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ARTICLE

Protective Roles of *Bacillus licheniformis* Preparation Against Gastrointestinal Dysfunction and Inflammation After Radiotherapy in Children With Medulloblastoma

Xing Wan[1], Jingnan Huang[2], Zhaodi Zeng[3], Zhijian Xu[1], Qi Tu[1], Huahui Chen[1], Minfeng Tong[1,*], Hu Xu[1,*]

[1]Department of Neurosurgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine (Jinhua Municipal Central Hospital), Jinhua, Zhejiang, China
[2]Department of Neurosurgery, Wencheng County People's Hospital, Wenzhou, Zhejiang, China
[3]Department of Paediatrics, Wencheng County People's Hospital, Wenzhou, Zhejiang, China
*Correspondence: tongminfeng777@163.com (Minfeng Tong); xhzey88@126.com (Hu Xu)

Abstract

Aims/Background Probiotics, including *Bacillus licheniformis*, have been shown to mitigate intestinal inflammation and mucositis by modulating gut microbiota and immune responses; however, their role in radiation-induced gastrointestinal (GI) injury remains unclear. This study aims to investigate the effects of *Bacillus licheniformis* supplementation on radiotherapy-induced GI dysfunction, inflammation, and survival rates in pediatric patients with medulloblastoma.

Methods A total of 205 pediatric patients with medulloblastoma admitted to Jinhua Municipal Central Hospital between March 2015 and March 2020 were divided into an experimental group and a control group based on treatment protocols. All patients received craniospinal irradiation (CSI). Patients in the experimental group received an oral *Bacillus licheniformis* preparation (one capsule, three times daily) starting one day before CSI and continuing through the completion of radiotherapy, while the control group did not receive the probiotic. Post-radiotherapy adverse reactions were recorded. Serum levels of endothelin (ET), C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6) were measured one day before the first radiotherapy session and one day after the final session. A five-year follow-up was conducted to assess patients' survival rates.

Results Most of the pediatric medulloblastoma patients developed varying degrees of gastrointestinal symptoms after CSI, with fewer cases observed in the experimental group compared to the control group (all $p < 0.05$). Serum levels of ET, CRP, TNF-α, IL-1β, and IL-6 significantly increased post-radiotherapy in both groups, but the rise was markedly attenuated in the experimental group (all $p < 0.001$). However, no significant differences were found in 5-year progression-free survival (hazard ratio [HR] = 1.060, log rank $p = 0.716$) or overall survival (HR = 1.275, log rank $p = 0.350$) rates between the two groups.

Conclusion *Bacillus licheniformis* preparation effectively alleviates CSI-induced gastrointestinal dysfunction and inflammation in pediatric patients with medulloblastoma, but does not significantly improve their survival rates.

Key words: medulloblastoma; *Bacillus licheniformis*; craniospinal irradiation; gastrointestinal tract; inflammation

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Introduction

Central nervous system (CNS) tumors exhibit remarkable clinical and biological heterogeneity, ranging from benign tumors curable by surgery alone (e.g., pilocytic astrocytoma) to highly aggressive malignancies resistant to most therapies

(e.g., glioblastoma) (Capper et al, 2018). Epidemiological data indicate that CNS tumors represent the second most common cause of pediatric cancer (Withrow et al, 2019). Prior to 1970, medulloblastoma represented the most common malignant CNS tumor in children, with a survival rate of only 20%; however, over three quarters of affected children with favorable risk factors can now be successfully cured (Frühwald and Rutkowski, 2011). In light of the high cure rates for medulloblastoma in children nowadays, more attention has been diverted to improving patients' quality of life after surgery.

Surgical resection remains the cornerstone of medulloblastoma management. Complete excision typically achieves cure for benign lesions. However, adjuvant radiotherapy and chemotherapy are often required for unresectable or partially resected benign tumors, as well as malignant neoplasms. Radiotherapy, which induces tumor cell death through disruption of DNA integrity and suppression of clonal proliferation, has become an essential component of oncologic regimens and one of the most widely employed anticancer strategies (Orth et al, 2014). Nevertheless, radiation-induced toxicities frequently necessitate treatment discontinuation in patients (Robbins and Gosselin, 2002). Common adverse effects include fatigue, pain, nausea, and vomiting (Henry et al, 2008), while anemia, alopecia, diarrhea, oral mucositis, and gastrointestinal injury may also occur (Robbins and Gosselin, 2002). The principal mechanism of radiotherapy involves DNA damage in tumor cells: low-dose radiation primarily triggers apoptosis, whereas high-dose exposure induces necrotic cell death (Rainaldi et al, 2003). Following radiation-induced tumor cell lysis, proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukins (ILs), and heat shock proteins (HSPs) are released, predisposing patients to severe gastrointestinal complications, particularly radiation enteritis (Derer et al, 2015; Ki et al, 2014). Therefore, it is necessary to explore treatment methods that can alleviate the side effects caused by radiotherapy.

At present, experimental and clinical studies have proved that probiotics can effectively regulate intestinal inflammation by altering the composition of indigenous intestinal flora, as well as their metabolic and functional characteristics (Timko, 2013). Additional studies have demonstrated that probiotics can mitigate gastrointestinal mucositis through multiple mechanisms, including reducing intestinal permeability, suppressing pro-inflammatory cytokine production, and stimulating the generation and secretion of anti-inflammatory cytokines, thereby achieving intact integrity of the protective mucosal layer (Lima et al, 2020). Among these, Gram-positive bacterial strains such as *Lactobacillus* and *Bacillus* species are widely utilized as probiotic agents (Rolfe, 2000). For instance, *Bacillus licheniformis* has been shown to alleviate dextran sulfate sodium (DSS)-induced colitis (Li et al, 2019). However, few studies have been conducted on the effects of *Bacillus licheniformis* on radiotherapy-induced gastrointestinal diseases.

This study aims to investigate the protective effects of *Bacillus licheniformis* preparation on gastrointestinal dysfunction and inflammation in pediatric patients with medulloblastoma undergoing craniospinal irradiation (CSI), and to explore its potential influence on long-term survival outcomes. These findings may provide

new insights into the prevention and management of radiotherapy-induced gastrointestinal injury in children.

Methods

General Information

A total of 205 pediatric patients with medulloblastoma who were admitted to the Department of Oncology at Jinhua Municipal Central Hospital between March 2015 and March 2020 were enrolled in this retrospective study. Any cases with missing core data were systematically excluded during initial screening. Patients were assigned to groups by their treating oncologists according to the institutional treatment protocols: subjects in the experimental group received both the standard care and the *Bacillus licheniformis* preparation, whereas subjects in the control group were treated with standard care only. This study protocol was approved by the Medical Ethics Review Committee of Jinhua Municipal Central Hospital (Approval No. Yan 2025–Ethics Review–168). This study is a retrospective analysis, and all included cases were derived from existing medical records. All data were anonymized during collection and analysis, containing no information that could identify individual patients. As the study only involved secondary analysis of pre-existing data and posed no risk to patients' treatment, health, or rights, the Institutional Medical Ethics Committee granted a waiver of informed consent. The study was conducted in strict accordance with the Declaration of Helsinki and relevant national and institutional regulations on clinical research ethics, ensuring that the study design complies with ethical standards and fully protects patient privacy.

Selection Criteria and Exclusion Criteria

Inclusion criteria of this study include the following: (i) histologically confirmed medulloblastoma; (ii) age 3 to 14 years; (iii) no medical contraindications; (iv) no history of radiotherapy or chemotherapy; and (v) normal immune function. Patients fulfilling the following criteria were excluded: (i) age less than 3 years or more than 14 years; (ii) recent use of immunosuppressants, antibiotics (within 4 weeks), or probiotics; (iii) intolerance to probiotic preparations; (iv) a history of radiotherapy or chemotherapy; (v) pre-existing autoimmune disorders or immunodeficiency; (vi) metastatic disease; (vii) concurrent malignant tumors or related metabolic diseases; and (viii) incomplete clinical records or non-adherence to treatment.

Treatment Perscription

Following tumor resection surgery, all patients with medulloblastoma underwent craniospinal irradiation (CSI) within 2–4 weeks. The total CSI dose was 36 Gy, conventionally fractionated at 1.8–2.0 Gy per day, five days per week, over an approximate course of 4–6 weeks, with a posterior fossa boost dose of 18–24 Gy delivered in additional fractions. Patients in the experimental group received oral *Bacillus licheniformis* capsules (manufactured by Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co., Ltd., Shenyang, China, National Medicine Approval No. S10950019), three times daily (one capsule per dose). The probiotic

regimen was initiated one day before radiotherapy and continued through the completion of the radiation course. Subjects in the control group were not given the *Bacillus licheniformis* intervention.

Evaluation Indicators

Serum levels of endothelin (ET; catalog number EIAET1), TNF-α (catalog number 88-7346-88), interleukin 1 beta (IL-1β; catalog number 88-7261-88), interleukin 6 (IL-6; catalog number EH2IL6), and C-reactive protein (CRP; catalog number KHA0031) were measured using commercial sandwich enzyme-linked immunosorbent assay (ELISA) kits from Invitrogen (Thermo Fisher Scientific, Waltham, MA, USA), following the manufacturers' protocols.

Occurrences of gastrointestinal reactions were monitored in the two groups of children after radiotherapy. Gastrointestinal symptoms were graded by clinicians in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) classification, v4.0.3 (NCI, 2010). Peripheral blood samples were collected from the children before and after radiotherapy. Children were followed up every 3 months during the first to second year after radiotherapy, and every 6 months during the third to fifth year. The survival status was verified quarterly through hospital medical record systems and telephone follow-ups. Survival rates were assessed using progression-free survival (PFS, defined as the time from radiotherapy completion to tumor recurrence or death) and overall survival (OS, defined as the time to all-cause mortality).

Statistical Methods

Statistical analysis was conducted using SPSS 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 7.04 (GraphPad Inc., San Diego, CA, USA). Categorical variables are expressed as counts and percentages. These variables were analyzed using the chi-square test. Data distribution of continuous variables was assessed for normality using the Shapiro–Wilk test; normally distributed data are presented as mean $\pm$ standard deviation (SD). For data conforming to a normal distribution, intergroup comparisons were performed using independent samples *t*-tests after verifying homogeneity of variance with Levene's test (all F-statistics $p > 0.05$). Paired sample *t*-test was used for intra-group comparisons. Kaplan–Meier survival analysis was used to analyze progression-free survival (PFS) and overall survival (OS) rates. To provide a more detailed assessment, the hazard ratio (HR) and its 95% confidence interval (CI) were subsequently calculated using the Cox proportional hazards model, and the log-rank test was used to compare OS and PFS between the two groups. Statistical significance was set at $p < 0.05$, with $p < 0.001$ indicating a high degree of statistical significance.

Results

Comparison of Baseline Characteristics Between the Experimental and Control Groups

The experimental group comprised 95 cases (46 males and 49 females). No statistically significant differences were found between the two groups in terms of

gender and age ($p > 0.05$, Table 1), demonstrating comparable baseline characteristics.

Table 1. Comparison of general data between the experimental and control groups.

Variables	Total ($n = 205$)	Control group ($n = 110$)	Experimental group ($n = 95$)	Statistic	p
Age, years	6.69 ± 1.72	6.80 ± 1.70	6.56 ± 1.75	$t = 1.00$	0.317
Gender, n (%)				$\chi^2 = 0.55$	0.456
Male	105 (51.22)	59 (53.64)	46 (48.42)		
Female	100 (48.78)	51 (46.36)	49 (51.58)		

Notes: t, t-test; χ^2, chi-square test.

Bacillus licheniformis Alleviates Gastrointestinal Symptoms Following Radiotherapy

We separately analyzed the gastrointestinal symptoms in children from the experimental and control groups after radiotherapy to evaluate the effects of *Bacillus licheniformis* on radiation-induced gastrointestinal toxicity. As presented in Table 2, all pediatric patients with medulloblastoma developed varying degrees of gastrointestinal symptoms following craniospinal irradiation (CSI). In the control group, 84 (76.36%) patients experienced nausea, 90 (81.82%) had vomiting, 51 (46.36%) reported abdominal pain, and 33 (30.00%) developed diarrhea. In contrast, in the experimental group, 48 (50.53%) patients experienced nausea, 39 (41.05%) had vomiting, 22 (23.16%) reported abdominal pain, and 12 (12.63%) developed diarrhea. The incidence of all four symptoms was significantly lower in the experimental group compared with the control group (all $p < 0.05$). These findings suggest that adjuvant administration of *Bacillus licheniformis* was associated with a reduction in craniospinal irradiation–related gastrointestinal reactions in children with medulloblastoma.

Bacillus licheniformis Attenuates Inflammatory Response to Radiotherapy

To investigate the inflammatory side effects following radiotherapy, we collected peripheral blood from the children before and after the treatment. We used ELISA to measure the levels of ET, TNF-α, IL-1β, IL-6, and CRP in the serum. The results showed that the serum levels of ET, TNF-α, IL-1β, IL-6, and CRP were significantly elevated in both the control and experimental groups after radiotherapy (Table 3), indicating that radiotherapy can induce an inflammatory response. We then compared the increase in the expression levels of inflammation-related cytokines in the experimental and control groups after radiotherapy (Table 3). It was found that the increase in ET, TNF-α, IL-1β, IL-6, and CRP in the experimental group, which received the *Bacillus licheniformis* preparation, was significantly lower than that in the control group (all $p < 0.001$), which did not receive the preparation. This result suggests that *Bacillus licheniformis* can help attenuate the inflammatory response in children with medulloblastoma who undergo radiotherapy.

Table 2. Incidence comparison of gastrointestinal symptoms in patients of the experimental and control groups.

Variables	Total (n = 205)	Control group (n = 110)	Experimental group (n = 95)	Statistic	p
Nausea, n (%)				χ^2 = 14.84	<0.001
No	73 (35.61)	26 (23.64)	47 (49.47)		
Yes	132 (64.39)	84 (76.36)	48 (50.53)		
Vomiting, n (%)				χ^2 = 36.31	<0.001
No	76 (37.07)	20 (18.18)	56 (58.95)		
Yes	129 (62.93)	90 (81.82)	39 (41.05)		
Abdominal pain, n (%)				χ^2 = 11.97	<0.001
No	132 (64.39)	59 (53.64)	73 (76.84)		
Yes	73 (35.61)	51 (46.36)	22 (23.16)		
Diarrhea, n (%)				χ^2 = 8.98	0.003
No	160 (78.05)	77 (70.00)	83 (87.37)		
Yes	45 (21.95)	33 (30.00)	12 (12.63)		

Note: χ^2, chi-square test.

Post-Treatment Survival Outcomes in Pediatric Patients

To investigate the impact of *Bacillus licheniformis* on the survival of children with medulloblastoma, we conducted a five-year follow-up study. All 205 enrolled patients (110 in control group, 95 in experimental group) completed the full follow-up period with complete survival data. The analysis of the follow-up data revealed that the 5-year PFS rate for patients in the experimental group was 60.75%, compared to 72.73% for those in the control group (Fig. 1A). The OS for patients in the experimental group was 66.38%, which was lower than 71.55% for those in the control group (Fig. 1B). A comparative analysis of the survival rates between the experimental and control groups revealed no significant differences in the PFS rate (p = 0.716) or the OS rate (p = 0.350), indicating that *Bacillus licheniformis* does not have a significant impact on the survival of children with medulloblastoma post-radiotherapy.

Discussion

Radiotherapy is a crucial component of cancer treatment and is considered highly cost-effective, accounting for only 5% of the total cost of cancer care (Ringborg et al, 2003). Approximately half of the cancer patients receive radiotherapy at some point during the course of their illness (Delaney et al, 2005). Radiotherapy inhibits the proliferation of cancer cells (Jackson and Bartek, 2009), but a series of side effects ensue post-treatment, such as nausea, vomiting, dyspnea and pain, which can add to the burden of patients (Redmond, 1996). At the same time, radiotherapy can damage endothelial cells, resulting in radiation-induced inflammation in patients (Jarosz-Biej et al, 2019). The current study aims to investigate the effects of *Bacillus licheniformis* preparation on gastrointestinal dysfunction and inflammation in children with medulloblastoma post-radiotherapy and on their survival rate.

Table 3. Changes in serum levels of ET, TNF-α, IL-1β, IL-6 and CRP before and after radiotherapy.

	Control group (n = 110)	Experimental group (n = 95)	Statistic	Cohen's d	p
ET					
Before RT	7.56 ± 2.55	7.58 ± 2.36	t = –0.07	0.01	0.945
After RT	25.61 ± 4.80***	17.21 ± 3.86***	t = 13.90	1.91	<0.001
Increased expression	18.06 ± 4.26	9.63 ± 3.02	t = 16.50	2.26	<0.001
TNF-α (pg/mL)					
Before RT	8.19 ± 3.81	8.56 ± 3.86	t = –0.70	0.01	0.486
After RT	31.16 ± 6.62***	24.29 ± 4.64***	t = 8.68	1.19	<0.001
Increased expression	22.97 ± 4.83	15.73 ± 2.75	t = 13.40	1.81	<0.001
IL-1β (pg/mL)					
Before RT	188.39 ± 17.08	191.29 ± 18.03	t = –1.18	0.17	0.238
After RT	261.95 ± 23.02***	235.86 ± 20.27***	t = 8.55	1.20	<0.001
Increased expression	73.56 ± 14.06	44.57 ± 8.11	t = 18.37	2.48	<0.001
IL-6 (pg/mL)					
Before RT	160.88 ± 23.13	158.12 ± 23.21	t = 0.85	0.12	0.395
After RT	249.01 ± 32.23***	204.42 ± 24.32***	t = 11.26	1.55	<0.001
Increased expression	88.13 ± 21.14	46.31 ± 7.83	t = 19.28	2.55	<0.001
CRP (μg/mL)					
Before RT	11.56 ± 2.05	11.39 ± 1.92	t = 0.62	0.09	0.539
After RT	28.48 ± 5.09***	21.22 ± 3.66***	t = 11.84	1.62	<0.001
Increased expression	16.92 ± 4.51	9.83 ± 2.98	t = 13.44	1.83	<0.001

Notes: *** $p < 0.001$ indicates that cytokine levels were significantly higher after radiotherapy compared with those before radiotherapy (intra-group comparison).
Abbreviations: CRP, C-reactive protein; ET, endothelin; RT, radiotherapy; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin 1 beta; IL-6, interleukin 6.

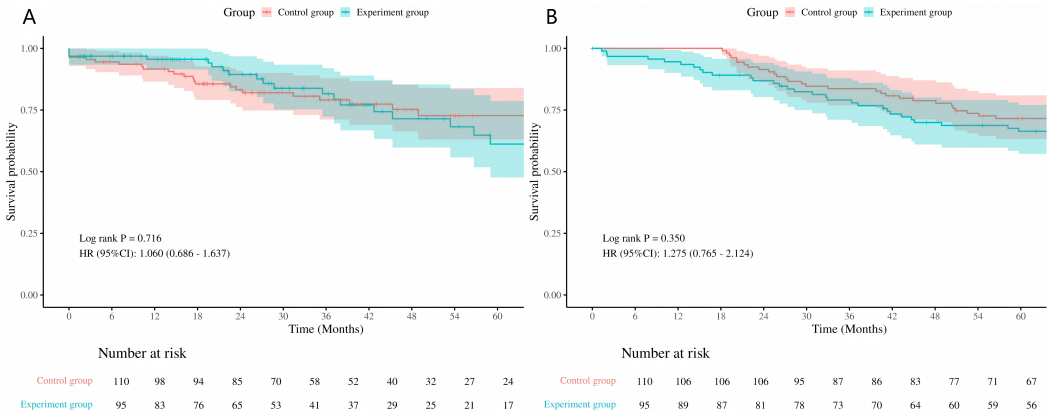

Fig. 1. Kaplan–Meier survival curves depicting five-year survival outcomes in pediatric patients of the experimental group and control group. (A) Survival curves of progression-free survival in the experimental group and the control group. (B) Survival curves of overall survival in the experimental group and the control group. HR, hazard ratio; CI, confidence interval.

Studies have revealed that probiotics can effectively prevent or treat diarrhea induced by chemotherapy or radiotherapy, reduce incidence of mucositis and improve mucositis symptoms in patients undergoing chemotherapy or radiotherapy

(Picó-Monllor and Mingot-Ascencao, 2019). In this study, we found that most of our patients presented with a range of gastrointestinal symptoms after the treatment, such as nausea, vomiting and diarrhea, and that *Bacillus licheniformis* preparation can alleviate gastrointestinal dysfunction and inflammatory response in children with medulloblastoma following radiotherapy. It is noteworthy that the incidence of these adverse reactions was significantly lower in the experimental group than in the control group, indicating that *Bacillus licheniformis* can relieve gastrointestinal symptoms after radiotherapy. In addition, serum samples of all children were collected before and after radiotherapy to detect the expression levels of ET, CRP, TNF-α, IL-1β and IL-6. The experimental results showed that compared with those before radiotherapy, the serum levels of ET, CRP, TNF-α, IL-1β and IL-6 of children in both groups increased significantly after radiotherapy. Meanwhile, it was found that after radiotherapy, the increase in the expression levels of these cytokines in the experimental group was significantly lower than that in the control group, indicating that *Bacillus licheniformis* can attenuate the inflammatory response after radiotherapy. Previous study has reported that probiotic preparations can reduce the incidence of intestinal mucositis and attenuate the elevation of inflammatory cytokines in patients undergoing chemotherapy or radiotherapy (Garczyk et al, 2022).

A study has shown that probiotic treatment can improve postoperative complications in children, but there is a lack of research on prognosis and survival (Reyna-Figueroa et al, 2021). The results of this study indicate that children treated with a supplementation of *Bacillus licheniformis* did not exhibit a comparatively higher survival rate post-radiotherapy, marked by the absence of a significant difference in the 5-year PFS and OS compared to the control group. This lack of effect may be attributable to several factors. Mechanistically, probiotics primarily contribute to modulating gut microbiota balance and enhancing intestinal barrier function (Lima et al, 2020), but they do not directly counteract tumor cell proliferation or invasion (Orth et al, 2014). Additionally, survival outcomes in pediatric patients with CNS tumors are predominantly governed by molecular subtypes and treatment sensitivity (Capper et al, 2018), meaning the indirect anti-inflammatory effects of probiotics may be insufficient to alter progression in high-risk malignancies. Furthermore, transient probiotics supplementation—typically administered during the radiotherapy period—is inadequate to sustain systemic immune modulation, potentially allowing for tumor recurrence over time (Wei et al, 2018).

It is important to emphasize that our results on the suppressive effects of *Bacillus licheniformis* against radiotherapy-induced gastrointestinal toxicity support its use as an adjuvant therapy, rather than as a component of standard care. Further multicenter trials should validate these findings and assess the long-term safety of *Bacillus licheniformis* in pediatric oncology protocols, while additional research is needed to explore the effects of different probiotic strains, dosages, or formulations on long-term survival and other critical aspects of patient care. Notably, the intersection of the PFS curves presenting the experimental and control groups in Fig. 1A is indicative of a delayed therapeutic effect of the *Bacillus licheniformis* preparation, but the underlying mechanisms remain to be elucidated in future studies.

This study has several limitations: First, although baseline demographic and clinical characteristics were comparable between groups, the non-randomized retrospective design may still introduce potential selection bias. Second, the selection of radiotherapy protocols may vary between clinicians and could involve unmeasured confounding factors that influence treatment outcomes investigated in the current study. Third, the single-center study design may limit the generalizability of findings. Finally, the modest observed survival difference, combined with the limited sample size (n = 205), may have limited the statistical power to detect a significant effect.

Conclusion

Bacillus licheniformis preparation provides a supplementary strategy to protect against gastrointestinal dysfunction and inflammation in children medulloblastoma undergoing CSI. This study provides new insights into optimizing treatment regimens to alleviate radiotherapy-related symptoms and enhance the quality of life in pediatric medulloblastoma patients.

Key Points

- *Bacillus licheniformis* significantly reduces radiotherapy-induced gastrointestinal symptoms, such as nausea, vomiting and diarrhea, in pediatric patients with medulloblastoma undergoing craniospinal irradiation (CSI).
- Probiotics supplementation attenuates post-radiotherapy inflammatory markers, including endothelin, C-reactive protein, tumor necrosis factor-alpha, interleukin 1 beta, and interleukin 6.
- *Bacillus licheniformis* contributes primarily to alleviating acute toxicity without impacting survival outcomes.

Availability of Data and Materials

The data and materials in the current study are available from the corresponding authors on reasonable request.

Author Contributions

XW, JNH, ZDZ, ZJX, QT, HHC, MFT and HX contributed to the study design. XW, JNH and ZDZ conducted the literature search. ZJX, QT and HHC acquired the data. MFT performed data analysis. XW wrote the article. All authors contributed to revising the manuscript critically for important intellectual content. 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

This study protocol was approved by the Medical Ethics Review Committee of Jinhua Municipal Central Hospital (Approval No. Yan 2025–Ethics Review–168). This study is a retrospective analysis, and all included cases were derived from existing medical records. All data were anonymized during collection and analysis, containing no information that could identify individual patients. As the study only involved secondary analysis of pre-existing data and posed no risk to patients' treatment, health, or rights, the Institutional Medical Ethics Committee granted a waiver of informed consent. The study was conducted in strict accordance with the Declaration of Helsinki and relevant national and institutional regulations on clinical research ethics, ensuring that the study design complies with ethical standards and fully protects patient privacy.

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Conflict of Interest

The authors declare no conflict of interest.

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