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COVID-19 may Forgotten but not Gone, Currently in Hidden Endemic Form Causing Unseen Havoc Among Older and Persons with Co-morbidities: An Innovative Observational Study on Diagnosis and Management of Clinical COVID-19 infection.

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Abstract

Background: The declaration of end of the COVID-19 (SAR-CoV-2) pandemic since September 2022, when a government determined that the associated public health crisis due to COVID-19 is no longer a threat to the social, economical and political costs of saving a life. Therefore, COVID-19 may forgotten , but it has not gone and persisting in endemic form. The COVID-19 not only a localized respiratory infection, but a multisystem disease caused by complex interplay of immunological, inflammatory and coagulation cascades and it is a heterogeneous disease with genetic and acquired differences in the host immune system with wide spectrum of clinical manifestations varying with age and presence of co-morbidities for its course and outcomes. COVID-19 is a highly inflammatory disease associated with elevated inflammatory biomarkers.

Objective :In absence of RT-PCR test , alternatively tests for clinical diagnosis of COVID-19 infection among highly suspected cases done by elevated acute inflammatory biomarkers criteria; if one or ≥ one of the following biomarkers criteria: such as elevated CRP, Ferritin, LDH, D-dimer and chest X-ray PA view showing pulmonary pathologies with high sensitivity and specificity :

Methods: A consecutive 100 hospitalized cases due to any causes in the Department of general Medicine (VSSIMSAR, Burla, Sambalpur, Odisha, India) were suspected to have COVID-19 infection and evaluated by elevated inflammatory biomarkers criteria and x-ray chest PA view to unravel diagnosis of hidden COVID-19 infection. Along with standard of care a short course (3-5 days) of high dose IV bolus Artesunate twice daily given for severe to critically ill clinical COVID-19 cases.

Results: About 95% of hospitalized cases fulfill the inflammatory biomarkers diagnostic criteria and or x-ray chest findings for hidden COVID-19 infection. A short course (3-5 days) of high dose IV bolus Artesunate twice daily along with standard of care associated with faster decrease of inflammatory biomarkers and faster resolution of symptoms and signs among moderate to severe cases.

Conclusions: Currently, COVID-19 existed in endemic form. Clinical diagnosis of COVID-19 infection can be done by elevated acute inflammatory biomarkers criteria and chest x-ray. A short course (3-5 days) of high dose IV bolus Artesunate twice daily associated with faster decrease of inflammatory biomarkers and faster resolution of symptoms and signs and decrease mortality and morbidity with excellent safety profile.

Keywords: Clinical COVID-19, Endemicity, SARS-CoV-2, Artesunate IV bolus, inflammatory blood biomarker

Introduction

COVID-19 may forgotten , but it has not gone .The end of pandemic, like their beginning is determined not only by the epidemiologic criteria but also by social, political, economic and ethical concerns. Given the challenges associated with eliminating pandemic virus, society have often chosen a less socially, politically and economically costly strategies by accepting as inevitable some deaths among certain groups of people. Pandemic therefore end when society adapts a pragmatic view of the sociopolitical

and economic cost of public health measures, and normalize the associated mortality and morbidity. Endemic disease typically cause occasional community level outbreak without saturating emergency department leading to endemicization. Currently, COVID-19 moves towards endemicity.[1]

After the emergence of less virulent Omicron variants of COVID-19 in November 2021 in South Africa, the virus has continued to rapidly spread due to its increased transmissibility with increasing immune escape from existing hybrid immunity (infection). In September 2022, USA declared that "the pandemic is over" and on April 10, 2023 terminated the COVID-19 national emergency putting COVID-19 in the rearview mirror. Several countries including India decided end of epidemic. There were sporadic cases reports of COVID-19 and surveillance of COVID-19 are no longer performed using RT-PCT test screening. 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. Now the lesser virulent Omicron COVID-19 exists in a hidden endemic form disguised with many faces and unsuspected. It is clear that SARS-CoV-2 will not be fully eradicated. The clinicians and community should keep SARS-CoV-2 in the list of causes of respiratory illness [2] or any acute deterioration of health among older and person with pre-existing co-morbidities needing hospitalization.

It seems that SARS-CoV-2 was moved towards endemicity and the infections are unsuspected, thus undetected. Mutations present in Omicron and its variants have been associated with increased transmissibility with immune evasion. The clinical features of Omicron virus may be asymptomatic, mild or are atypical and often neglected. [3] Mutations in spike protein escape the efficacy of natural immunity acquired by previous infection but with decrease in disease severity and about 20-25% reduced risk of hospitalization in comparison to previous Delta variant. Omicron variant is the predominant strain in U.S, and present in over 90 countries and made up over 58% of all new infections in these nations by December 25, 2021. 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.[4]

Clinical Features Of Hidden Covid-19:

COVID-19 is a complex heterogeneous multisystem disease with wide spectrum clinical manifestations varying with age and presence of co-morbidities. Clinically asymptomatic infection rates of those testing positive for COVID-19 may approximate 33%. The majority of patients have mild disease (80%). Although symptomatic COVID-19 patients exhibit a variety of signs and symptoms, most present with fever, changes in taste and/or smell (64-80%), myalgia, headache and respiratory tract symptoms such as cough (60-86%), shortness of breath (53-80%).Fever present in approximately half of patients at the time of initial presentation but overall present in 20-99% patients. However, there are no clinical features with high enough specificity to reliably differentiate COVID-19 from other infections. 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. [5]

Methods: **Suspicion Of Clinical Covid-19 And Innovative Strategies To Unveil Diagnosis Of Hidden Covid-19 Infection:**

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 copies/µl), different stages of infection, the skill of sample collection and the quality and consistency of the PCR assays being used.[6] In a systemic review of five studies among 957 patients by Steven et al, false RT-PCR negative results reported from 2-94%. (Fig.1).Thus, there are frequent false negative RT-PCR results and the clinicians should assume a negative result as 'false negative' in a person with typical symptoms and signs.[7] Currently, due to declaration of end of COVID-19 pandemic, it has been in endemicization and RT-PCT tests are not done routinely . The clinical manifestations COVID-19 are so subtle or atypical that, neither the treating physician nor the affected patients aware at the time of

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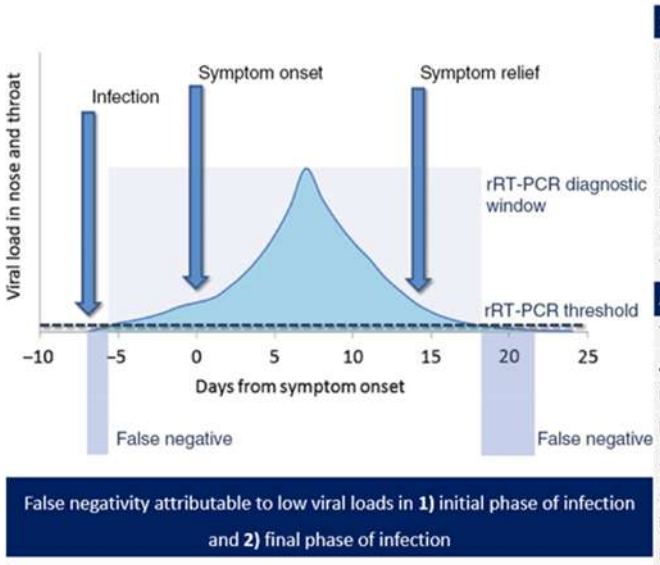
hospitalization for any medical reasons. When patients have history of fever, myalgia, arthralgia Elisa tests are done to exclude dengue, malaria, Scrubtyphus etc due to similar clinical features. The paradox is that there are incidences of false positive laboratory reports of dengue, malaria, Scrubtyphus, Hepatitis C, HIV etc. due to molecular mimicry of SARS-CoV-2 RNA, misleading and misguiding the physicians for the diagnosis and management. There are also incidences of multiple Elisa test positive in a single case. Therefore, the treating physician should very carefully correlate these laboratory reports with patient's detail clinical history and physical examinations in the epidemiological context.

Fig.1. Showing probability of false negative RT-PCR test.



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

Innovative Surrogate Diagnotic Tests For Suspected Hidden Clinical Covid-19 Infection:-

COVID-19 infection is a highly inflammatory disease associated with elevated acute inflammatory bio-markers. Therefore, any patient presented with or without any signs or symptoms of COVD-19 particularly elderly, obese and person with co-morbidities with acute exacerbation of health needing hospitalizations should be suspected to have underlying COVID-19 infection as the cause or exacerbating factor. To unravel the diagnosis of hidden COVID-19 infection diagnostic inflammatory biomarkers criteria can be done with panel of acute inflammatory serum biomarkers to determine the elevated bio-markers sensitivity and specificity for the diagnosis of hidden COVID-19 a surrogacy to RT-PCR test and by analyzing ROC curve, calculating the AUC and the cutoff value with a specificity of 89% was considered for following elevated blood biomarkers to met the diagnosis of COVID-19 infection: 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,(AUC = 0.847 and 0.804 in women and men, respectively).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) in comparison to RT-PCR, (91% of COVID-19 patients met one or more of the diagnostic inflammatory biomarkers criteria). Thus, these criteria can be used as a screening surrogate test to differentiate patients with and without COVID-19 infection. [9] (**Table. 1**). Additionally, X-ray chests PA view to detect abnormal pulmonary

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pathology further increase the diagnostic sensitivity and specificity of COVID-19 infection. Currently, about 95% of hospitalized patients in the department of Medicine,(VSSIMSAR,Burla,Odisha India) irrespective of their initial presentations meet the diagnostic criteria for underlying COVID-19 infection as a cause or exacerbating factor of existing co-morbidities. However, absences of elevated bio-markers or pulmonary involvement in chest x-ray alone, does not exclude diagnosis as it depends on host response, severity, system involved and stages of disease progression.

Table. 1. Sensitivity and specificity of 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

RESULTS:- OBSERVATIONS ON ELEVATED INFLAMMATORY BIOMARKERS CRITERIAS AND X-RAY CHEST AMONG CONSEQUITIVELY HOSPITALIZED 100 CASES IN THE DEPARTMENT OF MEDICINE. (Table.2.)

Table.2. Showing diagnostic elevated inflammatory biomarkers and pulmonary pathologies among 95% (95/100) of hospitalized cases.

Major Diagnostic Findings	**Percentages of cases**	**Major Diagnostic Findings**	**Percentages of cases**
CRP level ↑	87%	Abnormal x-ray chest + normal level biomarkers	4%
Serum Ferritin ↑	87%	Normal x-ray chest + raised biomarkers	5%
LDH ↑	87%	**Normal x-ray +normal biomarker**	5%
CRP+ Ferritin↑	56%	Age -20-39=24%, 40-50=15 %, 51-60=39%, 61-70=28%, 71-80=11%.	(≥ 50 years-75 %,)
CRP+ Ferritin+ LDH ↑	17%	Known co-morbidities present	78%

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Abnormal pulmonary pathologies only in X-ray chest PA View -	48%	Common co-morbidities: CKD, Cirrhosis, HTN, T2DM, Sickle cell disease, Obesity, ischemic stroke, Acute CVD.	
Abnormal pulmonary Pathologies & ↑markers-	46%		

Innovative Strategies For The Treatment Of Clinical Covid-19:

SARS-CoV-2 infection and immunity dysfunction are the two main courses driving the pathogenesis of COVID-19. Both the virus and host factors are potential targets for antiviral therapy. Hence, the current therapeutic strategies of COVID-19 have been classified into "**target virus**" and "**target host**" categories. In the early stage of infection progression, it is primarily driven by the robust viral replication cycle, which is mainly modulated by viral proteins. In the later stage of infection progression, it is driven by tremendous inflammatory/immune response (host factor) to SARS-CoV-2 that results in tissue damage.[10] Currently, the antiviral drugs used for treatment of COVID-19 are Remdesivir , Molnupiravir, Nirmatrelvir-Ritonavir (Paxlovid) etc. These antiviral therapies should ideally be started between the onset of symptoms and around the day of 5, during this period of robust viral replication for better effects. These antiviral target only on the early viral replication stages (viral factor), but not effective when started later during the hyperinflammation host response stages (host factors) when there no robust viral replication. Therefore, an ideal anti-COVID-19 drug used should be effective against both factors to prevent mortalities and morbidities.

Artesunate effectiveness in clinical trial of COVID-19 patients: In a prospective study of 43 cases of RT-PCR positive COVID-19 patients divided into routine treatment group (n=25) and Artesunate group (n=18), 60 mg IV twice daily along with routine treatment for 10 days. Among Artesunate group, time for significant improvement of symptoms was (days: 3.33±1.91 vs. 4.84±2.19), RT-PCR negative conversion time was (days: 4.72±2.16 vs. 6.68±3.76), lung lesion absorption starting time (days: 5.39±2.36 vs. 7.48±3.78), lung lesion absorption > 70% time (days: 14.11±4.16 vs. 17.04±4.42) and length of hospital stay (days: 16.56±3.71 vs. 18.04±3.97) were significantly shorter among Artesunate group, than those in routine treatment group with fewer adverse reactions.[11]

SCIENTIFIC RATIONALE OF HIGH DOSE IV BOLUS ARTESUNATE THERAPY FOR COVID-19 INFECTION:- Ruiyuan Cao, et al in their in vitro study, found the EC_{50} of Artesunate (AS) had 12.8±5.30µM and that of Dihydroartemisinin (DHA) had 13.31±1.24µM against SARS-CoV-2, indicating AS, is a potential countermeasure against COVID-19 infection. Artesunate could inhibit SARS-CoV-2 replication in a dose-dependent manner and might function at the post-entry stage of SARS-CoV-2 and inhibited by AS and DHA.[12] Bae JY et al, in their study in Vero cells, shown that AS inhibited SARS-CoV-2 replication with IC_{50} of 53.06 µM, CC_{50} of > 100 µM. Interestingly, in Calu-3 cells**,** (which are derived from human airway epithelial cells was more representative of susceptible cells in actual human airway infection) AS inhibitory effect had IC_{50} of 1.76 µM,CC_{50}> 100 µM, better than in Vero cells and reduced viral replication in a dose-dependent manner .[13] After 120mg of bolus IV AS produce Cmax of 11,343ng/ml (42µM) with t½ of 0.05 hrs and Cmax of DHA was 2,646ng/ml with t½ of 0.67 hrs (total 13,987ng/ml), [14] which were greater than EC_{50} of Artesunate and DHA against SARS-CoV-2. In another study 120mg IV bolus Artesunate produced Cmax of 29.5 µM with elimination $t^1/_2$ of 2.7 min and Cmax for DHA was 9.3 µM with t $^1/_2$ of 40 min and 100mg oral AS produce DHA Cmax of 2.6 µM only with t $^1/_2$of 39 min.[15] Gilmore K et al in vitro Vero E6 cells study: Artesunate EC_{50} had 7-12 µg/ml or (0.7-1.2 µM) was more potent artemisinin. The Cmax of AS exceeding EC_{50} can be achievable clinically in plasma and tissue concentrations of 15µg/ml and the typical doses of 2.4 mg/kg IV bolus produces Cmax of AS between 19.4 and 29.7µg/ml. In animal studies tissue concentrations including lung, kidney, intestine, and spleen were

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several-fold higher than plasma concentrations.[16] Artemisinins administration leads to autoinduction of hepatic drug metabolism and reduces its own bioavailability. The plasma concentrations of same daily dose of AS were ⅓rd less on day 3 onwards than on day 1.[17] The PK variability following 120mg IV AS with Cmax occurs with first exposure and Cmax variability ranges from 735-1890ng/ml (AS+DHA) and this variability was 25 fold among different clinical trials and this inter individual variability in some patients may have low Cmax associated with treatment failure in malaria. Thus, low dose regimen of AS to be avoided in treatment of viral diseases particularly in Covid-19 infection .[18] To achieve antiviral effects serum concentration of Artesunate should be >10µm and high dose (4mg/kg.bw or 240mg) IV bolus Artesunate is preferred to achieve higher free peak plasma levels (Cmax) of Artesunate and DHA with higher bioavailability to enter the human cells to inhibit SARS-CoV-2 replication effectively circumventing the PK/PD variability. [19] Patients with severe COVID-19 may also have many critical and variable conditions, co- morbidities with variable severity scores that may determine the drug's PK/PD characteristics and prognosis. The 4-8mg/kg loading dose is safe and in phase I-II study, IV AS 4-8mg/kg loading doses were extremely well tolerated in humane volunteers and malaria patients.[20] Artesunate Cmax is more important than AUC producing improved anti-COVID-19 efficacy and high dose IV bolus Artesunate provide sufficient high Cmax in patients avoiding inter-individual variability in PK/PD. Artesunate IV bolus injection following 4mg/kg produce Cmax of 36,100ng/ml and following 8mg/kg IV bolus ,Cmax of 89,340ng/ml, [21] Doses intervals for IV bolus Artesunate have not been determined. Therefore, in absence of well controlled dose-ranging studies and valid pharmacodynamic relationships, widely used empirical regimens remain unchallenged.[15] Coronavirus replication cycle is around 8-10 hrs.[22,23]Artesunate has Cmax dependent effects and high dose AS IV bolus (within 2-10 minutes) initiated at interval of 8-10 hr or 12hly can achieve higher plasma Cmax can be given for a short course of ≥ 3 to 5 days to cover 9 to 15 replication cycles of COVID-19 in the early stage of robust viral replication to inhibit viral replication , and to prevent disease progression as well as avoiding auto-induction of its own metabolism and low Cmax. Besides its antiviral effects, Artesunate have anti-inflammatory, immunomodulatory, antioxidant, anticytokine, anti-fibrotic and organs protective effects in hypoxia etc , thus effective even started in later stages of disease progression to reduce morbidity and mortality among patients with COVID-19 infection. [24 25, 26] Ghodke BA, et al. in a comparison study of 130 RT-PCR positive COVID-19 patients, 65 received add on bolus IV artesunate (2 mg/kg body weight) therapy followed by 2 mg/kg body weight after 6 h and 2 mg/kg body weight for next 2 days at an interval of 24 h) with the standard of care (SOC) versus 65 patients SOC only. About 93.8% of patients (61) recovered in Artesunate group compared with 72.3% of patients (47) recovered in SOC group. The overall death in Artesunate group was 6.2% (4/65) versus 27.7% (17/65) in SOC group ($P < 0.05$).[27]

Choice of Antibiotics with anti-COVID-19 effect for moderate to severe/critically ill COVID-19 hospitalized patients:-

Injection Cefepime and Ceftazidime are efficient for the management of moderate and severe cases of COVID-19 due to their potential anti-SARS CoV-2 activity and low side effects. The dose of either cefepime or ceftazidime was 1000 mg twice daily for five days. The mean recovery time for cefepime group (124) was 12 days, for ceftazidime group (136) was 13 days, and for control group (110) it was 19 days. Both ceftazidime and cefepime showed very good inhibitory activity towards SARS CoV-2′s M^{pro}, with IC_{50} values of 1.81 µM and 8.53 µM, respectively.[28]

Treatment of mild to moderately severe COVID-19 cases those able to take oraly treated with ACT-Artemether-Lumefantrine and Cefuroxime:-

(1).**Antimalarial ACT**: - In mild to moderate cases of COVID-19, patients who are able to take orally and clinically stable patients can be treated with a Artemisinin based Combination therapy (ACT) eg. Artemether - Lumefantrine (10mg/kg of Lumefantrine dose) as used in malarial for three days with fatty food is very safe and cost effective.[29] ACT –Artemether-Lumefantrine had SARS-CoV-2 clearance by day 7 was 56% (viral load 81(21-209)copies/ml VS 41% (viral load of 855-2883 copies/ml) by Pyronidine /Artesunate among patients co-infected with malaria and at day 14 was 96% vs 80%.[31]

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(2).**Oral Antibiotic:-** Cefuroxime is a broad spectrum antibacterial agent effective against associated bacterial infection, is the choice of oral antibiotic use for the treatment of mild to moderately severe COVID-19 infection. Several studies have reported cefuroxime as a potential inhibitor of three essential SARS-CoV-2 proteins; main protease, RNA-dependent RNA polymerase (RdRp) and ACE2-Spike complex.[32] Cefuroxime works as a multitarget inhibitor for 3 - SARS-CoV-2 proteins. Cefuroxime bind covalently irreversible bond with cys-145 of the active site of main protease (M^{Pro}) protein of SARS-Cov-2. Many studies reported that Cefuroxime may inhibit M^{Pro}. One study reported Cefuroxime may inhibit RdRp, while another reported Cefuroxime may inhibit the ACE-2 spike proteins binding complex. [32, 33, 34].

Conclusions:-

The end of COVID-19 pandemic has been declared since September 2022. At the end of the pandemic there was normalization of mortality and morbidity by means of routinization of disease and endemicization of COVID-19.Therefore, COVID-19 may forgotten but it has not gone. COVID-19 infection is a highly inflammatory disease associated with elevated inflammatory biomarkers, such as CRP, LDH, Ferritin, D-dimer levels. Diagnosis of clinical COVID-19 infection among highly suspected moderate to severe cases can be done by elevated inflammatory biomarkers criteria along with chest x-ray pulmonary pathologies with high sensitivity and specificity alternative to RT-PCR test. Surprise to our knowledge ≥ 95% hospitalized patient in the department of medicine fulfill the inflammatory diagnostic biomarkers criteria and/or x-ray chest have hidden COVID-19 infection a paradigms shift as a cause or exacerbating factor of pre-existing co-morbidities. Uses of high dose IV bolus Artesunate have anti-SARS-CoV-2 effects along with multiple favorable pleotropic effects on host. A short course of IV bolus Artesunate (240mg) twice daily for 3-5 days among moderate to severe / critically ill clinical COVID-19 along with standard of care injection Cefipime 1 gm IV twice daily associates with faster resolution of symptoms and signs and decreased morbidity and mortality with excellent safety profile. For less severe patients those able to take orally were treated with ACT – Artemether-Lumefantrine with fatty food twice daily for 3 days and oral Cefuroxime (500mg) twice daily for 5-10 days with high efficacy. Sequential ACT – Artemether-Lumefantrine and Cefuroxime was given to those able to take orally after 3 days of IV bolus Artesunate. We have treated more than twenty thousands of hospitalized moderate to severe/ critically ill COVID-19 cases since 1st November, 2020 to till date March, 2026, from the Alpha through Delta to Omicron waves with excellent results. (Unreported).

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