The Royal College of Pathologists
Pathology: the science behind the cure

Guidance on the use and interpretation of clinical biochemistry tests in patients with COVID-19 infection

17 April 2020

This document outlines the biochemical tests that have a role in the assessment and monitoring of patients with COVID-19 infection. It is intended to assist clinicians who are less familiar with these tests to understand the role and limitations of these markers in the management of patients with COVID-19.

In each hospital or unit, a panel of biochemistry tests and retest intervals should be agreed by clinicians leading the management of patients with COVID-19 infection.

Patients with mild symptoms who, based on clinical assessment, do not required hospital admission, also do not require additional laboratory tests. Analysis of inflammatory makers (along with haematology tests including white cell count and a coagulation panel) may assist in determining if a patient with moderate symptoms requires hospital admission.

It is likely that knowledge and understanding of the role of these biochemical tests in patients with COVID-19 infection will develop as the data are studied and analysed retrospectively.

C-reactive protein[1,2]

What is it? C-reactive protein (CRP) is a protein produced by the liver during inflammation, infection or tissue damage.

Why is it measured? CRP levels are elevated in up to 86% of patients admitted to hospital with COVID-19 infection and studies report significant differences in CRP level at baseline between those with mild and severe disease. It is therefore useful in assessing prognosis, and in monitoring for clinical improvement or deterioration.

When should it be measured? CRP should be measured at baseline in hospitalised patients and then at intervals determined by the clinical condition of the patient. A sudden increase will prompt surveillance for secondary bacterial infection or other causes of clinical deterioration, including cardiac injury.

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Unique document reference number: G217

Procalcitonin[2,3,4]

What is it? Procalcitonin is the peptide precursor of calcitonin. It is produced by the C cells of the thyroid, but during bacterial infection and severe inflammation it is also produced by most tissues.

Why is it measured? Procalcitonin is an acute-phase reactant that is released during inflammation and is particularly associated with bacterial infection. It is not usually elevated in viral infection, but levels can rise during severe systemic inflammation. Studies indicate that it is not increased in the majority of hospital inpatients with COVID-19 infection, but is more likely to be elevated in patients with severe disease.

When should it be measured? In contrast to CRP, assays for procalcitonin are not available in all laboratories. It may have a role in indicating secondary bacterial infection in patients with COVID-19 infection, but is not specific for this and elevated levels may occur in acute respiratory distress syndrome (ARDS) and cytokine storms.

Interleukin-6[1,2,5]

What is it? Interleukin-6 (IL-6) is a proinflammatory cytokine that stimulates the production of acute-phase proteins including CRP.

Why is it measured? IL-6 is measured to assess the inflammatory response in patients with COVID-19 infection. Studies indicate that IL-6 levels are significantly higher at admission in patients who develop more severe symptoms, and it may therefore have a role in identifying which patients are at higher risk of complications. It appears to track the progress of the condition, with levels increasing during clinical deterioration and reducing in association with clinical improvement.

When should it be measured? IL-6 has not been measured in routine clinical practice in the UK, however some laboratories have now implemented assays. If available, it should be measured on admission to stratify the severity of the disease (along with clinical findings) and then at intervals to monitor the condition.

Ferritin[1,6]

What is it? Ferritin is a protein that can store and release iron.

Why is it measured? Ferritin is typically measured to assess iron status, but it is used in patients with COVID-19 infection as it is also an acute-phase reactant that increases during inflammation. Studies indicate that ferritin levels are elevated in the majority of hospitalised patients with COVID-19 infection (approximately 60%). In patients who are severely ill with COVID-19, extremely high ferritin levels may indicate a cytokine storm and secondary haemophagocytic lymphohistiocytosis (sHLH) – a hyperinflammatory syndrome associated with multiorgan failure.

When should it be measured? Ferritin should be measured at baseline in hospitalised patients and then at intervals determined by the clinical condition of the patient. An increase indicates clinical deterioration.

Troponin[7,8]

What is it? Troponins are proteins that regulate muscle contraction. Highly sensitive (cardiac specific) troponin is measured, and the analytical platform in the laboratory will determine which component of the troponin complex is measured, either troponin I or troponin T.

Why is it measured? Of those patients admitted to hospital with COVID-19 infection, 7–23% have increased troponin levels. Higher troponin levels are associated with more severe infection and intensive care unit (ICU) admission. Mortality is higher in patients with elevated troponin levels. In some patients, troponin is low in the first phase of the illness and then increases around day 16. This is associated with clinical deterioration, signs of acute cardiac injury and a poor prognosis.

When should it be measured? Serial troponin levels may be measured in COVID-19 infection to track clinical progress in patients with severe disease. Troponin levels should be interpreted with caution in patients with COVID-19 infection who develop acute chest pain, and ischaemic heart disease will be difficult to rule in or out using troponin levels alone.

Brain natriuretic peptide[9]

What is it? Brain natriuretic peptide (BNP) is a natriuretic peptide synthesised and secreted by cardiac ventricles. NT-proBNP is the N-terminal fragment of the pre-hormone for BNP – proBNP. The exact analyte measured varies between analytical platforms, but they are used interchangeably in the clinical situation depending on the assay available in the laboratory.

Why is it measured? Both BNP and NT-proBNP are increased in heart failure and are primarily used as a ‘rule out’ test for this. Heart failure is very unlikely if BNP is within the reference range. Levels can increase in other cardiac disease including ischaemic and valvular heart disease. BNP has been found to be increased in patients with severe COVID-19 infection, and mortality is higher in patients with elevated BNP levels. This increase is associated with clinical deterioration and signs of cardiac injury.

When should it be measured? BNP measurement is not routinely indicated in patients with COVID-19 infection.

References

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

2. Yong G, Tuantuan L, Mingfeng H, et al. Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19. *J Med Virol*. 2020;1–6. https://doi.org/10.1002/jmv.25770

3. Cheng, Z., Chen, H. Higher incidence of acute respiratory distress syndrome in cardiac surgical patients with elevated serum procalcitonin concentration: a prospective cohort study. *Eur J Med Res* 2020; 25:11 https://doi.org/10.1186/s40001-020-00409-2

4. Meisner M. Update on procalcitonin measurements. *Ann Lab Med*. 2014;34(4):263–273. http://dx.doi.org/10.3343/alm.2014.34.4.263

5. Ruan, Q., Yang, K., Wang, W. et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020; https://doi.org/10.1007/s00134-020-05991-x

6. Mehta P, McAuley DF, Brown M, et al. UK COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 202:395:1022-1034. https://doi.org/10.1016/S0140-6736(20)30628-0

7. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;101623. https://doi.org/10.1016/j.tmaid.2020.101623

8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020; 395:1054–1062. https://doi.org/10.1016/ S0140-6736(20)30566-3

9. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020 epub. https://doi.org/10.1001/jamacardio.2020.0950