MAJOR ARTICLE

Dysregulated Host Response in Severe Acute Respiratory Syndrome Coronavirus 2-Induced Critical Illness

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Background. Impaired immune response has been reported to be the cause of the development of coronavirus disease 2019 (COVID-19)-related respiratory failure. Further studies are needed to understand the immunopathogenesis and to enable an improved stratification of patients who are at risk for critical illness.

Methods. Thirty-two severely ill patients hospitalized with COVID-19 were recruited in our center at the University Hospital Heidelberg. We performed a comprehensive analysis of immune phenotype, cytokine, and chemokine profiling and leukocyte transcripts in patients with severe COVID-19 and compared critically ill patients who required mechanical ventilation and high-flow oxygen therapy and noncritically ill patient who received low-flow oxygen therapy.

Results. Critically ill patients exhibited low levels of CD8 T cells and myeloid dendritic cells. We noted a pronounced CCR6^{+} TH17 phenotype in CD4 central memory cells and elevated circulating levels of interleukin-17 in the critical group. Gene expression of leukocytes derived from critically ill patients was characterized by an upregulation of proinflammatory cytokines and reduction of interferon (IFN)-responsive genes upon stimulation with Toll-like receptor 7/8 agonist. When correlating clinical improvement and immune kinetics, we found that CD8 T-cell subsets and myeloid dendritic cells significantly increased after disconnection from the ventilator.

Conclusion. Critical illness was characterized by a TH17-mediated response and dysfunctional IFN-associated response, indicating an impaired capacity to mount antiviral responses during severe acute respiratory syndrome coronavirus 2 severe infection.

Keywords. COVID-19; critical illness; IFN-responsive genes; inflammation; TH17 immunity.

To date, the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected approximately 72 million individuals and led to 1.6 million deaths worldwide. According to the World Health Organization (WHO), 15% of these cases are considered to be severe, requiring intensive care unit (ICU) admission and mechanical ventilation in some cases [1]. More than 600 clinical trials are currently being conducted to find effective therapeutic strategies against COVID-19. However, the current standard of care still relies on supportive treatment for the severe cases. Therefore, investigation of immunopathology and immune response of COVID-19-related acute respiratory distress syndrome (ARDS) is warranted for the development of effective drugs to improve the outcomes [2].

Several publications have indicated that a dysfunctional immune response is associated with the severity of COVID-19. So far, lymphopenia has been considered the hallmark of the disease. It has been reported that CD3, CD4, and CD8 counts are correlated with in-hospital mortality, organ injury, and severe pneumonia [2, 3]. Qin et al [4] showed higher neutrophil/lymphocyte ratio and an increased level of proinflammatory markers in patients with COVID-19. Further studies have described the so-called "cytokine storm," a strong indicator of the pathological host immune response [3].

In this study, we performed an in-depth immune phenotypic analysis of individual lymphocyte and myeloid cell populations obtained from patients with severe COVID-19 who were admitted to our ICU at the University Hospital Heidelberg. A multiplex assay was run to establish a link between immune phenotype and cytokine and chemokine expression. Interferon (IFN)-associated response reflecting the ability of mounting an antiviral response was investigated in an ex vivo stimulation assay.

METHODS

Patient Consent Statement and Study Approval

All patients provided written informed consent for the study. Patient care and research were conducted in compliance with the Declaration of Helsinki. Experiments were approved by the Ethics Committee of the University Hospital of Heidelberg, Germany (S148/2020). Whole blood was collected and processed immediately for flow cytometry analysis.

Flow Cytometry

The phenotyping was performed in whole blood within 4 hours, as recently described [5]. Absolute cell count was measured using the Multitest 6-color TBNK reagent (BD Biosciences). In brief, Panel-1 consisted of antibodies to characterize major T-cell populations (CD2, CD3, CD4, CD8, CD45RA, CD197). Panel-2 consisted of parameters (CD3, CD19, CD20, CD38), allowing the identification B cells as well as circulating plasma blasts. Panel-3 identified various monocyte and dendritic cell (DC) subsets (CD11c, CD123, CD14, CD16). The analysis was performed with LSR Fortessa Analyzer (BD Biosciences).

Gene Expression Analysis

A total of 0.5 mL heparinized whole blood was incubated with Roswell Park Memorial Institute (RPMI) 1640 medium or RPMI 1640 containing 10 µg/mL Resiquimod R848 (InvivoGen) for 3 hours at 37°C and 5% CO_2. Red cells were lysed with ACK-buffer. Ribonucleic acid (RNA) isolation from leukocytes and complementary deoxyribonucleic acid (cDNA) preparation were performed by using the MagNA-Pure (Roche) and First Strand cDNA Synthesis Kit (Roche) according to the manufacturer's instructions. Polymerase chain reaction was performed with the LightCycler FastStart DNA SYBR Green I kit (RAS). To correct for differences in the content of RNA, the calculated transcript numbers were normalized according to the expression of the housekeeping gene peptidylprolyl isomerase B (PPIB).

Quantification of Viral Ribonucleic Acid Load

Ribonucleic acid was isolated from nasopharyngeal swabs using QIAGEN Kits (QIAGEN) and by using various reagent mixes: LightMix Modular SARS and Wuhan CoV E-gene, LightMix Modular SARS and Wuhan CoV N-gene, LightMix Modular Wuhan CoV RdRP-gene and LightMix Modular EAV RNA Extraction Control (TIBMOLBIOL, Berlin, Germany), and LightCycler Multiplex RNA Virus Master (Roche) according to the manufacturer's instructions. Quantification of viral load was performed for E-gene using defined amounts of SARS-CoV-2 RNA standards.

Quantification of Cytokine and Chemokine

Blood serum was collected from each subject and was initially stored at −80°C for cytokine and chemokine profiling. For this purpose, multiplex analysis (Bio-Plex Pro Human Cytokine 48-PlexScreening Panel plus ICAM and VCAM; Bio-Rad, Munich, Germany) was performed, as previously described [6].

Statistical Analysis

Analysis was carried out by performing non-parametric tests (Mann-Whitney *U* test and Wilcoxon signed-rank test) using GraphPad Prism 8.0 (GraphPad, San Diego, CA). Figures were created by using GraphPad Prism 8.0.

RESULTS

Demographic and Clinical Characteristics of Patients With Coronavirus Disease 2019

Thirty-two COVID-19 cases, who were admitted to our ICU at the University Hospital Heidelberg from March 1, 2020 through May 19, 2020, were enrolled to analyze the immune response in severe patients with SARS-CoV-2 infection. According to the classification of WHO, criteria for severe COVID-19 illness included the following: clinical signs of pneumonia (fever, cough, dyspnea) plus 1 of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or SpO_2 <93% on room air. All patients in our cohort required supplemental oxygen therapy. We further divided the patients in 2 groups based on the oxygenation index calculated by the PaO_2/FiO_2 ratio. Subjects with oxygenation index ≤300 were assigned to the critical group (n = 15). Eleven of 15 critically ill patients (73.3%) required mechanical ventilation, while 26.6% (n = 4) of this group were treated with high-flow nasal cannula oxygen therapy. Demographic and clinical characteristics are described in Table 1. Laboratory results at admission are presented in Table 2.

Clinical Diagnosis of Severe Respiratory Failure Correlates With Decreased CD4 and CD8 Counts, But Not With Viral Ribonucleic Acid Load

We first examined the absolute counts and frequency of peripheral blood-derived lymphoid and myeloid cell populations from patients with severe COVID-19 at day 0–2 after hospitalization. Immunophenotypic analysis revealed that numbers of CD8 and CD4 T cells were significantly decreased in critically ill patients with COVID-19, compared with the noncritical group (Figure 1A). It is notable that critically ill patients with COVID-19 did not present with higher viral RNA load detected in nasopharyngeal swabs, compared with noncritically ill cases (Supplementary Figure 1A).

Among the myeloid populations, dendritic cells (DCs) were significantly reduced in critically ill subjects with COVID-19, compared with the noncritical group (Figure 1B). Monocyte and granulocyte counts did not differ between the cohorts (Supplementary Figure 1B).

We next explored the different myeloid subsets in the circulation of patients with COVID-19. Myeloid DCs

Table 1.   Basic Characteristics of 15 Critically Ill COVID-19 Patients Requiring Mechanical Ventilation or High-Flow Nasal Cannula Oxygen Therapy and Noncritically Ill COVID-19 Patients Receiving Low-Flow Oxygen Therapy

Characteristics	Critical (N = 15)	Noncritical (N = 17)
Age (years, mean ± SD)	67 ± 11	58 ± 15
Days from illness onset to admission (mean ± SD)	7 ± 4	9 ± 5
Mechanical ventilation (n, %)	11 (73.3)	0 (0)
High-flow oxygen therapy (n, %)	4 (26.6)	0 (0)
Low-flow oxygen therapy (n, %)	0 (0)	17 (100)
Maximum oxygen demand	70% FiO$_2$	5 L/min
Sex		
Female gender (n, %)	4 (26.6)	6 (35.3)
Main Comorbidities (n, %)		
Diabetes	3 (20)	3 (17.6)
Hypertension	7 (46)	7 (41)
Cardiovascular disease	2 (13)	3 (17.6)
Pulmonary disease	1 (6.6)	0 (0)
Malignancy	1 (6.6)	1 (5.8)
Outcome (n, %)		
Death	3 (20)	0 (0)
Recovery	12 (80)	17 (100)
Signs and symptoms (n, %)		
Fever	14 (93.3)	14 (82.4)
Cough	11 (73.3)	14 (82.4)
Myalgia or fatigue	5 (33.3)	11 (64.8)
Dyspnea	12 (80)	13 (76.5)
Diarrhea	5 (33.3)	3 (17.6)

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation.

were defined as CD11c$^+$CD123$^-$ population, whereas plasmacytoid DCs were identified as CD11c$^-$CD123$^+$ subset. The frequency of myeloid DCs was diminished in the critical group, compared with the noncritical group, whereas there was no difference in the frequency of plasmacytoid DCs (Figure 1B).

Table 2.   Laboratory Results in Critically (N = 15) and Noncritically Ill (N = 17) COVID-19 Patients at Initial Hospitalization

Laboratory Results (Mean ± SD)	Critical (N = 15)	Noncritical (N = 17)	P Value[a]
White blood count/nL	8.5 ± 4.1	6.8 ± 2.8	
Lymphocyte count/nL	0.6 ± 0.2	1.0 ± 0.4	.003
Hemoglobin (g/dL)	12.6 ± 2.5	13.5 ± 1.3	
Platelet count/nL	258 ± 100	257 ± 111.2	
Prothrombin time (%)	77.1 ± 21.7	88.1 ± 23.5	
D-dimer (mg/L)	3.0 ± 3.6	2.52 ± 5.73	
Albumin (g/L)	37.1 ± 4.8	41.9 ± 3.1	.005
Alanine aminotransferase (U/L)	55.3 ± 62	32.4 ± 7.5	
Aspartate aminotransferase (U/L)	70.1 ± 51.1	33.6 ± 16.3	.007
Total bilirubin (mmol/L)	0.8 ± 0.4	0.55 ± 0.15	.018
Potassium (mmol/L)	4.1 ± 0.6	4.1 ± 0.39	
Sodium (mmol/L)	136.1 ± 6.7	135.4 ± 5.1	
Creatinine (μmol/L)	1.4 ± 1.4	0.75 ± 0.18	
Creatine kinase, U/L	185.9 ± 186.7	108.4 ± 22.3	
Lactate dehydrogenase, U/L	543.9 ± 158.5	349.3 ± 126.5	.0008
Hypersensitive troponin I, pg/mL	19.3 ± 13.3	9.4 ± 5.53	.011
Nt-proBNP (ng/L)	4164.1 ± 8500.7	324.75 ± 491.8	
C-reactive protein (mg/L)	165.0 ± 67.5	64.9 ± 46.8	4.5e^{-05}
Procalcitonin (ng/mL)	0.95 ± 1.2	0.08 ± 0.06	.01

Abbreviations: COVID-19, coronavirus disease 2019; Nt-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation.

[a]P value calculated by 2-tailed t test.
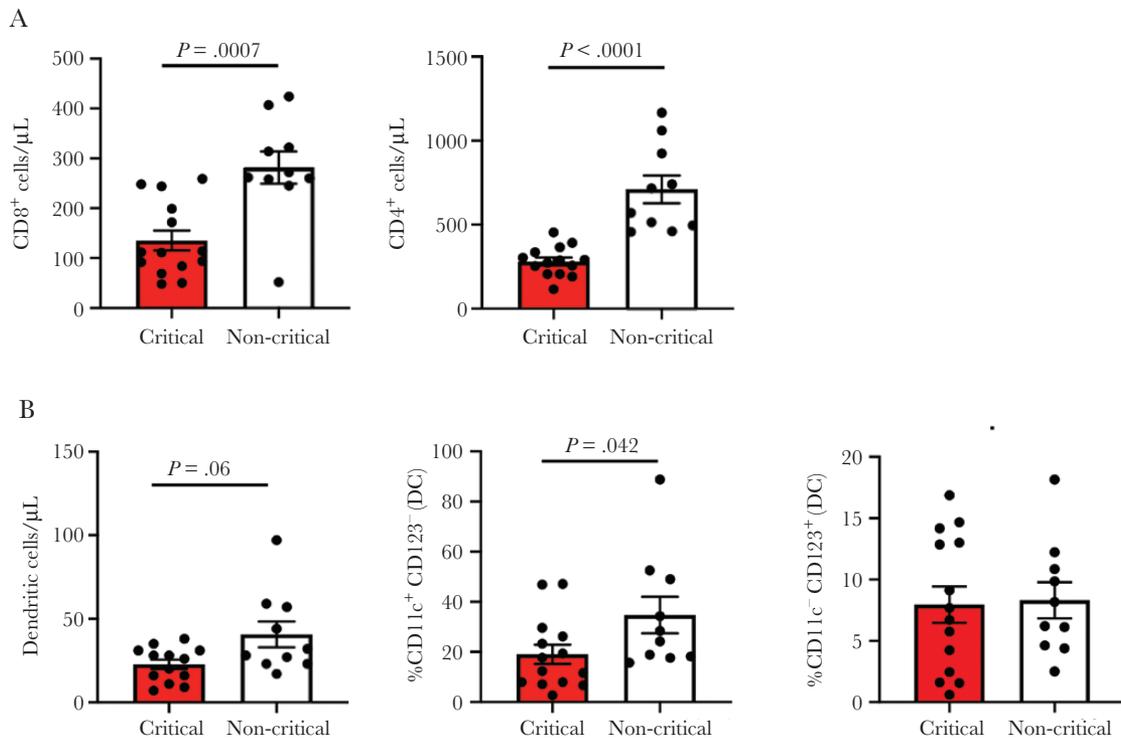
Figure 1. Clinical diagnosis of severe respiratory failure correlates with decreased CD4 and CD8 counts, but not with viral ribonucleic acid load. (A) Absolute counts of peripheral blood-derived CD8 and CD4 T cells in critically ill (N = 14) and noncritically ill (N = 10) patients at day 0–2 after admission. (B) Absolute counts of circulating dendritic cells (DCs) in peripheral blood of critically ill and noncritically ill patients. Frequency of CD11c and CD123 in the DC population, identifying myeloid and plasmacytoid DC, respectively. All bar figures represent mean ± standard error of the mean. P value calculated by Mann-Whitney U test.

Coronavirus Disease 2019-Related Acute Respiratory Distress Syndrome Is Correlated With an Enhanced TH17 Phenotype in the CD4 Central Memory T-Cell Subset

Because CD4 cell counts are significantly correlated with disease severity, we next sought to characterize CD4 T cells based on their memory function and T helper subset profile. We defined central and effector memory subsets based on their CD45-RA and CCR7 expression. CD4 central memory T cells (TCM) were marked as CD45-RA⁻CCR7⁺ cells, whereas CD4 effector memory T cells (TEM) were identified as CD45-RA⁻CCR7⁻ cells. Absolute counts of both CD4 memory T cells, particularly CD4 TCM, were significantly reduced in the critical group, compared with the noncritical group (Figure 2A).

To analyze the functional phenotype of CD4 helper cells, we subdivided this population based on the expression of CCR6 and CXCR3 cells. CD4 TCM from critically ill patients increased the proportion of CCR6⁺ cells, suggesting a TH17 phenotype (Figure 2A). Concomitantly, we found an increase of interleukin (IL)-17 and IL-6 in the serum of critically ill patients, compared with noncritical cases (Figure 2B).

Dysfunctional Interferon-Mediated Response in Patients With Severe Coronavirus Disease 2019 Upon Stimulation With Toll-Like Receptor 7/8 Agonist R848

Next, we assessed the ability of leukocytes derived from critically ill and noncritically ill patients with COVID-19 to respond upon activation by the Toll-like receptor 7/8-agonist Resiquimod (R848), an imidazoquinoline compound. Toll-like receptors serve as pathogen sensors and are key regulators of innate and adaptive immune responses during viral infection. Exposure of leukocytes to R848 for 3 hours resulted in significant induction of proinflammatory messenger RNA levels, such as *IL1B* and *IL18*, in leukocytes of critically ill subjects, compared with noncritically ill patients (Figure 3A). Concomitantly, we had found that critically ill patients exhibited higher level of circulating proinflammatory cytokines, such as IL-1β, and IL-18, compared with noncritically ill patients (Supplementary Figure 2A). In regard to the chemokine profile, critically ill patients exhibited higher levels of circulating chemokines, such as IFN-inducible CXCL10 and CCL7, compared with noncritically ill patients (Supplementary Figure 2B).

Because activation of the TLR7/8-dependent signaling pathway triggers an antiviral IFN-associated response [7], we evaluated IFN-responsive genes. We observed that *MX1*, *IFIT1*, and *IFI44L* transcripts were downregulated in leukocytes derived from critically ill patients, compared with noncritically ill subjects, postulating an impaired capacity to mount antiviral responses during SARS-CoV-2 severe infection (Figure 3B).
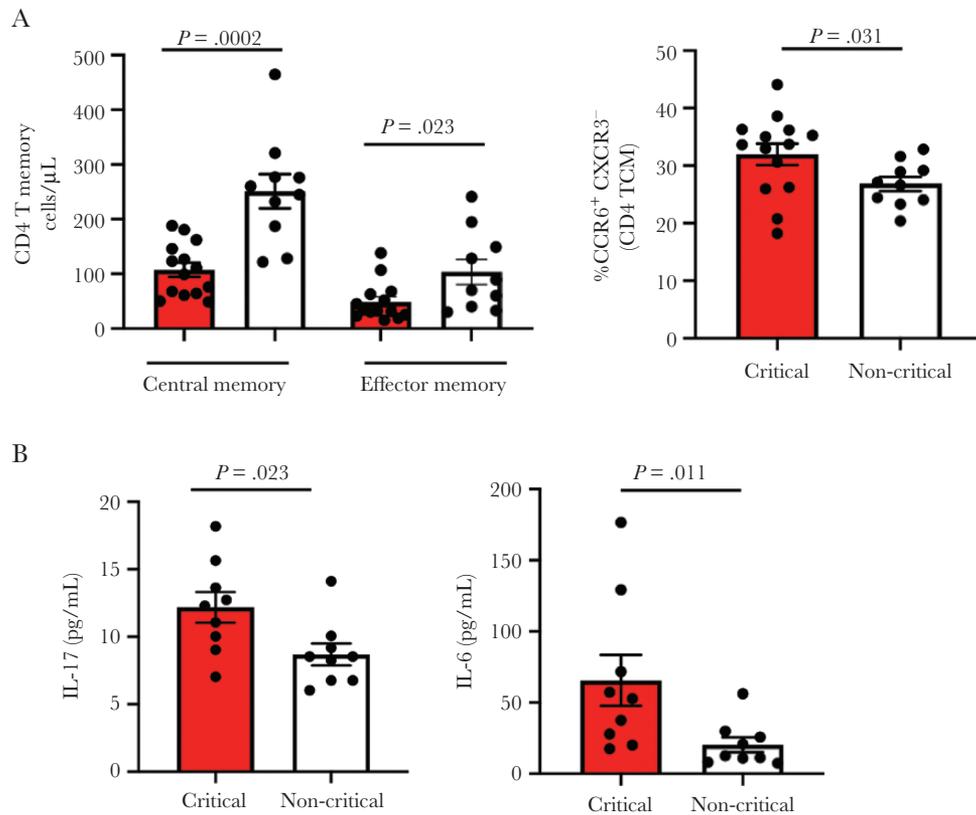
Figure 2. Coronavirus disease 2019 (COVID-19)-related acute respiratory distress syndrome is correlated with an enhanced TH17 phenotype in the CD4 T central memory cell (TCM) subset. (A) Cell counts of CD4 T central memory (TCM) and CD4 T effector memory (TEM) in critical (N = 14) and non-critical groups (N = 10). Frequency of CCR6+CXCR3- cells, identifying the TH17 cell subset, within the CD4 TCM population of critically ill and non-critically ill COVID19 cases. (B) Serum concentration of circulating IL-17 and IL-6 levels in the critical and non-critical group (n = 9 in each group). All bar figures represent mean ± standard error of the mean. P value calculated by Mann-Whitney U test.

Increase in CD8 Effector Memory T Cells, Activated CD8 T Cells, and Dendritic Cells Marks Clinical Improvement

To evaluate the immunological changes that occur during clinical improvement, we randomly selected 7 of our 15 critically ill patients and characterized the kinetics of immune subsets on the day of admission (time-point 1 [T1]) and on day 0/1 after disconnection from the ventilator (time-point 2 [T2]) for each subject.

The time course of oxygen support is depicted in Figure 4A. Although case 5 was successfully disconnected from the ventilator, his clinical condition deteriorated 2 days later, and he died 32 days after admission. All of the other patients, depicted here, survived and were discharged alive.

Analysis on immune kinetics demonstrated a significant increase in CD8 T-cell and myeloid DC counts, when mechanical ventilation or high-flow oxygen therapy was not needed (Figure 4B). It is notable that no difference in TH17 phenotype, shown as frequency of CCR6+ cells within the CD4 central memory population, was detected between the 2 time points (Figure 4C). When considering CD8 memory cells, we found that the absolute counts of CD8 TEM cells significantly increased at T2, compared with T1. When analyzing the frequency

of CD45-RA−CCR7− cells among the CD8+ lymphocytes, representing the effector memory phenotype, we noted a trend to increase in this cell subset at T2, compared with T1 (Figure 4D). No difference was observed for the central memory phenotype, when measuring the proportion of CD45-RA−CCR7+ cells among the CD8+ lymphocytes derived from critically and noncritically ill patients (Supplementary Figure 3A). We noted that clinical improvement was significantly associated with expansion of activated CD38+HLA-DR+ CD8 T cells (Figure 4E). In regard to CD4 T cells, our analysis showed (1) an increase in CD4 T-cell counts at T2 as well as (2) expansion of activated CD38+HLA-DR+ CD4 T cells that was associated with clinical improvement (Supplementary Figure 3B).

DISCUSSION

This study highlights the immunological features of peripheral blood cells derived from patients hospitalized with severe COVID-19. Our data show (1) a pronounced TH17 profile and elevated serum levels of IL-17 in critically ill patients, (2) marked alteration in DC counts with marked decrease in ventilated subjects and subsequent expansion
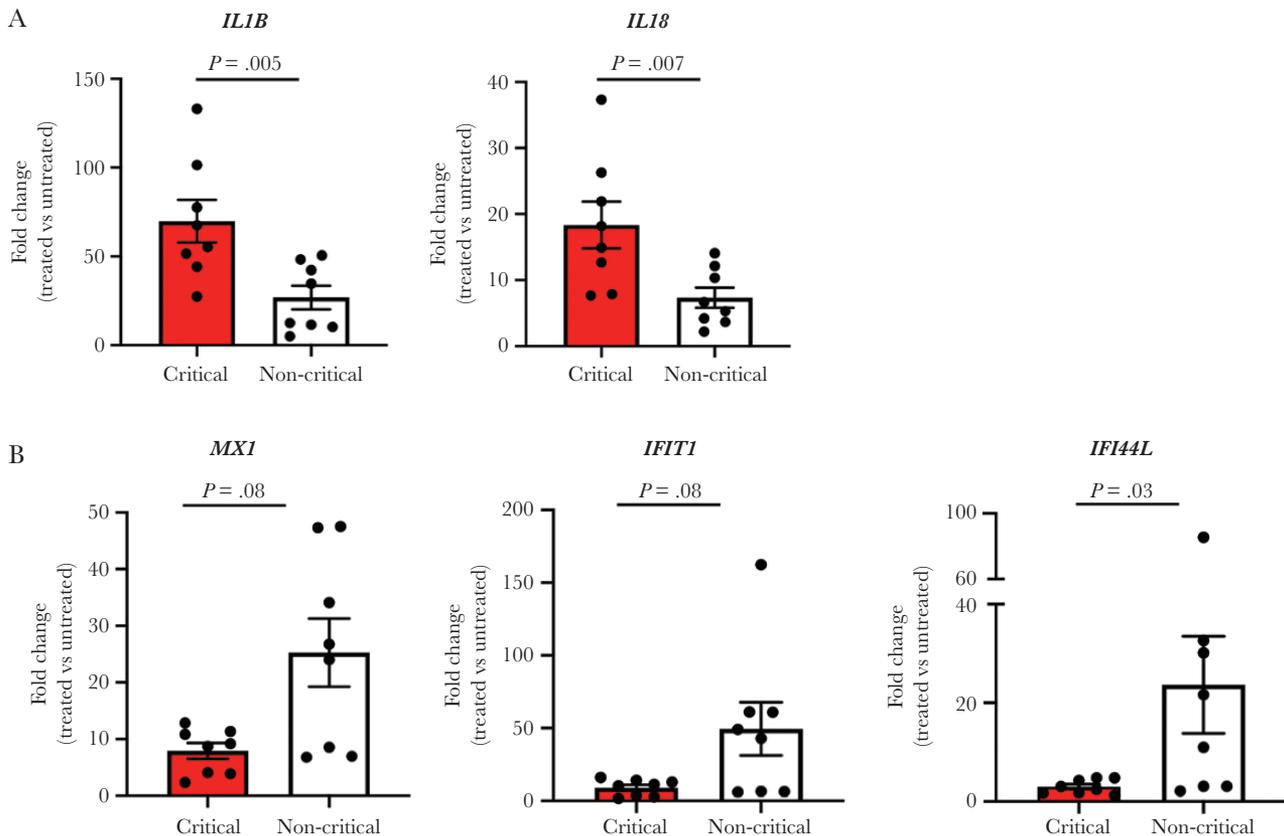
Figure 3. Dysfunctional interferon (IFN)-mediated response in severe coronavirus disease 2019 patients upon stimulation with TLR7/8 agonist R848. Human leukocytes derived from 8 individuals per group at day 0–2 after admission were used in the assay. (A) Relative messenger ribonucleic acid expression of *IL1B* and *IL18* in response to TLR7/8 agonist R848. (B) Response to R848, assessed by change in expression of the IFN-responsive genes, *MX1*, *IFIT1*, and *IF44L*, is shown. All bar figures represent mean ± SEM. Mann-Whitney *U* test was used to calculate *P* values.

after respiratory improvement, (3) increase in CD8 TEM and activated CD8 T cells along with clinical improvement, and (4) dysregulated antiviral response by impaired IFN response.

In our cytokine and chemokine expression panel, IL-17 and IL-6 were shown to be one of the most upregulated markers in critically ill patients with COVID-19. Concomitantly, the increased proportion of CCR6+ cells within the CD4 TCM subset supported the evidence for skewing towards TH17 cells in critically ill patients with COVID-19, compared with noncritical subjects. Consistent with other studies, this elevation of proinflammatory cytokines in the circulation might reflect the hyperactive state of critically ill patients with COVID-19 [3]. The differentiation of TH17 cells is promoted in a proinflammatory cytokine and hypoxic environment, suggesting that high IL-6 concentration and severe hypoxemia, seen in our patient cohort, might contribute to a pronounced TH17 cell activation [8–10].

So far, 1 case report indicated an increase in circulating CCR6+ CD4 T cells in a 50-year-old patient with severe COVID-19 [11]. Furthermore, elevated serum levels of IL-17 were noted in patients infected with Middle East respiratory

syndrome (MERS) and SARS-CoV [12, 13]. In addition, excessive production of IL-17 and a significant elevated proportion of TH17 cells were found in patients suffering from ARDS [14]. Animal models of influenza virus infection showed an acute pulmonary tissue injury that was mediated through IL-17 [15]. These findings raise the possibility that TH17-driven inflammation might be an important feature in the immunopathogenesis of COVID-19-related ARDS. Targeting TH17 signaling with commercially available monoclonal antibodies might be a promising therapeutic option to treat critically ill patients in the future.

When considering myeloid DCs, we observed decreased numbers and frequency of these cells in critically ill subjects, compared with noncritically ill patients at day 0–2 after hospitalization. Myeloid DCs are crucial for antigen presentation and are required for T-cell priming to induce a robust antiviral response. A reduced migration of myeloid DCs to the lung results in delayed T-cell kinetics in COVID-19, which leads to the pathogenic inflammatory exacerbation. This dysregulated response could explain the susceptibility to a severe outcome in elderly patients, due to the lack of function of antigen-presenting myeloid cells [16, 17]. Although our study sheds a light on a host
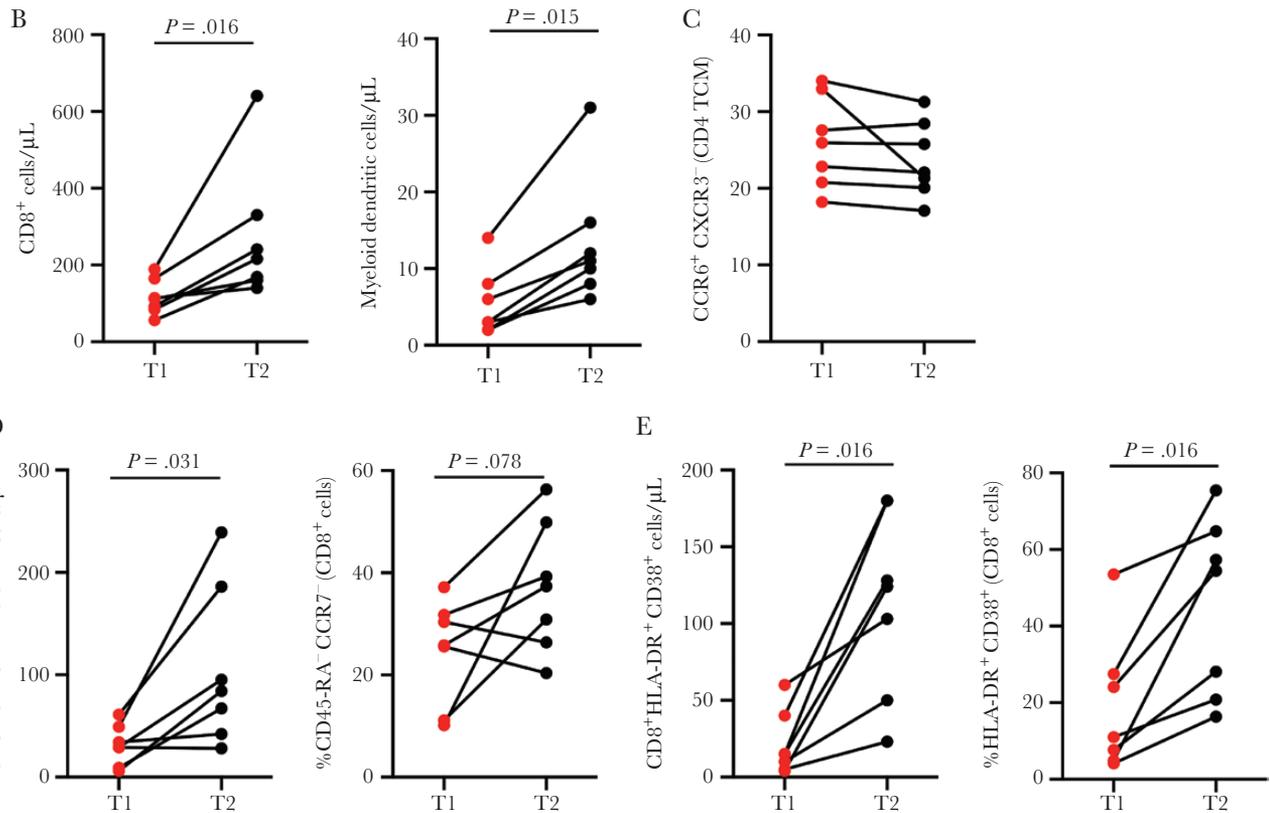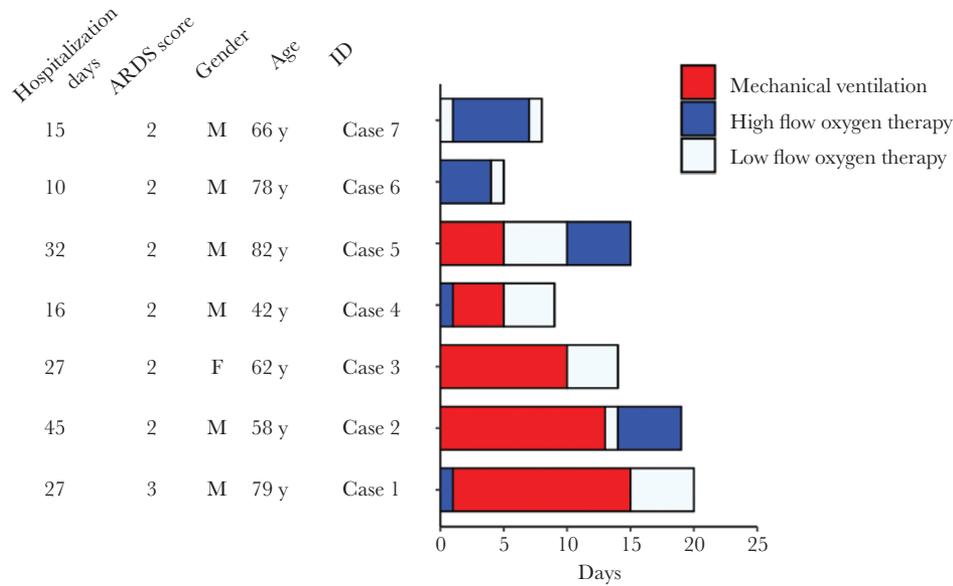
Figure 4. Increase in CD8 effector memory T cells (TEM), activated CD8 T cells, and dendritic cells marks clinical improvement. (A) Time course of oxygen support is depicted for each of the 7 critically ill patients. Comparisons are conducted between day of admission (T1) and day 0/1 after disconnection (T2) from the ventilator for each subject. (B) Changes in absolute counts of CD8 T cells and myeloid dendritic cells at T1 and T2. (C) Changes in the frequency of CCR6+CXCR3- cells, indicative of TH17 phenotype, within the CD4 T cell subset at the two time points. (D) Absolute counts of CD45-RA-CCR7- CD8 T cells and frequency of CD45-RA-CCR7- cells, indicative of effector memory cell function, within the CD8 T cell subset at the two time points. (E) Changes in the absolute counts of CD38+ HLA-DR+ CD8 T cells and frequency of CD38+ HLA-DR+ cells within the CD8 T cell subset before and after disconnection from the ventilator. P values are generated by using Wilcoxon signed rank test.

response mediated by myeloid DCs, further comprehensive analysis on this cell subset are needed to understand their role in the pathogenesis of COVID-19.

Furthermore, we discovered that clinical improvement was associated with increased CD8 TEM and DC counts. Zammit et al [18] have shown that DCs are major driver of CD8 memory

T-cell activation, particularly during a tissue-specific infection of the respiratory tract.

We also found that clinical improvement resulted in expansion of activated CD38+HLA-DR+ CD8 T cells. Previous investigations have demonstrated that this CD8 subset expands after vaccination and in acute viral infection, as in SARS-CoV-2 infection [19, 20].

One of the first effective strategies of antiviral defense is represented by an IFN-mediated innate immunity. We performed gene expression analysis to evaluate the capacity of leukocytes from COVID-19 patients to respond to R848, an agonist for TLR7/8. Although components of the nuclear factor κB-signaling cascade, such as *IL1B* and *IL18*, were increased upon activation of TLR7/8, induction of IFN-associated transcripts, such as *MX1* and *IFIT1*, was defective in leukocytes derived from ventilated COVID-19 subjects compared with noncritical cases. This observation indicates that for SARS-CoV and MERS infections, dysregulated IFN signaling in critically ill patients with COVID-19 might explain the impaired antiviral response and, consequently, the clinical manifestations in patients with severe COVID-19. Animal models of SARS-CoV-2 and in vitro studies on respiratory tract cell lines with SARS-CoV-2 revealed a reduced type I/III IFN response, despite strong expression of IFN-inducible chemokines, such as CXCL10 and CXCL9 [21]. Furthermore, another mechanism, which might explain the high concentration of the proinflammatory cytokines IL-1β and IL-18, is through the inflammasome activation. As recently reported, SARS-CoV2 can activate the NLRP3 inflammasome pathway, which ultimately results in a cleavage of the inactive precursors and release of the active cytokines IL-1β and IL-18. Further studies are needed to elucidate the pathomechanism for NLRP3-inflammasome-mediated ARDS [22, 23].

Our study has some limitations. First, we did not analyze the data based on days after onset of illness, but instead we focused on day 0–2 after admission, because the time point of sudden deterioration marks a significant event in the clinical course of this fatal disease. Because data on immune profiling at early time points before hospitalization are missing, the immunological changes that we have observed reflect the overall critical status of severely ill patients. Additional longitudinal studies are needed to further dissect immune phenotypes driving disease progression. Second, due to the nature of emergency-scene medical care, the blood sampling for research purposes was impaired in some cases, which might have led to selection bias for our immunological analysis.

As reported by others, we confirmed that severity of the disease was associated with low counts of circulating CD4 and CD8 cells [3, 4, 24]. It is notable that the viral RNA load did not differ between the 2 cohorts of patients, which suggests that virus load did not correlate with disease severity in our observed cohort. Although some authors hypothesize that a delayed T-cell response is triggered by high viral loads in the lung, it remains controversial whether the virus persistence is actually responsible for enhancing tissue damage in the lungs [25].

CONCLUSIONS

In summary, our study suggests that COVID-19-related ARDS is characterized by a TH17-driven inflammation and dysfunctional IFN-associated response reflecting an impaired capacity to mount antiviral responses. Moreover, respiratory improvement is correlated with dynamic change in CD8 T-cell and DC response.

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