Assessment of the effectiveness of tocilizumab on mortality and progression to mechanical ventilation or intensive care in patients with COVID-19 admitted to a tertiary hospital

Andrea Pinilla Rello, Arantxa Magallón Martínez, Cristina Vicente Iturbe, Angel Escolano-Pueyo, Elena Herranz Bayo, Irene Aguilo Lafarga

ABSTRACT
Objectives The evidence for tocilizumab in the treatment of COVID-19 is contradictory, with some clinical trials showing benefits in regard to progression to mechanical ventilation (MV) and/or mortality. The aim of this study is to evaluate in real clinical practice the effectiveness of tocilizumab in treating COVID-19 and to identify prognostic factors for patient outcomes.

Methods This was an observational, retrospective study of COVID-19 patients treated with tocilizumab between March 2020 and February 2021 in a tertiary hospital. Variables were demographics, comorbidities, vital signs, analytical parameters, COVID-19 treatment, progression to MV, intensive care unit (ICU) admission, hospital stay, and mortality.

Results A total of 685 patients (64.7% men, median 68 years) were included. Overall mortality was 23.4% (14.2% in the first 14 days post-tocilizumab) and 93.3% in patients with MV and/or in the ICU at 14 days post-tocilizumab. In addition, 61.5% of discharges occurred during the same period. In patients who died, statistically significant differences were observed in the baseline analytical parameters of C-reactive protein (CRP), D-dimer and higher lactate dehydrogenase (LDH) (p<0.05).

Conclusions In most patients the clinical results of tocilizumab were observed at 14 days post-administration and could benefit from earlier administration of treatment. Baseline levels of CRP, D-dimer and LDH could be prognostic factors for the evolution of the COVID-19 patient.

INTRODUCTION
The COVID-19 pandemic is a worldwide public health problem. There is still no treatment with proven efficacy to prevent mortality in patients with severe COVID-19 pneumonia, with the exception of corticosteroids in selected patients.1 2 Severe COVID-19 is associated with elevated inflammatory markers due to cytokine release syndrome. Interleukin 6 (IL-6) has been identified as a key cytokine in the cytokine storm associated with COVID-19,3 with tocilizumab being an anti-IL-64 antibody used for the treatment of these patients.

At the beginning of the COVID-19 pandemic, the available evidence on tocilizumab in COVID-19 was conflicting. In a meta-analysis including randomised controlled trials (RCTs) developed up to January 2021, no significant benefit was found in post-tocilizumab mortality among patients with COVID-19 (pooled hazard ratio 0.83, 95% CI 0.66 to 1.05; n=2057); however, the drug appeared to reduce the likelihood of progression to mechanical ventilation (MV).3

These results were variable according to the target population of each RCT, so that in non-critical patients hospitalised with COVID-19 pneumonia who did not receive MV, the trend to decrease the risk of MV at 144 and 28 days6 mentioned above was observed. However, an RCT involving critically ill or critically ill patients with COVID-19 was stopped early because of increased mortality at 15 days in patients treated with tocilizumab (16.9% vs 3.1% in the control group).7

The REDMAP-CAP trial8 was the first to demonstrate the benefit of tocilizumab. This trial concluded that in critically ill adult patients with COVID-19 receiving organ support, treatment with tocilizumab improved outcomes, including survival, since mortality was reduced by an additional 7% (28.0% vs 35.8% control). Another trial supporting these results was the RECOVERY trial,9 which demonstrated that tocilizumab in patients with COVID-19, hypoxia and inflammation achieved an absolute reduction in mortality by 4% (RR...
0.86, 95% CI 0.77 to 0.96), shortens time to hospital discharge, and reduces the need for MV.

In the prospective meta-analysis published in July 2021 by Shankar et al., based on 10,930 patients hospitalised for COVID-19 from 27 randomised clinical trials, the administration of anti-IL-6 compared with usual treatment or placebo was associated with lower all-cause mortality at 28 days. This was key to demonstrating and consolidating the benefit of tocilizumab in these patients.

There is published evidence from retrospective studies based on clinical practice in hospitalised patients. In a retrospective study in Spain, tocilizumab was associated with a lower risk of death or intensive care unit (ICU)/death in patients with higher C-reactive protein (CRP) levels (>150 mg/L), but no significant effect was found in patients with low CRP levels. In another retrospective study in the USA, the administration of tocilizumab was associated with a low rate of clinical improvement 7 days after administration in critically ill patients, lower white blood cell count (p=0.038) and lactate dehydrogenase (LDH) (p=0.015) at the time of drug administration, as well as a shorter time from the start of oxygen supplementation to drug administration (p=0.044), which were significantly associated with clinical improvement post-tocilizumab.

In this context, and in view of the persistence of COVID-19 in the population with continuous peaks in hospitalised patients, the aim of our study was to describe the use and clinical outcomes of tocilizumab by evaluating its effectiveness, in terms of mortality and progression to MV and/or ICU, in COVID-19 patients in the daily clinical practice of a tertiary hospital, as well as to identify possible prognostic factors for patient outcomes after receiving tocilizumab.

METHODS
This was an observational, retrospective study of all patients over 18 years of age diagnosed with COVID-19, which was confirmed by PCR or antigen test, and treated with tocilizumab between March 2020 and February 2021 in a tertiary hospital.

Patient identification was obtained from the outpatient module of the pharmacy service (Farmatools) as well as data regarding the drug and doses received. The electronic medical record was consulted to obtain the study variables.

The demographic variables collected included age, sex, comorbidities and Charlson Index. Liver failure was assessed according to Child Pugh and moderate-to-severe renal failure according to the consensus of the Spanish Society of Nephrology.

Regarding the infection process, we included the COVID-19 confirmation date, vital signs, and baseline pre-tocilizumab analytical parameters: heart rate, temperature, systolic blood pressure, diastolic blood pressure, oxygen saturation, CRP, ferritin, IL-6, D-dimer and LDH. These analytical parameters were also collected at 48 hours and 7 days post-tocilizumab. In addition, the need for oxygen supplementation at the time of drug administration was recorded.

With respect to treatment, the following were collected: date of symptom onset, days from symptom onset until receiving tocilizumab, days from hospital admission until administration of tocilizumab, administration of second dose and time between both (hours), and other drugs administered for COVID-19.

It should be mentioned that, in our centre, antibiotic treatment (specifically ceftriaxone for its preferred use in treating pneumonia and azithromycin for its immunomodulatory action) was started in COVID-19 patients according to clinical criteria based on chest x-ray, symptoms, comorbidities and patient history to avoid bacterial superinfection.

As clinical outcomes, effectiveness was evaluated based on mortality, the need for ICU admission and/or MV. These variables were collected 14 and 28 days after the first dose of tocilizumab.

The improvement or normalisation of baseline analytical parameters at 48 hours and 7 days post-tocilizumab was also studied. In addition, the profile of patients in whom greater effectiveness was observed was analysed, highlighting comorbidities and the time of tocilizumab administration.

Overall mortality (at 14 and 28 days, or later during admission, and whether or not death took place in the ICU), hospital stay and ICU stay, if applicable, were recorded. The date of discharge was also collected (if before 14 days, if at 28 days (period 15–28 days) or if it took place more than 28 days after admission).

The variables were collected in Microsoft Excel and the statistical analysis was performed with SPSS Statistics 22. For qualitative variables, percentages were detailed, and χ² or Fisher’s exact test were performed. For quantitative variables, measures of central tendency were provided, and we studied whether the variables followed a normal distribution (Kolgomorov-Smirnov test) and, according to normality, Student’s t-test or Mann-Whitney U test were performed.

The study was approved by the Clinical Research Ethics Committee of Aragón (CEICA) (reference P121/128).

RESULTS
A total of 685 COVID-19 patients treated with tocilizumab were included, 64.7% of whom were men. Demographic characteristics, comorbidities, treatment for COVID-19 infection and results of tocilizumab according to mortality are shown in table 1.

According to the need for MV and/or admission to the ICU post-tocilizumab, the characteristics of the patients, the treatment received for COVID-19 and outcomes of tocilizumab are shown in table 2.

Thirty-three patients (4.8%) did not receive oxygen therapy before receiving tocilizumab.

The treatment received by almost all patients for COVID-19 infection was systemic corticosteroids, low molecular weight heparin (99.0% and 96.8%) and oxygen therapy pre-tocilizumab (95.2%) (tables 1 and 2). As for oxygen therapy, patients who did not die or those who did not receive MV and/or ICU were mostly on nasal goggles or reservoir (79.0% and 82.8%, respectively), while those who died and those who received MV and/or ICU required MV to a greater extent (23.8% and 46.2%, respectively), these differences being statistically significant (tables 1 and 2);

According to clinical criteria to prevent bacterial superinfection during COVID-19 infection, 52.4% of patients treated with tocilizumab received antibiotics (42.2% ceftriaxone and 10.2% azithromycin) (tables 1 and 2).

Baseline vital signs, baseline, 48 hours post-tocilizumab and 7 days post-tocilizumab analytical parameters are shown in table 3.

The median number of days of hospital admission was 12 (1–134). A total of 325 (76.6%) patients were discharged after admission for COVID-19 while 160 (23.4%) died in hospital, occurring in 60.1% (97/160) of cases during the first 14 days post-tocilizumab. Similarly, 61.5% of discharges (323/525) occurred in the first 14 days post-tocilizumab. The clinical outcomes for tocilizumab are shown in table 4.
DISCUSSION

Tocilizumab remains a therapeutic option for COVID-19 patients, with evidence generated in actual clinical practice, beyond clinical trials, being essential in order to know the characteristics of treated patients and the effectiveness of treatment.

The comorbidities of COVID-19 patients have been studied throughout the pandemic. In the study by Klopfenstein et al., 15 60.0% of patients receiving tocilizumab had hypertension (HT), 40% cardiovascular disease (CVD) and 16.7% diabetes mellitus (DM); in the study by Moreno-Pérez et al., 16 33.3% had CVD, 25%DM and 15.6% HT; and in the study by Toniasi et al., 17 46% had HT, 17%DM and 13% CVD. The study by Li et al. 18 had similar findings, with 46.1% with HT, 25.6%DM and 25.6% CVD. In our study, DM is present as the most prevalent comorbidity in 24.1% of patients, followed by pulmonary disease at 16.6% and neoplasms at 10.8%, the latter two being

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics, comorbidities, and treatment for COVID-19 infection and results of tocilizumab therapy according to mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients n=685</td>
</tr>
<tr>
<td>Age (mean (SD))</td>
<td>68 (14)</td>
</tr>
<tr>
<td>Sex (n (%))</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>443 (64.7%)</td>
</tr>
<tr>
<td>Comorbidities (n (%))</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>71 (10.4%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Peripheral vascular disease</td>
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<tr>
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<tr>
<td>Diabetes</td>
<td>165 (24.1%)</td>
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<tr>
<td>Moderate or severe renal insufficiency</td>
<td>73 (10.7%)</td>
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<tr>
<td>Solid organ transplantation</td>
<td>7 (1.0%)</td>
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<td>Leukaemia/multiple myeloma</td>
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<td>6 (0.9%)</td>
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<tr>
<td>Neoplasm</td>
<td>14 (10.8%)</td>
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<tr>
<td>Metastases</td>
<td>13 (1.9%)</td>
</tr>
<tr>
<td>Charlson Index (mean (SD))</td>
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<tr>
<td>Tocilizumab second dose administration (n (%))</td>
<td>29 (4.2%)</td>
</tr>
<tr>
<td>Hours since first dose (median, range)</td>
<td>48 (12–288)</td>
</tr>
<tr>
<td>Concomitant treatment for COVID-19 (n (%))</td>
<td></td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>663 (96.8%)</td>
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<td>Hydroxychloroquine</td>
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<td>Corticosteroids (n (%))</td>
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<tr>
<td>Results of tocilizumab (n (%))</td>
<td></td>
</tr>
<tr>
<td>Need for MV and/or admission to ICU</td>
<td>104 (15.2%)</td>
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<tr>
<td>Median (range)</td>
<td></td>
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<tr>
<td>Days from admission–administration of tocilizumab</td>
<td>2 (0–183)</td>
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<tr>
<td>Days since start symptoms–administration of tocilizumab</td>
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<td>Days of hospital admission</td>
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ICU, intensive care unit; MV, mechanical ventilation.
comorbidities not mentioned in the studies described. In our case, CVD included acute myocardial infarction (10.4%) and congestive heart failure (6.9%), being overall (17.3%) one of the most prevalent comorbidities as in previous studies. Statistically significant differences were observed in the presence of DM (p=0.000), acute myocardial infarction (p=0.005), congestive heart failure (p=0.001), pulmonary disease (p=0.006) and moderate/severe renal failure (p=0.000), between patients who died and those who did not, with these diseases being more prevalent in patients who died (table 1). On the other hand, in our study, connective tissue disease had a prevalence of 5.5% and is the only comorbidity that presented statistical significance according to mortality (p=0.016), and according to the need for MV and/or ICU (p=0.015), being more prevalent in the group of deceased patients (9.4% vs 4.4%, table 1) and in those who required MV and/or ICU admission (10.6% vs 4.6%, table 2).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Demographic characteristics, comorbidities, treatment for COVID-19 infection and results of tocilizumab according to MV and/or ICU admission</th>
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<td>Results of tocilizumab</td>
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<tr>
<td>Death at 14 days</td>
<td>97 (14.2%)</td>
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<tr>
<td>Death at 28 days</td>
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ICU, intensive care unit; MV, mechanical ventilation.
On the other hand, in relation to comorbidities, it is necessary to mention that the physician in charge assessed each patient individually before the administration of tocilizumab, evaluating the risk/benefit of the treatment; tocilizumab was administered in all patients where the benefit outweighed the risk, including patients with dementia (3.5%), with moderate or severe renal failure (10.7%) and with moderate severe hepatic failure (0.1%) (tables 1 and 2), since in all cases the pathology was stable and monitored closely. Therefore, according to clinical judgement, they did not lead to a poor prognosis, in agreement with the

<table>
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<tr>
<th>Table 3</th>
<th>Baseline vital signs and baseline analytical parameters, at 48 hours post-tocilizumab and at 7 days post-tocilizumab, according to mortality and the need for MV and/or ICU</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Baseline vital signs pre-tocilizumab (mean (SD))</td>
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<tr>
<td>Cardiac output (L/min)</td>
<td>82 (16)</td>
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<tr>
<td>Temperature (°C)</td>
<td>37.0 (4.4)</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>129 (20)</td>
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<td>Diastolic blood pressure (mm Hg)</td>
<td>71 (13)</td>
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<tr>
<td>Oxygen saturation (%)</td>
<td>94 (3)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td></td>
</tr>
<tr>
<td>Ferritin (n=564)</td>
<td>1022.4 (1.4–4494.3)</td>
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<tr>
<td>IL-6 (n=446)</td>
<td>138.6 (2.9–7427)</td>
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<tr>
<td>D-Dimer (n=555)</td>
<td>1013 (142–131420)</td>
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<tr>
<td>LDH (n=560)</td>
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<td>Analytical parameters 48 hours post-tocilizumab (median (range))</td>
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<td>C-reactive protein (n=561)</td>
<td>2.8 (0.1–33.1)</td>
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ICU, intensive care unit; IL-6, interleukin-6; LDH, lactate dehydrogenase; MV, mechanical ventilation.
recommendations on the treatment of COVID-19 infection issued by the Spanish Agency of Medicines and Health Products, based on its technical data sheet, 4 since the use of tocilizumab was not recommended in the presence of comorbidity that could lead, according to clinical judgement, to a poor prognosis. 19 It was also not recommended in patients with aspartate transaminase/alanine transaminase (AST/ALT) values above 10 times the upper limit of normal, but none of the patients met this last condition, since their disease was stable as we have already detailed. 19

Regarding the time of administration, the mean number of days from the onset of the disease to the administration of tocilizumab was 10 days in the study by Moreno-Pérez et al., 16 11 days in the study by Smoke et al. 11 and 12 days in the study by Toniati et al. 17 In our study, the result was slightly lower, with the median number of days from symptom onset to administration being 9 days. The administration of tocilizumab in our study was earlier than in the studies by Toniati et al. 17 and Martínez-Sanz et al., 1 since the median number of days from patient admission to administration of tocilizumab was 5 and 4 days, respectively, and in our centre 3 days.

Regarding mortality and the need for MV and/or admission to the ICU, in the study by Klopfenstein et al., 13 mortality and/or the need for MV was lower in patients who received tocilizumab (26.7% vs 52.3%, p=0.009). In the study by Moreno-Perez et al., 16 mortality was 12.9%, and 49.4% of patients required MV while in the study by Menzella et al., 20 mortality was 24%, and the need for MV and/or mortality was 39%. In the study by Martínez-Sanz et al., 1 mortality was 14.7%, and 6.7% were admitted to the ICU. In the study by Li et al. 18 30.8% of patients died. In these studies, mortality ranged from 12.9–39%, while in our study mortality was 23.4%, a result at the midpoint of the previous studies and very similar to that of Menzella et al. 20

Regarding the need for MV and/or ICU, statistically significant differences were observed (p=0.000) between patients who died and those who survived, with these needs being higher in death (31.9% vs 10.1%).

Regarding the temporality of clinical outcomes, in the meta-analysis by Shankar et al., 16 they observed that administration of IL-6 antagonists was also associated with less progression to invasive MV or death, and with a greater likelihood of being discharged alive at 28 days. In our study, 14.2% of patients died at 14 days post-tocilizumab and 6.7% at 28 days, with more than twice as many patients dying at 14 days (tables 2 and 4). In addition, 61.5% of patients were discharged in these first 14 days post-tocilizumab, so that, in the majority of patients, clinical outcomes were observed in the first 14 days post-administration (table 4). Therefore, we observed in our centre an earlier administration that could have benefitted the patients when observing the clinical results in these first 14 days post-tocilizumab with mortality values intermediate to other studies, closer to the lower range of the mentioned studies, and overall only 15.2% of the patients required MV and/or ICU.

In relation to this, comparing patients who received MV and/or ICU and those who did not, the differences were statistically significant in mortality both at 14 days (p=0.023) and at 28 (p=0.000), being at 14 days an absolute difference (more than 90.0%) in patients with MV and/or ICU (93.3% vs 0.0%) and almost six times more at 28 days (21.2% vs 4.1%). Patients with MV and/or ICU were admitted for a median of 37 days versus 11 days in those without, this difference being very notable and statistically significant (p=0.000).

The reduction in progression to MV and/or ICU could be related to the administration of tocilizumab, as in the mentioned studies; however, since we do not have a comparator control group, we cannot state this with certainty, although we did observe that after the administration of tocilizumab, 84.8% (525/685) of the patients did not progress to MV and/or ICU.

The median number of days for hospitalisation was 12, a result higher than that of Sarhan et al., 21 with a median of 10 days. The maximum hospital stay in our study was 134 days, when following up during the entire hospital stay, including the time in ICU which is very long in these patients; in contrast, in the study by Sarhan et al., 21 the maximum range was 16 days, as they included patients during June 2020, and they were only followed up during that period of time. In addition, it should be mentioned that the lowest range of days of hospital admission was 1 day, since some patients died the day after admission. In relation to this, in the prospective, single-centre, open-label study by Broman et al., 22 comparing tocilizumab with standard therapy, the median duration of hospital admission was 9 days (IQR 7–12 days) for patients receiving tocilizumab and 12 days (IQR 9–15 days) for the control group, these differences being statistically significant (p=0.014). This result was also observed in the RECOVERY trial, 8 so that both concluded that tocilizumab reduced hospital stay. In our study, since we do not have a control group, we cannot establish this relationship, which would be a limitation.

After the second dose of tocilizumab, no statistically significant differences were found between patients who died and those who did not (p=0.582) or between those who received MV and/or ICU and those who did not (p=0.602) (tables 1 and 2). The result of our study is slightly superior to that observed by Li et al., 18 since 2.6% of patients received a second dose in the following 12 hours. In contrast, in the studies by Toniati et al. 17 and Klopfenstein et al., 13 almost all patients received second doses; specifically, in Toniati et al. 17 all patients received a second dose being the optional third dose, and in Klopfenstein et al. 13 90.0% of patients in the tocilizumab group (27/30) received a second dose 24–72 hours after the first dose. In these studies, it is possible to evaluate the results based on the two doses, but in our study, the small number of patients who received a second dose (4.2%) limits the possibility of evaluating this therapeutic option, so no conclusions can be drawn.

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**Table 4 Clinical outcomes of tocilizumab and mortality during hospitalisation**

<table>
<thead>
<tr>
<th>Clinical outcomes of tocilizumab (n=685)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for MV</td>
<td>75 (10.9%)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>86 (12.6%)</td>
</tr>
<tr>
<td>Death</td>
<td>97 (14.2%)</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>323 (47.2%)</td>
</tr>
</tbody>
</table>

Results after 28 days

| Need for MV | 64 (9.3%) |
| ICU admission | 72 (10.5%) |
| Death | 46 (6.7%) |
| Hospital discharge | 132 (19.3%) |

Results >28 days

| Death | 17 (2.5%) |
| Hospital discharge | 70 (10.2%) |
| Overall mortality | 160 (23.4%) |
| In-hospital mortality | 113 (16.5%) |
| Mortality in ICU | 47 (6.9%) |

ICU, intensive care unit; MV, mechanical ventilation.
The analytical parameters related to inflammation and infection have been the target of study since the beginning of the pandemic to find out how they influence the disease. In the study by Klopfenstein et al.15 on admission, ferritin, D-dimer and LDH parameters were higher than those of the control group (1496 ng/ml vs 952 ng/ml, 8344 mcg/l vs 2532 mcg/l, 482 U/l vs 409 U/l, respectively) and the difference was statistically significant (p=0.009, p=0.033 and p=0.024). In the Chachar et al.16 study, a downward trend in D-dimer, CRP and serum ferritin levels post-tocilizumab was observed. On the other hand, Menzella et al.17 observed that patients had significantly lower CRP values 72 hours and 7 days post-tocilizumab compared with those who received standard treatment (p=0.02 and p=0.01). Li et al.18 compared the analytical parameters between patients who died and those who improved after tocilizumab, as we did in our study, and observed statistically significant differences in the values of procalcitonin (p=0.0003), LDH (p=0.0056) and IL-6 (p=0.0191), with higher values in those who died. In contrast, in our study, we observed statistically significant differences in the baseline values of CRP (p=0.045), D-dimer (p=0.000) and LDH (p=0.000), these values being higher in the deceased, coinciding with the studies already mentioned, with the exception of ferritin where the baseline values were higher in patients who did not die (table 3). Similar to the study by Menzella et al.17 we studied the analytical parameters at 48 hours and 7 days post-tocilizumab; in our case, we observed statistically significant differences at 48 hours post-tocilizumab again in D-dimer and LDH in patients who died (p=0.018 and p=0.000, respectively) and at 7 days in D-dimer (p=0.000), with higher values in this same group. This was also observed in IL-6 values at 48 hours post-tocilizumab (p=0.000), being almost three times higher median in the deceased, but at 7 days the statistical analysis could not be performed since IL-6 values were collected in an unbalanced sample of patients corresponding mainly to the no MV and/or ICU and no death group. This is due to the fact that the analytical parameters at 48 hours and 7 days could not be collected in all patients, as they were not requested in the analyses performed during their hospital stay, this being a limitation of the study.

Depending on whether patients received MV and/or ICU, statistically significant differences were also observed in baseline D-dimer and LDH (p=0.036 and p=0.000, respectively), D-dimer and LDH 48 hours post-tocilizumab (p=0.019 and p=0.000, respectively) and 7 days post-tocilizumab (p=0.000 in both), with higher values in patients with MV and/or ICU. Ferritin 48 hours post-tocilizumab and 7 days post-tocilizumab also showed statistically significant differences (p=0.026 and p=0.001, respectively), with higher values in patients with MV and/or ICU being a possible prognostic value in this group of patients since no differences were observed depending on whether they died or not.

The main limitation of this study is that it is retrospective, so it presents weaknesses in determining whether the characteristics associated with the results obtained may have a causal relationship or are circumstantial. Another possible limitation is that we did not study the safety of treatment with tocilizumab because we focused on its effectiveness, and to study its effectiveness we needed to have a comparator control group; however, it seemed interesting to analyse the profile of tocilizumab use and to know its effectiveness by comparing patients according to clinical outcomes (mortality or need for MV/ICU), providing evidence of the use of tocilizumab from another point of view.

However, the power provided by the large sample size and the fact that it reflects routine clinical practice in COVID-19 patients are strengths of the study; it allows us to describe the characteristics of the patients treated and the patient profile that can benefit most from this treatment, as well as provide evidence for future prospective studies that could be considered, in order to minimise the contradictory evidence available on treatment with tocilizumab in COVID-19 patients.

Based on the observed data, we observed that the first 14 days after early administration of tocilizumab are key in the patient’s evolution, since it is during this period that most patients require MV and/or admission to the ICU, die, or are discharged after resolution of the COVID-19 infection. In relation to this, we observed that early administration of tocilizumab could delay progression to MV and/or ICU, in addition to benefiting patients in terms of mortality.

Moreover, we observed that baseline CRP, D-dimer and LDH levels could be prognostic factors for the evolution of COVID-19 patients because they are higher in deceased patients; therefore, it would be recommended to take them into account and initiate treatment with tocilizumab as soon as possible based on these parameters in order to improve the prognosis of these patients.


