Guidelines and Recommendations

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IFCC Interim Guidelines on Biochemical/ Hematological Monitoring of COVID-19 Patients

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Abstract: Routine biochemical and hematological tests have been reported to be useful in the stratification and prognostication of pediatric and adult patients with diagnosed coronavirus disease (COVID-19), correlating with poor outcomes such as the need for mechanical ventilation or intensive care, progression to multisystem organ failure, and/or death. While these tests are already well established in most clinical laboratories, there is still debate regarding their clinical value in the management of COVID-19, particularly in pediatrics, as well as the value of composite clinical risk scores in COVID-19 prognostication. This document by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Task Force on COVID-19 provides interim guidance on: (A) clinical indications for testing, (B) recommendations for test selection and interpretation, (C) considerations in test interpretation, and (D) current limitations of biochemical/ hematological monitoring of COVID-19 patients. These evidence-based recommendations will provide practical guidance to clinical laboratories worldwide, underscoring the contribution of biochemical and hematological testing to our collective pandemic response.

Keywords: biochemistry; COVID-19; hematology; SARS-CoV-2.

Along with the essential role for diagnosing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and for assessing the presence and extent of an immune response against the virus, laboratory medicine makes an important contribution towards risk stratification and monitoring of infected patients. Whilst “routine” hematology and biochemistry tests are not specific enough to diagnose SARS-CoV-2 infection, they play a role in several aspects of the coronavirus disease 2019 (COVID-19) care pathway, including patient management and prognosis.

This document by the IFCC Task Force on COVID-19 provides interim guidance on: (A) clinical indications for testing, (B) recommendations for test selection and interpretation, (C) considerations in test interpretation, and (D) current limitations of biochemical/hematological monitoring of COVID-19 patients.

A. Clinical indications for testing

Abnormal hematology and biochemistry test results in infected patients may help in:

- Diagnosing infection-related tissue and organ injury;
- Identifying infected patients at lower risk of severe disease;
- Recognizing patients who are likely to have poor prognosis (e.g., need for mechanical ventilation or intensive care, progression to multisystem organ failure, death);
- Monitoring disease course.

B. Recommendations for test selection and interpretation

Many review articles and meta-analyses have been published on the clinical utility of some conventional laboratory tests in SARS-CoV-2 infection. These are summarized and discussed below.

[B1] Key hematology tests to monitor COVID-19 patients

Leukocyte parameters

SARS-CoV-2 has been shown to have a direct cytopathic injury on lymphocytes, with a number of morphological changes seen on the peripheral blood smear of infected patients [1]. Lymphopenia has become a hallmark of SARS-CoV-2 infection and is present to a variable extent in almost all symptomatic patients. There is also evidence that the magnitude of lymphocyte count reduction associates with disease severity [2].

A low eosinophil count is another typical marker of COVID-19 infection [3]. The combination of lymphopenia and low eosinophil count in a symptomatic patient is a strong indicator of infection [4].

An elevated neutrophil count has been found to herald poor prognosis in COVID-19 infection [3, 5]. Taken in combination with low lymphocyte count, an elevated neutrophil-to-lymphocyte ratio (NLR) can be used as a marker of adverse outcomes [6].

Markers of coagulopathy

A marked coagulopathy is a key feature of SARS-CoV-2 infection. Coagulopathy most commonly manifests as a pro-thrombotic state with increased incidence of both venous and arterial thrombosis [7, 8]. The mechanisms underlying this complication are not fully understood, but are likely to involve a complex interplay between inflammatory and pro-thrombotic factors, with endotheliitis and the formation of intravascular neutrophil extracellular traps playing an important role [9–11]. In addition, a subset of patients with severe disease develop disseminated intravascular coagulation (DIC), with activation of the fibrinolytic pathway and consumption of platelets and clotting factors [12, 13].

An elevated D-dimer in infected patients has consistently been associated with unfavourable disease progression [3, 5, 14]. In addition, COVID-19-associated coagulopathy may present with prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT) [12], and with an increased fibrinogen concentration, as a result of the strong pro-inflammatory state [15]. Conversely, patients who develop DIC may have a low fibrinogen concentration and thrombocytopenia [7].

Thrombocytopenia is another aspect that characterizes unfavourable disease progression [16]. The low platelet count is attributable to many convergent mechanisms, encompassing enhanced platelet consumption, lung injury with associated megakaryocyte damage, drug-induced and immune thrombocytopenia, enhanced platelet clearance, and reduced thrombopoietin production and bone marrow depression [17].

Recommendation [B1]: key hematology tests to monitor COVID-19 patients.

- Key hematology tests recommended to monitor COVID-19 patients are presented in Table 1.

[B2] Key biochemical markers to monitor COVID-19 patients

Inflammatory markers

The development of a sustained and progressively systemic pro-inflammatory condition (the so-called “cytokine

Table 1: Recommended hematological tests in patients with COVID-19 infection.

Test	Findings	Clinical utility
Complete blood count	↓Lymphocytes ↓Eosinophils ↑Neutrophils	–Lymphopenia is a hallmark finding in symptomatic infection. –Elevated neutrophil-to-lymphocyte ratio is associated with poor clinical outcomes.
D-dimer	Increased	To identify those at risk of adverse outcome.
Platelets	Decreased	Associated with poor clinical outcomes.
PT/APTT	Increased	To identify and monitor coagulopathy
Fibrinogen	Increased/decreased	–Increased in COVID-associated coagulopathy. –Decreased in DIC.

PT, prothrombin time; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation.

storm") has been demonstrated in patients with adverse progression of COVID-19, at higher risk of requiring intensive care and suffering fatal outcomes [18, 19]. Therefore, the measurement of some inflammatory biomarkers is very important for early and accurate identification of COVID-19 patients at higher risk of unfavourable progression.

C-reactive protein (CRP) is a commonly measured non-specific biomarker of inflammation. Increased CRP concentration has consistently been shown to be associated with poor outcome in SARS-CoV-2 infection [3, 20, 21].

Erythrocyte sedimentation rate (ESR) is an inflammatory marker which may be considered as an alternative to CRP in resource-limited environments, with a similar relationship seen between adverse outcomes in SARS-CoV-2 infection and high biomarker values [22].

Ferritin is a positive acute phase protein, which is easily measured and may be a marker of adverse outcomes in individuals infected with SARS-CoV-2 [23].

Procalcitonin may be beneficial in identifying individuals with bacterial co-infections, who may require specific antibiotic therapy and who have a worse prognosis [24].

Many additional inflammatory biomarkers have been studied and associated with poor outcome in SARS-CoV-2 infection. Examples include interleukin-6 (IL-6), interferon gamma-induced protein 10, monocyte chemotactic protein-3 and presepsin [25–27]. However, given that such biomarkers cannot be easily assayed in all laboratories and that evidence is unclear as to whether they add any clinical value beyond that already obtained through measurement of more standard inflammatory markers, we would not currently recommend their routine measurement in the absence of further research on clinical utility.

Cardiovascular biomarkers

In line with the evidence that COVID-19 may progress to a systemic disease, cardiac involvement may frequently develop in patients with SARS-CoV-2 infection as a result of direct cytopathic injury, cytokine-mediated damage, ischemia or even exacerbation of preexisting cardiac diseases [28, 29]. Several studies have shown that cardiac troponins are higher in patients with more severe illness, compared to those with milder disease [30–32]. The American College of Cardiology (ACC) points out that increased cardiac troponins and NT-proBNP do not necessarily suggest acute coronary syndrome or heart failure and need to be interpreted in the right clinical context and with the key presenting features of the patient in mind [33]. An elevated cardiac troponin in COVID-19 is likely to reflect an acute myocardial injury induced by either the virus or host immune response, rather than myocardial infarction due to rupture of an atherosclerotic plaque [28]. It is now commonly acknowledged that there is strong association between elevated troponin and adverse outcomes in COVID-19 patients [34]. Similar relationships have been seen for other cardiac biomarkers, including creatine kinase-MB, myoglobin and natriuretic peptides [35], although these analytes do not necessarily add further clinical value to that already provided by cardiac troponins.

Biomarkers of multisystem organ failure/damage

COVID-19 can be associated with liver injury during disease progression and treatment, in patients with or without pre-existing liver disease. Elevated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin, and low albumin and prealbumin concentrations have all been associated with poor outcome [36–38] In addition, some drugs used in the treatment of COVID-19 are associated with the development of elevated liver biomarkers [39–41]. For this reason, at a minimum, it is recommended to monitor ALT, bilirubin and albumin during treatment of patients with hepatotoxic medications, and in those with pre-existing liver disease.

Kidney injury is a relatively frequent complication in patients with COVID-19, especially in those with severe illness. Elevations of both serum creatinine and urea (blood urea nitrogen, BUN) have been associated with unfavorable clinical outcome [3, 5].

Lactate dehydrogenase (LDH) is a non-specific marker of tissue damage. Probably because it is found in many different tissues, LDH emerges as one of the most consistently elevated markers in patients infected with COVID-19 at higher risk of developing adverse outcome [3, 5, 21].

Arterial blood gas parameters of respiratory function

Worsening SARS-CoV-2 infection is associated with hypoxemia and metabolic acidosis [42], which may progress to acute respiratory distress syndrome (ARDS). As such, there is a role for the measurement of **arterial blood gas** parameters especially **pH, pO_2, pCO_2, HCO_3^-** and **lactate** [43], in patients with progressive disease. Monitoring of arterial blood gases is considered routine for the management of any critically unwell patient, regardless of the underlying condition. Results from a blood gas analyzer may also have the benefit of providing a rapid assessment of electrolyte status, which is often abnormal in patients with severe disease [44].

Recommendation [B2]: key biochemical tests to monitor COVID-19 patients.

– Key biochemical tests recommended to monitor COVID-19 patients are presented in Table 2.

Table 2: Recommended biochemical tests in patients with COVID-19 infection.

Test	Findings	Clinical utility
Arterial blood gas	Variable	To identify and monitor hypoxemia and metabolic acidosis associated with severe infection.
CRP	Increased	Associated with worse clinical outcome.
Ferritin	Increased	Associated with worse clinical outcome.
ESR	Increased	Alternative to CRP/ferritin in resource-limited settings.
Procalcitonin	Increased	Associated with secondary bacterial infection.
Cardiac troponins	Increased	Associated with COVID-19- induced cardiac disease and poor prognosis.
ALT, bilirubin	Increased	To be monitored in patients treated with drugs known to affect liver function (e.g., lopinavir/ritonavir).
Albumin	Decreased	Reflects an acute inflammatory state and/or synthetic liver dysfunction.
Creatinine, urea (BUN)	Increased	Associated with poor prognosis.
LDH	Increased	Associated with worse clinical outcomes.
Interleukin-6, interferon gamma-induced protein 10, monocyte chemotactic protein-3, presepsin	Increased	*For research use only.* Associated with poor clinical outcomes (if validated assay clinically available).

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase.

[B3] Laboratory tests required in pediatric SARS-CoV-2 infection

In contrast to adults, SARS-CoV-2 infection in children tends to be comparatively mild. This observation is reflected by the fact that, when present, laboratory abnormalities in infected children are likely to be relatively less severe. Specifically, children are less likely to have abnormal white blood cell parameters, but mild elevations of inflammatory biomarkers (CRP, procalcitonin, IL-6) and D-dimer have been identified in some cases [45, 46]. There is a paucity of data regarding the correlation between biomarker concentration and disease severity in children, although it has been suggested that a CRP test result above the cut-off may be associated with radiological evidence of pneumonia [46].

A small proportion of pediatric cases develop a separate entity termed Multisystem Inflammatory Syndrome in Children (MIS-C). MIS-C is characterized by a hyper-inflammatory state progressing to severe end organ damage and multiple organ failure, which is hence not so different from the same detrimental inflammatory reaction observed in some adults. Elevated inflammatory biomarkers are considered to be part of the diagnostic criteria for MIS-C [47]. Laboratory abnormalities in children with MIS-C more closely represent those seen in adults, with lymphopenia, and elevations of inflammatory biomarkers, D-dimer, cardiac troponin and natriuretic peptides being commonly reported findings [45, 48, 49].

Recommendation [B3]: Laboratory tests required in pediatric SARS-CoV-2 infection.

- Measurement of hematological and biochemical markers is unlikely to be indicated in asymptomatic children.
- For those with clinical features of infection, measurement of a complete blood count and inflammatory markers (e.g. CRP and/or ferritin) and D-dimer may be indicated.
- Given the common occurrence of co-infection with other bacterial pathogens in children [56], procalcitonin measurement may also be warranted.

[B4] Role for clinical risk scores in the diagnosis or prognosis of COVID-19

Given the association between elevations in certain biomarkers and disease severity, laboratory results have been included in a number of clinical risk algorithms, developed for either diagnosing SARS-CoV-2 infection or identifying patients at higher risk of unfavourable disease progression [50–52]

The Corona-Score is a clinical risk score intended to predict the probability of SARS-CoV-2 infection in symptomatic patients presenting to emergency departments [52]. The score encompasses eight parameters, five of which are laboratory test results (absolute neutrophil count, absolute lymphocyte count, CRP, ferritin, LDH). A Corona-score <4 had 96% sensitivity for excluding SARS-CoV-2 infection using RT-PCR as a reference standard for diagnosis. This model was derived using laboratory data from 375 patients across three hospitals presenting to emergency departments with respiratory symptoms, or suspected COVID-19 infection, and was validated in an independent multi-centre cohort of 592 Dutch patients [52]. A separate study of the Corona-Score in the USA yielded a lower sensitivity (82 vs. 96%) and area under the receiver operating characteristic curve (AUC) (0.74 vs. 0.91) than in the original Dutch cohort [50]. Another study carried out in a metropolitan hospital in New York City at the peak of the SARS-CoV-2 outbreak used a machine learning model based on patient demographics combined with 27 routine laboratory tests to predict SARS-CoV-2 infection status. Diagnostic accuracy of the model was compared to viral RNA testing by RT-PCR as a reference test and the AUC was 0.854 (95% CI: 0.829–0.878) in the training set and 0.838 in an independent validation set [51].

Clinical risk scores have also been developed for identifying patients more likely to develop severe disease. One such example (COVID-GRAM) utilises three laboratory parameters (NLR, LDH, direct bilirubin) and seven clinical or radiological parameters to calculate a probability of developing severe disease [53].

The main limitation of these clinical risk scores (and in fact most tests for detecting SARS-CoV-2 infection) is that they perform differently depending upon the geographical location and local disease prevalence, or other differences in the selection of cases and reference standards used in test evaluations. A systematic review of clinical scores for SARS-CoV-2 infection reported a high risk of bias in the methodology used in such studies [54]. In addition, some of the assays used in clinical risk scores are not well-standardised across manufacturers. Therefore we recommend caution when applying a cut-off developed in one particular setting on one analyzer platform to that from a different setting and from a different manufacturer. Laboratories should carefully design their local verification of tests or testing algorithms, including diagnostic or clinical risk scores used in managing this pandemic.

Recommendation [B4]: role for clinical risk scores in the diagnosis or prognosis of COVID-19.

- Until clinical risk scores are validated in large, independent populations in whom these tests are to be used, we would advise against the use of clinical risk algorithms to diagnose or risk-stratify patients with COVID-19.

C. Test interpretation and limitations

[C1] Considerations for test interpretation

No single biochemical or hematological test can confer adequate information regarding the likely diagnosis or outcome of SARS-CoV-2 infection. None of the tests described in this section are specific for SARS-CoV-2 infection or its disease progression. Rather, the results of a group of relevant tests should be reviewed in the context of the patient's clinical presentation. Only in this way can these biomarkers provide useful information in the clinical management of COVID-19.

It is important to emphasize that some differences between laboratory results in patients with severe and non-severe disease can be modest. For example, in one meta-analysis, the weighted mean difference in ALT results between non-severe and severe patients was only 8 U/L [3]. This finding was nonetheless statistically significant and has been replicated in other studies. Based on these observations we recommend that test results are closely scrutinised in view of the overall clinical presentation, so that the significance of small deviations from the reference

interval or patient's baseline are not misinterpreted. Nevertheless, whilst most changes could be modest in absolute terms, they could become more meaningful during longitudinal monitoring, given that the intra-individual variability of clinical laboratory parameters is lower than the inter-individual variation.

Recommendation [C1]: considerations for test interpretation.

- No one test should be considered in isolation. Groups of relevant tests should be reviewed in the context of the patient's clinical presentation.
- Biological variation of the analyte, and analytical variation affecting test performance should be considered when interpreting intra-individual changes in results.

[C2] Current limitations of biochemical/ hematological monitoring in COVID-19 patients

As COVID-19 is a new condition, there are ongoing challenges regarding the translation of literature findings to current clinical practice. When writing these interim guidelines, we have attempted to include information replicated in multiple studies to add to the veracity of our recommendations. Nonetheless, most studies referenced suffer from limitations, including small sample sizes, restriction to a single site (or country), study population selection bias, considerable heterogeneity across the studies included in published meta-analyses and use of different endpoints of disease severity.

In addition, much of the published research does not include information on the analytical methods used for testing. For example, the wide variety of approaches used to measure and report D-dimer presents challenges when considering the expected changes in D-dimer concentration in COVID-19 patients [55].

Recommendation [C2]: Current limitations of biochemical/hematological monitoring in COVID-19 patients.

- We would urge caution when translating study findings to local laboratory practice, especially when diagnostic cut-offs are recommended.

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