

## Arteriovenous fistula thrombosis in hemodialysis patients with COVID-19: epiphenomenon or marker of severe clinical disease?

Editoriale

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### ABSTRACT

**Background:** Pandemic condition due to Coronavirus disease (COVID-19) caused a fastest augmentation of hospitalization, impairing the healthcare organization. As a consequence, diagnostic and therapeutic delays have been showed. COVID-19-associated coagulopathy is an endothelial disease related to SARS-CoV-2 infection. Our study evaluated the thrombosis of arteriovenous fistula (AVF) as risk marker of mortality.

**Methods:** the analysis included 24 dialysis-dependent patients admitted in a period between March 2020 and June 2021. Patients were divided based on AVF thrombosis: the A group without AVF thrombosis (13 patients), and the B group with AVF thrombosis events (11 patients). Pearson or Spearman' correlation tests were performed to detect possible confounding variable to include in multivariate models. Kaplan Meier and Cox regression analysis were performed to compute mortality analysis.

**Results:** Delta D-dimer (Rho: 0.613, p=0.007), over-infections (Rho 0.456; p= 0,026), C-reactive Protein (CRP) (Rho=0.417, p=0.043), death (Rho=0.492, p=0.027), positive pulmonary imaging (Rho 0.388, p=0.074), and high OLT (0.408, p=0.047) were related to AVF thrombosis, using Pearson or Spearman correlation tests. Kaplan Meier test showed a death average of 19 days in group B compared to a global average of 38 days (p=0.029), and Cox analysis showed an HR of 5.01, 95% CI 1.01-24.99, p=0.049. Furthermore, AVF thrombosis explained about the 68% of the mortality, evaluated through the Harrel's C test.

**Conclusion:** We can speculate that AVF thrombosis in hemodialysis patients with COVID-19 could be an early marker of both pro-coagulative process and severe clinical disease and it could be used to stratify patients and identify the ones that can be considered "frail".

**KEYWORDS:** COVID-19, Thrombosis, Hemodialysis, Survival analysis

## Background

Coronavirus disease (COVID-19) is caused by SARS-CoV2 and represents the agent of a potentially fatal disease. Although our analysis was performed on a too small sample, few studies about COVID-19 dialysis-dependent who required hospitalization were published. Furthermore, by evaluating the global impact of the pandemic working condition on hospitalization and healthcare, each thought marker could become useful. Thus, it is relevant to introduce our results in order to highlight the clinical relevance of the topic.

Coronavirus is one of the pathogens that primarily target the respiratory system. The first case of COVID-19 disease was reported in late December 2019 in Hubei province (Wuhan, China).

The global mortality rate is about 3.2%, with high mortality and morbidity in patients with another pre-existing chronic disease, including kidney disease. Terminal uremia determines chronic inflammation, immunosuppression [1], and deeply changes both in innate and adaptive immune system, making patients in chronic hemodialysis particularly susceptible developing severe SARS-CoV2 clinical manifestations.

COVID-19-associated coagulopathy [2, 3] is a frequent consequence of SARS-CoV-2 infection, an endothelial disease caused by a systemic prothrombotic chronic inflammation. People with multimorbidity are the most affected by it.

As reported by Moynihan R et al in their Systematic Review [4], therapeutic and diagnostic services got worse by about 30%. This has caused a delay in diagnosis and the worsening of outcomes for non-COVID-19 diseases. Furthermore, the fast augmentation of the COVID admission caused difficulties in the management both of the structures and of the staff. Another important role was played by the mental state, mostly in elder patients, due to the reduced contact caused by the required personal protective equipment [5]. Indeed, as reported by Chachkhiani D, length of hospital stay for patients with altered mental status was longer [6].

Also not COVID management has been impaired. Therefore, telemedicine was developed and it reduced mortality and improved the quality of care, despite the distance. Video calls among the team, dialysis centers and patients became the routine. They need to be simple to use and with the high graphic resolution, to detect aneurysms, infections, skin disease, edema, etc. [7]. Furthermore, a multidisciplinary approach is been facilitated by the implementation of virtual methods [8].

The combination of all these factors has made the management of the patients more difficult, especially in the first waves. For these reasons, finding earlier risk factors is very important.

Very few studies about the management were conducted in the pediatric population, except little observational studies or case reports [9].

We conducted an observational retrospective study on hemodialysis-dependent patients and COVID-19. In our analysis, thrombosis of arteriovenous fistula (AVF) was used as an independent variable to evaluate death in patients with COVID-19.

## Methods

From March 2020 and June 2021, 420 patients were hospitalized at COVID-Unit of the “Gaetano Martino” University Hospital, in Messina (Italy). Among these, we included in our study 24 patients affected by Chronic Kidney Disease (CKD) in hemodialytic treatment through AVF. Patients were split in two groups, based on the onset of AVF thrombosis: the A group without AVF thrombosis (13 patients), and the B group with AVF thrombosis events (11 patients).

Medical history, microbiological data, blood-chemical tests and instrumental exams were also assessed. Differences on baseline features between the two groups were detected using Student T test or Mann-Whitney Test for continuous variables, according to variable distribution, and Pearson's chi-squared test for categorical variables. Pearson or Spearman correlation tests were performed to detect possible confounding variable to include in multivariate models. Kaplan Meier and Cox analysis were performed to compute mortality analysis.

## Results

Our whole sample included 24 patients at the age of  $72\pm 12$  years,  $69\pm 12$  in group A and  $74\pm 13$  in group B. The only difference observed between the two groups, in blood tests, consists in Delta-D-dimer (1% vs 103%,  $p=0.005$ ). Although we didn't find other significant differences, we highlighted the differences in trends of IL-6 ( $152\pm 132$  vs  $47\pm 47$ pg/ml) and of over-infections (46% vs 90%,  $p=0.07$ ). No difference in dialysis monitor or dialytic technique were detected between the two groups.

Despite the small size of the population examined in the study, Pearson's or Spearman's tests showed significant correlation or trend among thrombosis and respectively delta D-dimer (Rho: 0.613,  $p=0.007$ ), over-infections (Rho 0.456;  $p=0.026$ ), C-reactive Protein (CRP) (Rho=0.417,  $p=0.043$ ), death (Rho=0.492,  $p=0.027$ ) and positive pulmonary imaging (Rho 0.388,  $p=0.074$ ), High OLT (0.408,  $p=0.047$ ).

Furthermore, partial correlation adjusted for superinfection, showed a significant correlation between Delta-D-dimer and thrombosis (Rho 0.699,  $p=0.003$ ).

Logistic regression was performed on the group as a dependent variable to discriminate related variables, as summarized in Table 1. It showed an impact of bacterial infections and  $\Delta$ D-dimer/ D-dimer  $T_0 \times 100$  on thrombosis events.

Mortality was evaluated using the Kaplan Meier test, which revealed an average of 19 days in group B compared to a global average of 38 days ( $p=0.029$ ) (Figure 1). Moreover, in group A, overall mortality probability was higher than 0.8. For this reason, days median and quartiles were not computed.

Cox analysis showed an HR of 5.01, 95% CI 1.01-24.99,  $p=0.049$ . Evaluated through Harrell's C test, thrombosis explained about the 68% of the mortality.

	OR	CI 95%	p
<b>Bacterial infection</b>	<b>10.5</b>	<b>1.015-108.6</b>	<b>0.049</b>
Reactive C protein	1.13	0.947-1.356	0.171
IL6	1.013	0.997-1.029	0.105
D-dimer	2.270	0.797-6.459	0.125
Rx	5.6	0.814-32.512	0.080
<b><math>\Delta</math>D-dimer/ D-dimer <math>T_0 \times 100</math></b>	<b>1.037</b>	<b>1.002-1.073</b>	<b>0.036</b>

**Table 1: Logistic regression with thrombosis as dependent variable**

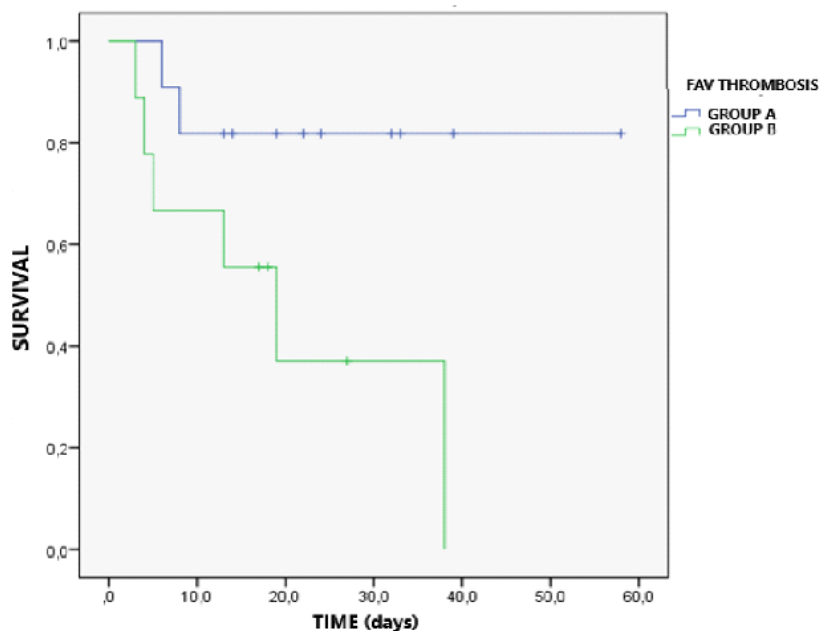


Figure 1: Kaplan Meier test

## Discussion

Our sample showed a higher incidence of thrombosis (46%) than literature data. To explain this result, compared to Desbuissons G. et al. [10], we would highlight the higher differences in age between the two groups in our sample, and our elder population compared to Desbuissons sample. However, also in Desbuissons G. population, the thrombosis rate was higher than not-COVID-19 incidence, perhaps due to the global difficulties in the pandemic management. It is interesting that the 82% of patients in group B manifested AVF thrombosis just before their respiratory condition got worse. This highlighted the possible weight of it in the management of dialyzed patients affected by COVID-19. D-dimer was a known risk factor of thrombosis, for this reason we evaluated its increment during the length in hospital stay (%); few data are published about the impact of the D-dimer increment on mortality or thrombosis. According to our results, increment of D-dimer was related to thrombosis risk, independently by baseline D-dimer. Although thrombosis could be considered as a late marker, management of its risk factors (included the increment of D-dimer) and the strength vascular evaluation of AVF should be detected to look in on the possible worsening of the patient's clinical condition.

According to our hypothesis, thrombosis was related with high O<sub>2</sub> therapy, highlighting it as a marker of several clinical disease.

## Conclusions

We can speculate that AVF thrombosis in hemodialysis patients with COVID-19 could be an early marker of both pro-coagulative process and severe clinical disease.

Although larger studies are needed to confirm it, based on higher mortality rate in patients that have experienced thrombosis, we supposed that AVF thrombosis could be used to stratify patients and identify the ones that can be considered "frail". Furthermore, it could be used to start specific early diagnostic-therapeutic processes to avoid further complications and *exitus*.

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