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Use of tocilizumab in kidney transplant recipients with COVID-19

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Abbreviations

ACEi, angiotensin converting enzyme inhibitor

AKI, acute kidney failure

ARB, angiotensin receptor blocker

ARDS, acute respiratory distress syndrome

BMI, body mass index

CI, confidence interval

CNI, calcineurin inhibitor

CRP, C-reactive protein

COVID-19, 2019 novel coronavirus disease

DM, diabetes mellitus

FiO2, fraction of inspired oxygen

HR, hazard ratio

ICU, intensive care unit

IL, interleukin

imTOR, mammalian target of rapamycin inhibitor

IQR, interquartile range

KT, kidney transplant

LDH, lactic acid dehydrogenase

MMF, mycophenolate mofetil

PaFi, PaO2/FiO2

PaO2, partial pressure of oxygen

ROC, receiver operating characteristic curve

RRT, renal replacement therapy

RT-PCR, reverse-transcriptase–polymerase-chain-reaction

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

SD, standard deviation

TNF, tumor necrosis factor-α

Abstract

Acute respiratory distress syndrome associated with coronavirus infection is related to a cytokine storm with large interleukin 6 (IL-6) release. The IL-6-receptor blocker tocilizumab may control the aberrant host immune response in COVID-19 patients. In this pandemic, kidney transplant (KT) recipients are a high-risk population for severe infection and showed poor outcomes. We present a multicenter cohort study of 80 KT patients with severe COVID-19 treated with tocilizumab during hospital admission. High mortality rate was identified (32.5%), related with older age (HR 3.12 for those older than 60 years, p=0.039). IL-6 and other inflammatory markers, including LDH, ferritin, and D-dimer increased early after tocilizumab administration and their values were higher in non-survivors. Instead, C-reactive protein (CRP) levels decreased after tocilizumab, and this decrease positively correlated with survival (mean 12.3 mg/L in survivors vs. 33 mg/L in non-survivors). Each mg/L of CRP soon after tocilizumab increased the risk of death by 1% (HR 1.01 [CI 1.004-1.024], p=0.003). Although patients who died presented with worse respiratory situation at admission, this was not significantly different at tocilizumab administration, and did not impact on outcome in the multivariate analysis. Tocilizumab may be effective in controlling cytokine storm in COVID-19 but randomized trials are needed.

1. Introduction

World Health Organization declared severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) outbreak as a pandemic on March 11th, 2020[1]. During the last nine weeks, Spain has been one of the most affected countries worldwide, with more than 235.000 people infected by May 26th and almost 27.000 deaths (fatality rate of 11.4%)[2]. At the same time, in Spain we have the privilege of enjoying one of the highest kidney transplantation (KT) rates across the world, with 72.8 procedures p.m.p performed in 2019 and more than 33.000 prevalent KT recipients with a functioning kidney[3]. This specific population is considered to be at risk for COVID-19 disease due to several conditions as their intrinsic comorbidities, the immunosuppressed status, and their frequent contact with health facilities[4–6]. In fact, more than 500 KT recipients have been reported to have COVID-19 through the Spanish Society of Nephrology registry[7,8], resulting in a global incidence of 1.5%, which triplicates general population.

The clinical presentation of COVID-19 includes fever, cough, dyspnea, gastro-intestinal symptoms and, eventually, respiratory failure[9]. So far, no treatment has solidly proven to be effective in stopping or ameliorating COVID-19 evolution[10,11]. Tocilizumab is a humanized antibody against the receptor of interleukin-6 (IL-6) that has been mostly used in rheumatoid arthritis, although its indications include other rheumatic conditions and severe cytokine release syndrome induced by CAR-T cells[12]. In the setting of transplantation, tocilizumab has been used to treat chronic antibody-mediated rejection[13]. Considering that the acute respiratory distress syndrome (ARDS) that occurs in some patients throughout COVID-19 is a consequence of an inflammatory response, tocilizumab appears as a reasonable drug to target the presumable cytokine storm triggered by the virus. Preliminary data in the general population[14–17] and transplant patients[18–20] show promising results.

Herein we present the results of tocilizumab use in a multicenter cohort of 80 Spanish KT recipients affected with SARS-CoV-2.

2. Methods

2.1. Patients

KT patients were identified from the Spanish Society of Nephrology COVID-19 registry, which included dialysis and KT patients with confirmed diagnosis of COVID-19 since 18th March 2020[7]. Only patients with a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) positive assay of a specimen collected on a nasopharyngeal swab or bronchoalveolar lavage were included. Initially, from 468 KT recipients included in the registry until the 9th of May, 73 were identified to have been treated with tocilizumab in 29 different hospitals in Spain. In a second step, a complete database was created in order to gather granular information from these patients. Each center was contacted and invited to participate in the study by

completing the additional variables. Twenty-seven centers completed the database and seven more patients were added, resulting in a final number of 80 patients. Median time to follow-up since symptoms onset was 25 days, interquartile range (IQR) 17-35 days.

2.2. Variables collected and definitions

The registry already included demographics, baseline kidney disease information, immunosuppressive and renin-angiotensin-system inhibitors treatments, and epidemiological and clinical data regarding COVID-19: date of diagnosis, symptoms, lymphopenia, pharmacological treatments, need of mechanical ventilation or intensive care and outcome. More specific and detailed data regarding tocilizumab treatment and inflammatory markers were added in the expanded database.

Obesity was defined as a body mass index (BMI) over 30 Kg/m^2. Respiratory symptoms included cough, sneezing and rhinorrhea but excluded dyspnea, which was collected separately. The ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2 expressed as a fraction) or PaFi index (Pa/FiO2) was calculated when available (n=38). If data to calculate it were missing, oxygen saturation was included (n=40).

Criteria for tocilizumab treatment was based on the protocol of each hospital although all patients presented with one of the following: increased levels or IL-6 (usually >40, ranged between >20 to >60 pg/mL), increased levels of other inflammatory markers (such as C-reactive protein (CRP), D-dimer, ferritin or lactic acid dehydrogenase (LDH)), and/or rapidly progressive ARDS (usually with PaFi<300).

Generally, tocilizumab dose was 8 mg/kg, adjusting to 600 mg for patients >75 or 80 kg body weight and 400 mg for those <75-80 kg. Depending on the clinical and analytical response, patients could receive two doses of tocilizumab, separated by 12 hours in the majority of the cases.

Clinical follow-up and lab tests were collected at three points: at admission, at the time tocilizumab was administered and early after tocilizumab infusion (median 72 h, IQR 48-96 h).

Outcomes were assessed as COVID-19-related mortality or recovery until May 15th, 2020. Recovery was defined as hospital discharge.

The study was performed under the principles of the Declaration of Helsinki and was approved by the hospital ethics committee.

2.3. Statistical analysis

Quantitative variables with a normal distribution are expressed as mean and standard deviation (SD) and the remaining as median and IQR. Categorical variables are summarized as counts and percentages. Univariate analyses were performed according to variables normality, with t-student test for normal

variables and non-parametric test for non-normal distributed ones. Cox multivariate analysis was assessed for predictors of patient mortality. Results are expressed as hazard ratio (HR) with their 95% confidence intervals (95% CIs). In the multivariate analysis only those variables with a p value <0.05 and clinically relevant for the outcome were included. A receiver operating characteristic (ROC) curve was plotted to illustrate the diagnostic ability of a binary classifier system as its discrimination threshold is varied. In general, a p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS V 22.0 (SPSS Inc., Chicago, IL).

3. Results

Fatality rate in this cohort was 32.5%. **Table 1** summarizes baseline characteristics of the entire cohort (n=80), patients who survived (n=54), and those who died (n=26). Mean age was 59.3 years and patients who died were five years older and more obese, with almost one third of them presenting with a BMI over 30 Kg/m^2. There were no other differences regarding recipient comorbidities. Most of them were on calcineurin inhibitors and mycophenolate. Clinical presentation most frequently included fever (81.3%) accompanied by other respiratory symptoms (cough, rhinorrhea) in 77.5% of them. Dyspnea and deteriorated respiratory situation (PaFi<300 or oxygen saturation<96%) were more frequent at the time of admission in those who died later on. Blood tests at admission showed a low lymphocyte count and elevated inflammatory markers, without relevant differences between those patients who died and those who survived, except for D-dimer, which was higher in patients who ultimately died.

COVID-19 management is summarized in **table 2**. All patients received tocilizumab at a median time of 5 days after admission. This elapsed time was longer in those who died in comparison with survivors (6 vs 4 days), though the difference was not statistically significant (p=0.13). Tocilizumab was more frequently administered at ICU in those who died, as median time from admission to administration was 6 days, and median time from admission to ICU was 5 days. Sixteen patients received more than one dose of tocilizumab. These patients were not more severely affected at baseline, but respiratory deterioration was more profound, with more frequent ICU admission and a higher mortality (**supplementary table 1**). Six patients treated with tocilizumab and steroids showed superimposed bacterial pneumonia.

Most patients received hydroxychloroquine (98.8%) and antibiotics (76.3%) while antivirals were less frequently used (48.8%). The use of steroid pulses together with tocilizumab was the most common practice (80%), and they were more often prescribed in those who died than in survivors (96.2% vs 72.2). Similarly, interferon was only administered in 5 patients and all of them died. Most patients withdrew immunosuppressive medications, either only antimetabolites (33.8%) or both antimetabolites and calcineurin inhibitors (55.8%). No differences were seen between survivors and deceased patients.

Outcomes are also detailed in **table 2**. Those who died were more often admitted to the ICU and had more frequent and severe acute kidney failure as COVID-19 complication.

The percentage of patients with severe respiratory disease (PaFi index <300 mmHg or Oxygen saturation <96%) at admission was higher in patients who ultimately died than in survivors (68% vs 41.5%, p<0.01). At the moment of tocilizumab treatment these percentages were not different between survivors and non-survivors (81.6% vs 87.5%) (**Figure 1)**.

Predictors for mortality were analyzed through multivariable Cox analysis (**table 3**). Recipient age over 60 and C-reactive protein (CRP) serum level after tocilizumab were associated with an increased risk of death. Each mg/L of CRP soon after tocilizumab administration increased the risk of death by 1% (p=0.003). A worse baseline respiratory situation and obesity were not significantly related to mortality in the multivariate adjustment. ARDS did not help on differentiating between survivors and non-survivors on final outcome.

We also analyzed laboratory parameters at different points during hospital stay (**figure 2**). At the time of tocilizumab administration all measurements had worsen compared to the status at admission, both in survivors and in those who had died at the end of follow-up. Early after tocilizumab administration only CRP levels decreased while other inflammatory markers increased even more. CRP levels markedly decreased after tocilizumab in survivors. In an attempt to identify which patients would have a favorable response to tocilizumab, we plotted a ROC curve for CRP levels soon after tocilizumab infusion, finding that values over 30 mg/L had a moderate estimation (0.648; p=0.042) for patient death.

The 80 patients treated with tocilizumab were compared with 335 ones not treated with tocilizumab but with COVID-19 symptoms and hospital admission. Age, gender, primary kidney disease, baseline immunosuppressive treatment and KT vintage were similar between both groups. Those patients treated with tocilizumab were more severely ill than those left untreated, as they had more frequently pneumonia, other concomitant drug treatments, ICU admission, non-invasive mechanical ventilation or endotracheal intubation, and a higher mortality (**supplementary table 2**).

4. Discussion

We present the results of the largest cohort of KT recipients with COVID-19 treated with tocilizumab. In our report, 80 patients have been analyzed and the fatality rate was 32.5%. Inflammatory markers increased early after tocilizumab administration, however CRP decreased, significantly more in survivors. There were no safety issues related to the administration of tocilizumab.

Several reports including low number of patients have reported outcomes of KT recipients with COVID-19[6,8,20–22]. In these studies, mortality ranged amongst 6 to 28%. The Spanish Society of Nephrology registry reported a mortality of 23.6% in 535 KT recipients with confirmed COVID-19[7]. Our study cohort has a high mortality, but given the severity of respiratory disease at baseline, it is likely that mortality may have been lower than expected. Our patient cohort presented with ARDS in 80% of cases and they required hospitalization and several pharmacological treatments, including tocilizumab.

Tocilizumab is a potent anti-inflammatory drug indicated for chronic conditions and mainly used in rheumatoid arthritis[12]. In the pathogenesis of severe COVID-19, a cytokine storm occurs, involving release of proinflammatory cytokines including IL-6, tumor necrosis factor-α (TNF-α), and others[23–25]. High plasma levels of cytokines have been found in COVID-19 patients admitted to the ICU, evidencing that the cytokine storm is related with the severity of the disease[9,26]. As dysregulated IL-6 synthesis is thought to play a key role in this cytokine storm, similar to what happens in autoimmune diseases and malignancy, targeting IL-6 is a potential therapeutic approach for severe and critical COVID-19. The largest series reported so far in the general COVID-19 population included 100 patients from Brescia, Italy[17]. After two doses of tocilizumab, 77% of patients improved respiratory distress. In another Chinese experience in 21 patients, the authors reported significant clinical improvement in all patients, including two who were critically ill, within five days after tocilizumab administration[16].

Previous published experience with tocilizumab treatment in transplant recipients is limited to the good outcomes in a liver transplant recipient[18] and a KT one[19], and a short series of 14 cases included in a report from New York[20]. In the latter, Pereira et al used tocilizumab in patients who deteriorated rapidly, with five of them receiving the initial dose after intubation. Of these 14 patients, three died and four remained in the ICU at last follow-up, so it is likely that the final mortality was around 40%, quite similar to ours. In our series, tocilizumab was used in around 20% of all Spanish COVID-19 registered KT recipients[7] and it is likely that this subset comprised the most severely affected patients.

Patients who finally died were more severely ill at the admission, but with similar severity at the time of tocilizumab administration. In addition, we did not find differences regards respiratory improvement 72h after tocilizumab administration between survivors and non-survivors, and, therefore, this might not be an early predictor of good outcome. Previous experiences have reported early response to tocilizumab administration regarding respiratory parameters[16,17], although in the largest series of patients this improvement seems to be more important 10 days after tocilizumab administration[17].

In terms of other drugs, patients who died received more frequently steroids and interferon. It is likely that this simply reflects a higher severity of the disease. We analyzed bacterial infections after tocilizumab

administration and 10% of patients presented with bacterial microbiological finding after tocilizumab infusion.

We observed that most inflammatory markers increased after tocilizumab in the whole cohort, although we could speculate that we had prevented an even higher increase. IL6 levels have been described to increase and then decrease in most patients after starting tocilizumab therapy[15,17]. The explanation is that binding of tocilizumab to IL-6 receptor inhibits receptor-mediated clearance of IL-6, leading to its accumulation in serum. A later decrease of IL-6 by interfering the stimulus for the exaggerated immune response might result in stabilization or improvement of clinical outcome. Additionally, not only IL-6 but also D-dimer may increase up to ten days after tocilizumab treatment[17]. In our study, CRP was the only marker that decreased within 72 hours after tocilizumab administration and differentiated those who finally resolved the infection from those who died. This is not an isolate finding from our data. CRP has been reported to decrease rapidly in patients treated with TCZ for COVID-19[15,17–19] and might help to predict outcomes soon after the treatment.

Our study has limitations. The retrospective nature of the study made it impossible to get the whole set of variables in all patients. Furthermore, we do not have a control group. Criteria for administration was disease severity and patients who received the drug were in worse conditions than an eventual control group not receiving the drug. A propensity cohort was not available for comparison, as very few KT patients with COVID-19 were left untreated when tocilizumab was indicated by center protocols. In fact, when we compared our 80 patients treated with tocilizumab with the 335 admitted ones not treated with tocilizumab, those treated with tocilizumab were more severely ill (more pneumonia, ICU admission and mechanical ventilation) than those left untreated. As a result, direct comparison between treated and untreated subgroups is not useful. Contrarily, the comparison between those who received tocilizumab and died and those who received the drug and survived was very informative. The disease presentation was different between them, and non-survivors were more severely ill since the beginning and received tocilizumab more frequently at the ICU. However, survivors and non-survivors presented equally affected at the time of tocilizumab administration and we could analyze the early response to treatment. Apart from the clinical response, we observed how inflammatory markers increased on both groups except for CRP -whose production is stimulated by IL6-, which decreased more significantly in the group of survivors.

In summary, we present a large cohort of KT patients treated with tocilizumab for COVID-19 management. Mortality in this group was high but it may have been lower than expected given the severity of respiratory disease. CRP levels early after tocilizumab administration together with clinical and radiological response might help to identify patients with poor outcomes. The efficacy of tocilizumab in treating

immunosuppressed patients with COVID-19 who develop ARDS needs to be further assessed in larger randomized controlled trials.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Figure legends

Figure 1. Percentage of patients with severe respiratory situation – defined as PaFi<300 or oxygen saturation <96%- at different points between patients who died and those who survived. Differences were found (p=0.02) only at the time of admission.

PaFi, arterial oxygen partial pressure/fraction of inspired oxygen

**p<0.01

Figure 2. Laboratory findings regarding COVID-19 infection evolution and tocilizumab (TCZ) use. Differences between alive and dead patients at three time points; admission, TCZ administration and 72 h after TCZ. **A**) Ferritin levels significantly increased in survivors along the inpatient stay. **B**) Lactic acid dehydrogenase (LDH) levels increased after TCZ in patients who died and were significantly higher than in survivors at TCZ and after TCZ. **C**) Procalcitonin decreased in survivors and levels after TCZ were higher in patients who died. **D**) Interleukin-6 (IL-6), remained increased during admission, and the increase was especially relevant after TCZ treatment in patients who finally died. **E**) D-dimer was significantly higher in those patients who died at TCZ and after TCZ, but levels increased along time in both subgroups. **F**) C-reactive protein (CRP) initially increased and levels were similar between groups at TCZ treatment, however, although levels decreased after TCZ in all patients, survivors experienced a higher decrease. *Continue lines* represent comparisons at different time points in recipients who survived. *Discontinue lines* represent comparisons at different time points in those who died. *Black asterisks* regard to comparison between different time-points and grey asterisks between dead and alive patients. *p<0.05; **p<0.01; ***p<0.001

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table 1. Baseline characteristics of all KT patients with COVID-19 infection who received tocilizumab as part of their treatment. Comparison between those who survived with those who died.

	All N=80	**Alive N=54**	**Dead N=26**	**p-Value**
Basal characteristics				
Recipient age (years, mean ± SD)	59.3 ± 11.7	57.6 ± 11.6	62.9 ± 11.2	**0.05**
Recipient age ≥60 years (n, %)	42 (52.2)	23 (42.6)	19 (73.1)	**0.01**
Female gender (n, %)	26 (32.5)	23 (33.3)	8 (30.8)	0.81
Caucasian race (n, %)	71 (88.8)	46 (85.2)	25 (96.2)	0.33
Underlying kidney disease				
Diabetic nephropathy (n, %)	15 (18.8)	11 (20.4)	4 (15.4)	0.66
Vascular (n, %)	7 (8.8)	5 (9.3)	2 (7.7)	
Glomerular disease (n, %)	17 (21.3)	12 (22.2)	5 (19.2)	
PKD (n, %)	14 (17.5)	7 (13)	7 (26.9)	
Other (n %)	27 (33.8)	19 (35.2)	8 (30.8)	
Retransplantation (n, %)	21 (26,2)	17 (31.5)	4 (15.4)	0.12
Smoking status (current or past) (n, %)	17 (21.3)	10 (18.5)	7 (26.9)	0.33
Comorbidities				
Lung disease (n, %)	7 (8.8)	4 (7.4)	3 (11.5)	0.54
Ischemic heart disease (n, %)	13 (16.3)	7 (13)	6 (23.1)	0.25
Hypertension (n, %)	71 (88.8)	50 (92.6)	21 (80.8)	0.11
Diabetes mellitus (n, %)	23 (28.7)	38 (70.4)	19 (73.1)	0.80
History of cancer (n, %)	17 (21.5)	9 (17)	8 (30.8)	0.16
Obesity – BMI > 30kg/m^2 (n, %)	14 (17.5)	6 (11.1)	8 (30.8)	**0.03**
ACEi or ARB treatment (n, %)	26 (32.5)	16 (29.6)	10 (38.5)	0.43

Immunosuppression				
Thymoglobulin induction (n, %)	33 (41.3)	24 (44.4)	9 (34.6)	0.34
Calcineurin inhibitor (n, %)	66 (82.5)	46 (85.2)	20 (76.9)	0.36
Prednisone (n, %)	73 (91.3)	50 (92.6)	23 (88.5)	0.54
Mycophenolate (n, %)	64 (80)	44 (81.5)	20 (76.9)	0.63
mTOR inhibitor (n, %)	14 (17.5)	10 (18.5)	4 (15.4)	0.73
At admission				
Time after transplant (months, median [IQR])	72 (16.5-165)	60 (18-143)	90 (16-186)	0.59
Time between onset of symptoms to admission (days, median [IQR])	-4 (-8 to -3)	-4 (-8 to -3)	-4.5 (-7 to -2.5)	0.72
Symptoms				
Fever (n, %)	65 (81.3)	43 (79.6)	22 (84.6)	0.59
Dyspnea (n, %)	46 (57.5)	27 (50)	19 (73.1)	**0.05**
Respiratory symptoms (n, %)	62 (77.5)	42 (77.8)	20 (76.9)	0.93
Gastrointestinal symptoms (n, %)	38 (48.1)	30 (56.6)	8 (30.8)	**0.03**
Respiratory situation				
PaO2/FiO2 (mmHg, median [IQR]) ***(n=38)***	319 (256-434)	324 (274-452)	281 (160-420)	0.26
ARDS moderate-severe (PaFi<200) (n, %)	6 (2.6)	2 (7.4)	4 (36.4)	**0.04**
ARDS (PaFi<300) (n, %)	17 (44.7)	10 (37)	7 (63.6)	0.13
Oxygen saturation (%, median [IQR]) ***(n=40)***	95 (91-97)	96 (93-97)	91 (90-96)	**0.007**
Oxygen saturation<96% (n, %) (n=40)	22 (55)	12 (46.2)	10 (71.4)	0.12
PaFi<300 or Oxygen saturation<96% (n, %) ***(n=78)***	39 (50)	22 (41.5)	17 (68)	**0.02**
Pneumonia demonstrated by X-ray (n, %)	78 (97.5)	52 (96.3)	26 (100)	0.32
Blood test				

White blood cells (x10*3/uL, mean ± SD)	6.8 (3.1)	6.8 (3.2)	6.7 (2.9)	0.55
Neutrophils (x10*3/uL, mean ± SD)	5.6 (3)	5.6 (3.1)	5.6 (2.8)	0.63
Lymphocytes (x10*3/uL, mean ± SD)	0.78 (0.6)	0.8 (0.9)	0.7 (0.4)	0.78
CRP (mg/L, median [IQR])	48.5 (10.1-48.5)	34.1 (9.1-114)	80 (20.8-174.2)	0.09
Procalcitonin (ng/mL, median [IQR])	0.24 (0.1-1.1)	0.19 (0.13-0.8)	0.53 (0.10-1.7)	0.37
IL-6 (pg/mL, median [IQR])	52 (33-110)	50 (28-90)	103 (45-128)	0.13
Log IL-6 (pg/mL, mean ± SD)	4.1 (1.1)	3.9 (0.9)	4.6 (1.2)	0.11
LDH (UI/L, median [IQR])	335 (257-485)	330 (256-479)	366 (257-526)	0.59
Ferritin (ng/mL, median [IQR])	698 (393-1677)	686 (358-1626)	1335 (581-2286)	0.15
D-dimer (mcg/L, median [IQR])	900 (475-1730)	605 (410-1196)	1684 (1109-2322)	**0.001**

SD, standard deviation; PKD, polycystic kidney disease; DM, diabetes mellitus; BMI, body mass index; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; IQR, interquartile range; PaO2, partial pressure of oxygen; FiO2, fraction of inspired oxygen; PaFi, PaO2/FiO2; ARDS, acute respiratory distress syndrome; mTOR, mammalian target of rapamycin; CRP, C-reactive protein; IL-6, interleukin-6; LDH lactic acid dehydrogenase

Table 2. Management and outcomes of KT with COVID-19 infection who received tocilizumab as part of their treatment. Comparison between those who survived with those who died.

	All **N=80**	**Alive** **N=54**	**Dead** **N=26**	**p-Value**
COVID-19 treatment				
Time since admission to tocilizumab treatment (days, median [IQR])	5 (2-8)	4 (2-7)	6 (3-10)	0.13
Time since onset of symptoms to tocilizumab treatment (days, median [IQR])	10 (7-15)	10 (8-15)	12 (6-15.7)	0.55
Tocilizumab >1 dose (%)	16 (20)	**7 (13)**	**9 (34.6)**	**0.02**
Hydroxychloroquine (n, %)	79 (98.8)	54 (100)	25 (96.2)	0.14
Azithromycin (n, %)	59 (73.8)	41 (75.9)	18 (69.2)	0.52
Other antibiotic (n, %)	61 (76.3)	41 (75.9)	20 (76.9)	0.92
Steroids (n, %)	64 (80)	**39 (72.2)**	**25 (96.2)**	**0.01**
Time since admission to steroids treatment (days, median [IQR])	3 (1-7)	3 (1-7)	2 (1-5)	0.85
Ritonavir/lopinavir/remdesvir (n, %)	39 (48.8)	23 (42.6)	15 (57.7)	0.12
Interferon (n, %)	5 (6.3)	**0**	**5 (19.2)**	**0.001**
IV immunoglobulins (n, %)	12 (15)	7 (12.9)	5 (19.2)	0.33
Anakinra (n, %)	6 (7.5)	2 (3.7)	4 (15.4)	0.08
Immunosuppression management				
Only CNI withdrawal (n, %)	4 (5.2)	3 (5.8)	1 (4)	0.73
Only MMF or imTOR withdrawal (n, %)	26 (33.8)	15 (28.8)	11 (44)	0.18
Both CNI and MMF or imTOR withdrawal (n, %)	43 (55.8)	31 (59.6)	12 (48)	0.33
Outcomes and follow-up				
ICU admission (n, %)	24 (30)	**9 (16.7)**	**15 (57.7)**	**<0.001**

Time since hospital admission to ICU admission (days, median [IQR])	7 (3.7-12)	9 (4.5-16.5)	5 (2.5-11)	0.92
Non-invasive mechanical ventilation (n, %)	33 (44)	**17 (33.3)**	**16 (66.7)**	**0.012**
Endotracheal intubation (n, %)	19 (25)	**5 (9.8)**	**14 (56)**	**<0.001**
Acute kidney injury (n, %)	36 (45)	**20 (37)**	**16 (61.5)**	**0.04**
with dialysis need (n, %)	15 (18.8)	**6 (11.1)**	**9 (34.6)**	**0.01**
Acute rejection (n, %)	1 (1.3)	0	1 (3.8)	0.14
Chest X-ray improvement after tocilizumab	32	**30 (56.6)**	**2 (7.7)**	**<0.001**

IQR, interquartile range; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; imTOR, mammalian target of rapamycin inhibitor; ICU, intensive care unit; AKI, acute kidney failure; RRT, renal replacement therapy

Table 3. Cox multivariate analysis showing predictors of patient death.

	HR	CI 95%	p-value
Age >60 years	**3.12**	1.05-9.26	**0.039**
CRP after tocilizumab	**1.01**	1.004-1.024	**0.003**
PaFi<300 or Oxygen saturation<96%	1.73	0.62-4.84	0.294
Obesity	1.65	0.66-4.10	0.278

HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; PaO2, partial pressure of oxygen; FiO2, fraction of inspired oxygen; PaFi, PaO2/FiO2

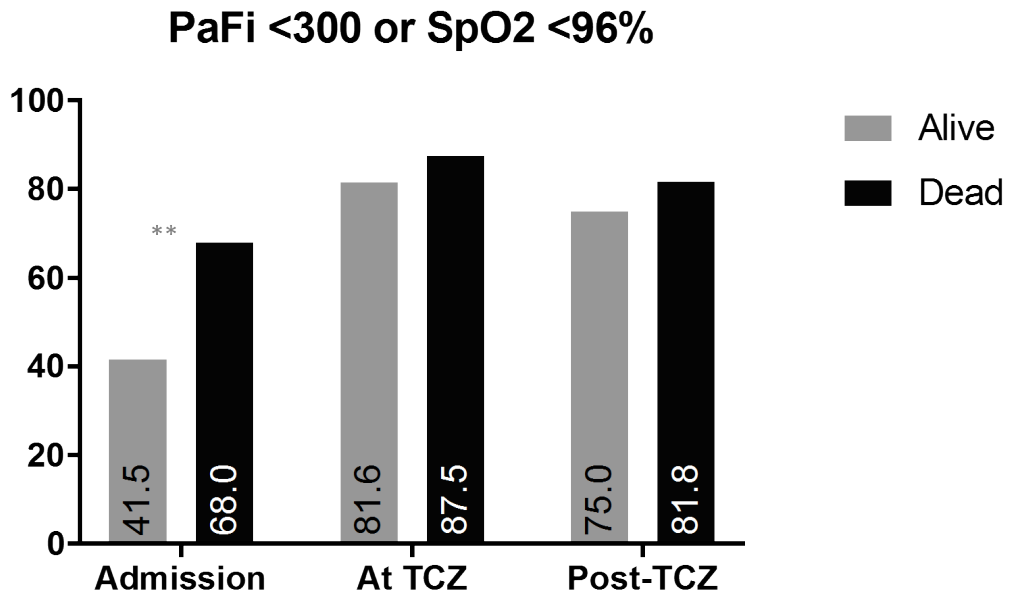

Figure 1. Percentage of patients with severe respiratory situation – defined as PaFi<300 or oxygen saturation <96%- at different points between patients who died and those who survived. Differences were found (p=0.02) only at the time of admission.

PaFi, arterial oxygen partial pressure/fraction of inspired oxygen**.** **p<0.01

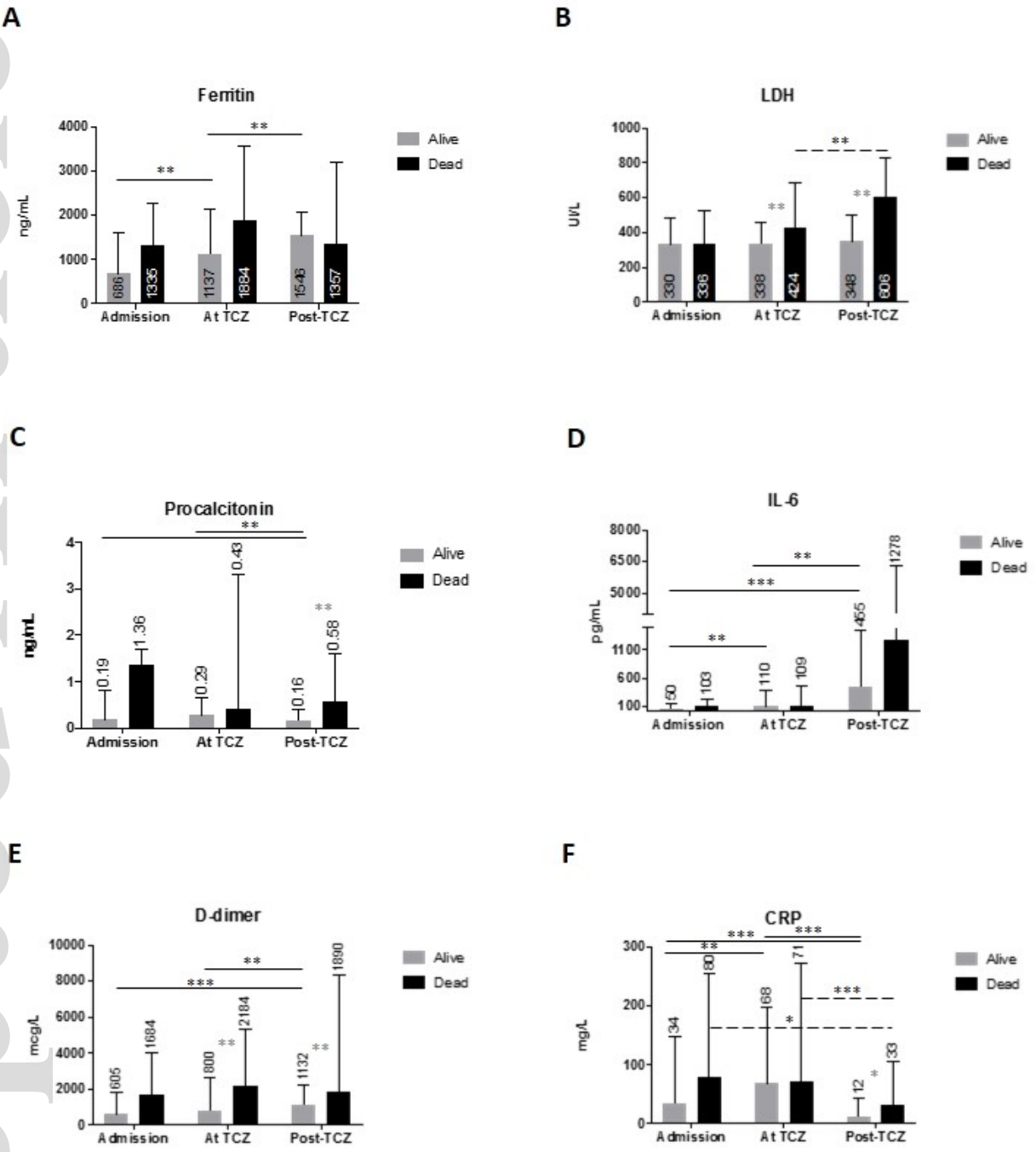

Figure 2. Laboratory findings regarding COVID-19 infection evolution and tocilizumab (TCZ) use. Differences between alive and dead patients at three time points; admission, TCZ administration and 72 h after TCZ. **A**) Ferritin levels significantly increased in survivors along the inpatient stay. **B**) Lactic acid dehydrogenase (LDH) levels increased after TCZ in patients who died and were significantly higher than in survivors at TCZ and after TCZ. **C**) Procalcitonin decreased in survivors and levels after TCZ were higher in patients who died. **D**) Interleukin-6 (IL-6), remained increased during admission, and the increase was especially relevant after TCZ treatment in patients who finally died. **E**) D-dimer was significantly higher in

those patients who died at TCZ and after TCZ, but levels increased along time in both subgroups. **F**) C-reactive protein (CRP) initially increased and levels were similar between groups at TCZ treatment, however, although levels decreased after TCZ in all patients, survivors experienced a higher decrease. *Continue lines* represent comparisons at different time points in recipients who survived. *Discontinue lines* represent comparisons at different time points in those who died. *Black asterisks* regard to comparison between different time-points and grey asterisks between dead and alive patients. *p<0.05; **p<0.01; ***p<0.001