Platelets

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iplt20

Anti-PF4/polyanion antibodies in COVID-19 patients are associated with disease severity and pulmonary pathology

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To cite this article: Thor Ueland, Ingvild Hausberg, Trude Victoria Mørtberg, Tuva Børresdatter Dahl, Tøri Vigeland Lerum, Annika Michelsen, Trine Ranheim, Katerina Nezvalova Henriksen, Anne Ma Dyrhol-Riise, Pål André Holme, Trond Mogens Aaløkken, Ole Henning Skjønsberg, Andreas Barratt-Due, Maria Therese Ahlén, Pål Aukrust & Bente Halvorsen (2022) Anti-PF4/polyanion antibodies in COVID-19 patients are associated with disease severity and pulmonary pathology, Platelets, 33:4, 640-644, DOI: 10.1080/09537104.2022.2042238

To link to this article: https://doi.org/10.1080/09537104.2022.2042238

http://www.tandfonline.com/iplt
ISSN: 0953-7104 (print), 1369-1635 (electronic)

platelets

Platelets, 2022; 33(4): 640–644
 DOI: https://doi.org/10.1080/09537104.2022.2042238

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DEFINITIVE REPORT

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Anti-PF4/polyanion antibodies in COVID-19 patients are associated with disease severity and pulmonary pathology

Thor Ueland[1,2,3], Ingvild Hausberg[4], Trude Victoria Mørtberg [4], Tuva Børresdatter Dahl[1,5], Tøri Vigeland Lerum[2,6], Annika Michelsen[1,2], Trine Ranheim[1], Katerina Nezvalova Henriksen[7], Anne Ma Dyrhol-Riise[2,8], Pål André Holme[1,2,9], Trond Mogens Aaløkken[2,10], Ole Henning Skjønsberg[2,6], Andreas Barratt-Due [5,11], Maria Therese Ahlén [4], Pål Aukrust[1,2,12], & Bente Halvorsen [1,2]

[1]*Research Institute of Internal Medicine, Oslo University Hospital, Oslo, Norway,* [2]*Institute of Clinical Medicine, University of Oslo, Oslo, Norway,* [3]*Department of Clinical Medicine, Thrombosis Research and Expertise Center (TREC), UiT-The Arctic University of Norway, Tromsø, Norway,* [4]*Norwegian National Unit for Platelet Immunology, University Hospital of North Norway, Tromsø, Norway,* [5]*Division of Emergencies and Critical Care, Department of Research and Development, Oslo University Hospital, Oslo, Norway,* [6]*Department of Pulmonary Medicine, Oslo University Hospital Ullevål, Oslo, Norway,* [7]*South-Eastern Norway Enterprise, Oslo University Hospital and Hospital Pharmacies, Oslo, Norway,* [8]*Department of Infectious Diseases, Oslo University Hospital, Oslo, Norway,* [9]*Department of Haematology, Oslo University Hospital, Oslo, Norway,* [10]*Department of Radiology and Nuclear Medicine, Oslo University Hospital Ullevål, Oslo, Norway,* [11]*Department of Immunology, Oslo University Hospital, Oslo, Norway, and* [12]*Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Oslo, Norway*

Abstract

Thromboembolic events are frequent and associated with poor outcome in severe COVID-19 disease. Anti-PF4/polyanion antibodies are related to heparin-induced thrombocytopenia (HIT) and thrombus formation, but data on these antibodies in unselected COVID-19 populations are scarce. We assessed the presence of anti-PF4/polyanion antibodies in prospectively collected serum from an unselected cohort of hospitalized COVID-19 patients and evaluated if elevated levels could give prognostic information on ICU admission and respiratory failure (RF), were associated with markers of inflammation, endothelial activation, platelet activation, coagulation and fibrosis and were associated with long-term pulmonary CT changes. Five out of 65 patients had anti-PF4/polyanion reactivity with OD ≥0.200. These patients had more severe disease as reflected by ICU admission without any evidence of HIT. They also had signs of enhanced inflammation and fibrinogenesis as reflected by elevated ferritin and osteopontin, respectively, during the first 10 days of hospitalization. Increased ferritin and osteopontin persisted in these patients at 3 months follow-up, concomitant with pulmonary CT pathology. Our finding shows that the presence of anti-PF4/polyanion antibodies in unselected hospitalized COVID−19 patients was not related to HIT, but was associated with disease severity, inflammation, and pulmonary pathology after 3 months.

Keywords

Anti-PF4/polyanion antibodies, COVID-19, HIT, intensive care unit, lung

History

Received 6 December 2021
Revised 22 January 2022
Accepted 22 January 2022

Introduction

Venous thromboembolic events are prominent clinical features of severe COVID-19 disease and autopsy studies suggest that pulmonary microthrombosis occurs early in patients with fatal COVID-19 [1], concurrently with high viral loads, enhanced inflammation and hypercoagulability [2,3]. A few studies have linked these features in severely affected patients to heparin-induced thrombocytopenia (HIT), a prothrombotic disorder caused by IgG antibodies against platelet factor 4 (PF4)/polyanion complexes that cause platelet activation through the FcγRIIA receptor [4–6], as well as PF4-independent immune complexes [7]. However, COVID-19 patients with suspected HIT may present strong anti-PF4/polyanion antibodies in immunoassays without the ability to activate platelets in functional testing [8], and it has been reported that a positive test may be a marker of severity of COVID-19 rather than a marker of thrombotic risk [9]. To further elucidate these issues, we evaluated if anti-PF4/polyanion antibodies in an unselected cohort of hospitalized COVID-19 patients also at lower levels than associated with HIT, could i) give prognostic information on disease severity as assessed by intensive care unit (ICU) admission and respiratory failure (RF), ii) were associated with markers of inflammation, virus load, endothelial activation, platelet activation and coagulation and fibrosis and iii) was associated with long-term effects of COVID-19 as assessed by persistent pulmonary CT pathology at 3-month follow-up.

Correspondence: Bente Halvorsen, Research Institute of Internal Medicine, Oslo University Hospital, University of Oslo, Sognsvannsveien 20, Oslo 0372, Norway. E-mail: b.e.halvorsen@medisin.uio.no

Methods

Patients

The NOR-Solidarity trial (n = 165) was an independent add-on study to the WHO Solidarity trial, evaluating hydroxychloroquine and remdesivir compared to standard of care in hospitalized COVID-19 patients [10]. Adults with PCR-confirmed SARS-CoV-2 infection were eligible for participation. Viral load in oropharynx and antibodies against SARS-CoV-2 was analyzed as previously reported [10]. In the NOR-Solidarity trial,

biobanking was not performed at all study sites (biobanking included 144 patients) and for this sub-study, adequate sample volumes were only available in 65 patients.

Biochemical and clinical variables

Antibodies to PF4/polyanion were screened for by ELISA (LIFECODES PF4 IgG assay; Immucor, Waukesha, WI) in serum collected at inclusion, at 5–10 days and at 3 months follow-up. Participants were classified as positive if they had optical density (OD) ≥0.200 during the first 10 days. The routine anti-PF4 IgG testing in classical HIT investigations has a validated positive cutoff of ≥0.400. However, by testing of series of healthy blood donors, we found the normal range to be lower [11]. The positive cutoff for ELISA was therefore set to OD ≥0.200 (mean +5SD: 0.068 + 0.131) after in-house testing of 150 healthy blood donors (range OD 0.038–0.187, 76/150 females, 74/150 males, mean age 44 years both genders). As such, we regard OD values in the range of 0.200–0.400 as positive IgG detection, as also reported among AZD1222 vaccinated individuals—although lower than associated with heparin-dependent IgG antibodies clinically relevant for classical HIT diagnosis [11].

A positive ELISA test was related to: (i) need for ICU admission or (ii) RF defined as [pO_2/FiO_2-(P/F)-ratio] <26.6 kPa during the first 10 days of hospitalization. PaO2/FiO2 (P/F) ratio is the ratio of arterial oxygen partial pressure, PaO2, to fractional inspired oxygen, FiO2 expressed as a fraction. The normal P/F ratio is ~55–65 kPa. Further, (iii) temporal profiles of C-reactive protein (CRP), ferritin, neutrophil and platelet counts, D-dimer, von Willebrand factor (vWF), α-2 anti-plasmin (A2AP), PF4, matrix metalloproteinase (MMP)-9 and osteopontin (OPN), a valuable marker of inflammation and matrix remodeling, in plasma collected at inclusion, at 3–5 and 7–10 days and at 3 months follow-up and (iv) presumably reversible or irreversible CT changes at 3 months follow-up [12, 13,14]. Serum inflammatory markers were measured by enzyme immunoassays (R&D Systems, Minneapolis, MN), vWF with antibodies from Dako Cytomation (Glostrup, Denmark), with intra-assay coefficient of variation <5%. Positive samples in PF4 IgG ELISA were further tested by PF4-dependent P-selectin expression assay (PEA) [13,15]. Briefly, platelets were pre-incubated with buffer, PF4 (30 μg/mL, ChromaTec, Greifswald, Germany), or PF4 and anti-FcγRIIA antibody (IV.3, 10 μg/mL) for 20 minutes. Patient serum was added and incubated for 1 hour at room temperature, prior to staining with anti-GPIIIa (AP-3, AF488) and anti-CD62P (AC1.2, PE) antibodies. Platelet activation was measured as integrated median fluorescence intensity (iMFI, PE, positive cutoff >2000) on GPIIIa-positive events in flow cytometry. A previously confirmed VITT serum served as positive control, and normal pooled sera as negative control.

Based on defined criteria, CT changes at 3 months after hospitalization that were thought to reflect inflammation were classified as presumably reversible changes and changes that were thought to reflect fibrosis were classified as presumably irreversible changes [13,14].

Statistics

Time to ICU admittance and respiratory failure was visualized by Kaplan–Meier curves with hazard ratios (HR) and 95% confidence intervals calculated by Cox regression, adjusting for randomized treatment and low-molecular-weight heparin (LMWH) use. As we did not have temporal samples from all patients at all timepoints, the temporal profile was evaluated with a univariate general linear model with marker as dependent, PF4 IgG group (i.e., OD ≥0.200 PF4+) and time as fixed factors whilst participant number was a random factor. Post-hoc testing was only performed on markers that had a significant group effect (Mann–Whitney U-test) or group*time effect (Wilcoxon paired test within PF4 groups). Markers dysregulated in the acute phase were also assessed at 3 months. Two-sided P-values were considered significant when <0.05.

Results and discussion

Sixty-five hospitalized COVID-19 patients were included in the study with a total number of serum samples of 195, of which 12 samples displayed OD values ≥0.200 in the anti-PF4/PVS IgG ELISA (Figure 1a). These were distributed in 5 patients (OD values on x-axis in Figure 3) where all had a positive sample on admission and were classified as the PF4+ group. Admission characteristics of these are shown in Table I. The PF4+ patients were males, had higher ferritin, but similar CRP, D-dimer, platelet and neutrophil counts, virus load and antibodies against SARS-CoV-2 as the PF4- group.

Of 65 patients, 15 were admitted to ICU and 16 experienced RF (P/F ratio <26.6 kPa) during the first 10 days of follow-up. The PF4+ patients had significantly higher risk of ICU admission (Figure 1b, HR = 3.7, p = .044), but not RF (HR = 3.4, p = .070), adjusting for randomized treatment and LMWH use. The P/F ratio in the PF4+ patients showed a significant interaction between PF4 group and time, but was not significant in post-hoc tests (Figure 2a). Evaluation of biomarkers revealed that the PF4+ patients had higher ferritin and OPN levels during the first 10 days of admission (Figure 2b), with trends for CRP and A2AP (Figure 2c, group effect p = .074). In contrast, no differences in

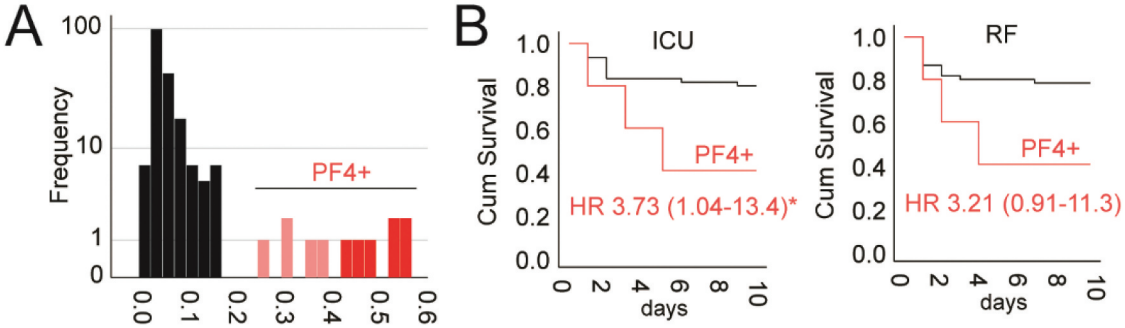

Figure 1. **Elevated anti-PF4 in relation to disease severity**. (a) Distribution of OD values from the anti-PF4/PVS IgG ELISA. (b) Kaplan–Meier curve for ICU admission and respiratory failure (RF) according to being PF4+ (see definition in results; red is PF4+ and black is PF4-) during the first 10 days of hospitalization. The numbers shown are the hazard ratio and (95% confidence interval) egression adjusting for randomized treatment and heparin use, *p < .05.

Table I. Demographics of the study population.

Parameter	PF4 IgG <0.2 OD (PF4- n = 60)	PF4 IgG ≥0.2 OD (PF4 + n = 5)	p-value
Age, years: mean (range)	61 (27–89)	64 (51–73)	.66
Male gender: n (%)	37 (62)	5 (100)	.091
Body Mass Index, kg/m^2: mean ± SD	27.9 ± 4.8	27.8 ± 4.0	.98
Randomized treatment Soc/HCQ/RDV: n	27/19/14	2/3/0	.32
Low-molecular-weight heparin use: n (%)	28 (47)	2 (40)	.57
P/F-ratio at admission, kPa: median (25th-75th)	45 (34–52)	39 (38–39)	.17
Neutrophil count, x10^9/L: mean ± SD	4.7 ± 2.5	6.0 ± 2.8	.28
Platelet count, x10^9/L: mean ± SD	218 ± 74	240 ± 95	.52
C-reactive protein, mg/L: median (25th-75th)	70 (43–129)	123 (87–182)	.17
Ferritin, µg/L: median (25th-75th)	617 (342–1022)	1298 (1292–1436)	.018
D-dimer, mg/L: median (25th-75th)	0.8 (0.5–1.2)	0.6 (0.5–2.5)	.90
Virus load (log$_{10}$/1000): median (25th-75th)	1.3 (0.1–2.6)	2.2 (1.1–2.6)	.50
Anti-SARS-CoV-2 RBD Ab ≥ 5, n (%)	29 (48)	3 (60)	.49

SoC, standard of care; HCQ, hydroxychloroquine; RDV, remdesivir; RBD, receptor binding domain. Data shown as mean and median levels were compared with Student's T-test and Mann-Whitney U test, respectively. Proportions were compared with Fisher's Exact Test.

virus load or SARS-CoV-2 antibodies (Figure 2d), platelet counts or platelet activation (i.e., plasma PF4 levels) were seen between the two PF4 groups during hospitalization (Figure 2e).

Ferritin (median 854 µg/mL versus 1298 µg/mL, p = .021) and OPN (median 38 ng/mL versus 52 ng/mL, p < .05, PF4- and PF4 +, respectively) remained higher at 3 months follow-up in the PF4

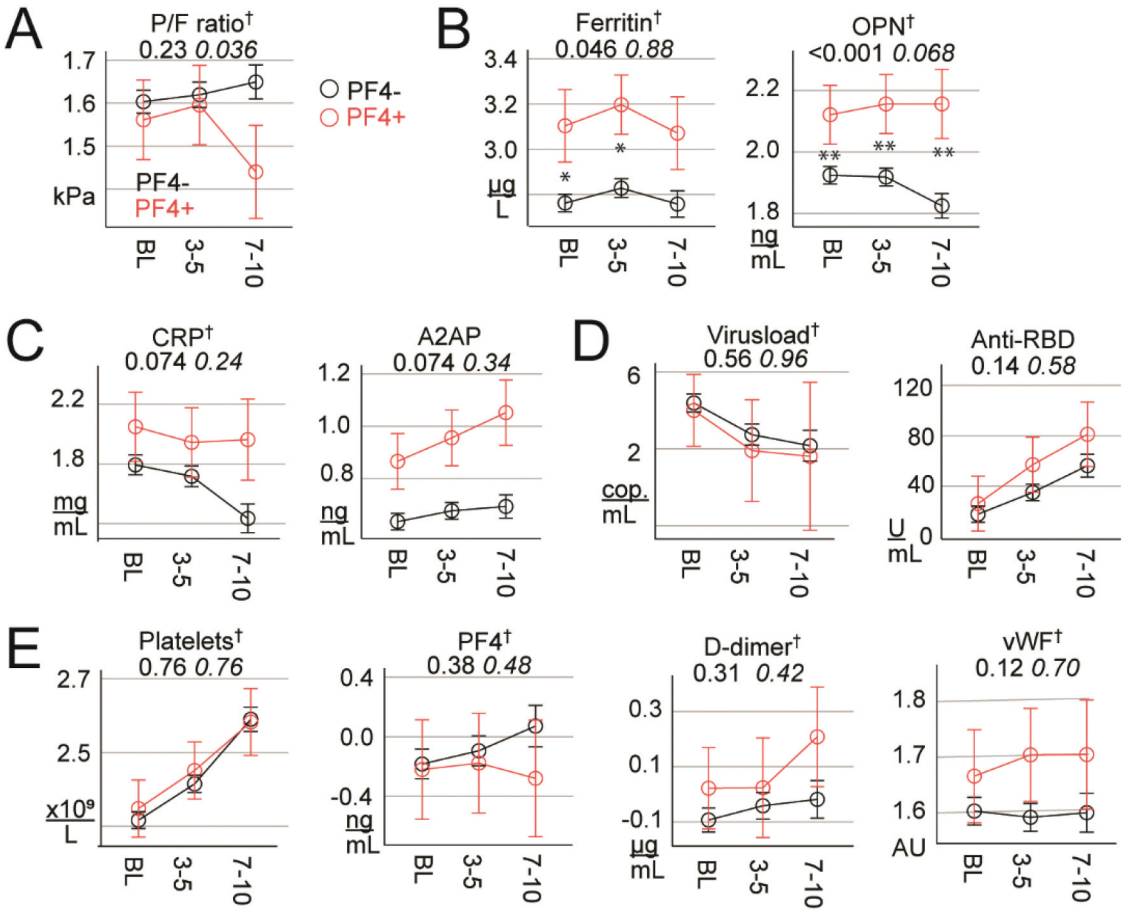

Figure 2. **Elevated anti-PF4 in relation to biomarkers. Temporal** profile of biomarkers according to being PF4+ (red lines) or PF4- (black lines) during the first 10 days after admission. (a) the PaO2/FiO2 (P/F) ratio (b) ferritin and osteoponectin (OPN) (c) C-reactive protein (CRP) and α2-antiplasmin (d) virus load and anti-SARS-CoV-2 RBD and (e) platelet counts, PF4 as a marker of platelet activation, D-dimer as a marker of fibrin degradation and thrombosis and vWF as a marker of endothelial cell activation. The p-values reflect the group effect (i.e. PF4±) from the general linear model analysis, whilst the italic p-values reflect the interaction between time and group. †log10 transformed. *p < .05; **p < .01 between PF4 groups at same time-point.

In Panel E both PF4 and D-dimer were skewed and log10 transformed prior to the regression analysis (indicated by the † in the graph). Some of the levels are therefore negative, i.e., this is not due to negative results from the standard curve.

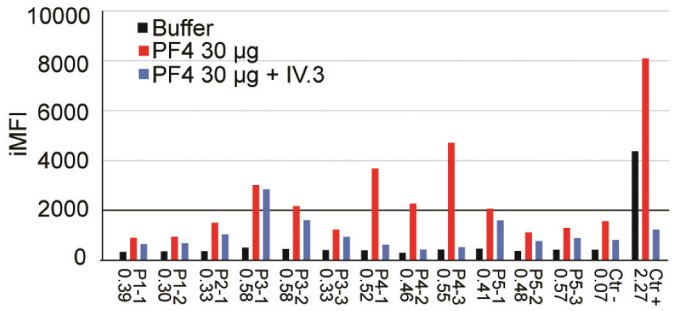

Figure 3. **Functional platelet activation in PF4-dependent P-Selectin Expression Assay (PEA)**. Positive samples in PF4 IgG ELISA were tested by PEA using pooled platelets collected from two blood donors. Patients are labeled 1–5 (P1-P5) with time point after (−1: baseline, −2: 5–10 days, −3: 3 months). Platelets were incubated with buffer, PF4 (30 µg/mL) or PF4 + anti-FcγRIIA antibody (IV.3, 10 µg/mL). Labels on x-axis corresponds to Patient/sample number and the anti-PF4 IgG ELISA OD value. A previously confirmed VITT serum served as positive control, and normal pooled sera as negative control.

+ patients. Fifty-five patients had CT evaluation at 3 months follow-up (PF4- n = 50, PF4 + n = 5). All PF4+ patients presented with CT changes compared to 32 (64%) PF4- patients (p = .10). The number of reversible CT changes was 29 (58%) versus 5 (100%) p = .065 and the number of irreversible CT changes was 23 (46%) versus 4 (80%) p = .15 for the PF4- and PF4+ patients, respectively.

Of the PF4+ sera, only those (n = 3) with OD ≥0.400 obtained in the PF4/PVS IgG ELISA induced platelet activation in the PEA assay in presence of PF4 (Figure 3), while this activation was efficiently inhibited by IV.3 in one patient only. The low effect of IV.3 blocking of activation seen for two patients indicate a non-FcγRIIA mediated activation.

Anti-PF4/polyanion antibodies, as a mediator of vaccine-induced immune thrombotic thrombocytopenia (VITT) (AstraZeneca, AZD1222), has received much attention [16–18]. We recently reported that six of 492 recently vaccinated with the first dosage of AZD1222 had detectable anti-PF4/polyanion antibodies without any thrombocytopenia or sign of thrombus formation [11]. The presence of such antibodies in COVID-19 patients with suspected HIT has also been reported, and that a high titer of anti-PF4/polyanion antibodies did not strongly predict clinically relevant HIT antibodies by functional testing [4,6,8,9]. A meta-analysis revealed HIT incidence to be comparable to non-COVID-19 patients [5]. Delrue et al. reported a prevalence of HIT-associated antibodies in 172 hospitalized SARS-CoV-2-infected patients, independent of suspected HIT, of 33% (IgG/A/M) and 11% (IgG) detected with ELISA (OD>0.500), with no significant relation to disease severity [19]. Herein, we show that in prospectively collected serum from an unselected cohort of hospitalized COVID-19 patients, five out 65 patients had anti-PF4/polyanion reactivity OD≥ 0.200 with induction of PF4-dependent platelet activation in PEA assay in three of the patients (iMFI>2000) – notably these three patients also all had ELISA OD≥0.400. The discrepancy between these data and the study by Delrue et al. [19] could potentially at least partly reflect differences in the patient selection.

None of the five PF4+ patients had thrombocytopenia and the presence of anti-PF4/polyanion antibodies was not related to the use of heparin. Although they had higher levels of A2AP that could attenuate fibrinolysis, HIT is very unlikely. However, the PF4+ patients had more severe disease as reflected by ICU admission. They also had signs of enhanced inflammation as assessed by elevated ferritin. The presence of various autoantibodies is relatively common in COVID-19 patients, most probably reflecting disease severity and the association with ICU in the present study, may reflect similar mechanisms. It is also possible that the anti-PF4 antibodies are just markers of general inflammation and overt immune activation.

Noteworthy, although not statistically different from PF4- patients, all the PF4+ patients had CT pathology 3 months after hospital admission and significantly elevated levels of ferritin and OPN at these time points. Persistent elevation of OPN, as a marker of extracellular matrix remodeling, inflammation and fibrogenesis, could reflect some association and potentially also a role in persistent pulmonary pathology [20,21].

The strength of the current study is the unsupervised selection of patients and the 3 months follow-up with clinical end-point such as pulmonary CT scan. However, the low number of patients (including only 40% of the NOR-Solidarity cohort), lack of long-term follow-up (> 3 month) and the hypothesis generating approach may be regarded as study limitations. The lack of serial CT thorax measurements to conclude if the changes at 3 months were truly reversible or irreversible is also a limitation of the study.

Our finding shows that the presence of anti-PF4/polyanion antibodies in an unselected cohort of hospitalized COVID-19 patients, without suspected HIT, was associated with disease severity and inflammation and although not statistically different from PF4- patients, all PF4+ patients had pulmonary pathology after 3 months. However, the pathogenic importance of these antibodies needs to be determined in larger studies with more long-term follow-up.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Author contributions

IHS, TVM, MTA, TBD, TR, AM, TVL, KNH, ABDTMA, PAH, OHS, ABD and AMDR data generation and assessments; TU, PA and BH designed, analysed data, and wrote the paper. All authors have critically reviewed and approved the paper.

ORCID

Trude Victoria Mørtberg http://orcid.org/0000-0003-0808-0183
Andreas Barratt-Due http://orcid.org/0000-0001-5408-7162
Maria Therese Ahlén http://orcid.org/0000-0002-3104-3818
Bente Halvorsen http://orcid.org/0000-0002-6529-6485

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