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, Hubei Province, 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. 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 4291 reported deaths. According to 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).

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. Sequence analysis of the genome of COVID-19 revealed 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.

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-week 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. 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 (a) provide background context about the origins and course of the pandemic, (b) discuss the laboratory’s role in the diagnosis of COVID-19 infection, (c) summarize the current state of biomarker analysis in COVID-19 infection, with an emphasis on markers derived from the hematology laboratory, (d) comment on the impact of COVID-19 on hematology laboratory safety, and (e) describe the impact the pandemic has had on organized national and international educational activities worldwide.

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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-week 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 comorbidities have been proposed which predispose patients to severe disease. Zhou et al addressed a wide range of comorbidities 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 PaO₂/FIO₂, 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 al8 identified reactivation in five patients from a cohort of 55 patients from China. 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.

2 | 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, two 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 three 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 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 two 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

3 | HEMATOLOGIC PARAMETERS OF PATIENTS WITH COVID-19 INFECTION

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 (Table 1). 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 has been established. A summary of the major hematologic features of importance in COVID-19-infected patients follows.
which is located ~450 miles from Wuhan. Conversely, in a series of COVID-19 patients from Singapore identified a much lower percentage of patients with lymphopenia, as did a paper reporting a series of COVID-19 patients who present with lymphopenia. For example, a recent meta-analysis noted that leukocytosis was a more common finding in children.

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. 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).

### 3.3 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. 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. Neutrophilia may also indicate superimposed bacterial infection. For example, Fan et al noted that neutrophilia is common in patients treated in the ICU during hospitalization (11.6 vs 3.5 × 10⁹/L).

### 3.4 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 are lacking. An exception is MDW (Beckman Coulter), 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. 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.

### 3.5 Thrombocytopenia

Thrombocytopenia is an important indicator of severe disease in COVID-19 patients, as highlighted by a recent review of the available evidence.
Increased arterial and venous thrombotic events such as cerebral infarction. 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.

### 4 | OTHER BIOMARKERS OF IMPORTANCE IN COVID-19 INFECTION

Several biochemical markers have been identified as being useful in identifying patients with severe COVID-19 disease (Table 2). 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, 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. It can be monitored with other biomarkers such as absolute lymphocyte count to assess whether patients are developing worsening infection.

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. On initial presentation, a majority of COVID-19 patients have procalcitonin levels in the normal range. As would be expected, patients with severe COVID-19 infection necessitating treatment in
an ICU frequently have marked elevation of calcitonin. Because of its association with bacterial co-infection and severe disease, it has been recommended to serially test calcitonin levels, particularly in ICU patients.\(^1\)\(^2\)\(^3\)

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.\(^4\) 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, 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 vs 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 excreted 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 comorbidities should have cardiac troponin level testing performed in a longitudinal fashion throughout hospitalization to assess for emerging myocardial damage.\(^3\)

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.\(^13\)

5  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.\(^3\)

### 6  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, USA) 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 (eg, proper risk assessment and training), rather than engineering, are 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. 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 the following:

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.

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.

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 (eg, 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.

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 regulates additional PPE for individuals working in high exposure risk and very high exposure risk categories, but not for individuals in the lower risk category.

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 nonessential international and/or domestic travel were recommended to prevent community spread. The CDC updates the guidelines as additional information becomes available.

7 | 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 prerecorded 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 22 June 2020 and 25 September 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.

8 | 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 laboratory 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.

CONFLICT OF INTEREST

The authors have no competing interest.

ORCID

John L. Frater https://orcid.org/0000-0002-4614-681X
Gina Zini https://orcid.org/0000-0003-0782-294X
Giuseppe d’Onofrio https://orcid.org/0000-0003-1948-3092
Heesun J. Rogers https://orcid.org/0000-0001-8491-224X

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