Effect of Ribavirin on Recovery Time in COVID-19 Patients: A Real-world Retrospective Cohort Study

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Research Article

Keywords: COVID-19; Ribavirin; Retrospective Real-world Study; Recovery Time

Posted Date: July 22nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-47356/v1

Abstract

Background: Up to now, there is still no specific drug against COVID-19. However, Ribavirin may bring clinical benefits to COVID-19 patients.

Methods: This study was designed as a real-world retrospective cohort study based on electronic medical record (EMR), and linear regression model was used to evaluate the effect of Ribavirin on recovery time.

Results: 342 patients were enrolled in this study. Both unadjusted and unadjusted models showed that interferon or Lopinavir-Ritonavir combined with Ribavirin could shorten the recovery time of patients, which was evident in all subgroups considered except the severe subgroup and after fine adjustments.

Conclusion: This study shows that interferon or Lopinavir-Ritonavir combined with Ribavirin can shorten the recovery time of patients with non-severe COVID-19.

1. Introduction

Up to now, there is still no specific drug against COVID-19. Ribavirin is a broad-spectrum nucleoside antiviral drug, which can interfere with the early transcriptional events of the virus to inhibit the replication and spread of the virus. There is only in silico[1-2] and in vitro experimental evidence[3] for treatment of COVID-19 with Ribavirin, and there is no clear clinical evidence for Ribavirin's benefits to COVID-19 patients. In addition, *Guideline for COVID-19 Management in China (Trial)* (Fifth Edition)[4] also comes from the clinical experience during the outbreak of SARS and MERS[5]. We conducted a real-world retrospective study to evaluate the efficacy of Ribavirin for SARS-CoV-2 infection.

2. Materials And Methods

2.1 Study design and population

This study was designed as a real-world retrospective cohort study based on EMRs. A total of 418 confirmed COVID-19 cases discharged from hospital from Shandong Provincial Chest Hospital, Jinan Infectious Diseases Hospital, Liaocheng Infectious Diseases Hospital, Qingdao Thoracic Hospital, Qingdao Municipal Hospital, Linyi Central Hospital, Binzhou Central Hospital, Weihai Thoracic Hospital, Linyi People's Hospital, Dezhou People's Hospital, Yantai Qishan Hospital and Huanggang Central Hospital between February 26, 2020 and March 9, 2020 were analyzed in this retrospective study. And, the baseline data of patient's EMRs must be complete.

The data for this study were obtained retrospectively from hospital EMRs. All confirmed cases in this study received basic antiviral therapy with interferon or Lopinavir-Ritonavir. The exclusion criteria were: (I) Patients received antiviral treatment with interferon or Lopinavir-Ritonavir combined with Ribavirin for less than 3 days; (II) Patients received no interferon or Lopinavir-Ritonavir combined with Ribavirin within 5 days of admission.

In Shandong Province, China, the government organized experts to consult COVID-19 patients. As the head of the Expert Committee on Prevention and Control of Epidemic Infectious Diseases and Emergency Treatment of Traditional Chinese Medicine in Shandong Province, doctors from the affiliated Hospital of Shandong University of traditional Chinese Medicine were sent to designated hospitals for consultation.

This study was approved by the Research Ethics Commission of Affiliated Hospital of Shandong University of Traditional Chinese Medicine, which waived the requirement for informed consent, as previously mentioned (KY-2020-001).

2.2 Data collection

Case Report Form was used to extract demographic information, comorbidities and clinical records from hospital EMRs. Before data extraction, personal identity information was replaced with codes for privacy concerns. All data were reviewed by two clinicians and a third-party researcher adjudicated any difference in interpretation between the two primary reviewers.

2.3 Definitions

The diagnosis and disease severity of COVID-19 were defined according to the *Guideline for COVID-19 Management in China* (version 7.0)[6]. Recovery time was regarded as the clinical outcome, defined as the time from the onset of the disease to the discharge of the patient. Pre-hospital delay was defined as the time from the onset of the disease to the admission of the patient.

2.4 Statistical analysis

All data analysis was run using R software (version 3.6.3) and Rstudio (version 1.2). Measurement data were described as mean±standard deviation or median with interquartile range, whereas count data were presented as numbers and percentages. Shapiro-Wilk test was performed to test the normality. Parametric or nonparametric tests were used to compare the baseline characteristics of COVID-19 patients receiving no treatment combined with Ribavirin and receiving treatment combined with Ribavirin. The linear regression model was used to evaluate the effect of Ribavirin on recovery time. Missing data was processed by Multivariate Imputation (MI) method using mice package (version 3.8.0), in which data is imputed multiple times to create 20 versions of the entire data set.

3. Results

3.1 Baseline characteristics of participants

Of the 418 COVID-19 patients recruited by searching medical records, 342 were enrolled in the study. Table 1 shows no statistical difference between baseline characteristics of the two groups.

Table 1. Baseline Characteristics of participants (N =342)

Variable	Uncombined	Combined	*P*-value
No. of participants	272	70	
Age, mean (SD)	44.73 (17.06)	43.79 (17.04)	0.680
Gender, n (%)			0.232
Female	112 (41.18)	35 (50.0)	
Male	160 (58.82)	35 (50.0)	
Underlying disease, n (%)			0.377
Yes	64 (23.5)	13 (18.6)	
No	208 (76.47)	57 (81.4)	
Disease severity status, n (%)			0.371
Mild	38 (14.0)	9 (12.9)	
Moderate	201 (73.9)	48 (68.6)	
Severe and critical	33 (12.1)	13 (18.6)	
Pre-hospital delay, median [IQR]	4.00 [0.00, 7.00]	3.00 [0.00, 8.00]	0.551

3.2 Univariate analysis

As shown in Table 2, univariate linear regression analysis showed that Ribavirin could shorten the recovery time. In addition, the results of univariate linear regression showed that age, disease severity status and pre-hospital delay were related to the recovery time. Compared with Mild type, Moderate type (β=7.17, 95%CI=4.20 to 10.15, p<0.001) and Severe type (β=13.95, 95%CI=9.84 to 18.05, p<0.001) tend to have a longer recovery time. The complete case analysis and multiple imputation analysis came to the same conclusion.

Table 2. Univariate analysis for recovery time

Variable	Complete case analysis		Multiple imputation analysis	
	β(95%CI)	*P*-value	β(95%CI)	*P*-value
Ribavirin				
Uncombined	Ref		Ref	
Combined	-3.35(-6.01,-0.70)	0.014*	-3.14(-5.72,-0.57)	0.017*
Age	0.08(0.01, 0.14)	0.022*	0.09(0.03,0.15)	0.004**
Gender				
Female	Ref		Ref	
Male	0.44(-1.82,2.70)	0.700	0.43(-1.71,2.56)	0.695
Underlying disease				
No	Ref		Ref	
Yes	2.02(-0.62,4.67)	0.132	2.19(-0.32, 4.70)	0.087
Disease severity status				
Mild	Ref		Ref	
Moderate	7.17(4.20,10.15)	<0.001***	7.45(4.61,10.28)	<0.001***
Severe and critical	13.95(9.84,18.05)	<0.001***	13.81(9.77,17.85)	<0.001***
Pre-hospital delay	0.60(0.40,0.79)	<0.001***	0.56(0.38,0.74)	<0.001***

Abbreviations: CI, confidence interval; Ref, Reference.

3.3 The results of relationship between Ribavirin and recovery time

Table 3 shows the relationship between Ribavirin and recovery time after adjusting for age, disease severity status and pre-hospital delay. Compared with treatment uncombined with Ribavirin, treatment combined with Ribavirin can shorten the recovery time after adjusting confounding variables.

Table 3. Relationship between Ribavirin and recovery time in complete case and multiple imputation analysis

Variable	Complete case analysis		Multiple imputation analysis	
	β(95%CI)	*P*-value	β(95%CI)	*P*-value
Ribavirin				
Uncombined	Ref		Ref	
Combined	-3.77(-6.10,-1.44)	0.002**	-3.58(-5.88,-1.28)	0.002**

Note 1: Abbreviations: CI, confidence interval; Ref, Reference.

Note 2: Model adjusted for age, disease severity status and pre-hospital delay.

3.4 The results of subgroup analysis

The stratified analysis of the relationship between Ribavirin and recovery time are presented in Table 4. The test for interactions were not statistically significant in age, gender, underlying disease and disease severity status (P for interaction=0.904, 0.240, 0.347 and 0.059, respectively). This negative effect was evident in all subgroups considered except the severe subgroup and after fine adjustments. In the severe subgroup, patients receiving treatment combined with ribavirin had a shorter recovery time than those receiving no treatment combined with Ribavirin, but the difference was not significant (β = 2.99, 95%CI =-6.17 to 12.16, p = 0.508).

Table 4. Effect size of Ribavirin on recovery time in prespecified and exploratory subgroups in each subgroup

Characteristic	No. of participants		β (95%CI)	*P*-value	*P* for interaction
	Uncombined	Combined			
Age					0.904
40	110	25	-4.33(-8.55,-0.11)	0.045*	
≥40	162	45	-2.97(-5.81,-0.12)	0.041*	
Gender					0.240
Female	112	35	-5.12(-8.50,-1.74)	0.003**	
Male	160	35	-2.08(-5.31,1.14)	0.204	
Underlying disease					0.347
No	208	57	-4.24(-6.80,-1.67)	0.001**	
Yes	64	13	-1.74(-7.92,4.44)	0.575	
Disease severity status					0.059
Non-severe	239	57	-4.34(-6.89,-1.79)	<0.001***	
Severe	33	13	2.99(-6.17,12.16)	0.508	

Note 1: Adjusted for age, disease severity status and pre-hospital delay(except the subgroup variable).

Note 2: Non-severe includes mild and moderate. Severe includes severe and critical.

Discussion

On February 11, 2020, the new coronavirus-infected pneumonia was named COVID-19 by WHO[7]. China's diagnosis and treatment plan "New Coronavirus-infected Pneumonia Diagnosis and Treatment Plan (Trial)" pointed out that the antiviral plan can adopt Alpha interferon Nebulized inhalation and oral

administration of Lopinavir/Ritonavir. In the fifth edition, Ribavirin was added[4], and in the sixth edition, Chloroquine Bis and Abidor were added[8].

The purpose of this study was to explore whether Ribavirin can benefit COVID-19 patients. What is encouraging is that in both unadjusted and adjusted models, the treatment combined with Ribavirin can indeed shorten the recovery time of COVID-19 patients. However, the treatment combined with Ribavirin in severe and critical patients was positively correlated with the recovery time. In addition, age, disease severity status and pre-hospital delay

By searching PubMed, we found no clinical studies evaluating the efficacy of Ribavirin on COVID-19. However, the clinical experience of SARS and MERS outbreaks shows that Ribavirin can provide clinical benefits to patients without septicemia and organ failure[9].

Ribavirin is a nucleoside analog with broad-spectrum antiviral effect, which was discovered in the 1970s. During the SARS epidemic in 2003, doctors tried to treat SARS patients with Ribavirin. Poutanen[10] reported on the experience of using Oseltamivir, Ribavirin combined with broad-spectrum antibiotics in the treatment of 7 SARS patients, of which 5 patients improved significantly, 1 improved, and 1 died. Booth[11]conducted a retrospective analysis of the clinical characteristics, treatment, and short-term prognosis of 144 SARS patients. Among them, 126 (88%) treatment regimens included intravenous infusion of Ribavirin. The results showed that patients receiving Ribavirin treatment had obvious improvement, but more adverse reactions occurred.

Ribavirin is also used in the treatment of MERS, though the effect is controversial. In a retrospective cohort study by Omrani[12], 20 patients with severe MERS were divided into 2 groups. One group received oral Ribavirin combined with subcutaneous injection of polyethylene glycol IFNα2a, and the other group did not use these two drugs. The survival rates of the two groups were 70% (14/20) and 29% (7/14) respectively, with statistically significant difference between the two groups(P = 0.004); after 28 days, the survival rates of the two groups were 30% (6/20) and 17% (4/24) respectively, without statistically significant difference between the groups (P = 0.54). Morra[13] collected 8 non-randomly controlled MERS treatment studies for meta-analysis. Among 116 patients, 68 were subcutaneously injected with IFN (IFNα2a for 34 cases, IFNα2b for 22 cases, IFNα1a for 12 cases) combined with oral or intravenous infusion of Ribavirin (observation group), and 48 cases did not use IFN and Ribavirin (control group). The mortality rates of the two groups were similar [71% (48/67) to 71% (34/48), P = 1.000], and there was no statistically significant difference between the mortality of patients receiving different types of IFN (P = 0.650).

Our analysis shows that patients with non-severe COVID-19 can benefit from the treatment combined with Ribavirin, while severe patients do not.

Lopinavir is an anti-HIV protease inhibitor. Chu[14] reported that Lopinavir and/or Ritonavir have anti-SARS-CoV activity in an in vitro virus sensitivity test; SARS patients were treated with Lopinavir/Ritonavir

and Ribavirin, and the incidence and mortality of acute respiratory distress syndrome [2.4% (1/41) and 0 (0/41)] after 21 days of medication were significantly lower than that in historically controlled patients treated with Ribavirin alone [22.5 % (25/111) and 6.3% (7/111)], with statistically significant difference (both P <0.001).

Chan[15] reported that Lopinavir/Ritonavir combined with IFN-β1b was effective in treating MERS-infected marmosets.

Bin Cao's[16] study showed that, in the hospitalized severe COVID -19 adult patients, the treatment with Lopinavir/Ritonavir brought no benefits beyond the standard treatment. 199 patients with laboratory-confirmed SARS-CoV-2 infection were divided into 2 groups, 99 in the Lopinavir/Ritonavir group and 100 in the standard care group. Lopinavir/Ritonavir treatment did not differ from standard treatment in terms of clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). The 28-day mortality rate of the Lopinavir/Ritonavir group and the standard care group was similar (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7).

Our study has several limitations. Firstly, this study is a real-world retrospective study, which provides only weak evidence. Secondly, all the data in this study are obtained from EMRs, which limits the collection of confounding variables. Thirdly, due to the limitation of sample size, the evaluation of the efficacy of Ribavirin in severe COVID-19 patients is not accurate. Finally, although MI was used to deal with the missing values, and the results obtained by complete case analysis and multiple imputation analysis were compared, the accuracy of statistical inference in this study was still affected.

In summary, this study shows that interferon or Lopinavir-Ritonavir combined with Ribavirin can shorten the recovery time of patients with non-severe COVID-19. These preliminary data can provide a research basis for Ribavirin in curing COVID-19.

Declarations

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[Authors' contributions]

WZ was responsible for the conception and design, analytical plan, critical revision of the manuscript for important intellectual content, approval of the final version to be published and agreement to be accountable for all aspects of the work. YL and XZ were responsible for the conception and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, approval of the final version to be published and agreement to be accountable for all aspects of the work. NS, XJ, XCZ, JH, ZQ, HL, YL and HM collected the data, critically revised the manuscript for important intellectual content and gave final approval for the version to be published. MY and CY were responsible for the

analytical plan, critical revision of the manuscript for important intellectual content, approval of the final version to be published and agreement to be accountable for all aspects of the work. All authors read and approved the final manuscript.

[Acknowledgements]

We thank all the colleagues who have helped with the research data collection.

[Funding]

Funding was provided by Shandong Province Major Science and Technology Innovation Project (2020SFXGY04-1) and Taishan Scholars (201712096).

[Ethical approval and consent to participate]

This article belongs to the final editorial and is exempt from ethical review.

[Availability of data and materials]

The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

[Competing interests]

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declared that Xinhua Jia, Yingying Liu, Huijie Ma and Zhanjun Qiu are members of Shandong Province's medical team assisting Wuhan; there are no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; there are no other relationships or activities that could appear to influence the submitted work.

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