%)	123 (85%)	121 (87%)	
Discharge	284	6 (5, 7)	6 (5, 7)	6 (5, 7)	0.7
Follow	284				0.7
Death		6 (2.1%)	4 (2.8%)	2 (1.4%)	
Discharge		278 (98%)	141 (97%)	137 (99%)	
CRP_T1	284	70 (55, 89)	67 (54, 80)	70 (56, 90)	0.14
CRP_T2	284	21 (15, 30)	21 (14, 30)	23 (16, 31)	0.025
CRP_T3	284	10 (7, 13)	11 (7, 14)	10 (7, 13)	0.4
IL6_T1	284	43 (35, 47)	41 (34, 46)	44 (37, 50)	0.005
IL6_T2	284	65 (50, 85)	68 (53, 88)	59 (48, 80)	0.10
IL6_T3	284	9 (7, 13)	9 (7, 13)	9 (7, 12)	0.2
IL8_T1	284	30 (24, 34)	30 (24, 34)	32 (24, 35)	0.13
IL8_T2	284	50 (43, 59)	53 (43, 61)	49 (42, 56)	0.4
IL8_T3	284	9 (8, 13)	10 (8, 13)	9 (8, 13)	0.14
delta_CRP	284	−58 (-75, −44)	−56 (-69, −44)	−60 (-76, −45)	0.2
delta_IL6	284	−32 (-39, −25)	−30 (-38, −24)	−35 (-41, −27)	0.003
delta_IL8	284	−20 (-25, −14)	−19 (-24, −12)	−21 (-26, −15)	0.032

Abbreviations: LDH; Lactate dehydrogenase, SGPT: Serum glutamate-pyruvate transaminase, SGOT; Serum glutamic-oxaloacetic transaminase, CAD; Coronary Artery Disease, CRP; C-reactive protein, IL-6; Interleukin 6, IL-8; Interleukin 8.
[1] n (%); Median (IQR)
[2] Pearson's Chi-squared test; Wilcoxon rank-sum test; Fisher's exact test

Also, the crucial stage in CRP biology is complement activation that has a pathogenic effect in COVID-19 patients [45–47]. Recently, it has been found that nitric oxide (NO) has a protective role against respiratory viral infection, including SARS-CoV-2 [48,49]; on the other hand, CRP can inhibit endothelial NO synthase, pointing to detrimental impacts through limiting NO generation, enhancing adhesion molecule production, and causing inflammation and vasoconstriction [50–52]. So, any medication which can reduce CRP levels might attenuate COVID-19 severity.

Our findings agree with the former investigation that revealed that the levels of IL-6 were elevated in cases with COVID-19 [53–55]. The result of our study demonstrated that the administration of lovastatin significantly decreased the levels of IL-6 in cases with COVID-19. These findings agree with previous studies, which revealed that lovastatin [25,56,57] and other statin decreased levels of IL-6 [57–59].

IL-6 have pleiotropic roles, including modulation of many aspects of immune response in the host. In the context of viral infection, the previous investigation demonstrated that IL-6 accompanying TNF-α and IL-1β could influence multiple parts and immune reactions in response to viral infections, especially the function of IL-6 in cases with COVID19 [60,61]. The investigation results in cases with COVID-19 have demonstrated that the IL-6 involves in the pathophysiology of COVID-19 through the modulating immune responses to the SARS-CoV-2 infection [61,62], lymphopenia [63,64], coagulation [65,66], tissue damage [67,68]. In sum, IL-6 levels were elevated in all cases with COVID-19; therefore, it may be considered a potential therapeutic target for investigators.

Regarding IL-8 levels, our finding agrees with previous research that displayed that IL-8 levels were elevated in patients with COVID-19 [69–71]. Recently, the accumulating evidence points out the significant function of neutrophils in the pathophysiology of SARS-CoV-2, especially in those with critical disease courses [72–74]. Also, IL-8 is a pro-inflammatory cytokine that may recruit neutrophils to the infected areas by act as neutrophil-activating chemokine (61). Thus, lovastatin may alleviate the pathogenicity of COVID-19 by decreasing IL-8 levels and then reducing neutrophil recruits to the inflammatory areas. Moreover, our study indicated that lovastatin administration could shorten the time of hospitalization time, which may reflect the reality that lovastatin may decline the pathogenesis of SARS-CoV-2 in ICU patients. Finally, according to Peymani et al. and Zhang et al., the result showed that the mortality rate decreased in patients receiving statins [27,28]; however, this finding was not statistically significant. Due to the small sample size, to better evaluate the role of lovastatin in reducing COVID-19 mortality, it is recommended to use a high sample size in future studies to interpret the results. It is also recommended that future studies will be performed as a prospective cohort study.

5. Conclusion

In the present work, we provide evidence for the possible beneficial role of lovastatin in ICU cases with COVID-19. Our findings divulged that lovastatin might have a protecting role in COVID-19 patients by reducing inflammatory markers, including CRP, IL-6, and IL-8. However, further investigations are needed concerning evaluating the effect of lovastatin on the COVID-19 cases, and more clinical trials are required to declare lovastatin as a beneficial option for the help to the treatment of COVID-19 patients

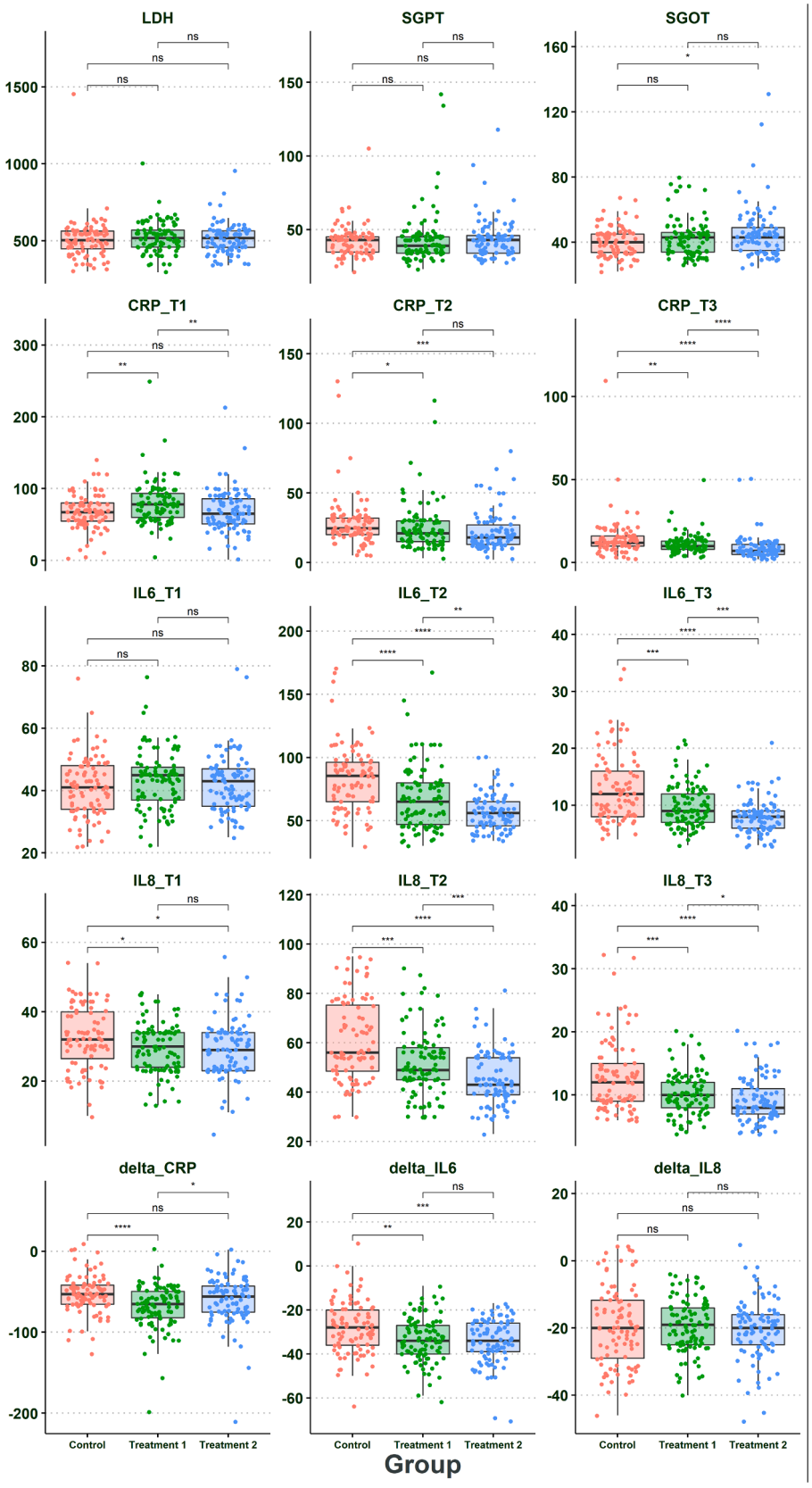

Fig. 1. The laboratory finding and dynamic changes in CRP, IL-6, and IL-8 levels in different study groups.

Table 3
Demographic and clinical parameters of dead patients versus alive patients.

Variable	N	Overall, N = 284[1]	Follow		p-value[2]
			Death, N = 6[1]	Discharge, N = 278[1]	
Group	284				0.068
Control		92 (32%)	4 (67%)	88 (32%)	
Treatment 1		99 (35%)	0 (0%)	99 (36%)	
Treatment 2		93 (33%)	2 (33%)	91 (33%)	
Sex	284				0.7
Female		145 (51%)	4 (67%)	141 (51%)	
Male		139 (49%)	2 (33%)	137 (49%)	
Age	284	45 (36, 54)	35 (31, 38)	45 (36, 54)	0.060
LDH	284	512 (457, 564)	492 (459, 584)	512 (458, 564)	0.9
SGPT	284	43 (34, 45)	50 (40, 56)	43 (34, 45)	0.076
SGOT	284	43 (34, 46)	42 (35, 44)	43 (34, 46)	0.8
Cigarette	284				>0.9
Negative		280 (99%)	6 (100%)	274 (99%)	
Positive		4 (1.4%)	0 (0%)	4 (1.4%)	
Kidney.**failure**	284				>0.9
Negative		282 (99%)	6 (100%)	276 (99%)	
Positive		2 (0.7%)	0 (0%)	2 (0.7%)	
Lung.disease	284				0.062
Negative		281 (99%)	5 (83%)	276 (99%)	
Positive		3 (1.1%)	1 (17%)	2 (0.7%)	
Cardiovascular. disease	284				0.001
Hypertension + CAD		3 (1.1%)	2 (33%)	1 (0.4%)	
Hypertension		37 (13%)	0 (0%)	37 (13%)	
Negative		244 (86%)	4 (67%)	240 (86%)	
Cardiovascular. Drug.regimen	284				0.004
Carvedilol		33 (12%)	0 (0%)	33 (12%)	
Carvedilol + Aspirin		2 (0.7%)	0 (0%)	2 (0.7%)	
Metoral		2 (0.7%)	0 (0%)	2 (0.7%)	
Metoral + Aspirin		3 (1.1%)	2 (33%)	1 (0.4%)	
None		244 (86%)	4 (67%)	240 (86%)	
CRP_T1	284	70 (55, 89)	86 (70, 113)	69 (55, 89)	0.090
CRP_T2	284	21 (15, 30)	28 (19, 38)	21 (15, 30)	0.2
CRP_T3	284	10 (7, 13)	12 (10, 14)	10 (7, 13)	0.3
IL6_T1	284	43 (35, 47)	40 (38, 45)	43 (35, 47)	0.9
IL6_T2	284	65 (50, 85)	101 (96, 107)	65 (50, 84)	0.014
IL6_T3	284	9 (7, 13)	10 (8, 16)	9 (7, 13)	0.5
IL8_T1	284	30 (24, 34)	30 (28, 33)	30 (24, 34)	0.9
IL8_T2	284	50 (43, 59)	52 (47, 66)	50 (43, 59)	0.6
IL8_T3	284	9 (8, 13)	8 (8, 14)	10 (8, 13)	0.8
delta_CRP	284	−58 (-75, −44)	−72 (-102, −58)	−58 (-75, −44)	0.12
delta_IL6	284	−32 (-39, −25)	−32 (-37, −20)	−32 (-39, −25)	0.6
delta_IL8	284	−20 (-25, −14)	−21 (-25, −16)	−20 (-25, −14)	>0.9

Abbreviations: LDH; Lactate dehydrogenase, SGPT: Serum glutamate-pyruvate transaminase, SGOT; Serum glutamic-oxaloacetic transaminase, CAD; Coronary Artery Disease, CRP; C-reactive protein, IL-6; Interleukin 6, IL-8; Interleukin 8.
[1] n (%); Median (IQR)
[2] Fisher's exact test; Wilcoxon rank-sum test

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

The Iran University of Medical Sciences Ethics Review Board approved this study (No. ECIUMS; IR.IUMS.REC.1399.185).

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