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The Effect of Antiviral Agents in the Treatment of COVID-19 Patients: A Propensity Score-Matched and a Stabilized Inverted Probability of Treatment Weight Study (SIPTW)

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Abstract

Earlier purpose: To evaluate the antivirals casual effects in the treatment of COVID-19 patients, focusing on recovery, the need for home oxygen therapy on discharge and in-hospital mortality.

Methods: A retrospective study of the admitted COVID-19 patients, the outcomes assessed were effect-difference between antivirals and controls for recovery, mortality, and the need for home oxygen. A Propensity Score Matched-Patients (PSM), variables entered for patients were age, gender, documented fever, tobacco, body mass index, LDH level, ferritin level, antivirals, imaging severity categories, D-dimer level, oxygen saturation. Other variables were excluded for multicollinearity. Outcomes were inferred from the PSM-adjusted patients and Stabilized Inverse Probability of Treatment Weight (SIPTW) analysis.

Results: All cohort and PSM-adjusted patients were described. Mortality was for 143 (12.7%) patients in the ICU was 124 (55.8%). SIPTW analysis demonstrated no significant difference between the antiviral treatment arm and control patients in recovered (P=NS), the need for home oxygen therapy (P=NS), and the difference in all-cause mortality between the treatment and control groups (P=NS). On multivariate analysis, recovery, the need for home oxygen and mortality with both favipiravir and remdesivir was not significantly different.

Conclusion: There was no evidence of significant benefit from the antiviral therapy in the treatment of COVID-19 patients in recovery, home oxygen requirements, and death.

Keywords: Remdesivir; Favipiravir; COVID-19 mortality; Recovery; Home oxygen therapy

Introduction

COVID-19 the beginning of the world devastation started in December 2019 from Wuhan, about 10-million inhabitant city in Hubei Province, China. A novel virus recognized as SARS-CoV-2 swept all continents [1]. Almost, no single region or country was spared from the infection with over 174 million confirmed case and over 3.5 million confirmed deaths so far [2]. The fast spread of this viral pandemic was unparalleled with the outbreaks in the last decades as in the 2003 coronavirus (SARS-CoV) [3], the 2009 influenza (H1N1pdm009) [4], and the MERS-CoV [5].

Since the attack of the 20th century pandemic caused by the "Spanish flu", the world was expectant of another viral pandemic [6-9]. In Jordan, the pandemic started in early March 2020, with a single SARS-CoV-2 infection case, 10 days later the number of cases rocketed, and in a few months, it was followed by an exponential increase in cases. The country was devastated by two large waves, peaking on November 20, 2020 and March 19, 2021. So far, the numbers of cases added up to over 742000 infected individuals with over 9570 deaths by 10 June 2021, in a country with 10.3 million inhabitants [10]. In the country, COVID-19 patients were treated exclusively in the Ministry of Health hospitals and military healthcare settings until November 2020, hitherto, private hospitals were authorized to admit and treat COVID-19 patients when an overwhelming explosion of admissions beyond the capacity of public hospitals occurred.

Unfortunately, the therapeutic options in the management of the novel virus and the clinical picture it manifests (COVID-19) fell short of a usual success, and acceptance was not uniform among the treating physicians and institutions due to the lack of an effective antiviral therapy [11-14]. In this study our aim was to focus on the repurposed antiviral treatment; favipiravir and remdesivir, portraying their therapeutic benefit for patients in recovery, the need for home oxygen therapy, and mortality. A propensity scores matched (PSM) and a Stabilized Inverted Probability of Treatment Weighing (SIPTW) for evaluating casual inferences on the treatment effect were used in the analysis to control for bias [15].

Materials and Methods

Study settings

Data for COVID-19 patients were collected from the three participating hospitals and were uploaded to a cloud excel sheet (Microsoft Corporation), the study was a cross sectional over about five and a half months (28 November 2020 to 6 May 2021). The analysis aimed to evaluate several aspects of the COVID-19 patient's therapeutic management; this study is a part of few other pending studies from the same database for several treatments. All records were included

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as patients presented for admissions in the hospitals the population is mostly belonging to the middle to middle-high socioeconomic classes in Amman, Jordan. The three hospitals are a private one, with bed capacity of around 700, special wards for the management of patients with COVID-19 were assigned with an approximate total capacity 155 floor beds and 47 ICU beds. The study was approved by the internal review board of the three hospitals, as an observational cross-sectional study. No consent was needed and the medical records for the patients were reviewed after the final disposition of the patients.

Treatment protocols

There was a current COVID-19 management protocol published by Jordan Ministry of Health (MOH), it has been updated regularly during the pandemic. In the private sector the treating physicians partially relied on the MOH protocol and directly from the updated publications in the world literature. This has caused to some extent heterogeneous management methods among the treating physicians. Physicians taking care of the patients were mostly chest and chest/critical care physicians, one Infectious diseases physician was available to contribute to the burden, and consults for the late effect of COVID-19 or secondary infections (The corresponding author).

COVID-19 patients and the treating physician's management questionnaire

Physicians taking care of COVID-19 patients were queried through a cloud Google Form on several medications being used in the country for the management of patients as they present early in the course of the disease for admission. The form was emailed to eight chest physicians that cover the three hospitals, all responded; the form focused on medications that were prescribed. Despite the heterogenous treatment regimens and timing of some medications in relation to some factors that patients may have developed, data were taken from the decisions taken in the first few days. The medications were: Steroids (dexamethasone or solumedrol), anticoagulants (Enoxaparin sodium, Apixaban, Rivaroxaban, and Fondaparinux), Vitamin D tablets (used as a three-days 50,000 I.U. regimen before March 15, then a seven-days 50,000 I.U., also a 2000 I.U. and 5000 I.U. daily were prescribed), Interleukin-6 inhibitors (tocilizumab), Antivirals (Favipiravir, Remdesivir), acetyl salicylic acid (ASA), colchicine, Zn tablets and Vitamin C (supplementary material).

Classification of radiological findings

Chest radiography scoring system, the degree of lungs involvement was reported by radiologists and the report was taken into consideration for classifying lungs involvement. Normal chest x-ray and/or normal CT chest with no infiltrate were considered as no involvement (score 1), a lobar infiltrate with 25% involvement (score 2), scattered ground glass appearance involving lungs with >25%-50% involvement (score 3), diffuse patchy infiltrate >50%-75% involvement was considered as (score 4), and multilobe infiltrate was considered as >75% involvement (score 5). This classification did not fit well with a previously published one [16].

Statistical analysis

Descriptive analysis of variables demonstrating the number of characteristics and features for the initial cohort, and the Propensity Score Matched (PSM) patients, in the antiviral treatment or control. All patients who were assigned receiving antivirals treatment or control were analyzed by Chi-square test ($\chi 2$) for the difference in proportions, with post hoc analysis by Bonferroni adjusted p-value to assure balanced variables and categories. Predicted probability was derived for continuous and binary variables using binary logistic regression, variables entered were: Age, gender, documented fever, tobacco, body mass index, LDH level, ferritin level, antivirals, imaging severity categories, D-dimer level and oxygen saturation. Predictors were tested for the normal distribution through skewness, histogram, and Q-Q blot, all closely fitted a normal curves distribution, skew ness for all were <1.0 and >-1.0, multicollinearity was evaluated by linear regression, tolerance was more than 0.644 for all predictors. VIF was for all <1.5, some continuous variables were Log 10 transformed to normalize the distribution before they were incorporated in the predicted probability model. A propensity score indices were deduced, match tolerance (caliper) was set at 0.1, without replacement. Stabilized Inverse Probability of Treatment Weight (SIPTW) was calculated for the treatment effects [15], and significance was evaluated for the difference between treated and control patients by Pearson $\chi 2$. Nested analysis with multivariate regression analysis to evaluate the difference among the patients who were on the antivirals "Favipiravir or Remdesivir" versus controls. SPSS version 25 with Python Essentials and Fuzzy extension command blog-ins was used in the analysis. Significance was considered for values <0.05.

Results

Characteristics of patients

The characteristics and feature of the 1220 patients were reviewed; ninety-three cases were not included due to excessively missing data. Analysis was for 1127 as the initial cohort (all patients), (PSM) analysis was for 580 patients, the same number of patients was analyzed as SIPTW. Overall, there was imbalance between the antiviral treatment and controls (P>0.05), however, they were balanced by PSM-adjustment except for colchicine and tocilizumab both remained significantly (but borderline) imbalanced after PSM adjustment (P<0.05), the rest of the characteristics were balanced (P=NS); in the initial cohort, age was well balanced except for the elder age group (≥ 76 years), but it was PSM-adjusted, gender was imbalanced in the initial cohort for males and females (P=0.013), it was PSM-adjusted antibiotics were PSM-adjusted, but antifungals were balanced in the initial cohort and in the PSM-adjusted population, some symptoms showed imbalance but were PSM adjusted, like chills, shortness of breath, cough and headaches. Comorbidities were balanced in the initial cohort except for "other" which was corrected by PSM (P=NS). Nested BMI analysis [17], and tobacco were well balanced for all cohort and the PSM adjusted population. The admission blood oxygen saturation was imbalanced for the categories 86%-90% and>95% in the initial cohort (P<0.05), however, the imbalance disappeared with the PSM score adjustment (P=NS). The admission radiological imaging (chest X-ray, CT scan or both) categories showed more patients allocated to no antivirals with significant difference for the 25% and >75% involvement (P<0.05), the imbalance disappeared on PSM score adjustment for all categories. For patients receiving oxygen, there was imbalance (P<0.05) between the two treatment allocations for using room air, simple mask, the combined method, the non re breather mask and the nasal prongs, all were balanced with PSM adjustment. Among laboratory markers, imbalance between the treatment allocations was evident for normal procalcitonin levels, D-dimer categories and for ferritin level <260 ng/ml [18], on PSM adjustment, PCT, D-dimer level>2000 ng/ml and serum ferritin level <260 ng/ml were balanced (Table 1) see the Supplementary material. All recorded complications for the followed-up patients had no significant difference (P=NS) between the antiviral treatment and controls in both the initial cohort and the PSM-adjusted patients (Table 1).

Characteristic	Patients' characteristic according to antiviral therapy allocation and Propensity score matching					
	All cohort N=1127			Propensity score match populations N=580		
	Antivirals n=725	Controls n=396	P*	Antivirals n=290	Controls n=290	P*
Age (years)						
Lowest thru 45	115	70	NS	56	48	
46 thru 55	129	63	NS	52	48	
56 thru 65	175	87	NS	73	69	0.536
66 thru 75	19	82	NS	60	60	
76 thru highest	127 (17.5)	91(23.2)	<0.05	49	65	
Gender						
Male	479 (66.1)	232 (58.6)	0.013	190	100	
female	246 (33.9)	164 (41.4)		171	119	0.104
Antivirals						
Favipiravir	667	0	-	255	-	-
Remdesivir	58	0	-	35	-	-
Colchicine	187 (25.8)	69 (17.4)	0.001	90 (31)	61 (21)	<0.05
Interleukin-6 inhibitors (Tocilizumab)	108 (14.9)	34 (8.6)	0.004	48 (16.6)	27 (9.3)	<0.05
Antibiotics	539 (74.3)	265 (66.9)	0.014	221	200	0.051
Antifungal	61	38	0.726	24	34	0.237
Presenting symptoms						
Temperature (exam)	711	386	NS	290	290	0.287
Chills	368 (50.8)	168 (42.4)	0.02	141	137	0.74
Sore throat	220	120	NS	96	95	0.996
Shortness of breath	623 (85.9)	303 (76.5)	0	249	239	0.256
Cough	607 (83.7)	304 (76.8)	0.011	238	237	0.914
Body aches	451	254	NS	186	204	0.111
Headaches	290 (40.0)	186 (47.0)	<0.05	135	154	0.163
Loss of smell	227	139	NS	94	118	0.067
Loss of Taste	236	153	NS	99	116	0.198
Diarrhea	110	47	NS	51	37	0.105
Rhinorrhea	49	20	NS	21	16	0.369
Comorbidities**						
Diabetes mellitus	37	26	NS	15	21	
Chronic lung disease	7	5	NS	5	6	
Heart disease	8	7	NS	3	4	
Hypertension	66	23	NS	25	17	0.637
Malignancy	3	3	NS	2	2	
Multiple comorbidities	387	196	NS	150	140	
Others	6 (0.8)	6 (2.3)	<0.05	2	7	
None	17	13	NS	9	11	
BMI$						
Lowest thru 18.49	140	65		61	45	
18.5-24.9	275	147	0.574	131	119	0.082
25-29.9	174	104		72	89	
30 thru highest	75	45		26	37	
Tobacco use	88	46		43	56	0.33
Blood oxygen saturation (%)						
>95	131 (18.1)	101 (25.5)	<0.05	56	60	
91-95	246	128	NS	88	100	
86-90	175 (24.1)	75 (18.9)	<0.05	76	63	0.48
80-85	88	51	NS	35	40	
<79	74	31	NS	35	27	
Radiological score (X-ray and CT)						
No involvement	54	22	NS	22	10	
25% Involvement	37 (5.1)	9 (2.3)	<0.05	6	8	
>25%-50% Involvement	220	131	NS	98	102	0.694
>50%-75% Involvement	187	119	NS	72	87	
>75% Involvement	198 (27.3)	78 (19.7)	<0.05	81	60	
Oxygen delivery method						
RA	90 (12.4)	72 (18.2)	<0.05	26	36	
Simple mask	107 (14.8)	41 (10.4)	<0.05	43	33	
High flow	33	10	NS	14	7	
Noninvasive ventilation	29	15	NS	13	12	
Combined	22 (3.0)	24 (6.1)	<0.05	10	20	0.072
IMV%	29	9	NS	13	8	
Non-rebreather mask	169 (23.3)	56 (14.1)	<0.05	62	45	
Nasal Prongs	236 (32.6)	155 (39.1)	<0.05	109	128	
Laboratory data						
PCT (ng/mL)						

<0.5	234 (32.2)	159 (40.2)	<0.05	116	135	
0.5 – or more	115	204	NS	42	36	0.391
D-Dimer (ng/mL)						
<500	480 (70.1)	308 (66.0)		235 (81)	259 (89.3)	<0.05
500-2000	127 (18.5)	36 (10.1)		37 (12.8)	22 (7.6)	<0.05
>2000	78 (11.4)	14 (3.9)		18	9	NS
			<0.05			
Ferritin ng/ml	<79	<79	<79	<79	<79	<79
<260	96 (13.6)	69 (19.8)	<0.05	34	54	
260-1000	330	162	NS	147	137	0.068
>1000	266	117	NS	109	99	
Complication by hospital discharge						
Pulmonary embolism	5	3		1	3	
Sepsis	2	1		0	0	
UTI	3	1		2	1	
HAP	3	0	0.815	0	0	0.552
Bleeding	2	1		0	1	
Others**	10	7		3	7	
No information	700	277		283	277	

*2-sided Significance (P-value) was tested by χ2, and adjusted by Bonferroni method; Numbers in (brackets) are the proportions for the adjacent numbers for the variables and or their category when statistical significance was demonstrated; $BMI: Body Mass Index; NS: Not Significant; **Comorbidities: Malignancy; 3 Haemato-malignancy and 3 solid tumors. Chronic lung disease; 8 Bronchial asthma and 4 COPD. Chronic heart disease; 8 Coronary disease and 7 chronic heart conditions; DM and HTN largely contributed to the "Multiple comorbidities"; % Invasive mechanical ventilation; **Others (complications): Others were nine; 1 liver injury, 1 coronary syndrome, 1 hyperglycemia, 1 acute kidney injury-hyperkalemia, 1 fibrosis, 1 hypotension, 1 brain dead, 1 barotrauma, and 1 emphysema pneumopericardium and 8 transfers to other hospitals/against medical advice; bleeding 2 hemoptysis and 1 GIT.

Table 1: The characteristics of COVID-19 patients and their epidemiological features according to treatment allocations.

Outcome measures

The all-cause mortality was in 143 patients (12.7%) and for those who stayed in the ICU were 124 patients (55.8%). In the all-cohort analysis, the recovered patients had a humble significant difference for patients who received the antiviral agents in favor of controls (P=0.032), which again was not significant in the PSM-adjustment (P=NS) and SIPTW (P=NS) respectively, there was no significant difference for the "needs home O2 therapy" among all outcome analysis groups (P=NS) respectively. Death was significantly increased in the initial cohort patients who were on antiviral therapy (P=0.014), on adjustment by PSM and SIPTW there was no significant difference compared with the control groups (P=NS) respectively. The antiviral treatment prescribed were favipiravir and remdesivir, sensitivity analysis using PSM and SIPTW demonstrated that recovered patients with both antivirals was not significantly different from controls for both analyses, favipiravir (P=NS) and remdesivir (P=NS). The need for home oxygen was similar for patients with favipiravir and remdesivir (P=NS). All-cause mortality was not significantly different for both favipiravir and remdesivir (13.8 vs. 20.8 respectively, χ2=4.409, P=0.110), on multivariate linear regression analysis, the mortality versus controls with favipiravir (P=NS), and with remdesivir (P=NS) (Table 2).

Discussion

As SARS-CoV-2 hit the globe signaling the start of the COVID-19 pandemic, an insight on the treatment in the country was sought, physicians dealing with the treatment of COVID-19 relied on the protocols drafted by Jordan Ministry of Health, and world literature. At the outset of the pandemic, our patients were provided an initial heterogeneous management that continued at a later stage of the pandemic, a consensus was not reached as it was revealed by a questionnaire (supplementary data), and remained heterogenous. Our study started with an acceptable sample size for a comfortable analysis even when using the PSM-adjusted population, which increases robustness [19,20]. The treatment population and controls were balanced, though a few confounders remained imbalanced, nonetheless with a humble significant difference, we believe that this occasional imbalance did not affect the robustness of outcome prior to the final outcome analysis (Table 1), but the majority of confounders and their sub-categories were well balanced (P>0.05).

Our all-cause 12.7% mortality and the 55.8% ICU mortality that we found in this study was not different from records for many countries, though initially, the idea was that mortality was higher in Jordan than

	Analysis of the casual effect of the antiviral therapy for patients with known outcomes								
Outcome	**All Cohort N=1059**			**Propensity Score Matched Population N=580**			**Stabilized Inverse Probability of Treatment Weighing N=420**		
	Yes n=679	No n=380	P	Yes n=281	No n=285	P*	Yes n=275	No n=145	P*
Recovered**	243 (33.5)	160 (40.4)	<0.05	103	105		98	54	
Needs home O2 therapy	304	166	NS	122	141	0.152	123	71	0.504
Death	105(14.5)	38(9.6)	<0.05	46	29		41	15	
Others$	27	16	NS	9	5		13	5	

*2-sided Significance was tested by χ2, and adjusted by Bonferroni method; Number in (brackets) are the proportions for the adjacent numbers for the variables and or their category when statistical significance was demonstrated; NS: not significant at 2-sided 0.05 level, **Recovered: no need for O2 therapy, no symptoms like (fever, headaches, myalgias, loss of taste, loss of smell, chills and other symptoms that were non-existent before the SARS-CoV-2 infection); $Others: Transferrers, Against Medical Advice, SOB, headache, loss of smell and the rest were unspecified.

Table 2: The outcome of antiviral agents in the treatment of the COVID-19 patients analyzed as unmatched initial cohort, propensity score-matched population (PSM), and stabilized inverted probability of treatment weight (SIPTW).

other world countries, however, the recorded ICU mortality in our study was similar to the rest of the worldwide where it ranged 50%-65% [21], this may indicate that COVID-19-associated mortality remained closely similar despite different protocols were adopted in various countries, hence, mortality was as an effect of the viral infection, the disease it causes and subsequent complications, treatment protocols may have not significantly altered the outcome in the absence of a "game changer" therapy.

In our study the antivirals therapy was significantly (P<0.05) prescribed in patients with higher oxygen saturation (>95%) in the initial cohort due to the wide scale use of the oral favipiravir, due to the ease of administrations, and most of those patients had a moderate COVID-19 that needed ward admission and the community-wide acceptance of the agent, however, this difference disappeared in the PSM adjustment. The imbalance in the oxygen delivery method for the room air, simple mask use, combined, non-rebreather mask, and prongs in the initial cohort was PSM-adjusted without imbalance. Among eleven symptoms and signs, four were imbalanced (P<0.05), because more patients with those symptoms visit the emergency rooms, again, all were balanced by the PSM-adjustment. More patients were treated with favipiravir in both the initial cohort and the PSM-adjusted population, favipiravir was commonly used due to a previous study demonstrating that favipiravir improves symptoms mostly fever and cough [22,23], in addition to a lower cost. It is noticed that the higher age (≥ 76 years) was a factor favoring the use of the antiviral treatment, this was abolished after the PSM adjustment (Table 1). Also, patients whom radiological score was 25% and >75% involvement were significantly on the antiviral therapy (P<0.05); this goes in hand with the previously noticed mild ambulatory and moderate patients admitted to the ward who had a relatively good oxygen saturation>95%, and those who had 75% of lung involvement were more on the antiviral therapy, anticipating some therapeutic effects in the very sick patients, the effects of both confounders disappeared with PSM-adjusted population (P=NS) representing a balanced populations. The higher levels of the serum procalcitonin in COVID-19 was not associated with initiating antiviral therapy as it is identified as an indicator of bacterial infection. D-dimer was imbalanced in the initial cohort, and only PSM-adjusted for the highest levels, serum ferritin level was not balanced for a level of <260 ng/ml in the initial cohort, but it was PSM adjusted. Inflammatory markers showed to some extent that lower levels go in hands with using favipiravir in the less severe patients, like the other covariates of less severs subcategories; like in patients with the relatively good oxygen saturation, being ambulatory and were admitted to the ward.

Worldwide, the repurposed antiviral agents; RNA-dependent RNA polymerase inhibitors were evaluated and prescribed for the treatment of COVID-19, almost before solid data were out. In Jordan, both agents, remdesivir and favipiravir, are available for use with a wide gab in cost, prohibiting the wide scale use of remdesivir, in addition to that remdesivir did not show a clear survival benefit but initially described as "shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection", the reference study was modified during its course [24]. Favipiravir was equally claimed to have clinical benefits like decreasing the length of hospital stay and the need for mechanical ventilation, in addition to shortening the time to viral clearance, and shortening the duration of some symptoms like fever and cough [22,25-27], furthermore, in a randomized, comparative, open-label, multicenter, phase 3 clinical trial, favipiravir was associated with the improvement in time to clinical cure (P=0.03) [28], and clinical recovery (P=0.001) [29]. Our physicians used the two antiviral agents but were dominated by favipiravir (favipiravir 667, and remdesivir 58 patients). The antiviral agents appeared to have no significant clinical benefit in patients' recovery, the need for the home oxygen, and mortality (P>0.05) when the outcomes were PSM-adjusted and reanalyzed as PSM and SIPTW. Remdesivir sensitivity analysis was in line with a meta-analysis that demonstrated remdesivir did not reduce significantly the time to recovery [30,31].

Conclusion

In conclusion, there was no significant clinical benefit for the currently evaluated antiviral agents, i.e., favipiravir and remdesivir in the treatment of COVID-19 patients in our focus outcomes of recovery, the need for home oxygen therapy, and all-cause mortality, all demonstrated no significant difference between the antiviral therapy and the control groups. We believe that PSM adjustment and outcome analysis by the SIPTW reduced bias, and made a robust study for the results we obtained.

Compliance with Ethical Standards

Funding

Not applicable.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Data Transparency

Analysis in supplementary materials and available database on request.

Ethical Approval

Ethical approval is obtained from the internal review board of each one of the three hospitals.

Informed Consent

Not applicable. The study has a retrospective design.

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