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Editorial

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LONG COVID - Never Ending Story

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Year 2019 presented the world with a pandemic of a nature the world had not seen for a century. The disease COVID 19 was a challenge at the beginning, a mystery with many unanswered questions and continues to be so to date since the onset. Severe acute respiratory syndrome corona virus 2 (SARS -CoV- 2) or Novel Corona virus is the causative organism for COVID-19 pandemic which was first identified in Wuhan in China. The devastating effects of it still seem to persist all over the world. Undoubtedly, it is the most crucial health crisis of our time with its potential to affect every community in the world irrespective of the wealth and development. It has significant morbidity and mortality with long term sequelae. Clinical and Scientific evidence is evolving on the sub-acute and long-term effects of COVID-19, which can affect multiple organ systems. It was evidenced similar long term clinically significant sequelae of survivors of previous coronavirus infections, including the SARS epidemic of 2003 and the Middle East respiratory syndrome (MERS) outbreak of 2012.

As a developing country, Sri Lanka has recognized COVID- 19 not only as a health crisis but also as an economic and social crisis.

The patients who recover keep on having distressing and disabling symptoms, presenting to their health care providers looking for help, presenting a challenging task to the health care provider in finding answers. This is long COVID, a story that appears to never end.

Definition and epidemiology

Long COVID syndrome is an umbrella term, Including post-acute COVID syndrome and post COVID syndrome. Long COVID syndrome is further divide in to two categories. Sub-acute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities present from 4-12 weeks beyond acute COVID-19. Chronic or post-COVID-19 syndrome, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses. It usually presents with cluster of symptoms that are often overlapping, which can fluctuate and change over time and can affect any system of the body, in any age or sex. It is also important to note that patients may present with post COVID syndrome even when they have had only mild symptoms and not hospitalized. Also, patients may not have had a positive COVID test (Figure 1, 2).

As all organ systems of the body are affected, it can have a wide range of presentations which include post viral fatigue, lasting organ damage, multi organ damage, post intensive care syndrome, PTSD and worsening of existing medical disorders.

The syndrome is estimated to be prevalent in one in ten, with one third of the affected not returning to normal work after 12 weeks and 30% having symptoms after 9 months.

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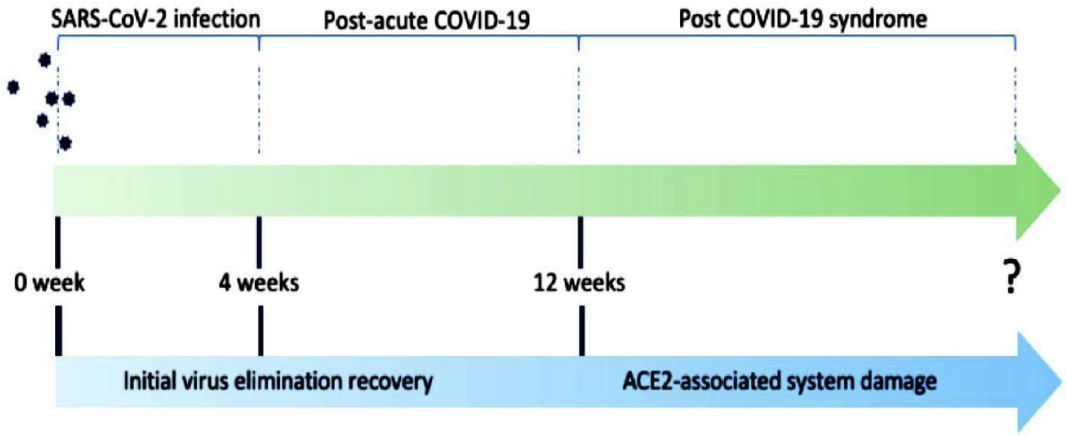


Figure 01

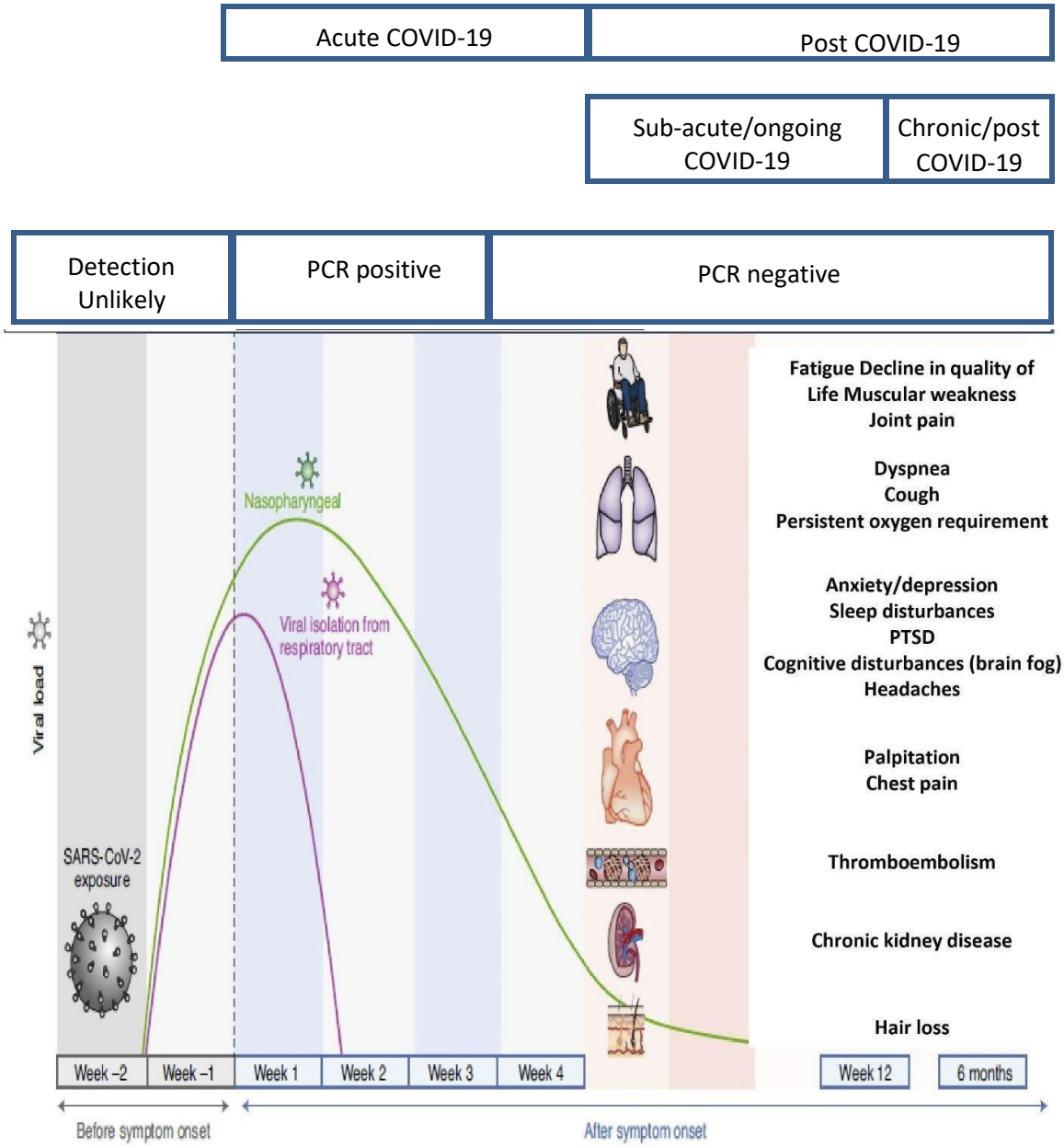


Figure 02

Pathophysiology

Just as COVID 19, the post COVID syndrome is still relatively new to the world. Thus, the pathophysiology of this syndrome is explained with what is well known so far as well as postulates. The potential mechanisms include virus specific pathophysiologic changes, immunologic aberrations, and inflammatory damage in response to the acute infection and expected sequalae post critical illness. Virus specific and related immune aberrations cause endothelial damage, micro vascular injury, immune disregulation, hyperinflammatory state, and hypercoagulability with resultant in situ thrombosis and macro thrombosis.

Clinical features and management

The syndrome of long COVID carries symptoms that are multiple, varied, and fluctuating over time. Fatigue is the most common symptom, which can be general as well as post exertional. Next are the Respiratory symptoms of persistent sob and cough, and musculoskeletal symptoms of muscle pain and fatigue. Psychiatric and psychological symptoms are also significant with sleep and mood disorders, anxiety, depression, and PTSD (Table 1).

Neurological symptoms include headache, dizziness and neurocognitive impairment. Cardiovascular system is affected with palpitations, arrhythmias, and postural tachycardia syndrome. Nausea indigestion and bowel changes represent the gastrointestinal system. There can be worsening of pre-existing diabetes and other metabolic disorders (Figure 3, 4)

Fatigue is reported to be one of the most consistent and persistent symptoms of the post COVID syndrome. There will be reduction of physical activity, aches, pains and reduced functional capacity, frustration, worry, anxiety, impairment of cognitive function and memory, the "brain fog. "Social and personal relations too can be affected.

The other most common symptom is shortness of breath which is multifactorial. It varies from person to person and does not depend on age, sex or co morbid status. Possibilities include development of secondary ILDSs such as Bronchiolitis obliterans organizing pneumonia, pulmonary embolism, cardiac causes, drug induced, post intensive care syndrome, opportunistic infections, and functional causes. Deconditioning and malnutrition or low BMI due to many causes are recognized as a major player of post COVID dysfunctional breathing (Table 2).

A total assessment of the patient is needed to find out the exact etiology of the patient's condition, to identify treatable causes and to explain the post COVID syndrome. A full work up from basic biochemistry to advanced imaging and invasive investigations may be needed (Figure 5).

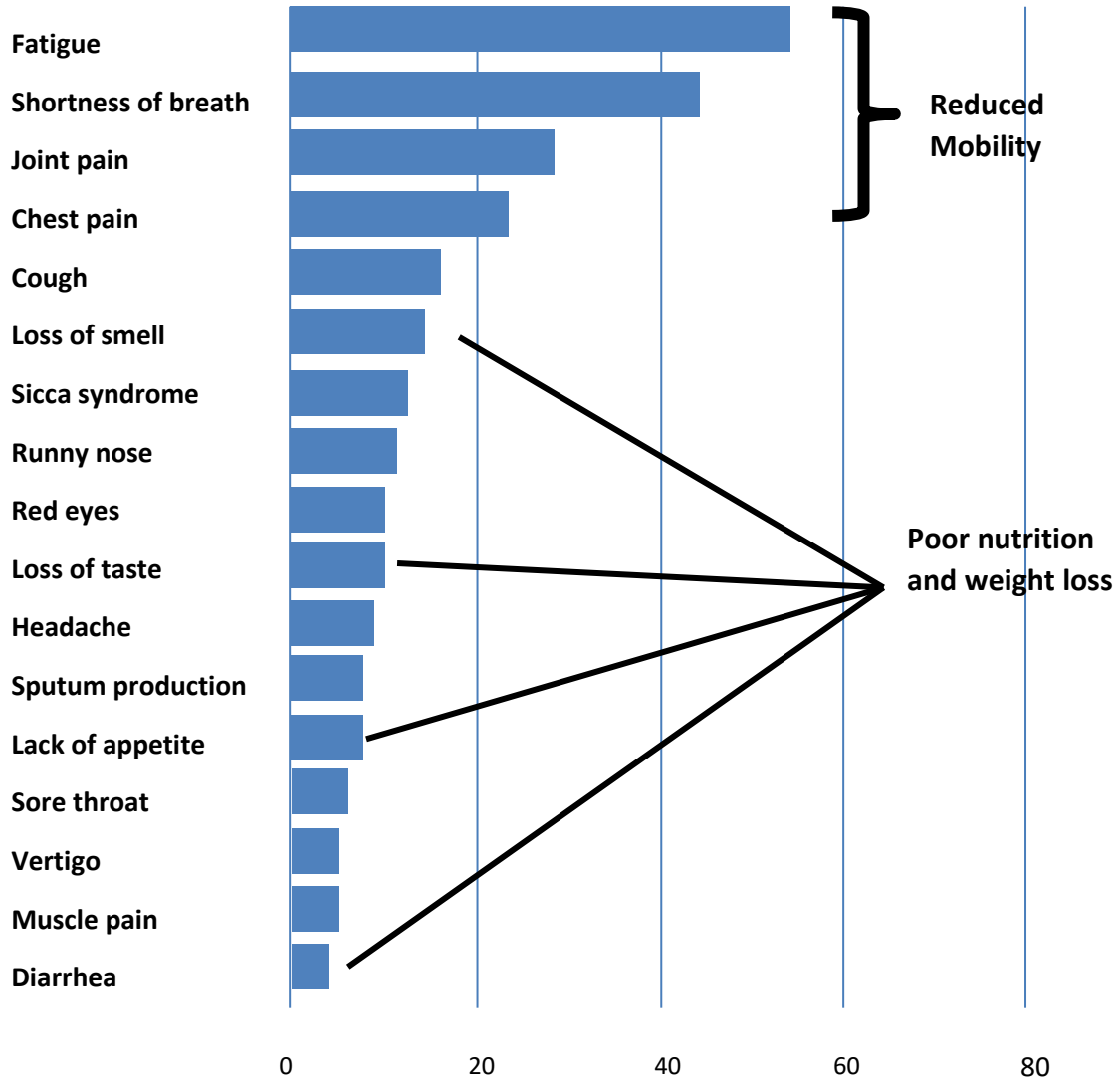
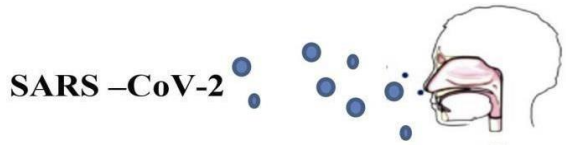


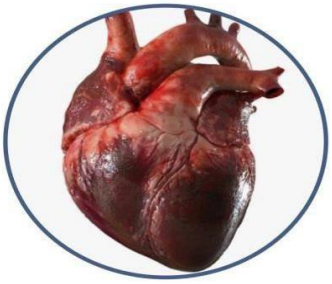
Figure 3: Long COVID symptoms

Table 01. Long COVID-19 syndrome on various systems: an evidence - based summery

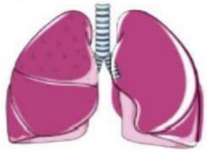
Table 01. Long COVID-19 syndrome on various systems : an evidence - based summery				
Systems	**Main Diagnosis**	**Features**	**Possible**	**Prognosis**
Respiratory system	Acute respiratory Syndrome (ARDS)	Extensive bilateral diffuse alveolar damage with cellular fibromyxoid exudates: Desquamation of pneumocytes and by aline memberane formation: diffusion impairment	SARS-Co-2 spike S1 domain protein binding to ACE2 receptor; Post-Acute Respiratory Distress Syndrome fibrosis with diffuse alveolar damage	Pulmonary function deficit 6 months after infection: extensive diffuse impairment; Long-term in- situ thrombosis

Cardiovascular system	Endothelitis: Micro-thrombosis, Capillary damage: hypercoagulability: Microangiopathy: Thromboembolism:myoc arditis: atrial fibrillation;	Increased target - to - blood pool ratio: capillary disturbance: impaired oxygen diffusion	Cytokine storm and macrophages activating syndrome-caused endothelial dysfunction	Majority (81%) of the COVID- 19 myocarditis patients survived the acute episode: ongoing subclinical myocarditis may evolve into myocardial dysfunction and sudden cardiac death.
Hematological system	Thromboembolism	Elevated convalescent D-dimer and C-reactive protein levels: persistently increased biomarkers of inflammation.	N/A	Prognostic biomarkers for monitoring clinical progression of long COVID-19 patients need to be investigated
Urinary system	Acute kidney injury: renal failure;	Declined glomerular filtration rate (eGFR): kidney infarction	High abundance pf ACE2 expression in kidneys	Significant risks of mortality and morbidity
Digestive system	Gastrointestinal impairment and dysfunction: hepatitis and cholestatic liver injury : pancreatic injury	Bowel diffuse damage: Enterocytes desquamation, lymphocytes infiltration and mesemteric nodes hemorrhage and necrosis	Rich in ACE2 and furin expression: fecal-oral transmission; plasma cells and lymphocytic infiltrations into lamina propria of intestinal tissues.	The liver enzymes remained persistently elevated 14 days after discharge, while the liver functions in majority survivors normalized 2 months after hospital discharge
Neurological system	Mood changes: cognitive difficulties: headache: fatigue: dizziness; memory loss: confusion: and attention deficit.	Hypoxic injury: microbleedings: Neuronal inflammation.	Blood vessel damage, impaired oxygen supply viral infiltration into the central nervous system and inflammatory cytokines-mediated cellular damage : indirect T-cell and microglia damage in the	Over 40% survivor without prior psychiatric conditions lived with depression within 90 days of recovery from severe COVID -19 associated respiratory failure ,while 70% of them did not receive treatment for depression
Metabolic system	Hyperglycaemia without diabetic mellitus: new- onset diabetic mellitus: starvation	High blood glucose level, impaired glucose metabolism	Intruding pancreatic - islet cells, triggering autoimmune responses because of the exposure of the antigen from damaged islet cells.	Long - term treatment of diabetic mellitus is needed.



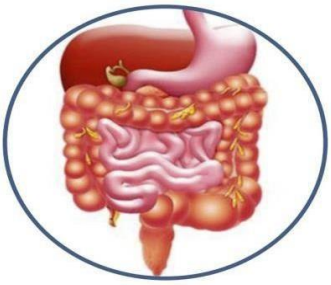


- Endothelial cell dysfunction
- Vasculitic changes
- Hypercoagulability
- Microangiopathy
- Thromboembolism
- Myocarditis

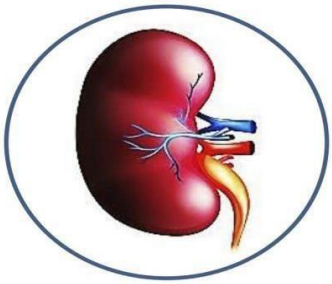


- Pulmonary function deficit
- Persistent lung pathology
- Thromboembolic

- Elevated convalescent D-dimer.
- Persistently increased cytokines and white blood cells.
- Decreased lymphocytes and platelet count.



- Bowel diffuse damage
- Enterocytes, desquamation, edema
- Small bowel dilation
- Lymphocyte infiltration
- Mesenteric nodes hemorrhage and necrosis.



- Acute kidney injury
- Renal failure
- Decreased glomerular filtration rate.

- Hyperglycemia without diabetes
- New onset diabetes

- Memory loss
- Attention deficit
- Slow processing speed
- Cognitive impairment.

Figure 04: Summery of Involvement

Table 2: Classified long-COVID and post-COVID symptoms summarized as per human body system.

System	Symptoms	Post-COVID	Long-COVID
Audio vestibular	-Ageusia	X	
	-Anosmia	X	
	-Hyposmia	X	
	-Hearing Loss	X	
Cardiovascular	-Myocarditis	X	
	-Heart Failure	X	
	-Myocardial Hypertrophy -	X	
	Mild to severe coronary artery atherosclerosis	X	X
	-Acute myocardial infraction Type 1		X
	-Acute myocardial infraction Type 2		X
	-Cardiogenic shock	X	
	-Arrhythmia	X	
	-Pericardial disease	X	
	-Takotsubo syndrome		X
	-Chronic heart disease		X
	-Severe coronary artery		X
Dermatological	-Psoriasis		X
	-Systemic Lupus erythematous		X
	-Vasculitis		X
	-Dermatomyositis		X
	-Chronic rheumatological disease.		X
Gastrointestinal	-Diarrhea	X	
	-Nausea	X	
	-Vomit	X	
	-Abdominal pain	X	
	-Anorexia	X	
	-Acid reflux	X	
	-Gastrointestinal bleeding	X	
	-Lack of appetite	X	
	-Constipation	X	
	-Changed in lung –intestine-brain axis		X
	-Changes in the intestinal flora -		X
	Disorders and disintegration of intestinal microorganisms		X
	-Microbiota dysbiosis		X
	-Dysfunction of intestinal metabolites		X
Hematological	-Breakdown of hemostasis	X	
	-Endoteliitis	X	
	-Disseminated intravascular coagulation	X	
	-Prothrombotic phenotype	X	
	-Coagulative disease	X	

Hepatic	-Alternation of inflammatory biomarkers of liver damage	**X**	
	-Macro and micro thromboembolic	**X**	
Immune system	-Secondary autoimmune symptoms associated with immunosuppression	**X**	
	-Vascular inflammation and myocarditis	**X**	
	-Guillain-Barret syndrome		
	-Motor paralysis	**X**	
	-Rheumatoid arthritis	**X**	
	-Arthralgia	**X**	
	-Myalgia	**X**	
	-Weakness	**X**	
	-Kawazaki disease	**X**	
		X	
Mental Health	-Depression	**X**	
	-Panic	**X**	
	-Anxiety	**X**	
	-Stress	**X**	
	-Psychiatric disorders	**X**	
	-Anguish	**X**	
	-Insomnia	**X**	
	-Negative psychological effects	**X**	
	-Panic syndrome	**X**	
Nervous system	-Headaches	**X**	
	-Spasms	**X**	
	-Convulsions	**X**	
	-Confusion	**X**	
	-Visual impairment	**X**	
	-Nerve pain	**X**	
	-Dizziness	**X**	
	-Conscience problems	**X**	
	-Nausea	**X**	
	-Vomiting	**X**	
	-Hemiplegia	**X**	
	-Ataxia	**X**	
	-Stroke (AVC)	**X**	
	-Cerebral hemorrhage	**X**	
	-Nonspecific neurological symptoms		**X**
	-Epileptic seizures		**X**
	-Myalgia		**X**
	-Anti-N-Methyl-D-Aspartate encephalitis(rNMDA)		**X**
	-Atypical postpartum reversibility encephalopathy syndrome	**X**	
Renal	-Renal disfunction	**X**	
	-Renal systemic microangiopathy with micro-thrombosis	**X**	

Pulmonary	-Pulmonary infarction	**X**	
	-Pulmonary Hemorrhage	**X**	
	-Respiratory failure	**X**	
	-Pulmonary thromboembolism	**X**	
	-Pulmonary embolism	**X**	
	-Pneumonia	**X**	
	-Secondary bronchopneumonia	**X**	**X**
	-Pulmonary vein thrombosis	**X**	
	-Post-viral pulmonary fibrosis	**X**	**X**
	-Chronic respiratory failure	**X**	
	-Dyspnea	**X**	
	-Cough	**X**	
	-Chest pain	**X**	
	-Hemoptysis	**X**	
Skeletomuscular	-Dermatomyositis		**X**
	-Generalized weakness		**X**
	-Fatigue		**X**
	-Muscle fiber atrophy		**X**
	-Extensive myalgia		**X**
	-Muscle dysfunction		**X**
	-Deficit in muscle strength and endurance		**X**
	-Generalized muscle atrophy		**X**
	-Sporadic and focal necrosis of muscle fibers		**X**
	-Neuronal demyelination		**X**

Table 3: Useful investigation tools for patients with long COVID-19 syndrome.

System	Main Diagnosis	Features	Useful Investigation tools	Abnormal to Look for
Respiratory system	Acute respiratory Distress syndrome (ARDS)	Extensive bilateral diffuse alveolar damage with cellular fibromyoxide exudates; desquamation of pneumocystis and hyaline membrane formation; diffusion impairment.	Pulmonary function test, high resolution CT, histology; pulmonary angiography.	Restrictive pulmonary function test; impaired gas transfer; reduced total lung capacity; fibrotic features on imaging; diffuse alveolar damage on histology ; pulmonary vasculature.

Cardiovascular system	Endothelitis; micro-thrombosis, capillary damage; Hypercoagulability: microangiopathy; thromboembolism : atrial fibrillation: supraventricular tachycardia.	Increased target-to-blood pool ratio; capillary disturbance; impaired oxygen diffusion.	Electrocardiogram; Echocardiography coronary angiography and cardiac catheterization; chest X Ray; electron-beam computed tomography; cardiac MRI.	Microcirculation disturbances: Increased target-to-blood pool ratio; impaired oxygen diffusion; myocardial inflammation; rhythmic abnormality.
Haematological system	Thromboembolism	Elevated convalescent D-dimer and c-reactive protein levels; Persistently increased biomarkers of inflammation.	Vein puncture for blood tests of D-dimer and c-reactive protein; duplex ultrasound for lower limb clots; CT-pulmonary angiogram for pulmonary embolism; electrocardiogram, echocardiography, coronary angiography and cardiac catheterization for evidence of cardiac or pulmonary embolism.	Thrombocytopenia ; blood cell abnormalities
Urinary system	Acute kidney injury; renal failure	Declined glomerular filtration rate (eGFR); kidney infraction	Urine analysis; glomerular filtration rate; ultrasound scanning; MRA; renal biopsy	Early recognition of kidney involvement ; kidney injury; renal infraction
Digestive system	Gastrointestinal impairment and dysfunction; Hepatic and cholestasis liver injury; pancreatic injury.	Bowel diffuse damage; enterocytes desquamation, edema, small bowel dilation, lymphocytes infiltration and mesenteric nodes hemorrhage and necrosis.	Barium beefsteak meal; colorectal transit study; computed tomography scan (CT or CAT scan); defecography ; Lower gastrointestinal series; MRI; magnetic resonance cholangiopancreatograhy (MRCP); oropharyngeal motility (swallowing) study.	Bowel damage; high fecal calprotectin level; gastrointestinal dysfunction; liver injury; pancreatic injury; hyperamylasemia

Neurological system	Mood changes; cognitive difficulties; headache; fatigue; dizziness; memory loss; confusion; and attention deficit.	Hypoxic injury; micro bleedings; neuronal inflammations	CT scan; electroencephalogram; MRI; electro diagnostic tests, such as electromyography (EMG) and nerve conduction velocity (NCV); position emission tomography (PET); arteriogram (angiogram); lumbar puncture; evoked potentials.	Neurological symptoms; ischemic damages to cerebral white matter; blood vessel damage; hypoxic injury, micro bleedings, and neuronal inflammations in different areas of the brain; brain hypo metabolism.
Metabolic system	Hyperglycemia without diabetic mellitus; new-onset diabetic mellitus; starvation ketoacidosis	High blood glucose level; impaired glucose metabolism	Blood tests for blood glucose and HbA1c level; plasma amino acid analysis; plasma Carnitine level; plasma acylcarnitine profile; plasma C-peptide level, Urine organic acid analysis; Urine and plasma ketone analysis.	Impaired glucose metabolism; increased ketone body.

Management

As post COVID syndrome is essentially a multisystem disorder it needs the best multidisciplinary approach in managing the patients. Majority of these patients will be in the community, those who had a mild infection and never hospitalized. The rest will be the ones discharged from a health care facility. The patients with the post COVID syndrome in community mostly never present to the hospitals thus need to be actively detected and cared for at the community level. Empowering the community level care providers and establishing specific post COVID care clinics will be of importance in managing the considerable number of these patients generated by the pandemic (Figure 5, 6)(Table 3).

Long COVID assessment and interventional pathways are well established in other parts of the world and include multidisciplinary teams (Figure 4, 6, 7, 8, 9). Family physicians and community care teams assess and intervene at community, with strategies that can easily be used in the community level. For majority of the post COVID patients, these multidisciplinary interventions are sufficient in the recovery from post COVID syndrome (Figure 8, 9), (Table 2,3). For those that are having complicated post COVID symptoms, referral centers with dedicated COVID clinics are established where comprehensive intra disciplinary interventions are provided (Figure 5, 9).

The basic structure of a COVID clinic should include structures pathways to assess post COVID patients, availability of necessary investigations and access to multidisciplinary care. Once assessed and deemed clear of other differentials and systemic illness, the patients will be referred on to a multidisciplinary rehabilitation process (Figure 5, 6, 7).

The process of rehabilitation and recovery should start while the patient is in acute care, “pre rehab”, and then referred onwards to the community care. Community based rehabilitation is continued until recovery is achieved (Figure 10).

In Sri Lanka, with a surge of patients presenting as a fourth wave, patients having post COVID syndrome has also risen significantly. With few established post COVID clinics, there is a huge need for improvement and interventions in providing the necessary care for these populations of patients. The well-established primary care system of our country is yet to be utilized for this purpose.

Efforts need to be taken to strengthen the primary care for the detection, assessment, rehabilitation, upward and downward referral of patients with post COVID syndrome for the best and cost-effective management of post COVID syndrome. Multidisciplinary teams, from administrators, specialists of all disciplines, family physicians, general practitioners, community nurses, physiotherapists, psychologists, and social workers need to work together in establishing the provision of care.

As the pandemic moves on to the third year with new variants emerging and new waves of patients appearing, post COVID syndrome will also be a never-ending story causing a significant and lasting burden on the community and country. Proactive and enduring efforts are needed to overcome this new added burden and to provide best possible care to the significant number of sufferers.

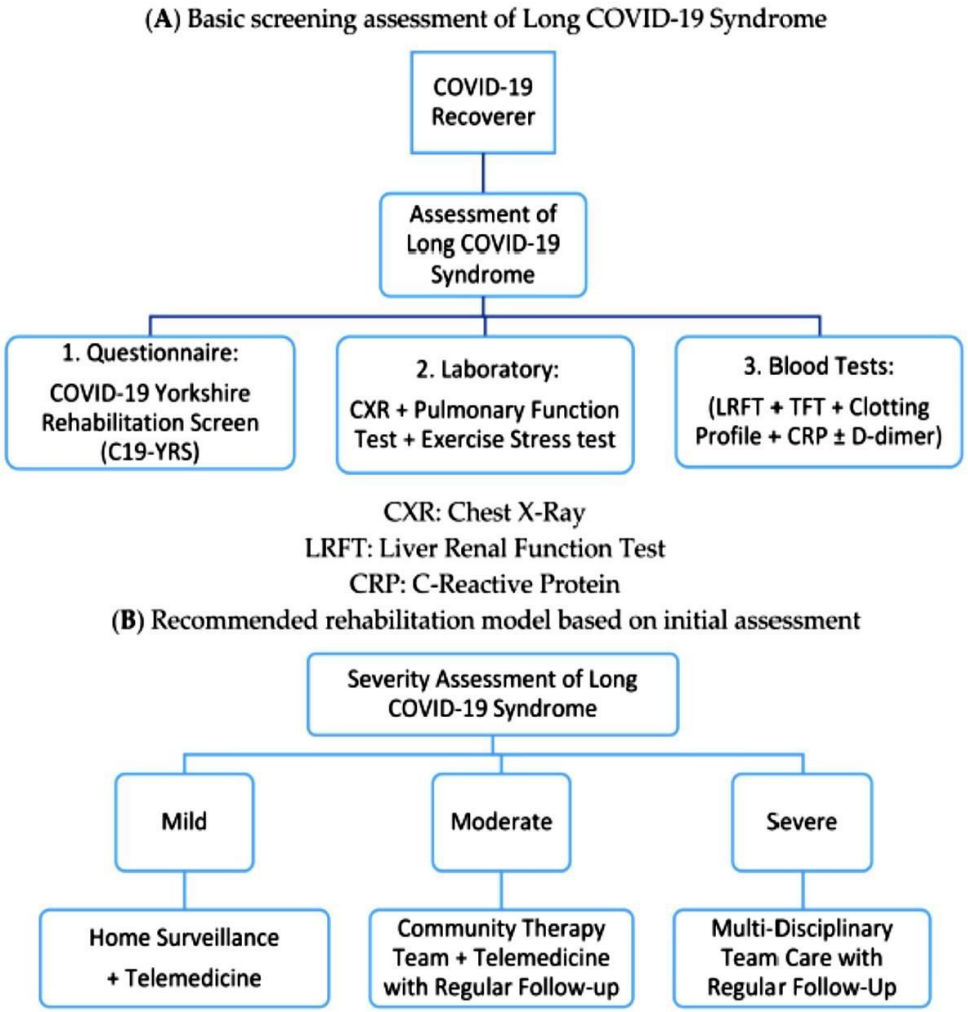


Figure 05: Recommended rehabilitation model for patient with COVID-19 syndrome.

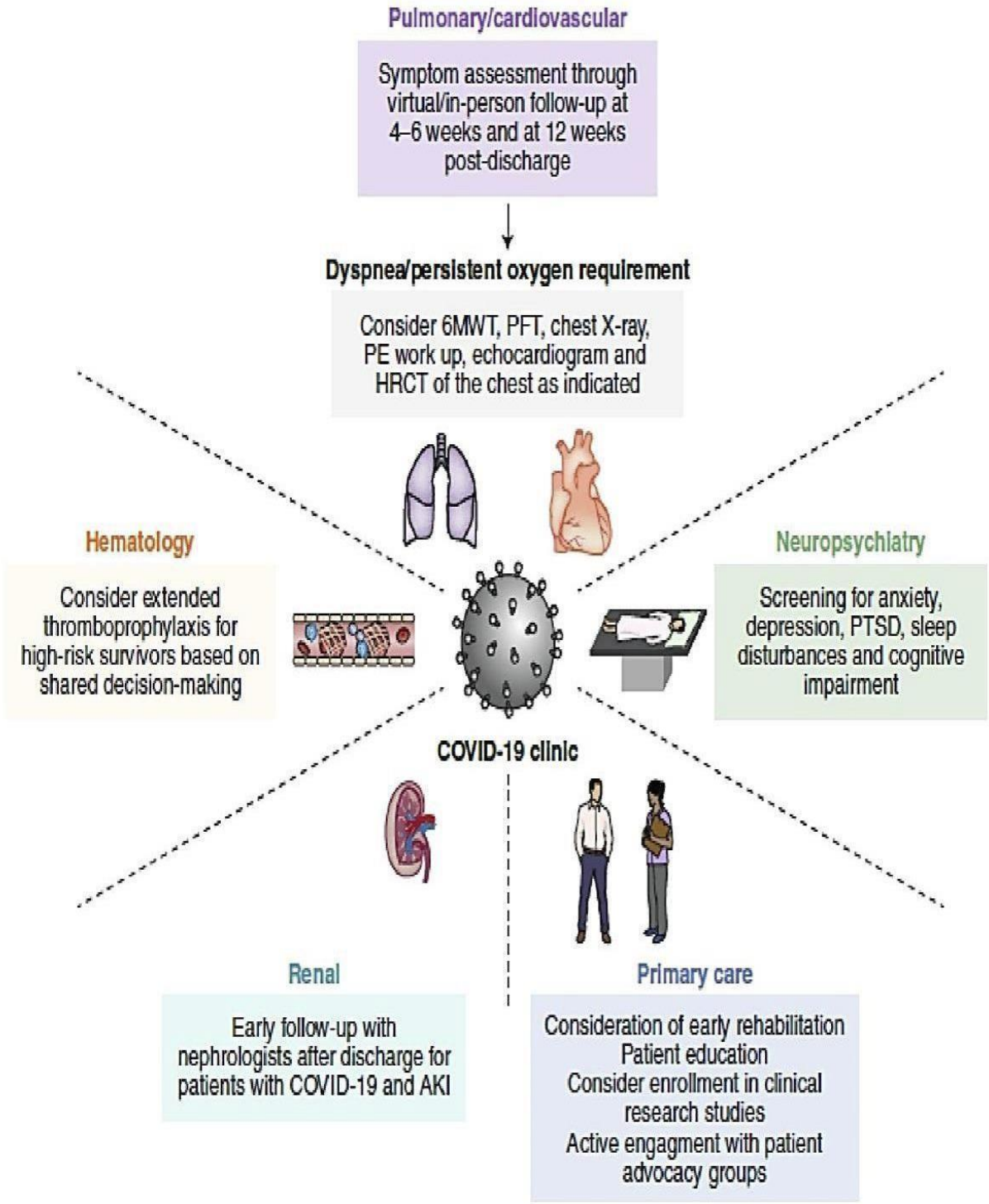


Figure 06: COVID clinic interdisciplinary approach

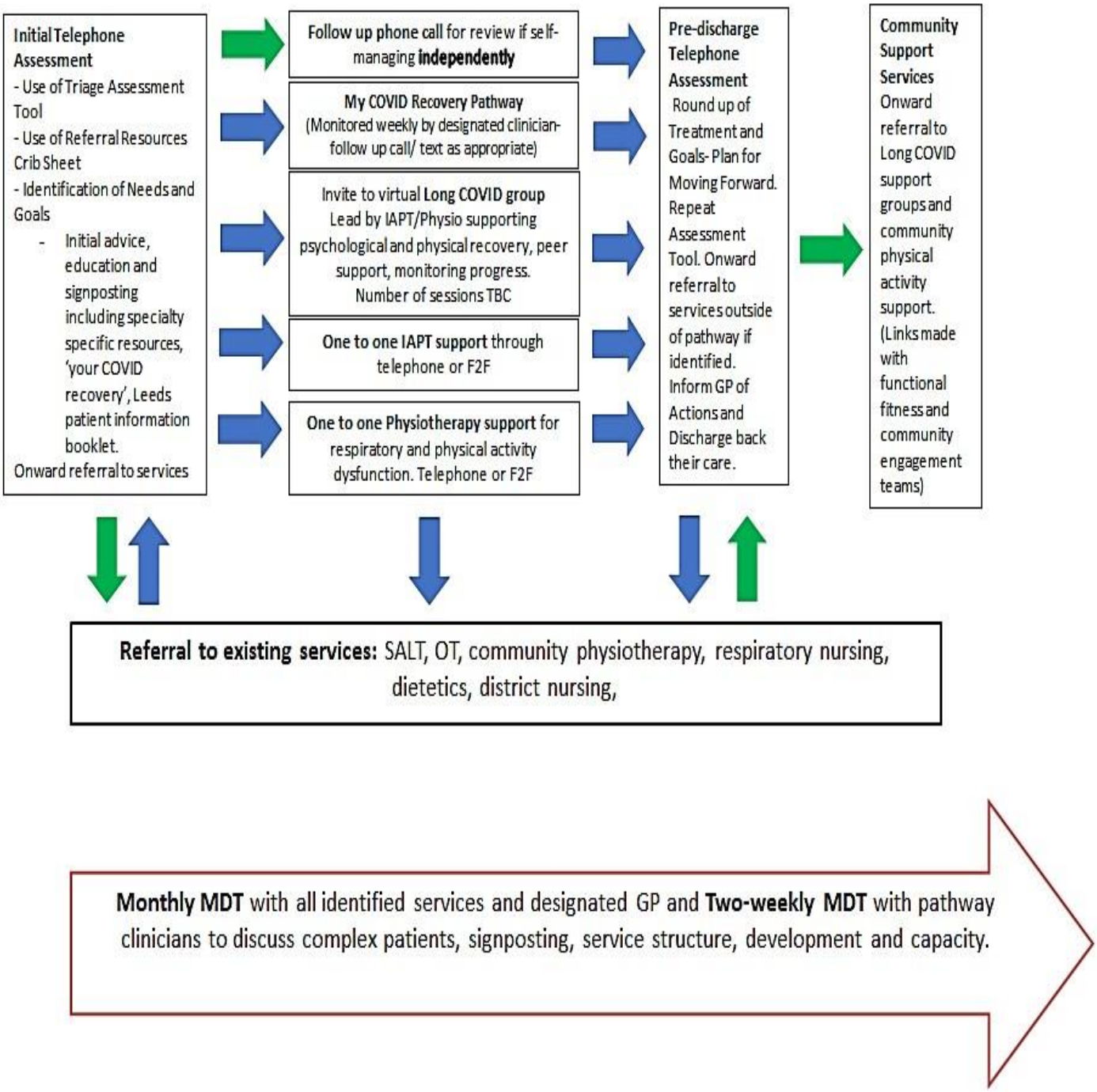


Figure 07: Long COVID Assessment and Intervention pathway

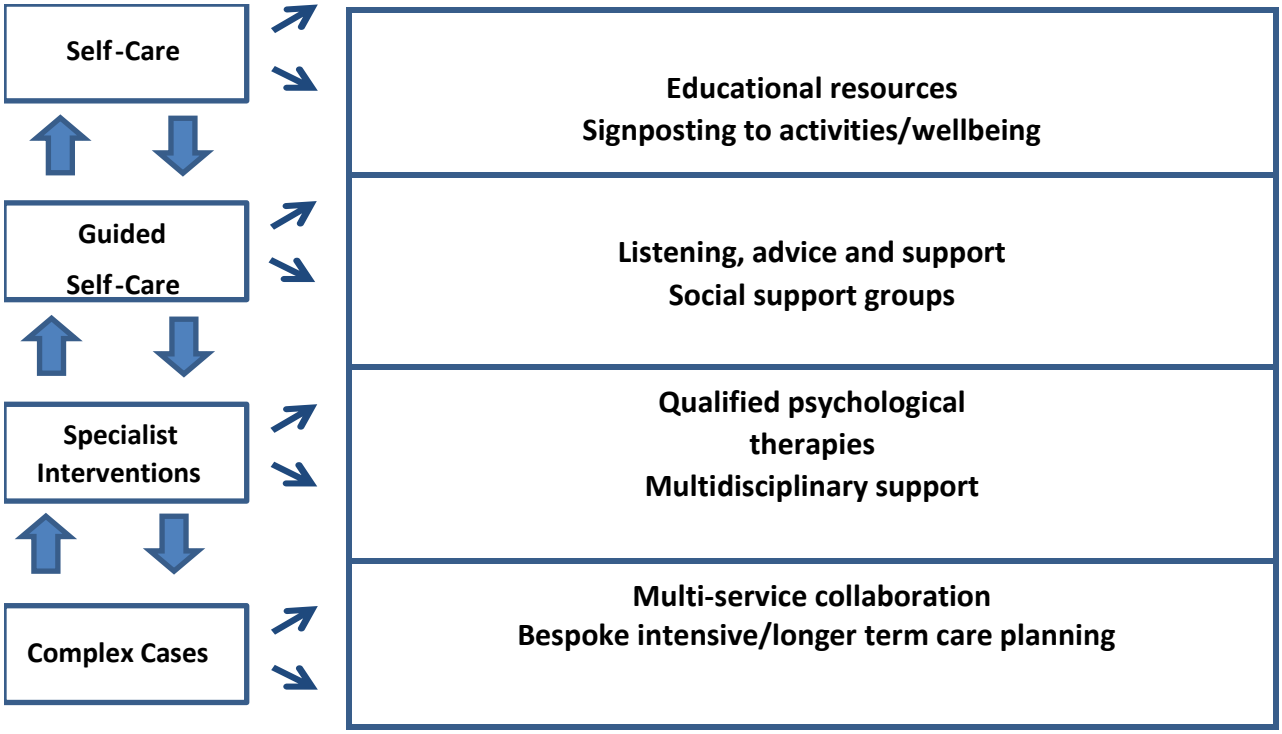


Figure 08: Service options

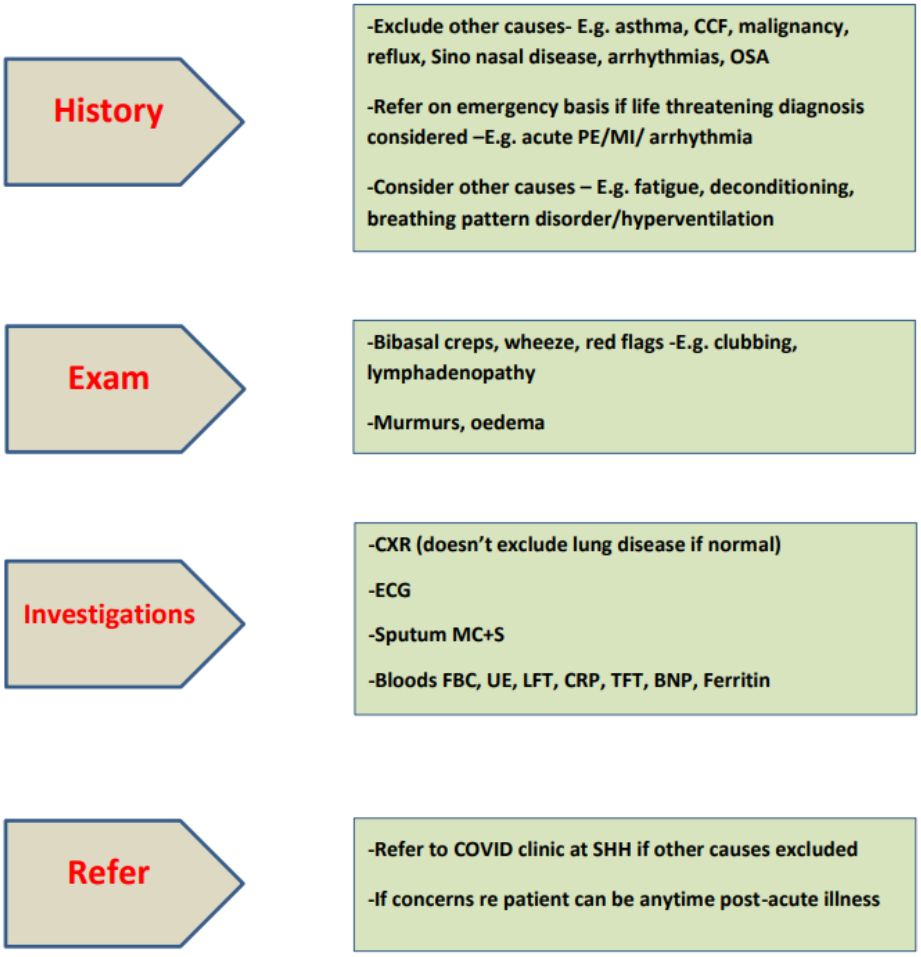


Figure 09: Clinical assessment primary care

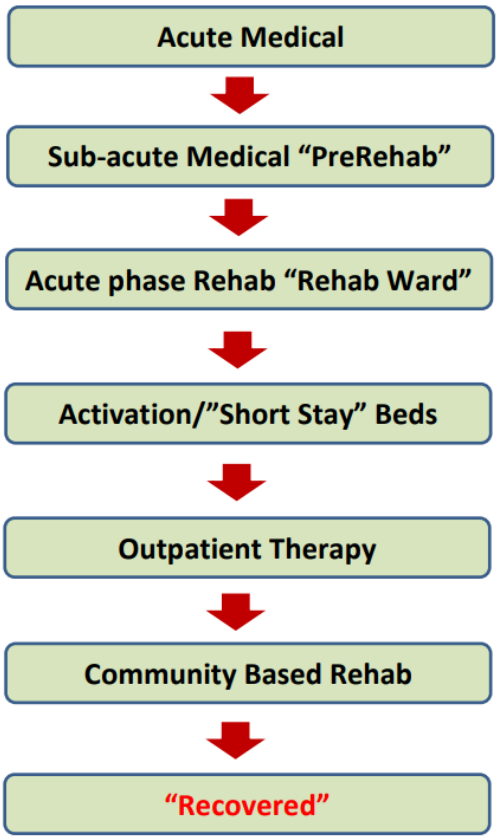


Figure 10: Typical rehabilitation services access and flow

CONCLUSION

COVID -19, the devastating illness with multi-organ involvement leads to significant mortality. Long COVID syndrome is the everlasting morbidity of survivors. Early diagnosis of suspected cases and planning of directed management are essential for normal or near normal functional status with maximum wellbeing. Multidisciplinary team with effective collaboration is the cornerstone of management of Long COVID Syndrome, the never ending story.

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