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Diagnosis of Hidden Clinical COVID-19 Infection among Hospitalized Patients with Acute Cardiovascular Manifestations and its Treatment: An Innovative Observational Study

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Abstract

Backgrounds: The spike glycoprotein of SARS-CoV-2 helps the virus to bind the ACE2 receptor to enter the host cells. ACE2 receptors are present in lung, heart, kidney, liver, brain and other organ. COVID-19 is recognized as a multi-organ disease with a broad spectrum of varied severity of clinical manifestations; can affect the cardiovascular system. COVID-19 infection is a highly inflammatory disease associated with elevated acute inflammatory blood biomarkers such as CRP, LDH, and Ferritin etc.

Objectives: To diagnose hidden clinical COVID-19 infection as a immediate major risk factor of acute cardiovascular manifestations and innovative short course treatment with high dose IV bolus Artesunate and its outcome.

Methods: Diagnosis of clinical COVID-19 infection was done by adopting a diagnostic criteria alternative to RT-PCR test among clinically suspected COVID-19 infected patients: if they met ≥ one of the following diagnostic inflammatory biomarkers, such as elevated levels of serum CRP, Ferritin, LDH, D-dimer and X-ray chest PA view. Acute cardiac manifestations were diagnosed by detail clinical history, physical examination, elevated serum Troponin-I, ECG, and echocardiography. Along with standard of care, patients were empirically treated with high dose (4mg/kg) IV bolus Artesunate for 3 to 5 days.

Results: Clinically hidden COVID-19 infection was diagnosed by acute inflammatory biomarkers criteria and x-ray chest PA view among 40 consecutive hospitalized cases with acute cardiovascular manifestations. High dose IV bolus Artesunate therapy along with standard of care appears to be very safe and effectively decreases inflammatory biomarkers with in very short periods and all patients recovered within a week.

Conclusions: Clinically COVID-19 can be diagnosed by elevated acute inflammatory criteria and imaging chest x-

ray. High dose IV bolus Artesunate for 3-5 days decreases inflammatory biomarkers rapidly and all patients recovered well within a week; there by decreased morbidity and mortality among COVID-19 associated acute cardiovascular manifestations.

Keywords: Clinical COVID-19, SARS-CoV-2, cardiovascular manifestations, high dose IV Bolus Artesunate, inflammatory biomarkers.

Introduction

In September 2022, USA declared that "the pandemic is over", when during that month there were >10,000 deaths due to COVID-19 and on April 10, 2023 terminated the COVID-19 national emergency putting COVID-19 in the rearview mirror in May 2023. Surveillance of COVID-19 is no longer performed using RT-PCT test screening. This was a result of vaccination and infection (Hybrid immunity), population immunity has increased. However, the hybrid immunity appears to be lowest among those aged 65 years old and wane over times and the decrease is faster among older adults and person with multiple pre-existing co-morbidities. After the emergence of Omicron and its sub-lineages, with lesser virulence, mild symptoms or may be asymptomatic, COVID-19 existed in a hidden endemic form disguised with many faces. The infections are unsuspected and undiagnosed. The clinicians should keep SARS-CoV-2 in the list of causes of acute respiratory illness or any acute deterioration of health among older and person with pre-existing co-morbidities needing hospitalization.[1] It seems that SARS-CoV-2 was moved towards endemicity and it is likely a gross underestimate of actual infections; because infections are unsuspected, thus undetected. The clinical features of currently circulating Omicron virus may be asymptomatic, mild or are atypical and often neglected.[2]

The COVID-19 pandemic has emphasized the importance of rethinking our concepts of disease based on dynamic and heterogeneous interrelationship: patients suffering from SAR-CoV-2 infection exhibit a high degree of heterogeneity in susceptibility to infections, disease manifestations and outcomes. This has been determined with respect to age, sex, race, underlying genetic variations, differential immune-response and preexisting co-morbidities, which are in turn subject to environmental and socioeconomic determinants. Genetic and acquired differences in the host immune system further complicate the host repertoire leading to wide heterogeneity in the clinical picture with varied manifestations, course and outcomes.[3] Extra-pulmonary complications are numerous and may be severe; can affect any organ or multiple organ system, including the cardiovascular, renal, neurologic, hematologic, gastrointestinal, hepatobiliary and dermatologic manifestations. [4]

The SARS-CoV-2 virus binds and enter through the ACE2 and results in systemic inflammation, multiorgan dysfunction and critical illness. Systemic inflammation can destabilize vascular plaque, while increase cytokine activity increase cardiac oxygen demand. The virus may cause direct damage to the heart utilizing ACE2 receptors located within cardiac tissues. Thus, the cardiovascular system affected with complications including myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysarrthythmias, and venous thromboembolic events.[5]

Suspicion of Hidden Clinical Covid-19 Infection and Strategies To Diagnosis

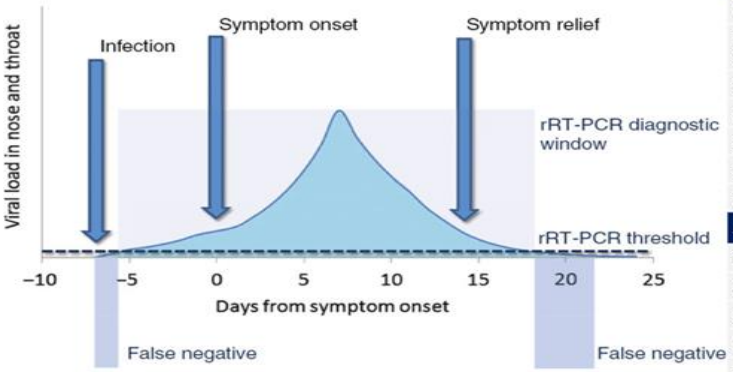
The pathophysiology of severe SARS-CoV-2 is characterized by overproduction of inflammatory cytokines (IL-6 & TNF-α) leading to systemic inflammation and multiple organ dysfunction syndrome

acutely affecting the cardiovascular system.SARS-CoV-2 tropism and interaction with RAAS system through ACE2 receptors, possibly enhances inflammatory response and cardiac aggression. Cardiac injury defined as elevated troponin-I, significantly related to inflammatory biomarkers (IL-6, CRP, hyperferritinemia and Leukocytosis) correlated between myocardial injury and inflammatory hyperactivity triggered by viral infection. Increased risk for myocardial infarction, fulminant myocarditis rapidly evolving with depressed systolic left ventricular function, arrhythmias, venous thromboembolism and cardiomyopathy mimicking STEMI presentation is one of the most prevalent cardiovascular complications. Preexisting cardiovascular disease and other risk factors can increase the severity of COVID-19 leading to the aggravation and decompenssation of chronic underlying cardiac pathology as well as acute onset of new cardiac complications. Myocardial injury can be present in approximately 12% of hospitalized patients with SARS-CoV-2 infection.[6]

The diagnostic performance of gold standard RT-PCR test for diagnosis of COVID-19 depends on many factors such as, the sample types, sample viral loads (>5000/µl), different stages of infection, the skill of sample collection and the quality and consistency of the PCR assays being used (Fig.1).[7] In a systemic review of five studies among 957 patients, false RT-PCR negative results reported from 2-94%.Thus, the clinicians should assume a negative result as 'false negative' in a person with typical symptoms and signs of COVID-19.[8]

Currently, RAT and RT-PCT tests are not done routinely or abandoned for diagnosis of COVID-19. The clinical manifestations COVID-19 are so subtle or atypical with varied clinical manifestation that, neither the treating physician nor the affected patients aware of its association at the time of clinic visit or hospitalization for any medical reasons. Further if the patients have history of fever, myalgia, and arthralgia; Elisa tests are done to exclude dengue, malaria, Scrubtyphus etc due to similar clinical features. The paradox is that there are incidences of false positive reports of dengue, malaria, Scrubtyphus, Hepatitis C, HIV etc. due to molecular mimicry of SARS-CoV-2 viral RNA, misleading and misguiding the physicians for the diagnosis and management. There are also incidences of multiple Elisa test positive in a single patient. Therefore, the treating physician should very carefully correlate these laboratory reports with patient's detail clinical history and physical examinations in the epidemiological context.[9,10]

Figure 1: Showing probability of false negative RT-PCR test



False negativity attributable to low viral loads in **1)** initial phase of infection and **2)** final phase of infection

Preanalytical Factors:
Lack of identification/misidentification
Inadequate specimen collection, handling, transport and storage
Collection of inadequate material for quality or volume
Presence of interfering substances
Manual (pipetting) errors
Sample contamination
Testing in patients receiving antiretroviral therapy
Analytical Factors:
Testing carried out outside of the diagnostic window
Active viral recombination
Use of non-adequately validated assays
Lack of harmonization of primers and probes
Instrument malfunctioning
Insufficient or inadequate material
Non-specific PCR annealing
Misinterpretation of expression profiles

Strategies for Diagnosis of Hidden Covid-19 Infection

As COVID-19 infection is a highly inflammatory disease associated with elevated acute inflammatory bio-markers. Currently, any elderly, obese and person with co-morbidities with acute exacerbation of health needing hospitalizations should be suspected to have underlying COVID-19 infection as a exacerbating factor. To unravel the diagnosis of hidden COVID-19 infection, acute inflammatory biomarkers diagnostic criteria can be used for diagnosis. Panels of acute inflammatory serum biomarkers tests were done to determine the sensitivity and specificity for the diagnosing of COVID-19 infection in comparison to RT-PCR test with a specificity of 89% for following elevated blood biomarkers criteria: If Serum ferritin levels >125% (1.25 times) of URL 300µg/L-(M) and 200µg/L(F) had sensitivity of 66% (56.8-76.4) and specificity of 85% (77.3-91.4) is the most accurate biomarker. Serum LDH levels >125% of URL-(290 IU/L (F) and 325 U/L for (M) with sensitivity of 62 % (51.1-71.5) and specificity of 77 % (67-83.8), and CRP level >80mg/L with sensitivity of 46 % (36.4-57.4) and specificity of 81 % (72.1- 87.7). Serum D-dimer levels >1.2mg/L with sensitivity of 33 % (23.6-43.4) and specificity of 79% (71.1-86.9). Over all, if ≥ one elevated bio-marker criteria present in a clinically suspected COVID-19 patients, diagnosis of COVID-19 infection was made with sensitivity of 91% (83.9-96.3) and specificity was 47% (38.1-57.5), versus (91% of RT-PCR positive COVID-19 patients met one or more of the diagnostic criteria with these blood biomarkers, and 47% in the non-COVID-19, did not met any diagnostic criteria).[11]

Table 1. Sensitivity and specificity of acute inflammatory blood biomarkers for the diagnosis of clinical COVID-19 infection

Serum acute inflammatory Biomarkers	Cut off value	Sensitivity	Specificity
Ferritin	URL 300µg/L-(M) 200µg/L(F)	66% (56.8-76.4)	85% (77.3-91.4)
CRP	>80mg/L	46 % (36.4-57.4)	81 % (72.1- 87.7)
LDH	290 IU/L (F), 325 U/L (M)	62 % (51.1-71.5)	77 % (67-83.8)
D-dimer	>1.2mg/L	33 % (23.6-43.4)	79% (71.1-86.9)
≥1 of above biomarkers elevated		91% (83.9-96.3)	47% (38.1-57.5)
X-ray Chest PA View	Abnormal pulmonary pathology	High	High

Further strong support of diagnosis of COVID-19 was made by evidences of pulmonary pathologies in the X-ray chest PA view with higher sensitivity and specificity. However, an absence of elevated bio-markers or pulmonary involvement in chest x-ray, alone does not exclude diagnosis of COVID-19 infection as it depends on host response, severity and stages of disease progression. In a study, Comparison of Clinical diagnosis of COVID-19 with Real Time Polymerase Chain Reaction in adult's representative Population. The Sensitivity and specificity of clinical diagnosis of COVID-19 against RT-PCR positive was 78%(95%CI,77-80%) versus RT-PCR positive of 93%(95% CI,93-93%)with positive predictive value (PPV)54%(95% ci,53-55%) and negative predictive value (NPV) was 98%(95% CI,98-98%). The accuracy of clinical diagnosis of COVID-19 is adequate regardless of gender, age, BMI, and asthma. Thus, clinical diagnosis

can be used for screening purpose to supplement RT-PCR which is costly, slow and test capacity, but at times been insufficient. [12]

Methods

There were 40 consecutive patients admitted in the indoor department of medicine (VSSIMAR BURLA, Odisha, India**)** with acute cardiovascular manifestations, with chief complains of acute chest pain, shortness of breaths, palpitations and pedal edema were undergone evaluation by adopted inflammatory biomarkers criteria (serum CRP, Ferritin and LDH) and X-ray chest PA view for the diagnosis of hidden COVID-19 infection.

Table 2: Results

Associated Major Findings	Percentages of cases
Age group(40-81 yrs) = 50 to 75 yrs(29 cases)	72%
Sex (M&F)	62.5% & 37.5%
Cases with raised CRP,LDH, Ferritin levels with X-ray chest abnormal pulmonary pathologies	87.5%
Cases with raised CRP,LDH, Ferritin levels without X-ray chest pathology	95%
Cases with abnormal pulmonary pathologies	92.5%
CRP elevated in	97.5%
Serum Ferritin elevated in all cases	100%
Serum LDH elevated	97.5%
Troponin –I elevated ng/mL	65%
ECHO abnormalities present	Only in 13 cases studied
Associated co-morbidities present in	80%
Most common co-morbidities	Hypertension, Obesity, Diabetes, Smoking ,Alcoholism

There were 40 consecutive cases (M-62.5%& F-37.5%) hospitalized with chief complain of chest pain, shortness of breaths, palpitations, pedal edema. Age ranged from 40-81 years,72% were between age 50-75 years old. There were 35 cases (87.5%) had elevated levels of CRP, LDH, Ferritin and abnormal pulmonary pathologies and 38 (95%) cases had cytokine storm ,all three biomarkers elevated without pulmonary pathology. Abnormal pulmonary pathologies were found in 37 cases (92.5%). CRP levels were elevated in 39 cases (97.5%), LDH level raised in 39 cases(97.5%) and Ferritin levels raised in 40 cases (100%). Troponin-I levels were raised in 26 cases (65%) and at least one co-morbidity was present in 32 cases (80%).

Innovative treatment of clinically proven COVID-19 infection

Artesunate have antiviral along with anti-inflammatory, immunomodulatory, antithrombotic effects and other favorable pleotropic effects.[13] After obtaining inform consent from patient's and their relatives, along with standard of care, empirical IV bolus (in 2-10 minute) Artesunate 4mg/kg body weight twice daily was administered at the time of diagnosis of COVID-19 infection for three to five days.[14,15] All patients recovered well and all inflammatory markers decreased within a week. Artesunate IV bolus therapy appears to be very safe and effectively decreases morbidities and mortalities

among patients presented with acute cardiovascular manifestations.

Discussion

The ACE-2 which is a key surface protein receptor for SARS-CoV-2 virus entry and part of rennin-angiotensin-aldosteron axis (RAAS) thought to be involved in the interactions. In addition to respiratory system uncontrolled SARS-CoV-2 infection can trigger a cytokine storm, where by pro-inflammatory cytokines and chemokines such as TNF-α, IL-6, IL-1β are overproduced by the immune system resulting in multiorgan damage, furthermore, it also causes coagulation abnormalities in substantial number of patients, which can lead to thromboembolic events. The high burden of systemic inflammation associated with COVID-19 has been proposed to accelerate the development of substantial disorders or cause de novo cardiovascular damage such as myocardial injury, arrythythmias, acute coronary syndrome, and venous thromboembolism. Some patients present without the typical symptoms of fever and cough have cardiac symptoms as the first clinical manifestation of COVID-19.These date indicate the presence of a bidirectional interaction between SARS-CoV-2 and the cardiovascular system.[16] Pre-existing cardiovascular diseases and traditional risk factors can increase the severity of COVID-19 leading to the aggravation and decompensation of chronic underlying cardiac pathology as well as acute onset of new cardiac complications.[17] Older individuals with underlying cardiovascular disease are susceptible to higher risk of adverse outcome and death during the severe and aggressive inflammatory response to COVID-19. Patients with long term coronary disease and those with risk factors for atherosclerotic cardiovascular disease have a heighten risk of developing acute coronary syndrome (ACS) during acute COVID-19 infection, such ACS could results from the severe increase in myocardial demand trigger by infection that precipitated myocardial injury or infarction(MI) akin to type-2 MI. Alternatively circulating cytokine released during severe systemic inflammatory stress could leads to atherosclerotic plaque instability and rupture. Similarly patients with heart failure are prone to hemodynamic decompensation during the stress of severe and aggressive inflammatory response to COVID-19.[18]

The virus can cause direct damage to the heart utilizing ACE-2 receptors located within the cardiac tissues. The patients with myocardial injury and myocarditis have serum troponin value abnormally high. ECG abnormalities are non-specific ST- segment, T –wave abnormalities- inversion and PR-segment and ST-segment deviation. In ECHO study differentiation of myocarditis and ACS is difficult. Most commonly focal wall motion abnormalities found with active significant ACS.[19] SARS-CoV-2 viral RNA was detectable and replicates in coronary lesions. SARS-CoV-2 targeted plaque macrophages and exhibited a stronger tropism for arterial lesions than the adjacent perivascular fats, correlating with macrophages infiltration levels. SARS-CoV-2 entry was increased in cholesterol loaded primary macrophages and dependent on part on neuropilin-1. SARS-CoV-2 induced a robust inflammatory response in cultured macrophages and human atherosclerotic vascular explants with secretion of cytokines known to trigger cardiovascular events including plaque inflammation –trigger acute cardiovascular complications and long term cardiovascular risk.[20]

Myocardial injury occurs approximately in one-quarter of hospitalized COVID-19 cases and is associated with greater need for mechanical ventilation support and higher hospital mortality. Direct viral myocardial invasion and myocardial stress induced cardiomyopathy,

microvascular thrombosis, macrovascular dysfunction, inflammation (increased IL-1.IL-6, TNF-α) related injury (cardiomyopathy) and oxygen supply demand imbalance (type-2 MI) can occurs. Inflammatory cytokines and excess Ang-II activity leads to endothelial activation associated with pro-thrombotic phenotype and increased endothelial permeability. SARS-CoV-2 can directly invade endothelial cells leading to endotheliitis. Myocardial injury associated with elevated Troponin, inflammatory biomarkers (eg. Ferritin, CRP,,D-dimer Pro-BNp and creatinine kinase (CK). Myocardial ischemic incidence is about 7-40% cases.[21]

Myocardial ACE-2 expression is increased in patients with underlying structural heart diseases (SHD). SDH is present in 83.60% of COVID-19 hospitalized patients. The myocardium is positive for SARS-CoV-2 in 65% of autopsy cases and in 91.67% patients have SHD. Myocardial presence of SARS-CoV- 2 was correlated with a significant down-regulation of ACE-2 versus normal hearts.[22] COVID-19 is associated with acute risk of major cardiac events (MACE) including myocardial infarction, stroke and mortality. Risk of MACE was elevated in COVID19 cases at all levels of severity and to a greater extent in cases hospitalized for COVID-19. Hospitalization for COVID-19 represented a coronary artery disease risk equivalent since incidence MACE risk among cases without history of cardiovascular disease was even higher than that observed in patients with cardiovascular disease without COVID-19. Rates of MACE is higher with MI, stroke or all cause mortality in COVID-19 patients are increased immediately after and during the first 30 days after infection as well as up to 2 years after infection. Hospitalization for COVID-19 represents a CAD risk equivalent with post-acute myocardial infarction and stroke risk, particularly heightened in non-O blood type, indicating gene-pathogen exposure interaction for thrombotic events. Non-O group patients (about 60% population) have 2 fold increase CAD risk.[23]

COVID-19 has a spectrum of potential heart manifestations with diverse mechanism. The recent past SARS-CoV-2 can lead to myocarditis, necrosis of the cells mimicking a heart attack, arrhythmias and acute or protracted heart failure. These complications which at times are the only features of COVID-19 clinical presentation have occurred even in cases with mild symptoms and in people who did not experience any symptoms. Recent finding of heart involvement in young athletes, including sudden death have raised concerns.

There is diverse spectrum of cardiovascular manifestations ranging from limited necrosis of the heart (injury) to myocarditis, to cardiogenic shock. Cardiac injury are associated with increased levels of troponin in at least one in five hospitalized patients and >50% of those with pre-existing heart conditions. Patients with marked increase levels of troponin have markers of severe increase of inflammatory biomarkers (CRP, Ferritin, IL-6, LDH, and high neutrophils counts and heart dysfunction (amino terminal Pro-B –type natriuretic peptide.

Myocarditis: usually representing a variable admixture of injury and inflammatory response to the injured heart that can extended throughout the three layers of human heart to the pericardium (infiltration of lymphocytes due to immune and inflammatory response). Involvement of myocytes, which orchestrate electrical conduction, can result in conduction block and malignant ventricular arrhythmias both of which can lead to cardiac arrest. MRI and ECHO study of heart, recently provided some new insight about cardiac involvement: - cardiac abnormalities including ongoing myocardial

inflammation. Majority of SARS-CoV-2 patients hospitalized have shown ECHO abnormalities. [24]

Conclusion

The SARS-CoV-2 (COVID-19) virus binds to the ACE-2 receptor to enter the host cells. ACE2 receptors are present in lung, heart, kidney, liver, brain and other organs. This leads to dysregulation of RAAS system and activation of a pro-inflammatory response with release of cytokines and a pro-thrombotic state. SARS-CoV-2 infection can damage the heart directly infecting myocardial cells, the endothelial cells that line the blood vessels of the heart and multiple vascular beds and indirectly as a result of elevation of systemic inflammatory cytokines. The cardiovascular system affected with complications including myocardial injury, myocarditis, acute myocardial infarction, acute or protracted heart failure, dysarrythmias and venous thromboembolic events. These complications which at times are the only features of COVID-19 clinical presentation have occurred even in cases with mild symptoms and in people who did not experience any symptoms. COVID-19 virus infection is a highly inflammatory disease associated with elevated acute inflammatory blood biomarkers such as CRP, LDH, and Ferritin etc. and in a suspected cases of COVID-19 infection, such biomarkers elevation can be used as diagnostic criteria for COVID-19 infection, as well as x-ray chest, as supplementary to RT-PCR test. Innovative treatment with high dose IV bolus Artesunate appears to be excellent safety profile and very effective for the treatment acute COVID-19 infection may decreases morbidity and mortalities among patients with cardiovascular manifestations. Further double blind placebo control large studies are required.

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