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Systematic Review

Regulatory T Cells in Immunopathogenesis and Severity of COVID-19: A Systematic Review

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Abstract

Background: Severe cases of coronavirus disease 2019 (COVID-19) often experience hyper-inflammatory reactions, acute respiratory distress syndrome (ARDS), blood clotting, and organ damage. The most prominent immunopathology of advanced COVID-19 is cytokine release syndrome, or "cytokine storm" which is attributed to a defect of immune-regulating mechanisms. This study aimed to evaluate the role of regulatory T cells (Tregs) as one of the main cells that maintain immune homeostasis.

Methods: A systematic search was performed on PubMed, Scopus and Google Scholar. All English articles related to Treg's role in COVID-19 were extracted and evaluated by two researchers independently. Study eligibility was assessed based on modified Evidence-based librarianship (EBL) checklist.

Results: Nineteen eligible studies comparing Treg cells in COVID-19 patients with the control group or comparing alterations of this cell in severe and moderate patients were evaluated. Currently, there is no consensus regarding the increase or decrease of Tregs in COVID-19 patients compared to the control group. However, it was observed that Tregs in severe COVID-19 patients were significantly lower than moderate patients, resulting in uncontrolled inflammation and cytokine storm.

Conclusion: Regulatory T cells can be one of the determinants of disease severity and prognosis in patients with COVID-19 by inhibiting rampant inflammation and preventing cytokine storms.

Keywords: COVID-19, Immune response, Regulatory T cell, SARS-CoV-2, Severity

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Introduction

T cells need to induce SARS-CoV-2-specific immune responses by detecting viral antigens through antigen receptors (TCR). By recognizing antigens as peptides attached to the major histocompatibility complex, T cells can recognize not only structural proteins such as spike (S) and nucleocapsid (N) but also nonstructural proteins including ORF3a and ORF7. Once a viral antigen is detected, CD4 + T cells are activated and can be differentiated into helper T cell subsets through the activity of transcription factors and specific cytokines for each subset.[1] However, in some diseases, such as coronavirus disease 2019 (COVID-19), the development of uncontrolled inflammation by the immune system with overproduction of pro-inflammatory cytokines including interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF- α), and IL-8 can lead to mortality.[2,3] Tregs are commonly defined by the forkhead box protein 3 (FoxP3) as $CD3^+$ $CD4^+$ $CD25^{high}CD127^{low}FoxP3^+$ T cells and are classically known for development of immune tolerance and preventing autoimmune diseases.[4] Numerous publications have observed that impaired production and performance of Tregs are associated with greater disease severity, as reported in patients with various inflammatory diseases. Tregs can limit effector T-cell function. The most critical population of Tregs, which expresses Foxp3, can limit the activation, proliferation, and effector roles in series of immune cells.[5-7] Studies have shown that the coronavirus and arterivirus lead to an increase in CD4 + CD25 + FoxP3 + lymphocytes. However, Treg activation results are different for each virus.[8] Since data were limited for Treg alterations for different severities of COVID-19 and its comparison between patients and controls, the aim of this study was to evaluate the alterations of Treg for different severities of COVID-19 and also the differences of this cell in patients and the control group.

Materials and Methods

We searched PubMed, Google Scholar and Scopus databases until May 1, 2021. Regulatory T-cells, Treg cells, Regulatory T-Lymphocytes, Regulatory T Lymphocytes, Th3 cells, and CD4 + CD25 + cells keywords were used to search databases. Also, the keywords for COVID-19 included: COVID-19, 2019-nCoV, 2019-nCoV infection, 2019-nCoV disease, 2019 novel corona virus, 2019 novel coronavirus infection, 2019 novel coronavirus disease, coronavirus disease 2019, coronavirus disease 2019 virus, 2019 novel coronavirus infection or coronavirus

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disease-19. All English-language studies evaluating Treg changes in COVID-19 patients were reviewed and no data limitations were applied. The search was conducted by two researchers independently and the consistency of the results was high. In contradictory cases, the third person reviewed the articles. For greater coherence of the results, mild and extremely severe patients were categorized into moderate and severe disease group, respectively (Supplementary file 1, Table S1).

Inclusion and Exclusion Criteria

All English-language studies were included with the following criteria: cross-sectional, case-control, and cohort studies that evaluated at least two of the following markers: CD4, FoxP3, CD25, and CD127. Studies that identified COVID-19 by real-time PCR were evaluated. All preprint articles, books, congresses, and duplicate studies were removed. In addition, case reports were removed due to the small sample size and the low accuracy of the results.

Eligibility Assessment

Based on the Evidence-based librarianship (EBL) criteria,[9] we created a checklist to evaluate the studies. In this questionnaire, there were three answers to the questions: "yes", "no" and "unclear". The total number of questions was 18. If the "yes" answer to the total questions for an article was less than 75%, it would be excluded from the study due to its low validity.

Results

Initially, 1352 studies were obtained. After deleting the duplicates, 319 articles remained. After initial evaluation, theses, books, and abstracts for conferences were removed. A total of 211 articles that met the study criteria were evaluated more precisely. Among them, 176 were review articles (often with subjects of Treg or COVID-19), 6 studies did not have a definition of Treg, 4 were commentary studies and 6 were case-reports. Finally, 19 articles that fully met the inclusion criteria of the study were reviewed (Figure 1).

Comparison of Treg Cells in Patients vs. Controls

There was a controversy in the comparison of Treg cells in patients with COVID-19 and the control group (Table 1). Some studies found that these cells increased significantly

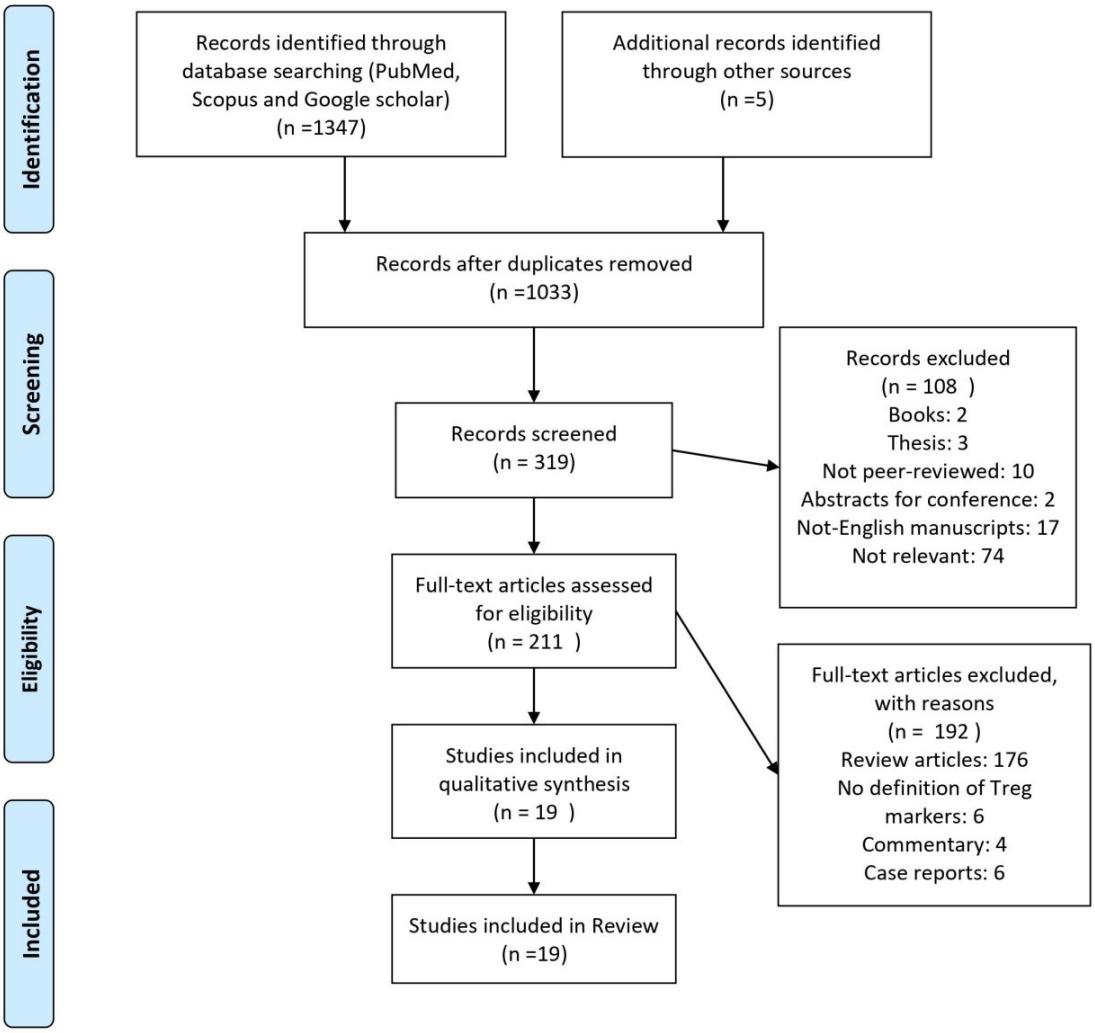

Figure 1. Flowchart of the Evaluated Studies.

in COVID-19 patients compared to the control group.[10,11] In one study, it was also observed that the number of regulatory cells in moderate patients, in contrast to severe patients, increased significantly compared to controls.[12] Opposite results were reported in other studies, which indicated a sharp increase in these cells in severe patients.[13,14] Finally, Song et al observed that the increase in regulatory cells in severe and moderate patients was not significant compared to the control group.[15]

In contrast, in some studies, a decrease of Tregs in patients compared to controls was reported. Mohebbi *et al* found that the number of these cells was significantly reduced in patients with COVID-19.[16] Mahmoud Salehi Khesht et al also observed that the number of regulatory T cells in both moderate and severe patients decreased significantly compared to the control.[17] These results were in line with the results of other studies.[18-20] The results of an evaluation in children with COVID-19 also showed that Treg cells decreased sharply in the acute phase of the disease and increased again in the convalescent phase (11–27 days after the onset of the disease).[21] An insignificant decrease in Tregs in patients compared to controls was also reported in one study.[22]

Comparison of Treg in Severe Patients vs. Moderate Patients

Although there was discordance in the results of assessment of this case among the studies, the most significant change was the decrease in Tregs in severe patients compared to the moderate ones (Table 2). Qin et al reported a significant reduction in Tregs in severe COVID-19 patients compared to moderate patients.[23] Similar results were observed in some other studies.[17,18,24] In contrast, Del Bello et al found a significant increase in Treg cell counts in severe compared to moderate COVID-19 patients who had undergone solid organ transplantation (SOT).[25]

Treg alterations reported in other evaluated studies were insignificant.[10,12,15,19,22,26-28] However, in two studies, the CD45RA + Treg cell population was assessed in moderate and severe COVID-19 patients. In both studies, it was

Table 1. Studies That Compared Tregs in COVID-19 Patients with Control Group

First Author	Number of Patients	Regulatory T Cell Markers	P Treg Patients/Control	P Treg Moderate/Control	P Treg Severe/Control
Chen [10]	102	$CD4^+CD25^+CD127^{low}$	<0.05	<0.001	<0.001
De Biasi [11]	39	$CD4^+CD25^+CD127^{low}$	<0.05	NM	NM
Tan [12]	56	$CD3^+CD4^+CD25^+CD127^{low}$	NM	<0.01	>0.05
Vigón [13]	109	$CD4^+CD25^+CD127^{low}$	>0.05	>0.05	<0.01
Rendeiro [14]	36	$CD4^+CD25^+CD127^{low}$	>0.05	>0.05	<0.01
Song [15]	41	$CD4^+CD25^+CD127^{low}$	>0.05	>0.05	>0.05
Mohebbi [16]	30	$CD4^+FoxP3^+$	<0.001	NM	NM
Mahmoud Salehi Khesht [17]	60	$CD4^+FoxP3^+$	NM	<0.05	<0.01
Schub [18]	50	$CD4^+CD25^+CD127^{low}$	NM	>0.05	<0.01
Laing [19]	63	$CD4^+CD25^+CD127^{low}$	NM	0.013	0.001
Sadeghi [20]	40	$CD4^+FoxP3^+$	<0.001	NM	<0.001
Jia [21]	19	$CD4^+CD25^+CD127^{low}$	0.027	NM	NM
Kang [22]	12	$CD4^+FoxP3^+$	NM	0.24	0.65

NM, Not mentioned.

Table 2. Studies That Compared Tregs in Severe and Moderate COVID-19 Patients

First Author	Number of Patients	Number of Moderate Patients	Number of Severe Patients	Regulatory T Cell Markers	P Treg Severe/Moderate
Chen [10]	21	10	11	$CD4^+CD25^+CD127^{low}$	>0.05
Tan [12]	56	31	25	$CD3^+CD4^+CD25^+CD127^{low}$	>0.05
Song [15]	41	29	12	$CD4^+CD25^+CD127^{low}$	>0.05
Mahmoud Salehi Khesht [17]	60	30	30	$CD4^+FoxP3^+$	<0.05
Schub [18]	50	36	14	$CD4^+CD25^+CD127^{low}$	<0.001
Laing [19]	63	32	31	$CD4^+CD25^+CD127^{low}$	>0.05
Kang [22]	12	8	4	$CD4^+FoxP3^+$	0.83
Qin [23]	44	17	27	$CD3^+CD4^+CD25^+CD127^{low}$	0.04
Meckiff [24]	40	18	22	$CD4^+FoxP3^+$	<0.001
Del Bello Bello[25]	51	29	22	$CD4^+CD25^+CD127^{low}$	0.02
Jiang [26]	103	86	17	$CD4^+CD25^+CD127^{low}$	0.85
Chen [27]	21	10	11	$CD4^+CD25^+CD127^{low}$	0.9
Wang [28]	65	30	35	$CD4^+CD25^+CD127^{low}$	>0.05

observed that the number of these cells in the more severe disease was significantly reduced compared to milder disease.[27,28]

Discussion

In this review, we evaluated the trend of Treg changes in COVID-19 patients compared to the control group at different clinical stages of the disease. Controversy was observed in the comparison of Tregs in COVID-19 patients compared to the control group which can be attributed to various reasons. This should be mainly due to the use of different markers in identifying Tregs because CD25 +/hi, CD127-/lo, FoxP3 + and their various combinations were used. In addition, the number of Tregs likely varies in patients with COVID-19 at different stages or with different disease intensities. CD25+/hi and CD127-/lo are just surrogate surface markers of FoxP3-expressing Tregs. Therefore, CD4 and FoxP3 markers are recommended to identify Tregs in future studies.[29,30] FOXP3 is induced in activated T cells by TCR signals and its transcription is further enhanced by IL-2 and TGF-b signaling. After expression in T cells, FOXP3 proteins bind to pre-existing transcription factors, particularly RUNX1 and ETS1, thereby transforming systems containing RUNX1-ETS1 for T cell activation and effective immune regulatory function.[31,32]

Regarding the comparison of Treg cell counts in severe and moderate COVID-19 patients, it was observed in most studies that these cells had a significant decrease in severe patients compared to moderate ones. It has been previously reported that in viral respiratory infections, Treg cells can prevent the cytokine storm, reducing the severity of viral pneumonia and acute lung injury.[33,34] In acute human and rat lung injury, Tregs accumulation is associated with reduction of immunopathology by inhibiting innate immune responses.[35] Therefore, Treg cells in patients with COVID-19 are more likely to prevent hyper-inflammation and cytokine storms. Significant reduction of Treg cells in these patients could be due to direct destruction of these cells by the virus, induction of apoptosis in activated cells, sequestration in infected tissue, and the inhibitory effect of IL-6 on Treg cells.[36-39] This is probably one of the reasons why IL-6 levels can be used to predict disease severity.[40] Decreased Treg cells upset the balance between regulatory and effector cells, leading to an uncontrolled inflammatory response, followed by local and systemic tissue damage.[41-44] Decreased proportion and dysfunction of Treg are of paramount importance in COVID-19-induced injury.[45-46] Treg cells can prevent cytokine storms, accelerate the healing process of acute respiratory distress syndrome (ARDS), and suppress the development of inflammatory disorders of the lung.[47-49] Treg cells prevent ARDS and cytokine storms through different mechanisms. These mechanisms include production of immunosuppressive cytokines (IL-10, IL-35 and TGFβ), IL-2 consumption, induction of death in effective cells through granzyme and perforin, inhibition of activation of antigen-presenting cells (APC) and metabolic disruption (such as adenosine production).[50] Thus, although Chen et al[10] reported a significant increase in Treg in patients compared to controls, a significant decrease in IL-10 in severe patients compared to controls may be due to the dysfunction of these cells despite an increase in their number. Also, in an experimental model of acute lung injury in mice, it was shown that infiltration of Treg cells in bronchoalveolar lavage fluid helps to resolve lung damage by inducing neutrophil apoptosis, macrophage efferocytosis, and decreased fibrocyte recruitment.[51] A study by Gladstone et al on the successful treatment of patients with COVID-19 and ARDS using allogeneic Tregs confirms the importance of Treg deficiency in the pathogenesis of COVID-19 and the potential therapeutic benefits of Treg.[52]

Bello et al observed that the number of Treg cells in SOT patients with severe COVID-19 increased significantly compared to moderate patients. Some studies have shown that Treg increases in SOT patients in order to increase the immune tolerance of the transplanted organ.[53-55] However, the increase in these cells in SOT patients with severe COVID-19 requires close investigation. Based on these various observations, it can be assumed that the delay and weakness of specific T cells and the neutralization of the humoral response to SARS-CoV-2 due to immune suppression lead to virus escape from immune neutralization and prevent rapid clearance of the virus, resulting in severe disease.[56]

In conclusion, the reported Treg cell alterations and function in COVID-19 are controversial. Although comparing these alterations between COVID-19 patients and healthy individuals in the studies yielded different results, it seems that in most studies, in more severe disease, a significant decrease in Tregs has been reported which disrupts immune homeostasis and creates a cytokine storm. However, early activation of this cell may also suppress the immune response and cause severe disease. However, the success of allogeneic Treg therapy could confirm the reduction of this cell in severe disease and the occurrence of rampant inflammatory response. Therefore, in order to more accurately evaluate the role of Treg cells in COVID-19, large studies are needed to compare the changes of this cell in COVID-19 patients and healthy individuals, as well as severe and moderate patients. Also, comparing the level of cytokines produced by Treg (such as IL-10) at different clinical stages of COVID-19 as well as with the control group, can evaluate the function of this cell (regardless of its decreasing or increasing number).

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Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SA, MR and HJ. The first draft of the manuscript was written by

SA, MR and DA. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

Ethical Statement

The study was performed in accordance with Declaration of Helsinki and was approved by Shahid Beheshti University of Medical Sciences ethical committee (ethical code: IR.AJAUMS.REC.1399.062)

Supplementary Materials

Supplementary file 1 contains Table S1.

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