Letter to the Editor

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Fibrin strands in peripheral blood smear: the COVID-19 era

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To the Editor,

An increase in the incidence of fibrin strands and platelet clumping was noticed in our hospital since the beginning of the COVID-19 pandemics. It is common believe that the presence of fibrin strands in peripheral blood smears (PBS) (Figure 1A) occurs, *in vitro*, after partial clotting of a blood specimen, because of difficulty in venipuncture [1]. When present, this phenomenon can translate in falsely low counts of platelets, as they can be clumped together with fibrin strands (Figure 1B) [2].

Although we could not prove this increase in the incidence of fibrin strands because we transitioned from the analyzer Sysmex® XE5000 to the analyzer Sysmex® XN10, we compared another marker of difficulties during blood collection – the number of coagulated samples (detected macroscopically) at the time of the study and in the corresponding non-COVID period (December 2018 to April 2019) and found a significative rise of coagulated samples from 0.21% to 0.28% (p-value <0.01).

On the other hand, it has been described that the presence of fibrin strands can be related to patients with a hypercoagulable state [1]. It is also known that most COVID-19 severely ill patients can develop coagulopathy, which is suggested by elevated levels of von Willebrand factor (vWf), fibrinogen and the fibrin degradation product D-dimer in the blood [3]. SARS-CoV-2 infects endothelial cells and causes cellular damage, decreasing the antithrombotic activity of the normal endothelium, it also activates the complement system that might induce endothelial cell injury and pro-inflammatory cytokines and chemokines released by activated macrophages amplifying the cycle of vascular integrity disruption, vessel coagulation and thrombosis [3, 4]. Activated endothelial cells initiate coagulation by expressing P-selectin, vWf and fibrinogen, leading to massive platelet binding, fibrin formation and clotting of red blood cells, ultimately resulting in systemic thrombosis and disseminated intravascular coagulation [4]. Several studies also reported a hypercoagulable state with massive fibrin formation in COVID-19 patients [5–7].

To address these findings, it is good laboratory practice not to release the report and to ask for a new sample, however this decision is not linear as the patient may no longer be in the hospital and the clinician may not need an accurate platelet count. Moreover, in our experience, not always do clinicians find it necessary to collect another blood sample in stable COVID-19 patients.

We retrospectively studied cases with fibrin strands found in PBS, from December 2020 to the end of April 2021 in the Laboratory serving outpatients and inpatients (including 21 intensive care unit [ICU] beds with 11 dedicated to COVID-19 patients). The presence of fibrin strands was suspected when platelet count and sometimes white blood cell count dropped from the normal values in patient history and, when the flag of "Clumps 300" was raised by our analyzer – Sysmex® XN 10. PBS was always observed to confirm the findings.

We then consulted the laboratory informatic system to collect demographic data, to determine if the patient had SARS-CoV-2 nucleic acid amplification test and history of fibrin strands, or fibrin strands in the follow-up hemogram, finally we also collected the D-dimer values, when determined.

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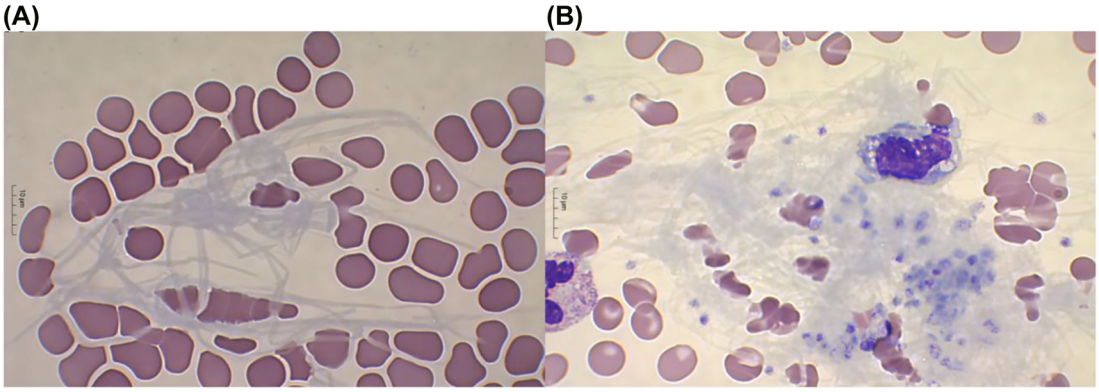

Figure 1: Fibrin strands.
(A) Fibrin strands in peripheral blood smear. (B) Fibrin strands with platelets and a white blood cell clumped together in peripheral blood smear.

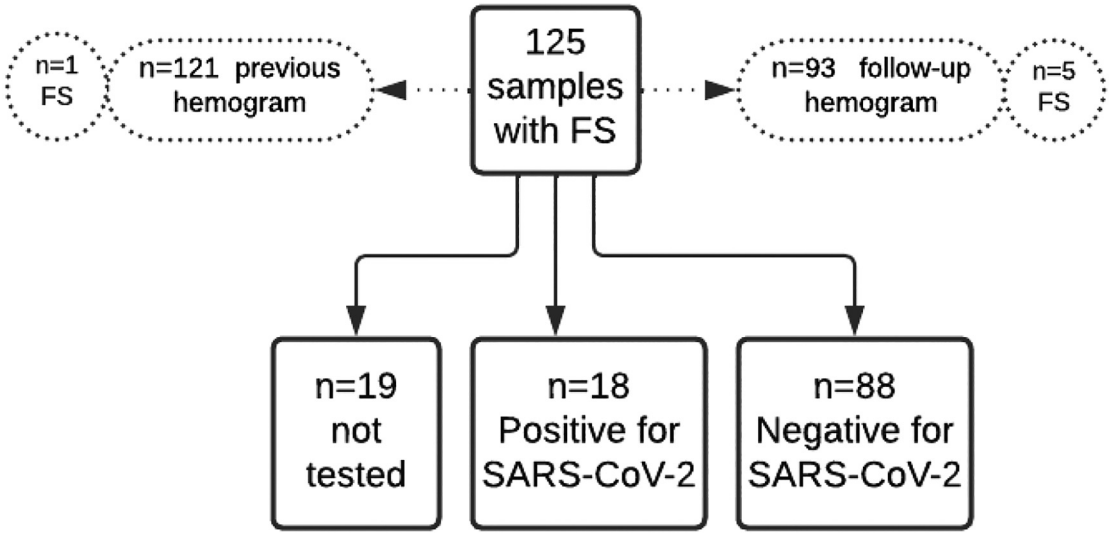

Figure 2: Distribution of cases.
FS – fibrin strands.

During this period, 125 samples positive for the presence of fibrin strands were found, corresponding to 1.96% of the total number of smears analyzed (n=6,375). Most patients (81.6%) were more than 60 years old and the prevalence in female patients was slightly superior (60%) to male patients (40%). Inpatients' samples corresponded to 61.6% (n=77), mostly from the internal medicine ward (63.6%; n=49). Only 1 sample from the ICU was found (1.3% of the hospitalized patients). Finally, 26.4% (n=33) were outpatients and 11.2% (n=14) were from the emergency department.

At first, we hypothesised this increase in fibrin strands detection was due to the coagulopathy developed by COVID-19 patients, however, after excluding 19 patients who were not tested, this study revealed only 17% of patients (n=18) were positive for SARS-CoV-2 and that 83% (n=88) of the tested patients were negative (Figure 2).

Regarding previous blood counts, out of the 121 patients who had a previous hemogram, only one patient had fibrin strands reported, this was a SARS-CoV-2 negative patient. On the other hand, 93 patients (74.4%), had a follow-up blood count, and only in 5 of them (5.4%), fibrin strands were once again present, all of them were negative for SARS-CoV-2 (Figure 2). We observed the interference indices from these 5 patients' reports and found three of them to have high hemolysis (measured in all samples for biochemical testing), probably indicating pre-analytical interferences.

Finally, we tried to correlate D-dimer values to the fibrin strands development, yet only 12 patients had a

D-dimer determination, but all had a high result. In the previous days 18 patients had a D-dimer determination, and in the following days – 11 patients, all of them with elevated values. Some of these patients were consecutive measurements and fibrin strands were not found in the previous or following days. We must remember COVID-19 patients do develop coagulopathy, and many patients were already under anticoagulant drugs.

Resuming, during the second COVID-19 wave in Portugal, we found only 17% of patients with fibrin strands in PBS were SARS-CoV-2 positive, out of all the patients tested. Regarding fibrin strands detection and D-dimer values, more studies are necessary as few patients had a D-dimer determination.

As an explanation for the increase in the incidence of fibrin strands, we thought that the personal protective equipment (PPE) may contribute to difficulties during blood collection, increasing the chance for a similar result if the blood collection is repeated. Besides the PPE, less experienced workers can also increase the number of preanalytical errors, and in our hospital, as in many others, several newly graduated healthcare workers were hired to face this pandemic. We believe that the need to repeat the blood collection, should be considered in an unstable patient and each case must be evaluated individually.

The transition from the analyzer Sysmex® XE5000 to the analyzer Sysmex® XN10 may have also contributed for this increase, as the new analyzer's flag may be more sensitive.

Finally, just as mentioned by Lippi et al., an additional effort should be made in order to optimize and standardize several preanalytical procedures [8]. We suggest new healthcare workers should be given an adequate integration time and that even during difficult periods adequate formation must be a priority.

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Informed consent: Not applicable.

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Data availability: The datasets generated during the current study are available from the corresponding author on reasonable request.

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