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Article type : Review

COVID-19 and the clinical hematology laboratory

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ijlh.13229

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Competing interest: The authors have no competing interest.

Abstract:

The ongoing COVID-19 pandemic originated in Wuhan, Hubei Province, China in December 2019. The etiologic agent is a novel coronavirus of presumed zoonotic origin with structural similarity to the viruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Like SARS and MERS, COVID-19 infection manifests most frequently with lower respiratory symptoms. A minority of patients progress to acute respiratory distress syndrome/ diffuse alveolar damage. In addition to its central role in the diagnosis of COVID-19 infection, the clinical laboratory provides critical information to clinicians regarding prognosis, disease course, and response to therapy. The purpose of this review is to 1) provide background context about the origins and course of the pandemic 2) discuss the laboratory's role in the diagnosis of COVID-19 infection 3) summarize the current state of biomarker analysis in COVID-19 infection, with an emphasis on markers derived from the hematology laboratory 4) comment on the impact of COVID-19 on hematology laboratory safety, and 5) describe the impact the pandemic has had on organized national and international educational activities worldwide.

Introduction: epidemiology and clinical features of the 2019-2020 COVID-19 pandemic

The current COVID-19 pandemic originated in December 2019 in the city of Wuhan, the capital of the Hubei province of China. Despite efforts to contain its spread, the epidemic spread to numerous other countries in Asia and by January 2020 infected patients were identified in Europe.(1) On March 11 the World Health Organization (WHO) declared a pandemic: at this point there were an estimated 118,000 cases in 114 countries, resulting in 4,291 reported deaths. According the WHO, as of April 9 , there were an estimated 1,436,198 cases in 212 countries and territories, resulting in 85,522 reported deaths. The countries with the largest numbers of confirmed cases were the United States (395,030 cases), Spain (146,690 cases), Italy (139,422 cases), Germany (108,202 cases) and China (83,249 cases).(2,3)

Early in the pandemic Zhu et al isolated and characterized the virus (preliminarily called 2019-nCoV, renamed SARS-CoV2, and finally COVID-19). Like the viral agents responsible for the severe acute respiratory syndrome (SARS) outbreak of 2002-2003 and the Middle East respiratory syndrome (MERS) outbreak of 2012-2013, COVID-19 is a coronavirus. Coronaviruses have a positive-sense single-stranded RNA genome and a helical capsid with an envelope composed of a lipid bilayer.(4,5) Sequence analysis of the genome of COVID-19 reveled that it has a strong homology to SARS-like coronaviruses that normally infect bats, and for this reason the pandemic is believed to be of zoonotic origin.(6)

Like the SARS and MERS outbreaks, the predominant clinical features demonstrated by individuals infected during the COVID-19 pandemic are respiratory. Following an incubation period of up to 2 weeks duration, patients become symptomatic. Fever (identified in ~99% of patients), cough (~50% of patients), and respiratory difficulty (~33% of patients) are the most common complaints. Approximately 80% of infected individuals have mild to moderate symptoms. The remainder have severe enough disease to necessitate hospitalization. Among severely ill individuals, the most severe complications are acute respiratory distress syndrome/ diffuse alveolar damage. Several co-morbidities have been proposed which predispose patients to severe disease. Zhou et al addressed a wide range of co-morbidities and laboratory abnormalities potentially impacting prognosis in COVID-19 patients. In their multivariate analysis the following features were associated with increased odds of death: older age; higher sequential organ failure assessment (SOFA) score (a scoring system based on PaO_2/FiO_2, Glasgow coma scale, mean arterial pressure, serum bilirubin, platelet count, and creatinine); and d-dimer greater than 1 μg/mL at admission.(7)

The disease trajectory and percentage of severe cases stands in contrast to patients identified in the SARS and MERS outbreaks, which had a shorter incubation and a higher fraction of severe cases and deaths from disease. As a result of the longer incubation period and presumed lower fatality rate, COVID-19 has infected a significantly larger number of individuals than those affected by the SARS and MERS outbreaks.(6)

A recently identified clinical phenomenon is reactivation of COVID-19 infection in a subset of patients following recovery from initial disease. Although it has not yet been widely reported in the peer-review medical literature, a report by Ye et al identified reactivation in 5 patients from a cohort of 55 patients from China.(8) Notably, influenza and H7 avian influenza virus were excluded by additional testing, but repeat testing for COVID-19 does not appear to have been performed. As of publication, all patients are alive without evidence of pneumonia. The hematologic characteristics of this group of patients with COVID-19 have not yet been definitively explored.

Laboratory confirmation of COVID-19 infection:

Because of the rapid spread of the COVID-19 pandemic, affected countries have taken a heterogeneous and evolving approach to diagnosis of infection in patients and continue to have different and in some cases evolving strategies to determine what segments of the population should be tested.

The molecular diagnosis of COVID-19 infection has been the subject of numerous scientific publications, many of which are beyond the scope of this review. Briefly, 2 major diagnostic approaches have been implemented in a majority of countries, both using RT-PCR. The first, which has the approval of the WHO, is that of Corman et al, which has 3 viral genes (*E*, *RdRp*, and *N*) as targets.(9,10) Screening is conducted using an assay directed at the *E* gene and is confirmed by testing for the *RdRP* and *N* genes. A second assay was developed by the Centers for Disease Control and Prevention (CDC) in the United States and uses a combined assay for the viral *N1/2/3 gene* with the *RNase P* gene as a control assay. This latter approach is the basis for many of the in-laboratory testing approaches developed by medical centers and commercial laboratories in the United States.(9)

Because of the rapid implementation of diagnostic testing for COVID-19, some features have become obvious only after widespread testing of patient populations. The first of these is the apparent suboptimal number of false negative RT-PCR results. In recent studies a small number (~3%) of patients with computerized

tomography (CT) findings strongly suggestive of COVID-19 infection initially were negative using the RT-PCR based testing. In at least one study all of the initially negative patients had a positive result on repeat testing after a mean interval of ~5.0 days.(11) This feature is understandable in view of the known disease trajectory in patients with severe COVID-19 disease. Since the mean incubation period is approximately 6 days, and viral load significantly increases during this period, testing conducted early in the symptomatic period may be falsely negative. Similarly, RT-PCR results may be falsely negative in recovering infection when patients are still presumably infectious, again due to the same features of disease kinetics. Both these scenarios have obvious negative implications for the use of molecular-based testing alone as the sole means of controlling the spread of infection.(9)

At least 2 important factors make the study of the epidemiologic features of COVID-19 challenging. The first is the lack of a uniformly applied diagnostic approach. Second, different nations have taken radically different approaches to population screening. Extreme examples of this heterogeneity are South Korea , a relatively small nation, which has tested over 65,000 individuals compared to the United States which was delayed in implementing RT-PCR which at the time of preparation of this manuscript has tested a much smaller number of individuals.(6)

As the pandemic matures, it will likely be useful to identify the overall number of individuals who have been exposed to COVID-19 and have developed a successful immune response. Since approximately 30% of adults and possibly a larger percentage of children have clinically silent infection, a mass screening approach of the general population may be informative. A combined IgG/IgM immunoassay has been developed which can achieve this goal in a simple and cost-effective manner.(9)

Hematologic parameters of patients with COVID-19 infection (Table 1):

On the basis of studies conducted in China and elsewhere, the clinical hematology laboratory plays an important role by providing the clinical team a number of useful prognostic markers. Although information is in some cases based on the results of limited amount of data and should be validated with additional studies, the available findings clearly establish the clinical hematology laboratory as an important partner in the triage and management of affected patients. Apart from RT-PCR testing for the organism, laboratory tests have not been assessed with regard to their sensitivity or specificity for the diagnosis of COVID-19, although their value as prognostic indicators have been established. A summary of the major hematologic features of importance in COVID-19 infected patients follows.

Lymphopenia

Lymphopenia is a common finding in patients with COVID-19 infection, and is believed to represent a defective immune response to the virus.(6) In their early study of 41 adults with RT-PCR confirmed COVID-19 infection, Huang et al noted that lymphopenia (defined as an absolute lymphocyte count $<1.0 \times 10^9$/L) was seen in 26 (63%) of patients.(12) This is typical for the series reported in the medical literature. A recent meta-analysis noted that 35–75% of patients developed lymphopenia, which was a more frequent feature of patients who died of disease.(13) In their analysis of 67 COVID-19 patients from Singapore, Fan et al identified an lymphocyte count of $<0.6 \times 10^9$/L being predictive for admission to the intensive care unit (ICU).(14)

There appears to be some geographic variability in the percentage of COVID-19 patients who present with lymphopenia. For example, a paper reporting a series of COVID-19 patients from Singapore identified a much lower percentage of patients with lymphopenia, as did a retrospective analysis of COVID-19 patients from Zhejiang Province, which is located ~450 miles from Wuhan.(14,15) Conversely, in a series of patients from Italy, patients presenting in the emergency department demonstrate lymphopenia in many cases.(16) The reasons for these and similar discrepancies are unclear, although they are likely multifactorial. Because of the apparent viral genomic mutations, it is possible that the immunologic response to the virus may change as the pandemic expands into other countries. Another possibility is that testing of patients is nonuniform and, depending on the time of presentation, the extent of lymphopenia may vary. A careful review of reported data for these issues is therefore recommended.

In children, lymphopenia is much less common. In their meta-analysis of 66 cases reported in the Chinese literature, Henry et al identified lymphopenia in 3% of patients. This is in contrast to other similar viral infections, such as SARS, in which lymphopenia was a much more common finding in children.(17)

Leukocytosis

Leukocytosis, irrespective of whether it represents a neutrophilia, lymphocytosis, or both, is noted in a minority of COVID-19 infected patients, and appears to herald bacterial infection or superinfection.(6) A meta-analysis of the extant literature noted that leukocytosis was identified in 11.4% of patients with severe disease compared to 4.8% of patients with mild to moderate disease (odds ratio [OR], 2.54; 95% confidence interval [CI], 1.43–4.52).(6)

Neutrophilia

The data on neutrophilia are incomplete and have not been widely addressed in the literature. The available data suggest that neutrophilia is an expression of the cytokine storm and hyperinflammatory state which have an important pathogenetic role in COVID-19 and related infections such as SARS (12,18-20). Cytoplasmic and nuclear morphological anomalies, from hyposegmented nuclei to apoptosis, have been described in circulating granulocytes at the time of hospital admission, possibly in relation with the hyperinflammatory state with cytokine storm. They usually precede the increase of reactive lymphocytes(21). Neutrophilia may also indicate superimposed bacterial infection.(6) For example, Fan et al noted that neutrophilia is common in patients treated in the ICU during hospitalization (11.6 vs $3.5x10^9$/L).(14)

Markers of systemic inflammation

In recent years a number of biomarkers of systemic inflammation including sepsis have become available as reportable elements of the major commercially available blood analyzers as part of the expanded CBC or as parameters measured in research mode. Among these are neutrophil CD64 expression, mean cell volume of neutrophils and monocytes, immature granulocyte fraction, delta neutrophil index, and monocyte distribution width (MDW). It is conceivable that many of these markers may be useful in identification of patients at risk for secondary bacterial sepsis, although data at this point in the pandemic is lacking. An exception is MDW (Beckman Coulter, Brea, CA, USA), which has been reported to be increased in nearly all COVID-19 infected patients, in particular in those with the worst clinical symptoms, based on non-peer reviewed personal data recently reported in a review.(6) The MDW data should be interpreted with caution, since the presence of reactive lymphocytes in COVID-19 positive patients may result in a falsely elevated MDW.

Another potential application of data derived from the CBC would be to use formulas such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio to act as surrogates to assess the extent of systemic inflammation. Although extensive study is at this point lacking, Qin et al have reported an increase in NLR in patients with severe disease compared to those without. (20)

Thrombocytopenia

Thrombocytopenia is an important indicator of severe disease in COVID-19 patients, as highlighted by a recent review of the available peer reviewed data. This is not surprising, since platelet count is used by

scoring systems such as the Multiple Organ Dysfunction Score (MODS), Simplified Acute Physiology Score (SAPS) II, and Acute Physiology and Chronic Health Evaluation (APACHE) II, and thrombocytopenia is an indicator of severe disease in these systems .(22) A meta-analysis pooling data from 9 studiesshowed that thrombocytopenia has been reported in a majority of patients. This is similar to data reported in the SARS outbreak, in which thrombocytopenia was reported in ~55% of cases and correlated with increased risk of severe disease.(22-24) In patients with severe infection, thrombocytopenia is identified in up to 57.7% of patients, vs. 31.6% of patients with less significant COVID-19 symptoms (OR 2.96, 95% CI, 2.07–4.22).(6) Interestingly, thrombocytosis has been identified in a minority of patients, for example by Chen et al who report this finding in ~4% of cases.(18)

The use of platelet count in conjunction with other factors associated with severe disease has to our knowledge not been reported for COVID-19 patients, although it has been revealed to be of use in SARS. For example, Zou et al reported that platelet count, in conjunction with hypoxemia, were used in prognostic model for SARS that predicted severe disease with 96.2% accuracy.(23,25) In addition, elements of the expanded CBC useful in evaluation of sepsis, such as mean platelet volume and reticulated platelet count, have not to our knowledge been reported in the COVID-19 literature, but may be of use in risk stratification and clinical decision making.

Coagulation parameters

Only rare articles are published related to coagulation parameters in COVID-19 patients, mainly from China.(26,27) A subset of severe pneumonia patients develop viral sepsis, disseminated intravascular coagulation (DIC) and multiorgan failure.(26) Coagulation parameters show abnormal results related to sepsis or DIC. Prothrombin time (PT), an assay used to evaluate the extrinsic and common coagulation pathways, and D-dimer are useful indicators of prognosis and severity of disease in COVID-19. (5) In a study with 183 coronavirus pneumonia, PT, activated partial thromboplastin time (APTT), fibrinogen, antithrombin, FDP and D-dimer were consecutively measured during 2-week hospitalization. The overall mortality was 11.5%. The non-survivors demonstrated significantly higher D-dimer and fibrin degradation product (FDP) levels, and longer PT and APTT compared to survivors on admission. The fibrinogen and antithrombin levels were significantly reduced in non-survivors during hospitalization, and D-dimer and FDP are markedly elevated in all non-survivors by the late hospitalization, which suggested a common coagulation activation, disregulated thrombin generation, impaired natural anticoagulants and fibrinolysis. Overt DIC (5 or higher

points according to the International Society on Thrombosis and Haemostasis diagnostic criteria for DIC)(28) was developed more frequently in non-survivors than survivors (71.4% vs 0.6%, respectively) in median 4 days from admission.(26,29). In addition, several critically-ill patients have been reported to develop coagulopathy, antiphospholipid antibodies and increased arterial and venous thrombotic events such as cerebral infarction.(30) Early recognition of these abnormal coagulation results will be useful to predict the disease severity, support to guide the therapy, and improve the patients' clinical outcome.(26)

Other biomarkers of importance in COVID-19 infection (Table 2)

Several biochemical markers have been identified as being useful in identifying patients with severe COVID-19 disease. Although these tests are outside the scope of laboratory hematology, based on their potential importance in conjunction with the aforementioned hematologic markers, a discussion of these biomarkers follows.

C-reactive protein (CRP), which is produced by the liver, is an acute phase reactant that is increased in a wide range of inflammatory conditions. It is increased in 75-93% of patients with COVID-19 infection, particularly in severe disease.(13) It can be monitored with other biomarkers such as absolute lymphocyte count to assess whether patients are developing worsening infection.(17)

Procalcitonin is a prohormone, a precursor of calcitonin, a hormone that plays a major role in calcium homeostasis. Elevated procalcitonin levels may be seen in sepsis and are particularly associated with septic shock and organ dysfunction requiring intervention.(31) On initial presentation a majority of COVID-19 patients have procalcitonin levels in the normal range.(12) As would be expected, patients with severe COVID-19 infection necessitating treatment in an ICU frequently have marked elevation of calcitonin.(13) Because of its association with bacterial co-infection and severe disease, it has been recommended to serially test calcitonin levels, particularly in ICU patients.(17,32)

Lactate dehydrogenase (LDH) is an enzyme expressed in nearly all human cells, including cells of the heart, liver, muscles, kidneys, lungs, and in bone marrow, and catalyzes the production of pyruvate to lactate. Elevated serum LDH may be identified following damage to any of the myriad cell types that normally express LDH. Fan et al in their series of COVID-19 patients from Singapore identified absolute lymphocyte count and LDH as discriminators between ICU and non-ICU patients.(14) As would be anticipated, elevation is LDH is common in COVID-19 patients in the ICU setting and indicates a poor outcome.(6,13,14)

Alanine aminotransferase (ALT), which is an enzyme produced by hepatocytes, is present at increased level in patients with liver disease. Like many other biochemical markers, it is present at increased level in COVID-19 patients with severe disease and as such may be useful to monitor in patients admitted to the ICU.(6,13,14)

Bilirubin, which is part of the heme catabolic pathway in vertebrates, is produced in hepatocytes. Increased serum bilirubin is identified in a number of disorders involving the liver and biliary apparatus and increased levels of total bilirubin have been shown to distinguish between COVID-19 patients admitted to the ICU versus those with less severe disease.(6,13)

Serum creatinine is a useful index of renal function. It is produced at a constant rate as a product of protein metabolism in the liver and excretion by the kidney, and increased levels may indicate a decreased glomerular filtration rate. Increased creatinine is more frequently identified in COVID-19 patients with severe disease compared to those with more mild features, and patients with combined increases in blood urea nitrogen and creatinine had a higher frequency of poor outcome.(13)

Increased serum levels of the cardiac-specific troponins (troponin I and troponin C) are mainstays in the diagnosis of myocardial infarction and acute coronary syndrome. It is now known that underlying cardiovascular disease is a significant indicator for severe disease in COVID-19 patients. Based on a meta-analysis of the extant literature, it was concluded that patients with hypertension and other cardiovascular co-morbidities should have cardiac troponin level testing performed in a longitudinal fashion throughout hospitalization to assess for emerging myocardial damage .(33)

Albumins are a family of water-soluble proteins commonly encountered in the blood. Decreased serum albumin is associated with a wide variety of conditions such as malnutrition, burns, sepsis, and renal disease. In COVID-19 patients, low serum albumin has been associated with poor outcome.(13)

Experiences in Italy

The COVID-19 pandemic has heavily impacted Italy, with a peak of positive cases around March 20 and a present trend toward a slow, apparently consistent decrease. As of April 6, 124,527 cases have been documented by molecular testing (53.1% males), with 14,860 fatalities.(34) The first case was diagnosed on February 21,(35) but it is now recognized that symptoms were already present in patients who subsequently were shown SARS-COV-2 positive, in the last days of January. There has been rapid spread from a few wealthy regions in the Northern part of the country, with an epicenter in several provinces of Lombardy.(36)

Besides the huge number of cases, COVID-19 infection in Italy is also characterized by a mortality rate (15.2%) which is very high compared to China or Germany. Different possible causes have been proposed to explain the easiness and rapidity of spread and the high fatality rate(37,38): an older age distribution (median age of deceased patients is 78, compared with the median age of 62 for the infected population)(34); the frequent presence of comorbidities (with no clear separation of patients died *of* SARS-COV-2 from those died *with* SARS-COV-2); the national inclination to socialization and clustering, the overcharge of hospitals, typically equipped with a limited number of ICU beds and, importantly, the limited use of molecular testing only for patients with severe symptoms. In addition, hospitals and family care facilities have initially represented a diffusion-enhancing factor, with spread from still undiagnosed infected patients to other patients and health workers. In Italy, 9% of documented cases have occurred in healthcare professionals, with more than 12,000 infected workers (67% women), with a median age of 48 years. Almost 100 doctors have died, with a high proportion of family physicians among them.

Hospitals had to modify their structure and organization(16) and massively improve their capacity for accommodation of patients requiring increasing levels of respiratory support. This has also put a strain on laboratory capacity for molecular testing and other analysis. From a diagnostic standpoint, hematologic data on 300 cases, reported by the hematology laboratory from Bergamo, at the epicenter of the spread, as confirm the frequency of lymphopenia, with presence of reactive lymphocytes and rare erythroblasts.(16) In another group of Italian cases, we have highlighted the frequency of granulocyte morphological anomalies, especially in patients with severe ARDS at admission(Figure 1).(21)

Implications for laboratory safety:

Maintaining a safe workplace is a cornerstone of good laboratory practice, and this is particularly important during a communicable disease outbreak. For guidance, national and international agencies have provided hospitals and private laboratories with a framework to keep employees safe and continue to perform their necessary work. Recommendations for hematology laboratories take into account the following features of COVID-19 epidemiology:

1. The disease has a primarily respiratory route of infection.

2. Social distancing, including maintaining at least 6 feet between individuals, decreases the likelihood of spread.

3. Coronaviruses such as COVID-19 can be effectively inactivated by a variety of alcohol and soap-based cleaning solutions.

The WHO, CDC, and Occupational Safety and Health Administration (OSHA, United States) have published safety recommendations for clinical laboratories. The WHO guidelines specify that blood should be handled using "good microbiological practices and procedures", a term used to emphasize that human factors (e.g. proper risk assessment and training), rather than engineering, is the best way to minimize injuries in the workplace. The WHO recommends that disinfectants known to act against enveloped viruses such as COVID-19 (including hypochlorite, alcohol, hydrogen peroxide, quaternary ammonium compounds and phenolic compounds) be used in all laboratories.(39) Both the WHO and CDC recommend that laboratories that employ automated blood analyzers or otherwise analyze blood from known or suspected COVID-19 patients operate using Biosafety level 2 precautions, which include:

1. Laboratory personnel have specific training in handling pathogenic agents and are directed by scientists with advanced training.
2. Access to the laboratory is limited when work is being conducted.
3. Extreme precautions are taken with contaminated sharp items.
4. Certain procedures in which infectious aerosols or splashes may be created are conducted in biological safety cabinets or other physical containment equipment.(40)

It is noteworthy that, although the predominant route of spread of COVID-19 is respiratory, ~1% of blood specimens tested by RT-PCR had evidence of COVID-19 viremia. Thus, although rare, infection though contaminated blood is possible.(16,41)

The OSHA guidelines offer guidance to employers regarding the risk of transmission of COVID-19 to employees. OSHA categorizes these risks on a scale ranging from very high exposure risk (e.g. healthcare workers performing aerosol-generating procedures) to lower exposure risk (jobs without exposure to people with known of expected COVID-19 infection and without frequent close contact of <6 feet with members of the general public). Apart from the microbiology laboratory, molecular genetic laboratory, or other laboratory facilities handling respiratory specimens, laboratory personnel including those working in a typical clinical hematology laboratory would most likely be categorized as lower exposure risk.(42)

The use of personal protective equipment (PPE) beyond that in general use in the clinical hematology laboratory varies depending on the institution and is dependent upon such factors as national/ international recommendations and availability of specific PPE items. Such regulations will likely change when increased information regarding risk of spread of the virus is more readily available. At Washington University, for example, apart from the general recommendations intended to limit community spread, no additional PPE is required in the hematology laboratory. The OSHA regulations additional PPE for individuals working in high exposure risk and very high exposure risk categories, but not for individuals in the lower risk category.(42)

The virus causing COVID-19 pandemic is known to spread easily and sustainably from person-to person. Although regulations will vary by country, proper social distancing (about 6 feet), restriction of group gatherings, and non-essential international and/or domestic travel were recommended to prevent community spread. The CDC updates the guidelines as additional information becomes available.

Implications for education:

Many community events, including national and international conferences that involve group gatherings and travel, have been cancelled or postponed during the outbreak, consequently interrupting continuing education. Organizations and faculty members of the planned events are suddenly thrust into virtual meetings, remotely accessible livestreaming or pre-recorded online meetings to maintain continuing education. Transitioning to virtual learning requires time and effort to re-plan, prepare and proceed with virtual events to minimize the potential for stigma associated with the lack of continuing education. The goal of the virtual meeting is to maintain the learning objectives and the quality of the original event, while preserving the health and wellbeing of the organizers, speakers and participants. If the virtual meetings are well structured and have high quality audio and video recording, interpersonal interactions may be the next consideration for a successful meeting. Interaction between speakers and participants, such as questions or comments by online chatting or emails, bulletin boards or discussion groups, is very important and will be the hallmark of an effective meeting

The International Society for Laboratory Hematology (ISLH), an international group of laboratory professionals, originally planned the annual ISLH 2020 meeting and educational workshop in Melbourne, Australia for May, 2020. However, due to the COVID-19 pandemic, ISLH 2020 was postponed and will proceed in a virtual meeting format between June 22 and September 25, 2020. This virtual meeting, including prerecorded online lectures and interaction among speakers and participants, will adapt the original speakers

and schedules to provide the same quality of the continuing education to participants. Also recorded educational workshop will be presented as a monthly webinar series to support continuing education of hematology laboratory professionals.

Concluding remarks:

In summary, the COVID-19 pandemic has significantly challenged the international laboratory hematology community. More than ever, the professionalism and collegiality that characterizes hematology laboratorians is critical to the success of the mission to effectively combat this risk. This review has emphasized the importance of laboratory information in the management of COVID-19, the importance of safe laboratory practices to minimize risk to laboratory personnel, and the efforts by professional societies to continue their vital educational mission in this challenging environment.

Figure legend:

Figure 1: Morphologic features of circulating cells from peripheral blood films of patients with COVID-19 infection. Neutrophils show hyposegmented nuclei (A-C), sometimes with pre-apoptotic chromatin (B), and hypergranular cytoplasm, sometimes with hypogranular basophilic areas (C). Such dysmorphism appears related to the accelerated and disorderly granulopoiesis associated with hyperinflammation. Reactive lymphocytes with large amounts of pale blue cytoplasm (D), lymphoplasmocytoid cells and large granular lymphocytes predominate in treated and recovering patients (May-Grünwald-Giemsa, original magnification x1000).

Table 1: Hematologic biomarkers of importance in COVID-19 infection [adapted by the authors from Reference (6)]. For details, see text.

Parameter	**Clinical significance**	**References**
Lymphopenia	Defective host response	(6,12,13)
Leukocytosis	Bacteria superinfection	(6)
Neutrophilia	Bacterial superinfection, cytokine storm	(6,12,14,18-20)
Thrombocytopenia	Consumptive coagulopathy	(6,22,25)

Abbreviation: MDW – monocyte volume distribution width

Table 2: Other laboratory biomarkers of importance in COVID-19 infection [adapted by the authors from (6)]. For details, see text.

Parameter	Clinical significance	References
Increased CRP	Severe viral infection, including viremia	(6,13,17)
Increased procalcitonin	Bacterial superinfection	(6,12,13,17)
Increased LDH	Pulmonary injury/ multiorgan damage	(6,13,14)
Increased aminotransferases	Liver injury/ multiorgan damage	(6,13,14)
Increased bilirubin	Liver injury	(6,13)
Increased creatinine	Renal injury	(6,13)
Increased cardiac troponins	Cardiac injury	(6,33)
Decreased albumin	Impaired liver function	(6,13)
Prolonged prothrombin time	Consumptive coagulopathy	(6), (24)
Prolonged APTT	Consumptive coagulopathy	(6), (24)
Increased D-dimer and/or FDP	Consumptive coagulopathy	(6), (24)

Abbreviations: CRP- C reactive protein; LDH – lactate dehydrogenase; APTT-activated partial thromboplastin time; FDP- fibrin degradation product.

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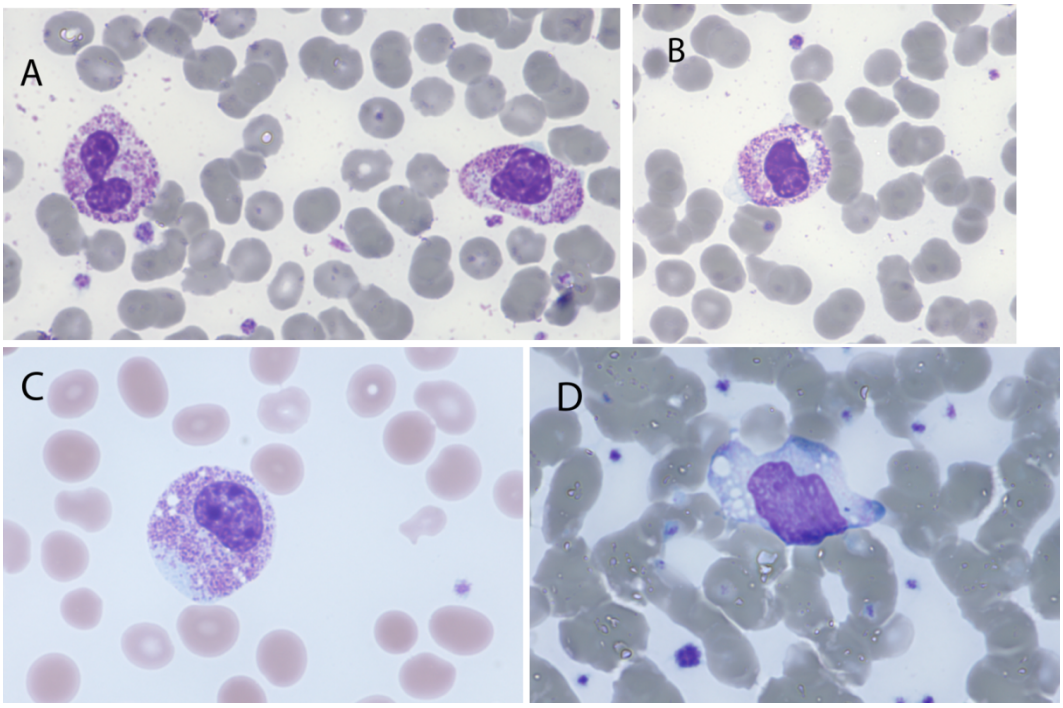

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