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Comparison of baricitinib and tocilizumab in clinical outcome among hospitalized patients with severe form of COVID-19 – our experiences

Компарација клиничког исхода барицитиниба и тоцилизумаба код хоспитализованих болесника са тешком формом ковида 19 – наша искуства

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Компарација клиничког исхода барицитиниба и тоцилизумаба код хоспитализованих болесника са тешком формом ковида 19 – наша искуства

SUMMARY

Introduction/Objective Severe acute respiratory syndrome caused by the coronavirus (SARS-CoV-2) manifested with an unpredictable clinical course that could rapidly progress, leading to serious and often fatal complications. The identification of effective laboratory biomarkers that could stratify patients at risk of developing severe forms of the disease is imperative to ensure they receive prompt medical treatment. The aim of our study is to compare baricitinib and tocilizumab in clinical outcome among hospitalized patients with severe COVID-19.

Methods A retrospective study included the analysis of data from 82 patients of both genders who were treated with biological immunosuppressive therapy at the Military COVID Hospital Karaburma. All patients who met the criteria for its application according to the guidelines of the national protocol for the treatment of COVID-19 version XIII had a consultative decision made for the application of biological immunosuppressive therapy. Half were treated with tocilizumab, and the other half with baricitinib.

Results The results of our study show that the mortality rate is lower in the group treated with tocilizumab compared to the group treated with baricitinib – 17.1% vs 26.8%, but without statistical significance (p = 0.286). Additionally, the use of tocilizumab reduces the need for mechanical ventilation compared to baricitinib – 53.6% vs 68.3%, without statistical significance (p = 0.454).

Conclusion The results obtained in our study indicate that both drugs are equally clinically effective.

Keywords: COVID-19; clinical outcome; cytokine storm; baricitinib; tocilizumab

САЖЕТАК

Увод/Циљ Тешки акутни респираторни синдрома изазван коронавирусом (*SARS-CoV*-2) манифестовао се непредвидивим клиничким током болести који се могао брзо развијати, изазивајући озбиљне и често смртоносне компликације. Индентификација ефикасних лабораторијских биомаркера који би могли стратификовати болесника за појаву тешких облика болести је императив како би им се гарантовао брз медицински третман. Циљ наше студије је упоређивање ефикасности барицитиниба и тоцилизумаба у клиничком исходу код хоспитализованих болесника са тешком формом ковида 19.

Методе. Ретроспективном студијом је обухваћена анализа података 82 болесника оба пола који су лечени биолошком имуносупресивном терапијом у Војној ковид болници Карабурма. Свим пацијентима који су испуњавали критеријуме за њену примену по смерницама националног протокола за лечење ковида 19 верзија XIII доношена је конзилијарна одлука за примену биолошке имуносупресивне терапије. Половина болесника је лечена тоцилизумабом, а друга половина барицитинибом.

Резултати Резултати наше студије показују да је стопа морталитета нижа код групе лечених тоцилизумабом у односу на групу лечених барицитинибом – 17.1% *vs*. 26.8%, али без статистичке значајности (*p* = 0.286). Такође, примена тоцилизумаба смањује потребу за механичком вентилацијом у односу на барицитиниб – 53.6% *vs*. 68.3%, без статистички значајности (*p* = 0.454).

Закључак Резултати наше студије указују да су оба лека подједнако клинички ефикасна.

Кључне речи: ковид 19; клинички исход; цитокинска олуја; барицитиниб; тоцилизумаб

INTRODUCTION

The pandemic caused by the coronavirus (COVID-19) was the greatest scientific, medical and social challenge since the Spanish flu pandemic of 1918. Severe acute respiratory syndrome caused by the coronavirus (SARS-CoV-2) manifested with an unpredictable clinical course that could rapidly progress, leading to serious and often fatal complications. The identification of effective laboratory biomarkers that could stratify patients at risk of developing severe forms of the disease is imperative to ensure they receive prompt medical treatment. One such biomarker is interleukin-6. It belongs to a group of molecules known as cytokines. These are part

of the "inflammatory cascade", which involves coordinated, sequential activation of immune response pathways and are responsible for the onset of a "cytokine storm" - a hyperinflammatory response to infection that significantly impacts mortality in COVID-19 patients [1].

Ponti et colleagues in 2020. study emphasize the role of systemic vasculitis and cytokine-mediated coagulation disorders as key contributors to multiple organ failure in patients with severe forms of COVID-19 [2]. The following biomarkers have been identified as correlating with an increased risk of developing disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS). Haematological markers: lymphocyte count, neutrophil count, and their ratio - the neutrophil-to- lymphocyte ratio (NLR); inflammatory markers: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT); immunological marker: interleukin (IL)-6 and biochemical markers: D-dimer, troponin, creatine kinase (CK), and aspartate aminotransferase (AST). Elevated concentrations of IL-6 have been shown to be a significant factor in damaging the host immune response in COVID-19 by stimulating a strong pro-inflammatory response, leading to a cytokine storm - a hyperinflammatory response to infection that has a significant impact on mortality in COVID-19 patients. Therefore, immunomodulatory therapies targeting IL-6 receptor antagonism have been explored as a countermeasure to host immune dysregulation and to support the beneficial effects of corticosteroids.

Tocilizumab is a recombinant humanized monoclonal antibody. It acts as an IL-6 receptor antagonist. Various observational studies have reported the beneficial effects of tocilizumab. Furthermore, subsequent randomized controlled trials have shown significant positive results regarding the efficacy and safety of tocilizumab, focusing on outcomes such as mortality, risk of admission to intensive care units, and the need for mechanical ventilation. A meta-analysis conducted by Wai and colleagues indicates that the introduction of tocilizumab in the treatment of patients with severe COVID-19 is associated with a lower risk of fatal outcomes and the need for mechanical ventilation [3].

In January 2022, the World Health Organization (WHO) recommended two new drugs for COVID-19, providing new options for treating more severe forms of the disease [4]. One of them was baricitinib, part of a class of drugs known as Janus kinase inhibitors (JAK1 and 2), which suppress excessive immune system stimulation (an oral medication used to treat rheumatoid arthritis by blocking the Interleukin 6 receptor), strongly recommended for patients with severe or critical forms of COVID-19. WHO recommends that it be administered together with corticosteroids.

The main problem in treating with biological therapy is the cost and availability of the drugs. WHO is in negotiations with manufacturers to ensure global supply capacity and equitable and sustainable access to newly recommended therapeutic agents. The Access to COVID-19 Tools Accelerator (ACT-A) therapeutic pillar is engaged with pharmaceutical companies to seek comprehensive access plans for low- and middle-income countries so that these treatments can be quickly implemented everywhere, not just in wealthy nations.

METHODS

This research was conducted at the Military COVID Hospital Karaburma in the period from 01 September to 31 December 2021 and it has had a retrospective character. The aim of our study is to compare the efficacy of baricitinib and. tocilizumab on mortality among hospitalized patients with severe form of COVID-19. We also investigated whether gender, cardiovascular comorbidities, diabetes, elevation of LDH, D-dimer, transaminases, NLR index, vaccination, and age affect mortality.

In our study we indicated the application of biological therapy based on the XIII version of the COVID-19 treatment protocol [5]. Tocilizumab was administered at a dose of 8 mg/kg i.v. per dose. Two doses were given (with a maximum of 800 mg per dose). The administration of Baricitinib depended on the eGFR value. The duration of therapy was limited to a maximum of 14 days or until clinical improvement occurred, if it happened within two weeks. For eGFR ≥60 mL/min/1.73m², Baricitinib was administered at 4mg once daily; for eGFR 30 to < 60 mL/min/1.73m², 2mg daily; for eGFR 15 to < 30 mL/min/1.73m², 1mg daily. Baricitinib was not recommended for eGFR < 15 mL/min/1.73m², and no such patients were included in the study.

The IBM SPSS Statistics package version 24 was used for statistical data processing (Statistical Package for the Social Sciences). Numerical features are presented through means (median, arithmetic mean) and measures of variability (standard deviation, range of values). Attribute features are shown using frequencies and percentages. The Likelihood Ratio Test and Mann-Whitney Test was used to test the relationship between the two categorical variables. The value of significance level $p \leq 0.05$ was considered statistically significant.

Ethics: The study was approved by the Ethics Committee of Military Medical Academy Belgrade (approval no. 48/2025) and complied with the revised ethical guidelines of the Declaration of Helsinki.

RESULTS

The study included 82 patients treated with biological immunosuppressive therapy, of which half, or 41 patients, were treated with tocilizumab (Actemra), and the other half with baricitinib (Olumiant). The age range of the patients was from 24 to 81 years, In discusionwith a median of Me = 60 years. The proportion of male patients was significantly higher, at 72%. A quarter of the patients were vaccinated (25.6%), with a fatal outcome recorded in 14.3% of vaccinated and 24.6% of unvaccinated patients.

In the intensive care unit, patients spent an average of Me = 10 days, with 37.5% being intubated. The fatal outcome occurred in older patients (Me = 64) compared to survivors, who were on average younger (Me = 59), but without statistical significance (p = 0.034). Mechanical ventilation was applied in 68.3% of patients who received baricitinib and in 53.6% of patients who received tocilizumab.

Patient hospitalization occurred on average on the 7th day, while treatment began on the 11th day. Treatment started earlier in surviving patients (Me = 11.00) compared to those with a fatal outcome (M = 13.00), p = 0.034. Survivors were treated on average for M = 23.5 days, while those who died were treated for an average of Me = 15.5 days, p < 0.001. The total time from the onset of illness to the final outcome (discharge or death) was Me = 35.5 days for the survivor group, and Me = 30.00 days for the group with a fatal outcome, p = 0.009.

The levels of IL-6, ESR and CRP were similar in the compared groups. D-dimer levels were significantly higher in those who died (Me = 13.16) compared to those who survived (Me = 1.90), p < 0.001.

The values of liver enzymes - alanine aminotransferase (ALT) were similar between the groups, while aspartate aminotransferase (AST) was higher in the group with fatal outcomes (Me = 70 vs Me = 53), although without statistical significance. Lactate dehydrogenase (LDH) levels were significantly higher in patients with a fatal outcome (Me = 598.50), p = 0.001.

A reduced lymphocyte count, or lymphopenia, was present in all 82 patients. The NLR index in all deceased patients was > 10. Of the total number of deceased patients, 64.3% had lymphocyte values below $0.5x10^6$, and 93% had values below $0.7x10^6$.

Clostridia was present in 20.7% of patients receiving biological therapy, and the study results did not indicate that it had an impact on mortality.

The results of our study show that the mortality rate was lower in the group treated with tocilizumab compared to the group treated with baricitinib 17.1% vs 26.8%, but without statistical

significance (p = 0.286). Additionally, the use of tocilizumab reduced the need for mechanical ventilation compared to baricitinib 53.6% vs 68.3%, without a statistically significant difference (p = 0.454).

Survival time (measured from the start of receiving biological therapy) for patients on baricitinib is M = 40.5, and for those on tocilizumab M = 49.3 days, but without a statistically significant difference. Total survival time measured from the start of biological therapy of all patients is M = 47.9 days. Survival time measured from the onset of the disease for vaccinated patients is M = 54.5, and for non-vaccinated patients M = 60.7 days, but without a statistically significant difference. Survival time (measured from the start of receiving biological therapy) for vaccinated patients is M = 45.2, and for unvaccinated M = 46.2 days, also without statistically significant difference. The Log Rank test shows that there are no statistically significant differences in treatment duration between vaccinated and unvaccinated patients, as well as between patients on tocilizumab and baricitinib. Furthermore, survival among vaccinated patients was somewhat higher compared to unvaccinated patients - 85.7% vs 74.4%, but without statistical significance (p = 0.388).

DISCUSSION

In our study including criteria for indication for biological therapy was: stages III and IV of the disease, with progression of lung findings and/or an increase in inflammatory markers, IL-6 levels ≥40 ng/l, and CRP > 50 mg/l, after the administration of adequate corticosteroid therapy without effect, respiratory rate ≥25 breaths/min, SpO2 (pulse oximetry) < 90%, and pO2 < 8.66 kPa on ambient air (without oxygen support). Similar recommendations are given in the Spanish treatment protocol for Covid-19 [6] when biological therapy being included in the event of respiratory insufficiency and at increase in the IL-6 value of more than 15ng/l.

In retrospective cohort study conducted by Conroy and colleagues [7] is concluded that ther is none difference in mortality or adverse effects was noted between tocilizumab and baricitinib. The results of our study show that the mortality rate were somewhat lower in the group treated with tocilizumab compared to the group treated with baricitinib 17.1% vs 26.8%, but without statistical significance (p = 0.286). The same conclusion was reached in the study by Cawcutt and Kalil [8]. In retrospective cohort study of the National Covid Collaborative, which includes more than 10.000 patients treated in the USA, baricitinib was associated with lower hospital mortality and shorter hospital length of stay compared with tocilizumab [9]. Vincent Marconi and colleagues evaluated the use of baricitinib in the COV- BARRIER study in a randomized,

placebo-controlled, double-blind trial [10]. The study's randomization was carried out strictly through an interactive response system and stratified according to disease severity, age, region, and steroid use. The trial was conducted in 101 centres across 12 countries and included 1,525 patients. Compared to the placebo, patients receiving baricitinib had a relative reduction of 38.2% and an absolute reduction of 5% in 28- day all-cause mortality. No other COVID-19 therapy has demonstrated such a significant reduction in mortality. For comparison, the other two immunomodulatory treatments associated with reduced mortality were dexamethasone - which showed a 17% relative reduction and a 2.8% absolute reduction in mortality - and tocilizumab - which showed a 15% relative reduction and a 4% absolute reduction in mortality. Further studies will provide clearer guidelines for optimal treatment Covid-19 patients.

The conclusion of the study by Choi and colleagues is that mortality is up to two times higher in men compared to women [11], which is consistent with the results of our study - 66.7% vs 33.3%. Additionally, mortality is up to five times higher in individuals with comorbidities compared to healthy individuals. In our study, cardiovascular comorbidities were recorded in 63.4% of patients receiving biological therapy, with a mortality rate of 25%, whereas in the population without cardiovascular disease, mortality was 16.7%. Diabetes was present in 19.5% of patients, with a mortality rate of 31.2% among diabetics, which is significantly higher than the 19.7% mortality rate in non-diabetic patients. Twelve patients had combined comorbidities, six in each group. Ten patients with diagnosed hypertension and diabetes (86% of them) required non-invasive ventilation (NIV) or full-face mask (FFM), leading us to conclude that dual comorbidities significantly increase the risk of respiratory failure and the need for mechanical ventilation.

The neutrophil-to-lymphocyte ratio (NLR) has proven its prognostic value in infections. It is considered that the normal NLR range is from 0.78 to 3.53 [12]. A meta- analysis by Badaraco and colleagues in 2021 indicates that NLR can be a useful prognostic biomarker in patients with severe forms of COVID-19, and that high NLR values may indicate a poor prognosis in these patients [13]. The NLR index in all deceased patients in our study was > 10.

A meta-analysis conducted by Tleyjeh and colleagues concluded that the use of tocilizumab reduces the risk of mechanical ventilation in hospitalized patients with COVID- 19 [14], which is also a result obtained in our study. Tocilizumab reduced the need for mechanical ventilation compared to baricitinib - 53.6% vs 68.3%, without a statistically significant difference ($p = 0.454$). Similar results were obtained in the study by Reid and colleagues [15].

CONCLUSION

The results obtained in our study indicate that both drugs are equally clinically effective, meaning that there is no statistically significant difference in the mortality rate ($p = 0.286$) between patients treated with tocilizumab and those treated with baricitinib.

Male gender, comorbidities, particularly dual comorbidities (diabetes mellitus and cardiovascular disease), elevated LDH and D-dimer values, NLR index > 10, and hypoalbuminemia are unfavorable prognostic factors, while vaccination status, elevated transaminases, and age do not impact mortality.

The obtained results should be confirmed in future studies to ensure optimal treatment for this group of severely ill patients.

Conflicts of interest: None declared.

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Table 1. General characteristics of patients treated with biological immunosuppressive therapy

General characteristics of patients	Treatment outcome						Test
	[All]		Survivors		Fatal outcome		p
	N = 82		N = 64		N = 18		
Sex							0.577[a]
Male	59	(72%)	47	(73.4%)	12	(66.7%)	
Female	23	(28%)	17	(26.6%)	6	(33.3%)	
Age (years) Median (min–max)	60	(24–81)	59	(24–81)	64	(31–78)	0.034[b]
Medication							0.284[a]
Baricitinib	41	(50%)	30	(46.9%)	11	(26.83%)	
Tocilizumab	41	(50%)	34	(53.1%)	7	(17.07%)	
Vaccination							0.309[a]
Yes	21	(25.6%)	18	(85.7%)	3	(14.3%)	
No	61	(74.4%)	46	(74.4%)	15	(24.6%)	
							0.388[a]
Sinopharm	18	(85.7%)	16	(88.9%)	2	(66.7%)	
Pfizer	2	(9.5%)	1	(5.6%)	1	(33.3%)	
Sputnik	1	(4.8%)	1	(5.6%)	0	(0%)	
							0.182[a]
ICU stay, days Median (min–max)	10	(3–44)	9	(3–44)	11	(4–24)	0.642[b]
Mechanical ventilation							
Invasive mechanical ventilation	18	(37.5%)	0	(0%)	18	(100%)	< 0.001[a]
Full-face mask	30	(62.5%)	30	(100%)	0	(0%)	

[a]Likelihood ratio test;

[b]Mann–Whitney Test

Table 2. Clinical characteristics of patients treated with biological immunosuppressive therapy

Clinical characteristics	Treatment outcome			Test
	[ALL]	Survivors	Fatal outcome	p
	N = 82	N = 64	N = 18	
Time from onset of illness to hospitalization (days)	7 (1–15)	7 (1–15)	7 (1–15)	0.282[b]
Time from onset of illness to start of treatment (days)	11 (5–26)	11 (5–26)	13 (9–26)	0.034[b]
Duration of treatment	22 (8–60)	23.5 (10–60)	15.5 (8–31)	< 0.001[b]
Time from start to end of treatment (days)	34 (19–77)	35.5 (19–77)	30 (19–44)	0.009
IL-6 (values at the beginning of th)	98.4 (41.1–366)	99.7 (41.1–333)	95.4 (42.1–366)	0.960[b]
CRP	125.5 (29–243)	122 (29–243)	129.5 (44–194)	0.758[b]
D-dimer	2 (0.41–34.55)	1.9 (0.41–34.55)	13.2 (1.28–34.47)	< 0.001[b]
ESR	60 (26–109)	64 (26–109)	56 (30–102)	0.023[b]
AST	57 (5–663)	53 (5–334)	70 (19–663)	0.330[b]
ALT	84 (21–817)	89 (21–451)	76.5 (24–817)	0.519[b]
LDH	466 (193–2743)	435.5 (193–1042)	598.5 (354–2743)	0.001[b]
ALB	35 (21–46)	35.5 (31–46)	33.5 (21–44)	0.210[b]
WBC	9.3 (2.27–45.9)	9 (2.27–45.9)	11.5(4.3–23.3)	0.010[b]
Lymphocytes	0.6 (0.2–40.9)	0.6 (0.2–0.9)	0.45 (0.2–1.2)	0.133[b]
Lymphocytes				0.048[a]
< 0.5	25 (30.5%)	16 (25.0%)	9 (50%)	
others	57 (69.5%)	48 (75.0%)	9 (50%)	
Clostridia				0.229[a]
Yes	17 (20.7%)	15 (88.3%)	2 (11.7%)	
No	65 (79.3%)	49 (75.4%)	16 (24.6%)	
Cardiovascular disease				0.373[a]
Yes	52 (63.4%)	39 (75.0%)	13 (25%)	
No	30 (36.6%)	25 (83.3%)	5 (16.7%)	
Diabetes mellitus				0.332[a]
Yes	16 (19.5%)	11 (68.25%)	5 (31.25%)	
No	66 (80.5%)	53 (82.8%)	13 (19.7%)	

CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; AST – aspartate aminotransferase; ALT – alanine aminotransferase; LDH – lactate dehydrogenase; ALB – albumin; WBC – white blood cell count;

[a]Likelihood ratio test;

[b]Mann–Whitney test;

Note: numerical variables shown as median (min–max)

Table 3. Mortality rate and mechanical ventilation between two patient groups

Parameter	Drug			p
	[All]	Baricitinib	Tocilizumab	
	N = 82	N = 41	N = 41	
Treatment outcome				0.286[a]
Survivors	64 (78%)	30 (73.2%)	34 (82.9%)	
Fatal outcome	18 (22%)	11 (26.8%)	7 (17.1%)	
Mechanical ventilation				
Invasive mechanical ventilation	18 (37.5%)	11 (42.3%)	7 (31.8%)	0.454[a]
Full-face mask	30 (62.5%)	15 (57.7%)	15 (68.2%)	

[a]Likelihood ratio test

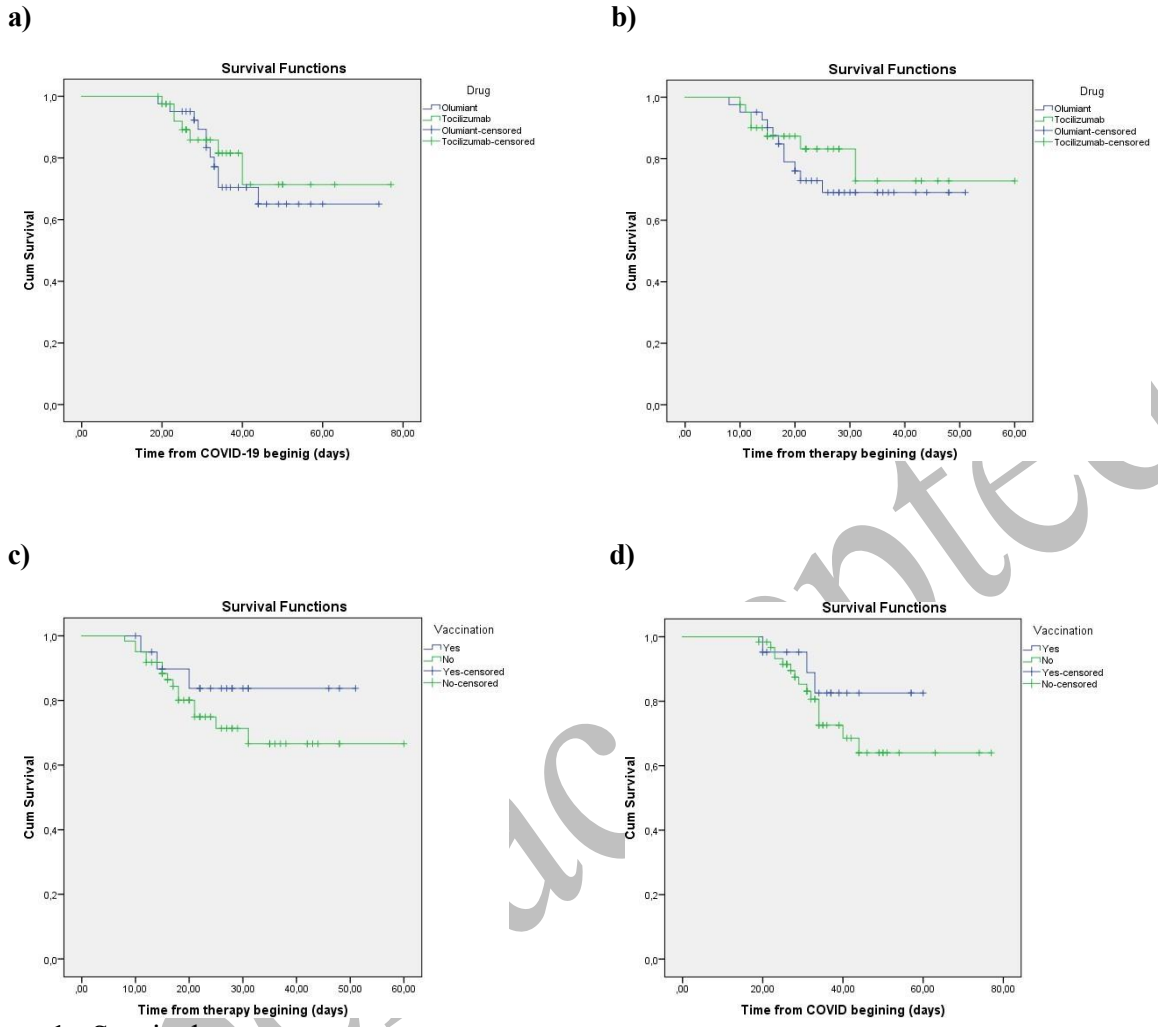

Figure 1. Survival curves

a) Treatment (from the onset of illness to outcome) of patients treated with baricitinib and tocilizumab (log rank (Mantel–Cox) = 0.240, df = 1, p = 0.624); b) treatment (from the start of biological therapy to outcome) of patients treated with baricitinib and tocilizumab (log rank (Mantel–Cox) = 0.433, df = 1, p = 0.510); c) treatment (from the onset of illness to outcome) in vaccinated and unvaccinated patients (log rank (Mantel–Cox) = 0.952, df = 1, p = 0.329); d) treatment (from the start of biological therapy to outcome) in vaccinated and unvaccinated patients (log rank (Mantel–Cox) = 0.889, df = 1, p = 0.3

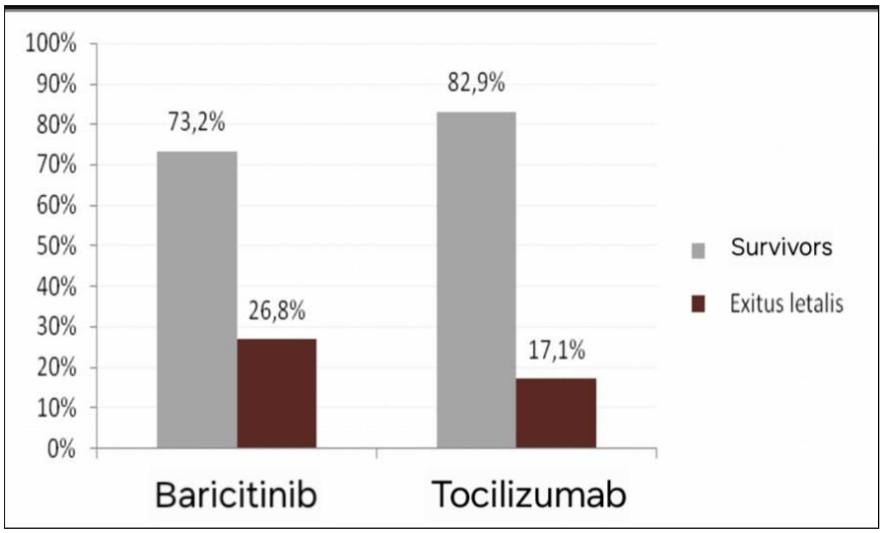

Figure 2. Mortality rate

