



Article

# Date of Admission during COVID-19 Pandemic Impacted Patient Outcomes in Addition to the Higher Efficacy of Tocilizumab Plus High-Dose Corticosteroid Therapy Compared to Tocilizumab Alone

Moncef Belhassen-García <sup>1,2,3,†</sup>, Antonio Sánchez-Puente <sup>4,5,†</sup> , Pedro-Ignacio Dorado-Díaz <sup>4,5</sup>, Amparo López-Bernús <sup>1,2,3</sup>, Jesús Sampredo-Gómez <sup>4,5</sup>, Raúl Azibeiro-Melchor <sup>6</sup>, Edgard Marcano-Millán <sup>7</sup>, Beatriz Rodríguez-Alonso <sup>3</sup> , María-Elisa Sánchez-Barrado <sup>8</sup>, Ignacio Hernández-García <sup>9</sup> , Ignacio Madruga <sup>3</sup>, Guillermo Hernández-Pérez <sup>1,2,3</sup>, Cristina Carbonell <sup>1,2,3</sup>, Judit García-Aparicio <sup>3</sup>, Laura Burgos <sup>3</sup>, Eugenia López-Sánchez <sup>3</sup>, Carlos Reina <sup>3</sup>, Ana-María Ramón <sup>3</sup>, Laura Cestero-Ramírez <sup>7</sup>, Fátima Boumhir <sup>3</sup>, Daniel Encinas-Sánchez <sup>3</sup>, María Sánchez-Ledesma <sup>3</sup>, Jacinto Herráez <sup>3</sup>, Patricia Araoz <sup>3</sup>, María-José Sánchez-Crespo <sup>3</sup>, Sandra Rodríguez-Rodríguez <sup>3</sup>, Ana-Elisa Rodríguez-Gude <sup>3</sup>, Miguel-Vicente Sánchez-Hernández <sup>8</sup>, Rafael Borrás <sup>10</sup>, Víctor Sagredo-Meneses <sup>7</sup>, Pedro-Luis Sánchez <sup>4,5</sup>, Miguel Marcos <sup>3,\*</sup> , and José-Ángel Martín-Oterino <sup>3,‡</sup>



**Citation:** Belhassen-García, M.; Sánchez-Puente, A.; Dorado-Díaz, P.-I.; López-Bernús, A.; Sampredo-Gómez, J.; Azibeiro-Melchor, R.; Marcano-Millán, E.; Rodríguez-Alonso, B.; Sánchez-Barrado, M.-E.; Hernández-García, I.; et al. Date of Admission during COVID-19 Pandemic Impacted Patient Outcomes in Addition to the Higher Efficacy of Tocilizumab Plus High-Dose Corticosteroid Therapy Compared to Tocilizumab Alone. *J. Clin. Med.* **2022**, *11*, 198. <https://doi.org/10.3390/jcm11010198>

Academic Editors: Antonio Muro and Jan Jelrik Oosterheert

Received: 19 November 2021

Accepted: 27 December 2021

Published: 30 December 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

- <sup>1</sup> Infectious Diseases Unit, Department of Internal Medicine, University Hospital of Salamanca-IBSAL, 37007 Salamanca, Spain; mbelhassen@saludcastillayleon.es (M.B.-G.); alopezb@saludcastillayleon.es (A.L.-B.); ghernandezp@saludcastillayleon.es (G.H.-P.); ccarbonell@saludcastillayleon.es (C.C.)
  - <sup>2</sup> Centro de Investigación de Enfermedades Tropicales de la Universidad de Salamanca (CIETUS), University of Salamanca, 37007 Salamanca, Spain
  - <sup>3</sup> Department of Internal Medicine, University Hospital of Salamanca-IBSAL, University of Salamanca, 37007 Salamanca, Spain; beamedicina@gmail.com (B.R.-A.); imadruga@saludcastillayleon.es (I.M.); jgarciaa@saludcastillayleon.es (J.G.-A.); lmartinez-burgos@saludcastillayleon.es (L.B.); eugeniamlsanchez@gmail.com (E.L.-S.); carlosreinabaez@gmail.com (C.R.); ramon.anamaria@gmail.com (A.-M.R.); fboumhir@saludcastillayleon.es (F.B.); dencinas@saludcastillayleon.es (D.E.-S.); mledesma@saludcastillayleon.es (M.S.-L.); jherraez@saludcastillayleon.es (J.H.); paraoz@saludcastillayleon.es (P.A.); mjsanchezcre@saludcastillayleon.es (M.-J.S.-C.); drusan\_13@hotmail.com (S.R.-R.); anaelisarodriguezgude@gmail.com (A.-E.R.-G.); jmoterino@saludcastillayleon.es (J.-Á.M.-O.)
  - <sup>4</sup> Department of Cardiology, University Hospital of Salamanca-IBSAL, University of Salamanca, 37007 Salamanca, Spain; asanchezpu@saludcastillayleon.es (A.S.-P.); pidorado@saludcastillayleon.es (P.-I.D.-D.); jmsampredo@saludcastillayleon.es (J.S.-G.); plsanchez@saludcastillayleon.es (P.-L.S.)
  - <sup>5</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, 28013 Madrid, Spain
  - <sup>6</sup> Department of Hematology, University Hospital of Salamanca-IBSAL, University of Salamanca, 37007 Salamanca, Spain; raulazi@usal.es
  - <sup>7</sup> Department of Intensive Care Medicine, University Hospital of Salamanca-IBSAL, University of Salamanca, 37007 Salamanca, Spain; ejmarcano@saludcastillayleon.es (E.M.-M.); lauracr\_91@icloud.com (L.C.-R.); vsagredo@saludcastillayleon.es (V.S.-M.)
  - <sup>8</sup> Department of Anesthesiology and Reanimation, University Hospital of Salamanca-IBSAL, University of Salamanca, 37007 Salamanca, Spain; mesanchezba@saludcastillayleon.es (M.-E.S.-B.); mvsanchezher@saludcastillayleon.es (M.-V.S.-H.)
  - <sup>9</sup> Department of Preventive Medicine and Public Health, Lozano Blesa University Clinical Hospital of Zaragoza, 50009 Zaragoza, Spain; ihernandezga@salud.aragon.es
  - <sup>10</sup> Department of Emergency Medicine, University Hospital of Salamanca-IBSAL, University of Salamanca, 37007 Salamanca, Spain; rborras@saludcastillayleon.es
- \* Correspondence: mmarcos@usa.es; Tel: +34-923-291100 (ext. 55437); Fax: +34-923-294739
- † Antonio Sánchez-Puente and Moncef Belhassen-García have contributed equally to this manuscript.
- ‡ Miguel Marcos and José-Ángel Martín-Oterino have contributed equally to this manuscript.

**Abstract:** Background: The evidence for the efficacy of glucocorticoids combined with tocilizumab (TCZ) in COVID-19 comes from observational studies or subgroup analysis. Our aim was to compare outcomes between hospitalized COVID-19 patients who received high-dose corticosteroid pulse therapy and TCZ and those who received TCZ. Methods: A retrospective single-center study was performed on consecutive hospitalized patients with severe COVID-19 between 1 March and 23 April 2020. Patients treated with either TCZ (400–600 mg, one to two doses) and methylprednisolone pulses (MPD-TCZ group) or TCZ alone were analyzed for the occurrence of a combined endpoint of death and need for invasive mechanical ventilation during admission. The independence of both treatment groups was tested using machine learning classifiers, and relevant variables that were potentially different between the groups were measured through a mean decrease accuracy algorithm. Results: An earlier date of admission was significantly associated with worse outcomes regardless of treatment type. Twenty patients died (27.0%) in the TCZ group, and 33 (44.6%) died or required intubation ( $n = 74$ ), whereas in the MPD-TCZ group, 15 (11.0%) patients died and 29 (21.3%) patients reached the combined endpoint ( $n = 136$ ;  $p = 0.006$  and  $p < 0.001$ , respectively). Machine learning methodology using a random forest classifier confirmed significant differences between the treatment groups. Conclusions: MPD and TCZ improved outcomes (death and invasive mechanical ventilation) among hospitalized COVID-19 patients, but confounding variables such as the date of admission during the COVID-19 pandemic should be considered in observational studies.

**Keywords:** COVID-19; SARS-CoV-2; infectious diseases; machine learning; tocilizumab; corticosteroids

## 1. Introduction

Coronavirus disease 2019 (COVID-19) has evolved into a global pandemic with a profound impact on public health. Approximately 20% of cases may develop severe COVID-19 infection with pneumonia, which could potentially lead to hypoxic respiratory failure, acute respiratory distress syndrome, and/or septic shock [1,2]. Patients with severe or critical COVID-19 usually display features of systemic inflammation, with increased levels of proinflammatory cytokines (interleukin (IL)-1 or IL-6) and other acute phase reactants (C-reactive protein (CRP), D-dimer or ferritin [3]). This hyperinflammatory response to SARS-CoV-2 has been suggested to play a key role in the pathogenesis of severe COVID-19, including lung damage and microvascular thrombosis [4].

Accordingly, immunomodulatory drugs such as glucocorticoids have been proposed as a treatment for patients with severe COVID-19 to tackle hyperinflammation and immune dysregulation [5]. Indeed, the use of dexamethasone and other glucocorticoids in severe COVID-19 has been associated with lower mortality in several trials [6]. Although controversial results have been reported, evidence also suggests that the use of interleukin (IL)-6 antagonists, such as tocilizumab (TCZ), is associated with a mortality benefit [7,8]. It is uncertain, however, whether the combined use of TCZ and glucocorticoids improves survival, but limited evidence from observational studies [9] and a subgroup analysis of an open-label trial [10] point toward a potential benefit of this combination. Observational studies, however, have potential limitations, such as differences in patients characteristics between groups, the availability of drugs at any given time, and mortality differences in different time points of the pandemic [11,12]. These limitations may be partially overcome with the use of advanced statistical techniques and previously validated prognostic scores to adjust baseline risk, such as the COVID-19 Salamanca Risk Score [13].

Therefore, the aim of our study was to compare, by means of machine learning methodology, the outcomes of hospitalized patients with COVID-19 who received TCZ compared with those who received TCZ and high-dose glucocorticoid pulse therapy.

## 2. Materials and Methods

### 2.1. Population and Study Design

We performed a retrospective study at a 1000-bed university tertiary care hospital located in Salamanca (northwestern Spain). Consecutive patients admitted due to severe COVID-19 from 1 March to 23 April (peak of the first wave in our center) were analyzed for this study. Patients with COVID-19 were considered to have severe disease because of respiratory failure or other organ dysfunction assessed by Sequential Organ Failure Assessment (SOFA) score  $> 2$ , which received per protocol in our center TCZ and/or corticosteroids. TCZ was administered according to our hospital protocol and the treatment consisted of two doses until 26 March (administered at a dosage of 8 mg/kg (max 800 mg) by two consecutive administrations 8 h apart) and one dose thereafter (600 mg (400 mg for weight  $< 70$  kg)), due to the recommendation issued on this date by the Spanish Agency of Medicines and Medical Devices (AEMPS) based on drug shortage. High-dose corticosteroid pulse therapy was administered according to the hospital protocol after 26 March (250 mg of intravenous methylprednisolone (MPD) for 3–5 days) and previously at the physician's discretion. Patients who received at least 125 mg of intravenous MPD (or dexamethasone equivalent in case the hospital was out of stock) for 2 to 5 days and intravenous TCZ composed the corticosteroid and TCZ (MPD-TCZ) group, and patients who received only intravenous TCZ composed the TCZ group. Patients within these groups were also able to receive hydroxychloroquine and lopinavir/ritonavir according to the protocol. These groups of patients (MPD and MPD-TCZ) were deemed comparable after stratification by our own validated prognosis score [13]. Thus, we proposed the hypothesis that since the choice of treatment was mainly based on the timing of admission and was not dependent on the characteristics of the patient, the effect of the treatment could be compared between both groups. To understand the potential differences between the patients in both treatment groups, we also analyzed baseline characteristics, comorbidities, outpatient treatments, symptoms, admission measures, and laboratory findings at the time of admission for these patients with three approaches: (a) univariate tests between measured variables in both groups; (b) a comparison using a previously validated machine learning prognostic score for the severity of the disease (COVID-19 Salamanca Risk Score [13]); and (c) the development of a newly trained machine learning model aimed at detecting differences between both treatment groups to be used as a multivariate test.

### 2.2. Data Collection

We collected data on demographic variables, the patients' individual comorbidities and Charlson Comorbidity Index scores, chronic medical treatments, clinical characteristics, physical examination parameters, and the laboratory findings available at hospital admission, as previously described [13]. Regarding patient outcomes, we defined the severity of disease progression during hospitalization as the use of invasive mechanical ventilation or death. Institutional approval was provided by the Ethics Committee of the University Hospital of Salamanca (2020/03/470), and the need for informed consent was waived. All datasets were anonymously analyzed, and the study was performed following the current recommendations of the Declaration of Helsinki [13].

### 2.3. Univariate Analysis

The differences in the measured variables between both treatment groups were analyzed using Student's *t*-test for continuous variables and Fisher's exact test for binary variables. If treatment was assigned randomly to all patients and the measured variables were independent, the *p* values of these tests would be distributed uniformly. Consequently, we would expect approximately six variables showing differences with statistical significance ( $p < 0.05$ ) between both treatment groups in univariate analysis. In addition, Kaplan–Meier curves were used to compare mortality rate between groups (long rank test).

#### 2.4. Machine Learning Severity Score Comparison by Means of COVID-19 Salamanca Risk Score

The relevance of the collected variables in the prognosis of the patients was previously analyzed in the same cohort of patients [13], where a prognostic score was developed through machine learning to predict severity (defined as death or intubation), regardless of treatment type. The internal validation results evaluated the predictive power with a value of 0.85 of the area under the receiver operating characteristic (ROC) curve [14]. Of note, an external validation using another cohort from the Hospital Clinic of Barcelona, Spain, obtained an area under the receiver operator characteristic (ROC) curve of 0.83, consistent with the internal validation results [13].

As previously described, the final model of this COVID-19 Salamanca Risk Score identified the following variables as predictors of severity in both our cohort and the external validation cohort [13]: the peripheral blood oxygen saturation (SpO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio, patient age, estimated glomerular filtration rate, procalcitonin levels, C-reactive protein levels, updated Charlson comorbidity index scores, and lymphocyte levels. We considered these predictors separately in the multivariate analysis, as differences in these variables between the treatment groups could have likely impacted our results. Additionally, due to the changing epidemiological situation and evolution of the COVID-19 pandemic, we performed a comparison of the mortality and severity in both treatment groups matched to both the basal risk score of the patients and the date of admission of the patients. This comparison was performed as a subclassification matching with five subclasses divided along quintiles [15], to assess the effects of the confounders within each treatment group, the effect of the treatment within each stratum, the distribution of each group along the subclasses, and the region of common support. A Mann–Kendall test was also performed to detect trends in the outcomes according to the date of admission.

#### 2.5. Multivariate Analysis through Machine Learning Methodology

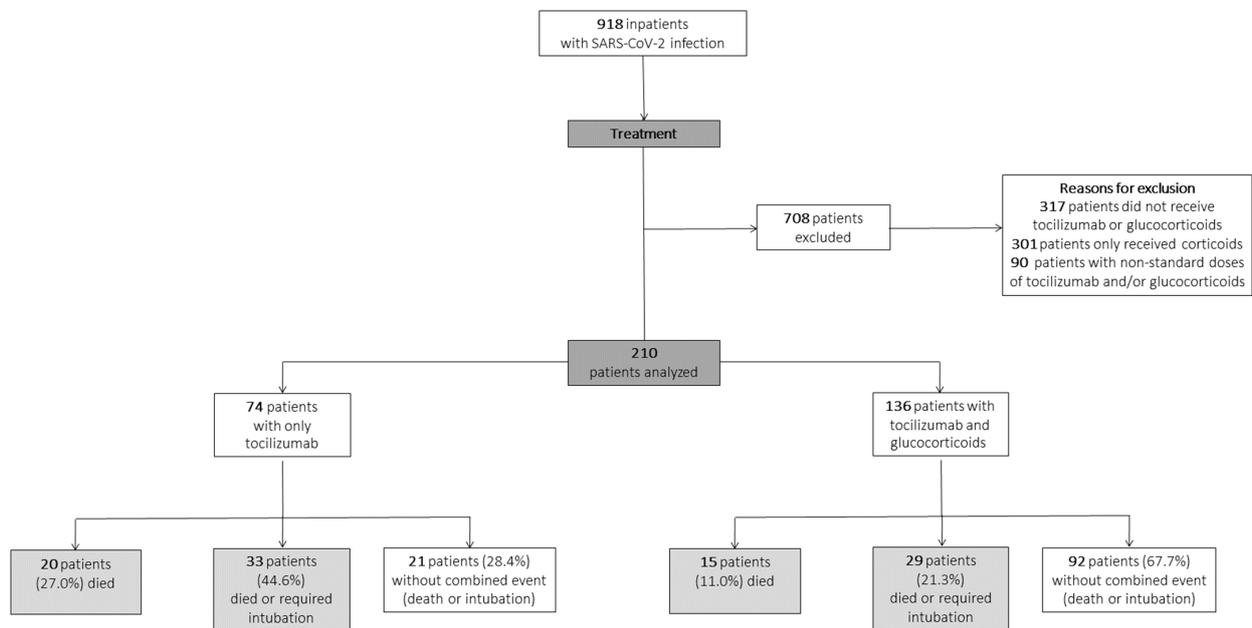
To test the independence between both treatment groups in a multivariate analysis, we developed a machine-learning algorithm for predicting whether a patient belonged to the TCZ or MPD-TCZ group. Machine learning methods were chosen because they encompass classical statistic models (such as logistic regression) while providing the benefits of regularization and cross-validation, and also offer different categories of models of greater discrimination power in case of non-linear relationships and interaction effects between the variables. The performance of this algorithm was given by the area under the ROC curve and the corresponding 95% confidence interval. The null hypothesis (lack of statistically significant differences between the groups) was rejected if the value of 0.5 for the area under the ROC curve fell outside the confidence interval. This analysis was performed both using all clinical variables and using only the variables included in the abovementioned COVID-19 Salamanca Risk Score [13].

In brief, machine learning methodology was described as follows [13]: data from patients in both treatment groups were preprocessed, variables with less than 70% completion were dropped, and missing values were filled using a 10-nearest neighbors algorithm [16]. Three classification algorithms that represented state-of-the-art approaches in machine learning, XGBoost [17], random forest [18], and regularized logistic regression, were trained within a stratified 10-fold cross-validation scheme with 10 repetitions for validation [19]. The evaluation metrics and their confidence intervals were obtained from the testing folds in the cross-validation scheme [20,21]. Additionally, we used a mean decrease accuracy algorithm [18] to identify the most relevant variables in the classification algorithms. In addition to the machine learning classifiers, we tested the discriminatory power of the date of admission, the SOFA score, and the abovementioned machine learning severity score to provide a reference.

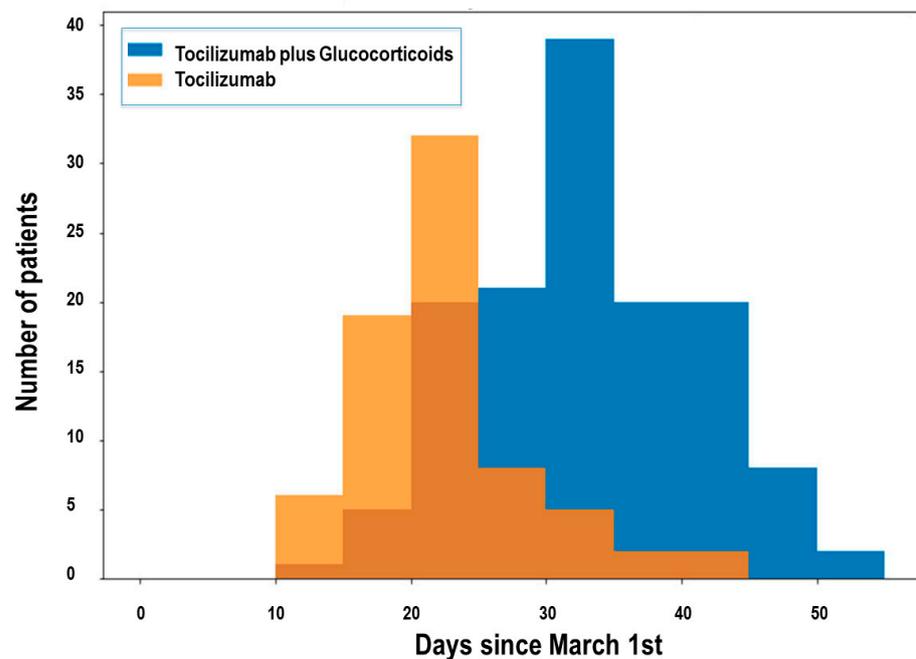
### 3. Results

Between 1 March and 23 April 2020, 918 patients were admitted to the University Hospital of Salamanca because of severe COVID-19 with PCR-confirmed infections. Of them,

74 patients received only TCZ, and 136 patients received TCZ and high-dose corticosteroids (126 received MPD and 10 received dexamethasone; Figure 1). The choice of treatment changed with the date of admission, according to modifications in our hospital protocol (Figure 2).



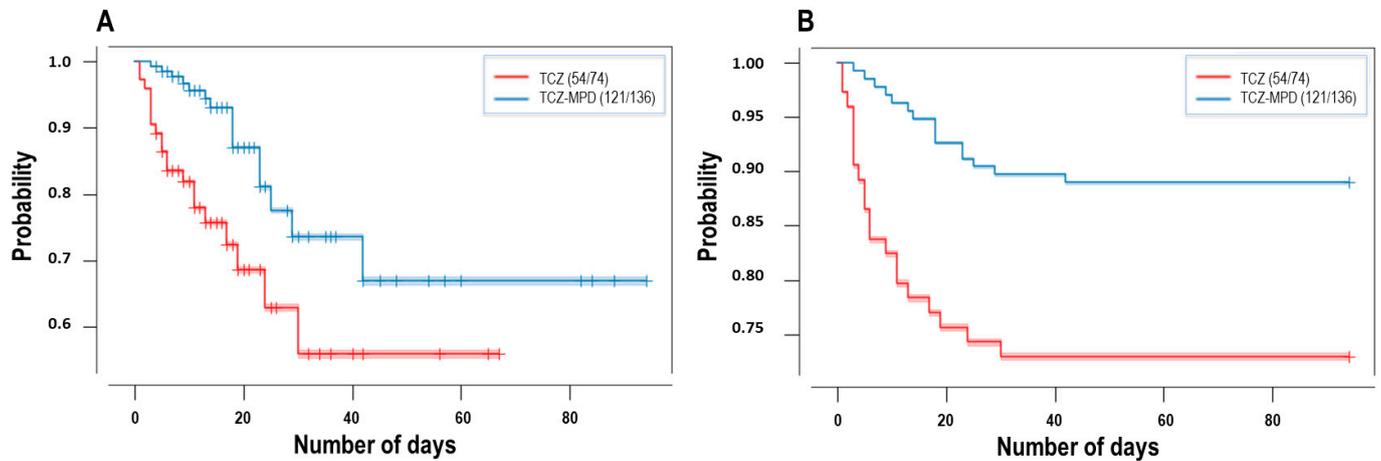
**Figure 1.** Flowchart of patient selection according to hospital protocol. Patients were included in the tocilizumab and glucocorticoid group if they received at least 125 mg of intravenous methylprednisolone (or dexamethasone equivalent) for 2 to 5 days and one or two doses of intravenous tocilizumab.



**Figure 2.** Distribution of patients according to date of admission.

A total of 20 patients died (27%) in the TCZ group and the combined event of death and need for invasive mechanical ventilation occurred in 33 patients (44.6%), whereas 15 patients died (11%), and 29 patients died or required intubation (21.3%) in the MPD-TCZ

group. These improved outcomes in the MPD-TCZ group were significant after univariate analysis ( $p = 0.006$  for mortality and  $p < 0.001$  for severity in favor of the MPD-TCZ group). Survival analysis and Kaplan–Meier curves also showed a significant effect ( $p = 0.002$ ) of MPD-TCZ in mortality (Figure 3).



**Figure 3.** (A) Kaplan–Meier survival curves of mortality in admitted patients with severe COVID-19 censoring patients on the date of their discharge ( $p = 0.00195$ , log-rank test). (B) Kaplan–Meier survival curves of mortality in admitted patients with severe COVID-19, without censoring patients ( $p = 0.00151$ , log-rank test).

Regarding other differences in patient characteristics between treatment groups, statistically significant differences between the measured variables can be found in Tables 1 and 2. In summary, differences were found in the following variables: fever, nasal congestion, hemoptysis, the SOFA score, treatment with hydroxychloroquine or azithromycin prior to hospital admission, and serum levels of calcium, magnesium, protein, creatine kinase, and fibrinogen.

**Table 1.** Admission characteristics of patients by treatment group.

Name	Tocilizumab and Glucocorticoids		Tocilizumab		p-Value
	n	Mean	n	Mean	
Age, years (mean ± SD)	136	64.3 ± 11.7	74	65.2 ± 10.9	0.578
Male, n (%)	136	92 (67.6%)	74	51 (68.9%)	0.878
<b>COMORBIDITIES</b>					
Classic Charlson comorbidity index, n (mean ± SD)	136	1.0 ± 1.6	74	0.9 ± 1.3	0.553
Updated Charlson comorbidity index, n (mean ± SD)	136	0.6 ± 1.4	74	0.5 ± 1.1	0.616
Myocardial infarction, n (%)	136	10 (7.4%)	74	6 (8.1%)	1
Congestive heart failure, n (%)	136	7 (5.1%)	74	5 (6.8%)	0.757
Peripheral vascular disease, n (%)	136	4 (2.9%)	74	3 (4.1%)	0.699
Arrhythmia, n (%)	136	10 (7.4%)	74	3 (4.1%)	0.55
Cerebrovascular accident, n (%)	136	5 (3.7%)	74	3 (4.1%)	1
Cognitive impairment, n (%)	136	2 (1.5%)	74	3 (4.1%)	0.348
Other central nervous system diseases, n (%)	136	3 (2.2%)	74	2 (2.7%)	1
Chronic obstructive pulmonary disease, n (%)	136	4 (2.9%)	74	5 (6.8%)	0.284
Asthma, n (%)	136	5 (3.7%)	74	2 (2.7%)	1
Other chronic pulmonary disease, n (%)	136	7 (5.1%)	74	6 (8.1%)	0.388
Rheumatological disorder, n (%)	136	7 (5.1%)	74	3 (4.1%)	1
Peptic ulcer disease, n (%)	136	4 (2.9%)	74	2 (2.7%)	1
Hemiplegia/paraplegia, n (%)	136	0 (0.0%)	74	1 (1.4%)	0.352
Chronic kidney disease (eGFR < 30), n (%)	136	1 (0.7%)	74	1 (1.4%)	1
Solid tumor, n (%)	136	11 (8.1%)	74	3 (4.1%)	0.387

**Table 1.** Cont.

	Tocilizumab and Glucocorticoids		Tocilizumab		
Neoplasia without metastasis, <i>n</i> (%)	136	10 (7.4%)	74	1 (1.4%)	0.101
Solid tumor metastasis, <i>n</i> (%)	136	1 (0.7%)	74	0 (0.0%)	1
Hematologic neoplasm, <i>n</i> (%)	136	3 (2.2%)	74	3 (4.1%)	0.427
Chronic acute leukemia, <i>n</i> (%)	136	1 (0.7%)	74	2 (2.7%)	0.284
Lymphoma, <i>n</i> (%)	136	3 (2.2%)	74	1 (1.4%)	1
Hypertension, <i>n</i> (%)	136	55 (40.4%)	74	32 (43.2%)	0.77
Other endocrine disease, <i>n</i> (%)	136	12 (8.8%)	74	9 (12.2%)	0.475
Inflammatory autoimmune disease, <i>n</i> (%)	136	9 (6.6%)	74	4 (5.4%)	1
Transplant recipient, <i>n</i> (%)	136	0 (0.0%)	74	1 (1.4%)	0.352
Obesity, <i>n</i> (%)	105	23 (21.9%)	60	19 (31.7%)	0.195
Dyslipidemia, <i>n</i> (%)	136	43 (31.6%)	74	34 (45.9%)	0.051
Current smoking, <i>n</i> (%)	116	9 (7.8%)	72	4 (5.6%)	0.769
Former/current smoking, <i>n</i> (%)	116	33 (28.4%)	72	14 (19.4%)	0.225
Diabetes, <i>n</i> (%)	136	31 (22.8%)	74	17 (23.0%)	1
Cancer, <i>n</i> (%)	136	13 (9.6%)	74	6 (8.1%)	0.806
<b>PREVIOUS MEDICATIONS, <i>n</i> (%)</b>					
Angiotensin-converting enzyme inhibitors	135	16 (11.9%)	73	7 (9.6%)	0.817
Angiotensin II receptor blockers	135	23 (17.0%)	71	20 (28.2%)	0.072
Chemotherapy	136	3 (2.2%)	74	0 (0.0%)	0.554
Immunosuppressants	136	4 (2.9%)	73	3 (4.1%)	0.697
Systemic corticosteroids	136	3 (2.2%)	73	4 (5.5%)	0.242
Inhaled corticosteroids	136	6 (4.4%)	73	2 (2.7%)	0.716
Acenocumarol	136	4 (2.9%)	74	1 (1.4%)	0.659
Low-molecular-weight heparin	136	5 (3.7%)	74	3 (4.1%)	1
Direct oral anticoagulants	136	10 (7.4%)	74	5 (6.8%)	1
New oral anticoagulants	136	1 (0.7%)	74	1 (1.4%)	1
Androgen antagonists	136	1 (0.7%)	74	0 (0.0%)	1
Hydroxychloroquine treatment prior to admission, <i>n</i> (%)	136	22 (16.2%)	74	5 (6.8%)	0.055
Azithromycin treatment prior to admission, <i>n</i> (%)	136	39 (28.7%)	74	10 (13.5%)	0.016
<b>SYMPTOMS/SIGNS</b>					
Duration of symptoms before admission (days), <i>n</i> (mean ± SD)	127	7.2 ± 4.5	71	7.2 ± 5.1	0.939
Fever, <i>n</i> (%)	136	101 (74.3%)	74	66 (89.2%)	0.012
Duration of fever before admission (days), <i>n</i> (mean ± SD)	90	6.7 ± 4.0	64	6.2 ± 3.5	0.396
Maximum temperature, <i>n</i> (mean ± SD)	92	38.3 ± 0.6	60	37.9 ± 4.1	0.357
Dry cough, <i>n</i> (%)	136	82 (60.3%)	74	48 (64.9%)	0.554
Productive cough, <i>n</i> (%)	136	8 (5.9%)	74	10 (13.5%)	0.072
Chest Pain, <i>n</i> (%)	136	15 (11.0%)	74	9 (12.2%)	0.823
Dyspnea, <i>n</i> (%)	136	84 (61.8%)	74	53 (71.6%)	0.174
Diminished level of consciousness, <i>n</i> (%)	136	9 (6.6%)	74	7 (9.5%)	0.587
Seizures, <i>n</i> (%)	136	1 (0.7%)	74	0 (0.0%)	1
Asthenia, <i>n</i> (%)	136	55 (40.4%)	74	33 (44.6%)	0.562
Myalgia/arthralgia, <i>n</i> (%)	136	28 (20.6%)	74	20 (27.0%)	0.306
Anosmia, <i>n</i> (%)	136	6 (4.4%)	74	2 (2.7%)	0.715
Ageusia, <i>n</i> (%)	136	9 (6.6%)	74	2 (2.7%)	0.335
Conjunctivitis, <i>n</i> (%)	136	1 (0.7%)	74	0 (0.0%)	1
Nasal congestion, <i>n</i> (%)	136	1 (0.7%)	74	5 (6.8%)	0.021
Headache, <i>n</i> (%)	136	12 (8.8%)	74	6 (8.1%)	1
Odynophagia, <i>n</i> (%)	136	5 (3.7%)	74	3 (4.1%)	1
Hemoptysis, <i>n</i> (%)	136	0 (0.0%)	74	5 (6.8%)	0.005
Nausea/vomiting, <i>n</i> (%)	136	19 (14.0%)	74	6 (8.1%)	0.267
Abdominal pain, <i>n</i> (%)	136	7 (5.1%)	74	1 (1.4%)	0.265
Diarrhea, <i>n</i> (%)	136	34 (25.0%)	74	15 (20.3%)	0.497

**Table 1.** Cont.

	Tocilizumab and Glucocorticoids		Tocilizumab		
BASELINE CHARACTERISTICS					
COVID-19 Salamanca Risk Score ( <i>n</i> )	136	28.6 ± 23.4	74	30.8 ± 26.0	0.543
SOFA Score ( <i>n</i> )	136	1.0 ± 1.2	74	1.4 ± 1.6	0.045
Pneumonia, (%)	136	130 (95.6%)	74	70 (94.6%)	0.744
Labored breathing, <i>n</i> (mean ± SD)	135	41 (30.4%)	74	26 (35.1%)	0.536
Heart rate, beats/min, <i>n</i> (mean ± SD)	136	87.3 ± 16.3	74	89.6 ± 16.2	0.339
Mean arterial pressure, <i>n</i> (mean ± SD)	136	87.6 ± 13.6	74	91.5 ± 13.5	0.048
Glasgow Coma Scale, <i>n</i> (mean ± SD)	136	14.8 ± 1.0	74	14.8 ± 0.9	0.903
Temperature, <i>n</i> (mean ± SD)	136	37.1 ± 0.9	74	37.1 ± 1.1	0.739
SpO <sub>2</sub> /FiO <sub>2</sub> ratio, <i>n</i> (mean ± SD)	136	368.5 ± 90.5	74	342.6 ± 116.6	0.076
Oxygen supplementation, <i>n</i> (mean ± SD)	136	67 (49.3%)	74	40 (54.1%)	0.564
Pulmonary infiltrates on chest X-ray, <i>n</i> (mean ± SD)	136	131 (96.3%)	74	71 (95.9%)	1
Bilateral pulmonary infiltrate, <i>n</i> (mean ± SD)	136	121 (89.0%)	74	65 (87.8%)	0.823
Lopinavir/ritonavir treatment	136	128 (94.1%)	74	72 (97.3%)	0.5

SD: standard deviation; SpO<sub>2</sub>/FiO<sub>2</sub>: arterial oxygen pressure/inspired oxygen fraction; SOFA: sequential organ failure assessment.

**Table 2.** Admission laboratory findings of patients from internal validation cohort by outcome.

Laboratory Findings					
Name	<i>n</i>	Mean	<i>n</i>	Mean	<i>p</i> -Value
Glucose (mg/dL)	128	136.4 ± 61.7	71	126.5 ± 35.2	0.216
Urea (mg/dL)	131	44.1 ± 30.0	72	43.8 ± 27.6	0.936
Urate (mg/dL)	112	4.9 ± 2.0	62	4.8 ± 1.8	0.95
eGFR (mL/min/1.73 m <sup>2</sup> )	133	70.9 ± 21.4	74	71.6 ± 20.8	0.813
Calcium (mg/dL)	125	9.0 ± 0.6	63	8.8 ± 0.5	0.003
Magnesium (mmol/L)	125	2.1 ± 0.3	63	2.0 ± 0.2	0.05
Sodium (mmol/L)	130	136.0 ± 3.3	71	136.5 ± 3.3	0.348
Potassium (mmol/L)	130	4.0 ± 0.5	71	4.0 ± 0.4	0.74
Alanine Aminotransferase (U/L)	129	49.5 ± 73.8	70	41.8 ± 37.7	0.418
Aspartate Aminotransferase (U/L)	107	54.4 ± 46.7	37	68.6 ± 51.3	0.123
Alkaline phosphatase (U/L)	126	87.6 ± 99.0	70	70.3 ± 28.2	0.153
Gamma-glutamyl transferase (U/L)	127	108.8 ± 287.9	70	67.1 ± 52.1	0.232
Lactate dehydrogenase (U/L)	128	394.4 ± 149.9	71	397.0 ± 142.4	0.905
Proteins (g/L)	125	7.6 ± 0.6	64	7.4 ± 0.5	0.012
Albumin (g/L)	122	3.8 ± 0.4	64	3.8 ± 0.4	0.956
Creatine kinase (U/L)	123	140.0 ± 136.3	63	215.1 ± 283.7	0.016
Procalcitonin (ng/mL)	82	0.4 ± 1.1	67	0.6 ± 1.7	0.548
Prothrombine time (%)	116	86.5 ± 16.9	67	84.6 ± 17.6	0.488
INR	115	1.2 ± 0.5	67	1.3 ± 1.2	0.391
Activated partial thromboplastine time (s)	63	34.7 ± 6.8	59	34.6 ± 4.9	0.904
Fibrinogen levels (mg/dL)	112	693.1 ± 192.3	61	626.2 ± 189.8	0.03
Hemoglobin (g/dL)	133	14.3 ± 1.9	72	14.3 ± 1.8	0.954
White blood cells count (×10 <sup>9</sup> /L)	116	11.9 ± 35.9	63	7.5 ± 6.3	0.339
Neutrophil cell count (×10 <sup>9</sup> /L)	131	6.2 ± 3.2	72	6.2 ± 3.7	0.948
Lymphocyte count (×10 <sup>9</sup> /L)	132	3.0 ± 23.3	72	1.2 ± 1.1	0.511
Monocyte count (×10 <sup>9</sup> /L)	130	0.5 ± 0.9	71	0.5 ± 0.3	0.667
C-reactive protein (mg/dL)	128	14.6 ± 11.0	71	14.5 ± 11.7	0.947
Interleukin-6 (pg/mL)	25	89.5 ± 104.9	16	183.7 ± 382.0	0.248
D-dimer level (pg/mL)	126	2.2 ± 7.9	64	2.9 ± 11.3	0.617
Platelet count (×10 <sup>9</sup> /L)	134	217.8 ± 90.1	74	195.7 ± 79.1	0.079

**Table 2.** Cont.

Name	Laboratory Findings				
	<i>n</i>	Mean	<i>n</i>	Mean	<i>p</i> -Value
Bilirubin (total) (mg/dL)	132	0.6 ± 0.3	73	0.6 ± 0.3	0.738
Creatinine (mg/dL)	133	1.1 ± 0.4	74	1.1 ± 0.5	0.973

Variables are presented as the mean ± standard deviation. eGFR: estimated glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; INR: international normalized ratio.

The average COVID-19 Salamanca Risk Score, as previously described [13], was 30.7% for the TCZ group and 28.7% for the MPD-TCZ group ( $p = 0.543$ ), which means that patients from both groups have a similar risk of severe outcomes according to this score and therefore that these groups may be considered comparable due to similar baseline risk. In addition, no statistically significant differences were found in any of the variables composing this score between both treatment groups. The comparison of the mortality and severity between the treatment groups matched to the score risk of patients is shown in Table 3. Worse outcomes were associated with higher COVID-19 Salamanca Risk Score in both groups, but patients in the MPD-TCZ group consistently had lower values for death and death or intubation. In addition, and due to the differences in the distribution of patients according to date of admission (Figure 2), data from Table 3 were also matched to date of admission, with the average risk score for each period (as shown in Table 4). After matching these data, we found that both mortality and combined end-point improved over time. Indeed, until 21st March mortality exceeded 30% and combined-end point reached 50% for both TCZ and MPD and TCZ alone but clearly declined thereafter for both groups. The baseline risk as calculated with COVID-19 Salamanca Risk Score of patients treated with tocilizumab also changed over time, although the average prognostic score was similar for both treatment groups. Very few patients were treated with tocilizumab alone after 26th March due to the change in protocol. A Mann–Kendall trend test showed that the combined endpoint events had a decreasing significant trend with admission date in both the TCZ group ( $p = 0.004$ ) and the MPD-TCZ group ( $p = 0.007$ ). Therefore, this finding shows that patients had worse outcomes in the first weeks of the analyzed period regardless of treatment type.

**Table 3.** Mortality and severity for each treatment group by risk score classification.

Average COVID-19 Salamanca Risk Score	Tocilizumab Group		Tocilizumab and Glucocorticoids Group		<i>p</i> -Value	
	Death or Intubation	Death	Death or Intubation	Death	Death or Intubation	Death
0–8.8%	2/16 = 12.5%	1/16 = 6.3%	3/26 = 11.5%	0/26 = 0%	1.0	0.381
8.8–15.7%	3/11 = 27.3%	2/11 = 18.2%	4/31 = 12.9%	0/31 = 0%	0.353	0.064
15.7–28%	6/16 = 37.5%	2/16 = 12.5%	4/26 = 15.4%	2/26 = 7.7%	0.142	0.628
28–49.5%	9/15 = 60%	4/15 = 26.7%	7/27 = 25.9%	5/27 = 18.5%	0.047	0.698
49.5–100%	13/16 = 81.3%	11/16 = 68.8%	11/26 = 42.3%	8/26 = 30.8%	0.024	0.026
TOTAL	33/74 = 44.6%	20/74 = 27%	29/136 = 21.3%	15/136 = 11%	<0.001	0.006

Therefore, univariate analysis and stratification according to baseline risk score calculated by means of COVID-19 Salamanca Risk Score and date of admission showed that patients who received tocilizumab and glucocorticoids had better outcomes than those receiving tocilizumab alone, without significant differences in baseline risk score but with differences regarding date of admission. In order to include other variables potentially associated with outcomes, machine learning models were built to test differences between the two treatment groups by means of multivariable analysis. Figure 4 shows the ROC curve for the machine learning models for predicting the treatment group of a patient. The best model built only with the seven variables included in the COVID-19 Salamanca Risk Score

(the peripheral blood oxygen saturation (SpO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio, patient age, the estimated glomerular filtration rate, procalcitonin levels, C-reactive protein levels, updated Charlson comorbidity index scores, and lymphocytes levels) was regularized logistic regression, which obtained an area under the ROC curve of 0.49 (0.40–0.57). However, the best model built with all the clinical variables was the random forest classifier, which obtained an area under the ROC curve of 0.60 (0.51–0.69), thus detecting statistically significant differences between both groups. Therefore, multivariable analysis including all potentially relevant variables confirmed a statistically significant difference between both treatment groups regarding outcomes. The most relevant variables used for this multivariable analysis as calculated by the mean decrease accuracy algorithm can be found in Table 5. Variables that were not included in this table and were not significant in the univariate analysis were less likely to impact mortality in our cohort, regardless of potential differences between groups.

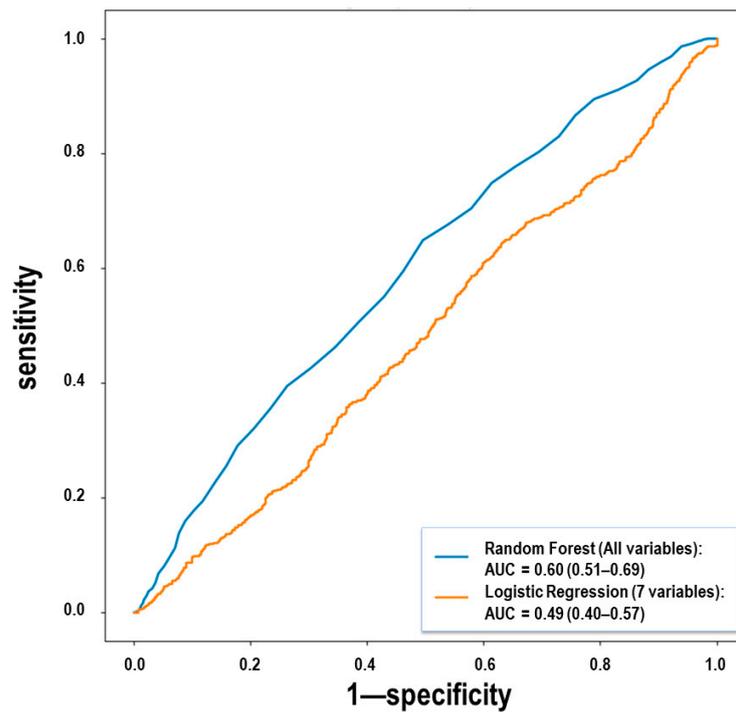
**Table 4.** Mortality and severity for each treatment group by date of admission.

Date of Admission	Tocilizumab			Tocilizumab and Glucocorticoids		
	Average COVID-19 Salamanca Risk Score	Death or Intubation	Death	Average COVID-19 Salamanca Risk Score	Death or Intubation	Death
March 1st–March 21st	33.2%	22/40 = 55%	13/40 = 32.5%	44.4%	6/12 = 50%	4/12 = 33.3%
March 22nd–March 25th	34.1%	9/21 = 42.9%	7/21 = 33.3%	27.8%	5/21 = 23.8%	2/21 = 9.5%
March 26th–March 31st	25.7%	2/7 = 28.6%	0/7 = 0%	29.9%	7/39 = 17.9%	4/39 = 19.3%
April 1st–April 7th	11.5%	0/4 = 0%	0/4 = 0%	24.4%	5/30 = 16.7%	1/30 = 3.3%
April 8th–April 14th	4.3%	0/2 = 0%	0/2 = 0%	25.9%	6/34 = 17.6%	4/34 = 11.8%
TOTAL	30.8%	33/74 = 44.6%	20/74 = 27%	28.6%	29/136 = 21.3%	15/136 = 11%

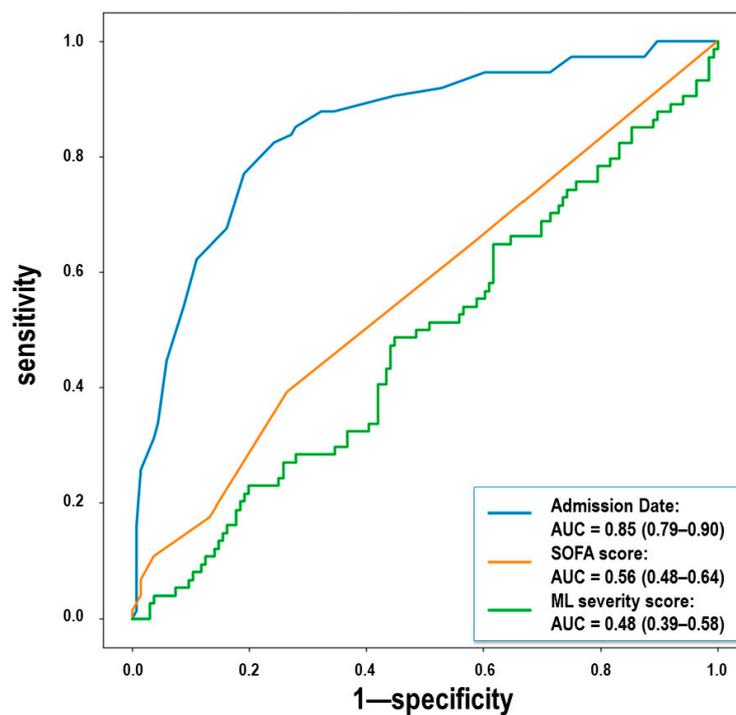
**Table 5.** Relative importance of top 10 variables used by the random forest classifier according to mean decrease accuracy algorithm (scaled to the most important one).

Variable	Relative Importance
Mean arterial pressure	1.000
Magnesium levels	0.822
Protein levels	0.759
Lactate dehydrogenase (ldh)	0.651
Sodium levels	0.434
Hemoptysis	0.429
D-dimer levels	0.404
Neutrophil count	0.380
Aspartate aminotransferase (ast) levels	0.370
Lymphocyte count	0.369

In addition, we compared whether the date of admission was more relevant than prognostic scores to differentiate between treatment groups. Figure 5 shows the ROC curves for the SOFA score, machine learning severity score, and date of admission, when used to distinguish between both treatment groups, showing no discriminant power for the first two and great discriminant power for the latter. Therefore, we confirmed that the date of admission was a significant variable potentially impacting outcome differences between treatment groups.



**Figure 4.** Receiver operating characteristic curves of the different classification algorithms for treatment difference, including best classifier (random forest with all variables) and logistic regression with 7 variables for comparison. The model with all variables was able to show statistically significant differences between both treatment groups but the model constructed with the 7 clinically relevant variables according to the COVID-19 Salamanca Risk Score did not find differences.



**Figure 5.** Receiver operating characteristic curves for treatment difference classification based on admission date, SOFA score and machine learning (ML) COVID-19 Salamanca Risk Score. There are no statistically significant differences between both treatment groups according to both prognostic scores, but admission date showed significant discriminant power.

#### 4. Discussion

In our study, we found that the combination treatment with glucocorticoids and TCZ, when compared with TCZ alone, is associated with both reduced mortality and a reduced risk of a composite endpoint of invasive mechanical ventilation and death. To allow comparison, we selected two groups with similar baseline risk according to our previously validated risk score, which made the presence of potential unknown confounders related to patient characteristics unlikely [13]. Additionally, we used a machine learning methodology to assess potential differences between groups after adjusting for other variables, and we found that a random forest classifier including all variables confirmed a significant difference between both treatment groups.

Our results are in line with data from other observational studies showing that this combination therapy is associated with better outcomes when compared with either TCZ or glucocorticoids alone [9,22–24]. In addition, subgroup analysis from the Recovery trial [10] found that patients who were receiving glucocorticoids were more likely to benefit from TCZ, and a similar result was reported from a recent meta-analysis including TCZ and other IL-6 antagonists [8]. The efficacy of this combination, however, is not yet fully established due to the lack of randomized trials and the presence of controversial results from other studies (e.g., improved outcomes with TCZ alone instead of with combination therapy [25]). Moreover, previous studies on this topic were prone to potential biases due to small sample sizes and retrospective and observational study designs, despite the different statistical techniques employed to reduce this risk, such as the inverse probability of the treatment weights technique [9] or propensity score matching [24].

In line with this, although we found a significant difference between the treatments after machine learning methodology, we also found that mortality improved over time as an independent variable associated with better outcomes. In our study, the choice of treatment for each patient was made according to the protocol at the time of admission: patients treated in the early stages of the pandemic received only TCZ, while in later stages, the protocol for treatment changed to include both TCZ and corticosteroids. Mortality improvement over time may have therefore been due, at least in part, to different treatment efficacies, as the random forest classifier also confirmed, but a potential confounding effect for the date of admission has to be considered. Indeed, improved mortality over time has already been described in other series of COVID-19 patients and may also be explained by the increased knowledge of the disease, different population groups being affected by the pandemic at different time points, and reduced hospital burden, regardless of treatment type [11]. This would support the hypothesis of the potential role of the date of admission as a confounding variable because such variable would be a risk factor for an effect (e.g., mortality) and would also be associated with the exposure subject of our study in the population from which the effect derives, without being an intermediate step in the causal pathway between the exposure and the effect that we have analyzed [26]. This variable is, however, complex, since a higher mortality risk has also been described at times of high incidence in comparison with inter-wave period [12] and an analysis of epidemiological time delay dynamics showed a marked decrease in the time from hospitalization to death and infection to death during high incidence periods when health care system was under the most pressure [27]. In any case, taking into account this variable could be of great interest since other studies that compared groups of patients with historical controls during the peak of the first pandemic wave have also found worse outcomes for the cohort admitted earlier in the pandemic [22,23]. Considering the striking differences in incidence in different periods of the pandemic, our data, along with the results from other authors, allow us to draw the conclusion that the date of admission should be considered as a variable in observational studies during the COVID-19 pandemic. In addition, this variable should be taken into account in other diseases when relevant temporal trends are present.

Another potential limitation of our study is the different sample sizes between groups and the use of different types and doses of steroids. Although the Recovery trial [6,28] used a low dose (6 mg) of dexamethasone for treatment, other studies, including a small

randomized trial, have shown the efficacy of pulse therapy with other steroids [29–31], such as MPD (which achieves higher lung tissue concentrations than dexamethasone). Regarding dose, a recent systematic review has shown that COVID-19 patients may be more likely to benefit from medium-high doses of steroids (defined as 90–250 mg/day or 1.5–4 mg/kg/day of MPD or an equivalent dose of other steroids), but higher or lower doses were both associated with improved survival rates [32]. Therefore, despite the lack of evidence regarding an optimal therapy, we do not think that combining the data of patients with equivalent corticosteroid dosages may have a major impact on our results, and other studies have also used this approach [24]. In any case, there is a lack of data on the comparison of corticosteroid pulse therapy with low-dose oral corticosteroids. Finally, although we only present data from the first wave of the pandemic, it is very unlikely to have data to compare tocilizumab vs. tocilizumab and corticosteroids after the first wave because corticosteroids became part of standard treatment in an early phase of the pandemic.

## 5. Conclusions

In conclusion, our data support the potential utility of the combination of glucocorticoids with TCZ, in line with previous findings but outcomes were influenced by date of admission regardless of treatment type and thus this variable as a potential source of bias should be considered in observational studies on this topic. Rigorous randomized trials are needed to assess the efficacy of TCZ and corticosteroids combined and to evaluate the optimal corticosteroid dose for treatment.

**Author Contributions:** M.M., M.B.-G., P.-L.S., A.S.-P., J.S.-G., P.-I.D.-D. and J.-Á.M.-O. participated in the design, analysis of data and interpretation of results, and drafted the manuscript; P.-L.S., A.S.-P., J.S.-G. and P.-I.D.-D. performed the machine-learning model; R.A.-M., E.M.-M., A.L.-B., B.R.-A. and C.C. contributed to the design, acquisition of data, analysis, interpretation of results, and revised the manuscript for intellectual important content; M.-E.S.-B., I.M., I.H.-G., G.H.-P., L.B., E.L.-S., C.R., A.-M.R., L.C.-R., F.B., D.E.-S., J.G.-A., M.S.-L., J.H., P.A., M.-J.S.-C., S.R.-R., A.-E.R.-G., M.-V.S.-H., R.B. and V.S.-M. collaborated in the collection of data, interpretation of results, and revising the manuscript for intellectual important content. A.S.-P. and M.B.-G. are both first-authors of this manuscript. J.-Á.M.-O. and M.M. are both senior-authors of this manuscript. All authors have read and agreed to the published version of the manuscript.

**Funding:** Partially funded by Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación (Madrid, Spain) and FEDER Funds “Una manera de hacer Europa”, by grants CIBERCV CB16/11/00374 to Pedro-L Sánchez and RD16/0017/0023 to Miguel Marcos, and by Institute of Biomedical Research of Salamanca (IBSAL) through a special grant for COVID-19 research.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University Hospital of Salamanca (2020/03/470), date of approval: 2 April 2020.

**Informed Consent Statement:** Institutional approval was provided by the Ethics Committee of the University Hospital of Salamanca (2020/03/470) and the need for informed consent was waived.

**Data Availability Statement:** Relevant anonymized patient level data are available on reasonable request. Code to develop machine learning model is already available.

**Acknowledgments:** We are indebted to Rafael Borrás, which passed away after the writing of this manuscript, for his inspiring leadership and hard work during COVID-19 pandemic. We acknowledge to María-Victoria Mateos and José-Ramón González-Porrás from the Hematology Department of the University Hospital of Salamanca as well as to all doctors and healthcare personnel involved in the COVID-19 Working Team from the Internal Medicine Department and others departments of the University Hospital of Salamanca including: José-Ignacio Martín-González, María-José García-Rodríguez, Ángela Romero-Alegría, Nora Gutiérrez-San Pedro, Leticia Moralejo-Alonso, José-Ignacio Herrero-Herrero, Antonio Chamorro, Mercedes Martín-Ordiales, Celestino Martín-Álvarez, Felipe Álvarez-Navia, Ronald Macías, Alejandro Rolo, Juan-Francisco Soto, Laura Manzanedo, Luis Seisdedos, Juan-Miguel Manrique, Alfredo-Javier Collado, Ana Rodríguez, Silvia Ojea, José-María Bastida,

María Díez-Campelo, Alberto Hernández-Sánchez, Luis-Mario Vaquero, Cristina de-Ramón, Estefanía Pérez, Borja Puertas, Daniel Presa, Ana Yeguas, Ana África, María-Victoria Coral, Rosa Tejera, Laura Gil, Javier Fernández, Elisa Acosta, Sonia Pastor, Marta Fonseca, María-de-los-Ángeles Pérez-Nieto, Ernesto Parras, María Cartagena, Víctor Barreales, Óscar Humberto, María Bartol, Olga Compán, Ana Ramón, Raquel Rodríguez, Silvia Ruiz, Sonsoles Garrosa, Alexis-Alan Rodrigo, Sara Alonso, Raquel Domínguez, Felipe Peña, María García-Duque, Ana Menéndez, Edgar Marcano-Millán, María-Teresa Moreira-Barroso, Noelia Cubino-Bóveda, María-Luisa Pérez-García, Sonia Peña-Balbuena, Eduardo Sobejano-Fuertes, Sandra Inés, Miriam López-Parra, Catalina Lorenzo, Adela Carpio, David Polo-San-Ricardo, and all the staff members. We want also to thank all COVID-19 patients admitted at the University Hospital of Salamanca and their families.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

## References

- Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N.; et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* **2020**, *395*, 565–574. [[CrossRef](#)]
- Wu, Z.; McGoogan, J.M. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA* **2020**, *323*, 1239–1242. [[CrossRef](#)]
- Gustine, J.N.; Jones, D. Immunopathology of Hyperinflammation in COVID-19. *Am. J. Pathol.* **2021**, *191*, 4–17. [[CrossRef](#)] [[PubMed](#)]
- Dorward, D.A.; Russell, C.D.; Um, I.H.; Elshani, M.; Armstrong, S.D.; Penrice-Randal, R.; Millar, T.; Lerpiniere, C.E.B.; Tagliavini, G.; Hartley, C.S.; et al. Tissue-Specific Immunopathology in Fatal COVID-19. *Am. J. Respir. Crit. Care Med.* **2021**, *203*, 192–201. [[CrossRef](#)] [[PubMed](#)]
- Hertanto, D.M.; Wiratama, B.S.; Sutanto, H.; Wungu, C.D.K. Immunomodulation as a Potent COVID-19 Pharmacotherapy: Past, Present and Future. *J. Inflamm. Res.* **2021**, *14*, 3419–3428. [[CrossRef](#)] [[PubMed](#)]
- Sterne, J.A.C.; Murthy, S.; Diaz, J.V.; Slutsky, A.S.; Villar, J.; Angus, D.C.; Annane, D.; Azevedo, L.C.P.; Berwanger, O.; Cavalcanti, A.B.; et al. Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis. *JAMA J. Am. Med. Assoc.* **2020**, *324*, 1330–1341. [[CrossRef](#)]
- Ghosn, L.; Chaimani, A.; Evrenoglou, T.; Davidson, M.; Graña, C.; Schmucker, C.; Bollig, C.; Henschke, N.; Sguassero, Y.; Nejtgaard, C.H.; et al. Interleukin-6 blocking agents for treating COVID-19: A living systematic review. *Cochrane Database Syst. Rev.* **2021**, *2021*, CD013881. [[CrossRef](#)]
- The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Domingo, P.; Mur, I.; Mateo, G.M.; Gutierrez, M.D.M.; Pomar, V.; de Benito, N.; Corbacho, N.; Herrera, S.; Millan, L.; et al. Association between Administration of IL-6 Antagonists and Mortality among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA* **2021**, *326*, 449–518. [[CrossRef](#)]
- Ruiz-Antorán, B.; Sancho-López, A.; Torres, F.; Moreno-Torres, V.; de Pablo-López, I.; García-López, P.; Abad-Santos, F.; Rosso-Fernández, C.M.; Aldea-Perona, A.; Montané, E.; et al. Combination of Tocilizumab and Steroids to Improve Mortality in Patients with Severe COVID-19 Infection: A Spanish, Multicenter, Cohort Study. *Infect. Dis. Ther.* **2021**, *10*, 347–362. [[CrossRef](#)] [[PubMed](#)]
- Abani, O.; Abbas, A.; Abbas, F.; Abbas, M.; Abbasi, S.; Abbass, H.; Abbott, A.; Abdallah, N.; Abdelaziz, A.; Abdelfattah, M.; et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. *Lancet* **2021**, *397*, 1637–1645. [[CrossRef](#)]
- Dennis, J.M.; McGovern, A.P.; Vollmer, S.J.; Mateen, B.A. Improving Survival of Critical Care Patients with Coronavirus Disease 2019 in England: A National Cohort Study, March to June 2020. *Crit. Care Med.* **2021**, *49*, 209–214. [[CrossRef](#)] [[PubMed](#)]
- Xiong, X.; Wai, A.K.C.; Wong, J.Y.H.; Tang, E.H.M.; Chu, O.C.K.; Wong, C.K.H.; Rainer, T.H. Impact of varying wave periods of COVID-19 on in-hospital mortality and length of stay for admission through emergency department: A territory-wide observational cohort study. *Influ. Other Respir. Viruses* **2021**. [[CrossRef](#)] [[PubMed](#)]
- Marcos, M.; Belhassen-García, M.; Sánchez-Puente, A.; Sampedro-Gomez, J.; Azibeiro, R.; Dorado-Díaz, P.-I.; Marcano-Millán, E.; García-Vidal, C.; Moreira-Barroso, M.-T.; Cubino-Bóveda, N.; et al. Development of a severity of disease score and classification model by machine learning for hospitalized COVID-19 patients. *PLoS ONE* **2021**, *16*, e0240200. [[CrossRef](#)] [[PubMed](#)]
- Hanley, J.A.; McNeil, B.J. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* **1982**, *143*, 29–36. [[CrossRef](#)] [[PubMed](#)]
- Stuart, E. Matching methods for causal inference: A review and a look forward. *Stat. Sci.* **2010**, *25*, 1–21. [[CrossRef](#)]
- Beretta, L.; Santaniello, A. Nearest neighbor imputation algorithms: A critical evaluation. *BMC Med. Inform. Decis. Mak.* **2016**, *16*, 197–208. [[CrossRef](#)]

17. Chen, T.; Guestrin, C. XGBoost: A scalable tree boosting system. In Proceedings of the ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, San Francisco, CA, USA, 13–17 August 2016; Association for Computing Machinery: New York, NY, USA, 2016; pp. 785–794.
18. Breiman, L. Random forests. *Mach. Learn.* **2001**, *45*, 5–32. [[CrossRef](#)]
19. Airola, A.; Pahikkala, T.; Waegeman, W.; De Baets, B.; Salakoski, T. An experimental comparison of cross-validation techniques for estimating the area under the ROC curve. *Comput. Stat. Data Anal.* **2011**, *55*, 1828–1844. [[CrossRef](#)]
20. Nadeau, C.; Bengio, Y. Inference for the generalization error. *Mach. Learn.* **2003**, *52*, 239–281. [[CrossRef](#)]
21. Bouckaert, R.R. Choosing between two learning algorithms based on calibrated tests. In Proceedings of the Twentieth International Conference on Machine Learning (ICML, 2003), Washington, DC, USA, 21–24 August 2003; pp. 51–58.
22. Ramiro, S.; Mostard, R.L.M.; Magro-Checa, C.; Van Dongen, C.M.P.; Dormans, T.; Buijs, J.; Gronenschild, M.; De Kruif, M.D.; Van Haren, E.H.J.; Van Kraaij, T.; et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: Results of the CHIC study. *Ann. Rheum. Dis.* **2020**, *79*, 1143–1151. [[CrossRef](#)]
23. Van den Eynde, E.; Gasch, O.; Oliva, J.C.; Prieto, E.; Calzado, S.; Gomila, A.; Machado, M.L.; Falgueras, L.; Ortonobes, S.; Morón, A.; et al. Corticosteroids and tocilizumab reduce in-hospital mortality in severe COVID-19 pneumonia: A retrospective study in a Spanish hospital. *Infect. Dis.* **2021**, *53*, 291–302. [[CrossRef](#)]
24. López-Medrano, F.; Asín, M.A.P.-J.; Fernández-Ruiz, M.; Carretero, O.; Lalueza, A.; de la Calle, G.M.; Caro, J.M.; de la Calle, C.; Catalán, M.; García-García, R.; et al. Combination therapy with tocilizumab and corticosteroids for aged patients with severe COVID-19 pneumonia: A single-center retrospective study. *Int. J. Infect. Dis.* **2021**, *105*, 487–494. [[CrossRef](#)]
25. Rodríguez-Baño, J.; Pachón, J.; Carratala, J.; Ryan, P.; Jarrín, I.; Yllescas, M.; Arribas, J.R.; Berenguer, J.; Muñoz, E.A.; Gil Divasson, P.; et al. Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: A multicentre cohort study (SAM-COVID-19). *Clin. Microbiol. Infect.* **2021**, *27*, 244–252. [[CrossRef](#)]
26. Delgado-Rodríguez, M.; Llorca, J. Bias. *J. Epidemiol. Community Health* **2004**, *58*, 635–641. [[CrossRef](#)] [[PubMed](#)]
27. Ward, T.; Johnsen, A. Understanding an evolving pandemic: An analysis of the clinical time delay distributions of COVID-19 in the United Kingdom. *PLoS ONE* **2021**, *16*, e0257978. [[CrossRef](#)] [[PubMed](#)]
28. Horby, P.; Lim, W.S.; Emberson, J.R.; Mafham, M.; Bell, J.L.; Linsell, L.; Phil, D.; Staplin, N.; Brightling, C.; Med, F.; et al. Dexamethasone in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* **2021**, *384*, 693–704. [[CrossRef](#)]
29. Ruiz-Irastorza, G.; Pijoan, J.-I.; Bereciartua, E.; Dunder, S.; Dominguez, J.; Garcia-Escudero, P.; Rodrigo, A.; Gomez-Carballo, C.; Varona, J.; Guio, L.; et al. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. *PLoS ONE* **2020**, *15*, e0239401. [[CrossRef](#)]
30. Cusacovich, I.; Aparisi, Á.; Marcos, M.; Ybarra-Falcón, C.; Iglesias-Echevarria, C.; Lopez-Veloso, M.; Barraza-Vengoechea, J.; Dueñas, C.; Martínez, S.A.J.; Rodríguez-Alonso, B.; et al. Corticosteroid Pulses for Hospitalized Patients with COVID-19: Effects on Mortality. *Mediat. Inflamm.* **2021**, *2021*, 6637227. [[CrossRef](#)] [[PubMed](#)]
31. Edalatifard, M.; Akhtari, M.; Salehi, M.; Naderi, Z.; Jamshidi, A.; Mostafaei, S.; Najafizadeh, S.R.; Farhadi, E.; Jalili, N.; Esfahani, M.; et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: Results from a randomised controlled clinical trial. *Eur. Respir. J.* **2020**, *56*, 2002808. [[CrossRef](#)]
32. Li, J.; Liao, X.; Zhou, Y.; Wang, L.; Yang, H.; Zhang, W.; Zhang, Z.; Kang, Y. Comparison of Associations between Glucocorticoids Treatment and Mortality in COVID-19 Patients and SARS Patients. *Shock*, 2021; *in press*. [[CrossRef](#)]