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# Immunosuppression Drugs Seize the Overacting Immune System by Preventing the Cytokine Storm In COVID-19 Symptoms

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**ABSTRACT**

The COVID-19 over-active other diseases within the human body especially respiratory system in which cytokine storm abnormally developed that results in the excessive killing of cells within the autoimmune system. To resolve this major issue, a systematic review paper is developed whose major aim is to propose such immunosuppression drugs that can easily seize the overacted immune system by blocking the cytokine storm action within human body, by systematically overview the previous scholars' articles, case reports and authentic websites based valid data. To justify this aim, different latest and authentic medicine's journals and papers are collected by posting four major keywords like "Cytokine Storm, Cytokine Storm in COVID-19 Symptoms, Immunosuppression Drugs and Immunosuppression Drugs to prevent the Cytokine storm." The major databases of this review paper are Science Direct, Wiley Online Library, Elsevier, Springer, Google Scholar, and other related ones. After collecting the random data, the proper inclusion and exclusion criteria implemented to synchronize the data into an authentic format for content analysis. According to the previous scholars' outcomes, Cyclosporine, Tocilizumab, Canakinumab, Corticosteroids are such immunosuppression drugs that play significant role in reducing the action of cytokine storm which becomes over-activated due to COVID-19 attack; also Remdesivir based immunopathology helps to reduce the auto-immune system of COVID-19 patient. But small dose of Tocilizumab and Hydroxychloroquine caused a major side effect on the COVID-19 patient. To further justify the hypothesis, rigorous studies are needed. Also, if the more searched papers considered for a review then more authentic outcomes will be generated.

**Keywords:** Cytokine Storm, COVID-19, Immunosuppression Drugs, autoimmune system

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## INTRODUCTION

### Cytokine Storm

A cytokine storm (CS) is also known as hypercytokinemia which is such a physiological reaction that is developed among human beings and other animals in which the innate immune system causes an excessive and uncontrolled release of the pro-inflammatory signaling molecules called as cytokines[1]. According to Krishna Kanty Gupta and others (2020), the targeting of cancer cells with the bispecific antibodies' administration and the natural extracts result in an elevated circulatory level of inflammatory cytokines named as interleukin and interferon. According to them, the cytokines' sustainable release due to hormonal and immunotherapy issues causes many kind of diseases[2]. In the cytokine syndrome, a diverse set of situations are unified by a clinical phenotype of multi-organ failure, systematic inflammation and hyperferritinemia, and mostly result into death in untreated scenarios. This clinical constellation is mostly generated by exaggeration of excessive amount of inflammatory mediators due to unchecked feed-forward immune amplification and activation[3]. The cytokine is an essential signal that helps to kill the disease-causing cell within an immune system[4], but if the excessive number of dead cells generated in the over-active immune system, then this cytokine storm signals generated within the human body that cause an uncontrollable infection within the body.

The previous literature depicts that IL-6 directly contributes to the host defense against any tissue injuries and infections. Within the human body, the excessive synthesis of IL-6 during fighting with environmental stress results in acute serious inflammatory outcomes known as storm that cause a high level of IL-6 to activate the vascular endothelial and coagulation pathway cells but inhibit the myocardial function[5]. In previous researches, this IL-6 therapy has been used by utilizing the humanized anti-IL-6 receptor antibody by proposing a systematic inflammatory response syndrome i.e. macrophage activation syndrome, sepsis and hemophagocytic lymphohistiocytosis. According to Ethan Sen and other (2019), the existence of such cytokine storm syndrome (CSS) majorly causes a failure of the appropriate

immune system with specific dysfunction of NK cells and cytotoxic T cells. Well, the most common virual infection triggering CSS is the Epstein-Barr virus and causes 74% of children affected by these symptoms[6]. In the COVID-19 pandemic, there are more chances to develop cytokine storm (CS) within the infectious body. In severe situation, the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) cause COVID-19 that result in acute respiratory distress syndrome (ARDS) and life-threatening pneumonia among a large number of individuals. Till now, the COVID-19 mechanism induced the lung injury, and the term of this cytokine storm resembles with pathophysiology. According to medical field scholars, sarilumab and tocilizumab are such monoclonal antibodies that directly targeted the interleukin (IL)-6 activity and helps to treat the patient[7].

## Cytokine Storm in COVID-19 Situation

In the peer review, many articles have been published to explore ways to overcome the cytokine storm in the COVID-19 situation. Pathogenesis is the complex but major helps to make a regulatory control of proinflammatory cytokine production at both the systematic and local levels[8]. As far as considering the involvement of chemokine and chemokine-receptor system within the cytokine storm occurrence in the COVID-19 pandemic, it becomes clear that chemokines are such low molecular weight proteins that powerful chemoattractant activity plays a major role in the immune cell recruitment during inflammation[9]. In the Autoimmunity Review based research article, the MAS-like syndrome mostly occurs in COVID-19 situation in which the abnormal activity of cells makes the situation more critical for patient survival[10]. Within this disease, melatonin act as an influencer who induces the circadian gene, Bmal1, which unconstraint the pyruvate dehydrogenase complex (PDC) that result in countering of Bmal1/PDC[11]. There are different types of cytokines and each is distinct in its response based on receptors like increase and decrease of inflammation, recruitment of more immune cells, and damage body tissues[12]. The cytokine storm's symptoms have been seen through high-grade fever, muscle & joint pain, rash, CNS symptoms, low blood pressure, vomiting & nausea, and worsening of dyspnea[13].

According to statistics, ARDS is such a common manifestation that followed by critical multiple organ failure because of the high mortality rate of 7-10% in the elderly population with underlying 1-3 disease[14]. In the current situation, majority of deaths and multi-organ failure are occurred due to widespread tissue damages and the ARDS aggravation because of excessive production of pro-inflammatory cytokines[15]. In the COVID-19 pandemic, the accumulation of monocyte and depletion of tissue-resident alveolar macrophages derived the inflammatory macrophages that directly linked with disease severity. In such situation, the inflammatory macrophages adopted the monocyte-recruiting and interferon-signaling chemokine programs that may cause ARDS[1]. This virus also has a detrimental impact on the neurological function and causes severe damages within human body along with severe acute respiratory syndrome CoV2 that results in many neurological diseases[16]. In that case, there is an urgent need to develop authentic prevention and treatment especially for TH17 type immune profiles[17].

## Immunosuppressant Drugs

In that case, the immunosuppressant drugs are efficient sources to reduce or suppress the strength of the body's immune system, and some of its drugs are used to reduce the ratio of transplanted organ i.e. kidney, heart and liver. They are mostly known as antirejection drugs and also majorly used to treat rheumatoid arthritis, psoriasis and lupus based autoimmune order[18]. This type of drug directly helps to reduce the risk of chronic or acute rejection of the allograft especially in Kidney transplant situations[19]. This immunosuppressive medication results in enhancing the quality of life, recurrent disease and natural development of co-morbidities. IS agents used in the liver transplantation's induction, the reversal of organ rejection and maintenance of organ[20]. In such immunosuppressive therapies, the proper vaccination guidance followed by the patients who have the immune-mediated disorder because such under observation treatment results in the resolving of complicated situations of patient[21]. In previous literature, there was also a discussion on ten major primary care things followed for the maintenance of immunosuppression for the transplant recipients; and they are 1) maintenance of appropriate immunosuppressive medication, 2) common drug-drug interaction with immunosuppressive medication, 3) therapeutic drug monitoring for immunosuppressive medication, 4) women with child-bearing potential, 5) non-adherence, 6) recurrent urinary tract infection in the kidney transplant recipients, 7) post-transplant diarrhea, 8) bone pain, 9) post-transplant erythrocytosis, and 10) elective surgeries[22]. Also, the longitudinal immunosuppression based medical data (i.e. granular and longitudinal) can easily reduce the misclassification bias in the solid organic transplantation cohorts[23]. A similar paper was generated by Steven Lvulich with others (2018) that enhancement of immunosuppression is a key factor of the ongoing success of lung transplantation in which the previous history of patient is essential to make a decision regarding which kind of mediation is given to the patient. Such kind of in-depth study on patient medical history helps the doctor to recommend the favorable drug to resolve the complications of the immune system[24]. In 2013, the number of immunosuppressed adults in the United States was unknown, but with time, their percentage becomes increases due to the improvement in medical science, its management, and the new indicators in the immunosuppressive treatment[25]. The implementation of immunosuppressive therapies for the immune-mediated disease is directly linked with infections elevated risk and the related comorbidities, and such disease can be prevented through vaccine[21]. In the treatment, the majority of immunosuppressive drugs are developed before identifying and function of Treg. Well, an authentic preclinical and clinical evidences help to develop treg-friendly immunosuppressive regimes[26]. According to studies, the surgical risk is much high in the transplanted patient and the modified gastrointestinal anatomy after the bariatric majorly leads to the pharmacokinetic alteration in the immunosuppressive drugs' absorption. To resolve this, doctors/ surgeons majorly studied the weight loss, changes in dosage, improvement in comorbidities and the immunosuppression drugs before and after the vaccination of patient[27]. A case report on the relevant topic depicts that this immunosuppression drugs also cause a side effect on the

health of patients like mostly children who have ascites and hepatomegaly and treated with such drugs are suffered from hepatosplenomegaly, pancytopenia and fever[28].

In coronavirus pandemic, there are more chances to reduce the death rate of people by using immunosuppression drugs after doctor prescription only[29]. Because its usage increases more chances to reduce the abnormal activity of the immune system. It's true that this disease faced many therapeutic challenges on which the patient mortality generated through acute respiratory factor syndrome (SRDS) and such cytokine release syndrome result in excessive inflammation and the IL-6 receptor inhibitors within an infectious body[30]. This severe acute respiratory coronavirus 2 (SARS-Cov2) outbreak makes human life in danger, so in that case, the previous literature only highlights the usage of efficient immunosuppression drugs and therapies by exploring its management in transplant recipients along with discussing the calcineurin, steroids and mycophenolic acid's role[31].

### Problem Statement

The problem statement of this informative paper is to critically understand the significance of immunosuppression drugs and their implication to prevent the existence of cytokine storms within an infected body COVID-19 patient by seizing the overacted immune system.

### Research Objectives and Hypothesis

After critically considered the previous background study of the selected variables of this systematic review paper, it becomes clear that its major aim is to critically examine the significant impact of immunosuppression drugs in the prevention of cytokine storm by critically reviewing the experiments, theories, and point of medicine scholars. This paper will be an informative and challenging approach to critically inspect how the proper medication treatment to a coronavirus disease patient can cause positive outcomes like normalize the efficient performance of cells within the immune system. However, the previous researches have been made on the related topic, but this review paper has a major aim to make authentic and highly acceptable research by majorly focused on the peer articles in the medical field. This paper is majorly attempted to consider and evaluate the latest relatively scare literature and answer some questions about the mechanism required for the selection and prescription of immunosuppression drugs to seize the overactive immune system of COVID-19 affected individuals. In addition to this, the previous scholars' work regarding such drugs and their significance in the current virus-based disease situation will be majorly considered within this informative study. This challenging study hypothesizes that there is a significant impact of immunosuppression drugs on reduction of cytokine storm occurrence due to SARS-Cov2 symptoms within a human body. This hypothesis is majorly derived from the previous scholars' work that are only based on exploring the immunosuppression drugs' significance for the liver transplant and other disease orientation vaccination mechanism, but nobody majorly works on exploring its diversified dose based implication for the presentation of coronavirus disease and its symptoms within the immune system of a person of any age and gender.

## MATERIAL AND METHODS

### Search Strategy

In this informative study, a systematic review-based search strategy has been majorly considered where the previous authentic and published articles, editorials and reliable website data were used to justify the hypothesis of this paper. In order to make an authentic search, some efficient keywords were used that completely relevant to the topic like Cytokine Storm, Cytokine Storm in COVID-19 Symptoms, Immunosuppression Drugs and Immunosuppression Drugs to reduce the Cytokine Storm.

These keywords were majorly considered because all of them were directly associated with the thesis statement of this review paper. Like the cytokine storm is the bone of contention in the severe acute respiratory system coronavirus 2 (SARS-Cov2) symptom whose occurrence causes a disaster within the immune system of a person due to lack of proper functioning of cell-cell communication. So, this variable was initially selected to understand the nature, performance and side effects of this signal to the cells. Its relevant articles' information helps to add value in the critical evaluation of this signal before considering its remedy drug. Secondly, Cytokine Storm in COVID-19 Symptoms based keyword used that helps to understand the generation of cytokine storm due to the SARS-Cov2 within a human body.

The major reason to utilize this keyword is to inspect how many cases regarding SARS-Cov2 has been seen and how this virus has easily spread throughout the human body. The previous scholars' information regarding this topic enhanced the reliability of its systematic review. This keyword is one of the highly effective to understand this cytokine storm cause a major change in the immune system signaling that the future increased the adverse impact of COVID-19 on the human body. The third keyword which was used to data collection mechanism based on Immunosuppression Drug in which different authentic and published articles were shown whose information furthers enhanced the authenticity of this paper analysis portion. This keyword was used to collect the relevant information regarding these drugs, their working, efficiency, and implications in many medical cases and resolve all the confusion regarding drug and its usage in the favorable outcomes for the prevention of cytokine storm within the immune system. Last but not the least, immunosuppression drug to prevent the cytokine storm based major independent variable used to collect the relevant information. This keyword helps a lot to understand the working of this drug for the COVID-19 patients in the current era and to develop an authentic systematic review of the peer articles. These last two keywords data were also collected from the official websites whose valid information enhanced the reliability of this review paper.

Overall all these key terms helped a lot to collect the relevant articles from different authentic medical science journals like Undergraduate Medical Research Journal, Journal of Canadian Association of Gastroenterology, Eastern Journal of Hospital Medicine, Transplant Infectious Disease journal, American Journal of Transplantation, Journal of cutaneous medicine and surgery, Journal of cutaneous medicine and surgery, Wiley Online Library, Elsevier, Springer and other related ones. The time duration of the relevant secondary data collection is based on ten years (from 2010-2019), but majorly

focused on collecting the relevant research articles because this review paper has a major aim to reduce the current coronavirus symptoms and their immune system prevention-based authentic systematic analysis of previous years researches. The search strategy which was adopted to collect the relevant data have been shown in table 1 which depicts that how many authentic articles, published journals and related results are generated after posting the eye-catching keywords associated with this paper. Its tabular representation has been seen in Table No 1 in the appendix. According to the table's outcomes, the majority of the authentic results are generated with the keyword of "Cytokine Storm in COVID-19 Symptoms" and "Immunosuppression Drugs to prevent the Cytokine storm" in the google chrome and google scholar websites. This search method helped a lot to make an efficient systematic review of the related medical journal's papers.

**Table 1:** Search Strategy Adopted for this Systematic Review

| Search Strategy Adopted for this Systematic Review | |
|---|---|
| **Search** | **Result** |
| Cytokine Storm | 6 |
| Cytokine Storm in COVID-19 Symptoms | 22 |
| Immunosuppression Drugs | 17 |
| Immunosuppression Drugs to prevent the Cytokine storm | 23 |

### Inclusion and Exclusion Criteria

In order to efficiently synchronize the data from the previous researches, the systematic inclusion and exclusion criteria technique was used which helped to divide the randomly collected data in the proper categorical format. This inclusion and exclusion criteria helped to set the boundaries for this systematic review after setting the research question before the search conducted and then scope the searches to determine the appropriate criteria; as shown in the appendix, figure no 1. That figure depicts that in the initial stage, all-around 68 articles associated with the thesis statement were considered in which the dispersed form of data was collected in the identification phase. After this in the screening phase, the duplicated record was eliminated and only 65 authentic articles remained for the authentic systematic review. After excluding the ineligible articles from the secondary source-based papers, only 25 highly acceptable papers are collected. In these 25 articles, 20 articles were excluded and, in the end, only 5 authentic articles remained for this qualitative hypothesis based systematic review. It becomes clear that from 68 papers data, only 5 of them are those whose information is directly linked with this paper.

## RESULTS

**Influence of Immunosuppression drugs to remove Cytokine storm based autoimmune disease**

According to the previous researches if becomes clear that majority of autoimmune diseases are treated through immunosuppression drugs like psoriasis, alopecia areata, rheumatoid arthritis, lupus, multiple sclerosis and Crohn's disease[32]. These drugs help to reduce the overacted immune system within the human body by significantly controlling the cytokine storm based abnormal signaling and overcome the excessive death of cells. When the list of medicines is considered, it comes to the knowledge that corticosteroids are based on prednisone, budesonide and prednisolone[33]. While the medication of Janus Kinase inhabitors includes tofacitinib and calcineurin inhibitors (tacrolimus and cyclosporine). According to studies, the mTOD inhibitors include sirolimus and everolimus; IMDH inhibitors are based on azathioprine, mycophenolate and lefunomide; and monocloinal antibodies consist of basiliximab and daclizumab. Also the biologics immunosuppression drugs are given to the patient named as abatacept, anakinra, golimumab, vedolizumab, tocilizumab, rituximab, ustekinumab, secukinumab, ixekizumab, infliximab, etanercept, adalimumab and certolizumab[34].

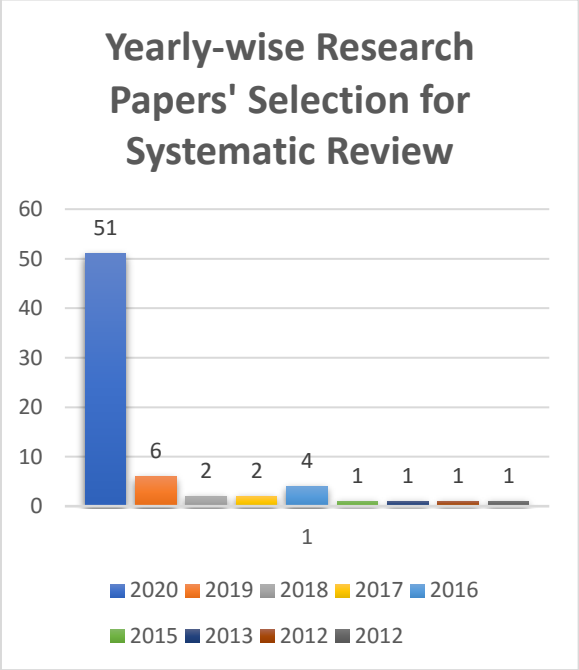


**Figure 1:** Selection of the studies to be included in the systematic review

All these drugs are used to reduce the abnormal working of the body cells that mostly activated in viral disease. The Melatonin is such an effective drug which is mostly used for insomnia and results in the beneficial effect in majority of other diseases like respiratory distress and atherosclerosis[35]. In SARS-CoV-2, there are more chances to increase the IFN-γ, IL-1β, MCP-1 and IP-10 in addition to IL-10 and IL-14 which result in the diminished in many patients with SARS[36]. The people in the worldwide used this type of therapy in case of urgent treatment in this viral disease.

### Immunosuppression Drugs implication in SARS-CoV2

Within the COVID-19 disease, the cytokine profile resembles with sHLH that result in the severity of this disease and end with the increase of interleukin (IL)-2 and IL-7, interferon-inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein, monocyte chemo-attractant protein 1 and the tumor necrosis factor[37]. In the current era, the majority of doctors made some efficient policies and supportive measures to reduce respiratory failure from acute respiratory distress syndrome (ARDS) which is the

major cause of mortality. Also, the haemophagocytic lymphohistiocytosis (sHLH) is such a hyperinflammatory and under-recognized syndrome that causes a fatal and fulminant hypercytokinaemia with the multiorgan failure. In majoroity of adults, this sHLH is occurred by this viral infection with 3.7%-4.3% of sepsis cases. Cardinal feature of such sHLH includes the cytopenia, unremitting fever and the hyperferritinemia; while the pulmonary involvement occurs in 50% of patients. However, the immunosuppression is considered as a beneficial source for such hyper inflammation[38]. According to previous scholars, those patients who have severe COVID-19 must be screened for the hyper inflammation by using laboratory trends like decreasing the platelet counts, increasing ferritin and the erythrocyte sedimentation rate, and the HScroe helps to consider the patients' medical report in order to implement the immunosuppression to enhance the mortality rate.

Both children and adults' immune system shows different responses in COVID-19 infection. In this case, the Ankinra based biologic immunosuppressant is safe and more effective in the auto-inflammatory and other inflammatory disorders, and could be a beneficial source to overcome the COVID-19 based cytokine storm syndrome within an infected body in which the disordered host responses directly contributed to pathology. Under this immunosuppressant process, the antiphospholipid antibodies, inflammatory endothelial activation, and complement activation directly promote the coagulopathy and proinflammatory state. In this case, the prospective controlled trials are essential to generate evidence for individualized treatment and stage-specific options in COVID-19[39].

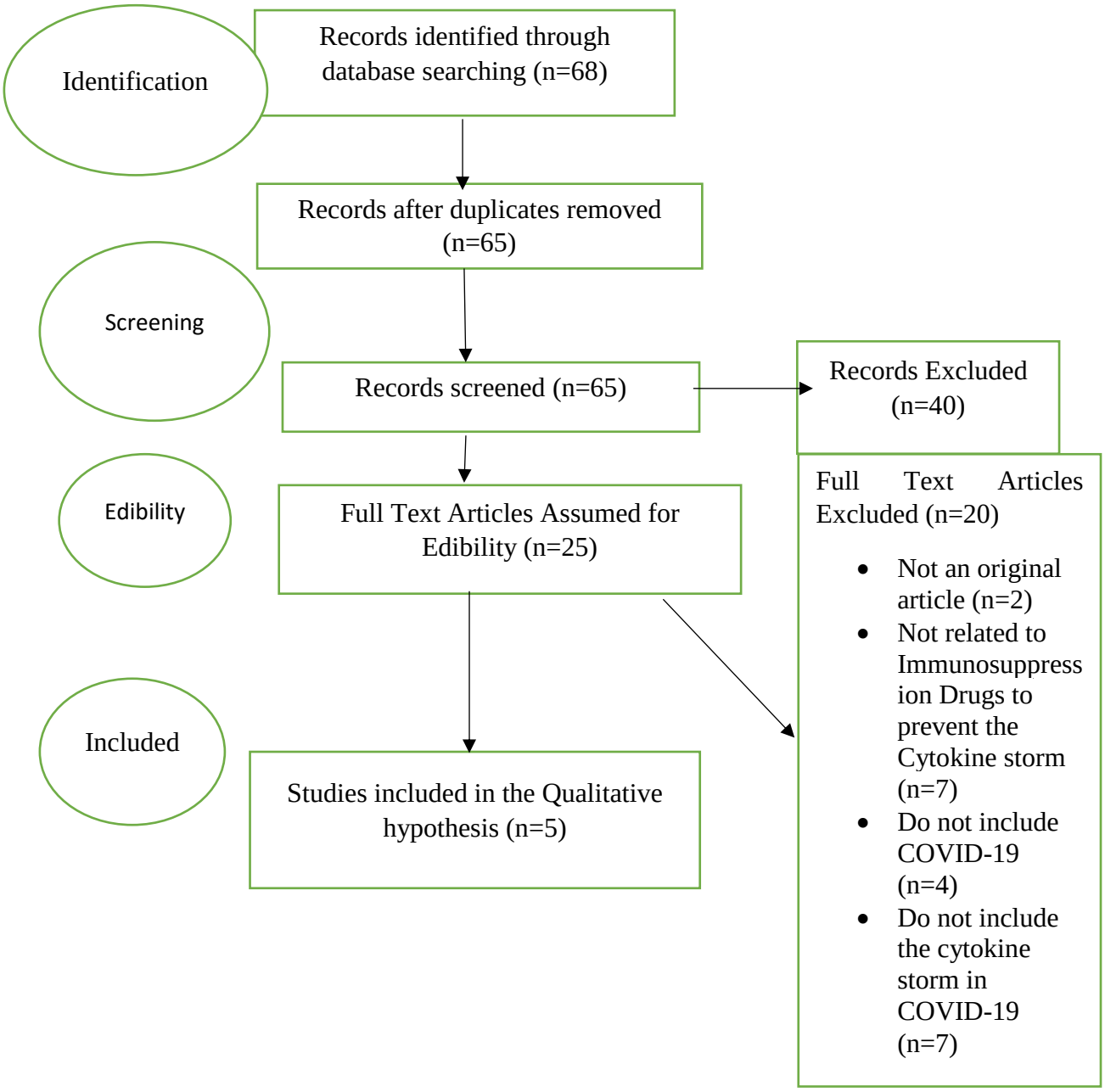


**Figure 2:** Yearly wise Research Papers' Selection for Systematic Review

## Corticosteroids

In that case of reducing the overactive immune system working within the human body, there is a need to majorly work to utilize the immunosuppressive supplements[40]. Like the Corticosteroid can effectively use to reduce the inflammation directly associated with the various condition[35]. Like they blind the cytoplasmic corticosteroid receptors which translate the nucleus and overcome the activity of the proinflammatory transcription factors named as activator protein-1 and NF-kB. Such activation of the corticosteroid receptors directly regulates the transcription of the anti-inflammatory genes that result in the mediators involved in the cytokine storm which directly reduce their abnormal action due to corticosteroid treatment. Within the coronavirus pandemic, such actions help to control the inflammation linked with the COVID-19[41]. One of the major reasons that hindered their utilization in the viral infection is their efficient immunosuppressive behavior. Like such corticosteroids directly boost the function of many immune cells e.g. inhibit the activation of T cells, antagonize the macrophages differentiation, suppress the dendritic cells, and reduce the number of circulating B cells.

Such corticosteroids were administered in many SARS outbreak where the implication oriented clinical data directly deteriorate the patient's condition[42]. The world health organization (WHO) on Han 28, 2020 also recommended treatment guidelines of corticosteroids after critically considering the COVID-19 patient condition[43]. It's true that dexamethasone is such widely available and inexpensive corticosteroid which directly associated with the reduction of the mortality in critically ill COVID-19 patients. In addition to this, dexamethasone use is also considered[44]. According to recent studies, the corticosteroid methylprednisolone medication to the hospitalized COVID-19 patients directly enhanced the favorable clinical outcomes like 81 patients who carry care therapy are compared with 132 patients who received early treatment with methylprednisolone (0.5 to 1 mg/kg/day divided into two intravenous doses for three days)[45]. In the end, those methylprednisolone groups shown fewer patients needing the transfer from the general medical unit to ICU, the fewer patients needed mechanical ventilation, and the mortality and hospital stay's length were both reduced. Such dexamethasone drug usage in server COVID-19 shows a favorable outcome[46].

## Canakinumab

Canakinumab is such an IL-1 indicator which mostly considered for the immunosuppression based medication for the COVI-19 patient[47]. It is also an anti-IL-1beta monoclonal antibody that helps to diagnose with the cryoprin-associated periodic syndrome and received the canakinumab as a treatment of a case. According to previous scholars, such interleukin blockade by the canakinumab helps to prevent COVID-19 possession[30]. This type of medication also helps to reduce the respiratory failure and hyper-inflammation by providing a single subcutaneous dose of the canakinumab along with the standard therapy to the COVI_19 patient[48]. According to previous statistics, such canakinumab dosing shows a remarkable decrease in the CRP levels and the rapid enhancement of the rapid improvement in the oxygenation as compared to the other standard treatment group. This shows that those patients who are treated with canakinumab do not show major systematic adverse events or any sign of server impression. So, it becomes concluded that it is a safe and effective treatment method to reduce the symptoms of cytokine storm symptoms of COVID-19 patients[49].

## Tocilizumab

Along with other prescriptions of the immunosuppression drugs, the Tocilizumab also shows the promissory outcomes to an overactive immune system within a body[50]. Those patients who are on the ventilator can utilize this Tocilizumab drug in order to survive in such a pandemic situation. This is considered as such a drug which is used to treat the various forms of arthritis and also known as the experimental treatment method for the coronavirus patient[51]. Such drugs can never be administered to the pregnant women and the eligible patients who have acute respiratory distress syndrome, impending respiratory compromise or ARDS. Majority of previous researches help to understand the influence of such immunomodulatory drug who act as a humanized monoclonal antibody against the interleukin-6 and used for the treatment of rheumatoid arthritis[52]. Its major purpose is to modulate the cytokine storm within the COVID-19 patient body where the hyper-immune response to pneumonia caused such a virus where the over-reactive immune system attack itself, just like Lupus. This drug is excessively used because it is cheap and also carry an old drug of Hydro chloroquine (HCQ) that used both Lupus and rheumatoid to efficiently modulate the immune response[53]. In the extreme situation, the cytokine storm directly damages the ability of the human body to fight against the virus and the double-pneumonia that result in the insufficient lung capacity to provide efficient support to the oxygenation of the heart that may result in heart failure or death. In that case, this Tocilizumab cased immunosuppression drug helps to sustain the COVID-19 patient health[54].

## Cyclosporine

Cyclosporine is used as such an immunosuppressive drug which is used to prevent organ rejection after the heart, kidney or liver transplant[55]. Many researchers considered it as a valid candidate to treat acute respiratory failure in COVID-19 patient. This drug helps to directly overcome the hyper inflammation-induced lung injury factors by directly inactivate the viral replication[56]. This drug is quite affordable and easily available and comparatively safer as compared to the other antivirus drugs. This drug is mostly used to prevent organ rejection and treat with T-cell directly associated with the autoimmune disease[53]. This drug exerts immunosuppressive and other anti-inflammatory impacts by binding to cyclophilin-A which directly prevents the activated T cell's nuclear factor activation and other genes' transcription that is required for T cell proliferation. This drug helps to dysregulated immune response in the setting of COVID-19 related to ARF. Also, it helps to promote the antiviral activity against the coronavirus within the human body by blocking the replication of all the coronavirus genera[57]. This type of drug is majorly used to prevent the rejection in organ transplantation. It was first used in the kidney transplant

patient in 1978 and now its implications enhanced its benefits to treat the COVID-19[58].

### Hydroxychloroquine (HCQ)

Also, the hydroxychloroquine and chloroquine based antiviral drugs are used for the potential therapies for COVID-19[59]. These drugs significantly reduce the CD154 expression in the T cells and also suppress the release of TNF and IL-6. Under the test of such drugs, the veroi cells explored that a low dose of HCQ result in the mitigation of the cytokine storm among those patients who have severe COVID-19[60]. Such an appropriate dose results in the significant reduction of the viral load, and the viral infection's duration also reduced due to this dose. This HCQ is considered as more harmful than the good based on its side effects which include cardiomyopathy, myopathy and neuropathy. Sometimes the high dose of HCQ also causes arrhythmia. This shows that till now, there is a need to upgrade the dosing influence of these drugs[61].

### Tocilizumab (TCZ)

Tocilizumab is such IL-6 receptor (IL) 6R antagonist which directly inhibits the cytokine storms by blocking the pathway of IL-6 signal transduction. This drug is mostly given to the critically ill patient of COVID-19[62]. According to previous statistics, out of 21 patients, 90% recovered after a few days of treatment with this TCZ dose[63]. In addition, there are also some risks associated with TCZ named as liver damage, severe infections, neutropenia and thrombocytopenia. Till now, the usage of this TCZ drug for the COVID-19 patient is under consideration that may cause a patient life in danger after extra dosing of this drug[64]. This type of immunosuppression is only used for trial testing in the current era.

### Remdesivir based Immunopathology

Within this immunopathology, the efficient changes had been expected on the human body after implementing the drugs and efficient clinical management. The combined use of both anti-inflammatory and antiviral drugs result in the prevention of this disease in a more productive way[65]. Based on the vitro evidence for inhabiting SARS-CoV-2 blocking and replication induced the pro-inflammatory cytokine production. In the nucleotide analogue remdesivir based antiviral drug helps to overcome the COVID-19 disease within human body[66]. This drug helps to develop a vaccine and the appropriate approaches that directly target on the virus or blocking the viral entry through proper treatment which address such immunopathology of the infected body[67].

## DISCUSSION AND CONCLUSION

After critically examine the previous studies regarding the implication of immunosuppression drugs for the prevention of cytokine storm based signaling in the COVID-19 patient's immune system, it becomes clear that each paper majorly highlights to develop more work on promoting the understanding regarding this drugs. In the current year, the SARS-CoV2 causes a fearsome disease based on pulmonary fibrosis, ARDS and even death. In this case, the transplant physician plays a major role to correctly diagnose and manage the infected coronavirus patient by optimizing the clinical management. The previous data shows that till now it is not clear which immunosuppression drug is 100% efficient for securing the lives of COVID-19 patients. But they majorly explored some drugs that are quite efficient to reduce the autoimmune activity within the human body by blocking the cytokine storm signaling to the other cells within this system. According to them, the Cyclosporine, Tocilizumab, Canakinumab, Corticosteroids are such cost-effective and highly recommended immunosuppression drugs that help to normalize the working of immune system within a hospitalized/ highly ill COVID-19 patient. In addition to this, some recommended immunopathology along with its drug named as remdesivir that helps to overcome the cytokine storm excessive working in coronavirus patients. But two major immunosuppression drugs are still under-observation and only used for the trail testing purpose like Hydroxychloroquine and Tocilizumab are such drugs that cause excessive adverse side effects on the human body like pregnant women, children and old age adults. According to previous case study and medical experiment-based statistics, their minor dose causes such harmful effects that their excessive dose can cause death. Majority of the papers are latest because this COVID-19 pandemic has recently occurred, and majority of these relevant researchers had been established in the last few months. Also, yearly wise authentic researches data have been shown in the appendix, fig 2. But due to lack of knowledge regarding the authentic and highly acceptable immunosuppression in the COVID-19 pandemic cause a major issue to resolve such issues in a quite effective way.

### Implications

This systematic review paper is an informative and attractive approach for the upcoming medical field scholars, pharmacists and other related bodies to understand the implication of the cost and quality of effective immunosuppression drugs for the survival of the COVID-19 patients. This paper will also add value in the practical, theoretical and policymaking based implications within this pharmacy/ medical field. Like this authentic source will add value to make a practical decision to adopt such recommended immunosuppression drugs whose side effects do not cause a major impact on the health and life of a COVID-19 patient. Also, this information helps to reduce the transplant option in front of the doctors by focusing on the implication of such drugs. Obviously, this authentic data also helps to directly safe the lives of people, In addition to this, its theoretical implication will help the future researchers within the field of medicines to evaluate the positive points and side effects of the immunosuppression drugs on the health of a patient who is suffering from SARS-CoV2 and other transplantation related chronic disease. This systematic paper will be a game-changer and wave a positive sign regarding the reduction of this viral disease all over the world. Till now, many researches have been working on a similar issue and this reliable source of peer-review will add value within this field of medical research. As far as its policymaking based implication is concerned, it becomes confirmed that its review data will also help the pharmaceutical company's administration and the relevant decision-makers to make some efficient decisions and rules regarding the adoption of such medicines for the prevention of autoimmune system and the blockage of cytokine storm within the human body.

## Limitations and Future Researches

The limitation of this review paper is that this study is majorly based on considering the literature on cytokine storm working COVID-19 situation and the implication of immunosuppression drugs which are released daily and have a systematic approach in the critical review portion. Besides all this, there is the heterogeneity of the reported cases and the imitated information regarding the immunosuppression drug provided within the articles which are majorly considered which render any conclusions speculative and unable to intend as guidance on the patient management. All the data was in a dispersed format. If the comparisons based systematic review is considered between the choice of immunosuppression drugs and transplantation situations, then a more versatile review paper will be generated. Also, rigorous studies are needed for appropriate analysis. As this paper is majorly based on only 68 papers on the relevant topic, so if more than 100 papers are critically studied for the systematic review purpose, then there will be more chances that more authentic information regarding the immunosuppression drug will be generated. So, for future researchers, there is an ample opportunity to work on its weakness and deri a constructive review approach.

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