The role of laboratory testing in hospitalised and critically ill COVID-19-positive patients

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The COVID-19 pandemic has placed healthcare resources around the world under immense pressure. South Africa, given the condition of its healthcare system, is particularly vulnerable. There has been much discussion around rational healthcare utilisation, ranging from diagnostic testing and personal protective equipment to triage and appropriate use of ventilation strategies. There has, however, been little guidance around use of laboratory tests once COVID-19 positive patients have been admitted to hospital. We present a working guide to rational laboratory test use, specifically for COVID-19, among hospitalised patients, including the critically ill. The specific tests, the reasons for testing, their clinical usefulness, timing and frequency are addressed. We also provide a discussion around evidence for the use of these tests from a clinical perspective.
Keywords. COVID-19, coronavirus disease, SARS-CoV-2, laboratory tests, diagnostics.

Within a few months of the World Health Organization declaring a global pandemic, there have been several million recorded cases of coronavirus disease 2019 (COVID-19) worldwide.[1-3] The broad clinical spectrum – from mild to life-threatening disease – highlights the importance of determining which groups develop severe disease.[4,5] The use of SOFA (sequential organ failure assessment) scores and additional laboratory data appears to have value in the assessment, prognostication and management of COVID-19 patients.[4] Laboratory tests used for COVID-19-positive patients have been briefly addressed in the literature.[6] We aim to further describe the clinical utility of these tests which will assist the clinician in their effective use. The role of diagnostic tests for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is beyond the scope of this paper.

Clinical staging

A clinically useful staging system has been proposed, and is shown in Table 1.[7] The model proposes an initial clinical stage attributed to the virus itself, which is subsequently followed by characteristically different stages evolving in relation to the host response. Laboratory features play an important part of the entire clinical picture and help to identify the disease stage.[7] This staging creates the platform to adjudge severity, disease progression, the level of care required, and also provides insights regarding the timing of stage-specific unique therapies such as targeting the virus in the initial stages and focusing on the role of exaggerated host immune response in the latter stages.

Laboratory role

The role of the laboratory in COVID-19 extends from epidemiological surveillance to patient management (Fig. 1). We deal specifically with the role of laboratory tests during the assessment and management of
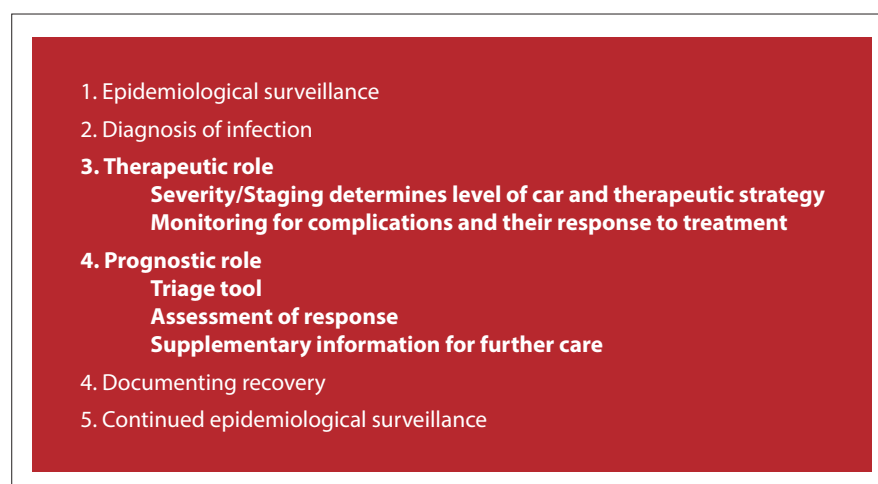

1. Epidemiological surveillance
2. Diagnosis of infection
3. **Therapeutic role**
   Severity/Staging determines level of car and therapeutic strategy
   Monitoring for complications and their response to treatment
4. **Prognostic role**
   Triage tool
   Assessment of response
   Supplementary information for further care
4. Documenting recovery
5. Continued epidemiological surveillance

Fig. 1. The multimodal role of the laboratory in COVID-19.[9]

Table 1. COVID-19 stage and clinical severity[7,8]

	Stage I	Stage IIa	Stage IIb	Stage III
Clinical	Mild	Moderate	Moderate	Severe
O_2 required	No	Yes	Yes	Yes
PaO_2/FiO_2 (P/F) ratio*	Normal	>300	<300	<300
Cytokine storm/MOD	None	None	Increasing cytokines	Present

PaO_2/FiO_2 = ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to the fraction of inspired oxygen (FiO_2); MOD = multiple organ dysfunction.
*PaO_2/FiO_2 (P/F) ratio is at sea level. Lower thresholds apply for locations above sea level e.g. in Johannesburg, the P/F threshold is ~250.

Table 2. Summary of laboratory tests and their utility

Test	Reason for testing	Clinical use	Timing and frequency*
FBC and differential white cell count	Assessment of lymphopenia, neutrophilia and thrombocytopenia	Severity, monitoring	On admission and at 24 - 72 hours
PT/INR, aPTT, fibrinogen D-dimer, TEG plasma anti-Xa levels	Identify presence of DIC Monitor anticoagulation	Severity, monitoring, prognostic and therapeutic	On admission: PT + D-dimer suggested as minimum. If SIC score ≥4 or D-dimer >1.5mg/L then DIC profile Monitoring: D-dimer 24 - 72 hours
Urine dipstick (chemistry)	Identify presence of protein and glucose in urine	Severity	On admission and thereafter as per standard unit protocols
Serum urea and creatinine	Identify presence AKI and SOFA calculation	Severity, triage and monitoring	On admission and at 24 - 72 hours
Serum electrolytes (K^+, Na^+, Cl^-, Ca^{2+}, Mg^{2+}, PO_4^{3-})	Detection of low K^+, Na^+ and Ca^{2+}	Monitoring and treatment of complications	On admission and at 24 - 72 hours
LFT and LDH	TB for SOFA score, AST and ALT to detect liver injury, Albumin	Severity, triage and monitoring	On admission: LFT and LDH Minimum suggested monitoring: TB, AST, ALT at 24 - 72 hours
CRP, ferritin, D-dimer, IL-6	Detect inflammation, cytokine storm and related DIC	Severity, monitoring, prognosis and timing of pharmacological interventions	On admission suggested minimum: CRP, ferritin with D-dimer. Minimum suggested monitoring: D-dimer and CRP or IL-6.
LDH	Detect lung-centric inflammatory process	Severity	See LFT above
Troponin	Identification of cardiac injury	Severity and guide treatment	Standard indications or haemodynamic compromise/tachycardia. Severity assessment where clinically relevant.
NT-pro-BNP , BNP	Identification of cardiac failure	Severity and guide treatment	As for troponin.
PCT	Possible identification/ exclusion of bacterial infection	Severity and guide treatment	On admission and at 24 - 72 hours.
Arterial blood gas analysis	Respiratory and metabolic assessment and SOFA calculation	Severity, monitoring and guide treatment, triage	On admission and apply standard unit protocols.
Blood glucose, muscle enzymes	Standard clinical indications	Monitoring	Apply standard protocols.

FBC = full blood count; PT = prothrombin time; INR = international normalised ratio; aPTT = activated partial thromboplastin time; TEG = thromboelastography; anti-Xa = anti-Factor Xa (active form of Factor X); DIC = disseminated intravascular coagulopathy; SIC = sepsis-induced coagulopathy; AKI = acute kidney injury; SOFA = sequential organ failure assessment; K^+ = potassium; = Na^+ = sodium; Cl^- = chloride; Ca^{2+} = calcium; Mg^{2+} = magnesium; PO_4^{3-} = phosphate; LFT = liver function test; LDH = lactate dehydrogenase; TB = total bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CRP = C-reactive protein; IL-6 = interleukin-6; pro-BNP (NT-proBNP) = B-type natriuretic peptide; PCT = procalcitonin.
*In general, we suggest that tests indicated for severity/staging, triage and prognostication be performed on admission. For monitoring: severe or progressive disease requires 24-hourly testing, while moderate disease or sustained improvement may require testing every 48 - 72 hours.

overt disease among COVID-19-positive patients who have disease severe enough to require hospitalisation, including critically ill patients.

The National Institute for Communicable Diseases guidelines suggest keeping broad local and clinically relevant differential diagnoses for patients presenting with severe illness (all hospitalised patients).[10] Blood cultures and assessment for other causes of community-acquired pneumonia, e.g. mycobacterial infection, *Pneumocystis jirovecii* pneumonia, influenza and other relevant atypical infections are suggested.

Discussion

Several laboratory tests may provide information for staging/severity and possible therapeutic interventions, prognostic information and monitoring. Timely identification of at-risk patients may enable prompt escalation of care. De-escalation may also enhance appropriate resource utilisation.

The white blood cell count, inclusive of neutrophil and lymphocyte counts, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, troponin, *D*-dimer and procalcitonin (PCT) levels are associated with increased odds of ICU admission.[11] In a separate study that included 140 COVID-19 patients, increased C-reactive protein (CRP), *D*-dimer and PCT levels were associated with greater severity of disease.[12] Other laboratory abnormalities demonstrated to be associated with poor outcomes include albumin, serum creatinine (sCr) and prothrombin time (PT/INR).[11]

Coagulation appears to have a role in COVID-19, with >70% of non-survivors shown to demonstrate overt disseminated intravascular coagulation (DIC).[13] These patients had significantly elevated *D*-dimers, PT and fibrin degradation products when compared with survivors. A *D*-dimer value above 1 mg/L at admission was associated with increased mortality.[4] Activated partial thromboplastin time, although higher, did not reach statistical significance. Elevated *D*-dimers may be used as an indication for admission, and monitored daily until improvement begins. The relevance of additional daily testing of PT, fibrinogen and platelet counts in the case of an elevated *D*-dimer value is to monitor for worsening of the coagulopathy.[14] In the analysis of 449 patients with severe COVID-19, those with a sepsis-induced coagulopathy score ≥4 and who were treated with heparin had a 24% lower mortality than those who were not treated.[15] The investigators also found a 20% reduction in mortality when heparin was used in patients with a *D*-dimer above 3 mg/L. Coagulation studies may therefore be useful for determining severity, progression (adaptive haemostasis to DIC and multiorgan failure), prognosis and guiding therapy.[16] Thromboelastography provides a point-of-care result, and this evaluation of coagulation factors, fibrinogen, platelet function and fibrinolysis has been recommended in some guidelines.[17]

Procalcitonin has not been found to be elevated initially among COVID-19 patients. An increase likely mirrors bacterial superinfection, and may be associated with a worse outcome.[11,18] A progressive increase may also occur with a dysregulated inflammatory response.[19]

Urine analysis performed on day 1 after admission also revealed a relationship between both urine protein and urine glucose and severity of disease. Patients with hypertension, diabetes and/or urinary tract infections were excluded from this study.[20]

Electrolyte abnormalities are significant among patients with severe COVID-19. Sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) were found to be low in these patients.[21] Hypokalaemia, reported to be low in as many as 60% of cases,[22] is likely the most relevant, as it has both clinical and pathophysiological significance. Clinically, hypokalaemia is associated with a worsening of cardiac complications and acute respiratory distress syndrome. The SARS-CoV-2 virus attaches to the angiotensin-converting enzyme receptor 2 (ACE-2). This enables viral entry into the alveolar cell, but also down-regulates the ACE-2 receptor, causing an increase in angiotensin II. This may explain K^+ loss and hypokalaemia at a renal level. Gastrointestinal symptoms, including diarrhoea, have been described in ~one-third of COVID-19 patients.[23] Monitoring will therefore enable appropriate fluid and electrolyte management. Monitoring of urea, creatinine and electrolytes is important for the assessment of severity/prognostication and therapeutic management.

Cardiac biomarkers including troponins and B-type natriuretic peptide (pro-BNP) may also be of value. Myocarditis with impaired systolic function has been reported in patients with COVID-19. Both troponins and pro-BNP values are elevated.[24] Abnormal troponin results were detected in 22.6% of 5 700 hospitalised patients.[25]

Identification of the cytokine storm, a clinical picture that has much in common with macrophage activation syndrome/haemophagocytic lymphohistiocytosis has been observed, but is largely lung-centric. Identification thereof may be key to timely therapeutic interventions.[26,27] This complication may be recognised by increases in CRP, ferritin, *D*-dimers and liver transaminases, as well as a shift from a predominant pulmonary disease state to one with multisystem complications/involvement. Interleukin-6 (IL-6) has been shown to correlate with qualitative serum viral loads (SARS-CoV-2 viraemia).[28] High CRP levels were significantly associated with the development of severe disease. The receiver operator curve reflected good accuracy for predicting severe disease (area under curve = 0.84).[29]

Arterial blood gas analysis is particularly useful for determination of the PaO_2/FiO_2 ratios, calculation of the alveolar arterial gradient (A-aDO$_2$) and the oxygenation index.[4,23] Blood gas information is valuable throughout hospitalisation, from the initial triage to the point of removal of supplementary oxygenation support.

The suggestions made above are time-limited. As our understanding of this disease rapidly unfolds, additional tests may be introduced or the use of currently recommended tests may be amended. Local experts should be consulted when available and modifications to these suggestions should be anticipated.

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