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REVIEW

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Immunity and inflammatory biomarkers in COVID-19: A systematic review

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Summary

Coronavirus disease 2019 (COVID-19) is a clinical syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Patients can be asymptomatic or present respiratory and gastrointestinal symptoms, and even multiple-organ failure which can lead to death. The balance between an effective antiviral response and dysregulated immune response is the key factor determining the severity of COVID-19 progression. A systematic review was performed using the NCBI-PubMed database to find the articles related to COVID-19 immunity and inflammatory response published from 1 December 2019 to 15 April 2020. Haematological, immunological and biochemical parameters were extracted and correlated with disease severity, age and presence of comorbidities. Twelve articles were analysed comprising a total of 1042 hospitalized patients infected with SARS-CoV-2 and 95 different parameters. Total lymphocyte count and levels of CD3+ and CD4+ T cells were decreased in severe and critical cases. Neutrophilia was found in patients who progressed to acute respiratory distress syndrome (ARDS). Interleukin-six (IL-6) was high in mild and severe patients regardless of comorbidities. Erythrocyte sedimentation rate (ESR) and count and C-reactive protein (CRP) levels were increased regardless of disease severity or presence of comorbidities. High levels of D-dimer and lactate dehydrogenase were present in diabetic patients and patients who developed ARDS. Procalcitonin levels were elevated to varying degrees in severe and critical patients. We conclude that the total lymphocyte count, CD3+ and CD4+ T cells are low, especially in severe and critical COVID-19 patients; ESR, CRP and IL-6 were elevated, independent of the severity of disease. Understanding the inflammatory response of COVID-19 patients is essential for the development of better therapeutic and management strategies.

KEYWORDS

COVID-19, cytokine, immune response, inflammatory response, SARS-COV-2

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TABLE OF ABBREVIATIONS

α-HBDH	α-hydroxybutyrate dehydrogenase
ACE-2	angiotensin-converting enzyme 2
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BNP;	brain natriuretic peptide
CK	creatine kinase
CK-MB	creatine kinase myocardial band
COVID-19	coronavirus disease 19
CRP	C-reactive protein
CT	computed tomography
DC	cendritic cell
ESR	crythrocyte sedimentation rate
GFR	glomerular filtration rate
Ig	immunoglobulin
IL	interleukin
INF	interferon
IP-10	gamma-induced protein 10
LDH	lactate dehydrogenase
MERS	Middle East respiratory syndrome
MPC-1	mitochondrial pyruvate
MSC	mesenchymal stem cells
NET	neutrophil extracellular traps
NK	natural killer
NO	nitric oxide
PRR	pattern recognition receptors
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TNF	tumour necrosis factors
Treg	regulatory T cell
WBC	white blood count

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new respiratory and systemic disease caused by the infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, a single-stranded RNA virus which belongs to the *Coronaviridae* family and *Betacoronavirus* sub-family.[1] COVID-19 is highly infectious; transmission is by inhalation of airborne particles or contact with fomites, and the incubation period ranges from 2 to 14 days.[2] While COVID-19 presents with striking non-uniformity, the primary clinical manifestations are fever, cough and malaise. Additional symptoms include gastrointestinal symptoms, sore throat, rash, headache, loss of taste and/or smell, and conjunctivitis.[3] The primary serious complications associated with COVID-19 are acute respiratory distress syndrome (ARDS) and sepsis.[4]

COVID-19 was first reported in December 2019 in the Hubei Province of China, in the city of Wuhan. The infection rapidly spreads around the globe, and on 11 March was declared a 'public health emergency of international concern' by the World Health Organization (WHO).[3] COVID-19 is currently reported in 235 countries. By 1 October 2020, over 33 million cases have been reported and over 1,010,000 deaths have been attributed to COVID-19. Brazil has reported around 672.4 deaths per 1 million population, the United Kingdom has reported around 620.8 deaths per 1 million population, the United States has reported around 618.3 deaths per 1 million population and China has reported 3.23 deaths per 1 million population (WHO). The global lethality is 0.035 (782,456/22,256,220), with patients over 60 years old and those presenting with comorbidities accounting for the majority of deaths.[5–10] Patients with comorbidities such as hypertension, liver disease, nervous system disease, chronic lung disease, chronic kidney disease, cardiovascular disease, cancer, smoking, and diabetes and other endocrine disorders represent 23%–48% of the overall cases and have the worst prognosis.[6,9,11–13] Reports of the mean age of patients with COVID-19 vary between 47 and 56 years.[5,6,14] Currently, general supportive treatments against COVID-19[1,13] have been supplemented with remdesivir and dexamethasone, licensed as the treatment for COVID-19, as well as inhaled interferon-beta, where a randomized controlled trial reports clinical benefit.[15–20]

SARS-CoV-2 infection can trigger a 'cytokine storm', which refers to the massive release of pro-inflammatory cytokines that contribute to acute lung injury and unfavourable prognosis.[21–26] Common laboratory findings of the virus include lymphocytopenia; neutrophilia; elevated levels of lactate dehydrogenase; C-reactive protein (CRP); D-dimer; IL (interleukin)-2, IL-6 and IL-10; and reduced levels of CD8 + T cells, in particular, as well as decreased CD4+ T cells, and natural killer (NK) cells.[7,14,21,26] The immune response to SARS-CoV-2 infection can cause tissue damage in the liver, kidneys, heart and lungs, and may account for the relationship between elevated pro-inflammatory cytokines and the most severe clinical manifestations of COVID-19.[11,14,21–23,25–28]

This systematic review aims to collate and critically appraise the literature relating to the inflammatory and immunological parameters of the SARS-CoV-2 in order to facilitate the development of new therapeutic approaches. Furthermore, because a significant volume of research has been published relating to COVID-19, this paper aims to gather, evaluate and consolidate data relating to the disease.

2 | METHODS

2.1 | Search strategy

We performed a literature search of COVID-19 and immune response using the NCBI-PubMed database to find the articles published from 1 December 2019 to 15 April 2020. 'COVID-19' and 'immune system,' 'immune response,' 'immunomodulation,' 'immunologic factors,' 'inflammatory response,' 'biomarkers,' 'immunologic characteristics,' 'inflammatory function,' 'immune mechanism,'

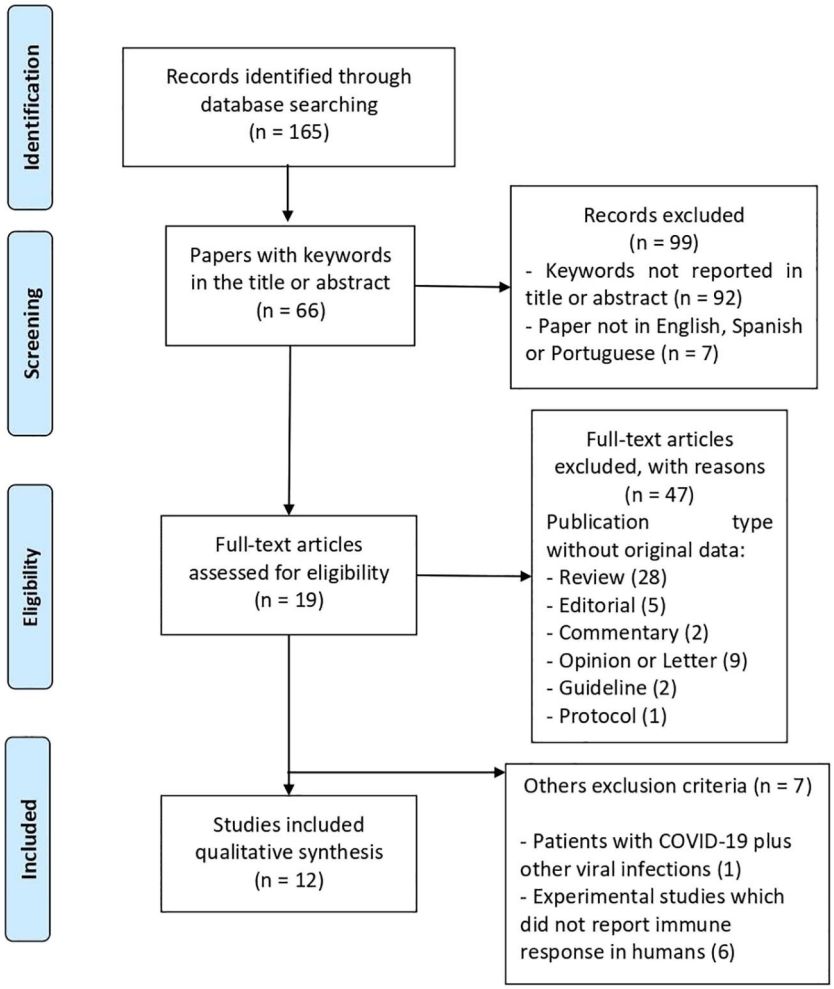

FIGURE 1 Flowchart: steps of study selection. The literature search resulted in 165 papers. Sixty-six articles remained after title/abstract and selection. Type of study, model used in the study and results were analysed. From 66 articles, 19 were included and 47 were excluded. Seven articles were excluded due to the absence of human host immune response data. Twelve papers remain for complete review

TABLE 1 Identification of articles. Articles included in this review: article number, reference, type of study and number of COVID-19 patients in each study

Article number	First author	DOI	Study type	Number of COVID-19 patients
1	Spezzani V	10.4414/smw.2020.20246	Case report	2
2	Tan C	10.1002/jmv.25871	Cohort	75
3	Wang L	10.1016/j.medmal.2020.03.007	Cohort	27
4	Liu Y	10.1007/s11427-020-1643-8	Cohort	12
5	Feng Y	10.1164/rccm.202002-0445OC	Cohort	476
6	Guo W	10.1002/dmrr.3319	Cohort	174
7	Qin C	10.1093/cid/ciaa248	Cohort	452
8	Marx D	10.1111/ajt.15919	Cohort	1
9	Zhou Y	10.21037/apm.2020.03.26	Cohort	17
10	Wu C	10.1001/jamainternmed.2020.0994	Cohort	201
11	Xiong Y	10.1080/22221751.2020.1747363	Cohort	6
12	Leng Z	10.14336/AD.2020.0228	Cohort	10

'immunoregulatory' and 'immunopathology' were included in the search strategy. All terms were searched as general terms to obtain the maximum search results. The review was registered in PROSPERO – International Prospective Register of Systematic Reviews (ID CRD42020180744). Additional search strategy information is presented in the Supplementary Material section.

2.2 | Study selection

The literature search resulted in 165 papers. After title and abstract evaluation, 66 articles remained for full-text analysis and primary data extraction. The data which were extracted from the articles included title, authors, type of study, model used in the study, country, population, patient groups (disease severity, presence of comorbidities, age and progression to ARDS), treatment and results. Among these 66 articles, 19 were eligible for inclusion and 47 were excluded due to not presenting the original data. A further seven articles were excluded because of the absence of data related to human host immune response. The reason for exclusion of each paper was documented (Figure 1). Finally, 12 papers were included in this review (Table 1).

Inclusion criteria required the presence of keywords in the title or abstract; papers publishing original data; full text available in English, Spanish or Portuguese; publication in a peer-reviewed journal; and study design/publication type as follows: case report, randomized controlled trial, cohort study, case–control study, cross-sectional study, experimental (in vitro and in silico) study, or other studies with original data. We excluded studies in which patients had other viral co-infections, and experimental studies that did not report immune response in humans. The reason for exclusion of each paper was documented in all cases (Figure 1). Two independent reviewers (AP and MR) evaluated and selected papers for inclusion following a checklist of requirements for each step. When a discrepancy arose in the inclusion or exclusion of a particular study, a third party (CP) blinded to the judgement of the previous reviewers evaluated the study following the same criteria as the other two reviewers, and determined its quality and suitability for inclusion.

2.3 | Quality assessment

The quality assessment of the articles included in this systematic review was performed according to the critical appraisal checklist recommended by the Joanna Briggs Institute.[29] The checklist is composed of eight questions for each study. The 'Yes' answer to each question received one point. Thus, the final scores for each study could range from 0 to 8.

2.4 | Data extraction and data synthesis

Data were extracted from the selected studies and study design, participants (total number and groups if applicable), stage of disease, and method were recorded using a Microsoft Excel spreadsheet. Immunological parameters, biochemistry indexes and other laboratory findings were evaluated (based on standard reference according to each article classification) in comparison to clinical and radiological outcomes.

Data were classified in groups (haematological and immunological parameters, biochemical parameters and organ-specific functional parameters) and, whenever possible, tested for association with specific clinical characteristics such as stage of disease, severity and population.

3 | RESULTS

The 12 studies included a total of 1480 patients; 1402 of whom were hospitalized with SARS-CoV-2 infection. For comparison, one study (article 2) included a group of 75 patients with influenza infection and another (article 11) included three healthy controls. The median age of COVID-19 patients was 52.4 years.

Following the COVID-19 classification scale,[30] patients in six paired groups (n = 973) were classified into three categories according to disease severity: mild (non-pneumonia and mild pneumonia; n = 541), severe (dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, PaO_2/FiO_2 ratio or P/F and the percentage of oxygen supplied <300, and/or lung infiltrates >50% within 24–48 h; n = 356), and critical (respiratory failure, septic shock, and/or multiple-organ dysfunction or failure; n = 76).[30] One article (article 3) classified patients as mild, moderate, severe and critical; one article (article 7) classified patients as severe or non-severe; and another article (article 9) classified patients as aggravated or non-aggravated. Based on the definition of classification in each article, we classified 'moderate', 'non-severe' and 'non-aggravation' as mild; and 'aggravated' as critical. Nine articles (articles 1, 2, 5, 6, 8–12) reported comorbidities including immunodeficiency or immunosuppression (0.97%), cardiovascular disease (8.1%), diabetes (13.9%), hypertension (25.3%) and other comorbidities (51.7%). One study (article 12) applied experimental therapy, and the other 11 studies clinically managed patients with supportive treatment for the disease. Laboratory tests were performed at hospital admission or as early as possible. In studies that showed patient outcomes (articles 1–3, 6, 8–12), the mortality rate was reported at 12.79% (54/422).

The 12 articles analysed 95 different haematological, immunological and biochemical parameters from blood, nasopharyngeal swabs and/or bronchoalveolar lavage. Lymphocyte count, CRP and white blood count (WBC) were the most commonly evaluated parameters. A complete list of analysed parameters is shown in Table S4.

Application of the critical appraisal checklist recommended by the Joanna Briggs Institute resulted in seven articles with a maximum score of 8. No article with a score below 5. The summary of scores applied for the twelve selected studies are shown in Table S2.

3.1 | Haematological and immunological parameters

The most frequently evaluated haematological parameters were lymphocyte, WBC, neutrophil and platelet counts. Lymphocytes subsets, mainly CD3+, CD4+, CD8+ T cells (measured by flow

TABLE 2 List of 19 immunological parameters and summary of the main results in each article

		Immunological parameters											
Article number	**First author**	**TCD3**	**TCD4**	**TCD8**	**Treg**	**B cell**	**IL-6**	**IL-1**	**IL-2R**	**IL-8**	**IL-10**	**TNF-α**	**CXCL1, CXCL2, CXCL6, CXCL8, CXCL10/MPC-1, CCL3/MPC-1a, CCL4/MIP1B**
4	Liu Y	[a]	Normal or low in critical	Low in critical	[a]		[a]	[a]	[a]	[a]	[a]	[a]	[a]
5	Feng Y	Low in severe and critical/age over 45	Low in severe and critical/age over 65	Low in severe and critical/age over 75	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
6	Guo W	[a]	[a]	[a]	[a]	[a]	High	[a]	[a]	[a]	[a]	[a]	[a]
7	Qin C	Low	[a]	[a]	Low in mild and severe	Normal	High	Normal	High in severe	Normal	Normal	High	[a]
8	Marx D	[a]	[a]	[a]	[a]	[a]	High	[a]	[a]	[a]	[a]	[a]	[a]
9	Zhou Y	[a]	Low in critical	Normal	[a]	-	[a]	[a]	[a]	[a]	[a]	[a]	[a]
10	Wu C	Low in patients with/without ARDS	Low in patients with/without ARDS	Low in patients with/without ARDS	[a]	-	High in ARDS deceased	[a]	[a]	[a]	[a]	[a]	[a]
11	Xiong Y	[a]	[a]	[a]	-	[a]	[a]	[a]	[a]	[a]	High	[a]	High
12	Leng Z	[a]	[a]	[a]	High in severe and critical with or without MSCT treatment	[a]	[a]	[a]	[a]	[a]	[a]	Low in mild, severe, critical with and without MSCT treatment	[a]

Abbreviations: ARDS, acute respiratory distress syndrome; Il, interleukin, MSCT, mesenchymal stem cell transplantation, TNF, tumour necrosis factor; Treg, regulatory T cell.

[a]Parameter not measured.

cytometry), ILs and chemokines were assessed to indicate the immunological status.

Nine articles (articles 1, 2, 4, 5, 7–10, 12) reported WBC at admission or as early as possible, of which seven (articles 2, 4, 5, 7–10) showed WBCs within normal range and one (articles 1) reported increased levels. WBC count was independent of the severity of SARS-CoV-2 infection.

Neutrophil count was reported in eight studies (articles 1, 2, 4–7, 10, 12). It was high in patients with ARDS who progressed to death (article 10; n = 44/201) and a single patient recently started chemotherapy treatment (article 1). Normal neutrophil levels were generally independent of the severity of COVID-19, presence of comorbidities and age (articles 2, 4–7, 12).

One article (article 12) presented the values of dendritic cells (DCs), reporting that the DC count was normal in patients with mild COVID-19, but increased in patients with severe and critical disease progression after the treatment with mesenchymal stem cell (MSC) transplantation.

Lymphocyte count was assessed in 11 studies (articles 1, 2, 4–12) and was increased only in one immunocompromised patient (article 1). Lymphocyte levels were most commonly low in patients with severe and critical COVID-19, regardless of ARDS. One study (article 7) showed low lymphocyte levels in mild and severe patients.

In three studies (articles 5, 7, 10), patients with critical or severe COVID-19 presented low CD3+ T cell count, while patients with mild COVID-19 showed normal levels of CD3+ T cells (article 5). Four articles (articles 5, 7, 9, 10) reported low CD4+ T cell counts in patients with severe or critical COVID-19 with or without ARDS. Patients with mild disease, aged below 65, presented CD3+ T cell count within normal range (articles 4, 5).

The studies that presented TCD8+ cell counts (articles 4, 5, 9, 10) that were contradictory are shown in Table 2. Two studies (articles 7, 12) reported divergent regulatory T cell (Treg) count; Treg was low in mild and severe cases (article 7). However, when patients were treated with MSC, the Treg count normalized (article 12). Similarly, tumour necrosis factor (TNF) levels were increased in severe and mild patients (article 7), while after the MSC treatment, TNF levels were low (article 12).

One study (article 7) investigated lymphocyte subsets in 44 patients (17 mild and 27 severe). They observed that B cells, naive Th cells, memory Th cells, and activated T cell count were within normal range. Tregs were increased in severe and mild patients. NK cells were low in the severe group but normal in the mild group, while naive Tregs were low in both groups.

Four studies (articles 6–8, 10) measured levels of IL-6. IL-6 levels were high in mild and severe patients (article 7), and high in the heterogeneous group, regardless of the presence of comorbidities (article 6). In one immunosuppressed patient, IL-6 was slightly increased (article 8). In ARDS patients, high IL-6 levels were observed only in patients who progressed to death (article 10) (Table 2).

Other ILs were evaluated in one study (article 7) that analysed 452 patients, and grouped according to the severity of disease. Only IL-2R was high in severe patients, while the other parameters were normal regardless of the severity of disease.

Pro-inflammatory chemokines were evaluated by transcriptome in one study (article 11) which included three patients with COVID-19 and three non-infected patients; high values were found in COVID-19 patients (Table 2).

Total immunoglobulin levels (IgG, IgM and IgA) were measured in two studies (articles 5, 7), and were in the normal range regardless of the severity of disease. Notably, both studies observed that, although in the normal range, patients with severe COVID-19 presented with lower levels of IgM than those with mild COVID-19.

Ferritin was evaluated in three studies (articles 6, 7, 10). Regardless of the severity of infection (article 7) and the presence of ARDS (article 10), ferritin was increased in patients with comorbidities, especially diabetes (article 6).

Platelets were reported by half the included studies (articles 1, 2, 4, 5, 10, 12; 6/12). Platelet levels were normal regardless of the severity of infection or presence of ARDS.

Three studies (articles 5, 6, 12) reported mostly high fibrinogen concentration regardless of severity of infection. One study (article 6) reported fibrinogen within normal range in patients without comorbidities. Another study (article 12) reported a critically severe patient with normal fibrinogen levels in the early phase of infection that progressed to increased levels in later stages of disease.

One article (article 10) investigated coagulation factors. Globulin and prothrombin time were normal while activated partial thromboplastin time was low in patients with or without ARDS.

3.2 | Biochemical parameters (inflammatory markers)

Erythrocyte sedimentation rate (ESR), lactate dehydrogenase rate (LDH), CRP, D-dimer and procalcitonin levels were reported as acute phase reactants. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase and total bilirubin were measured to assess hepatic function. Creatine kinase (CK), creatine kinase myocardial band (CK-MB), myoglobin and troponin levels were used as cardiovascular damage markers. Gasometrical parameters pO_2, pCO_2 and FiO_2 pO_2/FiO_2, together with chest x-ray and computed tomography scan were assessed to measure lung involvement and facilitate clinical decision management.

ESR was evaluated in five studies (articles 2, 5–7, 10). ESR was elevated regardless of the severity of infection or ARDS development in all five studies. However, it was within normal range in patients without comorbidities (article 6) and those in the early stage of mild disease, as reported by one study (article 2) that classified disease in progressive stages.

Eleven studies (articles 1–10, 12) reported CRP levels, nine of which (articles 3–10, 12) showed high CRP levels regardless of the severity of infection or age. Two studies (articles 1, 6) reported normal CRP in patients without comorbidities and in one immunocompromised patient.

D-dimer was measured in five studies (articles 5, 6, 8–10). High D-dimer levels were reported in both severe and mild patients, and those with comorbidities including diabetic patients, patients who developed ARDS and a post-kidney transplant patient.

LDH levels were reported by five studies (articles 4–6, 9, 10). Elevated LDH values were reported in diabetic patients and those who developed ARDS. However, data related to severity were contradictory in two studies. One large study (article 5; $n = 476$) showed high LDH levels in severe and critical patients ($n = 124/476$). Another (article 9) showed LDH within normal range in critical patients.

Procalcitonin levels were evaluated in four studies (articles 5, 4, 7, 9). All four studies reported elevated or slightly elevated levels in severe and critical patients. One study (article 5) reported normal levels in mild patients.

3.3 | Serial laboratory evaluation

Two articles (articles 8, 12) showed serial laboratory parameters. One article (article 8) presented a patient who had undergone kidney transplant and had mild COVID-19. The patient experienced rapid respiratory recovery after the treatment for a bacterial superinfection. The patient discontinued immunosuppressants (belatacept and mycophenolate mofetil), except prednisone, from the point of COVID-19 diagnosis until recovery. Leukocytes were 5.24 (10^9/L) prior to SARS-CoV-2 infection and decreased to 2.35 (10^9/L) during hospitalization. Initially, lymphocytes were 1.08 (10^9/L) and decreased to 0.51 (10^9/L) during hospitalization. After recovery, both parameters normalized. CRP and D-dimer levels increased during the COVID-19 disease course. After recovery, CRP decreased. The other article (article 12) reported a patient with critical COVID-19 who underwent MSC treatment. Lymphocytes were low at admission (0.94 10^9/L) and further decreased on the first day after MSC infusion (0.35 10^9/L). Lymphocyte levels replenished gradually until recovery (day 21). CRP peaked on day 1 following MSC infusion (191.00 mg/L) and then decreased until discharge (10.10 mg/L).

3.4 | Organ-specific consequences of SARS-CoV-2 inflammatory response

Liver function parameters (AST, ALT and/or bilirubin) were assessed in five studies (articles 4-6, 10, 12). In the majority of patients, liver function levels were normal, except for two critical patients who presented high AST and ALT (article 4). Three studies (articles 5, 10, 12) evaluated total bilirubin and reported no changes.

Cardiac function biomarkers such as α-hydroxybutyrate dehydrogenase (α-HBDH), myoglobin, brain natriuretic peptide (BNP) and CK-MB were reported in five studies (article 4–6, 10, 12). Two studies (articles 10, 6) evaluated α-HBDH levels. The first (article 10) reported high levels regardless of severity. The second (article 6) reported normal levels in patients without comorbidities. Three studies (articles 4, 5, 12) reported myoglobin (Mb) levels. Mb was within normal range in patients with mild and severe infection (articles 4, 5), and high in patients with critical infection (articles 4, 5, 12). One critical patient developed liver and cardiac damage during the disease course (article 12). Two studies evaluated BNP (articles 4, 5) and reported that, in general, BNP levels were normal. Only one patient showed a remarkably high viral load and this patient had fulminant myocarditis (article 5). Three studies (articles 5, 10, 12) reported that CK-MB presented no changes. Troponin was measured in one article (article 12) which reported normal levels in patients with mild disease, and high levels in severe and critical patients.

4 | DISCUSSION

We performed a systematic review of peer-reviewed articles presenting original data related to the various immune and inflammatory responses to SARS-CoV-2 infection. Among the 165 articles initially identified, 12 articles fulfilled the inclusion criteria.

The immune response to a virus is initiated by the engagement of pattern recognition receptors which deliver signals to recruit and activate cells from the innate immune system, producing cytokines, such as type I interferon (IFN I), TNF, IL-6, IL-1ß and CC-chemokine ligand 2 (CCL2), as well as reactive oxygen species (ROS), nitric oxide (NO) and neutrophil extracellular traps.[31–36] During the initial phase of COVID-19 infection, delayed cytokine production occurs in the epithelial cells of the respiratory tract, DCs and macrophages.[36] The number of phagocytes does not increase in all patients with COVID-19.[9] However, like other parameters, phagocyte levels are higher in patients with more severe infection (article 10, 12).[9,37]

In SARS-CoV and Middle East respiratory syndrome (MERS)-CoV infections, host viral clearance may be impaired due to vesicle production that enables viral replication from within.[38] IFN I is an important antiviral factor that inhibits virus replication and orchestrates the adaptive immune response to viral infection.[39] During SARS-CoV infection, low levels of IFNs are released by the innate immune cells which delays antibody response.[28] In contrast, IL-1ß, IL-6, TNF, CCL-2, CCL-3 and CCL-5 are produced at higher levels, which induces inflammatory cell infiltration.[28] Article 7 reported that TNF-α is increased in COVID-19 patients regardless of the severity of disease.[40] Elevated TNF-α leads to unregulated activation of neutrophils and macrophages, increased production of ROS, release of matrix metalloproteinases, pulmonary tissue degeneration and vascular endothelial dysfunction. These characteristics have been reported in patients with serious COVID-19.[39,41] Articles 6 and 7 reported that IL-6, a pro-inflammatory cytokine synthesized in the early stage of COVID-19, was high in patients with and without comorbidities, regardless of the severity.[40,42] In addition, the presence of IL-6 stimulates hepatocytes, which elevates the production of CRP, serum amyloid A, hepcidin and fibrinogen, which are hallmarks of inflammation. Article 5 indicated that COVID-19 patients with high levels of IL-6 also had high CRP.[43] Fibrinogen was high in all patients regardless of disease severity. Several articles (articles 2, 3, 5, 7, 10) reported that ESR was high in COVID-19 patients, while

others (articles 4, 5) report that procalcitonin and LDH were high in severe and critical patients.[5,9,40,43–45]

INF induces DC to mature, resulting in cell migration which is essential to initiation of antiviral T cell response and activation of NK cells that induce apoptosis in the infected cells.[46] Elevated response by NK cells has been observed in patients with SARS-CoV-2 infection, and resultant NK cell consumption leads to low NK cell counts in patients with severe COVID-19.[40,47,48] Migratory DCs present viral antigens to naive CD4+ and CD8+ T cells during respiratory viral infections. In the presence of specific cytokines, T cells differentiate into subsets, including Th1 and Th17, and release more pro-inflammatory cytokines.[48] One study which was not included in this review reported that IL-1ß, IFN-g, IP-10 and MPC-1 were elevated in COVID-19 patients.[27] Studies from the current review did not assess Th1-related cytokines. Article 7, from the included articles, showed high IL-2R levels in patients with severe COVID-19. This supports reports of an association between the severity of infection and IL-2R levels.[31,40] SARS-CoV-2 infection can trigger T helper-2 (Th2) (IL-4 and IL-10) secretion differently from other types of SARS-CoV infections.[27,28] However, in our review, one study (article 7) reported normal IL-10 levels in both severe and mild COVID-19 patients.[40]

Several included studies (articles 2, 4, 5, 7–10) reported that total peripheral WBC, a main indicator of immune response activation, was normal in the majority of patients, even among those with ARDS.[9,10,40,43-45,49] However, reduced total lymphocyte levels were observed in severe and critical patients (articles 2, 4–7, 9–12).[9,10,37,40,42-45,50] Because lymphocytes express angiotensin-converting enzyme (ACE2), a receptor employed by coronavirus to infect cells,[51] this could be a direct result of the effects of SARS-CoV-2 infection. Another possibility is related to the exhaustion of lymphocytes by the exacerbated inflammatory immune response which has been observed in some patients.[52] Moreover, the production of high levels of pro-inflammatory cytokines could directly inhibit the proliferation of lymphocytes and induce early apoptosis.[52] Among the T lymphocytes, TCD8 cells are particularly important in balancing the immune response against pathogens and guarding against the development of autoimmunity or hyper-inflammation.[25,53] Despite conflicting data among several included studies that evaluated TCD8 cells, the reduced TCD8 cell count observed in some patients with more severe COVID-19 (articles 4, 5, 7) may indicate a failure to control viral replication.[40,43,45]

Article 5, which enrolled 476 patients, reported low CD4+ T cell counts in severe, critical and aged patients (over 65 years).[43] Likewise, article 3 reported that in SARS-CoV-2 infections, T lymphocytes (both CD4+ and CD8+ T cell) were low in the early phase of infection.[5]

CD4+ T cells are involved in the process of immune memory, cytotoxic T-stimulating cytokines and innate immunity cells are released. In the context of SARS-COV-2 infection, a reduced number of TCD4+ may be associated with inadequate seroconversion and normal levels of IgA, IgM and IgG which have been reported by several papers that were not included in this review.[40,43,54,55] Article 7, included in the review, noted reduced regulatory T lymphocytes (CD4+CD25+FoxP3+) in COVID-19 patients.[40] As Tregs are essential in controlling the immune response (including the inflammatory processes), a lack of Treg control mechanisms may be crucial for the development and maintenance of the hyper-inflammation observed in some severe and critical cases of COVID-19.[56]

Viral infection triggers an innate immune response. While a well-coordinated and efficient response clears the pathogen, a massive dysregulated immune response may result in tissue damage.[28] Antigen presentation triggers pro-inflammatory cytokine production that attracts inflammatory cells, such as monocytes, macrophage and neutrophils, which infiltrate lung tissue.[57]

In some COVID-19 patients, the release of cytokines and chemokines is so excessive that a cytokine storm ensues, resulting in massive infiltration of inflammatory cells (in particular monocytes), into the lung tissue, resulting in thrombotic tendency and multiple-organ failure.[11] Article 4 reported a low PaO_2/FiO_2 ratio in critical COVID-19 patients, indicating excessive inflammatory tissue infiltration.[45]

Progression to the hyper-inflamed state occurs when NK cells and cytotoxic CD8 T cells fail to neutralize infected cells, and activated antigen-presenting cells trigger prolonged and massive production of pro-inflammatory cytokines such as TNF, IFN-g, IL-1, IL-6, IL-18 and IL-33.[52,58-60] This was evinced in article 7 which reported high DC numbers in severe and critical COVID-19 patients.[40] Increased macrophage activation causes lung tissue infiltration and bronchial and alveolar epithelium damage, which cascades to ARDS.[61] Thrombotic activity occurs due to endothelial damage which may be caused by SARS-COV-2 infection after binding to ACE-2 receptors, leading to elevated coagulation factors in critical patients.[60] Articles 5, 6 and 12[39,44,45] observed that fibrinogen concentration increased especially in the later stages of COVID-19 disease progression.[37,42,43]

Article 10 reported that COVID-19 patients who progressed to ARDS presented lymphopenia, decreased CD3+ and CD4+ T cells counts, and altered coagulation factors (increased LDH and D-dimer).[9] Neutrophilia, increased D-dimer and IL-6 were associated with COVID-19 patients with ARDS who progressed to death (article 10).[9] Thus, these are biomarkers associated with poor prognosis of COVID-19. The studies indicate that high virus titres and a disproportionate cytokine response cause a cytokine storm, leading to ARDS. This was also the main cause of death in SARS and MERS diseases.[28]

A cytokine storm can result in the extrapulmonary organ damage seen in critical COVID-19 patients.[62] In two studies which were not included in this review, liver injury was associated with increased AST and ALT.[45,63] Article 5, included in the review, showed increased BNP in one COVID-19 patient who presented fulminant myocarditis, and article 12 showed increased troponin levels in severe and critical COVID-19 patients.[37,43]

Longitudinal follow-up of COVID-19 patients during the course of the disease was present in articles 8 and 12.[37,49] Patients presented low levels of lymphocytes that increased during the recovery stage of the disease. A kidney-transplanted COVID-19 patient

exhibited normalization of lymphocyte levels after discharge, while another COVID-19 patient, after MSC transplantation therapy, had decreased lymphocyte levels in the final stage of the disease. Both patients initially had high CRP levels. One critical patient had the highest CRP levels during the first week of hospitalization, and one mild patient had high CRP levels during their entire hospitalization period. However, the mild patient achieved peak CRP levels during the third week. The differing CRP parameters between patients may be due to the difference in the severity of the disease. Both patients presented low levels of glomerular filtration rate (eGFR). In article 8, a patient presented a low level of eGFR even after discharge, while the patient from article 12 had increased levels one week after hospitalization.[37,49] The diverging results may be due to the transplant realized by the patients.

Biomarkers with potential to predict COVID-19 severity are essential for clinical management strategies. Patients identified with risk for poor prognosis could be evaluated in a more systematic way, with a sequential protocol for clinical and laboratory follow-up, in order to anticipate complications of the disease and to implement a timely effective treatment, as seen for the impact of dexamethasone for patients that require respiratory support.[15]

5 | CONCLUSION

The articles included in this systematic review indicate that during the course of SARS-CoV-2 infection, total lymphocytes, CD3+ and CD4+ T cell counts are low, especially in severe and critical patients, while CD8+ T cells were slightly more variable; WBC, neutrophil, platelet and immunoglobulin levels are normal; and ESR, fibrinogen, CRP, IL-6, TNF-α and Tregs are increased independent of the severity of the disease.

A more detailed compilation of information regarding the immune and inflammatory timeline of SARS-CoV-2 infection may facilitate the identification of new biomarkers and treatment strategies in the different stages of COVID-19 disease progression and enable better prognostic prediction.

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CONFLICT OF INTEREST

We have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Conceived the study: Carolina Prando. *Designed the study, performed literature search and study selection*: Carolina Prando, AnaPaula Diniz Iwamura and Marielen Ribeiro Tavares da Silva. *Performed data analysis, and drafted the paper*: Carolina Prando, AnaPaula Diniz Iwamura, Marielen Ribeiro Tavares da Silva and Ana Luísa Hümmelgen. *Commented on previous versions of the manuscript and critically revised the work contributing to the final version*: all authors.

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SUPPORTING INFORMATION

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