Respiratory Research

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The effect of immunosuppression on outcomes in elderly patients with community-acquired pneumonia

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Abstract

Background The effect of immunosuppression on clinical manifestations and outcomes was unclear in elderly patients with CAP.

Methods Elderly hospitalised patients with CAP were consecutively enrolled and were divided into immunocompromised hosts (ICHs) or non-ICHs groups. Clinical manifestations, severity, and outcomes were compared. The logistic regression model was used to determine the association between immunosuppression and outcomes. The primary outcome was 30-day mortality.

Results A total of 822 patients were enrolled, of whom 133 (16.2%) were immunocompromised. There were no differences between the two groups in vital signs, oxygenation, admission laboratory tests, need for mechanical ventilation and intensive care unit admission, except for a lower lymphocyte count in the ICH group (0.9*10^9/L, IQR 0.6–1.3*10^9/L [ICH group] vs. 1.2*10^9/L, IQR 0.8–1.7*10^9/L [non-ICH group]; $p < 0.001$). The 30-day mortality in ICHs was 15.8%, significantly higher than the 5.1% in non-ICHs ($p < 0.001$). The risk distribution of severity was similar between the two groups when assessed by CURB-65 on admission; however, the significant difference was found when assessed by PSI. Notably, in the CURB-65 low-risk group, the 30-day mortality was significantly higher in ICHs than in non-ICHs (9.7% vs. 1.1%, $p < 0.001$); but there was no difference between ICHs and non-ICHs in PSI low-risk group (3.7% vs. 0.6%; $p > 0.05$). After adjusting for age, sex, and comorbidities, immunosuppression was significantly associated with a higher risk of 30-day mortality (odds ratio 5.004, 95% CI [2.618–9.530]).

Conclusions Immunosuppression was independently associated with an increased risk of 30-day mortality. CURB-65 may underestimate the mortality risk of ICHs.

Keywords Community-acquired pneumonia, Immunocompromised, Elderly, Outcomes

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Introduction

Community-acquired pneumonia (CAP) is the leading cause of death among infectious diseases and remains a global health problem [1–3]. CAP is associated with high morbidity and mortality in the elderly patients [4, 5], resulting in significant healthcare costs. Immunocompromised hosts (ICHs) are at increased risk for developing pneumonia, hospitalization, and poor outcomes [6–8], which should be considered as a special concern. The prevalence of ICHs is gradually increasing due to the increased use of biological immune modulators and the prolonged survival of patients with cancer or organ transplantation [9]. In the US, the estimated prevalence of ICHs increased from 2.7% in 2013 [10] to 6.6% in 2021 [11], and the rate increased with increasing age. However, several CAP guidelines have excluded immunocompromised patients because of their need for complex treatment, the expanded spectrum of potential pathogens, and their exclusion from the large prospective studies of antibiotic efficacy used to support guideline recommendations [12–16]. To date, few high-quality studies have focused on the differences in clinical characteristics and outcomes between CAP patients with and without immunosuppression, particularly in the elderly. We aimed to compare the clinical characteristics, severity, and various outcomes between hospitalised ICHs and non-ICHs with CAP, and to explore the association between immunosuppression and adverse outcome.

Methods

Study design and participants

This was a retrospective cohort study conducted in the Department of Pulmonary and Critical Care Medicine, Beijing Hospital. This study was approved by the Research Ethics Committee of Beijing Hospital (2023BJYYEC-281-01), and the need for written informed consent was waived due to the retrospective design.

Patients aged ≥ 65 years hospitalized with CAP were consecutively enrolled between January 2021 and June 2023. The diagnosis of CAP was based on the criteria of the clinical practice guideline published by the Chinese Thoracic Society [15]. Patients were excluded from the study if they were diagnosed with a diagnosis other than CAP after admission. In addition, we aimed to compare the severity of pneumonia using the pneumonia severity scoring systems between ICHs and non-ICHs. Hence, patients were also excluded from the study if they had incomplete data within 24 h of admission, making it impossible to calculate the pneumonia severity scores. ICHs in our study include those receiving long-term (> 3 months) or high-dose (> 0.5 mg/kg/day) steroids or other immunosuppressant drugs, solid-organ transplant recipients, patients with solid tumour requiring chemotherapy in the last 5 years or with hematological malignancy whatever the time since the diagnosis and received treatments, and patients with primary immune deficiency [17].

Data collection and study outcomes

Data were extracted from the electronic medical history, including demographic characteristics, comorbidities, symptoms and signs during the acute infection, vital signs and mental confusion on admission, peripheral oxygen saturation or arterial blood gas, laboratory test results within 24 h of admission, chest images, treatment and clinical outcomes. Laboratory tests included, but were not limited to, a complete blood cell count, C-reactive protein, arterial blood gas, BNP or NT-proBNP, troponin I, creatinine, aspartate transaminase, alanine transaminase, blood urea, lactate dehydrogenase, albumin, d-dimer, and electrolytes. CURB-65 [18] and pneumonia severity index (PSI) [19] were used to evaluate the severity of pneumonia on admission. Patients with CAP were stratified into three risk groups according to CURB-65 and PSI scoring systems: low-risk (CURB-65 score 0–1 or PSI I-III), intermediate risk (CURB-65 score 2 or PSI IV) and high-risk groups (CURB-65 score ≥ 3 or PSI V). The primary outcome was 30-day mortality after hospitalization, and the secondary outcomes were in-hospital mortality, septic shock, need for vasoactive agents, mechanical ventilation and intensive care unit (ICU) admission.

Statistical analysis

Continuous variables were presented as median and interquartile range and categorical variables as numbers and percentages. The Mann-Whitney U test, χ^2 [2 test, or Fisher's exact test were used to compare the demographics, comorbidities, laboratory results, pneumonia severity scores, and outcomes between the ICH and non-ICH group, as appropriate. Wilcoxon rank-sum test was used to compare the pneumonia severity using CURB-65 and PSI score between the two groups. Multivariable adjusted logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence interval (CI) for the association between immunosuppression and adverse outcomes. Survival, ICU admission, and mechanical ventilation at 30 days after hospitalization of the two groups were presented in Kaplan–Meier curves and compared with log-rank tests. Statistical analysis was performed using IBM SPSS version 24.0 (IBM SPSS Statistics, IBM Corporation) and R software 4.0.2 (R Foundation for Statistical Computing). A two-sided $p < 0.05$ was considered statistically significant.

Results

Of the 822 patients enrolled, 133 (16.2%) were immunocompromised and 689 (83.8%) were immunocompetent. The most common immunocompromised population were those receiving chemotherapy for solid tumours (56.4% [75/133]), followed by those receiving prolonged corticosteroid therapy (32.3% [43/133]) and those receiving solid-organ transplantation or with hematologic malignancy (11.3% [15/133]) (Table 1).

Baseline characteristics of both groups are shown in Table 1. Patients in the ICH group were younger than those in the non-ICH group (median [IQR] age, 72.0 [69.0-79.5] years vs. 78.0 [71.0–84.0] years; $p < 0.001$). No gender difference was observed between the two groups. A higher percentage of patients never smoke in the non-ICH group than in the ICH group (64.3% vs. 50.4%; $p = 0.019$). Patients in the ICH group had a lower percentage of hypertension and coronary heart disease than those in the non-ICH group ($p < 0.05$), with no difference in other comorbidities. There were no significant differences in vital signs and oxygenation between the two groups, except for a statistically lower systolic

Table 1 Baseline characteristics of 822 elderly patients with CAP, by immune status

Characteristics	ICH (*n* = 133)	Non-ICH (*n* = 689)	*P* value
Age, years	72.0(69.0-79.5)	78.0(71.0–84.0)	< 0.001
65–74	78(58.6%)	265(38.5%)	
≥ 75	55(41.4%)	424(61.5%)	
Sex			0.054
Men	93(69.9%)	421(61.1%)	
Women	40(30.1%)	268(38.9%)	
Cigarette smoking			0.019
Never-smoker	67(50.4%)	443(64.3%)	
Current smoker	14(10.5%)	56(8.1%)	
Former smoker	52(39.1%)	188(27.3%)	
Comorbidity			
Chronic pulmonary disease	51(38.3%)	238(34.5%)	0.400
Hypertension	64(48.1%)	432(62.7%)	< 0.002
Diabetes mellitus	42(31.6%)	213(30.9%)	0.896
Coronary heart diseases	28(21.1%)	207(30.1%)	< 0.035
Cerebrovascular diseases	24(18.0%)	166(24.1%)	0.130
Chronic kidney disease	15(11.3%)	97(14.1%)	0.389
Chronic liver disease	12(9.0%)	65(9.4%)	0.881
Type of immunocompromised			
Solid-organ transplantation or hematologic malignancy	15(11.3%)		
Solid tumour receiving chemotherapy	75(56.4%)		
Prolonged corticosteroid therapy	43(32.3%)		
Clinical characteristics at admission			
Confusion	9(6.8%)	66(9.6%)	0.302
Fever	26(19.5%)	156(22.6%)	0.662
Respiratory rate, breaths per minute	20.0(19.0-21.5)	20.0(18.0–21.0)	0.184
Heart rate, beats per minute	86.0(78.0–96.0)	84.0(78.0–95.0)	0.484
Systolic blood pressure, mmHg	131.0(117.0-145.0)	136.0(121.0-148.0)	0.027
Diastolic blood pressure, mmHg	73.0(65.0–83.0)	74.0(66.0–82.0)	0.595
$PaO_2 \leq 60$mmHg or $SpO_2 \leq 90\%$	27(20.3%)	133(19.3)	0.790
White blood cell count, 10^9/L	6.7(4.7–9.8)	6.7(5.2–9.5)	0.666
Neutrocyte count, 10^9/L	4.8(3.2–7.8)	4.6(3.3–7.1)	0.541
Lymphocyte count, 10^9/L	0.9(0.6–1.3)	1.2(0.8–1.7)	< 0.001
C-reactive protein, mg/L	31.0(9.6–89.0)	26.3(6.3–76.0)	0.256
Haemoglobin, g/L	108.0(95.0-119.0)	115.0(101.0-128.0)	< 0.001
Urea, mmol/l	6.2(4.5–8.8)	5.9(4.4–8.4)	0.567
Albumin, g/L	33.0(29.0–38.0)	34.0(30.0–37.0)	0.486
ADL score	75.0(32.5–100.0)	80.0(30.0-100.0)	0.737

Data are n (%) or median (IQR). CAP = community-acquired pneumonia, eGFR = estimated glomerular filtration rate, ICH = immunocompromised host, ADL = activity of daily living scale

blood pressure in the ICH group compared to the non-ICH group. Patients in the ICH group were more likely to have lower lymphocyte count (0.9*10^9/L [0.6–1.3*10^9/L] vs. 1.2*10^9/L [0.8–1.7], $p<0.001$) and haemoglobin (108.0 g/L [95.0-119.0] vs. 115.0 g/L [101.0-128.0], $p<0.001$) on admission compared to those in the non-ICH group, with no difference in white blood cell count, neutrocyte count, and C-reactive protein between the two groups. Activities of daily living (ADL) scores were similar in the two groups (75.0[32.5–100.0] vs. 80.0[30.0-100.0], $p=0.737$).

Table 2 shows the results of the comparison of pneumonia severity scores and outcomes between the two groups. About half patients in the two groups were low risk (CURB-65 score 1), and there were no significant differences in the three risk levels of CURB-65 between the two groups. When assessed by PSI on admission, most of patients in the ICH group were intermediate risk (PSI IV), but were low risk (PSI II-III) in the non-ICH group. There were significant differences in the three risk levels of PSI between the two groups ($p<0.001$). Patients in the ICH group had a higher percentage of 30-day mortality than those in the non-ICH group (15.8%[21/133] vs. 5.1%[35/689]; $p<0.001$), and the trend was also seen for in-hospital mortality, septic shock, and need for vasoactive agents during hospitalization. A higher percentage of patients in the ICH group received high-flow nasal cannula therapy during hospitalization than those in the non-ICH group (13.5%[18/133] vs. 7.1[49/689]; $p<0.013$), with no difference in other oxygen therapies, such as nasal cannula or oxygen mask, non-invasive mechanical ventilation and invasive mechanical ventilation.

Table 2 Pneumonia severity and outcomes of 822 elderly patients with CAP, by immune status

Characteristics	ICH ($n=133$)	Non-ICH ($n=689$)	*P* value
CURB-65 at admission			0.377
Low risk (score 1)	62(46.6%)	360(52.2%)	
Intermediate risk (score 2)	52(39.1%)	227(32.9%)	
High risk (score 3–5)	19(14.3%)	102(14.8%)	
PSI at admission			< 0.001
Low risk (II-III)	27(20.3%)	344(49.9%)	
Intermediate risk (IV)	79(59.4%)	266(38.6%)	
High risk (V)	27(20.3)	79(11.5%)	
Outcomes			
Requiring oxygen therapy during hospitalization	100(75.2%)	482(70.0%)	0.224
Nasal cannula or oxygen mask	80(60.2%)	420(61.0%)	0.861
High flow nasal cannula	18(13.5%)	49(7.1%)	0.013
Non-invasive mechanical ventilation	33(24.8%)	131(19.0%)	0.115
Invasive mechanical ventilation	12(9.0%)	57(8.3%)	0.775
Mechanical ventilation	39(29.3%)	159(23.1%)	0.123
Septic shock	24(18.0%)	52(7.5%)	< 0.001
Vasoactive agents	27(20.3%)	61(8.9%)	< 0.001
Length of hospital stay, days	12.0(7.0–20.0)	11.0(7.0–17.0)	0.669
ICU admission	24(18.0%)	87(12.6%)	0.094
30-day mortality	21(15.8%)	35(5.1%)	< 0.001
In-hospital mortality	27(20.3%)	44(6.4%)	< 0.001

Data are n (%) or median (IQR). CAP = community-acquired pneumonia, PSI = pneumonia severity index, ICU = intensive care unit, ICH = immunocompromised host

The comparisons of 30-day mortality between ICHs and non-ICHs at the same risk level are shown in Fig. 1. In patients with CURB-65 score 1, ICH had a higher 30-day mortality compared to non-ICH (9.7% [6/62] vs. 1.1% [4/360]; $p<0.001$), and this significant difference was also shown in patients with CURB-65 score 2 (17.3% [9/52] vs. 3.1% [7/227]; $p<0.001$); however, no difference was observed between ICHs and non-ICHs in patients with CURB-65 score 3–5. ICHs in PSI IV were more likely to have a higher 30-day mortality (15.2% [12/79] vs. 5.6% [15/266; $p=0.006$); however, no differences were observed between ICHs and non-ICHs in patients with PSI II-III and PSI V. Patients were further divided into two age groups: aged 65–74 years or aged ≥ 75 years. In patients aged 65–74 years with a CURB-65 score of 2, the 30-day mortality was significantly higher in ICHs than in non-ICHs (20.7% vs. 1.4%; $p=0.003$). In patients aged ≥ 75 years, 30-day mortality was significantly higher in ICHs than in non-ICHs in patients with CURB-65 score 1 and patients with PSI IV.

The results of the association between immunosuppression and adverse outcomes are presented in Fig. 2. In the analyses adjusted for age and sex, ICHs had a significantly higher risk of 30-day mortality (OR, 4.829; 95% CI, 2.554–9.078; $P<0.001$), in-hospital mortality (OR 4.690; 95% CI 2.663–8.225; $P<0.001$), septic shock (OR 3.343; 95% CI 1.890–5.832; $P<0.001$), and need for vasoactive drugs (OR 3.280; 95% CI 1.907–5.576; $P<0.001$) compared to non-ICHs, but no difference in the need for mechanical ventilation and ICU admission (Table 3). This pattern was maintained when the model was further adjusted for comorbidities (Table 3).

Figure 2 shows the cumulative incidence of outcomes 30 days after hospitalization in ICH and non-ICH groups. The survival rate 30 days within hospitalization was significantly lower in ICH group than in non-ICH group (log-rank $P<0.0001$) (Fig. 2A). However, no significant differences were found between the two groups in the cumulative incidence of ICU admission (Fig. 2B), need for MV or IMV (Fig. 2C), and need for IMV (Fig. 2D) before day 30.

Discussion

To the best of our knowledge, this is the first study to systematically compare the clinical manifestations, pneumonia severity, and outcomes in elderly CAP patients

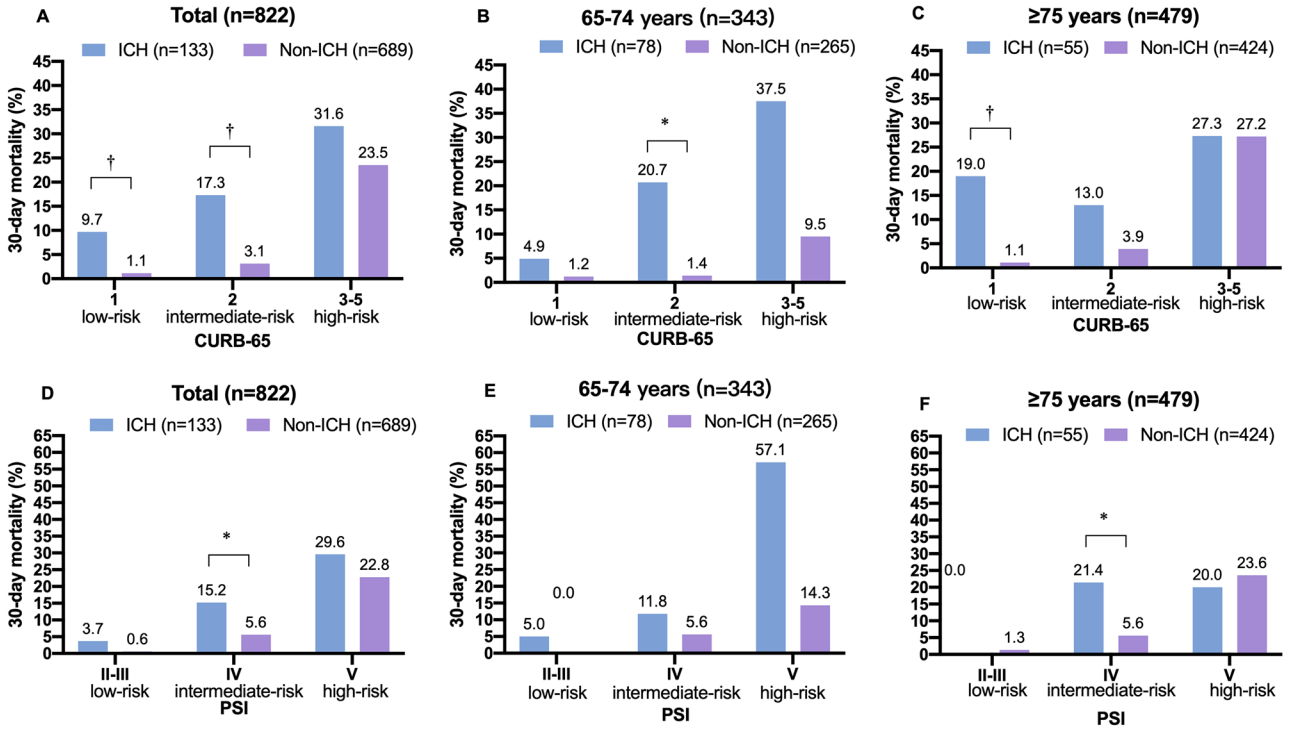

Fig. 1 30-day mortality rate of each risk group, grouped by immune status and age. ICH = immunocompromised host, PSI = pneumonia severity index. * $P < 0.05$, † $P < 0.001$

with and without immunosuppression. The lymphocyte count was significantly lower in the ICH group than in the non-ICH group. The ICH group were more likely to have adverse outcomes than the non-ICH group, including 30-day mortality, in-hospital mortality, septic shock, and need for vasoactive drugs; however, no difference was found between the two groups in the need for ICU admission and mechanical ventilation, and length of hospital stay. 30-day mortality was numerically higher in the ICHs group than in the non-ICHs group at each risk level, irrespective of age group. After adjustment of age, sex, and comorbidities, immunosuppression was independently associated with mortality and septic shock.

We found that 16.2% of elderly hospitalised patients with CAP were immunocompromised, which was consistent with the findings of an international multicenter study. Worldwide, up to 18% of hospitalised patients with CAP have at least one risk factor for immunosuppression [20]. The number of ICHs is increasing with the aging of the global population and more patients receiving immunosuppressive therapies for chronic diseases [21]. Although ICHs are generally recognized as being at high risk for CAP, there is a paucity of robust evidence on the management of CAP in this population, because the special population has been totally or partially excluded in the randomised controlled trials and observational prospective studies. Future large studies are needed to include this special population to describe their epidemiology, etiology, treatment, and outcomes. The most common risk factors for immunosuppression in current study were consistent with the above global survey [20], mainly including chemotherapy, chronic use of systemic steroids, and hematologic malignancy. The leading cause of immunosuppression in the global survey was chronic use of systemic steroids, but chemotherapy ranked first in current study. The prevalence and the ranking of the causes of immunosuppression in elderly patients with CAP may differ between continents, countries, and hospitals, probably partly due to the differences in healthcare systems, treatment site, and center profession.

The common pneumonia severity scoring systems, CURB-65 and PSI, were developed mainly from immunocompetent patients with CAP [18, 19], and their performance in immunocompromised patients were unclear. We found that half of the patients in the ICHs group were classified as low risk by CURB-65, but their 30-day mortality was almost nine times that of the CURB-65 low risk patients in the non-ICHs group (9.7%[ICHs] vs. 1.1%[non-ICHs]). In addition, approximately one in five patients were classified as low risk by PSI, and no statistical difference was found between PSI low risk patients with and without immunosuppression (3.7%[ICHs] vs. 0.6%[non-ICHs]). These findings support that the CURB-65 is likely to underestimate the mortality risk on admission in ICHs. The currently recommended hospital

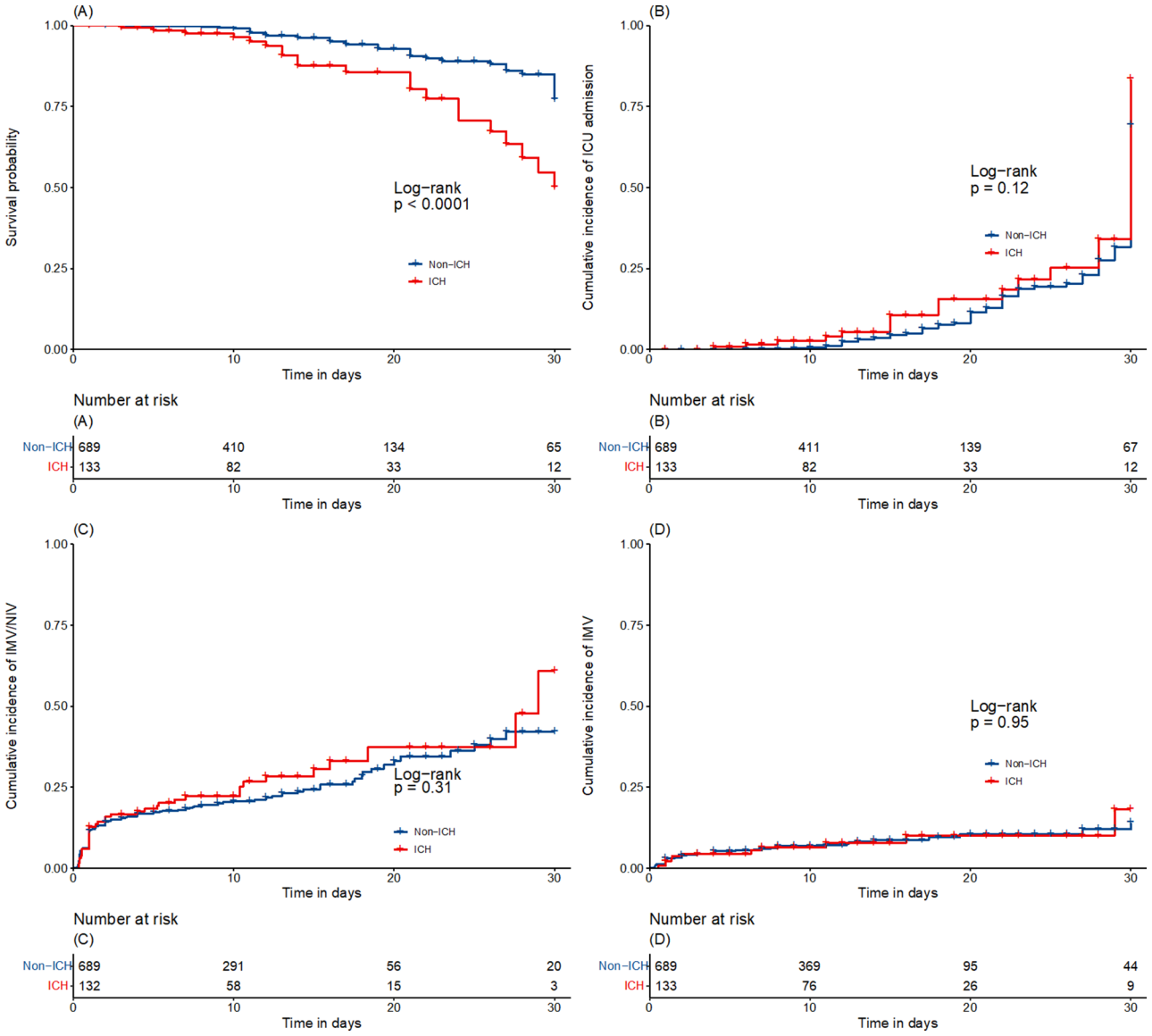

Fig. 2 Cumulative incidence of outcomes over 30 days by immune status. ICH = immunocompromised host, ICU = intensive care unit, IMV = invasive mechanical ventilation, NIV = non-invasive mechanical ventilation

admission criteria (CURB-65 ≥ 2) [2, 15] may result in many high-risk ICHs being managed on an outpatient basis, and a lower cut-off point may be more better for ICHs. Besides, we found that PSI may be optimal for assessing pneumonia severity in ICHs, which deserves a large sample study to further validate.

A previous small study with about 300 patients have shown that elderly ICHs with CAP had the similar rate of ICU admission and mechanical ventilation as well as length of hospital stay, but higher overall mortality [6]. These findings were totally consistent with our results. Besides, we further found that patients in the ICHs group were at higher risk for septic shock and need for vasoactive drugs. The risks for adverse outcomes between the two groups were further quantified. Patients in the ICH group have an approximately 5-fold greater risk of in-hospital or 30-day mortality, and 3-fold greater risk of septic shock than those in the non-ICH group. The higher risk for adverse outcomes in our ICH group may partly be due to the greater disease severity and the suppressed immune response, which can be shown from the PSI risk class and the lymphocyte count at admission. A prior study evaluated the mortality according to the function of the immune systems, and found that the mortality increased as immune function decreased [22]. The etiology difference between ICHs and non-ICHs may be another reason for the differences of clinical outcome. Streptococcus pneumoniae was the primary etiology of CAP in ICHs and non-ICHs [6, 20, 22], but identified opportunistic pathogen, especially fungi and

Table 3 Association between immunocompromised status and adverse outcomes

Outcomes	Model 1		Model 2	
	OR 95%CI	*P* value	OR 95%CI	*P* value
30-day mortality	4.829 (2.554–9.078)	< 0.001	5.004 (2.618–9.530)	< 0.001
In-hospital mortality	4.690 (2.663–8.225)	< 0.001	4.722 (2.645–8.414)	< 0.001
Mechanical ventilation	0.954 (0.496–1.994)	0.894	0.913 (0.468–1.932)	0.802
ICU admission	0.617 (0.373–1.048)	0.065	0.596 (0.358–1.021)	0.052
Septic shock	3.343 (1.890–5.832)	< 0.001	3.398 (1.890–6.007)	< 0.001
Vasoactive agents	3.280 (1.907–5.576)	< 0.001	3.426 (1.971–5.901)	< 0.001

ICU = intensive care unit, OR = odds ratio. Non-ICH group is the reference group

Model 1 is adjusted for age and sex

Model 2 is adjusted for model 1 and the following comorbidities: chronic pulmonary disease, hypertension, diabetes mellitus, coronary heart diseases, cerebrovascular diseases, chronic kidney disease, and chronic liver disease

pneumocystis, and virus as well as multidrug resistant pathogens were more common in ICHs [17, 22], which could be potentially related to poorer outcomes in ICHs.

Our study has several limitations. Firstly, although this is one of the few studies to focus on the effect of immunosuppression on clinical manifestations and outcomes in elderly patients with CAP, the design of retrospective single-center study determines its limited sample size. Our findings deserve further validation in a large sample study. Secondly, the limited number of immunocompromised patients resulted in the inability to compare the clinical characteristics and outcomes in patients with different risk factors of immunosuppression. Thirdly, in addition to guiding treatment, the etiology of CAP is associated with prognosis. Data on etiology were not collected in the current study, which mainly were contributed to the difficulty in determining the causative agents from the positive pathogens detected in this retrospective study.

About one in five elderly patients with CAP were immunocompromised, and chemotherapy was the leading risk factor. Immunocompromised patients have a higher risk of mortality and septic shock than immunocompetent patients. Immunosuppression was the independent risk factor for mortality and septic shock. CURB-65 may underestimate the risk of mortality in immunocompromised patients with CAP, which requires further validation in a future large sample study.

Author contributions

LH and YL conceived and designed the study. LH and BW collected data, did analysis, and drafted the paper. All authors participated in the diagnosis and treatment of elder patients with CAP, and collected data from medical records. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding

this work was supported by National High Level Hospital Clinical Research Funding(BJ-2023-159) and Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences under Grants(2021-I2M-1-044).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

our study was approved by the Research Ethics Committee of Beijing Hospital (2023BJYYEC-281-01).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 2 September 2024 / Accepted: 20 December 2024
Published online: 22 January 2025

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