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ORIGINAL RESEARCH

Clinical Outcomes of Hospitalized Immunocompromised Patients With COVID-19 and the Impact of Hyperinflammation: A Retrospective Cohort Study

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Purpose: Immunocompromised patients are at increased risk for severe outcomes from COVID-19 due to their altered immune responses, yet their inflammatory profiles and the interplay between immunosuppression remain poorly understood. We aimed to illustrate the inflammation profile and clinical outcomes of hospitalized immunocompromised patients with COVID-19.

Methods: We conducted a retrospective study using a multicenter database and included adult hospitalized patients with Corona virus disease 2019 (COVID-19) in China's late 2022 COVID-19 wave. Crude and adjusted 28- and 60-day mortality was compared between the two groups. Inflammatory phenotypes were evaluated by serum interleukin-6 (IL-6) and C-reactive protein (CRP) level. The interplay between overt inflammation and immunosuppression was analyzed.

Results: Among the 4078 included patients, 348 (8.5%) were immunocompromised. Immunocompromised patients had lower crude mortality but higher adjusted mortality at 28-day (hazard ratio [HR] = 1.55; 95% CI 1.08 to 2.23) and 60-day (HR = 1.47; 95% CI 1.05 to 2.06). Besides, immunocompromised patients had a higher risk of developing hyperinflammation (odd ratio [OR] =1.92; 95% CI 1.47 to 2.50, p <0.001). Moreover, hyperinflammation mediated a major part of the deleterious survival effect of immunosuppression on COVID-19.

Conclusion: Immunodeficiency not only increases short-term mortality risk but also predisposes patients to hyperinflammation. The complex interplay between immunosuppression, hyperinflammation, and COVID-19 outcomes warrants more detailed profiling of inflammation and immunity in this population.

Keywords: COVID-19, in-hospital mortality, immunosuppression, hyperinflammation

Introduction

Coronavirus disease 2019 (COVID-19) has significantly impacted global health and continues to pose a serious threat to the global population. Research has shown that immune dysregulation and excessive inflammation are key factors in the development of severe COVID-19 and are linked to poor outcomes.[1] Individuals with pre-existing immunosuppression, such as those with primary or acquired immune deficiencies, organ transplant recipients, cancer patients, and individuals

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with autoimmune diseases taking immunosuppressants, are at higher risk of COVID-19 infection and severe illness. The impact of COVID-19 on patients with compromised immune systems is a topic of ongoing discussion.[2,3] Some studies have found that organ transplant recipients do not have a higher risk of mortality from COVID-19 compared to non-transplant recipients.[4,5] On the contrary, solid organ transplant (SOT) was shown to be associated with more COVID-19-related death (HR 1.35, 95% CI 1.09–1.67) in a large national cohort study in the United States.[6] A population-level analysis of surveillance data on HIV and COVID-19 found that individuals with HIV were at increased risk of death from COVID-19.[7] For patients with autoimmune diseases, the COVID-19 associated mortality were reported to be 6–8% and not significantly different from the non-autoimmune patients.[8,9] For patients with active cancer, higher mortality was observed in patients with hematological malignant neoplasms.[10] Lung cancer was also significantly associated with higher COVID-19-related mortality.[11]

Excessive inflammation is a major contributor to organ damage and disease severity in COVID-19,[12] and immune-modulating drugs like Tocilizumab and Baricitinib have shown promise in reducing inflammation and preventing death.[13,14] Hyperinflammation is characterized by imbalanced innate and adaptive immune responses triggered by SARS-CoV-2 infection. The immune system, on one hand, fails to generate an effective antiviral response, while on the other hand, evokes potentially destructive inflammation marked by a rapid increase in interleukins (IL)-6, IL-8, IL-10, and tumor necrosis factor-alpha (TNF-α).[15] This excessive inflammatory response can result in pulmonary edema, fibrosis, and thrombosis, resulting in hypoxia, acute respiratory distress syndrome (ARDS), multi-organ failure, and even death.[12] Furthermore, hyperinflammation ultimately resulted in immune paralysis or suppression through upregulation of programmed death-1 (PD-1) expression on T lymphocyte,[16] which may account for the severe lymphopenia observed in critically ill COVID-19 patients, or leading to exhaustion of NK and CD8+ T lymphocyte via increasing expression of NKG2A.[17] These changes will lead to secondary infection and further exaggerate the disease.

However, the COVID-19 associated inflammation phenotypes in immunocompromised patients, including those with malignancies, SOTs, or immunosuppressive therapies, are less well understood. We hypothesized that a compromised immune response may actually have a protective effect by reducing excessive inflammation in COVID-19.[18] No studies have yet examined the combined effects and interactions of immune suppression and hyperinflammation on clinical outcomes in COVID-19 patients hospitalized, nor have they delved into the mechanistic role of hyperinflammation. This study seeks to investigate the relationship between immunosuppression and clinical outcomes in COVID-19 patients through a retrospective cohort study across multiple centers. Additionally, the study explores the inflammatory profile of immunocompromised patients and its impact on COVID-19 outcomes in this population.

Methods

Study Design

We conducted a retrospective cohort study to compare the clinical outcomes and inflammatory phenotypes of COVID-19 in general immunocompromised patients and the immunocompetent ones. In-hospital patients diagnosed with COVID-19 were included during the first wave of the omicron pandemic in China in late 2022. Patients were divided into immunocompromised group and immunocompetent group according to their comorbid diseases and medication history. Primary outcomes were all-cause mortality within 28 and 60 days of index hospital admission. We also analyzed the potential relationship between hyperinflammation and mortality.

Patient Selection

The Ethics Committee of Chinese PLA General Hospital, Beijing, China, approved all data analyses and exempted informed consent requirements on account of the minimal risk of this retrospective cohort study (number 309202302230712).

The study included all hospitalized adults diagnosed with COVID-19 for the first time[19] using antigenic tests or PCR, who were admitted to healthcare facilities within the Chinese PLA General Hospital health system between December 20, 2022, and January 20, 2023. Patient follow-up continued until March 22, 2023. Pregnant patients were excluded to eliminate cases related to childbirth in asymptomatic severe acute respiratory syndrome

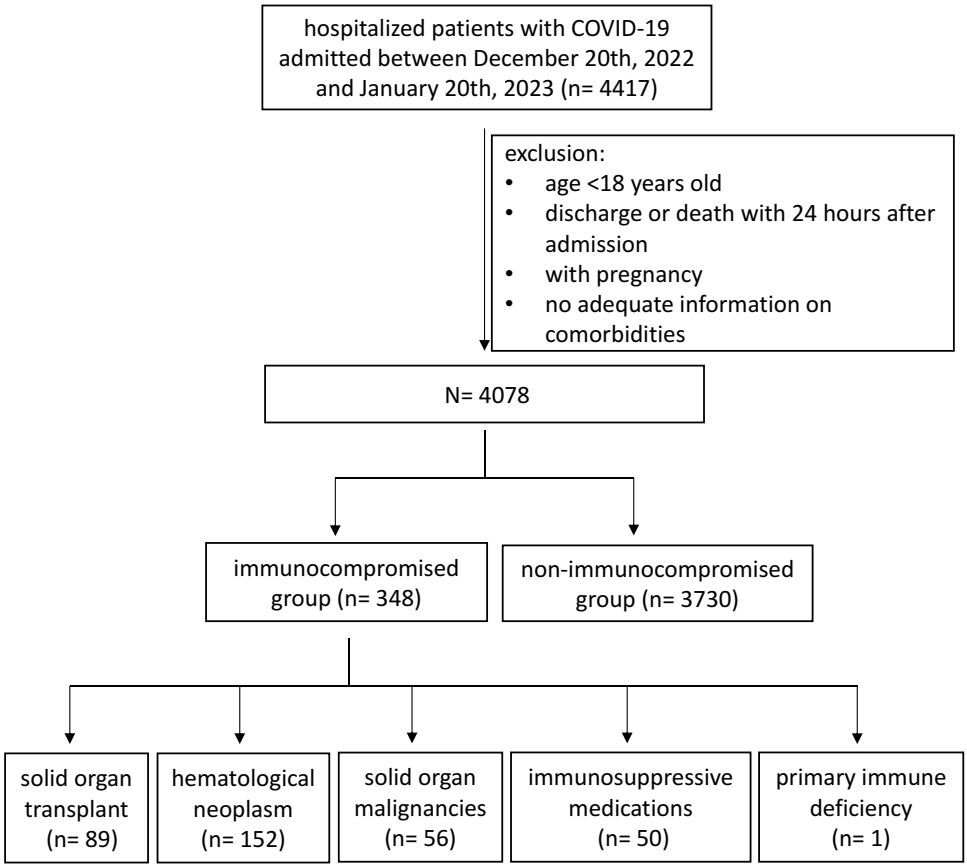

Figure 1 Participants selection flowchart. Flowchart presenting the participants selection procedure.

coronavirus 2 (SARS-CoV-2) positive mothers. Patients with incomplete comorbidity information were also excluded (see Figure 1). Demographic and baseline characteristics (including age, sex, comorbidities, and smoking history) of the included patients, as well as laboratory results were obtained from electronic medical records and analyzed.

Identification of Immune-Suppression Status

The following patients were categorized as immunocompromised per their medical history and recent medications reported at hospital admission:[20,21] i) patients with solid organ transplant ii) patients with malignant blood diseases with or without stem cell transplant, such as leukemia, lymphoma, multiple myeloma, severe aplastic anemia, etc. iii) patients with active solid organ malignancy who were treated with chemotherapy, radiation, hormonal therapy, targeted therapy or immunotherapy within 3 months prior to admission. iv) patients treated with immunosuppressants or corticosteroid equivalent to prednisone≥ 20 mg/day for more than 14 days within 3 months prior to admission for conditions other than the above-mentioned diseases, such as autoimmune diseases, interstitial lung diseases, etc. v) patients with primary or acquired immunodeficiency. Patients without above conditions were defined as immunocompetent ones.

Assessment of Hyperinflammation

C-reactive protein (CRP) and interleukin-6 (IL-6) levels were measured during hospitalization, with the highest recorded levels identified as peak CRP and peak IL-6. Hyperinflammation was defined as a peak CRP level exceeding 75mg/dl or a peak IL-6 level exceeding 30pg/mL during hospitalization.[14,22,23]

Ascertainment of Study Outcomes

Study outcomes included all-cause mortality within 28 and 60 days of index hospital admission. Patients were followed up to obtain survival data after discharge by telephone interviews. The final follow-up date was March 22, 2023.

Covariates

To address the potential confounding bias, we selected covariates for adjustment according to previous studies, including demographics, lifestyles, chronic conditions, clinical symptoms grade, and medication use based on previous literatures and experience.[6,24] Demographics included age and sex, while smoking status (current smoking or not) was adjusted for lifestyles. Chronic conditions included coronary heart disease, hypertension, diabetes, liver disease, Neurological disease, and chronic lung disease. Clinical symptoms grade was scored according to the WHO recommendations.[25] Medication usage included Baricitinib and anti-viral medication usage.

Statistical Analysis

The patients' characteristics are shown as the mean (standard deviation, SD) or the median with interquartile range (IQR) for continuous variables and as number (%) for categorical variables. Differences in baseline characteristics between the two immune-status groups were tested using Student's *t*-test, the Wilcoxon rank test, or the chi-square test.

The primary analysis aims to evaluate the associations between the immune-suppression and study outcomes, including 28-day and 60-day in-hospital mortality. The time to study outcome was defined as the number of days from the date of admission to the discharge date or date of death (whichever occurred first). We also calculated the crude incidence rate per 1000 person-days of outcomes. The Cox proportional hazard regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of study outcomes associated with the immune-suppression exposure. Proportional hazard assumption was checked for all included variables of Cox model using weighted Schoenfeld residual, with no significant violations for the variables included were observed ($P > 0.05$).[26] Crude in-hospital survival probability was derived from Kaplan-Meier estimator. We also calculated covariates-adjusted survival probability using direct standardization based on a previously fitted Cox regression model,[27] which controlled for age, sex, smoking status, chronic diseases, clinical symptom grade, and anti-viral medication usage.

Joint associations and additive interactions analysis were performed to delineate the interplay between immune-suppression and hyperinflammation status with in-hospital mortality. Additive interactions were assessed using relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI). The Delta method was applied for calculating confidence intervals of interaction measures.[28]

To evaluate the potential intermediating pathway of hyperinflammation in the associations between immune-suppression and mortality, we also conducted mediation analysis under a counterfactual framework. Compared with the traditional mediation analytical approach, counterfactual casual mediation analysis possesses the capability of handling exposure-mediator interactions and accounting for various data types, including binary outcomes and binary mediators. Under the counterfactual framework, the total effect (TE) can be divided into natural direct effect (NDE) and natural indirect effect (NIE), which was expressed on the scale of RERI. The NDE represented the effect of immune-suppression on mortality that was independent of hyperinflammation. The NIE represented the effect of immune-suppression on mortality that was explained via its associations with hyperinflammation. The proportion being mediated was calculated as NIE/TE × 100%, with the two-sided Wald 95% confidence intervals estimated for inference. We used the CAUSALMED procedure provided in the SAS software to conduct the mediation analysis, aligning with a previous study.[29]

Statistical analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC) and R 4.3.1 (R Foundation, Vienna, Austria), with a two-tailed alpha of 0.05 considered statistically significant.

Results

Baseline Characteristics

A total of 4078 patients who met the inclusion criteria were included in the study. Among them, 348 were identified as immunocompromised and the remaining 3730 were classified as immunocompetent. The immunocompromised group

consisted of 89 solid organ transplant patients (25.5%), 152 patients with blood malignancies (43.7%), 56 patients with solid organ tumors (16.1%), 50 patients taking preadmission immunosuppressive medications (14.4%), and 1 patient with primary immune deficiency (0.3%). SOT patients included 81 with kidney transplant, 6 with liver transplant, 1 with lung transplant and 1 with heart transplant. The time since organ transplantation ranged from 1 to 29 years, with an average time of 10.3 years and a median time of 8.5 years. The mean age for immunocompromised patients was 61.9 ± 15.1 years, compared to 68.0 ± 20.3 years for the immunocompetent group (p = 0.001, age presented as mean age ± SD). Immunocompromised patients exhibited a lower rate of cardiovascular diseases (CVD) and neurological diseases, and a higher rate of liver diseases, as outlined in Table 1. Despite these differences, COVID-19 illness severity at hospital admission, as measured by the Ordinal Scale for Clinical Improvement,[25] was similar in both groups (4.0 versus 4.0), indicating comparable disease severity upon admission for both groups. Lower neutrophil, CD4+ T lymphocyte counts and immunoglobulin G (IgG) levels in the immunocompromised group compared to the immunocompetent group were observed (Supplementary table). In contrast, CD8+ T lymphocyte counts did not exhibit a statistically significant difference between groups.

Associations Between Immunocompromised Status and Clinical Outcomes

The 28-day mortality rate of the immunocompromised group was 10.6% (37/348), which was lower than the 11.1% (413/3730, p = 0.020) observed in the immunocompetent group (Figure 2A). The crude 28-day death rate per 1000 person-days was 8.9 (95% CI 8.1 to 9.8) for the immunocompetent group and 6.4 (95% CI 4.5 to 8.9) for the immunosuppressed group (Table 2). Similarly, the 60-day mortality rate of the immunocompromised group was lower than that of the immunocompetent group, with mortality rates of 12.1% (42/348) and 12.7% (473/3730, p = 0.002) respectively (Figure 2C). The 60-day mortality incidence rate per 1000 person-days was 8.6 (95% CI 7.8 to 9.4) for the immunocompetent group and 5.3 (95% CI 3.9 to 7.3) for the immunocompromised group (Table 2).

After adjusting for age, sex, smoking status, comorbid diseases, clinical symptom grade, and anti-viral medication usage, mortality was found to be higher for patients with immune suppression compared to those with intact immunity (Figure 2B and D). The hazard ratio of adjusted 28-day mortality was 1.55 (95% CI 1.08 to 2.23, p=0.010) in the immunocompromised group versus the non-immunosuppressive group, and 1.47 (95% CI 1.05 to 2.06, p=0.020) for 60-day mortality, as shown in Table 2.

Table 1 Baseline Characteristics of Participants According to Immune-Suppression Status

Characteristics [a]	Immune-suppression Status		
	Without Immune-suppression (n=3730)	With Immune-suppression (n=348)	*P* for Difference [b]
Age, mean (SD), y	68.0 (20.3)	61.9 (15.1)	0.001
Men	2248 (60.3)	214 (61.5)	0.69
Current smoking	310 (8.3)	22 (6.3)	0.08
Coronary heart disease	1061 (28.4)	65 (18.7)	0.001
Hypertension	1783 (47.8)	181 (52.0)	0.15
Diabetes	1014 (27.2)	91 (26.1)	0.72
Neurological disease	759 (20.3)	31 (8.9)	0.001
Liver disease	529 (14.2)	75 (21.6)	0.001
Chronic lung disease	441 (11.8)	37 (10.6)	0.57
SCORE, median (IQR), points	4.0 [3.0–4.0]	4.0 [3.0–4.0]	0.02
Baricitinib	30 (0.8)	9 (2.6)	0.005
Anti-viral medication usage	1475 (39.5)	177 (50.9)	0.001

Notes: [a] Data are presented as mean (standard deviation, SD), n (%), or median (interquartile range, IQR). [b] P value reported for differences between two cohorts using *t*-test, chi-square test, or Wilcoxon rank test.

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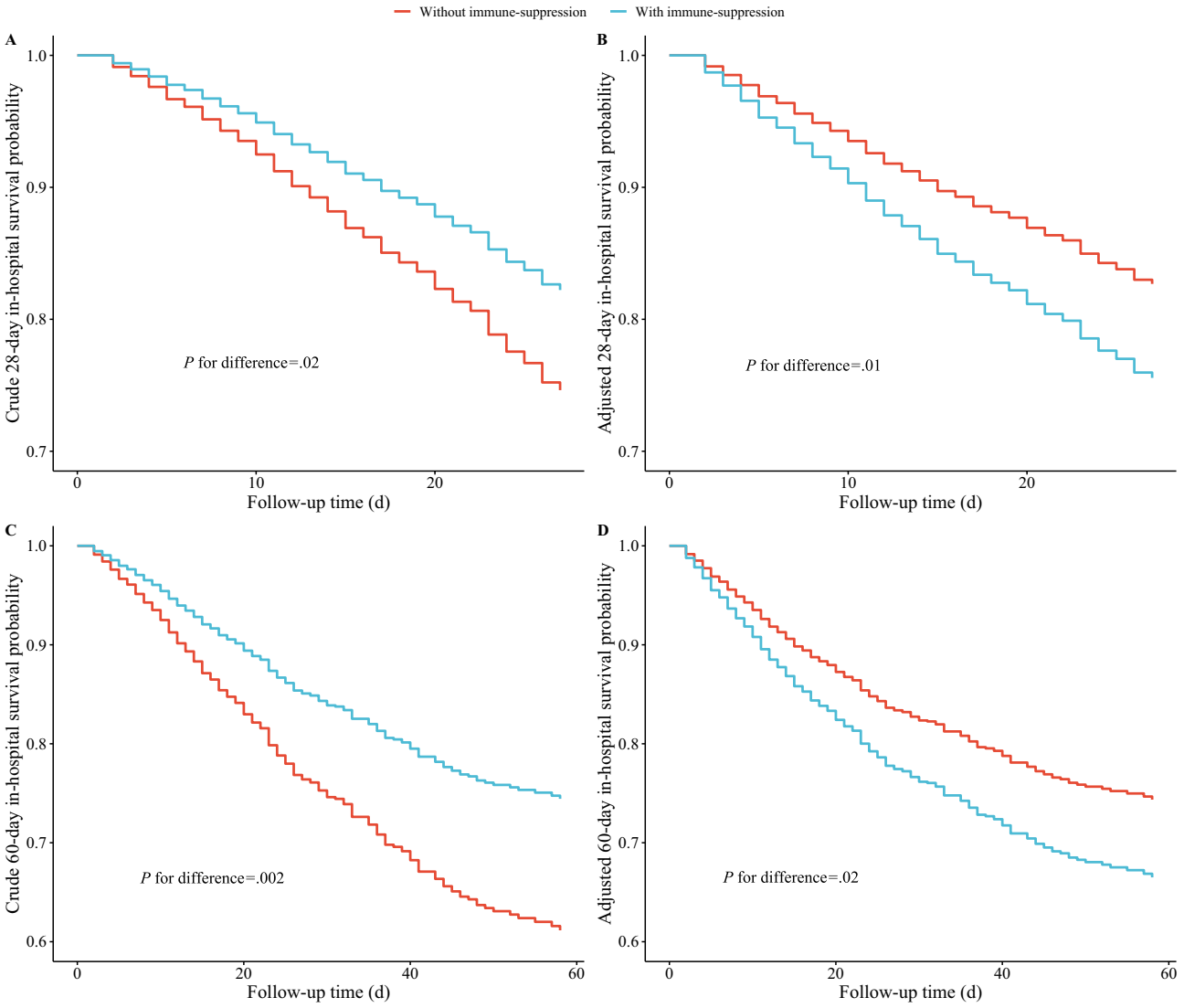

Figure 2 Crude and Adjusted In-Hospital Survival Probability According to Immune-Suppression Status. (**A**)Crude 28-day in-hospital survival probability according to immune-suppression status. (**B**)Adjusted 28-day in-hospital survival probability according to immune-suppression status. (**C**)Crude 60-day in-hospital survival probability according to immune-suppression status. (**D**)Adjusted 60-day in-hospital survival probability according to immune-suppression status. Crude in-hospital survival probability was derived from Kaplan-Meier estimator. Adjusted in-hospital survival probability was derived using direct standardization based on a previously fitted Cox regression model, which controlled for age, sex, smoking status, coronary heart disease, hypertension, diabetes, liver disease, Neurological disease, chronic lung disease, clinical symptom grade, Baricitinib, and anti-viral medication usage. Blue curves represent patients with immune suppression, and red curves represent patients without immune suppression.

Hyperinflammation and Death Risk in Immunosuppression Patients

Hyperinflammation was more prevalent in immunocompromised individuals, with an odds ratio (OR) of 1.92 (1.47 to 2.50, p <0.001). Factors associated with heightened inflammation included male gender (OR = 1.73, 1.47 to 2.04, p <0.001), diabetes (OR = 1.25, 1.06 to 1.47, p = 0.008), chronic renal diseases (OR = 1.96, 1.61 to 2.39, p <0.001), and a higher COVID-19 severity score (OR = 2.32, 2.03 to 2.65, p <0.001). The relative excess risk and attributable proportion for the interaction between immunosuppression and hyperinflammation in 28-day in-hospital mortality were 7.78 (0.28 to 15.84) and 0.44 (0.18 to 0.71), respectively (Figure 3A). For 60-day in-hospital mortality, these values were 5.10 (0.41 to 9.79) and 0.49 (0.24 to 0.73), respectively (Figure 3B). Furthermore, a significant portion of immunosuppression's impact on in-hospital mortality was influenced by excessive inflammation, with mediating proportions of 52.5% (34.8%, 70.2%, p < 0.001) and 45.4% (29.5%, 61.2%, p < 0.001) for 28-day (Figure 4A) and 60-day (Figure 4B) in-hospital mortality, respectively.

Table 2 Associations Between Immune-Suppression Status and Clinical Outcomes

Clinical outcomes	Events/Total	Person-days	Crude incidence rate (95% CI), per 1000 person-days	HR (95% CI) [a]
28-day in-hospital mortality				
Without immune-suppression	413/3730	45,693	8.9 (8.1 to 9.8)	1 [Reference]
With immune-suppression	37/348	5633	6.4 (4.5 to 8.9)	1.55 (1.08 to 2.23)
60-day in-hospital mortality				
Without immune-suppression	473/3730	55,173	8.6 (7.8 to 9.4)	1 [Reference]
With immune-suppression	42/348	7867	5.3 (3.9 to 7.3)	1.47 (1.05–2.06)

Notes: [a] For 28-day and 60-day in-hospital mortality, HR was estimated using Cox proportional hazard regression. All estimates controlled for age, sex, smoking status, coronary heart disease, hypertension, diabetes, liver disease, neurological disease, chronic lung disease, clinical symptom grade, Baricitinib, and anti-viral medication usage.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Discussion

Utilizing data from a significant multicenter cohort of hospitalized adults with COVID-19 during China's late 2022 COVID-19 wave, we conducted a comparative analysis of survival outcomes and inflammatory phenotypes between immunocompromised and immunocompetent patients. Our study revealed three key findings. Firstly, we observed higher 28- and 60-day mortality rates in immunocompromised patients compared to their immunocompetent counterparts. Secondly, immunocompromised patients were found to be at a heightened risk of developing hyperinflammation. Lastly, our results indicated that hyperinflammation played a significant role in mediating the adverse impact of immunosuppression on COVID-19 survival outcomes. Notably, this study represents the first of its kind to evaluate inflammatory status in the broader immunocompromised population with COVID-19 and investigate its implications on clinical prognosis.

The impact of COVID-19 on immunocompromised patients, particularly those who have undergone SOT, has been a topic of debate.[24,30] Research by Swan et al in 2022 suggests that SOT recipients may have similar short-term mortality outcomes from COVID-19 as non-SOT recipients in certain circumstances.[31] Similarly, a meta-analysis by Gatti et al in 2022 indicates that there is no significant increase in mortality risk for SOT recipients when adjusted for various factors.[32] On the contrary, Caillard et al in 2021 have shown that kidney transplant recipients (KTRs) may face higher COVID-19-related short-time mortality rates compared to nontransplant hospitalized patients.[33] Additionally, a large cohort study involving 600 SOT recipients (kidney, liver, heart, and lung) revealed a notably higher mortality rate from COVID-19 among SOT recipients than non-SOT recipients (14.7% versus 1.8%; $P < 0.0001$).[34] Moreover, a retrospective cohort study based on the first five waves of the SARS-CoV-2 pandemic in the UK highlighted that organ transplant recipients had an elevated risk of COVID-19-related death and individuals with immunosuppressive conditions may have reduced protection from SARS-CoV-2 vaccination.[35]

Here we reported a significant higher 28- and 60-day mortality in the general in-hospitalized immunocompromised population, with HR of 1.55 and 1.48, respectively. This aligns with a large prospective cohort study comparing immunocompromised and non-immunocompromised patients hospitalized with COVID-19, which reported an odds ratio (OR) of 1.55 for death in immunocompromised patients.[24] The discrepancy in clinical outcomes of COVID-19 may be attributed to differences in matching strategies. For instance, a propensity-matched cohort analysis that matched various factors like age, sex, race, comorbidities, and socioeconomic status showed similar COVID-19 mortality rates between solid organ transplant (SOT) and non-SOT populations.[31] Conversely, a different propensity score model that included fewer covariates found a higher risk of death in KTRs compared to non-KTRs.[33] Other factors contributing to conflicting results could include differences in cohort composition, such as age, comorbidities, socio-demographic factors, and severity of immunosuppression. Previous studies have highlighted older age and the presence of comorbidities as classical risk factors for mortality.[21,30] As illustrated by previous studies, older age and the presence or comorbidities are classical consequential mortality risk factors.[36,37] In our cohort, immunosuppressed patients were younger on average compared to immunocompetent patients, largely due to the lower average age of 56.8 years in the

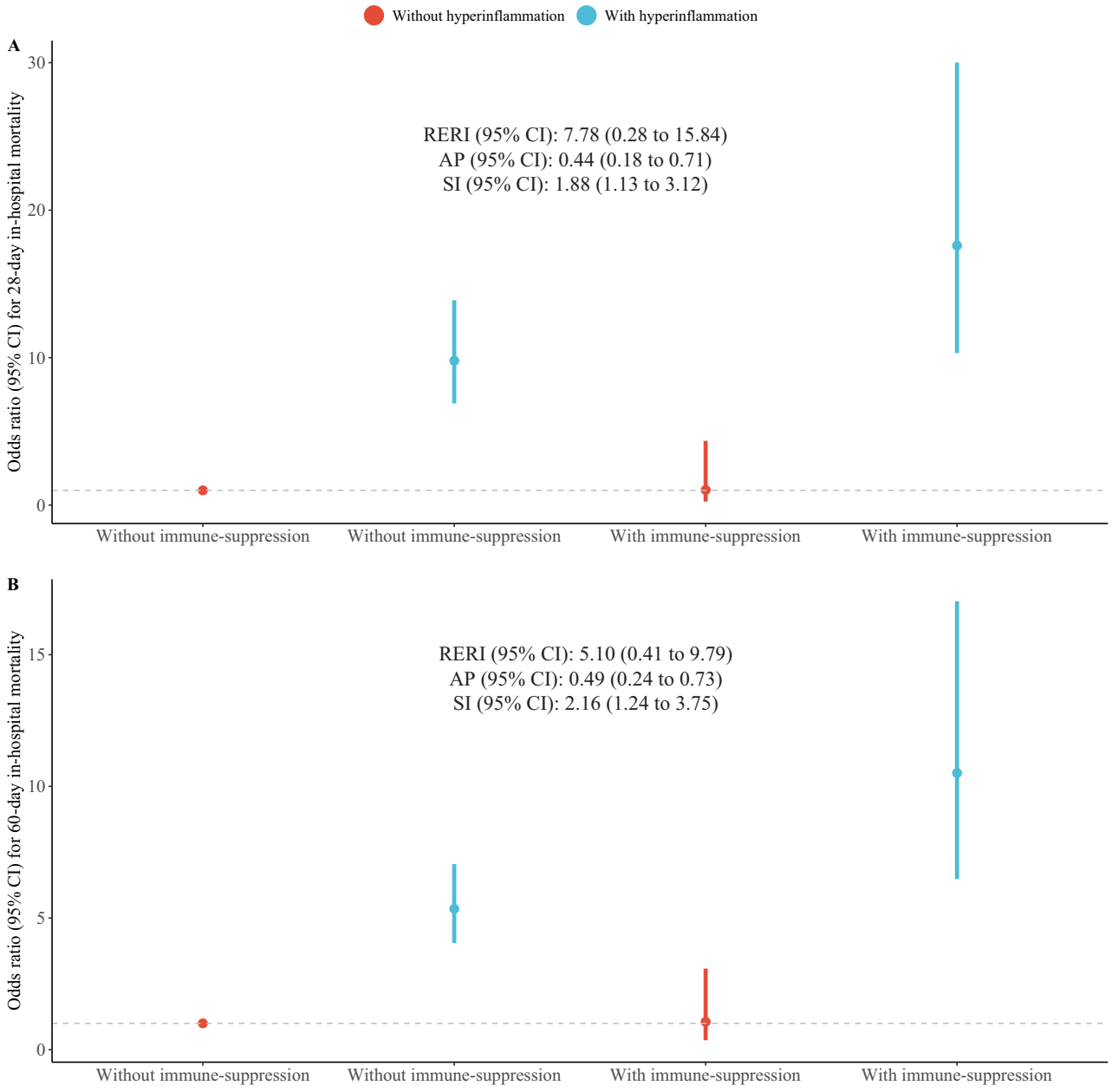

Figure 3 Joint Associations and Additive Interactions Between Immune-Suppression and Hyperinflammation Status with 28-Day and 60-Day In-Hospital Mortality. (**A**)Joint associations and additive interactions between immune-suppression and hyperinflammation status with 28-day in-hospital mortality. (**B**) Joint associations and additive interactions between immune-suppression and hyperinflammation status with -day in-hospital mortality. Odds ratio was derived using binary logistic regression, which controlled for age, sex, smoking status, coronary heart disease, hypertension, diabetes, liver diseases, Neurological disease, chronic lung disease, clinical symptom grade, Baricitinib, and anti-viral medication usage. Blue bars represent patients with hyperinflammation, and red bars represent patients without hyperinflammation.
Abbreviations: RERI, relative excess risk; AP, attributable proportion; SI, synergy index; CI, confidence interval.

SOT group. After adjusting for relevant covariates, including comorbid diseases, immunocompromised status remained an independent risk factor for death in COVID-19 hospitalized patients.

Excessive release of inflammatory cytokines against SARS-CoV-2 is a key aspect of COVID-19 pathogenesis. Immune modulators have been suggested to address this imbalance in a biomarker-driven approach.[38] When considering immunosuppression in COVID-19 treatment, the use of steroids or anti-cytokine therapies is a topic of deliberation. Previous research has shown that tocilizumab was less frequently administered to in-hospital immunocompromised patients compared to immunocompetent patients.[24,39] However, there is a lack of research on the intensity of

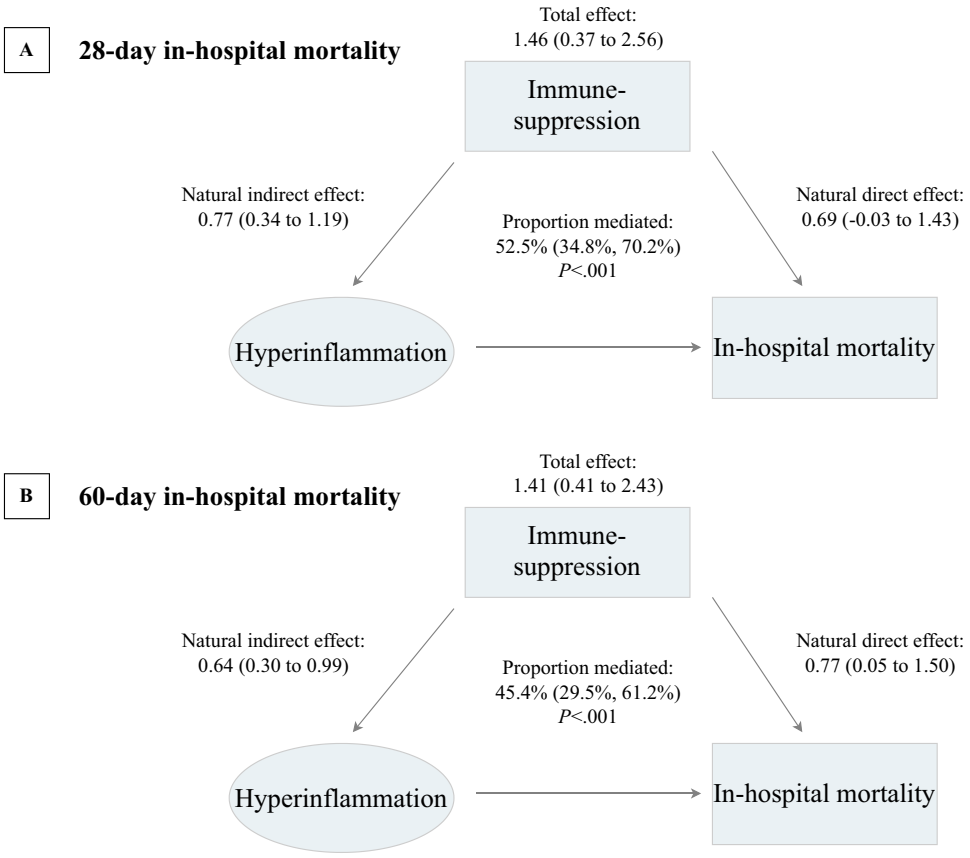

Figure 4 Counterfactual Mediation Models Assessing Associations Between Immune-Suppression and Hyperinflammation Status with 28-Day and 60-Day In-Hospital Mortality. (**A**) Mediation effects of hyperinflammation status in associations between immune-suppression 28-day in-hospital mortality. (**B**) Mediation effects of hyperinflammation status in associations between immune-suppression 60-day in-hospital mortality. Effect estimates were expressed as RERI and 95% confidence intervals. Counterfactual mediation models allowing for exposure-mediator interaction were applied for analyzing mediation effects, which controlled for age, sex, smoking status, coronary heart disease, hypertension, diabetes, liver disease, Neurological disease, chronic lung disease, clinical symptom grade, Baricitinib, and anti-viral medication usage.

inflammation in the immunocompromised population. Agustí et al in 2004 found a similar innate immune response in immunocompromised patients with pulmonary complications compared to non-immunosuppressed patients, with elevated levels of proinflammatory cytokines such as TNF-a, IL-6, and IL-8 etc.[40] We primarily focused on serum IL-6 and CRP levels for hyperinflammatory states. These markers were chosen because of their established role in reflecting systemic inflammation and cytokine storm severity in COVID-19, as well as their relevance in guiding therapeutic strategies like tocilizumab use during the pandemic.[14,23] Patients were categorized into hyperinflammation and non-hyperinflammation groups. Interestingly, hyperinflammation was more common in the immunocompromised group, suggesting that a compromised immune system does not necessarily result in a weaker inflammatory response.

Our results not only demonstrated a positive synergistic effect of inflammation overactivation and immunosuppression on COVID-19 mortality, but also highlighted that a significant portion of the prognostic impact of immunosuppression was influenced by hyperinflammation. These findings align with Benotmane et al study in 2021, which indicated that elevated levels of biomarkers associated with cytokine release syndrome, such as CRP, IL-6, high-sensitivity troponin I, and D-dimer, were strongly linked to severe disease and mortality in hospitalized kidney transplant recipients with COVID-19.[41] Additionally, our results were supported by previous studies suggesting that maintaining immunosuppressive medications could be beneficial for severe COVID-19 patients with immunosuppression.[42,43]

Currently there is no consensus on the definition of immunocompromised hosts. Similar to previous studies focusing on immunocompromised patients in the context of COVID-19[20,21] and other infectious scenarios,[44,45] we included patients with pre-existing diseases or conditions such as SOT, active malignancies or those receiving immunosuppressive medications, among others. Although often broadly labeled as immunocompromised, these clinical conditions vary in

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severity and types of immunosuppression.[3,21,44,46] For example, for SOT patients, intensity of immunosuppressive therapy may vary based on the time since transplantation, as well as individual patient factors, such as transplant type, comorbidities, and rejection episodes. The lack of detailed immune profiling such as immune functional tests when identifying immunosuppression represents a limitation not only in our study but also many previous studies, in which immunocompromised patients were included based on medical history. This was less accurate but more effective and feasible to recognize patients with incompetent immune systems when conducting retrospective studies.

In our cohort, the immunocompromised group exhibited fewer peripheral CD-4+ lymphocytes, reduced neutrophils counts and lower IgG levels, indicating the presence of suppressed immunity. Future investigations incorporating more comprehensive immune profiling, including biomarkers such as immune cell subsets, antibody titers, and functional immune assays, is warranted to further explore the immunologic heterogeneity within this population and to better understand the relationship between immunosuppression, hyperinflammation, and COVID-19 outcomes.

It is well established that vaccines can significantly reduce the incidence of severe diseases and enhance survival rates in COVID-19.[47,48] However for immunocompromised populations, the vaccine's protective effect may be less robust compared to the immunocompetent population.[49,50] Unfortunately, insufficient vaccination data prevented us from obtaining a comprehensive overview of vaccination status within the included population. Although no research has conclusively demonstrated that vaccination influences the level of patients' inflammatory responses to SARS-CoV-2, we cannot definitively determine whether vaccination contributed to the observed differences in inflammatory phenotype and prognosis between the two groups. We acknowledge that the lack of vaccination status information represents a limitation of our study. Future studies that incorporate vaccination records would provide a more comprehensive understanding of the interplay between immune status, inflammation, and COVID-19 outcomes.

Study strengths

Our study has various key strengths. Firstly, we demonstrated in a large cohort that hospitalized COVID-19 patients who were immunosuppressed had a higher risk of mortality. Secondly, this is the initial report indicating that immunocompromised individuals were more prone to hyperinflammation compared to those with a healthy immune system. Thirdly, we showed that an excessively activated inflammatory response was a contributing factor to COVID-19 mortality in individuals with compromised immune systems, as discussed in a previous study.[41] Our results, consistent with others, emphasize the importance of monitoring inflammatory biomarkers in COVID-19 patients with immunosuppression and suggest that timely administration of anti-inflammatory drugs based on biomarker levels could potentially improve prognosis in this population.

Study limitations

Several limitations need to be considered for the accurate interpretation of this study. Firstly, vaccination and BMI were not included in the adjusted analysis due to significant missing data. Despite that vaccination has limited effectiveness in immunocompromised populations,[51] we acknowledge that this omission might impact the final conclusion. Secondly, immunocompromised patients with different etiologies had varying risks of death due to the type and extent of immune suppression.[3,46] Unfortunately, the small sample size prevented a direct comparison of clinical outcomes among these groups.

Conclusions

Our study demonstrated that immunocompromised patients face a higher risk of mortality when hospitalized with COVID-19 compared to those with healthy immune systems. We emphasized the significant role of hyperinflammation in the negative clinical outcomes observed in this patient population. Our findings suggest that uncontrolled inflammation may be a key factor contributing to the severity of COVID-19 in individuals with compromised immune function, underscoring the importance of closely monitoring inflammation levels and utilizing biomarker-guided immunotherapy for severe cases. Given the complexity of immune responses and inflammatory processes, further research is needed to fully understand the mechanisms underlying immunosuppression and hyperinflammation in COVID-19 patients.

Ethics Approval and Informed Consent

This work did not involve any trials with human or animals. It complied with the Declaration of Helsinki and underwent approval by the Ethics Committee of the Chinese PLA General Hospital. Given the study was conducted retrospectively and the data was retrieved anonymously, the requirement for informed consent was therefore waived.

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Author Contributions

Lixin Xie conceived the study and obtained the funding. Wuxiang Xie and Junchang Cui designed the study. Xinxin Zhang, Xiaobo Han, and Chenglong Li wrote the initial draft and conducted the statistical analyses. Xin Yuan, Zhihan Han and Jiguang Meng participated in the planning and execution of this study. Junchen Xiong and Wei Chen extracted and collected the data. Xinjie Han participated in data acquisition and verified the data. Wuxiang Xie and Lixin Xie revised the manuscript for important intellectual content and interpreted the data. All authors have made significant contributions to the work reported, including the conception, study design, execution, acquisition of data, analysis, and interpretation. All authors have drafted, written, or substantially revised and critically reviewed the article. All authors have agreed on the journal to which the article will be submitted. All authors have reviewed and approved all versions of the article prior to submission, during revision, and the final version accepted for publication, and any significant changes introduced at the proofing stage. Furthermore, all authors have agreed to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors report no conflicts of interest in this work.

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