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# Human Immunoglobulin Therapy for End-Stage Liver Disease Complicated with Infection: Efficacy and Safety Analysis

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**Background: The incidence of liver diseases is high in China. Although the concept of end-stage liver disease (ESLD) has been proposed, it has not been strictly defined. Infection is a common complication of ESLD. Immunoglobulin has been used in the treatment of related diseases. To explore the efficacy and safety of human immunoglobulin (HIG) therapy for end-stage liver disease (ESLD) complicated with infection.**

**Materials and Methods: A retrospective analysis was conducted on 101 patients with ESLD complicated with infection admitted to the China Coast Guard Hospital of the People's Armed Police Force from May 2019 to May 2023, including 50 patients in the control group who were treated with conventional comprehensive treatment and 51 cases in the observation group receiving HIG in addition to conventional comprehensive treatment. The treatment efficacy, hepatic function parameters, immune function indices, complications, secondary infection rate, as well as mortality rate before and after treatment, were compared.**

**Results: Higher treatment efficacy was found in the observation group compared to the control group ($p < 0.05$). After treatment, a significant improvement was observed in the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBiL), and immunoglobulin (Ig) A/G/M in both groups, especially in the observation group ($p < 0.05$). There were no significant inter-group differences in the incidence of upper gastrointestinal bleeding and electrolyte disturbances ($p > 0.05$), but the incidences of hepatic encephalopathy and hepatorenal syndrome were lower in the observation group ($p < 0.05$). The observation group also exhibited lower secondary infection and mortality rates than the control group ($p < 0.05$).**

**Conclusions: The HIG therapy in patients with ESLD complicated with infection can effectively enhance therapeutic efficacy, improve hepatic and immune functions, and reduce the risk of complications and secondary infection, which is worth popularizing in clinical practice.**

**Keywords:** human immunoglobulin; end-stage liver disease; infection; efficacy; safety

## Introduction

In recent years, the incidence of hepatopathy in China has been at a high level, which seriously affects people's health and quality of life [1]. The concept of end-stage liver disease (ESLD) was proposed in the 1980s and is still not strictly defined [2]. Based on liver morphology and function, ESLD refers to the late stage of liver disease caused by various types of chronic liver damage, mainly characterized by the inability of hepatic function to meet the physiological needs of the human body; ESLD represents the end-stage of various chronic liver diseases like acute-on-chronic liver failure, acute decompensation of cirrhosis, chronic hepatic failure, and hepatocellular carcinoma [3,4]. Infection can induce or exacerbate ESLD and is one of the most common complications of ESLD, which can severely impair hepatic function and even lead to death if not treated promptly [5].

The key to treating ESLD lies in early control of infection and inhibition of further deterioration. At present, immunoglobulins (Igs) have been widely used in the treatment of infectious and autoimmune diseases [6]. Human immunoglobulin (HIG) is a biopharmaceutical. Besides its own anti-inflammatory effect, it can also regulate immune function, inhibit the production of inflammatory cytokines, neutralize cytotoxins, and reduce the damage of complement-mediated tissues and inflammation, thus improving patients' autoimmunity and helping restore hepatic function [7,8]. Previous study has found that HIG plays a certain role in preventing and combating infections, and its combination with antibiotics can improve the effectiveness against viral and bacterial infections [9].

We aimed to further analyze the efficacy and safety of HIG in treating ESLD patients with infection, and to provide more clinical evidence for the application of HIG in such a patient population.

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## Materials and Methods

### *Clinical Data*

This retrospective analysis included 101 ESLD patients with infection, admitted to the China Coast Guard Hospital of the People's Armed Police Force from May 2019 to May 2023, who were divided into a control group and an observation group based on the different treatment they received. The control group consisted of 50 patients treated with routine comprehensive treatment, whereas the observation group comprised 51 patients who received HIG in addition to routine comprehensive treatment. Inclusion criteria: Patients who (1) met the diagnostic criteria for ESLD complicated with infection [10], with (2) intact case data. Exclusion criteria: Patients with (1) malignant tumors, (2) other serious organ diseases, or (3) communication or mental disorders. We collected clinical data of patients, including age, gender, body mass index (BMI), smoking and drinking status, and other general demographic information, as well as the type of infection.

### *Treatment and Care*

Patients in both groups were given comprehensive treatment, with the goal of controlling infection, reducing hepatocyte necrosis, and preventing and treating various complications. In addition, cefotaxime sodium (SFDA Approval No. H20093075, Shandong Haibang Pharmaceutical Co., Ltd., Zibo, China) was given for anti-infection treatment, 1–2 g/time, 3 times/day, for 7 days. Other supportive therapies and corresponding treatment for complications were given. The observation group was additionally treated with intramuscular injection of HIG (Batch No.: 20181005, Zhengzhou RAAS Blood Products Co., Ltd., Zhengzhou, China) once a day for one month. During the treatment process, all patients were given corresponding care, including disease monitoring, knowledge education, nutritional assessment, and guidance. Attention was also paid to changes in the patient's dietary structure, mental symptoms, and vital signs. In addition, the ward was disinfected on a daily basis.

### *Endpoints*

(1) Treatment efficacy was evaluated as follows [11]: ① Significant effectiveness: Signs and symptoms were obviously improved, the neutrophil and peripheral leukocyte counts reached normal values, and ascites was significantly reduced or even disappeared. ② Effectiveness: Signs and symptoms were improved, the neutrophil and peripheral leukocyte counts were close to normal, and ascites was significantly reduced. ③ Ineffectiveness: Signs and symptoms were not effectively controlled or even aggravated, the volume of ascites increased, and the neutrophil and peripheral leukocyte counts decreased. Total effective rate = (significant effectiveness cases+effectiveness cases)/total cases × 100%. (2) We used an automatic analyzer (Olympus AU-800, Olympus Corporation, Tokyo, Japan) to detect hepatic function parameters before and after treatment, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (TBiL). (3) Before and after treatment, the immune function indices (IgA/G/M) were detected. (4) The complications of the two groups were recorded, including upper gastrointestinal bleeding, hepatic encephalopathy (HE), hepatorenal syndrome (HRS), and electrolyte disturbances. (5) Post-treatment, all patients received regular outpatient follow-up, and the rates of secondary infection and clinical mortality within a six-month period were compared between the two groups.

### *Statistical Methods*

Statistical analysis of the data was conducted using SPSS 20.0 (version 20.0, IBM Corp., Armonk, NY, USA). The mean ± standard deviation was used to statistically describe continuous variables, and inter- and intra-group comparisons were conducted using *t*-tests and paired *t*-tests, respectively. *Chi*-square tests were used to analyze categorical variables. $p$ values $< 0.05$ were considered statistically significant.

## Results

### *General Data*

A total of 101 patients were included in this study, with 51 in the observation group, including 31 males and 20 females; 22 patients aged ≤56 years and 29 patients aged >56 years; 27 patients had a BMI ≤23 and 24 patients had a BMI >23; there were 40 patients with a smoking history and 11 patients without; there were 41 patients with an alcohol history and 10 patients without; there were 25 patients with abdominal infections, 15 patients with lung infections, and 11 patients with infections in other sites. In the control group, there were 50 patients, including 27 males and 23 females; 22 patients aged ≤56 years and 28 patients aged >56 years; 26 patients had a BMI ≤23 and 24 patients had a BMI >23; there were 34 patients with a smoking history and 16 patients without; there were 39 patients with an alcohol history and 11 patients without; there were 24 patients with abdominal infections, 14 patients with lung infections, and 12 patients with infections in other sites. The observation and control groups were comparable in general data like gender, age, and BMI ($p > 0.05$; Table 1).

### *Comparison of Therapeutic Efficacy*

We conducted a comparative analysis of clinical efficacy. The numbers of significant effectiveness, effectiveness, and ineffectiveness cases in the observation group were 25, 18, and 8, respectively, with a total effective rate of 84.31%, compared with 16, 15, and 19 cases in the control group with a total effective rate of 62.00%. The total effective rate was significantly higher in the observation group than the control group ($p < 0.05$; Table 2).

**Table 1. General information of the two groups.**

| Variables | Observation group (n = 51) | Control group (n = 50) | $\chi^2$ | $p$ |
|---|---|---|---|---|
| Sex | | | 0.475 | 0.491 |
| Male | 31 (60.78) | 27 (54.00) | | |
| Female | 20 (39.22) | 23 (46.00) | | |
| Age (years) | | | 0.008 | 0.930 |
| ≤56 | 22 (43.14) | 22 (44.00) | | |
| >56 | 29 (56.86) | 28 (56.00) | | |
| BMI (kg/m$^2$) | | | 0.009 | 0.925 |
| ≤23 | 27 (52.94) | 26 (52.00) | | |
| >23 | 24 (47.06) | 24 (48.00) | | |
| History of smoking | | | 1.403 | 0.236 |
| With | 40 (78.43) | 34 (68.00) | | |
| Without | 11 (21.57) | 16 (32.00) | | |
| History of drinking | | | 0.088 | 0.767 |
| With | 41 (80.39) | 39 (78.00) | | |
| Without | 10 (19.61) | 11 (22.00) | | |
| Infection type | | | 0.088 | 0.957 |
| Abdominal infection | 25 (49.02) | 24 (48.00) | | |
| Pulmonary infection | 15 (29.41) | 14 (28.00) | | |
| Other infections | 11 (21.57) | 12 (24.00) | | |

BMI, body mass index.

**Table 2. Comparison of clinical efficacy of the two groups.**

| Groups | Observation group (n = 51) | Control group (n = 50) | $\chi^2$ | $p$ |
|---|---|---|---|---|
| Significant effectiveness | 25 (49.02) | 16 (32.00) | - | - |
| Effectiveness | 18 (35.29) | 15 (30.00) | - | - |
| Ineffectiveness | 8 (15.69) | 19 (38.00) | - | - |
| Total effective rate | 43 (84.31) | 31 (62.00) | 6.418 | 0.011 |

### *Comparison of Hepatic Function Parameters Between the Two Groups*

We tested and compared the hepatic function parameters before and after treatment. The two groups showed similar ALT, AST, and TBiL before treatment ($p > 0.05$). After treatment, the ALT, AST, and TBiL levels of both groups were significantly reduced ($p < 0.05$), with even lower levels in the observation group ($p < 0.05$; Fig. 1).

### *Comparison of Immune Function between the Two Groups before and after Treatment*

The two groups were not significantly different in pre-treatment levels of IgA, IgG, and IgM ($p > 0.05$). Both groups exhibited an increase in IgA, IgG and IgM levels after treatment ($p < 0.05$), particularly in the observation group ($p < 0.05$; Fig. 2).

### *Complications in the Two Groups*

Before the treatment, in the observation group and the control group, there were 3 and 2 cases of upper gastrointestinal bleeding, 0 and 1 case of hepatic encephalopathy, 1 and 2 cases of hepatorenal syndrome, and 14 and 12 cases of electrolyte disturbances, respectively. There were no statistically significant differences in the previous occurrences of complications between the two groups. During the treatment, among the 51 patients in the observation group, there were 4 cases of upper gastrointestinal bleeding, 6 cases of HE, 5 cases of HRS, and 29 cases of electrolyte disturbances, whereas the corresponding cases in the control group (50 patients) were 7, 19, 14, and 35. The incidences of HE and HRS in the observation group were 11.76% and 9.80%, respectively; these were significantly lower compared with those in the control group (38.00% and 28.00%) ($p = 0.003$ and 0.019, respectively); no significant inter-group differences were found in the incidence of other complications ($p > 0.05$; Table 3).

### *Comparison of Secondary Infection and Mortality Rates*

The number of patients in the observation group who developed secondary infections during hospitalization and the number of deaths from automatic discharge were 3 and 14, respectively, compared to 10 and 26 in the control group. The observation group had significantly lower secondary infection and mortality rates than the control group ($p < 0.05$; Table 4).

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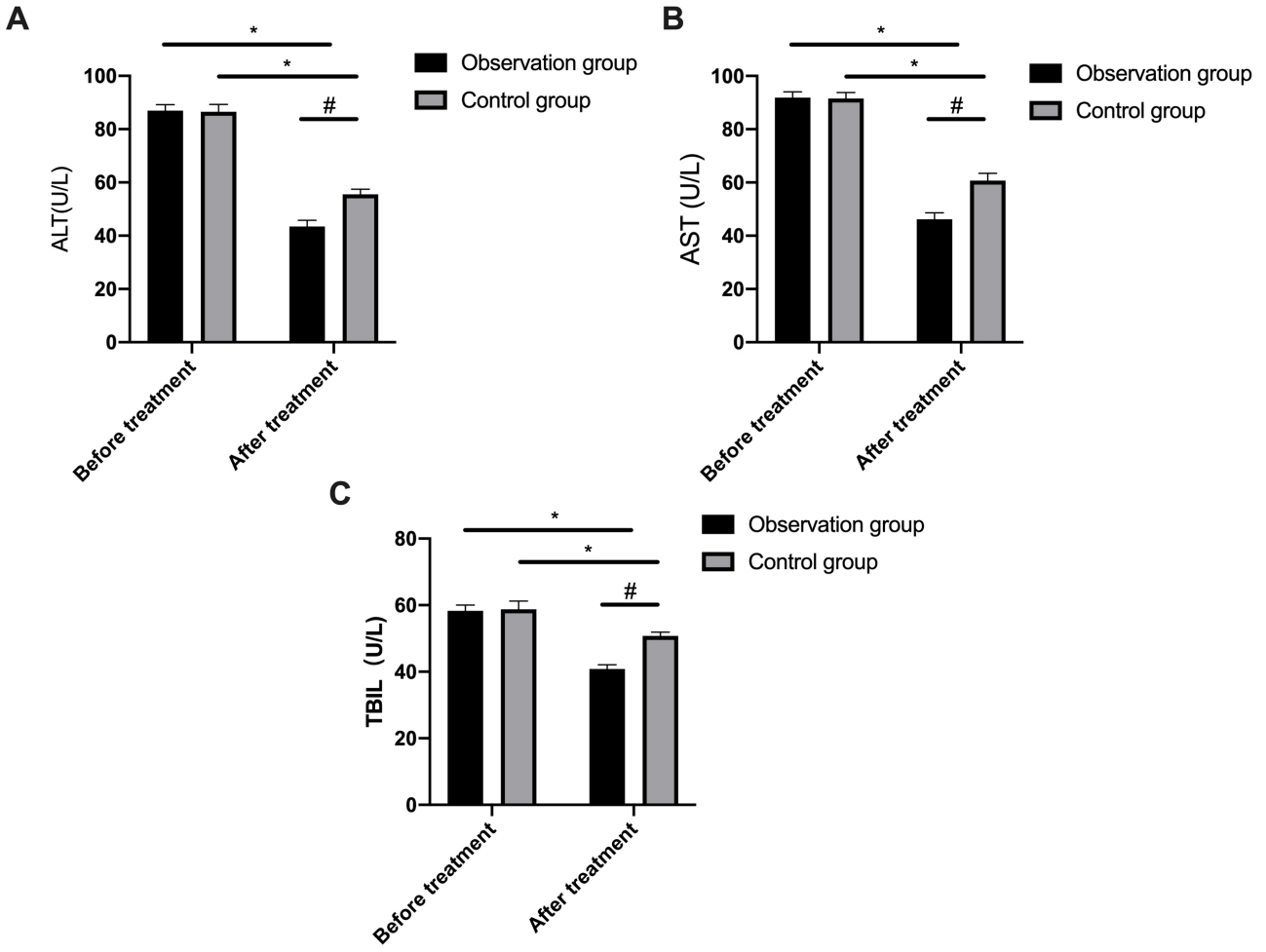


**Fig. 1. Comparison of hepatic function parameters between the two groups before and after treatment.** (A) Comparison of ALT before and after treatment. (B) Comparison of AST before and after treatment. (C) Comparison of TBiL before and after treatment. * denotes $p < 0.05$ in the intra-group comparison before and after treatment, and # denotes $p < 0.05$ in the inter-group comparison after treatment. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBiL, total bilirubin.

**Table 3. Complications in the two groups.**

| Complication | Observation group (n = 51) | Control group (n = 50) | $\chi^2$ | $p$ |
|---|---|---|---|---|
| Upper gastrointestinal bleeding | 4 (7.84) | 7 (14.00) | 0.986 | 0.321 |
| Hepatic encephalopathy | 6 (11.76) | 19 (38.00) | 8.955 | 0.003 |
| Hepatorenal syndrome | 5 (9.80) | 14 (28.00) | 5.473 | 0.019 |
| Electrolyte disturbances | 29 (56.86) | 35 (70.00) | 1.877 | 0.171 |

**Table 4. Comparison of secondary infections and mortality.**

| Categories | Observation group (n = 51) | Control group (n = 50) | $\chi^2$ | $p$ |
|---|---|---|---|---|
| Secondary infection | 3 (5.9) | 10 (20.00) | 4.487 | 0.034 |
| Mortality | 14 (27.45) | 26 (52.00) | 6.361 | 0.012 |

## Discussion

Infection is one of the most common complications of ESLD and a major contributor to liver failure and ultimately multi-organ failure [12]. Early control of infection is the key to achieving efficacy due to the fact that patients have extremely low immune defenses against infection and are prone to various infections that aggravate liver failure, leading to exacerbation of illness and even death [13].

Igs are mainly composed of IgG and its subgroup molecules. HIG is a biopharmaceutical that has been widely used to treat infectious and autoimmune diseases, with

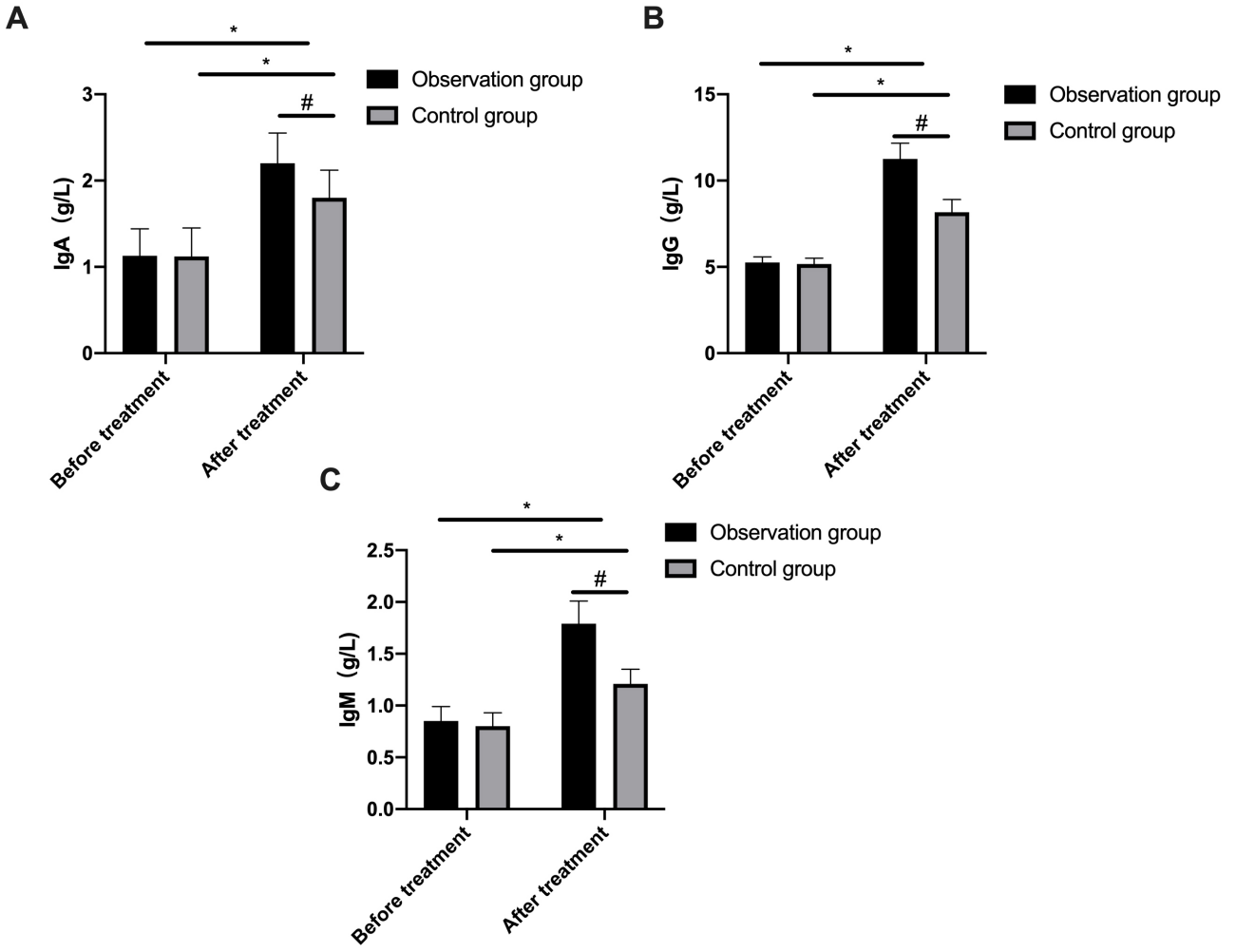


**Fig. 2. Comparison of immune function between the two groups before and after treatment.** (A) Comparison of IgA before and after treatment. (B) Comparison of IgG before and after treatment. (C) Comparison of IgM before and after treatment. * denotes $p < 0.05$ in the intra-group comparison before and after treatment, and # denotes $p < 0.05$ in the inter-group comparison after treatment. Ig, immunoglobulin.

anti-inflammatory and immunomodulatory actions [14]. Herein, we observed statistically higher overall efficacy in the observation group versus the control group, which suggests that the treatment of ESLD complicated with infection with HIG can significantly improve the treatment outcomes of patients. In addition, we compared hepatic function indices before and after treatment. Although both groups exhibited an improvement in hepatic function indices after treatment, the hepatic function enhancement was greater in the observation group, indicating that HIG can effectively improve the hepatic function of ESLD patients with infection. This is because the liver, as a critical organ for body's immune function, can lead to a decline in immune function when damaged. HIG has a high Ig molecule content, which has the effects of enhancing immunity, resisting bacteria, and diminishing inflammation. Clinically, intravenous injection of HIG is used to maintain the homeostasis of T lymphocyte subsets and enhance immunity, thus promoting growth factor secretion and accelerating hepatic function recovery [15,16]. Comparison of immune function indices revealed that immune function in the observation group recovered better than the control group. Previous literature has also found that HIG regulates the body's immune function, thereby increasing the secretion of growth factors, accelerating liver repair, and improving hepatic function [17], consistent with our observations.

ESLD patients have disordered cellular immune regulation and low non-specific immune function, such as decreased serum opsonin activity, complement component defects, and neutrophil function inhibition [18]. Endotoxins are an important inducement for ESLD to develop into liver failure. Endotoxins have a high affinity with Kupffer cells, prompting their release of inflammatory factors and forming an inflammation cascade and a vicious circle. In patients with ESLD, hepatic Kupffer cells in the liver are damaged and their phagocytic function is significantly reduced,

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in addition to hepatocyte necrosis and loss-of-function. As a result, bacteria from the intestine cannot be eliminated, and massive endotoxins from the portal vein enter the systemic circulation without detoxification, predisposing patients to endogenous infection and endotoxemia [19,20]. Endotoxins can also induce systemic metabolic and hemodynamic changes, participate in the onset and progression of a variety of complications, and induce HE, upper gastrointestinal bleeding, HRS, etc., further aggravating liver failure [21]. Therefore, in the treatment of cirrhosis complicated by infection, rapid and effective control of infection and reduction of complications are essential to improve patient survival and to curb the further development of liver failure. In this study, a notably lower incidence of HE and HRS was identified in the observation group compared to the control group, which shows that the use of HIG can also significantly reduce complications in ESLD patients with infection. A study [22] pointed out that the enhancement of immune function can increase the phagocytic function of Kupffer cells, thereby reducing endotoxins in the body, and ultimately reducing the occurrence of various complications like HE and HRS, which supports our findings. Finally, we compared the incidence of secondary infections and mortality. The results showed markedly lower secondary infection and mortality rates in the observation group than the control group. The reason is that Igs can provide the body with corresponding antibodies, which can act on invading pathogens and reduce the occurrence of secondary infections [23].

This study has some potential limitations, including constraints related to the retrospective design, potential sample selection bias, and the possibility of unaccounted confounding factors. Additionally, the short-term follow-up period and single-center design might affect the generalizability of the results. In the future, it is advisable to use larger sample sizes and multi-center designs, and to incorporate a more comprehensive range of potential factors to more comprehensively validate the efficacy and safety of HIG treatment in ESLD complicated with infection.

## Conclusions

Collectively, the HIG therapy in patients with ESLD complicated with infection can effectively improve treatment efficacy, enhance patients' liver and immune functions, and reduce the risk of complications and secondary infections, which deserves popularizing in clinical practice.

## Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the corresponding author if needed.

## Author Contributions

XGW, LHM, and DHC designed the research study. XGW and LHM performed the research and collected the data. XGW and DHC analyzed the data. XGW drafted this manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

All patients signed informed consent forms, and this study obtained approval from the Ethics Committee (WL2024-0402) and complied with the Declaration of Helsinki.

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## Conflict of Interest

The authors declare no conflict of interest.

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