Gastroenterology and Hepatology From Bed to Bench.


**ORIGINAL ARTICLE**

# Efficacy and safety of acetylcysteine for the prevention of liver injury in COVID-19 intensive care unit patients under treatment with remdesivir

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## ABSTRACT

**Aim**: The present double-blinded placebo-controlled randomized clinical trial evaluated prophylactic use of acetylcysteine for the prevention of liver injury in patients with severe COVID-19 pneumonia under treatment with remdesivir.

**Background**: Liver injury is reportedly common in patients with severe COVID-19 pneumonia and can occur not only as a result of disease progression, but as an iatrogenic reaction to remdesivir.

**Methods**: A total of 83 adult patients with severe COVID-19 pneumonia were randomly assigned in parallel groups to receive either acetylcysteine or placebo. All the patients received standard care according to institutional protocols, including remdesivir for a total of five days. One gram acetylcysteine was administered intravenously every 12 hours for 42 patients, and 41 patients received the same volume of 0.9% sodium chloride as placebo (Trial Registration: www.irct.ir identifier, IRCT20210726051995N1).

**Results:** After 5 days, median aspartate transaminase (AST) and alanine transaminase (ALT) levels were significantly lower in the acetylcysteine than in the placebo group. Of those who received the placebo, 30 (73.2%), 4 (9.7%), and 3 (7.3%) patients had serum AST levels elevated between 1-2.5, 2.5-5, and over 5 times the upper limit of normal (ULN), respectively; while in the acetylcysteine group, 33 (78.6%) and 0 patients had AST levels between 1-2.5 and over 2.5 times ULN, respectively ($p$-value=0.037). In the acetylcysteine group, 23 (54.8%), 1 (2.4%), and 1 (2.4%) patient had serum ALT levels elevated between 1-2.5, 2.5-5, and over 5 times ULN, respectively; in the placebo group, however, 24 (58.5%), 7 (17.1%), and 1 (2.4%) patient had serum ALT levels between 1-2.5, 2.5-5, and over 5 times ULN, respectively ($p$-value=0.073).

**Conclusion**: Intravenous administration of acetylcysteine significantly prevents liver transaminases elevation and liver injury in seriously ill COVID-19 patients treated with remdesivir.

**Keywords**: COVID-19, Coronavirus, Liver injury, Acetylcysteine, Remdesivir, Clinical trial.

**(**Please cite as: **Mousapour P, Hamidi Farahani R, Mosaed R, Asgari A, Hazrati E. Efficacy and safety of acetylcysteine for the prevention of liver injury in COVID-19 intensive care unit patients under treatment with remdesivir. Gastroenterol Hepatol Bed Bench 2022;15(3):241-248. https://doi.org/10.22037/ghfbb.v15i3.2565).**

## Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has now spread globally, imposing huge challenges to the global community. At least half of patients with the SARS-CoV-2 infection (the COVID-19 disease) requiring invasive mechanical ventilation have died in hospitals, and the disease-associated burden on healthcare systems, especially intensive care units, has been overwhelming in several affected countries (1, 2). A large proportion of COVID-19 patients, especially those with critical conditions, develop some forms of hepatocellular or liver injury regardless of the presence or absence of a pre-existing liver condition (3). Despite elevations in liver transaminase levels in 15% to 53% of COVID-19

*Received*: 24 June 2022 *Accepted*: 29 August 2022
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patients, most abnormalities are minor, as aspartate transaminase (AST) or alanine transaminase (ALT) levels rise over five times the upper limit of normal (ULN) in less than 20% and exceed 15 times the ULN in only 2% of patients (4). Previous investigations have reported elevated liver transaminase levels in 62% of patients in the intensive care unit (ICU) compared with 25% in those who have not required ICU admission (5), indicating a correlation between the worsening of liver transaminase levels and disease severity. Moreover, not only does liver injury develop due to COVID-19 progression, but remdesivir therapy can also play a role in the elevation of serum transaminases as observed in previous clinical trials. It has been shown that discontinuing remdesivir therapy improved serum transaminases promptly, suggesting an iatrogenic effect for this drug (6-8).

Remdesivir, an inhibitor of viral RNA-dependent RNA polymerase, is a monophosphoramidate prodrug of an adenosine analogue that has been shown to be safe and efficacious in patients with severe COVID-19. As a delayed translocation inhibitor of SARS-CoV-2 replication, remdesivir has also been demonstrated to reduce the need for invasive mechanical ventilation, shorten the time to recovery, and improve the recovery rate of patients hospitalized due to COVID-19 disease with signs of lower respiratory tract infection (9, 10). According to the literature, a 5-day course of remdesivir can provide similar benefits while causing fewer serious adverse reactions compared to a 10-day regimen of the drug (9). The use of remdesivir in treating COVID-19 pneumonia, however, places patients at risk for drug-associated acute liver injury, defined as increased serum ALT and/or AST levels at least 5 times the ULN, that is suggested as an indication for remdesivir discontinuation (7, 8, 11-14).

Acetylcysteine is a precursor of reduced glutathione and has a broad range of antioxidant, anti-inflammatory, and vasodilatory properties. This drug has shown promising results in the rapid treatment of liver injury in COVID-19 patients receiving remdesivir, atorvastatin, and amiodarone (6, 8, 15) and in preventing non-paracetamol-induced liver injury (16, 17). Nevertheless, there is no data on the potential prophylactic role of acetylcysteine in preventing liver injury in COVID-19 patients under treatment with remdesivir.

The objective of this double-blinded placebo-controlled randomized clinical trial was to evaluate prophylactic use of acetylcysteine for the prevention of liver injury as well as its clinical and antiviral efficacy in patients with severe COVID-19 under treatment with remdesivir.

## Methods

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has now spread globally, imposing huge challenges to the global community. At least half of patients with the SARS-CoV-2 infection (the COVID-19 disease) requiring invasive mechanical ventilation have died in hospitals, and the disease-associated burden on healthcare systems, especially intensive care units, has been overwhelming in several affected countries (1, 2). A large proportion of COVID-19 patients, especially those with critical conditions, develop some forms of hepatocellular or liver injury regardless of the presence or absence of a pre-existing liver condition (3). Despite elevations in liver transaminase levels in 15% to 53% of COVID-19 patients, most abnormalities are minor, as aspartate transaminase (AST) or alanine transaminase (ALT) levels rise over five times the upper limit of normal (ULN) in less than 20% and exceed 15 times the ULN in only 2% of patients (4). Previous investigations have reported elevated liver transaminase levels in 62% of patients in the intensive care unit (ICU) compared with 25% in those who have not required ICU admission (5), indicating a correlation between the worsening of liver transaminase levels and disease severity. Moreover, not only does liver injury develop due to COVID-19 progression, but remdesivir therapy can also play a role in the elevation of serum transaminases as observed in previous clinical trials. It has been shown that discontinuing remdesivir therapy improved serum transaminases promptly, suggesting an iatrogenic effect for this drug (6-8).

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## Results

Forty-two patients were allocated to the acetylcysteine group and 41 patients to the placebo group. The mean age of patients was 62.1 ± 15.2 years. The most common comorbidity was hypertension, followed by diabetes mellitus. The comparison of baseline characteristics between the study groups (Table 1) showed similar results for gender distribution, mean age, prevalence of comorbidities, red blood cell and white cell counts, prevalence of lymphocytopenia, median liver enzyme levels, platelet count, international normalized ratio (INR), serum total bilirubin levels, and kidney functional tests, while baseline median CRP was greater in patients who received acetylcysteine. Clinical assessment of patients in the acetylcysteine and placebo groups at baseline indicated 16 (38.1%) and 11 (26.8%) patients requiring high-flow non-invasive ventilation, and 2 (4.8%) and 1 (2.4%) patient requiring invasive mechanical ventilation, respectively. There was no significant difference in the six-point ordinal scale of clinical status at baseline.

All participating patients completed the 5-day course of remdesivir. Patients in the placebo group experienced a greater rise in AST and ALT levels compared with the acetylcysteine group within five days of the trial. After remdesivir discontinuation, however, transaminase levels improved in patients of both groups (Figure 1).

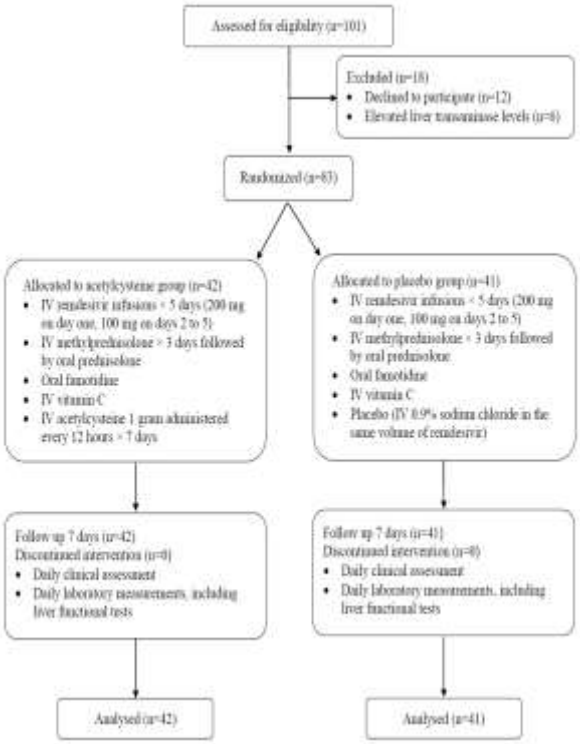


**Figure 1.** Study flowchart.

As shown in Table 2, at the third day of the trial, the median AST and ALT levels were significantly lower in the acetylcysteine group than the placebo group. No difference, however, was observed between the groups in grades of liver transaminase elevation. Of 42 patients in the acetylcysteine group, 20 (47.6%) had AST elevation between 1 and 2.5 times the ULN, and AST levels increased between 2.5 and 5 times the ULN in one (2.4%) patient. Of 41 patients in the placebo group, 26 (63.4%) experienced AST elevation between 1 and

**Table 1.** Subject demographics and baseline characteristics

| Variables | Acetylcysteine (N =42) | Placebo (N =41) | P-value |
|---|---|---|---|
| Age, years | 63.6 ± 15.1 | 60.5 ± 15.4 | 0.359 |
| Female sex, n (%) | 11 (26.2) | 15 (36.6) | 0.350 |
| Smoker, n (%) | 6 (14.3) | 7 (17.1) | 0.771 |
| Diabetes mellitus, n (%) | 10 (23.8) | 8 (19.5) | 0.791 |
| Hypertension, n (%) | 18 (42.8) | 15 (36.6) | 0.655 |
| Coronary artery disease, n (%) | 6 (14.3) | 4 (9.7) | 0.738 |
| Any comorbidities, n (%) | 22 (52.4) | 16 (39.0) | 0.158 |
| Systolic blood pressure, mmHg | 124.6 ± 6.3 | 128.4 ± 6.7 | 0.073 |
| Diastolic blood pressure, mmHg | 76.6 ± 3.2 | 77.9 ± 3.6 | 0.136 |
| Fever, n (%) | 17 (40.5) | 20 (48.8) | 0.511 |
| Hemoglobin, g/dL | 13.0 ± 2.2 | 13.2 ± 1.6 | 0.540 |
| Anemia, n (%) | 15 (35.7) | 12 (29.3) | 0.641 |
| White blood cell count, $10^9$ per L | 7.7 ± 3.6 | 8.8 ± 4.8 | 0.246 |
| White blood cell <4*$10^9$ per L, n (%) | 7 (16.7) | 5 (12.2) | 0.756 |
| Lymphocyte, $10^9$ per L | 1.0 ± 0.3 | 0.9 ± 0.3 | 0.109 |
| Lymphocyte <1*$0^9$ per L, n (%) | 16 (38.1) | 21 (51.2) | 0.505 |
| Platelet count, $10^9$ per L | 198.5 (133.1-251.4) | 237.5 (140.1-365.0) | 0.502 |
| Platelet <100*$10^9$ per L , n (%) | 1 (2.4) | 5 (12.2) | 0.109 |
| Aspartate aminotransferase, IU/L | 33.0 (25.0-38.2) | 32.0 (21.8-42.2) | 0.840 |
| Aspartate aminotransferase ≥40 IU/L, n (%) | 9 (21.4) | 10 (24.4) | 0.798 |
| Aspartate aminotransferase ≥100, n (%) | 0 (0) | 0 (0) | N/A |
| Alanine aminotransferase, IU/L | 37.5 (28.0-40.6) | 42.00 (27.0-51.0) | 0.111 |
| Alanine aminotransferase ≥40 IU/L, n (%) | 11 (26.2) | 18 (43.9) | 0.110 |
| Alanine aminotransferase ≥100 IU/L, n (%) | 0 (0) | 1 (2.4) | N/A |
| Alkaline phosphatase, IU/L | 207.4 (129.8-261.2)8 | 178.6 (144.3-196.1) | 0.121 |
| Total bilirubin, mg/dL | 1.0 ± 0.3 | 1.0 ± 0.4 | 0.799 |
| Total bilirubin ≥1.2 mg/dL, n (%) | 8 (19.0) | 7 (17.1) | 0.521 |
| CRP, mg/dL | 93.4 (84.4-103.0) | 81.1 (75.5-89.1) | 0.002 |
| International normalized ratio | 1.1 ± 0.1 | 1.1 ± 0.2 | 0.765 |
| Serum creatinine, μmol/L | 1.1 ± 0.3 | 1.1 ± 0.3 | 0.601 |
| Blood urea nitrogen, mg/dL | 17.2 ± 6.8 | 16.9 ± 7.0 | 0.835 |
| Six-category ordinal scale at day 1 | | | |
| 2-Hospital admission, not requiring supplemental oxygen | 12 (28.6) | 13 (31.7) | 0.602 |
| 3-Hospital admission, requiring supplemental | 12 (28.6) | 16 (39.0) | |
| 4-Hospital admission, requiring high-flow nasal cannula or non-invasive ventilation | 16 (38.1) | 11 (26.8) | |
| 5-Hospital admission, requiring invasive mechanical ventilation | 2 (4.8) | 1 (2.4) | |
| 6-Death | 0 (0) | 0 (0) | |

Categorical variables are represented as frequency (percent); Continuous variables are represented as mean ± SD or median (interquartile); ULN, upper limit of normal.

2.5 times the ULN, and no patients showed AST or ALT levels greater than 2.5 times the ULN. On the fifth day of the trial, median AST and ALT levels were significantly lower in the acetylcysteine group than in the placebo group. Of patients in the acetylcysteine group, 33 (78.6%) had AST levels between 1 and 2.5 times the ULN, and no patients revealed elevated AST levels over 2.5 times the ULN. In the placebo group, 30 (73.2%) patients had AST levels between 1 and 2.5 times the ULN, four (9.7%) patients displayed AST levels between 2.5 to 5 times the ULN, and three (7.3%) individuals developed a rise over five times the ULN. There was a significant difference in the grades of AST between the groups (*p*-value = 0.037).

Overall, 23 (54.8%) patients in the acetylcysteine group had ALT levels between 1 and 2.5 times the ULN; one (2.4%) patient had ALT levels over 2.5 times the ULN, and one (2.4%) patient had ALT levels over five times the ULN. In the placebo group, 24 (58.5%) patients had ALT levels between 1 and 2.5 times the ULN; seven (17.1%) individuals developed ALT levels between 2.5 to 5 times the ULN, and one (2.4%) patient showed ALT elevation over five times the ULN. However, the difference in ALT grades was not statistically significant between the groups on day five (*p*-value =0.073). On the third and fifth trial days, the prevalence rates of elevated serum total bilirubin, mean serum total bilirubin level, INR, and median platelet count were comparable between the groups.

**Table 2.** Liver function outcomes

| Variables | Acetylcysteine | Placebo | P-value |
|---|---|---|---|
| 3 days | | | |
| Aspartate aminotransferase | 35.0 (27.5-43.5) | 45.5 (31.6-55.0) | 0.010 |
| >1 to 2.5 times ULN | 20 (47.6) | 26 (63.4) | 0.250 |
| >2.5 to 5 times ULN | 1 (2.4) | 0 (0) | |
| >5 to 10 times ULN | 0 (0) | 0 (0) | |
| >10 times ULN | 0 (0) | 0 (0) | |
| Alanine aminotransferase | 39.5 (29.7-47.7) | 48.8 (34.6-59.8) | 0.046 |
| >1 to 2.5 times ULN | 16 (38.1) | 23 (56.1) | 0.251 |
| >2.5 to 5 times ULN | 1 (2.4) | 1 (2.4) | |
| >5 to 10 times ULN | 0 (0) | 0 (0) | |
| >10 times ULN | 0 (0) | 0 (0) | |
| Total bilirubin, mg/dL | 1.0 ± 0.3 | 0.9 ± 0.3 | 0.635 |
| Total bilirubin ≥1.2 mg/dL, n (%) | 9 (21.4) | 7 (17.1) | 0.304 |
| CRP, mg/dL | 92.5 (81.9-102.3) | 96.2 (88.3-106.9) | 0.425 |
| Platelet count, $10^9$ per L | 231.6 (185.3-306.7) | 231.5 (185.0-260.5) | 0.351 |
| International normalized ratio | 1.1± 0.1 | 1.0 ± 0.1 | 0.142 |
| International normalized ratio >1.1, n (%) | 9 (21.4) | 4 (9.7) | 0.227 |
| 5 days | | | |
| Aspartate aminotransferase | 50.0 (43.2-68.5) | 76.0 (55.9-97.6) | <0.001 |
| >1 to 2.5 times ULN | 33 (78.6) | 30 (73.2) | 0.037 |
| >2.5 to 5 times ULN | 0 (0) | 4 (9.7) | |
| >5 to 10 times ULN | 0 (0) | 3 (7.3) | |
| >10 times ULN | 0 (0) | 0 (0) | |
| Alanine aminotransferase | 42.9 (31.0-69.2) | 60.0 (45.0-83.0) | 0.013 |
| >1 to 2.5 times ULN | 23 (54.8) | 24 (58.5) | 0.073 |
| >2.5 to 5 times ULN | 1 (2.4) | 7 (17.1) | |
| >5 to 10 times ULN | 1 (2.4) | 1 (2.4) | |
| >10 times ULN | 0 (0) | 0 (0) | |
| Total bilirubin, mg/dL | 1.0 ± 0.3 | 0.9 ± 0.3 | 0.505 |
| Total bilirubin ≥1.2 mg/dL, n (%) | 11 (26.2) | 8 (19.5) | 0.216 |
| CRP, mg/dL | 85.5 (74.7-98.4) | 114.6 (101.7-121.8) | <0.001 |
| Platelet count, $10^9$ per L | 249.3 (180.5-313.3) | 230.4 (192.0-276.7) | 0.231 |
| International normalized ratio | 1.1± 0.2 | 1.0 ± 0.0 | 0.182 |
| International normalized ratio >1.1, n (%) | 8 (19.0) | 4 (9.7) | 0.350 |

Categorical variables are represented as frequency (percent); Continuous variables are represented as mean ± SD or median (interquartile);ULN, upper limit of normal; CRP, C-reactive protein.

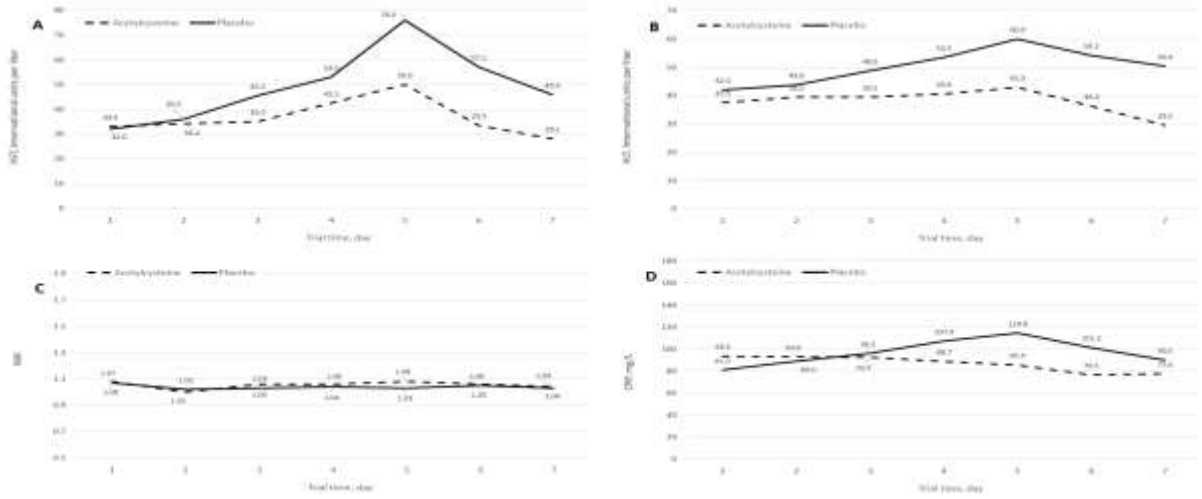


**Figure 2.** Trends of laboratory parameters over time; A. aspartate transaminase (AST), B. alanine transaminase (ALT), C. International normalized ratio (INR), D. C-reactive protein (CRP).

**Table 3.** Clinical outcomes

| Variables | Acetylcysteine (N =42) | Placebo (N =41) | P-value |
|---|---|---|---|
| | Improvement rate* | | |
| At day 7 | 6 (14.3) | 5 (12.2) | 0.779 |
| At day 14 | 17 (40.5) | 15 (36.6) | 0.716 |
| Six-category ordinal scale at day 7 | | | |
| 1-Discharge (alive) | 3 (7.1) | 4 (9.7) | 0.809 |
| 2-Hospital admission, not requiring supplemental oxygen | 4 (9.5) | 7 (17.1) | |
| 3-hospital admission, requiring supplemental oxygen | 22 (52.4) | 19 (46.3) | |
| 4-Hospital admission, requiring high-flow nasal cannula or non-invasive ventilation | 5 (11.9) | 4 (9.7) | |
| 5-Hospital admission, requiring invasive mechanical ventilation | 7 (16.7) | 7 (17.1) | |
| 6-Death | 1 (2.4) | 0 (0) | |
| Six-category ordinal scale at day 14 | | | |
| 1-Discharge (alive) | 11 (26.2) | 9 (21.9) | 0.981 |
| 2-Hospital admission, not requiring supplemental oxygen | 4 (9.5) | 5 (12.2) | |
| 3-hospital admission, requiring supplemental oxygen | 14 (33.3) | 12 (29.3) | |
| 4-Hospital admission, requiring high-flow nasal cannula or non-invasive ventilation | 3 (7.1) | 3 (7.3) | |
| 5-Hospital admission, requiring invasive mechanical ventilation | 6 (14.3) | 8 (19.5) | |
| 6-Death | 4 (9.5) | 4 (9.7) | |

All variables are represented as frequency (percent);* Clinical improvement was defined as a two-point reduction in patients' admission status on a six-category ordinal scale, or live discharge from the hospital, whichever came first.

No significant difference was observed in median CRP between the study groups on the third day of the trial; however, at day five, CRP was significantly lower in patients who received acetylcysteine than those in the placebo group.

Clinical outcomes after 7 and 14 days of admission are illustrated in Table 3. Improvement rates at days 7 and day 14 were numerically higher in patients who received acetylcysteine, however not significantly different between the groups, and most patients were in category 3 of the six-point ordinal scale of clinical status at both time points. Moreover, 7-day and 14-day mortalities were similar between the two groups.

## Discussion

Forty-two patients were allocated to the acetylcysteine group and 41 patients to the placebo group. The mean age of patients was 62.1 ± 15.2 years. The most common comorbidity was hypertension, followed by diabetes mellitus. The comparison of baseline characteristics between the study groups (Table 1) showed similar results for gender distribution, mean age, prevalence of comorbidities, red blood cell and white cell counts, prevalence of lymphocytopenia, median liver enzyme levels, platelet count, international normalized ratio (INR), serum total bilirubin levels, and kidney functional tests, while baseline median CRP was greater in patients who received acetylcysteine. Clinical assessment of patients in the acetylcysteine and placebo groups at baseline indicated 16 (38.1%) and 11 (26.8%) patients requiring high-flow non-invasive ventilation, and 2 (4.8%) and 1 (2.4%) patient requiring invasive mechanical ventilation, respectively. There was no significant difference in the six-point ordinal scale of clinical status at baseline.

All participating patients completed the 5-day course of remdesivir. Patients in the placebo group

experienced a greater rise in AST and ALT levels compared with the acetylcysteine group within five days of the trial. After remdesivir discontinuation, however, transaminase levels improved in patients of both groups (Figure 2).

As shown in Table 2, at the third day of the trial, the median AST and ALT levels were significantly lower in the acetylcysteine group than the placebo group. No difference, however, was observed between the groups in grades of liver transaminase elevation. Of 42 patients in the acetylcysteine group, 20 (47.6%) had AST elevation between 1 and 2.5 times the ULN, and AST levels increased between 2.5 and 5 times the ULN in one (2.4%) patient. Of 41 patients in the placebo group, 26 (63.4%) experienced AST elevation between 1 and 2.5 times the ULN, and no patients showed AST or ALT levels greater than 2.5 times the ULN. On the fifth day of the trial, median AST and ALT levels were significantly lower in the acetylcysteine group than in the placebo group. Of patients in the acetylcysteine group, 33 (78.6%) had AST levels between 1 and 2.5 times the ULN, and no patients revealed elevated AST levels over 2.5 times the ULN. In the placebo group, 30 (73.2%) patients had AST levels between 1 and 2.5 times the ULN, four (9.7%) patients displayed AST levels between 2.5 to 5 times the ULN, and three (7.3%) individuals developed a rise over five times the ULN. There was a significant difference in the grades of AST between the groups ($p$-value = 0.037).

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## Conflict of interests

The authors declare that they have no conflict of interest.

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