

Efficacy of Respiratory Physiotherapy and Remdesivir in Patients with COVID-19 Pneumonia: A Systematic Review and Meta-Analysis

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Abstract

Evaluated efficacy of Respiratory Physiotherapy and Remdesivir on patients with COVID-19 pneumonia. In current systematic review and meta-analysis study, articles published January 2019 to December 1, 2021 were reviewed in the databases of PubMed, Scopus, Web of Science, and EBSCO. Risk ratio and mean differences with 95% confidence interval (CI), fixed effect model and Mantel–Haenszel or Inverse-variance formula were calculated. The Meta analysis have been evaluated with the statistical software Stata/MP v.16 (The fastest version of Stata). Mean differences of PaO₂/FiO₂ ratio at 6h after chest Respiratory Physiotherapy was (MD, 66 mmHg 95 % CI 64.71 mmHg, 67.28 mmHg; p=0.0007). Risk ratio of recovery rate between experimental and control group was 0.20 (RR, 0.20 95 % CI 0.15, 0.25) with high heterogeneity (I² =78.84%; p=0.00). Risk ratio of mortality rate between experimental and control group was -0.34 (RR, -0.34 95 % CI -0.65, -0.03) with low heterogeneity (I²<0%; p=0.51). Based on the findings of meta-analysis, Respiratory Physiotherapy can play an effective role in respiratory therapy and rehabilitation of patients admitted to the ICU with COVID-19. A meta-analysis

showed that treatment with Remdesivir could increase the recovery rate, especially in the early days of COVID-19; also reduces the mortality rate.

Keywords: COVID-19, Respiratory Physiotherapy, Remdesivir

Introduction

Coronaviruses are a large family of viruses. From this collection, seven species transmitted to humans have been discovered so far, which cause diseases such as colds in humans(1). Coronaviruses often attack the respiratory tract and sometimes show symptoms in the intestines and stomach(2, 3).Coronaviruses usually first infect the mucous membranes of the respiratory tract in the throat and nose, causing symptoms similar to the common cold(4). Coronaviruses usually first infect the mucous membranes of the respiratory tract in the throat and nose, causing symptoms similar to the common cold(5). Sometimes can cause more serious illnesses such as bronchitis and exacerbation of asthma and chronic bronchitis in adults and even lung infection (pneumonia) in adults, the elderly and people with weakened immune systems(6).Covid-19 is an airway infection caused by a mutated version of the coronavirus and was first reported in Wuhan, China in December 2019(7).Initially, the mortality rate of patients with Covid-19 was announced at 3 to 5 percent, but recent reports have shown a reduction in mortality(8).Due to the fact that this disease is very new and emerging, so scientific and documented findings in this area are very few. Therefore, considering the secondary effects that this disease has on the pulmonary system and affects the pulmonary system, so specialized findings on the improvement of pulmonary patients and their conclusion are very helpful in advancing the goals(9). Physiotherapists, as a member of the multiple treatment team in the intensive care unit, play an effective role in reducing respiratory complications and preventing weakness due to hospitalization in the intensive care unit(10).Since one of the most important organs involved in Covid-19 disease is the respiratory system, Therefore, the role of physiotherapists, especially in the field of respiratory physiotherapy, along with other health professionals, plays an important role in the treatment and care of this group of patients and overcoming the respiratory symptoms of patients with Covid-19.In addition to medical treatment, rehabilitation techniques and pulmonary physiotherapy are essential for the treatment and improvement of patients' respiratory function. These measures are also recommended as self-care training and breathing exercises for quarantine patients at home(11).Pulmonary rehabilitation has a variety of techniques, including breathing exercises and chest physiotherapy that help clear the airways, create a deep breathing pattern, increase arterial oxygen saturation and improve pulmonary volume, and increase voluntary expiratory volume in the first second(12). Due to the increase in hospitalization costs, reducing the risk of nosocomial infections, reducing the number of hospitalizations, pulmonary rehabilitation programs for empowerment and also improving patients' self-care have been emphasized more than before; Therefore, the main role of physiotherapists to start patients' pulmonary rehabilitation programs at the time of hospitalization and the emphasis on continuing and following it at home becomes more apparent.Therefore, the aim of current study was evaluated efficacy of Respiratory Physiotherapy and Remdesivir on patients with COVID-19 pneumonia.

Method

In this systematic review study, Science direct, Google scholar, PubMed, Scopus, Web of Science, and EBSCO databases were used to search for articles. The present study is a systematic review and meta-analysis. In current study review of previous studies, the Preferred Reporting Items for Systematic Reviews (PRISMA) checklist was used to search for the studies(13).

Data Extraction and analysis method

The data were extracted from the research included years, study design, number of patients, mean of age. To extract the data, two blind and independent reviewers extracted the data from the abstract and full text of the studies. Prior to screening, kappa statistics were performed to confirm the level of agreement between the reviewers. Kappa values were higher than 0.80. Risk ratio and odds ratio with 95% confidence interval (CI), fixed effect model and Mantel–Haenszel formula; mean differences with 95% CI, fixed effect model and Inverse-variance formula were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. I^2 values above 50% signified moderate-to-high heterogeneity. The Meta analysis have been evaluated with the statistical software Stata/MP v.16.

Result

Respiratory Physiotherapy: A total of 5 articles were found in the initial search. After removing duplicates, entry criteria for the titles were applied to the remaining 5 articles, and a summary of the remaining articles was reviewed. In this step, 4 articles were excluded. In the next, full text of 1 article were reviewed, finally one study was selected.

Remdesivir: A total of 89 articles were found in the initial search. After removing duplicates, entry criteria for the titles were applied to the remaining 69 articles, and a summary of the remaining articles was reviewed. In this step, 53 articles were excluded. In the next, full text of 16 articles were reviewed and 13 articles were excluded, finally three studies were selected.

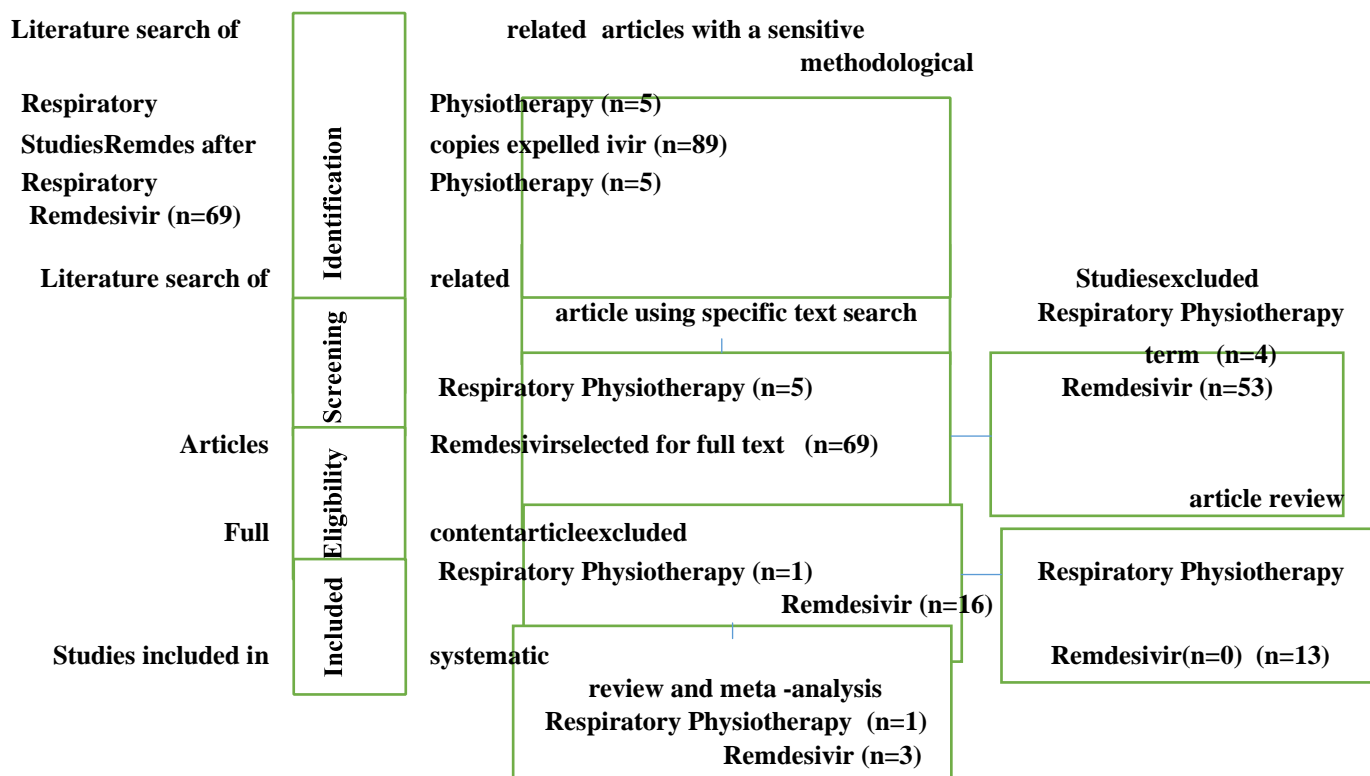


Figure 1. Flowchart of the literature search and selection criteria

Characteristics the studies included for evaluated Efficacy of Respiratory Physiotherapy One study (observational study) has been included in present article. The number of patients a total was 20 with mean age 63 years. Table 1 showed summary of studies for patient demographics, comorbidities, and clinical manifestations. Only one studies was found that evaluate Efficacy of Respiratory Physiotherapy in COVID-19 patients(14).

Table1. Summary of characteristics of included studies

Study. Years	Study design	Number of patients	Mean of age	Type of ventilation during RPT	ICU discharge characteristics
Battaglini et al.,2021 (14)	observational study	20	63	45% PSV 55% COT	% 5 Dead 95% Alive

PaO₂/FiO₂ ratio

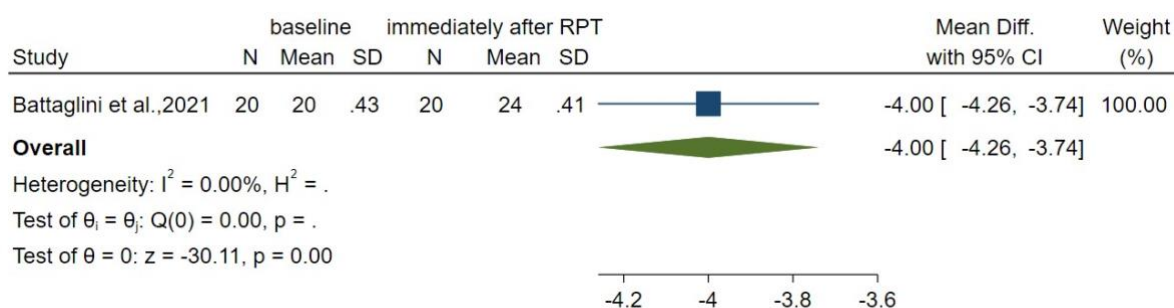
Battaglini et al.,2021 (14) reported that PaO₂/FiO₂ ratio improved at T1 (RPT) compared to T0 (baseline)(MD, 63 mmHg 95 % CI 61.83 mmHg, 64.16 mmHg; p=0.00), the mean differences of PaO₂/FiO₂ ratio at 6h after chest RPT was (MD, 66 mmHg 95 % CI 64.71 mmHg, 67.28 mmHg; p=0.0007), this result showed PaO₂/FiO₂ ratio improved at 6h after chest RPT than baseline (Table2).

Lung ultrasound score (LUS)

According to Battaglini et al.,2021 (14) study, the mean difference of LUS score between baseline and immediately after RPT was (MD, -4 95 % CI -4.26, -3.75; p=0.00).

Table2. Meta-analysis of PaO2/FiO2 ratio

Group	Study	Mean Diff.	[95% Conf. Interval]		% Weight
Baseline-immediately after RPT	Battaglini et al.,2021 (14)	63.000	61.838	64.162	54.92
baseline -6h after chest RPT	Battaglini et al.,2021 (14)	66.000	64.717	67.283	45.08
Meta-analysis summary		Number of studies = 2			
Fixed-effects model		Heterogeneity: I ² (%) = 91.33			
Method: Inverse-variance		H ² = 11.54			
Test of theta = 0: z = 146.42		Prob > z = 0.0000			
Test of homogeneity: Q = chi2(1) = 11.54		Prob > Q = 0.0007			



Fixed-effects inverse-variance model

Figure2. The Forest plot showed Mean differences of Lung ultrasound score

Battaglini et al.,2021 (14) reported Correlation between LUS and CT scan, volume of gas and hyperaeration at CT scan between baseline, immediately after RPT and 6h after chest RPT, the result showed there was statistically significant association between LUS score and lung gasvolume.

Characteristics the studies included for evaluated Efficacy of Remdesivir

Three studies have been included in present article. The number of patients in experimental and control group was 1125 with mean age 60.55 years and 799 with mean age 60 years, respectively. In all studies used 200 mg loading dose (IV), 100 mg maintenance dose from Second to Tenth day. The follow up period in two studies was 28 days and in one study was 29 days (Table3).

Table3. Summary of characteristics of included studies

Study. Years	Number of patients		Mean of age		Remdesivir arm	follow up period (day)
	treatment	control	treatment	control		

Spinner et al.,2002 (15)	384	200	58	57	200 mgloading dose (IV), 100 mg maintenance dose/ 2, 5 and 10 days	28
Wang et al., 2020 (16)	158	78	66	64	200 mgloading dose (IV), 100 mg maintenance dose/2-10 days	28
Beigel et al.,2020 (17)	583	521	58	59	200 mgloading dose (IV), 100 mg maintenance dose/2-10 days	29

Recovery rate

Risk ratio of recovery rate between experimental and control group was 0.20 (RR, 0.20 95 % CI 0.15, 0.25) with high heterogeneity ($I^2 = 78.84\%$; $p=0.00$) (Figure3). Subgroup metaanalysis showed Risk ratio of recovery rate on 7th day between experimental and control group was 0.19 (RR, 0.19 95 % CI 0.06, 0.33) with moderate heterogeneity ($I^2 = 52.24\%$; $p=0.12$) (Figure3); Risk ratio of recovery rate on 14th day between experimental and control group was 0.29 (RR, 0.29 95 % CI 0.20, 0.38) with high heterogeneity ($I^2 = 90.51\%$; $p=0.00$); Risk ratio of recovery rate on 28th day between experimental and control group was 0.13 (RR, 0.13 95 % CI 0.06, 0.20) with low heterogeneity ($I^2 = 49.21\%$; $p=0.14$). Remdesivir treatment significantly increased the recovery rate.

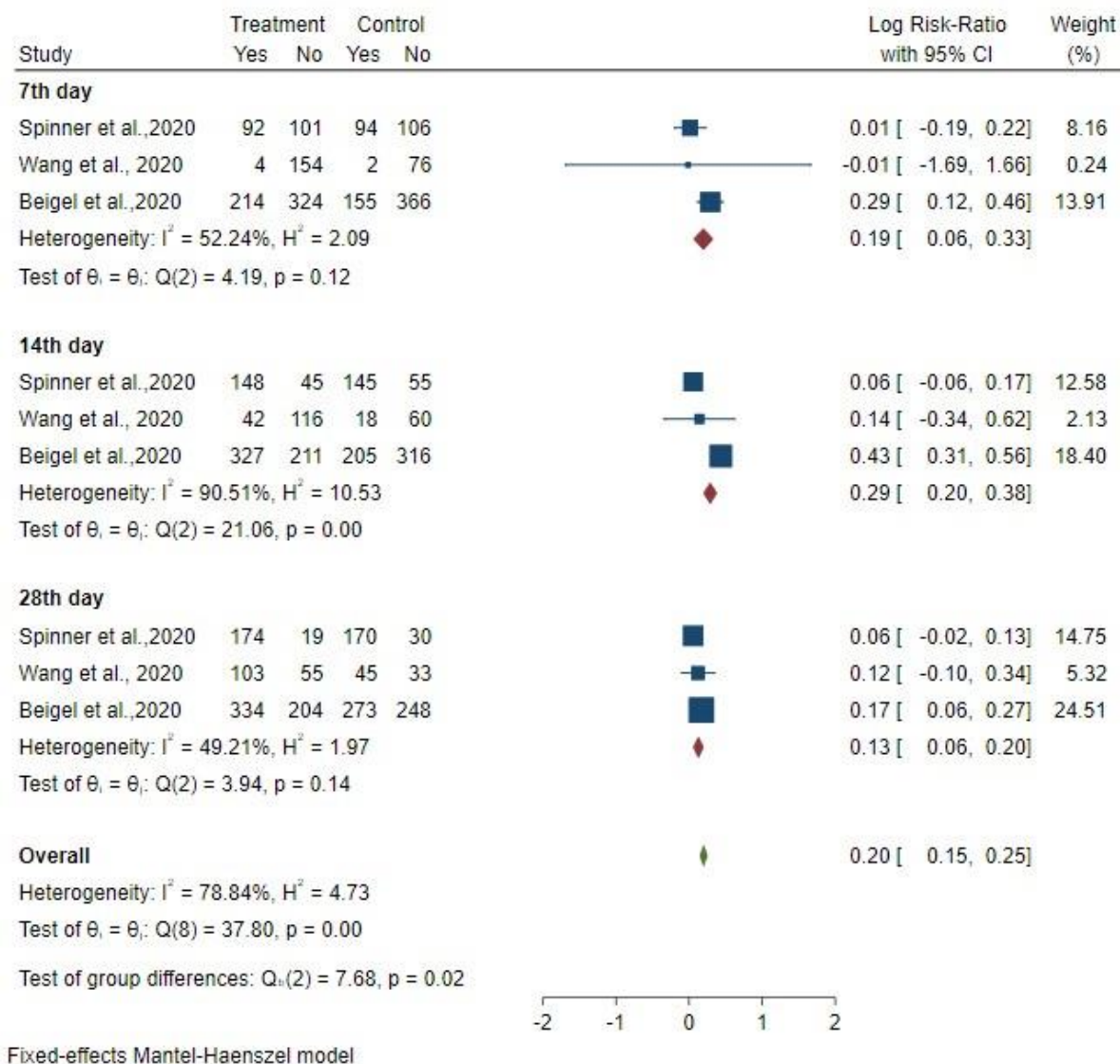


Figure3. The Forest plot showed recovery rate on 7, 14 and 28 days

Mortality rate

Risk ratio of mortality rate between experimental and control group was -0.34 (RR, -0.34 95 % CI -0.65, -0.03) with low heterogeneity ($I^2 < 0\%$; $p = 0.51$) (Figure4). Subgroup metaanalysis showed Risk ratio of mortality rate on 14th day between experimental and control group was -0.44 (RR, -0.44 95 % CI -0.82, -0.10) with low heterogeneity ($I^2 < 0\%$; $p = 0.52$); Risk ratio of Mortality rate on 28th day between experimental and control group was 0.04 (RR, 0.04 95 % CI -0.59, 0.67) with low heterogeneity ($I^2 < 0\%$; $p = 0.67$); Remdesivir treatment significantly reduction the mortality rate.

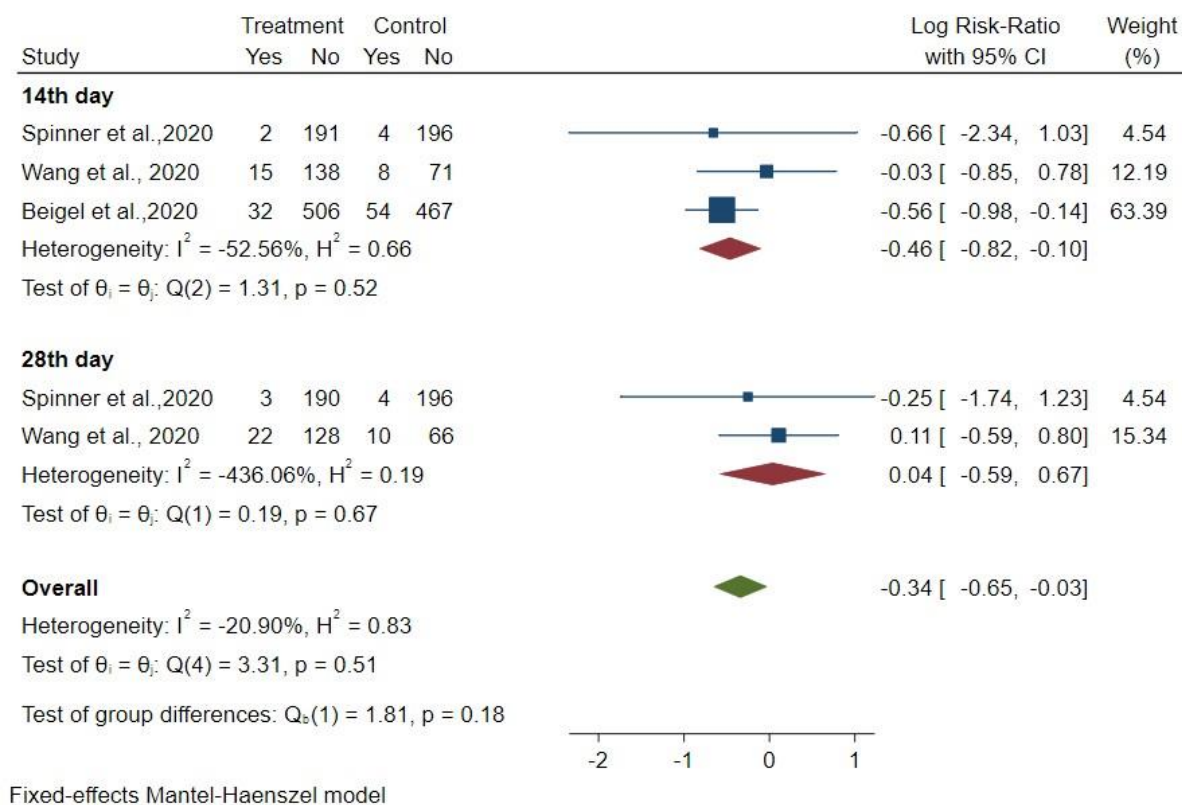


Figure4. The Forest plot showed Mortality rateon 14 and 28 days

Adverse effects

Riskdifference ofadverse effectsbetween experimental and control group was -0.01 (RD, 0.01 95 % CI -0.02, -0.00) with low heterogeneity ($I^2=27.92\%$; $p=0.17$) (Figure5).

Subgroup meta-analysis:

IncreasedSerum alanine aminotransferase

Riskdifference of Serum alanine aminotransferasebetween experimental and control group was-0.01 (RD, -0.01 95 % CI -0.02, -0.00) with high heterogeneity ($I^2=79.26\%$; $p=0.01$).

Increasedaspartate aminotransferase

Riskdifference of aspartate aminotransferasebetween experimental and control group was 0.02 (RD, -0.02 95 % CI -0.03, -0.00) with low heterogeneity ($I^2=34.50\%$; $p=0.22$).

Increased bilirubin

Riskdifference of bilirubinbetween experimental and control group was -0.00 (RD, -0.00 95 % CI 0.01, -0.01) with low heterogeneity ($I^2<0\%$; $p=0.96$).

Decreased Creatinine clearance

Riskdifference of Creatinine clearancebetween experimental and control group was -0.01 (RD, -0.0195 % CI -0.02, 0.01) with low heterogeneity ($I^2=33.40\%$; $p=0.20$).

Vomiting

Risk difference of Vomiting between experimental and control group was 0.02 (RD, 0.02 95 % CI -0.02, 0.07) with low heterogeneity ($I^2 < 0\%$; $p = 0.33$).

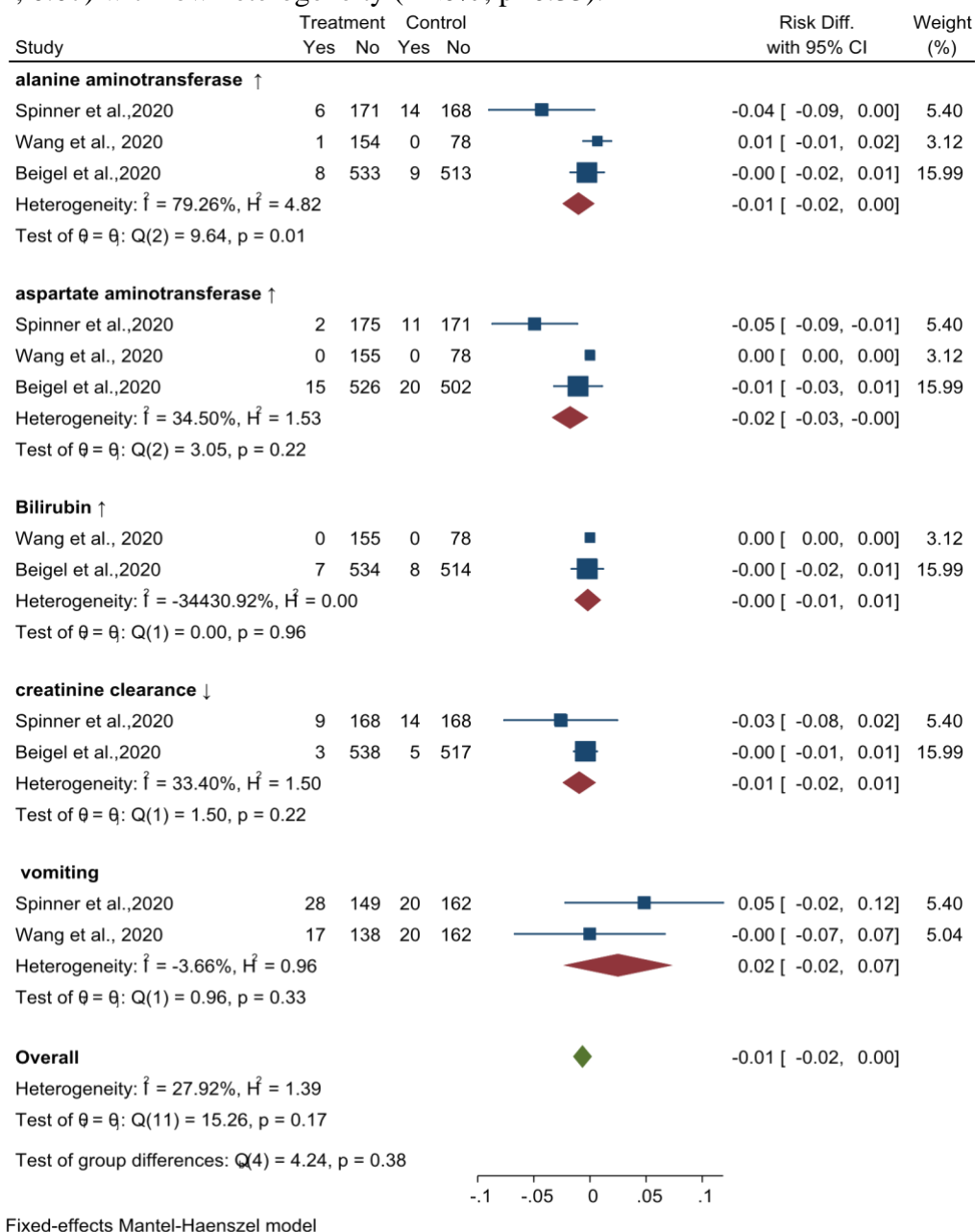


Figure5. The Forest plot showed adverse effects

Discussion

The aim of current systematic review and meta-analysis study was evaluating the efficacy of Respiratory Physiotherapy and Remdesivir on patients with COVID-19 pneumonia. Metaanalysis showed Respiratory Physiotherapy improves oxygenation in critically ill COVID-19 patients. Only one study (14) was found to investigate the role of respiratory physiotherapy in patients with COVID-19. Hence, further studies are needed to emphasize the findings. However, the findings showed that respiratory physiotherapy plays an important role in the rehabilitation of patients admitted to the ICU(18).A study did not find a role for respiratory physiotherapy in patients with different respiratory patterns.As the meta-analysis shows, the

LUS score improved, but these findings were not statistically significant. LUS is a diagnostic tool in the prognosis of COVID-19(19).To confirm this evidence, studies with larger sample sizes are needed to investigate the role of Respiratory Physiotherapy in patients with COVID19(14).Limitations of the present study on the role of Respiratory Physiotherapy are: the existence of only one study, small sample size, and observational study (retrospective), RCT studies were not found, the study was conducted at the peak of COVID-19 epidemic, No comparison was found with the control group to evaluate the effectiveness of Respiratory Physiotherapy.Therefore, summarizing the practical and effective techniques of pulmonary physiotherapy is valuable to increase the awareness of all audiences, including physiotherapists, nurses and patient caregivers. Most review studies indicate that pulmonary physiotherapy is a safe and effective intervention, especially in stable conditions, to clear the lungs and improve the patient's respiratory function. Of course, there are a number of precautions and time limits for performing these techniques that should be considered.According to the Guideline published in March 2020 for physiotherapists in the treatment of patients with COVID-19, cardiopulmonary physiotherapy focuses on the treatment and rehabilitation of acute and chronic respiratory conditions in patients and aims to improve the physical fitness of individuals seeking the disease. Accordingly, physiotherapy can play an effective role in respiratory therapy and physical rehabilitation of patients with COVID-19. To evaluated effectiveness of remdesivir, only three studies were found to be included in the meta-analysis. In these studies, the role of remdesivir on days 7, 14 and 28 in patients with COVID-19was investigated. Meta-analysis showed that the effectiveness of remdesivir in these patients increases the recovery rate and reduces the mortality rate.Studies show that Remdesivir is more effective on the seventh day in the early stages of the disease, and patients who do not require mechanical ventilation respond better to Remdesivir(20).According to the guidelines of the national institute of health, remdesivir works best in hospitalized patients with COVID-19who require less supplemental oxygen(21).However, further studies are needed to confirm these findings and provide sufficient and stronger evidence, as there is insufficient evidence to confirm the effectiveness of remdesivir in mild to moderate patients, and further studies are needed.Meta-analysis showed that the mortality rate on the 14th day of hospitalization was lower than on the 28th day, further studies are needed to confirm these findings (15, 22).The findings of this study are consistent with the results of previous meta-analysis studies(23, 24). However, the experimental studies reviewed in the current and previous meta-analysis were very few and, in most studies, the same, more RCT studies are needed in this area.Limitations of the study on the effectiveness of remdesivir in the treatment of patients with COVID-19 include: High heterogeneity in study results, time difference between results, age difference of patients, and low number of studies, low sample size and risk of bias not evaluated.

Conclusion

Meta-analysis showed that Respiratory Physiotherapy improves oxygen delivery in ICU patients with COVID-19, especially in less severe patients. It is recommended to review various Respiratory Physiotherapy techniques and their effectiveness in future studies. . All Respiratory Physiotherapy interventions should be carefully considered to reach a complete conclusion in this regard. Unfortunately, so far only one study has been performed to evaluate the

effectiveness of Respiratory Physiotherapy as a retrospective observational study (without control group); RCT and intervention studies are needed to confirm the effectiveness of Respiratory Physiotherapy techniques in patients with COVID-19. Based on the findings of meta-analysis, Respiratory Physiotherapy can play an effective role in respiratory therapy and rehabilitation of patients admitted to the ICU with COVID-19.

In the present study, a meta-analysis showed that treatment with Remdesivir could increase the recovery rate, especially in the early days of COVID-19; also reduces the mortality rate, although there is insufficient evidence in this regard because high heterogeneity was found between studies, so the reduction in mortality has not been proven. The efficacy of Remdesivir in patients with severe COVID-19 who do not require mechanical ventilation has been clearly demonstrated.

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