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AN OVERVIEW ON COVID-19 COMPLICATIONS (PULMONARY & EXTRA PULMONARY COMPLICATIONS)

Pulmonary Medicine

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ABSTRACT

Covid-19 is a respiratory illness caused by Novel corona virus , declared as pandemic by world health organization, as it affected globally and destroying worldwide economy and throwing challenges to various health care systems. Till date there is no clear pathophysiology, but most widely accepted mechanism is systemic inflammation – clinically significant inflammation is coagulopathy . Most of the literature presently available is on the treatment and management protocols of coivd 19 infection. Covid infection mainly affects respiratory system and there may be multi organ involvement in critically ill patients due to cytokine storm. Post covid infection phase is also as important as covid-19 infective phase. As we see persistent symptoms and few pulmonary and extrapulmonary complications during covid and post covid phase. So we will be discussing regarding the complaints and complication observed in the covid and post covid phase .

KEYWORDS

Covid, Pulmonary , Extrapulmonary, Complications , Inflammation , Cytokine Storm

INTRODUCTION:

Covid- 19 is a viral respiratory infection with frequent fatal lung complications in elderly or people with serious co morbidities. Lung destruction appear to be associated with cytokine storm related to increase levels of IL-6. Cytokine storm leads to multi organ involvement. Although there is not enough data to definitely establish and characterize the post covid syndrome, potential long term complications co-sequences can be inferred from emerging data. However there is no substantive discussion of potential long term effects of covid infection. After recovery, patient remains at risk for lung , heart disease and other mental health disorders. This may be also long term sequale of adverse events that developed in course of covid infection and its treatment. These complications likely to place additional medical, psychological and economical burden on all patients.

Many patients present with fever, cough, shortness of breath, myalgia , Upper respiratory tract infection with loss of taste and loss of smell during infective covid phase. Especially in post covid phase most common symptom we come across is fatigue, dyspnea (1) . Rapid detoriation can occur/ ventilation perfusion mismatch ranging from shunts to alveolar dead space ventilation is the central hall mark and affects various therapeautic targets. Happy hypoxemia - profound hypoxemia yet without proportional to signs of respiratory distress seen in not only covid patients but also seen in patients with Atelactasis and Arterio venous malformations. Main causes of hypoxemia in covid-19 are (2)

A. Intrapulmonary shunting
B. Loss of lung perfusion regulation
C. Intravascular Micro thrombi
D. Impaired diffusion capacity

So main pulmonary and extra pulmonary complications observed in covid 19 infected patients are:-

SL. NO	ORGAN AFFECTED	COMPLICATIONS
1.	Lung	Pulmonary scarring / Pulmonary fibrosis /Pulmonary embolisim / ARDS / Pneumonia
2.	Heart	Myocardial Injury / Cardiac Arrhytmia / Sudden cardiac Death / Heart failure
3.	Gastro Intestinal Hepatic	Loss of apetite / Diarrhea / vomiting Elevated enzymes / Elevated Bilirubin
4.	Renal	Acute Kidney injury / Renal failure / Haematuria / Protenuria
5.	Immune & Haematological	Septic shock / DIC / Thromboembolisim
6.	CNS	Strokes / seizures / GB Syndrome / Anosmia / Myalgia Increases risk of Parkinsons & Alzheimers disease
7.	Psychology	Anxiety / Fear / Frustration
8.	Reproductive system (Female)	Adverse pregnancy outcomes
9.	Endocrine	Hyperglycemia / Diabetic keto Acidosis

1.Lung Injury :

Although covid 19 mainly manifests as lung infection with symptoms ranging from mild upper respiratory tract infection to severe pneumonia , ARDS , Lung fibrosis and pulmonary embolisim.

Acute respiratory failure is the main leading cause of death. Lungs might not pump enough oxygen in to blood or might not take enough carbon dioxide out. Both these problems can appear at same time.

In pneumonia air sacs in lung becomes inflamed, making it harder to breath. If we see images of critically ill covid-19 patients, we can see lung filled with pus,fluid and cell debris.

Acute Respiratory Distress syndrome (ARDS) is one of the most common complication .Lungs are severely damaged ,that fluid begins to leak in to them. As a result body has trouble getting oxygen in to blood stream . You may need mechanical help to breath such as ventilator.

Pulmonary fibrosis results due to acute lung injury, attempt at repair by fibroproliferation and lung remodeling occur in covid disease. This leads to increase in risk of pulmonary fibrosis as a sequale of covid 19 infection. Once pulmonary fibrosis occurs there will be architectural distortion and irreversible lung dysfunction. Alveolar macrophages plays central role in process of phagocytising alveolar debris and production of cytokine and growth factor involved in repair (3) Risk factors for pulmonary fibrosis are Age, illness severity , length of ICU Stay and mechanical ventilation, smoking and chronic alcholisim .

Pulmonary embolisim – Thrombotic complications in patients with covid 19 infection are emerging as important sequale that contribute to morbidity and mortality. Pulmonary embolisim , Deep vein thrombosis ,Ischemic stroke, Myocardial infarction are examples of complications. Patients with covid-19 with following below mentioned features trigger thrombotic tendencies.

A. Excess inflammation
B. Hypoxia
C. Immobilization
D. Disseminated Intravascular coagulation (DIC)

Patients with covid infection receiving statin therapy prior to admission are less likely to develop pulmonary embolism . Statins are associated with decreasing risk of venous thrombo embolism and recurrent pulmonary embolisim (4).

2. ACUTE KIDNEY INJURY (AKI):

Kidney is one of the most common extrapulmonary organ involved in severe critically illed covid affected patients (5) . Mechanism of AKI is mainly due to maladaptive response of the immune system that induces cytokine storm and could be responsible for systemic inflammatory response syndrome induced AKI (6) . Critically ill patients requiring Mechanical ventilation , vasopresors drugs and nephrotoxic drugs all can aggrevate AKI. AKI is also found to be important risk factor for increasing hospital mortality (7) .

Rhabdomyolysis common finding in covid-19 affected patients, can lead to elevated serum Creatinine phosphokinase (CPK) more than 5 times to the baseline can lead to AKI (8) . Haemosiderin granules seen in tubular cells (9) .

As covid-19 induces thrombotic events- post mortem histopathology of kidney tissue who died of covid-19 observed severe tubular necrosis (9) (As virus binds to ACE2 receptor and this receptor rich in Tubules) and Erythrocyte aggregates obstructing peritubular capillaries and segmental thrombin in glomeruli. Few studies in covid-19 affected patients showed that there will be mild protenuria with increased Creatinine and Nitrogen levels.

AKI may be due to both Respiratory distress syndrome induced hypoxia and septic shock caused by SARS Cov2.

Sub clinical AKI (10)–Occurrence reflected by – Biomarkers of Tubular Damage

a) Increased Urinary levels of Beta 2 microglobulin
b) Increased urinary levels of alpha 1 microglobulin
c) N Acetyl Beta Glucosaminidase
d) Retinal binding protein

However large clinical trials are needed to test the risks and benefits of rigorous interactions in covid 19 patients specifically at risk of AKI.

3. Cardiac Complications:

Covid-19 infection cause direct or indirect cardiovascular sequale including Myocardial injury , Acute coronary syndrome , Cardiomyopathy, Acute Cor pulmonale, Arrhytmia and cardiogenic shock. Angiotensin Coverting enzyme-2 ACE2 has high expression in cardiovascular tissue including cardiac myocyte , fibroblast , endothelial cells, smooth muscle cells(11) .In view of direct viral injury - Myocarditis is presumed etiology of cardiac dysfunction. Isolation of virus from myocardial tissue has been reported in few autopsies. Direct viral infection to endothelium causing inflammation leading to Myocardial Infarction with circulatory failure. Cytokine storm is also another mechanism for myocardial injury. Patients with covid infection has high risk of MI(12) due to Hypercoagulability in affected people – Thrombotic mediated MI. Primary PCI is preferred approach in these patients.

Do not discontinue ACE /ARB in patients who are already on them at home (13) . Prefer ECG especially in patients who are receiving QT Prolongation drugs. Signs of myocardial injury reflects by increasing Trop – I and N-Terminal Pro BNP. Raise of cardiac Trop – I together with Pro – Inflammatory markers such as IL-6, LDH, D – Dimer might be an indicative of cytokine storm (14).

Cardiac Arrhytmia (15):

Another important cardiac complication in covid infection ranges from Tachycardia , Bradycardia and Asystole.

Sudden Cardiac Death mainly due to imbalance of Pulmonary ventilation perfusion ratio and decreasing capacity of pulmonary vasculature .

4. Liver Dysfunction / GI Complications :

GI Symptoms like Nausea , Vomiting , Diarrhea , Abdominal pain and loss of apetite may be associated with longer duration of illness. But have not been associated with increased mortality (16). Usual findings will be Increased hepatic Transaminase , Increased Bilirubin and Decreased albumin. Mild elevation of hepatic transminase levels should not be considered as contraindication to treatment.

Pathophysiology : Probably Multi factorial

a. Virus mediated direct tissue damage, in presence of ACE 2 receptors in Intestinal glandular cells (17) . visualisation of viral nucleocapsid protein in gastric, duodenal and rectal epithelial cells. Viral RNA isolated from stools with positivity rate of 54 percent (18) .

Live viral shedding of infectious virions in faecal matter has been reported even after resolution of symptoms. This needs further evaluation as potential source of transmission (17). Alteration of intestinal flora by virus may contribute to GI symptoms and severe disease progression (19).

Hepato Biliary Manifestations :

In severe critically ill patients , aminotransminase are typically elevated . But remains less than five times of upper limit of normal. Rarely Acute hepatitis is noted (20) . Elevated bilirubin at hospital admission time has also been linked to disease severity and progression to critical illness (21) . SARS Cov 2 can damage hepato biliary tree by binding to ACE2 receptor on cholangiocytes (22) . Hyper Inflammation seen with

a. Cytokine storm
b. Hypoxic Associated Metabolic Derangements (14)
c. Drug induced liver injury secondary to drugs like Remdesivir, Toclizumab , Lopinavir (23) .

One has to monitor Transaminase levels frequently when patient is receiving above mentioned treatments. Additional diagnostic tests are not needed for aminotransferase elevation unless additional features raises probability of findings like Increased bilirubin , Right upper quadrant pain and hepatomegaly (24) .

5. Haematological Manifestations :

Patient coming with covid infection may present with various lab abnormalities and Thrombotic complications. Common findings seen are

a. Lymphopaenia :- Cardinal lab finding. Marker of impaired cellular immunity. Low CD4 T cells is associated with severe covid-19 infection (25) .

b. Neutropaenia / Neutrophilia :- Neutrophilia less commonly seen. It is also a Negative prognostic marker (26) . Can be seen in some secondary bacterial infections or seen as a consequence of hyper inflammatory response to infection .

c. Thrombocytopaenia :- Although often mild associated with worse patient outcomes (27)

d. Coagulopathy:- Marked by increase in D-dimer and fibrinogen with minor abnormalities in PT / APTT / Platelet count in the initial stage of infection(28) . Thrombotic complications seen in arteries , veins and catheters . D – dimer increased at the time of admission and further elevation during hospital stay have been linked with increased mortality.

e. Inflammatory Markers :- Increased CRP / ESR / IL -6 / LDH

Lymphopaenia is mainly due to direct cytotoxic action of virus related to ACE-2 dependent / ACE- 2 independent entry in to lymphocyte (29) , leading to apoptosis mediated lymphocyte depletion. Atrophy of spleen / Destruction of lymphoid tissue seen in SARS and Covid infection. There will be inhibitory effect of lactic acid on Lymphocyte proliferation.

Cytokine release syndrome is usually associated with High grade fevers , Hypotension and Multi organ dysfunction - Mainly due to diffuse microvascular damage and is important cause of death in critically ill covid infected patient . Strongly consider Pharmacological prophylaxis for Venous Thrombo Embolisim in absence of absolute contraindications like Active bleeding or Thrombocytopaenia. Coagulation disorders and DIC plays an important role in increasing the risk of hospital mortality .Consider post hospitalized extended thromboprophylaxis particularly for those who had history critical illness. Parentral anticoagulation is preferred over oral anti coagulation especially in In Patient because of shorter half life and ready availability of reversal agents due to possibility of drug to drug interactions when they taken with Anti viral treatment such as Ribavarin and Antibacterial as Azithromycin.

Few of Autopsy studies on covid infection patient shows that high rates of micro and macro vascular thrombosis seen , especially in pulmonary circulation (30) .

6. Neurological Manifestations :-

Neurological symptoms can be divided in to 3 main clinical presentations.

a. Central Nervous system : - Headache, Dizziness , Acute cerebro vascular disease , Altered consciousness , Epilepsy.
b. Pheripheral Nervous system : - Anosmia , Ageusia , Loss of apetite
c. Skeletal muscle injury

Number of non specific and mild neurological symptoms are noted in covid infected hospitalized patients like Headache, Dizziness, myalgia

, fatigue, anorexia and loss of smell and taste (31). Direct viral invasion of neural parenchyma is possible. SARS COV2 may access central nervous system via Nasal mucosa / lamina cibrosa and olfactory bulb or via Retrograde axonal transport . Nasal epithelium has highest expression of ACE2 in respiratory tree (32) . This may lead to symptoms of altered sense of smell and taste. Proinflammatory and prothrombic cascade in wake of cytokine storm as it affects brain vasculature and blood brain barrier especially in settings of toxic metabolic sequale of multi organ dysfunction often seen in covid associated critical illness. Very rarely we also observe encephalopathy , encephalitis, GB Syndrome (33) . We have to delay the dosing of chronic immunomodulatory therapies in conditions such as multiple sclerosis in covid infection .

7. Endocrine manifestations :-

Patient with diabetes and obesity are more prone to develop covid-19 infection (34) . Most common issue we see from endocrine part of view are :-

a. Hyperglycemia
b. Ketoacidosis
c. Euglycemic ketosis
d. Severe illness in patients with pre existing diabetes or obesity.

Consider every patient for random sugar check for both diabetic and non diabetic patients. In case of non diabetic with hyperglycemia , measure Hb1AC. Early initiation of treatment for Diabetic ketoacidosis and consider glucose monitoring more frequently , who are on insulin drip. Consider increasing the dose of insulin in patients who are on steroids. As steroids can cause hyperglycemia. Avoid oral Hypoglycemic drugs due to potential renal damage, cardiac and hypoglycemia complications. Due to substantial elevation of cytokine levels may lead to impairment of pancreatic beta cell function and apoptosis. Consequently lead to decreased insulin production. ACE 2 expression has been reported in endocrine pancreas(35). Direct binding of SARS -2 to ACE 2 on beta cell might contribute to Insulin deficiency and Hyperglycemia. Obesity another risk factor for severe illness in covid infection(36) may be related to effects of pulmonary function such as reduced lung volume, reduced compliance and increased airway resistance,as well as an association with diabetes (37).

8. Covid-19 Infection in Pregnancy :-

Viral pneumonia is an important cause of morbidity and mortality among pregnant women (38) .. Maternal pneumonia associated with several adverse obstetricial outcomes including (39) Premature rupture of membranes (PROM)-

a. Pre Term Labour
b. Intra Uterine foetal death (IUFD)
c. Intra Uterine growth retardation (IUGR)
d. Neonatal death

With limited evidence exists, there is no vertical transmission of covid infection from pregnant mother to foetus . Infected mother can transmit covid-19 virus through respiratory droplets during breast feeding.

CONCLUSION :-

Covid infection mainly affects respiratory system and there may be multi organ involvement in critically ill patients due to cytokine storm. Covid-19 infection has to be managed aggressively especially in high risk individuals , both in covid phase and post covid phase. So that we can avoid both pulmonary / Extra pulmonary complications and also long term sequale due to covid-19 infection. Good amount of anticoagulation has to be initiated at earliest, especially to high risk hospitalized patients during the covid phase and also in post covid phase , so as to avoid thrombotic complications. Accordingly comprehensive knowledge of these complications will help health care providers to be attentive to these complications and diagnose and treat timely.

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