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Original Article

Effects of high-dose intravenous immunoglobulin on efficacy, inflammatory markers, and pulmonary function in adults with severe acute viral pneumonia

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Abstract: Objective: To elucidate the effects of high-dose intravenous immunoglobulin (HD-IVIG) therapy on inflammatory markers, and pulmonary function (PF) in adult patients with severe acute viral pneumonia (SAVP). Methods: A total of 178 adult patients with SAVP were selected and divided into two groups according to their actual treatment regimens. Eighty-eight patients receiving routine treatment were assigned to the control group, and 90 patients receiving HD-IVIG were assigned to the observation group. Clinical efficacy, symptom relief time, inflammatory markers, PF, humoral immunity, and quality of life (SF-36) were compared across multiple dimensions. Factors influencing treatment ineffectiveness in adult patients with SAVP were also investigated. Results: The overall clinical efficacy in the observation group was significantly better than that in the control group, with a significantly shorter symptom relief time. Compared with routine treatment, HD-IVIG therapy significantly reduced the levels of C-reactive protein (CRP) and procalcitonin (PCT) while substantially elevating the levels of interleukin (IL)-2, various PF indicators, humoral immunity markers, and scores on all dimensions of the SF-36. Age, coronary heart disease, CRP levels, and treatment modality are associated factors increasing the risk of treatment ineffectiveness in adult SEVP patients. Conclusion: HD-IVIG therapy has a definite clinical efficacy in treating adult patients with SAVP.

Keywords: High-dose intravenous immunoglobulin therapy, severe acute viral pneumonia in adults, therapeutic efficacy, inflammatory markers, pulmonary function

Introduction

Viral pneumonia is an inflammatory disease of the lungs. Its pathogenesis involves the invasion and damage of alveolar epithelial cells by influenza, parainfluenza, respiratory syncytial viruses, as well as adenoviruses, which in turn aggravates the host's immune response, causing abnormal gas exchange and impaired lung function. Severe cases can even induce multiple organ failure [1]. Patients usually experience symptoms such as fever, asthma, lung rales and cough, and may also be accompanied by adverse events such as respiratory distress, septic shock and coagulation dysfunction, which seriously endanger the patient's life and health [2]. Epidemiologically, the number of pneumonia cases worldwide reached 2.5 million in 2019 alone, ranking fourth among the world's leading causes of death [3]. This disease not only has high morbidity and mortality, but also brings a heavy economic burden to patients [4]. Severe acute viral pneumonia (SAVP) is a prevalent condition in intensive care units (ICUs), with an extremely high risk of death [5]. The routine clinical treatment for SAVP in adults is mainly anti-inflammatory, antiviral and maintenance of water and electrolyte balance, often using ceftriaxone in combination with azithromycin, oseltamivir, and ambroxol hydrochloride. Of these, ceftriaxone can effectively cover common pathogens such as Streptococcus pneumoniae and Haemophilus influenzae [6]; Azithromycin, as a macrolide antibiotic, plays an anti-inflammatory and immunomodulatory role [7]; Being a neuraminidase inhibitor, oseltamivir can shorten the duration of influenza symptoms and reduce mortality among severe patients, which is particularly indicated for those within 24 hours of admission [8, 9];

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Ambroxol hydrochloride solution is an expectorant that can help the body expel sputum [10]. Although this conventional treatment can control viral infection to some extent, it is slow to take effect and has limited efficacy. In addition, after passing the acute excessive inflammatory period, severe infection often leads to immune paralysis, which is characterized by suppression of innate immune function and a significantly increased risk of secondary infection. This phenomenon has been well documented in sepsis, where downregulation of key immune receptors such as CX3CR1 on the surface of monocytes leads to a decrease in pathogen clearance capacity and a worse clinical prognosis [11]. The specific mechanism of immune paralysis caused by severe viral pneumonia has not been fully elucidated, but the body is likely to experience a similar immune dysfunction process, which highlights the urgent need in clinical practice to develop a treatment plan that can both inhibit viral replication and repair and maintain the body's immune function. Intravenous immunoglobulin preparations are purified blood products with multiple immunomodulatory and anti-inflammatory effects [12]. The dosage of this preparation can be used according to different clinical indications, and the efficacy also varies with the dosage [13]. For example, high-dose intravenous immunoglobulin (HD-IVIG) therapy has been used to treat COVID-19 pneumonia, effectively relieving clinical symptoms, restoring body temperature to normal, and improving dyspnea [14]. When applied to severe H1N1 influenza patients in 2009, this therapy reduced viral load and inhibited cytokine storm, but had no significant effect on viral clearance rate or mortality [15].

Currently, research on HD-IVIG therapy for community-acquired, non-COVID-19 adult patients with severe acute viral pneumonia is still relatively scarce. Therefore, this study will focus on this direction and conduct in-depth analysis and verification.

Materials and methods

General data

This study selected 178 adult patients with SAVP who visited the our hospital from April 2022 to April 2025 as the research subjects. Among them, 88 patients received routine treatment and were set as the control group; 90 patients were treated with HD-IVIG and were set as the observation group. This retrospective study has been approved by the Ethics Committee of our hospital.

Inclusion criteria: the clinical diagnostic criteria for SAVP [16]; community-acquired infections (onset outside the hospital or within 48 hours of admission), with the pathogen identified as influenza/parainfluenza/respiratory syncytial viruses or adenovirus; a respiratory rate >30 breaths/minute; indications for medication; initial treatment; complete medical records.

Exclusion criteria: COVID-19; cardiovascular and cerebrovascular diseases, immune dysfunction, coagulation disorders; damage to the heart, liver, kidneys, or other organs; malignant tumors; neurological dysfunction or mental illness; allergic rhinitis or pharyngitis; use of immunosuppressants and/or glucocorticoids within the past six months; allergy or intolerance to the drugs used in the study; pregnancy or lactation.

Treatment plan

The control group received routine treatment, including anti-inflammatory and antiviral therapy, maintenance of electrolyte balance, and symptomatic drug intervention. Additionally, participants received intravenous ceftriaxone (1-2 g/day) combined with intravenous/oral azithromycin (0.5 g once daily) for 5-7 days; Oseltamivir was administered per os for antiviral treatment (150 mg twice daily for 5-10 days); Oral administration of ambroxol hydrochloride solution was also given (10 mL, three times daily).

The observation group received the routine treatment of the control group, plus HD-IVIG therapy. Intravenous immunoglobulin (2.5 g) was administered at a dosage calculated based on the patient's weight, ranging from 400 mg/(kg·d) to 1,000 mg/(kg·d), with a total daily dose not exceeding 40 g. Dosage is stratified according to the severity of the condition: critically ill patients (oxygenation index ≤200 mmHg or requiring non-invasive ventilation) were given 1,000 mg/(kg·d) for 3-5 days; moderate to severe patients (oxygenation index 200-300 mmHg) were given 400 mg/(kg·d) for 5-7 days. The calculated total dose of drug was diluted

with 5% glucose injection to 50-100 ml and infused using an infusion pump at a constant rate. The initial infusion rate was 0.5 mg/(kg·min), with a drip rate of approximately 5-10 drops/min. If there were no adverse reactions, the rate could be increased by 0.5 mg/(kg·min) every 30 minutes, with a maximum infusion rate not exceeding 4 mg/(kg·min), approximately 60-80 drops/min.

Both groups underwent a 7-day treatment course.

Observation indicators

Clinical efficacy

Evaluation criteria [17]: Marked efficacy was defined as complete disappearance of clinical symptoms, complete absorption of lung shadows on chest X-ray, and no shortness of breath after 3 minutes of activity. Effective efficacy was defined as relief of clinical symptoms, reduction of lung shadow area by >49% on chest X-ray, and no shortness of breath after 3 minutes of activity. Ineffective efficacy was defined as no improvement or even worsening of clinical symptoms, reduction of lung shadow area by <30% on chest X-ray, and persistent shortness of breath after 3 minutes of activity.

Symptom remission time [18]: The time for the resolution of fever, asthma, rales, and cough symptoms was recorded in both groups of patients after treatment.

Inflammatory markers [19]: Venous blood (3 mL) were collected from patients before and after treatment. Serum was separated by centrifugation, and the levels of interleukin (IL)-2, C-reactive protein (CRP), and procalcitonin (PCT) were detected by enzyme-linked immunosorbent assay (ELISA; Abbkine Scientific Co., Ltd., Wuhan, China, KTE6014-1, KTE6004-3, KTE4071-3).

Pulmonary function (PF) [20]: Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF) rate were measured in both groups before and after intervention using a PF testing instrument.

Humoral immune function [21]: Serum levels of immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM) were measured using a fully automated biochemical analyzer.

Quality of life

The Short-Form 36 Item Health Survey (SF-36) was used to assess the quality of life before and after intervention [22].

It included eight dimensions: physical functioning, social functioning, bodily pain, role-physical, role-emotional, mental health, vitality, and general health. The full score was 100 points, and the higher the score, the better the quality of life.

Statistical analysis

All measurement data were tested for normality using the Shapiro-Wilke test. Data that conformed to normal distribution were expressed as mean ± standard deviation (SD). The independent samples t-test was used for comparisons between groups, and the paired t-test was used for comparisons before and after treatment within groups. Data that did not conform to normal distribution were expressed as median (interquartile range) [M (Q1, Q3)], and the Mann-Whitney U test was used for comparisons between groups. Count data were expressed as number of cases (percentage) and the chi-square test was used. Univariate and multivariate logistic regression analyses were used to analyze the influencing factors of the efficacy of treatment in adult patients with severe adenovirus pneumonia. SPSS 22.0 software was used for data analysis. $P<0.05$ was considered statistically significant.

Results

Comparison of baseline data analysis

No statistically significant differences were found in terms of age, sex, disease duration, body temperature, body mass index (BMI), virus type, hypertension, diabetes, and coronary heart disease between the cohorts (all $P>0.05$, **Table 1**).

Comparison of efficacy assessment

The total effective rate in the control group was 75.00%, while in the observation group was 91.11%. The inter-group comparison showed that the overall efficacy in the observation group was significantly higher than that in the control group ($P=0.004$, **Table 2**).

Table 1. Comparison of baseline information

Data	Control group (n=88)	Observation group (n=90)	$Z/\chi^2/t$	P
Age (years)	57.60±6.91	58.21±6.50	0.607	0.545
Sex			0.099	0.753
Male	49 (55.68)	48 (53.33)		
Female	39 (44.32)	42 (46.67)		
Disease duration (d)	7.00 (5.00, 9.00)	7.00 (5.00, 9.00)	-0.895	0.371
Body temperature (°C)	39.22±0.63	39.08±0.85	1.246	0.214
Body mass index (kg/m^2)	22.59±2.10	22.48±2.13	0.347	0.729
Virus type			0.608	0.895
Influenza virus	18 (20.45)	16 (17.78)		
Parainfluenza virus	32 (36.36)	30 (33.33)		
Respiratory syncytial virus	28 (31.82)	32 (35.56)		
Adenovirus	10 (11.36)	12 (13.33)		
Hypertension	40 (45.45)	45 (50.00)	0.368	0.544
Diabetes	26 (29.55)	29 (32.22)	0.149	0.699
Coronary heart disease	13 (14.77)	18 (20.00)	0.845	0.358

Table 2. Comparison of efficacy assessment

Efficacy	Control group (n=88)	Observation group (n=90)	χ^2	P
Marked effectiveness	31 (35.23)	40 (44.44)		
Effectiveness	35 (39.77)	42 (46.67)		
Ineffectiveness	22 (25.00)	8 (8.89)		
Overall effectiveness	66 (75.00)	82 (91.11)	8.242	0.004

Table 3. Comparison of symptom remission time

Symptom remission time (d)	Control group (n=88)	Observation group (n=90)	Z	P
Fever	5.00 (3.00, 7.00)	3.00 (2.00, 9.00)	-3.897	<0.001
Asthma	6.50 (5.00, 8.00)	5.00 (4.00, 6.00)	-4.171	<0.001
Rales	7.00 (5.00, 8.75)	6.00 (5.00, 7.00)	-2.203	0.028
Cough	7.00 (5.00, 8.75)	6.00 (4.00, 7.00)	-2.900	0.004

Comparison of symptom remission time

The remission time of fever, asthma, rales, and cough symptoms was shorter in the observation group than in the control group (all P<0.05, **Table 3**).

Comparison of inflammatory markers

There were no significant differences in the levels of IL-2, CRP, and PCT between the two groups before treatment (all P>0.05). After treatment, IL-2 levels increased in both groups, while CRP and PCT levels decreased, and the changes in the observation group were significantly greater than those in the control group (P<0.01, **Figure 1**).

Comparison of PF evaluation

Before treatment, there were no statistically significant differences in various PF indicators, such as FEV1, FVC, and PEF, between the two groups (all P>0.05). After intervention, all these indicators increased significantly in both groups (all P<0.01), and the levels of all indicators in the observation group were higher than those in the control group (all P<0.01, **Figure 2**).

Comparison of humoral immune indicators

Before treatment, there was no significant difference in IgA, IgG and IgM levels between the two groups (all P>0.05). After intervention, all indicators in both groups showed a significant

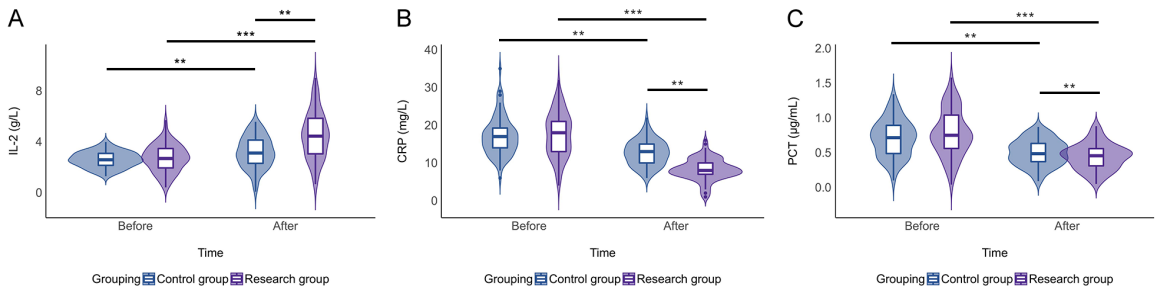

Figure 1. Comparison of inflammatory markers. A: Pre- and post-treatment IL-2. B: Pre- and post-treatment CRP. C: PCT changes pre- and post-treatment. Note: **P<0.01; ***P<0.001. IL, interleukin; CRP, C-reactive protein.

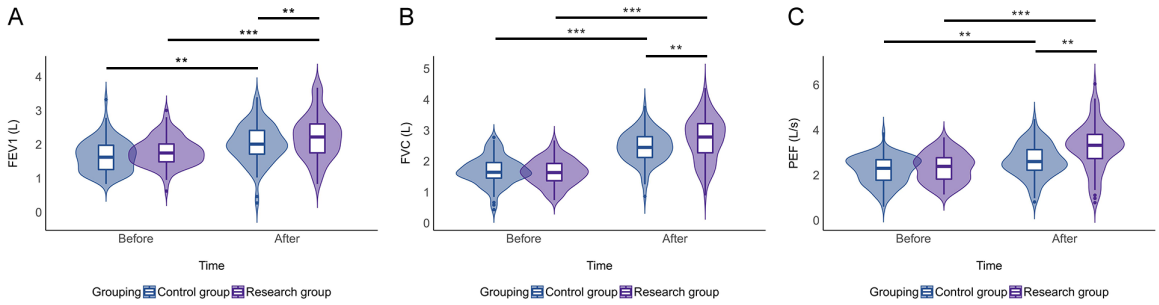

Figure 2. Comparison of pulmonary function evaluation. A: Pre- and post-treatment FEV1. B: FVC pre- and post-treatment. C: Pre- and post-treatment PEF. Note: **P<0.01; ***P<0.001. FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow.

Table 4. Comparison of humoral immune function

Categories	Control group (n=88)	Observation group (n=90)	t	P
IgA (g/L)				
Pre-treatment	0.87±0.42	0.88±0.42	0.159	0.874
Post-treatment	1.15±0.54**	1.61±0.85***	4.299	<0.001
IgG (g/L)				
Pre-treatment	8.20±3.44	8.51±3.72	0.577	0.565
Post-treatment	13.16±5.94***	15.66±5.40***	2.939	0.004
IgM (g/L)				
Pre-treatment	0.97±0.43	1.07±0.47	1.480	0.141
Post-treatment	1.67±0.67**	2.41±1.05***	5.591	<0.001

Note: Ig, immunoglobulin. **P<0.01, ***P<0.001 vs. pre-treatment.

increasing trend to varying degrees (all P<0.01), and the IgA, IgG and IgM levels in the observation group were higher than those in the control group (all P<0.01, **Table 4**).

Comparison of quality of life assessment

Before treatment, the baseline scores of each dimension of the SF-36 were similar between the groups (all P>0.05). After treatment, the scores of each dimension of the SF-36 in both groups were significantly improved compared with those before treatment (all P<0.001), and the improvement was more significant in the observation group (P<0.001, **Table 5**).

Analysis of factors influencing the treatment efficacy of adult patients with SAVP

As shown in **Table 6**, based on the efficacy assessment results, patients were divided into an ineffective group (30 cases) and an effective group (148 cases). Univariate analysis showed that age, diabetes mellitus, coronary

Table 5. Comparison of quality of life

Categories	Control group (n=88)	Observation group (n=90)	t	P
Physical functioning (points)				
Pre-treatment	64.43±6.23	64.86±5.54	0.487	0.627
Post-treatment	69.48±5.94***	79.58±7.68***	9.799	<0.001
Bodily pain (points)				
Pre-treatment	44.47±5.16	45.69±6.06	1.445	0.150
Post-treatment	61.66±6.12***	74.87±7.73***	12.623	<0.001
Role-physical (points)				
Pre-treatment	61.91±4.94	62.79±6.73	0.993	0.322
Post-treatment	71.91±6.69***	77.27±7.55***	5.009	<0.001
Role-emotional (points)				
Pre-treatment	52.52±4.98	53.70±5.56	1.490	0.138
Post-treatment	64.25±5.93***	72.69±7.29***	8.463	<0.001
Social functioning (points)				
Pre-treatment	41.69±4.33	40.80±4.87	1.288	0.200
Post-treatment	62.20±5.60***	72.86±6.80***	11.403	<0.001
Mental health (points)				
Pre-treatment	59.42±5.13	60.62±5.89	1.448	0.149
Post-treatment	70.93±5.89***	78.01±6.76***	7.443	<0.001
Vitality (points)				
Pre-treatment	46.94±4.77	46.88±4.81	0.084	0.934
Post-treatment	62.11±5.41***	72.76±6.17***	12.234	<0.001
General health (points)				
Pre-treatment	52.74±3.81	51.32±6.11	1.856	0.065
Post-treatment	64.27±7.08***	74.19±7.40***	9.135	<0.001

Note: ***P<0.001, compared with before treatment.

heart disease, CRP, IgG, and treatment modality were closely related to the treatment efficacy in adult patients with SAVP patients (all P<0.05), while gender, disease duration, body temperature, BMI, virus type, hypertension, IL-2, PCT, FEV1, FVC, PEF, IgA, and IgM had no statistically significant effect on efficacy (all P>0.05).

Further multivariate analysis showed that age (OR=2.589, 95% CI: 1.017-6.594), coronary heart disease (OR=3.057, 95% CI: 1.104-8.463), CRP (OR=2.892, 95% CI: 1.115-7.498), and treatment modality (OR=3.574, 95% CI: 1.382-9.240) were independent risk factors affecting the treatment efficacy in these patients (all P<0.05), while diabetes or IgG were not independent risk factors (both P>0.05, **Table 7**).

Discussion

In this study, HD-IVIG treatment of adult patients with SAVP can increase the overall effective rate from 75.00% to 91.11%, indicating that its efficacy is superior to conventional treatment alone. IVIG is a blood product isolated and concentrated from the blood of healthy donors, containing more than 95% IgG and a small amount of IgA or IgM. Its mechanism of action against viral pneumonia may be related to the inhibition of excessive activation of natural killer cells and their cytotoxicity [23]. The study reported by Cao et al. [24] showed that starting HD-IVIG treatment 14 days after the onset of severe novel coronavirus disease can reduce the 28-day mortality, suggesting the potential efficacy of this therapy. In our cohort, HD-IVIG exhibited significant clinical advantages in promoting symptom relief, significantly shortening the duration of symptoms such as fever, asthma, rales, and cough.

In the assessment of inflammatory markers, HD-IVIG can effectively regulate serum inflammation levels in adult patients with SAVP, such as upregulating IL-2 expression, and reducing

Table 6. Factors influencing curative effects in adult severe acute viral pneumonia patients by univariate analysis

Categories	Ineffective group (n=30)	Effective group (n=148)	χ^2	P
Age (years)			5.454	0.020
<58 (n=88)	9 (30.00)	79 (53.38)		
≥58 (n=90)	21 (70.00)	69 (46.62)		
Sex			0.020	0.889
Male (n=97)	16 (53.33)	81 (54.73)		
Female (n=81)	14 (46.67)	67 (45.27)		
Disease duration (d)			0.560	0.454
<7 (n=78)	15 (50.00)	63 (42.57)		
≥7 (n=100)	15 (50.00)	85 (57.43)		
Body temperature (°C)			0.444	0.505
<39.2 (n=87)	13 (43.33)	74 (50.00)		
≥39.2 (n=91)	17 (56.67)	74 (50.00)		
Body mass index (kg/m^2)			0.111	0.739
<22.50 (n=88)	14 (46.67)	74 (50.00)		
≥22.50 (n=90)	16 (53.33)	74 (50.00)		
Virus type			0.836	0.841
Influenza virus (n=34)	5 (16.67)	29 (19.59)		
Parainfluenza virus (n=62)	11 (36.67)	51 (34.46)		
Respiratory syncytial virus (n=60)	9 (30.00)	51 (34.46)		
Adenovirus (n=22)	5 (16.67)	17 (11.49)		
Hypertension			0.017	0.896
No (n=93)	16 (53.33)	77 (52.03)		
Yes (n=85)	14 (46.67)	71 (47.97)		
Diabetes			4.201	0.040
No (n=123)	16 (53.33)	107 (72.30)		
Yes (n=55)	14 (46.67)	41 (27.70)		
Coronary heart disease			6.356	0.012
No (n=147)	20 (66.67)	127 (85.81)		
Yes (n=31)	10 (33.33)	21 (14.19)		
IL-2 (g/L)			0.876	0.349
<2.64 (n=87)	17 (56.67)	70 (47.30)		
≥2.64 (n=91)	13 (43.33)	78 (52.70)		
CRP (mg/L)			6.099	0.014
<17.00 (n=84)	8 (26.67)	76 (51.35)		
≥17.00 (n=94)	22 (73.33)	72 (48.65)		
PCT (μg/mL)			1.777	0.183
<0.73 (n=85)	11 (36.67)	74 (50.00)		
≥0.73 (n=93)	19 (63.33)	74 (50.00)		
FEV1 (L)			1.610	0.205
<1.73 (n=88)	18 (60.00)	70 (47.30)		
≥1.73 (n=90)	12 (40.00)	78 (52.70)		
FVC (L)			2.787	0.095
<1.65 (n=88)	19 (63.33)	69 (46.62)		
≥1.65 (n=90)	11 (36.67)	79 (53.38)		

PEF (L/s)			0.160	0.689
<2.35 (n=89)	16 (53.33)	73 (49.32)		
≥2.35 (n=89)	14 (46.67)	75 (50.68)		
IgA (g/L)			1.443	0.230
<0.88 (n=89)	18 (60.00)	71 (47.97)		
≥0.88 (n=89)	12 (40.00)	77 (52.03)		
IgG (g/L)			6.103	0.014
<8.33 (n=88)	21 (70.00)	67 (45.27)		
≥8.33 (n=90)	9 (30.00)	81 (54.73)		
IgM (g/L)			0.538	0.463
<1.01 (n=88)	13 (43.33)	75 (50.68)		
≥1.01 (n=90)	17 (56.67)	73 (49.32)		
Treatment modality			8.242	0.004
High-dose intravenous immunoglobulin therapy (n=90)	8 (26.67)	82 (55.41)		
Conventional therapy (n=88)	22 (73.33)	66 (44.59)		

Note: IL, interleukin; CRP, C-reactive protein; PCT, procalcitonin; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; Ig, immunoglobulin.

Table 7. Efficacy determinants in adults with severe acute viral pneumonia (multivariate analysis)

Categories	B	SE	WALD	P	OR	95% CI
Age (years)	0.951	0.477	3.979	0.046	2.589	1.017-6.594
Diabetes	0.698	0.459	2.313	0.128	2.010	0.817-4.944
Coronary heart disease	1.117	0.520	4.627	0.031	3.057	1.104-8.463
CRP (mg/L)	1.062	0.486	4.770	0.029	2.892	1.115-7.498
IgG (g/L)	-0.883	0.475	3.455	0.063	0.413	0.163-1.049
Treatment modality	1.274	0.485	6.907	0.009	3.574	1.382-9.240

Note: SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval; CRP, C-reactive protein; Ig, immunoglobulin.

CRP and PCT levels. Zhang et al. also had similar research results, confirming that HD-IVIG can significantly improve the overall treatment efficacy of patients with Kawasaki disease, accelerate the relief of clinical symptoms, and inhibit the levels of inflammatory factors such as CRP and IL-6 [25]. HD-IVIG exert anti-inflammatory effects by inhibiting Toll-like receptor expression and blocking the ineffective T cell/B cell co-stimulation pathway [26]. It can also achieve anti-inflammatory effects by blocking leukocyte surface adhesion molecules [27]. It has also been pointed out that the large amount of IgG contained in HD-IVIG can regulate the inflammatory balance by interacting with the fragment crystallizable region, Fc gamma receptors, and neonatal Fc receptor [28]. In terms of PF function assessment, adult patients with SAVP treated with HD-IVIG revealed more significant improvement in FEV1, FVC, and PEF compared to the control group. A rat experiment on acute lung injury showed that HD-IVIG can improve PF by inhibiting lung inflammation and downregulating transforming growth factor-β (TGF-β) expression, which to some extent explains the protective effect of this therapy on PF among adult patients with SAVP [29].

In the assessment of humoral immunity-related indicators, adult patients with SAVP treated with HD-IVIG therapy showed more significant improvement in humoral immune function. Its mechanism of action may be as follows. HD-IVIG neutralizes proliferation-inducing ligand, B cell activating factor, apoptosis-associated antigen Fas, and regulates the Toll-like receptor 9 signaling cascade, thereby inhibiting B cell activation and regulating the body's humoral immune status [30]. From the perspective of quality of life, HD-IVIG treatment can comprehensively improve the quality of life of adult patients with SAVP. Shao et al. [31] also reported that early intervention with HD-IVIG

within 7 days of admission improved the 60-day clinical prognosis of patients with severe COVID-19. This study further determined that the independent influencing factors of efficacy in adult patients with SAVP were age, coronary heart disease, CRP, and treatment modality. Specifically, clinical factors such as age ≥58 years, coronary heart disease, CRP≥17.00 mg/L, and conventional treatment significantly increase the risk of treatment failure in such patients; while the presence of diabetes did not show independent statistical significance. This might because the chronic inflammation and microvascular complications induced by diabetes in severe acute conditions are highly heterogeneous, weakening its risk effect. In multivariate analysis, there was no statistical difference in endogenous IgG, mainly due to the large fluctuation range of its level caused by leakage and consumption interference in the acute phase. HD-IVIG can directly exert anti-inflammatory effects by neutralizing antigens and regulating Fc receptors, thus to some extent getting rid of the dependence on the body's own endogenous IgG. Furthermore, an antifungal immune-related study showed that using specific vaccines to activate the Dectin-1 signaling pathway can induce the production of high-affinity protective antibodies, which have a strong defensive effect against fungal infections [32]. This finding underscored that the protective effect of antibodies depends not only on the total amount, but more importantly on antigen specificity and functional affinity. Therefore, endogenous IgG levels were not significantly correlated with treatment efficacy. This may be because HD-IVIG can supplement patients with a large amount of functionally defined, broad-spectrum antiviral IgG, compensating for deficiencies in the patient's humoral immunity. Thus, the levels of IgA, IgM, and IgG were not significantly associated with treatment efficacy, suggesting that the overall humoral immune level in adult patients with SAVP is not an independent influencing factor on treatment outcomes.

This study still has several limitations and requires further improvement. First, the analysis of efficacy based on chest imaging did not include quantitative indicators such as changes in lesion volume on CT scans. Future studies should use high-resolution CT to quantitatively assess lung lesions to minimize subjective bias. Second, core immune cell subset indicators such as the CD4+/CD8+ T cell ratio and the TH1/TH2 cytokine balance were not detected. These need to be supplemented in future studies to comprehensively evaluate the regulatory effect of HD-IVIG therapy on cellular immune function. Third, the study lacks evaluation of immune cell subsets and key pathway molecules (such as Toll-like receptor and Fcγ receptor expression). Fourth, the direct correlation between changes in key cytokines such as IL-2 and viral clearance was not analyzed; prospective studies combining these tests with functional experiments are needed to provide more direct molecular evidence for mechanistic research. Finally, viral load and key inflammatory pathway molecules (nuclear factor κB, tumor necrosis factor-α, etc.) before and after treatment were not measured; supplementing this data would help to preliminarily explore the potential synergistic mechanism between anti-inflammatory and antiviral effects of HD-IVIG, distinguishing its direct anti-inflammatory effect from its indirect anti-inflammatory effect achieved through viral clearance.

Based on the latest advances in basic immunology, future prospective studies should focus on exploring the specific molecular pathways behind the therapeutic effects observed in this study. For instance, studies have confirmed that the stability of UFL1-mediated interferon gene-stimulating protein (STING) is a key mechanism for regulating antiviral immune responses [33]; caspase-8 has been identified as a key molecular switch for panapoptosis (pyroptosis, apoptosis, programmed necrosis) and plays a central role in the pathogenesis of various inflammatory diseases [34]. Therefore, in addition to the conventional inflammatory factors detected in this study, further research is needed on key molecules in the STING/TBK1/IRF3 pathway and the caspase-8-mediated cell death pathway. Elucidating the mechanisms of action of these pathways will help to analyze the mechanism of HD-IVIG in regulating inflammation and immune responses at a more refined molecular level, and is also expected to discover new targets for optimizing clinical treatment of severe viral pneumonia.

In summary, compared with conventional treatment alone, HD-IVIG therapy for adult patients with SAVP has more prominent clinical

advantages, significantly improving treatment efficacy, alleviating clinical symptoms, inhibiting serum inflammatory response, improving humoral immune function, and improving patients' quality of life. Meanwhile, adult patients with SAVP who are ≥58 years, have coronary heart disease, have a CRP level ≥17.00 mg/L, or are receiving routine treatment have a significantly increased risk of treatment failure.

Disclosure of conflict of interest

None.

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