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Case Report

Long Covid Patients Successfully Treated by Means of Heparin-Mediated Extracorporeal LDL Precipitation (H.E.L.P.) Apheresis

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Abstract

Many COVID-19 infected patients develop a chronic state of disease that hinders them for months or even years due to severe persisting pulmonary, neurologic, cardiac, and other deficits. This debilitating condition was coined by patients as 'Long COVID', for which there is currently no proven effective treatment. It is increasingly apparent that a key mechanism of COVID-19 infection is a systemic endotheliitis and microembolization which affects various organs. Mounting evidence suggests that the plasma of individuals with acute COVID-19 or Long COVID contains fibrin amyloid-like microclots that are comparatively resistant to fibrinolysis. A biologically plausible explanation links the presence of such fibrin amyloid-like microclots to the blockage of capillaries, with the inhibition of oxygen transport to tissues. This may contribute to many of the Long COVID symptoms such as breathlessness, fatigue, cognitive dysfunction, post-exertional symptom exacerbation, and autonomic dysfunction. Thus, an extracorporeal method such as Heparin-mediated Extracorporeal Low-density lipoprotein (LDL) Precipitation (H.E.L.P.) apheresis that eliminates cholesterol, clotting factors, endotoxins, and inflammatory mediators such as cytokines and tumour necrosis factor-α toxins, could also potentially eliminate the SARS-CoV-2 spike protein and fibrin amyloid-like microclots present in Long COVID and consequently restore vascular homeostasis in persisting COVID-19 infection. We randomly assigned 17 Long COVID patients to receive repeated H.E.L.P. apheresis treatments in short intervals (1-7 sessions) until they recovered from major clinical symptoms. Of these 17 treated patients, 16 patients felt immediate improvement and 12 patients nearly reached full recovery after completion of the treatment. A 6–10-month follow-up revealed that 15 patients maintained their improvements. Thus, of the 17 patients with severe Long COVID symptoms, 16 patients had experienced a great benefit. One patient did not improve, although his oxygen saturation ameliorated. Therefore, H.E.L.P. apheresis serves as a promising and safe treatment option for Long COVID patients. These improvements in symptoms highlight the benefits of H.E.L.P. apheresis as an effective treatment for Long COVID and stresses the urgent need for larger controlled-studies-into-this-treatment.

List of Abbreviations

ACE-2: angiotensin converting enzyme-2; ATP: adenosine triphosphate; CRP: C-reactive protein; CT: computerized tomography; H.E.L.P.: Heparin-mediated Extracorporeal Low-density lipoprotein (LDL) Precipitation; IL: interleukin; LDL: low-density lipoprotein; Lp(a): lipoprotein(a); ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; NO: nitric oxide; PASC: post-acute sequelae SARS-COV-2 infection; PEM: post-exertional malaise; PFIB: plasma fibrinogen; SARS CoV-2: severe acute respiratory syndrome coronavirus 2; VEGF: vascular endothelial growth factor; VLDL: very-low-density lipoprotein; VWF: von Willebrand Factor; WHO: World Health Organization; MRI: magnetic resonance imaging

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) can cause a severe acute multi-organ illness which subsequently leads to the chronic debilitating illness post-acute sequelae SARS-COV-2 infection (PASC); more commonly referred to as "Long COVID" (hereafter termed Long COVID). The acute illness does not have the clinical, radiological, or pathological features of a classic infectious pneumonia.

Endothelial cells and platelets are both activated by SARS CoV-2 through angiotensin converting enzyme-2 (ACE-2) [1,2].

This disrupts clotting physiology, characterised by increased levels of von Willebrand Factor (VWF), platelet hyperactivation, activation of the intrinsic clotting pathway, and impaired fibrinolysis [3]. Subsequently, this leads to a state of persistent hypercoagulation characterised by widespread microthrombi and fibrinoid deposits, which are resistant to fibrinolysis [4]. The early characterization of acute COVID-19 by assessing platelet dysfunction and the presence of circulating fibrin amyloid-like microclots using fluorescence microscopy has been proposed as a rational framework for diagnosis [3].

Long COVID is a clinical syndrome most characterised by disabling fatigue, cognitive dysfunction, and post-exertional malaise (PEM) [5]. Nearly half of patients (hospitalised or otherwise) report persistent symptoms after one year post their initial acute COVID-19 infection [6]. The precise cause of Long COVID is unknown; however, endotheliitis has been demonstrated and there are multiple reports of late thrombotic events [7-9]. Furthermore, there is evidence of persistent circulating fibrin amyloid-like microclots in plasma which could adversely affect organ function [10-13]. These fibrin amyloid-like microclots trap alpha-2-antiplasmin, fibrinogen, and amyloids, and are particularly resistant to fibrinolysis [10,12].

Long COVID is a debilitating condition with currently no proven effective treatment. In this case series, H.E.L.P. apheresis was used to treat patients with Long COVID. Developed in 1984 by Seidel and Wieland, H.E.L.P. apheresis was used primarily for patients with severe hyperlipidaemia or familial homozygous

hypercholesterolemia, and has been in clinical use for 38 years [14]. Furthermore, it is used for improved blood flow in coronary heart disease, heart transplantation, aortocoronary bypass surgery, pre-eclampsia, cerebrovascular disease, and unstable angina pectoris [15]. In pilot studies by Bengsch et al., [16] H.E.L.P. apheresis has been tested in septic multi-organ failure and in haemolytic uremic syndrome [16].

It has been proposed that H.E.L.P. apheresis could benefit acute and Long COVID patients [17] owing to its anti-inflammatory effects, including the removal of cytokines such as interleukin (IL)-6, IL-8, and TNF-α. It also reduces C-reactive protein (CRP) concentrations by more than 50% [16]. Furthermore, H.E.L.P. apheresis, exhibits anticoagulant properties reducing the pro-coagulation and fibrinolytic cascades by 35% to 50% [18], while antithrombin III is only reduced by 25% [18]. Fibrinogen is a main determinant in microcirculation, plasma viscosity, and erythrocyte aggregability [19]. Hence, decreased fibrinogen concentrations will relieve the rheology of the pulmonary circulation without a reduction in erythrocyte concentration [17]. It will also facilitate oxygen exchange and significantly reduce the plasma viscosity and erythrocyte aggregability by 19% and 60%, respectively [20]. Additionally, H.E.L.P. apheresis has been found to remove circulating fibrinolysis-resistant microclots [18,19]. Vascular endothelial growth factor (VEGF) and nitric oxide (NO) are also favourably influenced by H.E.L.P. apheresis [20], and an improvement in cerebral blood flow in cardiac patients has been observed, with a 63% increase in the CO_2 reserve capacity [21]. Additionally, H.E.L.P. apheresis lowers low-density lipoprotein (LDL) cholesterol and lipoprotein(a) [Lp(a)] concentrations [22,23], improving endothelial function [24,21,20]. Hence, H.E.L.P. apheresis has the potential to de-escalate the coagulation cascade while minimizing risks of bleeding [17].

Furthermore, heparin used in the H.E.L.P. apheresis system can bind and remove COVID-19 particles as well as bind the SARS-CoV-2 S1 spike protein [25]. Lastly, the heparin adsorber eliminates endo- and exotoxins, regardless of their bacterial or viral origin [26,16]. Since the SARS-CoV-2 virus is able produce neurotoxic "conotoxins" by acting as a bacteriophage on the gut and lung microbiome of infected patients [27], this property of H.E.L.P. apheresis would prove beneficial in this patient group. In essence, these vascular, anti-inflammatory, and anticoagulant effects could be helpful in COVID-19 disease and Long COVID [17]. In this article, where "apheresis" is mentioned, it can be assumed that it is H.E.L.P apheresis, except if explicitly stated otherwise.

Methods

In this pilot study, we have observed 17 patients (Age 23-63, median 40 years; 10 males, 7 females). The group was a combination of self-referred individuals and those referred by their physicians. The history of acute COVID-19 infection was either confirmed by the presence of a positive PCR or antibody test in the patient's medical history or diagnosed as a case of probable COVID-19 infection based on symptom presentation at the time of acute illness using World Health Organization (WHO) recommendations. All patients had either received a formal diagnosis of Long COVID from their primary care practitioner or from a clinician experienced in the condition (Dr. BR Jaeger) at the H.E.L.P. apheresis centre. Participants were pre-screened with a detailed intake form prior to the study, which was also used to acquire baseline characteristics. Additionally, the participants signed an informed consent form before the H.E.L.P apheresis treatments. All participants had been in full-time employment and had normal exercise function prior to COVID-19. Any patient comorbidities are illustrated in Figure 1 below. After acute COVID-19, they developed severe symptoms of Long COVID (symptom duration 2-12 months, median 3 months).
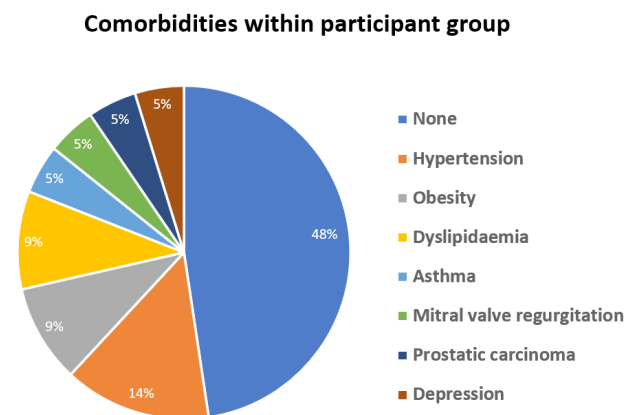
Comorbidities within participant group

Figure 1: Comorbidities within the participant group. Seven different comorbidities were reported within the study group. These comorbidities were experienced prior to the COVID-19 infection. Among the 17 patients; 21 comorbidity instances were reported. Each instance is represented by one of the seven comorbidities. These comorbidities likely could have affected the intensity and severity of symptoms experienced.

The patients were treated with an average of four H.E.L.P. apheresis treatments, (minimum 1; maximum 7) an average of seven days between each treatment. During H.E.L.P. apheresis, blood cells are separated from plasma in an extracorporeal circuit, 400 000 units of unfractionated heparin are added to the plasma, and the pH is lowered to 5.12 using an acetate buffer. This is the isoelectric point for the optimal precipitation of the apolipoproteins from LDL cholesterol, Lp(a), and very-low-density lipoprotein (VLDL), which are removed in the precipitation filter, together

with 60% of fibrinogen. Excess heparin is adsorbed, and bicarbonate dialysis restores the pH balance, eliminating the risk of haemorrhage. The patient's blood cells are reinfused in parallel with a saline solution. During each treatment, between 2 and 4 litres of blood are treated and depending on the flow rate achieved, lasts between 2 and 4 hours. This process is illustrated in Figure 2.
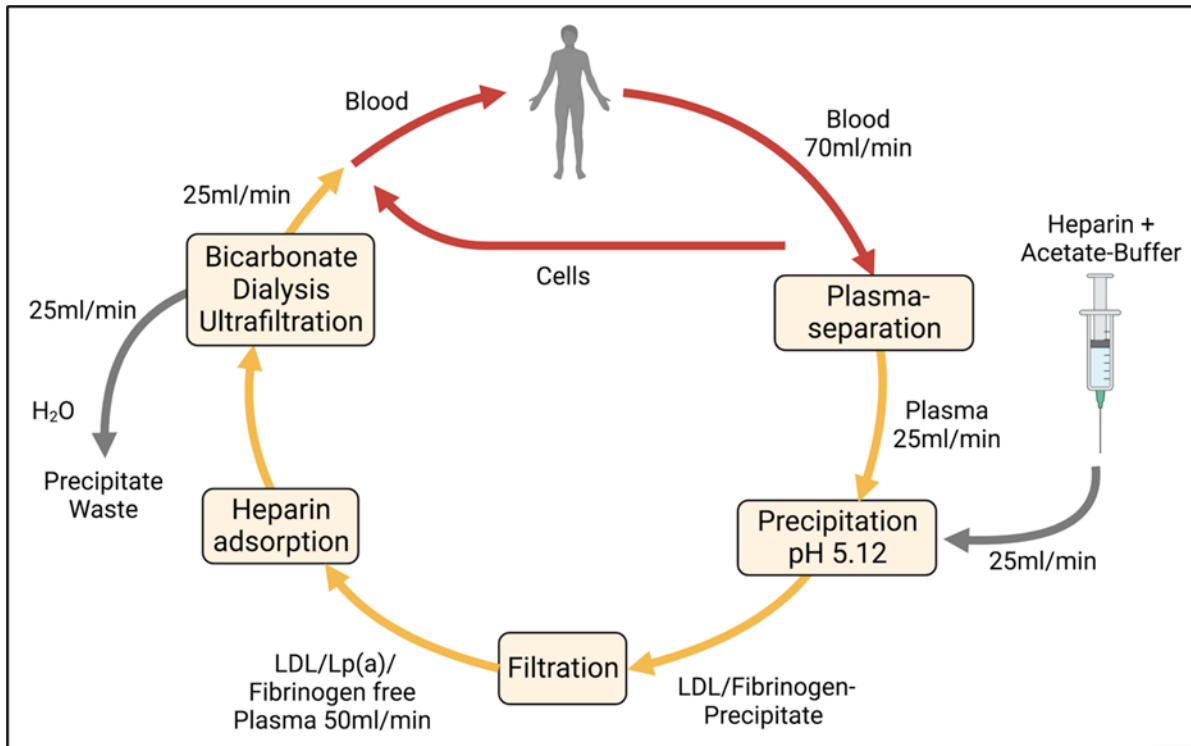

Figure 2: H.E.L.P. apheresis flow scheme. Blood cells are first separated from plasma in an extracorporeal circuit, 400,000 units of unfractionated heparin are added to the plasma, and the pH is lowered to 5.12 using an acetate buffer. This is the isoelectric point for optimal precipitation of apolipoproteins from LDL cholesterol, Lp(a), and VLDL. Excess heparin is then adsorbed, and bicarbonate dialysis balances the pH to counter any risk of haemorrhage. The blood cells are then reinfused in parallel with a saline solution. This marks the completion of one H.E.L.P. apheresis cycle. The duration of the procedure is usually 1.5 to 3 hours, depending on the flow rate achieved, and between 2.5 and 4 litres of blood are treated per session.

The aim of this retrospective study was to treat patients and to establish whether H.E.L.P. apheresis treatment assists in the symptom relief and treatment of Long COVID patients. This was assessed in the form of a questionnaire before and after the patients underwent treatment, and a follow-up with the patients 6-10 months after the last apheresis treatment.

Furthermore, blood tests were conducted before and after each H.E.L.P apheresis treatment to measure, amongst others, fibrinogen, D-Dimer, and CRP concentrations. Although valuable, our aim was not to compare before and after concentrations related to an individual H.E.L.P apheresis treatment. It has been thoroughly reported that a H.E.L.P apheresis treatment successfully decreases the concentrations of these biomarkers. Instead, we are interested in the maintenance of improvements i.e., can the lowered concentration seen directly after a H.E.L.P apheresis treatment be preserved in Long COVID patients, at least until the next treatment. Furthermore, we aim to evaluate the change in the concentrations of these biomarkers over the course of consecutive H.E.L.P apheresis treatments. Therefore, we will group blood results in 'before' (B) and 'after' (A) groups for each patient and each biomarker. The change in biomarker concentration due to the number of H.E.L.P apheresis treatments will be evaluated within each group (before group and after group) in the form of linear regression. We aim to express the results in terms of the slope (m) of the linear regression. In the case of fibrinogen, D-Dimer, and CRP, a negative linear regression ($m_{A/B} < 0$) will indicate an improvement in coagulability due to the number of H.E.L.P apheresis treatments (n_H), whereas a positive linear regression ($m_{A/B} > 0$) will indicate an increase in coagulation risk. Additionally, no change is represented by $m_{A/B} = 0$. The number of 'before' values available are expressed as n_B and the number of 'after' values are expressed as n_A.

Results

The procedure resulted in the removal of substantial amounts of solid material which could be observed in the filter (Figure 3). 16 of the 17 patients had substantial improvement in all symptoms after the completion of all their H.E.L.P. treatments, including breathlessness, fatigue, and cognition. Although many of the patients had a reduction in their former exercise habits/regimens and working abilities after their acute COVID-19 infection, 12 patients reported complete or near-complete resolution of all symptoms after treatment, with many restored to their pre-infection baseline levels and being able to work full-time again. An extensive description of every patient's case can be found below. A telephonic review in December 2021 revealed that the benefits were either preserved or continued to increase in 15 patients (follow-up 6-10 months; median 7 months). Only two patients had significant new or continued symptoms.

Figure 3: Solid fibrinogen material in the H.E.L.P apheresis machine filter. After a H.E.L.P apheresis treatment, the filters contain a white/yellow gel-like substance. This is the precipitated and filtered solid fibrinogen, LDL, VLDL, and Lp(a). This filter also removes other molecules not visible to the naked-eye, such as inflammatory mediators, clotting factors, SARS-CoV-2 S1 spike protein, and neurotoxic "conotoxins".

A summary of patient responses to the H.E.L.P. apheresis treatments can be seen in Figure 4, as well as a detailed description of the symptom alleviation in Figure 5.
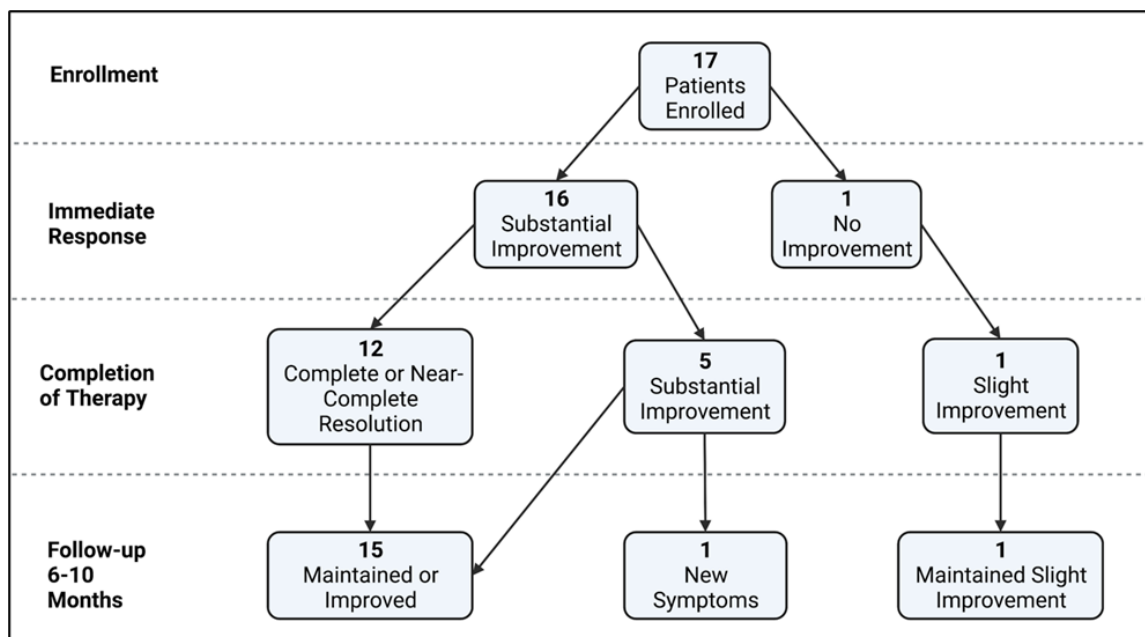

Figure 4: Changes in symptoms experienced due to H.E.L.P. apheresis treatments. Summary of patient recruitment, their immediate response to H.E.L.P. apheresis treatment, any symptoms experienced after the last apheresis session, and their symptoms present at a 6–10-month follow-up.
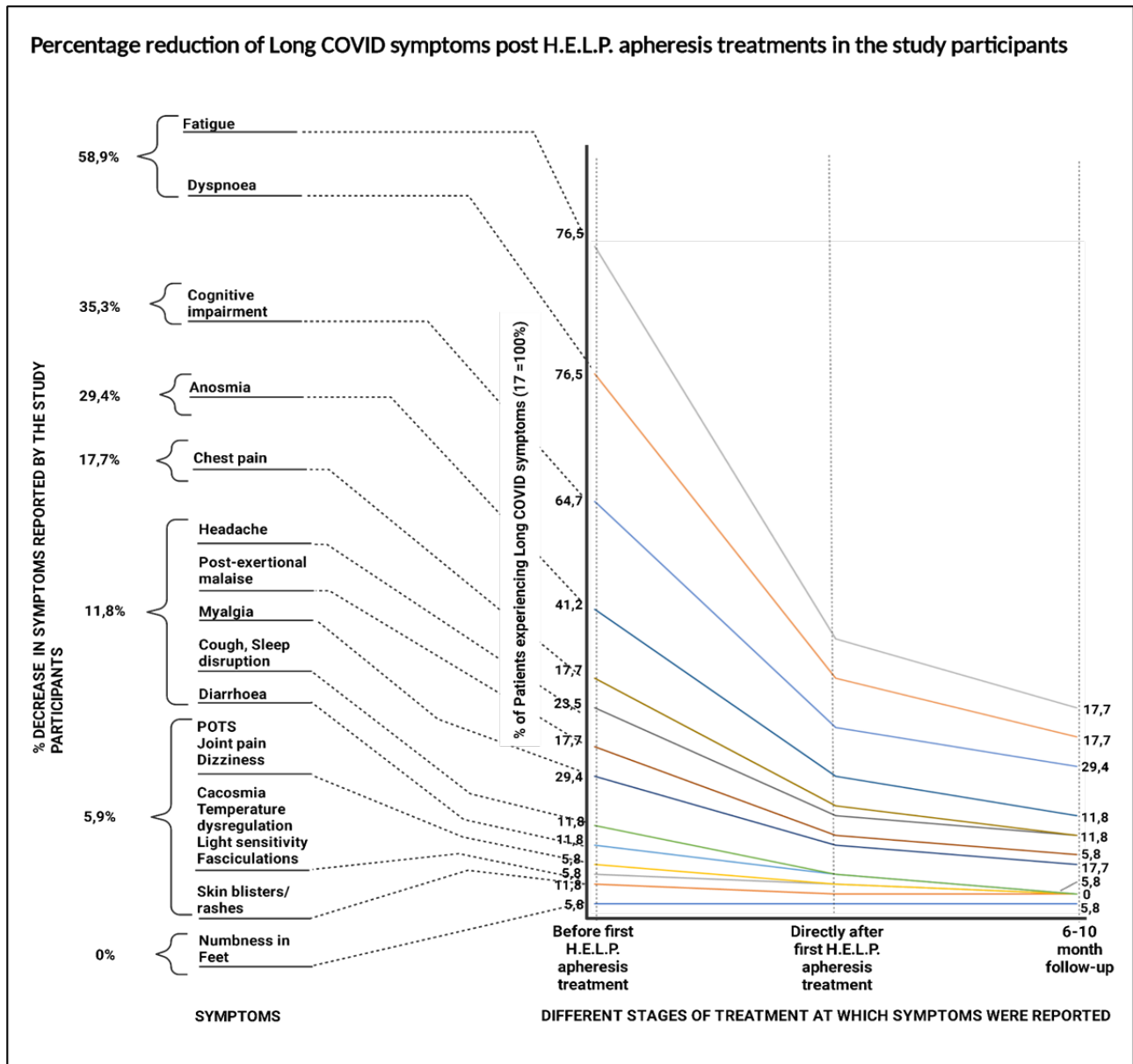
Figure 5: The percentage of patients that experienced Long COVID symptoms at different stages of the H.E.L.P. apheresis treatments. Symptoms experienced were reported before the start of the H.E.L.P. apheresis treatments, directly after the first H.E.L.P. apheresis treatment, and 6-10 months after the last H.E.L.P. apheresis treatment at a follow-up consultation. From the study group (n=17) one symptom, numbness in feet, did not resolve or improve with the H.E.L.P. treatments. This symptom was experienced by one patient (5,8%). Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Case Reports

Patient 1

30-year-old caregiver, Krupp Hospital, Essen, was infected November 2020 while on duty in the Corona ward and tested positive on the 24th of November 2020. Despite contracting pneumonia in 2017, he healed completely and was healthy and athletic prior to his COVID-19 infection. During the infection period he developed fever and exhaustion and could barely walk between his bedroom and kitchen. He had also protracted dyspnoea, which prevented him from climbing steps. By December 2020, he tried physical activity such as walking, and on the 20th of that month he noted that he was unable to walk for longer than 50–60 minutes at a time. He received three H.E.L.P. apheresis treatments, on the 2nd, 10th, and 16th of February 2021, respectively. After his first apheresis, his breathing improved and was evaluated by giving 40 steps at a fast pace. He managed this easily, despite his breathing rate accelerating faster than normal. The day after the second apheresis he was completely symptom-free and discontinued his salbutamol spray medication. Two days later he was able to jog 20km. Thoracic computerized tomography (CT) showed complete healing with no residuals. Overall, there was a decrease in blood coagulation factors directly after the first apheresis (Table 1). Plasma fibrinogen ([PFIB]) levels decreased by 32% from 320mg/dl to 101 mg/dL, measured before and after the first H.E.L.P. apheresis (Figure 6). A month after the first H.E.L.P. apheresis, [PFIB] levels were elevated.

Table 1: Patient 1 blood coagulation factors results before and after H.E.L.P. apheresis treatments. Factor X, - XII, -VII and -IX all decreased when compared to before the H.E.L.P. apheresis treatment indicating a decrease in coagulation risk.

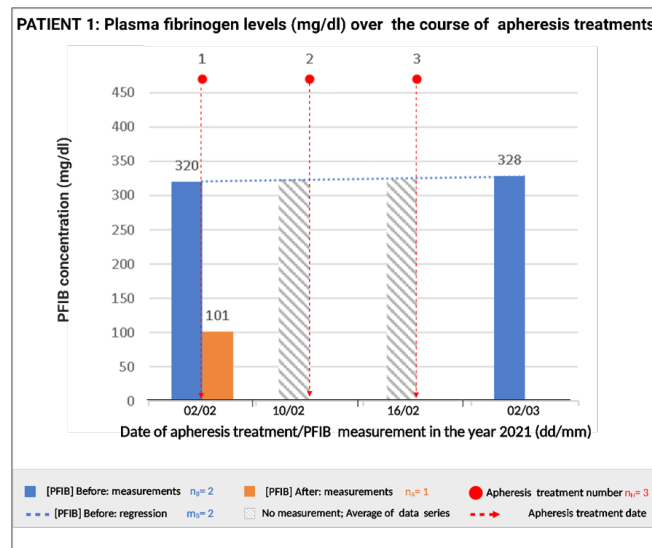| 1st H.E.L.P. Apheresis in Patient 1				
Blood coagulation factors	**Before**	**After**	**Change in concentration**	**Effect on coagulation**
Factor X (%)	107	42	Decrease	Decrease
Factor XII (%)	144	63	Decrease	Decrease
Factor VII (%)	62	41	Decrease	Decrease
Factor IX (%)	153	62	Decrease	Decrease

Figure 6: Fibrinogen levels of patient 1. Patient 1 completed three H.E.L.P apheresis treatments (n_H=3). [PFIB] measurements were taken before treatment 1 and 2, and 20 days after the 3rd. The fibrinogen levels decreased with 32% over just more than a month. [PFIB] follows a linear positive regression in relation to the number of apheresis treatments with a slope of m_b=2. Where [PFIB] values were unavailable, the average of the data series was used in order to determine the regression. Abbreviations: PFIB: Plasma fibrinogen. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 2

40-year-old heating engineer from Bottrop was infected with COVID-19 in May 2020 and was in hospital for suspected myocarditis. He complained of very severe headaches, experienced persistent weakness in his performance, and lost his sense of smell lasting six months. His symptoms were alleviated completely after one H.E.L.P. apheresis treatment, that was carried out on 12/04/2021. A thoracic CT revealed no pathological findings, except for low-grade ventilation disturbances.

Patient 3

A 53-year-old nurse and Long COVID sufferer was infected with COVID-19 in February 2021 during her service at a care-home in Bochum. The patient has suffered from bronchial asthma and mitral valve insufficiency since childhood. Her COVID-19 infection initially caused severe headaches, a persistent fever of 40°C, fatigue, severe pain in both legs and shortness of breath at the slightest exertion. She used a fluticasone/vilanterol spray. A pulmonary CT revealed a lung infarction (scarring and calcifications), and she reported severe concentration problems that has lasted more than a month without improvement. During March and April of 2021, she received three apheresis treatments in total. After her first apheresis on the 30th of March, she reported a slight improvement. The day after the second apheresis (06/04/2021) she felt unwell: describing an altered body awareness. After her third apheresis on the 20th of April, she experienced a breakthrough and was able to breathe deeply and effortlessly. Her physical resilience i.e., tolerance to physical activity, continually improved; she could recommence her exercise, including walking on inclines.

She also reported that the discomfort in her legs notably decreased. A decrease can be seen in D-Dimer levels after each apheresis treatment (Table 2). However, after test two, D-Dimer was slightly more elevated than the values measured at the time of test 1. When comparing measurements before and after each treatment, a decrease was also observed in [PFIB] (Figure 7).

Table 2: Patient 3 blood coagulation marker D- Dimer results before and after apheresis treatments. Apheresis treatment resulted in an immediate decrease in D-Dimer levels; however, this decline was not maintained by the time of the second apheresis test, which in turn also resulted in an immediate decrease.

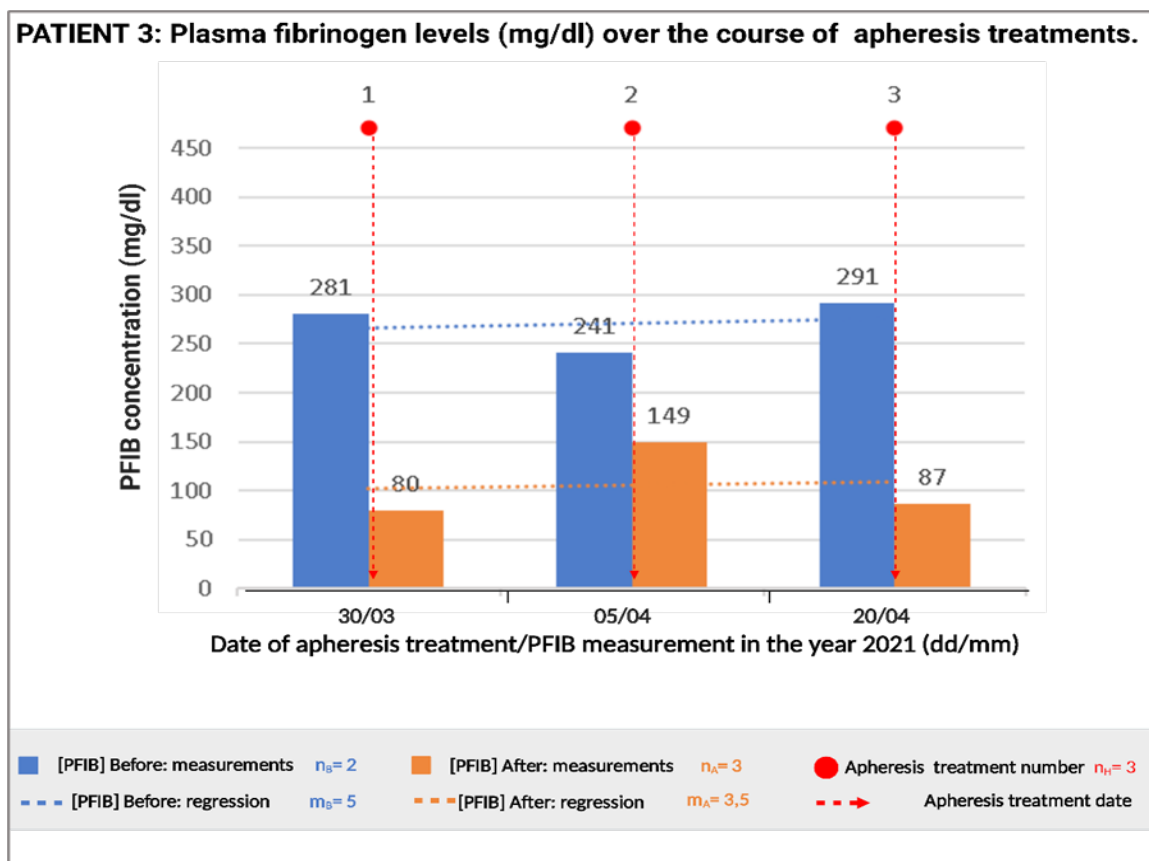| H.E.L.P. Apheresis in Patient 3					
Blood coagulation markers	Test number	Before	After	Change in concentration	Effect on coagulation
D-Dimer	1	360	<190	Decrease	Decrease
D-Dimer	2	359	313	Decrease	Decrease

Figure 7: Fibrinogen levels of patient 3. Patient 3 completed three apheresis treatments (n_H=3). [PFIB] measurements were taken before (n_B=2) and after (n_A=3) each treatment. When comparing the [PFIB] obtained before each treatment, a decrease is seen from treatment 1 to 2. Before test 3, [PFIB] was elevated again. [PFIB] after each treatment was higher after treatment 2 compared to treatment 1, but lower after treatment 3 compared to treatment 2. The [PFIB] follows a positive linear regression in relation to the number of apheresis treatments for both before and after measurements with slopes of m_B=5 and m_A=3,5, respectively. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 4

The husband of patient 3, age 58, was diagnosed with prostate carcinoma in 2018. He was tested for COVID-19 as part of a planned cataract surgery in February 2021 and the results returned positive. During his acute COVID-19 infection he developed a fever, cough, massive headache, and pain in his limbs described as being like "rheumatism in terminal stage". He felt continuously tired and weak, had a low breathing capacity i.e., struggled to take a deep breath, had problems with his memory, struggled to complete sentences, and a partial loss of smell. After his first apheresis on the 30th of March 2021, he reported improvement in his concentration and fewer problems in his speech. After his second apheresis on the 5th of April 2021, he reported a "bad body feeling". However, one day later, this had disappeared, and he had noticed improvement in his neurological limitations. After the third apheresis on the 20th of April 2021, both neurological deficits and shortness of breath were massively alleviated. His sense of smell recovered only partially. For example, he could smell vanilla, but he couldn't smell lemon. After two further apheresis treatments (1st and 8th of June), his venous oxygen saturation prior to treatments increased and stabilized around 80%, compared to the previous treatments being only 63% and 70%, respectively. Plasma fibrinogen levels decreased when comparing values before and after each treatment. Furthermore, when comparing the measurements taken before each treatment (n_B) and after each treatment (n_A), a decrease was observed (Figure 8). D-Dimer and CRP levels decreased when comparing measurements taken before test five, to measurements taken before test one (Table 3).
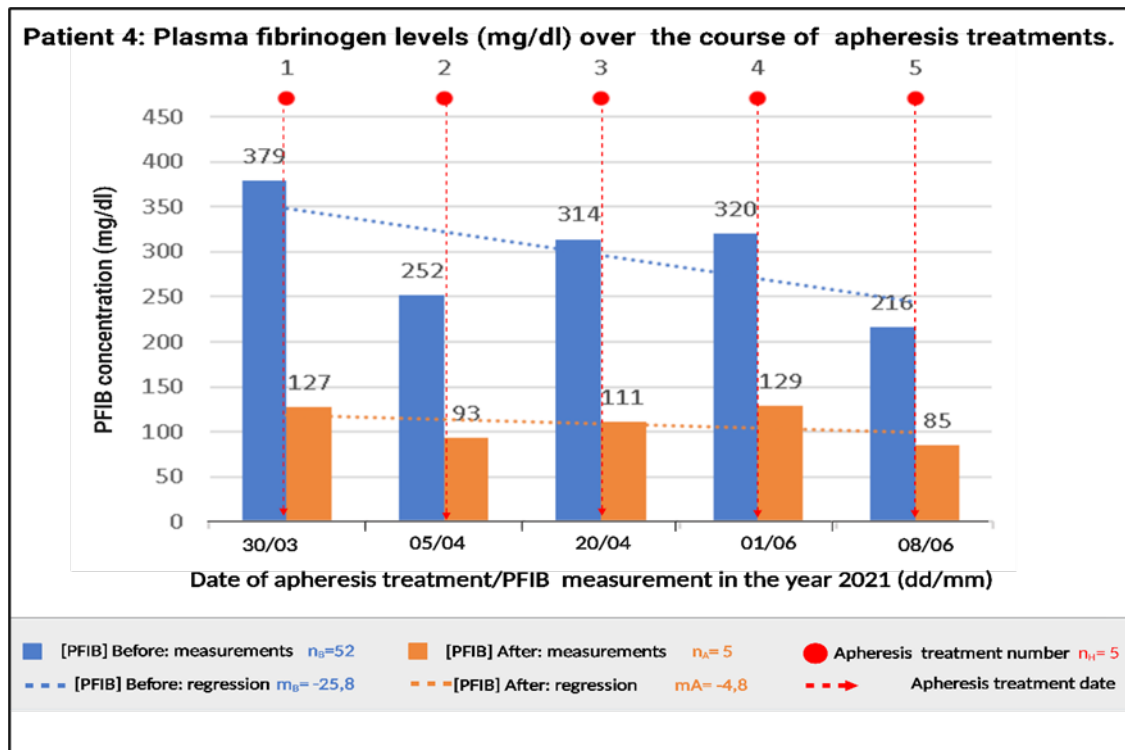

Figure 8: **Fibrinogen levels of patient 4.** Patient 4 completed five apheresis treatments (n_H=5). Before and after each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before each apheresis treatment (n_B=5) showed an overall decrease in [PFIB]. Both before and after [PFIB] are indirectly proportional to the number of apheresis treatments and follow a negative linear regression, in relation to the number of apheresis treatments, with slopes of m_B=-25,8 and m_A=-4.8. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Table 3: D-Dimer and CRP concentrations of patient 4. D-Dimer and CRP levels increased when comparing measurements taken from before tests 1,2, and 3. However, in both D-Dimer and CRP measurements from before test number 5, a decrease was observed when compared to measurements taken before test 1. CRP concentrations follow a negative linear regression when compared to the number of apheresis treatments with a slope of -0,004, and D-Dimer follows a positive linear regression with a slope of 4,7.

H.E.L.P. Apheresis in Patient 4						
Blood coagulation markers	**Measurement**	**Test Number**				**Linear Regression Slope**
		1	**2**	**4**	**5**	
D-Dimer (ng/ml FEU)	Before	464	469	552	452	4,7
CRP (mg/dL)	Before	0,14	0,15	0,23	0,1	-0,004

Patient 5

In December 2020 a 32-year-old architect from Gelnhausen was infected with COVID-19. He was athletic, despite being slightly overweight and had arterial hypertension. He initially developed severe headaches, dizziness, earaches, shortness of breath, and angina pectoris, which lasted more than 14 days. He could only walk 200m and post-walk he had to rest. He felt "endlessly limp" and was unable to work under pressure. The man was admitted to the Main-Kinzig-Klinikum on the 23rd of March 2021 as an inpatient. Cardiac magnetic resonance imaging (MRI) revealed perimyocarditis with fibrosis, scarred areas subepicardially, pericardially-laterally, and inferolaterally. In parallel, he developed weakness in his right leg and had to drag it when walking. Head MRI revealed two lacunar defects (medullary camp frontally left). He received H.E.L.P. apheresis treatments on the 6th, 9th, and 23rd of April 2021. During his first apheresis his angina pectoris reoccurred. However, he noted afterwards that his head was clearer, and he could breathe with more ease. After his second apheresis his symptoms improved drastically: his headaches subsided, his gait improved, and he was able to handle much more physical strain - such as jogging. By the time he completed his third apheresis, he was able to return to his lifestyle as it was before the COVID-19 infection. Over the course of three apheresis treatments, his [D-Dimer] decreased (Table 4) as well as [PFIB] (Figure 9).

Table 4: D-Dimer levels for Patient 5. A decrease was seen in the D-Dimer concentration over the course of two apheresis treatments. This could indicate that H.E.L.P apheresis decreases the risk of hypercoagulation.

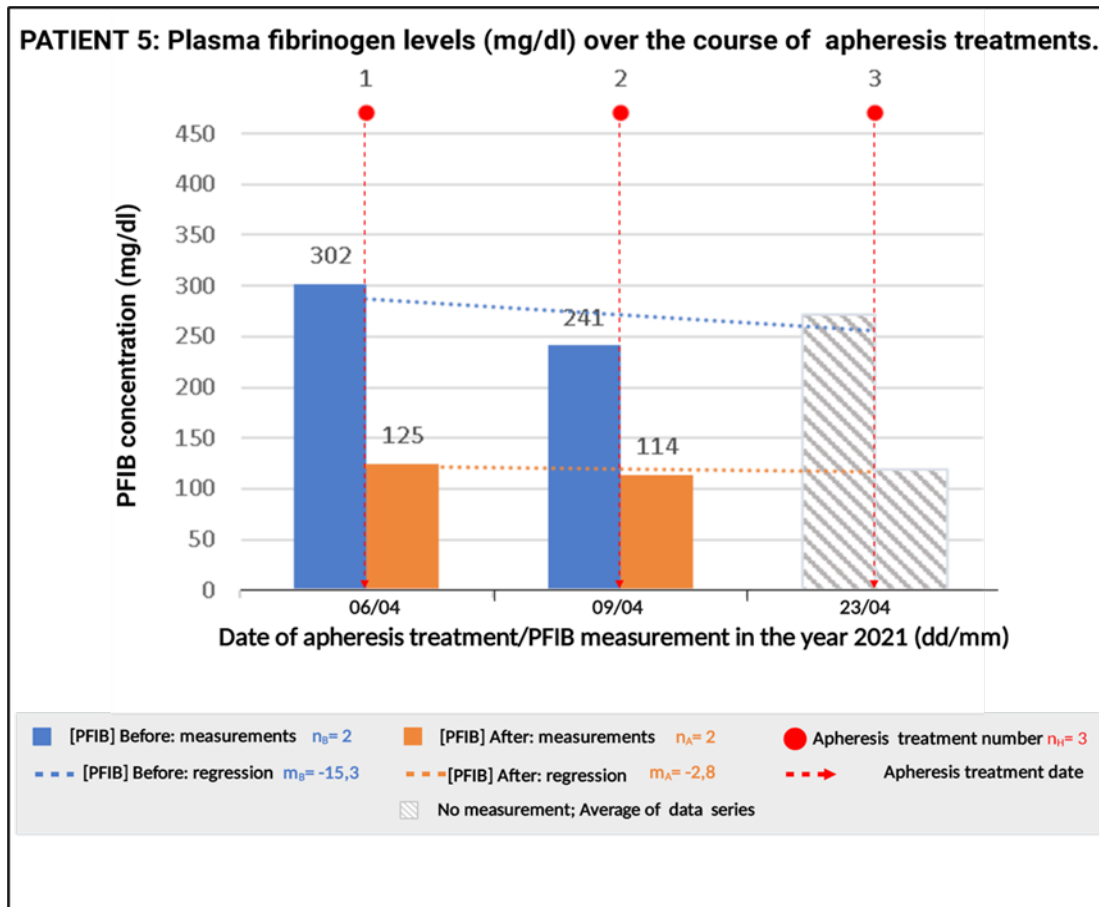| H.E.L.P. Apheresis in Patient 5					
Blood coagulation markers	**Test number**	**Measurement before treatment**	**Measurement after treatment**	**Change in concentration**	**Effect on coagulation**
D-Dimer (ng/ml FEU)	1	667	505	Decrease	Decrease
	2	649	526	Decrease	Decrease

Figure 9: Fibrinogen levels of patient 5. Patient 5 completed three apheresis treatments (n_H=3). Before (n_B=2) and after (n_A=2) the first two apheresis treatments, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after each apheresis treatment showed an overall decrease in [PFIB]. Both before and after [PFIB] are indirectly proportional to the number of apheresis treatments and follow a negative linear regression in relation to the number of apheresis treatments, with slopes of m_B=-15,3 and m_A=-2,8, respectively. Where [PFIB] values were unavailable, the average of the data series was used in order to determine the regression. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 6

A 52-year-old anaesthetic nurse from Krupp Hospital, Essen, tested positive for COVID-19 in December 2020 after a shift in the operating theatre. Following the infection, the patient suffered depressive episodes, experienced headaches, loss of smell and taste, decreased appetite, and she had difficulties in speaking, thinking, and concentrating. Additionally, she experienced air hunger after minimal physical strain such as climbing one flight of stairs. Furthermore, she reported skin rashes, hair loss, and black streaks on her nails (possibly embolic). She underwent several H.E.L.P. apheresis treatments conducted on the 13th, 16th, 22nd, and 29th of April 2021 as well as the 4th and 5th of May 2021 and the 2nd of June 2021. After the second apheresis she felt clearer and could breathe better. After the fourth apheresis there were remarkable improvements in her articulation and memory. Her sense of smell and taste recovered partially. She could climb more stairs and felt less depressed. By the end of June, she started rehabilitation to aid persisting (but non-consecutive) headaches and memory problems, although already much attenuated with the H.E.L.P. apheresis treatments. Over the course of seven apheresis treatments, CRP (Table 5) and [PFIB] (Figure 10) decreased, whereas D-Dimer increased (Table 5).

Table 5: D-Dimer and CRP levels for Patient 6. An increase in [D-Dimer] and a decrease in [CRP] was seen over the course of seven H.E.L.P. apheresis treatments.

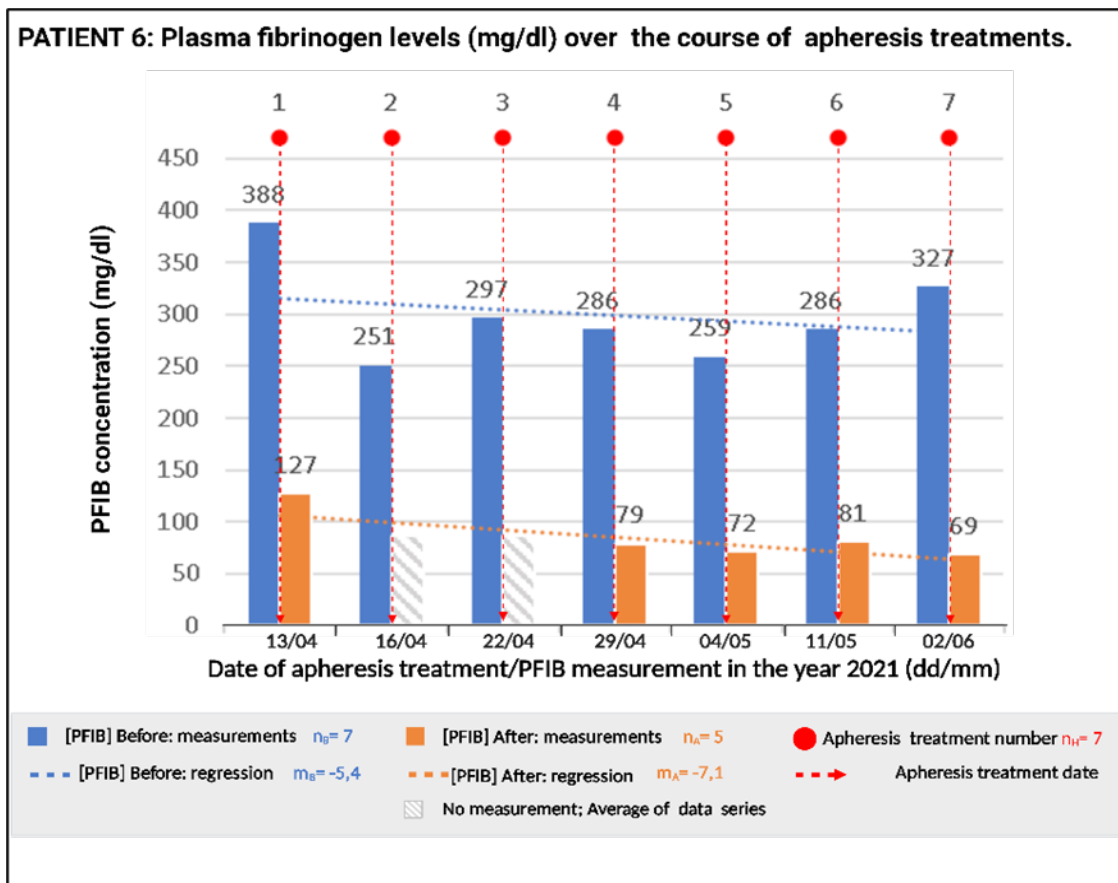| H.E.L.P. Apheresis in Patient 6							
Blood coagulation markers	**Measurement**	**Test number**					**Linear Regression Slope**
		1	**4**	**5**	**6**	**7**	**(m)**
D-Dimer (ng/ml FEU)	Before	396	434	417	476	453	15,6
CRP (mg/dL)	Before	0,14	-	-	0,08	0,06	-0,04

Figure 10: Fibrinogen levels of patient 6. Patient 6 completed seven apheresis treatments (n_H=7). Before (n_B=7) and after (n_A=5) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after each apheresis treatment showed an overall decrease in [PFIB]. Both before and after [PFIB] are indirectly proportional to the number of apheresis treatments and follow a negative linear regression in relation to the number of apheresis treatments, with slopes of m_B=-5,4 and m_A=-7.1, respectively. Where [PFIB] values were unavailable, the average of the data series was used in order to determine the regression. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 7

In January 2021, a 53-year-old chief physician from Soest contracted COVID-19. Before his acute infection, he could walk 5km and regularly partook in sports. Initially, the infection caused flu-like symptoms such as fevers that reached up to 39.3°C in a wave-like course and a dry-cough. His resilience was clearly limited; climbing stairs caused shortness of breath and he experienced thoracic pain

during deep respiration. Initially he also experienced anosmia and headaches, which later subsided. Furthermore, he experienced daytime fatigue, concentration problems, restless legs, and gastrointestinal irregularities. No lung-damage was observed during a pulmonological examination conducted on the 10th of February 2021. Other than bifrontal medullary lagliosis and an arachnoid cyst, a head MRI revealed no abnormal findings. The patient described that he was "no longer able to strain himself and unable to concentrate and work for more than four hours". After mowing his lawn, he was "half-dead", fatigued and had to rest for up to three days. H.E.L.P. apheresis treatments were conducted on the 13th, 15th, and 20th of April 2021. He reported a significant decrease in all symptoms and called it "a striking improvement". He received two more treatments on the 27th of April and the 6th of May which allowed him to return to work full-time. Fibrinogen concentrations (Figure 11) were measured after each treatment, showing a clear decrease in concentration, while D-Dimer and CRP concentrations were measured before each treatment (Table 6).
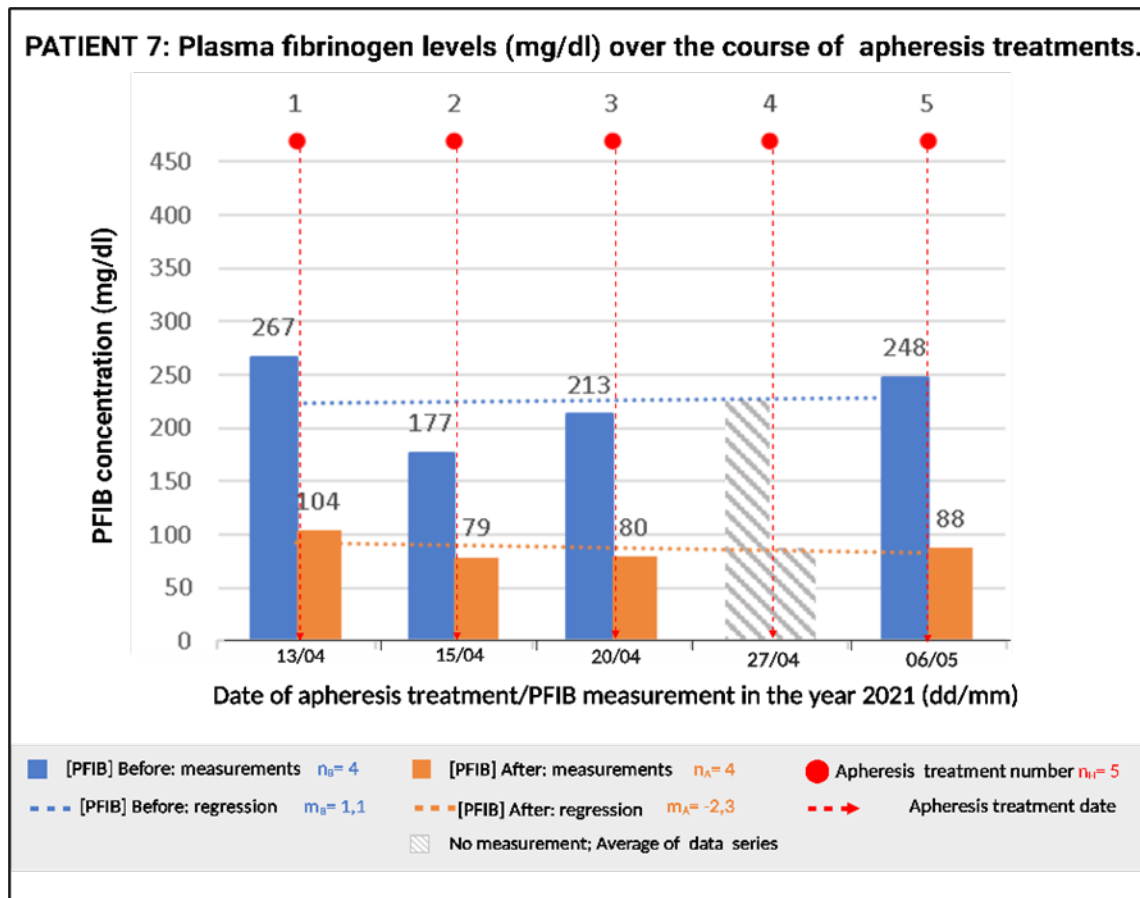

Figure 11: Fibrinogen levels of patient 7. Patient 7 completed five H.E.L.P. apheresis treatments (n_H=5). Before (n_B=4) and after (n_A=4) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The before measurements showed an overall increase and follow a positive linear regression in relation to the number of apheresis treatments, with a slope of m_B=1.1 The after measurements show an overall decrease in [PFIB] following a negative linear regression, in relation to the number of apheresis treatments, with a slope of m_A=-2,3. Where [PFIB] values were unavailable, the average of the data series was used to determine the regression. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Table 6: D-Dimer and CRP levels for patient 7. Both D-Dimer and CRP level decreased over the course of H.E.L.P apheresis treatments.

H.E.L.P. Apheresis in Patient 7					
Blood coagulation markers	**Measurement**	**Test Number**			**Linear Regression Slope (m)**
		1	**2**	**5**	
D-Dimer (ng/ml FEU)	Before	247	190	213	-17
CRP (mg/dL)	Before	0,04	0,03	0,03	-0,005

Patient 8

In October 2020, a 35-year-old firefighter from Neukirchen-Vluyn contracted COVID-19. Initially he had a fever of up to 40°C that continued for 6 days. He would experience shortness of breath after speaking only a few words. His lips became cyanotic, and he experienced repeated hypertensive crises, with a resting heart rate of 60 bpm (twice presyncopal). The performance deficit persisted. Before the COVID-19 infection, he was able to pedal 270 watts on the ergometer and regularly jogged between 15 and 20km. Post COVID-19 infection, he could only manage 2km of walking. He experienced sleep disturbances every night accompanied by gasping for air several times per night. The thoracic CT revealed left basal scarring. He received a COVID-19 vaccination on the 31st of December 2020 and his condition worsened. After the first apheresis on the 22nd of April 2021, his breathing improved noticeably and his sleep disturbances subsided, allowing him to sleep through the night again. The second and third apheresis took place on the 27th and 30th of April, respectively. Consequently, his physical ability improved, allowing him to jog for up to 30 consecutive minutes. After the fourth apheresis on the 8th of May 2021, he reported that he jogged 8km every other day. He underwent three more treatments on the 17th and 25th of May, as well as the 1st of June 2021. This allowed for a full recovery, and he returned to work. At this point, his arterial oxygen saturation was 98%. Fibrinogen (Figure 12) and D-Dimer concentrations were measured before and after treatment. CRP concentrations were measured before treatments and decreased over the course of H.E.L.P apheresis treatments.
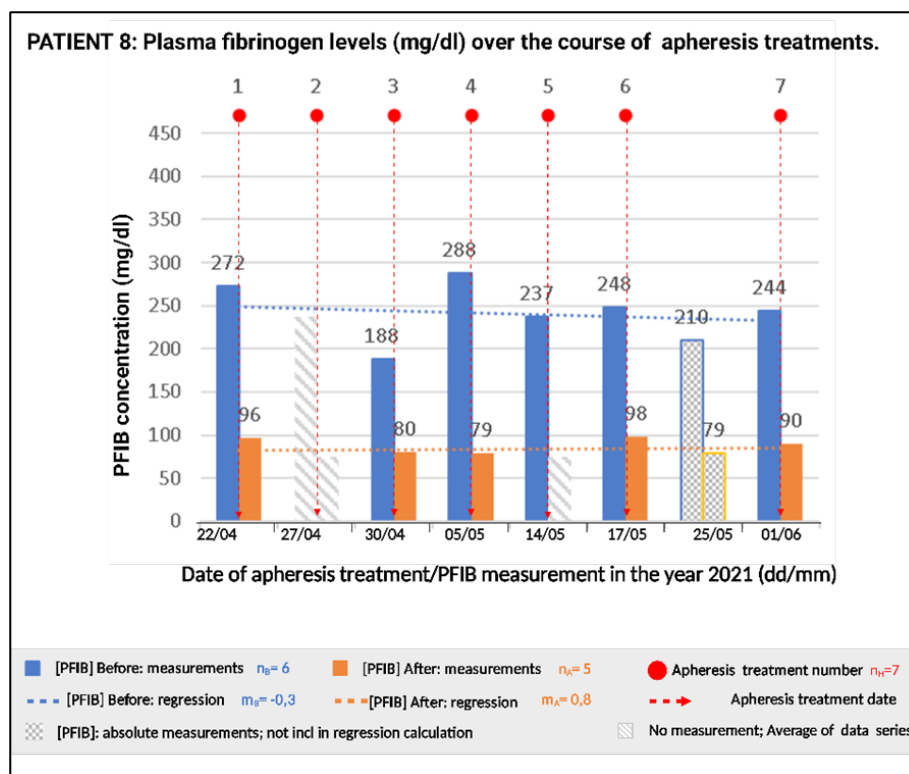

Figure 12: Fibrinogen levels of patient 8. Patient 8 completed seven H.E.L.P. apheresis treatments (n_H=7). Before (n_B=6) and after (n_A=4) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The before measurements showed an overall decrease and follow a negative linear regression in relation to the number of apheresis treatments, with a slope of m_B=-0,3. The after measurements show an overall increase in [PFIB] following a positive linear regression in relation to the number of apheresis treatments, with a slope of m_A=0,8. Where [PFIB] values were unavailable, the average of the data series was used to determine the regression. Data that was available, but was not taken around a treatment, were excluded from the calculation of the regression. Where apheresis treatment is mentioned, it refers to H.E.L.P. apheresis.

Table 7: D-Dimer and CRP concentrations for patient 8. D-Dimer and CRP concentrations measured before, and D-Dimer concentrations measured after H.E.L.P apheresis treatments decreased over the course of the seven treatments. CRP concentrations measured after treatments increased slightly. Measurements that correlate to test 2 were unavailable.

H.E.L.P. Apheresis in Patient 8								
Blood coagulation markers	**Measurement**	**Test number**						**Linear Regression**
		1	**3**	**4**	**5**	**6**	**7**	**Slope (m)**
D-Dimer (ng/ml FEU)	Before	372	252	321	342	304	316	-2,94
	After	351	190	192	190	190	190	-23,06
CRP (mg/dL)	Before	0,1	0,16	0,07	0,17	0,08	0,01	-0,02
	After	0,04	0,08	0,02	0,07	0,04	0,06	0,001

Patient 9

A 40-year-old physiotherapist was infected with COVID-19 in a Mülheim hospital ward and tested positive on the 1st of January 2021. The next day she developed a headache, ear rashes, circulation collapse, chest pain, cough, shortness of breath and hoarseness, depressive moods, and strong fatigue - with symptoms persisting throughout the quarantine. Additionally, she struggled to concentrate on reading. Two days later, she developed a fluttering pulse, heart rhythm irregularities, and resting dyspnoea, as well as prominent muscle/ankle pains. Her movements resembled Parkinson´s disease together with general weakness and permanently feeling cold (temperature dysregulation). A month later, on the 30th of January, she experienced persistent and painful burning sensations in her legs and feet, and direct sunlight caused severe headaches. She received five H.E.L.P. apheresis treatments, and after her third treatment, her feeling of being cold faded and she could breathe with more ease. Her fourth treatment was interrupted because the needle clogged. A 10cm long intravenous coagulum was found. The fifth treatment gave a significant breakthrough: her respiration and mobility improved greatly and paranaesthesia in her legs diminished. She could also take part in light physical activities - she was able to ride a bicycle for 30 minutes. Furthermore, her concentration improved, and she could tolerate bright light again. A spirometry test and chest X-ray revealed no pathologic findings. All symptoms improved and nearly diminished after the completion of treatments. D-Dimer (Table 8), CRP (Table 8), and fibrinogen (Figure 13) concentrations measured before each treatment showed an overall decrease over the course of the H.E.L.P apheresis treatment.

Table 8: D-Dimer and CRP concentrations for patient 9. D-Dimer and CRP concentrations measured before, and CRP concentrations measured after H.E.L.P apheresis treatments decreased over the course of five treatments. D-Dimer concentrations measured after treatments increased. Measurements correlating with before test 1 and after test 5 were unavailable.

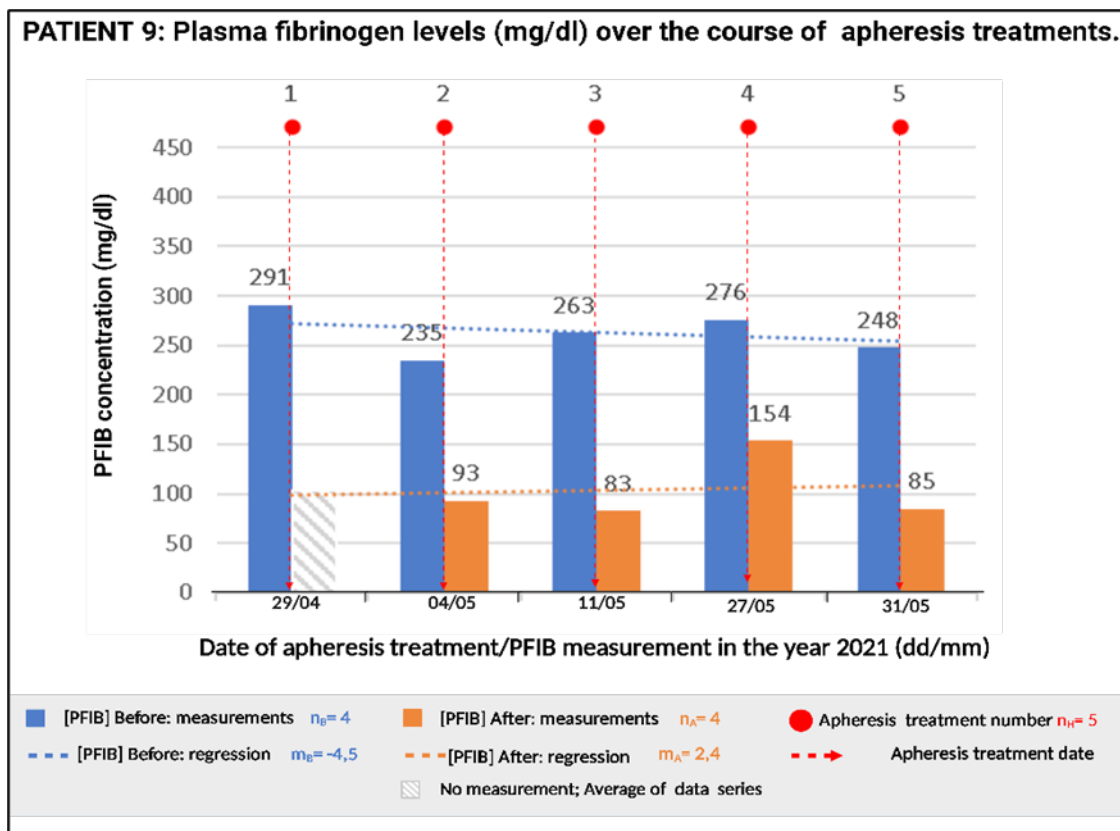| H.E.L.P. Apheresis in Patient 9						
Blood coagulation markers	**Measurement**	**Test number**				**Linear Regression Slope (m)**
		2	**3**	**4**	**5**	
D-Dimer (ng/ml FEU)	Before	458	453	528	432	-0,3
	After	263	226	464	212	8,5
CRP (mg/dL)	Before	0,09	0,06	0,07	0,04	-0,01
	After	0,06	0,02	0,02	0,03	-0,01

Figure 13: Fibrinogen levels of patient 9. Patient 9 completed five H.E.L.P. apheresis treatments (n_H=5). Before (n_B=5) and after (n_A=4) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The before measurements showed an overall decrease and follow a negative linear regression in relation to the number of apheresis treatments, with a slope of m_B=-4,5. The after measurements show an overall increase in [PFIB] following a positive linear regression, in relation to the number of apheresis treatments, with a slope of m_A= -2,4. Where [PFIB] values were unavailable, the average of the data series was used to determine the regression. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 10

A 50-year-old medical assistant from Erwitte was infected with COVID-19 in a rehabilitation clinic on the 10th of January 2021. The patient developed persistent shortness of breath, fatigue, and neurological problems causing vocabulary issues, difficulties with memory, and concentration deficits. H.E.L.P apheresis treatments were performed on the 5th of May, as well as the 1st and 4th of June 2021. Each treatment brought her relief in respect to breathing and coughing. She experienced an improved fitness level, decreased fatigue, and recovered neurologically. A decrease in fibrinogen (Figure 14) and CRP (Table 9) levels were seen over the course of the treatments.
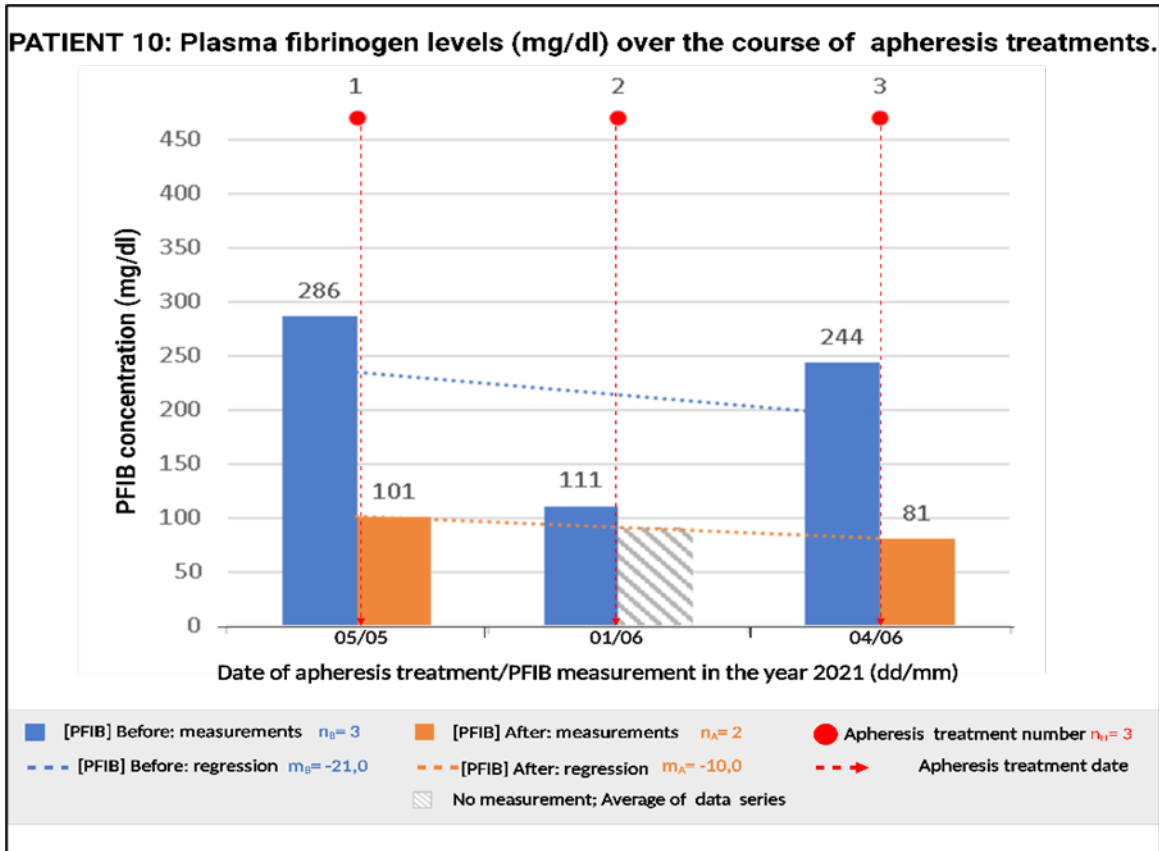

Figure 14: Fibrinogen levels of patient 10. Patient 10 completed three H.E.L.P. apheresis treatments (n_H=3). Before (n_B=3) and after (n_A=2) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after showed an overall decrease and follow a negative linear regression in relation to the number of apheresis treatments, with a slope of m_B=-21 and m_A=-10. Where [PFIB] values were unavailable, the average of the data series was used to determine the regression. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Table 9: D-Dimer and CRP concentrations of patient 10. D-Dimer concentrations remained the same and CRP concentrations decreased over the course of three H.E.L.P. apheresis treatments.

H.E.L.P. Apheresis in Patient 10					
Blood coagulation markers	Measurement	Test number			Linear Regression
		1	2	3	Slope (m)
D-Dimer (ng/ml FEU)	After	190	217	190	0,00
CRP (mg/dL)	After	0,15	0,11	0,12	-0,02

Patient 11

A 63-year-old caretaker at the Ruhrland Klinik in Essen was infected with COVID-19 in April 2020, possibly during a night shift. He had arterial hypertension and hypercholesterolemia prior to the infection. Initially he only experienced a cough, but soon developed muscle pain and severe short-term memory loss. Furthermore, intermittent headaches, concentration problems, and dyspnoea developed and persisted for a year. He received four H.E.L.P apheresis treatments. During his first apheresis on the 28th of April 2021, and second apheresis on the 4th of May, his venous oxygen saturation increased from 28,8% to 72,8%, and 48,5% to 65,7%, respectively. Following the third apheresis on the 10th of May 2021, it dropped from 79,7% to 71,0%. Finally, after the fourth and final apheresis on the 25th of May 2021, it increased from 43,0% to 84,4 %. Hence, an improvement in venous oxygen saturation was seen overall. However, he did not experience a relief in symptoms and treatment was terminated when his rehabilitation started. D-Dimer and CRP (Table 10), as well as fibrinogen (Figure 15) decreased over the course of four treatments.

Table 10: D-Dimer and CRP levels for patient 11. Overall, the concentrations of D-Dimer and CRP measured before and after the treatments decreased. Measurements that correspond to test 1 were unavailable.

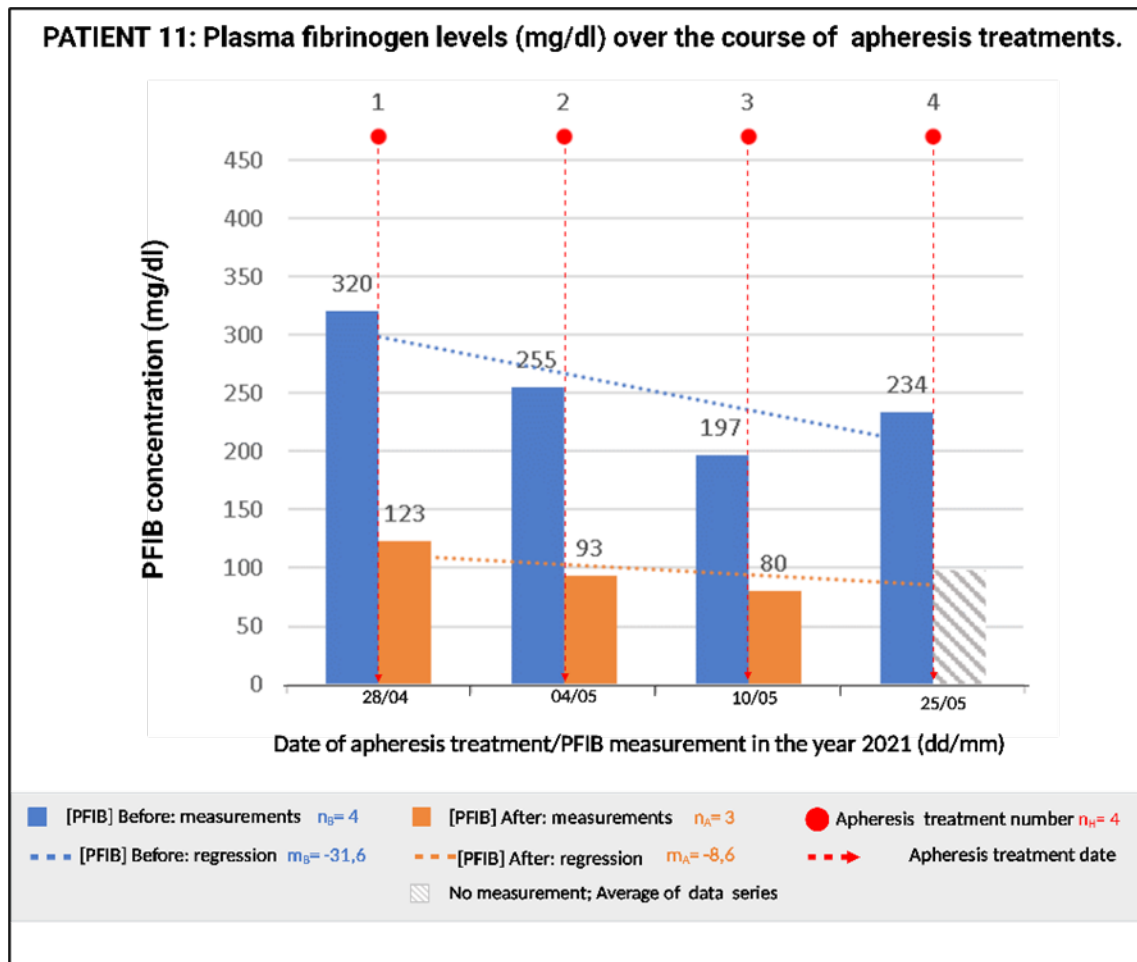| H.E.L.P. Apheresis in Patient 11						
Blood coagulation markers	Measurement	Test number				Linear Regression Slope
		1	2	3	4	
D-Dimer (ng/ml FEU)	Before	665	634	434	542	-56,9
	After	-	488	491	247	-120,5
CRP (mg/dL)	Before	0,74	0,27	0,12	0,09	-0,21
	After	-	0,32	0,1	0,06	-0,13

Figure 15: Fibrinogen levels of patient 11. Patient 11 completed four H.E.L.P. apheresis treatments (n_H=4). Before (n_B=4) and after (n_A=3) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after showed an overall decrease and follow a negative linear regression in relation to the number of apheresis treatments, with a slope of m_B=-31,6 and m_A=-8,6. Where [PFIB] values were unavailable, the average of the data series was used to determine the regression. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 12

A 29-year-old and physically active accountant from Hamburg tested positive for COVID-19 on the 7th of March 2021. Initially, she experienced symptoms such as fatigue, fever, coughing, and sneezing. Furthermore, persistent symptoms included a loss of olfaction, and enduring physical weakness and dyspnoea which prevented her from continuing her usual physical exercise. She received her first apheresis on the 3rd of May 2021. Two days later, during a walk, she noted that her olfaction returned - she was able to smell the surrounding grass and woods. After her second apheresis on the 6th of May 2021, her breathing improved and she could recommence her normal exercise regime (jogging three times per week). After her third apheresis on the 7th of June, she was relieved from all symptoms. Fibrinogen (Figure 16) concentrations decreased.
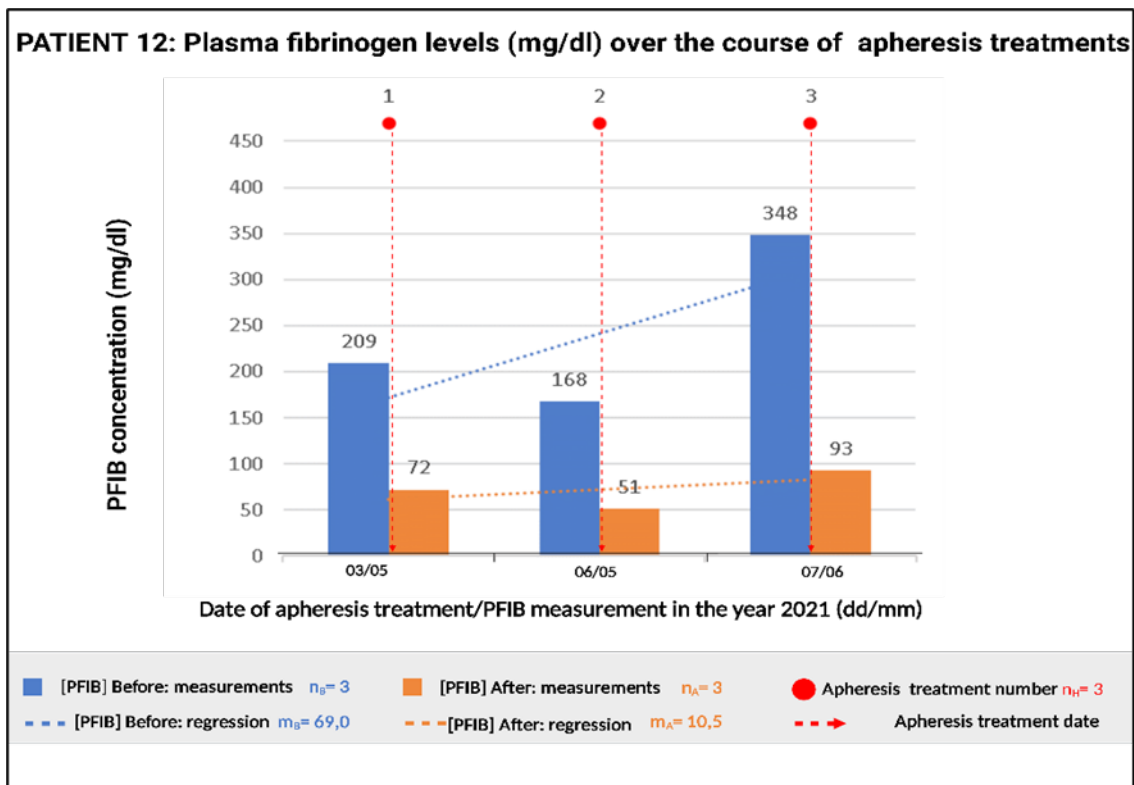
Figure 16: Fibrinogen levels of patient 12. Patient 12 completed three H.E.L.P. apheresis treatments (n_H=3). Before (n_B=3) and after (n_A=3) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after show an overall increase in [PFIB] following a positive linear regression, in relation to the number of apheresis treatments, with a slope of m_B=69,0 and m_A =10,5. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 13

A 21-year-old, physically fit, bugler from Saarbrücken was infected with COVID-19 on the 8th of November 2020. His symptoms comprised of fever, muscle/ankle pain, headaches, coughing, and gastrointestinal trouble. Two days later, he lost his sense of smell and taste and developed difficulty breathing, saying that his lungs felt like they were "full of sawdust". Some of the symptoms persisted, including shortness of breath, cough, fatigue, and muscle/ankle pain, making it difficult to undertake physical exercise. He had tremendous difficulty with concentration, especially when playing instruments. Three H.E.L.P. apheresis treatments were conducted within one week, on the 14th, 16th, and 18th of June 2021. This alleviated all his symptoms, allowing him to return to his normal lifestyle which includes jogging and play horn again. Fibrinogen (Figure 17) and CRP concentrations (Table 11) decreased, whereas D-Dimer (Table 11) increased.
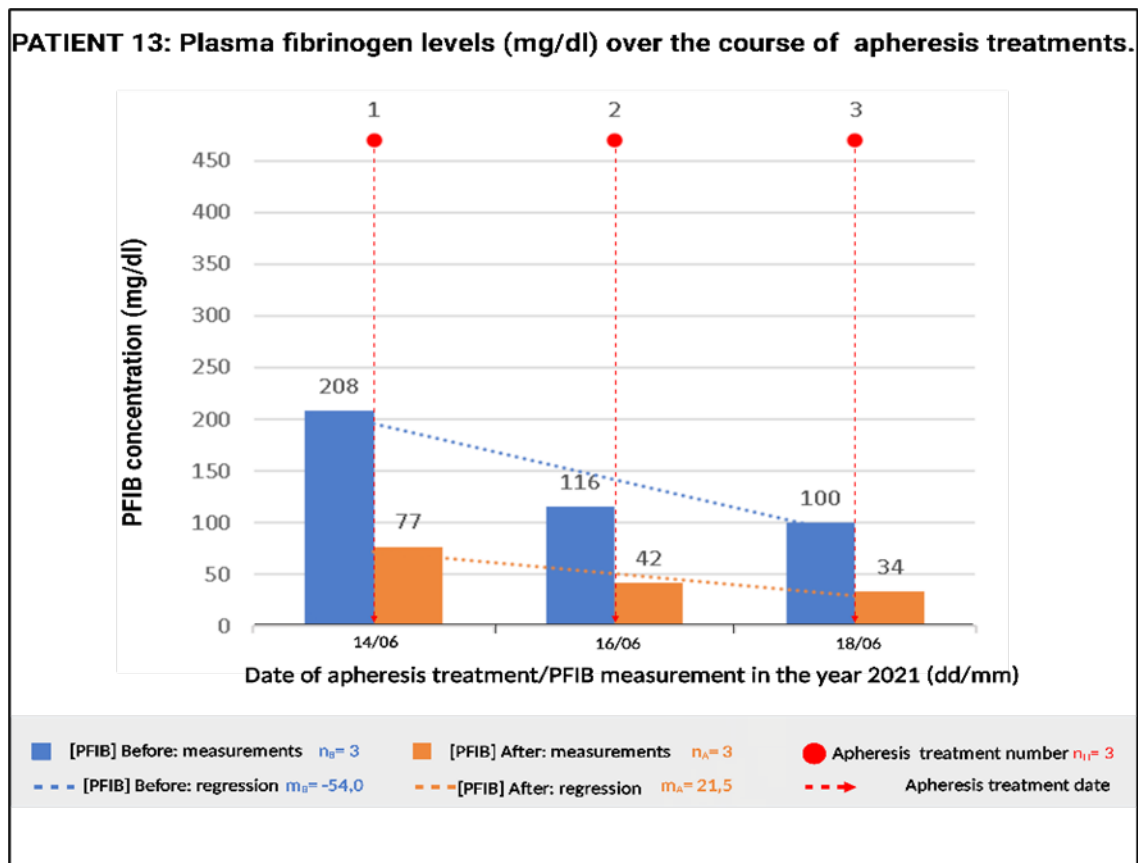
Figure 17: Fibrinogen concentrations of patient 13. Patient 13 completed three H.E.L.P. apheresis treatments (n_H=3). Before (n_B=3) and after (n_A=3) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after show an overall decrease in [PFIB] following a negative linear regression, in relation to the number of apheresis treatments, with a slope of m_B=-54,0 and m_A=-21,5. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Table 11: D-Dimer and CRP levels of patient 13. D-Dimer levels increased whereas CRP levels decreased.

H.E.L.P. Apheresis in Patient 13					
Blood coagulation markers	**Test number**	**1**	**2**	**3**	**Linear Regression Slope**
D-Dimer (ng/ml FEU)	Before	236	190	305	34,5
CRP (mg/dL)	Before	0,04	0,05	0,03	-0,005

Patient 14

A 42-year-old entrepreneur from Nicosia was infected with COVID-19 on the 20th of November 2020. At first, he experienced a cough, fever, hoarseness, headaches, and spine-, muscle-, and joint pain. As the disease progressed, he developed depression and severe anxiety, insomnia, night sweats, brain fog, a lost sense of smell and taste, and the skin on his fingertips cracked. He was left bed-ridden with concentration deficits, extreme fatigue, and PEM. He went on to develop neurological problems with wording and short-term memory. Additionally, his pulmonary gas exchange dropped to 78%. After his first apheresis on the 18th of June 2021, his symptoms were alleviated, except for short-term memory and concentration deficits. After the second apheresis on the 21st of June, his concentration deficits were gone. On the 24th of June, after the third apheresis, his sense of hot, cold, and pain returned fully (which he had previously not identified as a problem). During the initial stage of the recovery period post-apheresis, he experienced minor vein pain, and his resting heart rate was 15-20% higher than normal. However, the patient regained his tolerance to exercise, his oxygen levels recovered fully during rest and exercise, and his short-term memory quickly improved. Although delayed, his vision also improved. Fibrinogen (Figure 18), D-Dimer (Table 12), and CRP (Table 12) concentrations decreased over the course of four H.E.L.P apheresis treatments.
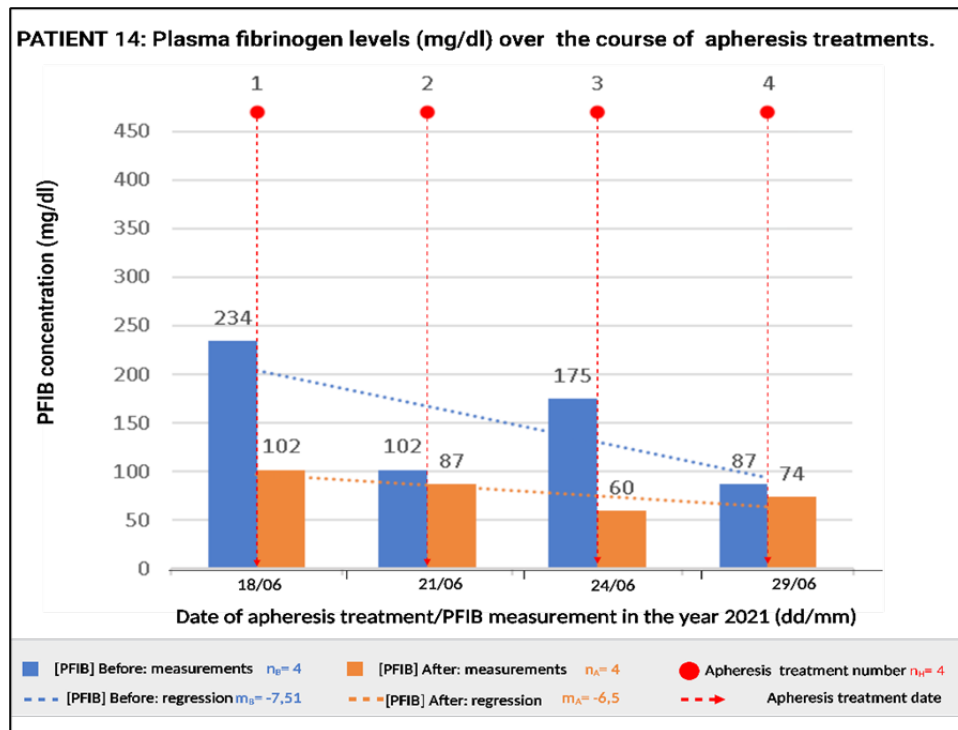

Figure 18: Fibrinogen levels of patient 14. Patient 14 completed four H.E.L.P. apheresis treatments (n_H=4). Before (n_B=4) and after (n_A=4) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after show an overall decrease in [PFIB] following a negative linear regression, in relation to the number of apheresis treatments, with a slope of m_B=-7,51,0 and m_A=-6,5. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Table 12: D-Dimer and CRP concentrations for patient 14. Concentrations of D-Dimer and CRP decreased over the course of four H.E.L.P. apheresis treatments.

H.E.L.P. Apheresis in Patient 14						
Blood coagulation markers	**Measurement**	**Test number**				**Linear Regression Slope (m)**
		1	**2**	**3**	**4**	
D-Dimer (ng/ml FEU)	Before	351	219	303	205	-35,4
	After	190	210	190	190	-2
CRP (mg/dL)	Before	0,13	0,16	0,11	0,09	-0,017
	After	-	0,06	0,04	0,04	-0,01

Patient 15

In November 2020, an overweight, 24-year-old caregiver was infected with COVID-19 during a shift in Dortmund municipal hospital. Before the infection he regularly did strength and endurance exercises and played football. The patient's arterial hypertension was treated with ramipril. He fell ill on the 16th of November 2020, seven hours after his positive swab for COVID-19. His pulse rate increased to 140 bpm, he developed fever, and lost his sense of taste and smell. His physical condition deteriorated rapidly and at one stage, he slept on the floor because he lacked enough strength to walk back to his bed. For seven days, his body temperature remained at 39.2°C, after which it dropped to 37.2°C. During the acute illness he used paracetamol. His main symptoms included complete exhaustion, diarrhoea, and shortness of breath during even the lightest physical exertion. His GP administered ampicillin 8g, dexamethasone, and heparin for 12 days. A thoracic CT on the 5th of December revealed no pathological findings. He had trouble sleeping through the night, something he did not struggle with pre-infection. Due to shortness of breath, he could barely climb two flights of stairs - disabling him from fulfilling his duties as caregiver. He had H.E.L.P. apheresis treatments on the 9th and 12th of March 2021. Two days after his second H.E.L.P.

apheresis treatment, he was symptom-free and resumed his usual exercise habits to a full extent.

Patient 16

A 56-year-old pharmaceutical scientist was infected in March 2020 during the first wave of COVID-19 while on holiday in Ischgl, Austria. After an acute phase with fever, she complained mainly of severe dyspnoea lasting for months, accompanied by a cough, poor resilience, severe concentration disorders, memory lapses, sentence interruptions, temporary paralysis, and skin symptoms on her hands (blisters and peeling skin). On the 30th of March, during and after the first of the three H.E.L.P. apheresis treatments, she was able to breathe with greater ease, and her concentration ability improved. After her second apheresis on the 6th of April, she felt like she was "reborn". Her symptoms improved, and her skin symptoms resolved. She reached full recovery after the third and final apheresis on the 15th of April. She could return to horse-back riding and playing golf - during which she did not experience any shortness of breath. Her ability to concentrate improved even further. Fibrinogen (Figure 19) concentrations measured before and after each treatment decreased over the course of the four H.E.L.P apheresis treatments.
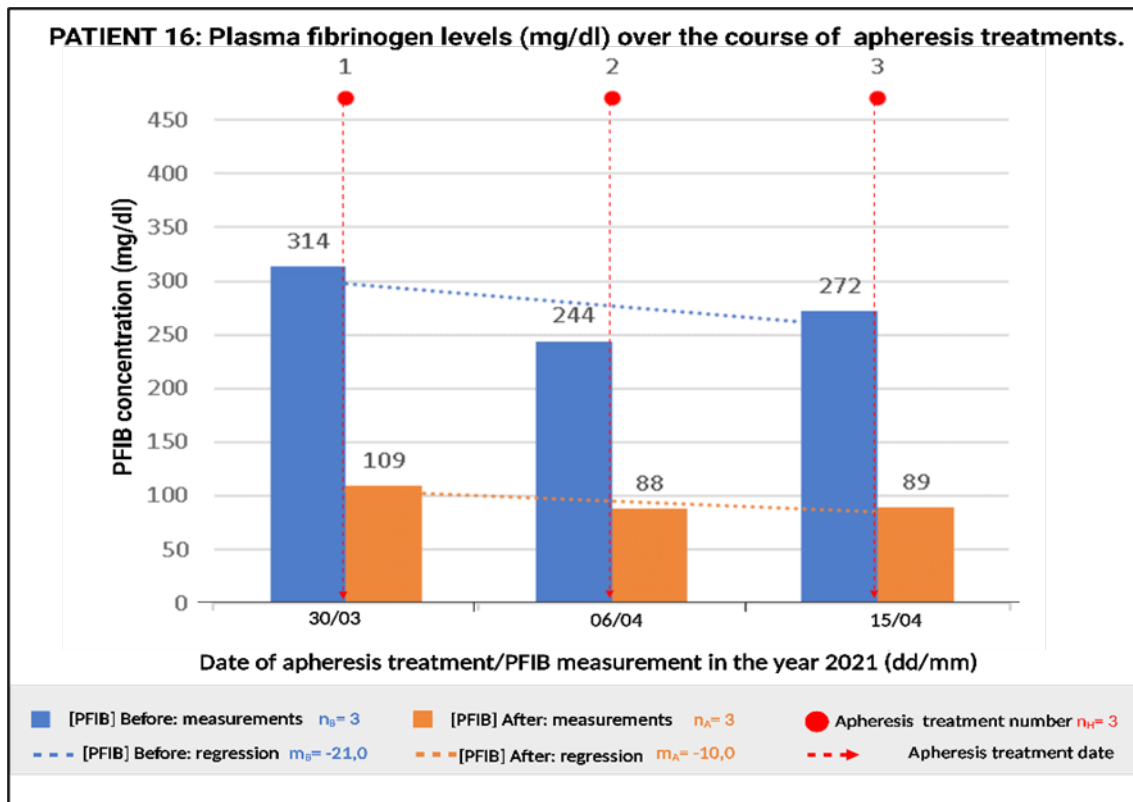
Figure 19. Fibrinogen levels of patient 16. Patient 16 completed three H.E.L.P. apheresis treatments (n_H=3). Before (n_B=3) and after (n_A=3) each apheresis treatment, plasma fibrinogen levels (PFIB mg/dl) were measured. The measurements before and after show an overall decrease in [PFIB] following a negative linear regression, in relation to the number of apheresis treatments, with a slope of m_B=-21,0 and m_A=-10. Where apheresis treatment is mentioned, it refers to H.E.L.P apheresis.

Patient 17

28-year-old female from Bad Sassendorf was infected on duty as an ergo-therapist and tested positive on the 2nd of January 2021. Shortly after her acute infection, she developed a cough as well as throat and chest pain, all of which continually worsened. She lost her sense of smell and taste and suffered from concentration deficits and fatigue. No muscle or ankle pain was reported. During quarantine, she was unable to climb more than three steps without experiencing shortness of breath. Before her first and single apheresis treatment on the 5th of April 2021, she could barely climb two flights of stairs. The H.E.L.P apheresis procedure was stopped prematurely after only 1338mL plasma volume owing to a coagulum that clogged the needle. Nonetheless, after H.E.L.P. apheresis all her symptoms were alleviated, except for her impaired sense of smell. The patient terminated the treatments because she fell pregnant.

Discussion and Clinical Observations

In this pilot study, H.E.L.P. apheresis made an apparent step-change improvement in patients' clinical symptoms, with restoration of normal long-term function in majority of the patients. We hypothesise that this was primarily through removal of circulating microclots, renewal of normal clotting function, and restoration of oxygen to organs. The H.E.L.P. apheresis procedure is already well described, and no harm has been reported after many years of it being in use. Patients have only mentioned only slight discomfort in the treatment in terms of the venepuncture and bruising. Other risks include allergies to heparin and vasovagal reactions. Additionally, since the H.E.L.P. procedure is effective in removing LDL-c and Lp(a), the treatment removes over 2000 calories per session. Hence, it is advised that the patients eat a sufficient meal prior to the treatment.

Additionally, it is worth mentioning that H.E.L.P. apheresis is not restricted to a two-hour treatment time [17]. The H.E.L.P. system can be circulated for many hours until the precipitate filter is saturated. The precipitate filter can also be exchanged during the procedure, meaning the fibrinogen concentration can theoretically be reduced by up to 99.9999%. The H.E.L.P. machine can also be adapted to eliminate different circulating molecules/substances. For example, an alternative filter can be added to the machine to target the specific removal of various aspects from the blood, such as heavy metals for example. This means the treatment can be adapted to make it patient-specific.

However, we recognise that this is only a first step. The mechanism of benefits provided by H.E.L.P. apheresis needs to be elucidated and there is a need for a controlled treatment study with identification of the best objective pre- and post-acute and long-term outcomes; including symptom and quality of life scores, walk testing, evaluation of dysautonomia, pulmonary diffusion capacity, and cognitive testing. Hence, H.E.L.P. apheresis requires rigorous evaluation before it can be considered as a standardised treatment for Long COVID patients. A trial of H.E.L.P. apheresis for acute severe COVID-19 should also be considered. Additionally, we are aware that the inclusion of a control group would be beneficial to elucidate the safety aspect of the treatment. However, it is difficult to include a control group in these studies, considering the cost of the H.E.L.P. treatment and the limited number of machines available. Owing to these limitations, only a small sample size was included in this pilot study.

Furthermore, it is important to elucidate the number of H.E.L.P. apheresis treatments required by patients, and why some patients require more sessions than others. On average, Long COVID patients appear to require six apheresis treatments, but some patients have also had as few as one treatment and as many as 20 treatments. It appears that the longer the duration of symptoms, the more apheresis treatments the patient will require. However, in some patients suffering since the beginning of the COVID-19 pandemic for example, it appears that H.E.L.P. apheresis alone may not target the root of the disease, but instead only aid in short-term relief of symptoms. In these patients, an autoimmune aspect has been hypothesised, but this requires further investigation.

Additionally, the potential therapeutic role of anticoagulation medication also requires further investigation. It has been seen that the most successful method to prevent the formation of new fibrin amyloid-like microclots and restore the normal clotting physiology is to combine anticoagulant medication with H.E.L.P. apheresis to lower fibrinogen levels and bind the SARS-CoV-2 spike protein between apheresis sessions. Such an anticoagulant regimen includes a commonly used "triple therapy" approach [11] comprised of an oral/injectable anticoagulant such as unfractionated heparin or aspirin, combined with two drugs inhibiting platelet activation such as the $P2Y_{12}$ inhibitor clopidogrel and a gastric proton pump inhibitor to reduce any possibilities of gastric bleeding. Incorporating these anticoagulants would be promising to decrease proinflammatory platelet-endothelial interactions and the formation of future fibrin amyloid-like microclots. In future, other studies should investigate how a combined group of H.E.L.P. apheresis and anticoagulant treatment compares to an anticoagulant treatment alone and a control group. This would allow us to assess the difference in efficacy between the differing regimens currently prescribed to patients.

We also acknowledge that H.E.L.P. apheresis and anticoagulant mediation may not be a permanent solution for all patients. Due to the cost of treatment, it may not be affordable for all patients to continue this regimen for an optimal time, as well as there being a limited number of H.E.L.P. machines available. Hence, H.E.L.P. apheresis in combination with other treatments, such as cryotherapy and light therapy for example, should be considered.

Not only has H.E.L.P. apheresis now been used in vascular diseases and Long COVID, but there is also promise for its use in other diseases lacking treatment regimens, such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Many overlapping mechanisms have been identified between Long COVID and ME/CFS, such as inflammation, redox imbalances, immune dysregulation, metabolic dysregulation and a reduced adenosine triphosphate (ATP) production, and a general hypometabolic state [28-32]. Additionally, autoimmune mechanisms appear to be prominent in ME/CFS [31]. Owing to this, immunoadsorption therapy has shown promise in ME/CFS, a type of non-specific apheresis that removes immunoglobulin G from plasma [33,34] independently of their antigen specificity [35]. Hence, the mechanism of an even more specific apheresis such as H.E.L.P. may be beneficial in treating and lowering the symptoms of ME/CFS patients.

Conclusion

Long COVID impairs the lives of the patients significantly, leaving many unable to participate in their previous activities, social lives, and work or studying. Long COVID is ever increasing in prevalence and has a growing impact on global healthcare, so there is a desperate need for a treatment regimen. This pilot study demonstrates the potential benefits of H.E.L.P. apheresis treatment in Long COVID cases to reduce clinical symptoms and improve long-term function in patients. These results are sufficiently positive to give some optimism to patients with Long COVID.

Conflict of Interest

The authors declare that they have no conflict of interest.

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