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Early View

Research letter

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Title

Impact of *N*-Acetylcysteine on SARS-CoV-2 pneumonia and its sequelae: results from a large cohort study

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N-Acetylcysteine, COVID-19, SARS-CoV-2 pneumonia, mortality, intensive care unit admission

Take-Home Message

Patients receiving N-Acetyl-L-cysteine (NAC) during hospitalisation for SARS-CoV-2 pneumonia and discharged alive present a significantly shorter length of hospital stay compared to those who did not receive NAC.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may cause pneumonia and acute respiratory distress syndrome, whose pathogenesis has been partially related to an increased systemic inflammatory response with great production of pro-inflammatory cytokines causing a "cytokine storm" and an oxidative stress imbalance.(1)

N- Acetyl- L- cysteine (NAC) is a precursor of reduced glutathione (2) that has antioxidant, anti-inflammatory and immunomodulating properties that may prove beneficial in modulating the excessive inflammatory activation during coronavirus disease (COVID-19).(3) Furthermore, NAC has been extensively used as mucolytic agent to improve airway clearance in chronic respiratory diseases.

During COVID-19 pandemic research hypothesis on the role of NAC have been formulated and randomized control trials (RCT) are ongoing, however so far only a few case reports have been conducted.(3,4)

Aim of our study is to evaluate the impact of NAC administered during hospitalisation for SARS-CoV-2 pneumonia on short-term and long-term outcomes. As short-term outcomes we considered in-hospital mortality, intensive care unit (ICU) admission, length of ICU stay and length of hospital stay (LOS) in patients discharged alive; as long-term outcomes we included diffusion capacity for carbon monoxide (DLCO) impairment, chest X-ray alterations, reduced distance walked at six-minute walking test (6MWT) and dyspnea score (Modified Medical Research Council (mMRC) scale) at 6 months follow-up on a subset of patients included in a follow-up study. Furthermore, we will also evaluate the impact of NAC on the development of atelectasis during hospitalisation, a possible complication of SARS-CoV-2 pneumonia.

We performed a retrospective monocentric study on 1083 consecutive adult patients hospitalised for SARS-CoV-2 pneumonia at the San Gerardo Hospital, Monza, Italy, between February 2020 and April 2021. Given that the aim was to evaluate the impact of a least 5 days of NAC administration, patients were excluded if they died or were discharged within 5 days from admission (n=177) to avoid immortal time bias. NAC was introduced, as per institutional protocol, on admission and administered at a dosage of 300 mg intravenous TID, switched to 600 mg per os BID once reached clinical stability and continued until discharge. The study (STORM) was approved by national Institutional Review Board (Spallanzani Hospital), ClinicalTrials.gov: NCT04424992.

As part of a multi-center prospective study to evaluate pulmonary sequelae caused by SARS-CoV-2 pneumonia (5) (ClinicalTrials.gov: NCT04435327), we also had available follow-up data on 102 patients from the original cohort alive at discharge. The follow-up consisted of a pneumological visit at 6 months including complete pulmonary function tests and DLCO, 6MWT, mMRC scale and chest X-ray.

A propensity score method was used to evaluate the impact of NAC on outcomes on the full cohort adjusting for potential confounders: we created a pseudo-population by weighting our cohort by the inverse of stabilised inverse probability of treatment weights (IPTW) computed by a multivariable logistic model on the propensity of NAC assumption with the following covariates: gender, age, days from symptoms onset to hospital admission, period of diagnosis (before/after 01/07/20), chest X-ray (bilateral, unilateral or absence of pulmonary involvement) and ventilation support on admission, direct admission to the ICU, comorbidities (cardiovascular and cerebrovascular diseases, asthma, chronic obstructive pulmonary disease, other pulmonary diseases, diabetes, connective tissue diseases, chronic neurological disorders, dementia and anemia), cough and dyspnea as symptoms and concomitant assumption of systemic steroid or Remdesivir. We checked balancing among the two treatment groups after weighting by standardised mean difference and compared them by weighted two-sample rank tests (6) and weighted logistic model. Similar approach was adopted with the subsample of subjects with a follow-up visit at 6 months.

Nine hundred six patients (601, 66% males, median age 64 years, first-third quartiles (IQR) 55-75) were included in the study, 585 (64%) received at least 5 days of NAC and 321(36%) did not receive NAC or received less than 5 days of therapy (n=27). Demographic and clinical characteristics of the study population are summarised in Table 1. Patient's characteristics were well balanced in the two groups (NAC vs others) after weighting with standardised mean difference always lower than 0.1.

In regards to the main outcomes, 133 patients died during hospital stay (91 in NAC group and 42 in the other group), Odds Ratio (OR) of mortality from the IPTW weighted logistic regression resulted 1.22 (95% Confidence Interval, CI, 0.83,1.81, p=0.3) for the NAC group versus the other. One hundred fifty-four patients were admitted to the ICU with a median (IQR) of 2 (0-5) days after hospital admission and with a median (IQR) time spent in the ICU of 14 (8-24) days. After adjusting by the IPTW, no differences were observed between the two groups in regards to ICU admission and length of ICU stay. LOS in patients discharged at home was lower in NAC patients (weighted median (IQR) 15 (10-24) days) compared to those who did not receive NAC (weighted median (IQR) 17 (12-30) days, p=0.013), Table 1. Occurrence of atelectasis was not different among the two groups (2% in both groups, p=0.913), Table 1.

When considering the 102 patients (78% males, median (IQR) age 59 (53-63) years) who were followed up at 6 months with a pneumological visit, no differences were observed in regards to DLCO impairment (weighted percentage 24% vs 19%, OR=1.35, 95%CI: 0.50,3.92), chest-X-ray abnormalities (weighted percentage 18% vs 14%, OR=1.04, 95%CI 0.88,1.22) and distance walked at 6MWT (weighted median (IQR) 482 (424-540) meters vs 480 (432-541) meters, p=0.909)

between patients who received NAC (N=64) and those who did not (N= 38), respectively. mMRC was not statistically different between the two groups (p=0.281), although the weighted percentage of mMRC ≥ 2 (walks slower than people of the same age because of dyspnea) resulted 11% in patients who received NAC and 28% in others.

Despite the preliminary evidence of a few studies, up to date there are no definitive data on the efficacy of NAC in preventing short- and long-term negative outcomes in patients with SARS-CoV-2 pneumonia (7-9). Indeed our results nicely fit with those of the only double-blind RCT available till now that showed no benefit of high dose NAC administration for 20 hours in the emergency department on the development of severe acute respiratory failure requiring mechanical ventilation (MV) (7). Nevertheless, LOS and long-term outcomes were not evaluated in this RCT. Similarly, a pilot study by *Taher et al.* did not observe any benefit from NAC administered 40 mg/kg/day intravenously for 3 days in mild-to-moderate COVID19-associated acute respiratory distress syndrome (ARDS) on long-term (overall mortality over 28-day) and short-term outcomes (including the proportion of patients requiring MV and changes in ARDS-severity 48 and 96 h after intervention) (9).

Among the main strengths of our study, we acknowledge the inclusion of consecutive patients from a tertiary care center with a standardized protocol to manage COVID-19. This allowed patients to receive a homogeneous treatment. The standardized protocol followed the indications from the evidence based medicine: from March to July 2020 hydroxychloroquine, prophylactic heparin and, in case of oxygen supplementation requirement, remdesivir were administered. Use of hydroxychloroquine was then discontinued from May 2020, due to the lack of efficacy in COVID-19 patients (10). During the subsequent months (August 2020 – April 2021) and after publication of the RECOVERY trial's preliminary data (11), corticosteroid therapy was administered to all patients requiring oxygen supplementation.

Among the study limitations the following must be acknowledged: the reasons that led physicians to administer or not administer NAC were not clear, leading to possible biases despite propensity matching.

In conclusion, our study does not suggest an impact of NAC on short- and long-term outcomes including in-hospital mortality, ICU admission, DLCO impairment and chest X-ray alterations at 6-month follow-up. Patients receiving NAC during hospitalization for SARS-CoV-2 pneumonia presented a shorter LOS in comparison to those who did not receive NAC. However, results of the ongoing RCTs may shed further light on the role of NAC as add-on therapy to the standard treatment for SARS-CoV-2 pneumonia.

Declarations:

Declaration of Competing interest:

The authors declare they have no conflict of interest

Funding:

The authors have no funding to declare.

Ethical approval:

The STORM study was approved by national Institutional Review Board (Spallanzani Hospital). The SequelaeCoV study received Ethics Committee approval (ASST Monza, 3389, May 21st 2020).

Authors' contributions:

AP and MGV are the guarantors of this research. PF, PR, ER, SB and AP were responsible for study concept and design. PF, SdG, FM, LG, SB and FL contributed to patient recruitment and follow-up. All authors contributed to data acquisition. PF, PR, ER, SB and MGV performed data analysis. PF, PR, SB and FL contributed to the drafting of this manuscript. All authors read and approved the final manuscript.

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Table 1: Baseline patients' characteristics and outcomes in the total original sample and in the pseudo-population weighted for the propensity score of N- Acetyl- L- cysteine

	ORIGINAL DATA			WEIGHTED DATA		
	N-Acetyl-L-cysteine assumption			N-Acetyl-L-cysteine assumption		
	No (N=321)	Yes (N=585)	SMD	No (N=329)	Yes (N=572)	SMD
	N(%)	N(%)		N(%)	N(%)	
MALES	192 (60)	409 (70)	0.213	209 (64)	381 (67)	0.060
AGE (MEDIAN [Q1,Q3])	68[57, 79]	63[55, 72]	0.232	64[54, 75]	64[55, 73]	0.003
OXYGEN / VENTILATORY SUPPORT			0.736			0.098
NONE	101 (31)	41 (7)		49 (15)	78 (14)	
OXYGEN THERAPY ALONE	168(52)	379(65)		193 (59)	354 (62)	
CPAP	51 (16)	147 (25)		82 (25)	128 (22)	
ETI AND IMV	1 (0)	18 (3)		5 (1)	12 (2)	
CARDIOVASCULAR DISEASES	187 (58)	319 (55)	0.075	178 (54)	315 (55)	0.016
HYPERTENSION	151 (47)	275 (47)	0.001	151 (46)	270 (47)	0.021
DIABETES	69 (21)	84 (14)	0.187	53 (16)	90 (16)	0.006
OBESITY	39 (23)	126 (33)	0.219	53 (26)	117 (33)	0.156
CEREBROVASCULAR DISEASES	25 (8)	30 (5)	0.108	19 (6)	36 (6)	0.019
COPD	25 (8)	20 (3)	0.191	15 (5)	25 (4)	0.017
MODERATE OR SEVERE CHRONIC KIDNEY DISEASES	31 (10)	41 (7)	0.096	26 (8)	43 (7)	0.022
MODERATE OR SEVERE LIVER DISEASES	7 (2)	13 (2)	0.003	6 (2)	16 (3)	0.078
CHRONIC NEUROLOGICAL DISORDERS	60 (19)	52 (9)	0.287	41 (12)	74 (13)	0.014
CANCER	37 (12)	47 (8)	0.118	33 (10)	52 (9)	0.030
IMMUNE SYSTEM DISORDER	8 (2)	14 (2)	0.006	7 (2)	12 (2)	0.004
TREATMENT DURING HOSPITALISATION						
SYSTEMIC STEROID	76 (24)	265 (45)	0.467	122 (37)	217 (38)	0.016
REMDESIVIR	13 (4)	68 (12)	0.285	34 (10)	52 (9)	0.035
OUTCOMES						
	N(%)	N(%)		N(%)	N(%)	p
ICU ADMISSION	20 (7)	134 (23)		46 (15)	107 (19)	0.360
DAYS TO ICU (MEDIAN [Q1,Q3])	4 [1, 6]	2 [0, 5]		2 [0, 4]	2 [0, 5]	0.972
DAYS SPENT IN ICU (MEDIAN [Q1,Q3])	9 [4, 19]	14 [9, 24]		20 [8, 32]	14 [9, 23]	0.191
HOSPITAL DISCHARGE						0.523
DEATH	42 (13)	91 (16)		44 (13)	91 (16)	
DISCHARGED AT HOME	229 (71)	396 (68)		224 (68)	392 (68)	
TRANSFERRED TO OTHER FACILITY	50 (16)	98 (17)		61 (19)	89 (16)	
LENGTH OF HOSPITAL STAY IN SUBJECTS DISCHARGED AT HOME (DAYS, MEDIAN [Q1,Q3])	16 [11, 25]	16 [10, 25]		17 [12, 30]	15 [10, 24]	**0.013**
ATELECTASIS DURING HOSPITAL STAY	3 (1)	14 (2)		7 (2)	11 (2)	0.913

Footnotes: Q1= first quartile; Q3= third quartile; ICU= intensive care unit; SMD= standardised mean difference; COPD= chronic obstructive pulmonary disease; CPAP= continuous positive airway pressure; ETI= endotracheal intubation; IMV= invasive mechanical ventilation.