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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Predictors of Mortality in Severe and Critical COVID-19 Patients Receiving High Dose Intravenous Anakinra

Yüksek Doz İntravenöz Anakinra Alan Ciddi ve Kritik COVİD-19 Hastalarında Mortalite Öngördürücüleri

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Abstract

Objectives: In this study, we aim to evaluate the predictive factors associated with mortality in patients with severe and critical COVID-19 receiving high dose intravenous anakinra.
Methods: This is an observational retrospective study was conducted at a tertiary referral center between 01.09.2021 and 01.02.2022 in Turkey. COVID-19 disease severity was evaluated according to National Institute of Health (NIH) severity scale. Inflammatory state of the patients was calculated according to COVID hyperinflammatory syndrome (cHIS) score. Clinical (patients characteristics, disease severity, inflammatory state) and laboratory parameters such as lymphocyte count, CRP, LDH, ferritin and d-dimer levels were compared in patients had mortality and those had not.
Results: Data of 148 patients (n=78; 53% male) were analyzed. Mean±standard deviation (SD) patient age was 66.8±17 years and median (interquartile of range; IQR) duration of hospitalization was 11 (12) days. In this cohort, 57 patients (38.5%) severe, 91 patients (61.5%) had critical disease and mean±SD cHIS score was 3.4±1.2. Overall, 56 patients (37.8%) died during the follow-up and ICU admission was in 60 patients (40.5%) and intubation was in 54 patients (36.5%).
Conclusion: In our study mortality was developed in third of anakinra receiving severe and critical ill COVID-19 patients. Mortality was independently associated with advanced age, critical illness and higher cHIS score reflecting higher inflammatory burden. Furthermore, highest levels of CRP, LDH, ferritin, D-dimer and higher cHIS score predict higher mortality in patients with COVID-19 receiving anakinra.

Keywords: COVID-19, Anakinra, Cytokine Storm, Hyperinflammation, Predictors

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Öz

Amaç: Bu çalışmada, yüksek doz intravenöz anakinra alan ciddi ve kritik COVID-19 hastalarında mortalite ile ilişkili öngörücü faktörleri değerlendirmeyi amaçladık**.**

Yöntem: Bu çalışma, 01.09.2021 ile 01.02.2022 tarihleri arasında üçüncü basamak referans merkezinde gerçekleştirilmiştir. Çalışmamız geriye dönük gözlemsel bir çalışmadır**.** COVID-19 hastalık şiddeti NIH şiddet ölçeğine göre değerlendirildi. COVID hiperinflamatuar sendrom (cHIS) skoru hastaların inflamatuvar durumlarını değerlendirmek için hesaplandı. Klinik (hasta özellikleri, hastalık şiddeti, inflamatuvar durum) ve laboratuvar parametreleri (lenfosit sayısı, CRP, LDH, ferritin ve d-dimer düzeyleri) mortalite gerçekleşen ve gerçekleşmeyen hastalarda karşılaştırıldı.

Bulgular: 148 hastanın (n=78; %53 erkek) verileri analiz edildi. Ortalama±standart sapma (SS) hasta yaşı 66.8±17 yıl ve ortanca (çeyrekler arası aralık; IQR) hastanede kalış süresi 11 (12) gündü. Bu kohortta 57 hasta (%38.5) şiddetli, 91 hasta (%61.5) kritik hastalığa sahipti ve hastaların ortalama±SD cHIS skoru 3.4±1.2 idi. Toplamda 56 hastada (%37.8) takip sırasında mortalite gerçekleşti ve 60 hastada (%40.5) yoğun bakım ünitesine yatış ve 54 hastada (%36.5) entübasyon ihtiyacı oluştu.

Sonuç: Çalışmamızda ciddi ve kritik seyirli COVİD-19 hastalarının yaklaşık üçte birinde mortalite gerçekleşmiştir. Mortalite hızı ileri hasta yaşı, kritik hastalık şiddeti ve inflamatuvar yükü yansıtan cHIS skoru ile ilişkili bulundu. Dahası, yüksek CRP, LDH, ferritin, d-dimer seviyeleri ve cHIS skoru anakinra alan COVİD-19 hastalarında yüksek mortaliteyi öngördürmekteydi.

Anahtar Kelimeler: COVİD-19, Anakinra, Sitokin Fırtınası, Hiperinflamasyon, Öngördürücüler

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially life-threatening disease that caused by SARS-Cov-2 (1). Clinical findings of COVID-19 are ranged from asymptomatic to severe pneumoniae, acute respiratory distress syndrome, multiorgan failure and death (2). Severe COVID-19 patients are usually accompanied by a higher inflammatory response with the release of a large amount of pro-inflammatory cytokines in an event known as "cytokine storm" (3). Several cytokines such as interleukin 1 (IL-1), tumor necrosis factor-alfa (TNF-α) and interleukin-6 (IL-6) may play a driver role into the development of cytokine storm in patients with COVID-19. Downstream production of interferons by SARS-Cov-2 induces intracellular antiviral defenses in neighboring epithelial cells which may limit viral dissemination, while the release of pro-inflammatory cytokines from immune cells promotes recruitment of neutrophils and T cells and causes cytokine storm (4). Severe disease course as well as poor outcome including intensive care unit (ICU) requirement and death were mainly associated with development of cytokine storm in patients with COVID-19 (5). Although the definition of cytokine storm is a challenge in COVID-19, several scoring systems such as COVID-19–associated hyperinflammatory syndrome (cHIS) score, the Caricchio COVID-Cytokine Storm (COVID-CS) score, and the CSS Quick Score have been described so far (6) (7) (8).

Several biological agents targeting some cytokines such as IL-1 and IL-6 have been proposed for treating cytokine storm associated with various inflammatory conditions (9). Anakinra, an IL-1 receptor antagonist, which is used in treatment of autoinflammatory conditions such as hereditary periodic fever syndromes, adult onset still disease and also was proven to be helpful in hyperinflammatory condition

such as macrophage activation syndrome secondary to various diseases (10). In the light of these findings, anakinra has been started to be used during the pandemic period in severe or critical COVID-19 patients, since the COVID-19-associated cytokine storm has common pathogenetic mechanisms with other hyperinflammatory syndromes. Several predictive factors such as age, gender, comorbidities, and inflammatory burden were described in COVID-19 disease course during the pandemic, however there is limited data in severe and critically ill patients who received biologic therapies including anakinra (11). In this study, we aimed to evaluate the predictive factors of mortality in patients with severe and critically ill COVID-19 receiving anakinra.

MATERIAL AND METHODS

Patients and Data

This is an observational retrospective study was conducted at a tertiary referral center between 01.09.2021 and 01.02.2022 in Turkey. Diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) in addition to clinical signs and symptoms as well as typical computer tomography (CT) findings. The patients who had negative PCR results and inconsistent CT findings with COVID-19 were excluded from the study. COVID-19 disease severity was evaluated according to National Institute of Health (NIH) severity scale and only severe (NIH score 3) and critically ill (NIH score 4) patients receiving anakinra in the ward were included into the study.

Laboratory Evaluation

Laboratory values such as hemogram, liver enzymes, creatinine, procalcitonin, C-reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH) at admission; the highest levels of CRP, ferritin, D-dimer and LDH and lowest lymphocyte count during to the follow-up and at the last day of hospitalization were recorded. Inflammatory state of the patients was evaluated according to COVID hyperinflammatory syndrome score (cHIS) and it was calculated according to combination of neutrophil and lymphocyte counts at admission and the highest levels of CRP, ferritin, D-dimer and LDH during to the follow-up (6).

Clinical (patients characteristics, disease severity, inflammatory state) and laboratory parameters such as lymphocyte count, CRP, LDH, ferritin and d-dimer levels were compared in patients had mortality and those had not.

Treatment Protocol

All patients received background corticosteroid therapy with 80 mg/day methylprednisolone (or its equivalent) and enoxaparin 0.4 mg/day at admission and consecutive days. Anakinra was started in patients who did not respond to steroid therapy at least two days or concomitantly with steroids in all patients with critical illness at admission and in severe patients if needed during the follow-up. Average starting dose of anakinra was 400 mg/day intravenously and increased gradually to maximum 1600 mg/day if necessary. Anakinra dose adjustment was performed by the same rheumatologist (MB) according to daily clinical and laboratory findings including need of oxygen supply, lymphocyte, ferritin, CRP, LDH, and d-dimer levels. Severe infection was defined as development of opportunistic infection, intravenous antibiotics, sepsis or requirement of ICU admission or development of death due to infection.

Statistical Analysis

In our study, 21.0 version (IBM, Armonk, NY, USA) of SPSS (Statistical Package for the Social Sciences) program was used for statistical analysis of data. Descriptive statistics, discrete and continuous numerical variables were expressed as mean, ± standard deviation or median (minimum-maximum). Categorical variables were expressed as number of cases (%). Cross table statistics was used to compare categorical variables (Chi-Square, Fisher' exact test). Normally distributed parametric data were compared with Student's t-test and non-parametric data that did not meet normal distribution were compared with Mann Whitney U and Kruskal Wallis tests. Kaplan-Meier and log-rank methods were used for survival analysis. Multivariate analysis was performed by using logistic regression. Sensitivity and specificity analysis were performed by Receiver operating characteristic (ROC)

analysis. p<0.05 value was considered statistically significant.

Local ethic committee approval and written individual patient consent were obtained for this study (date/number: 24.02.2022, 2022/04-09)

RESULTS

Data of 148 patients (n=78; 53% male) were analyzed. Baseline clinical and laboratory findings of patients were described in table 1. Mean±standard deviation (SD) patient age was 66.8±17 years and median (interquartile of range; IQR) duration of hospitalization was 11 (12) days. In this cohort, 57 patients had (38.5%) severe and 91 patients had (61.5%) critical disease and mean±SD cHIS score was 3.4±1.2. Overall, 56 patients (37.8%) died during the follow-up and ICU admission was in 60 patients (40.5%) and intubation was in 54 patients (36.5%).

In univariable analysis, only dementia among comorbidities significantly differed between patients had mortality and had not (6.3% vs 27%; p=0.002, odds ratio; [OR]:9.8). Additionally, mean±SD patient age (63.4±18 vs 72.3±14; p=0.001), median (IQR) neutrophil to lymphocyte ratio (NLR) (5.6 [5] vs 10 [9]; p<0.001), mean±SD cHIS scores (3±1 vs 4.1±1.1; p<0.001) were higher in patients had mortality. Higher median (IQR) baseline and peak levels of CRP (107 [110] vs 136 [126]; p=0.004 and 137 [100] vs 194 [134]; p<0.001, respectively) and d-dimer (1 [1] vs 1.5 [1.7]; p=0.016 and 2.8 [7] vs 12.4 [24]; p<0.001, respectively), higher peak levels of ferritin (555 [606] vs 1212 [2336]; p<0.001) and LDH (513 [200] vs 676 [528]; p<0.001) were observed in patients had mortality compared to those had not. Mortality was also higher in patients with critically ill (n=55, 60.4%) compared to severe disease (n=1, 1.8%) (p<0.001; OR:51) (table 2).

Table 1: Baseline characteristics of patients with study group

Variables	Results
Age (years) (mean±SD)	66.8±17
Gender, male (n, %)	78 (52.7)
Duration of hospitalization (days) (median, IQR)	11 (12)
Comorbidities	
Diabetes mellitus (n=146)	41 (28.1)
Hypertension (n=143)	84 (58.7)
Coronary heart disease (n=143, %)	27 (18.9)
Heart failure (n=143, %)	18 (12.6)
Chronic renal failure (n, %)	31 (20.9)
Chronic obstructive lung disease (n=144, %)	23 (16)
Dementia (n=117, %)	15 (12.8)
Malignancy (n=146, %)	16 (11)
Rheumatic disease (n=142, %)	8 (5.6)
Immunosuppressive usage (n=146, %)	18 (12.3)
Disease severity (n, %)	
NIH score 3 (severe)	57 (38.5)
NIH score 4 (critical)	91 (61.5)
Laboratory values	
At admission	
Leucocyte (10^9/L), median (IQR)	7.8 (5)
Neutrophil (10^9/L), median (IQR)	6.5 (4.5)
Lymphocyte (10^9/L), median (IQR)	1 (0.74)
Hemoglobin (g/dL), mean±SD	13.2±2.2
Platelets (10^9/L), median (IQR)	189 (100)
Neutrophil to lymphocyte ratio, median (IQR)	6.7 (8.1)
Procalcitonin (ng/mL), median (IQR)	0.2 (0.46)
Creatinine (mg/dL), median (IQR)	0.9 (0.5)
C-reactive protein (mg/L), median (IQR)	120 (110)
Lactate dehydrogenase (U/L), median (IQR)	398 (216)
Ferritin (ng/mL), median (IQR)	393 (616)
D-dimer (mcg/mL), median (IQR)	1.24 (1.2)
Peak levels	
C-reactive protein (mg/L), median (IQR)	153 (124)
Lactate dehydrogenase (U/L), median (IQR)	589 (285)
Ferritin (ng/mL), median (IQR)	717 (1023)
D-dimer (mcg/mL), median (IQR)	4.3 (14.8)
cHIS score (mean±SD)	3.4±1.2
Outcomes	
Severe infection (n=128, %)	19 (14.8)
Myocardial infarction (n=132, %)	3 (2.3)
Pneumothorax (n=134, %)	3 (2.2)
Pulmonary embolism (n=134, %)	4 (3)
ICU admission (n, %)	60 (40.5)
Intubation (n, %)	54 (36.5)
Mortality (n, %)	56 (37.8)

SD: Standard deviation, IQR: Interquartile range, NIH: National Institute of Health, ICU: Intensive care unit

In multivariate analysis; higher patient age (p=0.01, OR:1.05, 95% confidence interval [CI]: 1.01-1.09), higher cHIS score (p=0.002, OR:2.6, 95% CI:1.4-4.9) and critical illness (compared to severe disease) (p=0.02, OR:14, 95% CI:1.6-122) were associated with higher mortality (table 2).

Table 2: Univariable and multivariable analysis of mortality in patients with COVID-19

Variables	Univariable analysis			Multivariable analysis
	Alive patients (n=91)	Deceased patients (n=55)	p value (OR)	p value, (OR) [95 % CI]
Age (years) (mean±SD)	63.4±18	72.3±14	***0.001****	***0.01, (1.05) [1.01-1.09]***
Gender, male (n, %)	44 (48)	34 (61)	0.1	
Duration of hospitalization (days) median (IQR)	10.5 (12)	12 (14)	0.8	
Comorbidities				
Diabetes mellitus (n=146)	23 (25)	18 (33.3)	0.3	
Hypertension (n=143)	52 (56.5)	32 (62.7)	0.5	
Coronary heart disease (n=143, %)	15 (16.3)	12 (23.5)	0.3	
Heart failure (n=143, %)	11 (12)	7 (13.7)	0.8	
Chronic renal failure (n, %)	16 (17.4)	15 (26.8)	0.2	
Chronic obstructive lung disease (n=144, %)	14 (15.2)	9 (17.3)	0.7	
Dementia (n=117, %)	5 (6.3)	10 (27)	***0.002 (9.8)***	
Malignancy (n=146, %)	9 (9.8)	7 (13)	0.6	
Rheumatic disease (n=142, %)	5 (5.6)	3 (5.8)	1	
Immunosuppressive usage (n=146, %)	10 (11)	8 (14.5)	0.5	
Disease severity (n, %)				
NIH score 3 (severe) (n=57)	56 (98.2)	1 (1.8)	***<0.001 (51.3)***	***0.02, (14), [1.6-122]***
NIH score 4 (critical) (n=91)	36 (39.6)	55 (60.4)		
cHIS score (mean±SD)	3±1	4.1±1.1	***<0.001****	***0.002, (2.6), [1.4-4.9]***
Laboratory results				
Neutrophil to lymphocyte ratio, median (IQR)	5.6 (5)	10 (9)	***<0.001***[ɨ]	
Hemoglobin (g/dL), mean±SD	13.4±2.2	13±2.3	0.3	
Platelets (10^9/L), median (IQR)	215±77	192±82	***0.01***[ɨ]	
C-reactive protein (mg/L), median (IQR)				
1	107 (110)	136 (126)	***0.004***[ɨ]	
2	137 (100)	194 (134)	***<0.001***[ɨ]	
Ferritin (ng/mL), median (IQR)				
1	326 (531)	557 (767)	0.06	
2	555 (606)	1212 (2336)	***<0.001***[ɨ]	
D-dimer (mcg/mL), median (IQR)				
1	1 (1)	1.5 (1.7)	***0.016***[ɨ]	
2	2.8 (7)	12.4 (24)	***<0.001***[ɨ]	
Lactate dehydrogenase (U/L), median (IQR)				
1	399 (193)	391 (245)	0.9	
2	513 (200)	676 (528)	***<0.001***[ɨ]	
Procalcitonin (ng/mL), median (IQR)	0.17 (0.3)	0.27 (0.6)	***0.01***[ɨ]	
Creatinine (mg/dL), median (IQR)	0.84 (0.52)	1 (0.4)	0.1	

SD: Standard deviation, IQR: Interquartile range, OR: Odds ratio, CI: Confidence interval, NIH: National Institute of Health, ICU: Intensive care unit
1: at admission, 2: Peak level
*Independent t test
[ɨ] Mann Whitney U test

In ROC analysis; a cut-off value for cHIS score was 3.5 with 72% sensitivity and 72% specificity, NLR 7.1 with 69% sensitivity and 70% specificity, CRP 160.5 mg/L with 70% sensitivity and 69% specificity, LDH 581 U/L with 72% sensitivity and 75% specificity, ferritin 771 ng/mL with 70% sensitivity and 72% specificity, d-dimer 7.56 mcg/mL with 70% sensitivity and 73.4% specificity were found, respectively (table 3).

Table 3: ROC analysis of laboratory values for mortality

ROC analysis	AUC	cut-off	p value (95 % CI)	Sensitivity (%)	Specificity (%)
cHIS score	0.77	3.5	<0.001 (0.69-0.86)	72	72
NLR	0.72	7.1	<0.001 (0.6-0.82)	69	70
At admission					
CRP	0.64	118.5	0.005 (0.55-0.73)	62.5	55.4
LDH	0.5	NA	0.9 (0.4-0.6)		
Ferritin	0.59	NA	0.06 (0.495-0.69)		
D-dimer	0.62	1.3	0.016 (0.52-0.71)	61	62
Peak level					
CRP	0.73	160.5	<0.001 (0.63-0.82)	70	69
LDH	0.78	581	<0.001 (0.69-0.86)	72	75
Ferritin	0.76	771	<0.001 (0.68-0.85)	70	72
D-dimer	0.74	7.56	<0.001 (0.65-0.83)	70	73.4

NLR: Neutrophil to lymphocyte ratio, AUC: Area under curve, CI: Confidence interval, CRP: C-reactive protein, LDH: Lactate dehydrogenase, NA: Not available

DISCUSSION

Several risk factors and predictors have been described for mortality in patients with COVID-19, so far. Advanced age, male gender, presence of comorbidities such as diabetes mellitus, hypertension are well-defined risk factors for severe COVID-19 course (12). In our study higher mortality with advanced age was compatible with previous results (13). Although no differences in other comorbidities, higher mortality in patients with dementia was a remarkable finding in our study. It may be due to higher average age and accompanying more comorbidities in these patients. On the other hand, possible role of NLRP3 inflammasome leading higher IL-1 levels in the pathogenesis of Alzheimer's disease was speculated in previous studies (14) (15). Considering mainstay role of IL-1 in cytokine storm and in the pathogenesis of Alzheimer's disease may cause more systemic inflammatory response as well as poor outcome in patients with COVID-19 accompanying Alzheimer's disease. Additionally higher secondary bacterial infection risk such as pneumoniae and urinary tract infection in patients with dementia may be another explanation for higher mortality in these patients because of immobility and immunocompromised status due to more prevalent hospitalization, inefficacy to excrete their secretions and urinary catheterization (16) (17). Further studies are needed to confirm these findings.

SARS-Cov-2 binds to angiotensin-converting enzyme type 2 (ACE2) receptor (18) and leads to release of viral ssRNA and binding to pattern recognition receptors (PRR). Among the PRR, three major receptors are involved in viral infections; toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (19). SARS-Cov-2 viral ssRNA binds TLR 7-8 leading activation of nuclear factor-kappa B (NFKB) with activation of JAK-STAT pathway therefore production of several proinflammatory cytokines such as type 1 interferon ([IFN] alpha and beta), interleukin-6 (IL-6) and TNF-α and others (20). There is also another important pathway in the pathogenesis of COVID-19 associated cytokine storm. Recent evidence showed that, SARS-CoV-2 also activates an intracellular multiprotein complex which is called '*inflammasome*' after binding TLRs. Inflammasomes present in innate immune cells such as neutrophils, macrophages and dendritic cells and have

essential role in the host defense against microorganisms including viruses. The inflammasome is coordinated by the NLRP3 sensor (NOD, Leucin-rich repeat, Pyrin domain, adaptor protein ASC, as well as the effector protein caspase 1) and also drives cleavage of pro-IL-1βby caspase-1, followed by the production of active IL-1β (21). Several hyperinflammatory conditions such as macrophage activation syndrome, hemophagocytic lymphohistiocytosis, cytokine release syndrome were described due to various immune mediated, infectious or malignant diseases and recently grouped in an umbrella definition that is called, 'cytokine storm' (22) (23). Cytokine storm is the main cause of the development of severe disease, poor outcome as well as mortality in patients with COVID-19 (24). Preliminary results revealed higher immune response with higher levels of IL-1β, IL-6, IL-8, IL-12, IL-2, IL-7, TNF-α, MCP-1, and IFN-γ reflecting cytokine storm in patients with COVID-19 (25). These proinflammatory cytokines are responsible for the increased acute phase reactants (APR) such as CRP and ferritin but also d-dimer and LDH levels reflecting tissue damage and immunothrombosis. There are several studies to reveal higher mortality risk with elevated APR in patients with COVID-19 (26) (27) (28). Although, the clear role of cytokine storm is well known in the development of severe COVID-19, the definition of COVID-19-associated cytokine storm is controversial. There are few scoring scales attributed to COVID-19-associated cytokine storm so far (6) (7). Among these scales cHIS score was developed by Webb et al. and validated in the same study (6). Furthermore, higher mortality rate and increase by gradually with cHIS score ≥2 was also established in this study.

There are inconsistent results with mortality rate in patients with COVID-19. Mortality rate in COVID-19 could be affected by features of the study population such as hospitalized vs outpatient patients or ward vs ICU, inflammatory burden, and disease severity of participants. In Grasselli et al. study with 3988 patients in ICU, overall mortality was 53.4% (29). In another observational study with hospitalized COVID-19 patients, mortality was observed in 50.5% severe and critical disease according to Brescia-COVID respiratory severity scale, 58% according to CURB-65 scale which were higher compared to our study (30). However, treatment scheme in this study is unclear. Our study population consisted of severe and critically ill patients for whom a higher risk of mortality expected. Furthermore, the fact that mean cHIS score is 3.4 also reflects higher inflammatory burden in our study. Therefore, our study group had more severe disease and higher mortality risk at admission.

In a comparative study from Italy with 392 patients who consisted of 62 anakinra and 55 anti-IL-6 treatment, overall mortality was 25%, 32% in biologic-naive, 14% in anakinra and 18% in tocilizumab receiving patients (31). In previous study, survival rate was higher in patients receiving IL-1 inhibitor compared to IL-6 inhibitors. In this study, higher CRP levels at baseline and decreasing levels of LDH with treatment predicted higher IL-1 and IL-6 inhibitor response and reduced mortality. Although anti-cytokine treatment was applied to patients with CRP≥100 mg/L or ferritin≥900 ng/mL and partial pressure of oxygen to the fraction of inspired oxygen of 300 mm Hg of less, the detail of hyperinflammation and disease severity in these study participants were unclear. Furthermore, differences in study dates (February and March 2020) with the former study compared to our study may have caused difference in the mortality rate due to potentially different COVID-19 variants since delta variant was not dominant into this period. Higher disease severity and poor outcome with delta variant compared to other variants was established in previous studies (32) (33). In a prospective comparative study that was carried out between June and July 2020, mortality was lower in patients receiving anakinra compared to those with standard of care (29% vs 46%; p=0.082). On the other hand, anakinra was applied subcutaneously with lower doses in the former study compared to our study (34). Furthermore, difference into the study period was another important limitation to make comparison between the former study and our study as mentioned above. In a randomized controlled study

in early COVID-19 patients with anakinra, favorable outcome was observed in patients with higher CRP, NLR, ferritin and AST levels (35). In this study, at least two CRP >50 mg/L, NLR> 5.5, ferritin >700 ng/ml or AST >44 U were associated with favorable outcome in patients receiving anakinra compared to placebo. These results were not consistent with our study probably due to difference in study design between two studies (prospective versus retrospective). In the former study, lower mortality was also revealed in patients with receiving anakinra than those without.

Intravenous and high dose administration of anakinra is an emerging issue both in rheumatology and COVID-19 daily practices. Intravenous dose of anakinra enables higher and fast maximum plasma concentration compared to subcutaneous administration (36). Recently there are growing evidence with high dose intravenous anakinra administration in hyperinflammatory syndromes (37) (38). Safety and efficacy of high dose intravenous anakinra treatment was established by Cavalli et al in a preliminary retrospective study from Italy in patients with COVID-19 (39). In another prospective controlled study (ESCAPE open label study) with critically ill COVID-19 patients, high dose intravenous anakinra had lower mortality rate than standard of care as well as tocilizumab treatment (40). Furthermore, similar results were observed in other observational studies with COVID-19 (41).

This study has some limitations. First, retrospective design of the study was the main limitation. Additionally, absence of control group was another limitation. On the other hand, the fact that the study is conducted in a single center ensures homogeneity in terms of patient population and treatment decisions that made by a single physician.

CONCLUSION

In our study mortality was developed in third of anakinra receiving severe and critical ill COVID-19 patients. Mortality was independently associated with advanced age, critical illness and higher cHIS score reflecting higher inflammatory burden. Furthermore, highest levels of CRP, LDH, ferritin, D-dimer and higher cHIS score predict higher mortality in patients with COVID-19 receiving anakinra. It is important to identify the patients with higher mortality risk to improve outcome.

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Conflicts of Interest:

Authors declare no conflicts of interest.

Ethical Declaration:

Local ethic committee approval and written individual patient consent were obtained for this study (date/number: 24.02.2022, 2022/04-09)

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