Letter to the Editor

Peter A. Kavsak*, Kerstin de Wit and Andrew Worster

Clinical chemistry tests for patients with COVID-19 – important caveats for interpretation

https://doi.org/10.1515/cclm-2020-0436
Received April 3, 2020; accepted April 5, 2020

Keywords: analytical; clinical chemistry; COVID-19; emergency setting; preanalytical; postanalytical.

To the Editor,

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has recently posted a list of laboratory tests for monitoring patients with COVID-19 (IFCC Information Guide on COVID-19; published Thursday, March 26: https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/). Besides hematology (i.e. complete blood count) and coagulation (i.e. d-dimer and prothrombin time), the list also includes specific clinical chemistry tests for the biochemical monitoring of patients with COVID-19, which are supported by the initial clinical course of patients from Wuhan, China [1]. These tests have also been recently highlighted in *Clinical Chemistry and Laboratory Medicine* [2] (Table 1). Importantly, the original list omits blood gas panels as well as urea, with the latter needed for the CURB-65 community-acquired pneumonia severity score used in the emergency setting [3]. We have added these tests to the list and have provided important caveats for the interpretation of these tests as preanalytical, analytical and postanalytical issues can affect interpretation.

Briefly, for clinical chemistry tests related to liver function, there are preanalytical, analytical and postanalytical variables that can influence test interpretation [4–9]. Both aspartate aminotransferase (AST) and

***Corresponding author: Dr. Peter A. Kavsak,** Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; and Juravinski Hospital and Cancer Centre, 711 Concession Street Hamilton, Hamilton, ON L8V 1C3, Canada, Phone: +905-521-2100, Fax: +905-575-2581, E-mail: kavaskp@mcmaster.ca
Kerstin de Wit and Andrew Worster: Division of Emergency Medicine, Department of Medicine, McMaster University, Hamilton, ON, Canada

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

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 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

Table 1 (continued)

Clinical chemistry tests	Lab value direction for unfavorable prognosis in patients with COVID-19	Preanalytical, analytical and postanalytical caveats for interpretation
Blood gas panel	Predicted 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

lactate dehydrogenase (LD) results can be affected by preanalytical factors such as pneumatic tube system transportation and *in vitro* hemolysis which will result in higher levels [4, 5]. For transportation via pneumatic tube systems, careful validation and monitoring of the system for force and acceleration may mitigate these effects, even when hemolysis is not present [4, 5]. Bilirubin is photosensitive and alanine aminotransferase (ALT) should be interpreted based on sex-specific reference intervals for both the pediatric and adult populations [6, 7]. Albumin levels are affected by the analytical method used to generate the results (e.g. bromocresol green versus bromocresol purple) [8, 9]. Here, the bromocresol green method for albumin measurement is less specific than the bromocresol purple method and binds other proteins. This effect is most noticeable at low concentrations; thus, physicians need to be mindful of this if comparing results from different laboratories, especially with low albumin levels [8, 9].

Of the inflammatory-related clinical chemistry tests listed, C-reactive protein (CRP) is more widely available at hospitals and in the emergency setting. Both high-sensitivity CRP (hs-CRP) and CRP can be used for the detection of an acute phase response. Finally, both cardiac troponin and high-sensitivity cardiac troponin (hs-cTn) can identify myocardial injury with hs-cTn superior for identifying low-risk individuals [10]. Importantly, survivors of COVID-19 at admission had a median hs-cTnI level of 3 ng/L [1]; as such low hs-cTn levels, in combination with other algorithms, may be helpful in this setting [1, 3, 10].

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: Dr. Kavsak has received grants/reagents/consultant/advisor/ honoraria from several diagnostic companies, including Abbott Laboratories, Abbott Point of Care, Beckman Coulter, Ortho Clinical Diagnostics, Randox Laboratories, Roche Diagnostics and Siemens Healthcare Diagnostics. McMaster University has filed patents with Dr. Kavsak listed as an inventor in the acute cardiovascular biomarker field. Dr. de Wit has received a research grant from Bayer.
Ethical approval: The local Institutional Review Board deemed the study exempt from review.

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
2. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med 2020. pii: /j/cclm.ahead-of-print/cclm-2020-0240/cclm-2020-0240.xml. doi: 10.1515/cclm-2020-0240.
3. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377–82.
4. Kavsak PA, Mansour M, Wang L, Campeau S, Clark L, Brooks D, et al. Assessing pneumatic tube systems with patient-specific populations and laboratory-derived criteria. Clin Chem 2012;58:792–5.
5. Nybo M, Lund ME, Titlestad K, Maegaard CU. Blood sample transportation by pneumatic transportation systems: a systematic literature review. Clin Chem 2018;64:782–90.
6. Pacifico L, Ferraro F, Bonci E, Anania C, Romaggioli S, Chiesa C. Upper limit of normal for alanine aminotransferase: quo vadis? Clin Chim Acta 2013;422:29–39.
7. Parker ML, Adeli K, Lévy É, Delvin E. Are universal upper reference limits for alanine aminotransferase (ALT) appropriate for assessing pediatric liver injury? Clin Biochem 2018;53:55–7.
8. Bachmann LM, Yu M, Boyd JC, Bruns DE, Miller WG. State of harmonization of 24 serum albumin measurement procedures and implications for medical decisions. Clin Chem 2017;63:770–9.
9. van de Logt AE, Rijpma SR, Vink CH, Prudon-Rosmulder E, Wetzels JF, van Berkel M. The bias between different albumin assays may affect clinical decision-making. Kidney Int 2019;95:1514–7.
10. Neumann JT, Twerenbold R, Ojeda F, Sörensen NA, Chapman AR, Shah AS, et al. Application of high-sensitivity troponin in suspected myocardial infarction. N Engl J Med 2019;380:2529–40.