**DIAGNOSTICS**

# The COVID-19 Pandemic: Global Healthcare Agency and Society Observations of Supportive Laboratory Diagnostic Testing Values with Clinical Status

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## INTRODUCTION

Much has been learned by physicians and other clinicians since the World Health Organization declared the COVID-19 Pandemic on March 11, 2020. COVID-19 is the disease state caused by the SARS-COV-2 virus. RNA tests have been developed to detect the virus in individuals with early active infections as have antigen and antibody tests, which aid in diagnosis, determining community prevalence and surveillance. Managing patients diagnosed with COVID-19, has led to increased understanding of additional diagnostic tests that appear to be valuable in determining patient status and prognosis while helping to guide treatment and supportive care.

Given the rapidity with which this pandemic has progressed many papers have been published discussing diagnostic test results and their interpretation. Importantly, many governmental health sites such as the Centers for Disease Control (CDC) in the United States, the Robert Koch Institute (RKI) in Germany, Various National Health Service Trusts in the United Kingdom as well as several professional societies such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Society of Cardiology (ESC), have summarized statements regarding laboratory tests and associated results, publishing these to provide information to the medical community at large. The purpose of this paper is to present a broad overview of the statements of these organizations and provide references to these sites.

## THE CDC

For clinicians in the United States, the CDC website makes a clear statement of the laboratory findings that the CDC has found to be relevant. Further, the CDC provides analysis as to which variables may be associated with greater disease severity and critical illness. The statement from the United States CDC reads:

Lymphopenia is the most common lab finding in COVID-19 and is found in as many as 83% of hospitalized patients[1]. Lymphopenia, neutrophilia, elevated serum alanine, aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenase, high CRP and high ferritin levels may be associated with greater illness severity.[1]

Elevated D-dimer and lymphopenia have been associated with mortality[1]. Procalcitonin is typically normal on admission but may increase among those admitted to the ICU.[1] Patients with critical illness had high plasma levels of inflammatory makers, suggesting potential immune dysregulation.[1]

The CDC makes additional recommendations regarding non-laboratory radiographic studies, currently stating that 'given the variability in chest imaging findings, chest radiograph or CT alone is not recommended for the diagnosis of COVID-19'.[1]

Finally, the CDC notes that some patients with COVID-19 may develop signs of a hypercoagulable state and be at increased risk for venous and arterial thrombosis of large and small vessels.[1] Laboratory abnormalities commonly observed among hospitalized patients with COVID-19-associated coagulopathy include: mild thrombocytopenia, increased D-dimer levels, increased fibrin degradation products, and prolonged prothrombin time.[1] Elevated D-dimer levels have been strongly associated with greater risk of death.[1]

## THE RKI

The German Governmental authority, the RKI, has made a similar statement regarding laboratory diagnostic tests. Although published in German, the English translation reads: Further Diagnostics: regular blood sampling with differential blood count, clinical chemistry depending on the course of the disease with control of CRP, LDH, renal and liver function parameters, electrolytes, and, depending on the course of the disease, procalcitonin, troponin, D-dimer, IL-6. (German: Weitere Diagnostik: - Regelmäßige Blutabnahme mit Differential-Blutbild, klinischer Chemie je nach Verlaufsform der Erkrankung mit Kontrolle von CRP, LDH, Nieren- und Leberfunktionsparametern, Elektrolyten, und, je nach Verlaufsform der Erkrankung, Procalcitonin, Troponin, D-Dimer, IL-60[2]).

## UNITED KINGDOM

Two National Health Trusts in the UK joined with two medical schools to publish statements regarding additional laboratory testing during the pandemic. The Imperial College Healthcare NHS Trust and the Barts Health NHS Trust joined together with the Barts and London School of Medicine and Dentistry and the UCL Medical School, University College London to publish 'Evidence Based Management Guideline for the COVID-19 Pandemic-Review Article.' These organizations make similar statements as noted below.

Key laboratory results on admission include leucocytes below or above the normal range; neutrophils above the normal range; lymphocytes, hemoglobin and platelets below the normal range.[3] Key liver findings may include elevated alanine aminotransferase, aspartate aminotransferase, C-reactive protein, creatine kinase, lactate dehydrogenase, blood urea nitrogen, and serum creatinine levels.[3] Regarding the infection index, procalcitonin levels may be above the normal range.[3]

## IFCC

Medical professional societies have also published on the topic of laboratory test results and provided analysis regarding association of test results associated with disease state or severity. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), presented an initial statement which was then updated to include both blood gas panels and also urea. IFCC notes that urea is necessary for the CURB-65 community acquired pneumonia severity score used in the emergency situation[4].

The IFCC statement with their interpretation for prognosis associated with COVID-19 and caveats for interpretation is presented below:

| Clinical Chemistry Tests | Lab Value direction for unfavorable prognosis in patients with COVID-19 | Preanalytical, analytical and postanalytical caveats for Interpretation |
|---|---|---|
| **Tests widely available as Stat at hospital laboratories** | | |
| Albumin | Decreased | There are two main types of albumin assays: Bromocresol green reports higher concentrations than bromocresol purple |
| Lactate dehydrogenase (LD) | Increased | Preanalytical factors such as handling via pneumatic tube |

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|---|---|---|
| | | systems and *in vitro* hemolysis may cause elevations |
| Alanine aminotransferase (ALT) | Increased | Sex-specific reference intervals should be used |
| Aspartate aminotransferase (AST) | Increased | Can be elevated from many different tissues and factors, such as *in vitro* hemolysis, may cause elevations |
| Total bilirubin | Increased | Photosensitive, so testing should not be delayed, used in SOFA score |
| Creatinine | Increased | eGFR by CKD-EPI equation would be a useful adjunct, used in SOFA score |
| C-reactive protein (CRP) | Increased | There are two main types of assays, hs-CRP and CRP; both assays are appropriate for acute phase response |
| Cardiac troponin | Increased | There are two main types of assays, hs-cTn and cTn; both assays are appropriate for detecting myocardial injury, with hs-cTn testing preferred for risk stratification |
| Urea | Predicted to be increased | Used for CURB-65 score |
| Blood gas panel | Predicated to have increased and decreased levels for many different tests | Many blood gas analyzers provide pH, $pO_2$, $pCO_2$, bicarbonate, glucose, lactate, free calcium, Na, K, Cl. Testing needs to be performed promptly |
| **Tests that may not be available at hospital laboratories** | | |
| Ferritin | Increased | May not be available for STAT testing |
| Procalcitonin | Increased | Is not available in all hospitals |
| Cytokines (Il-6) | Increased | Is not available in all hospitals and many tests are for research use |

**Table 1**: Clinical chemistry tests for patients with COVID-19 in the emergency setting (modified from the IFCC list and ref.[2])[4]

## ESC

The European Society of Cardiology (ESC) supplied guidance for the diagnosis and management of cardiovascular (CV) disease during the COVID-19 Pandemic.[5] ESC assembled a group of experts and practitioners with experience in the care of COVID-19 patients to provide a guidance document relevant

for all aspects of CV care during the COVID-19 pandemic and included statements regarding cardiac biomarkers. The ESC noted that this is a guidance document not guidelines and that the guidance is only in effect as long as Pandemic status is maintained by the World Health Organization (WHO).[5]

There were several significant statements in the ESC guidance. Similar to the CDC, RKI and IFCC, it is stated that factors associated with ARDS in COVID-19 were neutrophilia, lymphocytopenia, elevated laboratory markers of organ dysfunction (e.g. lactate dehydrogenase [LDH]), inflammation (C reactive protein) and D-dimer.[5] The ESC also notes that high serum IL-6 levels are a common feature in CRS. IL-6 is a clinical predictor of mortality in COVID-19.[5]

In their guidance document, the ESC noted that the diagnostic work-up of critically ill patients with confirmed or suspected COVID-19 infection requires specific considerations. Specifically, cited were[5]:

- Key diagnostic testing in patients with suspected CS, including electrocardiogram (ECG) although no specific changes attributed to COVID-19 were identified, bedside echocardiography, and urgent/emergent coronary angiography, should be integrated into local diagnostic protocols.
- Cardiomyocyte injury, as quantified by cardiac troponin T/I concentrations, and haemodynamic stress, as quantified by B-type natriuretic peptide (BNP) and N-terminal B type natriuretic peptide (NT-proBNP) concentrations, may occur in COVID-19 infections as in other pneumonias. The level of those biomarkers correlates with disease severity and mortality;
- Cardiac troponin T/I and BNP/NT-proBNP concentrations should be interpreted as quantitative variables;
- In patients hospitalized with COVID-19, mild elevations in cardiac troponin T/I and/or BNP/NT-proBNP concentrations are in general the result of pre-existing cardiac disease and/or the acute injury/stress related to COVID-19;
- In the absence of typical angina chest pain and/or ischaemic ECG changes, patients with mild elevations (e.g. < 2–3 times the upper limit of normal [ULN] do NOT require work-up and/or treatment for Type 1 myocardial infarction [T1MI]);
- In patients with COVID-19, as in patients with other pneumonias, it is suggested to measure cardiac troponin T/I concentrations only if the diagnosis of T1MI is being considered on clinical grounds, or in new onset LV dysfunction. Independently from diagnosis, monitoring of cardiac troponin T/I may help for the purpose of prognostication;
  D-Dimers can be increased in a third of patients with COVID-19 for miscellaneous reasons. Monitoring of D-Dimer concentrations might help to anticipate deteriorating cases but could also cause confusion regarding the presence of acute PE. Therefore, D-dimer should only be determined in case of clinically suspected PE and in accordance with recommended diagnostic algorithms. Other markers of coagulation activation could be monitored for the purpose of prognostication.

The ESC states that as in patients without COVID-19, cardiac troponin T/I concentrations should be measured whenever on clinical grounds T1MI is suspected and that BNP/NT-proBNP should be measured whenever on clinical grounds HF is suspected[5]. ESC concludes, however, that at this point in time, no specific therapeutic intervention can be justified based on the use of cardiac troponin T/I as a prognostic marker for COVID-19 and that routine measurements of cardiac troponin T/I and/or BNP/NT-proBNP in patients with COVID-19 given the current very limited evidence for incremental value for clinical decision-making, is discouraged[5]. Markers of haemostasis including activated partial thromboplastin

time, prothrombin time, fibrin degradation products and D-Dimers should be monitored routinely according to the ESC.[5]

The ESC guidance states that patients with symptoms and ECG changes suggestive of T1MI should be treated according to ESC-guidelines irrespective of COVID-19 status.[5] Mild elevations in cardiac troponin T/I concentrations (e.g. < 2–3 times the ULN), particularly in an older patient with pre-existing cardiac disease, do NOT require work-up or treatment for T1MI, unless strongly suggested by angina chest pain and/or ECG changes.[5] The concentrations of cardiac troponin I/T in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease AND the acute injury related to COVID-19.[5] Concentrations remained in the normal range in the majority of survivors. In non-survivors, troponin levels progressively increased in parallel with the severity of COVID-19 and the development of ARDS.[5]

## CONCLUSION

During this COVID-19 Pandemic, clinical medical information is rapidly changing as medical professionals provide care to patients, ranging from those who are mildly symptomatic to those who are critically ill. Laboratory tests always play an important role in the clinical management of patients including during this time of pandemic. This has led several governmental organizations and medical or laboratory societies to provide information to help clinicians and laboratorians select laboratory tests that will best help guide patient care.

For additional questions please contact Abbott Core Diagnostics Medical or Scientific Affairs.

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