Immunology and Infections

CONCEPTUAL PAPER

Pulse rate variability as a biomarker of COVID-19 infection, hospital risk stratification, and post hospitalization recovery

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Rapid and reliable COVID-19 biomarkers are needed:

Biomarkers that can rapidly identify novel coronavirus 2019 (COVID-19) infection are in high demand. COVID-19 infection is expected to present as fever, dry cough, fatigue, and the gradual development of respiratory symptoms [1], however, fever was present in only 12% of individuals who tested positive for COVID-19 infection [2]. Although individuals are screened for fever related to COVID-19 in airports, some businesses, and other public gatherings before entering, it is possible that many people carrying the virus do not have a fever or potentially do not display any symptoms at all.

Of additional consideration is that the symptoms of COVID-19 are common among a variety of viral and bacterial ailments; fever is a common symptom associated with many other infectious diseases such as influenza and may be even less indicative of COVID-19 infection during flu season, necessitating a rapid, accessible, and reliable biomarker of COVID-19 infection to distinguish from other common infectious diseases.

In addition to identifying individuals with active COVID-19 infection, the ideal biomarker would also distinguish which symptomatic COVID-19-infected individuals are at the greatest risk of developing a severe clinical course requiring mechanical ventilation or hemodialysis. Further, many patients recovering from COVID-19 infection experience a prolonged convalescent phase lasting more than 30 days and are diagnosed with post intensive care syndrome (PICS) [3]. A biomarker able identify individuals at risk for post-hospitalization complications would help assign post hospitalization follow-up management.

Potential utility for COVID-19 biomarkers:

- Early diagnosis of infection
- Prognosis of clinical outcome
- Identify risk of post-COVID-19 complications

Considering c-reactive protein as a biomarker of COVID-19:

C-reactive protein (CRP) is a marker of systemic inflammation and is an indicator of early infection, prognosis, and risk of PICS. CRP is produced by the liver in response to the production of IL-6 by macrophages and T-cells and is a reliable biomarker of acute and chronic inflammatory activity [4]. COVID-19 infection is associated with an excessive release of pro-inflammatory cytokines, referred to as a cytokine storm, including CRP and IL-6, and increased levels of cytokines correlate with a higher risk of complications during hospitalization due to COVID-19 [5].

CRP may be a useful biomarker in distinguishing COVID-19 infection from other common respiratory infections; during evaluation of patients for possible infection, CRP levels changed before other blood test parameters including leukocytes, monocytes, lymphocytes, and hemoglobin in patients ultimately diagnosed with COVID-19 [6]. The ratio between these blood parameters and CRP was significantly increased in symptomatic patients who had indirect contact with the disease while traveling in an epidemic area, suggesting that the change in reactivity of CRP in COVID-19 infection is greater than the response of other blood parameters. Another study in children determined that CRP was the most accurate indicator of an infectious or inflammatory process compared to neutrophil count or estimated sedimentation rate [7].

CRP has shown promise in clinical settings as an independent discriminator of COVID-19 severity upon hospital admission according to chest CT severity and was also a predictor of adverse outcomes and mortality [8-13] (Figure 1). In non-COVID-19 patients, preoperative CRP levels correlate with an increased risk of systemic inflammatory response syndrome following percutaneous nephrolithotomy [14, 15].

A biomarker like CRP should be used in combination with other relevant elements such as oxygen level, vital signs (fever, respiration rate, pulse rate), symptoms, exposure, and travel history of the patient. Collectively, these data could aid the identification of individuals at risk for COVID-19 infection

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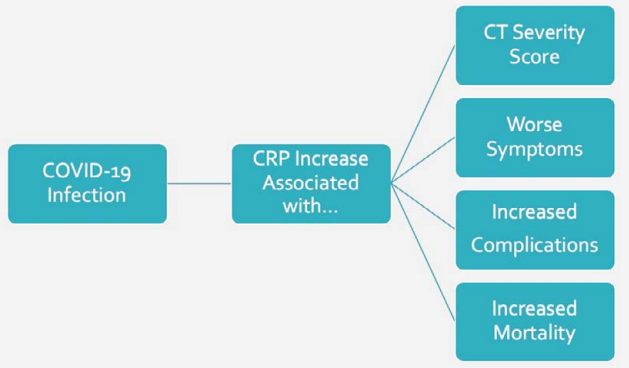

Figure 1: CRP correlates with severity of outcomes in COVID-19 infection.

when symptomatic or pre-symptomatic and could help stratify the intensity of care required after laboratory diagnosis of COVID-19 infection.

The major drawback of using CRP as a COVID-19 screening tool is that measuring CRP requires a blood sample and laboratory analysis. Although this is not a significant hurdle when a patient is being evaluated in a hospital, access to a laboratory can be difficult and costly in the outpatient clinical setting or when screening or contact tracing individuals quickly and in large numbers. Fortunately, CRP increase is inversely correlated with a measure of autonomic nervous system function known as heart rate variability (HRV). HRV is quickly and reliably measured with small handheld portable devices that provide immediate and accurate results, making HRV a useful surrogate for a CRP blood test.

HRV as an indicator of inflammation and clinical outcome:

The autonomic nervous system maintains whole-body homeostasis and HRV is a measure of autonomic health. HRV determines the variation in time between each successive pair of heartbeats and is non-invasive, providing information about the balance between the sympathetic and parasympathetic nervous systems. Variations in HRV are closely related to the presence of illness and pathologic conditions (inflammation) and the degree of HRV variation is an indicator of the severity of disease [16, 17]. A high degree of variability in HR indicates a healthy person with a well-functioning autonomic nervous system and low inflammation. A low degree of HRV indicates autonomic nervous system dysfunction and is associated with elevated levels of pro-inflammatory cytokines and worse outcomes in a variety of medical conditions including myocardial infarction, diabetes, metabolic syndrome, end-stage renal disease, chronic liver disease, hypoxic lung disease, congestive heart failure, hypertension, and obesity [18-22]. The inflammatory biomarkers commonly correlated with HRV in these studies include CRP, TNF-α, IL-1, IL-6, and white blood cell count.

IL-6 levels are negatively correlated with HRV and predictive of response to therapy and survival [23]. This indicates that reduction in HRV is associated with elevated pro-inflammatory cytokines. Indeed, an assessment of heart rate variability measuring CRP serum levels within 24 hours of admission in 531 patients with unstable cardiac pain found a significant negative correlation between CRP levels and HRV [24].

An investigation of the association between HRV, CRP, IL-6, and fibrinogen in a cohort of 862 subjects found that HRV was inversely associated with inflammatory indices after adjustment of all covariates [25], also supporting HRV as an indicator of inflammation. Additionally, HRV measures by a hospital rapid response team over the first 24 hours after resuscitation accurately predicted both the need for ICU admission and survival outcomes in critically ill hospitalized patients [26], suggesting that HRV can be used to quickly perform risk assessment.

Infections and the predictive value of HRV:

Low HRV and autonomic dysfunction are reported alongside infectious conditions such as community acquired pneumonia [27], dengue viral infection, HIV [28, 29], leprosy [30], and tetanus [31]. When comparing HRV in patients with community-acquired pneumonia to healthy control subjects, pneumonia was correlated with a decline in HRV. Interestingly, the degree of HRV suppression was correlated with severity of illness and increased time to clinical stability after admission. Another study assessing post-operative complications in older people suggests that low HRV is associated with a six-fold increase in the likelihood of pneumonia in this patient population. Additional studies implicate HRV as an early indicator of sepsis 12 to 24 hours before traditional clinical methods [32-34]. One study observed changes in HRV as early as three to four days before the onset of sepsis [35]. Many of these complications are also observed in COVID-19 patients, suggesting that HRV may act as a surrogate for CRP levels in predicting negative outcomes (Figure 2).

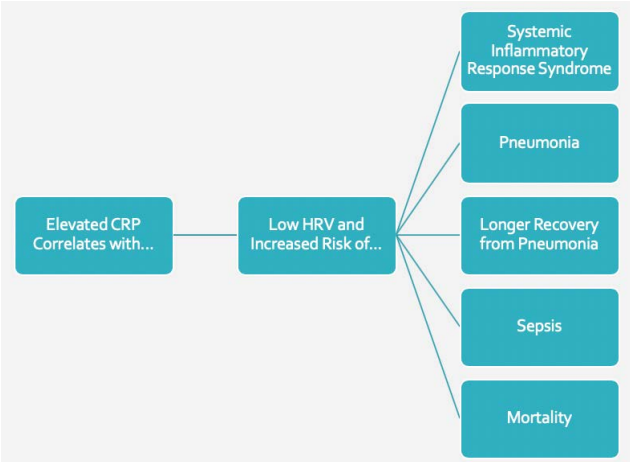

Figure 2: CRP and HRV are both associated with complications also found in COVID-19 infection.

An association between low HRV and general complications, postoperative infections, and postoperative pneumonia after hip fracture demonstrated that HRV may be used to identify patient groups that need increased surveillance and prophylactic treatments [36]. Although pro-inflammatory conditions are associated with a decline in HRV, a significant degree of autonomic nervous system dysfunction, as represented by low HRV, may predispose patients to a worse clinical outcome.

Measuring the influence of inflammation on HRV with a smartphone:

A five-minute electrocardiogram (ECG) is traditionally used to measure HRV by analyzing the variation in time between R to R intervals of successive beats. An alternate method of HRV determination is photoplethysmography (PPG), which does not require the use of an ECG and can be performed in less time. Each R peak on the ECG corresponds with a contraction of the ventricle and each contraction can be detected by pulsation of blood within the capillary bed of the fingernail via PPG.

PPG is an optical method that detects cardiac beats by analyzing changes in light absorption and the color of skin and is the basis for common digital pulse oximetry. The PPG sensor detects the alteration in intensity of light via transmission through or reflection from the tissue [37, 38] and can be determined and displayed using a smartphone.

Variations in light intensity are related to changes in blood perfusion of the tissue of the nail bed and based on these changes, heart-related information can be retrieved. HRV determined by this method is specifically referred to pulse rate variability (PRV) and has a high degree of concordance with HRV determined by ECG [39-42]. Our group has developed a PRV measurement device called the My Vagus Sensor that is worn on the fingertip just like a typical pulse oximeter (Figure 3).

We developed a smartphone app called MyAutonomic Health that detects the Bluetooth signal from the My Vagus Sensor to provide the user with PRV measurement. Measuring PRV for 1 minute allows the user to accurately monitor the health of their autonomic nervous system via PRV/HRV determination. Scores can be graphically displayed to provide the user with feedback about whether their systemic inflammatory status is increasing or decreasing (Figure 4). An additional method of utilizing PPG with a smartphone is by placing the subject's finger over a single lens of the smartphone camera.

Figure 3 (a): MyVagus Sensor is a modified pulse oximeter used to capture PPG signal.

Figure 3(b): Example PRV measurements determined by PPG technology.

Summary:

Considering the ubiquitous presence of smartphones, the monitoring of PRV through photoplethysmography is a potential biomarker of COVID-19 infection, especially for use outside of the hospital environment necessitating a reliable, rapid, and laboratory-free screening method.

Smartphone-based PRV determination can be coupled with oxygen saturation levels, symptom surveys and even therapy adherence tracking all of which can easily be shared with clinicians overseeing the recovery of patients with COVID-19 infection.

As large numbers of persons continue to be infected with COVID-19 worldwide, it is imperative that clinically useful, inexpensive, and rapidly deployable biomarkers are developed.

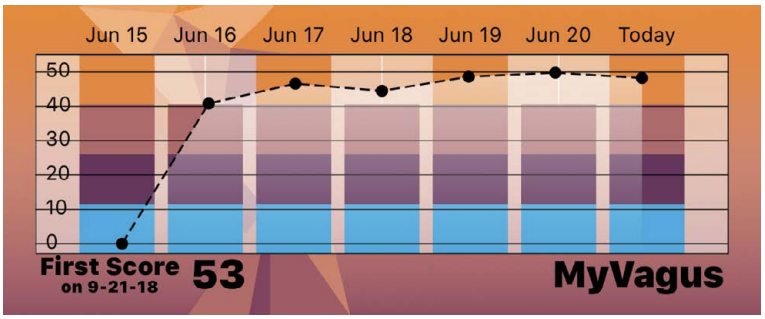

Figure 4: PRV and adherence tracking to therapies as indicated by color bars.

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