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Lymphopenia in the COVID-19 Patient: More than a Predictor of Poor Prognosis?

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I N F O

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A B S T R A C T

The COVID-19 pandemic, caused by the infectious agent SARS-CoV-2, has claimed the life of thousands of people around the world following its rapid expansion from Wuhan, China, in early January 2020. Since then, multiple groups worldwide have attempted to describe predictive models for adverse clinical outcomes in patients affected by this disease. Within laboratory findings, the first Chinese cohorts described an inverse relationship between the absolute lymphocyte count and disease severity, and about 80% of severe patients exhibited lymphopenia. However, there are discrepancies regarding the predictive value of this clinical manifestation, as well as in the pathophysiological mechanisms involved. Here, we review current evidence regarding lymphopenia in patients with COVID-19, and the potential utility of this hematological finding as a disease biomarker.

Keywords: Coronavirus Disease, SARS-Cov-2, Lymphopenia, Biomarker, Prognosis

Introduction

Coronaviruses (CoV) are cause of common cold and serious respiratory illnesses, such as the Severe Acute Respiratory Syndrome (SARS). A recent outbreak of pneumonia occurred in Wuhan, China, in December 2019, and the causative agent was identified as a novel coronavirus, SARS-CoV-2, genetically related to SARS-CoV and Middle East respiratory syndrome (MERS)-CoV. The clinical manifestations of SARS-CoV-2 disease (COVID-19) include fever, cough, fatigue, muscle pain, diarrhea, and pneumonia, which can evolve to acute respiratory distress syndrome, metabolic acidosis, septic shock, coagulation dysfunction, liver, kidney and heart failure.[1,2]

Several biomarkers, such as the levels of C Reactive Protein (CRP), ferritin, procalcitonin, D-dimer and thrombocytopenia, have been associated with COVID-19 severity. Moreover, lymphopenia has emerged as an important independent predictor of poor prognosis in COVID-19 patients.[3] Nonetheless, it is not clear the pathophysiological mechanism of COVID-19-associated lymphopenia, its clinical significance, and the potential therapeutic implications related to this hematological disorder.[4] Here, we review the characteristics, epidemiology, and associated clinical features of lymphopenia induced by SARS-CoV-2 infection, and discuss the potential pathophysiological and therapeutic implications of this alteration.

Definition and Incidence of COVID-19-associated Lymphopenia

Lymphopenia is a common clinical feature among SARS-CoV,

MERS-CoV and SARS-CoV-2 infections. Several studies have shown absolute lymphocyte counts below 1500 cells/ µL in COVID-19 patients, and less than 700 cells/µL in individuals with severe disease.[5] A predominant reduction in the proportion and absolute numbers of T cells has also been observed.[6,7] Interestingly, lymphopenia is developed as early as 3 days after disease onset and is maintained even after 16 days of disease.[6] Lymphopenia is evidenced in up to 80% of COVID-19 patients,[7] whereas this proportion increases to 96% in patients with severe disease.[8]

Clinical Characteristics of COVID-19

COVID-19 is a clinically dynamic disease, with manifestations ranging from asymptomatic forms and mild flu-like syndromes, to life-threatening acute respiratory disease syndrome (ARDS) and multi-organ dysfunction. The transmission of COVID-19 is through person-to-person when the infected individual cough and sneezes, or through invasive procedures such as orotracheal intubation.[7] Symptomatic individuals are infectious even 3 days before onset of symptoms, and the rate of transmission by these individuals rises to 40 to 50% (in asymptomatic individuals; on the other hand, the viral shedding dynamics is not completely understood, but some investigations have suggested that approximately 2.6% of these individuals are capable of transmitting the infection).[7] The most common symptom as studied from various cohorts of COVID-19 patients are fever (83-98%) followed by fatigue (70%) and dry cough (59%); gastrointestinal symptoms can occur between 4-26%: abdominal pain, nausea, vomiting, diarrhea.[1,3] Typically, the onset of symptoms occurs at 4 to 5 days of infection9, with a chronology depicted in Figure 1. Clinically, COVID-19 can be classified as follows:

Mild: Symptoms include fever, cough, myalgia, anorexia and diarrhea. A minor fraction (10%) of the individuals also present anosmia and ageusia.[7] The symptoms usually resolve spontaneously in most of the individuals, so that this group of patients does not need additional evaluation, depending on the risk profile.[8,9] Indeed, a fraction of them (20.3%) can develop moderate or severe disease, with risk factors that include age >65 years, cardiovascular disease, chronic lung disease, hypertension, diabetes, obesity, kidney disease, immunosuppression, cancer and Human Immunodeficiency Virus infection (HIV).[1,9]

Moderate: Dyspnea characterizes this group of individuals (40% of the cases), together with laboratory findings such as increased levels of D-dimer, lactate dehydrogenase, C-reactive protein and ferritin.[10] Other findings associated with poor outcomes include lymphopenia, prolonged prothrombin time, and elevated levels of liver enzymes.[5,7] Typical imaging findings are ground-glass opacification or consolidation (>50% of the lung field).[6,8] Patients with moderate disease should receive hospital-based management.[9]

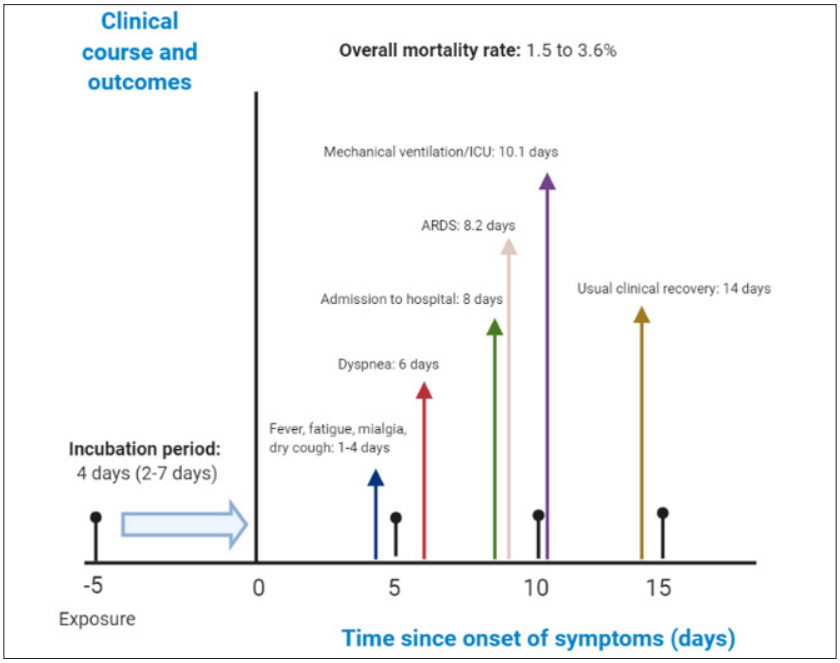

Figure 1.Timeline of COVID-19 clinical manifestations. Incubation period is defined as the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (i.e. cough, fever, fatigue or myalgia). The median incubation period is 4 days (interquartile range 2–7 days). Most of SAR-CoV-2 infections are mild (81%) with a usual recovery period of 2 weeks. ADRS: acute respiratory distress syndrome; ICU: Intensive care unit.

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Severe: In these individuals, there is worsening of dyspnea, along with tachypnea (>30 breaths per minute), hypoxemia (oxygen saturation <93% and ratio of PaCO2 to FiO2<300) and abnormal lung auscultation (crackles). In addition to Lymphopenia, biomarkers of poor prognosis include increased d-dimer, CRP, ferritin and Lactate Dehydrogenase (LDH) levels in serum, as well as prothrombin time.[8,9] A high proportion of these individuals (32.8%) develop ARDS1, requiring clinical management in an Intensive Care Unit (ICU), including strategic mechanical ventilation.[10]

In severe disease, the recovery period rises to 3-6 weeks to critical disease (ARDS, sepsis, septic shock or MODS) in 5%, with highest case fatality (8-15%) among those aged over 80 years.[1,3,44,46]

Mechanisms of Lymphopenia in SARS-COV-2 Infection

SARS-CoV-2 genome exhibits a 79% and 50% sequence similarity with SARS-CoV and MERS-CoV, respectively.[11,12] Besides, SARS-CoV-2 and SARS-CoV share the cell entry receptor Angiotensin-Converting Enzyme 2 (ACE2).[12,13] This similarity is reflected in common clinical manifestations, as well as specific immunological disturbances, such as lymphocyte loss.[14] In addition to lymphopenia and profound decrease in T cell counts, COVID-19 patients exhibit high levels of the functional T cell exhaustion, with increased expression of programmed death 1 (PD-1) and T cell immunoglobulin and mucin-domain containing-3 (TIM3),[15] and lower production of interferon (IFN)-α in severe patients.6 However, the mechanisms of lymphopenia in SARS-CoV-2 infection, as well as in the original SARS-CoV disease, are yet undefined. These potential mechanisms can be classified as direct, product of viral infection and subsequent lymphocyte death and indirect, because of the immune response mounted against the virus.

SARS-CoV-2 Replication in Lymphocytes

SARS-CoV-2 entry to the cell is facilitated by the virus spike protein, which binds the ACE2 receptor. This process requires additional cellular factors, particularly the serine protease TMPRSS2, which primes the S protein for ultimate fusion of viral and cellular membranes.[13,18] However, ACE2 is not expressed by lymphocyte populations,[18-21] and only a small fraction of T cells and B cells in oral mucosa has been found to express ACE2 transcripts.[22] Consistently, a previous study failed to detect SARS-CoV-2 RNA in peripheral blood mononuclear cells from infected patients.[21] Thus, although SARS-CoV particles have been found in several immune cells, including lymphocytes,[23] it is controversial if SARS-CoV-2 readily infects lymphocytes. Therefore, active viral replication and cytopathic effects probably do not account as a major mechanism of lymphocyte loss. Nonetheless, it should not be discarded that the potential process of viral binding and entry into cells activates several intracellular pathways leading to cell death, as evidenced for MERS-CoV[24] and other viruses.[25] Inflammasome activation and pyroptosis triggered by abortive infection may be important mechanisms of T cell death in COVID-19, similar to what occurs in HIV infection.[26] Moreover, activation of Toll-like receptors by structural proteins of SARS viruses might lead to lymphocyte death.[27,28]

Indirect Mechanisms of Lymphocyte Loss in SARS-CoV-2 Infection

SARS and MERS are characterized by a massive immune cell activation, release of inflammatory cytokines, increase in acute-phase proteins, and coagulability disorders. These immunological disturbances, also known as cytokine storm syndrome, constitute a hallmark of severe COVID-19.[29] Indeed, there is increasing evidence of a systemic inflammatory profile in individuals with SARS-CoV-2 infection, particularly with severe disease, exhibiting high plasma/ serum levels of cytokines such as interleukin (IL)-6, IL-1b, IL-1RA, IL-2R, IL-7, IL-8, tumor necrosis factor (TNF)-α, and the regulatory cytokine IL-10.[6,7,14,16] Peripheral blood mononuclear cells and bronchoalveolar lavage fluid also contain elevated transcripts of the chemokines CCL2, CXCL10, CCL3, and CCL4.[21] Lung chemokines induce lymphocyte migration into this organ,[30] also reflecting in peripheral lymphopenia. Importantly, the levels of IL-6, IL-10, and TNF-α negatively correlate with T cell numbers in COVID-19 patients,[17] supporting the role of systemic inflammation in the development of lymphopenia. Certainly, cytokines of the TNF-α family induce apoptosis of activated T cells,[31,32] and in SARS-CoV-2 infection there is an increase in the proportion of HLA-DR+ CD38+ activated T cells,[16,33] pointing to cytokine-induced cell death as an important mechanism of lymphocyte loss in COVID-19.

Another mechanism that may contribute to the cytokine syndrome storm and T cell activation is the downregulation of ACE2 after virus entry into cells. Although this event has not been formally proven for SARS-CoV-2,[13] it was evidenced for SARS-CoV.[34] ACE2 inactivates angiotensin 2, preventing its binding to the angiotensin receptors 1 and 2. By this mechanism, ACE2 regulates the global proinflammatory response induced by the renin-angiotensin system.[35] This anti-inflammatory effect of ACE2 is beneficial in the context of vascular and renal inflammation and atherosclerosis,[36,37] as well as acute lung injury.[38] Thus, the reduction in ACE2 levels might also contribute to immune dysregulation and lung injury seen in COVID-19 and the modulation of the renin-angiotensin system is a potential therapeutic strategy.

Apart from cytokine-induced cell death, T cells also suffer Activation-Induced Cell Death (AICD) following T cell receptor triggering.[39] This is a regulatory mechanism that assures the contraction of the T cell effector phase and

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involves the upregulation and ligation of death receptors such as Fas[40,41] and the activation of p53-related apoptotic pathways.[41] Precisely, apoptosis and p53-related genes are enriched in peripheral blood mononuclear cells from COVID-19 patients[21] and death receptors such as PD-1 are upregulated in T cells from these individuals,[17] supporting AICD as another mechanism of T cell loss in this disease.

In summary, multiple pathways contribute to the development of lymphopenia in COVID-19. These mechanisms, summarized in Figure 2, may also be potential therapeutic targets to counteract infection or prevent potential comorbidities.

Lymphopenia as a Biomarker of Severity in COVID-19

Several observational studies have indicated the importance of lymphopenia as a predictive marker of poor prognosis in COVID-19. The first clinical characterizations in Wuhan, China, early demonstrated the predominant lymphocyte loss in individuals with COVID-19.[42,43] Other studies have found that lymphopenia, and predominantly CD4+ T cell loss, as well as an elevated neutrophil/ lymphocyte ratio, is more frequent in severe cases.[49] Systematic reviews have also shown that lymphopenia is a feature of severe COVID-19 with critical patients exhibiting a median lymphocyte count of 800 cells/µL, and non-survivors showing persistent lymphopenia.[44,45]

Lymphopenia have included within prognostic scales by several observational studies. Ji et al. propose a predictive model called CALL, which includes comorbidity, age, lymphocyte count and LDH levels.[46] A nomogram with four variables was developed, reporting adjusted calibration curves and good concordance indices (0.86, 95% CI 0.81 - 0.91).

Chen J et al. also explored prognostic factors for ICU

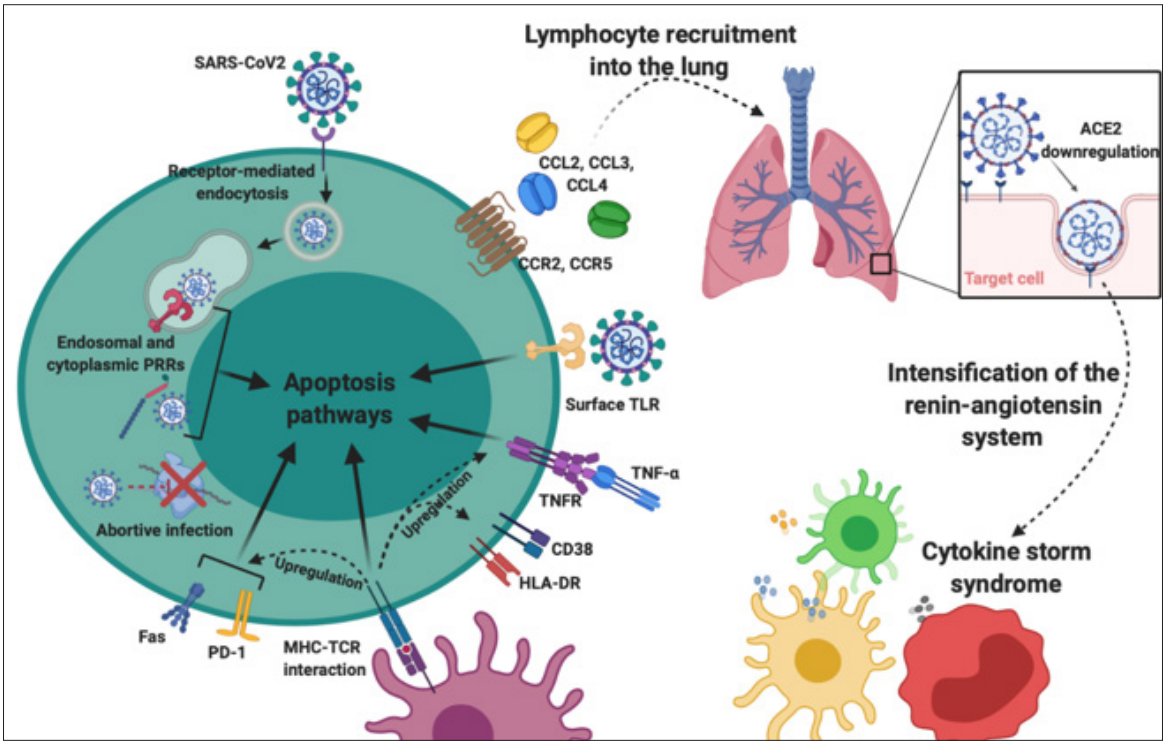

Figure 2.Mechanisms of lymphopenia in COVID-19. SARS-Cov2 might enter T cells via receptor-mediated endocytosis and exert abortive infection, but this process is still controversial. However, multiple pattern recognition receptors (PRR), both in the cell surface, endosomes, or cytoplasm, recognize viral proteins, and trigger apoptotic pathways. COVID-19 is characterized by a cytokine storm syndrome, with the high secretion of inflammatory cytokines such as IL-6 and TNF-α internalization could also limit the regulatory role of this receptor on the renin-angiotensin system, further exacerbating the inflammatory process driven by this endocrine axis. Besides, multiple chemokines such as CCL2, CCL3, and CCL4 are released in the lung and systemically, promoting T cell sequestration into the lung. Inflammatory cytokines, as well as major histocompatibility (MHC)/T cell receptor (TCR)-mediated signals promote T cell activation and render them more susceptible to cell death. Specifically, these signals directly lead to the activation of apoptotic pathways, induce the expression of activation markers such as HLA-DR and CD38, and cause the upregulation of death receptors such as Fas and programmed death 1 (PD-1), which in turn activate apoptotic pathways.

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admission, finding that only age and CD4+ T cell counts were independently associated with this outcome.[47] Likewise, among the prognostic factors of mortality, Zhao Q et al. propose a predictive model at[7,14,21] and 28 days, which includes the age, LDH and CRP levels.[48] However, in this study, lymphopenia had a strength of association for fatal outcome when absolute counts are lower than 1-x-10^9 cells/µL than D-dimer levels.

Some meta-analyses focused on the evaluation of Lymphopenia in COVID-19 are summarized in Table 1.

Conclusion

Table 1.Lymphopenia as a predictor of severe COVID-19

Author	Study objective	Type of study	Criteria for severe COVID-19	Cut-points for lymphopenia	Conclusion
Zhao Q et al.[48]	To explore the relationship between lymphocyte count and the severity of COVID-19.	13 case-series with a total of 2282 cases were included in the study	Requirement for intensive care, mechanical ventilation or death	Lymphocyte count of less than 1.1x109/L in four studies and as less than 1.5x109/L in one study	The presence of lymphopenia was associated with nearly threefold increased risk of severe COVID-19 (Random effects model, OR = 2.99, 95% CI: 1.31-6.82). Lymphopenia is a prominent part of severe COVID-19 and a lymphocyte count of less than 1.5x109/L may be useful in predicting the severity clinical outcomes.
Huang I, Pranata R42	To investigate the association of lymphocyte count on admission and the severity of COVID-19. To analyze whether age and comorbidities affect the relationship between lymphocyte count and COVID-19	23 studies with a total of 3099 cases were included in the study	Patients who had any of the following features at the time of, or after, admission: (1) respiratory rate ≥ 30 breaths per min, (2) oxygen saturation ≤ 93% (at rest), (3) ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air (PaO2 to fiO2 ratio) ≤ 300mmHg, or (4) specific complications, such as septic shock, respiratory failure, and or multiple organ dysfunction	A cut-off point of less than 1100 cells/µL was established because there were 4 studies using it as a cutoff point.	Lymphopenia can be used as a marker for poor prognosis in COVID-19 and in younger patients in particular. Lymphopenia defined as lymphocyte count ≤ 1100 cells/µL is associated with threefold risk of poor outcome

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Huang W et al.50	To evaluate prognostic information for COVID-19 disease severity of lymphopenia in patients hospitalized with infection	20 publications selected for meta-analysis included a total of 3017 subjects with CD4+ cell counts where 2311 were classified as Mild/Moderate (76.6%) and 706 were classified as Severe/Critical (23.4%).	Decreased, non-survival, critical and patients with disease aggravation were all classified into the "Severe/Critical" group	No mention of cut-points Compared the results of peripheral blood lymphocyte subset counts in patients with mild/moderate disease (average: 1134 cells/ µL) to those with severe/ critical disease average: 705 cells/µL) hospitalized in China with a diagnosis of COVID-19 pneumonia.	Absolute counts of major lymphocyte subsets are significantly and substantially decreased in severe COVID-19 disease. Multivariate analyses reviewed here establish immune cell subset counts, particularly CD4+ and CD8+ T cell counts, as independent predictors of COVID-19 outcomes.

Lymphopenia is a common characteristic of COVID-19 and other CoV infections. The mechanisms of lymphopenia in COVID-19 are not fully understood, but may include direct cytophatic viral effects, activation of apoptosis pathways via pattern recognition receptors and cell death induced by the inflammatory environment and T cell activation.

The absolute lymphocyte count is a parameter highly accessible in the clinical setting, so that the evaluation of Lymphopenia, as well as the neutrophil/ lymphocyte ratio, should be considered for the clinical follow-up of COVID-19 patients, in order to anticipate the development of disease complications and comorbidities

Declaration of Interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval

Does not apply.

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