N-Acetylcysteine Treatment Accelerates Patient-Reported Outcomes Improvement in Patients With COVID-19 A Prospective Study

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Research Article

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Abstract

Background: Since its outbreak in late December 2019, the coronavirus disease 2019 (COVID-19) has culminated in a global pandemic, and its causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has continued to mutate, with increasing rates of transmission and pathogenicity, having a serious worldwide impact. This study aims to assess the benefits of the health-related quality of life of using N-acetylcysteine(NAC).

Methods: In this prospective observational research, 63 confirmed COVID-19 patients who were treated between the ends of January and March 2020 were divided into patients treated with NAC-treatment (32 cases) and non-NAC-treatment groups (31 cases). Patients were followed up at discharge and at 1, 3, and 6 months after discharge. The clinical treatment effects of the two groups were compared, and the St. George's Respiratory Questionnaire (SGRQ) evaluated patient-reported outcomes.

Results: There were strong correlations between SGRQ component scores (0.728, 0.749, 0.850; $P < 0.001$ for all items) as well as between each SGRQ component score and the total patient score (0.822, 0.958, 0.957; $P < 0.001$ for all items). In the univariate analysis, the change differences of one month after discharge compared with discharge between two groups patients were statistically significant in the impacts and total scores (753.000, $P < 0.001$; 644.000, $P = 0.042$); the change differences of three months after discharge compared with discharge were also significant in the activity, impacts, and total scores (660.500, $P = 0.022$; 800.000, $P < 0.001$; 707.000, $P = 0.004$). In the multivariate analysis, the factors that have statistically significant influence on the unit value of SGRQ total score difference (UVD_{SGRQ}) is NAC treatment ($\beta = 1.954$, $P < 0.001$), disease severity ($\beta = 3.179$, $P < 0.001$), follow-up duration ($\beta = -0.232$, $P = 0.001$), as well as NAC treatment and follow-up duration interaction item ($\beta = -0.436$, $P = 0.004$).

Conclusion: Our study shows as the follow-up time increases, the SGRQ total scores of patients treated with NAC decreases significantly faster than those who were treated without NAC. In the treatment of COVID-19 patients, increasing the use of NAC has clinical significance.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has culminated in a global pandemic. As of 25 February 2022, a total of 430,257,564 cases and 5,922,049 deaths had been confirmed worldwide. [1]Although the vast majority of patients experience mild-to-moderate symptoms, a large number of infected people continue to die from the disease.[2]At present, clinical drug research for COVID-19 is predominantly focused on the development of new crown vaccines, antiviral therapy, and antibody neutralization therapy,[3–5] and to date, there are few studies on the therapeutic effects of N-acetylcysteine on COVID-19 patients .

The main cause of death from COVID-19 is acute respiratory distress syndrome (ARDS),[6] and studies have shown that excessive immune activation and cytokine storm is the causes of COVID-19-related lung injury.[7] It is currently believed that prolonged oxidative stress, increased production of reactive oxygen species (ROS), and decreased glutathione levels [8]lead to an imbalance in redox homeostasis, thus leading to excessive immune activation and cytokine storms. It is used as a direct scavenger of ROS to regulate the redox state, regulate the inflammatory response, and exhibit indirect antioxidant properties. It has been confirmed by in vitro and in vivo studies,[9] and it is widely used in clinics, for example, in the treatment of liver poisoning due to paracetamol toxicity, chronic obstructive pulmonary disease,[10] and so on.

The first COVID-19 death autopsy in China[11]was conducted on an 85-year-old patient, and it revealed white foamy mucus in the trachea and jelly-like mucus in the bronchus lumen of the right lung, suggesting the presence of secretions in the airway of the COVID-19 patient. The secretions are considerably viscous and not easily discharged, possibly contributing to the acceleration of patient death. Therefore, the use of expectorant drugs has become an important part of the adjuvant treatment of patients with COVID-19. N-acetylcysteine (NAC) is an N-acetyl derivative of the natural amino acid L-cysteine. The active free -SH group in the NAC molecule potentially promotes the breakage of the acid glycoprotein polypeptide disulphide bond (-SS) in the sputum and directly splits the DNA molecular chain and mucin in the hydrolysed sputum, thereby decomposing the respiratory mucus. Keeping the respiratory tract moist may reduce irritation.[12] In a prospective, randomized, controlled trial in Shandong Province, China,[13]recruited adult patients with bronchiectasis who had experienced at least two acute exacerbations in the previous year. The results demonstrated that oral NAC (600 mg twice a day for 12 months) potentially reduces the risk of acute exacerbation.

In addition, the protective effect of NAC in influenza and other respiratory viral diseases has been confirmed, and it has been proven to reduce the incidence and severity of influenza and influenza-like diseases.[14]The mechanism includes the inhibition of viral matrix protein expression, caspase activation, and fatty acid synthase upregulation,[15] thereby inhibiting virus replication and reducing viral load. Simultaneously, it inhibits influenza A and B viruses as well as a respiratory syncytial virus by regulating the overexpression and release of MUC5AC and inhibiting the translocation of interleukin (IL)-8, IL-6, tumor necrosis factor-alpha, and nuclear factor kappa B to the nucleus as well as the phosphorylation of mitogen-activated protein kinase p38.53. The mechanism that leads to the production of ROS and release of mucin from epithelial cells increases inflammation and apoptosis events.[14]

Based on the foregoing theory, we believe that NAC can play an important role in the treatment of COVID-19.

Clinical data sources include objective indicators such as laboratory tests, imaging tests, patient signs, and subjective indicators such as patient-reported outcomes (PROs). However, the use of clinical objective indicators alone may overlook a patient's certain symptoms and overestimate the effectiveness

of medical interventions.[16] The verbal characterization of the symptoms conveyed by the patient, and recorded by care providers is central to the practice of clinical medicine, and increasing importance is attached to patient-centered clinical care.[17] The United States Food and Drug Administration defines a patient-reported outcomes as any report regarding the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else[18]. PROs is the only measure that can reflect the impact of the patient's disease. It helps to obtain the patient's treatment license and establishes beneficial communication between the patient and healthcare staff to determine treatment efficiency. Therefore, a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else),PROs, [19]necessarily need to be included to realistically assess the effectiveness and safety of the intervention.

The results of some foreign studies have shown that the St. George's Respiratory Questionnaire (SGRQ) questionnaire correlates well with pulmonary function and clinical symptoms, [20–22]and most of the questions are required to be self-reported by patients, which is more realistic. Therefore, the SGRQ questionnaire was chosen to assess the quality of life of COVID-19 patients in this study. The SGRQ is a patient-reported questionnaire used to measure the impact of respiratory diseases and their treatment on the patient's health-related quality of life (HRQoL). It has been used in patients with asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, and lung transplantation.[23] The SGRQ includes 50 items, divided into three parts: symptoms (frequency and severity), activities (activities that can cause shortness of breath or restricted activities), and impact on daily life (social impairment and psychological disorders caused by airway diseases). The SGRQ total score ranges from 0 to 100 points, with a lower score indicating superior HRQoL.

Therefore, we conducted a multi-center observational study (www.chictr.org.cn; number: ChiCTR2100049355). The main purpose of the study was to evaluate the effectiveness of NAC against COVID-19 and observe its impact on the patient-reported outcomes.

Materials And Methods

Design and data collection

This study used a prospective, observational research design to investigate the effectiveness of NAC against COVID-19. A flowchart of this research is displayed in Fig. 1. To improve the accuracy and completeness of this research report, we consulted the STROBE[24]guidelines to standardize each stage's work and the report writing. Data were collected by researchers using a case report form, which was developed by the Key Laboratory of Major Disease Risk Assessment of Shanxi Medical University, Shanxi Province. Data on demographics, clinical signs and symptoms, comorbidities, laboratory examinations, chest imaging, and treatment plans were collected on admission. There were thirty-two patients t who received NAC treatment and thirty-one patients who did not receive NAC treatment. NAC 600 mg/time was

administered twice/day, orally. Thirty-one patients with COVID-19 who did not use NAC constituted the control group. When the two groups were discharged from the hospital, data on clinical symptoms and signs, laboratory examinations, and chest imaging were collected, and the SGRQ was completed. After discharge from the hospital, the treatment group continued receiving NAC. Patients in both groups were followed up through face-to-face or telephone interviews at 1, 3, and 6 months after discharge, and they completed the SGRQ. All data were analyzed anonymously. Figure 1 shows the flow diagram of this N-acetylcysteine's effectiveness study for COVID-19 patients.

Participants

This study was conducted in five hospitals, including the Fourth People's Hospital of Taiyuan City, a hospital designated for COVID-19 treatment in Shanxi Province. Patients admitted between February and March 2020 were screened for eligibility. They were followed up in person or by phone at discharge as well as at 1, 3, and 6 months after discharge. The sample size was determined using the number of COVID-19 cases in the region during the study period.

The inclusion criteria were as follows: (a) age > 18 years; (b) SARS-CoV-2-positive real-time reverse transcription-polymerase chain reaction tests for nasal swabs or lower respiratory tract samples; (c) chest computed tomography (CT) images confirming pneumonia; and (d) willingness to participate in the study. The exclusion criteria were as follows: (a) pregnancy and childhood and (b) inability to provide informed consent.

Ethics approval and informed Consent

The study was approved by the Institutional Review Committee of the chief investigator's hospital (the Second Hospital of Shanxi Medical University, China (No: 2020YX017) and the institutional review committees of participating hospitals. According to the approval of the Local Ethics Committee, informed consent was obtained during hospitalization.

Quality control

A relatively widespread source of patients with the novel coronavirus pneumonia was available, the possibility of recall after discharge from the hospital was minimal, and compliance with regular follow-up visits was poor, resulting in a considerably large percentage of missing data on patient follow-up visits. Therefore, to obtain the HRQoL data of patients with the new coronavirus pneumonia and minimise bias caused by loss to follow-up, the SGRQ was used to regularly follow-up these patients and measure the damage to their health. Concomitantly, free medication was used during the follow-up period to improve patient compliance, thus ensuring a high questionnaire response rate during regular follow-up. Facts have proven that the above measures significantly improve patient compliance, with the questionnaire response rate reaching 100%. All staff who conducted follow-up visits were uniformly trained.

Statistical methods

1. Research on the correlation between statistical descriptions and research object scores:

Measurement data are presented as mean values ± standard deviations ($\bar{X} \pm S$) e, and the composition ratio was used to describe counted data. Correlations between symptoms, activity, impacts and total scores on the SGRQ scale were all evaluated and tested using Pearson's correlation coefficient.

2. Univariate analysis:

Stratified by follow-up time, the Mann–Whitney *U* test was used to analyse the symptoms, activity, impacts, and changes in total scores and compare them with those at hospital discharge in the NAC-treatment and non-NAC-treatment groups.

According to the presence or absence of NAC treatment, the Kruskal–Wallis *H* test was used to analyse the changes in symptoms, activity, impacts, and total scores at all follow-up time points.

3. Multi-factor analysis

The generalized estimation equation was used to conduct a multi-factor analysis to minimize the influence of confounding factors that could affect the SGRQ score. In the modeling process, this study relied on minimal clinical significance changes to effectively reduce the dispersion of variables in the model (mainly to reduce the impact on the overall model when the variance of the variables was large) and render the interpretation of model parameters more clinically meaningful. The minimal clinically important difference (MCID) value constructs the unit value of the difference (UVD) of the corresponding variable. For the total score, its UVD is:

$$\mathrm{UVD}_{\mathrm{SGRQ}} = \frac{\mathrm{SGRQ}_i}{\mathrm{MCID}_{\mathrm{SGRQ}}}$$

In the above formula, the SGRQi is the total SGRQ score at follow-up time *i*, and the $\mathrm{MCID}_{\mathrm{SGRQ}}$ is the MCID of the total score. According to previous research reports by scholars, the MCID of the total score is usually set to 4 points.[25] The $\mathrm{UVD}_{\mathrm{SGRQ}}$ was incorporated as a dependent variable into the generalized estimation equation for analysis. Its meaning in the generalized estimation model was as follows: when other variables remain unchanged, the total score increases (or decreases) by several units due to changes in certain factors. Further, when the absolute value of the $\mathrm{UVD}_{\mathrm{SGRQ}}$ change in the model exceeds 1, it often suggests that the change in the total score may have practical clinical significance.

Data analysis software

We used EpiData software (version 3.1; The EpiData Association, Odense, Denmark) for double-entry and to verify all patient data. All statistical analyses were performed using SPSS (version 25.0; IBM, Armonk, NY, USA). Significance threshold $\alpha = 0.05$.

Results

1. Baseline status of patients with COVID-19

As shown in Table 1 (at the end of the document text file), the average age of patients with the new coronavirus pneumonia was 44.65 years, and the average hospital stay was 16.24 days. The proportion of men in the patient group was higher, that of overweight was higher, that of smoking was lower, that of frequent or occasional drinking was lower, that of occasional physical exercise was higher, that of having a history of the respiratory system disease was lower, that of other system comorbidities was lower. and the proportion of lightness was higher.

Table 1
Baseline situation of patients with COVID-19

	All patients(n = 63)
Age(years)	44.65 ± 19.46
Length of hospital stay (days)	16.24 ± 7.79
male	38(60.3%)
BMI	
thin	3(4.76%)
normal	17(26.99%)
overweight	29(46.03%)
obesity	10(15.87%)
unknown	4(6.35%)
Smoking	9(14.29%)
Drinking	
often	5(7.94%)
occasionally	9(14.28%)
no	49(77.78%)
Physical exercise	
often	19(30.16%)
occasionally	43(68.25%)
unknown	1(1.59%)
Have a history of respiratory system	3(4.76%)
Have other systemic comorbidities	19(30.16%)
Severity of illness	
Light	45(71.43%)
serious	18(28.57%)

2. Correlation analysis between the SGRQ series scores of all patients

Table 2
Correlations of SGRQ series scores in all patients

	Symptoms score	Activity score	Impacts score	Total score
Symptoms score	1.000	0.728*	0.749*	0.822*
Activity score	0.728*	1.000	0.850*	0.958*
Impacts score	0.749*	0.790*	1.000	0.957*
Total score	0.822*	0.958*	0.957*	1.000
Note: Pearson correlation coefficient is used for the correlation between the scores; * item tested P < 0.001				

The Pearson correlation coefficient was used to evaluate the correlation between the scores. Consistent with the study findings of Bacârea et al.,[26] Table 2 shows that there were strong correlations between the scores of the SGRQ components as well as between the score of each component and the total score (α = 0.05). Among these correlations, the total score exhibited the strongest correlation with the activity score, followed by the impacts and symptoms scores in that order.

3 Single-factor analysis affecting the changes in patients' SGRQ series scores

(1) Differences in score change between the two patient groups at each follow-up time

Table 3
Changes in SGRQ scores of the two groups of COVID-19 patients at each follow-up time

	NAC treatment (n = 32)	Without NAC treatment (n = 31)	*U*	*P*
Change of one month after discharge compared with discharge				
Symptoms score	13.10 ± 17.32	7.60 ± 12.94	555.000	0.411
Activity score	12.12 ± 15.72	8.74 ± 11.95	573.500	0.281
Impacts score	12.12 ± 17.80	2.24 ± 9.44	753.000	**< 0.001**
Total score	12.28 ± 15.54	5.08 ± 10.05	644.000	**0.042**
Change of three months after discharge compared with discharge				
Symptoms score	18.06 ± 18.25	10.04 ± 14.94	632.000	0.061
Activity score	24.19 ± 27.52	11.70 ± 15.21	660.500	**0.022**
Impacts score	15.39 ± 21.01	2.41 ± 10.04	800.000	**< 0.001**
Total score	18.49 ± 21.25	6.80 ± 11.99	707.000	**0.004**
Change of six months after discharge compared with discharge				
Symptoms score	18.53 ± 19.66	11.22 ± 13.97	612.500	0.108
Activity score	24.19 ± 27.52	11.70 ± 15.21	660.500	**0.022**
Impacts score	15.57 ± 21.02	2.74 ± 10.29	793.000	**< 0.001**
Total score	18.65 ± 21.38	6.33 ± 12.23	723.000	**0.002**

Note: Mann-Whitney *U* test was used for the comparison of differences in score changes between groups

Table 3 shows that the change differences in the impacts scores of the two patient groups 1 month after hospital discharge and median difference in the total score were statistically different. The median differences in the changes in the activity, impacts, and total scores of the patients at 3 months after hospital discharge were statistically significant; further, the two patient groups exhibited statistical differences in their activity scores at 6 months after discharge. The median difference in the amount of change, change in the impacts score, and change in the total score were also statistically different.

(2) Differences in the changes in patient scores at each follow-up time in the two groups

Table 4
Changes in SGRQ scores of patients at each follow-up time in the two groups

	Change of one month after discharge compared with discharge	Change of three months after discharge compared with discharge	Change of six months after discharge compared with discharge	*H*	*P*
NAC treatment					
Symptoms score	13.10 ± 17.32	18.06 ± 18.25	18.53 ± 19.66	3.413	0.182
Activity score	12.12 ± 15.72	24.19 ± 27.52	24.19 ± 27.52	5.233	0.073
Impacts score	12.12 ± 17.80	15.39 ± 21.01	15.57 ± 21.02	0.625	0.732
Total score	12.28 ± 15.54	18.49 ± 21.25	18.65 ± 21.38	2.769	0.250
Without NAC treatment					
Symptoms score	7.60 ± 12.94	10.04 ± 14.94	11.22 ± 13.97	3.564	0.168
Activity score	8.74 ± 11.95	11.70 ± 15.21	11.70 ± 15.21	2.658	0.265
Impacts score	2.24 ± 9.44	2.41 ± 10.04	2.74 ± 10.29	0.709	0.701
Total score	5.08 ± 10.05	6.80 ± 11.99	6.33 ± 12.23	3.007	0.222
Note: The Kruskal-Wallis *H* test is used for the overall comparison of the differences in the changes in the scores at different follow-up times					

Table 4 shows the overall differences in the median changes in the scores of the two patient groups at different follow-up times were not statistically significant. The scores of the two patient groups at different follow-up times could not be considered equal.

4 Multivariate analyses of the UVD's influence on patients' SGRQ scores

We constructed a generalized estimation equation to analyse the factors affecting patients' UVD_{SGRQ}. The analysis results are shown in Fig. 2. NAC treatment, severe illness, and follow-up time were all statistically significant for UVD_{SGRQ}. Moreover, the interaction between NAC treatment and follow-up time was also statistically significant.

Under the premise that disease severity remains the same when a patient was not followed up, the UVD_{SGRQ} of NAC-treated patients was 1.954 higher than that of non-NAC-treated patients. That is, the total SGRQ score for NAC-treated patients increased by 1.954 units on average. The MCID value contradicted the expected result. Provided the NAC treatment and follow-up statuses remained unchanged, the UVD_{SGRQ} increased by 3.179 on average in severe patients than in mild patients. On the premise of similar disease severity, the follow-up time increased by 1 month and UVD_{SGRQ} decreased by an average of 0.232 in non-NAC treated patients, and the minimum clinically significant change value was not achieved.

5 Contour plot of marginal mean patient SGRQ score

According to the parameter estimation results of the model's interaction term of the model, the total patient score for NAC-treated patients increased at 1 month of follow-up compared with that for non-NAC treated patients; therefore, the total patient score in the NAC-treatment group decreased faster than that in the non-NAC treatment group. Based on an MCID decrease of 0.232 units, the MCID continued to decrease by an average of 0.436 units. Further, Fig. 3 shows that the slope of the average change in the total score for NAC-treated patients was greater than that for non-NAC-treated patients in the same period.(Figure 3)

Discussion

Data from survivors of previous viral outbreaks, such as SARS and the Middle East respiratory syndrome (MERS) coronavirus, show that pulmonary, as well as physical and mental function, may be impaired for months after discharge[27].And reports on persisting physical and mental health impairments are emerging, raising concerns about a potentially impeding chronic health issue[28]. And, as the medical model shifts to a bio-psycho-social model, doctors are no longer concerned with just physical recovery, but are more concerned with improving the quality of life of their patients. However, clinical physiological indicators do not provide a comprehensive assessment of quality of life. Therefore, in this study, the benefits of using NAC on patients' quality of life were analyzed using the SGRQ questionnaire to assess patients' quality of life on the basis of a patient self-report format.

NAC has been widely used in respiratory diseases due to its anti-oxidation, expectorant, and virus-inhibiting effects, and many reviews have demonstrated its feasibility in the adjuvant treatment of COVID-19.[29, 30] There are case reports of [31]COVID-19 patients with right-sided capsular empyema. Based on anti-infection, respiratory support, and other treatments, combined with the NAC-inhalation solution and repeated bronchoalveolar lavage, the patients' refractory hypercapnia gradually improved. Another study reports[32] severe COVID-19 infection in a glucose-6-phosphate dehydrogenase-deficient patient treated with hydroxychloroquine. After reverse hemolysis, the patient received intravenous NAC to significantly improve his clinical symptoms. However, in a double-blind, randomized, placebo-controlled, single-center trial[33] involving 135 patients with severe COVID-19, the experimental group was administered NAC 21 g (approximately 300 mg/kg) for 20 h. The result was that the experimental group and the control group

were given NAC 21 g (approximately 300 mg/kg) for 20 h. There were no significant differences in the number of patients requiring mechanical ventilation, laboratory examinations, and chest CT images in the group, suggesting that the administration of high-dose NAC may not affect the progression of severe COVID-19. In a single-center, randomized controlled study of patients with mild-to-moderate COVID-19-related ARDS,[34] the experimental group received intravenous NAC at a dose of 40 mg/kg/day for three consecutive days, and 28-day clinical indicators were observed. Although the clinical status distribution of the NAC-treatment group showed improvement on day 28, it did not achieve statistical significance, indicating insufficient evidence to corroborate the potential benefit of intravenous NAC in the treatment of patients with COVID-19-related ARDS. To date, no research has been published that investigates the long-term use of NAC for COVID-19 using the SGRQ as a PRO measurement tool for evaluating follow-up.

NAC use in our study lasted up to 6 months. Since this study was observational and used completely real-world data, the clinical treatment of all patients with the novel coronavirus had to be carried out in strict accordance with ethical requirements. Therefore, for patients with serious illnesses, clinical treatments had to be conducted in strict accordance with ethical requirements. NAC has commonly been used in the past, and patients with mild symptoms have received NAC less frequently. This has led to failure in achieving a balance in disease severity between the two patient groups (NAC-treatment and non-NAC-treatment groups), that is, disease severity influences the utility of NAC treatment. Therefore, it is likely that the strong effect of disease severity resulted in the following situation: ‘when the mild patients were not followed up, the UVD_{SGRQ} in NAC-treated patients increased by 1.954 compared to that in non-NAC patients, that is, the total score increased by 1.954 MCID values’.

This study has certain limitations. The sample size of this study complied with the minimum 10 events per predictor variable principle [35]proposed by Harrell. However, due to objective restrictions on scientific research funding, investigators, and the number of local patients, all samples in this study were limited to one province. Hence, research results may inevitably exhibit regional characteristics. In the future, we intend to conduct this research in more provinces, expand the sample size based on increasing sample sources, and further improve the representativeness of the research samples and the reliability of the research results.

Conclusion

NAC treatment decreases the total score of NAC-treated patients more rapidly than that of non-NAC-treated patients. The findings suggest that the long-term use of NAC potentially improves the quality of life of patients with COVID-19.

Abbreviations

COVID-19
coronavirus disease 2019
SARS-CoV-2

severe acute respiratory syndrome coronavirus 2
NAC
N-acetylcysteine
SGRQ
the St. George's Respiratory Questionnaire
ARDS
cute respiratory distress syndrome
ROS
reactive oxygen species
PROs
patient-reported outcomes
HRQoL
health-related quality of life
MCID
minimal clinically important difference
UVD
unit value of the difference
MERS
Middle East respiratory syndrome.

Declarations

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Author contributions

HZ design the work, LL drafted the paper, YZ revised the article critically, HH analyzed the data, CC, JZ, MQu, YW, AZ and HD acquired the data. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Research Manager repository, (http://www.medresman.org.cn).

Ethics approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations. The study was approved by the Institutional Review Committee of the chief investigator's hospital (the Second Hospital of Shanxi Medical University, China (No.2020YX017) and the institutional review committees of participating hospitals. According to the approval of the Local Ethics Committee, informed consent was obtained during hospitalization.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

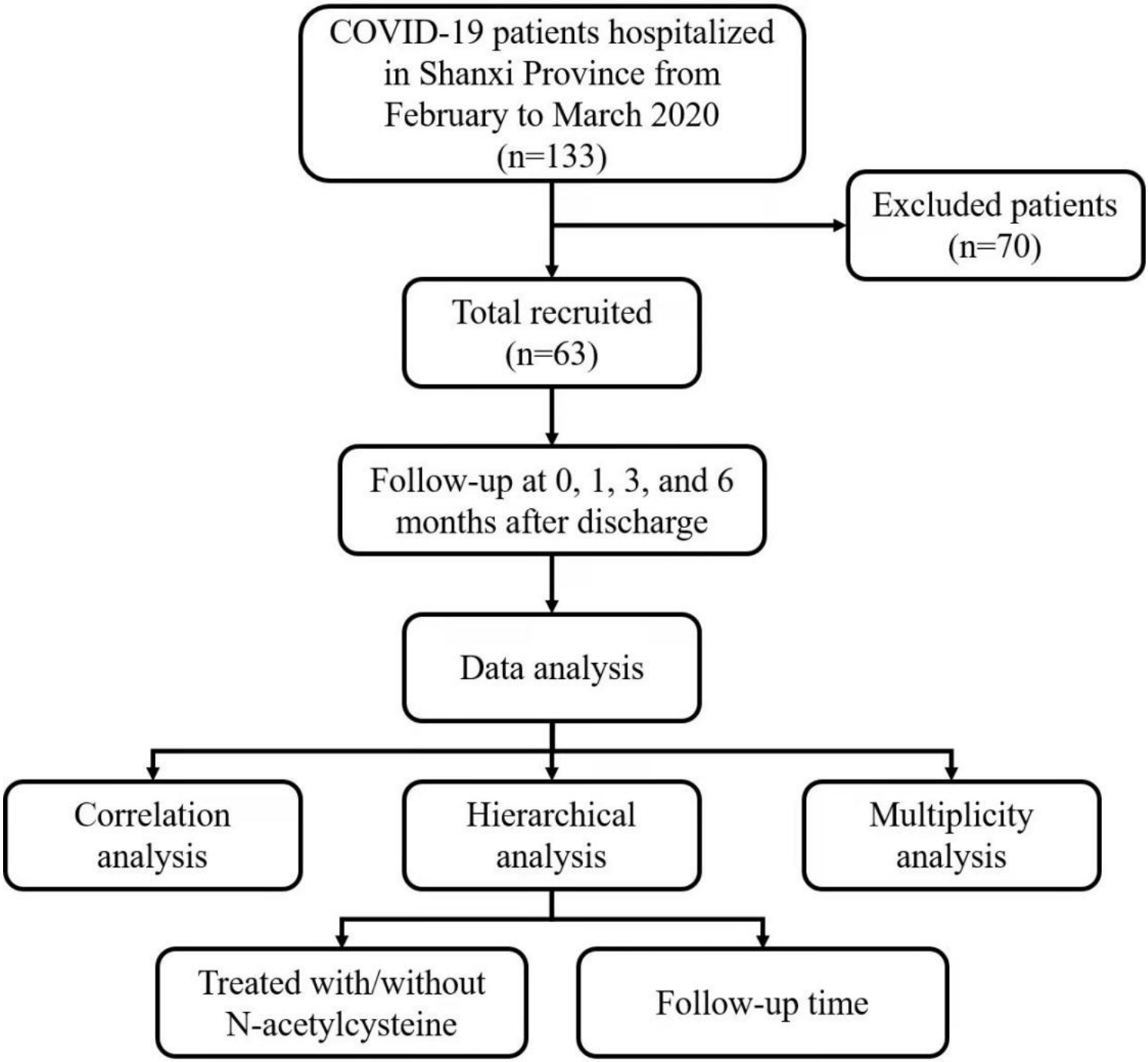

Figure 1

Flow diagram of this N-acetylcysteine's effectiveness study for COVID-19 patients

Variables	$S_{\bar{x}}$	Ward χ^2	Estimation and 95% confidence interval of β		P
			Estimation (95%CI)	Forest plot	
Constant term	0.234	19.279	1.029 (0.570, 1.488)		<0.001
NAC treatment	0.516	14.358	1.954 (0.943, 2.964)		<0.001
Severity	0.500	40.467	3.179 (2.199, 4.158)		<0.001
Follow-up time	0.070	10.900	-0.232 (-0.369, -0.094)		0.001
NAC treatment × Follow-up time	0.150	8.515	-0.436 (-0.729, -0.143)		0.004

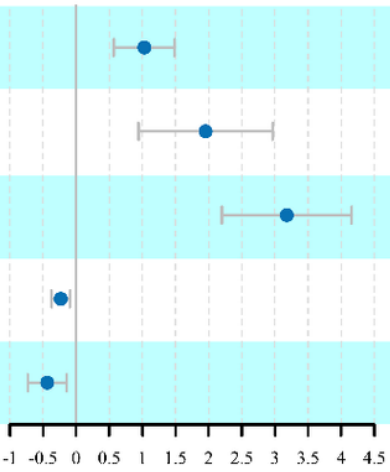

Figure 2

Parameter estimation results of the generalized estimation equation

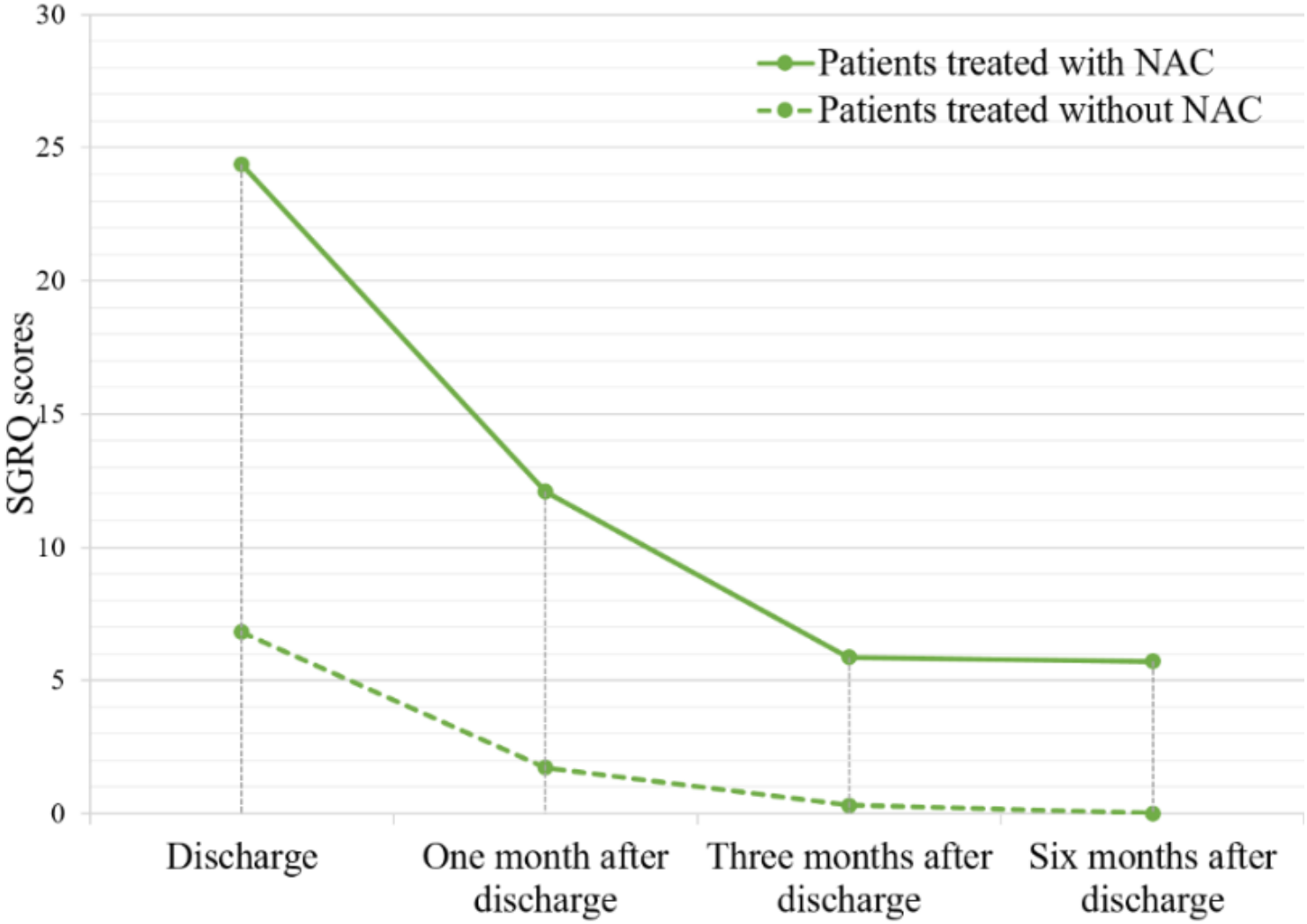

Figure 3

Contour map of the marginal mean of the total score of patients with COVID-19