Routine Laboratory Biomarkers Detecting COVID-19

Subjects: Medical Informatics
Contributor: Jana Suklan

No routine laboratory biomarkers perform well enough in diagnosing COVID-19 in isolation for them to be used as a standalone.

Keywords: Routine Laboratory Biomarkers ; COVID-19

1. Introduction

In this meta-analysis of routine laboratory biomarkers, we found that white blood cell, neutrophil, lymphocyte, eosinophil and platelet counts were decreased in COVID-19-positive patients, while lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase were increased in COVID-19-positive patients in a hospital setting.

2.Utility of Routine Laboratory Biomarkers to Detect COVID-19

Previous attempts have been made using routine laboratory biomarkers for diagnosing COVID-19. In a study of 200 hospitalised patients with suspected COVID-19, Mardani, Ahmadi and Vasmehjani [1] suggested lactate dehydrogenase, C-reactive protein, alanine aminotransferase, and neutrophil count were useful for diagnosing COVID-19. In their study, these biomarkers were significantly different in COVID-19-positive compared to -negative patients, but only lactate dehydrogenase and C-reactive protein values were outside of the normal ranges. Another study reported eosinopenia (<0.02 109/L) alone or in combination with elevated high-sensitivity C-reactive protein (≥4 mg/L) could be used for separating the two groups and thus providing a biomarker with predictive capacity for diagnosing COVID-19 [2]. A decrease in circulating eosinophils was also reported to have a good predictive value for COVID-19 and is more common in COVID-19-positive patients compared to patients with other types of pneumonia [3]. Lactate dehydrogenase and lymphocyte counts were particularly interesting, with the mean lactate dehydrogenase levels in COVID-19-positive patients raised above the normal range, while individuals with COVID-19 are often lymphopenic [4]. Lymphocytes and lactate dehydrogenase were also identified in prognostic systematic literature reviews as useful markers of severe disease [5]. However, whilst all COVID-19-positive individuals had lower mean lymphocyte counts, they were not rendered lymphopenic, meaning lymphocyte counts surprisingly had limited utility in differentiating COVID-19-positive from COVID-19-negative pneumonia patients [6]. However, the included studies were predominantly from China, where early molecular diagnostics were likely to have lacked sensitivity and had a high limit of detection. This could have introduced diagnostic bias amongst pauci-symptomatic individuals, who potentially have lower level viraemias than those with highly symptomatic infection [7].

Inflammatory markers may be useful in supporting the diagnosis of COVID-19 and differentiating it from other viral pneumonias. C-reactive protein is associated with overproduction of inflammatory cytokines in patients, which is linked with the degree of severity and mortality of patients with COVID-19 [8]. It was even reported as being a promising biomarker that could potentially be used for assessing disease mortality [9]. This review indicates that inflammatory markers seem unlikely to differentiate COVID-19 from bacterial pneumonia. Procalcitonin is another inflammatory marker thought to be more specific for bacterial infection. In this meta-analysis, the standard mean difference was lower in COVID-19-positive patients, but the literature is somewhat inconsistent [10][11][12][13]. Some studies reported that procalcitonin levels correlate with disease severity in COVID-19-positive patients and can, as such, help to predict the prognosis in confirmed COVID-19 cases [14]. A meta-analysis even demonstrated a ~5-fold increased risk of severe SARS-CoV-2 infection in patients with elevated procalcitonin [15]. However, concurrent bacterial infection could bias these results, and it would act as a strong confounding factor.

The impact of these results in the emergency department will need to be further evaluated. The standard mean difference of certain biomarkers shows a statistically significant difference, but the means are often within the normative ranges. This implies that a non-negligible number of individual patients with COVID-19 would have normal levels of the biomarkers. Thus, no single biomarker will have the sensitivity and specificity to diagnose or exclude COVID-19. In parallel to our

review, a Cochrane review [16] analysing the increased or decreased test results compared to normal range values was published. This review explored whether routine laboratory tests were sufficiently accurate to diagnose COVID-19 and concluded that these tests cannot accurately differentiate between COVID-19 and other diseases.

There is a suggestion that multiple biomarkers could be combined and added into a composite reference standard for diagnosing COVID-19 [17]. This option seems reasonable when considering the biomarkers identified by the current review; where low neutrophil, lymphocyte, and platelet counts are unlikely to discriminate between respiratory infections and COVID-19; but lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase levels seem a more characteristic feature of COVID-19 [1][5][18][19][20]. These biomarkers are increased when tissues are damaged and, in particular, when the liver is affected [21]. COVID-19 does not just cause respiratory symptoms, clearly demonstrated by its ability to cause thromboembolic events, and gastrointestinal and even central nervous system infection [22][23]. However, further studies and analyses are required to compare COIVD-19 to seasonal influenza viruses, which may mimic COVID-19 infection.

Currently RT-PCR is the most commonly used reference standard [24][25], but its imperfect performance means that a composite gold standard could be used to better classify disease status [17][26]. In COVID-19, this would include not only RT-PCR but also radiology, expert opinion, and laboratory test results to correctly identify COVID-19. This method is used when only imperfect tests exist, with no established gold standard [27]; and would provide a reference to test the performance of novel COVID-19 diagnostics against. This will be of upmost importance in the immediate future, where there is an urgent desire to identify sensitive POC tests for both symptomatic and asymptomatic individuals. However, without a careful selection of an accurate gold standard, the evaluation of such diagnostics is problematic, and sensitivity can be over-estimated.

From the start of the COVID-19 outbreak in the UK, the RT-PCR testing infrastructure has expanded dramatically [28]. In the study conceptualisation phase, during the first wave there was an increase in demand for testing that lengthened the time to obtain a RT-PCR result, and the current hospital bed pressures have further placed a high demand on side rooms and isolation facilities. As the testing infrastructure continues to develop, improvements in sensitivity, the increase in high-throughput diagnostics and reductions in time to result are likely to increase the use of molecular tests at the expense of the biomarkers in the study. However, biomarkers often have the advantage of faster turn-around times, when compared to current COVID-19 diagnostics, meaning results are often available before the RT-PCR results. Clinically, this is extremely relevant, as it could be used to guide the isolation of patients with suspected COVID-19. Suspected COVID-19 patients require isolation, before being de-escalated with a negative RT-PCR result [29]. However, due to a lack of sensitivity, often patients with a high clinical suspicion of COVID-19 remain in isolation pending repeat testing, further imaging or alternative investigations. This places additional pressures on hospital infection control resources.

The development of a clinical scoring algorithm using biomarkers to inform triage and isolation strategies upon admission could have a significant impact on infection control when resources are scarce. Biomarkers may also have a role in identifying disease severity. There is evidence that biomarkers such as D-dimer are correlated with complications such as pulmonary embolism and poor outcomes. Further research is required to see whether biomarkers be used to help predict mortality and morbidity [30].

References

1. Mardani, R.; Ahmadi Vasmehjani, A.; Zali, F.; Gholami, A.; Mousavi Nasab, S.D.; Kaghazian, H.; Kaviani, M.; Ahmadi, N. Laboratory parameters in detection of COVID-19 patients with positive RT-PCR; a diagnostic accuracy study. Arch. Acad. Emerg. Med. 2020, 8, e43.
2. Li, Q.; Ding, X.; Xia, G.; Chen, H.-G.; Chen, F.; Geng, Z.; Xu, L.; Lei, S.; Pan, A.; Wang, L.; et al. Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: A retrospective case-control study. EClinicalMedicine. 2020, 23.
3. Xie, G.; Ding, F.; Han, L.; Yin, D.; Lu, H.; Zhang, M. The role of peripheral blood eosinophil counts in COVID-19 patients. Allergy 2020, 76, 471–482.
4. Huang, G.; Kovalic, A.J.; Graber, C.J. Prognostic value of leukocytosis and lymphopenia for coronavirus disease severity. Emerg. Infect. Dis. 2020, 26, 1839–1841.
5. Kermali, M.; Khalsa, R.K.; Pillai, K.; Ismail, Z.; Harky, A. The role of biomarkers in diagnosis of COVID-19—A systematic review. Life Sci. 2020, 254, 117788.

6. Soraya, G.V.; Ulhaq, Z.S. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. Med. Clin. 2020, 155, 143–151.
7. Fajnzylber, J.; Regan, J.; Coxen, K.; Corry, H.; Wong, C.; Rosenthal, A.; Worrall, D.; Giguel, F.; Piechocka-Trocha, A.; Atyeo, C.; et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat. Commun. 2020, 11, 5493.
8. Ali, N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J. Med. Virol. 2020.
9. Sahu, B.R.; Kampa, R.K.; Padhi, A.; Panda, A.K. C-reactive protein: A promising biomarker for poor prognosis in COVID-19 infection. Clin. Chim. Acta Int. J. Clin. Chem. 2020, 509, 91–94.
10. Gendrel, D.; Bohuon, C. Procalcitonin, a marker of bacterial infection. Infection. 1997, 25, 133–134.
11. Gilbert, D.N. Procalcitonin as a biomarker in respiratory tract infection. Clin. Infect. Dis. 2011, 52, S346–S350.
12. Vazzana, N.; Dipaola, F.; Ognibene, S. Procalcitonin and secondary bacterial infections in COVID-19: Association with disease severity and outcomes. Acta Clin. Belg. 2020, 1–5.
13. Yan, S.T.; Sun, L.C.; Jia, H.B.; Gao, W.; Yang, J.P.; Zhang, G.Q. Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria. Am. J. Emerg. Med. 2017, 35, 579–583.
14. Hu, R.; Han, C.; Pei, S.; Yin, M.; Chen, X. Procalcitonin levels in COVID-19 patients. Int. J. Antimicrob. Agents 2020, 56, 106051.
15. Lippi, G.; Plebani, M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin. Chim. Acta 2020, 505, 190–191.
16. Stegeman, I.; Ochodo, E.A.; Guleid, F.; Holtman, G.A.; Yang, B.; Davenport, C.; Deeks, J.J.; Dinnes, J.; Dittrich, S.; Emperador, D. Routine laboratory testing to determine if a patient has COVID-19. Cochrane Database Syst. Rev. 2020.
17. Graziadio, S.; Hicks, T.; Allen, A.J.; Suklan, J.; Urwin, S.G.; Winter, A.; Price, D.A.; Body, R. A Composite Reference Standard for COVID-19 Diagnostic Accuracy Studies: A Roadmap; PAHO: Washington, DC, USA, 2020.
18. Rodriguez-Morales, A.J.; Cardona-Ospina, J.A.; Gutiérrez-Ocampo, E.; Villamizar-Peña, R.; Holguin-Rivera, Y.; Escalera-Antezana, J.P.; Alvarado-Arnez, L.E.; Bonilla-Aldana, D.K.; Franco-Paredes, C.; Henao-Martinez, A.F.; et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med. Infect. Dis. 2020, 101623.
19. Henry, B.M.; Lippi, G.; Plebani, M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin. Chem. Lab. Med. 2020, 20200272.
20. 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.
21. Ali, N. Relationship between COVID-19 infection and liver injury: A review of recent data. Front. Med. 2020, 7.
22. Gavriatopoulou, M.; Korompoki, E.; Fotiou, D.; Ntanasis-Stathopoulos, I.; Psaltopoulou, T.; Kastritis, E.; Terpos, E.; Dimopoulos, M.A. Organ-specific manifestations of COVID-19 infection. Clin. Exp. Med. 2020, 20, 493–506.
23. Gupta, A.; Madhavan, M.V.; Sehgal, K.; Nair, N.; Mahajan, S.; Sehrawat, T.S.; Bikdeli, B.; Ahluwalia, N.; Ausiello, J.C.; Wan, E.Y.; et al. Extrapulmonary manifestations of COVID-19. Nat. Med. 2020, 26, 1017–1032.
24. Corman, V.M.; Landt, O.; Kaiser, M.; Molenkamp, R.; Meijer, A.; Chu, D.K.; Bleicker, T.; Brünink, S.; Schneider, J.; Schmidt, M.L. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance 2020, 25, 2000045.
25. Dramé, M.; Teguo, M.T.; Proye, E.; Hequet, F.; Hentzien, M.; Kanagaratnam, L.; Godaert, L. Should RT-PCR be considered a gold standard in the diagnosis of Covid-19? J. Med. Virol. 2020, 92, 2312–2313.
26. Umemneku Chikere, C.M.; Wilson, K.; Graziadio, S.; Vale, L.; Allen, A.J. Diagnostic test evaluation methodology: A systematic review of methods employed to evaluate diagnostic tests in the absence of gold standard—An update. PLoS ONE 2019, 14, e0223832.
27. Naaktgeboren, C.A.; Bertens, L.C.M.; Smeden, M.v.; Groot, J.A.H.d.; Moons, K.G.M.; Reitsma, J.B. Value of composite reference standards in diagnostic research. BMJ Br. Med. J. 2013, 347, f5605.
28. Testing in UK. Coronavirus (COVID-19) in the UK. GOV.UK. Available online: (accessed on 20 April 2021).
29. Public Health England. COVID-19: Guidance for The Remobilisation of Services within Health and Care Settings Infection Prevention and Control Recommendations; Public Health England: London, UK, 2020.
30. Yao, Y.; Cao, J.; Wang, Q.; Shi, Q.; Liu, K.; Luo, Z.; Chen, X.; Chen, S.; Yu, K.; Huang, Z.; et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J. Intensive Care 2020, 8, 49.