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# Impaired T-cell Reactivity in Hematological Malignancy Patients: Insights into SARS-CoV-2 Omicron Infection and Clinical Implications

**Xiaodan Luo[1,a,#], Ao Chen[1,b,#], Xian Long[2], Liang Peng[2], Jianli Tang[1], Jianbo Liu[1], Jiayu Huang[1], Lian Liu[1], Huo Tan[1], Runhui Zheng[1,*]**

*[1]Hematology Department, Key Laboratory of Biological Targeting Diagnosis, Therapy and Rehabilitation of Guangdong Higher Education Institutes, The Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, China*
*[2]Department of Laboratory Medicine, Key Laboratory of Biological Targeting Diagnosis, Therapy and Rehabilitation of Guangdong Higher Education Institutes, The Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, China*
*[a]xdluo@gzhmu.edu.cn, [b]1131343416@qq.com*
*[#]Xiaodan Luo and Ao Chen contributed equally to this article.*
*[*]Corresponding author: zhengrunhui@gzhmu.edu.cn*

***Abstract:*** *The SARS-CoV-2 Omicron variant has posed global health challenges, particularly for individuals with haematological malignancies. This study aimed to characterize clinical and immunological aspects of Omicron-infected haematological malignancy patients and compare them to the general population. In a retrospective study from Dec 3, 2022, to Apr 30, 2023, we assessed SARS-CoV-2-positive patients in the Haematology Department (study group) and randomly selected control patients from other departments. Clinical symptoms were similar, but pneumonia was more common in the patients with haematological malignancies. Haemoglobin and platelet levels were notably lower in the study group, and they had a higher viral load with lower intracellular ATP levels in CD4+ and CD8+ T cells. CD8+ ATP levels were further reduced in lymphocytic malignancies. Risk factors for mortality included age >60 years, ECOG score >3, CRP >50 mg/L, and NLR ≥6.5. This study emphasizes the significance of cellular immune responses in Omicron-infected haematological malignancy patients. Tailored clinical strategies and close monitoring are crucial for this vulnerable group due to potential immune impairments and associated risks.*

***Keywords:*** *Omicron, Haematological Malignancy, T-cell Reactivity, ATP*

## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has highly variable disease severity. Immunocompromised patients have been reported to experience more severe cases and worse clinical outcome due to impaired immune defenses resulting from both underlying disease and treatment. Within three years, the SARS-CoV-2 Omicron variant become the dominant variant worldwide and has since evolved into several variants. The emergence of the highly infectious Omicron and its subvariant has greatly increased the prevalence of breakthrough infection. As China transitions away from zero – COVID strategy, COVID-19 is now classified as a Class B infectious disease and is subject to the preventive and control measures designated for a Class B infectious disease. In the post - COVID 19 era, as the nation prepares for an unprecedented wave of infections spreading from its major cities to its vast rural areas, symptoms and clinical outcomes of immunocompromised patients considered a highly vulnerable population to Omicron infection-merit attention. Recent studies have reported an overall COVID-19 related mortality rate of 32 to 40% in hematological patients, which is higher than that in general population [1-4]. The Omicron variant is reported to be milder than the Delta variant, primarily affecting the upper respiratory tract with considerable clinical symptoms but exhibiting low mortality [5]. The in-hospital mortality rate for general population stood at 7.1% in the United States [6]. In a Chinese survey of 1690 patients with autoimmune inflammatory rheumatic diseases and confirmed SARS-CoV-2 infection, 3.4% were hospitalized and 2.7% developed severe disease, and the mortality rate was only 0.4% [7]. Do immunocompromised patients exhibit atypical clinical manifestations, an increased risk for severe cases, or higher mortality? The relationship between

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hematological malignancies and clinical outcomes after contracting the SARS-CoV-2 Omicron variant remains ambiguous, and adverse prognostic factors are not well-defined.

It has been reported that patients with hematological malignancies and those who have undergone hematopoietic stem cell transplantation are more likely to develop severe infections or experience higher mortality, partly due to prolonged viral shedding especially in the elderly [8-13]. However, patients presumed to be at a higher risk of severe disease might also exhibit reduced detrimental inflammatory responses [8]. Numerous studies have indicated that the T cell response is crucial for protection against SARS-CoV-2, but it is relatively impaired in severe cases, which present with both intense T cell activation and lymphopenia [14-18]. Evaluating T cell reactivity in patients with hematological malignancies could potentially predict clinical outcomes and guide the timely management of SARS-CoV-2 infections. In this context, we detail the demographic characteristics, laboratory and imaging findings, cellular immune functions, and outcomes among patients with hematological malignancies infected with the Omicron variant. Our findings suggest that intracellular adenosine triphosphate (ATP) levels in stimulated T cells could serve as a potential prognostic factor, aiding risk assessment and decision-making for effective supportive care following acute Omicron infection.

## 2. Patients and methods

### *2.1. Study design and participants*

This retrospective study involved patients with PCR-documented SARS-CoV-2 infection diagnosed between Dec 3rd, 2022, and Apr 30th, 2023, in the Hematology Department. Cases with hematological malignancy were included in the study group. Patients without hematological or solid organ neoplasms who were admitted to other departments were randomly assigned to the control group. The study received approval from the Ethical Committee of The Fifth Affiliated Hospital of Guangzhou Medical University, and informed consent was obtained from all participants.

### *2.2. Data collection*

Baseline characteristics, treatments (chemotherapy or targeted therapy) for underlying diseases, laboratory data, and clinical outcomes were compiled, with data collection completed by May 31, 2023. The performance status at the time of COVID-19 diagnosis was graded based on the Eastern Cooperative Oncology Group (ECOG) score [19]. Disease status at the time of SARS-CoV-2 detection was categorized according to the revised criteria specific to each disease, such as leukemia, myeloproliferative neoplasm, multiple myeloma, and lymphoma. Baseline laboratory variables, including absolute lymphocyte and neutrophil counts, neutrophil to lymphocyte ratio (NLR), hemoglobin levels, platelet counts, lymphocyte subsets, T cell ATP levels, C-reactive protein (CRP), serum amyloid protein (SAA), T helper cell (Th) 1/Th2 cytokines, and D-dimer levels, were collected within 3 days post SARS-CoV-2 detection. Pneumonia was identified by the presence of a new or progressing infiltrate on a chest CT scan. The majority of patients were monitored weekly until SARS-CoV-2 was no longer detected, particularly when their conditions improved or deteriorated.

### *2.3. Statistical analysis*

For continuous variables, both the median and range were used. Group means were compared using the independent group t-test for normally distributed data and the Mann–Whitney test for non-normally distributed data. Laboratory variables at each measurement point during the SARS-CoV-2 infection were analyzed using the repeated measurement test. A P-value of $< 0.05$ was deemed statistically significant. Survival outcomes were evaluated using the Kaplan–Meier estimator. Overall survival (OS) was defined as the duration from SARS-CoV-2 detection to either death from any cause or the last follow-up date. Analyses were conducted using IBM SPSS version 20.0 and GraphPad Prism v10.0.

## 3. Results

### *3.1. Patient characteristics*

This study comprised 60 patients with laboratory-confirmed SARS-CoV-2, of which 30 had hematological malignancy (forming the study group) and 30 served as controls (control group). The

ISSN 2618-1584 Vol. 6, Issue 2: 10-16, DOI: 10.25236/FMSR.2024.060202

median age at the time of COVID-19 diagnosis in the study group was 59 years (range: 16 – 85). This group included 14 patients with myeloid malignancy and 16 with lymphocytic malignancy. Only two patients had undergone allogeneic hematopoietic stem cell transplantation (allo-SCT), with the time from transplantation to SARS-CoV-2 infection being 38 and 172 days, respectively. Among those in the study group, 19 patients were either currently receiving or had recently received (within the past 30 days) chemotherapy. This includes eight patients who were in the phase of treatment-related bone marrow suppression. One patient was on a Bruton tyrosine kinase (BTK) inhibitor, six on venetoclax, three on Fms-like tyrosine kinase 3 (FLT3) inhibitor, three on histone deacetylase (HDAC) inhibitor, two on a tyrosine kinase inhibitor, and one on an isocitrate dehydrogenase 2 (IDH2) inhibitor. Both chemotherapy and oral immunosuppressants or targeted drugs were postponed until SARS-CoV-2 was no longer detected. Patient and disease characteristics are detailed in Table 1. Characteristics such as age, gender, and ECOG score were well-balanced between the two groups.

*Table 1: Clinical and laboratory characteristics.*

| Characteristics | Hematological disease (n = 30) | non-Hematological disease (n = 30) | *p* value |
|---|---|---|---|
| **Age (years), median (range)** | 59 (16 – 85) | 63 (14 – 75) | 0.305 |
| ≤ 60 years, n (%) | 16 (53.33) | 12 (40.00) | |
| > 60 years，n (%) | 14 (46.67) | 18 (60) | |
| **Gender, Male/Female** | 15/15 | 13/17 | 0.608 |
| **Baseline disease, n (%)** | | | |
| AML | 12 (40.00) | N/A | |
| ALL | 4 (13.33) | N/A | |
| MPD | 2 (6.67) | N/A | |
| NHL | 12 (40.00) | N/A | |
| **Disease status, n (%)** | | N/A | |
| CR | 15 (50) | N/A | |
| non-CR | 15 (50) | N/A | |
| **Allo-SCT, n (%)** | 2 (6.67) | N/A | |
| **Chemotherapy within 30 days, n (%)** | 19 (3.33) | N/A | |
| **Under targeted or immunosuppressive drugs, n (%)** | 14 (46.66) | N/A | |
| **Performance status, n (%)** | | | 0.757 |
| ECOG < 3 | 20 (66.67) | 24 (80) | |
| ECOG ≥ 3 | 10 (33.33) | 6 (20) | |
| **Symptoms, n (%)** | | | |
| Fever | 20 (66.67) | 16 (53.33) | 0.798 |
| Myalgia | 12 (40) | 9 (30) | 0.421 |
| Fatigue | 11 (36.67) | 6 (20) | 0.155 |
| Pharyngitis | 11 (36.67) | 14 (46.67) | 0.436 |
| Cough | 22 (73.33) | 21 (70) | 0.776 |
| Short breath | 7 (23.33) | 11 (36.67) | 0.264 |
| **Abnormal radiological pulmonary finding, n (%)** | 17 (56.67) | 9 (30) | 0.039 |
| **Laboratory characteristics** | | | |
| Ct values, median (range) | 28.94 (21.16 - 39.29) | 35.28 (21.17 - 39.22) | 0.003 |
| ANC ($\times 10^9$/L), median (range) | 2.03 (0.00 - 21.59) | 5.04 (0.02 - 20.39) | 0.128 |
| ANC < 1, n (%) | 7 (23.33) | 1 (3.33) | |
| ANC < 0.5, n (%) | 6 (20) | 1 (3.33) | |
| ALC ($\times 10^9$/L), median (range) | 0.67 (0.09 - 81.94) | 1.24 (0.23 - 3.14) | 0.138 |
| ALC < 1, n (%) | 23 (76.67) | 11 (36.67) | |
| HGB (g/L), median (range) | 94 (33 - 156) | 120.5 (58 - 141) | 0.009 |
| HGB < 100, n (%) | 17 (56.67) | 8 (26.67) | |
| PLT ($\times 10^9$/L), median (range) | 121.5 (7 - 306) | 212 (1 - 370) | 0.000 |
| PLT < 100, n (%) | 13 (43.33) | 5 (16.67) | |
| SAA > 100 mg/L, n (%) | 18 (60) | 12 (40) | 0.305 |
| CRP > 20 mg/L (n, %) | 16 (53.33) | 9 (30) | 0.188 |
| D-dimer > 500 ng/mL (n, %) | 19 (63.33) | 6 (20) | 0.262 |
| $ATP_{CD4}$ (ng/ml), mean ± SD | 152.43 ± 173.42 | 367.05 ± 161.8 | 0.000 |
| $ATP_{CD8}$ (ng/ml), mean ± SD | 103.72 ± 132.12 | 326.92 ± 125.96 | 0.000 |
| **COVID-19 related mortality, n (%)** | 4 (13.33) | 6 (20) | 0.812 |
| **Median time from diagnosis to death, days (range)** | 23 (16-32) | 66 (53-71) | 0.016 |

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MPD: myeloproliferative disorders; NHL: Non-Hodgkin's lymphomas; CR: complete remission; allo-SCT: allogeneic hematopoietic stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; Ct values: cycle threshold values; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; HGB: hemoglobin; PLT: platelet; SAA: serum amyloid A; CRP: C-reactive protein.

ISSN 2618-1584 Vol. 6, Issue 2: 10-16, DOI: 10.25236/FMSR.2024.060202

### *3.2. Clinical manifestations and laboratory characteristics*

The most common clinical features in both the study group and the control group were cough (73.3% vs 70%) and fever (66.7% vs 53.3%). Other symptoms included myalgia (50% vs 30%), fatigue (36.7% vs 20%), pharyngitis (36.67% vs 46.67%), and shortness of breath (23.33% vs 36.67%). Only one patient, who had undergone allo-SCT 38 days prior to SARS-CoV-2 infection, developed myocarditis. No patient in either group developed diarrhea. Pneumonia, confirmed by CT scan, was observed in 17 (56.67%) patients with hematological malignancy, of which 5 (29.41%) developed acute respiratory distress syndrome (ARDS). In the control group, 9 (30%) patients developed pneumonia, with 2 (22.22%) of them developing ARDS.

Full blood count results indicated that the neutrophil count was not statistically different between the study group and the control (3.76 ± 4.82 vs 5.46 ± 3.61 × $10^9$/L, $P = 0.128$). However, more patients in the study group exhibited agranulocytosis ($P = 0.046$). One patient diagnosed with chronic lymphocytic leukemia was excluded from the lymphocyte count analysis due to extremely high lymphocyte counts. Lymphocyte counts, which were reduced in 23 of 29 patients in the study group and 11 of 30 in the control group, showed no significant difference between the two groups (0.86 ± 0.97 vs 1.18 ± 0.63 × 109/L, $P = 0.138$). The neutrophil to lymphocyte ratio (NLR) was 9.27 ± 11.62 in the study group and 5.95 ± 6.10 in the control, with no significant difference ($P = 0.611$). Hemoglobin (HGB) levels and platelet count were significantly lower in the study group compared to the control group (HGB: 56.67% vs 26.67%, $P = 0.039$; PLT: 43.33% vs 16.67%, $P = 0.013$), registering at 89.77 ± 33.98 vs 110.90 ± 55.94 g/L ($P = 0.009$) and 116.63 ± 79.81 vs 206.4 ± 97.23 × 109/L ($P = 0.000$), respectively.

The median cycle threshold (Ct) value of SARS-CoV-2 for patients in the study group was 28.94 (range 21.16 - 39.29), which was significantly lower than that of the control group (35.28, range 21.17 – 39.22) ($P = 0.003$). Biomarkers for SARS-CoV-2 infection showed no difference between the two groups. Most patients had elevated CRP and SAA levels (CRP > 20 mg/L: 53.33% vs 30%, $P = 0.188$; SAA > 100 mg/L: 60% vs 46.67%, $P = 0.305$). However, levels of acute-response cytokines, such as interleukin (IL) - 6, 2, 4, 10, interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α), were not elevated.

### *3.3. Analysis of T cell immune function*

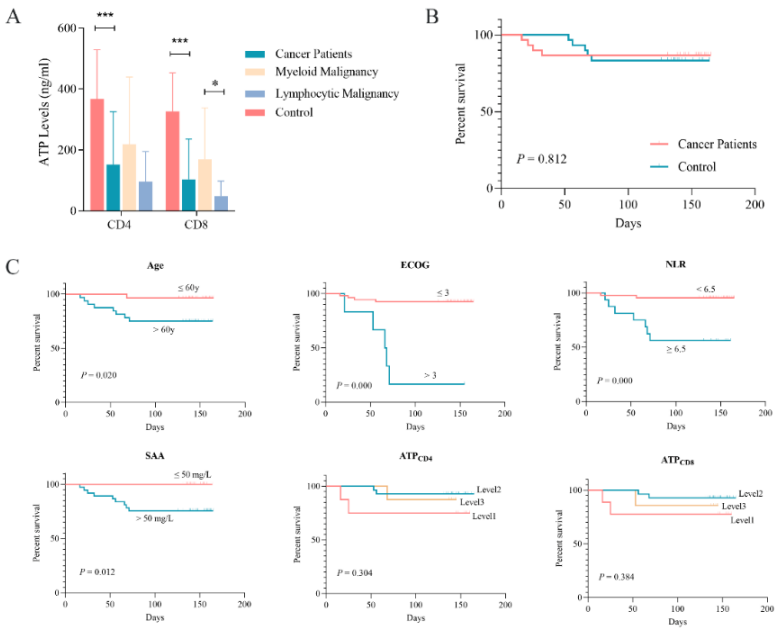


*Figure 1: A. ATPCD4 and ATPCD8 of patients with hematological malignancy were significantly lower than those in the control group (P = 0.000). ATPCD8 were significantly higher in patients with myeloid malignancy compared to those with lymphocytic malignancy (P = 0.041). B. The mortality rates between the two groups were not statistically different (P = 0.812). C. Risk factors for mortality, from the time of SARS-CoV-2 detection to the last follow-up, included age > 60 years, an ECOG score > 3, SAA > 50 mg/L, and NLR ≥ 6.5, but ATPCD4 and ATPCD8 were not significantly associated with mortality.*

ISSN 2618-1584 Vol. 6, Issue 2: 10-16, DOI: 10.25236/FMSR.2024.060202

T cell activity in patients with hematological malignancies was assessed through lymphocyte subtype analysis and the quantification of intracellular ATP levels in stimulated T cells. The percentages of CD4, CD8, B cells, and NK cells were 31.84 ± 17.63 (%), 31.34 ± 11.91 (%), 8.16 ± 17.32 and 13.47 ± 11.01 (%), respectively. There was a notable decrease in the percentages of CD4 and NK cells compared to the reference values (CD4: t = -2.223, $P$ = 0.034; NK: t = -4.989, $P$ = 0.000). Intracellular ATP levels in CD4+ and CD8+ ($ATP_{CD4}$ and $ATP_{CD8}$) were compared between 24 patients with hematological malignancy and 20 patients in the control group. In the study group, $ATP_{CD4}$ and $ATP_{CD8}$ were 152.43 ± 173.42 ng/ml and 103.72 ± 132.12 ng/ml, respectively. These values were significantly lower than those in the control group, which were 367.05 ± 161.80 ng/ml and 326.92 ± 125.96 ng/ml, respectively ($P$ = 0.000 for both, Figure 1A).

### *3.4. Myeloid malignancy versus lymphocytic malignancy*

Among the patients with hematological malignancies, we further compared the clinical and laboratory parameters between those with myeloid malignancies and those with lymphocytic malignancies. The characteristics of both groups were similar in terms of all baseline covariates used for analysis. When comparing the myeloid and lymphoid groups, there were no significant differences in full blood count, NLR, infection biomarkers, lymphocyte subtypes, or levels of acute-response cytokines ($P$ > 0.05 for all). $ATP_{CD4}$ were 96.28 ± 98.63 ng/ml in the lymphocytic group and 218.79 ± 220.35 ng/ml in the myeloid group, with no significant difference between the two ($P$ = 0.084). However, $ATP_{CD8}$ were significantly higher in patients with myeloid malignancy (169.28 ± 168.76 ng/ml) compared to those with lymphocytic malignancy (48.25 ± 49.52 ng/ml) ($P$ = 0.041) (Figure 1A). Furthermore, patients with myeloid malignancies took less time to test negative for SARS-CoV-2 compared to those with lymphocytic malignancies (18.43 ± 7.82 vs 30.06 ± 23.88 days, $P$ = 0.034).

### *3.5. Outcome and mortality*

After a median follow-up of 142 days (range: 16 - 165), 26 patients with hematological malignancies had fully recovered, with a median recovery time of 21 days (range: 7 - 116) from SARS-CoV-2 detection. Four of these patients died, resulting in a mortality rate of 13.33%. In the control group, five patients had died by the end of the last follow-up. However, the recovery time for those who survived could not be recorded, as many did not undergo a retest for SARS-CoV-2. The mortality rates between the two groups were not statistically different ($P$ = 0.812) (Figure 1B). Risk factors for mortality, from the time of SARS-CoV-2 detection to the last follow-up, included age > 60 years, an ECOG score > 3, SAA > 50 mg/L, and NLR ≥ 6.5 ($P$ values: 0.020, 0.000, 0.012, and 0.000, respectively, Figure 1C). The predictive value of NLR for mortality was divided into two subgroups: a "high cut-off value" (cut-off ≥ 6.5) and a "low cut-off value" (< 6.5), based on Li's study [20]. Factors such as diagnosis, disease status, chemotherapy or targeted therapy, pneumonia status, full blood count, $ATP_{CD4}$ and $ATP_{CD8}$ were not significantly associated with mortality ($P$ > 0.05 for all) (Figure 1C).

## 4. Discussion

We present a report of patients with hematological malignancies infected by the SARS-CoV-2 Omicron variant in the post-COVID-19 era. We compared clinical symptoms, laboratory characteristics, and outcomes between patients with and without hematological malignancies, with a particular focus on T cell responses to SARS-CoV-2. Our results indicate an overall mortality rate of 13.33% in patients with hematological malignancies within a median follow-up of 142 days from Omicron detection. This mortality rate is higher than the in-hospital mortality for the general population in the United States and a large cohort study in England [6, 21]. These findings align with previously reported results [2, 12, 22]. Mortality related to Omicron varies among immunocompromised patients, with cancer or organ transplantation considered high-risk factors for severe cases [23]. The TERAVOLT study reported an Omicron-related mortality rate of 3.2% in 346 patients with thoracic malignancies [24]. Pinato *et al*. reported a 28-day case-fatality rate of less than 13% in cancer patients with Omicron [25]. In our study, the Omicron mortality rate among patients with hematologic malignancies is slightly higher than the rates mentioned above. However, it did not show a significant increase compared to the control group, which might be attributed to the overall lower mortality rate of the Omicron variant.

COVID-19 mortality in this study was influenced by advanced age, poor performance status, and a severe inflammatory state, including elevated SAA levels and NLR. These factors showed no difference between the two groups. However, the clinical characteristics and immune indicators of patients with hematological malignancies may offer insights to identify potentially severe cases early and initiate timely, effective management. Most COVID-19 symptoms in patients with hematological malignancies resembled those in the general population. Yet, these patients exhibited a higher incidence of pneumonia

ISSN 2618-1584 Vol. 6, Issue 2: 10-16, DOI: 10.25236/FMSR.2024.060202

and a lower Ct value compared to the control group. Given that the Ct value is inversely related to viral load, this suggests that cancer patients might be more susceptible to higher viral loads, leading to pneumonia or even severe infections [9, 10, 21]. Both CRP and SAA, sensitive biomarkers of infection, were elevated in all patients, especially SAA, with no significant difference observed between the two groups. Does the susceptibility of cancer patients to Omicron relate to reduced granulocyte or lymphocyte counts due to cancer or its treatments? Our findings show no significant difference in neutrophil and lymphocyte counts between the groups, even though hemoglobin and platelet levels are significantly lower in patients with malignancies. High NLR has been reported to predict COVID-19 severity and mortality [20]. In this study, NLR was not statistically different between the groups, though a high NLR contributes to the mortality rate.

Cellular immune responses against SARS-CoV-2 during acute infection are crucial for controlling the infection, and the cellular immune system might clear infections before the humoral immune response is fully established [16-18]. Patients in immunosuppressed states often show a slow decline in viral load, possibly due to a delayed and inadequate T-cell immune response [17, 26, 27]. We measured ATP $_{CD4}$ and ATP $_{CD8}$, previously confirmed as predictive indicators for disease relapse and poor prognosis in malignancies [28-30], to assess patients' cellular immune responses. Both ATP $_{CD4}$ and ATP $_{CD8}$ were significantly reduced in patients with malignancies, even though lymphocyte counts were similar in both the study and control groups. We hypothesize that this reduced T-cell reactivity is linked to impaired reactivity against SARS-CoV-2, leading to a higher viral load. We also compared T cell ATP levels between the lymphocytic and myeloid groups, observing a significant decrease in ATP $_{CD8}$ and a longer recovery time in patients with lymphocytic malignancies. Defective $CD8^+$ T cell function is known to correlate with impaired lymphocyte proliferation and apoptosis [31]. CD8+ T cells, more so than $CD4^+$ T cells, might mediate or contribute to the rapid termination of SARS-CoV-2 [26, 27]. Patients with lymphocytic malignancies might have an underlying condition of T-cell exhaustion, with $CD8^+$ T cells exhaustion being more prevalent. The combined effects of cancer and related treatments further weaken $CD8^+$ T cell function, leading to delayed viral clearance. Additionally, it has been reported that SARS-CoV-2 infection might inhibit $CD4^+$ T cell responses to certain related viruses [26, 27, 31], reducing immune function against other viruses in non-cancer patients. We speculate that this could explain the lack of mortality rate difference between the groups after Omicron infection.

## 5. Conclusion

Patients with hematological malignancy infected by the SARS-CoV-2 Omicron variant exhibited similar clinical symptoms to the general population but had a higher incidence of pneumonia and a tendency for higher viral loads. The study highlighted the importance of cellular immune responses in controlling the infection. Specifically, decreased T-cell reactivity in patients with hematological malignancy might be associated with impaired defense against SARS-CoV-2, potentially leading to delayed viral clearance, emphasizing the need for close monitoring and early intervention in this patient population.

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