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Impact of early interferon-β treatment on the prognosis of patients with COVID-19 in the first wave: A post hoc analysis from a multicenter cohort

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ABSTRACT

Background: Interferon-β is an attractive drug for repurposing and use in the treatment of COVID-19, based on its in vitro antiviral activity and the encouraging results from clinical trials. The aim of this study was to analyze the impact of early interferon-β treatment in patients admitted with COVID-19 during the first wave of the pandemic.
Methods: This post hoc analysis of a COVID-19@Spain multicenter cohort included 3808 consecutive adult patients hospitalized with COVID-19 from 1 January to 17 March 2020. The primary endpoint was 30-day all-cause mortality, and the main exposure of interest was subcutaneous administration of interferon-β, defined as early if started ≤ 3 days from admission. Multivariate logistic and Cox regression analyses were conducted to identify the associations of different variables with receiving early interferon-β therapy and to assess its impact on 30-day mortality. A propensity score was calculated and used to both control for confounders and perform a matched cohort analysis.
Results: Overall, 683 patients (17.9%) received early interferon-β therapy. These patients were more severely ill. Adjusted HR for mortality with early interferon-β was 1.03 (95% CI, 0.82–1.30) in the overall cohort, 0.96 (0.82–1.13) in the PS-matched subcohort, and 0.89 (0.60–1.32) when interferon-β treatment was analyzed as a time-dependent variable.

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Conclusions: In this multicenter cohort of admitted COVID-19 patients, receiving early interferon-β therapy after hospital admission did not show an association with lower mortality. Whether interferon-β might be useful in the earlier stages of the disease or specific subgroups of patients requires further research.

1. Introduction

Since the pandemic of coronavirus disease 2019 (COVID-19) beginning in December 2019, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, more than 272 million cases and 5.3 million deaths have been reported around the world as of 16 December 2021 [1]. Compared to the other beta coronaviruses that have caused epidemics over the last two decades, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 exhibits higher infectivity and lower fatality; hence, its destructive and expansive nature has led to the most devastating pandemic of the century [2].

Symptomatic SARS-CoV-2 infection presents a characteristic sequence of phases, beginning with accelerated viral replication that can escape the immune system, manifesting as an influenza-like illness. Within 7–10 days from symptom onset, an inflammatory phase develops in up to 20% of infected individuals, typically heralded by an organizing pneumonia [3]. Around 5% of patients subsequently deteriorate, with immune system dysregulation and stimulation of a hyperinflammatory state leading to acute respiratory distress syndrome (ARDS), endothelial damage and microvascular injury, and hypercoagulability [4].

In the absence of an antiviral drug with proven clinical efficacy against SARS-CoV-2, physicians across the world began treating patients with agents such as hydroxychloroquine, azithromycin, lopinavir/ritonavir, ivermectin, and remdesivir based on their empirically observed in vitro activity against coronaviruses. Most of these drugs are not used today because they did not demonstrate clinical efficacy in clinical trials, and there is currently no antiviral agent that can unequivocally reduce mortality. In this context, knowing the role of the inflammatory response in the development of severe complications, it is likely that developing a compound with both antiviral and immunomodulatory effects would be the most powerful approach to combat COVID-19.

Interferons (IFNs) are a group of cytokines that are crucial not only for antiviral immunity but also to dampen the innate response, preventing damage from pathogen-induced inflammation. However, coronaviruses encode interferon antagonists that actively interfere with host interferon induction and/or signaling [5]. There is evidence that the severity of COVID-19 is correlated with highly impaired type I IFN activity, characterized by no IFN-β and low IFN-α production [6]. Furthermore, it has been reported that at least 10% of patients with life-threatening pneumonia have neutralizing auto-antibodies (auto-Abs) against type I IFNs, which, like the abovementioned inborn errors, are associated with persistent blood viral load and an exacerbated inflammatory response [7]. The most important barriers to the use of type I IFNs as therapy are the lack of knowledge about timing and appropriate dosing and the increased chance of immunopathology by further stimulation of proinflammatory signals [8,9]. Promising results obtained from three randomized controlled trials with small sample sizes showed that subcutaneous injection of IFN-β in patients with moderate-to-severe COVID-19 improved clinical outcomes with no specific side effects [10–12]. However, two other multicenter randomized controlled trials, mostly in adult inpatients with mild-to-moderate COVID-19, did not show clinical efficacy of interferon treatment [13,14].

With these data, we hypothesized that early administration of IFN-β would be associated with lower mortality compared to standard treatment alone. Therefore, we conducted a post hoc study using data from the multicenter retrospective COVID-19@Spain cohort to assess the protective effect of early IFN-β treatment compared with no IFN-β administration in patients hospitalized with COVID-19 [15].

2. Methods

2.1. Study design, sites, and participants

This post hoc analysis of the multicenter retrospective COVID-19@Spain cohort included 4035 consecutive adult patients with COVID-19 confirmed by real-time polymerase chain reaction (RT-PCR) assay, hospitalized in 127 Spanish centers between 1 January and 17 March 2020 and followed for 30 days after admission. The methodology has previously been described in detail [15–18]. In summary, all data were collected using an electronic case report form (eCRF) and added to a database built with Research Electronic Data Capture (REDCap) tools hosted at the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)/AIDS Study Group (GESIDA) Foundation [19]. The Ethics Committee for Research with Medicines of Hospital General Universitario Gregorio Marañón approved the study and waived informed consent for the collection of clinical data. Approval was also obtained at each participating center, conforming with local requirements. Hospitals in which IFN-β was not used in any patient were excluded because they would cause a cluster effect not amenable to the control. Patients who died less than 48 h after admission were excluded from the study, whether they received IFN-β or not. This analysis was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (Table S1) [20].

2.2. Variables and definitions

The outcome variable was 30-day all-cause mortality, and the main exposure of interest was subcutaneous administration of IFN-β, which was classified as early IFN-β treatment (EIT) if started within $\leq$ 3 days (day of hospital admission was considered day 0), late IFN-β treatment (LIT) if started from day 4 onward, or no IFN-β treatment (NIT) if only standard treatment (not including IFN-β) was provided.

Additional exposure variables recorded at hospital admission were demographic data, chronic underlying conditions, admission symptoms and signs, laboratory findings, and severity according to the COVID-19 SEIMC score (14) and the WHO Clinical Progression Scale [21]. Additionally, other treatments for COVID-19 and use of respiratory support during hospitalization were recorded (Table 1).

2.3. Statistical analysis

The χ^2 or Fisher's exact test was used to compare categorical variables. When appropriate, continuous variables were dichotomized using data classification analysis, according to their association with mortality. Hospitals were classified into those with lower (<30%) and higher (≥30%) mortality as well as lower (<40%) and higher (≥40%) IFN-β prescription based on the 75th percentile cut-off point, and these variables were retained in the models. Cox regression was used to analyze the impact of EIT on 30-day mortality. Variables with $p < 0.10$ in univariate comparisons and those considered of clinical importance were entered into the multivariate models. The variables in the models were selected manually using a backward stepwise process. Interactions and collinearity were evaluated. Sensitivity analyses for 30-day mortality were performed, including changes in covariables and specific categorizations, using the variable IFN-β treatment as a time-dependent variable considered from the admission date. In addition, a propensity score (PS) for receiving EIT instead of NIT was calculated, and its ability to predict the observed data was assessed using the area under the receiver operating characteristic curve (AUROC) with a 95% confidence interval

Table 1
Features of Patients with COVID-19 According to Interferon Group.

Variable	EIT (n = 683)	LIT (n = 440)	NIT (n = 2685)	*P* Value (Early vs NIT)	*P* Value (Late vs NIT)
Male sex	451 (67)	297 (68.1)	1559 (58.8)	< .001	< .001
Age > 75 years	193 (28.3)	140 (31.9)	968 (36.1)	< .001	.09
Comorbidities					
Hypertension	337 (49.8)	240 (54.9)	1337 (50.1)	.90	.06
Diabetes	150 (22)	103 (23.7)	553 (20.8)	.49	.16
Obesity (BMI >30)	101 (16.3)	73 (18.3)	283 (11.9)	.003	< .001
Chronic heart disease	138 (20.3)	100 (23.3)	632 (23.8)	.05	.81
Chronic pulmonary disease (not asthma)	132 (19.4)	92 (21.3)	456 (17.1)	.16	.04
Asthma	52 (7.6)	33 (7.7)	197 (7.4)	.83	.85
Liver cirrhosis	5 (.7)	10 (2.3)	33 (1.2)	.17	.08
Chronic kidney disease stage 4 (eGFR <30 mL/min/1.73 m^2)	24 (3.5)	17 (3.9)	149 (5.6)	.03	.15
Chronic neurologic disorder	36 (5.3)	24 (5.6)	278 (10.4)	< .001	.002
Solid/hematologic neoplasm (active)	28 (4.1)	38 (8.8)	267 (10)	< .001	.42
Admission symptoms and signs					
Headache	65 (10)	47 (11.3)	292 (11.6)	.23	.85
Myalgia/arthralgia	178 (27.2)	119 (29)	611 (24.1)	.10	.03
Cough	547 (81)	320 (74.1)	1850 (69.7)	< .001	.07
Dyspnea	411 (60.8)	213 (49.1)	1191 (45)	< .001	.12
Vomiting/nausea	76 (11.4)	54 (12.7)	329 (12.6)	.43	.92
Diarrhea	92 (13.8)	62 (14.6)	290 (11.1)	.05	.04
Low SpO_2 (age-adjusted)[a]	261 (43.8)	101 (26.6)	498 (20.9)	< .001	.01
Heart rate ≥ 100 bpm	175 (27)	90 (21.5)	565 (22)	.007	.83
SBP < 90 or DPB ≤ 60 mmHg	122 (19.1)	73 (17.8)	468 (18.3)	.64	.84
Temperature ≥ 38.5 ºC	82 (12.5)	70 (16.5)	257 (9.9)	.06	< .001
More than 7 days from symptoms onset to admission	142 (20.8)	66 (15.0)	415 (15.5)	.001	.81
Admission laboratory findings					
Neutrophil count > 7500/μL	122 (17.9)	51 (11.6)	388 (14.8)	.047	.08
Lymphocyte count < 1000/μL	406 (59.9)	254 (58.1)	1357 (51.7)	< .001	.01
Platelets < 150,000/μL	239 (35.3)	163 (37.4)	783 (29.9)	.007	.002
D-dimer levels > 500 ng/mL	192 (62.7)	95 (55.9)	557 (56.2)	.04	.94
Lactate dehydrogenase > 250 U/L	369 (83.1)	197 (68.2)	1008 (58.8)	< .001	.003
C-reactive protein > 100 mg/L	295 (46.3)	112 (26.7)	603 (25.1)	< .001	.47
Treatment during hospitalization					
Remdesivir	30 (4.5)	10 (2.3)	8 (.3)	< .001	< .001
Lopinavir/ritonavir	635 (93.1)	413 (94.1)	1660 (62.4)	< .001	< .001
Tocilizumab	150 (22.4)	97 (22.5)	117 (4.5)	< .001	< .001
Corticosteroids	260 (38.4)	175 (40.1)	615 (23.3)	< .001	< .001
NIV or high flow (score of 6)[b]	178 (26.4)	116 (26.9)	214 (8.1)	< .001	< .001
Intubation and mechanical ventilation (score of 7)[b]	283 (41.4)	142 (32.3)	169 (6.3)	< .001	< .001
Vasopressors (score of 8)[b]	226 (33.4)	114 (26.5)	118 (4.5)	< .001	< .001
Dialysis or ECMO (score of 9)[b]	62 (9.2)	33 (7.6)	42 (1.7)	< .001	< .001
Outcome					
Alive currently hospitalized	110 (16.1)	56 (12.7)	132 (4.9)	< .001	< .001
Discharged alive	346 (50.7)	215 (48.9)	1930 (71.9)	< .001	< .001
Mortality at day 30	227 (33.2)	169 (38.4)	623 (23.2)	< .001	< .001
Center with high mortality	239 (35)	196 (44.5)	1042 (38.8)	.07	.02
Center with high interferon-β prescription	420 (61.5)	168 (38.2)	522 (19.4)	< .001	< .001
COVID-19 SEIMC Score (Median [IQR])[c]	8 (5–13)	8 (5–13)	8 (4–16)	.89	.92
COVID-19 SEIMC Score Risk category[c]					
Low (0–2 points)	34 (5.9)	22 (5.9)	307 (13.8)	< .001	< .001
Moderate (3–5 points)	122 (21.3)	75 (20.3)	473 (21.2)	.99	.89
High (6–8 points)	140 (24.4)	92 (24.9)	410 (18.4)	.046	.04
Very high (9–30 points)	277 (48.3)	181 (48.9)	1040 (46.6)	.72	.65
Days from hospital admission to intubation (Median [IQR])	2 (1–4)	5 (3–7)	4 (1–7)	.01	.05

Data are presented as No. (%). P values are calculated by $\chi 2$, Fisher's test or Mann-Whitney's *U* test.
Abbreviations: EIT, early interferon-β treatment; LIT, late interferon-β treatment; NIT, no interferon-β treatment; BMI, body mass index; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus infection; AIDS, acquired immunodeficiency syndrome; SpO_2, peripheral capillary oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIV, non-invasive ventilation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.
[a]Age-adjusted low SpO_2 ≤ 90% for patients aged > 50 years and ≤ 93% for patients aged ≤ 50 years.
[b]Severity rating according to the WHO Clinical Progression Scale, ranged from 0 (not infected) to 10 (dead).
[c]Simple scoring system to predict 30-day mortality on presentation in hospitalized patients with COVID-19 based on age (years), low SpO_2 (age-adjusted), neutrophil-to-lymphocyte ratio, estimated glomerular filtration rate (CKD-EPI), dyspnea and sex (14).

(CI). The PS was used in two ways: as a covariate to control for residual confounders in multivariate models and to perform a matched cohort analysis in which patients undergoing EIT and NIT were paired (1:1) according to their PS using calipers with 0.01 standard deviation. Mortality in the matched pairs was compared by Cox regression. Regarding missing data, Little's MCAR test was used to verify a random pattern, and imputation was performed using the Markov chain Monte Carlo method. All statistical analyses were carried out using SPSS software (SPSS 26.0, IBM Corp., Armonk, NY, USA).

3. Results

In all, 4035 patients with COVID-19 included in the COVID-19@Spain cohort were eligible for analysis; 130 patients were excluded for being treated at one of 19 centers where IFN-β was not used, and 97 because they died ≤ 48 h after hospital admission. Finally, 3808 patients were included in this study: 683 (17.9%) received early IFN-β treatment (median (IQR) days from admission, 1 (1−2)), 440 (11.6%) received late IFN-β treatment (median (IQR) days from

admission, 5 (4−8)), and 2685 (70.5%) received no IFN-β treatment. The study flowchart is presented in Fig. 1.

The patient characteristics are shown in Table 1. Compared to patients who underwent EIT, those in the NIT group were more frequently over 75 years old; had chronic heart, kidney, and neurological diseases; and suffered from active solid or hematologic neoplasms. Notwithstanding, they presented a significantly lower proportion of severe symptoms and signs (i.e., dyspnea, peripheral oxygen desaturation, and tachycardia), in conjunction with fewer laboratory indicators of high risk (i.e., neutrophilia, lymphopenia, thrombocytopenia, and elevated levels of D-dimer, lactate dehydrogenase, and C-reactive protein), which is consistent with a diminished prevalence of the inflammatory phase of COVID-19 on admission (142 patients in EIT and 415 in NIT; $p = 0.001$). Thus, patients in the NIT group less often reached higher disease severity scores (from 6 to 9, according to the WHO Clinical Progression Scale; from 6 to 8, according to the COVID-19 SEIMC score) [18,21] and did not receive as broad therapy (including remdesivir, tocilizumab, and corticosteroids) as patients in the EIT group.

3.1. Variables associated with EIT

The association of different variables with EIT is shown in Table 2. Patients receiving EIT more frequently had severe signs and symptoms and high values of inflammatory biomarkers, and received treatment with tocilizumab, corticosteroids, and respiratory and hemodynamic support in higher proportions.

3.2. Mortality analysis

The mortality rates were 33.2% (227/683), 38.4% (169/440), and 23.2% (623/2685) in patients with EIT, LIT, and NIT, respectively ($p < 0.001$ for EIT vs. NIT) (Table 1). Univariate and multivariate analyses of variables associated with 30-day mortality are shown in Table 3. The multivariate analysis selected the following factors as being associated with mortality: age > 75 years (HR, 2.37; 95% CI, 2.00–2.81; $p < 0.001$), dyspnea (HR, 1.49; 95% CI, 1.24–1.78; $p < 0.001$), low peripheral capillary oxygen saturation (SpO_2) (HR, 1.55; 95% CI, 1.26–1.90; $p < 0.001$), lymphocyte count < 1000/μL (HR, 1.28; 95% CI, 1.08–1.53; $p = 0.01$), platelets < 150,000/μL (HR, 1.29; 95% CI, 1.08–1.53; $p = 0.004$), lactate dehydrogenase > 250 U/L (HR, 1.44; 95% CI, 1.19–1.76; $p < 0.001$), C-reactive protein > 100 mg/L (HR, 1.42; 95% CI, 1.19–1.69; $p < 0.001$), and corticosteroids (HR, 1.32; 95% CI, 1.11–1.56; $p = 0.002$). Early IFN-β treatment did not show an association with mortality. The model exhibited good predictive ability (AUROC, 0.86 (95% CI, 0.84–0.91; $p = 0.004$)). No important interactions were identified.

We then investigated the impact of EIT vs. NIT, including the PS for EIT (LIT patients were excluded from this analysis) (Table 3). No significant collinearity was found between PS and other variables. Similarly, no difference was observed among the patients undergoing EIT (adjusted hazard ratio (HR), 1.03 (95% CI, 0.82–1.30; $p = 0.78$)); AUROC for this model: 0.81 (95% CI, 0.77–0.83; $p < 0.001$).

The estimations of the associations of EIT with mortality in the sensitivity analyses were consistent with the analysis of the whole cohort. When including the COVID-19 SEIMC score as a continuous variable instead of the component variables (age, dyspnea, low SpO_2, and lymphocyte count), the adjusted hazard ratio for EIT was 1.08 (95% CI, 0.93–1.25; $p = 0.32$) (Table S2). When excluding the covariates lopinavir/ritonavir, tocilizumab, and corticoids, the adjusted hazard ratio for EIT was 1.10 (95% CI, 0.96–1.27; $p = 0.16$) (Table S3). Therefore, these treatments were not confounding factors for the association between EIT and mortality. We also studied interferon treatment as a time-dependent covariate within the entire cohort, having an adjusted hazard ratio of 0.89 (95% CI, 0.59–1.32; $p = 0.55$) (Table S4).

Finally, we matched 144 pairs of patients receiving EIT or NIT based on PS. Matched subcohorts had similar exposure frequency to all variables (Table 4). Early IFN-β treatment did not show an association with mortality in this analysis (HR, 0.96 (95% CI, 0.82–1.13; $p = 0.99$)).

4. Discussion

In this post hoc analysis of a multicenter cohort from the first wave of the COVID-19 pandemic, we analyzed the association of early IFN-β administration with mortality. Patients receiving EIT more frequently had severe symptoms and signs in addition to high values of inflammatory biomarkers, and a higher proportion required respiratory and/or hemodynamic support than those receiving LIT or NIT. The crude mortality rates were 33.2%, 38.4%, and 23.2% in patients with EIT, LIT,

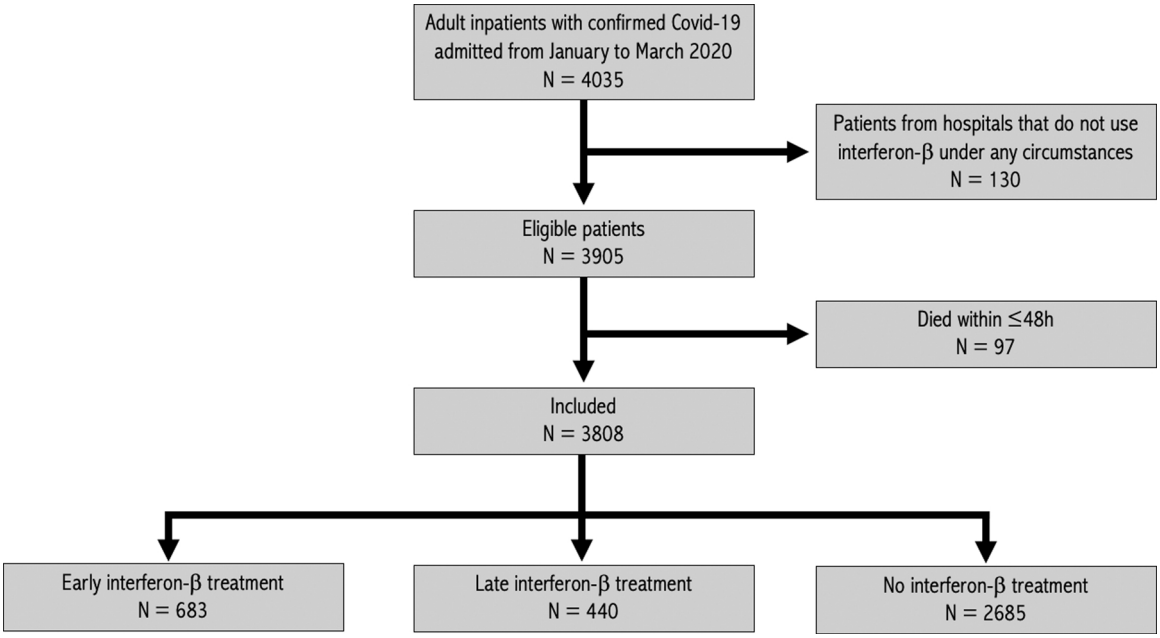

Fig. 1. Study flowchart showing the initial patients from the COVID-19@Spain cohort and the reasons for exclusion, for being treated at centers where IFN-β was not used and because they died ≤ 48 h after hospital admission. Finally, 3808 patients were included for analysis of the impact of early interferon-β treatment.

Table 2
Analysis of the Association of Different Variables with Early Interferon-β Treatment.

Variable	EIT (n = 683)	LIT or NIT (n = 3125)	Crude OR (95% CI)	*P* Value
Male sex	451 (67)	1856 (60.1)	1.34 (1.25–1.44)	< .001
Age > 75 years	193 (28.3)	1108 (35.5)	.72 (.67–.77)	< .001
Obesity (BMI >30)	101 (16.3)	356 (12.8)	1.31 (1.19–1.43)	< .001
Chronic heart disease	138 (20.3)	732 (23.7)	.81 (.75–.89)	< .001
Dyspnea	411 (60.8)	1404 (45.6)	1.84 (1.72–1.98)	< .001
Low SpO_2 (age-adjusted)[a]	261 (43.8)	599 (21.7)	2.69 (2.51–2.89)	< .001
Heart rate ≥ 100 bpm	175 (27)	655 (21.9)	1.31 (1.21–1.42)	< .001
More than 7 days from symptoms onset to admission	142 (20.8)	481 (15.4)	1.44 (1.33–1.57)	< .001
Neutrophil count > 7500/μL	122 (17.9)	439 (14.4)	1.30 (1.19–1.42)	< .001
Lymphocyte count < 1000/μL	406 (59.9)	1611 (52.6)	1.34 (1.26–1.44)	< .001
Platelets < 150,000/μL	239 (35.3)	946 (30.9)	1.22 (1.13–1.31)	< .001
D-dimer levels > 500 ng/mL	192 (62.7)	652 (56.2)	1.32 (1.18–1.46)	< .001
Lactate dehydrogenase > 250 U/L	369 (83.1)	1205 (60.2)	3.26 (2.93–3.63)	< .001
C-reactive protein > 100 mg/L	295 (46.3)	715 (25.3)	2.55 (2.37–2.74)	< .001
Lopinavir/ritonavir	635 (93.1)	2073 (66.9)	6.70 (5.91–7.59)	< .001
Tocilizumab	150 (22.4)	214 (7)	3.83 (3.49–4.20)	< .001
Corticosteroids	260 (38.4)	790 (25.7)	1.80 (1.68–1.94)	< .001
NIV or high flow (score of 6)[b]	178 (26.4)	330 (10.7)	2.96 (2.73–3.22)	< .001
Intubation and mechanical ventilation (score of 7)[b]	283 (41.4)	311 (10)	5.94 (5.51–6.41)	< .001
Vasopressors (score of 8)[b]	226 (33.4)	232 (7.6)	6.00 (5.52–6.53)	< .001
Center with high interferon-β prescription[c]	420 (61.5)	690 (22.1)	5.64 (5.25–6.06)	< .001

Data are presented as No. (%) unless otherwise indicated.
Abbreviations: EIT, early interferon-β treatment; LIT, late interferon-β treatment; NIT, no interferon-β treatment; OR, odds ratio; CI, confidence interval; BMI, body mass index; SpO_2, peripheral capillary oxygen saturation; NIV, non-invasive ventilation.
[a]Age-adjusted low SpO_2 ≤ 90% for patients aged > 50 years and ≤ 93% for patients aged ≤ 50 years.
[b]Severity rating according to the WHO Clinical Progression Scale, ranged from 0 (not infected) to 10 (dead).
[c]The centers were dichotomized into low (<40%) and high (≥40%) proportion of IFN-β prescription.

and NIT, respectively. The factors independently associated with 30-day mortality were age > 75 years, dyspnea, low peripheral capillary oxygen saturation, lymphopenia, thrombocytopenia, high values of lactate dehydrogenase and C-reactive protein, and the use of corticosteroids. Early IFN-β treatment did not show an association with mortality. Moreover, the analysis of 144 pairs of patients receiving EIT or NIT based on PS did not reveal an association of EIT with lower mortality.

To the best of our knowledge, this is the biggest study providing information on the effectiveness of systemic early IFN-β administration vs. standard treatment alone in patients with moderate-to-severe COVID-19 addressing the confounding effects of other potential targeted drugs. Our hypothesis, that early administration of IFN-β would be associated with lower mortality compared to standard treatment alone, is shared by the currently ongoing INTERCOP study, an open-label monocentric phase II randomized controlled trial (Clinical Trials.gov identifier: NCT04449380) [22].

The unprecedented emergency of the COVID-19 pandemic, with no available medications of fully proven efficacy, provided a compelling reason to repurpose drugs already marketed for other indications. Among these, the use of IFN-β seemed immediately feasible for a number of reasons: (i) direct in vitro antiviral activity against SARS-CoV-2 [23]; (ii) previous encouraging experience in mice and nonhuman primate models of MERS [24,25]; (iii) promising results in reducing mortality when combined with lopinavir–ritonavir and started within seven days after symptom onset [26]; and (iv) safety in patients with ARDS, in addition to long-term consolidated evidence of tolerability as an established treatment for multiple sclerosis [27,28].

The very promising results from a Chinese multicenter randomized trial with 127 patients enrolled suggest that subcutaneous INF-β is a key component for success in shortening the viral shedding of a combined therapy that also includes lopinavir–ritonavir and ribavirin [10]. However, the analysis was confounded by the exclusion of a 34-patient subgroup (admitted ≥7 days after symptom onset), for whom INF-β was omitted due to concerns about proinflammatory side effects. Furthermore, critically ill patients were not eligible for the study, impeding the application of the findings to severe cases. Another single-center randomized controlled trial in Iran recruited 60 severely ill patients to evaluate the efficacy of subcutaneous INF-β. In short, the intervention group had a shorter time to clinical improvement, and their mortality rate was almost half that of the control group, although the difference was not statistically significant [11]. Including moderate patients and earlier administration of exogenous INF-β (mean time from enrollment to first dose was 5.4 days) might have yielded more substantial results and minimized the adverse effects (essentially abnormalities in liver injury biomarkers). A third single-center randomized controlled trial showed a significant decrease in mortality in patients receiving early therapy (less than 7–10 days from the onset of symptoms) with subcutaneous INF-β, but not late administration of INF-β [12].

The WHO Solidarity Trial [13], a multicenter randomized controlled trial, did not show lower mortality in the interferon group vs. control (11.8% vs. 10.5%, p = 0.11). Both groups were similar, but contrary to our study, only 6.7% (INF-β) and 6.3% (control) of patients were on ventilation support, and only 33.7% and 34.7% were hospitalized ≥ 2 days. Similarly, a multicenter randomized controlled trial by Kalil et al. did not show efficacy of INF-β combined with remdesivir compared to remdesivir alone concerning time to recovery [14]. Patients had mostly mild-to-moderate COVID-19, with only 7% in both groups requiring non-invasive ventilation or high-flow oxygen therapy.

Finally, Monk et al. assessed the efficacy and safety of inhaled INF-β vs. placebo for the treatment of patients admitted with non-severe COVID-19 (only 2 out of 98 patients requiring non-invasive ventilation or high-flow oxygen), showing a significant improvement in the clinical condition, on the basis of the WHO Ordinal Scale for Clinical Improvement, during the dosing period in the intention-to-treat population [29].

With this as background, we conducted a post hoc propensity score-adjusted study of 3808 consecutive patients with moderate-to-severe COVID-19, investigating the effectiveness of subcutaneous INF-β treatment. In this observational study, we mimicked the assignment of patients to treatment arms and the intention-to-treat analysis inherent in any randomized trial. Therefore, before performing any analysis, we defined EIT as IFN-β started ≤ 3 days from admission and excluded patients for whom the endpoint was reached in this period or those who started treatment from day 4 onward in order to avoid immortal time bias. We used a single robust primary outcome, mortality, because some

Table 3
Univariate and Multivariate Analyses of Risk Factors Associated with All-cause 30-Day Mortality Using Cox Regression.

Variable	Deceased (n = 1019)	Alive (n = 2789)	Crude Analysis		Adjusted Analysis[a]		EIT vs NIT, Adjusted by PS[b]	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Male sex	700 (69.5)	1607 (58.4)	1.31 (1.15–1.50)	< .001	…	…	…	…
Age > 75 years	621 (61)	680 (24.4)	2.66 (2.34–3.01)	< .001	2.37 (2.00–2.81)	< .001	2.51 (2.06–3.05)	< .001
Obesity (BMI > 30)	163 (18.3)	294 (11.7)	1.29 (1.09–1.52)	.004	…	…	…	…
Chronic heart disease	399 (39.6)	471 (17.1)	1.87 (1.65–2.13)	< .001	…	…	…	…
Dyspnea	613 (61.2)	1202 (43.7)	1.74 (1.54–1.98)	< .001	1.49 (1.24–1.78)	< .001	1.39 (1.12–1.71)	.003
Low SpO_2 (age-adjusted)[c]	366 (42.9)	494 (19.8)	2.05 (1.75–2.41)	< .001	1.55 (1.26–1.90)	< .001	1.67 (1.30–2.14)	< .001
Heart rate ≥ 100 bpm	239 (24.5)	591 (22.4)	1.15 (.99–1.33)	.06	…	…	…	…
More than 7 days from symptoms onset to admission	99 (9.7)	524 (18.8)	.67 (.54–.83)	< .001	…	…	…	…
Neutrophil count > 7500/μL	244 (24.3)	317 (11.6)	1.60 (1.38–1.84)	< .001	…	…	…	…
Lymphocyte count < 1000/μL	650 (64.9)	1367 (49.9)	1.55 (1.36–1.77)	< .001	1.28 (1.08–1.53)	.01	1.25 (1.03–1.51)	.03
Platelets < 150,000/μL	382 (37.9)	803 (29.4)	1.30 (1.14–1.48)	< .001	1.29 (1.08–1.53)	.004	1.28 (1.05–1.56)	.01
D-dimer levels > 500 ng/mL	233 (67.1)	611 (54.6)	1.27 (1.01–1.59)	.04	…	…	…	…
Lactate dehydrogenase > 250 U/L	458 (73.4)	1116 (61.2)	1.49 (1.25–1.78)	< .001	1.44 (1.19–1.76)	< .001	1.50 (1.20–1.88)	< .001
C-reactive protein > 100 mg/L	407 (44.1)	603 (23.7)	1.87 (1.65–2.14)	< .001	1.42 (1.19–1.69)	< .001	1.47 (1.21–1.79)	< .001
Lopinavir/ritonavir	743 (72.9)	1982 (71.1)	.93 (.81–1.07)	.29	.92 (.75–1.13)	.42	.88 (.64–1.20)	.41
Tocilizumab	122 (12.2)	242 (8.9)	.90 (.75–1.09)	.27	.80 (.63–1.03)	.08	.76 (.46–1.26)	.28
Corticosteroids	439 (43.6)	611 (22.3)	1.52 (1.34–1.72)	< .001	1.32 (1.11–1.56)	.002	1.33 (1.08–1.63)	.01
Interferon-β treatment								
No interferon-β treatment	623 (61.1)	2062 (73.9)	Reference	.01	Reference	.34	Reference	…
Early interferon-β treatment	227 (26.7)	456 (18.1)	1.28 (1.10–1.49)	.001	1.01 (.80–1.26)	.97	1.03 (.82–1.30)	.78
Late interferon-β treatment	169 (21.3)	271 (11.6)	1.08 (.91–1.28)	.37	1.19 (.95–1.49)	.14	Excluded	…
Center with high mortality	543 (53.3)	934 (33.5)	1.72 (1.52–1.95)	< .001	1.69 (1.43–2.00)	< .001	1.68 (1.39–2.03)	< .001
Propensity score[d]	…	…	…	…	…	…	.98 (.27–3.62)	.97

Data are presented as No. (%) unless otherwise indicated. Crude and adjusted HR have been calculated from imputed data.
Abbreviations: EIT, early interferon-β treatment; NIT, no interferon-β treatment; PS, propensity score; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SpO_2, peripheral capillary oxygen saturation.
[a]The area under the receiver operating characteristic (AUROC) curve of the model was.86 (95% CI,.84–.91), $P = .004$.
[b]Patients in the late interferon-β treatment group were excluded from this analysis.
[c]Age-adjusted low $SpO_2 \leq 90\%$ for patients aged > 50 years and ≤ 93% for patients aged ≤ 50 years.
[d]Calculated only for patients in the early interferon-β treatment and no interferon-β treatment groups. The variables included in the propensity score were sex, age, obesity, chronic heart disease, dyspnea, low SpO_2, hyperinflammation phase, neutrophil count, lymphocyte count, platelets, D-dimer, lactate dehydrogenase, C-reactive protein, lopinavir/ritonavir, tocilizumab, corticosteroids, and high-mortality hospital. The AUROC curve of the PS model was.83 (95% CI,.81–.87), $P < .001$.

patients may be candidates for additional medical treatment but not for intensive care, owing to previous conditions. Regarding confounders, we used propensity scores in different ways to control for indication bias. In the crude analysis, the EIT group showed higher mortality, as it was administered to patients with more severe disease. After adjustment for other well-known risk mortality predictors [15,30,31], EIT was not found to be associated with mortality.

Regarding IFN treatment, studies supporting its use in COVID-19 are still scarce and certainly do not address the phase of the disease in which to start administration. Data on the increased severity of COVID-19 in patients with no endogenous IFN-β and low IFN-α production [6] or with neutralizing auto-Abs against type I IFNs [7] suggest a potential role for early IFN treatment. In addition, a cohort analysis of patients with multiple sclerosis showed that IFN administration is preventive of severe COVID-19 [32]. Other issues also have to be considered, such as the dosage and PEGylation to prolong the antiviral effect, as per the methods used in other mammals for acute and chronic viral diseases [33,34]. An important aspect in our study is the fact that a substantial proportion of patients already had > 7 days of symptoms when admitted, and this was more frequent among those with EIT, meaning that the window of opportunity for benefiting from IFN-β treatment may have already passed when the drug was administered.

The present study has several limitations. First, controlling for confounders in any observational study can be incomplete despite all efforts. Second, a wide range of dosing regimens was used in all groups. Third, the investigators were not blinded to the exposure; however, we used a hard outcome and included consecutive cases. Fourth, our data were not specific to or complete for adverse events, and this is a crucial aspect that should be considered in more detail in future studies. Moreover, we had no access to the follow-up RT-PCR results; thus, we were unable to determine the time to a negative test or to shed further light on the effect of IFN-β on viral dynamics. Regarding the association found between the use of corticosteroids and mortality, the weaknesses are that the study was not designed to evaluate their efficacy, the late time of administration in many cases, and the probable different dosages depending on the clinical situation of the patients. Finally, the cohort

Table 4
Comparison of Matched Patients According to Propensity Score.

	Overall Cohort (N = 3368)[a]			Propensity Score-Matched Cohort (N = 288)[b]		
Variable	EIT (n = 683)	NIT (n = 2685)	*P* Value	EIT (n = 144)	NIT (n = 144)	*P* Value
Male sex	451 (67)	1559 (58.8)	< .001	97 (67.4)	98 (68.1)	.90
Age > 75 years	193 (28.3)	968 (36.1)	< .001	30 (20.8)	38 (26.4)	.27
Obesity (BMI >30)	101 (16.3)	283 (11.9)	.003	23 (16)	19 (13.2)	.50
Chronic heart disease	138 (20.3)	632 (23.8)	.05	23 (16)	24 (16.7)	.87
Dyspnea	411 (60.8)	1191 (45)	< .001	93 (64.6)	86 (59.7)	.40
Low SpO_2 (age-adjusted)[c]	261 (43.8)	498 (20.9)	< .001	59 (41)	53 (36.8)	.47
Heart rate ≥ 100 bpm	175 (27)	565 (22)	.01	40 (27.8)	39 (27.1)	.90
> 7 days from onset to admission	142 (20.8)	415 (15.5)	.001	29 (20.1)	31 (21.5)	.77
Neutrophil count > 7500/μL	122 (17.9)	388 (14.8)	.047	21 (14.6)	23 (16)	.74
Lymphocyte count < 1000/μL	406 (59.9)	1357 (51.7)	< .001	91 (63.2)	83 (57.6)	.34
Platelets < 150,000/μL	239 (35.3)	783 (29.9)	.01	48 (33.3)	54 (37.5)	.46
D-dimer levels > 500 ng/mL	192 (62.7)	557 (56.2)	.04	96 (66.7)	91 (63.2)	.54
Lactate dehydrogenase > 250 U/L	369 (83.1)	1008 (58.8)	< .001	115 (79.9)	117 (81.3)	.77
C-reactive protein > 100 mg/L	295 (46.3)	603 (25.1)	< .001	66 (45.8)	68 (47.2)	.81
Lopinavir/ritonavir	635 (93.1)	1660 (62.4)	< .001	142 (98.6)	142 (98.6)	.99
Tocilizumab	150 (22.4)	117 (4.5)	< .001	32 (22.2)	36 (25)	.56
Corticosteroids	260 (38.4)	615 (23.3)	< .001	63 (43.8)	64 (44.4)	.91
Deceased	227 (33.2)	623 (23.2)	< .001	38 (26.4)	38 (26.4)	1.00
Center with high mortality	239 (35)	1042 (38.8)	.07	50 (34.7)	47 (32.6)	.71

Data are presented as No. (%). P values are calculated by Cox regression.
Abbreviations: EIT, early interferon-β treatment; NIT, no interferon-β treatment; BMI, body mass index; SpO_2, peripheral capillary oxygen saturation.
[a]Patients in the late interferon-β treatment group were excluded from this analysis.
[b]The Propensity score was calculated only for patients in the early interferon-β treatment and no interferon-β treatment groups. The variables included in the propensity score were sex, age, obesity, chronic heart disease, dyspnea, low SpO_2, hyperinflammation phase, neutrophil count, lymphocyte count, platelets, D-dimer, lactate dehydrogenase, C-reactive protein, lopinavir/ritonavir, tocilizumab, corticosteroids, and high-mortality hospital. The AUROC curve of the PS model was.83 (95% CI,.81–.87), $P < .001$.
[c]Age-adjusted low $SpO_2 \leq 90\%$ for patients aged > 50 years and ≤ 93% for patients aged ≤ 50 years.
[d]Severity rating according to the WHO Clinical Progression Scale, ranged from 0 (not infected) to 10 (dead).

was built during the first wave of the pandemic in Spain; management may have changed afterward. The strengths include the multicenter nature of participation, adequate sample size, and the use of standardized scoring systems and a clear, solid endpoint together with advanced statistical analyses, including the imputation of missing data using the Markov chain Monte Carlo method.

In conclusion, our findings did not find an association between early IFN-β therapy after hospital admission and any mortality benefit in patients admitted because of COVID-19. Additional data are needed for IFN-β administration at even earlier stages of the disease and in association with other drugs such as tocilizumab or corticosteroids. Finally, whether the drug would be useful specifically in patients with low IFN production needs to be investigated.

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Conflict of interest statement

JRA declares the following advisory fees and speaker fees: GSK, MSD, Serono, Lilly, Roche. The rest of the authors declare that there are no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2021.112572.

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