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# The impact of lymphoid memory cells in different ages of COVID-19 patients

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## ABSTRACT

Coronaviruses are highly pathogenic and transmissible viruses. The SARS-CoV-2 virus that emerged in December 2019 is increasingly recognized as a serious, worldwide public health concern. Respiratory infections and the hyper-inflammatory response induced by SARS-CoV-2 play a key role in disease severity and death in infected COVID-19 patients. However, much uncertainty still exists about the pathogenesis and various effects of COVID-19 on immune system. It seems that memory T cells can reduce the severity of COVID-19 infection by inducing a protective immune response. Memory T cells along with protective antibodies are the main defenses and also protective barrier against recurrent COVID-19 infection. The role of Memory T cells varies in different ages and the severity of COVID-19 infection varies between children, adults and the elderly. Furthermore, the aim of this review is to evaluate the role of memory cells in mild, moderate and severe infected COVID-19 patients with different ages.

## 1. Introduction

Since December 2019, an outbreak of coronavirus disease (COVID-19) appeared in Wuhan, China, and then spread all around the world causing significant numbers of deaths in many countries. COVID-19 became a major public health problem and was the main cause of respiratory distress syndrome with a 3% fatality rate (Yang et al., 2020; Calisher et al., 2020). Patients with underlying diseases such as; cardiovascular disease, diabetes, hypertension, and immune deficiencies, are at a high risk of death. In addition, approximately 80% of adults aged above 65 years who get a severe COVID-19 infection are hospitalized and admitted to intensive care unit (ICU), but there were rare ICU admissions and less than 0.1% of deaths in people aged under 19. The reports showed the percentage of hospitalization development in age (Weaver et al., 2021; Serpa et al., 2021). According to the infrequency of severe COVID-19 in children and adolescents, the knowledge of its

pathogenesis mechanisms is still restricted. However, features of the immune and inflammatory response in children, besides age-related extra-immunological factors, like angiotensin I converting enzyme 2 (ACE2) receptor expression could remarkably help to distinguish the different clinical phenotype and disease severity between adult and pediatric patients. T cell-dependent cytokine release and direct cellular cytotoxicity can also contribute to tissue inflammation and toxicity, increasing the possibility that immunosuppression, owing to T cell depletion and exhaustion, causes COVID-19 viral persistence and mortality (Li et al., 2020). In this regard, the majority of virus-specific T cells undergo apoptosis following viral clearance; however, maintenance of a virus-specific memory T cell population is required for long-term antiviral immunity (Zheng et al., 2020). This review illustrates the main immunopathogenic aspects of COVID-19 and the impact of lymphoid memory cells, with a focus on the age-related differences between adult and children patients deriving clinical implications.

**Abbreviations:** COVID-19, coronavirus disease-19; ICU, intensive care unit; CNS, central nervous system; ACE2, angiotensin-converting enzyme 2; NK, natural killer (NK) cells; CRP, C-reactive protein; MNPs, mononuclear phagocytes; BALF, broncho-alveolar fluid; CRS, cytokine release syndrome; TNF, tumor necrosis factor; CCL, CC-chemokine ligand; CXCL, CXC-chemokine ligand; EDTA, ethylenediaminetetraacetic acid.

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### 1.1. Symptoms and genomic characterization

The incubation period for COVID-19 can be up to 14 days, but age and immune system conditions can shorten this period. The most common symptoms of COVID-19 infected patients are fever, fatigue, dry cough, loss of appetite, body aches, gastrointestinal problems, and shortness of breath (Yang et al., 2020; Calisher et al., 2020; Weaver et al., 2021; Serpa et al., 2021). Recent evidence has examined the effects of COVID-19 on the lungs, cardiovascular system, kidneys, gastrointestinal organs, and central nervous system (CNS), although the lungs are the most affected organ (Li et al., 2020; Zheng et al., 2020; Wadman et al., 2020; Gu et al., 2020; Baig et al., 2020; Sarda et al., 2020). COVID-19 also engaged angiotensin-converting enzyme 2 (ACE2) as a cell receptor to enter respiratory cells, gastrointestinal cells, and renal cells (Huisman et al., 2018; Suleiman et al., 2021). The genome sequences of COVID-19 revealed coding regions of COVID-19 including the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The spike protein is divided into the two S1 and S2 domains that are responsible for receptor binding and cell membrane fusion, respectively (R. Lu et al., 2020; Z. Liu et al., 2020; Tang et al., 2020). It seems that specific antibodies against S and N proteins can be used to diagnose COVID-19 (Y. Liu et al., 2020; Chan et al., 2009; Raheem et al., 2021a).

### 1.2. Pathogenesis

Many studies are describing the role of the immune response in patients with COVID-19. The innate immune system is the first layer of defense against pathogens that involves different cells and humoral components such as neutrophils, eosinophils, macrophages, mast cells, dendritic cells, natural killer (NK) cells, C-reactive protein (CRP), and antimicrobial peptides. In addition, innate immunity provides an important contribution to initiating adaptive immune response (Turvey, 2010). Studies have reported patients with COVID-19, especially in severe cases, have an increased neutrophil count and a decreased lymphocyte count, as well as high levels of the inflammatory mediators and acute-phase protein (like inflammatory cytokine/chemokines and CRP) in serum. Since the entrance of COVID-19, pattern recognition receptors for coronaviruses such as Toll-like receptor 7, RIG 1, and MDA-5 initiate immune response and expression of IFN- $\gamma$  and inflammatory cytokines. Results showed that the portion of mononuclear phagocytes (MNP) in broncho-alveolar fluid (BALF) of patients with severe conditions was higher than mild cases, which led to hyper inflammation. The release of a large number of cytokines in patients with severe conditions is similar to the cytokine release syndrome (CRS). High serum levels of IL-6, IL-1, IL-7, tumor necrosis factor (TNF), and also inflammatory chemokines including CC-chemokine ligand 2 (CCL2), CCL7, CCL3, and CXC-chemokine ligand 10 (CXCL10), were observed in individuals with severe COVID-19 caused hyper inflammation and death, even in younger patients (Merad and JCJNRI, 2020; Shi et al., 2020; Moore and June, 2020). Furthermore, lymphocyte subsets were significantly decreased in patients with COVID-19. Helper T (Th) cells, suppressor T cells, memory Th cells, and regulatory T cells were reduced, seen more clearly in severe cases, but, the percentage of naive Th cells were enhanced (Qin et al., 2020; Schett et al., 2020).

## 2. Discussion

According to similar inflammatory and pathogenicity features of COVID-19 in different infected patients, finding a resistant strategy against disease is crucial. About one-third of COVID-19 infected patients have no symptoms, this is dependent on the patient's human leukocyte antigen (HLA) polymorphism, immune system response, presence of antibodies, and CD4<sup>+</sup> and CD8<sup>+</sup> memory cells. Earlier findings demonstrated that humoral immune system response (IgG, IgM, and IgA antibodies) might not be protective in all COVID-19 patients and cannot

prevent reinfection. Therefore, the role of CD4<sup>+</sup> and CD8<sup>+</sup> memory cells in the immune response against COVID-19 is significant. Regarding imposed since of memory cells in the inhibition of viral disease progression, the purpose of this study is to assess the role of subsets of memory cells in mild and severe COVID-19 patients of different ages.

### 2.1. Memory T cell subsets and protective role

In contrast to naïve T cells, memory T cells circulate in peripheral tissues (such as lung, skin, and gut) in addition to lymph nodes, and blood, which enhances their ability to respond more effectively and faster to infections. They also require less co-stimulation and can respond to lower antigen doses (Woodland and Kohlmeier, 2009). Memory T cells are divided into numerous subsets: central memory T cells (T<sub>CM</sub> cells), effector memory T cells (T<sub>EM</sub> cells) (Saule et al., 2006), tissue-resident memory T cells (T<sub>RM</sub>) (Mueller and Mackay, 2016), virtual memory T cells (TVM) (Lee et al., 2011; Marusina et al., 2017) and stem memory T cells (T<sub>SCM</sub>) (Gattinoni et al., 2011a) that are determined by their homing, phenotype and migratory properties.

Although the function and tissue homing of all memory CD4<sup>+</sup> T cell subsets are different, they play a fundamental role in eliminating pathogens (Mueller et al., 2013). CD4<sup>+</sup> T<sub>CM</sub> cells can produce IL-2 cytokine more than CD4<sup>+</sup> T<sub>RM</sub> cells, which led to having a considerable capacity of proliferation as well as developing B cell expansion and antibody production (Wang et al., 2012; MacLeod et al., 2011). While CD4<sup>+</sup> T<sub>EM</sub> cells produce IL-4, IL-17, and IFN- $\gamma$  and supply Ag-specific effector T cells rapidly (Jain et al., 2018; Kaech et al., 2002). In addition, CD4<sup>+</sup> T<sub>EM</sub> cells can suppress *P. chabaudi*, a mouse model of malaria, through the effects of IFN- $\gamma$  and IL-10 (Stephens and Langhorne, 2010). CD4<sup>+</sup> T<sub>RM</sub> cells operate as the first line of defense in peripheral tissues and elevate quick local response to entry sites of infection. They have a regulatory function via the expression of the transcription factor Foxp3 (Seneschal et al., 2012) and the production of IFN- $\gamma$ , TNF, and IL-22 (Watanabe et al., 2015). Previous researches have indicated that CD4<sup>+</sup> T<sub>RM</sub> cells can boost protection against different viruses and bacteria. Lung, mucosal, and skin resident memory CD4<sup>+</sup> T<sub>RM</sub> cells provide appropriate protection against secondary respiratory viral challenge with influenza virus, *Chlamydia* infection, and *Leishmania* (Tejaro et al., 2011; Stary et al., 2015; Glennie et al., 2015). Findings have been reported that IFN- $\gamma$  secreted from CD4<sup>+</sup> T<sub>RM</sub> cells, improve *Chlamydia trachomatis*, genital tract herpes simplex virus (HSV), and *Helicobacter pylori* amelioration (Stary et al., 2015; Nogueira et al., 2015; Shin and Iwasaki, 2012; Liu et al., 2019). Moreover, CD4<sup>+</sup> T<sub>RM</sub> cells can enhance the distribution of lung CD8<sup>+</sup> T<sub>RM</sub> cells in infection with influenza (Laidlaw et al., 2014). In contrast, studies showed that memory CD4<sup>+</sup> T cell subsets promote pathogenesis in multiple sclerosis (MS), psoriasis, rheumatoid arthritis (RA), systemic lupus erythematosus, colitis, and type 1 diabetes autoimmune disease (Raphael et al., 2020). Furthermore, in Parkinson's disease, memory CD4<sup>+</sup> T cells increased, while naïve T cells decreased (Saunders et al., 2012).

There is an apparent relationship between CD4<sup>+</sup> and CD8<sup>+</sup> T cells. CD4<sup>+</sup> T cells enhance the generation and maintenance of effector and memory CD8<sup>+</sup> T cells population, via direct ligation of CD40 on naive CD8<sup>+</sup> T cells by CD40L on CD4<sup>+</sup> T cells (Bourgeois et al., 2002) and IL-6, IL-1, IL-15, and TNF cytokines (Oh et al., 2008). Memory CD8<sup>+</sup> T cells enable robust protection against invading intracellular pathogens, particularly viral infections and tumors (Phan et al., 2016). CD8<sup>+</sup> T<sub>CM</sub> and T<sub>EM</sub> cells recirculate into blood but, CD8<sup>+</sup> T<sub>RM</sub> cells reside in non-lymphoid peripheral tissues (e.g., salivary glands, skin, lung, liver, kidney, gastrointestinal tract, female reproductive tract (FRT), and brain), and lymphoid tissues (e.g., thymus and secondary lymphoid organs). Earlier findings demonstrated IL-15 and IL-7 are essential for the longevity of recirculating memory CD8<sup>+</sup> T cells in secondary lymphoid organs (Wu et al., 2018; Schenkel and Masopust, 2014). CD8<sup>+</sup> T<sub>RM</sub> cells play a vital role in anti-viral infection diseases. The protective effects of CD8<sup>+</sup> T<sub>RM</sub> cells have been explored in several studies. Several

researches have reported that through vaccinia virus (VACV) (Jiang et al., 2012), pulmonary influenza virus (Zarnitsyna et al., 2016; Wu et al., 2014), respiratory syncytial virus (RSV) (Kinnear et al., 2018), herpes simplex virus (HSV) (Gebhardt et al., 2009), and local murine cytomegalovirus (MCMV) infections (Thom et al., 2015), CD8<sup>+</sup> T<sub>RM</sub> cells are generated and produce IFN- $\gamma$  and TNF- $\alpha$  cytokines to orchestrate strong antiviral immune response (McMaster et al., 2015).

## 2.2. Age-associated vulnerability in response to COVID-19

As mentioned, COVID-19 is an age-related disease, and the mortality rate increases with aging. It is also noticeable that COVID-19 outbreak and mortality is higher in men than in women at the same age (Palaiodimos et al., 2020; Jin et al., 2020; Raheem et al., 2021b). Aging is a sophisticated mechanism that includes deadly and non-deadly diseases and suppresses the immune system response. Age-related changes can lead to the decline in production of new naïve T cells at the end of puberty (Chinn et al., 2012) and at 40–50 years of age (Naylor et al., 2005), decrease in proliferation and differentiation of B and T cells in lymph nodes (Brien et al., 2009) and dysregulation of T cells migration (Li et al., 2012), which could diminish the quick response of the immune response to infections (Schett et al., 2020; Richner et al., 2015). However, patients with underlying diseases are more vulnerable to COVID-19, even at a young age (Blagosklonny, 2020).

## 2.3. COVID-19 in infants and children

Several researchers have reported that in addition to adults, infants and children are susceptible to COVID-19 (Ludvigsson, 2020; Zhou et al., 2021). Infants are extremely vulnerable to respiratory viral pathogens, and their mortality rate is enlarged which is probably due to an immature immune response. The findings demonstrated that in influenza infection, CD4<sup>+</sup>, and CD8<sup>+</sup> lung tissue-resident T<sub>RM</sub> cells of infants produce a protective response (Siegrist, 2007). Although, most of their peripheral T cells are naïve (Thome et al., 2016) and lung-localized T<sub>RM</sub> cells are reduced in adults. In contrast, in infants, transcription factor T-bet level is enhanced, this is correlated with reduced development of T<sub>RM</sub> cells and the survival factor CD127 (Zens et al., 2017). Investigators also have examined the effects of COVID-19 on children. A recent study demonstrated, unlike the other respiratory infections, COVID-19 was milder in children, and most of the children were asymptomatic (Sinha et al., 2020). But, the evidence showed *Streptococcus pneumoniae* and *Haemophilus influenzae type B* caused pneumonia in children, and they have been identified as major contributing factors for death under the age of 5 (Adkins et al., 2011). The researchers observed clinical symptoms of COVID-19 in children were less severe than in adults, and the mortality rate is low. Cough, pharyngeal erythema, and fever are the majority of symptoms among children (X. Lu et al., 2020; Suksatan et al., 2021).

Most recently research indicated that national dissimilarities in COVID-19 impact could be a limited extent elucidated by the different national BCG childhood vaccination policies (Miller et al., 2020; Netea et al., 2020). According to cross-protection, in vitro memory T cells which are specific for unrelated pathogens, probably can play important role in protective immunity arising from heterologous infectious agents. Analogous epitopes shared between BCG and SARS-CoV-2 have been recognized as the potential for cross-reactive in adaptive immunity (Welsh and Selin, 2002; Eggenhuizen et al., 2021) Although in vivo effect of cross-reactive T cells in BCG vaccinated individuals, particularly memory T cell subsets should be characterized.

Recently, Cohen and et al. investigated SARS-CoV-2 specific T cell responses in children. Infected children had notably lower CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses to SARS-CoV-2 structural compared to infected adults. Effector and memory CD4<sup>+</sup> T cells responses to structural SARS-CoV-2 proteins remarkably elevated with age, whereas CD8<sup>+</sup> T cell responses enhanced with time post-infection (Cohen et al., 2021).

Also, laboratory tests in children showed neutrophil counts reduced, but lymphocytes counts were not different from adults. Inflammatory mediators such as CRP and IL-6 were not elevated, and enhanced LDH was observed in children, which cause cardiopulmonary disease. Although lung injuries were observed in some cases in children, clinical symptoms were mild compared to adults (Du et al., 2020). A possible explanation for these results may be the lack of adequate inflammatory memory cells, low ability to cell-mediated attacks on lung tissue, and fewer ACE2 receptors in the lungs, and other organs in early life. Another possible explanation is the lack of devastating inflammatory response and cytokine storm that leads to exacerbation of the disease.

## 2.4. COVID-19 mild, moderate, and severe infections among adults and elderly patients

To realize how immune responses make processes in the elderly and young hosts differently, we require to discover how the innate and adaptive systems differ during the natural aging process. The reduction of hematopoietic output causes an age-related diminution of naïve lymphocytes in the circulation. Besides the B cells population, there is a vast range of age-related functional changes in peripheral B cells that could alter antibody responses to infections and vaccines in the elderly (Riley et al., 2017). In addition, since T lymphocyte cells leave their developmental sites and resettle to secondary lymph tissue, they encounter age-related stromal failure (Masters et al., 2019). In opposition to young people, older adults are exposed to the coronaviruses, therefore, memory cells level is enhanced, and the inflammatory response is more intense, which in the elderly and patients with underlying disease contribute to multi-organ dysfunction and a severe form of the disease (Abdulmir, 2020). The relationship between cytokine profile and age has been widely investigated. The findings showed that cytokine profiles are age-related, and the T cell population presented various functions in children, adults, and the elderly. Also, data suggested that children's cells are rarely susceptible to stimulation compared to adults (Booth et al., 2014). Along with COVID-19 growth in children, there is increasing concern over the progression of the disease in the elderly. In elderly infected patients, hyper-functional immune response causes cellular exhaustion (e.g., lymphopenia), hyper-inflammation, and cytokine storm that give rise to death. On the other hand, it has been shown that in older adults D-dimer levels, more than 1  $\mu\text{g/mL}$  and elevated Sequential Organ Failure Assessment (SOFA) scores, were predisposing factors for death with COVID-19 (Zhou et al., 2020). In other words, hyper-functional immune response and following outcomes, are stronger reasons than COVID-19 virus numbers for death (Smits et al., 2010). In addition, differentiation of naïve T cells to memory T cells enhanced with age (Davenport et al., 2019). Some authors have speculated that diminished myeloid cell antigen-presenting cell (APC) function in older adults, probably aggravated immune evasion by SARS-CoV-2 infection (Zhao et al., 2016).

Bronchoalveolar lavage fluid analysis (single-cell RNA-seq technique) demonstrated the whole number of tissue-resident CD8<sup>+</sup> T cells was greater in moderate disease patients than that in those with severe disease. Also, this study deduced that lung macrophages present in Bronchoalveolar lavage fluid of severe COVID-19 patients expressed chemokines highly likely to recruit inflammatory monocytes, while lung macrophages expressed higher amounts of T cell-recruiting chemokines in moderate COVID-19 patients, supporting the hypothesis that T cell migration to the lungs is not the leading cause of lymphopenia which is observed in the severe forms of the disease (Liao et al., 2020a). In respiratory infections cases, T<sub>RM</sub> can provide protection against severe pulmonary disease by blocking the spread of viral disease from the upper to lower respiratory tract which has been demonstrated obviously in influenza A infection (Pizzolla et al., 2017).

In line with recent studies, pre-existing T cell immunity against SARS-CoV-2 is likely against common cold viruses in 20–50% of the unexposed individuals (Grifoni et al., 2020a). Severe COVID-19 patients

demonstrated lower TCR avidity and clonal expansion. As memory T cells have a less activation threshold, numerous low avidity memory cells may be involved and prohibit naïve T cell activation and high-affinity selection (Lanzer et al., 2018). Additionally, evaluation of immunological age-related interaction memory on COVID-19 severity indicates that SARS-CoV-2 reactive T cells in hospitalized patients demonstrate notably lower functional avidity compared to non-hospitalized patients. Increasing T cell abundance in severe COVID-19 did not arise from an expansion of individual clones but instead reflected a broad polyclonal response. In mild disease, the most expanded clones were generally exclusive to the cytotoxic cluster while several clusters were observed in more severe disease. (Bacher et al., 2020) This evidence indicates a need to understand the various aspects of COVID-19 that exist among mild, moderate, and severe patients.

In a major study, Wen, W. et al. found that in patients in the early recovery stage of COVID-19 (who recovered in less than seven days), CD4<sup>+</sup> and CD8<sup>+</sup> T cells, NK and naïve B cells diminished significantly, while plasma cells and inflammatory genes increased. On the other hand, in patients in the late recovery stage, NK and T cells were elevated, and inflammatory genes decreased (Wen et al., 2020). Also, the magnitude of memory cells responses and COVID-19 disease severity were investigated up to 8 months in hospitalized and non-hospitalized adults. Given to result, memory CD8<sup>+</sup> T cell frequencies were not higher in hospitalized cases compared to non-hospitalized cases, and memory CD4<sup>+</sup> T cell frequencies were lower in hospitalized cases compared to non-hospitalized individuals. Moreover, memory B cells specific for the spike protein existed in almost all COVID-19 individuals, with no apparent half-life at 5 to 8 months after infection (Dan et al., 2021), while other studies of B cell memory against other infections has been distinguished to be long-lived (Palm and Henry, 2019). In other research on the magnitude of memory cells against COVID-19 particularly in the elderly, it was found CD4<sup>+</sup> T cell responses appear to be more substantial than those of CD8<sup>+</sup> T cells. In other words, the COVID-19-specific CD4<sup>+</sup> T lymphocytes' existence is significantly associated with decline COVID-19 severity than the antibodies and CD8<sup>+</sup> T cells (García-Torre et al., 2021). Interestingly, in hematological malignancy elderly patients who became infected with SARS-CoV-2, although titers of SARS-CoV-2-specific IgG were reduced on account of anti-CD20 therapy, it was not associated with increased mortality, disease severity, or viral load (Bange et al., 2021). It stands to reason that when the humoral immune response is inadequate, effector and memory T cells have a host protective role in COVID-19 patients particularly. Also, 'virtual memory' CD8<sup>+</sup> T cells (TVM) have been most broadly studied in mice, but a human similar population has been recognized (CD45RA<sup>+</sup>KIR<sup>+</sup>NKG2A<sup>+</sup>Eomes<sup>+</sup>) that is related to age. Cytokines (IL-15, IL-18, and type I IFNs) trigger the activity of Virtual memory CD8<sup>+</sup> T. Regardless of cognate antigen during viral infections. Although this could be considered a benefit in the elimination of the virus, it could also have detrimental effects on the host if remained unregulated. However, the role of these cells in COVID-19 patients should be further investigated (Kim and Shin, 2019). Furthermore, Thevarajan, I. et al. showed activated CD4<sup>+</sup> and CD8<sup>+</sup> T cells, follicular T-helper cells, antibody-secreting cells, and IgM/IgG SARS-CoV-2-binding antibodies, were enhanced in mild-to-moderate COVID-19 hospitalized patients (Thevarajan et al., 2020).

### 2.5. Role of memory cells in protective immunity against COVID-19

There has been little agreement on what mechanisms can give rise to the progression or inhibition of disease. A considerable amount of literature has been published on the role of antibodies in COVID-19. Several studies have revealed that the presence of CD4<sup>+</sup> T cells is necessary for generating antibody responses against infection with coronavirus, vesicular stomatitis virus (VSV), yellow fever virus, or vaccinia virus (Swain et al., 2012). Yuchun, N. et al. point out neutralizing antibodies response to SARS-CoV, can enlarge approximately 20

days post-infection against viral N and S proteins and can last for 150 days (Yuchun et al., 2004), whereas in SARS-CoV-2, neutralizing antibodies are not protective (Pan et al., 2020). Recent evidence suggests that restriction in antibody response in COVID-19 may be due to the absence of germinal centers. They observed in thoracic lymph nodes and spleens of deceased COVID-19 patients, germinal centers were absent, and the absence of germinal centers interacted with a defect in Bcl-6<sup>+</sup> TFH cell differentiation, antibody affinity maturation, somatic hypermutation, and accumulation of extra-follicular TNF- $\alpha$ . Whereas in mild and convalescent COVID-19 patients, virus-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells, B cells, TFH cells, and circulating IgG, and IgM in their periphery were perceived (Kaneko et al., 2020; Duan et al., 2020).

In contrast to some other evidence, Duggan, NM. et al. claimed reinfection in COVID-19 patients is possible. They reported that an old male with underlying diseases that previously recovered from COVID-19, re-infected with newly positive RT-PCR, 48 days after the first presentation (Duggan et al., 2020). It seems possible that these results are due to a strong viral immune escape mechanism that contributes to virus escape from innate immune cells, neutralizing antibodies, and reduction in interferons production (Weisblum et al., 2020). Although differences of opinion still exist, there appears to be some compromise that amelioration of COVID-19 refers to adaptive immunity and memory cells. Prior studies have argued about a dual role for T cells in COVID-19 infection. Some authors have demonstrated that lung injuries may be due to the overreaction of T cells (Xu et al., 2020) but, others support the protective role of T cells in disease progression (Diao et al., 2020). However, depending on time and adaptive immune response value, both of the two theories can happen (Peeples, 2020). Peng, Y. et al. confirm the association between SARS-CoV-2-specific T cell responses and recovery from COVID-19. They have illustrated in severe subjects, memory T cells responses were greater than mild COVID-19 subjects, which are associated with response to ORF3a, membrane, and spike proteins. In contrast, in mild cases, nucleoprotein-specific CD8<sup>+</sup> T cells were elevated (Dong et al., 2020). This finding corroborates the ideas of Liao, M. et al. who suggested that adaptive T cell responses are probably protective in SARS-CoV-2 infection. They observed clonal expansions of CD8<sup>+</sup> T cells in BALF of mild COVID-19 patients (Liao et al., 2020b). Moreover, Sahin, U. et al. has been reported that the BNT162b1 mRNA vaccine against COVID-19, activated virus-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells, produced neutralizing antibodies and improved IFN- $\gamma$  secretion. They indicated that CD4<sup>+</sup> and CD8<sup>+</sup> T cells immune responses were not dose-dependent and may provide permanent immunity against COVID-19 (Sahin et al., 2020). Additionally, some studies showed the development of a unique, innate memory cell population of natural killer cells (NKG2C) in response to viral and bacterial infections, such as cytomegalovirus (Foley et al., 2012; Jaiswal et al., 2019), influenza (Goodier et al., 2016; Jaiswal et al., 2020a), HIV (Gondois-Rey et al., 2017), Hantavirus (Björkström et al., 2011) and *Mycobacterium tuberculosis* (Suliman et al., 2016), that inhibit expansion of lower respiratory infections. In addition, the absence of NKG2C<sup>+</sup> NK cells, in other coronavirus infections in particular SARS-CoV-1, contributed to the exacerbation of the disease (National Research Project for SARS BGJA-JoCP, 2004). These findings support the idea that NKG2C<sup>+</sup> NK cells may constrain the deterioration of COVID-19 infected cases (Jaiswal et al., 2020b). The reported data supports the assumption that memory cell cross-reactions can have an effect on SARS-CoV-2 control. A widespread phenomenon is heterologous viral immunity that happens when humans are exposed to various antigens following vaccination and infection, and particular virus memory T cells, cross-react with epitopes expressed by other, unrelated viruses (Welsh et al., 2010). Grifoni, A. et al. reported SARS-CoV-2-specific CD4<sup>+</sup> T cell responses were observed in both recovered from COVID-19 and unexposed cases. Furthermore, they showed CD8<sup>+</sup> memory responses to SARS-CoV-2 were established in 70% of recovered patients. This result may be explained by the pre-existent cross-reactive immune memory to other coronaviruses (Grifoni et al., 2020b). These findings match those observed in some other

studies. According to Guo, T. et al. and Li, C.K. et al. studies, memory T and B cells of SARS-CoV-1 infection can be sustained for a long time and improve adaptive immune response against SARS-CoV-2 infection (Guo et al., 2020; Li et al., 2008). Although the evidence showed in SARS-CoV-1 infection, memory B cell responses were momentary (Channappanavar et al., 2014a; Channappanavar et al., 2014b), while memory T cell responses were a strength for a long time (Le Bert et al., 2020). Studies showed that in COVID-19 infected patients, memory B cells declined. However, plasmablasts were significantly increased, and in some cases, IgG was available in plasma that can be attributed to the expansion of immunoglobulins by pre-existing specific memory B cells for other coronaviruses (De Biasi et al., n.d.). Although some former studies on SARS-CoV-1 and MERS-CoV infection have indicated that T cell responses were more supporting compared to antibody responses, there is no precise information on how long adaptive immune memory lasts in COVID-19 convalescent patients (Tang et al., 2011; Zhao et al., 2017). In another major study into this area, Sekine, T. et al. demonstrated memory T cells have a fundamental role in inducing long-lasting immunity in individuals with COVID-19. They observed in the acute and recovery phase of COVID-19, T cells exhibited a cytotoxic and stem-like memory phenotype, respectively. In addition, they reported in mild cases or antibody-seronegative family members, COVID-19 specific T cells were identified and robust memory T cell response can hamper recurrent severe COVID-19 (Sekine et al., 2020). Lately, stem cell-like memory T ( $T_{SCM}$ ) cells were considered to possess the capacity for self-renewal and multipotency to revive the broad spectrum of memory and effector T cell subsets (Gattinoni et al., 2017; Gattinoni et al., 2011b). In this regard, Hyung Jung et al. demonstrated the preservation of SARS-CoV-2-specific memory T cell responses in COVID-19 convalescent patients over 10 months post-infection. Interestingly, SARS-CoV-2-specific  $T_{SCM}$  cells scarcely expressed PD-1 and TIGIT, illustrating that SARS-CoV-2-specific  $T_{SCM}$  cells are not exhausted-like progenitors (Jung et al., 2021).

### 3. Conclusion

Memory cells play a pivotal role in the rapid and appropriate response to infectious agents, especially viral agents. The role of memory cells in the induction of effector T cells and the production of protective and neutralizing antibodies has been identified and demonstrated. In this study, by confirming the effective and protective role of antibodies in patients with COVID-19, the role of memory cells was fully investigated and mentioned. The function of memory cells in individuals of different ages as well as various genetics and history of Ag exposure indicate the role of memory cell importance. A high percentage of patients do not show any symptoms after exposure to the COVID-19. Even the antibody titer is not detectable in many of these people, which may be due to the inhibition of the virus through the protective effect of memory cells. On the other hand, a small percentage of patients who develop symptoms, have different outcomes depending on the type and population of memory cells (whether they produce antibodies or not). A large percentage of these patients can overcome the disease due to the strength of the immune system and the type of memory cells and about less than 5% of patients will die as a result of immune system activation and cytokine storm. In infants and children, the absence of inflammatory memory cells is considered a protective factor to prevent cytokine storms and severe forms of COVID-19. But in adults, cross-reactive memory cells determine the degree of disease. In fact, the patients with cross-reactive memory cells can show low or mild symptoms, while patients with inflammatory memory cells can move to a severe form of the disease and establish the inflammation expansion. Moreover, Pre-existing memory indicated a general mechanism of immune-modulation towards neo-antigens, commonly in the elderly. Low avidity pre-existing T cell memory negatively impacts the T cell response quality against SARS-CoV-2, which may give rise to unsuitable immune responses chiefly in elderly patients. Unfocused and low avidity

response may consequence of preferential recruitment of a vast pre-existing memory repertoire generally existing in the elderly. All in all, pre-existing SARS-CoV-2 cross-reactive memory T cells in unexposed individuals are prevalent in humans and develop with the immunological age but do not demonstrate aspects of a protective cross-reactive T cell population. Also,  $T_{RM}$  could prevent the spread and replication of upper respiratory tract SARS-CoV-2 infection. Although the role of cross-reactive  $T_{RM}$ , induced by seasonal coronaviruses, can block transferring SARS-CoV-2 from the upper respiratory tract to the lung and finally weaken severe COVID-19 remains unresolved. Besides, whether SARS-CoV-2-specific  $T_{RM}$  are induced after COVID-19 and if these cells will provide enough protection for a long-time also have been remaining unanswered. According to the relationship between COVID-19 severity and age, it will be substantial to perceive whether the elderly have been exposed to more human coronavirus infections and whether this exposure makes strong memory T cell responses. Because with age insufficient TCR diversity may prevent vast memory T cell development.

Therefore, given the importance of vaccination, vaccines under development should focus on the characteristics, population, and response of memory cells, more than the production of neutralizing antibodies, because memory cells can produce antibodies. On the other hand, monitoring the population of memory cells in healthy or at-risk individuals is very important for proper prevention or treatment.

### Declaration of competing interest

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

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