SARS-CoV-2 Spike Protein-Induced Dysfunction of the NRP-1/VEGF-A Complex

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Long coronavirus disease-19 (COVID-19) is a newly discovered syndrome characterized by multiple organ manifestations that persist for weeks to months, following the recovery from acute disease. Occasionally, neurological and cardiovascular side effects mimicking long COVID-19 have been reported in recipients of COVID-19 vaccines. Hypothetically, the clinical similarity could be due to a shared pathogenic role of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein produced by the virus or used for immunization. The S protein can bind to neuropilin (NRP)-1, which normally functions as a coreceptor for the vascular endothelial growth factor (VEGF)-A. By antagonizing the docking of VEGF-A to NRP-1, the S protein could disrupt physiological pathways involved in angiogenesis and nociception. One consequence could be the increase in unbound forms of VEGF-A that could bind to other receptors. SARS-CoV-2-infected individuals may exhibit increased plasma levels of VEGF-A during both acute illness and convalescence, which could be responsible for diffuse microvascular and neurological damage.

Keywords: SARS-CoV-2 ; NRP-1 ; VEGF-A ; COVID-19 ; COVID-19 vaccine ; long COVID-19 ; post-COVID-19 ; spike protein ; small fiber neuropathy

1. Disruption of the Neuropilin (NRP)-1/VEGF-A Pathway by SARS-CoV-2 in Acute COVID-19

COVID-19 is a polyhedral disease characterized by a range of manifestations of varying intensity [1]. Despite being less common with the Omicron variant infection, reported symptoms usually include fever, fatigue, myalgia, cough, headache, hypo-anosmia, and hypo-ageusia [2][3]. The prognosis is generally more severe in the case of viral pneumonia with subsequent development of hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) [4]. Occasionally, patients may suffer from cardiac symptoms (arrhythmia, myocarditis, acute coronary syndrome, and heart failure), neuropsychiatric manifestations (stroke, seizure, encephalopathy, demyelinating disorders, or psychosis), and thromboembolic events [4].

A growing body of evidence suggests that COVID-19 is due to a profound alteration of the endothelium triggered directly by SARS-CoV-2 or indirectly by the increase in proinflammatory cytokines [5]. This view is supported by manifestations consistent with diffuse or organ-specific endotheliitis, altered nailfold capillaroscopy patterns in COVID-19 patients, and increases in markers of endothelial injury in blood samples from infected individuals, such as circulating endothelial cells (CECs), von Willebrand factor, soluble intercellular adhesion molecule-1 (sICAM-1), and angiopoietin-2 (Ang-2) [5][6][7][8]. In addition, COVID-19 patients exhibit increased plasma levels of VEGF-A during both acute disease and convalescence, possibly reflecting diffuse microvascular injury [9][10][11]. Endothelial dysfunction leading to local tissue hypoxia could be another stimulus for VEGF-A secretion, triggering a self-perpetuating mechanism [12]. The increase in VEGF-A and other angiogenic factors may impair pericyte function and lead to intussusceptive angiogenesis in the lungs of infected individuals, contributing to endothelial hyperpermeability and massive interstitial edema [13][14][15].

Recent studies have downplayed the role of ACE2 in enabling SARS-CoV-2 entry into endothelial cells and nervous cells [5][16]. Although ACE2 can be detected in human endothelium, mature human cortex and olfactory cells, its expression is very low and probably insufficient to cause direct infection. Therefore, endothelial and neurological damages that occur during COVID-19 may depend on alternative mechanisms, including the exploitation of various cell receptors by the virus [17]. A number of experiments have shown that SARS-CoV-2 may be capable of interacting with the membrane neuropilin (NRP)-1 via its S protein and subsequently being internalized through this pathway [18][19][20][21][22]. Specifically, the B1 domain of NRP-1 has been predicted to interact with furin-cleaved ligands that contain a shared motif with arginine amino acid residues, also known as R/KXXR sequence, that is common to VEGF members [23]. A computational study revealed that a polybasic sequence in the C-terminus of the furin-cleaved SARS-CoV-2 S1 subdomain may also associate with

NRP-1 in the B1 domain, potentially displacing the VEGF ligand from the binding site [24], as shown in **Table 1**. However, this kind of binding appeared to be flexible and transient, and thus less effective than other molecular conformational interactions.

Table 1. Amino acid sequences of VEGF members and isoforms and SARS-CoV-2 S1 subdomain predicted to bind to the B1 domain of NRPs. Abbreviations: NRP: neuropilin; VEGF: vascular endothelial growth factor.

NRP Ligand	Binding Sequence (C-Terminus)
VEGF-A165	**DKPRR**
VEGF-B167	**RKLRR**
VEGF-B186	**RPQPR**
VEGF-C	**SIIRR**
spike S1 subdomain	**TNSPRRAR**

The emergence of new SARS-CoV-2 variants may indeed affect the binding affinity of the S protein to its receptors, modulating viral infectivity; however, data concerning changes in the avidity for NRP-1 receptors are unclear [25][26].

Given the abundant expression of NRP-1 in the endothelium as well as in the nervous system, olfactory epithelium, and respiratory system, this alternative mechanism could explain the COVID-19 endotheliitis and other complications such as anosmia, dizziness, and headache [27][28][29][30]. Interestingly, a recent experiment on induced pluripotent stem cell (iPSC)-derived brain organoids and primary human astrocytes from the cerebral cortex found that SARS-CoV-2 may invade astrocytes by using NRP-1 as the primary receptor [26]. Furthermore, as shown by Moutal et al. in a preclinical assay using rat models and spinal ganglion neurons [18], the binding of the S protein to NRP-1 may also impede nociception and explain a more rapid viral transmission in asymptomatic individuals. Moreover, the release of proinflammatory cytokines during acute illness may upregulate the expression of NRP-1 in the cardiomyocytes of SARS-CoV-2-infected patients, facilitating viral infectivity and cellular injury [31].

The inflammatory background associated with acute COVID-19 may also promote the activation of the VEGF-A/VEGF-R2 pathway and induce angiogenesis, increased vascular permeability, nitric oxide production, and disruption of endothelial cell junctions [5]. The excess of VEGF-A may then promote cardiac edema, inflammation, and remodeling of myocyte interstitial spaces, eventually leading to cardiac arrhythmias, as shown in a study of animal models [32]. Finally, VEGF-A may affect nociception and contribute to COVID-19 neuropathy [18].

As previously mentioned, the upregulation in the VEGF pathway is not exclusive to COVID-19, also being observed during other viral infections. Different trends, however, emerged when comparing VEGF expression during SARS-CoV-2 infection and infections sustained by other respiratory viruses. In a prospective cohort study evaluating the immune profile of moderate-to-severe COVID-19 and pandemic influenza A(H1N1) patients, a higher serum expression of VEGF was found in the former group compared to the latter [33]. Similarly, a Chinese study conducted on hospitalized COVID-19 children, children with acute respiratory tract infections caused by RSV, influenza virus, and adenovirus, and 20 matched healthy controls reported a panel of dysregulated cytokines in all the diseases, among which VEGF was the only one significantly associated with COVID-19 [34].

Based on these findings, VEGF-A has been considered a potential biomarker for COVID-19 and as such has been included among candidate pharmacological targets for combating the severe forms of the disease. The use of VEGF-A inhibitors such as bevacizumab in critically ill patients is currently being investigated in clinical trials with encouraging results [14][35]. In parallel, work is underway to identify potential compounds that prevent SARS-CoV-2 from binding to NRP-1 [36][37][38].

2. Disruption of the Neuropilin (NRP)-1/VEGF-A Pathway by SARS-CoV-2 in Long COVID-19

Long COVID-19 is a recently described syndrome characterized by multiple organ symptoms that may occur in more than 50% of individuals infected with SARS-CoV-2 four weeks after recovery from acute illness [39][40][41][42]. Fatigue, cardiac arrhythmias, muscle weakness, impaired ability to perform activities of daily life, and neuropsychiatric disorders are among the most common manifestations [39][43]. The duration of symptoms varies widely, ranging from three weeks to more than three months according to various reports [44]. There is still uncertainty about the pathogenic mechanisms

underlying the development of long COVID-19. Female gender and previous hospitalization due to severe illness are considered important risk factors. However, long COVID-19 can also occur in individuals with mild symptoms or without symptoms [44]. Sahanic et al. divided the post-COVID-19 sequelae into three phenotypes (hyposmia/anosmia phenotype, fatigue phenotype, and multi-organ phenotype), supporting the hypothesis that different pathogenic mechanisms may trigger the disease [42]. The clinical manifestations of long COVID-19 can be mild or severe and are likely due to both the cytopathic effects caused by the virus and the hyperactivation of the immune system. Patients with long COVID-19 may have impaired clearance of SARS-CoV-2, leading to a dysregulated immune response, which is in turn associated with increased thromboembolic risk [44]. In this context, neuropsychiatric and cardiovascular symptoms may be either due to organic injury (thromboembolism, local inflammation, fibrofatty substitution) or endothelial dysfunction and virus-induced demodulation of signaling pathways [28][40].

Very limited evidence links long COVID-19 to dysregulation of the NRP-1/VEGF-A pathway. An isolated cohort observational study of 103 SARS-CoV-2-infected patients, 48 of whom developed long COVID-19, reported significantly increased serum concentrations of VEGF in long COVID-19 patients compared with fully recovered subjects [45]. Three months after being discharged or onset of symptoms, patients with long COVID-19 also had higher anti-SARS-CoV-2 IgG titers and serum levels of granulocyte–macrophage colony-stimulating factor (GM-CSF). However, VEGF proved to be the only biomarker for long COVID-19 in univariate analysis. The study by Lim et al. also showed an increase in VEGF-A plasma levels in early (≤28 days) and late (>28 days) convalescent patients [10]. The authors also found that plasma levels of VEGF-A correlated directly with the severity of convalescence and circulating HLA-DR+CD38+CD8+ memory T lymphocytes and were instead negatively associated with CD8+CD56- mucosal-associated invariant T (MAIT) cells. HLA-DR+CD38+CD8+ T cells, which are typically elevated in severe forms of COVID-19 [46][47][48], reflect an exhausted T cell phenotype, whereas MAIT cells play a critical role in immune surveillance against pathogens [49]. Taken together, these data suggest that patients with worse COVID-19 outcomes have an altered immune profile with impaired clearance of SARS-CoV-2, which may accelerate inflammation and facilitate VEGF-A release. Indeed, epidemiological data show that long COVID-19 is more likely to follow severe forms of acute illness [44]. In the lung, the release of proinflammatory cytokines such as IL-1, IL-6, and TNF-α could stimulate the secretion of VEGF-A from alveolar epithelial cells and enhance lung inflammation [50]. However, in a Turkish study of 99 post-acute COVID-19 patients (who had been recovering for 3–12 weeks), the authors observed a significant decrease in serum concentration of VEGF-A in patients with evidence of pulmonary fibrosis on computed tomography (CT) of the chest compared with patients without pulmonary sequelae or healthy controls [51]. Thus, although VEGF-A appears to be a critical mediator of alveolocapillary permeability in ARDS, it may not be equally important in pulmonary fibrosis.

On the other hand, the results from other studies indicate that VEGF levels may be downregulated rather than increased during COVID-19 convalescence. A cross-sectional study on 20 healthy blood donors without previous SARS-CoV-2 infection and 140 convalescent plasma donors (median time since SARS-CoV-2 molecular positivity: 44 days) reported higher plasma levels of some cytokines, such as IFN-γ and IL-10, and lower plasma levels of VEGF-A in previously infected individuals compared to controls [52]. In another study, VEGF serum levels were reported to decrease in convalescent patients (time since symptoms: 35.75 ± 5.68 days) compared with the acute phase of disease and to be lower in asymptomatic SARS-CoV-2-infected individuals than in symptomatic patients [53]. Hence, the disturbance in the NRP-1/VEGF-A system by SARS-CoV-2 during long COVID-19 appears still uncertain. The conflicting results of the cited studies may depend on different methodologies, symptom persistence, concomitant cytokine milieu, viral clearance capacity, formation of neutralizing antibodies against the S protein, and medications.

Evidence of the dysregulation of VEGF-A-related signaling pathways during both acute and long COVID-19 is summarized in **Table 2**.

Table 2. Summary of the studies reporting altered VEGF-A expression in acute and long COVID-19/convalescent patients or suggesting the efficacy of anti-VEGF-A interventions in acute disease.

Author, Year	Type of Study	Population Studied	Main Results
Rovas et al., 2021 [9]	**Prospective, observational, cross-sectional study**	**-23 pts with moderate–severe COVID-19 -15 HCs**	**Increase in plasma VEGF-A levels and significant correlation with 60-day in-hospital mortality**

Author, Year	Type of Study	Population Studied	Main Results
Lim et al., 2021 [10]	Cross-sectional study	-37 pts with acute COVID-19 -40 convalescent pts -10 HCs	Increase in VEGF-A plasma levels during both acute disease and convalescence; positive correlation between VEGF-A plasma levels and convalescence severity; inverse correlation between VEGF-A plasma levels and CD8+CD56- MAIT cells during convalescence; positive association between VEGF-A plasma levels and HLA-DR+CD38+ CD8+ T cells in convalescent pts
Medeiros et al., 2022 [11]	Longitudinal study	-82 hospitalized moderate-to-severe COVID-19 pts, 41.5% of whom developing AKI	Increased serum levels of VEGF in pts with COVID-19-related AKI compared to pts without renal involvement
Choreño-Parra et al., 2021 [33]	Prospective cohort study	-10 pts with acute moderate COVID-19 -24 pts with acute severe COVID-19 -23 pts with pandemic influenza A(H1N1)	Increased serum levels of VEGF along with systemic, Th1 and Th2 cell cytokines in pts with COVID-19 but not in those with influenza
Zhang et al., 2022 [34]	Case control study	-20 hospitalized COVID-19 children -58 children with ARTI caused by RSV, influenza virus, and ADV -20 HCs	Significantly increased VEGF serum levels in SARS-CoV-2-infected pts compared to the other groups
Pang et al., 2021 [35]	Single-arm trial	-26 pts with severe COVID-19 treated with a single dose of bevacizumab	Improvement in PaO2/FiO2 parameters at days 1 and 7 from baseline; improvement in oxygen-support status in 92% of pts at day 28 from baseline; decrease in lung lesions on chest CT or X-ray within 7 days; normalization of body temperature within 72 h in 93% treated pts
Torres-Ruiz et al., 2021 [45]	Observational cohort study	-103 pts with previous COVID-19, 46.6% of whom diagnosed with long COVID-19	Higher VEGF serum levels in pts with long COVID-19 than in pts without; VEGF appearing as the sole biomarker strongly associated with long COVID-19 in univariate analysis
Arslan et al., 2022 [51]	Observational, cross-sectional study	-32 pts with a previous COVID-19 diagnosis and no lung fibrosis on CT scan -32 pts with a previous COVID-19 diagnosis and lung fibrosis on CT scan -26 HCs	Higher VEGF serum concentration in pts with a previous COVID-19 diagnosis and no lung fibrosis compared to the other groups
Bonny et al., 2021 [52]	Observational, cross-sectional study	-20 healthy blood donors without previous SARS-CoV-2 infection -140 COVID-19 convalescent plasma donors	Higher plasma levels of IFN-γ, IL-10, IL-15, IL-21, and MIP-1 and lower levels of IL-1RA, IL-8, IL-16, and VEGF-A in convalescent plasma donors compared to controls
Chi et al., 2020 [53]	Observational, cross-sectional study	-70 SARS-CoV-2-infected pts (4 asymptomatic; 66 symptomatic) -4 convalescent pts -4 HCs	Higher VEGF serum levels in symptomatic cases compared with asymptomatic cases; lower serum levels of VEGF in convalescent pts than in symptomatic pts; positive correlation between VEGF serum concentration and male gender; weakly positive correlation between VEGF serum concentration and SARS-CoV-2 viral load

Abbreviations: ADV: adenovirus; AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARTI: acute respiratory tract infection; COVID-19: coronavirus disease-19; CT: computed tomography; IL: interleukin; IL-1RA: IL-1 receptor antagonist; IFN: interferon; HCs: healthy controls; HLA: human leukocyte antigen; MAIT: mucosal-associated invariant T; MIP-1: macrophage-inflammatory protein-1; PaO2/FiO2: ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen; RSV: respiratory syncytial virus; pts: patients; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; VEGF-A: vascular growth factor-A.

3. Disruption of the NRP-1/VEGF-A Pathway by COVID-19 Vaccines

COVID-19 vaccines have been rapidly developed using various technologies to counteract the global spread of infection. Currently approved formulations include nucleic acid-based vaccines, vector-based vaccines, recombinant protein vaccines, and inactivated SARS-CoV-2 vaccines. Although they have different pharmacological properties, they all encode or carry the SARS-CoV-2 S protein, which can elicit a selective immune response [54]. As of October 2022, more than 900 million doses of COVID-19 vaccines have been administered to people in the EU and the European Economic Area. Since their launch, the European Medicines Agency (EMA) has periodically been confirming the efficacy and safety profile of COVID-19 vaccines as determined in clinical trials, with serious adverse events considered extremely rare [55]. According to the most recent EudraVigilance report, adverse events are more common in women aged 18–64 years and include, in particular, constitutional, neurological, and musculoskeletal symptoms [56]. Serious cardiovascular events have also been described in rare cases. These data are consistent with Vaccine Adverse Event Reporting System (VAERS) reports and the published literature [57][58]. Occasionally, adverse events mimicking long COVID-19 manifestations have been reported, as shown in **Table 3** [59][60][61][62].

Table 3. Constitutional, musculoskeletal, neuropsychiatric, and cardiovascular manifestations reported during long COVID-19 or listed among the COVID-19 vaccine side effects.

Clinical Domain	Long COVID-19	COVID-19 Vaccine Side Effects
Constitutional	• Fatigue • Sleep disturbances	• Fever • Fatigue
Musculoskeletal	• Arthralgias • Myalgias • Arthritis	• Arthralgias • Myalgias
Neuropsychiatric	• Paresthesia • Hypoesthesia • Dysesthesia • Headache • Dizziness • SFN • PTSD • Anxiety • Depression • Emotional disturbances • Brain fog • Hyposmia • Hypogeusia	• Weakness • Headache • Dizziness • Transient sensory symptoms • SFN • Seizures • Guillain–Barré syndrome • Transverse myelitis • Encephalopathy • Cerebral vascular events • Psychosis and confusional states • New-onset bipolar disorder • Anxiety

Clinical Domain	Long COVID-19	COVID-19 Vaccine Side Effects
Cardiovascular	• Palpitations • Chest pain • Dyspnea • Increased CV disease risk	• Syncope • Palpitations • Myocarditis • Pericarditis • Thrombosis

Abbreviations: COVID-19: coronavirus disease-19; CV: cardiovascular; PTSD: post-traumatic stress disorder; SFN: small fiber neuropathy.

Excessive reactogenicity to vaccine components or autoimmune phenomena have been proposed as possible mechanisms to explain neurological and cardiovascular side effects [63]. However, it has not been investigated whether the dysfunction of the NRP-1/VEGF-A system caused by the SARS-CoV-2 S protein may be directly associated with adverse events in COVID-19 vaccine recipients. A recent study has characterized the immune profile of six COVID-19-vaccinated male individuals, among whom there was one case of myopericarditis, and five male controls. Blood samples were collected 2–4 days after vaccination. By using a multiplex cytokine assay, the researchers reported a set of dysregulated cytokines and angiogenic mediators in recipients of COVID-19 vaccine versus healthy controls, including VEGF-A [64]. Remarkably, plasma concentrations of VEGF-A were lower in the vaccinated patient developing myopericarditis compared to the group of vaccinated individuals without any complications. Hence, even though preclinical evidence linked VEGF-A to the potential risk of some cardiac complications, such as arrhythmia [32], the real role of this mediator in post-vaccine cardiomyopathy remains undetermined. Interestingly, a recent Israeli cohort study examined 951 patients infected with SARS-CoV-2 and found that post-acute COVID-19 symptoms (fatigue, headache, limb weakness, and muscle pain) were lower in the vaccinated compared to the unvaccinated individuals [65]. These results could be due to a lower cytopathic effect of the virus or a more limited inflammatory response during infection in vaccinated subjects compared with unvaccinated subjects, although they could also reflect the antinociceptive function of the S protein [18].

Although current knowledge on circulating VEGF-A levels in COVID-19 vaccine recipients is limited to one study [64], the RS3PE syndrome has been described in two case reports as a consequence of vaccination, suggesting that an increase in this mediator may occur in a proportion of vaccinated individuals [66][67].

A number of studies have also demonstrated an association between COVID-19 vaccines and the risk of small fiber neuropathy (SFN) [68][69][70][71]. This is a clinical entity characterized by quantitative or qualitative damage to the small somatic and autonomic Aδ and C fibers, manifested by spontaneous pain, allodynia, hyperesthesia, or various autonomic dysfunctions [72]. In 50% of cases, the underlying cause is unknown and the disease is referred to as idiopathic; in the remaining cases, it may be the result of diabetes and other medical conditions. The occurrence of SFN has also been observed in SARS-CoV-2-infected patients, in whom it may accompany or follow acute symptoms of COVID-19 [73][74][75][76][77]. SARS-CoV-2 infection and COVID-19 vaccines may induce SFN via an immunological mechanism involving the proliferation of autoreactive T and B cells during seroconversion. Indeed, most reports describe the onset of SFN weeks after SARS-CoV-2 infection or vaccination, consistent with the activation of the adaptive immune response. Symptoms occurring within a week have been attributed to unmasking or flare-up of preexisting autoimmune or neurological diseases [69][77]. Conversely, there is still uncertainty about the role of the NRP-1/VEGF-A complex in the development of SFN. A study of skin punch biopsies from patients with diabetes-related SFN reported that the altered epidermal expression of NRP-1 may contribute to neuropathic pain and other neurological symptoms via the semaphorin-3A-mediated inhibition of C fiber sprouting and regeneration [78]. Other studies in diabetic animal models suggest that the *VEGF* gene transfer may improve SFN by increasing vascularization of nerves via the vasa nervorum [79]. The interplay of NRP-1, VEGF-Rs, and VEGF-A in nerves and blood vessels makes the association between SFN developing after COVID-19 or COVID-19 vaccination and increased VEGF-A levels plausible, but further research is needed.

References

1. Talotta, R.; Robertson, E. Autoimmunity as the Comet Tail of COVID-19 Pandemic. World J. Clin. Cases 2020, 8, 3621–3644.
2. Lechien, J.R.; Chiesa-Estomba, C.M.; Place, S.; Van Laethem, Y.; Cabaraux, P.; Mat, Q.; Huet, K.; Plzak, J.; Horoi, M.; Hans, S.; et al. Clinical and Epidemiological Characteristics of 1420 European Patients with Mild-to-Moderate Coronavirus Disease 2019. J. Intern. Med. 2020, 288, 335–344.
3. Stokes, E.K.; Zambrano, L.D.; Anderson, K.N.; Marder, E.P.; Raz, K.M.; El Burai Felix, S.; Tie, Y.; Fullerton, K.E. Coronavirus Disease 2019 Case Surveillance—United States, January 22–May 30 2020. MMWR Morb. Mortal. Wkly. Rep. 2020, 69, 759–765.
4. Long, B.; Carius, B.M.; Chavez, S.; Liang, S.Y.; Brady, W.J.; Koyfman, A.; Gottlieb, M. Clinical Update on COVID-19 for the Emergency Clinician: Presentation and Evaluation. Am. J. Emerg. Med. 2022, 54, 46–57.
5. Ma, Z.; Yang, K.Y.; Huang, Y.; Lui, K.O. Endothelial Contribution to COVID-19: An Update on Mechanisms and Therapeutic Implications. J. Mol. Cell. Cardiol. 2022, 164, 69–82.
6. Sulli, A.; Gotelli, E.; Bica, P.F.; Schiavetti, I.; Pizzorni, C.; Aloè, T.; Grosso, M.; Barisione, E.; Paolino, S.; Smith, V.; et al. Detailed Videocapillaroscopic Microvascular Changes Detectable in Adult COVID-19 Survivors. Microvasc. Res. 2022, 142, 104361.
7. Çakmak, F.; Demirbuga, A.; Demirkol, D.; Gümüş, S.; Torun, S.H.; Kayaalp, G.K.; Ömeroglu, R.E.; Somer, A.; Uysalol, M.; Yıldız, R.; et al. Nailfold Capillaroscopy: A Sensitive Method for Evaluating Microvascular Involvement in Children with SARS-CoV-2 Infection. Microvasc. Res. 2021, 138, 104196.
8. Natalello, G.; De Luca, G.; Gigante, L.; Campochiaro, C.; De Lorenzis, E.; Verardi, L.; Paglionico, A.; Petricca, L.; Martone, A.M.; Calvisi, S.; et al. Nailfold Capillaroscopy Findings in Patients with Coronavirus Disease 2019: Broadening the Spectrum of COVID-19 Microvascular Involvement. Microvasc. Res. 2021, 133, 104071.
9. Rovas, A.; Osiaevi, I.; Buscher, K.; Sackarnd, J.; Tepasse, P.R.; Fobker, M.; Kühn, J.; Braune, S.; Göbel, U.; Thölking, G.; et al. Microvascular Dysfunction in COVID-19: The MYSTIC Study. Angiogenesis 2021, 24, 145–157.
10. Lim, J.; Puan, K.J.; Wang, L.W.; Teng, K.W.W.; Loh, C.Y.; Tan, K.P.; Carissimo, G.; Chan, Y.H.; Poh, C.M.; Lee, C.Y.P.; et al. Data-Driven Analysis of COVID-19 Reveals Persistent Immune Abnormalities in Convalescent Severe Individuals. Front. Immunol. 2021, 12, 710217.
11. Medeiros, T.; Guimarães, G.M.C.; Carvalho, F.R.; Alves, L.S.; Faustino, R.; Campi-Azevedo, A.C.; Peruhype-Magalhães, V.; Teixeira-Carvalho, A.; de Souza Gomes, M.; Rodrigues do Amaral, L.; et al. Acute Kidney Injury Associated to COVID-19 Leads to a Strong Unbalance of Circulant Immune Mediators. Cytokine 2022, 157, 155974.
12. Zhou, Y.; Zhu, X.; Cui, H.; Shi, J.; Yuan, G.; Shi, S.; Hu, Y. The Role of the VEGF Family in Coronary Heart Disease. Front. Cardiovasc. Med. 2021, 8, 738325.
13. Ackermann, M.; Verleden, S.E.; Kuehnel, M.; Haverich, A.; Welte, T.; Laenger, F.; Vanstapel, A.; Werlein, C.; Stark, H.; Tzankov, A.; et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19. N. Engl. J. Med. 2020, 383, 120–128.
14. Meini, S.; Giani, T.; Tascini, C. Intussusceptive Angiogenesis in COVID-19: Hypothesis on the Significance and Focus on the Possible Role of FGF2. Mol. Biol. Rep. 2020, 47, 8301–8304.
15. Smadja, D.M.; Mentzer, S.J.; Fontenay, M.; Laffan, M.A.; Ackermann, M.; Helms, J.; Jonigk, D.; Chocron, R.; Pier, G.B.; Gendron, N.; et al. COVID-19 Is a Systemic Vascular Hemopathy: Insight for Mechanistic and Clinical Aspects. Angiogenesis 2021, 24, 755–788.
16. Mayi, B.S.; Leibowitz, J.A.; Woods, A.T.; Ammon, K.A.; Liu, A.E.; Raja, A. The Role of Neuropilin-1 in COVID-19. PLoS Pathog. 2021, 17, e1009153.
17. Alipoor, S.D.; Mirsaeidi, M. SARS-CoV-2 Cell Entry beyond the ACE2 Receptor. Mol. Biol. Rep. 2022, 49, 10715–10727.
18. Moutal, A.; Martin, L.F.; Boinon, L.; Gomez, K.; Ran, D.; Zhou, Y.; Stratton, H.J.; Cai, S.; Luo, S.; Gonzalez, K.B.; et al. SARS-CoV-2 Spike Protein Co-Opts VEGF-A/Neuropilin-1 Receptor Signaling to Induce Analgesia. Pain 2021, 162, 243–252.
19. Simonetti, B.; Daly, J.L.; Simón-Gracia, L.; Klein, K.; Weeratunga, S.; Antón-Plágaro, C.; Tobi, A.; Hodgson, L.; Lewis, P.A.; Heesom, K.J.; et al. ESCPE-1 Mediates Retrograde Endosomal Sorting of the SARS-CoV-2 Host Factor Neuropilin-1. Proc. Natl. Acad. Sci. USA 2022, 119, e2201980119.
20. Gao, J.; Mei, H.; Sun, J.; Li, H.; Huang, Y.; Tang, Y.; Duan, L.; Liu, D.; Pang, Y.; Wang, Q.; et al. Neuropilin-1-Mediated SARS-CoV-2 Infection in Bone Marrow-Derived Macrophages Inhibits Osteoclast Differentiation. Adv. Biol. 2022, 6, 220

0007.

21. Benedetti, F.; Silvestri, G.; Mavian, C.; Weichseldorfer, M.; Munawwar, A.; Cash, M.N.; Dulcey, M.; Vittor, A.Y.; Ciccozzi, M.; Salemi, M.; et al. Comparison of Sars-Cov-2 Receptors Expression in Primary Endothelial Cells and Retinoic Acid-Differentiated Human Neuronal Cells. Viruses 2021, 13, 2193.
22. Zhang, F.; Li, W.; Feng, J.; da Silva, S.R.; Ju, E.; Zhang, H.; Chang, Y.; Moore, P.S.; Guo, H.; Gao, S.J. SARS-CoV-2 P seudovirus Infectivity and Expression of Viral Entry-Related Factors ACE2, TMPRSS2, Kim-1, and NRP-1 in Human Ce lls from the Respiratory, Urinary, Digestive, Reproductive, and Immune Systems. J. Med. Virol. 2021, 93, 6671–6685.
23. Eldrid, C.; Zloh, M.; Fotinou, C.; Yelland, T.; Yu, L.; Mota, F.; Selwood, D.L.; Djordjevic, S. VEGFA, B, C: Implications of the C-Terminal Sequence Variations for the Interaction with Neuropilins. Biomolecules 2022, 12, 372.
24. Li, Z.-L.; Buck, M. Neuropilin-1 Assists SARS-CoV-2 Infection by Stimulating the Separation of Spike Protein S1 and S 2. Biophys. J. 2021, 120, 2828–2837.
25. Baindara, P.; Roy, D.; Mandal, S.M.; Schrum, A.G. Conservation and Enhanced Binding of SARS-CoV-2 Omicron Spike Protein to Coreceptor Neuropilin-1 Predicted by Docking Analysis. Infect. Dis. Rep. 2022, 14, 243–249.
26. Kong, W.; Montano, M.; Corley, M.J.; Helmy, E.; Kobayashi, H.; Kinisu, M.; Suryawanshi, R.; Luo, X.; Royer, L.A.; Roa n, N.R.; et al. Neuropilin-1 Mediates SARS-CoV-2 Infection of Astrocytes in Brain Organoids, Inducing Inflammation Le ading to Dysfunction and Death of Neurons. mBio 2022, e0230822.
27. Jobe, A.; Vijayan, R. Neuropilins: C-End Rule Peptides and Their Association with Nociception and COVID-19. Comput. Struct. Biotechnol. J. 2021, 19, 1889–1895.
28. Saleki, K.; Banazadeh, M.; Miri, N.S.; Azadmehr, A. Triangle of Cytokine Storm, Central Nervous System Involvement, and Viral Infection in COVID-19: The Role of SFasL and Neuropilin-1. Rev. Neurosci. 2022, 33, 147–160.
29. Chaudhary, J.K.; Yadav, R.; Chaudhary, P.K.; Maurya, A.; Roshan, R.; Azam, F.; Mehta, J.; Handu, S.; Prasad, R.; Jain, N.; et al. Host Cell and SARS-CoV-2-Associated Molecular Structures and Factors as Potential Therapeutic Targets. C ells 2021, 10, 2427.
30. Needham, E.J.; Chou, S.H.Y.; Coles, A.J.; Menon, D.K. Neurological Implications of COVID-19 Infections. Neurocrit. Ca re 2020, 32, 667–671.
31. Tangos, M.; Budde, H.; Kolijn, D.; Sieme, M.; Zhazykbayeva, S.; Lódi, M.; Herwig, M.; Gömöri, K.; Hassoun, R.; Robins on, E.L.; et al. SARS-CoV-2 Infects Human Cardiomyocytes Promoted by Inflammation and Oxidative Stress. Int. J. Ca rdiol. 2022, 362, 196–205.
32. Mezache, L.; Struckman, H.L.; Greer-Short, A.; Baine, S.; Györke, S.; Radwański, P.B.; Hund, T.J.; Veeraraghavan, R. Vascular Endothelial Growth Factor Promotes Atrial Arrhythmias by Inducing Acute Intercalated Disk Remodeling. Sci. Rep. 2020, 10, 20463.
33. Choreño-Parra, J.A.; Jiménez-Álvarez, L.A.; Cruz-Lagunas, A.; Rodríguez-Reyna, T.S.; Ramírez-Martínez, G.; Sandov al-Vega, M.; Hernández-García, D.L.; Choreño-Parra, E.M.; Balderas-Martínez, Y.I.; Martinez-Sánchez, M.E.; et al. Clin ical and Immunological Factors That Distinguish COVID-19 From Pandemic Influenza A(H1N1). Front. Immunol. 2021, 12, 593595.
34. Zhang, Z.Z.; Chen, D.P.; Liu, Q.B.; Gan, C.; Jiang, L.; Zhu, K.; Zhang, X.Y.; Xu, H.M.; Huang, A.L.; Long, Q.X.; et al. Cli nical Features of Chinese Children with COVID-19 and Other Viral Respiratory Infections. Pediatr. Pulmonol. 2022, 57, 49–56.
35. Pang, J.; Xu, F.; Aondio, G.; Li, Y.; Fumagalli, A.; Lu, M.; Valmadre, G.; Wei, J.; Bian, Y.; Canesi, M.; et al. Efficacy and Tolerability of Bevacizumab in Patients with Severe COVID-19. Nat. Commun. 2021, 12, 814.
36. Perez-Miller, S.; Patek, M.; Moutal, A.; Duran, P.; Cabel, C.R.; Thorne, C.A.; Campos, S.K.; Khanna, R. Novel Compou nds Targeting Neuropilin Receptor 1 with Potential to Interfere with SARS-CoV-2 Virus Entry. ACS Chem. Neurosci. 202 1, 12, 1299–1312.
37. Charoute, H.; Elkarhat, Z.; Elkhattabi, L.; El Fahime, E.; Oukkache, N.; Rouba, H.; Barakat, A. Computational Screenin g of Potential Drugs against COVID-19 Disease: The Neuropilin-1 Receptor as Molecular Target. VirusDisease 2022, 3 3, 23–31.
38. Perez-Miller, S.; Patek, M.; Moutal, A.; Cabel, C.R.; Thorne, C.A.; Campos, S.K.; Khanna, R. In Silico Identification and Validation of Inhibitors of the Interaction between Neuropilin Receptor 1 and SARS-CoV-2 Spike Protein. bioRxiv 2020.
39. Yong, S.J. Long COVID or Post-COVID-19 Syndrome: Putative Pathophysiology, Risk Factors, and Treatments. Infect. Dis. 2021, 53, 737–754.
40. Joshee, S.; Vatti, N.; Chang, C. Long-Term Effects of COVID-19. Mayo Clin. Proc. 2022, 97, 579–599.

41. Blomberg, B.; Mohn, K.G.I.; Brokstad, K.A.; Zhou, F.; Linchausen, D.W.; Hansen, B.A.; Lartey, S.; Onyango, T.B.; Kuwelker, K.; Sævik, M.; et al. Long COVID in a Prospective Cohort of Home-Isolated Patients. Nat. Med. 2021, 27, 1607–1613.

42. Sahanic, S.; Tymoszuk, P.; Ausserhofer, D.; Rass, V.; Pizzini, A.; Nordmeyer, G.; Hüfner, K.; Kurz, K.; Weber, P.M.; Sonnweber, T.; et al. Phenotyping of Acute and Persistent Coronavirus Disease 2019 Features in the Outpatient Setting: Exploratory Analysis of an International Cross-Sectional Online Survey. Clin. Infect. Dis. 2022, 75, e418–e431.

43. Carfì, A.; Bernabei, R.; Landi, F. Persistent Symptoms in Patients after Acute COVID-19. JAMA—J. Am. Med. Assoc. 2020, 324, 603–605.

44. Batiha, G.E.-S.; Al-kuraishy, H.M.; Al-Gareeb, A.I.; Welson, N.N. Pathophysiology of Post-COVID Syndromes: A New Perspective. Virol. J. 2022, 19, 158.

45. Torres-Ruiz, J.; Lomelín-Gascón, J.; Lira-Luna, J.; Pérez-Fragoso, A.; Tapia-Conyer, R.; Nuñez-Aguirre, M.; Alcalá-Carmona, B.; Absalón-Aguilar, A.; Maravillas-Montero, J.L.; Mejía-Domínguez, N.R.; et al. FANSY POSTCOV: A Composite Clinical Immunological Predictive Index for Post-COVID-19 Syndrome Unveils Distinctive Features in a Cohort Study of Mild to Critical Patients. Clin. Transl. Med. 2021, 11, e623.

46. Du, J.; Wei, L.; Li, G.; Hua, M.; Sun, Y.; Wang, D.; Han, K.; Yan, Y.; Song, C.; Song, R.; et al. Persistent High Percentage of HLA-DR+CD38high CD8+ T Cells Associated With Immune Disorder and Disease Severity of COVID-19. Front. Immunol. 2021, 12, 735125.

47. Bobcakova, A.; Petriskova, J.; Vysehradsky, R.; Kocan, I.; Kapustova, L.; Barnova, M.; Diamant, Z.; Jesenak, M. Immune Profile in Patients With COVID-19: Lymphocytes Exhaustion Markers in Relationship to Clinical Outcome. Front. Cell. Infect. Microbiol. 2021, 11, 646688.

48. Bobcakova, A.; Barnova, M.; Vysehradsky, R.; Petriskova, J.; Kocan, I.; Diamant, Z.; Jesenak, M. Activated CD8+CD38+ Cells Are Associated With Worse Clinical Outcome in Hospitalized COVID-19 Patients. Front. Immunol. 2022, 13, 861666.

49. Garner, L.C.; Klenerman, P.; Provine, N.M. Insights into Mucosal-Associated Invariant T Cell Biology from Studies of Invariant Natural Killer T Cells. Front. Immunol. 2018, 9, 1478.

50. Maloney, J.P.; Gao, L. Proinflammatory Cytokines Increase Vascular Endothelial Growth Factor Expression in Alveolar Epithelial Cells. Mediat. Inflamm. 2015, 2015, 387842.

51. Arslan, N.G.; Aksakal, Ş.; Yılmam, İ.; Görgün, S. VEGF, IL-17 and IgG4 Levels of Patients with Lung Sequelae in Post-COVID-19 Period. Tuberk Toraks 2022, 70, 179–186.

52. Bonny, T.S.; Patel, E.U.; Zhu, X.; Bloch, E.M.; Grabowski, M.K.; Abraham, A.G.; Littlefield, K.; Shrestha, R.; Benner, S.E.; Laeyendecker, O.; et al. Cytokine and Chemokine Levels in Coronavirus Disease 2019 Convalescent Plasma. Open Forum Infect. Dis. 2021, 8, ofaa574.

53. Chi, Y.; Ge, Y.; Wu, B.; Zhang, W.; Wu, T.; Wen, T.; Liu, J.; Guo, X.; Huang, C.; Jiao, Y.; et al. Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China. J. Infect. Dis. 2020, 222, 746–754.

54. Velikova, T.; Georgiev, T. SARS-CoV-2 Vaccines and Autoimmune Diseases amidst the COVID-19 Crisis. Rheumatol. Int. 2021, 41, 509–518.

55. European Medicines Agency Safety of COVID-19 Vaccines. Available online: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-COVID-19/treatments-vaccines/vaccines-COVID-19/safety-COVID-19-vaccines (accessed on 13 October 2022).

56. EudraVigilance—European Database of Suspected Adverse Drug Reaction Reports. Available online: https://www.adrreports.eu/en/search_subst.html# (accessed on 13 October 2022).

57. SeyedAlinaghi, S.; Karimi, A.; Pashaei, Z.; Afzalian, A.; Mirzapour, P.; Ghorbanzadeh, K.; Ghasemzadeh, A.; Dashti, M.; Nazarian, N.; Vahedi, F.; et al. Safety and Adverse Events Related to COVID-19 MRNA Vaccines; a Systematic Review. Arch. Acad. Emerg. Med. 2022, 10, e41.

58. Rabail, R.; Ahmed, W.; Ilyas, M.; Rajoka, M.S.R.; Hassoun, A.; Khalid, A.R.; Khan, M.R.; Aadil, R.M. The Side Effects and Adverse Clinical Cases Reported after COVID-19 Immunization. Vaccines 2022, 10, 488.

59. Garg, R.K.; Paliwal, V.K. Spectrum of Neurological Complications Following COVID-19 Vaccination. Neurol. Sci. 2021, 43, 3–40.

60. Patone, M.; Mei, X.W.; Handunnetthi, L.; Dixon, S.; Zaccardi, F.; Shankar-Hari, M.; Watkinson, P.; Khunti, K.; Harnden, A.; Coupland, C.A.C.; et al. Risks of Myocarditis, Pericarditis, and Cardiac Arrhythmias Associated with COVID-19 Vaccination or SARS-CoV-2 Infection. Nat. Med. 2021, 28, 410–422.

61. Allahyari, F.; Molaee, H.; Hosseini Nejad, J. COVID-19 Vaccines and Neurological Complications: A Systematic Review. Z. Naturforsch. C 2022.

62. Roberts, K.; Sidhu, N.; Russel, M.; Abbas, M.J. Psychiatric Pathology Potentially Induced by COVID-19 Vaccine. Prog. Neurol. Psychiatry 2021, 25, 8–10.

63. Escudero, C.; Prieto-Montaño, P.; Audicana, M.T. Adverse Reactions to Anti-Infective Vaccines: An Emerging Problem i n the COVID-19 Era. Curr. Treat. Options Allergy 2022, 9, 250–272.

64. Won, T.; Gilotra, N.A.; Wood, M.K.; Hughes, D.M.; Talor, M.V.; Lovell, J.; Milstone, A.M.; Steenbergen, C.; Čiháková, D. Increased Interleukin 18-Dependent Immune Responses Are Associated With Myopericarditis After COVID-19 MRNA V accination. Front. Immunol. 2022, 13, 851620.

65. Kuodi, P.; Gorelik, Y.; Zayyad, H.; Wertheim, O.; Wiegler, K.B.; Abu Jabal, K.; Dror, A.A.; Nazzal, S.; Glikman, D.; Edelst ein, M. Association between BNT162b2 Vaccination and Reported Incidence of Post-COVID-19 Symptoms: Cross-Sect ional Study 2020-21, Israel. NPJ Vaccines 2022, 7, 101.

66. Parperis, K.; Constantinou, M. Remitting Seronegative Symmetrical Synovitis with Pitting Oedema Following BNT162b 2 MRNA COVID-19 Vaccination. BMJ Case Rep. 2021, 14, e244479.

67. Arino, H.; Muramae, N.; Okano, M.; Mori, K.; Otsui, K.; Sakaguchi, K. Acute Onset of Remitting Seronegative Symmetri cal Synovitis with Pitting Edema (RS3PE) Two Weeks after COVID-19 Vaccination with MRNA-1273 with Possible Activ ation of Parvovirus B19: A Case Report With Literature Review. Cureus 2022, 14, e24952.

68. Khokhar, F.; Khan, A.; Hussain, Z.; Yu, J. Small Fiber Neuropathy Associated with the Moderna SARS-CoV-2 Vaccine. Cureus 2022, 14, e25969.

69. Watad, A.; De Marco, G.; Mahajna, H.; Druyan, A.; Eltity, M.; Hijazi, N.; Haddad, A.; Elias, M.; Zisman, D.; Naffaa, M.E.; et al. Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following Mrna/Dna Sars-Cov-2 Vaccina tion. Vaccines 2021, 9, 435.

70. Schelke, M.W.; Barcavage, S.; Lampshire, E.; Brannagan, T.H. Post–COVID-19 vaccine small-fiber neuropathy and tin nitus treated with plasma exchange. Muscle Nerve 2022, 66, E21–E23.

71. Abbott, M.G.; Allawi, Z.; Hofer, M.; Ansorge, O.; Brady, S.; Fadic, R.; Torres, G.; Knight, R.; Calvo, M.; Bennett, D.L.H.; et al. Acute small fiber neuropathy after Oxford-AstraZeneca ChAdOx1-S vaccination: A report of three cases and revie w of the literature. J. Peripher. Nerv. Syst. 2022, 27, 325–329.

72. Hovaguimian, A.; Gibbons, C.H. Diagnosis and Treatment of Pain in Small-Fiber Neuropathy. Curr. Pain Headache Re p. 2011, 15, 193–200.

73. Abrams, R.M.C.; Simpson, D.M.; Navis, A.; Jette, N.; Zhou, L.; Shin, S.C. Small Fiber Neuropathy Associated with SAR S-CoV-2 Infection. Muscle Nerve 2022, 65, 440–443.

74. Agnihotri, S.P.; Luis, C.V.S.; Kazamel, M. Autonomic Neuropathy as Post-Acute Sequela of SARS-CoV-2 Infection: A C ase Report. J. Neurovirol. 2022, 28, 158–161.

75. Novak, P. Post COVID-19 Syndrome Associated with Orthostatic Cerebral Hypoperfusion Syndrome, Small Fiber Neur opathy and Benefit of Immunotherapy: A Case Report. Eneurologicalsci 2020, 21, 100276.

76. Oaklander, A.L.; Mills, A.J.; Kelley, M.; Toran, L.S.; Smith, B.; Dalakas, M.C.; Nath, A. Peripheral Neuropathy Evaluation s of Patients With Prolonged Long COVID. Neurol. Neuroimmunol. Neuroinflamm. 2022, 9, e1146.

77. Shouman, K.; Vanichkachorn, G.; Cheshire, W.P.; Suarez, M.D.; Shelly, S.; Lamotte, G.J.; Sandroni, P.; Benarroch, E. E.; Berini, S.E.; Cutsforth-Gregory, J.K.; et al. Autonomic Dysfunction Following COVID-19 Infection: An Early Experien ce. Clin. Auton. Res. 2021, 31, 385–394.

78. Van Acker, N.; Ragé, M.; Vermeirsch, H.; Schrijvers, D.; Nuydens, R.; Byttebier, G.; Timmers, M.; De Schepper, S.; Stre ffer, J.; Andries, L.; et al. NRP-1 Receptor Expression Mismatch in Skin of Subjects with Experimental and Diabetic Sm all Fiber Neuropathy. PLoS ONE 2016, 11, e0161441.

79. Schratzberger, P.; Walter, D.H.; Rittig, K.; Bahlmann, F.H.; Pola, R.; Curry, C.; Silver, M.; Krainin, J.G.; Weinberg, D.H.; Ropper, A.H.; et al. Reversal of Experimental Diabetic Neuropathy by VEGF Gene Transfer. J. Clin. Investig. 2001, 107, 1083–1092.