

Survival and Biomarkers of COVID-19 Patients Treated with Remdesivir and Favipiravir in ICU: A Single Center Experience in Bangladesh

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Abstract

Background: Since the first detection of a bunch of COVID-19 in late 2019, it become a global concern due to its transmissibility and ability to progress patients in severe respiratory failure and acute respiratory distress syndrome, which need intensive care unit support for a long time. We observed the repurposing use of remdesivir and favipiravir whether considered as a therapeutic option or not through survival rate and changes in biomarker during 10-day treatment stay in ICU.

Materials and method: The retrospective observational study in a tertiary care hospital dedicated to COVID-19 at Dhaka, Bangladesh was done at the peak of COVID-19 pandemic in Bangladesh. The mortality rate, length of ICU stays and eight prognostic biomarkers of patients treated with remdesivir and favipiravir was observed as one of the first ever reported experience in Bangladesh.

Results: Among the critically ill patients in ICU, 26 (44.8%) died and 32 (55.2%) were cured during the study period and highest mean duration of stay in ICU was observed (14.33 days and 18.13 days) in FPV-treated patients. Mean of means for all biomarkers CRP (26.0) and d-Dimer (2.64) was recorded higher in favipiravir treated patients in death cases, but NLR, d-NLR, platelet, PLR was much higher in remdesivir treated patient of both death and improved cases. Though overall outcome variables between death and improved cases were not statistically significant ($p < 0.39$)

Conclusion: The severity of disease progression in critically ill COVID-19 patients in ICU depends on comorbidities and hyper responsive inflammatory or immunological biomarkers to predict. Though the emergency use authorization and repurposing use of different antivirals are still on trial, but remdesivir and favipiravir revealed not much hope in improving prognostic biomarkers, survival rate and disease progression at the initial peak of pandemic in Bangladesh.

Introduction

Since the cluster of novel respiratory viral infections first recognized in China in late December 2019, it was observed with growing apprehension as infections with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus— named Coronavirus Disease of 2019 (COVID-19) have also spread to hospitals in Bangladesh. The progression and severity of COVID-19 have placed critical care physicians in to attention. Its transmissibility caused spread of the disease throughout a population quite rapidly and case counts might increase by hundreds or even thousands per day in densely populated metropolitan area as no herd immunity exists to COVID-19. Unlike influenza virus infection, COVID-19 is manifested by a severe hypoxic respiratory failure requiring long time intensive care with specialized support.

The common presenting complaints of COVID-19 patients are fever, cough, dyspnea, myalgia or weakness, sputum production, cerebral pain, hemoptysis and loose motion. COVID-19 patients may present with solely neurological manifestations like loss of smell, loss of taste, stroke, vertigo or respiratory failure even without having any respiratory symptoms.¹ Studies showed the incubation period of this disease could be up to 14 days. The median time was found 4-5 days from the day of exposure to the virus. One study found that 97.5% of COVID-19 affected person will develop the symptoms within 11.5 days². One of the Chinese cohort studies, comprises of more than 44 thousand COVID-19 patients divided the symptoms into mild to moderate (81%), sever (14%) and critical (5%). Severe cases had dyspnea, hypoxia or more than pulmonary involvement in imaging. Critical cases presented with multi-organ dysfunction, shock or respiratory failure with overall mortality rate of 49%.³

In intensive care unit (ICU), critically ill COVID-19 patients usually develop shortness of breathing within 5 to 8 days and develop acute respiratory distress syndrome (ARDS) within 8 to 12 days. Nearly one-third of admitted patient required

ICU.⁴ Among all the admitted patients, 3% to 7% patients developed ARDS and this percentage was 67% to 82% for ICU patients. The mortality of ICU patients varied from 39% to 72% in different studies. For the survivors, the average duration of hospital staying was 10 to 13 days⁵. Commonest complications of COVID-19 patients are septic shock, ARDS, pneumonia, cardiopathy and acute kidney diseases. Some patients develop prolonged hospitalization related complications like gastrointestinal bleeding, secondary bacterial infections, thromboembolism and polyneuropathy.⁶ Some novel corona virus affected patients may develop hypercoagulable state featured with arterial and venous thrombosis of large and small vessels. Coagulopathy related common laboratory abnormal findings are prolonged prothrombin time, increased D-dimer, increased fibrin degradation products and mild to moderate thrombocytopenia. Increased D-dimer has been found strongly associated with greater risk of death.⁷

In Bangladesh, the treatment guideline initially included several medications for the critically ill patients requiring ICU support. Besides oxygen therapy, HFNC, NIV and invasive ventilation, different pharmacotherapy was tried under different protocol in search of remedy. As the COVID-19 belongs to the same family as SARS and MERS and patients present with same pneumonia like symptoms, variety of antiviral agents have been tried according to the clinical experience from SARS and MERS. Most commonly used broad-spectrum antiviral agent used against SARS and MERS was ribavirin, protease inhibitor lopinavir and ritonavir, oseltamivir and immune up-regulator interferon. Similar agents are also being tried purposefully for COVID-19 patients⁸. Remdesivir and favipiravir are one of the proposed antiviral medicines which were attempted during the attack of EBOLA though Food and Drug Administration (FDA) of USA rejected the drug due to lack of significant evidence in favor of it. This time also remdesivir was expected to be one of the promising options for treatment of COVID-19 based on some laboratory experiments and reports from some compassionate use and case reports⁹. Repurposing use of lot of pharmacological compounds/drugs has been tried as a remedy. Favipiravir is one of the proposed antiviral medicine which was attempted during the attack of EBOLA. At first china and Japan, then many countries around the world started to use favipiravir against SARS-CoV-2, though scarcity of published RCTs reflects a lack of significant evidence in favor of it¹⁰. The safety and efficacy of these drugs in COVID-19 require evidence based, quality-designed and sufficiently-powered clinical trials with large sample size for defined decision. Still some clinical prognostic biomarkers of critically ill patients in ICU who were treated with remdesivir and/or favipiravir needed to be monitored and evaluated to add in search of effective pharmacotherapy.

In this retrospective study, the overall treatment outcome was compared as improved or death cases along with different prognostic biomarkers of the critically ill patients treated with remdesivir and/or favipiravir in ICU of a tertiary care teaching hospital dedicated for COVID-19 during the peak of pandemic in the capital city of Bangladesh.

Methodology

The cross sectional retrospective descriptive study was done on the critically ill patients admitted in Intensive Care Unit (ICU) of Holy Family Red Crescent Medical College Hospital, Dhaka, Bangladesh during the peak two months of pandemic in Bangladesh from 1 June 2020 to 31 July 2020. The aim of the study was to observe the survival outcome of COVID-19 patients in ICU treated with remdesivir and favipiravir in the tertiary care hospital of Bangladesh. The primary objective of this study was to observe the mortality and prognostic biomarkers of 10-day treatment outcome of different treatment groups among ICU admitted COVID-19 patients. The relationship between gender and age group, change and relationship of biomarkers with different groups of patients treated with remdesivir and favipiravir, along with convalescent plasma were also observed in the study.

Inclusion criteria: All diagnosed (by RT-PCR) COVID-19 patients admitted in the ICU of Holy Family Red Crescent Medical College Hospital, Dhaka divided into 5 treatment groups were included.

Exclusion criteria: COVID-19 patients admitted anywhere other than ICU were not included, patients who did not receive Remdesivir (RDV) and/or Favipiravir (FPV), patients without documented predictor / outcome variables.

The study protocol was approved by the institutional ethics board (IRB) of Holy Family Red Crescent Medical College Hospital. Data was collected from electronic medical information system database. Death and improved were set as primary outcome variable along with the duration of ICU stays and eight biomarkers (d-dimer, ferritin, CRP, INR, NLR, d-NLR, platelet) were recorded during the 10 days of treatment with RDV and/or FPV as prognostic outcome variables. Convalescent plasma (CP) therapy was also observed as adjuvant with RDV and FPV. Data were transferred to SPSS IBM 23 spreadsheet. After the completion of enrollment data were calculated. Survival outcome among 5 treatment groups were calculated by one-way ANOVA and the *t*-test were done to evaluate the significance of variations of the biomarkers between RDV and FPV treated groups.

Results

In total, 58 patients with confirmed COVID-19 were treated in ICU, of whom 45 (77.5%) were male and 13 (22.5%) were female. Most of the critically ill patients (25) were in the age range of 40-69 years. Among the critically ill patients in ICU, 26 (44.8%) died and 32 (55.2%) were cured during the study period from June 1, 2020 to July 31, 2020. Total 22 patients were treated with remdesivir only (RDV), 5 with favipiravir only (FPV), 14 with both remdesivir and favipiravir (RDV+FPV), 21 with remdesivir and convalescent plasma (RDV+CP), 7 with remdesivir, favipiravir and plasma (RDV+FPV+CP) as per national guideline of Directorate General of Health Services (DGHS) in Bangladesh (Table-I).

Most of the improved patients (71.42%) were observed in the remdesivir, favipiravir and plasma (RDV+FPV+CP) treated group, whereas most of the died patients (60.00%) were found in FPV group (Fig-1). The difference was found statistically significant ($p < .05$) with *t*-value = 2.46789 and *p*-value = 0.019419 by *t*-test.

The mean duration of stay in ICU was observed highest (14.33 days and 18.13 days) in FPV-treated patients and lowest (11.22 days and 9.18 days) in RDV+Plasma treated patients in both the death and improved cases.

Comparing the mean of means for all available biomarkers of 10-day treatment, the CRP (26.0) and d-Dimer (2.64) was recorded higher in FPV-treated patients in death cases, but NLR, d-NLR, platelet, PLR was much higher in RDV-treated patient of both death and improved cases as shown in table-II. Though overall outcome variables between death and improved cases were not statistically significant ($p < 0.39$) between RDV and FPV treated groups.

Discussion

The experimental antiviral drug remdesivir (manufactured by Gilead) was granted Emergency Use Authorization by the US-FDA in May 2020 for patients hospitalized with severe COVID-19¹¹. Besides US and much of Europe, licensing agreement with manufacturers in Egypt, India, Pakistan, Philippines and Bangladesh that permit the sale of generic version of the drug^{12,13,14}. But at that time, only two randomized clinical trials (RCTs) were completed that compared a 10-day course of remdesivir with placebo. One of the bigger was the National Institutes of Health–sponsored Adaptive COVID-19 Treatment Trial (ACTT-1) on 1063 patients found that those assigned a 10-day course of remdesivir had a shorter recovery time by 4 days (median, 11 vs 15 days) compared with placebo^{8,9,15}. In this study, the mean duration of ICU stay was 11.78 days in RDV-treated patients whereas 18.13 days in FPV-treated patients who survived and improved. But among the death cases, this duration was 12.11 and 14.13 days respectively.

Favipiravir (T-705) is a synthetic prodrug first discovered antiviral active against the influenza virus in Toyoma Chemicals laboratory and has been approved in Japan in 2014 for the management of emerging pandemic influenza.

Favipiravir inhibits 53 types of influenza viruses including seasonal flu, swine flu, avian influenza. Over the past few months, different clinical studies have been performed around the world including China, Japan, USA, Saudi Arabia, India to assess the efficacy of favipiravir against SARS-CoV-2^{8,10,16}. In various prospective, open-label multi-centric trial with favipiravir (1600 mg twice daily followed by 600 mg twice daily up to 10 days) revealed clinical recovery at day 7 among moderate COVID-19 patients^{17,18}. The main advantages of favipiravir are that it is administered orally and can be given in patients who are symptomatic but not severe enough to be hospitalized. In this study, severely ill COVID-19 patients in ICU were found treated with favipiravir, that might be due to deterioration of condition or exacerbation of comorbid conditions.

Given that d-dimer, ferritin, CRP, INR, NLR, d-NLR, platelet used as predictive biomarkers to identify and differentiate the severity of COVID-19 patients were limited. Yang et al. revealed eight potential factors to identify the progression of the severity¹⁹. The applicable thresholds for NLR, d-NLR, PLR, and LMR were observed using the ROC curve. The optimal threshold at 3.3 for NLR showed a superior prognostic option of clinical symptoms to change from mild to severe, which had the maximum of sensitivity and specificity and the largest of AUC. Several reports on the feasibility of either NLR or PLR in predicting prognosis in patients with SARS-CoV-2 infection have been published. In particular, Qu et al. suggested a possible prognostic role of PLR by analyzing the data of a cohort of 30 patients²⁰. Another study by Qin et al. showed a significantly higher NLR in patients with severe forms of COVID-19 in a cohort of 452 hospitalized patients. A higher NLR at hospital admission was associated with a more severe outcome: in particular, a NLR of > 4 was a predictor of admission to the ICU²¹. Patients with severe disease presented a significantly higher NLR at admission compared with patients with a milder form of COVID-19, which was in agreement with the present study, where the mean NLR, d-NLR was much higher in all the critically ill patients in ICU with 7.87 in death cases and 3.31 in improved cases who were treated with favipiravir only.

C-reactive protein (CRP) levels are increased in COVID-19 patients and study revealed strong correlation with disease severity and prognosis with median CRP values of approximately 40 mg/L among survivors, while non-survivors had median values of 125 mg/L²².

Among hematological parameters, lymphopenia is clearly associated with disease severity; patients who have died from COVID-19 have had significantly lower lymphocyte counts than survivors. In fact, repletion of lymphocytes may be an important factor for recovery²³. Other blood cells including neutrophils, eosinophils, WBC, platelets and CD8 cell counts were partial predictors in discriminating mild from severe COVID-19.

In the present study, the role of two commonly used antivirals (RDV and FPV) in the treatment of COVID-19 patients in ICU revealed not much hope in improving hematological biomarkers in limiting the disease progression. Some independent biomarkers like NLR (7.48 vs 3.31), d-NLR (5.10 vs 2.51) and d-Dimer (0.32 vs 1.10) showed significant variations ($p < .00001$) in improved cases between RDV and FPV treated patients for 10-day treatment in ICU.

Conclusion

The clinical status and coexisting comorbidities of COVID-19 patients largely determine the admittance in ICU. The cut-off line for SpO₂ to differentiate severe or critical status of patients vary with time and corresponding biomarkers to predict inflammatory and immunological responses caused by cytokines activity. Though the retrospective study was not inclusive of large or multi-center sampling, but a preliminary observation at the peak of COVID-19 pandemic in Bangladesh was indicative to develop, modify and revise treatment protocol for later versions.

Declarations

Conflict of interest:

The authors declare no potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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References

1. Khandaker A Talha, Selina F, Nasir M, Rahman M, Islam S, et al. (2020) Systematic Review on Neurological Manifestations of COVID-19 Corona Virus. *J Neuroinfect Dis* 11: 291.
2. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med* 2020.
3. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020.
4. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.
5. Wu C, Chen X, Cai Y, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020.
6. Bikdeli B, Madhavan M, Jimenez D et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *Journal of American College of Cardiology*. April 2020, S0735-1097(20)35008-7
7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* Feb 2020. <https://doi.org/10.1111/jth.14768>.
8. Perveen RA, Nasir M, Talha KA, Selina F, Islam MA. Systematic review on current antiviral therapy in COVID-19 pandemic. *Med J Malaysia*. 2020 Nov; 75(6): 615-621.
9. Nasir M, Talha KA, Islam T, Saha SK, Selina F, Parveen RA. Use of Remdesivir in the Management of COVID-19: A Systematic Review on Current Evidences. *Mymensingh Med J*. 2020 Apr;29(2):481-487. PMID: 32506110.
10. Nasir M, Perveen RA, Saha SK, Talha KA, Selina F, Islam MA. Systematic Review on Repurposing Use of Favipiravir Against SARS-CoV-2. *Mymensingh Med J*. 2020 Jul;29(3):747-754. PMID: 32844821.
11. US Food and Drug Administration. Coronavirus (COVID-19) update: FDA issues Emergency Use Authorization for potential COVID-19 treatment. Published May 1, 2020. Accessed August 11, 2020. <https://www.fda.gov/news-events/pressannouncements/coronavirus-covid-19-update-fdaissues-emergency-use-authorization-potential-covid-19-treatment>
12. Gilead. Voluntary licensing agreements for Remdesivir. www.gilead.com/purpose/advancingglobal-health/covid-19/voluntary-licensing-agreements-for-remdesivir.

13. Cohen E. Covid-19 drug rationed in the US is plentiful in developing countries. CNN. Sept. 2020. www.cnn.com/2020/09/09/health/covid-remdesivir-us-vs-other-countries/index.html.
14. Dutton G. EU faces Remdesivir shortages amidst sharp spikes in new covid-19 cases. BioSpace. 9 October 2020. www.biospace.com/article/eu-faces-remdesivir-shortages-amidst-sharp-spikesin-new-covid-19-cases.
15. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19—preliminary report. *N Engl J Med*. Published online May 22, 2020. doi:10.1056/NEJMoa2007764
16. Agarwal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. *Med J Armed Forces India*. 2020 Oct; 76(4): 370–376. PMID: 32895599
17. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv; 2020. DOI: 10.1101/2020.03.17.20037432.
18. Investigational antiviral study finds faster clinical improvement in patients with COVID-19 [Internet]. Pharmacy Times, [cited 24 July 2020]. Available from: <https://www.pharmacytimes.com/news/favipiravir-study-finds-fasterclinical-improvement-in-patients-with-covid-19>; 2020.
19. Yang A, Liu J, Tao W, Li H. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *Int Immunopharmacol*. 2020 Jul; 84: 106504. PMID: 32304994
20. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. *J Med Virol* 2020 Mar 17 [Epub ahead of print]. doi: 10.1002/jmv.25767
21. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020 Mar 12 [Epub ahead of print]. doi: 10.1093/cid/ciaa248
22. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive care med*. 2020; 46(5):846-8.
23. Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. *The Lancet Respiratory Medicine*. 2020 Apr 1;8(4):e24.

Tables

Table-I: Mortality outcome in different treatment groups in ICU

Medications received	Patients treated	Death cases		Improved cases		Statistical values
		Number	Percentage	Number	Percentage	
Remdesivir only (RDV)	22	08	36.36%	14	63.63%	<i>t-value</i>
Favipiravir only (FPV)	05	03	60.00%	02	40.00%	-2.46789
RDV + FPV	14	05	35.71%	09	64.28%	<i>p-value</i>
RDV + plasma	21	09	42.85%	12	57.14%	0.019419
RDV + FPV + plasma	07	02	28.57%	05	71.42%	Significant at <i>P < .05</i>

Table- II: Prognostic biomarkers of patients treated with remdesevir and favipiravir in ICU

	RDV		<i>t</i> -test	FPV		<i>t</i> -test
	Death	Improved		Death	Improved	
ICU stay	12±11.86	11.78±6.33	The <i>t</i> -value is 0.2647. The <i>p</i> -value is .397311. The result is not significant at <i>p</i> < .05.	14.33±15.37	18.13±4.96	The <i>t</i> -value is 0.26371. The <i>p</i> -value is .397685. The result is not significant at <i>p</i> < .05.
d-Dimer	1.88±2.23	0.32±0.58		2.64±3.10	1.10±1.39	
Ferritin	1122.50±863.93	671.73±635.69		1120.80±1104.5	457.0±443.15	
CRP	19.50±19.20	27.27±19.96		26±21.07	27.0±24.89	
INR	1.16±0.13	1.25±0.13		1.27±0.14	1.57±0.18	
NLR	8.49±8.72	7.48±5.08		7.87±7.05	3.31±3.37	
d-NLR	7.87±6.07	5.10±2.65		5.90±3.22	2.51±0.26	
Platelet	298.66±108.26	370.60±120.54		166.00±50.91	386.50±139.19	
PLR	236.34±235.76	264.97±126.23		113.92±46.84	238.53±131.82	

Figures

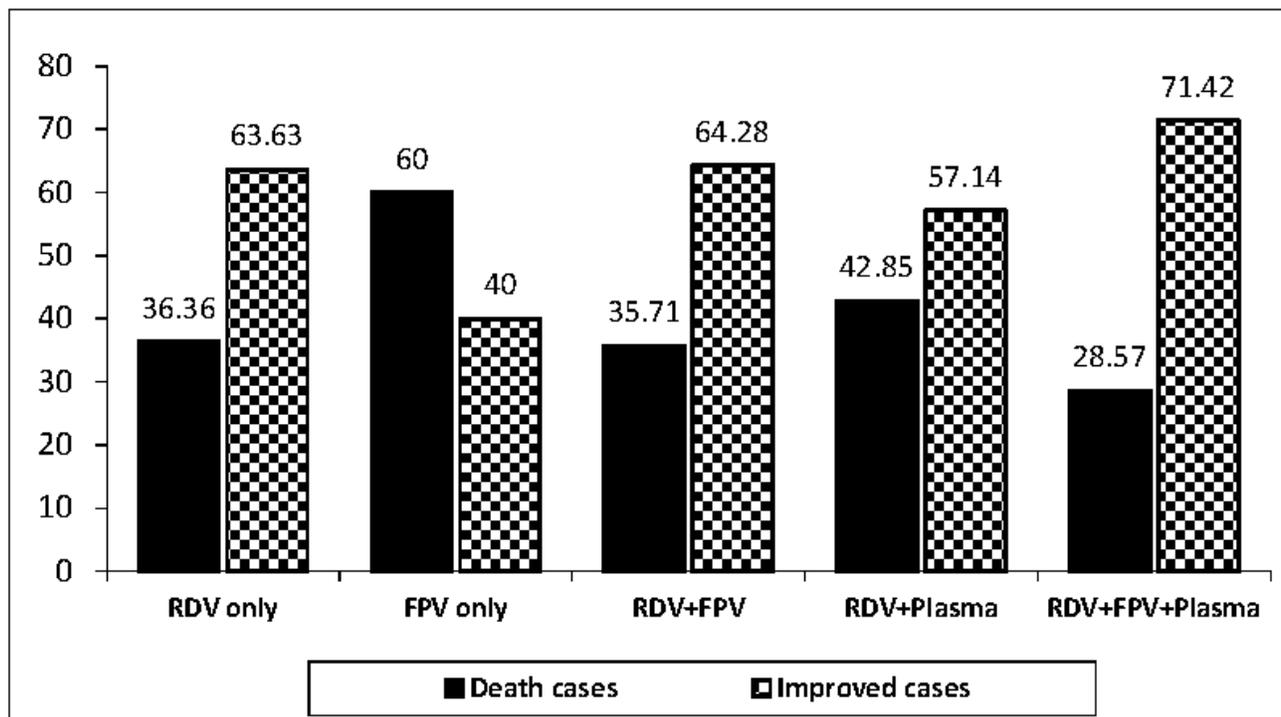


Figure 1

Survival outcome in different treatment groups