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Cytokine Storm Magnifies the Mortality Rate in COVID-19 - A review

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Abstract:

The knowledge on the association between cytokine storm and CoViD-19 helps in effective treatment planning. With this background, the present review highlights the association between cytokine storm and CoViD-19 and the effective treatment planning options.The number of articles used in the present study is around 50 - 60 articles. These articles are collected from various search engines like Google Scholar, PubMed, MeSH core, MedRxiv, Cochrane, BioRxiv. Also, two primary Chinese databases for Biomedical Research purposes which includes CNKI and WanFang were used as a source for articles in this study. The relevant articles were collected from the period of 2000 to 2020 (till date). The article collection involves five steps.Cytokine storm is an excessive immune response which mediates the Pathogenesis CoViD 19 and increases the death rate. Cytokine storm is the major cause for Acute Respiratory Distress Syndrome and progresses further leading to death.Cytokine storm has to be managed at an inappropriate time to prevent the magnification of mortality. The control of the cytokine storm in the early stages through immunomodulators and cytokine antagonists is the main therapeutic option which increases the success rate and reduces the mortality rate of CoViD-19 infection. From this review study, we can see that there is a strong association between cytokine storm and CoViD-19 infection.

Keywords: CoViD-19, Cytokine storm, Corticosteroid therapy, Immunomodulators, Tocilizumab, TNF blockers

Introduction:

CoViD-19 is caused by a group of coronavirus belonging to the family of Coronaviridae. Coronaviruses are primarily the respiratory system (Girija As and Priyadharsini J, 2019; Guo *et al.*, 2020). Coronaviruses are positive RNA single-stranded spherical, enveloped virus particles of 150 – 160 nm in size (Pratha, AshwathaPratha and Geetha, 2017; Cascella*et al.*, 2020). The amino acid sequence of coronaviruses is exclusive of different types, 1ab poly protein S surface glycoprotein or S protein. The coronaviruses invading the human beings are of 7 different types namely, HCoV – 229E, HCoV – NL63, HCoV – OC43, HCoV – HKU1, SARS-CoV, MERS – CoV and finally nCoV – 19 (Ashwin and Muralidharan, 2015; Chan *et al.*, 2020). nCoV – 19 is classified as a highly pathogenic form of coronavirus. The first incidence of CoViD-19 was started in Wuhan, China in December 2019. The patient reported with the symptoms like fever,

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respiratory depression, cough and other symptoms. CT scan of the lung revealed various opacities as dense and confluent a suggestion of Pneumonia, but with a further diagnosis, it was identified as CoronaVirus(Liu *et al.*, 2020; Lu *et al.*, 2020). The mode of transmission of coronaviruses is by the inhalation of infected droplets, contact with infected persons leads to coronavirus infection (Shahana and Muralidharan, 2016; Selvakumar and Np, 2017). CoViD-19 started as a small disease and now it became a pandemic threat, and WHO declared it a global threat (Zhang *et al.*, 2020).

There are fours stages in the progression of CoViD-19 which have been reported as following (1) presymptomatic phase which reports symptoms like fever, malaise, cough and there is an increased viral load in the body (2) Pneumonia is reported due to the increasing load of virus in the lower respiratory tract and decreased viral load in the upper respiratory tract. In this stage, the humoral immune response develops and also acts as a protective barrier (Marickar, Geetha and Neelakantan, 2014). (3) Stage of increased release of cytokines (Cytokine Release Syndrome) (4) Stage of Acute Respiratory Distress Syndrome (ARDS), which when progress leads to multiple organ failure and finally death of the patient (Girija, SmilineGirija, Shankar, *et al.*, 2020; Li *et al.*, 2020).

Cytokine Release Syndrome (CRS) is a systemic inflammatory response which is caused due to an infection, drugs etc. In CRS there is increased release in pro-inflammatory mediators, cytokines, interleukins which as result produces HyperInflammation(Rothan and Byrareddy, 2020). The cytokine storm is due to an increase in IL -1β, IFN – γ, IP -10 and IL – 37, 38, magnifies the progression of the disease. Cytokine storm leads to Acute Respiratory Distress Syndrome (ARDS) and leads to multiple organ failure and finally leads to the death of the patient. IL – 6 plays a major and vital role in the cytokine storm and increases the mortality rate in CoViD-19 (Zhang *et al.*, 2008).

The knowledge about cytokine storm is essential to manage any respiratory diseases as in the pandemic CoViD-19 to manage and effective treatment planning. There is previous literature which suggests that it is also associated with respiratory diseases of the same Coronaviridae family-like SARS, MERS diseases. Similar cytokine storm is also reported in SARS and MERS-CoV where the virus gets accumulated in the lungs and leads to fibrosis of the lung and also poor disease progression. Lung fibrosis is due to the damage in the lungs as a result of cytokine storm i.e, increased levels of cytokine and C-Reactive Protein (Law *et al.*, 2005). There are studies which suggest that association between cytokine storm and respiratory diseases plays a key role in the progression of CoViD-19 disease. The knowledge and management of cytokine storm help in effective treatment planning by suppressing the release of cytokines and helps in reducing the mortality rate (Weiss and Navas-Martin, 2005).

The knowledge on the association between cytokine storm and CoViD-19 helps in effective treatment planning. With this background, the present study aims to review the association

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between cytokine storm and CoViD-19 and the effective treatment planning options. Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Arigaet *al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy*et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and Antony, 2018; Manohar and Sharma, 2018; Menon *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan*et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy*et al.*, 2019; Gheena and Ezhilarasan, 2019; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar*et al.*, 2019; Sharma *et al.*, 2019; Siddique *et al.*, 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

Retrieval Of Data:

The number of articles used in the present study is around 50 - 60 articles. These articles are collected from various search engines like Google Scholar, PubMed, MeSH core, MedRxiv, Cochrane, BioRxiv. Also, two primary Chinese databases for Biomedical Research purposes which includes CNKI and WanFang were used as a source for articles in this study. The relevant articles were collected from the period of 2000 to 2020 (till date).

The article collection involves five steps: Identification of clear objectives, Identification of all relevant articles, Selection of all articles, Data extraction from the collected articles and analysing the data extracted and reporting. Articles related to Cytokine storm associated with COVID - 19, SARS, the pathogenesis behind COVID - 19, inflammatory mediators and mortality related to COVID - 19 were included in the present study and Articles with general information, articles related to MERS were excluded from the present study.

Mechanism Of Cytokine Storm In CoViD - 19:

In the pathogenesis of any viral disease, Cytokines play a vital role in exaggerating the disease progression. The first line of defence in a viral infection is the innate immune response, however excessive and irregular immune responses produce damage to the human body. There is clinical evidence in previous literature which suggests that the Cytokine storm is exacerbating the disease progression (Perlman and Netland, 2009). An in-vitro experimental study concluded that cytokines and chemokines are released by the macrophages present in the Respiratory epithelial cells during the early stages of CoViD-19 Infection. And during the later stages, these cells secrete Interferons in low levels whereas cytokines IL -1 β, IL - 6, Tumour Necrosis Factor (TNF), Chemokines - 2, 3, 5 (CCL) are increased. The mechanism of the Cytokine storm is similar to that seen in MERS respiratory infection (Girija, Jayaseelan and Arumugam, 2018; Chen *et al.*, 2020).

Another mechanism by which COVID -19 affects the lung is with the involvement of Fas- ligand or TRAIL death receptor 5, which causes apoptosis in the alveolar epithelial cells and thereby it

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blocks the respiratory tract. When endothelial cells present in the airway undergo apoptosis it leads to vascular leakage and Alveolar oedema which finally leads to Acute Respiratory Distress Syndrome (ARDS) (Cao *et al.*, 2020). Production of IFN - α or β plays a vital role in the natural defence mechanism and during the early stages of the viral infection. However delayed immune response i,e The release of IFN inactivates the body's response to the invaded viruses. The main cause for the death of a patient with COVID - 19 is due ARDS. The factors which contribute to the pathogenesis of ARDS include IL - 6, IL - 8, IL - 1β, Granulocyte Macrophage Colony Stimulating Factor (GSF) and CCL - 2, 5, 3 , IFN - γ induced Protein. From these data we can summarise that Cytokine Strong leads to ARDS, extrapulmonary again failure and even it may lead to death (Wu *et al.*, 2020) (Figure -1).

Association Between Cytokine Storm And Disease Progression:

In CoViD 19, the subjects have increased levels and expression of IL -1β, IFN - γ, IP - 10, MCP 1. In a study from the previous literature, it is reported that IL -2R and IL -6 are increased in the serum which suggests that it increases the disease prognosis and also the severity of the disease (Yang *et al.*, 2020). The serum levels of IL-2R and IL-6 are associated with disease progression. Also, there are studies which report that CoViD-19 patients in the ICU have elevated levels of Granulocyte colony-stimulating factor, IP-10, MCP-1, Macrophage Inflammatory Protein 1A and TNF - α in addition to IL-2R and IL-6 (Vaishali and Geetha, 2018; M, Geetha and Thangavelu, 2019). Cytokine storm is fatal and is characterised by rapid proliferation and hyperactivation of T-cells, macrophages and more than 150 inflammatory cytokines and chemical mediators are released by The immune and non-immune cells. Activation of the type-1 T-helper cells is the key event (Marchingo*et al.*, 2020).

In contrast to SARS and MERS, CoViD-19 the levels of IL - 2, IL -7, IL -10, GSF, IP -10, TNF - α, were significantly increased In the blood of CoViD-19 patients when compared to SARS and MERS. A biopsy report from a patient who died of CoViD-19, Showed that there were increased levels of CCR - 4+, CCR 6+, Th 17+, CD 4 T-cells and which is an indication of T - cell hyperactivation And the severe immune response (Channappanavar*et al.*, 2019). Cytokine storm produces severe Immune damage to the tissues and organs while the immune system is also suppressed and it is not able to eradicate the virus from the body. However few studies contraindicate that cytokine storm Is independent in only CoViD-19 bye but it is associated with ARDS, SARS, MERS and other respiratory infection (Carcillo and Shakoory, 2019).

Current Management And Treatment Protocols:

The increased viral load and titre value and the levels of cytokine and chemokines can magnify the mortality rate in CoViD-19 disease (Smiline, Vijayashree and Paramasivam, 2018). The previous treatment strategies which were employed during SARS and MERS concluded that reducing the viral load with the help of the drugs which decrease inflammatory mediators was effective in the management. Therapeutic strategies for treating CoViD-19 Is based on the

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pathogenesis of CoViD-19 So it requires some special care. The management therapy for pneumonia which resulted from CoViD-19 includes supplemental oxygen therapy, Conservative fluid management, hypoxia treatment (Stockman, Bellamy and Garner, 2006). Chloroquine was recommended as an effective drug in the treatment which is also controversial as few studies suggest that it is ineffective in the treatment of COVID--19. Earlier during the SARS epidemic, Corticosteroids were used by clinicians, as corticosteroids produce an immune modulatory effect on the immune system (Arabi *et al.*, 2020).

Corticosteroid Therapy :

Corticosteroids contain steroid hormones Which have anti-inflammatory, immunosuppressive functions, Corticosteroids are primarily used for their immune suppression function. During the SARS epidemic, Corticosteroids was used as the drug of choice, because of its immunomodulatory effect. Since CoViD-19 Belongs to the same family of viruses corticosteroids can be used for treatment. In SARS, early treatment with corticosteroids increased the virus Load in the plasma which exaggerates the disease (Zha*et al.*, 2020).

When glucocorticoids are used in the treatment, it is essential to note the timing and stage in which it is administered. When corticosteroids are administered during the early stages of the disease it leads to immune suppression and also the body's defence mechanism is also suppressed which increases the viral load in the body and leads to some adverse consequences. Corticosteroids are preferred in Critically ill patients, late stages of the disease and also in conditions like cytokines storm. In Cytokine storm corticosteroids are administered in the early stage so that hyper inflammation can be prevented. Usage of corticosteroids in cytokine Storm might lead to complications like hyperglycaemia and some secondary infections (Shang *et al.*, 2020; Zhao *et al.*, 2020).

Contradicting a study reported that administration of corticosteroids during SARS, Produced twentyfold increase in the adverse effects. The adverse effects produced include dizziness, hypertension, Hyperglycaemiaetc(Wang *et al.*, no date). Besides, an increase in serum LDH enzyme level is also noted which might lead to ineffective treatment. Administrations of corticosteroids in the early stage produce various adverse effects and exaggerate the disease progression (Li *et al.*, no date) .

IL - 6 Antagonist And IFN - αβ Inhibitor:

Tocilizumab is an IL - 6 antagonist which has an immunosuppressive function. It is usually preferred for autoimmune diseases like Rheumatoid arthritis, Juvenile arthritis etc(Tanaka, Narazaki and Kishimoto, 2016). Tocilizumab inhibits IL - 6 by binding to SIL - 6R and mIL-6R receptors and blocks the signal transduction. In CoViD-19, due to hyper inflammation, there is a marked elevation of IL - 6 (Xu *et al.*, 2020). There are studies which suggest that tocilizumab can be used as a treatment for cytokine storm. In a retrospective study conducted in China, with

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20 severe cases of CoViD-19 patients administered with Tocilizumab, 50 % subjects had improved and there was a reduction in the opacity of lesion in the lung and the lymphocyte ratio was also recovered. The recommended dosage of Tocilizumab for the first dose is 4-8mg/kg body weight, in case of inefficiency of first dose second dose of the same dosage after 12 hours is recommended (Fu, Xu and Wei, 2020; Klopfenstein *et al.*, 2020).

Treatment of Tocilizumab for influenza virus did not increase the susceptibility to the infection. The adverse effects of this drug are increased susceptibility to opportunistic infections like candidiasis, aspergillosis etc., In literature, there are no studies which contradict the usage of CoViD-19 but all precautionary measures should be taken and high safety is necessary during the administration (Kawada *et al.*, 2013).

IFN - αβ inhibitor acts by Limiting the viral replication by inducing IFN stimulated genes. IFN - αβ exaggerates the progression by enhancing the recruitment and function of macrophages and other immune cells. A study conducted in the animal model by infecting with SARS - CoV, delayed IFN - αβ signalling which leads to anti-SARS-CoV immune response (Davidson, Maini and Wack, 2015). Contraindicating this IFN - αβ inhibitor is not used in humans as treatment of choice in CoViD-19 but it can be prescribed. When IFN - αβ inhibitor is to be administered the timing of drug administration is crucial i.e., it should be administered during the later stages of the disease so that hyper inflammation can be prevented (Dong, Hu and Gao, 2020).

Tumour Necrosis Factor (TNF) BLOCKERS:

Tumour Necrosis Factor is a key factor which triggers the cytokine storm. Blocking TNF is an important target in controlling the cytokine storm. A meta-analysis by Qiu P et al., suggested that Anti TNF therapy can reduce the sepsis and also increased the survival rate in CoViD-19 infection. A study conducted in mice infected with SARS-CoV infection revealed that protection from SARS-CoV is achieved due to neutralisation of TNF activity or loss of TNF receptor and thereby decreasing the mortality rate. During the later stages of CoViD-19 TNF is not detected in the serum (Qiu*et al.*, 2013).

Contraindicating these TNF blockers is not given to patients but it can be suggested that it can be used as a therapeutic option. The exploration of TNF Blockers has to be done to use it in patients. There is no evidence indicating that TNF blockers are harmful and cannot be used for SARS, CoViD-19 infection (Ye, Wang and Mao, 2020).

Effectiveness Of Chloroquine:

Chloroquine is a drug which is generally used for the treatment of malaria and is a derivative of Hydroxychloroquine. Chloroquine has anti-malarial, antiviral and anti-inflammatory, by virtue of its anti-inflammatory property it is also used in the treatment of autoimmune diseases like

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rheumatoid arthritis and Systemic Lupus Erythematosus, here it acts by inhibiting MHC-Class II cells. In recent times, it was reported to be an effective drug in the treatment of CoViD-19 (Sun *et al.*, 2020). It acts by reducing the effect of the cytokine storm by inhibiting the release of TNF and IL-6. Chloroquine has the ability to get accumulated in the acidic organelles like lysosome, endosomes and inhibits the replication of the virus by increasing the pH of these organelles. In a study by Gao et al., among the 100 Chinese patients with CoViD-19 concluded that Chloroquine receiving patients showed good clinical improvement. The recommended dosage of hydroxychloroquine is 200mg, three times per day for 10 days (Gao, Tian and Yang, 2020).

Blood Purification Treatment And Stem Cell Therapy:

Plasma exchange, adsorption, blood filtration, perfusion, plasma filtration etc are some of the blood purification systems, can be employed for the removal of the inflammatory factors from the blood and reduce the cytokine storm and the damage caused in the body because of the inflammatory response to some extent (Girija*et al.*, 2019). During the early stages, blood purification treatment is effective and not that effective in the later stages of the CoViD-19 disease. Li Lanjuan from China introduced the method of artificial liver technology, helps in the elimination of the inflammatory factors and reduce the effect of cytokine storm in CoViD-19. Renal replacement therapy can also be used for reducing the effect of the cytokine storm (Paramasivam, VijayashreePriyadharsini and Raghunandhakumar, 2020; Zuccari *et al.*, 2020).

Mesenchymal stem cells are a group of undifferentiated stem cells which possess the ability of self-renewal capacity and differentiation into any particular cell or tissue. These stem cells have immune-regulation and anti-inflammatory functions, abnormal activation of T-lymphocytes and Macrophages can also be inhibited (Priyadharsini*et al.*, 2018a). It also possesses the potential to inhibit the inflammatory cytokines and prevent/reduce the occurrence of cytokine storm in CoViD-19. It not only helps in the prevention of cytokine storm also helps in regeneration and repairing of the damaged lung tissues. Stem cell therapy can also be used in the treatment of CoVid-19 (Lee *et al.*, 2011).Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; VijayashreePriyadharsini, SmilineGirija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramaduraiet *al.*, 2019; Sridharan *et al.*, 2019; VijayashreePriyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

Development Of Vaccine :

Vaccines are preparation which is developed and can be used as immunoprophylactic agents /sources. It takes around 12 years for development and getting approval for the vaccine (Shahzan*et al.*, 2019). But in the case of pandemic CoViD-19 vaccine, development duration for different phases is reduced. Currently, the different vaccine preparation characteristics are LNP-encapsulated mRNA vaccine encoding S protein (mRNA-1273 Candidate), DNA plasmid

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encoding S protein delivered by electroporation (INO-4800 Candidate), Adenovirus type 5 vector that expresses S protein (Ad5-nCoV candidates) are in phase I of the clinical trials (Le *et al.*, 2020). If the vaccines which are developed are effective and potential in all the three phases of the clinical trials, vaccines would be available within a time period of 6 months to 1 year. During the development of vaccines there are different challenges and limitations like structural modifications in the domain receptor, the vaccine is developed should be safe, effective and provide long term immunity etc. In Silico docking approach, usage of microbial bioinformatics for choosing the vaccine candidates can also be used (Priyadharsini*et al.*, 2018b; Girija, SmilineGirija, Shoba, *et al.*, 2020).

Conclusion:

Inflammation being a part of the immune system helps in generating immune response to successfully eliminate the microbes from the body. But in the case of CoVid-19, there is hyper inflammation due to excessive release of inflammatory mediators like cytokines and chemokines resulting in cytokine storm. Cytokine storm has to be managed at an inappropriate time to prevent the magnification of mortality. The control of the cytokine storm in the early stages through immunomodulators and cytokine antagonists is the main therapeutic option which increases the success rate and reduces the mortality rate of CoViD-19 infection. This review thus had provided an insight into the strong association between cytokine storm and CoViD-19 infection with the immune-blockers and their mechanisms.

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Author Contribution :

V.T.ThamaraiSelvi :

1. Execution of the work
2. Data collection
3. Drafting of manuscript

SmilineGirija .A.S. :

1. Concept and design of the study
2. Validation of the data collection
3. Revision and proof-reading of the review

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BrundhaM.P. :

1. Validation of the data collection
2. Revision and proof-reading of the review

Conflicts Of Interest :

None to declare

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Title of the figure

Figure 1: Mechanism Of Cytokine Storm In Covid-19

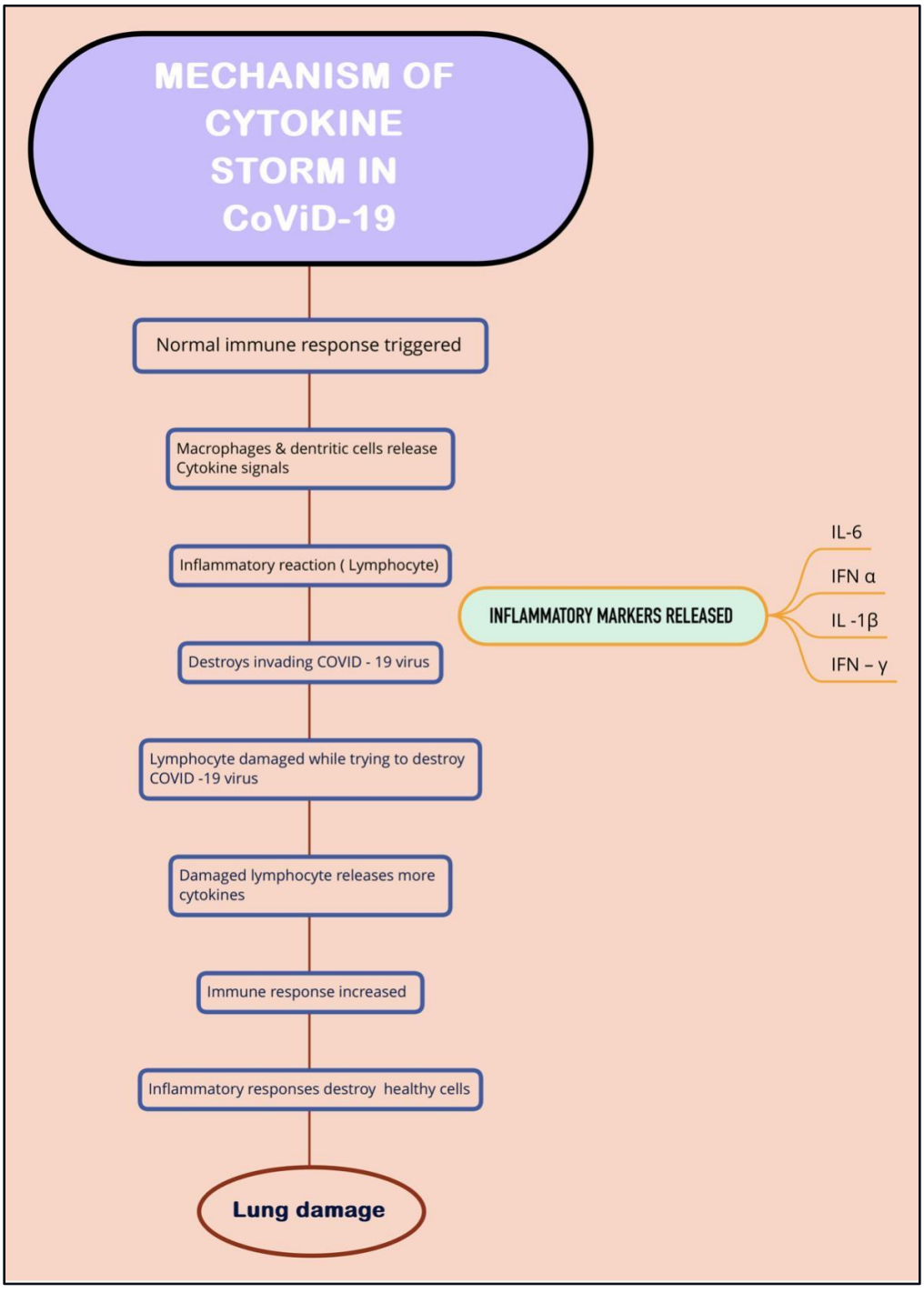

Figure 1 Elucidating the mechanism of cytokine storm in CoViD-19