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Effect of Therapeutic Agents on Outcome of Different level of Progression of COVID-19 Infection in Pakistani Population

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ABSTRACT

Background: **Cytopathic effects of virus and cytokine release syndrome complicate acute respiratory distress syndrome and ultimately leads to multi-organ failure which can eventually culminate to mortality in COVID-19 patients. Many therapeutic agents have been tried from different aspects in desperation to control the unrestricted spread of virus, although the evidence of benefit was sparse.**

Material and method: **It is a retrospective cohort study of the treatment given to the patients admitted at Indus hospital Karachi from March 2020 to September 2020. In this study, we aim to evaluate therapeutic response of the treatment recommended in COVID-19 patients which included Methylprednisolone, Remdesivir, Tocilizumab and Hydroxychloroquine. We categorized the patients according to the CALL score (Comorbid, Age, Lymphocyte count, LDH) in to mild, moderate and at severe risk of progression of disease.**

Results: **Overall, out of 704 patients, 238(33.8%) patients died while 466(66.2%) survived. Least deaths were observed in low-risk group 30(12.6%) as compared to intermediate group 98(41.2%) and high risk patients 110(46.2%). In low, intermediate, and high risk groups, patients who didn't receive treatment showed better recovery [61(95.3%) vs 90(76.9%)], [59(75.6%) vs 137(63.4)] and [31(63.3%) vs 88(48.9%)] respectively. Similarly, in Remdesivir group, the patients who did not receive the treatment showed good outcome [(132 (86.6%) vs15 (62.5%)], [164 (69.8%) vs 32 (54.2%)] and [103 (56.3%) vs 16 (34.8%)]. In the same way Tocilizumab [136 (86.6%) vs 15(62.5%)], [166 (72.5%) vs 30 (46.2%)] and [103 (57.9%) vs 16 (31.4%)]. Lastly, Hydroxychloroquine [133 (86.4%) vs 18 (66.7%)], [169 (67.3%) vs27 (62.8%)] and [102 (52%) vs17 (51.5%)]. Over none of the treatment showed any beneficial effect on hospital stay and mortality.**

Conclusion: **Therapeutic option for treatment is limited and that these drugs as currently used should no longer be considered viable treatment options for COVID-19. There is need of research in developing new therapeutic options.**

Keywords: COVID-19, Methylprednisolone, Remdesivir, tocilizumab, Hydroxychloroquine, COVID-19 treatment, Pakistan.

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I. Introduction

It has been one year since the emergence of COVID-19 pandemic, and the treatment of the disease is still speculative. Many therapeutic agents have been tried from different aspects, in desperation to rein the untrammelled spread of virus, although the evidence of benefit is sparse [1], [2]. There are at least three strategies evident by which course of the disease was challenged. Firstly, by inhibiting viral replication (Remdesivir, lopinavir), secondly by muting immune response to prevent manifestation such as cytokine release syndrome (glucocorticoids, Interlukin-6 blocker) and lastly by neutralizing the virus through passive immunity (Convalescent–phase plasma, monoclonal antibody) [3]. The

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evidence in support of any favourable effect by these therapies is not substantial and still under extensive research [4], [5].

There are many factors which affect the outcome of the treatment like at what stage of the disease the treatment was started, comorbid conditions, age, and immune status of the patients. [6]. There is need of more data in different populations to see the effect of the different pharmacological treatments used to treat COVID-19 patients with different severity and comorbid conditions. The objective of our study was to review the progression of disease in our patients and the effect of treatment on outcome.

II. Material and Method

This is a retrospective observational cohort study of COVID-19 patients admitted in COVID-19 unit of Indus Hospital Karachi from 1st of March 2020 to 30th of Sep 2020. We included patients of all ages and the diagnosis of COVID-19 was made by RT-PCR, performed through nasopharyngeal. Permission from the institutional ethical review committee was taken prior to conduction of study. Patient's clinical characteristic and laboratory parameters were acquired from the Health Management Information System (HMIS) record of the patients. Data was collected on a structured proforma which included variables like age, gender, comorbid conditions, disease progression, COVID specific treatment, hospital stay, lab parameters and outcome. Disease progression was calculated according to CALL (Comorbid, Age, Lymphocyte count, LDH) score (7) into low risk (< 10% progression risk, intermediate risk (10%-40% progression risk) and high risk (>50% progression risk) (Table I).

TABLE I: Calculation of Call Score

Call score predictor n (%)			Call score
Age	<60 years	391 (55.5)	1
	≥ 60 years	313(44.5)	3
Comorbid	No	188 (26.7)	1
	At least one	516 (73.3)	4
Lymphocyte count	≤ 1× 10 9 /L	594 (84.4)	1
	> 1× 10 9/L	110 (15.6)	3
LDH	≤ 25	56 (8)	1
	251 – 500	321(45.6)	2
	>500	327 (46.4)	3

A. Statistical Analysis

The data was entered and analyzed in IBM SPSS version 21. Cleaning and coding of data was done prior to analysis. Frequencies and percentages were obtained for categorical variables, while mean± std was observed for continuous parameters. All continuous variables were categorized at the stage of analysis. Stratification of data was done according to three level of progression of disease and Chi square test was applied to observe any association between variables. Cox regression survival analysis was done to find the median hospital stay of patients according to the disease progression and treatment. The binary logistic regression analysis was executed to obtain odds ratio with 95% Confidence interval (CI) to predict death of the patients due to COVID-19. P value of ≤ 0.05 was consider significant.

III. Results

The description and division of study population according to CALL score is explained in Table I. Majority of our patients admitted with intermediate progression of disease 294 (41.8%), patients' distribution according to the progression of disease is depicted in Fig. 1.

Overall, out of 704 patients, 238(33.8%) patients died while 466(66.2%) survived. Least deaths were observed in low-risk group 30(12.6) as compared to intermediate group 98(41.2) and high risk patients 110(46.2) (Fig. 2). There were 539(76%) patients who received one or more than one form of treatment, while 165(23%) patients who didn't receive any form of COVID-19 specific treatment mentioned below. Methylprednisolone (MPS): In low risk group the patients who did not receive MPS showed better recovery as compared to those who received it [61(95.3%) vs 90(76.9%)]. Similar results were found in intermediate and high-risk groups in which the patients who did not received the MPS had more recovery than the patients who were treated with it 75.6% vs 63.4% and 63.3% vs 48.9% respectively (Table II).

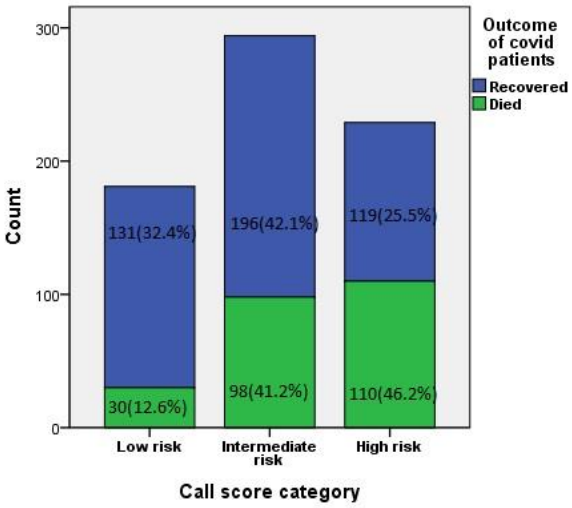

Fig. 2. Outcome of patients according to CALL.

A. Methylprednisolone (MPS)

In low-risk group, the patients who did not receive MPS showed better recovery as compared to those who received it [61(95.3%) vs 90(76.9%)]. Similar results were found in intermediate and high-risk groups in which the patients who did not received the MPS had more recovery than the patients who were treated with it 75.6% vs 63.4% and 63.3% vs 48.9%, respectively (Table II).

B. Remdesivir (RD)

In low risk of disease progression, the RD was given to few patients and among them 19(76%) patients recovered. Similarly, only 59(20.1%) of patients in intermediate group received the RD in which 32(54.2%) patients recovered, on the other hand, 164(69.8%) patients recovered from untreated group. In addition to this when RD was given to high-risk group only 16(34.8%) patients recovered while majority of the patients died 30(65.2%), as compared to the patients who

did not receive the treatment in which 103(56.3%) patients recovered and 80(43.7%) patients died (Table II).

TABLE II: ASSOCIATION OF TREATMENT WITH OUTCOME OF COVID-19, STRATIFIED BY CALL SCORE

Progression of disease according to Call score	Treatment		Outcome n (%) Recovered 466 (66.2%)	Died 238 (33.8%)	Total	P value
Low risk 181(25.7%)	Methylprednisolone	Yes	90 (76.9)	27 (23.1)	117 (64.6)	0.001
		No	61 (95.3)	3 (4.7)	64 (35.4)	
	Remdesivir	Yes	19 (76)	6 (24)	25 (13.8)	0.282
		No	132 (86.6)	24 (15.4)	25 (13.8)	
	Tocilizumab	Yes	15 (62.5)	9 (37.5)	24 (13.3)	0.001
		No	136 (86.6)	21 (13.6)	154 (85.1)	
	Hydroxychloroquine	Yes	18 (66.7)	9 (33.3)	27 (14.9)	0.001
		No	133 (86.4)	21 (13.6)	154 (85.1)	
	Total		151(32.4)	30(12.6)	181(25.7)	
Intermediate risk 294(41.8%)	Methylprednisolone	Yes	137 (63.4)	79 (36.6)	216 (73.5)	0.05
		No	59 (75.6)	19 (24.4)	78 (26.5)	
	Remdesivir	Yes	32 (54.2)	22 (45.8)	59 (20.1)	0.023
		No	164 (69.8)	71 (16.6)	239 (79.9)	
	Tocilizumab	Yes	30 (46.2)	35 (53.8)	65 (22.1)	<0.001
		No	166 (72.5)	63 (27.5)	229 (77.9)	
	Hydroxychloroquine	Yes	27 (62.8)	16 (37.2)	43 (14.6)	0.56
		No	169 (67.3)	82 (32.7)	251 (85.4)	
	Total		196(42.1)	98(41.2)	294(41.8)	
High risk 229(32.5%)	Methylprednisolone	Yes	88 (48.9)	92 (51.1)	180 (78.6)	0.074
		No	31 (63.3)	18 (36.9)	49 (21.4)	
	Remdesivir	Yes	16 (34.8)	30 (65.2)	46 (20.1)	0.009
		No	103 (56.3)	80 (43.7)	183 (79.9)	
	Tocilizumab	Yes	16 (31.4)	35 (68.6)	51 (22.3)	0.001
		No	103 (57.9)	75 (42.1)	178 (77.7)	
	Hydroxychloroquine	Yes	17 (51.5)	16 (48.5)	33 (14.4)	0.955
		No	102 (52)	94 (48)	196 (85.6)	
	Total		119(25.5)	110(46.2)	229(32.5)	

C. Tocilizumab: (TOCI)

Same as the Remdesivir, the TOCI also given to a smaller number of patients in low-risk group and among them 15(62.5%) patients recovered, while the patients who did not received the TOCI 136(86.6%) recovered. Likewise, in intermediate group the patients who did not receive the TOCI, recovered more than the patients who received it 166(72.5%) vs 30(46.2%). Consistently, the TOCI had negative outcome in the high-risk group, in which 51(22.3%) patients received TOCI and among them 35(68.6%) patients died while only 16(31.4%) recovered as compared to non-receivers in which 103(57.9%) patients recovered and 75(42.1%) patients died (Table II).

D. Hydroxychloroquine (HCQ)

Only 27(14.9%) patients who were in low-risk group treated with HCQ in which 18(66.7%) recovered while among the patients who were not treated with HCQ 133(86.4%) patients recovered. In intermediate group the outcome of both patients who were treated or not treated with HCQ was almost the same [27(62.8%) vs 169(67.3%)] respectively. In the same way, recovery in patients with high risk of disease progression was the same when treated with HCQ or not 17(51.5%) and 102(52%) (Table II).

Survival analysis showed that patients who had mild disease and did not receive any covid specific treatment had least hospital stay as compared with other patients. The median stay was of 5 days (95%CI 4.4-5.6). On the other hand, the patients with high risk of progression of disease and received multiple drugs like MPS, RD and TOCI to control the disease during hospital stay suffered longest stay in hospital, their median stay was 19 days (95% ci 12.9-25.1) (Fig. 3 and Table III).

We also observed the individual effect of disease progression and treatment on survival and found that the patients with high risk of progression died 4.7 times more than the patients with low-risk progression of the disease. Similarly, patients who needed MPS or any combination along with MPS died more than the patients who did not need immunosuppressions or antiviral treatment. The worst outcome was observed in those patients who received combination of MPS, RD and TOCI as they died 8 times more than the patients with no treatment (Table III).

TABLE III: MEDIAN HOSPITAL STAY OF PATIENTS ACCORDING TO DISEASE SEVERITY AND TREATMENT, AND THEIR ASSOCIATION WITH DEATH

Disease severity and Treatment	Median hospital stay in days	95% CI Lower-Upper	Odds ratio	95% CI Lower-Upper	p value
Overall	7	6.6-7.4	-	-	-
Low risk	5	4.4-5.6	-	-	-
Intermediate risk	7	6.4-7.6	2.5	1.6-4	<0.001
High risk	11	9.3-12.7	4.7	2.9-7.4	<0.001
No Immunosuppressive treatment	5	4.4-5.6	1	-	-
Methylprednisolone	7	6.4-7.6	2.5	1.6-4.1	<0.001
Methylprednisolone +Remdesivir	9	7-11.1	3.5	1.8-6.6	<0.001
Methylprednisolone +Tocilizumab	14	10.9-17.1	6.3	3.5-11.6	<0.001
Methylprednisolone +Remdesivir+ Tocilizumab	19	12.9-25.1	8	4-15.5	<0.001

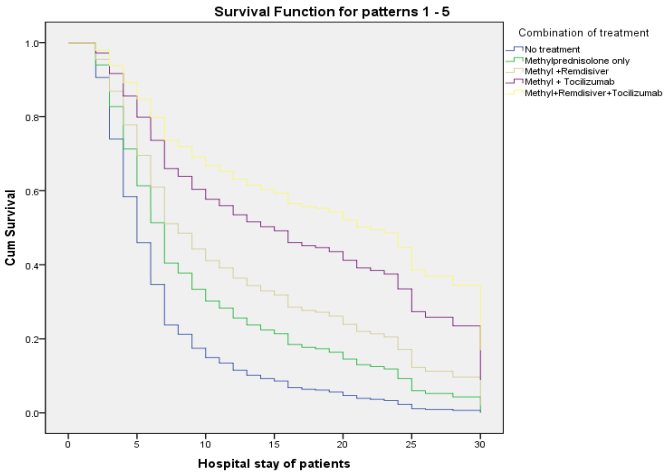

Fig. 3. Survival analysis of the patients treated with different medications.

IV. DISCUSSION

This is the first study from this country which evaluated the effects of almost all important therapeutic agents which are still in the armamentarium of COVID-19 treatment. It is dismaying that almost one year has passed and we are still in search of a breakthrough treatment of this fatal disease. The impression that we got from this data is that these medications need to be identified with their specific place with the patients in whom they have the best effect on.

In our study steroids did not show any beneficial effect on hospital stay and on survival as well. Steroids have been linked with reduced clearance of virus and increased viral load in both Middle East respiratory and SARS Cov pneumonia and caused a compromised outcome in influenza pneumonia [8], [9]. On the other hand in non-COVID-19 pneumonia with ARDS, it showed contradictory results. [10], [11]. In COVID-19, steroids showed conflicting results, for example, in The CoDEX Randomized Clinical Trial comprises of 299 patients, comparing dexamethasone vs placebo in moderate to severe ARDS, investigators found statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days, with the use of intravenous dexamethasone plus standard care compared with standard care alone [12]. On the contrary, in another multicentred randomized double-blind sequential trial conducted in France, patients were randomized to receive low-dose hydrocortisone vs placebo. The investigators concluded that the hydrocortisone did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. Although, the study was terminated early and likely was underpowered to find a statistically and clinically important difference in the primary outcome [13].

RD entered into the treatment regimen after authorization of its emergency use granted by US Food and Drug Administration as well by European medicine agency for the management of COVID-19 in patients 12 years of age or older with pneumonia who require supplemental oxygen [14], [15]. The effect of RD was also very marginal in our patients, and it did not show any benefit in improving the survival and hospital stay. Although, in other studies it showed some benefit in time to recover from ventilator. For instance, in a large double blind RD placebo-controlled ACCT-1 trial, RD was found to be superior to placebo in shortening the time to recover in severe COVID-19 as compared with those receiving placebo which was 11 days vs 15 days [16]. In another randomized open label trial assigned to 1:1 ratio to receive RD for either 5 to 10 days, it was concluded that the patients with severe COVID-19 who did not require mechanical ventilation did not show any significant difference between 5 days and 10 days course [17]. TOCI, which is an interleukin-6 receptor monoclonal antibody, was approved by FDA for the treatment of cytokine release syndrome. Interleukin-6 levels are correlated with viral load, disease severity and prognosis. In a large observational cohort, Gupta and Wang found lower in-hospital mortality in patients treated with TOCI in first 2 days of ICU admission compared with patients whose treatment did not include early use of TOCI [18]. Similarly, Jordan et al also found a beneficial effect of TOCI in reducing inflammation, oxygen requirement, vasopressor support and mortality [19]. Our results were very disappointing with TOCI as no retardation in the progress of disease was found in any group. Rather, we experienced that the patients who received TOCI developed more hospital acquired infections and bacterial sepsis. In this connection, we also want to mention (although not included in this study) that in a subgroup of the patients who developed acute kidney injury and received TOCI succumbed to worse outcome that compared patients who received TOCI and standard care, the investigators found that the patients who received TOCI showed no benefit on disease progression as compared with standard care [21]. In another randomized, double blind placebo-controlled trial involving confirmed severe COVID disease, the treatment assigned was standard care plus TOCI and standard care plus placebo. The investigators concluded that TOCI was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 [22].

However, in a randomized control trial comparing with usual care and usual care alone in French population, Hermine et al found no difference on the day 28 mortality and was neither able to reduce WHO-CPS score on day 4 [20]. Similarly in a prospective, open label, randomized Italian trial

Lastly, the Hydroxychloroquine was used in a smaller number of patients in our population but its effect was neutral

as its effect was same on the outcome in all risk groups whether it was used or not, although its use was associated with cardiac rhythm abnormalities. Recently published interim WHO Solidarity trial showed similar results.

There are few limitations of the study. This is an observational study in nature and the data was collected retrospectively, although size of the population is adequate as no other data is published with this number from this area. Our population is different from the western population in respect of median age, socioeconomical status, health care structure and provision. The epidemiology and demography of COVID-19 is different in this population. Therefore, despite the presence of the factors which were thought to deteriorate the outcome of the disease in this population, the mortality was not as high as we are still observing in the western population [23]. We have the same observation of our study which the editorial writers of Solidarity trial have "*Viewed collectively with previous studies, the Solidarity trial sends the clear message that these drugs as currently used should no longer be considered viable treatment options for COVID-19"* [24].

V. Conclusion

Therapeutic options for treatment are limited and that these drugs as currently used should no longer be considered viable treatment options for COVID-19. There is need of research in developing new therapeutic options.

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