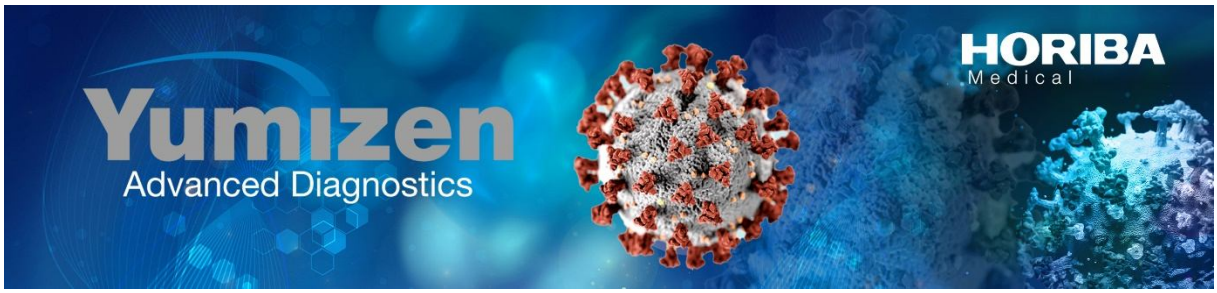

How biological markers could contribute to the monitoring of COVID-19?

Focus Note #1 : Hematology Biological 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.

Hematology Parameters

Different authors have published findings regarding the effect on hematology parameters in COVID-19 infected patients. The vast majority concur on an unbalanced white blood cells panel (37).

White Blood Cells

In the hematological panel, a study that evaluated 1099 positive COVID-19 samples showed on admission and 83.2% of lymphocytopenia (fewer than 1500 cells per mm 3) and leukopenia in 33.7% (16), other authors support these observations especially lymphocytopenia in severe patients (see figure 1) (38) (39) (40) (41) (42) (43) and others reported normal levels of leukocytes (44) (45). Furthermore, neutrophils seem to increase according to the severity of the COVID-19 (14) (17). In a study with 13 patients admitted to ICU and 28 to non-ICU care, the medians of the neutrophil count were 10.6 and 4.4 × 10^9/L, respectively (14). Consequently, due to a significant decrease of lymphocytes and neutrophil increase, the neutrophil-lymphocyte ratio, along with the age of patient, has been suggested as a combined parameter to evaluate the severity of patients with pneumonia caused by COVID-19 for improving risk stratification and management (45) (36).

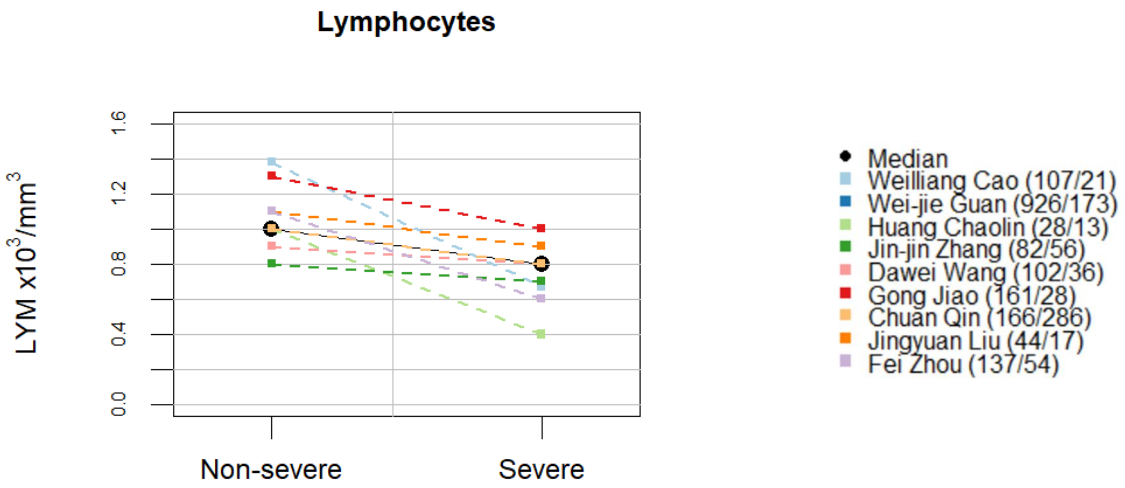


Figure 2: Lymphocyte mean count in non-severe and severe patients from different authors.

The definition of severity varies slightly among references. In all the references inspected, a decrease of lymphocytes was observed in association of COVID-19 severity. The numbers inside the parenthesis are the numbers of non-severe and severe patients per study.

Platelets

A meta-analysis was performed of platelet number in COVID-19 patients with or without severe disease and odds ratio (OR) of thrombocytopenia for severe form of COVID-19 (42). The pooled analysis revealed that platelet count was significantly lower in patients with more severe COVID-19. A subgroup analysis comparing patients by survival, found an even lower platelet count was observed with mortality. In this study, a low platelet count was associated with over fivefold enhanced risk of severe COVID-19 (42). The low platelet count could be associated with increased risk of severe disease and mortality in patients with COVID-19.

2. The HORIBA Medical Solution

2.1. The Full Blood Count analysis on new Yumizen hematology systems

As major hematology IVD specialist, HORIBA Medical is capable to deliver hematology solutions to clinical labs in the world. The new **Yumizen®** hematology products line consist of automated testing systems designed to perform Full Blood Count (FBC) analysis in small labs with **Yumizen H500 and H550**; and in big labs with **Yumizen H1500 and H2500**.

Yumizen H500

OT Model

CT model

Yumizen H550

Auto sampling autoloader

- Dedicated to small size laboratories: small hospital, emergencies, satellites, back up, POLs,…
- 27 parameters with 6 Diff WBC
- Compact analyzer & very ease of use
- Suitable for infectious sample monitoring

Yumizen H1500

Yumizen H2500

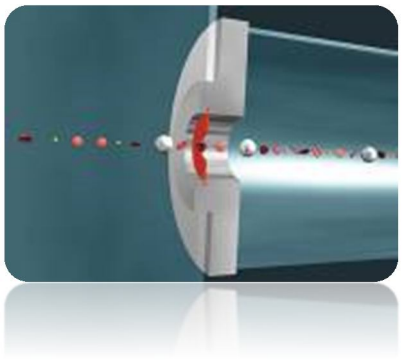
Yumizen SPS

Yumizen P8000

- Dedicated to big size laboratories: hospitals, private chain labs,...
- 56 parameters with 8 Diff WBC, Retic, Body Fluid.
- Fully automated HELO* solution with Yumizen P8000 (middleware), Yumizen SPS (slide maker stainer), Cellavision (digital cells examination) and Yumizen T6000 (track system)
- Suitable for extensive hematological diagnosis

*HORIBA Evolutive Laboratory Organization

2.2. Technologies & performances for monitoring blood cells parameters



- **Reference impedance method**

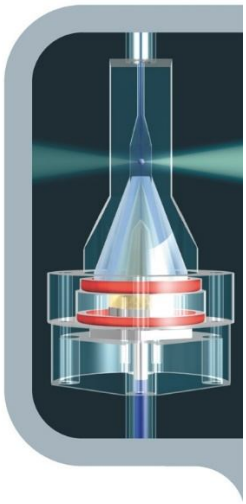
⇨ for Complete Blood Count :

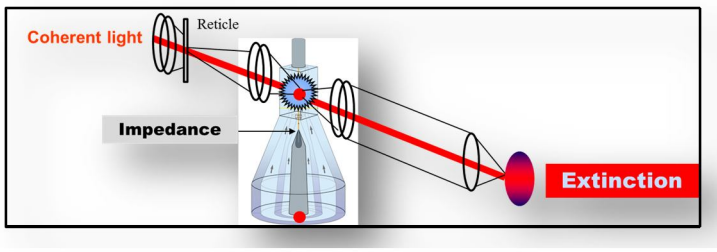
Red Blood Cells : RBC, HGB, HCT, MCV, MCH, MCHC, RDW-CV, RDW-SD, MIC*, MAC*

*available on Yumizen H1500/2500

Platelets : PLT, MPV, PDW, PCT, P-LCC*, P-LCR*

*available on Yumizen H500/550





- **Flow Cytometry:** Double Hydrodynamic Sequential System, DHSS®
- **Impedance** for cells volume measuremnt
- **Optical Extinction** for refractive index measurement (absorbance)

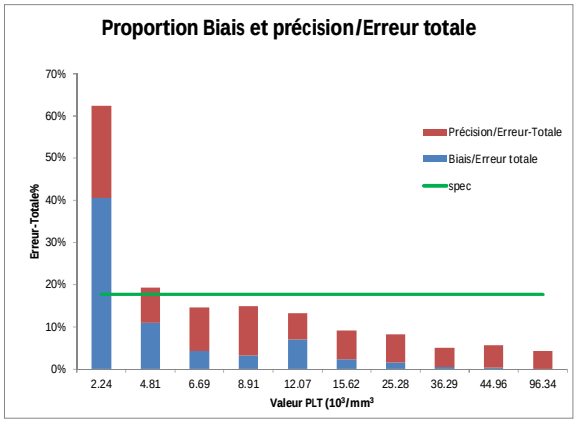
⇨ for Differential Leucocytes Count

White Blood Cells :

- WBC, LYM # %, MON # %, NEU # %, EOS # %, BAS # %, LIC # % : on YH500 & YH550
- WBC, LYM # %, MON # %, NEU # %, EOS # %, BAS # %, LIC # %, ALY # %, IMG # %, IML # %, IMM # % : on YH1500 & YH2500

Platelets Count

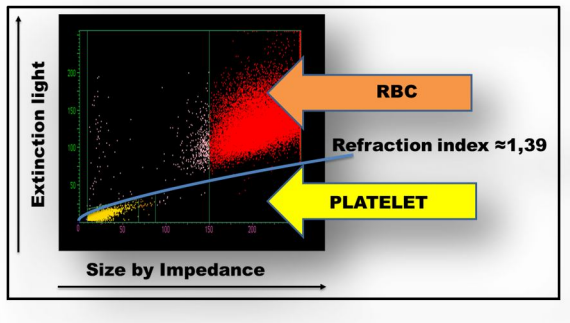
On new Yumizen analyzers range, the PLT measurement by impedance has been enhanced in such way to reach the lowest acceptable concentration _ **Limit Of Quantification** (LOQ) _ below **10**.10^9/L fitting the clinical threshold to help the clinicians to take the appropriate decision of blood transfusion.

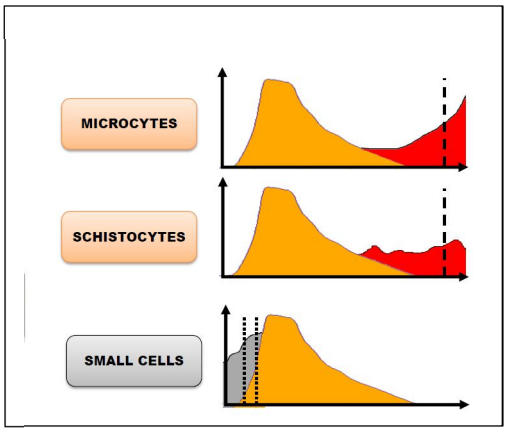


The LOQ has been obtained with an imprecision claim (total error) of 17,7% as per the clinical standard of Gröner & Simpsons

Clinical Assessment of LOQ on Yumzien H500/550

On **Yumizen H1500/H2500**, an alternative measurement of Platelets can be performed from optical extinction technology. The called **PLTox** parameter can be obtained by reflex testing and especially useful in case of platelets interferences.





Leucocytes Count

- **White Blood Cells Count (WBC)**

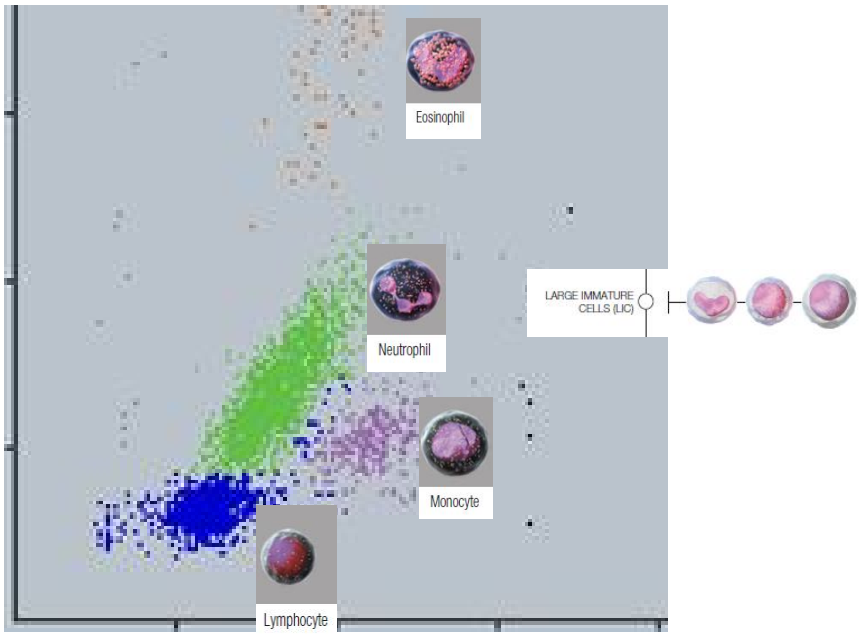
The WBC count is ensured trough different measurements technologies on the different HORIBA Medical hematology analyzers available:

WBC Measurement	Impedance CBC/HGB Chanel	Impedance Baso Channel	Optical LMNE Channel	WBC & Diff Parameters
Micros range	✓			WBC, 3 Diff
Pentra range	✓	✓	✓	WBC, 5 Diff
Yumizen H500/550			✓	WBC, 6 Diff
Yumizen H1500/2500	✓	✓	✓	TNC, WBC, 8 Diff

- **Differential Leukocytes Count (WBC DIF)**

Detection of WBC abnormalities in term of size and content is perfectly detected with great sensitivity and specificity. Thanks to the technology of double hydro-focalization system sampling (DHSS®), the Yumizen systems are able to give you the size of cells, the content and also the distribution per sub leucocytes population: Lymphocytes, Monocytes, Neutrophils, Eosinophils and Basophils. The clusters of each population are automatically surrounded with a specific attention around Lymphocytes population with LN flags, ALY,...

The HORIBA Medical technology embedded in Yumizen analyzers are particularly powerful for detecting inflammations or infections. It also helps you monitor therapies – elevated white blood cell counts going down can show therapies are working.



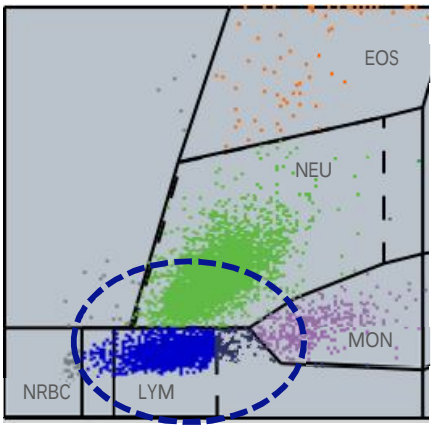
Current LMNE Matrix for Differential WBC on Yumizen range

Lymphocytes Count (LYM)

The HORIBA Medical hematology analyzers integrate in the DIF mode sub leucocytes population in a specialized area to count Lymphocytes (LYM). It is of particular interest for samples with detected abnormalities either on cells enumeration or cells morphologies.

Lymphocytes are very small, round shaped cells with a condensed cytoplasm and a large nucleus. These cells are normally positioned in the lower part of the Y-axis, as well as in the left part of the X-axis, of differential matrix, because of their small size.

An expert flagging system is capable to trigger out flags and alarms in case of pathological abnormalities in order to provide comprehensive diagnosis help to clinicians for validating their hematology results.

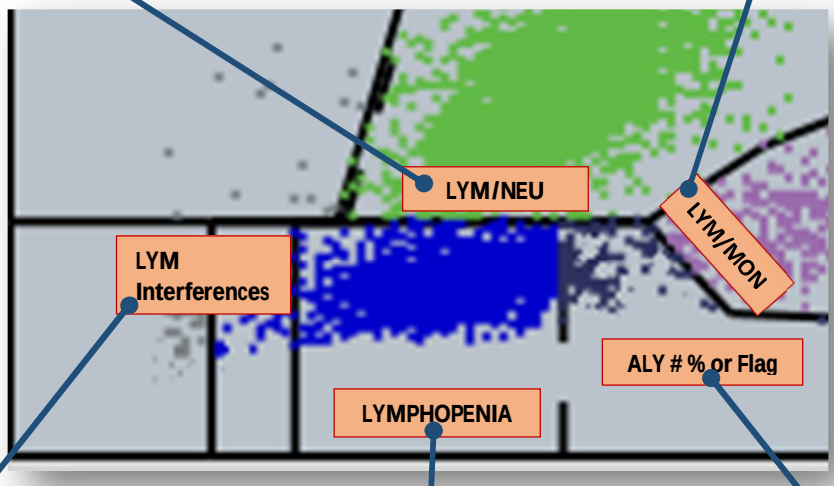


Abnormal Differentiation Lympho/Neutro:

- Small neutrophils without granules and/or slightly segmented
- Lymphocytes with a segmented nucleus
- Activated lymphocytes
- Large granular lymphocytes
- Neutrophils with membrane weakness

Abnormal Differentiation Lympho/Mono:

- Reactive lymphoid forms
- Atypical Lymphocytes
- Blasts
- Small monocytes



Lymphocytes Interferences:

- Platelet aggregates
- NRBC
- Small Lymphocytes
- Lyse resistant RBC

Lymphopenia:
Pathology flag triggered out when LYM# > Panic value

Atypical Lymphocytes (ALY):
Large lymphocytes are usually detected in the ALY area where reactive lymphoid forms, Sezary cells, tricholeucocytes,... activated lymphocytes, and plasmocytes are also found.

- **Neutrophil-To-Lymphocytes Ratio (NLR)**

The ratio between Neutrophils count and Lymphocytes count can be used when combined with other parameters as an indicator of inflammation and infection.

Recent Chinese publication on Covid-19 monitoring highlight the clinical value of NLR when combined with age criteria as an early indication of severe illness.

This ratio can be now set up on Yumizen P8000 middleware of Yumizen H1500/2500 and hence provide the users with the NLR value in the FBC report.

The NLR will be also available on next version of Yumizen H550, and then, on future version of H500.

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3. Conclusion : Monitoring Covid-19 through Hematology Testing

The hematology analyzers such as **Yumizen** are capable to deliver reliable hematology diagnosis by combining enhanced technologies and providing multiple parameters; from small care units to much bigger laboratories centers. More and more sophisticated flagging system are implemented to help the clinicians to interpret cells abnormalities and provide safe pathological diagnosis.

Infectious diseases cannot be only monitored with dedicated infectious diagnostics tools but also **biological testing systems** are more and more suitable for delivering significant markers to help and contribute to their monitoring.