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Post COVID Cardiopulmonary Symptoms: Self-limiting or life threatening? (An unexplored and mysterious status): Needs evaluation

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Abstract: A good proportion of patients complain of cardiopulmonary symptoms even after COVID recovery. Post-COVID symptoms were reported most often as mild and self-limiting. On the other hand, severe post COVID cardiopulmonary complications had also been reported. Therefore, the status of extent and severity of underlying cardiopulmonary disease in this group of patients is very mysterious. Evaluation of underlying disease in such patients is extremely essential. Whereas evaluation is a tough challenge during this COVID pandemic due to the high epidemiological burden of symptomatic post COVID patients. Therefore a systemic review was conducted, collecting and compiling all the literature related to post COVID cardiopulmonary symptoms to understand their pathophysiology and severity of underlying disease. At the same time, an attempt was initiated to derive an approach and strategy for evaluation. During analysis, we obtained useful information as described below. Post COVID cardiopulmonary symptoms can arise due to causes like cardiac, pulmonary, psychogenic, neurogenic, and endocrine, etc. COVID manifests a spectrum of post COVID cardiopulmonary sequelae like myocarditis (2/3rd cases), pericarditis (3% cases), pericardial effusion (5% cases), LV dysfunction (12% cases), pulmonary fibrosis (20% cases), pulmonary function abnormalities (40% cases) etc., which can manifest cardiopulmonary symptoms in post COVID patients. However, the extent and severity of cardiopulmonary involvement is very limited. Reported abnormalities during cardiopulmonary evaluation were found to be mild and self-limiting. However, there is higher chance of developing life threatening complications like pulmonary embolism, acute coronary syndrome, left ventricular failure and arrhythmia in a few rare post COVID cases due to the persistence of hyper inflammatory and hypercoagulable states. Stratification of cases based on past history, records during acute COVID period, clinical findings and biomarkers, can guide in identifying high risk cases. A selective, systemic, and step wise clinical and laboratory approach can help in proper evaluation of patients. However, exclusion of other non COVID

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related causes is extremely essential, before designating symptoms as post COVID symptoms.

Key word: Post COVID, Cardio-pulmonary symptoms, Sequelae, Evaluation, Strategy

Introduction

COVID 19 became the deadliest pandemic that ever happened. It sustains its inflammatory and hypercoagulability state in patients, even months after its recovery (1, 2). Therefore, a good proportion (10–35% overall and 80% hospitalized) of patients manifest with post COVID symptoms (3, 4). Post COVID symptoms were reported most often as mild and self-limiting (5). As ACE II receptor is the main target for entry pathway in COVID infection and found most abundantly in heart and lung,(6) therefore majority of patients presents with persistent cardio pulmonary symptoms as manifestations of post COVID sequelae (6). Life threatening cardiopulmonary complications [like pulmonary embolism, pulmonary artery hypertension (PAH), myocarditis, and extensive pulmonary fibrosis] also have been reported among patients after COVID recovery (7-11). Therefore the status of severity and extent of underlying cardiopulmonary disease is unclear. Evaluation of underlying disease in patients with such symptoms is extremely essential. On the other hand evaluation of post COVID cardiopulmonary symptoms is a tough challenge during this COVID pandemic, as epidemiological burden of symptomatic post COVID patients is disproportionately higher with respect to limited health resources and manpower. Therefore, a systemic review was conducted with following objectives

1. To understand pathophysiology of cardiopulmonary symptoms in patients after COVID recovery.
2. To discuss the approach for evaluation based on pathophysiological causes of post COVID cardiopulmonary symptoms
3. To discuss the severity of underlying cardiopulmonary disease in patients with post COVID cardiopulmonary symptoms
4. To discuss a strategy for proper evaluation of post COVID cardiopulmonary symptoms with limited health resources and manpower.

Methodology: A systematic search was performed using PubMed, EMBASE, and Scopus databases. A list of terms relating to post COVID cardiopulmonary symptoms like dyspnea, chest pain, syncope, cough etc. has been utilised to find relevant articles. English literatures published between July.2020 to July 2022 detailing follow-up period longer than 4 weeks from the onset of COVID 19 infection (in accordance with the timeline prescribed for the post COVID period by integrative classification for post COVID symptom)(12) were included. Studies not meeting the inclusion criteria were excluded. All the relevant articles were collected and compiled. Data synthesized and analysed systemically in order to achieve the study objectives.

Definition: As per integrative classification, symptoms arising within 4 weeks of detection of COVID were considered COVID related symptoms. Whereas symptoms that continue, relapse or remit after 4 weeks of COVID infection were considered post COVID symptoms. Such symptoms are further classified as: acute post-COVID symptoms (from week 5 to week 12), long post-COVID symptoms (from week 12 to week 24), and persistent post-COVID symptoms (lasting more than 24 weeks) (12).

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Pathophysiology of cardiopulmonary symptoms: Patients manifest a spectrum of clinical cardiopulmonary symptoms like dyspnea, fatigue, chest pain, cough, syncope, etc. during post COVID period. Such symptoms can arise in patients due to post COVID cardiopulmonary sequelae arising from complex pathophysiological phenomena as described subsequently. ACE II receptor is the primary pathogenesis pathway for COVID virus infection (6). As ACE II receptor more abundantly found in heart and lung, therefore such organs are mainly victimized during deadly COVID infection (6). By releasing IL1, 6 AND TNF alpha through this receptor, the virus volcanizes a cascade of inflammation hosting different inflammatory cell and breaking the structural integrity of cardiovascular and pulmonary structures (6). Besides COVID 19 disarranges coagulation system, platelet function, micro vascular integrity resulting a hypercoaguable state (13).Unlike other viruses like MERS, SARS , COVID 19 sustains its inflammatory and hypercoagulable state for a pretty long period after COVID recovery,(1-2) leading to disastrous post COVID complications . Persistent inflammation in myocardium has been reported in 70-80% of post COVID cases (14). Chronic recurrent myocarditis can cause diastolic dysfunction at an early stage and later, on long run, can progress to systolic dysfunction in post COVID patients (15). Besides chronic inflammation can form scar in myocardium, making susceptible to deadly arrhythmias like ventricular tachycardia, atrial fibrillation etc. (16). Besides pericarditis, pericardial effusion can also develop in patients with chronic inflammation of pericardium (17). Complications like PAH can arise secondary to hemodynamic changes in the pulmonary vasculature arising as a result of persistent or recurrent inflammatory and embolic episodes. RV (right ventricle) dysfunction can arise in patients after an acute insult to right ventricle or secondary to PAH (18). Micro vascular dysfunction, plaque destabilization or rupture caused by chronic inflammatory infiltration in the context of hypercoagulability raises the risk of deadliest complication like acute coronary syndrome (19). Besides complications like deep vein thrombosis, pulmonary embolism, and coronary embolism, etc. can arise due to post COVID sustained hypercoagulable state (13).Persisting inflammation in the lung due to COVID infection can organise as a residual lesion or progress further to develop lung fibrosis (1-2).

However non cardiopulmonary causes (like autonomic, neurological, psychological and endocrine) also responsible for cardiopulmonary symptoms in post COVID patients. Chronic inflammation destabilises the immune system and develops auto-antibodies against the alpha/beta adrenergic receptor and the muscarinic receptor leading to autonomic dysfunction (20). Autoantibodies like anti thyroglobulin and anti-thyroid peroxidase antibodies can lead to thyroid abnormalities, manifesting systemic cardiac symptoms like palpitations, fatigue etc. Neuro-inflammation and neuro-immunomodulation of vagal sensory nerves can cause symptoms like cough (21). Psychological causes like post-traumatic stress disorder, chronic fatigue syndrome, etc. also responsible for cardiopulmonary symptoms after COVID recovery (22-23).

APPROACH FOR EVALUATION OF CARDIOPULMONARY SYMPTOMS: Evaluation of post COVID patients with cardiopulmonary symptoms can avoid future catastrophic events at an early stage. History taking, clinical examination and laboratory evaluation are three important pillars of clinical evaluation. History taking provides important clues for

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diagnosis. Clinical examination helps physician reach a provisional diagnosis. Whereas laboratory evaluation helps in confirming the diagnosis and assessing its severity.

Evaluation of past history and records: The clinical history during or prior to an acute COVID event can provide useful information while evaluating cardiopulmonary symptoms in post COVID patients. Patients with histories (like severe pneumonia, ventilator use, ICU admission, longer hospital stay etc.) during acute COVID event are more likely to experience dyspnea during the post COVID period (24-26). Patients with pre-existing bronchial asthma are more likely to experience polypnea, even months after COVID recovery (27). Patients with comorbidities like hypertension and diabetes mellitus more prevalently experience fatigability (28).

Besides, the evaluation of the past records (like HRCT severity score, troponin, D-dimer, CRP etc.) during acute COVID episodes can also provide useful information, while evaluating post COVID patients. Patients with elevated troponin during acute COVID events are more likely (around three times as likely) to develop adverse cardiac events during post COVID period as compared to age, sex and risk factor matched healthy controls (29). Patients with higher lung CT severity score are more likely to have persistent dyspnea during the post COVID period due to residual lung lesions (1). Patients having persistently elevated d dimer value during acute COVID period are more likely develop an embolic complication like pulmonary embolism (30). Patients with persistent elevations of CRP more likely to complain of fatigue during post COVID period. Therefore evaluation of past record during acute COVID episode is an important part of strategy.

Evaluation of clinical findings: Post COVID patients manifest a spectrum of clinical symptoms like dyspnea, fatigue, chest pain, cough, syncope etc. Post COVID symptoms can arise due to cardiac, pulmonary, autonomic, neurological, psychological, endocrine etiologies. Typical clinical symptoms and signs with specific characteristics can provide a clue for diagnosis of etiology (as described below).

Dyspnea: Around half and 1/4 of the post COVID patients complain dyspnea with activity and at rest respectively even after 7 months of COVID recovery (31). Females, obese and older people are more likely experience dyspnea during post COVID period (32). Dyspnea in post COVID patients can arise due to pulmonary causes like residual organising pneumonia, pulmonary fibrosis or cardiac causes like myocarditis, cardiomyopathy and pulmonary embolism. Besides hyperventilation, chronic fatigue syndrome has also been reported as a cause of exercise-induced dyspnea in post COVID patients (23). Typical symptoms like paroxysmal nocturnal dyspnea, orthopnea etc. along with clinical signs like LV S3, bilateral basal fine crepitation can provide a clue for the diagnosis of left heart failure due to myocarditis, coronary artery disease or post COVID cardiomyopathy (33). Whereas clinical findings like parasternal lift, RV apex, loud P2, RV s3 etc. can provide a clue for the diagnosis of RV failure, which can arise secondary to PAH. Further clinical signs suggestive of atrial fibrillation and deep vein thrombosis can help in diagnosis of pulmonary embolism in the background of RV failure. Muffled heart sound, increased cardiac dullness, pulsus paradoxus can be observed in cases with post COVID pericardial tamponodes. Coarse crepitation with bronchial breath sounds can be observed in patients with residual organised pneumonia (33).Whereas decreased breath sounds, stony dullness, and deviated trachea to the same side can be noticed in extensive lung fibrosis (33).

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Cough: Cough is a symptom observed in 15% of patients after COVID recovery (21). Cough in post COVID patients can arise due to different causes like pulmonary, cardiac or neugenic e.t.c. (15,17-18,21). Cough with expectoration in post COVID patients can be observed due to residual organising pneumonia or bronchiectasis (34). Whereas persistent dry cough can be observed in cases with pulmonary fibrosis (34). Paroxysmal nocturnal cough can provide a clue for heart failure due to post COVID cardiac sequelae (34). Besides cough in post COVID patients can be neurogenic. Several pathophysiological mechanisms (neurotropism, neuroinflammation and neuroimmunomodulation of vagal sensory nerves) have been postulated for neurogenic cough in post COVID patients (21). Whereas other causes such as reinfection of COVID, pulmonary tuberculosis, and malignancy also need to be excluded before assuming cough as a post COVID symptoms.

Chest pain: Chest pain was reported in around 1/5 of post COVID patients. [35] Chest pain can develop in patients due to different causes like post COVID pericarditis, coronary artery disease, pulmonary embolism or pleurisy, etc. (17-19). Proper interpretation of history can distinguish chest pains of different origins. Chest pain increasing with inspiration along with associated pleural rub indicates a diagnosis of pleurisy associated with organising residual COVID pneumonia (36).Whereas shooting or stabbing chest pain, which radiates to shoulders and decreases with leaning forward along with pericardial rub, can provide a clue for diagnosis of the post COVID pericarditis (36). Burning, squeezing chest pain or heaviness, that intensifies with exertion can be due to coronary artery disease (CAD) (36).

Palpitation: Palpitation is a symptom observed in 8% of patients after COVID recovery (37). Palpitation can arise in post COVID patients due to different causes like coronary artery disease, arrhythmia, autonomic dysfunction or post-traumatic stress disorder (16,19-20,22). Palpitation, along with other dysautonomic symptoms (like dizziness, night sweats, poor temperature control etc.) and signs (like a positive orthostatic test) can provide clue for autonomic dysfunction (38). Palpitation with exertion can provide a clue for CAD. Recurrent, paroxysmal onset of palpitation can be due to arrhythmias like paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation (AF) etc.

Syncope: Syncope in post COVID patients is rare. It can be cardiac, neurogenic, postural, or reflex mediated. In a study including COVID patients, most (87.9%) of episode of syncope reported to be unexplained origin. Whereas reflex generated syncope noticed found in 8% cases, orthostatic syncope reported in 2.2% cases and cardiac syncope noticed in another 2.2% cases (39).

Fatigability: It is the most common symptom observed in more than 2/3 of patients (31). Fatigability can develop in patients due to multiple etiologies like cardiac (myocarditis, coronary artery disease, post COVID cardiomyopathy, or RV dysfunction), pulmonary (post COVID residual pneumonia, or bronchospasm), endocrinal (post COVID hypothyroidism) or psychogenic (post-traumatic stress disorder, chronic fatigue syndrome), etc.(14-20,22-23)

Laboratory evaluation:

Laboratory investigation helps in both diagnosing and prognosticating the cases. Routine procedures such as electrocardiography, X-ray chest, pulmonary function test can be utilised for initial screening purposes. Whereas selective procedures such as echocardiography,

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HRCT thorax, CMR imaging, CT pulmonary angiography etc. can be utilised as per abnormality detected during clinical examination and routine procedures. Such procedures not only diagnose, but also help in assessing the severity of an underlying disease. Blood investigations like cardiac, inflammatory biomarkers also help in diagnosing and prognosticating cases.

Routine laboratory procedures

Electrocardiography: Electrocardiography can be used as a routine screening procedure to evaluate post COVID patients with suspected cardiac disease. Diseases like post COVID pericarditis, CAD, and pulmonary embolism can be suspected from electrocardiographic manifestations. Dynamic ST-T changes can provide a clue for the diagnosis of acute coronary syndrome in the background of typical angina (40). E.C.G findings like new onset RBBB, RAE, RVH, [S1, Q3,T3]pattern, etc. can provide a clue for the diagnosis of pulmonary embolism (40). Electrocardiographic signs like ST depression in AVL with PR prolongation or depression can be observed in patients with post COVID pericarditis (40). Low voltage complex can be observed in patients with post COVID pericardial effusion (40). Persistent sinus tachycardia is a common finding in post COVID patients, which can arise in patients due to post COVID autonomic dysfunction (40).Arrhythmias like atrial fibrillation, supraventricular tachycardia (SVT), ventricular tachycardia (VT), premature VPC, bradycardia can occur in post COVID patients due to different etiologies like post COVID myocarditis, CAD, cardiomyopathy etc. (40).

X-ray chest: X-ray chest is a cost effective screening procedure that can be utilised in post COVID patients for detection of both cardiac and pulmonary abnormalities like residual organising COVID pneumonia, pulmonary fibrosis, heart chamber enlargement, and PAH. Dilated right atrium and ventricle with associated radiological signs of PAH, pulmonary infarct, can provide a clue for RV dysfunction associated with pulmonary embolism. Whereas cardiomegaly with LV type of apex, left atrial enlargement, interstitial edema, kerly lines, batwing wing appearance can provide a clue for underlying Left ventricular dysfunction (41).An enlarged cardiac contour with a smooth cardiac border and typical water bottle shape can be observed in post COVID pericardial effusion (41).

Beside cardiac abnormalities, residual pulmonary abnormalities like organising pneumonia, lung fibrosis, and bronchiectasis can be detected in post COVID patients. As per a study residual pulmonary lesions persist in 2/5 of patients even at 54 days follow up (1). Approximately 1/10 of patients' lung lesion deteriorate after post discharge. Surprisingly out of this group, around 1/10 of patients reported having normal x-ray findings during the COVID period (1). Therefore patients with cardiopulmonary symptoms during the post COVID period should be evaluated at least with a chest X- ray, despite having previous normal chest X-ray during COVID period.

Pulmonary function test: The pulmonary function test is a cost-effective screening procedure, that can be utilized for evaluation of patients with dyspnea after recovery of COVID. Pulmonary function test abnormality associates well with post COVID symptoms. Around 2/5 of patients with post COVID symptoms, found to have abnormalities in pulmonary function, however most of the cases were reported to be mild in nature. Out of this group, around half of the cases found to have mild impairment of FEV1 or FEV1/FVC (42) and most of them were obstructive in nature (43). Remaining cases had mild impairment of

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lung diffusion capacity (42) Most of the patients with such impairments were in the older age group and had history of hospitalisation in the ICU due to severe COVID pneumonia (43).

Selective laboratory procedures:

Echocardiography: Echocardiography is a very important tool to evaluate post COVID patients with clinical, electrocardiographic or radiological signs suggestive of an underlying cardiac disorder. Echocardiography can be utilized for evaluation of LV and RV function, PAH, wall motion abnormalities, pericardial involvement in post COVID patients.

Left ventricular function: As per a recent study, abnormal left ventricular (LV) systolic function reported in 12% post COVID patients (15). Majority of patients found to have EF greater than 40% (15). Besides LV diastolic dysfunction observed in 16.8% cases, but majority of them were grade I or II severity (15).

Wall motion abnormality: Wall motion abnormality is defined as kinetic alteration in cardiac wall motion during cardiac cycle (44). It can be global or regional. It was reported in 5% of post COVID patients (45). Regional wall motion abnormalities (like hypokinesia, akinesia or dyskinesia) in the area of distribution of the coronary artery can be observed in post-COVID patients with CAD (44). Whereas regional wall motion abnormality (not distributed to any coronary artery) can be observed in patients with post COVID myocarditis, stress induced cardiomyopathy (44). Global hypokinesia can be noted after chronic extensive myocardial inflammation (44).

RV function: PAH can develop in post COVID patients due to secondary pathophysiological changes in pulmonary artery. RV dysfunction can develop in post COVID patients due chronic RV insult (direct/indirect) or secondary to PAH (18). Around 1/10,1/4 of post COVID patients reported to have PAH and RV dysfunction during post COVID periods respectively (46). Therefore, assessment of RV function in addition to LV function extremely essential in post COVID patients.

Evaluation of pericardium: Echocardiography has an important role in assessing severity of pericardial effusion. Post COVID pericardial effusion was reported in 5% of patients (47). Most of cases were mild and asymptomatic in nature. Pericardial tamponode was very rare in post COVID patients (47-48).

HRCT (High resolution computed tomography) thorax: It has an important role in further evaluation of a residual lesion, noticed during routine chest X-ray in post COVID patients. Residual lesion returns to normal in 82% patients after 3 months and 100% after 5 months (49-50). Residual lesions more commonly observed in older groups of patients due to delayed resolution. Ground glass opacity and irregular lines are most common (2/3 of cases) pattern of residual lesion noticed in post COVID patients (51). Besides reticulation and interstitial thickening, mosaic attenuation, linear consolidation or band-like and perilobular opacities were also observed in post COVID patients (51). Evidence of lung fibrosis like parenchymal band, irregular interfaces, honeycombing and traction bronchiectasis were observed in 1/5 of patients during follow up at 3-4 months post COVID (15). Most (9/10 of cases) of them were reported to be sub-pleural involving less than 25% of lung parenchyma (15).Whereas a few rare cases of post COVID extensive lung fibrosis were reported in case reports and case series (7).

Surprisingly, it has been noticed that, post COVID symptoms do not associate well with HRCT finding. Even though their lung lesions were completely resolved on HRCT chest,

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more than half of the COVID survivors presented with chest symptoms dyspnea , cough etc.(50). Therefore, lung HRCT is not a sensitive tool to screen patients with post COVID pulmonary symptoms (50).

Cardiac magnetic resonance (CMR) imaging: CMR is a potentially valuable diagnostic tool for the detection of myocardial injury, inflammation, scar etc. As per a CMR study, COVID inflammation in myocardium persists in 75%-80% of patients even months after recovery of COVID. On-going active inflammations were detected in 60% of post COVID cases (14). Myocardial scarring surprisingly reported in one in five post COVID patients (48). Though such statistics were very frightening, however it was surprising to learn that, only 10% patients diagnosed to have myocarditis during endomyocardial biopsy (52) and that only 3% patients met updated Lake louise criteria of active myocarditis (53). Myocardial injury usually (in 9 out of 10 cases) limited to 3 or fewer myocardial segments (48). RV and LV function were found to be in the normal range despite having active myocardial inflammation in CMR imaging (54). Most of the patients found to be completely asymptomatic, despite the abnormal CMR findings. Conversely, some patients with normal CMR imaging were found to be symptomatic (55).It implies that, status of post COVID symptoms does not correlate well with CMR findings. Therefore, it is not a sensitive tool for initial screening of patients.

Besides myocardium, CMR imaging can be utilised for evaluation of the pericardium. Pericarditis also reported in 0.03% of post COVID patients during CMR imaging, however, most of the cases were asymptomatic (56).

Tilt table test (TTT); It is an orthostatic test to evaluate patients with symptoms of dysautonomia like palpitation, dizziness, night sweats and poor temperature control (57). Transient baro-reflex failure, sympathetic withdrawal due to prolonged bed rest and virus induced autoimmunity, and molecular mimicry have an important role in the pathogenesis of dysautonomia in post COVID patients (20). Approximately 2.5% of patients with a post COVID condition reported having dysautonomia (58). Around 2/3 of post COVID patients attending a dysautonomia clinic were found to have orthostatic intolerance. Half of the patients with such symptoms met criteria for postural orthostatic syndrome (POTS) (59).Therefore TTT has an important role in evaluating post COVID autonomic symptoms.

Holter monitoring: Holter monitoring is a diagnostic procedure,that can be utilised for further evaluation of patients with palpitation or syncope suggesting cardiac causes and an unremarkable ECG (60). Paroxysmal arrhythmias (such as PSVT, AF, NSVT etc.), that are frequently missed during ECG, can be detected by 24 hour holter monitoring (60). As post COVID patients are more likely to present an arrhythmia as compared to the control group, (16) therefore, patients complaining of intermittent palpitation or syncope can be evaluated by holter monitoring in the case of inconclusive ECG findings.

Coronary angiography-Coronary angiography is a diagnostic invasive procedure used to detect obstruction in coronary artery. Hypercoagulability, endothelial dysfunction and plaque rupture due to ongoing inflammation are the mechanism for obstruction in coronary artery, resulting type I MI (19) However approximately half of the patients during COVID and post COVID period reported type II MI (due to myocardial oxygen demand and supply mismatch) having non obstructive coronary arteries during angiography (61-62). Also many case reports of micro-vascular angina with a normal epicardial coronary artery had been

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reported as a cause of chest pain in post COVID patients (63).Therefore, angiographic findings can be normal in post COVID patients despite having typical angina.

Venous Doppler ultrasound: Venous Doppler ultrasound has an important role in diagnosing deep vein thrombosis in post COVID patients. As COVID infection sustains its hypercoagulable state beyond the COVID period, therefore chances of developing deep vein thrombosis (DVT) in patients are very high, which can lead to further complications like pulmonary embolism, coronary embolism etc. (64). Therefore the presence of DVT in patients with an acute onset of shortness of breath , can provide an additional clue for the diagnosis of embolic events as described above.

CT pulmonary angiography: It has an important role in evaluating post COVID patients with suspected pulmonary embolism. The prevalence of pulmonary embolism is 30 times higher in patients with COVID-19 pneumonia due to their hypercoagulable state as compared to critically ill patients without COVID-19 disease (65). As hypercoagulable state can last months after COVID recovery, (1-2) therefore post COVID patients more likely to develop pulmonary embolism. Patients with echocardiographic evidence of right heart strain/failure, PAH, free-floating right ventricular (RV) thrombus can be evaluated with CT pulmonary angiography to find out if there is any embolism in pulmonary vasculature (66).An invasive procedure like this can assess not only the presence, but also the severity of pulmonary embolism (67).

Laboratory blood investigation:

Laboratory blood tests like cardiac, inflammatory biomarkers (D-dimer, troponin, CRP, NT-probnp) have an immense role in diagnosing and prognosticating post COVID cases. Such tests can provide an additional clue for diagnosis.

D-dimer-D-dimer is an intravascular coagulation related inflammatory marker . Unlike MERS and SARS infections, COVID 19 sustains its hypercoagulable state even months after COVID recovery. Around 1/4 of patients were found to have elevated D-dimer, even after 4 months of post COVID recovery (68). Around 1/6 of patients were detected to have D dimer value two times above the threshold for pulmonary embolism (67). Post COVID patients with such a high level of D-dimer are more susceptible to develop embolic events like pulmonary embolism, cardio-embolic stroke and coronary embolism (30). Therefore D dimer can provide a clue for the diagnosis of pulmonary embolism in patients with acute new onset or worsening breathlessness.

Troponin -Troponin is a cardiac biomarker, that represents the acute onset of myocardial injury. It can be elevated in myocarditis, acute myocardial infarction, pulmonary embolism and pericarditis in post COVID patients (69). The troponin test can be falsely positive in some nonspecific conditions like hypoxia, hypotension, sepsis and renal impairment, however negative results reduce uncertainty about any adverse cardiac event like AMI (69). Therefore, correlation between clinical and laboratory findings has an immense role in diagnosing disease.

NT-probnp- It is a sensitive biomarker of heart failure. It can be elevated in patients with heart failure due to chronic pulmonary embolism, active myocarditis or coronary artery disease (70). Patient with post COVID syndrome found to have higher level of NT pro BNP than age, sex, risk factor matched controls (71). Persisting increased circulating concentrations of NT-pro BNP associated with adverse cardiac prognosis on long run (71).

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CRP-It is non-specific inflammatory marker, that has reported to be persistently elevated in 10% post COVID patients (1). Patients with such findings with post COVID syndrome should be evaluated for other inflammatory markers like serum ferritin, LDH and interleukin. Beside biomarkers, a thyroid function test has an important role in evaluating patients with palpitation or fatigability. It has been noticed that, around 5% of post COVID patients had elevated TSH (42). 15% of patients were found to have elevated anti thyroglobulin and anti-thyroid peroxidase antibodies (42).Therefore it is wise to evaluate thyroid function in post COVID patients presenting with symptoms like chronic fatigability, palpitation etc.

Severity of underlying cardiopulmonary disease in patients with post COVID cardiopulmonary symptoms: COVID can cause different serious post COVID cardiopulmonary sequelae such as myocarditis (2/3rd cases),(14) pericarditis (0.03% cases),(17) pericardial effusion (5% cases),[47] LV dysfunction (12% cases),(15) pulmonary fibrosis(20% cases),(15) Pulmonary function abnormality (40% cases),(43) organizing pneumonia (51) and others, during post COVID period manifesting cardiopulmonary symptoms. However extensive and severe cardiopulmonary involvement was observed in very few cases. Reported post COVID myocarditis most often extends into few segments of myocardium (48). Observed ejection fraction in patients with post COVID LV systolic dysfunction rarely crosses below 40% (15). It normalises over a period of 12 months (72). Post COVID pericardial effusion invariably mild to moderate in nature (47).Pericardial tamponode is very rare in post COVID patients (47). Half of the cases of myocardial infarction during and post COVID period were reported to have non-obstructive coronary arteries (62).Pulmonary function abnormalities most often reported as mild in post COVID patients (43). Residual lung lesions resolved completely over the 5 month post COVID period in most of the cases (50).Post COVID lung fibrosis was most often found to be sub-pleural and doesn't extend beyond 25% of lung parenchyma (15). Extensive lung fibrosis is very uncommon (15). However, there is a higher chance of developing life threatening complications (like pulmonary embolism, acute coronary syndrome, left ventricular failure, and arrhythmia) in few rare post COVID cases due to persistence of hyper inflammatory and hypercoagulable states (64,70).

Strategy for evaluation of post COVID cardiopulmonary symptoms:

Despite the fact, COVID caused post COVID cardiopulmonary symptoms in significant proportion of patients, (3, 4) the severity of symptoms in patients were mild (5). Reported cardiopulmonary sequelae and abnormalities were also self-limiting (15, 43, 47, 50, 62, 72). However, life threatening complications can develops in few rare cases manifesting cardiopulmonary symptoms (7-11). Aside from non COVID related cardiopulmonary disease like pulmonary tuberculosis, malignancy, which can be overlooked, when symptoms are misdiagnosed as post COVID symptoms.Therefore such symptoms can't be ignored as such.As a result following strategies can aid in for proper evaluation of cardiopulmonary symptoms in post COVID patients, discouraging over utilization of health resources and manpower.

1. Stratification of cases: Stratification of cases based on history or records, severity of clinical findings can help in identifying high risk cases, so that catastrophic cardiopulmonary events can be avoided in them at an early stage. History (like severity of pneumonia,

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coronary or embolic events, heart failure, ventilator use, ICU admission, length of hospital stay during hospitalisation etc.) and past records (like higher HRCT severity score, troponin, D-dimer etc.) during acute COVID events can play an important role in stratifying patients with symptoms after COVID recovery (24-26,29-30). The history of pre-existing pulmonary, cardiac disease or comorbidities can play an immense role in assessing the severity of cases (27-28). Besides clinical findings suggestive of LV/RV failure, PAH, persisting pneumonia along with associated corroborative ECG and X-ray chest findings, elevated inflammatory or cardiac marker can help in identifying high risk cases.

2. Specific selective clinical approach: Adapting a general approach for evaluation of all symptomatic post COVID patients in the context of ongoing COVID pandemic, is an extremely tough challenge. A specific selective approach based on clinical symptoms and signs instead of generalized approach can help in the proper evaluation of patients. Past medical history and clinical findings with specific characteristic can provide important clues for the next step. At the same time over utilization of health resources and manpower can be avoided during the COVID pandemic.

3. Systemic step wise laboratory approach: During this COVID pandemic, selective diagnostic procedure such as HRCT thorax, echocardiography, CMR imaging have been utilised to evaluate COVID and post COVID patients. However such diagnostic procedures may not be accessible in every part of the world. Secondly, clinical experts like cardiologists, radiologists may not be available in every remote part of the world. Thirdly, such procedures are costly and can put an extra economic burden on the patients on the eve of this COVID pandemic. Whereas routine procedures such as ECG, chest X ray, spirometry etc. are easily affordable and accessible. Therefore, evaluation of patients can be initiated with routine procedures and later more selective procedures can be utilised as per clinical findings. Besides cardiac and inflammatory biomarkers have an important role in diagnosing and prognosticating post COVID cases (29-30, 69, 71). Negative laboratory results reduce uncertainty about diagnosis. Whereas falsely positive results can create diagnostic dilemma (69). Therefore such blood test should be ordered selectively with specific clinical indications, derived from careful history taking and clinical examination (75) .

4. Exclusion of other possible causes: As post COVID cardiopulmonary symptoms can arise due to non-cardiopulmonary causes involving other disciplines like neurology, endocrinology, psychiatry etc., therefore consultation from respective disciplines should be sought, as when needed. Secondly chances of reinfection of COVID is not uncommon on the eve of ongoing COVID pandemic (76). Symptoms of COVID infection can be mistaken as post COVID symptom. Therefore COVID reinfection should be excluded before diagnosing symptoms as post COVID symptoms. Besides symptoms can arise in patients during post COVID period due to other non-COVID related causes like tuberculosis, malignancy, which can be missed due to the bias of presuming as post COVID symptoms. During the COVID pandemic, screening for lung malignancy and tuberculosis became highly compromised, resulting in an increased prevalence of late stage diseases (77-78). Therefore, exclusion of other non COVID related causes is extremely essential before designating symptoms as a manifestation of post COVID cardiopulmonary sequelae.

Conclusion:

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COVID manifests a spectrum of cardiopulmonary symptoms even after COVID recovery. Most of those symptoms were found to be mild in nature. Reported cardiopulmonary sequelae and abnormalities were also found to be mild and self-limiting. However life threatening post COVID complications can arise in few rare high risk cases due to persistence of inflammatory and hypercoagulable states. Stratification of cases based on past history, records during COVID period, clinical findings and biomarkers can help in the identification high risk cases at an early stage. A selective, systemic and stepwise approach can be helpful in the evaluation of all symptomatic post COVID cases, despite high epidemiological burden. However exclusion of other non COVID causes is extremely essential before designating symptoms as post COVID cardiopulmonary symptoms. As post COVID cardiopulmonary symptoms can arise due to non-cardiopulmonary causes (i.e. neurogenic, psychogenic, endocrine etc.), therefore consultation from respective disciplines should be sought, as when needed.

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