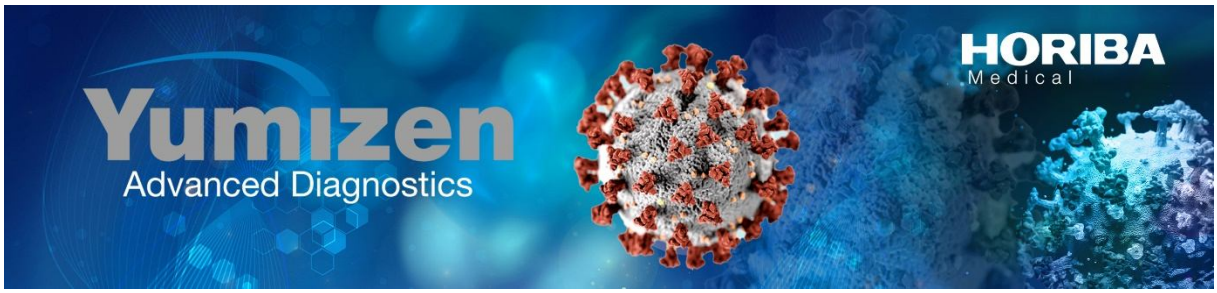

How biological markers could contribute to the monitoring of COVID-19?

Focus Note #3 : Hemostasis Markers

1. Extract from Article on Hematology Biomarkers

COVID-19 screening, prognosis and severity assessment with biomarkers for management of patients

Published April 8, 2020

Summary

This global epidemic of coronavirus that we are currently experiencing, need an over view on the biological markers that allow the monitoring of COVID-19 disease. After a synopsis of the clinical characteristics and the management of patients, we propose a literature review of the diagnostic tests which include molecular and serological diagnosis. The aim of this document is to show the biological markers involved in screening, triage and prognosis, which involves white blood cells, platelets, D-dimer, CRP and fibrinogen. While acknowledging that these parameters are not exhaustive, they nonetheless represent essential biological markers for the management of this epidemic.

Christian Siatka, Marion Eveillard, Jun Nishimura, Christophe Duroux and George Ferrandi

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Biological Markers for Screening, Triage and Prognosis

Several biomarkers have been observed to be abnormal in COVID-19 infected patients and the relevance of identifying them resides on decreasing the possibility of misdiagnosing severe COVID-19 (36) and to provide more insightful information for better management of COVID-19 patients. Many cohorts of different populations have been reported, principally from China, showing abnormal laboratory

assessments consisting mainly of complete blood count, liver and renal function, biochemical and coagulation testing, inflammatory factors, and others.

D-dimer

In addition to the unbalanced white blood cell differential, a coagulation testing parameter called D-dimer has been reported to increase in association with the severity of the disease and related to clotting disorders and microthrombotic formation in peripheral blood vessels (46). D-dimer levels in ICU patients (0.6-14.4 mg/L) was higher than non-ICU (0.3-0.8 mg/L) with p-value of 0.0042 (14). In another study, D-dimer shown to be higher in non-survivor patients than survivor patients, particularly a significant difference was observed in the ninth onset day (17), other authors agree that the increasing of D-dimer is linked to the severity of the disease (47) (48) (13) (49).

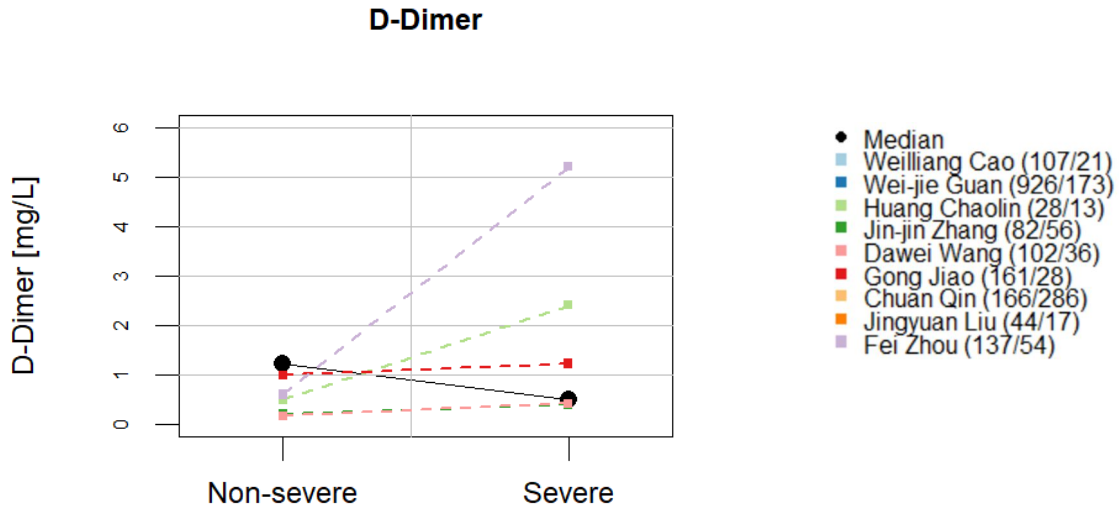

Figure 3: D-dimer mean count in non-severe and severe patients of different authors.

The definition of severity varies slightly among references. In all the references inspected, an increase of D-dimer was observed in association of COVID-19 severity. In (47) & (49) elevation of D-dimer was associated with the survival of infected patients. The numbers inside the parenthesis are the numbers of non-severe and severe patients per study.

Fibrinogen

Fibrinogen degradation products (FDP), and Fibrine (FIB) were found to be higher than in a control healthy population, thus confirming earlier similar findings. Reported data from 94 patients show that FDP (33.83 vs. 1.55 mg/L; $p<0.001$) were higher in patients than those in controls, FIB values in SARS-CoV-2 patients were also higher than those in the control group (5.02 vs. 2.90 g/L; $p<0.001$). The analysis of blood coagulation in COVID-19 patients seems to be clearly deranged compared with a healthy control population. More specifically, FDP, and FIB values were found to be significantly increased (49).

2. The Hemostasis Guidelines for COVID-19 Monitoring & Prognosis

Coagulopathy is common in hospitalized COVID-19 patients including a thrombotic risk (**Pulmonary Embolism** or **DIC**). It has long been recognized that activation of coagulation and/or fibrinolysis occur as part of the acute inflammatory response.

Zhou et al performed a retrospective multicenter cohort study of 191 adults with laboratory confirmed COVID-19 from Wuhan Hospitals. Coagulopathy, defined as a 3 second extension of prothrombin time (PT) or a 5 second extension of activated partial thromboplastin time (APTT), was present in 50% of the no survivors but only 7% of the survivors ($p< 0.0001$).

Guidelines

- **GIHP/GFHC:** The French Working Group on Perioperative Hemostasis (**GIHP**) and the French Study Group on Thrombosis and Hemostasis (**GFHT**) published recommendations for anticoagulant treatment and hemostasis monitoring for the prevention of thrombotic risk in hospitalized COVID-19 patients. For patients hospitalized with COVID-19, prevention of thromboembolic disease by LMWH is the option of choice. Certain biological tests has proven to be very useful for patients monitoring. The recommendation is to check at least every 48 hours **Platelet count, PT, aPTT, Fib and D-dimer**.

- **ISTH**: Jecko Thachil et al (2020) Interim guidance on recognition and management of coagulopathy in COVID-19. Prelease from jth. Online version. First published: 25 March 2020.
  Guideline: use **PT/INR or aPTT** ratio in order to manage bleeding: "Manage bleeding with blood product replacement as per managing major bleeding as above: i.e. if PT/INR or APTT ratios are greater than 1.5 then give FFP 15-25mg/Kg; if fibrinogen is < 50x 109/l then give platelets"

- **BHS**: The DIC score is of prognostic value in COVID-19 pneumonia. The DIC score is calculated from measurement of the **platelet count, D-dimer, fibrinogen and prothrombin time** (Taylor et al, 2001) as shown in this table:

Parameter	Score
Platelet Count	
>100 x 10^9/L	0
50-100 x 10^9/L	1
<50 x 10^9/L	2
D-dimer	
No increase	0
Moderate increase (1 – 10 times upper limit of normal)	2
Strong increase (> 10 times upper limit of normal)	3
Fibrinogen	
> 1.0 g/L	0
≤ 1.0 g/L	1
Prothrombin time prolongation	
< 3 s	0
3 – 6 s	1
> 6 s	2
Overt Disseminated Intravascular Coagulation	**≥ 5**

"Hematologists should support use of the score in the clinical assessment of patients hospitalized with proven COVID-19 infection. This may involve modifying laboratory order sets so that when a coagulation screen is requested in an affected patient D-dimer and fibrinogen are automatically added to the prothrombin time"
From the BSH Hemostasis and Thrombosis Task Force, 18-03-2020.

3. The HORIBA Medical Solution

3.1. The new hemostasis Yumizen G range

The new hemostasis comprehensive Yumizen G range meets those expectations for all required parameters PT, aPTT, Fib and D-dimer including mainly liquid and ready to use reagents formulations.

All those parameters are available on semi-automatic and fully-automatic systems.

Semi-automatic range

Compact 2 and 4-channel instruments *designed for small and satellite laboratories to perform hemostasis screening and monitoring*

Yumizen G200

Yumizen G400

Fully automatic range

Automatic benchtop hemostasis analyzer *for routine and specialized laboratories*

Yumizen G800

Yumizen G1500 Yumizen G1550

4. Conclusion : Monitoring Covid-19 through Hemostasis Testing

Scientific experts have issued therapeutic recommendations for monitoring COVID-19. The **biological markers** for monitoring and prognosis are platelet count, PT, aPTT, Fib and D-dimer.

All the hemostasis parameters are available on semi-automatic and fully automatics analyzers **Yumizen G**. With the Yumizen G range, it is possible to meet the demands of routine laboratories, emergency and satellites laboratories.