The sharp edge of immunosuppressive treatments; infections

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Informed consent

As this study is not an experimental investigation, obtaining informed consent was deemed unnecessary.

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Abstract

Background and aim: Different side effects, including infections, are encountered in patients receiving anti-cytokines used for the treatment of severe COVID-19. The aim of our study is to evaluate the infections and the effects of these infections that develop in this patient group.

Materials and Methods: This study included 208 patients who were followed up with the diagnosis of severe COVID-19 in two different hospitals. Patients' data were obtained retrospectively from the hospital information system.

Results: Of the 208 patients included; 54 patients were in the anakinra, and 154 patients were in the tocilizumab group. 73 of them (35.1%) developed infection, 160 (76.9%) were monitored in the intensive care unit (ICU), and the 30-day mortality rate was 46.6%. ICU admission, 30-day mortality and infection rates were higher in the anakinra group but it was not statistically significant ($p=0.137$, $p=0.127$, $p=0.132$, respectively), while pneumonia and blood stream infection (BSI) rates were higher ($p=0.043$, $p=0.010$ respectively). The 30-day mortality rate was significantly higher in patients who developed infection, especially in the tocilizumab group ($p<0.001$, $p=0.001$). The independent risk factors affecting the development of infection were evaluated via regression analysis; age, gender, and type of immunosuppressive treatments had no significant effect, while ICU admission increases the risk of infection by 32.8 times (95% CI 4.4–245.8) and each day of hospitalization slightly increases the risk of infection by 1.06 times (95% CI 1.03–1.09).

Conclusion: Infection rates were higher in patients receiving anakinra therapy, especially pneumonia and BSI rates were higher than in other group. 30-day mortality rates were higher in patients who had an infection, especially in the tocilizumab group. This is one of the rare studies that evaluated infections developing in patients treated with anakinra and tocilizumab together.

Key words: Anti-cytokine, anakinra, tocilizumab, infection, COVID-19

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There is no conflict of interest.

1. Introduction

Immunosuppressive therapies have long been used to treat hyperinflammation caused by autoimmune diseases or infections. The oldest known immunosuppressive drugs are corticosteroids, and new treatments, which are more effective and have fewer side effects, are coming into use every day. These molecules, which can be beneficial if used appropriately, can also have severe side effects, including death. This situation has been encountered quite frequently with the immunosuppressive drugs used in the treatment of Coronavirus Disease (COVID-19), which has affected the world for the past four years.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is the causative agent of COVID-19, enters the cell by attaching to the ACE-2 receptor in the cells, initiating the replication cycle, while also triggering the innate and adaptive immune response, causing a cytokine storm and uncontrolled hyperinflammation. Various cytokines, chemokines, and immune cells are activated during this cytokine storm, particularly the macrophages. Studies have shown that the most important factor causing serious disease is the uncontrolled and excessive immune response of the host [1, 2]. As a result, pneumonia, organ damage, acute respiratory distress syndrome (ARDS), and in some cases, mortality develop.

MAS is a condition caused by a cytokine storm and characterized by hyperferritinemia and coagulopathy. It is thought that COVID-19-related immune exhaustion or defective antiviral response causes this syndrome. For this reason, studies have been conducted to use anti-IL-1 and IL-6 agents used in the treatment of MAS in the treatment of severe COVID-19 cases [3]. It has been shown that immunosuppressive

and anti-cytokine treatments, at the right time, in the right doses, and correctly selected, increase survival in the treatment of hyperinflammatory response [4-6]. Hence, the COVID-19 treatment guidelines suggest administering corticosteroids to hospitalized, hypoxic patients and considering immunomodulatory therapies like anakinra (Kineret®) or tocilizumab (Actemra®) for individuals who do not show reduced oxygen requirements or systemic inflammatory response improvement following steroid treatment [6-10]. It is known that these drugs, which are used to reduce morbidity and mortality, may cause side effects such as application-related local reactions, secondary infections, hypertension, disorders in liver function tests, gastrointestinal bleeding, pulmonary embolism, and even intestinal perforation [6, 11-13].

Our research seeks to investigate the occurrence rate of infections, the pathogens responsible for these infections, and the impact of this situation on mortality among patients being treated with anakinra or tocilizumab. These medications were commonly utilized during the pandemic and are anticipated to remain key in managing hyperinflammation following autoimmune diseases or infections.

2. Materials and Methods

Patients over the age of 18, who were followed up between 01.03.2020 and 31.12.2021 with a diagnosis of COVID-19 at the 2nd level state hospital and 3rd level university hospital in our city, who received anakinra or tocilizumab with the diagnosis of MAS due to COVID-19, were included in the study. Patients were examined in two groups as anakinra or tocilizumab. The patient's age, gender, immunosuppressive treatment received, intensive care unit (ICU) follow-up, presence of 30-day mortality,

length of hospital stay, infections that developed after receiving immunosuppressive treatment, the causative agents of these infections, and the effect of infection development on mortality were retrospectively scanned from the hospital data system. Only the infections in which the agent could be isolated in blood, sputum, tracheal aspirate, and urine sample cultures were included. Bloodstream infections (BSI) secondary to another infection focus, sequential culture positivities, asymptomatic candiduria, and culture results evaluated in favor of colonization were excluded.

2.1. Treatment administration and selection: All hypoxic patients who were hospitalized with the diagnosis of COVID-19 were started on standard dose or high-dose corticosteroid treatments. Patients who failed to improve with first-line treatment were evaluated for MAS and the need for anti-cytokine therapy.

MAS was diagnosed according to the COVID-19 treatment guide of the Ministry of Health of the Republic of Turkiye. Patients with resistant fever, ongoing elevation of C-Reactive Protein, ferritin level that is above normal or continues to increase, elevated D-dimer levels, lymphopenia, neutrophilia, thrombocytopenia, and deterioration in liver function tests were evaluated for MAS [14]. Anti-cytokine therapy was started in patients whose procalcitonin levels were negative and who had no evidence of secondary infection according to clinical evaluation. Tocilizumab treatment was administered as an intravenous infusion at a dose of 8mg/kg in two consecutive doses, while anakinra was started at a dose of 2-10 mg/kg (subcutaneous) and discontinued by reducing the dose according to patients' situation. The choice of tocilizumab or anakinra was made considering the physician's preference and the availability of the drugs.

2.2. Ethics Committee Approval was obtained from the Ethics Committee of our center, where the pre-research study was carried out, with the decision numbered 2023/54, dated 23.2.23.

2.3. Statistical analysis performed with IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp). The distribution of the data was checked by visual (histogram) and Kolmogorov-Smirnov tests. Age and length of hospital stay variables distributed non-parametrically. In the presentation of data, we used numbers (n), percent (%), and median with minimum-maximum values. Pearson's Chi-Square test and Fisher's Exact test were used in the statistical analysis of categorical data. We used the Mann-Whitney U test for the parametric comparison of the numerical data of two groups. We used binomial regression to determine the factors that affect infection diagnosis. The statistical significance of the p-value is accepted as $p<0.05$ at a 95% confidence interval.

3. Results

A total of 208 patients were included in our study in two groups: 54 patients receiving anakinra treatment, and 154 patients receiving tocilizumab treatment. All patients receiving anakinra or tocilizumab treatment had received standard-dose or pulse-dose steroids simultaneously or before. 79 of the patients (38%) were women, their median age was 63.5 years (range 24–94 years), and their length of hospital stay was 18 days (range 6–75 days). There were 160 (76.9%) patients monitored in the ICU, and the 30-day mortality was 46.6%. Secondary infection developed during hospitalization in 73 patients (35.1%) (Figure 1). There were 33 (15.9%) patients with

BSI, three of the patients had more than one BSI attack. 57 (27.4%) patients developed pneumonia, seven of them had more than one pneumonia attack. 19 (9.1%) patients developed urinary tract infection and two (1%) patients developed invasive fungal infection (IFI). The most frequently identified microorganisms in BSIs were gram-positive cocci, (*Enterococcus* spp. and coagulase negative streptococci), followed by *Acinetobacter baumannii,* and *Stenotrophomonas maltophilia*. *A. baumannii* was also the leading causative agent in pneumonia. In urinary tract infections; *Escherichia coli* was the most frequently isolated microorganism. *Candida albicans* was the most common agent identified in IFIs. The distribution of causative agents is shown in Figure 2.

Since ICU follow-up was thought to be a risk factor for the development of infection, this patient group was evaluated separately. 65 of 160 patients (40.6%) were women, the median age was 64 years (range 24 - 88 years). 46 (28.7%) of the patients received anakinra, and 114 (71.3%) received tocilizumab.72 (45%) of the patients developed an infection during hospitalization, the 30-day mortality rate was 58.1%.

When all patients in two groups were evaluated, there was no difference in the mean age values and rates of ICU admission, 30-day mortality, secondary infection, UTI, and IFI. The ICU follow-up, mortality and infection development rates were higher in the anakinra group than in the tocilizumab group, but this was not statistically significant. Pneumonia and BSI rates of patients receiving anakinra were higher than in patients receiving tocilizumab ($p=0.043$ and $p=0.010$, respectively). In the Anakinra group, the average length of hospital stay of the patients was lower ($p=0.046$). When the patients followed in the ICU were evaluated separately, no statistically significant relationship was found between the treatment groups in terms of 30-day mortality and

infection development rates (p=0.533, p=0.326, respectively). The BSI rate was significantly higher in those receiving anakinra treatment than in those receiving tocilizumab (p=0.021) (Table 1).

The factors affecting the development of infection were evaluated, and no significant difference was found in terms of gender or median age (p=0.496, p = 0.715, respectively). The rate of infection in patients who stayed in the ICU department was significantly higher than in others (p<0.001). Among all patients and patients monitored in the ICU, the median length of hospital stay in patients who developed infection was longer than in those who did not (p<0.001, p=0.009, respectively) (Table 2).

The 30-day mortality rate in patients who developed infection was significantly higher than in those who did not (p<0.001). When the treatment groups were evaluated separately, there was no significant relationship in the anakinra group (p=0.141), and in the tocilizumab group, the 30-day mortality rate in patients who developed infection was significantly higher than in those who did not (p=0.001) (Table 3).

Independent risk factors that were thought to affect the development of infection in patients diagnosed with COVID-19 and receiving immunosuppressive treatment were evaluated by regression analysis. The odds ratio of infection among all patients increased by 1.048 times (95% CI 1.015–1.082) for each day of hospitalization, and ICU admission increased by 32.819 times (95% CI 4.382–245.821). For patients who stayed in ICUs, each day's increase in the length of stay increased the probability of infection by 1.048 times (95% CI 1.015–1.082) (Table 4). The immunosuppressive treatments received by the patients in both groups did not increase the risk of infection.

4. Discussion

Unlike previous reviews that analyzed similar topics, this article is one of the rare studies in which infections developed in patients who received anakinra and tocilizumab treatment were evaluated together. In the anakinra group, ICU admission, 30-day mortality and infection rates were lower but not statistically significant, whereas pneumonia and BSI development rates were significantly higher than tocilizumab group ($p= 0.137$, $p= 0.127$, $p= 0.132$, $p= 0.043$ and $p= 0.01$, respectively). Development of an infection increases 30-day mortality rate in all patients, especially in tocilizumab group ($p=0.001$ and $p= 0.001$ respectively). ICU admission and length of stay are independent risk factors for the development of infection.

Suppressing hyperinflammation is one of the building blocks of COVID-19 treatment. Studies have been conducted on the effectiveness and side effects of anti-cytokine treatments such as anakinra, tocilizumab, sarilumab, and canakinumab [7, 9, 10, 15, 16].

Anakinra, an IL-1 receptor antagonist, has been used to treat hyperinflammation and MAS caused by COVID-19 [17]. In a systematic review evaluating serious infections in patients using biological agents the rate of severe infections was 5.1%, pneumonia (23.8%) was the most common infection in the anakinra group [12]. Another study comparing anakinra and standard treatment in COVID-19 patients; 26.8% of the patients receiving anakinra had infections (8% BSI, 3.6% pneumonia) and 3.6% of these patients died; there was no statistically significant difference between the groups [10]. In our study 44.4% of the anakinra group developed an infection, 38.9% of them had pneumonia and 27.8% had BSI. The higher infection rates in our study group

may be due to the high rate of ICU admission and mortality which may show that our study group had more severe conditions. In addition, the fact that all patients received steroids simultaneously may have caused the immune system to be more suppressed. The reason for the higher pneumonia rates is that our patients likely already had damaged lung tissues due to COVID-19 pneumonia.

Tocilizumab is a competitive inhibitor of the receptor for IL-6, a cytokine with pro- and anti-inflammatory effects [18, 19]. In the radomised, controlled, REMAP-CAP and RECOVERY studies, which evaluates the effectiveness of IL-6 receptor antagonists in the treatment of COVID-19, secondary infection rates ranged from 0.07 to 0.3% . Also, secondary infection rates differed from 14.2 to 40.4% in different cohorts[20, 21]. 74% of the patients included in our study who received tocilizumab treatment were monitored in the ICU, the mortality rate was 56.5%, and 31.8% developed an infection. Infection rates were higher than RCTs, but similar to cohorts, the reason of this high rate may be very high ICU admission rates and patients' prior use of corticosteroids.

Looking at the studies that compare side effects of immunosuppressive treatments, in a review including 3073 patients receiving anti-cytokine therapy and 6572 patients as the control group evaluating the effectiveness of these treatments and secondary infections in COVID-19 patients, anti-cytokine therapy did not increase the infection rate. The infection rate was higher in patients receiving anakinra (OR = 1.44, 95% CI=0.47–4.43, p=0.520) compared to those receiving tocilizumab (OR=1.12,95% CI=0.87–1.43, p=0.376) but it was not statistically significant [22]. In another study including 235 patients which compared anakinra and tocilizumab, secondary infection rates were found to be similar between the two groups (6.3% vs. 9.2%, p = 0.44). Also

28-day mortality rates and ICU admission rates were similar (p= 1 and p=0.30 respectively) [23].

In our study, secondary infections cause an increase in 30-day mortality rates in patients, especially in tocilizumab group. In a study evaluating factors affecting mortality in COVID-19 patients receiving tocilizumab; secondary bacterial co-infections were found to be associated with mortality (p=0.002)[24], however, there are also studies that find the opposite [25].

The limitations of our study are that it is retrospective, the initial clinical conditions of the patients are not known, and there is no control group. The strength of our study is that it is one of the rare studies in which both treatment groups are examined together, the developing infections and infectious agents were analyzed in detail, and the effect of infection development on mortality was examined. Randomized controlled studies on this subject are needed for clearer data.

5. Conclusion

Although the pandemic is over and the number and severity of cases has decreased, the anti-cytokines used in the treatment of COVID-19 will continue to be used in the treatment of hyperinflammatory syndrome and MAS that develop due to infections or rheumatological diseases. It should be kept in mind that infections may develop as a side effect of anakinra and tocilizumab, and especially anakinra has a higher risk in this regard. Treatment selection and patient follow-up should be shaped accordingly. Prospective, randomized studies are needed to further elucidate this issue.

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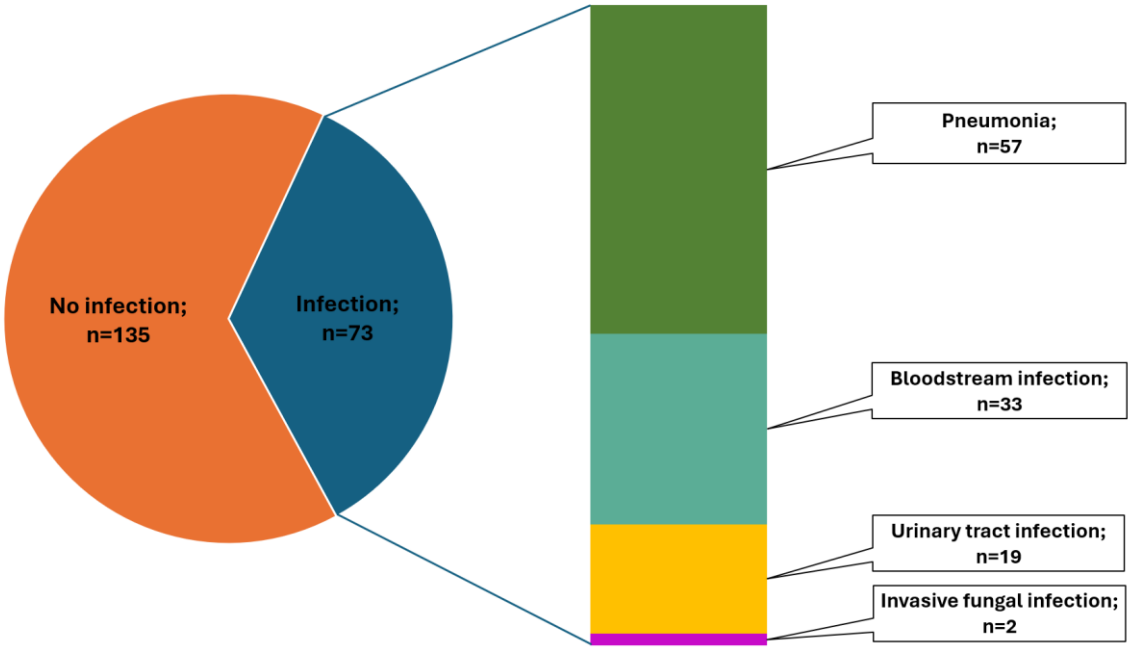

Figure 1. Infections developing in patients receiving immunosuppressive therapy.

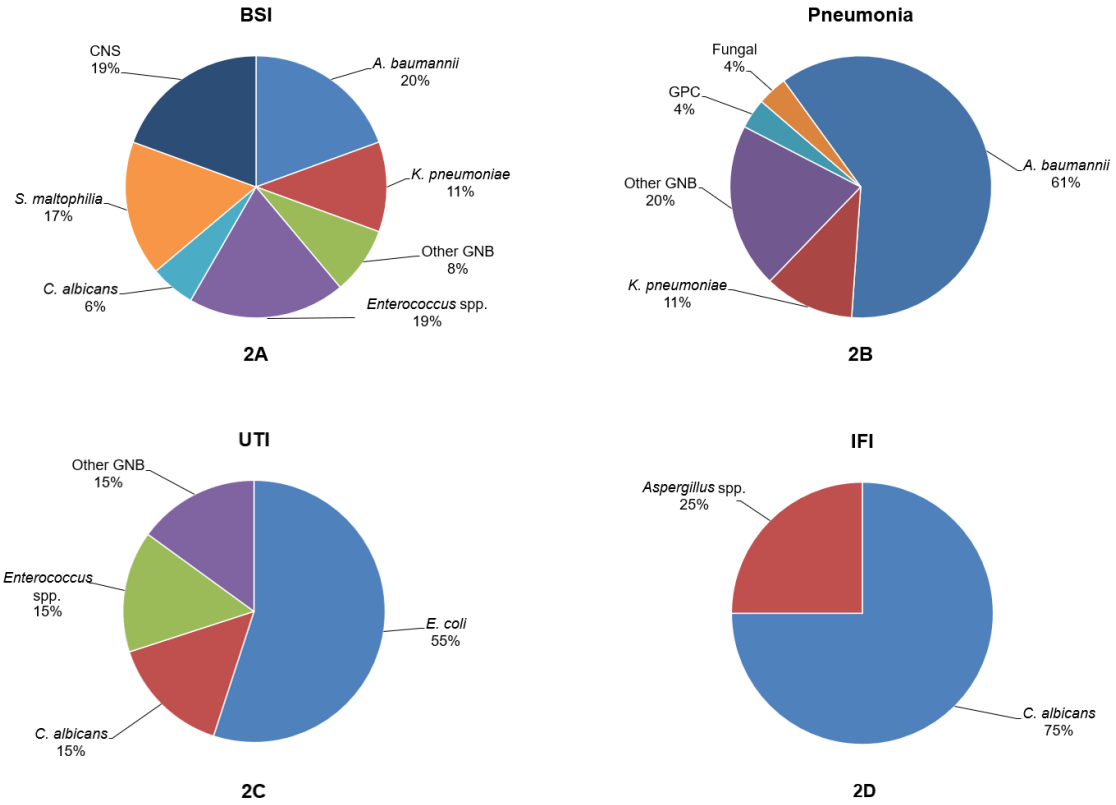

Figure 2: Causative agent distribution of BSI (2A), pneumonia (2B), UTI (2C) and IFI (2D).

2A: BSI: Blood stream infection, CNS: Coagulase negative staphylococci, Other GNB: *E. coli, B. cepacia*
2B: Fungal infections: *C. albicans*, *Aspergillus* spp.; GPC: *Enterococcus* spp., *S. pneumoniae*, Other GNB: *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. maltophilia*, *Enterobacter* spp., *B. cepacia*,
2C: UTI: Urinary tract infection, Other GNB: *K. pneumoniae*, *P. aeruginosa*
2D: IFI: Invasive fungal infection

Table 1: Distribution of patients according to the treatments they received, gender, need for intensive care and infection rates.

			Anakinra	Tocilizumab	p
ALL PATIENTS (n=208)	**Gender (n/%*)**				
		Female	29 (53.7)	50 (32.5)	**.006#**
		Male	25 (46.3)	104 (67.5)	
	Age (years)**		66 (27 – 94)	63 (24 – 88)	.650¥
	Length of hospital stay (days)**		17 (6 – 61)	21 (7 – 75)	**.046¥**
	ICU (n/%*)				
		No	8 (14.8)	40 (26.0)	.137#
		Yes	46 (85.2)	114 (74.0)	
	30-day mortality (n/%*)				
		No	24 (44.4)	87 (56.5)	.127#
		Yes	30 (55.6)	67 (43.5)	
	Infection (n/%*)				
		No	30 (55.6)	105 (68.2)	.132#
		Yes	24 (44.4)	49 (31.8)	
	Pneumonia (n/%*)				
		No	33 (61.1)	118 (76.6)	**.043#**
		Yes	21 (38.9)	36 (23.4)	
	BSI (n/%*)				
		No	39 (72.2)	136 (88.3)	**.010#**
		Yes	15 (27.8)	18 (11.7)	
	UTI (n/%*)				
		No	47 (87.0)	142 (92.2)	.277#
		Yes	7 (13.0)	12 (7.8)	
	IFI (n/%*)				
		No	54 (100)	152 (98.7)	1.000
		Yes	0 (0.0)	2 (1.3)	
PATIENTS FOLLOWED IN ICU (n=160)	**30-day mortality (n/%*)**				
		No	17 (37.0)	50 (43.9)	.533#
		Yes	29 (63.0)	64 (56.1)	
	Infection (n/%*)				
		No	22 (47.8)	66 (57.9)	.326#
		Yes	24 (52.2)	48 (42.1)	
	Pneumonia (n/%*)				
		No	27 (58.7)	78 (68.4)	.323#
		Yes	19 (41.3)	36 (31.6)	
	BSI (n/%*)				
		No	31 (67.4)	97 (85.1)	**.021#**
		Yes	15 (32.6)	17 (14.9)	
	UTI (n/%*)				
		No	39 (84.8)	102 (89.5)	.575#
		Yes	7 (15.2)	12 (10.5)	
	IFI (n/%*)				
		No	46 (100)	112 (98.2)	1.000
		Yes	0 (0.0)	2 (1.8)	

*Column percentage, **Median (Minimum – Maximum) #Pearson chi-square test was used, ¥Mann-Whitney U test was used,

Abbreviations: ICU: Intensive care unit, BSI: Blood stream infection, UTI: Urinary tract infection, IFI: Invasive fungal infection

Table 2: Factors Affecting Infection Development.

			Infection		p
			No	Yes	
ALL PATIENTS (n=208)	**Gender(n/%*)**				
		Female	49 (62.0)	30 (38.0)	.496**
		Male	86 (66.7)	43 (33.3)	
	Age (years) (median [min – max])		64 (24 – 94)	63 (27 – 88)	.715#
	Length of hospital stay (day) (median [min – max])		17 (6 – 54)	22 (9 – 75)	**<.001#**
	ICU (n/%*)				
		No	47 (97.9)	1 (2.1)	**<.001****
		Yes	88 (55.0)	72 (45.0)	
PATIENTS FOLLOWED IN ICU (n=160)	**Gender (n/%*)**				
		Female	35 (53.8)	30 (46.2)	.135**
		Male	53 (55.8)	42 (44.2)	
	Age (year) (median [min – max])		65.5 (24 – 88)	63 (27 – 88)	.483#
	Length of hospital stay (day) (median [min – max])		18 (6 – 54)	22 (9 – 75)	**.009#**

*Percentage of rows, **Pearson chi-square test used, #Mann-Whitney U test used.

Table 3: Effect of infection development on 30-day mortality.

		Infection (n/%*)		p
30-day mortality		**No**	**Yes**	
All patients; (n=363)				
	No	85 (63.0)	26 (35.6)	**<.001****
	Yes	50 (37.0)	47 (64.4)	
Anakinra; (n=54)				
	No	16 (53.3)	8 (33.3)	0.232**
	Yes	14 (46.7)	16 (66.7)	
Tocilizumab; (n=154)				
	No	69 (65.7)	18 (36.7)	**0.001****
	Yes	36 (34.3)	31 (63.3)	

*Column percentage, **Pearson chi-square test used

Table 4. Factors affecting the development of infection; regression analysis.

Risk Factor Analysis of Infection				
ALL PATIENTS *	**Factors**	**p value**	**Odds Ratio**	**95% CI**
	Age	.865	-	-
	Sex - Male	.961	-	-
	Treatment - Anakinra	.499	-	-
	ICU (+)	**.001**	**32.819**	**4.382-245.821**
	Length of hospital stay	**.004**	**1.048**	**1.015-1.082**
PATIENTS FOLLOWED IN ICU**	**Factors**	**p value**	**Odds Ratio**	**95% CI**
	Age	.727	-	-
	Sex - Male	.979	-	-
	Treatment - Anakinra	.462	-	-
	Length of hospital stay	**.004**	**1.048**	**1.015-1.082**

*Hosmer and Lemeshow Test p value is: 0.356, Cox&Snell R Square value is .217, Nagelkerke R Square value is .299. The model was significantly significant, $\chi 2$ (1, *n total*=208) = 51.010, p<.001, which suggests model can distinguish between Infection and Non-infection situations. Our model explained between %21.7 (Cox&Snell R Square) and %29.9 (Nagelkerke R Square) of the variance in the infection variable and overall prediction of classification was %69.2.

**Hosmer and Lemeshow Test p value is: 0.271, Cox&Snell R Square value is .067, Nagelkerke R Square value is 090.The model was significantly significant, $\chi 2$ (1, *n total*=160) = 11.122, p=0.025, which suggests model can distinguish between Infection and Non-infection situations. Our model explained between %6.7 (Cox&Snell R Square) and %9.0 (Nagelkerke R Square) of the variance in the Infection variable and overall prediction of classification was %59.4.