Technical Bulletin

Current information on increased D-dimer, cardiac Troponin (cTn), and BNP biomarkers in patients with laboratory-confirmed SARS-CoV-2 infections

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In response to the number and diversity of studies that have emerged surrounding SARS-CoV-2 infections and the suspected link to thrombotic and cardiac events, Quidel has felt it prudent to summarize and provide a technical bulletin of the recent literature on these topics. Please note that there is no direct link to our products and their intended use, as stated in the Package Inserts.

There are limitations of the data aggregated in this technical bulletin due to the changing environment surrounding SARS-CoV-2 and the lack of controlled studies. We recommend that customers continue to keep up to date with the latest literature and relevant society recommendations. These guidelines and recommendations change rapidly, so please reference them online for real time updates: ESC, ACC, IFCC, WHO, CDC, NIH, AMA, AHA.

SARS-CoV-2 and D-dimer

Background

- COVID-19 disease is associated with thrombosis: large vessel clots, DVT/PE (deep vein thrombosis/ pulmonary embolism), potentially arterial events and small vessel disease as well as microvascular thrombosis.[1]
- It has been postulated that the high mortality observed among COVID-19 patients may be partly due to unrecognized pulmonary embolism (PE) and pulmonary in situ thrombosis.[2]

Mechanisms of Thrombosis

- One potential mechanism of thrombosis is an infection-induced endothelial damage of blood vessels with subsequent clotting that is accompanied by increased D-dimer levels. Foundation of this hypothesis is that the SARS-CoV-2 virus enters cells via ACE2-receptors (angiotensin-converting enzyme), which are most commonly found in alveolar epithelial cells, followed by endothelial cells.[1]
- Endothelial cells are prolific in every organism, and therefore, it is not surprising that thrombus and microthrombus formations caused by a SARS-CoV-2 infection affect not only the lungs, but also other organs like heart, liver or kidneys.[1]

Clinical Studies and Outcomes

- ***Fei-Zhou et al. (2020; N = 191)***: In patients with simultaneously increased D-dimer levels (>1 µg/mL), the mortality risk was 18-times higher (OR: 18.42, 2.64 – 128.55; p=0.0033).[3]
- ***Tang et al. (2020; N = 183):*** D-dimer (µg/mL) levels in survivors of COVID-19 pneumonia have been significantly lower than in deceased patients: 0.61 (0.35 – 1.29) versus 2.12 (0.77 – 5.27); p<0.001.[4]

Conclusions

- Hospitalized patients with COVID-19 were characterized by substantial in-hospital mortality and a high rate of thromboembolic complications. Rapidly increasing D-dimer levels were observed in non-survivors, reflecting the inflammatory and procoagulant state of COVID-19.[2]
- The risk factors related to COVID-19, the development of ARDS (Acute Respiratory Distress Syndrome), and the progression from ARDS to death included older age, neutrophilia, higher SOFA (Sequential Organ Failure Assessment) score, and coagulation dysfunction (e.g., D-dimer).[3,5]

SARS-CoV-2 and Troponin/BNP

Background

- COVID-19 patients with pre-existing cardiovascular conditions represent large proportions of patients with symptomatic infection, and experience disproportionately worse outcomes with a 5 to 10-fold increase in mortality.[6]
- Patients with new COVID-19 infections can also develop cardiovascular complications, such as heart failure, myocarditis, pericarditis, vasculitis, and cardiac arrhythmias.[6]

Mechanisms of Cardiac Injury

- For patients with underlying CVD (cardiovascular disease), viral illness can further damage myocardial cells through several mechanisms including direct damage by the virus, systemic inflammatory responses, destabilized coronary plaque, and aggravated hypoxia.[7, 10,11]
- Mechanistic data are extremely limited for COVID-19, but they offer proof of concept of direct cellular injury in tissues with ACE2 (angiotensin-converting enzyme) expression. The myocardial cellular targets for SARS-CoV-2 may include pericytes, cardiomyocytes, fibroblasts, and immune cells.[8]
- ACE2, which is expressed in the lungs, heart and vessels, is a key member of the renin angiotensin system (RAS) important in the pathophysiology of CVD. CVD associated with COVID-19, likely involves dysregulation of the RAS/ACE2 system which causes hypertension.[9]

Clinical Studies and Outcomes

- **Lippi et al. (2020; N = 341):** Results from a meta-analysis revealed abnormal cTnI values (>99th percentile) in 8-12% of patients hospitalized with COVID-19 and elevations were associated with more severe complications and worse outcomes.[12]
- **Shi et al. (2020; N = 416):** In patients that had increased cTn levels (20%) at hospital admission, the mortality risk has been about 10-times higher (51% versus 5%, adjusted HR: 3.41 (95% CI 1.62 – 7.16).[13]
- A similar proportion of patients also manifest elevations of natriuretic peptides (BNP). Troponin and BNP, together with the presence of underlying cardiovascular diseases or cardiovascular risk factors, are highly prognostic of requirement for ICU admission, ventilation and death.[6]

Conclusions

- If clinicians are reluctant to measure cardiac troponin in these patients, the consequence may be to ignore the plethora of ischemic and non-ischemic causes of myocardial injury related to COVID-19, which may be directly or indirectly associated with poor outcomes.[14]

- The early presence of cardiac injury and stress, as evidenced by biomarkers of elevated troponin and/or natriuretic peptides, are important to ascertain especially in higher risk patients.[6]
- In the clinical course of patients with COVID-19, detectable hs-cTnI was observed in most patients, and hs-cTnI was significantly elevated in more than half of the patients that died.[11]

Pertinent guidance links:

- ESC - escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance
- ACC - acc.org/latest-in-cardiology/features/accs-coronavirus-disease-2019-covid-19-hub
- IFCC - ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19
- WHO - who.int/emergencies/diseases/novel-coronavirus-2019
- CDC - coronavirus.gov
- NIH - nih.gov/health-information/coronavirus
- AMA - ama-assn.org
- AHA - heart.org/en/coronavirus

Literature

1. Phend C. Anticoagulation Guidance Emerging for Severe COVID 19 https://www.medpagetoday.com/infectiousdisease/covid19/85865
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3. Fei Zhou et al. The Lancet 2020; Vol.: 395, Issue 10229; 1054 – 1062)
4. Tang et al. J Thromb Haemost. 2020; 18: 844 – 847
5. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020
6. Liu et al. 10.1161/CIRCULATIONAHA.120.047549
7. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA cardiology. 2020 Mar 27. PMID: 32219356
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10. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nature Reviews Cardiology. 2020 Mar 5:1-2. PMID:32139904
11. American College of Cardiology. Troponin and BNP Use in COVID-19. 28 Mar 2020
12. Lippi et al. https://doi.org/10.1016/j.pcad.2020.03.001
13. Shi S et al. JAMA Cardiol. 2020 Mar 25. doi: 10.1001/jamacardio.2020.0950
14. Chapman et al. Circulation 2020. https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.119.042960

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