Clinical Hemorheology and Microcirculation xx (2022) x–xx
DOI 10.3233/CH-229105
IOS Press

Influence of Covid-19 disease on hemostasis dynamics during extracorporeal membrane oxygenation (ECMO)[1]

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Abstract.
INTRODUCTION: COVID-19 causes a considerable degradation of pulmonary function to the point of an acute respiratory distress syndrome (ARDS). Over the course of the disease the gas exchange capability of the lung can get impaired to such an extent that extracorporeal membrane oxygenation (ECMO) is needed as a life-saving intervention. In patients COVID-19 as well as ECMO may cause severe coagulopathies which manifest themselves in micro and macro thrombosis. Previous studies established D-dimers as a marker for critical thrombosis of the ECMO system while on admission increased D-dimers are associated with a higher mortality in COIVD-19 patients. It is therefore crucial to determine if COVID-19 poses an increased risk of early thrombosis of the vital ECMO system.
METHODS: 40 patients who required ECMO support were enrolled in a retrospective analysis and assigned into 2 groups. The COVID group consist of 20 COVID-19 patients who required ECMO support ($n = 20$), whereas 20 ECMO patients without COVID-19 were assigned to the control group. D-dimers, fibrinogen, antithrombin III (AT III), lactate dehydrogenase (LDH) and platelet count were analysed using locally weighted scatterplot smoothing and MANOVAs.
RESULTS: The analysis of both groups shows highly significant differences in the dynamics of hemostasis. The increase in D-dimers that is associated with thrombosis of the ECMO systems occurs in COVID-19 patients around 2 days earlier ($p = 2{,}8115\ 10^{-11}$) while fibrinogen is consumed steadily. In the control group fibrinogen levels increase rapidly after ten days with a plateau phase of around five days ($p = 1{,}407\ 10^{-3}$). Both groups experience a rapid increase in AT III after start of support by ECMO ($p = 5{,}96\ 10^{-15}$). In the COVID group platelet count decreased from 210 giga/l to 130 giga/l within eight days, while in the same time span in the control group platelets decreased from 180 giga/l to 105 giga/l ($p = 1{,}1\ 10^{-15}$). In both groups a marked increase in LDH beyond 5000 U/l occurs ($p = 3{,}0865\ 10^{-15}$).
CONCLUSION: The early increase in D-dimers and decrease in fibrinogen suggests that COVID-19 patients bear an increased risk of early thrombosis of the ECMO system compared to other diseases treated with ECMO. Additionally, the control group shows signs of severe inflammation 10 days after the start of ECMO which were absent in COVID-19 patients.

1. Introduction

The COVID-19 disease caused by the SARS-CoV-2 Virus leads in severe cases to a serious reduction in the functionality of the lung up to an acute respiratory distress syndrome (ARDS) and pulmonary embolisms. In course of this respiratory and circulatory support via extracorporeal membrane oxy-

[1]This article was presented at the 40th Conference of the German Society for Clinical Microcirculation and Hemorheology (DGKMH), Senftenberg, Germany, 20– 21 May 2022.

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ISSN 1386-0291/$35.00

genation (ECMO) might become necessary as a lifesaving action. COVID-19 causes a sever immune response know as cytokine storms which in terms of virus-related diseases are novel [1]. The coagulopathies caused by COVID-19 are like disseminated intravascular coagulopathy (DIC) which occur during sepsis and other infections but differs in major aspects [2, 3]. COVID-19 distinguishes itself by oscillation between thrombotic and fibrinolytic phase which leads to micro and macro thrombi and consumption of important products for coagulation [4–6]. This high build up and lysis of thrombi [7, 8] is shown by highly elevated d-dimers and a steady consumption of fibrinogen. Elevated d-dimers on admission in COVID-19 patients are associated with worsen prognosis 12]. While COVID-19 causes a wide spectrum of coagulopathies the necessary ECMO with its foreign surfaces and unphysiological flow conditions leads to an activation of the haemostatic and inflammatory systems [13]. Over the course of ECMO support thrombi may accumulate inside the ECMO system and threaten functionality. In operation these thrombi are difficult to spot. A sharp increase in d-dimers several days after start of ECMO has been established as a sign of thrombi formation inside the EMCO [14–16]. In this case with decreased fibrinogen, worsen oxygenation performance and other soft factors exchange of the ECMO system should be considered.

The complex reactions of the haemostatic system may lead to complications during support of the patients. COVID-19 with its wide variety of coagulopathic characteristics adds another layer to the already complex human-machine interactions. How the interaction between COVID-19 and ECMO alters the known dynamics of the haemostatic systems is unknown for now. The comparison between ECMO patients with COVID-19 to patients with diseases common for ECMO give new information about these complex interactions.

2. Methods

2.1. Study design

Data from 40 patients was used for a retrospective analysis. The patients were assigned to a COVID-19 group and control group. The COVID-19 group consists of 20 patients ($n = 20$) who contracted COVID-19 due to wildtype SARS-CoV-2 Virus and needed support via ECMO. 20 patients needing ECMO support without COVID-19 were assigned to the control group ($n = 20$). Additional requirements for both groups were an age $\geq$18 years and a ECMO support duration of at least 7 days. The ethics commission of the Justus-Liebig-University Giessen approved the retrospective analysis of patients' data (AZ 140/21).

2.2. Study population

The COVID-19 group with an average of 27 (median 20 d) days was supported almost twice as long in comparison to the control group with 15 days (median 10 d). In both groups the number of patients under support declines over time (Fig. 1).

2.3. Parameters and data acquisition

D-dimers, fibrinogen, platelet count, antithrombin III (AT III) and lactate dehydrogenase (LDH) were collected from the hospital internal ICU data base.

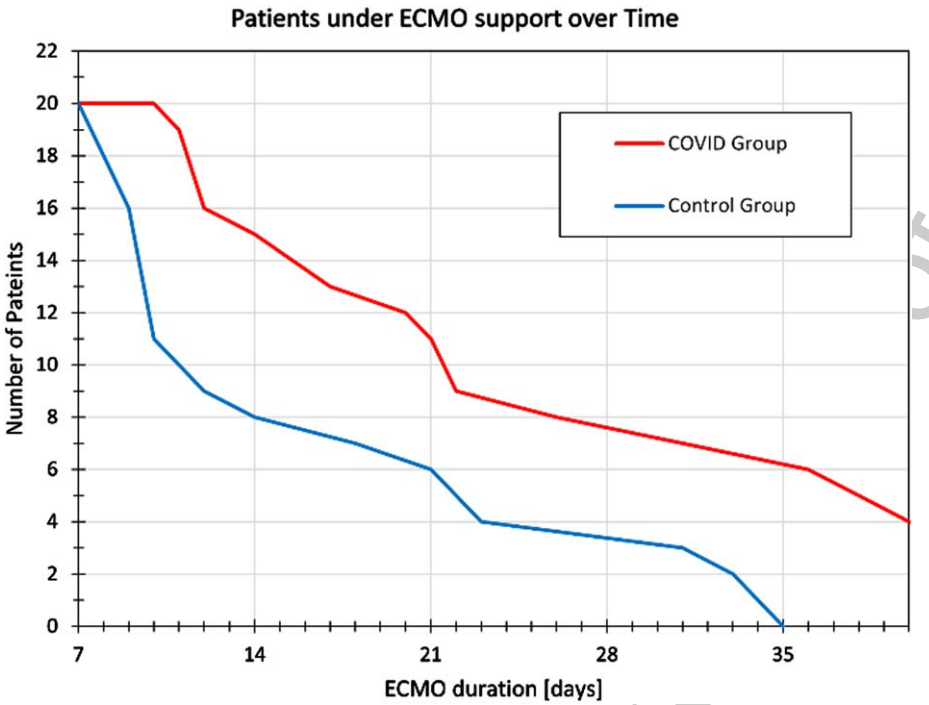

Fig. 1. Number of patients supported by EMCO over time. In the COIVD-19 group the longest support time is up to 94 days.

2.4. Statistical analysis

Analysis was performed in RStudio using locally weighted scatterplot smoothing (LOWESS) and MANOVAS's for hypothesis testing. The MANOVA was used to test if groups differ in a combination of the parameters value and time in the first 34 days. In the MANOVA only D-Dimers over 20 mg/dl were chosen to control their unspecific nature. 20–25 mg/dl were identified as the range in which the peaks occur [14, 15]. For D-dimers, fibrinogen, AT III and the platelet count a linear regression was plotted.

3. Results

3.1. Coagulation parameters

The red gradients show the COVID-19 group, the blue the ones of the control group and the black jitter is the respective raw data. In the COVID-19 group the first peak in D-dimers (Fig. 2) is around 12 days while the control group takes around 14 days to reach the first peak. The MANOVA results in a p-value = 2,8115 10^{-11} for D-dimers above 20 mg/l. Over the course of the support both groups experience smaller increases in D-dimers continuously. The regression of both groups shows that D-dimers in the COVID-19 group increase 50 % faster than the control group

In contrast to the D-dimers the course of fibrinogen differs greatly between the groups. While in the COVID-19 group a steady decline in fibrinogen is observable the control group undergoes rapid changes in trend around the days eight to ten. Besides these marked differences the regression analysis reveals that fibrinogen is consumed at a similar pace in both group for the first ten days. The data for fibrinogen results in $p = 1{,}407\ 10^{-3}$.

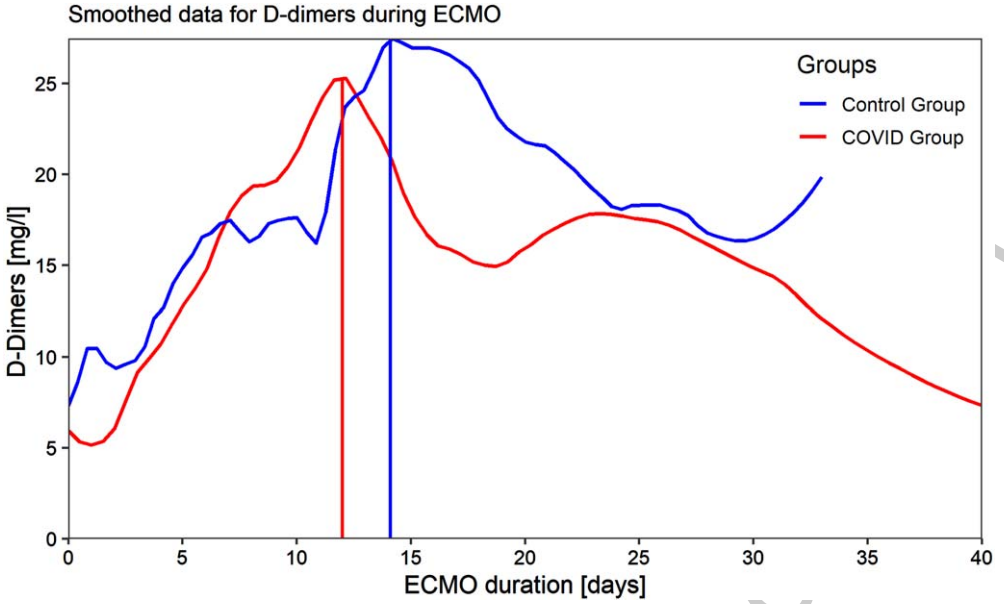

Fig. 2. D-Dimer levels over time for both groups with their respective peaks at 12 and 14 days of ECMO support.

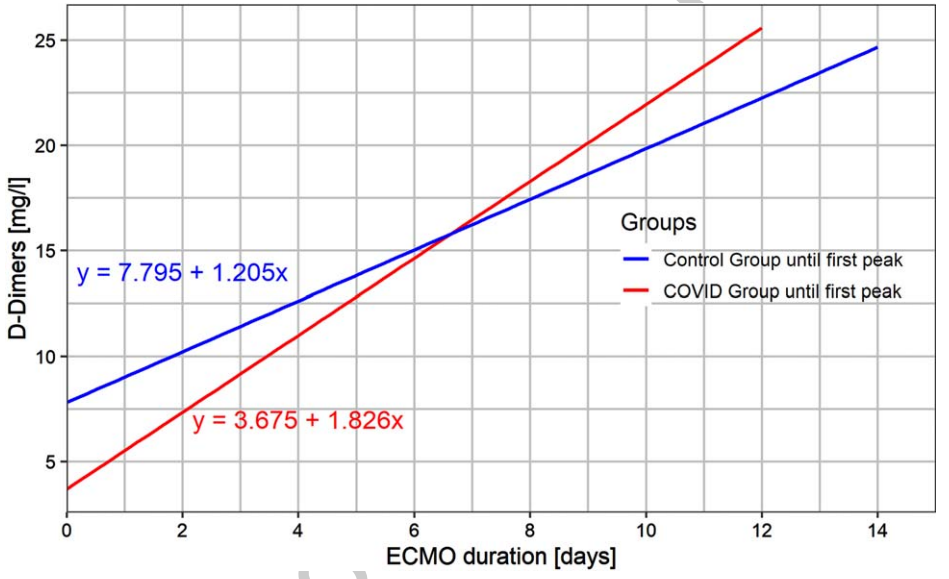

Fig. 3. Regression for D-Dimers until their respective first peaks in the COVID-19 group.

This change in dynamics after 10 days is also observable in AT III and LDH within the control group. AT III increases sharply from as low as 50 % to the maximum values of 130% in both group after start of ECMO. Around days 8 to 10 the control group experiences a sharp decline in AT III for several days. MANOVA: p-value = 5,96 10^{-15} for the AT III and time data.

Besides the sudden change in direction in the control group the regression shows a very similar increase in AT III over time for both groups.

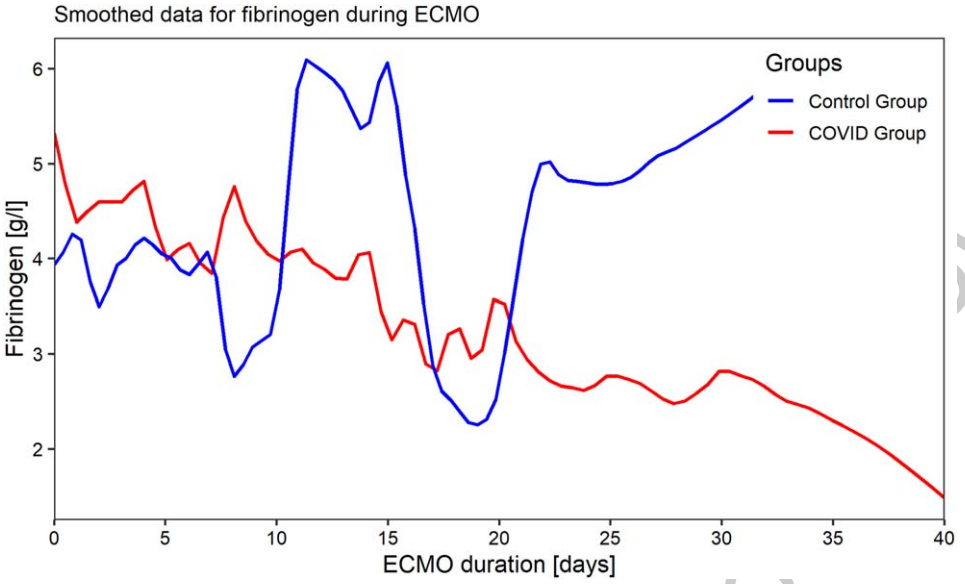

Fig. 4. Fibrinogen levels over time show a steady consumption with a rapid change around day 10.

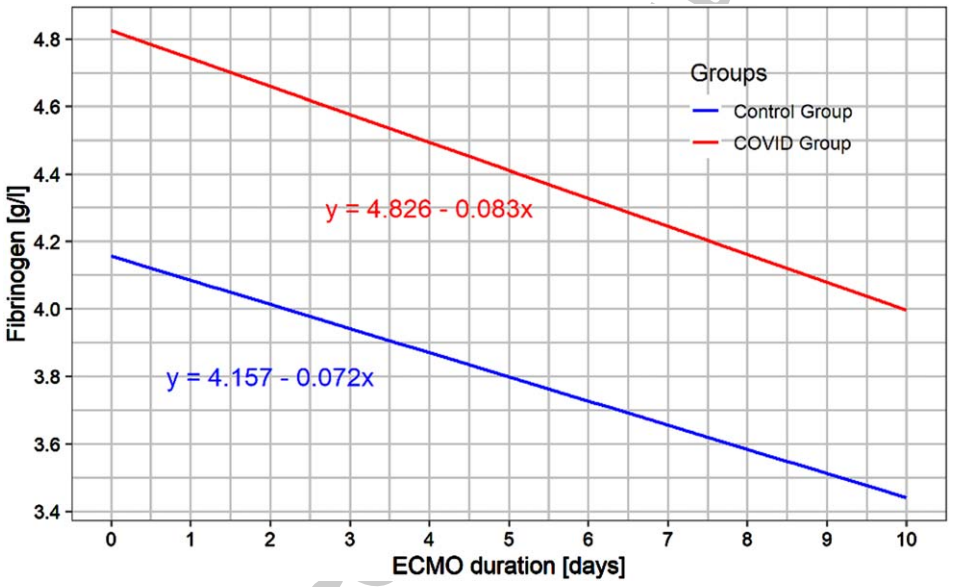

Fig. 5. Regression of the fibrinogen levels in both groups up to day 10.

LDH remains highly elevated in both groups with levels above 800 U/l. For the shown data the MANOVA results in p-value = 3,0865 10^{-15}. Around day 10 a marked increase in LDH in the control similar to the one in fibrinogen can be seen.

In both groups platelets are consumed at a high rate with a decrease from 210 Giga/l to 130 Giga/l in 6 days and low point at around eight days of support. The MANOVA results in (p-value = 1,1 10^{-15} for the show data (Fig. 9). The regressions shows that platelet count in the COVID-group decreases at more than double the rate of the control group despite higher initial values.

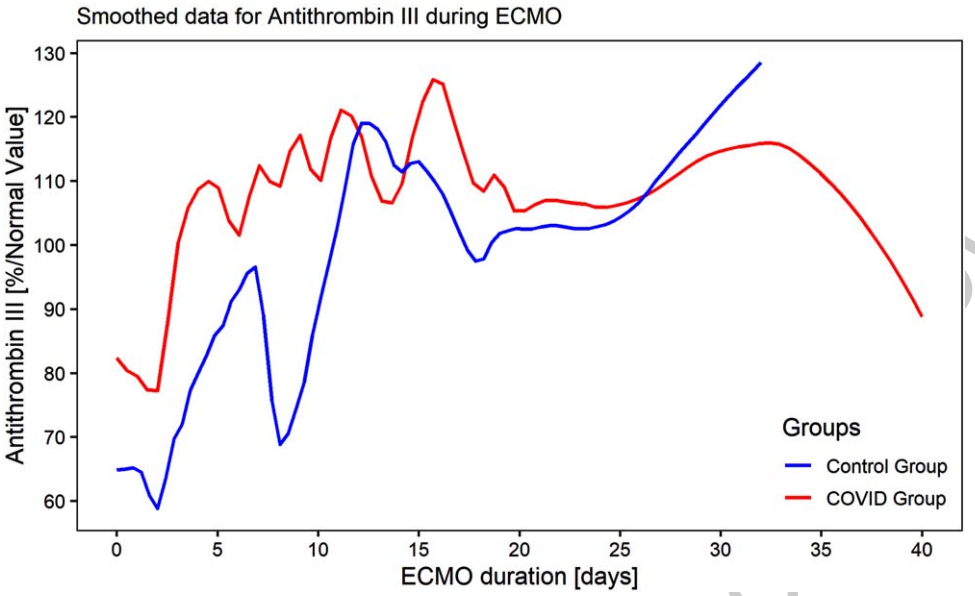

Fig. 6. Antithrombin III levels during ECMO support.

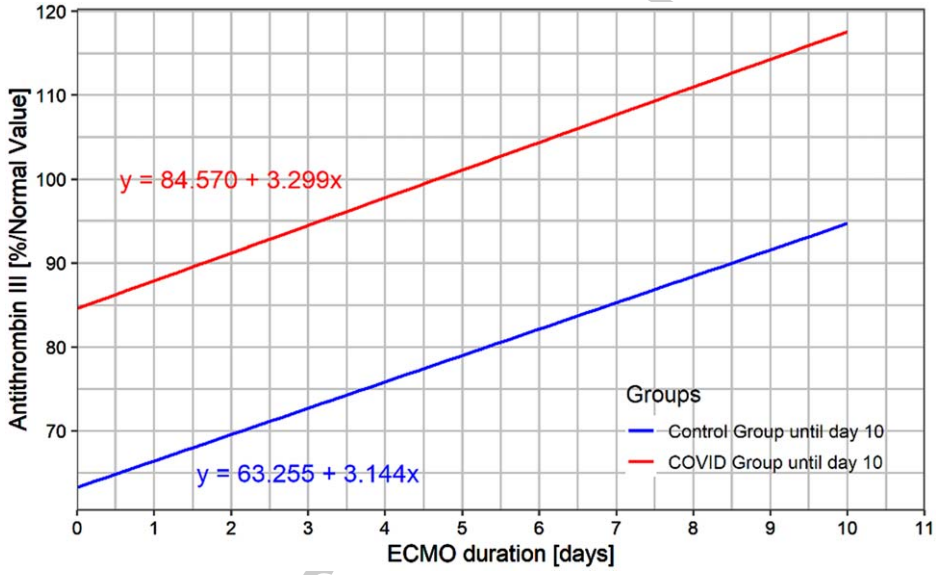

Fig. 7. Regression for Antithrombin III levels until day 10.

4. Discussion

COVID-19 as well as ECMO may induce coagulopathies that cause excessive thrombus formation and consumption of coagulation products. A comparison in amplitudes for this data set is not sensible because D-dimers (max. 32,5 mg/l), fibrinogen (max. 7,5 g/l) and AT III (max. 130 %) constantly exceed the measurable range. Therefore, an analysis of curve dynamics and support time is more sensible.

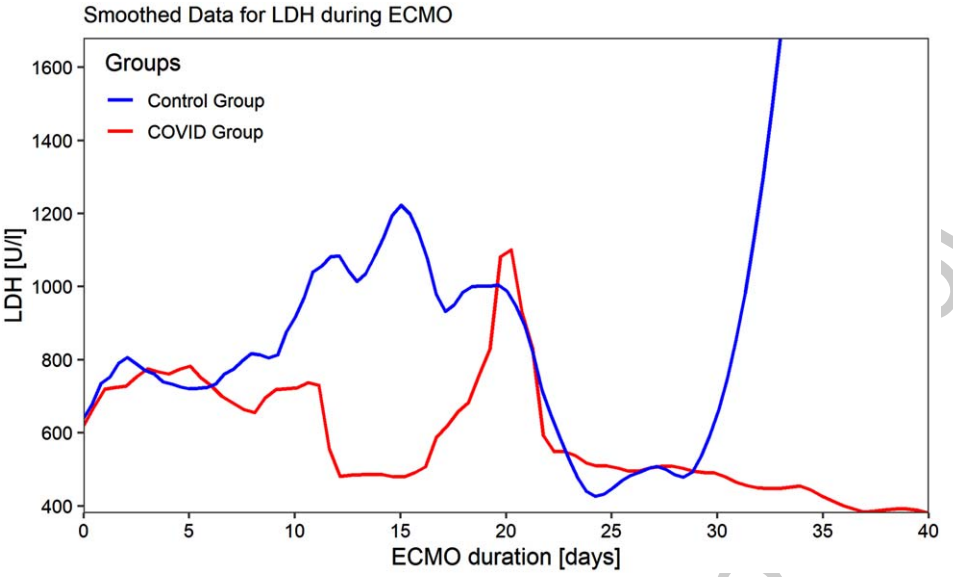

Fig. 8. LDH levels during ECMO support.

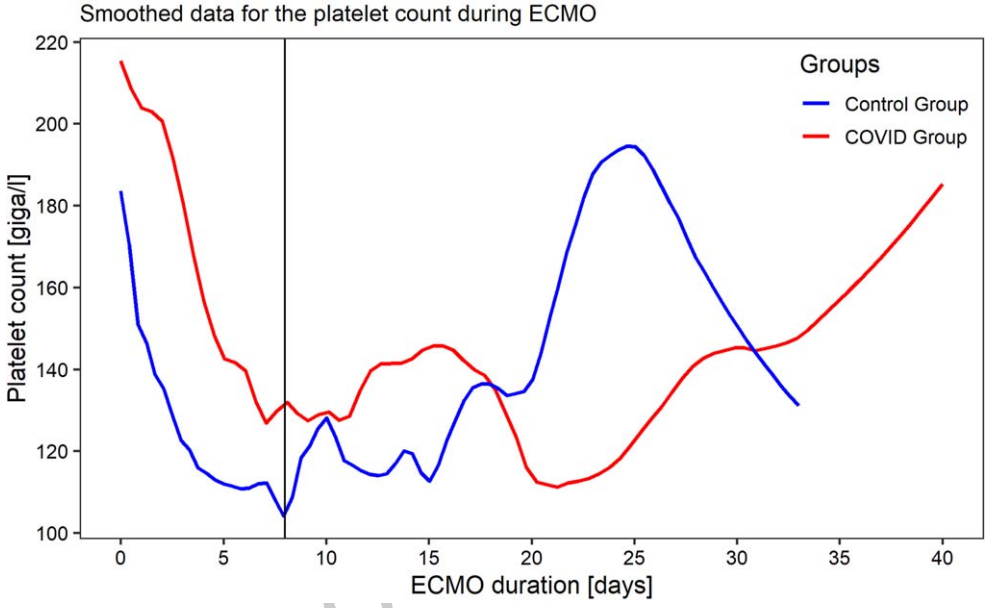

Fig. 9. Platelet count levels over time with the respective low points after four days of support.

Considering the earlier occurrence of the spike and fast increase in D-dimers level in the COIVD-group suggests that thrombosis of the ECMO system happens considerably earlier in COVID-19 cases. The periodic rise in D-dimers afterwards that is seen in both groups and is likewise described by Gehron et al. is caused by periodic exchanges of the ECMO system. Dornia et al. could observe similar dynamics in D-dimers during ECMO [14, 16]. The data suggest that COVID-19 does not have an impact on the frequency of these spikes but creates an offset of around 5 days.

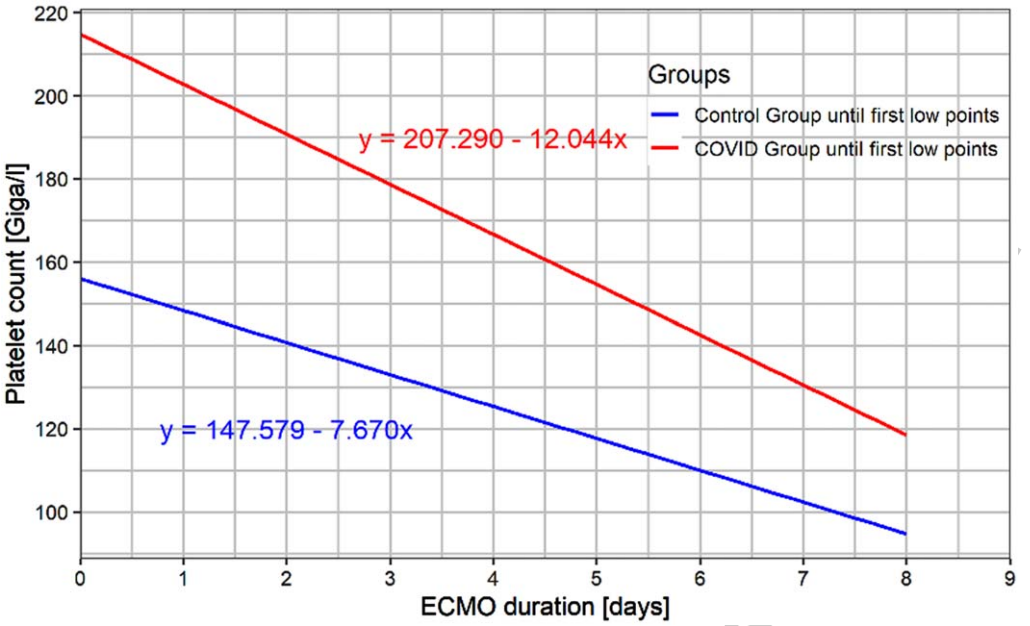

Fig. 10. Regression of platelet count levels until the first low point.

Table 1
Characteristics of COVID-19 and non-COVID-19 ECMO support

Variable	COVID group	Control group
n	20	20
Age [mean ± SD]	56 ± 11	53 ± 15
Male [*n*]	12	16
Female [*n*]	8	4
Mortality [%]	60	35
Support time [days]		
Mean ± SD	27 ± 20	15 ± 9
Minimum	11	7
Maximum	94	34
Mean for mortal outcome	28 ± 24	21 ± 17

While the D-dimers behave very similar in both groups fibrinogen level reveals paint a different picture. In both groups a constant consumption of fibrinogen due to the thrombotic nature of extracorporeal support. The consumption of fibrinogen in patients with COVID-19 and ECMO is also observed by Hayakawa et al. [17]. Overall, this study's result in respect to D-dimers and fibrinogen dynamics is very similar to the single patient case report of Hayakawa et al.

In view of fibrinogen's role as acute phase protein [18] together with an increase in LDH and sharp decline in Antithrombin III at the same time we assume inflammation or even sepsis to be the cause of this marked change in parameters. This assumption is supported by Sharma's study that shows an increase in fibrinogen and D-dimers in children with sepsis while Matsubara's results associate a decline in fibrinogen and Antithrombin III with sepsis [19, 20]. While we could not observe this decline in fibrinogen a sharp decrease in Antithrombin III is noticeable. The cause for this unexpected heavy

Table 2
Results for the collected data

Variable	COVID group	Control group
D-Dimer [mg/l]		
Mean ± SD	15.0 ± 10.7	16.7 ± 12.9
Min	0.7	0.4
Max	35.2	35.2
Median	12.9	12.6
Fibrinogen [g/l]		
Mean ± SD	3.7 ± 1.8	4.1 ± 1.7
Min	0.5	0.4
Max	7.5	7.5
Median	3.2	4.3
Antithrombin III [%/Normal value]		
Mean ± SD	108 ± 23	86 ± 27
Min	36	20
Max	130	130
Median	112	78
Platelet count [giga/l]		
Mean ± SD	150 ± 70	130 ± 68
Min	24	20
Max	481	515
Median	139	125
LDH [U/l		
Mean ± SD	619 ± 489	824 ± 880
Min	13	189
Max	5181	5623
Median	469	486

inflammation in the control group during support is thus far unknown. Additionally, the heterogeneity in the underlying diseases of the control group makes it difficult to pinpoint the exact cause of larger curve changes and resulting noise in the data. An overall increase in AT III after start of ECMO is also observed by Bembea at al. although not as sharp as seen in this study [21].

The steady decrease in platelet count is often seen during extracorporeal circulation and known [22]. Contact reactions and the unphysiological flow conditions during ECMO and it's foreign surfaces cause a decline in platelets over time [23]. It is unlikely that the overall decline in platelets is caused by COVID-19 but in respect to the pace of decline plays COVID-19 seems to play a considerable role in the decline of platelet numbers. Together with the steady consumption of fibrinogen this decline in platelet numbers supports the assumption that during COVID-19 consumptive thrombotic processes similar to DIC happen.

In view of the heterogeneity of the underlying diseases of the control group a more extensive analysis including further parameters is advisable. New sub-variants of the SARS-CoV-2 Virus might change dynamics further.

5. Conclusion

COVID-19 can alter the patient's hemostatic system during ECMO. The early rise in D-Dimers and steady consumption of fibrinogen suggest an increased risk of early thrombosis of the ECMO system due to COVID-19. Therefore, close-knit monitoring of D-Dimers, fibrinogen and other parameters showing ECMO performance is paramount. The suspected strong inflammatory reaction in the control group needs a larger pool of data for further investigation.

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