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Coronavirus Pandemic

Intravenous high dose vitamin C and selected antiviral drugs in hospitalized COVID-19 patients: a descriptive cohort study

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Abstract

Introduction: There is lack of universal agreement on the management of COVID-19. Intravenous high dose vitamin C (HDVC), remdesivir (RDV), and favipiravir (FPV) have been suggested as part of the treatment regimens and only RDV is approved by the Food and Drug Administration (FDA) so far. There is no study in Lebanon that addresses the descriptive cohort of HDVC and antiviral therapy amongst COVID-19 inpatients. Our goal was to highlight such a cohort.

Methodology: A retrospective electronic chart review of COVID-19 inpatients was done over a period of 10 months (August 2020 to April 2021). Comparative data analysis was performed between HDVC and non-HDVC (NHDVC) groups, and RDV and FPV groups.

Results: Among HDVC patients, 70.1% ($p = 0.035$) and 67.2% ($p = 0.008$) had dyspnea and desaturation respectively. Patients on HDVC were less likely to remain in hospital for more than 20 days ($p = 0.003$). HDVC patients were more likely to be on oxygen therapy with 74.7% ($p = 0.002$). RDV patients were more likely to be on other COVID-19-related medications during hospitalization including the use of tofacitinib, baricitinib, tocilizumab, and anticoagulation as recommended in the guidelines. Statistical significance was noted for the status on discharge as 90.1% of the patients that received RDV were discharged after clinical improvement, compared to the 74.2% of the FPV patients.

Conclusions: Further research is needed to establish local guidelines for the treatment of COVID-19. A significant role of HDVC and FPV might resurface if randomized control trials are conducted.

Key words: COVID-19; Remdesivir; Favipiravir; Vitamin C; retrospective study; Lebanon.

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Introduction

Over 500 million confirmed coronavirus disease 2019 (COVID-19) cases have been recorded worldwide [1]. Although this is not the first coronavirus outbreak, the global response to the SARS-CoV-2 outbreak, took a different course in terms of agility, vigilance, and awareness. However, uncertainty looms over internationally unified strategies in the management of the disease as the world is still in the slow recovery phase from battling an ambiguous pathological force for nearly two years. With the continuous establishment and updating of international guidelines for treatment [2], it is essential to acknowledge the level of doubt behind setting and publishing any scientific recommendations especially in the case of a rapidly growing pandemic where scholars and healthcare workers seek immediate resolution and disease containment. The pressure on researchers to publish results prevents well-founded robust clinical trials. There is a lack of clear evidence on the administration of drugs resulting in therapeutic and ethical dilemma. In addition, the patients and healthcare systems are also challenged by the high costs of medical care, side effects of medications, and false hopes from ambiguous treatment guidelines [3].

COVID-19 results in a very heterogeneous spectrum of illnesses, ranging from asymptomatic carriage, to severe life-threatening conditions such as acute respiratory distress syndrome, systemic manifestations of sepsis, septic shock, cardiac injury,

and multiple organ failure. Disease severity seems to increase with age, and with the presence of pre-existing medical comorbidities including cardiovascular disease (CVD), diabetes mellitus (type 1 and type 2 [T1DM and T2DM]), chronic lung disease, hypertension (HTN), dyslipidemia (DL), cancer, and others. The main array of presenting symptoms includes fever, dry cough, and shortness of breath, while other symptoms such as chest pain, sore throat, headaches, muscle aches, rhinorrhea, diarrhea, nausea, and vomiting are less frequently reported [4,5]. Approximately 14-20% develop severe SARS-CoV-2 symptoms that require instant hospital admissions, with 1 in 4 of these patients requiring Intensive Care Unit (ICU) admission [4,6]. The severity of the disease is also related to certain clinical and paraclinical presentations including dyspnea, respiratory rate > 30 breaths/min, blood oxygen saturation (SpO_2) < 94%, and PaO_2/FiO_2 < 300 [7]. Lebanon has had a total of > 1 million confirmed cases with more than 10,300 mortalities since its first reported case in February 2020 [8].

Several investigational approaches have been developed in response to the high morbidity and mortality associated with COVID-19, and its impact on healthcare systems. However, the results of most trials remain underway. Some clinicians have suggested the use of intravenous high dose vitamin C (HDVC) to improve the prognosis of severe and critical cases. It is widely considered that ascorbic acid (VC) is a relatively safe and inexpensive nutrient. Its insufficiency was first described by Alfred Hess in patients with scurvy who, as he postulated, were more susceptible for broncho-pneumonia [9]. Since then, there have been additional scholarly work to understand the therapeutic potential of ascorbic acid. Its effect on the actions of immune cells is thought to include maturation of T-lymphocytes, cytokine production and possible regulation – especially interferons, and a role in promoting phagocytosis [10,11]. It is suggested that VC deficiency exacerbates lung pathology in viral pneumonia as was found in influenza A-infected mice [12]. These animals had a rise in pulmonary pathology compared to control mice, which further reinforces VC's role in boosting immunity. In vivo studies have reported that HDVC protects multiple vital organs from hemorrhagic shock [13]. This is likely achieved through the inhibitory effects of HDVC on inflammatory cytokines and oxidative factors, which is achieved by the activation of the Sirtuin1 pathway – a cellular process involved in numerous regulatory functions.

The pathophysiology of COVID-19 suggests that a strong inflammatory response, known as cytokine storm (CS), occurs. This inflammatory process is defined as a severe immune reaction where the body releases massive amounts of cytokines into the blood. Cytokines are a normal component of immune responses. When they are released in excess quantities within a short time frame, a severe and often life-threatening condition occurs. During a CS, neutrophils accumulate in the lungs causing destruction of the alveolar capillaries [14]. The antioxidant properties of VC may play a role in fending off the CS. A retrospective cohort study looked into the efficiency of HDVC in 76 COVID-19 inpatients, classified into a 46-individual HDVC group and a 30-individual standard therapy group [15]. HDVC was defined as a 6 g intravenous (IV) loading dose on day 1, followed by 6 g once every 24 hours for 4 days. Although no apparent safety events were linked to its therapy, HDVC patients had lower 28-day mortality and improved oxygenation status compared to the standard regimen group. A 2021 systematic review and meta-analysis of HDVC infusion in COVID-19 patients further highlighted the need for more research-based evidence to confirm the alleged efficacy and safety of ascorbic acid [16].

A challenging aspect of SARS-CoV-2 is the need for an indeterminate near-universal agent to combat the virus. A few existing antiviral drugs have been repurposed for use in treatment of COVID-19. Among these drugs are remdesivir (RDV) and favipiravir (FPV). RDV has been approved by the United States Federal Drug Agency (FDA) for treatment of COVID-19 and is an adenosine analogue with RNA-dependent RNA polymerase (RdRp) inhibitory activity. It has proven impact on multiple viral diseases like Middle East respiratory syndrome (MERS), severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), respiratory syncytial virus (RSV), and Ebola virus (EBOV) [17]. RDV has been shown to be effective in decreasing recovery time in COVID-19 adult patients (10 days with RDV vs 15 days with placebo) and had lower mortality on day 15 (6.7% with RDV vs 11.9% with placebo) and day 29 (11.4% with RDV vs 15.2% with placebo) [18]. FPV is another synthetic viral RdRp competitive inhibitor which is being repurposed for COVID-19. The antiviral has some virucidal effect since it is capable of inducing in vitro lethal mutagenesis of the influenza A H1N1 virus [19]. FPV was approved for treatment of the Japanese pandemic influenza spread in 2014 [20]. This drug was previously repurposed in the proposed treatment of the EBOV, with a retrospective study highlighting that FPV-treated patients had overall better, yet statistically insignificant, survival [21]. In the case of COVID-19, a 2021

systematic review by Özlüşen *et al*. showed no better effect of FPV usage over other standard regimens, including the already proven ineffective drugs like hydroxychloroquine, chloroquine, and lopinavir, in terms of moderate to severe COVID-19 infections [22]. The results are still inconclusive over the approval of FPV for SARS-CoV-2 with the proposed method of its activity based on the intracellular concentration of its active metabolites [23]. Since SARS-CoV-2-RdRp is 10-fold more active than other similar viral RNA polymerases, the appropriate dose of favipiravir needed in therapy is unclear [24]. The optimal dose of favipiravir for the treatment of COVID-19 pneumonia is debatable, and the doses used include 1800 or 1600 mg oral loading dose twice on day 1 followed by 800 or 600 mg twice daily for 7-14 days [25].

Further research is needed to clarify the inconclusive data on the use of VC and repurposed antivirals. The goal of this study was to highlight the descriptive cohort of HDVC and antiviral therapy amongst COVID-19 inpatients at the Lebanese American University Medical Center – Rizk Hospital (LAUMC-RH), a large tertiary care center at Beirut, Lebanon. To our knowledge, there has not been a similar study in Lebanon or the Arab World.

Methodology

Study design and sample

The study is an observational retrospective cohort based on reviews of medical record forms of COVID-19 patients admitted to LAUMC-RH from the inclusive dates of 1 August 2020 to 14 April 2021. Eligible subjects were adults (≥ 18 years old) male and non-pregnant female COVID-19 inpatients (confirmed based on real-time reverse transcription–polymerase chain reaction [RT-PCR] analysis). Patients with known allergy or newly established allergy to VC, breastfeeding females, and those admitted for less than 24 hours were excluded from the study. Patients with body mass index [BMI] values ≤ 15 kg/m^2 and ≥ 50 kg/m^2 were also excluded. Duplicate entry subjects were included only once. A total of 491 patients were included based on these criteria.

Data extraction and selection

We obtained all the data from the Infection Control department. All patients had a medical record form filled by the healthcare personnel (HCP) at the hospital. Patient demographics and anthropometric data, medical history, and overall medical condition were used in our analysis, after removing all subject identifiers and assigning unique study IDs to each patient. Patients were selected based on the mentioned inclusion and exclusion criteria. The study's electronic documents remained on a separate log sheet and was accessible to the research team if needed for data verification.

The following data were included in our study: age, gender, weight, length of stay (date of admission – date of discharge), chief complaints (dyspnea, desaturation [SpO_2 < 94%], chest pain, sore throat, abdominal pain, fever, chills, cough, myalgia, diarrhea, nausea and vomiting), past medical history (T2DM, cardiac disease, HTN, DL, cancer, obstructive lung disease, and chronic kidney disease), smoking status, oxygen need, length of stay in ICU, use of invasive ventilation, use of vasopressors, radiological studies and findings on admission, on-admission lab values (White blood cells [WBC], neutrophil %, lymphocyte %, C-reactive protein [CRP], d-dimer, Troponin T, Creatine kinase-MB [CKMB], lactic acid, and IL-6), COVID-19 related medications (remdesivir, tocilizumab, baricitinib, tofacitinib, dexamethasone, antibiotics, anticoagulation, zinc, colchicine, and azithromycin), convalescent plasma transfusion, and the status on hospital discharge.

Key Definitions

BMI was classified into four groups corresponding to the World Health Organization (WHO) recommendation to define healthy weight (18.5-24.9 kg/m^2), underweight (< 18.5 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥ 30 kg/m^2) [26]. Average male (1.78 m) and female (1.63 m) heights were extracted from the World Data website since the HCP had not recorded the height of patients [27]. Smoking status was classified into smoker (active or has quit smoking for less than 15 years from the admission date), ex-smoker (has stopped smoking more than 15 years ago), and never smoker. HDVC was defined as a continuous intravenous (IV) infusion of 12 g over 24 hours. The patients who received IV RDV got 200 mg on day 1, followed by 100 mg daily for 5-10 days, while those who took oral FPV received 1.6 g twice on day 1, followed by 600 mg twice daily for a total of 7-14 days. The patients were considered "cured" and ready for discharge after two consecutive negative RT-PCRs for COVID-19 at least 24 hours apart along with clinical improvement. "Abnormal Chest X-ray" was defined as an X-ray with any patterns that would reflect pathological findings (e.g., infiltrates, pleural effusion, consolidation, pneumothorax etc.). The normal laboratory ranges were based on the values recommended by LAUMC-RH.

Statistical Analysis

Data extracted from patient medical charts were coded and imported into Statistical Package for the Social Sciences 25.0 [SPSS] for analysis. Patients diagnosed with COVID-19 pneumonia on HDVC and non-HDVC (NHDVC) were compared to the rest using the Pearson Chi-square test. The same was done for RDV and FPV. The comparison included patients' general characteristics, symptomatology, medical history, laboratory results, radiographic findings, and clinical outcomes. All analyses were evaluated at 0.05 significance level.

Results

The use of VC with respect to inpatients' variables

Majority of the inpatients who received both NHDVC (34.7%) and HDVC (41.4%) were in the 45-64 years age group ($p = 0.503$). This was followed by the age groups 65-74 years and ≥ 75 years. 69.0% of the patients on HDVC were men, and a similar percentage was found among the NHDVC patients ($p = 0.964$). The overweight category had the largest share of VC administration with 40.3% for NHDVC and 39.8% for HDVC (Table 1a).

Among the patients on HDVC, 70.1% ($p = 0.035$) and 67.2% ($p = 0.008$) had dyspnea and desaturation respectively (Table 1b). HTN, DL, and T2DM predominated in both HDVC and NHDVC groups. At least 50% of the patients in both groups had HTN (Table 1c). Patients on HDVC were less likely to stay for > 20 days than those receiving NHDVC ($p = 0.003$). 74.7% of the patients received oxygen therapy, indicating that HDVC patients were more likely to be on oxygen therapy during their stay ($p = 0.002$). Among the patients who were in the ICU, 13.2% ($p = 0.544$) HDVC patients used vasopressors and 16.1% ($p = 0.109$) used invasive ventilation. In comparison, 11.4% and 11.0% of the NHDVC patients used vasopressors and invasive ventilation respectively (Table 1d). HDVC was most prominent in patients who stayed in the ICU for 5 days or less and those who remained for 10 to 15 days, with 28.8% for each group (Figure 1a).

Approximately 95.4% of patients on HDVC had abnormal chest X-ray (CXR) compared to 88.7% in the NHDVC group ($p = 0.021$). Both VC patient groups had ground glass opacities (GGOs) on chest CT scan, with frank consolidations coming in second. Among the patients on HDVC, 49.5% had ≥ 50% GGOs on admission while those on NHDVC had 40.0% ($p = 0.111$). Those on HDVC were also more likely to be lymphopenic and 83.2% of them had lymphocyte content < 19%. CRP and D-dimer were high at the time of admission for those who received both VC dosages; these values for HDVC and NHDVC were 98.2% and 93.2% ($p < 0.001$) for CRP, and 76.4% and 73.6% for D-dimer (Supplementary Table 1).

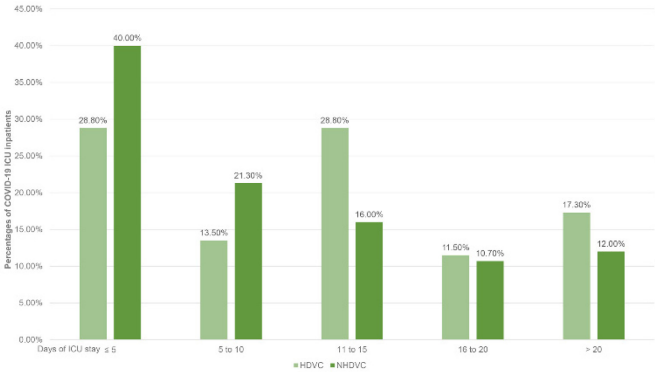
HDVC patients were also more likely to have steroids in their regimen with dexamethasone reported in 90.8% compared to 81.7% in NHDV ($p = 0.007$). Among the HDVC patients, 61.1% received at least one dose of therapeutic anticoagulation +/- prophylactic dosing during their stay, while only 38.9% received prophylactic therapy ($p = 0.001$). A higher proportion (90.8%) of HDVC patients received zinc as part of the regimen ($p < 0.001$). In contrast, < 50% received azithromycin and colchicine during their therapy. A higher proportion of patients receiving HDVC also received antibiotics and majority (47.7%) of them received ceftriaxone ($p = 0.001$). There was not much difference between NHDVC and HDVC in terms of status of discharge. 88.3% of NHDVC and 85.5% of HDVC patients improved and left the medical center ($p = 0.362$) and there was no significant difference in mortality (Table.1e and Figure.1b).

The use of antivirals with respect to inpatients' variables

Tables 2a-2e summarize the administration of two antivirals, RDV and FPV, with respect to multiple inpatient admission variables. The analysis was based on the patients receiving either of the antivirals during their hospital stay but never both. The majority of patients who received either of the drugs fell in the 45-64 years age group and 38.6% and 51.6% received RDV and FPV respectively ($p = 0.697$). The majority of the patients in both groups were males, and this proportion was higher in the case of RDV with 73.9% males ($p = 0.470$). Among the patients receiving RDV, 44.7% were overweight, while 36.7% of the patients receiving FPV were overweight ($p = 0.661$) (Table 2a).

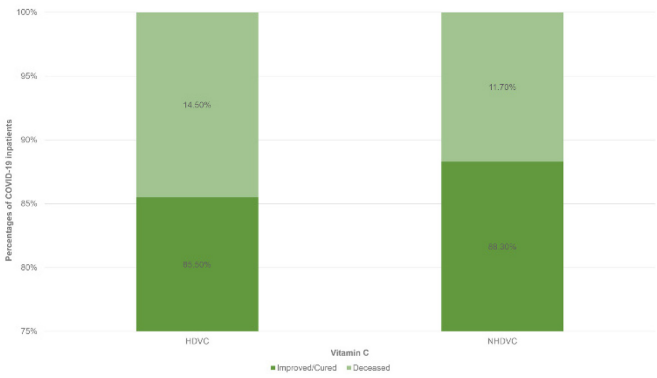
The chief complaints at the time of admission in the case of patients who were administered RDV were fever (73.4%), dyspnea (72.0%), and desaturation (67.1%). In the case of the patients who received FPV, the main complaints at the time of hospital admission included desaturation (77.4%), dyspnea (71.0%), and fever (61.3%) (Table 2b). T2DM, HTN, and DL were present in both inpatient groups and HTN had the highest occurrence (Table 2c). The duration of hospital stay in the case of the patients on RDV was 5-10 days, while those patients who received FPV stayed for ≤ 5 days ($p = 0.279$). A relatively high percentage of patients on RDV (74.4%) and FPV (77.4%) received oxygen therapy ($p = 0.718$).

Figure 1a. The use of HDVC and NHDVC with respect to the ICU stay of COVID-19 patients.



HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; ICU: Intensive Care Unit; %: Percentage; p = 0.273.

Figure 1b. The use of HDVC and NHDVC with respect to the status of patients on discharge.



HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; %: Percentage; p = 0.362.

Table 1a. The use of HDVC and NHDVC with respect to the demographics of COVID-19 patients on hospital admissions.

Demographics	HDVC		NHDVC		*p* value
	N	%	N	%	
Age (years): mean ± stdev	63.34	15.716	62.28	15.960	0.477
17 to 44	23	13.2%	43	13.6%	
45 to 64	72	41.4%	110	34.7%	
65 to 74	37	21.3%	80	25.2%	
≥ 75	42	24.1%	84	26.5%	0.503
Gender					
Males	120	69.0%	218	68.8%	
Females	54	31.0%	99	31.2%	0.964
BMI: mean ± stdev					
< 18.5	2	1.2%	3	1.0%	
18.5-24.99	49	29.5%	89	30.4%	
25–29.99	66	39.8%	118	40.3%	
≥ 30	49	29.5%	83	28.3%	0.990
Smoking status					
Never-smoker	128	77.1%	226	76.1%	
Ex-smoker	6	3.6%	7	2.4%	
Smoker	32	19.3%	64	21.5%	0.644

HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; BMI: Body mass index; N: Number of patients; %: Percentage; stdev: standard deviation.

Table 1b. The use of HDVC and NHDVC with respect to the chief complaints of COVID-19 patients at the time of hospital admission.

Chief Complaints	HDVC		NHDVC		*p* value
	N	%	N	%	
Fever	116	66.7%	218	68.8%	0.633
Temperature range (°C)					
< 38.3	125	72.7%	235	75.1%	
38.3-39.3	41	23.8%	65	20.8%	
≥ 39.3	6	3.5%	13	4.2%	0.708
Chills	52	29.9%	72	22.7%	0.080
Cough	84	48.3%	146	46.1%	0.637
Dyspnea	122	70.1%	192	60.6%	0.035
Desaturation	117	67.2%	174	54.9%	0.008
Diarrhea	32	18.4%	69	21.8%	0.376
Abdominal pain	9	5.2%	24	7.6%	0.310
Nausea/Vomiting	18	10.3%	26	8.2%	0.426
Myalgia	51	29.3%	97	30.6%	0.766
Chest pain	14	8.0%	23	7.3%	0.751
Sore throat	5	2.9%	21	6.6%	0.076

HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; °C: Degree Celsius; N: Number of patients; %: Percentage.

Table1c. The use of HDVC and NHDVC with respect to the past medical history of COVID-19 patients on hospital admissions.

Medical history	HDVC		NHDVC		*p* value
	N	%	N	%	
Type 2 diabetes mellitus	52	29.9%	100	31.5%	0.703
Hypertension	87	50.0%	168	53.0%	0.525
Dyslipidemia	53	30.5%	123	38.8%	0.065
Coronary artery disease	32	18.4%	61	19.2%	0.818
Heart failure	11	6.3%	30	9.5%	0.229
Obstructive lung disease	16	9.2%	25	7.9%	0.616
Chronic kidney disease	3	1.7%	24	7.6%	0.007
Cancer	14	8.0%	32	10.1%	0.456
Breast	5	35.7%	6	18.8%	
Gastrointestinal	1	7.1%	8	25.0%	
Gynecologic	1	7.1%	1	3.1%	
Respiratory	1	7.1%	1	3.1%	
Hematologic	3	21.4%	8	25.0%	
Prostate	3	21.4%	1	3.1%	
Testicular	0	0.0%	3	9.4%	
Papillary	0	0.0%	1	3.1%	
Melanoma	0	0.0%	2	6.3%	
Head and neck	0	0.0%	1	3.1%	0.323

HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; N: Number of patients; %: Percentage.

Table 1d. The use of HDVC and NHDVC with respect to the variables during the hospital stay of COVID-19 patients.

Hospital stay	HDVC		NHDVC		*p* value
	N	%	N	%	
Length of hospitalization					
≤ 5 days	50	28.7%	128	40.4%	
5 to 10 days	58	33.3%	105	33.1%	
10 to 15 days	21	12.1%	35	11.0%	
15 to 20 days	24	13.8%	15	4.7%	
> 20 days	21	12.1%	34	10.7%	0.003
Median and (IQR)	8.00	11.00%	6.00	7.00%	< 0.001
Oxygen therapy					
Received oxygen therapy	130	74.7%	194	61.2%	0.002
ICU stay					
Total ICU stay	52	29.9%	75	23.7%	0.132
Originally admitted to ICU	26	50.0%	45	60.0%	0.264
Use of invasive ventilation	28	16.1%	35	11.0%	0.109
Use of vasopressors	23	13.2%	36	11.4%	0.544

HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; N: Number of patients; %: Percentage; IQR: Interquartile range.

Table 1e. The use of HDVC and NHDVC with respect to the medical therapy received during the hospital stay of COVID-19 patients.

Medical Therapy	HDVC		NHDVC		*p* value
	N	%	N	%	
Tocilizumab	18	10.3%	29	9.1%	0.666
1 dose	9	50.0%	21	72.4%	
2 doses	3	16.7%	6	20.7%	
3 doses	3	16.7%	2	6.9%	
4 doses	3	16.7%	0	0.0%	0.079
Tofacitinib	48	27.6%	62	19.6%	0.041
Baricitinib	18	10.3%	23	7.3%	0.237
Dexamethasone	158	90.8%	259	81.7%	0.007
Anticoagulation					
Therapeutic +/- Prophylactic	102	61.1%	133	44.9%	
Prophylactic only	65	38.9%	163	55.1%	0.001
Zinc	158	90.8%	220	69.4%	< 0.001
Zithromax	56	32.2%	83	26.2%	0.158
Colchicine	6	5.5%	17	7.0%	0.601
Antibiotics Received	125	71.8%	201	63.4%	0.058
Ceftriaxone	83	47.7%	103	32.5%	0.001
Meropenem	41	23.6%	69	21.8%	0.648
Ciprofloxacin	14	8.0%	32	10.1%	0.456
Transfusion Received	7	4.0%	11	3.5%	0.755
1 Transfusion	4	2.3%	6	1.9%	
2 Transfusions	1	0.6%	2	0.6%	
3 Transfusions	2	1.1%	0	0.0%	0.293

HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; N: Number of patients; %: Percentage.

Use of invasive ventilation and vasopressors were higher in patients on FPV with 22.6% (p = 0.110) receiving invasive ventilation and 16.1% (p = 0.319) receiving vasopressors (Table 2d). For patients on FPV, the length of ICU stay was at its highest in the 5 to 10 days group with 33.3%, while for the RDV patients, the maximum percentage was in the 5 or less days group with 31.0% (Figure 2a).

Abnormal findings on admission CXR were higher (95.2%) among the patients on RDV (p = 0.049). GGOs were the found in 96.1% RDV and 100.0% FPV patients. More than 80.0% of the patients in both groups had lymphopenia at the time of admission. CRP and D-dimer levels were high for both groups. An IL-6 level of ≥ 40 pg/mL was recorded at the time of admission of the 62.9% patients who received RDV and 48.0% patients who received FPV (p = 0.244) (Supplementary Table 2).

Among the RDV inpatients, 22.2% received tocilizumab (p = 0.003), and among them 63.0% received a single dose. Dexamethasone was administered to 95.2% RDV and 90.3% FPV patients (p = 0.268). The patients on RDV who received at least one dose of therapeutic anticoagulation +/- prophylactic dosing during their stay were 61.4%, while those that got FPV were 55.2% (p = 0.522). Zinc was included as part of the treatment regimen for 76.8% RDV and 90.3% FPV patients (p = 0.97). However, < 50% patients received azithromycin and colchicine. Both the antiviral groups received antibiotics. Ceftriaxone was administered to 38.2% RDV group and 51.6% FPV patients. At the time of discharge, 90.1% of the patients who received RDV were discharged after clinical improvement, while 74.2% of the FPV patients showed clinical improvement. 25.8% FPV patients and 9.9% RDV patients died in the hospital (p = 0.011) (Table.2e and Figure.2b).

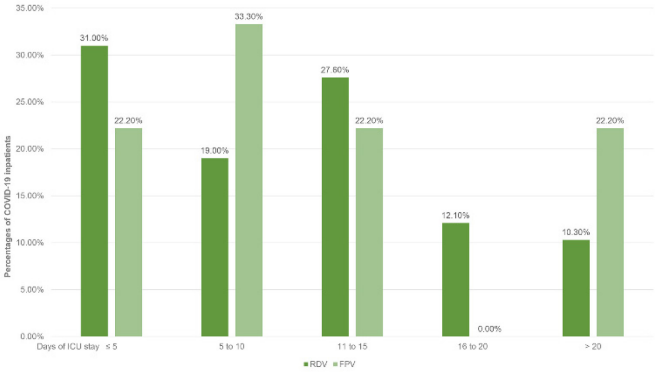
Discussion

COVID-19 has affected nearly all age groups to varying extent across countries. Severe infection is usually more common among the adults and the majority of the deaths are reported in the older population [28-31]. In addition, higher severity and fatality are reported in males. This is possibly because of the higher proportion of males in the population and the likelihood of men having compromised pulmonary function due to smoking tobacco [32]. In addition, it has been reported that males have higher expression levels of angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2), both of which are used by SARS-CoV-2 for entering host cells [33]. A Taiwanese retrospective study analysed the public surveillance data of 398 inpatients with COVID-19 across approximately 3 months in 2020 [34]. This study concluded that disease severity, represented by chest X-ray infiltration, was associated with males, elderly and females with T2DM or with chief complaints of cough, fever, and dyspnea. In our analysis, the 45-64 years age group was the most prominent in the VC and antiviral groups and this aligns with the previous report. The mean age of the patients in the NHDVC and HDVC groups were 62.28 years and 63.34 years respectively. Thus, the mean age in our NHDVC group exceeds that of another retrospective cohort (57 years) and nearly equates the HDVC mean age (63 years) [6]. The majority of patients in our study were males and a relatively higher proportion of them received VC and antivirals than the female counterparts.

Our findings suggest that among the patients admitted with COVID-19, those in the overweight category received most of the medications. Several studies have reported on the dangers of overweight and obesity, and these conditions are also considered as epidemics. Approximately 2.8 million individuals die annually due to obesity and obesity-related comorbidities [35]. It has been suggested that with the rise in body weight, obese individuals start to develop a chronic and slow-growing inflammatory state mediated by various pro-inflammatory cytokines. IL-6 is one of these cytokines whose action is implicated in COVID-19 and it leads to a CS. Therefore, obese and overweight individuals are at risk of presenting with severe forms of COVID-19. A French retrospective study concluded that 75.8% of 124 ICU inpatients had a BMI exceeding 30 kg/m^2 [36]. A study from Italy concluded that amongst the studied 482 COVID-19 inpatients in a single hospital, those that had a BMI ≥ 30 kg/m^2 exhibited or were at risk of developing severe illness, while patients with a BMI ≥ 35 kg/m^2 had a higher risk of death [37]. Despite the lack of statistical significance, our findings suggest that overweight, and to some extent obese, inpatients were admitted with more severe symptoms than those in the lower weight classes, thus foreshadowing the use of HDVC and antivirals. When comparing the absolute numbers, RDV seemed to be the drug of choice in compliance with international guidelines.

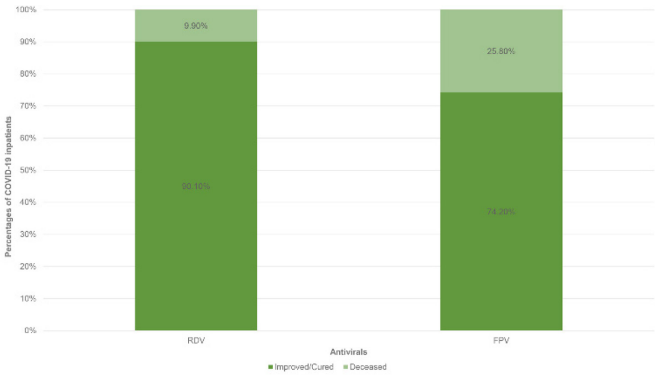
Among the patients who received a higher proportion of antivirals and VC were those who had pre-existing metabolic diseases, especially HTN, T2DM, and DL, at the time of admission.

Figure 2a. The use of RDV and FPV with respect to the ICU stay of COVID-19 patients.



RDV: Remdesivir; FPV: Favipiravir; ICU: Intensive Care Unit; %: Percentage; p = 0.547.

Figure 2b. The use of RDV and FPV with respect to the status of patients on discharge.



RDV: Remdesivir; FPV: Favipiravir; %: Percentage; p = 0.011.

Table 2a. The use of RDV and FPV with respect to the demographics of COVID-19 patients on hospital admissions.

Demographics	RDV		FPV		*p* value
	N	%	N	%	
Age (years): mean ± stdev	62.72	15.002	61.58	16.703	0.697
17 to 44	25	12.1%	4	12.9%	
45 to 64	80	38.6%	16	51.6%	
65 to 74	52	25.1%	4	12.9%	
≥ 75	50	24.2%	7	22.6%	0.411
Gender					
Males	153	73.9%	21	67.7%	
Females	54	26.1%	10	32.3%	0.470
BMI: mean ± stdev					
< 18.5	1	0.5%	0	0.0%	
18.5–24.99	50	25.1%	9	30.0%	
25–29.99	89	44.7%	10	33.3%	
≥ 30	59	29.6%	11	36.7%	0.661
Smoking status					
Never-smoker	153	78.1%	25	80.6%	
Ex-smoker	4	2.0%	1	3.2%	
Smoker	39	19.9%	5	16.1%	0.823

RDV: Remdesivir; FPV: Favipiravir; BMI: Body mass index; N: Number of patients; %: Percentage; stdev: standard deviation.

Table 2b. The use of RDV and FPV with respect to the chief complaints of COVID-19 patients on hospital admissions.

Chief Complaints	RDV		FPV		*p* value
	N	%	N	%	
Fever	152	73.4%	19	61.3%	0.161
Temperature range (°C)					
< 38.3	145	70.7%	25	80.6%	
38.3–39.3	52	25.4%	6	19.4%	
≥ 39.3	8	3.9%	0	0.0%	0.373
Chills	58	28.0%	7	22.6%	0.526
Cough	106	51.2%	14	45.2%	0.530
Dyspnea	149	72.0%	22	71.0%	0.907
Desaturation	139	67.1%	24	77.4%	0.251
Diarrhea	41	19.8%	4	12.9%	0.360
Abdominal pain	16	7.7%	0	0.0%	0.109
Nausea/Vomiting	17	8.2%	1	3.2%	0.327
Myalgia	59	28.5%	10	32.3%	0.667
Chest pain	9	4.3%	4	12.9%	0.051
Sore throat	7	3.4%	1	3.2%	0.964

RDV: Remdesivir; FPV: Favipiravir; °C: Degree Celsius; N: Number of patients; %: Percentage.

Table 2c. The use of RDV and FPV with respect to the past medical history of COVID-19 patients on hospital admissions.

Medical history	RDV		FPV		*p* value
	N	%	N	%	
Type 2 diabetes mellitus	69	33.3%	12	38.7%	0.556
Hypertension	110	53.1%	19	61.3%	0.396
Dyslipidemia	77	37.2%	11	35.5%	0.854
Coronary artery disease	42	20.3%	5	16.1%	0.587
Heart failure	12	5.8%	4	12.9%	0.141
Obstructive lung disease	19	9.2%	3	9.7%	0.929
Chronic kidney disease	5	2.4%	3	9.7%	0.036
Cancer	18	8.7%	2	6.5%	0.674
Breast	4	22.2%	0	0.0%	
Gastrointestinal	2	11.1%	0	0.0%	
Gynecologic	1	5.6%	0	0.0%	
Respiratory	1	5.6%	0	0.0%	
Hematologic	5	27.8%	2	100.0%	
Prostate	2	11.1%	0	0.0%	
Testicular	2	11.1%	0	0.0%	
Papillary	1	5.6%	0	0.0%	
Melanoma	0	0.0%	0	0.0%	
Head and neck	0	0.0%	0	0.0%	0.765

RDV: Remdesivir; FPV: Favipiravir; N: Number of patients; %: Percentage.

Table 2d. The use of RDV and FPV with respect to the past medical history of COVID-19 patients on hospital admissions.

Hospital stay	RDV		FPV		*p* value
	N	%	N	%	
Length of hospitalization					
≤ 5 days	50	24.2%	12	38.7%	
5 to 10 days	86	41.5%	8	25.8%	
10 to 15 days	28	13.5%	6	19.4%	
15 to 20 days	20	9.7%	3	9.7%	
> 20 days	23	11.1%	2	6.5%	0.279
Oxygen therapy					
Received oxygen therapy	154	74.4%	24	77.4%	0.718
ICU stay					
Total ICU stay	58	28.0%	9	29.0%	0.907
Originally admitted to ICU	30	51.7%	4	44.4%	0.684
Use of invasive ventilation	25	12.1%	7	22.6%	0.110
Use of vasopressors	21	10.1%	5	16.1%	0.319

RDV: Remdesivir; FPV: Favipiravir; N: Number of patients; %: Percentage.

Table 2e. The use of RDV and FPV with respect to the medical therapy received during the hospital stay of COVID-19 patients.

Medical therapy	RDV		FPV		*p* value
	N	%	N	%	
Tocilizumab	46	22.2**%**	0	0.0**%**	0.003
1 dose	29	63.0%	0	0.0%	
2 doses	9	19.6%	0	0.0%	
3 doses	5	10.9%	0	0.0%	
4 doses	3	6.5%	0	0.0%	.[a]
Tofacitinib	70	33.8**%**	7	22.6**%**	0.212
Baricitinib	31	15.0**%**	2	6.5**%**	0.200
Dexamethasone	197	95.2**%**	28	90.3**%**	0.268
Anticoagulation					
Therapeutic +/- Prophylactic	124	61.4%	16	55.2%	
Prophylactic only	78	38.6%	13	44.8%	0.522
Zinc	159	76.8%	28	90.3%	0.087
Zithromax	52	25.1%	5	16.1%	0.274
Colchicine	7	4.6%	1	5.3%	0.903
Antibiotics received	139	67.1**%**	23	74.2**%**	0.433
Ceftriaxone	79	38.2%	16	51.6%	0.154
Meropenem	50	24.2%	9	29.0%	0.557
Ciprofloxacin	19	9.2%	4	12.9%	0.513
Transfusion received	8	3.9**%**	3	9.7**%**	0.151
1 transfusion	5	2.4%	2	6.5%	
2 transfusions	1	0.5%	0	0.0%	
3 transfusions	1	0.5%	1	3.2%	0.247

RDV: Remdesivir; FPV: Favipiravir; N: Number of patients; %: Percentage; [a]: No statistics are computed because Remdesivir or Favipiravir are constant.

This observation is in agreement with a meta-analysis of 87 scientific reports that concluded that HTN (40.8%) and T2DM (22.3%) were the primary comorbidities among COVID-19 inpatients [38]. A study from England reported that COVID-19 patients with T2DM and T1DM had higher mortality rates; these individuals were mainly men and the high mortality was associated with advancing age, elevated BMI, poor glycemic control, CVD, and associated renal disease [39]. In our study, 29.9% of the HDVC patients and 31.5% of the NHDVC patients had T2DM. It is beyond the scope of this study to do an in-depth analysis of the trend of the blood capillary glucose levels; nevertheless, it is interesting that HDVC might play a role in prolonging hyperglycemia in hospitalized patients [40]. The actual interference timeline is still a mystery as researchers postulate that it could range from a few hours to more than a day after the IV infusion has ceased [41]. Another explanation might be that a chemical interference between ascorbic acid and the glucometer strips results in pseudo-hyperglycemia [40]. This is more logical considering the role of ascorbic acid in anti-inflammation. To our knowledge, there is no study detailing a direct effect of either the antivirals on diabetes. A single prospective observational study conducted in Pakistan showed a relatively delayed recovery time in COVID-19 diabetic patients who received RDV as compared to the nondiabetic patients [42]. However, this could be due to the high inflammatory state of diabetes in addition to the viral infection and not an effect of RDV.

Our data indicates that a higher proportion of the patients who received HDVC were those who were admitted to the critical care units, needed invasive ventilation, and necessitated vasopressors for hemodynamic and clinical stability. In addition, those who were admitted to the ICU were more likely to receive RDV, while among the individuals who received FPV a higher proportion were intubated and/or received vasopressors than the RDV group. Previous reports have suggested that RDV has a positive effect on the survival of patients who are under invasive ventilation. A study in California reported that approximately 42% of non-RDV patients required intubation while only 25% of the patients who were administered RDV required intubation [43]. However, the report did not mention at which stage of the disease, hospitalization, or symptoms the patients required invasive ventilation, nonetheless it indicates a possible efficacy of the antiviral in combating COVID-19. In another study by Lapadula *et al*, RDV-treated groups had lower mortality (15.2%), higher extubation rates (88%), and more frequent hospital discharges (85%) when compared to the non-RDV groups [44]. Our results indicate similar statistically significant outcomes on discharge as 90.1% of the patients who received RDV were discharged, and 9.9% died. In the case of the effect of VC on the overall health of inpatients, previous studies have reported on the efficiency of VC in reducing mortality [15], although there are also studies that indicate otherwise. Zhang *et al* found out that very large doses of HDVC (24 g/day) failed to decrease the 28-day mortality of critically ill patients, but they might have had a role in improving oxygenation as a steady increase in PaO_2/FiO_2 was noted [45]. Our study showed that patients were more likely to have shorter duration of hospital stay when administered VC, in addition to receiving medications related to their critical state like tofacitinib, baricitinib, tocilizumab, anticoagulation, and ceftriaxone.

Limitations

Our study is a retrospective chart review, a trait that is a limitation by itself. The previously mentioned height estimation and our adjustment of the BMI limits accuracy of its values. However, the World Data engine is a considerably reliable source of estimation that we followed based on the expert opinions of local scholars and researchers. The relatively small sample size puts the study at a disadvantage which was observed in the lack of statistical significance in some findings. In addition, the study results are based on a single university hospital in the capital of Lebanon, thus making it somewhat difficult to generalize to all the Lebanese population. This is especially the case since LAUMC-RH attracts mainly patients of the upper-middle to upper social class. However, this study is the first in Lebanon to look at such a descriptive analysis in relative detail, which would pave the way for future studies.

An important limitation is the striking variance in absolute numbers between RDV and FPV. It is important to note that FPV was administered most of the times instead of RDV because of depletion in stock of the latter or the relatively higher cost. Some changes in the variable absolute numbers can be related to the subjectivity in management and variations in diagnosis by different attending physicians that rotate according to a specialty service system. An example of that would be the preferred usage of colchicine or zinc by some physicians, their opinion on the lack of effectiveness of HDVC effect and consequent non-use of HDVC, and the subjectivity in estimating the period of infection which would rely on the usage of antivirals or not. In

spite of existing international or local guidelines, some attending physicians still use their own experience in the field to determine how severe the patient's illness truly is. This, by itself, is a limitation due to the lack of a standardized clinical judgement in research. However, our physicians attempted to mirror international guidelines as much as possible in order to achieve a coherent body of research data for the future, and, more importantly, provide optimum care for the patients.

An important point to highlight is the number of days over which VC was administered. Our patients received VC as long as the signs of active infection were present, therefore there was no fixed range of days over which VC was administered. There is lack of agreement in previous reports with regard to the duration of VC treatment needed. Some reports have suggested that the optimum duration for COVID-19 patients is at least 7 days [46]. A systematic review indicated that VC in septic non-COVID-19 patients is most efficient if administered for 3-5 days [47]. We recorded the laboratory values of patients only at the time of admission; therefore, we did not follow the change in these parameters during treatment. However, the aim of our study was to describe the health of the patients at the time of admission and the outcome during discharge.

Conclusions

The COVID-19 pandemic is spreading rapidly throughout the world and is characterized by rapid spread of the virus, deterioration of health of the infected persons, and the ability of the virus to mutate and become resistant to the proposed therapy. Scientists were forced to fast-track development and deployment of vaccines to contain the pandemic. The COVID-19 vaccines have certainly helped slow down spread of the virus globally. There is still a lack of international agreement over a standardized therapy for COVID-19, either with new antivirals or by repurposing existing drugs. There is lack of consensus on supplementary therapy such as HDVC. Despite the National Institutes of Health's treatment guidelines, further research, ideally through randomized control trials, is needed that is focused on the Lebanese population to establish local recommendations that might help improve efficiency of treatment of SARS-CoV-2.

Authors' Contributions

MF: data collection, data analysis, and manuscript writing. JM, TH, RA, and GEH: data collection. HD and RH: data analyses. RHS, JM, and AF: project design, data analysis, and manuscript editing. All authors contributed to the article and approved the submitted version.

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Annex – Supplementary Items

Supplementary Table 1. The use of HDVC and NHDVC with respect to the paraclinical data of COVID-19 patients on hospital admissions.

Paraclinical Data	HDVC		NHDVC		*p* value
	N	%	N	%	
Chest X-ray					
Normal chest X-ray	7	4.6%	30	11.3%	
Abnormal chest X-ray	145	95.4%	236	88.7%	0.021
Missing	22		51		
CT scan:					
CT scan done	161	92.5%	271	85.5%	0.022
Pleural effusion	18	11.2%	39	14.4%	0.340
Consolidation	94	58.4%	147	54.2%	0.402
GGOs	152	94.4%	259	95.6%	0.587
GGOs percentages (%)					
< 50	56	50.5%	108	60.0%	
≥ 50	55	49.5%	72	40.0%	0.111
Missing	63		137		
Labs					
White Blood Cell count (in 10^9 cells/L)					
< 5.2	52	30.1%	111	35.4%	
5.2–12.4	105	60.7%	175	55.7%	
> 12.4	16	9.2%	28	8.9%	0.491
Missing	1		3		
Neutrophil percentage (%)					
< 40	2	1.2%	9	2.9%	
40–74	39	22.5%	81	25.8%	
> 74	132	76.3%	224	71.3%	0.317
Missing	1		3		
Lymphocyte percentage (%)					
< 19	144	83.2%	248	79.0%	
19–48	25	14.5%	63	20.1%	
> 48	4	2.3%	3	1.0%	0.163
Missing	1		3		
C-Reactive Protein levels (mg/L)					
< 0.7	3	1.8%	19	6.7%	
≥ 0.7	161	98.2%	265	93.3%	0.022
Missing	10		33		
Creatinine levels (mg/L)					
≤ 1.17	156	90.2%	231	74.8%	
> 1.17	17	9.8%	78	25.2%	< 0.001
Missing	1		8		
D-dimer levels (mcg/mL)					
< 0.5	38	23.6%	72	26.4%	
≥ 0.5	123	76.4%	201	73.6%	0.521
Missing	13		44		
Troponin-T (ng/dL)					
≤ 4	18	11.6%	37	14.7%	
> 4	137	88.4%	215	85.3%	0.379
Missing	19		65		
CK-MB (IU/L)					
≤ 25	151	99.3%	237	99.2%	
> 25	1	0.7%	2	0.8%	0.843
Missing	22		78		
Lactic acid (mmol/L)					
≤ 2.20	70	74.5%	79	62.2%	
> 2.20	24	25.5%	48	37.8%	0.054
Missing	80		190		
IL-6 (pg/mL)					
< 7	10	7.0%	16	6.9%	
7–39.99	53	37.1%	86	37.2%	
≥ 40	80	55.9%	129	55.8%	0.999
Missing	31		86		

HDVC: High dose vitamin C; NHDVC: Non-high dose vitamin C; GGOs: Ground glass opacities; CK-MB: Creatine kinase myocardial band; IL-6: Interleukin-6; N: Number of patients; %: Percentage.

Supplementary Table 2. The use of RDV and FPV with respect to the paraclinical data of COVID-19 patients on hospital admissions.

Paraclinical data	RDV		FPV		*p* value
	N	%	N	%	
Chest x-ray					
Normal chest x-ray	9	4.8%	4	14.3%	
Abnormal chest x-ray	179	95.2%	24	85.7%	0.049
Missing information	19		3		
CT scan: performed	180	87.0%	27	87.1%	0.983
Pleural effusion	20	11.1%	6	22.2%	0.104
Consolidation	114	63.3%	13	48.1%	0.131
GGOs	173	96.1%	27	100.0%	0.297
GGOs percentages (%)					
< 50%	65	52.4%	15	62.5%	
≥ 50%	59	47.6%	9	37.5%	0.364
Missing	83		7		
Labs					
White blood cell count (in 10^9 cells/L)					
< 5.2	66	32.2%	9	29.0%	
5.2–12.4	121	59.0%	19	61.3%	
> 12.4	18	8.8%	3	9.7%	0.936
Missing	2		0		
Neutrophil percentage (%)					
< 40%	6	2.9%	0	0.0%	
40–74%	34	16.6%	8	25.8%	
> 74%	165	80.5%	23	74.2%	0.312
Missing	2		0		
Lymphocyte percentage (%)					
< 19%	172	83.9%	25	80.6%	
19–48%	30	14.6%	4	12.9%	
> 48%	3	1.5%	2	6.5%	0.197
Missing	2		0		
C-Reactive Protein levels (mg/L)					
< 0.7	6	3.1%	0	0.0%	
≥ 0.7	188	96.9%	29	100.0%	0.337
Missing	13		2		
Creatinine levels (mg/L)					
≤ 1.17	174	84.5%	26	83.9%	
> 1.17	32	15.5%	5	16.1%	0.932
Missing	1		0		
D-dimer levels (mcg/mL)					
< 0.5	46	24.2%	8	28.6%	
≥ 0.5	144	75.8%	20	71.4%	0.618
Missing	17		3		
Troponin-T (ng/dL)					
≤ 4	22	12.4%	5	17.2%	
> 4	156	87.6%	24	82.8%	0.469
Missing	29		2		
CK-MB (IU/L)					
≤ 25	170	100.0%	27	100.0%	
> 25	0	0.0%	0	0.0%	.[a]
Missing	37		4		
Lactic acid (mmol/L)					
≤ 2.20	62	67.4%	16	84.2%	
> 2.20	30	32.6%	3	15.8%	0.144
Missing	115		12		
IL-6 (pg/mL)					
< 7	11	5.9%	1	4.0%	
7-39.99	58	31.2%	12	48.0%	
≥ 40	117	62.9%	12	48.0%	0.244
Missing	21		6		

RDV: Remdesivir; FPV: Favipiravir; GGOs: Ground glass opacities; CK-MB: Creatine kinase myocardial band; IL-6: Interleukin-6; N: Number of patients; %: Percentage; [a]: No Statistics are computed because Remdesivir or Favipiravir are constant.