

## TOCILIZUMAB FOR COVID-19 TREATMENT. AN ARGENTINE REPORT

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**Abstract** Recently it has been demonstrated the clinical effectiveness of tocilizumab (TCZ) associated with systemic steroids for the treatment of severe SARS-CoV-2 pneumonia with rapid progression. The objective of this work was to describe the epidemiological, clinical, laboratory and evolution characteristics of the patients who received this treatment. Between March and June 2021, TCZ was administered in a cohort study of adults with severe SARS-CoV-2 pneumonia, in a private hospital in the City of Buenos Aires; 30 patients were included, 63% men, middle age 55 years. Obesity (33%), arterial hypertension (26%) and diabetes (25%) were the most frequent comorbidities. We found associated infections during hospitalization in half of the cohort, within them, pneumonia associated with mechanical ventilation was the most frequent and methicillin-sensitive *Staphylococcus aureus*, the most prevalent germ. Patients with secondary infections had a higher requirement for invasive mechanical ventilation (IMV) (100% vs. 19%  $p < 0.001$ ) and more days of hospitalization (median 23 vs. 15  $p = 0.009$ ). Of the entire cohort, seven who died during hospitalization had the highest requirement for IMV (100% vs. 43%  $p = 0.010$ ) and secondary infections (100% vs. 35%,  $p = 0.006$ ). In this relatively young cohort of patients with severe or critical SARS-CoV-2 pneumonia, obesity does not appear to be a predisposing factor for superinfection or death. The presence of secondary infections, organ failure and shock are presented as probable factors of worse evolution, as well as the requirement of IMV.

**Key words:** COVID-19, SARS CoV-2, tocilizumab

**Resumen** *Tocilizumab en el tratamiento de COVID-19. Informe argentino.* Recientemente se demostró la efectividad clínica del tocilizumab (TCZ) asociado a esteroides sistémicos para el tratamiento de la neumonía grave por SARS-CoV-2 con rápida progresión. El objetivo de este trabajo fue describir las características epidemiológicas, clínicas, de laboratorio y evolución de los pacientes que recibieron este tratamiento. Entre marzo y junio, 2021, se realizó un estudio de cohorte en un sanatorio privado de la Ciudad de Buenos Aires en adultos con neumonía grave por SARS-CoV-2 que recibieron TCZ. Se incluyeron 30 pacientes, hombres 63%, mediana edad 55 años, obesidad (33%), hipertensión arterial (26%) y diabetes (25%) fueron las comorbilidades más frecuentes. Encontramos infecciones asociadas durante la hospitalización en la mitad de la cohorte, dentro de ellas, la neumonía asociada a la ventilación mecánica fue la más frecuente y el *Staphylococcus aureus* metilicilino sensible, el germen más prevalente. Los enfermos con infecciones secundarias tuvieron un mayor requerimiento de ventilación mecánica invasiva (VMI) (100% vs. 19%  $p < 0.001$ ) y más días de internación (mediana 23 vs. 15  $p = 0.009$ ). De la totalidad de la cohorte, siete que fallecieron durante la internación tuvieron el mayor requerimiento de VMI (100% vs. 43%  $p = 0.010$ ) e infecciones secundarias (100% vs. 35%,  $p = 0.006$ ). En esta cohorte relativamente joven de pacientes con neumonía grave o crítica por SARS-CoV-2, la obesidad no parece ser un factor predisponente para sobreinfección o muerte. La presencia de infecciones secundarias, falla orgánica y *shock* se presentan como probables factores de peor evolución, como así también el requerimiento de VMI.

**Palabras clave:** COVID-19, SARS CoV-2, tocilizumab

### KEY POINTS

- Several therapeutic alternatives have been developed for the treatment of severe COVID-19 pneumonia. TCZ combined with dexamethasone decreases mortality in patients who require oxygen supply.
- In this cohort, obesity and CRP values do not seem to be associated with a higher risk of superinfection or death. The absence of invasive mechanical ventilation, shock and superinfection resulted in better prognosis.

Since the initial description on December 31, 2019, in Wuhan City, Hubei province (China); of an acute respiratory disease<sup>1</sup> caused by a new coronavirus (SARS-CoV-2) and its spread worldwide, multiple, and different treatment approaches have been studied.

Among these therapeutic interventions, use of systemic steroids showed clear reduction in mortality in hospitalized patients with Coronavirus disease (COVID-19) that required oxygen supply<sup>2</sup>.

Tocilizumab (TCZ) is a humanized recombinant monoclonal antibody against interleukin-6 (IL-6) receptor, that inhibits the binding of IL-6 cytokine. IL-6 is involved in inflammation, and it regulates the immune response. National Administration of Medicines, Food and Medical Technology (ANMAT)<sup>3</sup>, United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have authorized its use for treatment of rheumatological illnesses (rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and polyarticular juvenile idiopathic arthritis). The hypothesis of a potential use of TCZ in severe COVID-19 patients is linked to the fact that the virus induces cytokine release (especially IL-6) in those patients with severe disease<sup>4</sup>.

TCZ most common side effects include headache and hypertension, and rarely, hepatotoxicity, that ranges from mildly elevated transaminases to severe drug-induced liver injury (DILI)<sup>5</sup>. Currently, data on TCZ hepatotoxicity in COVID-19 patients are limited and inconclusive<sup>6</sup>.

Despite the potential risk for secondary infections reported by some authors when using IL-6 pathway inhibitors, there are many randomized clinical trials that demonstrated there is no such higher risk<sup>7, 8</sup>. The RECOVERY study<sup>9</sup> showed that TCZ reduced the 28-day mortality in SARS-CoV-2 pneumonia patients that required oxygen support of any type and had C-reactive protein (CRP) levels above 75 mg/l. Besides, the REMAP-CAP<sup>10</sup> database showed that TCZ reduced hospital mortality in patients who had started high-flow oxygen or more intensive respiratory support in the previous 24 hours.

In our institution, we considered current evidence and used the National Institute of Health (NIH, United States) recommendations<sup>11</sup> and the American Society of Infectious Diseases (IDSA) guidelines<sup>12</sup> for treatment of COVID-19

patients. The aim of this study was to describe clinical and laboratory characteristics and outcome of patients receiving TCZ and systemic steroids as treatment for severe or critical SARS-CoV2 pneumonia in Sanatorio Finochietto in Buenos Aires City.

### Materials and methods

We conducted a retrospective observational study based on electronic records of patients 18 years of age or older with severe or critical pneumonia due to SARS-CoV-2, who received treatment with TCZ (8 mg/kg/dose) and systemic steroids (dexamethasone  $\geq$  6 mg/day or another steroid at equivalent doses) from March to May 2021. Demographic and clinical data were gathered. The study took place at *Sanatorio Finochietto*, a private health center that provides health care services in prevalent clinical and surgical pathologies. It is a reference center in Buenos Aires City, which has an Emergency Department, Maternity Ward, General Ward, Intensive Care Unit; as well as complementary services, such as laboratory, radiology, and hemodynamics departments. The protocol was approved by the institution's Ethics Committee.

In the descriptive analysis, quantitative data was expressed as median and interquartile range 25-75 (IQR) according to their distribution. Data normality was evaluated using charts and Kolmogorov-Smirnov's test. Qualitative data was expressed as absolute and relative frequency in percentage. For comparison between groups, chi2 or Fisher test were used according to assumptions for qualitative data and Wilcoxon for quantitative data according to their distribution. The Wilcoxon signed-rank test, a non-parametric statistical hypothesis test was used to compare CRP levels between TCZ and death or discharge. A significance level of less than 0.05 was considered. R software version 4.0.3 was used.

### Results

The first 31 severe COVID-19 patients receiving TCZ treatment were included in the analysis. A patient was later excluded because he was referred to another facility within 24 hours of TCZ administration and due to inability to obtain data. Thus, 30 patients were finally included in the analysis. Median age was 56.5 (IQR 45.0- 66.2) and 19 (63.3%) were men.

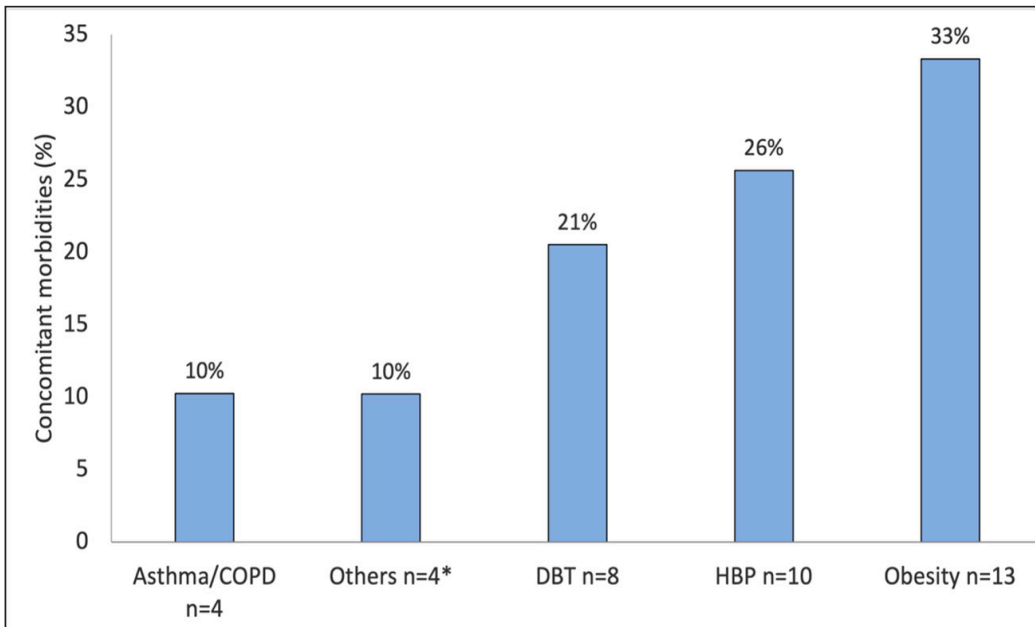
Figure 1 shows patient's concomitant morbidities.

All patients were admitted to the Intensive Care Unit. Median APACHE at admission was 8.0 (IQR 6.0-9.7). Quantitative biomarkers (CRP, ferritin and D-dimer) were evaluated at the time of TCZ administration (Fig. 2).

Median number of days between COVID-19 symptoms onset and TCZ administration was 10.0 days (IQR 7.25-11.0). All patients received systemic steroids; the median number of days was 14.0 (IQR 10.0-20.7). Five patients (16.7%) also received methylprednisolone pulses. Only one received convalescent plasma. All of them received only one TCZ infusion, and the dose did not exceed 800 mg.

Only two patients did not require ventilatory support beyond a non-rebreather mask. Of the remaining 28 (93.3%), twenty (66.6%) required high-flow nasal oxygen (HFNO)

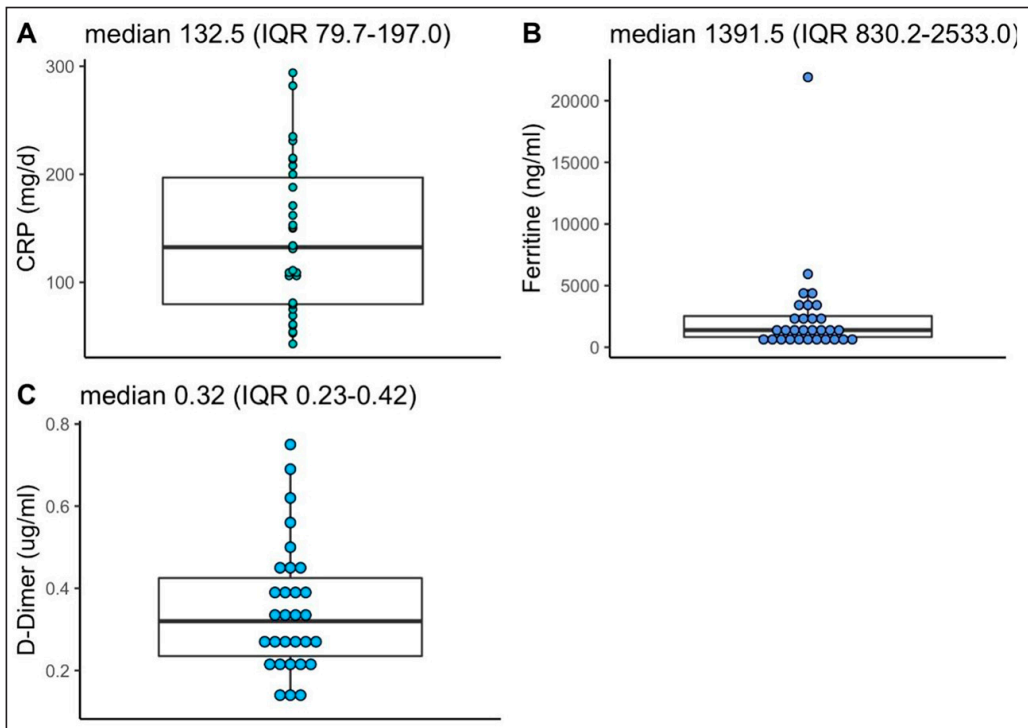
Fig. 1.– Concomitant morbidities n = 39



DBT: diabetes; HBP: high blood pressure

\*Others: Coronary heart disease n = 2, solid tumor n = 2

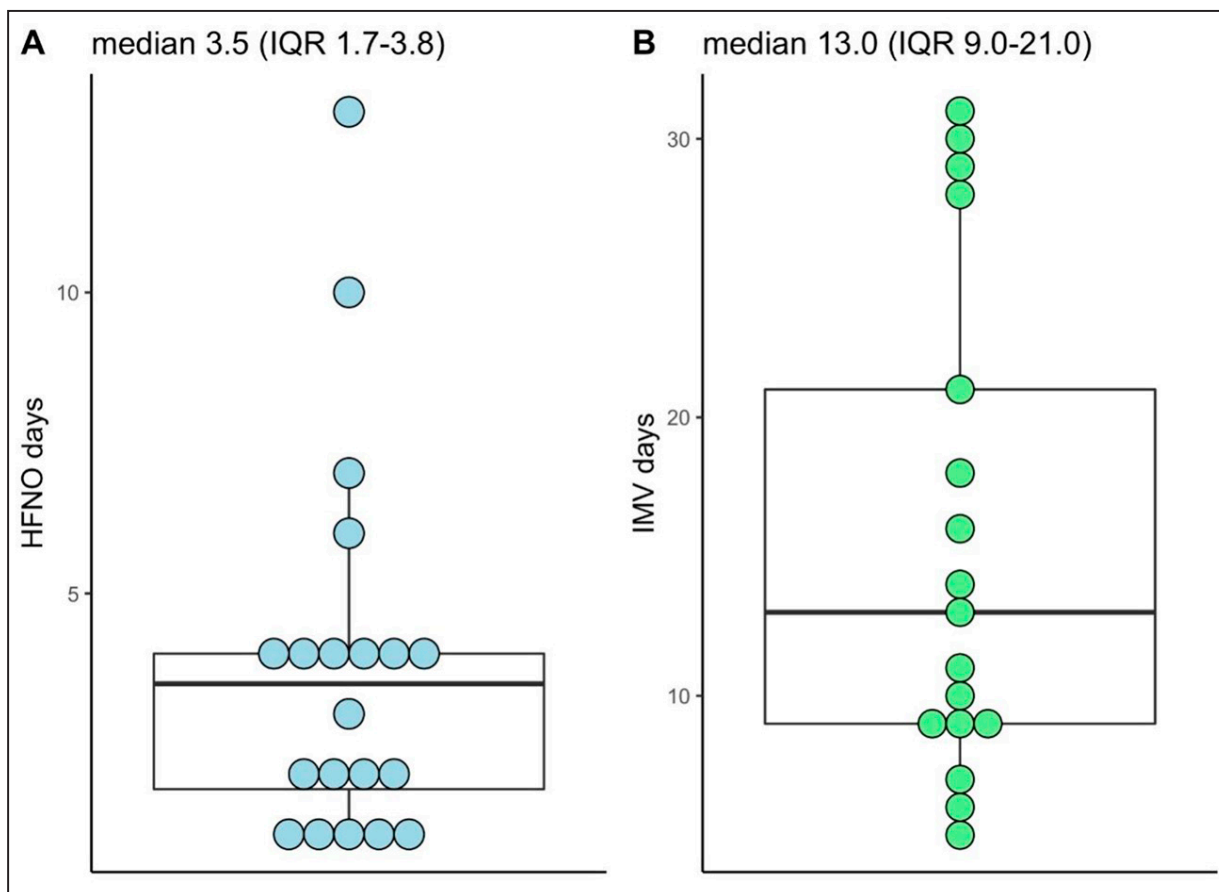
Fig. 2.– Biomarkers at the time of TCZ administration. A) C-reactive protein (mg/dl) B) Ferritin (ng/ml) C) D-dimer (ug/ml)



CRP: C reactive protein

Each dot represents a patient

Fig. 3.— Days of requirement for each type of ventilatory support. A) High nasal flow oxygen B) Invasive mechanical ventilation



HFNO: high nasal flow oxygen; IMV: invasive mechanical ventilation  
Each dot represents a patient with requirement of ventilatory support

and 17 (56.7%) required invasive mechanical ventilation (IMV). A total of 11 patients required both HFNO and IMV due to worsening in the ventilation parameters. These patients and those who required IMV from admission were included in the IMV group. Figure 3 shows the days required for each type of ventilatory support.

Median length of hospitalization was 17.0 days (IQR 13.0-23.7) and 14 patients (46.7%) presented secondary infections. When comparing patients according to whether they had secondary infections or not, the former had a higher frequency of shock, multiorgan failure, IMV requirement and total length of hospitalization (Table 1).

There were 22 secondary infections, and 6 patients had more than one event. Most of them were ventilation-related pneumonia or tracheobronchitis (11, 50%). Secondary infections and microorganisms found are described in Figure 4.

CRP levels decreased from the administration of TZC to death or discharge (Fig. 5 A). Seven patients died (23.3%). Compared to those who survived, they had a

lower decrease in CRP levels between TCZ administration and discharge or death (Fig. 5 B). There was no association between obesity and death, this frequency was 3/7 (42/9%) in patients that didn't survive and 10/23 (43.5%) in those who survived ( $p = 0.999$ ). All patients who died required IMV (100%) versus 10 in those who survived (43.5%,  $p = 0.01$ ). Shock, multi-organ failure and secondary infections were more frequent in those patients (in percent) 6 versus 2 ( $p < 0.001$ ); 4 versus 1 ( $p = 0.006$ ) and 7 versus 8 ( $p = 0.006$ ), respectively. Neutrophil counts were normal. Elevated liver enzymes (five times above normal range) were only observed in two patients.

## Discussion

This cohort represents a relatively young group of patients with severe SARS-CoV2 pneumonia, with an average age that fall below the age reported in Argentina for patients admitted to multiple intensive care units (UCI)<sup>13-15</sup> and, with a prevalence of males in a 2:1 ratio compared to

TABLE 1.– Clinicopathological features of patients with or without secondary infections

	No secondary infection N = 16	Secondary infection N = 14	p value
Age <sup>2</sup>	55.5 (41.2-62.5)	57.5 (45.7- 69. 0)	0.708
Male <sup>1</sup>	9 (56.2)	10 (71.4)	0.630
BMI <sup>2</sup>	29.6 (26.9-35.0)	25.1 (22.8-29.6)	0.088
<i>Comorbidities</i>			
High blood pressure <sup>1</sup>	3 (18.8)	7 (50.0)	0.122
Obesity <sup>1</sup>	7 (43.8)	6 (42.9)	0.999
Coronaryartery disease <sup>1</sup>	1 (6.2)	1 (7.1)	0.999
Solid tumor <sup>1</sup>	0 (0)	2 (14.3)	0.209
<i>Measures at TCZ administr.</i>			
Apache.II <sup>2</sup>	8.50 (5.0-10.5)	8.0 (6.0- 8.0]	0.815
CRP(mg.dl) <sup>2</sup>	150.4 (99.7-175.2)	110.0 (76.1-213.2)	0.803
Ferritin (ng/ml) <sup>2</sup>	1382.5 (615.2-2274.2)	1391.5 (844.5-3211.0)	0.589
D-dimer (ug.ml) <sup>2</sup>	0.3 (0.2-0.4)	0.4 (0.3-0.5]	0.349
<i>Treatments</i>			
TCZ doses <sup>2</sup>	720.0 (600.0-800.0)	800.0 (600.0- 800.0)	0.801
Days from symptoms to TCZ <sup>2</sup>	9.50 (8.0-12.0)	10.0 (6.2-11.0)	0.629
Metilpredison <sup>1</sup>	23.5 (16.5-28.0)	1 ( 6.2)	0.013
Dayscorticoids <sup>2</sup>	12.5 (9.7-17.0)	14.5 (12.2-31.0)	0.630
Convalescence plasma <sup>1</sup>	0 (0)	1 (7.1)	0.467
<i>Ventilatory parameters</i>			
HFNO <sup>1</sup>	11 (68.7)	9 (64.3)	0.809
Days HFNO <sup>2*</sup>	4.0 (3.7-6.2)	2.0 (1.0-2.0)	0.013
IMV <sup>1</sup>	3 (18.8)	14 (100.0)	<0.001
Days IMV <sup>2*</sup>	10.0 (8.0-11.5)	15.0 (9.0-26.2)	0.256
Shock <sup>1</sup>	1 (6.2)	7 (50.0)	0.012
Organic failure <sup>1</sup>	0 (0)	5 (35.7)	0.014
Days hospitalization <sup>2</sup>	15.0 (12.0-17.7)	23.5 (16.5-28.0)	0.013
CRP(mg.dl) <sup>2†</sup>	1.9 (1.1-6.1)	33.0 (3.0-49.0]	0.035
Death <sup>1</sup>	0 (0)	7 (50.0)	0.002

BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; TCZ: tocilizumab; HFNO: high flow nasal oxygen; IMV: invasive mechanical ventilation

<sup>1</sup>Absoluty N and relative frequency (%)

<sup>2</sup>Median (IQR)

<sup>†</sup>Measure to discharge or death

\*Only in who had HFNO or VNI

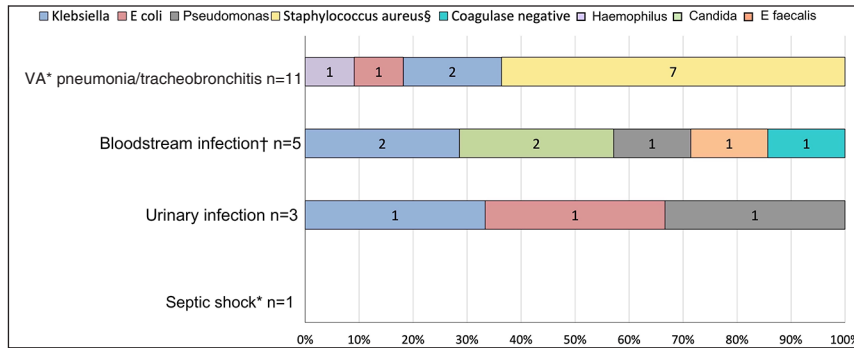
females. Interestingly, one out of three patients evaluated didn't present any of the known risk factors for severe COVID-19. This may be related to the patient's younger age. We did not find previous publications in Argentina of a cohort of consecutive severe COVID-19 patients who received TCZ treatment associated with standards of care.

Obesity found in our study population is similar than that reported in a recent publication of ventilated patients in ICU in Argentina in 2020<sup>13</sup>, being this the most frequent concomitant morbidity in our series. Hypertension, which

has the highest prevalence in Argentine publications<sup>13-15</sup> came second. The same was reported for patients receiving TCZ as treatment for SARS-CoV-2 pneumonia in Chile<sup>16</sup> in 2020, and Barcelona<sup>17</sup> in 2021.

TCZ was infused in all patients within 24 hours of clinical worsening, and in most cases in the hyper inflammatory phase, eight patients (26.6%) received TCZ within the first 7 days of symptoms onset. All patients received parenteral corticosteroids and had a CRP value greater than 75 mg/dl, thus, standard indications suggested by RECOVERY were accomplished.

Fig. 4.– Associated infections and isolated microorganisms

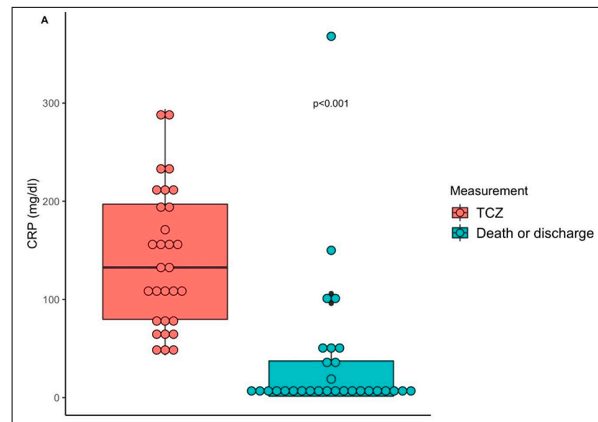


VA: ventilation-associated

\*Without isolation † bacteremia or candidemia bloodstream infection

§Methicillin-sensitive = 6 methicillin-resistant = 1

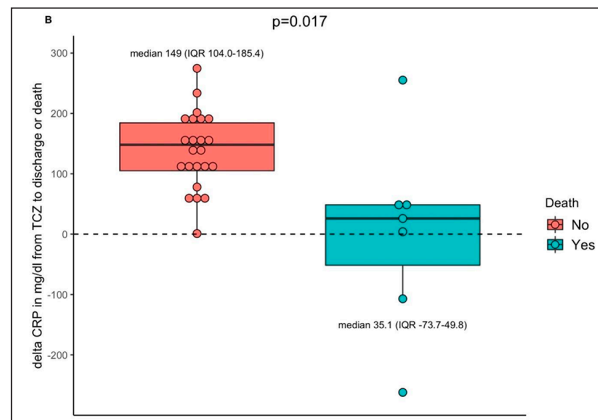
Fig. 5.– A) Measurement of C-reactive protein levels(mg/dl) at TCZ treatment and at death or discharge



CRP: C reactive protein; TCZ: tocilizumab

Each dot represents a patient with CRP measurement. Measurement at TCZ infusion (pink) and before hospital discharge or death (light blue)

Fig. 5.– B) Changes in C-reactive protein levels (delta in mg/dl) after TCZ treatment in patients before hospital discharge or death according to death or survival



CRP: C reactive protein; TCZ: tocilizumab

Each dot represents a patient with CRP measurement. Changes in CRP levels (delta) after TCZ treatment in patients before hospital discharge (pink) or death (light blue)

Our series shows that at TCZ administration, all patients had biomarker levels compatible with an augmented inflammatory response (CRP and ferritin). Unlike other publications<sup>16-18</sup>, none of them showed elevated D-dimer values.

Half of our patients developed secondary infections during hospitalization, most of them caused by bacteria. Ventilator-associated pneumonia (VAP) and methicillin-susceptible *Staphylococcus aureus* (MSSA) were the most prevalent infections and bacteria found, respectively.

Although IMV was related with an increase of secondary infections ( $p < 0.001$ ), there was no association between IMV time and infection. Neither there was any association between secondary infections and CRP or ferritin values at clinical worsening.

We found an increase in mortality in patients that presented IMV requirements, shock, multiorgan dysfunction and secondary infection, and CRP values had a lesser decrease from TCZ to death. Although obesity is widely reported as a risk factor for bad outcomes for COVID-19 patients, in our cohort it does not seem to be a risk factor for secondary infections nor it seems to be associated with an increased mortality. Remarkably, Estenssoro et al<sup>13</sup> found that the body mass index was higher in patients without secondary infections compared to those who survived.

Use of TCZ was safe and there were no adverse events during infusion and no need for discontinuation. No subsequent development of neutropenia was found. Elevated liver enzymes (five times above normal range)<sup>16</sup> was only observed in two patients (6.7%) and this was lower to that reported in registry trials (10-40%)<sup>6</sup>. None of them had liver failure.

Our study has several limitations. It is a single center, observational study, with no control group and with a small number of patients. Long-term survival and patient's condition after hospital discharge was not assessed. Despite this, the strength of this study relies on the fact that it is an Argentine experience of the use of TCZ for treatment of severe COVID-19 patients, with a survival rate greater than 75%.

Neither obesity nor CRP values at clinical worsening seem to be risk factors for higher chance of secondary infections or death, although more studies are needed to draw further conclusions.

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**Conflict of interest:** None to declare

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#### **BASIC IMPLICATIONS OF CLINICAL OBSERVATIONS**

*The Clinical Implications of Basic Research series has focused on highlighting laboratory research that could lead to advances in clinical therapeutics. However, the path between the laboratory and the bedside runs both ways: clinical observations often pose new questions for laboratory investigations that then lead back to the clinic.*

#### **IMPLICACIONES BÁSICAS DE LAS OBSERVACIONES CLÍNICAS**

La serie de Implicaciones clínicas de la investigación básica se ha centrado en destacar la investigación de laboratorio que podría conducir a avances en la terapéutica clínica. Sin embargo, el camino entre el laboratorio y la cabecera de la cama es bidireccional: las observaciones clínicas a menudo plantean nuevas preguntas para las investigaciones de laboratorio que luego conducen a la clínica.

En: Clinical Implications of Basic Research, NEJM.org; November 24, 2021,  
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