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Original Article

Efficacy of High-Dose Nebulized Interferon α 2b in Severe COVID-19 Pneumonia

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Abstract

OBJECTIVE: The COVID-19 pandemic is progressing rapidly, sending the world into a great panic. Healthcare professionals have responded by embarking on a concerted search for therapies to cure and prevent COVID-19. Recently, interferon (IFN) has emerged as a potential therapy as it is associated with reducing lung inflammation and suppressing viral replication. This research paper assessed the efficacy of high-dose nebulized IFN α 2b in severe COVID-19 pneumonia.

METHODS: This is a retrospective study. It commenced on April 9 and ended on June 17, 2020. Researchers selected participants from hospitalized patients aged 18 years and above who were diagnosed with severe COVID-19 pneumonia. Other inclusion criteria were bilateral pneumonia on lung or chest X-ray scan and severe respiratory distress. SMART-COP, which is a risk stratification scoring tool, and radiologic severity index (RSI) were used to assess pneumonia severity. Patients in the treatment cohort received nebulized IFN α 2b at a dose of 10 million IU every 12 hours for 5 days, in addition to standard treatment. Patients in the control cohort received standard treatment only.

RESULTS: Seventy-three patients met the inclusion criteria; 37 were included in the treatment cohort and 36 in the control cohort. Mechanical ventilation was needed in 14 of 36 (38.9%) patients in the control cohort, compared with 6 of 37 (27.4%) patients in the treatment cohort (HR 5.62 [95% CI 1.81-17.48]; *P* = .003). For pneumonia severity, there was a hazard ratio (HR) of 3.72 [95% CI 1.74-7.98]; *P* = ·.01. After 5 days of treatment, chest X-rays indicated significant beneficial changes in the treatment group (HR 2.24 [CI 1.05-4.79]; *P* = .036). Multivariate analysis revealed that pneumonia severity and RSI remained higher in the control group. The HR was 3.44 [95% CI 1.49-7.94]; *P* = .004 and 2.26 [95% CI 0.99-5.16]; *P* = .05, respectively. There was an increase in liver aminotransferases in 5 (14%) participants in the control cohort and 3 (8%) participants in the treatment cohort.

CONCLUSION: High-dose nebulized IFN α 2b has potential efficacy in mitigating severe COVID-19 pneumonia. This study established that administering high-dose nebulized IFN α 2b significantly reduces pneumonia severity in COVID-19 patients. We also found a strong relationship between using nebulized IFN α 2b and reduced need for mechanical ventilation among patients with severe COVID-19 pneumonia. However, a well-designed control trial is needed to confirm the drug's efficacy in reducing the COVID-19 pneumonia severity.

KEYWORDS: Efficacy, IFN α 2b, severe pneumonia, COVID-19, SARS-COV 2
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INTRODUCTION

COVID-19 has recently become a major public health concern globally. This condition was first observed in December 2019 in Wuhan, Hubei Province, China. It has since then spread across the globe.[1] On March 11, 2020, numerous cases of this disease had been reported outside China, prompting WHO to declare COVID-19 as a global pandemic.[1] Healthcare professionals maintain that this disease is caused by severe acute respiratory syndrome coronavirus-2, also called SARS-CoV-2.[2,3] About 30% of hospitalized COVID-19 patients develop acute respiratory distress (ARDS) and require intensive care units (ICUs) for ventilation assistance.[4] Doctors warn of a possible second-wave of pandemic outbreak, sending the world into a continuous panic.[4] Consequently, healthcare providers need to search for a specific treatment to keep the COVID-19 pandemic under control, considering efficacy, reliability, and safety.[5]

The potential pathophysiology of COVID-19 revolves around cytokines.[5] While most of the cytokines, such as type-I interferon (IFN) and interleukin-7, are beneficial in reducing the severity of COVID-19, others, such as interleukin-1β, -6, and TNF-α, seem detrimental, particularly in bringing about a cytokine storm.[6] According to Nile et al.,[7] viral replication and dissemination may be restrained through an early and robust type-I IFN response. For instance, type-I IFN is associated with stimulating intracellular RNA degradation and virus reduction, inducing tissue repair, and triggering an extended adaptive immune response.[6] However, data extracted from MERS-CoV and SARS-CoV outbreaks show that coronaviruses may suppress the response of type-I IFN by interfering with type-I IFN or pattern recognition

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receptor (PRR)-signaling pathways.[4] Gao et al.[6] state that type-I IFNs play a vital role in antiviral response. In addition, delayed or low IFN response is associated with poor clinical results.[7] Therefore, IFN-β and IFN-α could serve as a potentially effective intervention for patients with SARS-CoV-2.

Research done by Davidson et al.[8] implicated type-I IFNs in reducing viral replication in vitro. Further research demonstrated the benefits of type-I IFNs in primate models of infection.[8] Pegylated and non-pegylated interferons that were utilized in the management of coronavirus infection were found to occur in combinatory interventions along with antivirals such as ribavirin and lopinavir/ritonavir, with prospective beneficial effects in mixed human and animal models.[9] Earlier administration was marginally beneficial in decreasing viral load and contributed to modest development in clinical manifestations.[9] However, delayed administration did not have any benefit compared to placebo controls.[8,9,10] Numerous adverse effects were noted with subcutaneous IFN therapy.[10] Additionally, it was found that aerosolized therapy can maximize drug concentrations at the site of infection and reduce the risk of potential side effects.[9]

IFN-α 2a was given in combination with ribavirin and lopinavir/ritonavir as triple therapy for MERS-CoV in South Korea. Interestingly, SARS-CoV-2 is far more vulnerable to IFNs compared to SARS-CoV, and inhaled IFN-α 2b decreased the infection rate significantly.[11] Treatment guidelines in China include vapor inhalation of IFN-α along with ribavirin as an option for the treatment of COVID-19. This type of drug administration has the advantage of delivering IFN-α directly to the respiratory tract.[12] Nebulized IFN-α 2b, with or without arbidol, was found to shorten the duration of a detectable viral load in the upper side of the respiratory tract, and simultaneously decreased the levels of inflammatory markers.[12] From these findings, it can be hypothesized that a high dose of nebulized IFN-α 2b could offer an efficient adjunctive intervention for severe forms of COVID-19.

MATERIAL AND METHODS

Study Design and Participants

This was a single-center retrospective observational cohort study. The participants were patients who had severe COVID-19 pneumonia, confirmed by the reverse transcriptase reaction of polymerase chain assay (RT-PCR), and were consequently admitted to a public hospital in Dubai, betweeen April 9 and June 17, 2020. The time frame defined in this study represents the time between the publication of the first unified COVID-19 national management guidelines and the initiation of data collection. The participants included in this study had the following characteristics:

i. Only adults were included (age ≥ 18 years).
ii. Patients with bilateral pneumonia on chest X-ray and/or lung CT scan.
iii. Patients with symptoms such as fever, dyspnea, and cough.
iv. Patients with severe respiratory distress, SpO2 < 90% on room air, and respiratory rate > 30 breaths/min.

Main Points

- The early use of 5-day high-dose nebulized interferon α 2b at 20 million units daily as an adjunctive treatment reduced significantly the severity of COVID-19-associated pneumonia in hospitalized patients in need of oxygen therapy.
- It noticeably decreased the need of either non-invasive or invasive mechanical ventilation, and therefore, limited ICU admission and ventilator-related complications.
- The use of a nebulized form of interferon prevented the potential incidence of its common side effects.

Procedure

During this study, patients in the treatment cohort received nebulized IFN α 2b at a dose of 10 million IU. This treatment was repeated every 12 hours for 5 days, in addition to standard treatment care. Patients in the control cohort, on the other hand, received standard treatment care only, without IFN. Standard treatment was given in several steps. The first treatment was hydroxychloroquine (400 milligrams twice on the first day, and 200 mg twice per day on days 2-7) or chloroquine (500 mg twice a day for 7 days). The second treatment involved lopinavir/ritonavir (400/100 mg twice per day for 5-7 days) or Favipiravir (1600 mg twice loading on the first day, then 600 mg twice daily from days 2-7). The third treatment was IV antibiotics. The final treatment was IV steroid and IV tocilizumab (400 mg administered twice, 12 hours apart) if cytokine release syndrome existed.

A SMART-COP score and Radiologic Severity Index (RSI) were used to assess the severity of pneumonia. According to Charles et al.,[13] a SMART-COP score is a risk stratification tool that has been designed to assess the seriousness of community-acquired pneumonia. It is also used to predict the need for aggressive oxygenation or ICU admission. It is used to measure elements such as systolic blood pressure, confusion, multi-lobar chest radiography involvement, arterial pH, albumin level, oxygenation, respiratory rate, and tachycardia, as depicted in Figure 1. Participants with a score of 5 and above were considered to be at a high risk and required ICU admission. The next step was to calculate the score for both groups on days 1 and 7 post-admission.

This paper uses the term "radiologic severity index (RSI)" to refer to a semi-quantitative scoring tool that is designed to monitor disease progression, predict mortality of lower respiratory tract infections, and treatment response.[14] To apply this tool, one needs to divide each lung into 3 zones: the lower zone, the upper zone, and the middle zone. Therefore, a total of 6 zones are obtained. To calculate the score, the predominant pattern score of each lung zone is multiplied by the score of the extent of the volumetric radiologic involvement in each zone. The sum of scores obtained from all the 6 zones offers the final reading of the RSI. In our study, scores ranged from 0 to 72, as shown in Table 1. The calculation of the RSI of chest x-ray performed in these days was done by. The patients' full medical history, chronic comorbidities, and baseline laboratory investigations were obtained from the hospital's electronic medical records. This study protocol was approved by the local Research Ethics Committee (Reference No: MOHAP/DXB-REC/ JJJ/No. 87/2020).

Outcomes

This study focused on two primary objectives. First, to identify a potential intervention for reducing pneumonia severity. Second, to find a possible therapy to prevent the need for either non-invasive or invasive mechanical ventilation. Clearing the virus was our secondary objective. It was defined as the period from hospital admission to the time of 2 negative RT-PCR assays done with at least a 24-hour gap, and with no positive result afterward.

Statistical Analysis

Numerical data were summarized using mean and standard deviation or median and range. Categorical data were summarized as numbers and percentages. Numerical data was explored for normality using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. The baseline characteristics of both cohorts were compared. Comparison between the two groups for normally distributed numeric variables was made using the Student's *t*-test, while the Mann–Whitney test was used for non-normally distributed data. Chi-square test was used to analyze categorical variables. Time-dependent events (ventilation and pneumonia severity) were analyzed with a hazard ratio (HR) and 2-sided 95% CIs using univariate and multivariate cox proportional-hazards models, the associated Kaplan–Meier survival estimates for the time from admission to discharge or death. Besides age and smoking, 3 comorbidities (diabetes, hypertension, and cardiovascular disease) were considered for multivariate cox analysis. Time to viral RNA clearance in both groups was analyzed by Kaplan–Meier, and the curves were statistically compared using the Mantel–Cox log-rank test. Post-hoc power analysis was performed to determine the statistical validity of our sample size.

All *P* values were 2-sided. *P* values < .05 were considered significant. Statistical calculations were done by Statistical Package for Social Sciences Version 26 and Stata power cox Version 14.

RESULTS

As mentioned, the results for this study were collected from April 9 to June 17, 2020. During this period, 405 admitted patients were identified consecutively for the study. Seventy-three patients (37 in the treatment cohort and 36 in the control cohort) met the inclusion criteria. The baseline characteristics of both cohorts were listed as shown in Table 2. Several observations were made, shown in the results depicted in Table 2. First, there were more females than males in both cohorts (mean difference 9 females [95% CI 1.12-1.42]; *P* = .004). Second, there was lower total bilirubin (Z = −2.3 mean rank [31.65 to 42.5]; *P* = .029) in the IFN group than in the control group. Third, there was a higher proportion of patients treated with IV antibiotics (16.7%; *P* = .022) in the IFN group than in the control group. Fourth, there was a negligible difference in comorbidities between both groups.

Besides, baseline inflammatory markers (CRP and ferritin) were significantly high in both groups when starting standard COVID-19 therapeutic regimen with regard to the set national guidelines. The need for mechanical ventilation (non-invasive or invasive) was assessed using a univariate cox regression analysis which revealed that 14 of 36 (38.9%) patients in the control cohort received mechanical ventilation compared with 6 of 37 (27.4%) patients in the IFN cohort (HR 5.62 [95% CI 1.81-17.48]; *P* = .003; as shown in Figure 2A). Related findings were observed for pneumonia severity (HR 3.72 [95% CI 1.74-7.98]; *P* = .001; Figure 2B). The chest X-rays, on the other hand, indicated significant beneficial changes in the radiological imaging of the IFN group after 5 days of treatment compared to the control group (HR 2.24 [1.05-4.79]; *P* = .036; Figure 2C).

With regard to pneumonia severity and RSI, it was observed that both remained higher in the control group after adjusting for age, diabetes, hypertension, cardiovascular disease, and smoking. The HR was 3.44 [95% CI 1.49-7.94]; *P* = .004 and 2.26 [95% CI 0.99-5.16]; *P* = .05, respectively. As it can be seen in Table 3, the radiological deterioration was more significant among patients older than 50 years (HR 3.7 [95% CI 1.09–12.52]; *P* = .03). There was no noticeable difference in the duration of viral RNA clearance between IFN group and control group, the duration's estimated mean was 13.51 days versus 12.5 days; log-rank test *P* = .334 (Figure 3). With regard to liver enzymes, it was observed that 5 (14%) patients in the control cohort and 3 (8%) in the IFN cohort recorded hypertransaminasemia. For instance, the increment in the liver aminotransferases was found to be more than 3 times that of the upper limit of the normal. In this paper, the term "normal alanine transaminase" is defined as 63 IU per L based on the national laboratory references. Lymphocytopenia was found in 4 (11%) patients in the control cohort and 3 (11%) in the IFN cohort a week post-admission.

Post hoc power analysis of cox regression showed that a sample size of 73 patients was very well powered (>99.9%) to

Table 1. Scoring Algorithm for RSI

Predominant Radiological Pattern in the Lung Zone	Pattern Score	Extent of Volumetric Radiological Involvement (%)	Volumetric Score
Normal lung	1	0 (normal)	0
Ground glass opacities	2	1-24	1
Consolidation	3	25-49	2
		50-74	3
		75-100	4

Radiologic Severity Index (RSI) scores are calculated by multiplying the predominant pattern score for each lung zone by the volumetric involvement score for that zone. The sum of scores from all six zones gives the final RSI, ranging from 0 to 72.

Table 2. Baseline Demographic and Clinical Characteristics

	Interferon Cohort	Control Cohort	
	(*n* = 37)	(*n* = 36)	*P*
Age, years	51.03 (14.8)	51.69 (12.6)	.836
Age category			.897
> 50 years	17 (45.9%)	16 (44.4%)	
≤ 50 years	20 (54.1%)	20 (55.6%)	
Sex			.004
Male	27 (73%)	35 (97.2%)	
Female	10 (27%)	1 (2.8%)	
Comorbidities			
Diabetes	19 (51.4%)	11 (30.6%)	.71
Hypertension	12 (32.4%)	10 (27.8%)	.665
Cardiovascular disease	5 (13.5%)	4 (11.1%)	.755
Smoking	3 (8.1%)	3 (8.3%)	.972
Lab investigations			
WBC	8.86 (3.14)	8.86 (3.52)	.996
Hemoglobin	13.02 (1.78)	12.68 (1.65)	.392
Platelets	284.73 (108.11)	294.69 (122.34)	.713
Absolute lymphocyte count	0.98 (0.56)	1.06 (0.66)	.728
Absolute nNeutrophil count	7 (3.08)	6.56 (3.63)	.847
D Dimer	0.89 (6.11)	0.92 (6.04)	.608
Serum creatinine	81 (54.13)	76 (84.87)	.31
ALT	56 (73.91)	56 (52.12)	.483
AST	46 (43.41)	45 (28.3)	.386
Total Bilirubin	12 (7.05)	14.3 (10.4)	.029
Ferritin	792.8 (1575.86)	1374 (966.92)	.631
Troponin-I	7.6 (115.24)	9.3 (128.54)	.318
Pro BNP	158 (2019.7)	171.5 (3617.3)	.925
C- reactive protein	95.9 (87.99)	71.05 (72.95)	.843
Serum procalcitonin	0.15 (0.65)	0.09 (0.32)	.433
Concomitant medications			
Chloroquine/ Hhydroxychloroquine	34 (91.9%)	30 (83.3%)	.266
Lopinavir/-ritonavir	22 (59.5%)	28 (77.8%)	.092
Favipiravir	24 (64.9%)	17 (47.2%)	.129
IV antibiotic	36 (97.3%)	29 (80.6%)	.022
IV steroids	35 (94.6%)	30 (83.3%)	.124
Tocilizumab	9 (24.3%)	7 (19.4%)	.614

Data are displayed as mean (SD), median (SD) or *n* (%).

Table 3. Estimation of Radiological Deterioration, After Adjustment for Potential Confounding Factors, Using a Multivariable Cox Proportional-Hazards Model

	Hazard Ratio	95% CI	*P*
Group (control vs. interferon)	2.26	0.99-5.16	.05
Age > 50 years	3.7	1.09-2.52	.03
Diabetes	0.99	0.41-2.42	.98
Cardiovascular disease	2.7	0.82-8.83	.1
Hypertension	0.66	0.22-1.96	.45
Smoking	0.55	1.24-2.49	.44

detect the desired main outcomes. All numerical indicators that were used in this analysis are demonstrated in Table 4.

DISCUSSION

As depicted in the research methods and results above, this was a single-center retrospective observational cohort study that provided reliable information regarding the efficacy of high-dose nebulized IFN α 2b in severe COVID-19-associated pneumonia. The study found that an early 5-day course of nebulized IFN α 2b as adjunctive therapy significantly reduced both pneumonia severity and the need for mechanical ventilation. The study also established that the drug has no serious side effects on the enrolled patients. Besides, it became apparent from the study that the most frequent complication in COVID-19 was acute respiratory distress syndrome (ARDS). Anemia was the second in severity, followed by acute cardiac injury and secondary bacterial infection.

These study findings were consistent with those of earlier research on the topic. For example, a study conducted by Geng et al.[15] had proved that severe pneumonia and consequently respiratory failure and death were triggered by acute immune-related inflammation rather than direct harm caused by the virus as previously thought. Therefore, the best intervention that can be provided at early stage to patients with severe hypoxemia is controlling virus replication and boosting the immune system.

Researchers associated IFN with 2 primary biological activities: antiviral and immunomodulation.[15] Dhochak et al.[16] pointed out that the early induction of IFN and low secretion threshold are behind the lower mortality and morbidity rates of COVID-19 in children than in adults. In addition, neutralizing antibodies against IFN increase significantly with age.[15] From this observation, it can be deduced that IFN-based therapies might be effective against COVID-19, especially in the early phase of its pathogenic cycle. Nevertheless, literature reviews show that controversial information exists regarding the importance of IFN-α2 b in the clearance of COVID-19 RNA and hospitalization.

For example, Rehman et al.[17] found that there was no significant difference between a combination of arbidol and IFN-α2 b and IFN-α2 b as a monotherapy in the clearance

Table 4. Post-Hoc Analysis of Cox Regression Using Power Cox Stata 14

Outcomes	*P*	Hazard Ratio	Standard Deviation	R squared	Probability of event	Sample Size	Post Hoc Power
Need of mechanical ventilation	.003	5.62	4.94	0.7	0.27	73	1
Pneumonia severity	.001	3.72	3.32	0.47	0.48	73	1
Radiological deterioration	.036	2.246	3.31	0.08	0.41	73	1

of COVID-19 RNA and hospitalization. However, a retrospective cohort study conducted by Xu et al.[18] indicated a significant role for IFN-α 2b, either with or without arbidol, in shortening viral clearance duration and reducing elevated inflammation markers in mild to moderate symptoms of COVID-19 pneumonia.[19] Despite the absence of consistent conclusions, both studies confirmed that nebulized IFN-α 2b can significantly reduce the virus-induced inflammation.

The findings of the current research and the earlier studies give an insight into the potential role of nebulized IFN-α 2b in reducing COVID-19 pneumonia severity and preventing the need for mechanical ventilation. So far the dose of nebulized IFN-α 2b that was used in all observational studies was confined to 5 million units twice daily for 5 days.[15,17,18,19] However, considering the reduction in both pneumonia severity and the necessity of mechanical ventilation, our hospital's physicians decided to use a high dose of 20 million units daily in 2 divided doses for the same duration as they were dealing with severe COVID-19 pneumonia cases. A consensus statement from a Chinese expert committee that consisted of more than 30 pediatricians revealed that nebulized IFN-α is an antiviral option for COVID-19 and can be administered with a dose of 2-4 μg/kg or 200 000-400 000 IU/kg, twice daily, as a course of 5-7 days.[12]

The administration of high doses demonstrated promising outcomes in reducing viral virulence in terms of pneumonia severity and need for mechanical ventilation.

This study had 3 primary limitations. First, the current study was conducted using a small sample of 73 patients at a single center. Perhaps future studies should use a larger sample size to make the results reliable for generalization to the whole population. Second, the current research used a cohort study design. It would, therefore, be imprudent to rule out the probability of several confounding factors such as co-administered medicines. Future studies should focus on using a randomized controlled study design to prove efficacy. Finally, referral cases from other healthcare centers posed a challenge in accounting for the accumulative process of the disease's severity and progression.

Despite these limitations, the current study is unique and justifiable for several reasons. First, the study used a single-brand version of IFN-α 2b, and hence could be used to make an accurate prediction of the drug's efficacy. Second, the study used 2 different scoring systems to predict the desirable outcomes, SMART-COP and RSI. Third, this study was among the first to show an optimistic outcome of high-dose nebulized IFN-α in preventing mechanical ventilation and ICU admission. Therefore, it not only enables healthcare professionals to develop an excellent interventional framework for curbing the COVID-19 pandemic, but also forms the basis for future studies into the topic to find a long-lasting solution to contain the pandemic.

CONCLUSION

In conclusion, this study confirms the efficacy of 5-day high-dose nebulized IFN α 2b in severe COVID-19 pneumonia as an adjunctive therapy. The study finds a significant relationship between nebulized IFN α 2b and the reduction of pneumonia severity, as well as decreasing the need of mechanical ventilation among patients requiring supplemental oxygen. In this regard, future studies should focus on further testing of nebulized IFN α 2b using randomized trials to confirm efficacy.

Ethics Committee Approval: This study was approved by Ministry of Health and Prevention, Research Ethics Committee (Reference No: MOHAP/DXB-REC/ JJJ/No. 87/2020).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer Review: Externally peer-reviewed.

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SMART-COP

A risk stratification tool to assess the severity of community acquired pneumonia and predict the need of aggressive oxygenation or ICU admission

CAP confirmed by CXR

S	Systolic BP < 90 mmhg	2 points
M	Multilobar CXR involvement	1 point
A	Albumin < 3.5 g/dl	1 point
R	Respiratory rate – age adjusted cut-offs	1 point

Age	≤ 50 years	> 50 years
RR	≥ 25 br/min	≥ 30 br/min

T	Tachycardia ≥ 125 bpm	1 point
C	Confusion (new onset)	1 point
O	Oxygen low – age adjusted cut-offs	2 points

Age	≤ 50 years	> 50 years
PaO2	< 70 mmhg	< 60 mmhg
Or O2 saturation	≤ 93 %	≤ 90 %
Or PaO2/FiO2	< 333	< 250

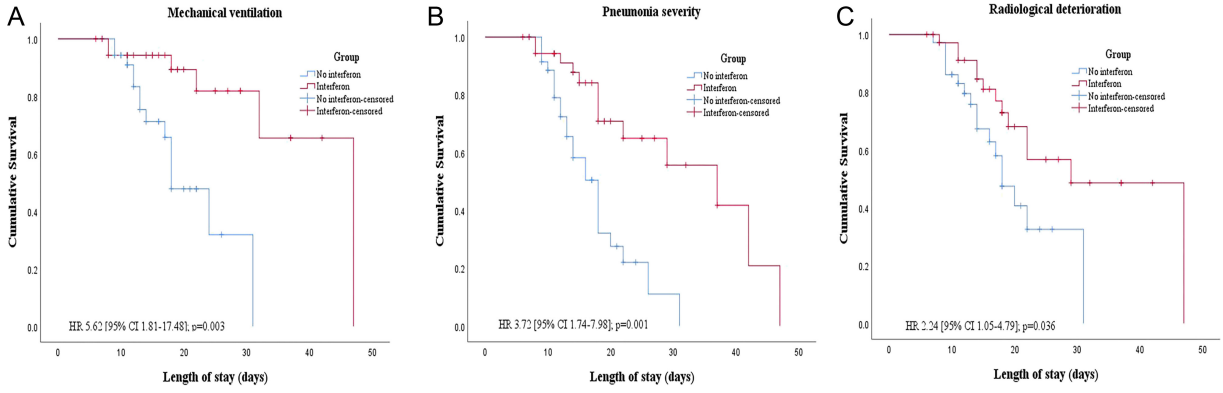
P pH (Arterial) < 7.35 — 2 points

Interpretation

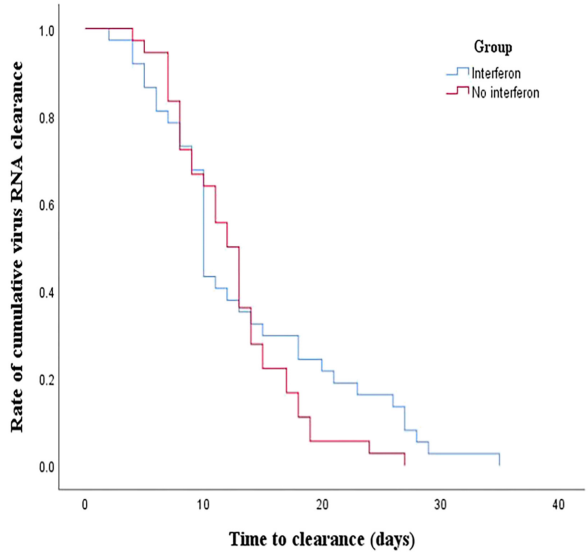
0–2	Low risk of needing IRVS
3–4	Moderate risk of needing IRVS
5-6	High risk of needing IRVS
≥ 7	Very high risk of needing IRVS

IRVS (Intensive Respiratory or Vasopressor Support)

Supplementary Figure 1. SMART-COP scoring to.



Supplementary Figure 2. (A) Kaplan-Meier cumulative survival of mechanical ventilation in the interferon group compared with the control group. (B) Kaplan-Meier cumulative survival of pneumonia severity in the interferon group compared with the control group. (C) Kaplan-Meier cumulative survival of radiological deterioration in the interferon group compared with the control group.



Supplementary Figure 3. Kaplan-Meier plot comparing the cumulative rate of virus RNA clearance between the two groups.