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ORIGINAL ARTICLE

Analysis of the effectiveness of the administration of tocilizumab in patients admitted to an intermediate respiratory care unit with a diagnosis of severe coronavirus disease 2019 pneumonia: a prospective observational study with propensity score matching

Análisis de la efectividad de la administración de tocilizumab en pacientes ingresados en una unidad de cuidados respiratorios intermedios con diagnóstico de neumonía grave por enfermedad por coronavirus 2019: un estudio observacional prospectivo con pareamiento por puntaje de propensión

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Abstract

Background: *The use of tocilizumab might counteract the inflammatory hyperresponsiveness associated with the most severe cases of coronavirus disease 2019 (COVID-19) and thus improve the vital prognosis, although this fact is controversial in the scientific literature.* **Objectives:** *We evaluated the effects of tocilizumab therapy in semi-critical patients with severe COVID-19 pneumonia.* **Material and method:** *We conducted a prospective observational study in patients admitted to an intermediate respiratory care unit (IRCU) for severe COVID-19 pneumonia requiring non-invasive respiratory support (NIRS). We established two groups of patients according to whether or not they had received tocilizumab, respectively. In order to reduce the derived selection bias, we used the propensity score matching. The most important outcomes were death, receipt*

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of invasive mechanical ventilation (IMV), and the composite of receipt of IMV or death (clinical failure). **Results:** *We included 1306 patients: 532 (40.7%) received tocilizumab and 774 (59.3%) did not receive tocilizumab. We matched 321 patients in each group. After matching, we did not detect any statistically significant differences between the two groups in mortality within 30 days (36/321 vs. 35/321; 11.2% vs. 10.9%) (hazard ratio [HR] = 1.03; HR 95% confidence interval [CI] = 0.65-1.64; p = 0.896) (odds ratio [OR] = 1.03; OR 95% CI = 0.63-1.69; p = 0.900), nor in the probability of receipt of IMV within 30 days (89/301 vs. 76/302; 29.6% vs. 25.2%) (HR = 1.22; HR 95% CI = 0.90-1.66; p = 0.194) (OR = 1.25; OR 95% CI = 0.87-1.79; p = 0.225), nor in the probability of clinical failure within 30 days (104/321 vs. 89/321; 32.4% vs. 27.7%) (HR = 1.22; HR 95% CI = 0.92-1.62; p = 0.167) (OR = 1.25; OR 95% CI = 0.89-1.75; p = 0.197). We also did not observe any statistically significant difference in in-hospital mortality (59/321 vs. 49/321; 18.4% vs. 15.3%) (OR = 1.25; OR 95% CI = 0.83-1.89; p = 0.291).* **Conclusion:** *In our sample of patients admitted to the IRCU for severe COVID-19 pneumonia under NIRS, tocilizumab therapy did not demonstrate any effectiveness in terms of reducing the probabilities of death, receipt of IMV, and clinical failure.*

Keywords: *Tocilizumab. COVID-19 pneumonia. Intermediate respiratory care unit. Non-invasive respiratory support. Mortality. Invasive mechanical ventilation. Clinical failure.*

Resumen

Antecedentes: *El uso de tocilizumab podría contrarrestar la hiperrespuesta inflamatoria asociada con los casos más graves de enfermedad por coronavirus 2019 (COVID-19) y así mejorar el pronóstico vital, aunque este hecho es controvertido en la literatura científica.* **Objetivos***: Evaluamos los efectos de la terapia con tocilizumab en pacientes semicríticos con neumonía grave por COVID-19.* **Material y método:** *Realizamos un estudio observacional prospectivo en pacientes ingresados en una unidad de cuidados respiratorios intermedios (UCRI) por neumonía grave por COVID-19 con necesidad de soporte respiratorio no invasivo (SRNI). Establecimos dos grupos de pacientes según si éstos habían recibido o no tocilizumab, respectivamente. Para la disminución del sesgo de selección derivado, efectuamos la técnica de pareamiento por puntaje de propensión. Las variables de resultado más importantes fueron la muerte, la recepción de ventilación mecánica invasiva (VMI) y la composición de recepción de VMI o muerte (fracaso clínico).* **Resultados:** *Incluimos 1306 pacientes: 532 (40,7%) recibieron tocilizumab y 774 (59,3%) no recibieron tocilizumab. Pareamos 321 pacientes en cada grupo. Después del pareamiento, no se detectaron diferencias estadísticamente significativas entre ambos grupos en la mortalidad hasta los 30 días (36/321 vs. 35/321; 11,2% vs. 10,9%) (HR = 1,03; IC 95%HR = 0,65-1,64; p = 0,896) (OR = 1,03; IC 95%OR = 0,63-1,69; p = 0,900), ni en la probabilidad de recepción de VMI hasta los 30 días (89/301 vs. 76/302; 29,6% vs. 25,2%) (HR = 1,22; IC 95%HR = 0,90-1,66; p = 0,194) (OR = 1,25; IC 95%OR = 0,87-1,79; p = 0,225) ni en la probabilidad de fracaso clínico hasta los 30 días (104/321 vs. 89/321; 32,4% vs. 27,7%) (HR = 1,22; IC 95%HR = 0,92-1,62; p = 0,167) (OR = 1,25; IC 95%OR = 0,89-1,75; p = 0,197). Tampoco se observaron diferencias estadísticamente significativas en la mortalidad intrahospitalaria (59/321 vs. 49/321; 18,4% vs. 15,3%) (OR = 1,25; IC 95%OR = 0,83-1,89; p = 0,291).* **Conclusiones:** *En nuestra muestra de pacientes ingresados en UCRI por neumonía grave por COVID-19 bajo SRNI, la terapia con tocilizumab no mostró efectividad alguna en términos de reducción de probabilidades de muerte, recepción de VMI y fracaso clínico.*

Palabras clave: *Tocilizumab. Neumonía por COVID-19. Unidad de cuidados respiratorios intermedios. Soporte respiratorio no invasivo. Mortalidad. Ventilación mecánica invasiva. Fracaso clínico.*

Introduction

In stage IIb of coronavirus disease 2019 (COVID-19), a localized inflammatory response is initiated in the lungs, leading to significant acute hypoxemia[1] with the need for conventional oxygen therapy (COT) (in ascending order: conventional nasal cannulas [NC], single mask or Venturi mask, and reservoir mask) in a conventional hospitalization area[2]. Progression of inflammation in stage III (systemic inflammatory response syndrome: "cytokine storm") results in acute respiratory distress syndrome (ARDS)[1,3] with the need for non-invasive respiratory support (NIRS) (high-flow nasal cannulas [HFNC], continuous positive airway pressure [CPAP], and/or bilevel positive airway pressure [BPAP]) or invasive respiratory support (IRS) (invasive mechanical ventilation [IMV] through orotracheal intubation [OTI] or tracheostomy and veno-venous extracorporeal

membrane oxygenation [ECMO]), as required, in an intermediate respiratory care unit (IRCU) or intensive care unit (ICU), respectively[2]. Mortality reaches 49.0% among intubated patients (OTI)[3,4].

The use of anti-inflammatory/immunomodulatory therapies such as glucocorticoids, tocilizumab, anakinra, and baricitinib may decrease the inflammatory hyperresponsiveness associated with the most severe cases of COVID-19 and, thereby, improve the vital prognosis[1,3,5-13]. The use of dexamethasone has been shown to reliably decrease mortality in patients diagnosed with COVID-19 pneumonia who present with hypoxemia and, therefore, require COT, in less severe cases; or NIRS or IRS, in more severe cases. In these latter cases, the mortality-decreasing effect of dexamethasone is of greater magnitude[6,7]. However, this survival benefit of tocilizumab, a recombinant monoclonal IgG1 antibody antagonist of the interleukin-6 receptor (both membrane-bound and soluble), is controversial[5]. There is a large discrepancy, with studies finding conclusive results in favor of a decrease in mortality with tocilizumab, such as the REMAP-CAP[8] and, especially, RECOVERY[9] trials; and others against this decrease in mortality (without statistically significant differences), such as the BACC Bay[14], EMPACTA[15], COVACTA[16], and REMDACTA[17] trials.

To clarify the effect of tocilizumab on mortality among patients hospitalized for severe COVID-19 pneumonia, we conducted an observational study in an IRCU of a COVID-19 monographic hospital. We also aimed to analyze the effect of tocilizumab on the probability of receiving IMV and on the composite probability of receiving IMV or death.

Methods

Study design and participants

Our study had a prospective longitudinal analytical observational design, that is, a cohort study ("the Zendal IRCU cohort").

This study was conducted at the IRCU of the Hospital de Emergencias Enfermera Isabel Zendal (Nurse Isabel Zendal Emergency Hospital) (HEEIZ) in Madrid (Spain)[18] between December 14th, 2020, and September 28th, 2021 (first with the alpha variant and then with the delta variant of severe acute respiratory syndrome coronavirus 2)[19].

We included adult patients aged ≥ 18 years old with a microbiologically confirmed diagnosis of severe COVID-19 pneumonia who came to require NIRS in one or more of the following three types: HFNC, CPAP, or BPAP.

The need for NIRS was established by the presence of severe acute hypoxemia (SpO_2 < 92%, PaO_2 < 67 mmHg, and/or PaO_2/FiO_2 ratio < 200) and/or inadequate respiratory mechanics (tachypnea ≥ 30 breaths/min, significant use of accessory respiratory musculature, thoraco-abdominal respiratory desynchronisation, and/or pronounced dyspnea) that was not controllable with COT devices in a conventional hospitalization area after an escalation of these in the following order: NC, single mask or Venturi mask, and reservoir mask. The requirement of COT at an FiO_2 ≥ 0.40 to achieve an SpO_2 ≥ 92% constituted a criterion for escalation to NIRS[2].

As NIRS, all patients used HFNC, either alone or in combination with CPAP or BPAP.

Tocilizumab was generally administered to patients with a value of C-reactive protein (CRP) ≥ 75 mg/L on admission to the IRCU, based on the RECOVERY trial[9,20,21].

Procedures

We established two groups of patients according to whether or not they had received tocilizumab. All patients had received standard of care (SOC).

All patients admitted to the IRCU were escalated from COT to NIRS.

As part of our IRCU protocol[18], from admission to the IRCU, all patients received dexamethasone in intravenous boluses of 20 mg/24 h for the first 5 days, followed by 10 mg/24 h for the next 5 days, in accordance with previous studies of ARDS due to COVID-19[22,23].

Tocilizumab was administered as a single intravenous infusion over 60 min at a dose of 8 mg/kg (maximum of 800 mg), based on the RECOVERY trial[9,21]. The date of receipt of tocilizumab coincided exactly or was very close to the date of admission to the IRCU in the tocilizumab + SOC group.

We followed up with the patients throughout their hospital stay from the date of admission to the IRCU.

Baseline variables

We collected the following baseline variables: demographic data (sex and age), previous diseases, time of evolution of COVID-19 symptoms, time from hospitalization to admission to the IRCU, PaO_2/FiO_2 ratio, SpO_2/

FiO_2 ratio, RR, use of accessory respiratory musculature, ROX index ([SpO_2/FiO_2]/RR ratio), type of NIRS required, blood analytical parameters, radiological extent of pneumonic lung involvement, symptomatology, candidacy for OTI-IMV, use of dexamethasone, and use of remdesivir.

Outcome variables

The most important (primary) outcome variables were death, receipt of IMV, and the composite of receipt of IMV or death (clinical failure), measured up to (within) 30 days and throughout (during) the hospital stay (in-hospital), from the date of admission to the IRCU.

As less important (secondary) outcome variables, we measured the following: de-escalation to NC up to 30 days; discharge to home up to 30 days; and medians of the following times: from the date of admission to the IRCU to the date of death up to 30 days and during the hospital stay (among patients who died), to the date of receipt of IMV in ICU (among patients who escalated to OTI-IMV), to the date of the composite of receipt of IMV or death during the hospital stay (among patients who as a composite escalated to OTI-IMV or died), to the date of de-escalation to NC in conventional hospitalization area during the hospital stay (among patients who neither escalated to OTI-IMV nor died), and to the date of discharge to home during the hospital stay (among patients who neither escalated to OTI-IMV nor died).

For the analysis of the outcome variables related to the probability of receiving IMV up to 30 days and during the hospital stay, we excluded from the total sample all patients deemed non-candidates for OTI-IMV due to advanced age, frail baseline state (patients dependent on basic activities of daily living), and major comorbidities.

Statistical analysis

To eliminate the bias (selection bias) that was committed when selecting which patients would or would not be administered tocilizumab based on certain baseline characteristics (confounding factors), and that, therefore, would significantly interfere with the estimation of the effects of tocilizumab treatment on the outcome variables (death, IMV, clinical failure…), potentially leading to erroneous conclusions, we performed propensity score matching (PSM) at a ratio of 1:1, using the nearest neighbor search algorithm. To obtain the final propensity score (PS), we included the following baseline variables (covariates) in a multiple binary logistic regression model: PaO_2/FiO_2 ratio, number of days since symptom onset, use of CPAP, value of CRP in blood, and radiological extent of pneumonia. We drew a love plot to examine the balance of the PS and its component covariates between the tocilizumab + SOC group and the SOC group, both before and after matching (Fig. 1).

Qualitative variables were expressed as numbers (n) or fractions (n/N) and percentages (%), along with their estimates using 95% confidence intervals (95% CIs). Quantitative variables were expressed as means ± standard deviation (SD) or medians with interquartile range (Q1-Q3).

For associations between two qualitative variables, we employed the Chi-square test or Fisher's exact test as appropriate, and we measured their magnitudes by odds ratios (ORs) along with their 95% CIs. For comparisons of means and medians (ranges) of quantitative variables between two groups of a qualitative variable (tocilizumab + SOC group vs. SOC group), we employed the Student's t-test (with Levene's test) and Mann-Whitney U-test, respectively.

For the time-to-event analyses (death, IMV, clinical failure, and discharge to home up to 30 days), we used the Kaplan–Meier method for descriptive purposes, the bivariate log-rank method to compare between the tocilizumab + SOC group and the SOC group, and the Cox regression method (proportional hazards model) for the subsequent calculation of the hazard ratio (HR) along with its 95% CI to measure their magnitudes of association taking into account the follow-up time of each patient.

We established a $p \leq 0.05$ as the threshold for statistical significance.

We used software packages R version 4.1.3 and SPSS version 22 for all statistical analyses.

Results

Patients: baseline characteristics

We included 1306 patients: 532 (40.7%) received tocilizumab + SOC and 774 (59.3%) received SOC alone (Fig. 2A). Patients from both groups were then matched at a ratio of 1:1, id est, 321 (50.0%) and 321 (50.0%), respectively, totaling 642 patients (100.0%) (Fig. 2B).

Before matching, we observed statistically significant differences ($p \leq 0.05$) between the tocilizumab + SOC group and the SOC group in many of the baseline characteristics: age, cerebrovascular disease, time of evolution of symptoms, PaO_2/FiO_2 ratio, type of NIRS, CRP, radiological extent of pneumonia, dyspnea, and

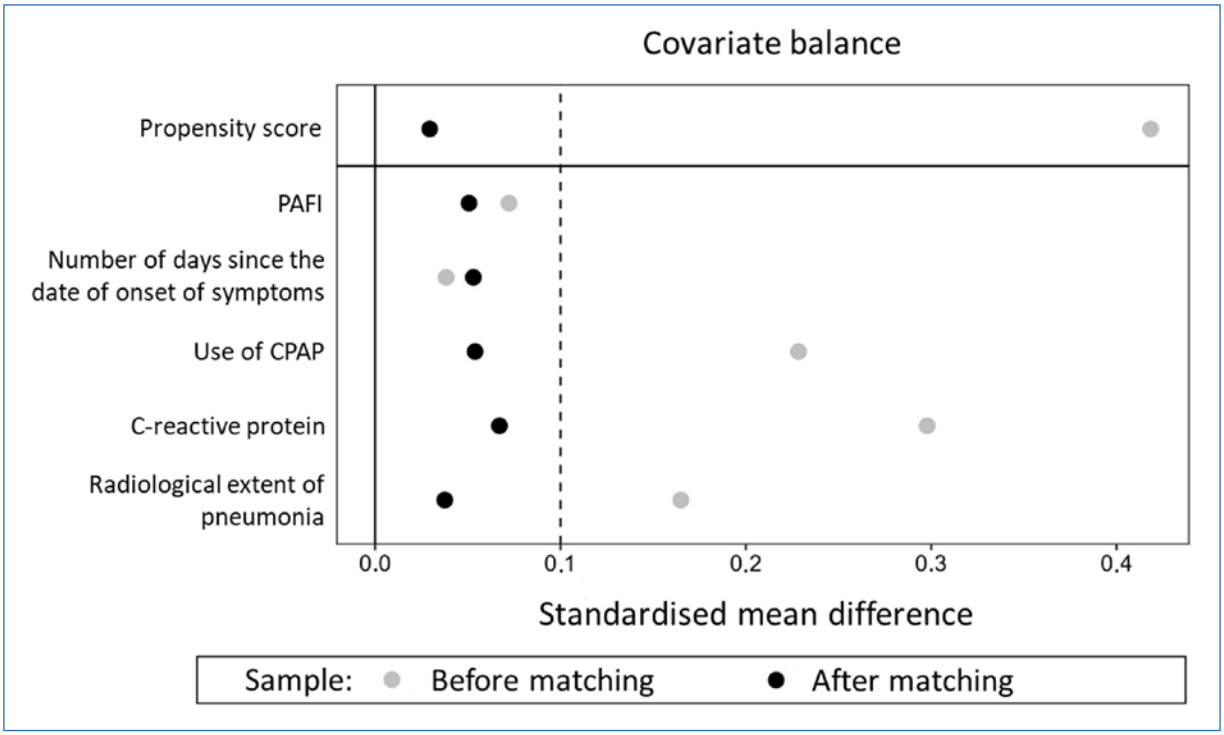

Figure 1. Love plot of the standardised mean differences between the tocilizumab + SOC group and the SOC group in the sample before matching (all patients) and after matching (matched patients) on a series of confounding variables (covariates) and the propensity score integrating these variables. These confounding variables were: PAFI, number of days since symptom onset, use of CPAP, C-reactive protein, and radiological extent of pneumonia. The dashed vertical line represents a standardised mean difference between the two groups of 0.1 for the variable in question. Differences of greater than 0.1 indicated a significant imbalance (distancing, heterogeneity) in the values of these variables between the subjects of both groups (tocilizumab + SOC group vs. SOC group) in the sample, as was the case before matching. In contrast, differences of less than 0.1 indicated an appropriate balance (proximity, homogeneity) in the values of these variables between the subjects of both groups (tocilizumab + SOC group vs. SOC group) in the sample, as was the case after matching. CPAP: continuous positive airway pressure; PAFI: PaO2/FiO2 ratio; SOC: standard of care.

chest pain (Table 1). There was a significant imbalance of the covariates between the two groups (Fig. 1).

After matching, we did not observe any statistically significant differences ($p > 0.05$) between the two groups in any of the baseline characteristics, except for lymphocyte count ($p = 0.026$) and dyspnea ($p = 0.002$) (Table 2). We achieved an adequate balance of the covariates between the two groups (Fig. 1).

Death

After matching, we did not detect any statistically significant difference in 30-day mortality between the tocilizumab + SOC group and the SOC group (36/321 vs. 35/321; 11.2% vs. 10.9%; 95% CI = 8.1-15.3% vs. 95% CI = 7.8-15.0%) (HR = 1.03; HR 95% CI = 0.65-1.64; $p = 0.896$) (OR = 1.03; OR 95% CI = 0.63-1.69; $p = 0.900$) (Fig. 3A and Table 3). The median (Q1-Q3) of time until these patients died within 30 days was not modified by whether or not they had received tocilizumab (15.5 [9.0-20.0] days vs. 14.0 [11.0-20.0] days; $p = 0.913$) (Table 3).

After matching, we did not detect any statistically significant difference in in-hospital mortality between the tocilizumab + SOC group and the SOC group (59/321 vs. 49/321; 18.4% vs. 15.3%; 95% CI = 14.4-23.1% vs. 95% CI = 11.6-19.8%) (OR = 1.25; OR 95% CI = 0.83-1.89; $p = 0.291$) (Table 3). The median [Q1-Q3] of time until these patients died at any time throughout the hospital stay was not modified by whether or not they had received tocilizumab (23.0 [12.0-38.0] days vs. 19.0 [12.5-33.5] days; $p = 0.301$) (Table 3). If we focused on patients who had escalated from NIRS to IMV in the ICU, no statistically significant difference in in-hospital mortality was detected between the two groups (44/89 vs. 36/76; 49.4% vs. 47.4%; 95% CI = 38.8-60.2% vs. 95% CI = 35.9-59.1%) (OR = 1.09; OR 95% CI = 0.59-2.00; $p = 0.791$).

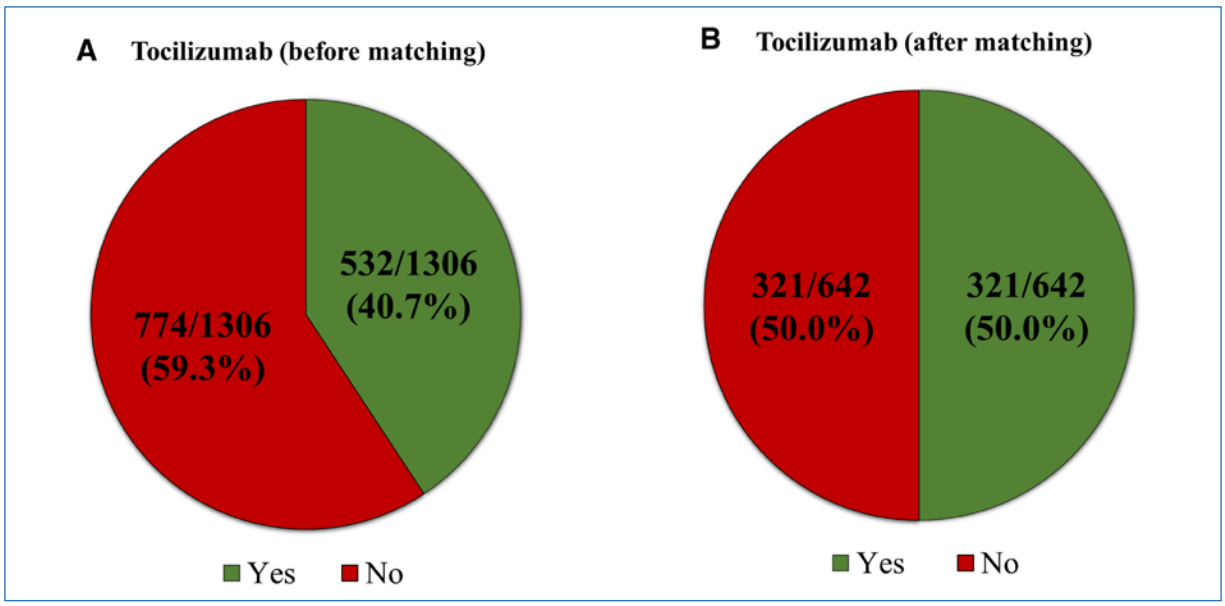

Figure 2. Distribution of patients admitted to the IRCU for severe COVID-19 pneumonia with need for NIRS (HFNC, CPAP, and/or BPAP) according to whether or not they received tocilizumab therapy (tocilizumab + SOC group vs. SOC group), before **(A)** and after **(B)** propensity score matching at a ratio of 1:1. BPAP: bilevel positive airway pressure; COVID-19: coronavirus disease 2019; CPAP: continuous positive airway pressure; HFNC: high-flow nasal cannulas; IRCU: intermediate respiratory care unit; NIRS: non-invasive respiratory support; SOC: standard of care.

Table 1. Baseline characteristics of patients before propensity score matching

Before propensity score matching				
Characteristic	**All patients (n = 1306) (100%)**	**Tocilizumab + SOC group (n = 532) (40.7%)**	**SOC group (n = 774) (59.3%)**	**p***
Sex (%)				
Male	844 (64.6)	353 (66.4)	491 (63.4)	0.279
Female	462 (35.4)	179 (33.6)	283 (36.6)	
Age in years				
Mean ± SD	54.7 ± 13.7	53.2 ± 13.6	55.7 ± 13.6	0.001
Median (Q1-Q3)	55.0 (45.0-65.0)	54.0 (44.0-63.0)	56.0 (46.0-66.0)	0.003
Categories (%)				
< 60 years	800 (61.3)	347 (65.2)	453 (58.5)	0.015
≥ 60 years	506 (38.7)	185 (34.8)	321 (41.5)	
Previous diseases (%)				
Obesity	518 (39.7)	220 (41.4)	298 (38.5)	0.301
Diabetes mellitus	190 (14.5)	69 (13.0)	121 (15.6)	0.180
COPD	110 (8.4)	51 (9.6)	59 (7.6)	0.209
Bronchial asthma	145 (11.1)	63 (11.8)	82 (10.6)	0.481
Sleep apnea	98 (7.5)	39 (7.3)	59 (7.6)	0.844
Ischemic heart disease	54 (4.1)	18 (3.4)	36 (4.7)	0.258
Heart failure	40 (3.1)	11 (2.1)	29 (3.7)	0.084
Cerebrovascular disease	27 (2.1)	5 (0.9)	22 (2.8)	0.018
Cognitive impairment	3 (0.2)	3 (0.6)	0 (0.0)	0.067

(*Continues*)

Table 1. Baseline characteristics of patients before propensity score matching (*continued*)

Before propensity score matching				
Characteristic	**All patients (n = 1306) (100%)**	**Tocilizumab + SOC group (n = 532) (40.7%)**	**SOC group (n = 774) (59.3%)**	**p***
Connectivopathy	32 (2.5)	9 (1.7)	23 (3.0)	0.142
Gastroduodenal peptic ulcer	36 (2.8)	14 (2.6)	22 (2.8)	0.819
Chronic liver disease	61 (4.7)	27 (5.1)	34 (4.4)	0.566
Chronic kidney disease	27 (2.1)	11 (2.1)	16 (2.1)	1.000
Solid malignant neoplasm	58 (4.4)	21 (3.9)	37 (4.8)	0.473
Leukemia and/or lymphoma	9 (0.7)	3 (0.6)	6 (0.8)	0.745
HIV infection	5 (0.4)	0 (0.0)	5 (0.6)	0.084
Number of days since the date of onset of symptoms‡				
Median (Q1-Q3)	10.0 (8.0-11.0)	9.0 (8.0-11.0)	10.0 (8.0-12.0)	0.007
Mean ± SD	9.7 ± 3.3	9.5 ± 3.1	9.9 ± 3.5	0.013
Categories, n (%)				
≤ 10 days	844/1305 (64.7)	364/532 (68.4)	480/773 (62.1)	0.019
> 10 days	461/1305 (35.3)	168/532 (31.6)	293/773 (37.9)	
Number of days of hospitalization since the date of hospitalization-median (Q1-Q3)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	0.354
PAFI-median (Q1-Q3)‡	103.1 (80.0-145.0)	108.5 (83.3-149.8)	102.0 (78.2-140.0)	0.009
PAFI-mean ± SD‡	119.4 ± 55.1	123.2 ± 54.0	116.7 ± 55.7	0.039
Degrees of ARDS according to PAFI‡, n (%)				
Not ARDS (PAFI > 300)	13/1247 (1.0)	3/520 (0.6)	10/727 (1.4)	0.022
Mild ARDS (200 < PAFI ≤ 300)	97/1247 (7.8)	53/520 (10.2)	44/727 (6.1)	
Moderate ARDS (100 < PAFI ≤ 200)	549/1247 (44.0)	231/520 (44.4)	318/727 (43.7)	
Severe ARDS (PAFI ≤ 100)	588/1247 (47.2)	233/520 (44.8)	355/727 (48.8)	
SAFI-median (Q1-Q3)	98.0 (95.0-118.0)	98.0 (96.0-118.0)	98.0 (95.0-118.5)	0.791
SAFI-mean ± SD	108.5 ± 20.9	106.7 ± 17.4	109.7 ± 22.9	0.007
Respiratory rate				
Median (Q1-Q3)	22.0 (19.0-25.0)	22.0 (19.0-26.0)	22.0 (19.0-25.0)	0.282
Mean ± SD	22.5 ± 5.2	22.7 ± 5.3	22.3 ± 5.1	0.156
Categories, n (%)				
RR ≤ 20 breaths/min	518 (39.7)	207 (38.9)	311 (40.2)	0.517
20 < RR < 30 breaths/min	651 (49.8)	263 (49.4)	388 (50.1)	
RR ≥ 30 breaths/min	137 (10.5)	62 (11.7)	75 (9.7)	
Use of accessory respiratory musculature†	651/1278 (50.9)	262/514 (51.0)	389/764 (50.9)	0.984
ROX index-median (Q1-Q3)	4.8 (4.0-5.9)	4.8 (3.9-5.7)	4.8 (4.0-6.0)	0.107
ROX index-mean ± SD	5.1 ± 1.6	5.0 ± 1.5	5.2 ± 1.7	0.017
Type of NIRS required‡, n (%)				
HFNC alone	530 (40.6)	178 (33.5)	352 (45.5)	< 0.001
HFNC + CPAP / BPAP	776 (59.4)	354 (66.5)	422 (54.5)	< 0.001
HFNC + CPAP	766 (58.7)	350 (65.8)	416 (53.7)	< 0.001
HFNC + CPAP without BPAP	690 (52.8)	312 (58.6)	378 (48.8)	< 0.001
HFNC + BPAP	86 (6.6)	42 (7.9)	44 (5.7)	0.114
HFNC + BPAP without CPAP	10 (0.8)	4 (0.8)	6 (0.8)	1.000
HFNC + CPAP + BPAP	76 (5.8)	38 (7.1)	38 (4.9)	0.090

(*Continues*)

Table 1. Baseline characteristics of patients before propensity score matching (*continued*)

Before propensity score matching				
Characteristic	**All patients (n = 1306) (100%)**	**Tocilizumab + SOC group (n = 532) (40.7%)**	**SOC group (n = 774) (59.3%)**	**p***
Blood analytical parameters-median (Q1-Q3)†				
Lymphocytes in cells/mm3	670.0 (490.0-940.0)	695.0 (520.0-922.5)	650.0 (470.0-960.0)	0.150
C-reactive protein in mg/L	75.5 (36.0-137.9)	100.9 (47.2-152.5)	63.7 (31.3-118.0)	< 0.001
Ferritin in ng/mL	933.0 (518.5-1400.5)	941.0 (486.5-1385.3)	929.0 (535.0-1403.0)	0.937
Lactate dehydrogenase in IU/L	397.0 (333.8-491.3)	399.0 (338.0-497.0)	394.0 (331.0-483.0)	0.478
Procalcitonin in ng/mL	0.10 (0.06-0.18)	0.12 (0.06-0.19)	0.10 (0.06-0.17)	0.057
D-dimer in ng/mL	610.0 (410.0-950.0)	600.0 (417.5-955.0)	610.0 (400.0-950.0)	0.768
Creatinine in mg/dL	0.70 (0.59-0.84)	0.71 (0.61-0.83)	0.70 (0.59-0.84)	0.365
Total bilirubin in mg/dL	0.43 (0.34-0.57)	0.42 (0.32-0.53)	0.45 (0.34-0.58)	< 0.001
Microbiological detection test (RT-PCR or rapid antigenic test) positive for SARS-CoV-2 in nasopharyngeal exudate, n (%)	1306 (100)	532 (100)	774 (100)	1.000
Radiological extent of pneumonia†, n (%)				
No quadrants	19/952 (2.0)	7/348 (2.0)	12/604 (2.0)	0.007
One quadrant	23/952 (2.4)	4/348 (1.1)	19/604 (3.1)	
Two quadrants	210/952 (22.1)	59/348 (17.0)	151/604 (25.0)	
Three quadrants	231/952 (24.3)	86/348 (24.7)	145/604 (24.0)	
Four quadrants	469/952 (49.3)	192/348 (55.2)	277/604 (45.9)	
Symptomatology†, n (%)				
Fever	789/1126 (70.1)	366/515 (71.1)	423/611 (69.2)	0.502
Cough	1111/1296 (85.7)	462/527 (87.7)	649/769 (84.4)	0.098
Dyspnea	768/1232 (62.3)	294/510 (57.6)	474/722 (65.7)	0.004
Chest pain	125/584 (21.4)	65/247 (26.3)	60/337 (17.8)	0.013
Diarrhea	222/1278 (17.4)	100/522 (19.2)	122/756 (16.1)	0.161
Headache	335/1295 (25.9)	146/528 (27.7)	189/767 (24.6)	0.224
Anosmia	97/1276 (7.6)	42/522 (8.0)	55/754 (7.3)	0.618
Candidacy for OTI-IMV if worsening, n (%)	1238 (94.8)	507 (95.3)	731 (94.4)	0.494
Use of glucocorticotherapy (dexamethasone) by systemic route, n (%)				
No	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Yes, standard dose of 6 mg/24 h	0 (0.0)	0 (0.0)	0 (0.0)	
Yes, iv a bolus of 20 mg/24 h	1306 (100)	532 (100)	774 (100)	
Use of remdesivir†	57/957 (6.0%)	24/349 (6.9%)	33/608 (5.4%)	0.362

*For the comparison between two qualitative variables, we used the Chi-square test or Fisher's exact test, depending on whether < 20% or > 20% of the cells had an expected frequency < 5, respectively. For the comparison of a quantitative variable between two groups of a dichotomous nominal qualitative variable (tocilizumab yes vs. no), we used the Student's t-test if means were compared and Mann-Whitney U test if medians (ranges) were compared.
†Values of patients have been lost in these variables; hence, the denominator is smaller.
‡The variable type of NIRS required was divided into several groups, taking into account that all patients used HFNC: (a) HFNC alone (no use of CPAP or BPAP); (b) HFNC + CPAP/BPAP (use of CPAP or BPAP or both); (c) HFNC+CPAP (use of CPAP regardless of whether or not the patient had also used BPAP afterward); (d) HFNC + CPAP without BPAP (use of CPAP excluding cases that had used BPAP afterward); (e) HFNC + BPAP (use of BPAP regardless of whether or not the patient had also used CPAP before); (f) HFNC + BPAP without CPAP (use of BPAP excluding cases that had used CPAP before); (g) HFNC + CPAP + BPAP (use of both devices, CPAP and BPAP, excluding cases that had only used CPAP or BPAP separately). Data are expressed as n (%), n/N (%), mean ± SD, or median (Q1-Q3).
ARDS: adult acute respiratory distress syndrome; BPAP: bilevel positive airway pressure; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; HFNC: high-flow nasal cannulas; HIV: human immunodeficiency virus; IMV: invasive mechanical ventilation; IV or iv: intravenous route; N or n: sample size or number of observations; NIRS: non-invasive respiratory support; OTI: orotracheal intubation; p-value: statistical significance level; PAFI: PaO2/FiO2 ratio; Q1: first quartile; Q3: third quartile; ROX index: (SpO2/FiO2)/RR ratio; RR: respiratory rate; RT-PCR: reverse transcriptase polymerase chain reaction; SAFI: SpO2/FiO2 ratio; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation; SOC: standard of care.

Table 2. Baseline characteristics of patients after propensity score matching

After propensity score matching				
Characteristic	**All patients (n = 642) (100%)**	**Tocilizumab + SOC group (n = 321) (50%)**	**SOC group (n = 321) (50%)**	**p***
Sex, n (%)				
Male	429 (66.8)	208 (64.8)	221 (68.8)	0.276
Female	213 (33.2)	113 (35.2)	100 (31.2)	
Age in years				
Mean ± SD	58.0 ± 12.4	57.4 ± 12.0	58.6 ± 12.8	0.217
Median (Q1-Q3)	59.0 (49.0-67.0)	58.0 (49.0-66.0)	59.0 (49.0-68.0)	0.196
Categories, n (%)				
< 60 years	342 (53.3)	181 (56.4)	161 (50.2)	0.114
≥ 60 years	300 (46.7)	140 (43.6)	160 (49.8)	
Previous diseases, n (%)				
Obesity	295 (46.0)	146 (45.5)	149 (46.4)	0.812
Diabetes mellitus	95 (14.8)	43 (13.4)	52 (16.2)	0.317
COPD	54 (8.4)	28 (8.7)	26 (8.1)	0.776
Bronchial asthma	86 (13.4)	47 (14.6)	39 (12.1)	0.354
Sleep apnea	66 (10.3)	31 (9.7)	35 (10.9)	0.603
Ischemic heart disease	28 (4.4)	15 (4.7)	13 (4.0)	0.699
Heart failure	17 (2.6)	7 (2.2)	10 (3.1)	0.461
Cerebrovascular disease	16 (2.5)	5 (1.6)	11 (3.4)	0.129
Cognitive impairment	2 (0.3)	2 (0.6)	0 (0.0)	0.499
Connectivopathy	18 (2.8)	9 (2.8)	9 (2.8)	1.000
Gastroduodenal peptic ulcer	25 (3.9)	13 (4.0)	12 (3.7)	0.838
Chronic liver disease	31 (4.8)	15 (4.7)	16 (5.0)	0.854
Chronic kidney disease	16 (2.5)	9 (2.8)	7 (2.2)	0.613
Solid malignant neoplasm	35 (5.5)	18 (5.6)	17 (5.3)	0.862
Leukemia and/or lymphoma	5 (0.8)	1 (0.3)	4 (1.2)	0.373
HIV infection	3 (0.5)	0 (0.0)	3 (0.9)	0.249
Number of days since the date of onset of symptoms				
Median (Q1-Q3)	10.0 (8.0-11.0)	9.0 (8.0-11.0)	10.0 (8.0-12.0)	0.250
Mean ± SD	9.8 ± 3.6	9.7 ± 3.3	10.0 ± 3.8	0.222
Categories (%)				
≤ 10 days	406 (63.2)	210 (65.4)	196 (61.1)	0.252
> 10 days	236 (36.8)	111 (34.6)	125 (38.9)	
Number of days of hospitalization since the date of hospitalization-median (Q1-Q3)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-3.5)	0.853
PAFI-median (Q1-Q3)	96.0 (76.0-129.0)	98.0 (78.9-130.5)	95.0 (72.0-125.0)	0.103
PAFI-mean ± SD	110.5 ± 50.5	111.7 ± 47.3	109.3 ± 53.6	0.548
Degrees of ARDS according to PAFI, n (%)				
Not ARDS (PAFI > 300)	5 (0.8)	1 (0.3)	4 (1.2)	0.521
Mild ARDS (200 < PAFI ≤ 300)	39 (6.1)	21 (6.5)	18 (5.6)	
Moderate ARDS (100 < PAFI ≤ 200)	242 (37.7)	125 (38.9)	117 (36.4)	
Severe ARDS (PAFI ≤ 100)	356 (55.5)	174 (54.2)	182 (56.7)	
SAFI-median (Q1-Q3)	97.0 (95.0-117.0)	98.0 (95.0-117.0)	97.0 (95.0-117.0)	0.320
SAFI-mean ± SD	106.4 ± 19.5	105.4 ± 15.7	107.4 ± 22.7	0.203

(*Continues*)

Table 2. Baseline characteristics of patients after propensity score matching (*continued*)

After propensity score matching				
Characteristic	**All patients (n = 642) (100%)**	**Tocilizumab + SOC group (n = 321) (50%)**	**SOC group (n = 321) (50%)**	**p***
Respiratory rate				
Median (Q1-Q3)	22.0 (19.0-25.0)	22.0 (19.0-25.0)	22.0 (19.0-25.0)	0.403
Mean ± SD	22.7 ± 5.2	22.5 ± 5.1	22.8 ± 5.4	0.479
Categories, n (%)				
RR ≤ 20 breaths/min	244 (38.0)	129 (40.2)	115 (35.8)	0.320
20 < RR < 30 breaths/min	328 (51.1)	162 (50.5)	166 (51.7)	
RR ≥ 30 breaths/min	70 (10.9)	30 (9.3)	40 (12.5)	
Use of accessory respiratory musculature‡, n (%)	368/641 (57.4)	182/320 (56.9)	186/321 (57.9)	0.784
ROX index-median (Q1-Q3)	4.7 (3.9-5.6)	4.8 (3.9-5.6)	4.6 (3.9-5.6)	0.554
ROX index-mean ± SD	5.0 ± 1.5	4.9 ± 1.4	5.0 ± 1.7	0.662
Type of NIRS required‡, n (%)				
HFNC alone	185 (28.8)	96 (29.9)	89 (27.7)	0.542
HFNC + CPAP/BPAP	457 (71.2)	225 (70.1)	232 (72.3)	0.542
HFNC + CPAP	452 (70.4)	222 (69.2)	230 (71.7)	0.489
HFNC + CPAP without BPAP	393 (61.2)	189 (58.9)	204 (63.6)	0.224
HFNC + BPAP	64 (10.0%)	36 (11.2)	28 (8.7)	0.292
HFNC + BPAP without CPAP	5 (0.8%)	3 (0.9)	2 (0.6)	1.000
HFNC + CPAP + BPAP	59 (9.2%)	33 (10.3%)	26 (8.1%)	0.339
Blood analytical parameters-median (Q1-Q3)				
Lymphocytes in cells/mm3†	630.0 (460.0-895.0)	660.0 (500.0-905.0)	590.0 (440.0-880.0)	0.026
C-reactive protein in mg/L	95.4 (44.8-152.5)	103.6 (45.3-155.3)	88.7 (43.9-151.3)	0.469
Ferritin in ng/mL†	970.5 (543.0-1396.0)	928.0 (517.3-1349.3)	1015.0 (581.8-1430.3)	0.093
Lactate dehydrogenase in IU/L†	407.0 (339.0-499.5)	399.0 (338.0-496.0)	414.0 (342.8-509.3)	0.388
Procalcitonin in ng/mL†	0.12 (0.06-0.20)	0.12 (0.06-0.20)	0.11 (0.07-0.21)	0.768
D-dimer in ng/mL†	655.0 (440.0-1060.0)	630.0 (440.0-1040.0)	670.0 (440.0-1090.0)	0.737
Creatinine in mg/dL†	0.70 (0.60-0.84)	0.70 (0.60-0.83)	0.71 (0.60-0.84)	0.752
Total bilirubin in mg/dL†	0.43 (0.33-0.57)	0.42 (0.31-0.54)	0.46 (0.35-0.59)	0.002
Microbiological detection test (RT-PCR or rapid antigenic test) positive for SARS-CoV-2 in nasopharyngeal exudate, n (%)	642 (100)	321 (100)	321 (100)	1.000
Radiological extent of pneumonia, n (%)				
No quadrants	13 (2.0)	6 (1.9)	7 (2.2)	0.841
One quadrant	6 (0.9)	3 (0.9)	3 (0.9)	
Two quadrants	113 (17.6)	54 (16.8)	59 (18.4)	
Three quadrants	148 (23.1)	80 (24.9)	68 (21.2)	
Four quadrants	362 (56.4)	178 (55.5)	184 (57.3)	
Symptomatology, n (%)				
Fever†	367/537 (68.3)	207/309 (67.0)	160/228 (70.2)	0.433
Cough	563 (87.7)	285 (88.8)	278 (86.6)	0.400
Dyspnea†	326/600 (54.3)	148/307 (48.2)	178/293 (60.8)	0.002
Chest pain†	25/157 (15.9)	12/67 (17.9%)	13/90 (14.4)	0.714
Diarrhea‡	85/626 (13.6)	47/315 (14.9)	38/311 (12.2)	0.324
Headache	155 (24.1)	82 (25.5)	73 (22.7)	0.407
Anosmia‡	36/626 (5.8)	20/315 (6.3)	16/311 (5.1)	0.517

(*Continues*)

Table 2. Baseline characteristics of patients after propensity score matching (*continued*)

After propensity score matching				
Characteristic	**All patients (n = 642) (100%)**	**Tocilizumab + SOC group (n = 321) (50%)**	**SOC group (n = 321) (50%)**	**p***
Candidacy for OTI-IMV if worsening	603 (93.9)	301 (93.8)	302 (94.1)	0.869
Use of glucocorticotherapy (dexamethasone) by systemic route, n (%)				
No	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Yes, standard dose of 6 mg/24 h	0 (0.0)	0 (0.0)	0 (0.0)	
Yes, iv a bolus of 20 mg/24 h	642 (100)	321 (100)	321 (100)	
Use of remdesivir, n (%)	39 (6.1)	22 (6.9)	17 (5.3)	0.409

*For the comparison between two qualitative variables, we used the Chi-square test or Fisher's exact test, depending on whether < 20% or > 20% of the cells had an expected frequency < 5, respectively. For the comparison of a quantitative variable between two groups of a dichotomous nominal qualitative variable (tocilizumab yes vs. no), we used the Student's t-test if means were compared and Mann-Whitney U test if medians (ranges) were compared.
†Values of patients have been lost in these variables; hence, the denominator is smaller.
‡The variable type of NIRS required was divided into several groups, taking into account that all patients used HFNC: (a) HFNC alone (no use of CPAP or BPAP); (b) HFNC + CPAP/BPAP (use of CPAP or BPAP or both); (c) HFNC + CPAP (use of CPAP regardless of whether or not the patient had also used BPAP afterward); (d) HFNC + CPAP without BPAP (use of CPAP excluding cases that had used BPAP afterward); (e) HFNC + BPAP (use of BPAP regardless of whether or not the patient had also used CPAP before); (f) HFNC + BPAP without CPAP (use of BPAP excluding cases that had used CPAP before); (g) HFNC + CPAP + BPAP (use of both devices, CPAP and BPAP, excluding cases that had only used CPAP or BPAP separately). Data are expressed as n (%), n/N (%), mean ± SD, or median (Q1-Q3).
ARDS: adult acute respiratory distress syndrome; BPAP: bilevel positive airway pressure; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; HFNC: high-flow nasal cannulas; HIV: human immunodeficiency virus; IMV: invasive mechanical ventilation; IV or iv: intravenous route; N or n: sample size or number of observations; NIRS: non-invasive respiratory support; OTI: orotracheal intubation; P value: statistical significance level; PAFI: PaO2/FiO2 ratio; Q1: first quartile; Q3: third quartile; ROX index: (SpO2/FiO2)/RR ratio; RR: respiratory rate; RT-PCR: reverse transcriptase polymerase chain reaction; SAFI: SpO2/FiO2 ratio; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation; SOC: standard of care.

Need for invasive mechanical ventilation

After matching, no statistically significant difference was detected in the probability of receiving IMV up to 30 days between the tocilizumab + SOC group and the SOC group (89/301 vs. 76/302; 29.6% vs. 25.2%; 95% CI = 24.5-35.1% vs. 95% CI = 20.5-30.5%) (HR = 1.22; HR 95% CI = 0.90-1.66; p = 0.194) (OR = 1.25; OR 95% CI = 0.87-1.79; p = 0.225) (Fig. 3B and Table 3).

Since no patients were escalated to OTI-IMV after 30 days, the OR was equal for the receipt of IMV throughout the hospital stay (Table 3). The median (Q1-Q3) of time until these patients received IMV was not modified by whether or not they had received tocilizumab (4.0 [2.5-7.0] days vs. 4.5 [2.3-7.8] days; p = 0.937) (Table 3).

Clinical failure

After matching, when analysing the composite probability of receiving IMV or death (clinical failure) up to 30 days, no statistically significant difference was detected between the tocilizumab + SOC group and the SOC group (104/321 vs. 89/321; 32.4% vs. 27.7%; 95% CI = 27.4-37.9% vs. 95% CI = 23.0-33.0%) (HR = 1.22; HR 95% CI = 0.92-1.62; p = 0.167) (OR = 1.25; OR 95% CI = 0.89-1.75; p = 0.197) (Fig. 3C and Table 3).

Since no patients experienced the composite event of IMV or death after 30 days, the OR was equal for the composite of receiving IMV or death (clinical failure) throughout the hospital stay (Table 3). The median (Q1-Q3) of time until these patients as a composite received IMV or died was not modified by whether or not they had received tocilizumab (5.0 [3.0-8.0] days vs. 5.0 [3.0-8.0] days; p = 0.673) (Table 3).

De-escalation to conventional nasal cannulas up to 30 days

After matching, regarding the probability of de-escalation from NIRS (HFNC, CPAP, and/or BPAP) (with patients potentially having escalated to IMV in between if they had required IMV) to NC within 30 days, no statistically significant difference in this was observed between the tocilizumab + SOC group and the SOC group (242/321 vs. 250/321; 75.4% vs. 77.9%; 95% CI = 70.2-79.9% vs. 95% CI = 72.9-82.2%) (OR = 0.87; OR95% CI = 0.60-1.25; p = 0.456) (Table 3). Within the subgroup of patients who neither received IMV nor died, the median (Q1-Q3) of length of stay in the IRCU under NIRS until de-escalation to NC in the conventional hospitalization area was statistically similar between the tocilizumab + SOC group and the SOC group (7.0 [5.0-10.0] days vs. 7.0 [5.0-10.0] days; p = 0.249) (Table 3).

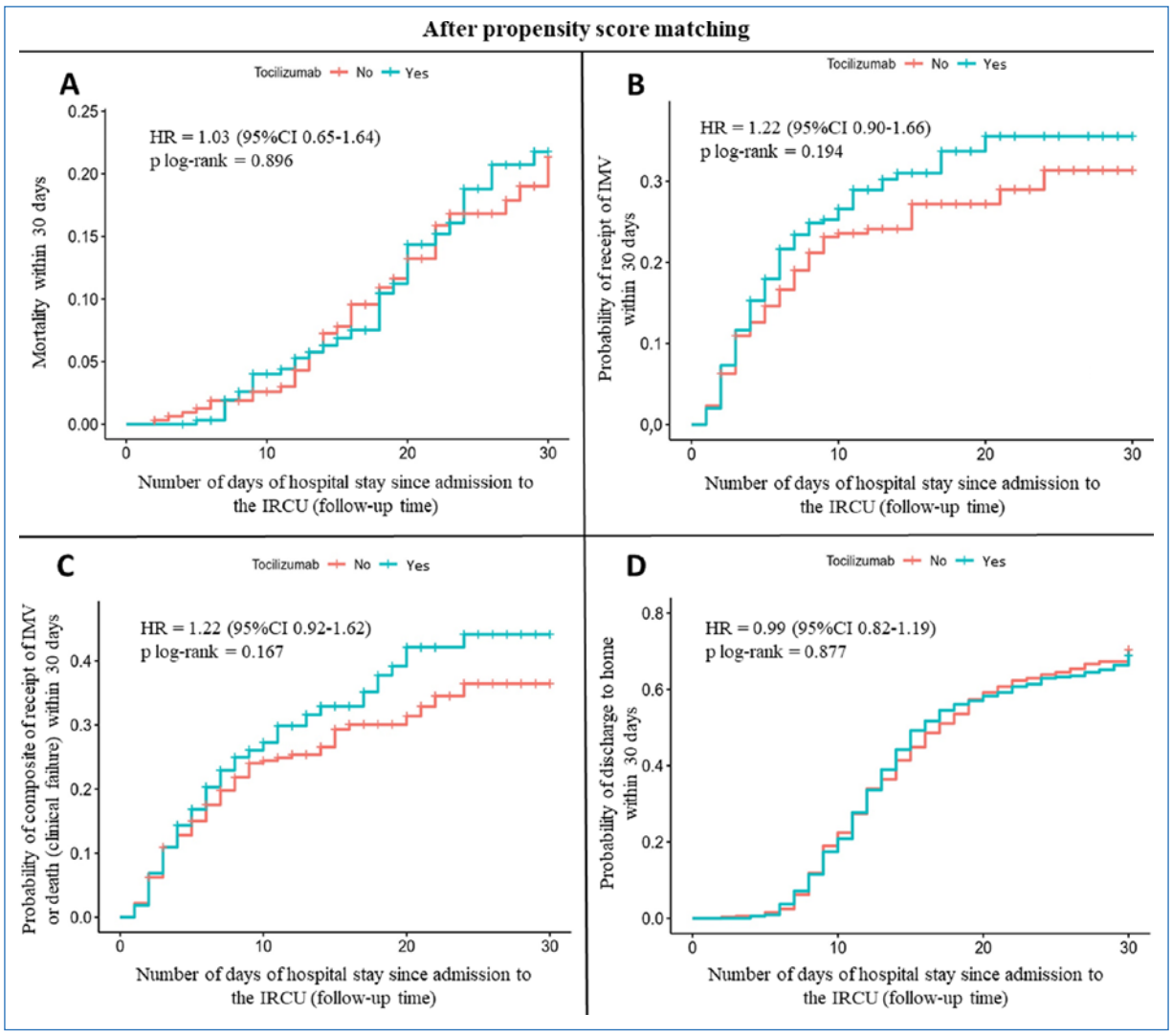

Figure 3. Effect of administration of tocilizumab on mortality up to 30 days **(A)**, on the probability of receiving IMV up to 30 days **(B)**, on the probability of composite of receiving IMV or death up to 30 days **(C)**, and on the probability of discharge to home up to 30 days **(D)**, after propensity score matching. To analyse the receipt of IMV in figure 3B, patients (39; 6.1%) deemed non-candidates for OTI-IMV due to advanced age, frail (dependent) baseline life, and major comorbidities were excluded from the total sample of 642 patients. HR: hazard ratio; IMV: invasive mechanical ventilation; IRCU: intermediate respiratory care unit; NC: conventional nasal cannulas; NIRS: non-invasive respiratory support; OTI: orotracheal intubation.

Discharge to home up to 30 days

After matching, regarding the probability of discharge to home up to 30 days, no statistically significant difference in this was observed between the tocilizumab + SOC group and the SOC group (221/321 vs. 226/321; 68.8% vs. 70.4%; 95% CI = 63.4-73.8% vs. 95% CI = 65.0-75.3%) (HR = 0.99; HR 95% CI = 0.82-1.19; p = 0.877) (OR = 0.93; OR 95% CI = 0.66-1.30; p = 0.668) (Fig. 3D and Table 3). Within the subgroup of patients who neither received IMV nor died, the median (Q1-Q3) of length of stay from admission to the IRCU to discharge to home was statistically similar between the tocilizumab + SOC group and the SOC group (13.0 [9.0-16.0] days vs. 13.0 [9.0-19.0] days; p = 0.308) (Table 3).

Discussion

We presented a 1:1 matched cohort of 642 patients diagnosed with severe COVID-19 pneumonia who required NIRS (HFNC, CPAP, and/or BPAP) in an IRCU, where we observed that tocilizumab treatment was ineffective (showing no significant differences with its

Table 3. Effects of tocilizumab on study outcome variables after propensity score matching

After propensity score matching					
Outcome variable	**All patients (n = 642) (100%)**	**Tocilizumab + SOC group (n = 321) (50.0%)**	**SOC group (n = 321) (50.0%)**	**Hazard ratio and/ or odds ratio (95% CI)**	**p**
Death within 30 days (95% CI)*	71/642 11.1% (8.8-13.8%)	36/321 11.2% (8.1-15.3%)	35/321 10.9% (7.8-15.0%)	HR: 1.03 (0.65-1.64) OR: 1.03 (0.63-1.69)	0.896 0.900
Median of time (days) to death within 30 days [Q1-Q3][§]	15.0 [9.0-20.0]	15.5 [9.0-20.0]	14.0 [11.0-20.0]	HR: Not valued OR: Not valued	0.913
Death during the hospital stay (95% CI)[†]	108/642 16.8% (14.1-20.0%)	59/321 18.4% (14.4-23.1%)	49/321 15.3% (11.6-19.8%)	HR: Not valued OR: 1.25 (0.83-1.89)	Not valued 0.291
Median of time (days) to death during the hospital stay (Q1-Q3)[§]	20.0 (12.3-36.0)	23.0 (12.0-38.0)	19.0 (12.5-33.5)	HR: Not valued OR: Not valued	0.301
Receipt of IMV within 30 days (95% CI)[*‡]	165/603 27.4% (23.9-31.1%)	89/301 29.6% (24.5-35.1%)	76/302 25.2% (20.5-30.5%)	HR: 1.22 (0.90-1.66) OR: 1.25 (0.87-1.79)	0.194 0.225
Receipt of IMV during the hospital stay (95% CI)[†‡]	165/603 27.4% (23.9-31.1%)	89/301 29.6% (24.5-35.1%)	76/302 25.2% (20.5-30.5%)	HR: Not valued OR: 1.25 (0.87-1.79)	Not valued 0.225
Median of time (days) to receipt of IMV (Q1-Q3)[¶]	4.0 (2.5-7.0)	4.0 (2.5-7.0)	4.5 (2.3-7.8)	HR: Not valued OR: Not valued	0.937
Composite of receipt of IMV or death (clinical failure) within 30 days (95% CI)*	193/642 30.1% (26.6-33.8%)	104/321 32.4% (27.4-37.9%)	89/321 27.7% (23.0-33.0%)	HR: 1.22 (0.92-1.62) OR: 1.25 (0.89-1.75)	0.167 0.197
Composite of receipt of IMV or death (clinical failure) during the hospital stay (95% CI)[†]	193/642 30.1% (26.6-33.8%)	104/321 32.4% (27.4-37.9%)	89/321 27.7% (23.0-33.0%)	HR: Not valued OR: 1.25 (0.89-1.75)	Not valued 0.197
Median of time (days) to composite of receipt of IMV or death (clinical failure) (Q1-Q3)**	5.0 (3.0-8.0)	5.0 (3.0-8.0)	5.0 (3.0-8.0)	HR: Not valued OR: Not valued	0.673
De-escalation to NC within 30 days (95% CI)[†]	492/642 76.6% (73.1-79.8%)	242/321 75.4% (70.2-79.9%)	250/321 77.9% (72.9-82.2%)	HR: Not valued OR: 0.87 (0.60-1.25)	Not valued 0.456
Median of time (days) to de-escalation to NC (Q1-Q3)[††]	7.0 (5.0-10.0)	7.0 (5.0-10.0)	7.0 (5.0-10.0)	HR: Not valued OR: Not valued	0.249
Discharge to home within 30 days (95% CI)*	447/642 69.6% (65.9-73.1%)	221/321 68.8% (63.4-73.8%)	226/321 70.4% (65.0-75.3%)	HR: 0.99 (0.82-1.19) OR: 0.93 (0.66-1.30)	0.877 0.668
Median of time (days) to discharge to home [Q1-Q3][††]	13.0 (9.0-17.0)	13.0 (9.0-16.0)	13.0 (9.0-19.0)	HR: Not valued OR: Not valued	0.308

Data are expressed as n/N and % (95% CI) or median (Q1-Q3).
*For these variables, the HR was used as the main measure of association, and the OR was used as the secondary measure of association. The difference lies in the fact that the HR takes into account the follow-up time of the patients (therefore, it provides more information and is more complete), while the OR is independent of the follow-up time of the patients.
**Selecting only the subgroup of patients who, as a composite, received OTI-IMV in the ICU or died due to unfavourable evolution of respiratory failure.
[†]For these variables, the OR, which is independent of patient follow-up time, was used as the single main measure of association.
[††]Selecting only the subgroup of patients who neither received OTI-IMV in the ICU nor died due to favourable evolution of their respiratory status, so that they could be de-escalated from NIRS to NC and transferred from IRCU to a conventional hospitalisation area.
[‡]To analyse the receipt of IMV, patients (39; 6.1%) deemed non-candidates for OTI-IMV due to advanced age, frail (dependent) baseline life, and major comorbidities were excluded from the total sample of 642 patients.
[§]Selecting only the subgroup of patients who died due to unfavorable evolution of respiratory failure.
[¶]Selecting only the subgroup of patients who received OTI-IMV in the ICU due to unfavourable evolution of respiratory failure.
95% CI: 95% confidence interval; HR: hazard ratio; ICU: intensive care unit; IMV: invasive mechanical ventilation; IRCU: intermediate respiratory care unit; N or n: sample size or number of observations; NC: conventional nasal cannulas; NIRS: non-invasive respiratory support; OR: odds ratio; OTI: orotracheal intubation; p-value: level of statistical significance; Q1: first quartile; Q3: third quartile; SOC: standard of care.

non-use) in terms of avoidance of death, IMV, and clinical failure, both up to 30 days and during the hospital stay, and in terms of promotion of de-escalation to NC and discharge to home up to 30 days.

Among subjects under IMV in the ICU, tocilizumab treatment was also ineffective in avoiding in-hospital death.

The benefit of tocilizumab therapy in reducing mortality for moderate (need for COT) or severe (need for NIRS or IRS) COVID-19 pneumonia is controversial[5]. We observed a large discrepancy in the scientific literature[5].

On the one hand, similar to our study, we found studies against the significant decrease in mortality with tocilizumab such as: the retrospective observational studies by Li et al.[24] (n = 1428; OR = 2.9; p = 0.0004) (where mortality was even significantly higher among those patients who had received tocilizumab), Okoh et al.[25] (n = 60; 10% vs. 8%; p = 0.823), Hill et al.[26] (n = 88; HR = 0.57; HR 95% CI = 0.21-1.52; p = 0.26), and Cardona-Pascual et al.[27] (n = 542; OR = 1.03; OR 95% CI = 0.63-1.68); the meta-analysis of seven retrospective observational studies by Lan et al.[28] (n = 592; 39/240 vs. 85/352; 16.3% vs. 24.1%; risk ratio = 0.62; risk ratio 95% CI = 0.31-1.22; p = 0.16; I^2 = 68%); and the randomized double-blind clinical trials BACC Bay[14] (n = 243; 9/161 vs. 3/82; 5.6% vs. 3.8%; HR = 1.52; HR 95% CI = 0.41-5.61), EMPACTA[15] (n = 377; 26/249 vs. 11/128; 10.4% vs. 8.6%; weighted difference = +2.0%, with 95% CI from –5,2% to +7.8%), COVACTA[16] (n = 438; 58/294 vs. 28/144; 19.7% vs. 19.4%; weighted difference = +0.3%, with 95% CI from –7.6% to +8.2%; p = 0.94), and REMDACTA[17] (n = 640; 78/430 vs. 41/210; 18.1% vs. 19.5%; HR = 0.95; HR 95% CI = 0.65-1.39; p = 0.79).

On the other hand, in contrast to our study, we found studies with conclusive results in favor of a significant decrease in mortality with tocilizumab such as: the retrospective observational studies by Guaraldi et al.[29] (n = 544; 13/179 vs. 73/365; 7% vs. 20%; HR = 0.38; HR 95% CI = 0.17-0.83; p = 0.015), Biran et al.[30] (n = 630; 102/210 vs. 256/420; 49% vs. 61%; HR = 0.71; HR 95% CI = 0.56-0.89; p = 0.0027), and Gupta et al.[31] (n = 3924; 125/433 vs. 1419/3491; 28.9% vs. 40.6%; HR = 0.71; HR 95% CI = 0.56-0.92; p = 0.004); the meta-analysis of 10 retrospective observational studies by Zhao et al.[32] (n = 1675; 132/675 vs. 283/1000; 19.5% vs. 28.3%; OR = 0.47; OR 95% CI = 0.36-0.60; p < 0.00001; I^2 = 74%; fixed-effect model); the randomized open-label clinical trials REMAP-CAP[8] (n = 755; 99/353 vs. 142/402; 28.0% vs. 35.3%; HR = 0.63; HR 95% CI = 0.49-0.81 [conversely, in survival: HR = 1.59; HR 95% CI = 1.24-2.05]) and RECOVERY[9] (n = 4116; 621/2022 vs. 729/2094; 30.7% vs. 34.8%; rate ratio = 0.85; rate ratio 95% CI = 0.76-0.94; p = 0.0028); and the meta-analysis of 19 randomized clinical trials by the World Health Organisation (WHO)[10] (n = 8048; 960/4299 vs. 1023/3749; 22.3% vs. 27.3%; OR = 0.83; OR 95% CI = 0.74-0.92; p < 0.001; I^2 = 3.3%; fixed-effect model).

Regarding the probability of receiving IMV, similar to our study, among all the previously mentioned studies, tocilizumab therapy did not significantly reduce it in the following studies: the retrospective observational studies by Guaraldi et al.[29] (n = 544; 33/179 vs. 57/365; 18% vs. 16%; p = 0.41) and Li et al.[24] (n = 1428; OR = 6.6; p < 0.0001) (it was even significantly higher in the group that had received tocilizumab); the meta-analysis of seven retrospective observational studies by Lan et al.[28] (n = 413; 47/134 vs. 44/279; 35.1% vs. 15.8%; risk ratio = 1.51; risk ratio 95% CI = 0.33-6.78; p = 0.59; I^2 = 86%); and the randomized double-blind clinical trials BACC Bay[14] (n = 243; 11/161 vs. 8/82; 6.8% vs. 10.0%; HR = 0.65; HR 95% CI = 0.26-1.62) and COVACTA[16] (n = 273; 51/183 vs. 33/90; 27.9% vs. 36.7%; weighted difference = –8.9%, with 95% CI from –20.7% to +3.0%).

However, in contrast to our study, these other studies did show a benefit of tocilizumab in terms of significantly reducing the probability of receiving IMV: the randomized open-label clinical trial RECOVERY[9] (n = 3554; 265/1754 vs. 343/1800; 15.1% vs. 19.1%; risk ratio = 0.79; risk ratio 95% CI = 0.69-0.92; p = 0.0019).

Regarding the composite probability of receiving IMV or death (clinical failure), similar to our study, among all previously mentioned studies, tocilizumab therapy did not significantly modify it in the following two studies: the randomized double-blind clinical trials BACC Bay[14] (n = 243; 17/161 vs. 10/82; 10.6% vs. 12.5%; HR = 0.83; HR 95% CI = 0.38-1.81; p = 0.64) and REMDACTA[17] (n = 640; 123/430 vs. 61/210; 28.6% vs. 29.0%; HR = 0.98; HR 95% CI = 0.72-1.34; p = 0.90).

However, in contrast to our study, these other studies did show a benefit of tocilizumab in terms of a significant reduction in the composite probability of receiving IMV or death (clinical failure): the retrospective observational study by Guaraldi et al.[29] (n = 544; 40/179 vs. 133/365; 22.6% vs. 36.5%; HR = 0.61; HR 95% CI = 0.40-0.92; p = 0.020); the randomized double-blind clinical trials COVACTA[16] (n = 273; 53/183 vs. 38/90;

29.0% vs. 42.2%; HR = 0.61; HR 95% CI = 0.40-0.94) and EMPACTA[15] (n = 377; 30/249 vs. 25/128; 12.0% vs. 19.3%; HR = 0.56; HR 95% CI = 0.33-0.97; p = 0.04); the randomised open-label clinical trial RECOVERY[9] (n = 3554; 619/1754 vs. 754/1800; 35.3% vs. 41.9%; risk ratio = 0.84; risk ratio 95% CI = 0.77-0.92; p < 0.0001); and the meta-analysis of 19 randomized clinical trials by the WHO[10] (n = 6838; 1009/3657 vs. 1126/3181; 27.6% vs. 35.4%; OR = 0.74; OR 95% CI = 0.66-0.82; I^2 = 0%).

Our study had several limitations. First, although analytical, it was an observational design instead of an experimental design, thus providing more restricted evidence (lower validity) for assessing the effectiveness of tocilizumab in patients with severe COVID-19 pneumonia receiving NIRS. Second, this resulted in selection bias, given the absence of randomization, reflected as heterogeneity (p ≤ 0.05) in many of the baseline characteristics between the tocilizumab + SOC group and the SOC group. This was a very important problem that seriously affected the validity of our study (potentially leading to erroneous conclusions), since the results obtained for the outcome variables (death, IMV, clinical failure...) could not be explained by the action of tocilizumab, but by the greater or lesser previous severity of the patients in one group compared to the other, according to the differences in the aforementioned baseline variables. However, we were able to overcome this serious problem using the PSM statistical method at a 1:1 ratio to balance the two groups with each other, thereby greatly reducing selection bias. After matching, both groups were homogeneous (p > 0.05) with each other on almost all baseline characteristics. Nonetheless, this came at the cost of a decrease in the sample size from 1306 to 642 patients, which increased the random error of the study, although not severely, as the sample size was still large. Third, it is possible that in the PSM we did not take into account other confounding baseline variables due to lack of knowledge or availability; for example, the prior COVID-19 vaccination status, although we knew that the vast majority of our patients had not been vaccinated against COVID-19 due to problems of accessibility to the vaccine during the study period or refusal of the vaccine. Fourth, this was an open-label study instead of a masked study, with no use of a placebo as a control group, which could have increased differential classification bias. Moreover, fifth, the administration of dexamethasone in intravenous boluses of 20mg/24h to all our patients could have caused an anti-inflammatory effect of such intensity that the subsequent addition of tocilizumab did not provide a significant anti-inflammatory synergy, resulting in a lack of effectiveness of tocilizumab. Although no studies have demonstrated a statistically significant superiority (especially in terms of mortality reduction) of the intravenous bolus compared to the standard dose in systemic glucocorticotherapy among patients admitted to the IRCU/ICU under NIRS/IRS for ARDS due to severe COVID-19 pneumonia (see clinical trials by Salton et al.[33], Salvarani et al.[34], Maskin et al.[35], Bouadma et al.[36], and Granholm et al.[37]), it cannot be entirely ruled out[38,39].

We highlight several strengths in our study. First, it had a large sample size (n = 642 after matching), which reduces random error. Second, although observational, it was a prospective longitudinal study, offering greater validity in its conclusions compared to a retrospective longitudinal study or a cross-sectional study. Third, the homogeneity achieved between both groups (tocilizumab + SOC group vs. SOC group) in the baseline characteristics after the matching process, which, as previously explained, eliminated the influence of these characteristics (CRP, time of evolution of symptoms, type of NIRS used, radiological extent of pneumonia, PaO_2/FiO_2 ratio...) on the results obtained for the outcome variables (death, IMV, clinical failure...) of our study; thus ensuring that these results were explained solely by the effect of tocilizumab, without interferences. In this way, we managed to provide our study with robust validity, avoiding erroneous conclusions. Fourth, to compare the results obtained for the outcome variables of death, IMV, clinical failure, and discharge to home within 30 days between the two groups, we performed survival analyses, which not only assessed whether or not the event in question occurred, but also how long it took for the event to occur (that is, they took into account the exact follow-up time of each patient); in this way, they provided more complete information. Moreover, fifth, following the clinical guidelines of our center, based on expert consensus[18,22,23], all patients (100%) received dexamethasone in intravenous boluses of 20mg/24h upon admission to the IRCU, thus completely eliminating selection bias related to the use and dosage of systemic glucocorticotherapy, an achievement that had not been attained in such a decisive manner in any of the previous studies.

Scientific literature, both observational (retrospective and prospective) and experimental (randomized clinical trials), including meta-analyses, remains heterogeneous regarding the effectiveness of tocilizumab in

terms of reducing death, IMV, and clinical failure among patients with moderate or severe COVID-19 pneumonia[5,40]. We consider that our study, despite being observational and non-experimental, contributes to increasing the existing scientific evidence on this issue, specifically in patients receiving NIRS. Although numerous clinical trials addressing this issue have already been published, we believe that the observational design of our study may be closer to the daily clinical practice environment ("real conditions") when treating this type of patients, a nuance that may be more difficult to achieve in clinical trials, which tend to have a much more controlled environment ("ideal conditions"). In addition, the application of the PSM statistical technique in our observational study has allowed us to correct selection bias to some extent and, therefore, to approach the validity of an open-label clinical trial, in which the randomization technique is used to eliminate selection bias. Taking into account the results of our study and the (very heterogeneous) results of all the aforementioned studies, we cannot yet take a definitive stance on the advisability or not of using tocilizumab in patients with severe COVID-19 pneumonia receiving NIRS, neither for nor against. If we refer to the highest levels of evidence, it is true that the meta-analysis of randomized clinical trials by the WHO[10], with a very large sample size (n = 8048), and represented above all by the open-label trial RECOVERY[9] (n = 4116), demonstrated that tocilizumab was effective in reducing mortality. However, on the other hand, the randomized clinical trials BACC Bay[14] (n = 243), EMPACTA (n = 377)[15], COVACTA[16] (n = 438), and REMDACTA[17] (n = 649), although they had much smaller sample sizes (greater randomized error), were double-blinded (greater validity, give the avoidance of classification bias), and demonstrated no effectiveness of tocilizumab in terms of mortality reduction.

Conclusion

In our study, among patients admitted to the IRCU with a diagnosis of severe COVID-19 pneumonia who required NIRS (HFNC, CPAP, and/or BPAP), tocilizumab therapy was not shown to reduce mortality nor the probability of receiving IMV, not even when combining these two variables (clinical failure), neither up to 30 days nor during the hospital stay. Furthermore, tocilizumab therapy did not influence the probability of de-escalation to NC nor the probability of discharge to home up to 30 days.

Supplementary data

Supplementary data are available at DOI: 10.24875/RPR.25000027. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Authors' contributions

All the authors were involved in the annotation of data in the patients' electronic medical records and in the subsequent creation of a database into which they transcribed the annotated data.

All the authors had access to the study data and took responsibility for the integrity of the data.

M. Lorente-González, J.R. Terán-Tinedo, C. Funes-Moreno, and P. Landete were responsible for the overall study design.

F. Neria-Serrano performed all statistical analyses for this study. M. Lorente-González was secondarily involved in many of the statistical analyses.

M. Lorente-González, J.R. Terán-Tinedo, F. Neria-Serrano, and P. Landete took equal responsibility for the accuracy of the data analysis.

M. Lorente-González carried out the complete writing of this manuscript and the preparation of all tables and figures, and performed all the bibliographic review necessary for the preparation of this manuscript.

M. Lorente-González, J.R. Terán-Tinedo, F. Neria-Serrano, and P. Landete performed data interpretation,

and they undertook an exhaustive process of critical review and revision of this manuscript once it was drafted by M. Lorente-González. They approved the final version of this manuscript for publication.

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Conflicts of interest

All the authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

M. Lorente-González, J.R. Terán-Tinedo, A. Zevallos-Villegas, P. Mariscal-Aguilar, M. Suárez-Ortiz, E. Cano-Sanz, M.A. Ortega-Fraile, J. Hernández-Núñez, E.M. Saiz-Lou, and P. Landete were medical researchers in the HEEIZ in an open-label randomized phase 3 clinical trial, NEPTUNO, to determine the efficacy and safety of plitidepsin (an antiviral drug) compared to control in adult patients requiring hospitalization for moderate COVID-19. P. Landete was the primary researcher. The rest of the authors mentioned were secondary researchers. PharmaMar payments were made to all the researchers.

P. Landete and E.M. Saiz-Lou are members of PharmaMar's Advisory Board.

J.R. Terán-Tinedo, C. Funes-Moreno, D. Laorden, and P. Landete were also researchers in the HEEIZ in an open-label phase 3 clinical trial, OSCAR, to evaluate the efficacy and safety of otilimab (an anti-GM-CSF monoclonal antibody) in patients ≥ 70 years requiring admission to the IRCU for severe COVID-19. P. Landete was the primary researcher. The rest of the authors mentioned were secondary researchers. GlaxoSmithKline (GSK) payments were made to all the researchers.

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Ethical considerations

Protection of humans and animals and ethical approval. All the authors declare that no experiments on humans or animals were performed for this research. It was an observational study. This observational study was approved by the Research Ethics Committee with Medical Products of the La Paz University Hospital, located in Madrid, Spain, under code PI-4865. All the authors were certified in standards of Good Clinical Practice (GCP) by The Global Health Network (TGHN). All the authors adhered to the ethical principles for medical research involving human subjects stated in the Declaration of Helsinki by the World Medical Association (WMA).

Informed consent, confidentiality of data, and right to privacy. Informed consent was obtained from all patients, verbally, since at the time of the study, we were faced with an enormous healthcare burden in the midst of the COVID-19 pandemic situation. This article does not contain any patient data that could compromise their confidentiality, infringe on their privacy, or enable their identification.

Use of artificial intelligence for generating text. All the authors declare that no generative artificial intelligence was used in the production of this manuscript, including its figures and tables.

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