Gynecologic Oncology Reports 57 (2025) 101682

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

N-acetylcysteine (NAC) supplementation improves dyspnea and may normalize von Willebrand plasma levels in gynecologic patients with Post-Acute-COVID-Sequela (PASC)/Long COVID

Stefania Bellone [a], Eric R. Siegel [b], Alessandro D. Santin [a,*]

[a] Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520, USA
[b] Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

ARTICLE INFO

Keywords:
N-Acetylcysteine (NAC)
Long COVID/PASC
Von Willebrand factor
Micro-clotting

ABSTRACT

Objectives: A subset of COVID-infected cancer patients may develop post-acute sequelae of COVID-19 (PASC), also known as Long COVID (LC). While LC is considered multifactorial in its pathogenesis, growing evidence suggests that persistent microvascular inflammation (ie, spike-induced endotheliosis) causing chronically elevated levels of clotting factors including von Willebrand factor (vWF), clumping/clotting of red blood cells and platelets, and thrombotic complications may be at the root of PASC/LC symptoms. N-Acetylcysteine (NAC), a precursor of glutathione, is an inexpensive FDA-approved drug/supplement endowed with mucolytic, antioxidant, anti-inflammatory and thrombolytic properties. Multiple reports have recently demonstrated the potential clinical activity of NAC in COVID-19 patients. We retrospectively evaluated responses to NAC supplementation in a total of 9 PASC/LC patients, 3 of which reporting regular use of NAC, followed in our Gynecologic Oncology clinic.
Methods: Gynecologic patients using NAC supplement (3 patients) vs controls (6 patients) with persistent LC/PASC symptoms and with elevated plasmatic vWF levels were identified in our Gynecologic Oncology clinic database and evaluated for improvement/normalization in LC/PASC symptoms and vWF levels.
Results: Subjective improvement in shortness of breath, brain fog and fatigue with normalization of vWF levels were noted in 3 out of 3 PASC/LC patients using oral NAC (600–1200 mg BID) vs none of the randomly selected cancer control patients with PASC/LC (Fisher's exact P = 0.0119).
Conclusions: These preliminary results suggest that NAC may represent an inexpensive, safe and potentially effective supplement to improve many PASC/LC-related symptoms. Prospective randomized studies with NAC in PASC/LC patients are needed to confirm these findings.

1. Introduction

Up to one-third of healthy individuals and a large subset of cancer patients recovering from COVID-19 infection may develop prolonged debilitating symptoms consistent with Post-Acute Sequelae of COVID-19 (PASC), also known as Long COVID syndrome (LC). The most common reported symptoms include, but are not limited to fatigue, decreased exercise tolerance, shortness of breath, brain fog, cognitive dysfunction, postural orthostatic tachycardia syndrome (POTS), chest pain, chronic pain, palpitations, and gastrointestinal symptoms (Soriano et al., 2022; Ceban et al., 2022; Dagher et al., 2023; Cortellini et al., 2023; Ford et al, 2023). In many of these studies, a gender unbalance/predisposition was noted with female cancer patients more likely than male patients to report persistence of PASC/LC symptoms (Bai et al., 2022). With at least 65 million individuals worldwide estimated to have LC/PASC (Davis et al., 2023), the syndrome has emerged as a central public health issue. Unfortunately, regardless the major NIH initiative/investment to identify the causes and ultimately the means of prevention and treatment of individuals who have been sickened by COVID-19 (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid), currently no broadly effective treatments exist for LC/PASC patients.

While multiple pathophysiological mechanisms behind PASC/LC have been hypothesized including persistent viral infection, dysregulated interferon (IFN) response, chronic inflammation, alterations in cellular metabolism, dysbiosis, neuroinflammation, autoimmune

* Corresponding author at: 333 Cedar Street, LSOG 305, PO Box 208063, New Haven, CT 06520, USA.
E-mail address: alessandro.santin@yale.ed (A.D. Santin).

https://doi.org/10.1016/j.gore.2025.101682
Received 4 December 2024; Received in revised form 13 January 2025; Accepted 17 January 2025
Available online 25 January 2025

processes and mast cell activation syndrome (MACS) (Davis et al., 2023), recent growing evidence suggests that the core root component of PASC/LC is related to a persistent COVID-19-associated coagulopathy triggered by the ability of long-lasting viral Spike-1 protein to cause clumping and clotting of red blood cells and platelets (Scheim, 2022; Boschi et al., 2022; Scheim et al., 2023) and disruption of normal endothelial function leading to prolonged thrombotic and microvascular complications (Kruger et al., 2022; Pretorius et al., 2022; Turner et al., 2023; Kell et al., 2022). In this regard, while acute COVID-19 infection typically initiates with penetration of the virus into the upper airway leading to lung inflammation, multiple studies have identified the vascular endothelium as the primary target of COVID-19 pathology, causing microvascular occlusion in lungs and other organ systems with accompanying morbidities such as intravascular clotting and peripheral ischemia (Ackermann et al., 2020; O'Sullivan et al., 2020). Autopsy studies have reported widespread microthrombi disseminated throughout the pulmonary vasculature, demonstrating that vasculopathy is paramount in COVID-19 pathogenesis (Wichmann et al., 2020). Importantly, in a recent report, we identified persistent elevation of von Willebrand and Factor VIII but not d-dimer in a series of PASC/LC gynecologic cancer patients followed in our cancer clinic (Bellone et al, 2024), while other investigators have reported the identification and isolation of fibrin amyloid micro-clots able to block capillaries and inhibit the transport of O_2 to tissue (Kruger et al., 2022; Pretorius et al., 2022; Turner et al., 2023; Kell et al., 2022). Importantly, the combined treatment of fibrin amyloid micro-clots and platelet pathology with a combination of anticoagulation and antiplatelet therapy (ie, triple anticoagulation treatment) has been recently demonstrated to improve/resolve most of PACS/LC persistent symptoms (Pretorius et al., 2021). Unfortunately, patients on this triple regime must be followed under strict and qualified medical guidance to obviate the risk of hemorrhagic bleeding (Pretorius et al., 2021). Taken together, these data suggest that endothelial cell damage and platelet inflammation/activation causing chronic release of clotting factors including von Willebrand and triggering intravascular formation of difficult-to-dissolve fibrin amyloid micro-clots may play a key role in orchestrating not only the unusual pulmonary intravascular coagulopathy associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection but also PASC/LC.

N-acetylcysteine (NAC) is a thiol-containing free-radical scavenger and precursor of glutathione which exerts potent antioxidant and anti-inflammatory effects (reviewed by Pedre et al, 2021; Ershad et al, 2024). It was initially patented over 60 years ago as a mucolytic agent in respiratory infections and as an antidote for paracetamol toxicity. NAC is on the World Health Organization's List of Essential Medicines and is available as an inexpensive generic drug over-the-counter supplement all over the world. Multiple preclinical and clinical studies have demonstrated its potent antioxidant and anti-inflammatory actions able to decrease immune activation and prevent cytokine release during infections by reducing oxygen species and oxidative stress, which are able to activate important redox-sensitive transcription factors (ie, nuclear factor-kappa B, NF-KB), leading to the expression of multiple proinflammatory cytokines including but not limited IL-6, IL-8, and TNF-a (Pedre et al, 2021; Ershad et al, 2024). Importantly, these cytokines have been reported to play a major role during the hyper-inflammatory phase developed in a small subset of COVID-19-infected patients defined as "cytokine storm" (Fajgenbaum and June, 2020). Clinical reports in acutely infected COVID-19 patients have demonstrated NAC treatment not only to be safe even at high doses (ie, up to 150 mg/kg/day IV), but also able to improve systemic oxygenation and treatment outcome (reviewed in Shi and Puyo, 2020). Of interest, other studies have demonstrated a previously unrecognized thrombolytic effect of NAC in human and mouse plasma, in which it was able to reduce the size of vWF multimers, which polymerize in a manner similar to mucins, by reducing disulfide bonds connecting the monomers and eventually causing the lysing of von Willebrand factor-made micro-clots (Chen et al., 2011; Martinez de Lizarrondo et al., 2017). Since micro-clots enriched in von Willebrand factor are abundant in LC/PASC patients (Kruger et al., 2022; Pretorius et al., 2022; Turner et al., 2023; Kell et al., 2022) and our group has recently reported that von Willebrand factor is significantly and persistently increased in the circulation of symptomatic LC/PASC gynecologic oncology patients, in this study we retrospectively evaluated the charts of 9 LC/PASC patients including a subset (ie, 3 patients) reporting regular supplementation of their diet with NAC. We investigated clinical signs of activity in LC/PASC symptoms including SOB, fatigue and brain fog as well as changes in biomarker (ie, Von Willebrand Factor) levels and compared such findings to a control group of gynecologic LC/PASC patients not using NAC.

2. Methods

A retrospective chart review of the EMR identified nine patients followed in our Gynecologic Oncology clinic who fulfilled study inclusion criteria (ie, previous Covid-19 infection, persistent LC/PASC symptoms as well as availability of multiple von Willebrand lab evaluations/values over the 4-year study period). Information about the regular use of the NAC supplement or the lack of its use as well as the type and severity of reported symptoms were extracted from the Epic charts of the identified LC/PASC patients. No specific symptoms' questionnaire was available for this retrospective review study. Out of the 9 LC/PASC patients identified 3 reported regular use of NAC during the study period. We evaluated and compared vWF levels before and after starting NAC treatment to those detected in a control group of 6 randomly selected gynecologic patients with PASC/LC symptoms who did not use the supplement. Levels of vWF were tested for variance equality with the folded F-test, then compared accordingly for group differences with either Student's equal-variance *t*-test or Welch's unequal-variance *t*-test. We considered the vWF level to be elevated if it exceeded the Yale Laboratory's reference range of 62–175 %. Groups were compared via Fisher's exact test for differences in the elevated vWF rate at baseline vs follow-up visits. A p value < 0.05 was considered statistically significant. The study was conducted according to the tenets of the Declaration of Helsinki. The retrospective chart review was approved by the Yale Human Research Protection Program, Institutional Review Boards, IRB Protocol ID: 2000030512.

3. Results

We retrospectively evaluated changes in clinical symptoms including SOB, brain fog and fatigue and in plasmatic levels of vWF, in a total of 9 patients affected by PASC/LC with a history of gynecologic tumors and/or benign gynecologic conditions followed in our clinic. Three out of nine reported supplementation of their diet with over-the-counter NAC (600–1200 mg BID) at different time points after the diagnosis with PASC/LC. Patients using NAC supplementation experienced subjective improvement in SOB at rest and/or while walking with decreased brain fog and fatigue. Since plasmatic levels of vWF were collected during the COVID-19 pandemic in PASC/LC patients at the time of follow up visits as part of their blood-workup monitoring, we were also able to evaluate and compare vWF levels before and after starting NAC treatment to those detected in a control group of randomly selected gynecologic patients with PASC/LC symptoms who did not use the supplement. The characteristics of the study patients, date of COVID-19 infection and of the blood collections used for vWF evaluation are described in Table 1 and Table 2. We found elevated baseline vWF level in all 9 symptomatic PASC/LC patients evaluable for the study (range = 206 % to 462 %, Table 2). When divided by group, baseline vWF levels were significantly higher among controls than among NAC supplementers. Group means ± SDs in baseline vWF for controls versus NAC supplementers respectively were 334 % ± 95 % versus 215 % ± 9 % (Welch's *t*-test P = 0.0271; folded F-test P = 0.0181). The same pattern of differences in vWF was seen at the 1st follow-up visit. Group means ± SDs in 1st-

Table 1
Characteristics of PASC/LC patients.

Case Number	Age	Race	Gyn Pathology	Date of COVID infection	Long COVID Symptoms	NAC Supplement
1	66	White	endometrial cancer	2/2020	Yes	No
2	72	White	complex ovarian cyst	12/2022	Yes	No
3	66	White	endometrial cancer	9/2023	Yes	No
4	65	White	ovarian cancer	10/2020	Yes	No
5	58	Black	ovarian cancer	11/2020	Yes	No
6	81	White	Endometrial cancer	12/2020	Yes	No
7	71	White	ovarian cancer	9/2020	Yes	Yes
8	42	White	cervical dysplasia	11/2021	Yes	Yes
9	36	White	bladder incontinence	10/2023	Yes	Yes

Table 2
Levels of vWF in PASC/LC patients treated with NAC vs controls.

Case Number	Level of vWF	Level of vWF at Follow-up	Level of vWF at Follow-up	Level of vWF at Follow-up	NAC Supplement
1	235 % (8/23)*	230 % (11/23)	247 % (2/24)	233 % (6/24)	No
2	462 % (3/23)	222 % (8/23)	n/a	n/a	No
3	405 % (11/23)	400 % (4/24)	359 % (4/24)	340 % (8/24)	No
4	300 % (12/20)	215 % (2/21)	n/a	n/a	No
5	370 % (1/21)	363 % (3/21)	n/a	n/a	No
6	229 % (1/21)	233 % (2/24)	221 % (9/24)	n/a	No
7	214 % (6/23)	**156 % (2/24)**	**163 % (5/24)**	n/a	Yes
8	206 % (9/23)	**173 % (5/24)**	n/a	n/a	Yes
9	224 % (11/23)	**151 % (1/24)**	n/a	n/a	Yes

* Date of the blood collection (month/year). Values shown in bold are within normal reference range (Von Willebrand Factor normal range = 62 % – 175 %).

follow-up vWF for controls versus NAC supplementers respectively were 277 % ± 82 % versus 160 % ± 12 % (Welch's *t*-test P = 0.0165; folded F-test P = 0.0391). However, three out of 3 (100 %) of the PASC/LC patients supplementing their diet with NAC decreased vWF values to normal levels at the time of subsequent evaluations, whereas none (0 %) of the 6 symptomatic PASC/LC control patients did so (Fisher's exact P = 0.0119)(Table 2). Importantly, as representatively demonstrated in Fig. 1, NAC PASC/LC users regardless to the length of time they experienced PASC/LC symptoms and/or elevation in vWF plasmatic levels reported subjective improvement in their long-lasting debilitating symptoms including SOB, brain fog and fatigue and normalization of vWF level (Fig. 1) versus none of the PASC/LC control patients.

4. Discussion

Cancer patients have been reported to be more susceptible to SARS-CoV-2 infection than otherwise similar age healthy patients and to be at a higher risk of severe COVID-19 complications than the general population (Wang et al., 2020). Moreover, recent data have suggested that cancer patients may also be more susceptible to develop long-lasting debilitating symptoms after COVID-19 infection with up to 60 % reported to develop PASC/LC (Dagher et al., 2023; Cortellini et al., 2023).

The pathophysiologic mechanisms underlying the post-COVID prolonged and disabling symptoms remain poorly understood and are likely multifactorial. However, several studies have demonstrated that SARS-CoV-2 may remain detectable for months in a subset of PASC/LC patients after the acute infection, hiding in multiple organs and inflammatory cells such as monocytes/macrophages (de Melo et al., 2021; Bussani et al., 2020; Craddock et al., 2023; Zollner et al., 2022; Cheung et al., 2022; Patterson et al., 2022; Schultheiß et al., 2023; Wang et al., 2020). Chronic production of spike protein in the body of PASC/LC patients might therefore trigger a persistent state of inflammation in vessels/organs, in particular in the microcirculation, causing a status of chronic coagulopathy and systemic micro thrombosis (Kruger et al., 2022; Pretorius et al., 2022; Turner et al., 2023; Kell et al., 2022). Consistent with this view, SARS-CoV-2 spike protein has been demonstrated to mediate not only direct lung injury but also vascular damage by inducing endothelial barrier dysfunction and inflammation (i.e., endotheliitis), platelet activation and formation of difficult to lyse "fibrinaloid" microclots after the recovery from the acute infection (Kruger et al., 2022; Pretorius et al., 2022; Turner et al., 2023; Kell et al., 2022). In other studies, binding of spike proteins to mammalian cells has been reported to downregulate not only the surface expression of ACE2,

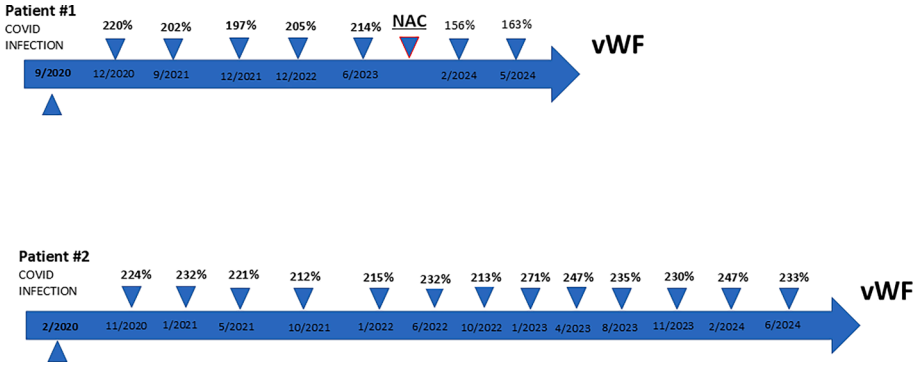

Fig. 1. Longitudinal von Willebrand Factor plasma values in two representative PASC/LC cancer patients follow for 4 years after the initial COVID-19 infection (ie, date in bold) with multiple vWF evaluations available. Upper panel: Patient #7 (NAC user) vs Lower panel: Patient #1 (Control). Values shown in bold are above vWF normal reference range.

(ie, the main SARS-CoV-2 binding receptor), but also that of the α7 nicotinic acetylcholine receptor (ie, α7nAChR), the core receptor under the control of the vagus nerve regulating the parasympathetic nervous system and the cholinergic anti-inflammatory pathway) (Lei et al, 2021; Pavlov et al, 2003). Importantly, spike-induced α7nAChR down-regulation has been shown to impair neuronal and immune function and dramatically increase platelet activation and aggregation status (Tillman et al, 2023; Kooijman et al., 2015). These findings combined with the recent demonstration that fibrin binds to spike S1 protein forming proinflammatory micro clots enriched in vWF driving thrombus inflammation and neuropathology in COVID-19 patients (Ryu et al, 2024), further support the notion that persistent COVID-19-associated coagulopathy may represent the root component of PASC/LC symptoms.

In a recent report we found that similarly to acutely infected COVID-19 patients (Goshua et al., 2020), many highly symptomatic PASC/LC patients demonstrate persistently elevated levels of vWF and Factor VIII in their plasma (Bellone et al, 2024). These results obtained in both acutely infected and PASC/LC patients have provided biochemical evidence that endotheliopathy and platelet activation are ubiquitous in acute and chronically infected COVID-19 patients and, accordingly, may lead to the clinical prothrombotic manifestations of COVID-19-associated coagulopathy, which include microvascular thrombosis (Goshua et al., 2020). Since the production of vWF is exclusive to endothelial cells and megakaryocytes (Lenting et al., 2015), and since vWF is secreted by endothelial cells in response to high shear stress and other inflammatory mediators (Lenting et al., 2015), it is likely that resting endothelial cells and inflamed platelets may continue to release large amounts of long vWF multimers into circulation when activated/damaged by the persistent production/presence of spike protein in PASC/LC patients. However, regardless to this emerging knowledge about PASC/LC pathogenesis, no safe, effective and inexpensive treatments are currently available to treat patients affected by PASC/LC.

NAC is an amino acid derivative available over the counter with decades of scientific validation as mucolytic, antioxidant, and anti-inflammatory agent. At therapeutic doses (ie, 1200 mg/day), due to its free thiol group, NAC has demonstrated the ability to restore the physiologic intracellular level of glutathione (GSH), a powerful cellular antioxidant, and be also able of decreasing mucin size and viscosity in patients with obstructive lung disease. Accordingly, NAC has been used for over 60 years in clinical practice to treat multiple medical conditions including paracetamol intoxication, acute respiratory distress, and a variety of chronic inflammatory diseases (reviewed by Pedre et al, 2021; Ershad et al, 2024). As antiviral agent against flu infection, prospective randomized double blind studies having as main objective the evaluation of the effect of long-term treatment with NAC (600 mg twice daily for 6 months) vs placebo on influenza and influenza-like episodes, demonstrated NAC treatment to be well tolerated and able to cause a significant decrease in the frequency of influenza-like episodes, severity, and length of time confined to bed (de Flora et al, 1997). When used in COVID-19 patients with pneumonia, NAC significantly reduced the risk for mechanical ventilation and mortality (Assimakopoulos et al, 2021) while a remarkable benefit of IV NAC has been reported in series of patients with severe COVID-19 infection (Ibrahim et al, 2020). Of interest, a recent study demonstrated in a series of twelve patients with "brain fogs" and LC/PASC symptoms treated with guanfacine and NAC significant improvement in memory, concentration, and executive functions including the resumption of normal workload (Khasnavis et al., 2024).

Accordingly, in this study we retrospectively evaluated the potential activity of NAC supplement in 9 LC/PASC patients followed in our Gynecologic Oncology clinic. In agreement with the report of Khasnavis et al., 2024 in LC/PASC, we found patients reporting regular use of NAC to subjectively demonstrate improvement in SOB, brain fog and fatigue. Of interest, although we noticed the plasmatic concentration of vWF to decrease with time in both groups of patients, only NAC supplementers were able to normalize their vWF levels after treatment (ie, 3 out of 3), whereas 0 % of the control PASC/LC gynecologic patients did so (ie, 0 out of 6) regardless to their baseline starting level of vWF or follow up time. Importantly, in our small series, subjective improvement in performance status and decrease/normalization in the levels of vWF were detected even in PASC/LC patient symptomatic for years.

In conclusion, we report that NAC supplementation may improve SOB and fatigue while decreasing/normalizing the levels of vWF in the plasma of symptomatic gynecologic PASC/LC patients. NAC may represent a safe and potentially effective alternative to the use of antithrombotic agents to restore micro vessel patency and improve tissue oxygenation in PASC/LC patients. Prospective clinical trials are warranted.

5. Consent

Written informed consent was obtained from the patients for publication of this case series. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Stefania Bellone, Eric Siegel and Alessandro D. Santin participated in drafting and revising this manuscript. All authors read and approved this manuscript to be submitted.

CRediT authorship contribution statement

Stefania Bellone: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eric R. Siegel:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Alessandro D. Santin:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [ADS reports grants from VERASTEM, PUMA, GILEAD, SYNTHON, MERCK, BOEHINGER-INGELHEIM, GENENTECH, and personal fees for consulting services from TESARO, EISAI, GSK, MERCK, and GILEAD. The other authors declare no conflict of interest].

References

Ackermann, M., Verleden, S.E., Kuehnel, M., et al., 2020. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N. Engl. J. Med. 383, 120–128. https://doi.org/10.1056/NEJMoa2015432.

Assimakopoulos, S.F., Aretha, D., Komninos, D., Dimitropoulou, D., Lagadinou, M., Leonidou, L., Oikonomou, I., Mouzaki, A., Marangos, M., 2021. N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center retrospective cohort study. Infect Dis (Lond). 53 (11), 847–854. https://doi.org/10.1080/23744235.2021.1945675. Epub 2021 Jun 29 PMID: 34182881.

Bai, F., Tomasoni, D., Falcinella, C., et al., 2022. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin. Microbiol. Infect. 28, 611. e619–611.e1616. https://doi.org/10.1016/j.cmi.2021.11.002.

Bellone, S., Siegel, E.R., Scheim, D.E., Santin, A.D., 2024. Increased von Willebrand and Factor VIII plasma levels in gynecologic patients with Post-Acute-COVID-Sequela (PASC)/Long COVID. Gynecol Oncol Rep. 4 (51), 101324. https://doi.org/10.1016/j.gore.2024.101324. PMID: 38273933; PMCID: PMC10809113.

Boschi, C., Scheim, D.E., Bancod, A., et al., 2022. SARS-CoV-2 spike protein induces hemagglutination: implications for COVID-19 morbidities and therapeutics and for vaccine adverse effects. Int. J. Mol. Sci. 23, 15480. https://doi.org/10.3390/ijms232415480.

Bussani, R., Schneider, E., Zentilin, L., et al., 2020. Persistence of viral RNA, pneumocyte syncytia and thrombosis are hallmarks of advanced COVID-19 pathology. EBioMedicine 61, 103104. https://doi.org/10.1016/j.ebiom.2020.103104.

Ceban, F., Ling, S., Lui, L.M.W., et al., 2022. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: a systematic review and meta-analysis. Brain Behav. Immun. 101, 93–135. https://doi.org/10.1016/j.bbi.2021.12.020.

Chen, J., Reheman, A., Gushiken, F.C., Nolasco, L., Fu, X., Moake, J.L., Ni, H., López, J. A., 2011. N-acetylcysteine reduces the size and activity of von Willebrand factor in human plasma and mice. J. Clin. Invest. 121 (2), 593–603. https://doi.org/10.1172/JCI41062. Epub 2011 Jan 25. PMID: 21266777; PMCID: PMC3026714.

Cheung, C.C.L., Goh, D., Lim, X., et al., 2022. Residual SARS-CoV-2 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-19. Gut 71, 226–229. https://doi.org/10.1136/gutjnl-2021-324280.

Cortellini, A., Tabernero, J., Mukherjee, U., et al., 2023. SARS-CoV-2 omicron (B.1.1.529)-related COVID-19 sequelae in vaccinated and unvaccinated patients with cancer: results from the OnCovid registry. Lancet Oncol. 24, 335–346. https://doi.org/10.1016/S1470-2045(23)00056-6.

Craddock, V., Mahajan, A., Spikes, L., et al., 2023. Persistent circulation of soluble and extracellular vesicle-linked Spike protein in individuals with postacute sequelae of COVID-19. J. Med. Virol. 95, e28568. https://doi.org/10.1002/jmv.28568.

Dagher, H., Chaftari, A.-M., Subbiah, I.M., et al., 2023. Long COVID in Cancer Patients: Preponderance of Symptoms in Majority of Patients over Long Time Period. eLife 12, e81182. https://doi.org/10.7554/eLife.81182.

Davis, H.E., McCorkell, L., Vogel, J.M., et al., 2023. Long COVID: major findings, mechanisms and recommendations. Nat. Rev. Microbiol. 21, 133–146. https://doi.org/10.1038/s41579-022-00846-2.

De Flora, S., Grassi, C., Carati, L., 1997. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. Eur. Respir. J. 10 (7), 1535–1541. https://doi.org/10.1183/09031936.97.10071535. PMID: 9230243.

de Melo, G.D., Lazarini, F., Levallois, S., et al., 2021. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. Sci. Transl. Med. 13, eabf8396. https://doi.org/10.1126/scitranslmed.abf8396.

Ershad M, Naji A, Patel P, et al. N-Acetylcysteine. [Updated 2024 Feb 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537183/.

Fajgenbaum, D.C., June, C.H., 2020. Cytokine Storm. N. Engl. J. Med. 383, 2255–2273.

Ford, N.D., Slaughter, D., Edwards, D., et al., 2023. Long COVID and Significant Activity Limitation Among Adults, by Age - United States, June 1-13, 2022, to June 7-19, 2023. MMWR Morb Mortal Wkly Rep 72, 866-870. 10.15585/mmwr.mm7232a3.

Goshua, G., Pine, A.B., Meizlish, M.L., et al., 2020. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol 7, e575–e582. https://doi.org/10.1016/s2352-3026(20)30216-7.

Ibrahim, H., Perl, A., Smith, D., Lewis, T., Kon, Z., Goldenberg, R., Yarta, K., Staniloae, C., Williams, M., 2020. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. Clin. Immunol. 219. https://doi.org/10.1016/j.clim.2020.108544. Epub 2020 Jul 22. PMID: 32707089; PMCID: PMC7374140.

Kell, D.B., Laubscher, G.J., Pretorius, E., 2022. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem. J 479, 537–559. https://doi.org/10.1042/bcj20220016.

Khasnavis, S., Belliveau, T., Arnsten, A., Fesharaki-Zadeh, A., 2024. Combined use of guanfacine and N-acetylcysteine for the treatment of cognitive deficits after traumatic brain injury. Neurotrauma Rep. 5 (1), 226–231. https://doi.org/10.1089/neur.2023.0124. PMID: 38524728; PMCID: PMC10960163.

Kooijman, S., Meurs, I., van der Stoep, M., Habets, K.L., Lammers, B., Berbée, J.F., Havekes, L.M., van Eck, M., Romijn, J.A., Korporaal, S.J., Rensen, P.C., 2015. Hematopoietic α7 nicotinic acetylcholine receptor deficiency increases inflammation and platelet activation status, but does not aggravate atherosclerosis. J. Thromb. Haemost. 13 (1), 126–135.

Kruger, A., Vlok, M., Turner, S., et al., 2022. Proteomics of fibrin amyloid microclots in long COVID/post-acute sequelae of COVID-19 (PASC) shows many entrapped pro-inflammatory molecules that may also contribute to a failed fibrinolytic system. Cardiovasc. Diabetol. 21, 190. https://doi.org/10.1186/s12933-022-01623-4.

Lei, Y., Zhang, J., Schiavon, C.R., He, M., Chen, L., Shen, H., Zhang, Y., Yin, Q., Cho, Y., Andrade, L., Shadel, G.S., Hepokoski, M., Lei, T., Wang, H., Zhang, J., Yuan, J.X., Malhotra, A., Manor, U., Wang, S., Yuan, Z.Y., Shyy, J.Y., 2021. SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE 2. Circ. Res. 128 (9), 1323–1326.

Lenting, P.J., Christophe, O.D., Denis, C.V., 2015. von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends. Blood 125, 2019–2028. https://doi.org/10.1182/blood-2014-06-528406.

S. Martinez de Lizarrondo C. Gakuba B.A. Herbig Y. Repessé C. Ali C.V. Denis P.J. Lenting E. Touzé S.L. Diamond D. Vivien M. Gauberti, Potent Thrombolytic Effect of N-Acetylcysteine on Arterial Thrombi Circulation. 136 7 2017 646 660 10.1161/CIRCULATIONAHA.117.027290 Epub 2017 May 9. PMID: 28487393; PMCID: PMC5560034.

O'Sullivan, J.M., Gonagle, D.M., Ward, S.E., Preston, R.J.S., O'Donnell, J.S., 2020. Endothelial cells orchestrate COVID-19 coagulopathy. Lancet Haematol 7, e553–e555. https://doi.org/10.1016/s2352-3026(20)30215-5.

Patterson, B.K., Francisco, E.B., Yogendra, R., et al., 2022. Persistence of SARS CoV-2 S1 protein in CD16+ monocytes in post-acute sequelae of COVID-19 (PASC) up to 15 months post-infection. Front. Immunol. 12, 5526.

Pavlov, V.A., Wang, H., Czura, C.J., Friedman, S.G., Tracey, K.J., 2003. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. Mol. Med. 9 (5–8), 125–134. PMID: 14571320; PMCID: PMC1430829.

Pedre, B., Barayeu, U., Ezeriņa, D., Dick, T.P., 2021. The mechanism of action of N-acetylcysteine (NAC): the emerging role of H2S and sulfane sulfur species. Pharmacol. Therapeut. 228. https://doi.org/10.1016/j.pharmthera.2021.107916. ISSN 0163-7258.

Pretorius, E., Venter, C., Laubscher, G.J., et al., 2021. Combined triple treatment of fibrin amyloid microclots and platelet pathology in individuals with Long COVID/ Post-Acute Sequelae of COVID-19 (PASC) can resolve their persistent symptoms. Research Square. https://doi.org/10.21203/rs.3.rs-1205453/v1.

Pretorius, E., Venter, C., Laubscher, G.J., et al., 2022. Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with Long COVID/Post-Acute Sequelae of COVID-19 (PASC). Cardiovasc. Diabetol. 21, 148. https://doi.org/10.1186/s12933-022-01579-5.

Ryu JK, Yan Z, Montano M, Sozmen EG, Dixit K, Suryawanshi RK, Matsui Y, Helmy E, Kaushal P, Makanani SK, Deerinck TJ, Meyer-Franke A, Rios Coronado PE, Trevino TN, Shin MG, Tognatta R, Liu Y, Schuck R, Le L, Miyajima H, Mendiola AS, Arun N, Guo B, Taha TY, Agrawal A, MacDonald E, Aries O, Yan A, Weaver O, Petersen MA, Meza Acevedo R, Alzamora MDPS, Thomas R, Traglia M, Kouznetsova VL, Tsigelny IF, Pico AR, Red-Horse K, Ellisman MH, Krogan NJ, Bouhaddou M, Ott M, Greene WC, Akassoglou K. Fibrin drives thromboinflammation and neuropathology in COVID-19. Nature. 2024 Sep;633(8031):905-913. doi: 10.1038/s41586-024-07873-4. Epub 2024 Aug 28. PMID: 39198643; PMCID: PMC11424477.

Scheim, D.E., 2022. A Deadly Embrace: Hemagglutination Mediated by SARS-CoV-2 Spike Protein at its 22 N-Glycosylation Sites, Red Blood Cell Surface Sialoglycoproteins, and Antibody. Int. J. Mol. Sci. 23, 2558. https://doi.org/10.3390/ijms23052558.

Scheim, D.E., Vottero, P., Santin, A.D., Hirsh, A.G., 2023. Sialylated glycan bindings from SARS-CoV-2 spike protein to blood and endothelial cells govern the severe morbidities of COVID-19. Int. J. Mol. Sci. 24 (23), 17039. https://doi.org/10.3390/ijms242317039.

Schultheiß, C., Willscher, E., Paschold, L., et al., 2023. Liquid biomarkers of macrophage dysregulation and circulating spike protein illustrate the biological heterogeneity in patients with post-acute sequelae of COVID-19. J. Med. Virol. 95, e28364. https://doi.org/10.1002/jmv.28364.

Shi, Z., Puyo, C.A., 2020. N-Acetylcysteine to Combat COVID-19: an Evidence Review. Ther. Clin. Risk Manag. 2 (16), 1047–1055. https://doi.org/10.2147/TCRM.S273700. PMID: 33177829; PMCID: PMC7649937.

Soriano, J.B., Murthy, S., Marshall, J.C., Relan, P., Diaz, J.V., 2022. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect. Dis. 22, e102–e107. https://doi.org/10.1016/s1473-3099(21)00703-9.

Tillman, T.S., Chen, Q., Bondarenko, V., Coleman, J.A., Xu, Y., Tang, P., 2023. SARS-CoV-2 spike protein downregulates cell surface α7nAChR through a helical motif in the spike neck. ACS Chem. Neurosci. 14 (4), 689–698. https://doi.org/10.1021/acschemneuro.2c00610. Epub 2023 Feb 6. PMID: 36745901; PMCID: PMC9923440.

Turner, S., Khan, M.A., Putrino, D., et al., 2023. Long COVID: pathophysiological factors and abnormalities of coagulation. Trends Endocrinol Metab 34, 321–344. https://doi.org/10.1016/j.tem.2023.03.002.

Wang, L., Sun, Y., Yuan, Y., Mei, Q., Yuan, X., 2020. Clinical challenges in cancer patients with COVID-19: aging, immunosuppression, and comorbidities. Aging (Albany NY) 12, 24462–24474. https://doi.org/10.18632/aging.104205.

Wichmann, D., Sperhake, J.-P., Lütgehetmann, M., et al., 2020. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann. Intern. Med. 173, 268–277. https://doi.org/10.7326/M20-2003.

Zollner, A., Koch, R., Jukic, A., et al., 2022. Postacute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. Gastroenterology 163, 495–506.e498. https://doi.org/10.1053/j.gastro.2022.04.037.