

Improvement of neurological function, immune function and inflammatory response in patients with severe cerebral hemorrhage by probiotic low-fat enteral nutrition

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Abstract: After the occurrence of cerebral hemorrhage (CH), patients generally develop neurological disorders and dysphagia, requiring enteral nutrition support. In this study, the research team explored the impact of predictive management-assisted probiotic low-fat nutritional supplements on CH patients. A total of 114 CH patients admitted to our hospital from August 2022 to June 2024 were selected as the study subjects. They were divided into a control group (n=57) using low-fat nutritional supplements and an experimental group (n=57) using probiotic combined with low-fat nutritional supplements. After treatment, the NIHSS of the experimental group was found to be lower than that of the control group, while the ADL was higher than that of the control group ($p < 0.05$). In addition, glutamate (Glu), aspartic acid (Asp), CD8+ and inflammatory factors were lower in the experimental group than in the control group after treatment, whereas glycine (Gly), gamma-aminobutyric acid (GABA), cluster of differentiation (CD)3+, CD4+, CD4+/CD8+ were higher than in the control group ($P < 0.05$). In conclusion, probiotic low-fat nutrition combined with predictive management significantly improves neurological function.

Keywords: Cerebral hemorrhage; Enteral nutrition support; Inflammatory factors; Low-fat enteral nutrition; Neurotransmitters; T lymphocyte subsets

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INTRODUCTION

Cerebral hemorrhage (CH) is a primary non-traumatic intracerebral hemorrhage commonly seen in patients with hypertension complicated with arteriosclerosis (Magid-Bernstein *et al.*, 2022). According to the survey by the World Health Organization, the annual incidence of CH is about 60-80/100,000, accounting for 20-30% of all acute cerebrovascular diseases (Montano *et al.*, 2021). The mortality rate of CH in the acute phase is as high as 30-40%, which is the highest among acute cerebrovascular diseases, with over 60% of patients developing irreversible nerve damage, significantly reducing their quality of life (Al-Kawaz *et al.*, 2020). Intracranial hematoma removal is the most direct treatment for CH, but patients are at high risk of postoperative complications such as bleeding and infection due to the special surgical site (Wan *et al.*, 2023). Clinically, more individualized management strategies are required for CH patients to improve treatment safety and patient prognosis (Kase & Hanley, 2021). Disturbance of consciousness and dysphagia are common in CH, warranting enteral nutrition support in clinical treatment to maintain life activities (Kang *et al.*, 2023). Recently, it has been confirmed that gut microbiota is closely related to CH inflammation and early hematoma expansion and improving gut microbiota may help to improve the prognosis of CH patients (Jiang *et al.*, 2025). Similarly, the

meta-analysis also confirmed that probiotics can enhance the function of the human vagus nerve (Morkl *et al.*, 2025), which emphasized the important role of probiotics in the rehabilitation treatment of CH. In this regard, we propose to use a new enteral nutrient-probiotic low-fat nutritional supplement, which may be more conducive to the rehabilitation of CH patients.

Probiotics are an excellent adjunctive therapeutic drug, which not only can regulate neurological disorders through the gut-brain axis (probiotics regulate neurotransmitters through the vagus nerve, short-chain fatty acids and immune pathways), improve neuronal survival and reduce neuronal decline, but also have anti-inflammatory effects, which can inhibit inflammatory responses and prevent inflammation from occurring in the brain (Naomi *et al.*, 2021). In an animal experiment by Cho H and others, they found that probiotics can promote the normal operation of the intestinal closure function, which can prevent bacteria or viruses from invading the blood circulation and help to reduce the damage to the brain (Cho *et al.*, 2023). In other words, probiotics also have great potential in the treatment of CH, but there are no studies yet to confirm this idea.

Predictive management is a prospective nursing model based on patients' risk factors and personalized intervention plans are formulated by a multidisciplinary

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team. It covers the prevention of respiratory, urinary, thrombosis, constipation and other complications (such as regular turn and pat on the back, early extubation, passive limb movement, etc.) (Blackman & Mudd, 2023). This management model has achieved remarkable application results in patients with chronic obstructive pulmonary disease and pressure sores (Chen *et al.*, 2025; Indraswari *et al.*, 2024), but its influence on CH remains unclear.

Therefore, in this study, we observed the effect of predictive management-assisted probiotic low-fat nutritional supplements on the neurological function, immune function and inflammatory response of CH patients, so as to provide more reliable reference and guidance for future clinical treatment of CH.

MATERIALS AND METHODS

Study population

G-Power software was used to estimate the sample size of the study. Based on $\alpha=0.05$ and $\beta=0.2$, it was estimated that 100 cases were needed and the dropout rate was extended to 114 cases. The study population was 114 patients with CH (August 2022 to June 2024), all of whom were given enteral nutrition support and cared for by the predictive management and nursing model, with obvious dysphagia. They were divided into a control group ($n=57$) using low-fat nutritional supplements and an experimental group ($n=57$) using probiotics combined with low-fat nutritional supplements [using block random method (block size=4)]. All subjects were unaware of the group assignments. In the control group, there were 37 males and 20 females, with a mean age of (64.65 ± 7.15) years and a mean body mass index of (23.11 ± 2.96) kg/m²; in the experimental group, there were 41 males and 16 females, with a mean age of (64.33 ± 6.47) years and a mean body mass index of (22.29 ± 1.52) kg/m².

Inclusion criteria: The patient was diagnosed with new-onset CH by craniocerebral computerized tomography and magnetic resonance imaging, with dysphagia, complete clinical data and no obstacles in cognition and communication and received intracranial hematoma trepanation and drainage in our hospital. **Exclusion criteria:** Previous history of craniocerebral surgery and venous thrombosis; mental disorders or referrals; other acute or chronic infection symptoms; seriously damaged or impaired heart, liver, kidney and other important organs; progressive stroke; gastrointestinal bleeding and intestinal obstruction; allergies to nutrients; previous history of cognitive impairment or irritable bowel syndrome.

Methods

The same surgical team in our hospital completed trepanation and drainage of intracranial hematoma. After the procedure, conventional treatments such as supplementing cranial nerve nutrition, correcting water and electrolyte imbalances and oxygen inhalation were given.

Predictive management: A predictive risk management team composed of neurologists, head nurses, responsible nurses and nutritionists was established. All members of the team fully understood the contents and characteristics of CH, treatment nursing, etc., collected relevant information through evidence-based access and learned and mastered the key nursing points and emergency treatment methods of CH. According to the characteristics of CH patients and the actual situation in our hospital, a predictive risk care scheme was discussed and formulated, with measures taken from the following perspectives: (1) *Respiratory risk management.* To maintain the smooth airway of the patient, the nursing staff helped the patient to remove oral secretions and food residues in time and regularly assisted in turning over and patting the back. Atomized sputum suction was used when necessary if the sputum was sticky and difficult to cough up. (2) *Urinary system risk management.*

Attention was paid to the patient's indications for extubation to shorten the duration of catheterization as far as possible. Besides, the cleanliness of the bladder and perineum was strengthened and the signs of infection were regularly evaluated. If there was any abnormality, the doctor was immediately reported for symptomatic treatment. (3) *Thrombosis risk management.* In the acute stage of the disease, the nursing staff told the patient to maintain absolute bed rest and insisted on helping the patient to do passive limb activities, passive ankle joint extension and flexion exercises, limb massage and so on every day.

After the patient regained consciousness, the patient was encouraged to increase the range of activity. (4) *Constipation risk management:* The viscosity of food was adjusted. For postoperative coma patients, adequate nutrients and water were given and vegetables and fruits were stirred, homogenized and injected into the patient's nasogastric tube to stimulate gastrointestinal peristalsis and soften feces. For those who were awake after surgery, water was replenished as soon as possible. In addition, patients were given guidance on defecation, instructing them to take deep breaths, exert force on the lower abdomen and stimulate the rectum by pressing on the abdomen with their hands to induce bowel movements, avoiding forced defecation. (5) *Language rehabilitation risk management:* A vocabulary list presented in the form of words and pictures, such as washing clothes, drying quilts, cooking, etc., with bright colors, complex vision and consistent appearances, was made for patients to guide them to carry out situational imagination.

Combined with their interests and hobbies, patients were given visual stimulation of pictures and guided to perform oral output. During this period, timely encouragement was given to strengthen their confidence in recovery. (6) *Psychological rehabilitation risk management:* Patients

were fully understood and supported. During communication with patients, nurses maintained a smile on their faces, a gentle tone and a proactive attitude. In response to the questions raised by patients and their families, nurses patiently made relevant explanations to eliminate their doubts. Meanwhile, past successful recovery cases were listed to enhance patients' confidence in recovery and guide them to actively cooperate.

Furthermore, the ideological work of the patient's family members was done well, enabling them to understand the patient's specific condition, psychological state, etc. Family members were also informed of the importance of support and encouraged to give care and support to patients. On the second day after admission, a clinical pathway for enteral nutrition was opened as soon as possible according to the patient's condition and intestinal function. Enteral nutrition via a nasogastric feeding tube (500 mL on the first day, with a 500 mL increment every 2 days) was given in a slow to rapid and small to adequate amount manner. The nutritional supplement of the control group was composed of 90g of low-fat nutrient powder (Xi'an Libang Clinical Nutrition Corporation Ltd.) + glutamine + cellulose. In the experimental group, 10g of probiotic compound powder (Shandong Junyi Bioengineering Co., Ltd.) was added to the control group (bifidobacterium longum BB536, Lactobacillus rhamnosus GG, viable bacteria $\geq 1 \times 10^9$ CFU/g).

Endpoints

Patients' neurological function was assessed before and after treatment using the National Institute of Health Stroke Scale (NIHSS) (Alemseged *et al.*, 2022) and the Activity of Daily Living (ADL) scale (Zhang *et al.*, 2021). A higher NIHSS score suggests a more serious nerve defect and a higher ADL score indicates a better self-care ability. Fasting venous blood of 3mL was collected before and after treatment and divided into two portions. One portion was tested for T-lymphocyte subsets [cluster of differentiation (CD)3+, CD4+, and CD8+], which were measured by flow cytometry and CD4+/CD8+ were calculated. The other copy of serum taken after centrifugation (3000 rpm/min) for 10 min was tested for aspartic acid (Asp) using colorimetric assay and glutamate (Glu), glycine (Gly), gamma-aminobutyric acid (GABA), Tumor necrosis factor-alpha (TNF- α), Interleukin-6 (IL-6) and High mobility group box-1 protein (HMGB1).

Statistical analysis

Statistical analyses were performed using SPSS2 4.0, significance level $\alpha=0.05$, 95% confidence intervals were calculated. The chi-square test was used to compare count data [n (%)]. Measurement data described in the form of ($\bar{x} \pm s$), an independent sample t-test was used for inter-group comparison and a paired t-test was used for intra-group comparison. A significance level of $P < 0.05$ was used in all analyses.

RESULTS

Comparison of neurological function

The results of NIHSS and ADL scores showed that the two scale scores elevated in both groups after treatment ($P < 0.05$), but with no statistical inter-group difference ($P > 0.05$), indicating no significant difference in neurological function between the two groups (Fig. 1).

Changes in neurotransmitters

After treatment, Glu and Asp were lower in both groups and the experimental group was lower than the control group ($P < 0.05$); while Gly and GABA were higher and the experimental group was higher than the control group ($P < 0.05$), which indicated that although the neurotransmitters of the two groups of patients were improved after treatment, the experimental group was better than the control group (Fig. 2).

Changes in T lymphocyte subsets

After treatment, CD3+, CD4+ and CD4+/CD8+ in both groups increased, with more significant increases in the experimental group compared with the control group; while CD8+ decreased and was even lower in the experimental group ($P < 0.05$). It is suggested that the immune function of the experimental group was better after treatment (Fig. 3).

Changes in inflammatory factors

Before treatment, there was no difference in the comparison of inflammatory factors between the two groups ($P > 0.05$). After treatment, TNF- α , IL-6 and HMGB1 were lower in both groups and the experimental group was even lower than the control group ($P < 0.05$), suggesting that the experimental group had a lower inflammatory response after treatment (Fig. 4).

The safety

During the treatment, the incidence of adverse reactions was 7.02% in the experimental group and 21.05% in the control group. The inter-group comparison revealed a lower incidence of adverse reactions in the experimental group versus the control group ($P < 0.05$), indicating higher treatment safety in the experimental group (Table 1).

DISCUSSION

CH, is mainly managed through surgical approaches to effectively reduce intracranial pressure and save patients' lives (Garg *et al.*, 2022). Enteral nutrition support is one of the necessary means in the treatment process. First of all, comparing patients' neurological function, it was found that the NIHSS score decreased and the ADL score increased after treatment in both groups (Fig. 1), suggesting effectively improved neurological functions in both groups, which we believe is related to the positive influence of predictive management.

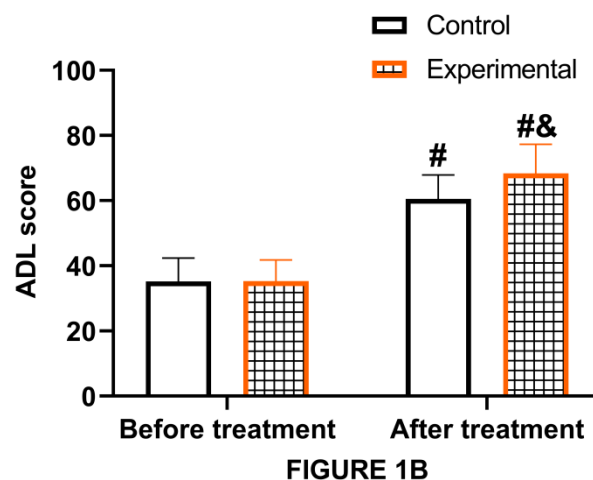
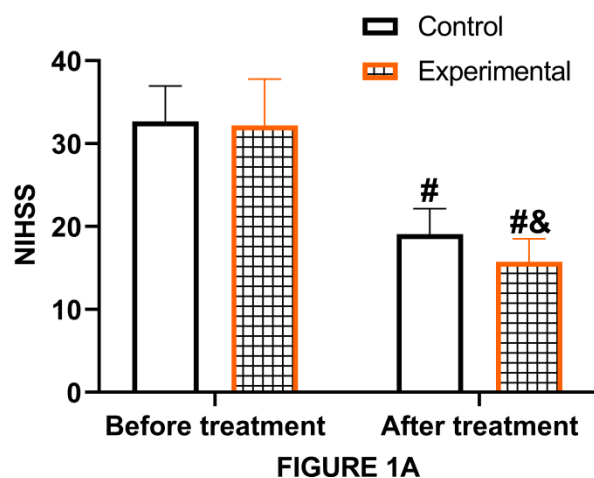


Fig. 1: Comparison of A) NIHSS, B) ALD score. vs before treatment, # indicates $P < 0.05$ compared with before treatment, & indicates $P < 0.05$ compared with experimental group.

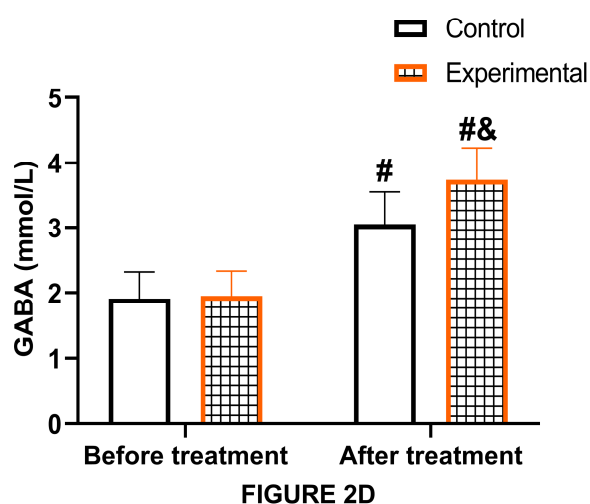
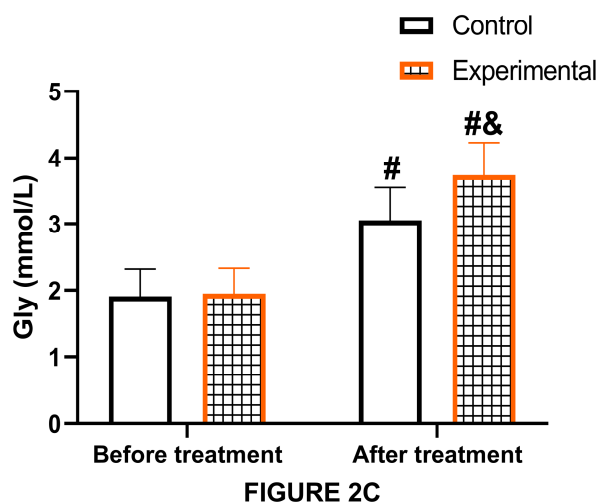
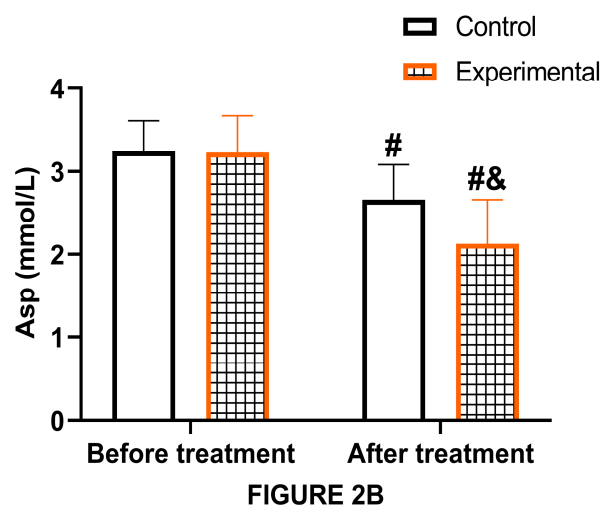
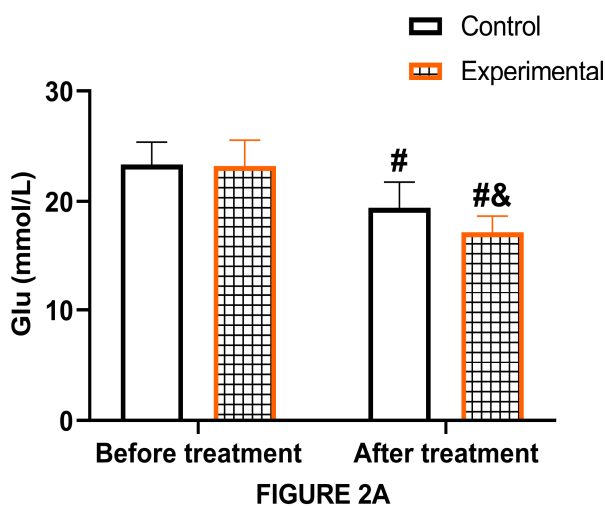


Fig. 2: Comparison of A) Glu, B) Asp, C) Gly, and D) GABA # indicates $P < 0.05$ compared with before treatment, & indicates $P < 0.05$ compared with experimental group.

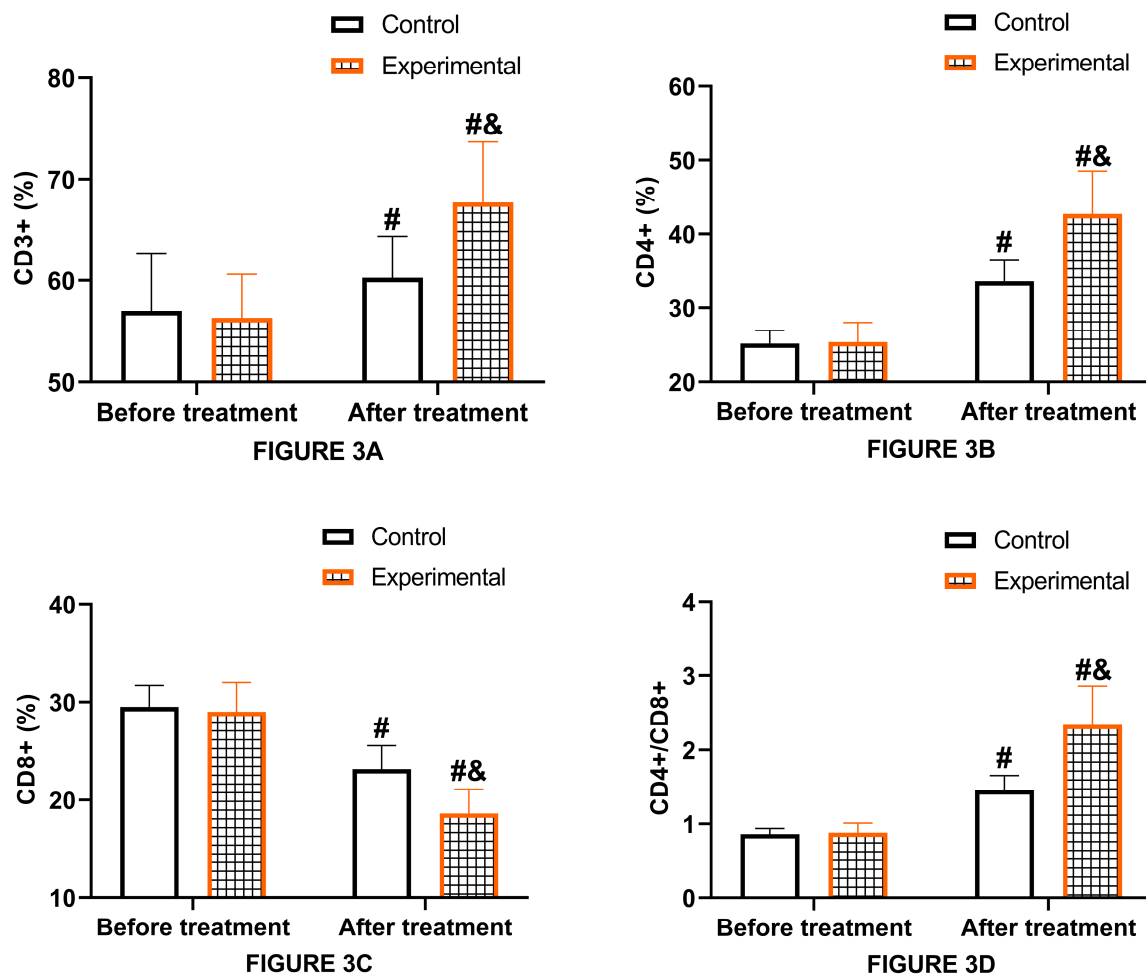


Fig. 3: Comparison of A) CD3+, B) CD4+, C) CD8+, D) CD4+/CD8+. # indicates $P < 0.05$ compared with before treatment, & indicates $P < 0.05$ compared with experimental group.

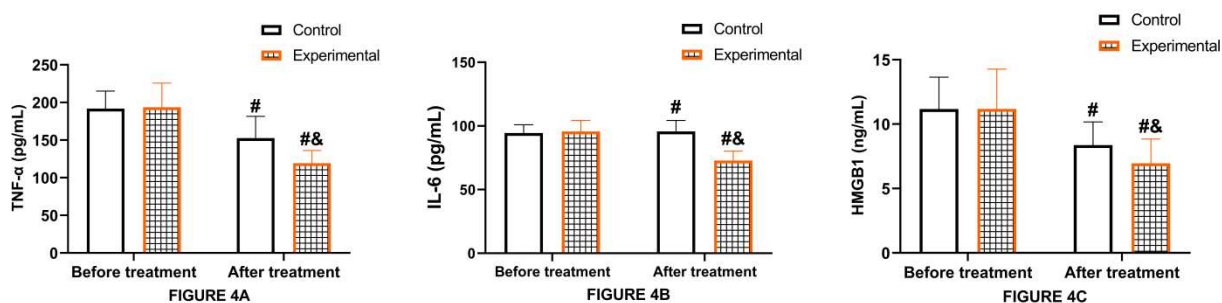


Fig. 4: Comparison of A) TNF- α , B) IL-6, C) HMGB1. # indicates $P < 0.05$ compared with before treatment, & indicates $P < 0.05$ compared with experimental group.

Table 1: Comparison of safety.

Groups	n	Diarrhea [n(%)]	Bloating [n(%)]	Gastric retention [n(%)]	Vomiting [n(%)]	Fever [n(%)]	Total incidence [n(%)]
Control	57	3 (5.26)	4 (7.02)	2 (3.51)	2 (3.51)	1 (1.75)	12 (21.05)
Experimental	57	1 (1.75)	2 (3.51)	0 (0.0)	1 (1.75)	0 (0.0)	4 (7.02)
χ^2							4.653
P							0.031

By analyzing the possible problems in advance and formulating intervention measures, the clinical intervention ability of nursing staff can be effectively improved and the nursing effect can be improved and accelerating patient recovery. In a research study, predictive management reduces the risk of complications in diabetic patients (Rubin & Shah, 2021), which is consistent with our results.

In the comparison of neurotransmitters (Fig. 2), immune function (Fig. 3) and inflammatory responses (Fig. 4), the improvement was more pronounced in the experimental group compared to the control group. *Reason for analysis:* Probiotics contain four types of probiotics and a variety of prebiotics that help to improve the body's microbiome. The probiotics contained in it are beneficial active microorganisms that can activate endogenous bacterial metabolism, maintain the intestinal barrier, regulate intestinal flora, improve immunity and promote intestinal function recovery. In the case of severe diseases, probiotics can effectively prevent gastrointestinal dysfunction complicated by enteral nutrition (Huang & Wang, 2022). In addition, probiotics regulate the immune system and can reduce bacterial infections as well as inflammatory responses, which can prevent brain damage (Juan *et al.*, 2022). Network pharmacology studies have shown that apoptotic pathways, such as ERK1/2, are key targets for ICH treatment (Deng *et al.*, 2021). In this study, probiotics may exert anti-apoptotic effects through a similar pathway, such as down-regulation of the pro-apoptotic factor HMGB1, which may reduce neuronal apoptosis through the TLR4/NF- κ B pathway or reduce IL-6 and other cytokines to indirectly inhibit the apoptosis cascade mediated by microglia. This is synergistic with the effect of probiotics on repairing the intestinal barrier and reducing systemic inflammation. In an analysis of the correlation between antibiotics and functional gastrointestinal disorders, they mentioned that probiotic use helps to improve neurotransmitter levels in patients with gastrointestinal disorders (Karakan *et al.*, 2021), which is consistent with our results. Glu, Gly, GABA and Asp play a central role in the balance of cortical inhibition/excitation (Hsao *et al.*, 2020). The decrease of Glu/Asp indicates the reduction of excitotoxicity and the increase of Gly/GABA reflects the enhancement of inhibitory neurotransmission, which is consistent with the improvement of neurological function scores. This is consistent with the pathological model of excessive activation of glutamatergic neurons after CH (Li *et al.*, 2023). At the same time, this finding is highly consistent with Jiang's CSF multi-omics study: This study suggests that disorders of lipid metabolism after ICH (e.g., inhibition of sphingomyelin degradation) can exacerbate excitotoxicity and that probiotics may reduce neuronal damage by regulating metabolic pathways along the gut-brain axis (e.g., increasing SCFFA) and promoting synthesis of inhibitory neurotransmitters (Jiang *et al.*,

2025). Therefore, we hypothesized that the synergistic effect of nutritional interventions (such as probiotics) and lipid metabolism may achieve neuroprotection through the following mechanisms: (1) direct activation of GABAergic neurons by probiotic metabolites (such as butyrate); (2) Low-fat nutrition reduced oxidative stress and inhibited excessive glutamate release. Similarly, the study of Aghamohammad also mentions the excellent application of probiotics in neurological diseases (Aghamohammad *et al.*, 2023). This was confirmed by the fact that the experimental group in the current study had even lower levels of inflammatory factors after treatment than the control group. Therefore, the use of probiotic low-fat nutritional supplements can not only strengthen the neurological function of the human body more effectively, but also promote the recovery of immune function and improve safety during rehabilitation (Table 1). We hypothesized that the modulation of T cell subsets by probiotics may be the result of multiple mechanisms: (1) direct immune regulation: after colonization of the gut, probiotics promote Th1 differentiation by activating dendritic cells and up-regulate the CD4+/CD8+ ratio. (2) Indirect anti-inflammatory effect: Improving intestinal barrier function and reducing endotoxin translocation, thereby reducing the inhibition of T cells by systemic inflammatory factors.

Based on the results obtained in this study, we suggest that the regulation of probiotics on CH may involve the following mechanisms: (1) Probiotics play an anti-inflammatory role by inhibiting TLR4/NF- κ B pathway and reducing TNF- α /IL-6. (2) Low-fat nutrition reduces bile acid secretion and probiotics up-regulate the expression of occluding (Li *et al.*, 2022), thereby achieving the repair of intestinal barrier function. (3) Probiotic metabolites (such as butyrate) promote GABA synthesis, correct excitation/inhibition imbalance and improve neurological function of patients.

However, there are many limitations of this study. For example, 114 cases in a single center may affect the statistical power, which needs to be verified by a large sample from multiple centers. Similarly, due to the limited number of cases, this study was not stratified according to the location of bleeding, such as anterior/posterior circulation. Studies have indicated that patients with posterior circulation variants may have unique vascular risk factors (Zheng *et al.*, 2024) that may affect the response to nutritional interventions. Therefore, future subgroup analyses with larger sample sizes are needed and should focus on the efficiency of gut-brain axis regulation in patients with posterior circulation hemorrhage. Second, microbiome analysis was missing and did not detect changes in the composition of the fecal microbiota (e.g., the ratio of Bacteroides to Firmicutes). Finally, although all the patients underwent a standardized drilling and drainage procedure for intracranial hematoma, performed by the same surgical team, the procedure itself may have affected

prognosis. To minimize confounding bias, we used block randomization (block size =4) to ensure a balanced distribution of surgical procedures between the two groups. All patients were given the same basic treatment (neuronutrition and electrolyte balance) after operation. According to a study (Zhang *et al.*, 2024), future research needs to record more detailed surgical parameters (such as hematoma clearance rate) to quantify its potential impact on the effect of nutritional intervention. In the future, more indicators need to be observed to comprehensively evaluate the influence of predictive management-assisted probiotic low-fat nutritional supplements on CH. In addition, the sample size should be expanded to improve the comprehensiveness of the research results.

CONCLUSION

To sum up, predictive management-assisted probiotic low-fat nutritional supplements can improve the postoperative recovery of severe CH patients, enhance their neurological function and immune function, which is recommended for clinical use.

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Authors' contributions

Kai Wang and Xulei Li conceived and designed the study, Bei Yuan wrote and revised the manuscript, Qiannan Qi collected and analyzed data, and Bei Yuan and Qiannan Qi contributed to the work equally and should be regarded as co-first authors. All authors read and approved the final submitted manuscript.

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Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical approval

Ethical approval obtained from the Ethics Committee of Affiliated Hospital of Hebei University (No. HDFYLL-KY-2023-019), this study was conducted strictly following the Declaration of Helsinki. All the subjects' immediate family members signed the informed consent form.

Conflict of interest

The authors report no conflict of interest.

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