CRITICAL ROLE OF LAB MEDICINE IN PATIENTS WITH COVID 19

Diagnostic Reasoning, Managed Care And Therapeutic Monitoring

Introduction:

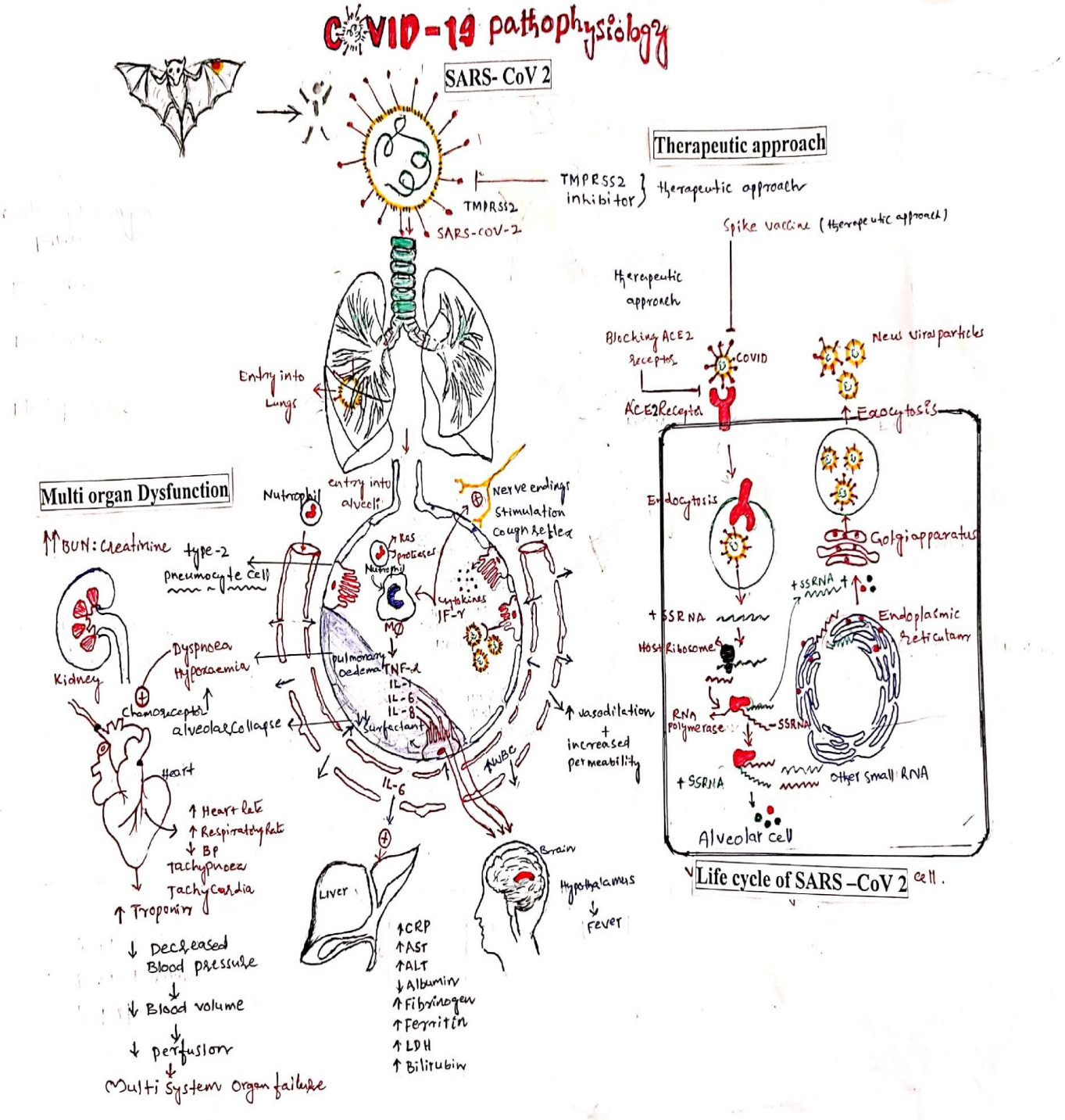
The recent pandemic of COVID 19 has created a havoc in the health industry. The clinical consequences were so rapid and variant that there was very little scope in understanding the aetiopathogenesis. The course of the disease was attributed mainly due to the theory of cytokine storm. The devastating effects of this cytokine storm was severe ARDS , MODS and DIC. The confirmation of the disease was done by RT-PCR that detects unique sequences of the virus that causes COVID-19 (SARS-CoV-2) in respiratory tract specimens

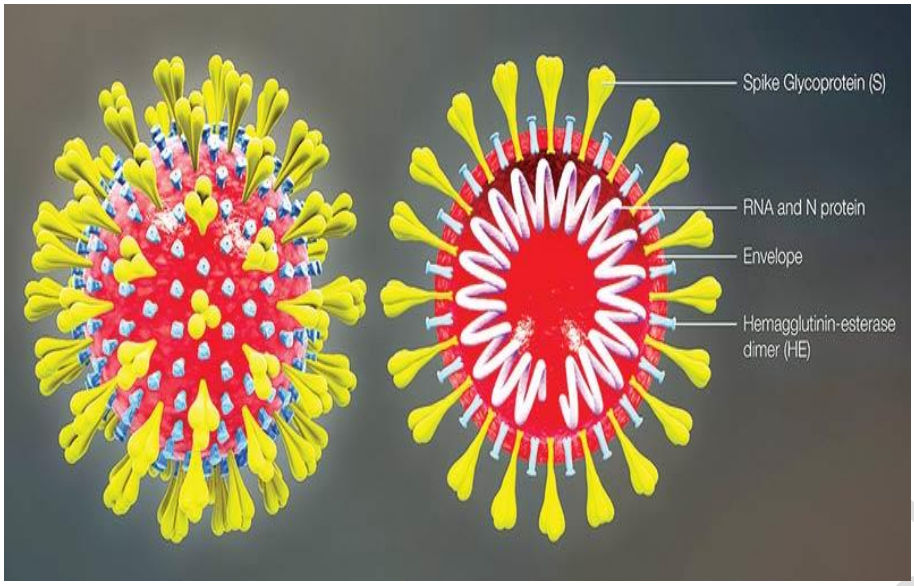
All viral infections are superimposed with bacterial infections. There are very few studies establishing the critical role of Biochemistry parameters in the course of the COVID 19. Biochemistry sepsis markers can be considered to understand the course of the disease, to monitor the patients in understanding the severity and prognosis. Also these parameters can be a guideline in establishing the treatment modalities or in fact the change in the treatment modality and intervention at the correct juncture so that more cases would not end up in sepsis mode or either of the severe complications like the ARDS, MODS or DIC.

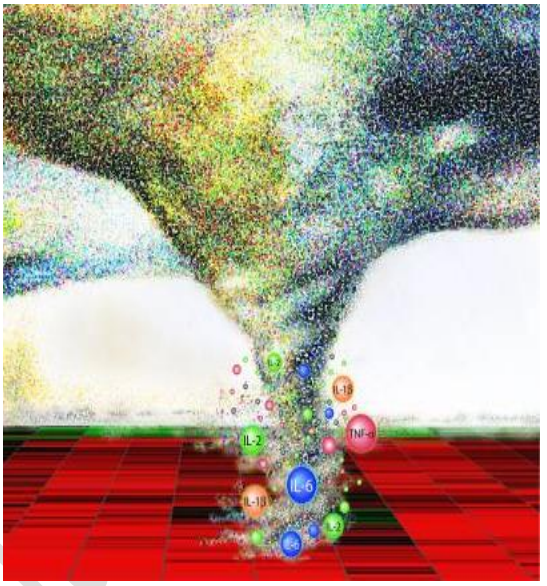
A word about the COVID19 structure and the etiopathogensis of the cytokine storm and hence the change in the Biochemical parameters.

nCOV Genome is 30 kb in size, it contains 29891 nucleotides encoding for 9860 proteins. It is a spoky virus , a single stranded RNA with numerous spikes on its surface. These spikes are glycoproteins and help in anchoring to the host cell receptors. Virus enters through nose, ears, mouth, eye and it binds to ACE 2 receptors, on lungs, liver, kidney and GIT. Receptor binding domain of s protein binds to ACE2 after primed by serine proteases. Virus attaches to the receptor, then is internalized into host cell, releases RNA, and virions (viral particles) cause the disease. These virions later burst out and bring a dysregulation to immunomodulatory system cytokine storm.

Etiopathogenesis







Whenever there is an inflammatory reaction due to an imbalance or dysregulation in the cytokine inflammatory markers it will start at a local site and spread throughout the body via systemic circulation. These inflammatory responses often occur at the expense of local organ function, particularly when tissue edema causes a rise in extravascular pressures and a reduction in tissue perfusion. The body starts a repair process as a soon after inflammation begins, and in many cases the repair process completely restores tissue and organ function. When severe inflammation or the primary etiological agent triggering inflammation damages local tissue structures, healing occurs with fibrosis, which can result in permanent organ damage.

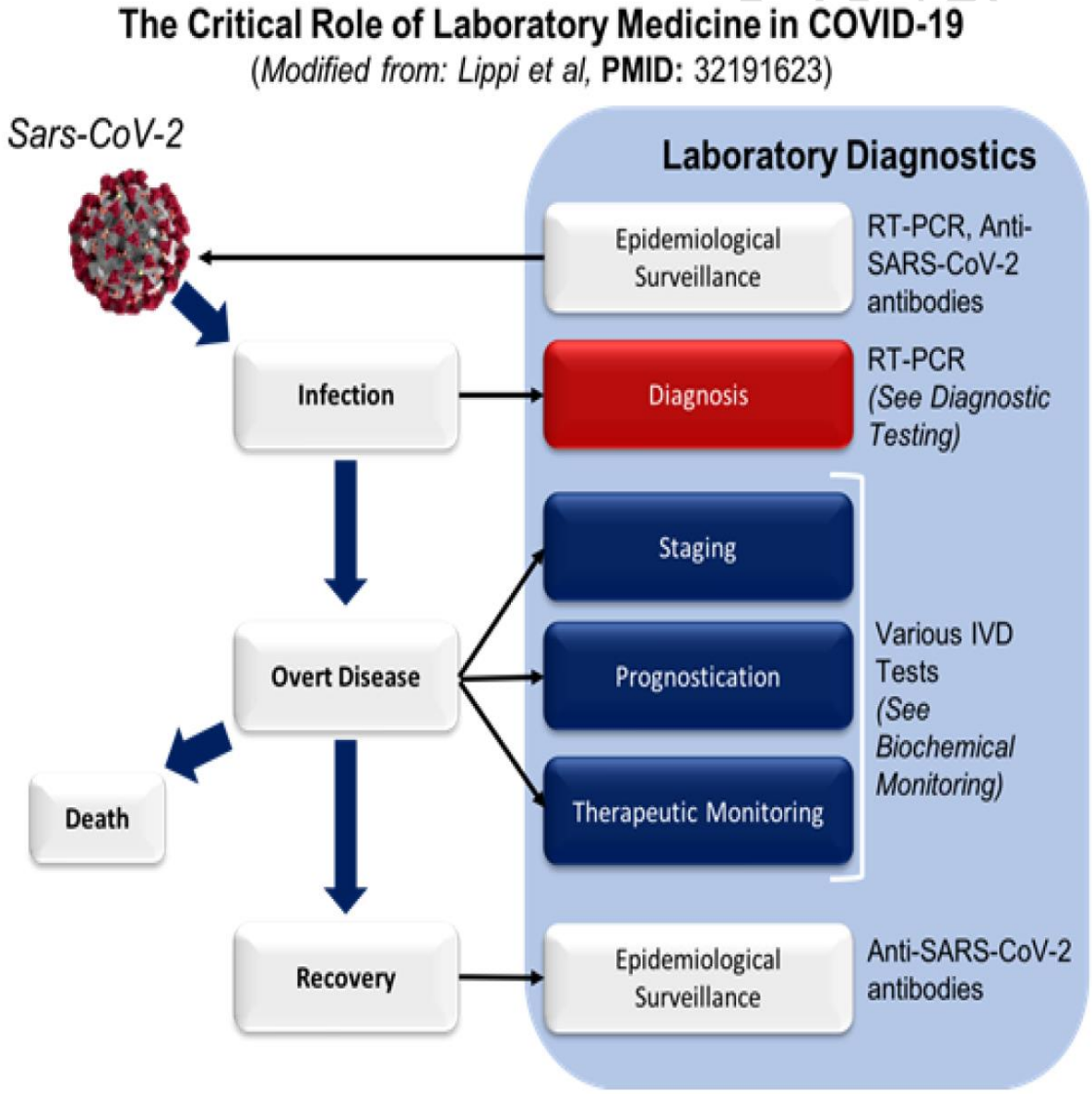
SARS-CoV infects type II pneumocytes in the alveolar walls and lead to acute lung injury. with respiratory failure, sepsis, and a cytokine storm. TNF is the main mediator of bringing inflammation, it is expressed by all cell types and ensures widespread effects of cytokine. TNF promotes IL-1 generation, and induces a change in the endothelial membrane, local cell environment, and exert broad systemic effects beyond the site of infection. The central role of TNF was attributed in other viral disease like Influenza Dengue and Ebola virus.

Another mechanism involved in regulating the proinflammatory responses is the production of anti-inflammatory cytokines, mainly IL-10 by macrophages and certain types of T cells (Th2 and regulatory T cells) and B cells .IL -10 has a significant role in fibrosis where increased Il-10 expression leads to induction of collagen production and fibrocyte recruitment into the lung . In contrast, interactions between IL-6 and its soluble receptor enhance the activity of IL-

6 on target cells, providing a mechanism for enhancing the activity of TNF and IL-1β when the concentrations of soluble TNF receptors and IL-1RA are very high.

A balance of pro- and anti-inflammatory mechanisms is critical to maintain the lung immune homeostasis, if one or more of these regulatory mechanisms are absent or differently regulated, then the outcome is devastating.

Lab medicine has an important role in coming to a comprehensive diagnosis and monitoring, so our review suggests the role of sepsis markers in defining the fatal course of COVID 19 and if required a change in the treatment modalities and appropriate interventions.



IFCC Information Guide on COVID-19 - IFCC Recommended Test List

Laboratory Test	**Main laboratory abnormalities observed in adult patients with unfavorable COVID-19 progression**	**Significant difference noted in those who need ICU admission**	**Potential clinical and biological significance**
Complete blood count	Increased white blood cell Increase neutrophil count Decreased lymphocyte count Decreased platelet count	1.5 fold increased 1.7 fold increased 0.9 fold decreased	Bacterial (super)infection Bacterial (super)infection Decreased immunological response to the virus Consumption (disseminated) coagulopathy
Albumin	Decreased	0.8 fold decreased	Impairment of liver function
Lactate Dehydrogenase	Increased	2.1 fold increased	Pulmonary injury and/or widespread organ damage
Alanine Aminotransferase	Increased	1.5 fold increased	Liver injury and/or widespread organ damage
Aspartate aminotransferase	Increased	1.8 fold increased	Liver injury and/or widespread organ damage
Total bilirubin	Increased	1.2 fold increased	Liver injury
Creatinine	Increased	1.1 fold increased	Kidney injury
Cardiac troponin	Increased	2.2 fold increased	Cardiac injury
D-Dimer	Increased	2.5 fold increased	Activation of blood coagulation and/or disseminated coagulopathy
Prothrombin Time	Increased	1.5 fold increased	Activation of blood coagulation and/or disseminated coagulopathy
Procalcitonin	Increased	1.2 fold increased	Bacterial (super)infection
C-reactive protein	Increased	1.7 fold increased	Severe viral infection/viremia/viral sepsis
Ferritin	Increased	3.0 fold increased	Severe inflammation
Cytokines (IL-6)	Increased	3.0 fold increased	Cytokine storm syndrome

Suggested Biochemical Parameters to Assess the Severity of Disease

MILD	**MODERATE**	**SEVERE**
Albumin	Albumin	Albumin
Ferritin	Ferritin	Ferritin
AST (aspartate aminotransferase)	LFT (liver function tests)	LFT (liver function tests)
ALT (alanine amino transferase)	CRP (C- reactive protein)	RFT (Renal function tests)
Creatinine	RFT (Renal function tests)	Cardiac Troponin I
		Prothrombin time
		Procalcitonin
		CRP
		IL-6

Related research work:

- Wang et al has examined 6 lab parameters through 19 days of Hospital admission in 138 patients, 33 with severe disease and 5 died during hospital stay and they observed that,
- If Procalcitonin value is raised 3fold then ICU admission is a must, studies have shown that admission in ICU vs Non admission in ICU, 75% vs 22%; $p<0.001$
- Zhang et al had considered 140 COVID cases, out of them 58 with severe disease had D-Dimer – 2fold rise, CRP -1.7 raise and procalcitonin – 2fold raise compared with milder cases.
- Huang et al , total 140 cases , 13 with severe disease .Significant predictors of ICU admission was increase in PT (1.4 fold), D-Dimer- (4.8 fold), Albumin(0.8 decreased), T.Bilirubin (1.3 fold) and LDH (1.4 fold)
- Tang et al, followed up 183 patients and found coagulation parameters were more frequently de arranged in those who die. Significantly there was increase in values of PT (1.14 fold), D-Dimer (3.5 Fold) Fibrin / Fibrinogen degraded products (1.9 Fold)
- Amyloid A is increased before fibrosis, but studies are inconclusive and this is area of further statistically significant studies

Normal Reference values:

PARAMETER	REFERENCE RANGES
Total bilirubin	Males – 0.2-1.1mg/dl Females- 0.1-0.9mg/dl
Direct bilirubin	0.11-0.42mg/dl
AST	18-34 U/L
ALT	18-78 U/L
ALP	M- 50-116 U/L, F -46-122 U/L
GGT	9-48 U/ L
Total Protein	6.5-7.8 gm/dl
Albumin	3.9- 5 gm/dl
A/G Ratio:	1.5: 1
Creatinine	M- 0.71-1.16mg/dl, F- 0.56-0.96mg/dl
Urea	15-45mg/dl
BUN	M- 9-22mg/dl, F- 8-19 mg/dl
Uric acid	M- 3.7-7.7mg/dl, F- 2.5-6.2 mg/dl
Electrolytes:	
Sodium	136-143 mmol/L
Potassium	3.8-4.9m mol/L
Chloride	102-108 mmol/L
Albumin	3.9 – 5 gm/dl
Ferritin	New born - 25 -200ng/ml 6 months -15y- 7-140 ng/ml Adult –Male- 20-250ng/ml Female- 10-120ng/ml
Cardiac Troponin I	0.00 to 0.04 ng/ml
Prothrombin time	12.7-15.4 seconds
Procalcitonin	Adults & children more than 72hrs - 0.15 ng/ml or less
CRP	Adult (20-60 y)- < 5mg/L
IL-6	Upto 1.8 pg/ml

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