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Review

COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences

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ABSTRACT

Worldwide there have been over 760 million confirmed coronavirus disease 2019 (COVID-19) cases, and over 13 billion COVID-19 vaccine doses have been administered as of April 2023, according to the World Health Organization. An infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to an acute disease, i.e. COVID-19, but also to a post-acute COVID-19 syndrome (PACS, "long COVID"). Currently, the side effects of COVID-19 vaccines are increasingly being noted and studied. Here, we summarise the currently available indications and discuss our conclusions that (i) these side effects have specific similarities and differences to acute COVID-19 and PACS, that (ii) a new term should be used to refer to these side effects (post-COVID-19 vaccination syndrome, PCVS, colloquially "post-COVIDvac-syndrome"), and that (iii) there is a need to distinguish between acute COVID-19 vaccination syndrome (ACVS) and post-acute COVID-19 vaccination syndrome (PACVS) – in analogy to acute COVID-19 and PACS ("long COVID"). Moreover, we address mixed forms of disease caused by natural SARS-CoV-2 infection and COVID-19 vaccination. We explain why it is important for medical diagnosis, care and research to use the new terms (PCVS, ACVS and PACVS) in order to avoid confusion and misinterpretation of the underlying causes of disease and to enable optimal medical therapy. We do not recommend to use the term "Post-Vac-Syndrome" as it is imprecise. The article also serves to address the current problem of "medical gaslighting" in relation to PACS and PCVS by raising awareness among the medical professionals and supplying appropriate terminology for disease.

1. Introduction

Starting with the first cases reported in China in December 2019 [1,2], as of April 2023, there have been over 760 million confirmed coronavirus disease 2019 (COVID-19) cases (generally defined as positive tests for the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) worldwide, and over 13 billion COVID-19 vaccine doses have been administered, according to the World Health Organization (WHO).

In most people, COVID-19 disease progresses without major complications or escalation to a more severe course. Disease severity is associated with several factors [3], including older age and pre-existing health conditions like diabetes, arterial hypertension and obesity [4] as well as the individual vitamin D level [5–7], pre-existing immunity to circulating human coronaviruses before the SARS-CoV-2 pandemic [8], previous SARS-CoV-2 infection [9,10], co-infections (e.g. with Epstein-Barr virus) [11,12] and gut microbial dysbiosis [13]. From an epidemiological point of view, environmental factors including air pollution, climate and chemical exposures also play a role in relation to the pandemic [14]. The COVID-19 case fatality rate is mainly age-dependent [15] and generally fell over the course of the pandemic parallel to the occurrence of novel SARS-CoV-2 variants [16,17].

After the acute phase of a SARS-CoV-2 infection, a proportion of those infected show persistent somatic symptoms over weeks, months and even years, including general tiredness, muscle pain, difficulties when breathing, tingling extremities, chest pain or a lump in the throat [18]. This post-COVID-19 condition is termed "long COVID" and is also referred to as "post-acute sequelae of COVID-19", "post-COVID-19 syndrome", "post-COVID conditions" or post-acute COVID-19 syndrome (PACS) (a term we recommend and use in this work). PACS "has a

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multifactorial nature and multiple pathophysiological factors at play" [19] and is a "multisystemic illness encompassing ME/CFS [myalgic encephalomyelitis/chronic fatigue syndrome], dysautonomia, impacts on multiple organ systems, and vascular and clotting abnormalities" [20] whereby specific types of PACS can be defined depending, for example, on the type of symptoms [21–24], severity of symptoms [25] or the timeline of the symptoms' appearance [26,27]. The probability of developing PACS depends on many factors, including the type of SARS-CoV-2 variant infected with. For example, the odds of PACS development is reduced with the SARS-CoV-2 omicron variant, compared to the delta variant [28]. According to data from the UK (December 2021 to March 2022, n = 56003 adults), 4.5% people experienced PACS (after infection with the Omicron variant), and 10.8% (after infection with the Delta variant) [28].

While according to the WHO more than 350 COVID-19 vaccines are currently in preclinical or clinical development (January 2023), ten have already been approved by the WHO for global use. The vaccines can be divided into four different types: "inactivated virus vaccines (Sinopharm's Covilo, Sinovac's CoronaVac, and Bharat Biotech's Covaxin), messenger RNA (mRNA) vaccines (Moderna's Spikevax mRNA-1273 and Pfizer–BioNTech's Comirnaty BNT162b2), adenovirus vector–based vaccines (AstraZeneca's Vaxzevria and Covishield ChAdOx1 and Johnson & Johnson–Janssen's Ad26. COV2. S), and adjuvanted protein vaccines (Novavax's Nuvaxovid and Covovax NVX-CoV2373)." [29]. In addition, there are other vaccines in use that have been approved by other regulatory authorities (e.g. the self-amplifying COVID-19 mRNA vaccine GEMCOVAC-19 and the DNA plasmid based COVID-19 vaccine, both approved for emergency use in India).

The global COVID-19 vaccination campaign started in December 2020 and is ongoing. Currently the global COVID-19 vaccine campaign faces two challenges: a decrease in the vaccine's efficacy in preventing a more severe COVID-19 disease course and/or death, and in parallel an increased recognition and awareness in relation to possible problems with the vaccine's safety.

While a recent mathematical modelling study estimated that the global COVID-19 vaccination campaign prevented 14.4 million deaths from COVID-19 in 185 countries and territories [30] (but see also a critical evaluation of the methodology of this study [31]), the efficacy of the available COVID-19 vaccines is declining as novel SARS-CoV-2 variants emerge [32,33]. The current use of a bivalent booster for the two available mRNA COVID-19 vaccines (including the wild-type (Wuhan-Hu-1) and Omicron (BA.1) SARS-CoV-2 spike messenger RNAs) "likely only represents a temporizing measure until variants emerge", and the "need to repeatedly vaccinate at-risk populations, combined with the documented emergence of a new dominant SARS-CoV-2 variant approximately every 3–4 months, presents a public health dilemma." [34]. In addition, the "long-term consequences of ongoing, repeated vaccination campaigns against COVID-19 for viral ecology and viral mutations inducing vaccine resistance" is seen as a potential problem, and there is also the serious concern of the risk of "repeated vaccination to cause vaccine exhaustion and, consequently, reduce protection against microbial infection" [35]. Repeated vaccination with the same antigen has been shown to induce overstimulation of $CD4^+$ T cells and subsequent development of autoantibody-inducing $CD4^+$ T cells [36].

The protection gained from a COVID-19 vaccination booster dose diminishes with increasing number of booster doses received, as recently found [37]. Repeated vaccination and confrontation with novel antigen variants are associated with the immune memory phenomenon of "original antigenic sin" (leading to less efficient immune responses in comparison to the original antigen variant) and "immune imprinting" (leading to a progressively narrowed immune response towards a new antigen variant) [38]. That the "vaccine-induced immune imprinting against the S [spike] protein partially inhibits the response against the N [nucleocapsid] protein after SARS-CoV-2 infection" has been shown already [39], and a recent study came to the conclusion that "protective effects from the humoral immunity and cellular immunity established by the conventional immunization were both profoundly impaired during the extended vaccination course." [40]. Immune imprinting was also concluded to be the reason for the unexpectedly reduced efficacy of the novel bivalent COVID-19 vaccines since the "immune systems of people immunized with the bivalent vaccine, all of whom had previously been vaccinated, were primed to respond to the ancestral strain of SARS-CoV-2" [41]. Also the "antibody dependent enhancement" (ADE) mechanism becomes relevant, as demonstrated by new results showing the "possible emergence of adverse effects caused by these [antibodies] in addition to the therapeutic or preventive effect"; some sera of mRNA-vaccinated individuals were observed to "gradually exhibited dominance of ADE activity in a time-dependent manner" [42]. The recent documentation of an immunoglobulin G4 (IgG4) dominated immune response after three doses of the Pfizer BNT162b2 COVID-19 vaccine [43], possibly inducing immune tolerance [44], must also be considered in this context.

With regard to the safety of the vaccines, adverse effects following COVID-19 vaccination are increasingly being noticed and studied, including cardiovascular [45–49], neurological [50–53] as well as autoimmune and inflammatory [54–59] disorders.

Researchers and doctors around the world are confronted with patients with various symptoms after SARS-CoV-2 infection and/or COVID-19 vaccination. In the work presented here, we address the current need for appropriate medical terminology that classifies the syndromes associated with SARS-CoV-2 infection and COVID-19 vaccination, based on specific similarities and differences of these conditions.

2. The need for a new unified medical terminology: COVID-19, PACS, PCVS, ACVS and PACVS

Based on the facts summarised so far in the introduction, we hypothesise that (i) the COVID-19 vaccination side effects have specific similarities and differences to acute COVID-19 and PACS, that (ii) a new term should be used to refer to these side effects (post-COVID-19 vaccination syndrome, PCVS, colloquially "post-COVIDvac-syndrome"), and that (iii) there is a need to distinguish between an acute COVID-19 vaccination syndrome (ACVS) and a post-acute COVID-19 vaccination syndrome (PACVS) – in analogy to acute COVID-19 and PACS ("long COVID").

Fig. 1 visualises the definition of the terms. Based on this concept, the syndromes can be classified according to their cause (infection/vaccination) and according to their general temporal manifestation (acute/chronic). The transition from the acute to the chronic phase is fluid and not abrupt.

Fig. 2 visualises our concept, according to which the acute phases (COVID-19, ACVS) and the chronic phases (PACS, PACVS) of both syndrome types (infection-related and vaccination-related) show

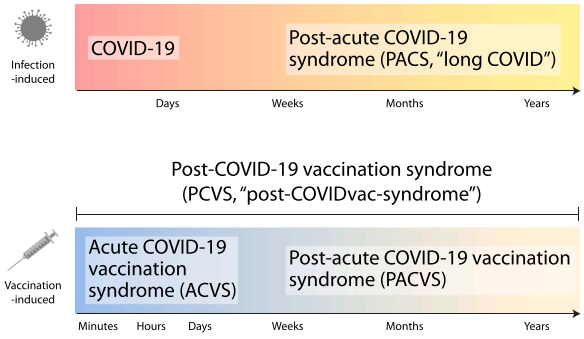


Fig. 1. Definition of the terminology of syndromes with respect to the causative factor (infection/vaccination) und their general temporal manifestation. The colour gradient shows that it is a spectrum where the initial syndrome can change to the following syndrome.

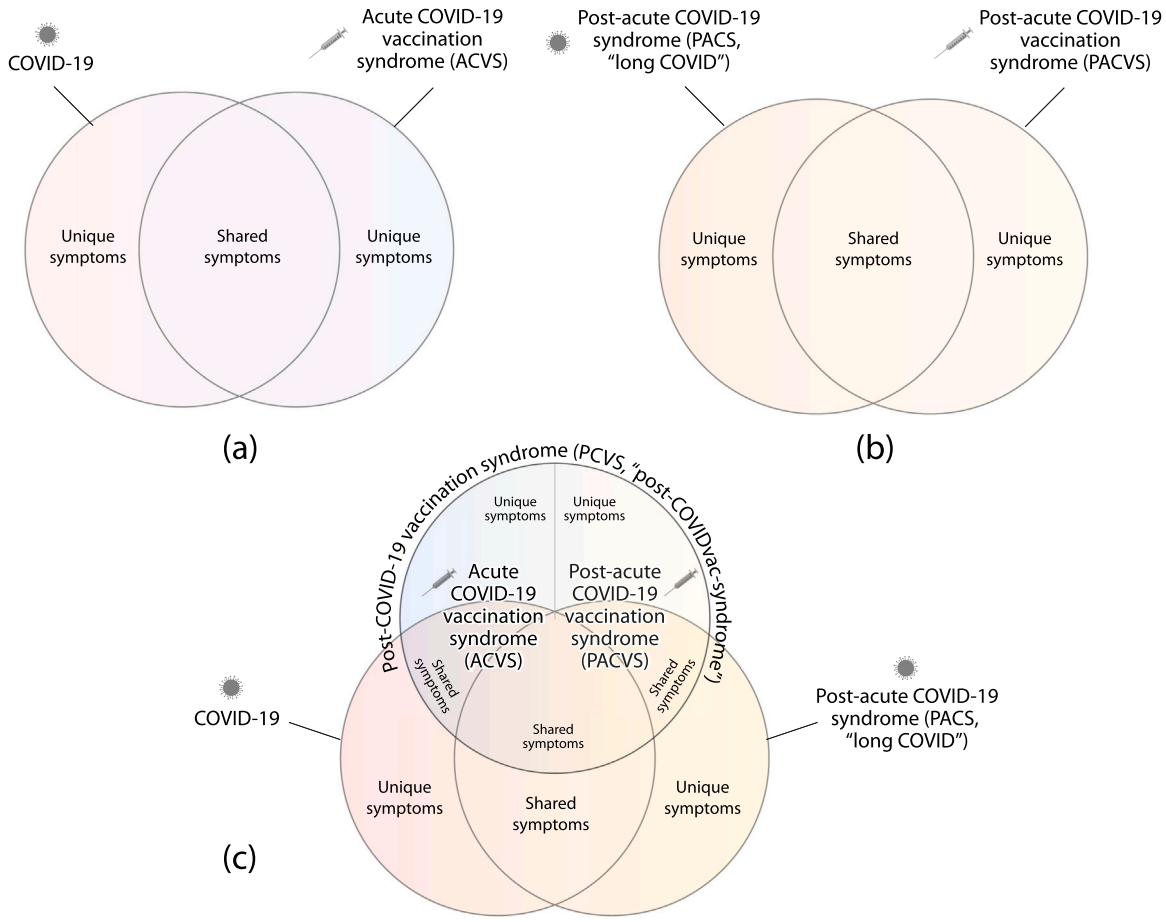


Fig. 2. Visualisation of the terminology in the form of Venn diagrams based on overlapping symptoms, in terms of (a) COVID-19 and ACVS, (b) PACS and PACVS, and (c) COVID-19, PCVS and PACS.

similarities in symptomatology, although characteristic differences also exist (Fig. 2 **(a,b)**). The entire symptom spectrum of PCVS thus has similarities but also characteristic differences to COVID-19 and PACS (Fig. 2 **(c)**).

Table 1 provides translations of the three newly defined terms into major European languages to facilitate the application of the new terms in the local language.

Table 1
The three newly defined terms for COVID-19 vaccine-induced syndromes in major European languages.

	Post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome")	**Acute COVID-19 vaccination syndrome (ACVS)**	**Post-acute COVID-19 vaccination syndrome (PACVS)**
German	Post-COVID-19-Impfsyndrom (PCIS, "Post-COVIDvac-Syndrom")	Akutes COVID-19-Impfsyndrom (ACIS)	Post-akutes COVID-19-Impfsyndrom (PACIS)
French	Syndrome post-vaccination COVID-19 (SPVC)	Syndrome aigu de vaccination COVID-19 (SAVC)	Syndrome post-aigu de vaccination COVID-19 (SPAVC)
Italian	Sindrome post vaccinazione COVID-19 (SPVC)	Sindrome acuta da vaccinazione COVID-19 (SAVC)	Sindrome post-acuta da vaccinazione COVID-19 (SPAVC)
Hispanic	Síndrome postvacunación COVID-19 (SPVC)	Síndrome agudo de vacunación COVID-19 (SACV)	Síndrome postvacunal agudo por COVID-19 (SPAVC)

3. SARS-CoV-2 infection- and COVID-19 vaccination-induced syndromes: similarities and differences

The clinical symptoms of COVID-19 depend on the disease severity and most commonly include fever, cough, fatigue and dyspnoea [60,61] while the symptoms are differentially present through the disease course [61] and, dependent on the severity of the disease, may lead to manifestation of an acute respiratory distress syndrome [62,63]. The types and severity of COVID-19 symptoms were found also to depend on the SARS-CoV-2 variant of infection [64–67].

In a subset of people infected with SARS-CoV-2 and developing COVID-19, symptoms can persist after the acute phase for months and even years [68]. Common symptoms of this post-COVID-19 condition (PACS, "long COVID") include fatigue, dyspnoea, myalgia, chest pain, cough and sputum production [69–71] but can also include ones associated with pathophysiological states and processes in all organ systems. There is therefore a clear overlap between the symptoms of COVID-19 and PACS. The number of PACS symptoms was shown to be also dependent on the type of SARS-CoV-2 variant of infection (e.g. higher number of symptoms in individuals infected with the original (Wuhan) variant compared to those with the Alpha or Delta ones [66]). For the definition of PACS, the time interval between SARS-CoV-2 infection/-COVID-19 and the duration of the subsequent symptoms is relevant as well. According to the WHO, PACS is characterized by "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation" [72]. According to the US Centers of Disease Control and Prevention (CDC) however, the symptoms need to be present for "4 weeks or more after the initial phase of infection" [73]. COVID-19 and

PACS appear to represent specific states (acute vs. chronic) in a spectrum of the disease caused by the SARS-CoV-2 infection, where the transition between COVID-19 and PACS is fluid (with the temporal boundary still defined differently) and there is an asymmetry of the two syndromes (PACS without prior SARS-CoV-2 infection: not possible; SARS-CoV-2 infection without subsequent PACS: possible). The PACS symptoms can last for years; a recent study found that "the proportion of patients with at least 1 post-COVID-19 symptom 2 years after acute infection was 59.7% for hospitalized patients and 67.5% for those not requiring hospitalization" [74]. Although PACS has unique characteristics, post-acute infection syndromes (PAIS) can also be present after other types of infections [75–79]. For example, "post-infectious fatigue" (also termed "post-infectious fatigue syndrome") and ME/CFS has been documented after infection with influenza viruses [80–82], Dengue virus [83,84], Puumala virus [85], Epstein-Barr virus [86–89], enterovirus [90], human parvovirus B19 [91], the spirochete Borrelia [92–95], bacterium *Coxiella burnetii* [96] and the protozoan Giardia [97–103]. A relatively widespread and increasingly researched PAIS is for example the "post-treatment Lyme disease syndrome" (also known as "post-Lyme syndrome") with fatigue also a key symptom [104–107]. PACS is therefore a type of PAIS. What must also be taken into account is that after acute illnesses, physical and cognitive impairments can occur, especially if intensive medical care has been provided. This phenomenon, known as "post-intensive care syndrome" (PICS) [108–112], is also relevant for PACS [113–119] (and in principle also for PACVS).

With regard to the side-effects of COVID-19 vaccinations, the most frequent ones are mild to moderate, non-serious and include fatigue, pain at the site of injection, fever, chills, muscle pain, joint pain, and headache lasting a few days [120–134], indicating generally a transient production of type I interferons as part of the immune system's reaction to a pathogen [135]. In addition, severe adverse events (side effects) can occur and the phenomenon of long-lasting non-severe side effects is reported. The symptoms a person experiences after a COVID-19 vaccination (independent of the time after vaccination and the duration of the symptoms) can be generally assigned to the newly defined PCVS ("post-COVIDvac-syndrome"). Although in most of the vaccinated people the acute symptoms after vaccination disappear after a few days, the symptoms remain for weeks or months in some. For example, Riad et al. [121] reported that 3% of the vaccine recipients experienced side effect symptoms for longer than 1 week, and 1.4% for longer than 1 month. A similar results was published by Klugar et al. [125] (4.6% for > 1 week and 0.2% > 1 month). This supports our notion that there is a need to distinguish between an acute and a chronic form of PCVS: ACVS (acute) and PACVS (chronic).

Concerning the similarity of symptoms between acute COVID-19 and ACVS, fatigue is a non-severe adverse event symptom shared by both conditions [60,136]. ACVS can manifest in different ways, with for example anaphylaxis [137–142] and vasovagal syncope/presyncope [143] that can follow immediately after vaccination. In 2021, a specific lot (41L20A) of the Moderna COVID-19 vaccine was discovered in the USA associated with a disproportionately frequent triggering of severe allergic reactions and the California Department of Public Health recommended to pause the administration of vaccines from this lot [144].

In the worst case, COVID-19 and ACVS (and PACVS) can lead to death. What distinguishes death in both cases is the timing between infection/vaccination and occurrence of death (see. Fig. 3). While the distribution of time intervals with respect to COVID-19 symptom onset to death peaks at about 1–3 weeks (depending on many factors including the SARS-CoV-2 variant of infection, age and sex of the deceased infected) [145,146] (Fig. 3**(a,b)**), the distribution of time intervals between COVID-19 vaccination and associated deaths follows a double-exponential decay function with the most cases immediately after vaccination [147] (Fig. 3**(c)**).

Severe side effects of COVID-19 vaccination have particularly an overlap with symptoms of COVID-19. For example, myocarditis and pericarditis have been found in association with COVID-19 [148–156] and COVID-19 vaccination [46,148,157–174] with the onset of cardiovascular symptoms after vaccination normally occurring a few days after vaccination [158,160–162,174,175]. While COVID-19 vaccine induced myocarditis/pericarditis generally fall in the category ACVS, cases in the category PACVS seem to occur too (e.g. 3 months after vaccination [176]). More precise data is currently virtually non-existent, as the observation period of the approval and post-marketing studies does not take this long period of time into account and as the data is also much more difficult to collect. For example, proof must be provided that the vaccination is causally responsible for the disease. This can be done, for example, through the detection of mRNA and/or spike proteins from the COVID-19 vaccine. The spike protein (but not the nucleocapsid protein)

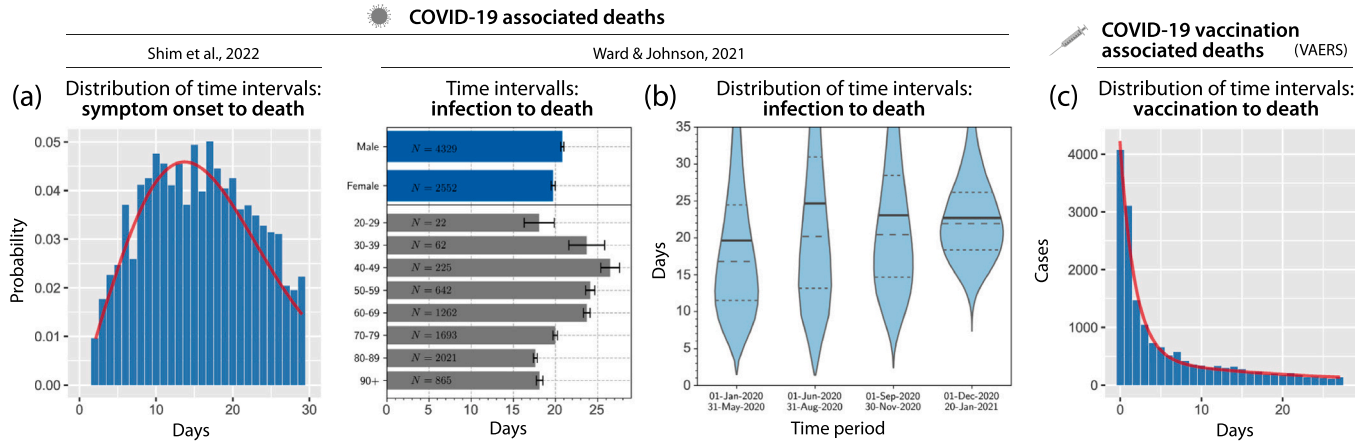


Fig. 3. Latency between COVID-19 disease onset or COVID-19 vaccination and associated death. (a) Distribution of time intervals of COVID-19 symptom onset to death ($n = 3478$, range: 1–97 days) based on data from South Korea (19 January 2020–10 January 2022, covering the phase of the pandemic where the wild-type (Wuhan-Hu-1), alpha, delta and omicron (BA.1) variants were present) [145]. A double-exponential function is fitted to the data ($r^2 = 0.9597$). (b) Distribution of time intervals between SARS-CoV-2 infection to death ($n = 63,855$) as a function of sex, age and four time periods during the pandemic based on data from the United Kingdom (1 January 2020–20 January 2021, covering the phase of the pandemic where the wild-type (Wuhan-Hu-1) and alpha variants were present) [146]. (c) Distribution of time intervals between COVID-19 vaccination and associated deaths ($n = 33,904$) according to data from the US Vaccine Adverse Event Reporting System (VAERS) (based on 1509,410 reports through January 20, 2023). The distribution follows a double-exponential decay function (red) ($r^2 = 0.9819$). However, it should be noted that there is very likely a reporting bias, i.e. the probability of reporting deaths after vaccination is higher the closer the death occurred to the time of vaccination. Therefore, it must be assumed that the exponential decline in reality is slower than the data shows.
(b) Reprinted and modified from Ward & Johnson [146], with permission from the publisher.

could be detected, for example, "within the foci of inflammation in both the brain and the heart, particularly in the endothelial cells of small blood vessels" in an individual that collapsed 2 weeks after the third dose of the COVID-19 vaccine and died 1 weeks after this incidence [177]. The SARS-CoV-2 spike protein was also detected in cardiac tissue in individuals experiencing intramyocardial inflammation after COVID-19 vaccination, including a case with symptoms 21 days after vaccination and successful mRNA detection [178]. Furthermore, the presence of the SARS-CoV-2 spike protein was found in varicella zoster virus (VZV) lesions in a patient suffering from VZV reactivation after COVID-19 vaccination [179].

Besides myocarditis/pericarditis due to SARS-CoV-2 infection/COVID-19 and COVID-19 vaccination, other severe health conditions were observed, including neurological ones and issues by the reactivation of chronic infections. For example, transverse myelitis has been documented due to COVID-19 [180–186] and COVID-19 vaccination [187–194]. In addition, VZV and herpes simplex virus, cytomegalovirus and Epstein-Barr virus reactivation was found to be possibly occurring due to COVID-19 [11,12,195–204] and COVID-19 vaccination [205–213]. The reactivation of chronic infection seems to be also associated with PACS. For example, Gold et al. found 66.7% of long COVID patients to be positive for Epstein-Barr virus reactivation (compared to 10% in control subjects) [214]. Another complication is thrombosis which has been documented in association with COVID-19 [215–229] and COVID-19 vaccination [230–233]. In case of COVID-19 vaccination, vaccine-induced immune thrombotic thrombocytopenia (VITT), which can lead to cerebral venous sinus thrombosis, has been found to be particularly associated with the adenovirus vector-based COVID-19 vaccines [234–242]. Another example are retinal artery/vein occlusions induced by SARS-CoV-2 infection [243–262] and COVID-19 vaccination [263–292], which can thus be considered part of the symptoms of COVID-19 and PCVS. Noteworthy, induced retinal artery/vein occlusions induced COVID-19 vaccination were found to be "more common than anticipated" [263]. According to a case-series by Ashkenazy et al. [245], the median time from COVID-19 diagnosis to onset of retinal vein/artery occlusion symptoms was 6.9 weeks (range: 1–13 weeks). Shorter time-spans have been documented too, e.g. 3 days [248] as well as a case of central retinal vein/artery occlusion 8 months after COVID-19 (and thus falling in the category PACS) [293]. For the case of retinal vein/artery occlusion symptoms after COVID-19 vaccination, the median time from vaccination diagnosis to onset of retinal vein/artery occlusion symptoms is significantly shorter, i.e. median 9 days (range: 15 min to 61 days) (based on the case reports cited above) with cases of fast onset of symptoms, e.g. within 15 min after vaccination [267], and late onsets in the range of 1–2 months after vaccination [269,274,288]. While most cases therefore can be classified as part of ACVS, cases of vaccine-induced central retinal vein/artery occlusion associated with PACVS can apparently happen too. The time to onset of symptoms of central retinal vein/artery occlusion is therefore one aspect that generally distinguishes SARS-CoV-2 infection- and COVID-19 vaccination-induced cases. With regard to hepatitis after COVID-19 vaccination, several cases have been reported [294–303] and vaccine SARS-CoV-2 mRNA has been found in the cytoplasm of hepathocytes in a case of COVID-19 vaccine-related hepatitis about 2 weeks after vaccination, demonstrating that "lipid nanoparticles bearing mRNA molecules encoding SARS-CoV-2 proteins can reach hepatocytes under certain circumstances and deliver mRNA in high quantities that could be used by the translational machinery of the cells to produce spike" [304].

The examples given here illustrate that COVID-19, PACS and PCVS can cause overlapping illnesses with corresponding overlapping symptoms. An important distinguishing factor seems to be the length of time between the onset of the disease/symptoms and the infection or vaccination.

With regard to the two subtypes of PCVS, the chronic form, i.e. PACVS, is increasingly being addressed and researched. In January 2022 this topic was addressed in an article in *Science* concluding that the COVID-19 vaccines "may cause rare, Long Covid–like symptoms". Different terms were used so far to refer to this conditions, including "Long post-COVID vaccination syndrome (LPCVS)" [305,306], "post-vaccination individuals with PASC-like symptoms" [307] or "autoimmune post-COVID vaccine syndromes" [57]. In German speaking countries, the term "Post-Vakzin-Syndrom" or "Post-Vac-Syndrom" (translated into "post-vac syndrome") is increasingly used in the media to refer to this condition. Also the Swiss Agency for Therapeutic Products (Swissmedic) adopted this term recently in their communications [308]. According to the innovative study of Patterson et al. [307], the predominant (non-severe) shared symptoms of PACS and PACVS are fatigue, neuropathy, brain fog and headache, where shortness of breath and loss of taste/smell is less frequent in PACVS compared to PACS. The symptoms associated with the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have a significant overlap with the symptoms of PACS [309–313] and PACVS (see for example the Individual Case Safety Reports for "chronic fatigue syndrome" associated with COVID-19 vaccination documented in the EudraVigilance European Database for Suspected Adverse Drug Reaction Reports, EDSADRR) [314]. Unfortunately, studies that explicitly investigate the occurrence of ME/CFS after COVID-19 vaccination, i.e. as part of PACVS, have not yet been published. Such studies are also urgently needed because there is already "epidemiological, clinical and experimental evidence that ME/CFS constitutes a major type of adverse effect of vaccines" [315].

According to an observation in 120 PACVS patients, the syndrome is generally characterized by fatigue with post exercise malaise, cognitive disorders, headaches, visual disturbances, joint and muscle pain, disturbances of the heat-cold regulation and sudden fast heartbeat without apparent reason (Jörg-Heiner Möller, personal communication).

With respect to fundamental pathophysiological processes underlying COVID-19, PACS and PCVS, the following aspects are of importance: autoantibodies, vascular disorders, amyloid fibrin microclots, hyperactivated platelets as well as circulating SARS-CoV-2 mRNA and proteins.

Autoantibodies were detected during the acute phase of COVID-19 [316–333], months afterwards (predicting PACS symptoms) [334,335], in PACS [336–340], and in PCVS [295,298,341–365]. In the absence of PCVS after COVID-19 vaccination, autoantibodies are generally not present [366–368]. However, in some documented cases, individuals have shown a significant increase in antiphospholipid IgM autoantibody levels, for example, after each COVID-19 vaccine dose (with accompanying transient fatigue and malaise) [368].

Endotheliitis has been documented occurring in the acute phase of COVID-19 [369–374], but also after COVID-19 vaccination [375,376]. Endotheliopathy has been also shown in PACS [377,378]. Disturbances of the blood-brain barrier integrity were found during COVID-19 [379–381] and after COVID-19 vaccination [382–384].

Amyloid fibrin microclots and hyperactivated platelets have been found in the blood plasma of patients with COVID-19 [385,386] and PACS [386–389] (see Fig. 4). No study about amyloid fibrin microclots and hyperactivated platelets in the blood of living individuals with PCVS (i.e. ACVS and PACVS) have been published yet but corresponding observations have already been made during medical examinations (Beate R. Jaeger, personal communication). Microthrombi were detected in biopsies of tissue in case of COVID-19 [390–393] and PCVS (in general in the case of VITT) [394–402].

In COVID-19 and PACS, circulating SARS-CoV-2 proteins and mRNA in the blood were detected by several groups (see Fig. 5).

Schultheiß et al. [403] found circulating SARS-CoV-2 spike protein S1 subunits in the blood plasma in 64% of unvaccinated patients with ongoing PACS (and in 35% with prior COVID-19 but no PACS) (Fig. 5 **(a)**). Interestingly, circulating spike protein S1 subunit levels showed a trend toward a positive correlation with SARS-CoV-2 nucleocapsid antibody levels.

Swank et al. [404] reported the detection of SARS-CoV-2 spike (full-length and S1 subunit) and nucleocapsid protein in in the blood

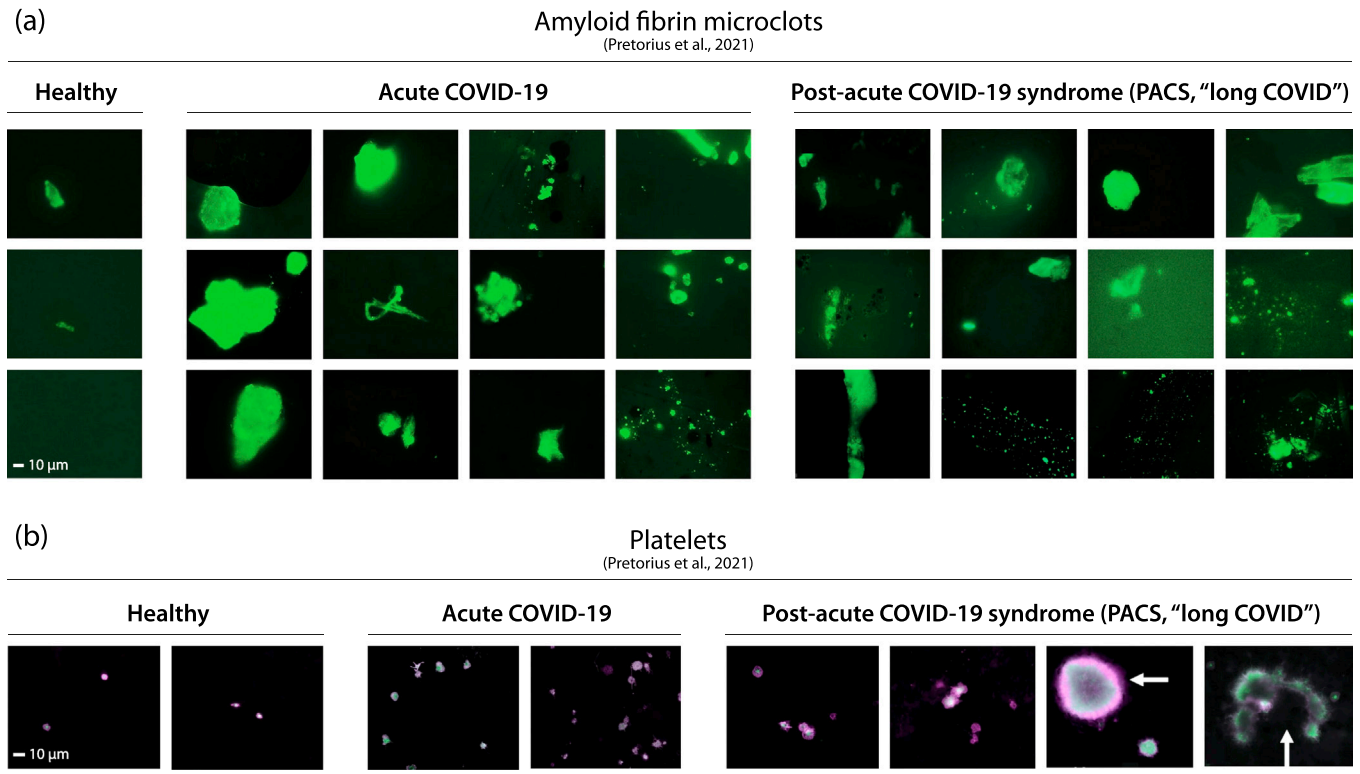


Fig. 4. (a) Amyloid fibrin microclots and (b) hyperactivated platelets in in the blood plasma (platelet poor plasma) in COVID-19 and PACS, compared to healthy controls. Aggregated platelets are indicated by white arrows. Amyloid fibrin microclots are visualized with Thioflavin T (green fluorescence) and platelets with PAC-1 (green fluorescence) and CD62P-PE (purple fluorescence).
(a) Reprinted and modified from Pretorius et al. [386], with permission from the publisher.

plasma from patients with PACS (Fig. 5**(b)**). Analyses were performed up to 12 months post PACS diagnosis and spike proteins were detected in a certain number of samples by this time. However, a drawback of the study is that 58.3% of PACS patients received one or more COVID-19 vaccinations during the respective study interval, which is a confounder.

Patterson et al. [405] found that the SARS-CoV-2 spike protein S1 subunit was expressed in non-classical monocytes ($CD14^{low}CD16^{+}$) from the blood of individuals with severe COVID-19 and PACS (up to 15 months post-infection) (Fig. 5**(c)**). The S1 protein subunit in non-classical monocytes was interpreted by the authors to be "retained from prior infection or phagocytosis of infected cells undergoing apoptosis and is not the result of persistent viral replication". An "immune response to persistent viral antigens, specifically the S1 fragment of the spike protein" is considered by the authors to be an important pathophysiological process of PACS.

Ram-Mohan et al. [406] used quantitative (qPCR) and digital polymerase chain reaction (dPCR, i.e. the third generation of PCR enabling absolute quantification without a standard curve) to quantify SARS-CoV-2 mRNA from blood plasma of COVID-19 patients. In 23.0% (44 of 191) of them, viral mRNA could be detected in the plasma with dPCR (compared to 1.4% (2 of 147) by qPCR). The mRNA load was correlated with maximum disease severity (Fig. 5**(e)**). In a subsequent study, Ram-Mohan et al. [407] found that COVID-19 patients in which SARS-CoV-2 mRNA could be detected in the blood had a higher chance of developing PACS symptoms later on (at least 4 weeks afterwards) compared to those where mRNA could not be detected (83% vs. 41.2%). mRNA detected on presentation with COVID-19 was associated with significantly higher rates of PACS for moderate COVID-19 severity.

Craddock et al. [408] detected SARS-CoV-2 mRNA (using droplet-digital PCR, ddPCR) in 59% of PACS patients, where the probability of detection correlated with days of hospitalization. SARS-CoV-2 spike protein was found in 64% in the blood of PACS patients, and in 33% of the PACS patients, both SARS-CoV-2 mRNA and SARS-CoV-2 spike protein could be detected. None of the subject of the control population (subjects who had a SARS-CoV-2 infection in the past but did not develop PACS) had both detected at the same time. PACS patient tended to show an increased number of small extracellular vesicles (EVs) (25–150 nm) in the blood plasma compared to the controls. In 43% of the plasma samples from PACS patients in which the SARS-CoV-2 spike protein could be detected, the EVs showed positivity for the SARS-CoV-2 spike protein. The SARS-CoV-2 spike protein was not detected in any of the EVs of the subjects in the control group. The results are shown in Fig. 5**(f)**).

In PACS patients, SARS-CoV-2 proteins and mRNA were also found in the tissue. Goh et al. [409] reported the detection of the SARS-CoV-2 nucleocapsid protein and spike protein in the appendix of an individual with PACS and loymphoid hyperplasia of the appendix 426 days after symptom onset. The SARS-CoV-2 nucleocapsid protein was also detected in the skin. In another patient with breast cancer and PACS, viral mRNA as well as the SARS-CoV-2 nucleocapsid protein and spike protein were found in the tumor-adjacent area 175 days after COVID-19 infection and related symptom onset.

Regarding circulating SARS-CoV-2 proteins and mRNA in the blood of individuals after COVID-19 vaccination and in patients with PCVS, some important research work on this has also been published so far (Fig. 6).

Castruita et al. [410] detected in 9.3% of a cohort of vaccinated Hepatitis C virus positive patients full-length or traces of SARS-CoV-2 spike mRNA vaccine sequences up to 28 days after COVID-19 vaccination (Fig. 6**(a)**). The mRNA nucleotide sequences detected in the blood plasma was almost 100% identical to those used in the specific mRNA COVID-19 vaccines (Pfizer-BioNTech (BTN162b2) and Moderna (mRNA-1273)).

Bansal et al. [411] demonstrated the presence of SARS-CoV-2 spike

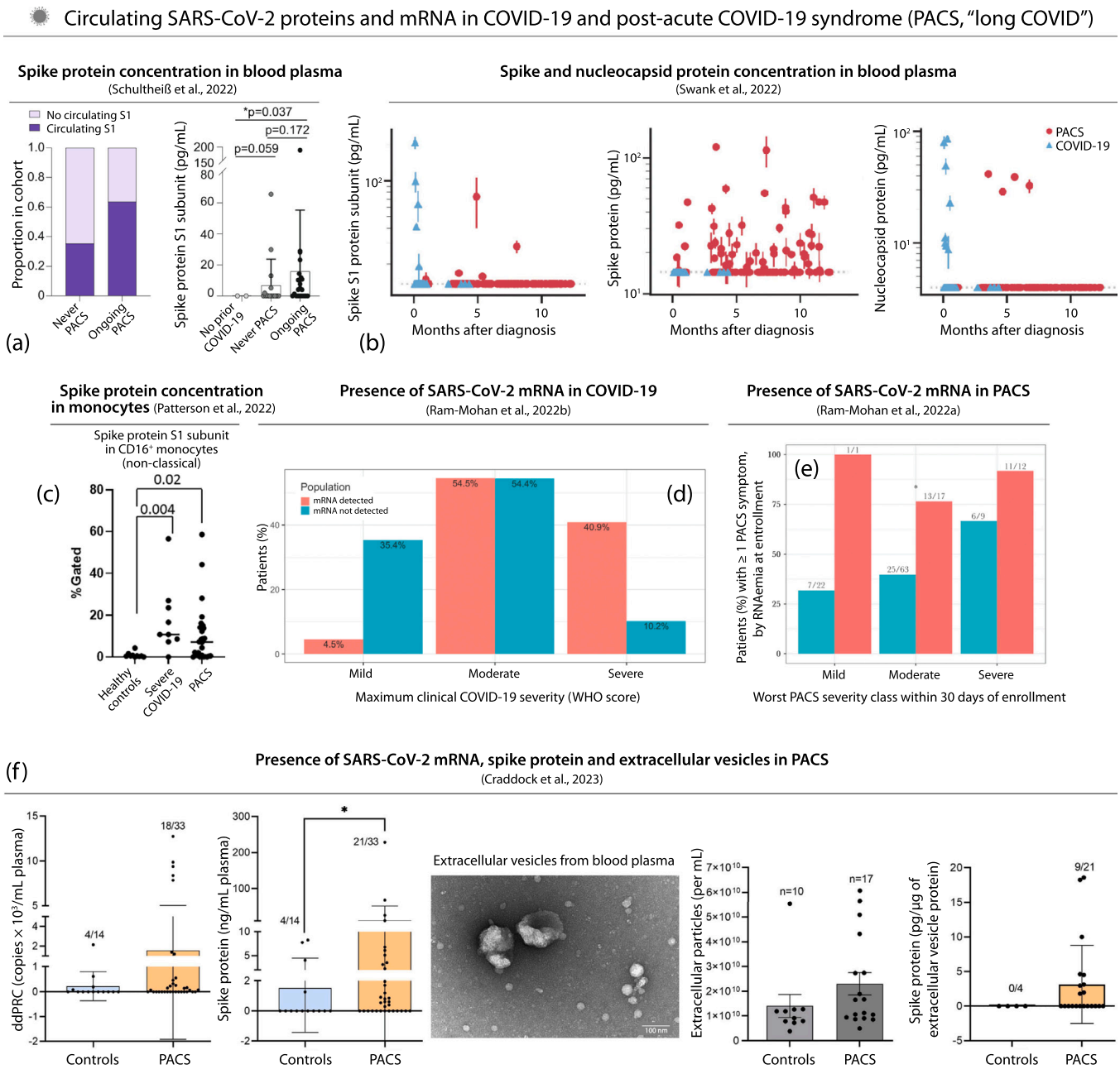


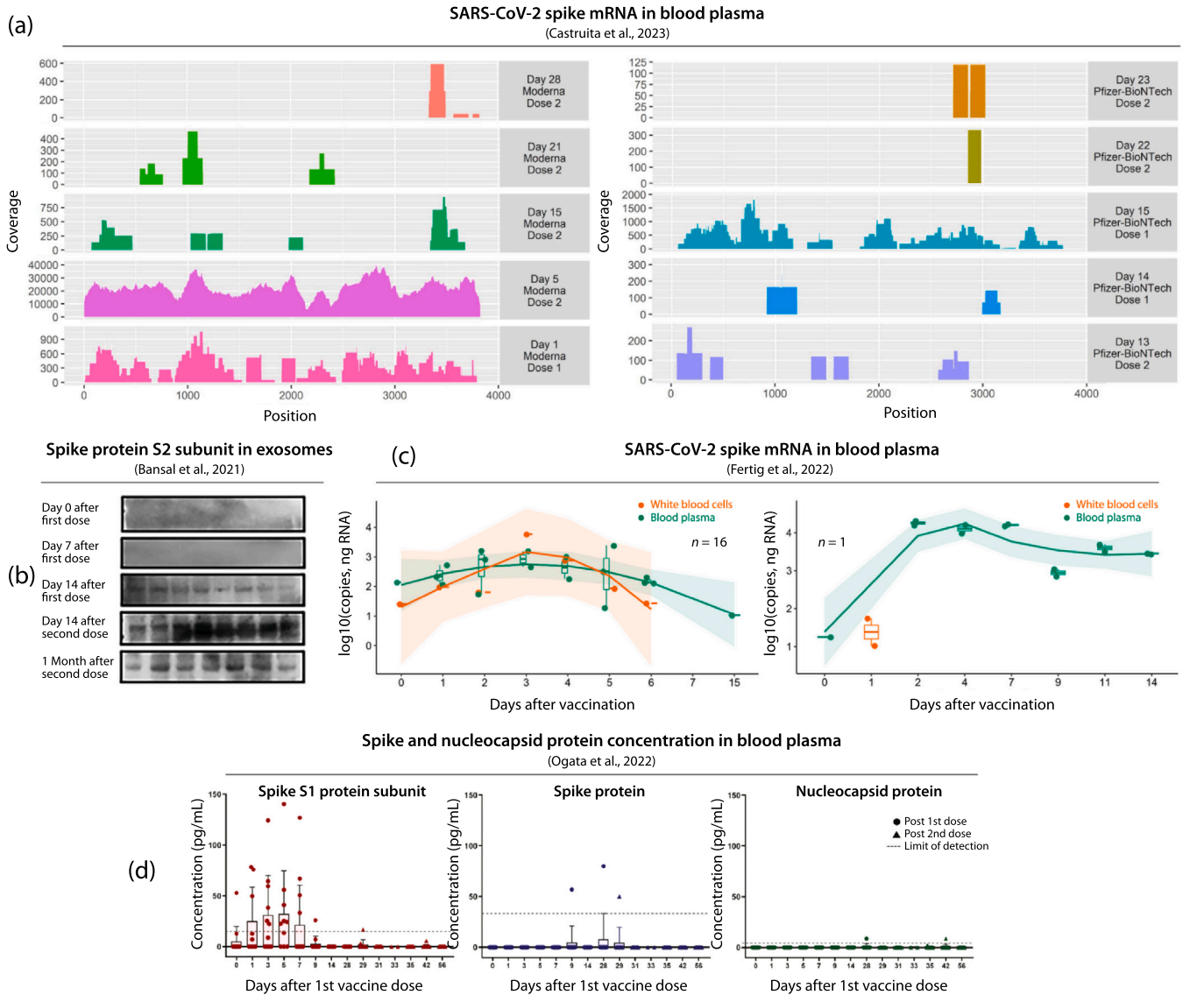
Fig. 5. Circulating SARS-CoV-2 proteins and mRNA in COVID-19 and PACS. (a) Spike protein concentration in blood plasma in individuals with and without PACS. (b) Time-dependent spike and nucleocapsid protein concentration in blood plasma in individuals with PACS and COVID-19. (c) Spike protein concentration in non-classical monocytes in healthy controls and individuals with severe COVID-19 and PACS. (d) Presence of SARS-CoV-2 mRNA in individuals with COVID-19 as a function of the maximum clinical COVID-19 severity. (e) Presence of SARS-CoV-2 mRNA in individuals with PACS as a function of the PACS severity. (f) Presence of SARS-CoV-2 mRNA (obtained with droplet digital-PCR (ddPRC), spike protein and extracellular vesicles (EV) with (with spike protein) in the blood plasma of individuals with PACS. A representative transmission electron microscopy (TEM) micrograph shows EVs (50.000 × magnification). The bar plot depicting the differences in EVs in controls and PACS refers to small EVs.
(a) Reprinted and modified from Schultheiß et al.[403], with permission from the publisher. (b) Reprinted and modified from Swank et al. [404], with permission from the publisher. (c) Reprinted and modified from Patterson et al. [405], with permission from the publisher. (d) Reprinted and modified from Ram-Mohan et al. [407], with permission from the publisher. (e) Reprinted and modified from Ram-Mohan et al., with permission from the publisher. (f) Reprinted and modified from Craddock et al. [408], with permission from the publisher (TEM image directly obtained by the author).

protein S2 subunit content in EVs (i.e. exosomes) from the blood plasma of COVID-19 vaccinated individuals 14 days after the first vaccine dose, 14 days after the second one and 4 months after the second one (Fig. 6 **(b)**). The finding was confirmed with electron microscopy showing the SARS-CoV-2 spike protein in exosomes. The immunogenic potential of the exosomes was shown by immunizing mice with these exosomes.

Fertig et al. [412] showed that "BNT162b2 vaccine mRNA remains in the systemic circulation of vaccinated individuals for at least 2 weeks, during which it likely retains its ability to induce S-protein expression in susceptible cells and tissues." (Fig. 6**(c)**). The vaccine mRNA was overwhelmingly detected in the plasma fraction.

Ogata et al. [413] found that the spike protein S1 subunit is present in the blood plasma as early as day 1 after COVID-19 vaccination (mRNA-1273) and its concentration peaks on average 5 days after the vaccination with the first dose followed by a decline and reaching the limit of detection by day 14 (Fig. 6**(d)**). Spike protein S1 subunits could

Circulating SARS-CoV-2 proteins and mRNA after COVID-19 vaccination



Circulating SARS-CoV-2 proteins and mRNA in post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome")

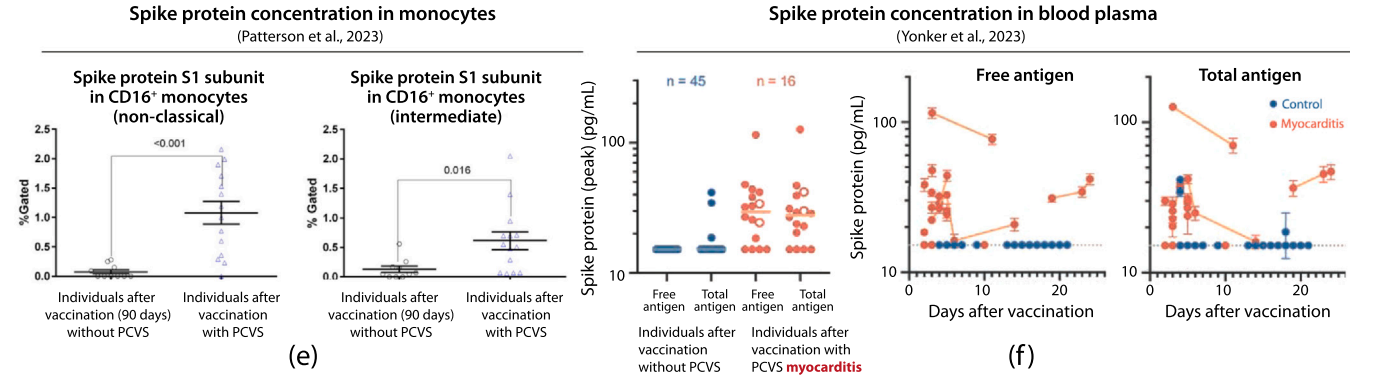


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Fig. 6. Circulating SARS-CoV-2 proteins and mRNA after COVID-19 vaccination and in PCVS. (a) SARS-CoV-2 spike mRNA in blood plasma as a function of type of vaccine and time after vaccination. Shown is the mapping of trimmed and filtered reads to the coding regions of the specific SARS-CoV-2 spike protein from the two COVID-19 vaccines. (b) Western blot showing the detection of SARS-CoV-2 spike protein S2 subunit in exosomes from blood plasma at 14 days after the first dose, 14 days after the second dose and 4 months after the second dose of the COVID-19 vaccine. (c) Circulating mRNA in blood (plasma and white blood cells) at different time-points after BNT162b2 COVID-19 vaccination. Left shows the group average, right an example from a single individual. (d) SARS-CoV-2 spike and nucleocapsid protein concentration after COVID-19 vaccination. (e) Spike protein concentration in non-classical monocytes in the blood of COVID-19 vaccinated individuals with and without experiencing PCVS symptoms. (f) Free and total full-length SARS-CoV-2 spike protein concentrations in COVID-19 vaccinated individuals who developed myocarditis compared to healthy ones. Shown is also the concentration of free full-length and S1 subunit spike protein as a function of time after vaccination and for the two cohorts (myocarditis and healthy controls).
(a) Reprinted and modified from Castruita et al. [410], with permission from the publisher. (b) Reprinted and modified from Bansal et al. [411], with permission from the publisher. (c) Reprinted and modified from Fertig et al. [412], with permission from the publisher. (d) Reprinted and modified from Ogata et al.[413], with permission from the publisher. (e) Reprinted and modified from Patterson et al. [307], with permission from the publisher. (f) Reprinted and modified from Yonker et al. [414], with permission from the publisher.

not be detected after the second vaccine dose. The full-length spike protein was detectable in around 23% (3/13) of the individuals about 2 weeks after receiving the first dose of the vaccine. The nucleocapsid protein could not be detected (as expected). The study highlighted that the spike protein S1 subunit "can be detected by day 1 and is present beyond the site of injection and the associated regional lymph nodes", proving that the vaccine reaches systemic circulation. The study was conducted with vaccine recipients that did not experience PCVS symptoms.

Patterson et al. [307] investigated 50 post-vaccinated individuals who experienced PACS-like symptoms, i.e. PCVS symptoms (or PACVS symptoms, to be more precise), more than 4 weeks after vaccination and found significantly more spike protein S1 subunit concentrations in non-classical $CD14^{low}CD16^{+}$ monocytes in the blood of vaccinated individuals who experienced PCVS symptoms compared to those who did not (Fig. 6**(e)**). This investigation also demonstrated that "$CD16^{+}$ cells from post-vaccination patients also contained S1 protein months after vaccination" and that "these S1 positive, $CD16^{+}$ cells also contained peptide sequences of S2, and mutant S1 peptides". Furthermore, a link between elevations of specific cytokines (CCL5 (RANTES), sCD40L, IL-6, and IL-8) and "post-vaccination PASC-like symptoms" (i.e. PCVS/PACVS symptoms) was found where the IL-8 was identified as a "unique marker relative to PASC in post-vaccination individuals with PASC-like symptoms".

Yonker et al. [414] showed that adolescents that developed myocarditis after COVID-19 vaccination had higher levels of free full-length spike protein (unbound by antibodies) in their blood plasma compared to age-matched asymptomatic COVID-19 vaccinated control subjects (Fig. 6**(f)**). However, the time between vaccination and sample collection was different between these two groups (post-vaccine myocarditis: 4 days (1–19 days) (median, range), vaccinated control subjects: 14 days (4–21 days)). Nevertheless, the development of the free full-length spike protein levels in both groups over the days post vaccination were different, which reinforces the conclusion that circulating spike protein levels are elevated in cases of post-COVID-19 mRNA vaccine myocarditis, i.e. PCVS (ACVS).

In a case of a subject experiencing subacute monomelic radiculoplexus neuropathy, antibody testing in the cerebrospinal fluid (CSF) for the SARS-CoV-2 nucleocapsid protein was negative but positive for the SARS-CoV-2 spike protein, 2 months after the second COVID-19 vaccine dose and 2.5 months after the first one (and symptoms onset) [415]. This case confirms that the proteins induced by COVID-19 vaccination can be present in the CSF for a long time (months).

Trace amounts of COVID-19 vaccine mRNA (from the Pfizer-BioNTech (BTN162b2) and Moderna (mRNA-1273) COVID-19 mRNA vaccines) could be detected in breastmilk of lactating mothers up to 45 h after vaccination (with an increased concentration in EVs compared to whole milk) [416]. Low levels of COVID-19 vaccine mRNA were also found in some breast milk samples from vaccinated mothers in a further study [417]. Another study, however, could not detect COVID-19 vaccine-associated mRNA in breast milk collected 4–48 h after vaccination [418] (but the validity of the study has been criticised [419]).

Roltgen et al. [420] could demonstrate the presence of abundant SARS-CoV-2 spike protein in axillary lymph nodes of vaccinated individuals 16 days post-second dose and a still detectable amount 60 days post-second dose. The SARS-CoV-2 spike protein was present in the lymph node tissue as a reticular pattern around the germinal center B cells.

From what has been presented and summarised here, it is clear that the SARS-CoV-2 spike protein plays an important role in COVID-19, PACS and PCVS. However, it must also be taken into account that the vaccine-induced protein is not identical to the natural one; in the Pfizer-BioNTech (BTN162b2) and Moderna (mRNA-1273) COVID-19 mRNA vaccine, for example, the RNA nucleobase N1-methylpseudouridine is incorporated to enhance protein expression and immune evasion [421]. These modifications could be relevant for differences in infection- and vaccine-related pathophysiological processes.

The difference in the transmission of the SARS-CoV-2 genetic material into humans (by infection via the nose and mouth, or by vaccination via injection into the muscle) can also make a difference in the pathophysiological processes triggered by it. It should also be noted here that an accidental direct injection into the bloodstream can in principle also occur in the case of vaccination into the muscle, which is probably associated with an increased complication rate [422,423]. Rzymski and Fal pointed out that "in vivo evidence suggests that intravenous injection of [the] mRNA vaccine can potentially lead to myocarditis, while introducing adenoviral vector to bloodstream can possibly result in thrombocytopenia and coagulopathy" [422] (a reference to two studies in this regard [424,425]).

Cosentino and Marino [426] pointed out that adverse effects of the COVID-19 vaccines could be related to excess SARS-CoV-2 spike production in specific individuals "for too long and/or in inappropriate tissues and organs", while the probability of this occurrence "is at present unpredictable, since systemic biodistribution and disposition of the COVID-19 mRNA vaccine has so far never been considered an issue, and as a consequence it has never been studied as it would have actually deserved." According to these authors, the problem is therefore the possibility of an excess of SARS-CoV-2 production, which can also last too long and/or at the same time can also happen at the wrong place (i.e. not primarily at the injection site).

Another point to note is that contaminants (process- and product-related impurities) have been found in the COVID-19 vaccines. In a recent analysis of vials of the bivalent Pfizer-BioNTech (BTN162b2) and Moderna (mRNA-1273) COVID-19 mRNA vaccine, McKernan et al. [427] found DNA contaminations exceeding the safety limits of the European Medicines Agency (EMA) (330 ng/mg) and the U.S. Food and Drug Administration (FED) (10 ng/dose).

Krutzke et al. [428] investigated the content of the adenovirus vector–based COVID-19 vaccines from AstraZeneca (ChAdOx1) and Johnson & Johnson–Janssen (Ad26. COV2. S) and found significant protein contaminations. In the three lots investigated of the AstraZeneca (ChAdOx1) vaccine, "about 70% of the detected protein content was of human and only 30% of virus origin" in one lot, and "approximately 50% of detected proteins were of human origin" in the two other lots.

More than 1000 different human proteins could be identified that originate from the human T-REx-293 cells (human embryonic kidney cells from a female fetus transformed with adenovirus 5 DNA) used in the vaccine production. The specification limit for protein contamination defined by the EMA (400 ng), was significantly exceeded by the amount of protein contamination detected. In the Johnson & Johnson–Janssen (Ad26. COV2. S) vaccine samples, the protein contamination was significantly less (less than 1% of human origin). With regard to possible health-related effects of these process- and product-related impurities the authors concluded that given the significant amount of protein contamination in the AstraZeneca (ChAdOx1) vaccine "the question imposes itself, whether or not (some of) the impurities might have long-term immune-related side effects in some of the vaccinees".

As pointed out by Milano et al. [429] another concern are double-strand RNA (dsRNA) contaminations in COVID-19 mRNA vaccines. The presence of dsRNA has been documented by the EMA for the Moderna (mRNA-1273)) [430] and the Pfizer-BioNTech (BTN162b2) [431] COVID-19 vaccines. Since dsRNA has a high potential to induce immune-inflammatory reactions, Milano et al. concluded that this dsRNA contamination "could be hypothetically suspected to trigger the induction of myocarditis among other possible factors."

Another possibility to cause adverse effects of the COVID-19 vaccines are additives, such as the polyethylene glycol (PEG) contained in mRNA-based formulations [432–440] of the additives polysorbate 80, L-histidine, ethylenediaminetetraacetic acid (EDTA), tromethamine and tromethamine hydrochloride [441–443].

4. Summary, conclusion and outlook

In the previous sections, we presented our conclusion that three new terms for COVID-19 vaccination induced syndromes need to be introduced (PCVS, ACVS and PACVS) for conditions that share similarities and differences to COVID-19 and PACS. We provided a literature review supporting the conclusion for the need to introduce these new terms, and studies were reviewed concerning similar and different symptoms associated with these infection- and vaccination-associated syndromes. In addition, possible underlying pathophysiological conditions were discussed.

Two calls for action result from what has been presented so far.

Firstly, the newly introduced technical terms (post-COVID-19 vaccination syndrome, PCVS; acute COVID-19 vaccination syndrome, ACVS; and post-acute COVID-19 vaccination syndrome, PACVS) should be used in medical communication and documentation (scientific publications, medical documentation, etc.). The general and simplified version for PCVS, the term "post-COVIDvac-syndrome", is recommended for communication with the public. The term "post-vac-syndrome", which has been used from time to time in the media, should be replaced by the new terms, as they are more precise. The term "post-vac-syndrom" should not be used as it does not specify that this is a specific syndrome caused by the COVID-19 vaccines and not a syndrome caused by vaccination in general. The use of the new terms may help to ensure that vaccine-related side-effect syndromes are taken more seriously and reduce the likelihood that they will be mistaken for infection-related disease syndromes. It must not happen that people with side effects due to vaccination are not taken seriously and get misdiagnosed. The issue of diseases not being taken seriously has been the case in the past and is still partly prevalent for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CSF) [444,445] and PACS [446,447]. In the case of ME/CSF, many of those affected are frustrated by the "widespread negative stereotyping of patients and the marginalization and exclusion of patient voices by medical authorities" [445]. Concerning PACS, the "serious implications for individuals and society have been missing from public communication and pandemic policy" [447]. In a survey with PACS patients they described "encountering medical professionals who dismissed their experience, leading to lengthy diagnostic odysseys and lack of treatment options for Long Covid" [446]. This phenomenon, which has been called "medical gaslighting", must not occur with the infection-related PACS or with the vaccination-related PCVS. In this context, it must also be remembered that the term was first coined by patients and not by doctors or scientists. The same happened with the term "Long Covid", which was also first introduced by those affected [448]. According to Turner et al. "there is hesitancy among patients and researchers to acknowledge and openly discuss vaccine injury, due to fear of being labeled 'anti-vax'. Patients with vaccine injury should be able to access medical care without fear of being stigmatized, and vaccine injury should be researched like any other disease." [19]. Just as the term "Long Covid" (i.e. PACS) is now a recognised medical term, so too should the three new terms introduced here (PCVS, ACVS and PACVS). These new terms should also be introduced in the International Classification of Diseases (ICD) system, which already includes (in version ICD-10) the "post COVID-19 condition" (U09.9) (i.e. PACS) and COVID-19 (U09.9). The two present COVID-19 vaccine-associated codes T50. B95A (adverse effect of other viral vaccines, initial encounter) and U12.9 (COVID-19 vaccines causing adverse effects in therapeutic use, unspecified) should be replaced with the three newly introduced terms to provide clear ICD diagnostic codes for the COVID-19 vaccination-induced disease conditions. At least the ICD diagnostic code "post-COVID-19 vaccination condition, unspecified" (in analogy to U09.9: "post COVID-19 condition, unspecified") should be immediately introduced in the upcoming version of the ICD.

Secondly, more research is urgently needed to further define and characterise the vaccine-induced syndromes. The similarities and differences of the symptoms of these syndromes with COVID-19 and PACS need to be studied in detail. In addition, there needs to be detailed research into the pathophysiology of PCVS (i.e. ACVS and PACVS) and therapeutic options to help those affected. As there is already a specialisation on the part of physicians in private practice or facilities in hospitals for persons with PACS, this should also be implemented for PCVS. As far as the diagnosis of infection- and vaccine-related diseases is concerned, it must be noted that the situation has now been complicated by the fact that mixed forms between both causes are also possible. In general, four cases can be defined and should be distinguished (see Fig. 7): (i) COVID-19/ACVS (i.e. COVID-19 + ACVS), (ii) COVID-19/PACVS (i.e. COVID-19 + PACVS), (iii) PACS/ACVS (i.e. PACS + ACVS), and (iv) PACS/PACVS (i.e. PACS + PACVS). Unfortunately, there is almost no research on these second-order syndromes. Future studies are needed to precisely define these types of combined syndromes in terms of symptoms and pathophysiology. It should also be noted that the order of events will be relevant for the characteristics of the syndromes, i.e. it will probably be relevant whether the infection-related disease came first or the vaccination-related disease.

In the course of differential diagnostics (with respect to the first-order syndromes (Fig. 1) and second-order syndromes (Fig. 7)), it

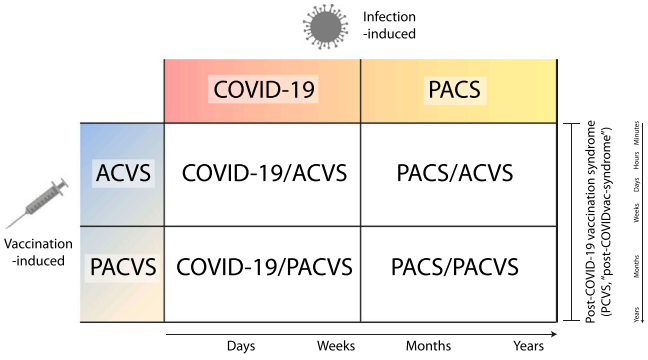

Fig. 7. Definition of the terminology of second-order syndromes as a combination of infection- and vaccination-induced syndromes. PACS: post-acute COVID-19 syndrome. ACVS: acute COVID-19 vaccination syndrome, PACVS: post-acute COVID-19 vaccination syndrome.

could be useful to search for SARS-CoV-2 mRNA and proteins from infection and vaccination in the blood and tissue samples of patients. Since both mRNA COVID-19 vaccine sequences "have been modified and are only ~70% identical to the spike reference genome on a nucleotide level" [410], this helps in the differential diagnosis in terms of finding the cause of the disease (infectious or vaccine-related). Also the detection of COVID-19 vaccine associated SARS-CoV-2 proteins in non-classical $CD14^{low}CD16^{+}$ monocytes, as pioneered by Patterson et al. [307], is promising in this respect. The examination of the blood of the sick person for amyloid fibrin microclots and hyperactivated platelets [385,386,388,389] is also obvious and probably also essential for patients with PACS and/or PACVS (and PCVS in general).

Consent statement/ethical approval

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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