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ORIGINAL

Efficacy and Safety of Pd-1 Inhibitors in the Treatment of Advanced Esophageal Cancer in Athletic Patients

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ABSTRACT

Objective: To study the efficacy and safety of PD-1 inhibitors in the clinical treatment of athletic patients with advanced esophageal cancer. **Methods:** The observation objects of this study were selected from athletic patients with advanced esophageal cancer who were treated in our hospital. The number of samples was 74 cases, and the treatment period was from August 2019 to August 2021. The medical records of the above athletic patients were retrospectively analyzed, and the athletic patients were grouped according to the treatment plan. The athletic patients in the control group were treated with docetaxel, fluorouracil and other drugs, while the athletic patients in the observation group were treated with programmed death molecule (PD-1) inhibitors during the course of chemotherapy. The survival time, clinical efficacy and the occurrence of adverse reactions were comparing the two groups, and the neutrophil count to lymphocyte count ratio (NLR), neutrophil count/ (white blood cell count - neutrophil count) (dNLR) levels and changes in quality of life were analyzed in both groups. **Results:** The objective efficiency rate and overall controlling rate of the observing group were above those of the controlling group, $P < 0.05$; the duration of progression-free survival and general survival of the observing group were prolonged than those of the controlling group, $P < 0.05$; among the therapy-related adverse reactions of the observing group, there was no significant discrepancy in the incidence of various symptoms for the two groups, $P > 0.05$; the occurrence of immune-related adverse reactions of the two groups was analyzed. There was no obvious discrepancy in the occurrence of skin mucosal reaction, endocrine damage, hematotoxicity, immune pneumonia, immune myocarditis, and nephritis in both groups, $P < 0.05$; NLR and dNLR after therapy in the observing group were below those in the controlling group, $P < 0.05$; the

scores of each item of quality of living score in the observing group were clearly superior to those in the controlling group, P < 0.05. **Conclusion:** The clinical application of PD-1 inhibitor has considerable efficacy in the clinical treatment of advanced esophageal cancer athletic patients, and the safety of this regimen is high, which is valuable for being further promoted and applied.

KEYWORDS: PD-1 inhibitor; Advanced esophageal cancer; Quality of life; Efficacy; Safety

1. INTRODUCTION

Esophageal cancer is a malignancy of the gastrointestinal system with extremely high clinical incidence. Clinical statistics show that (Lu et al., 2022) globally, the number of athletic patients with esophageal cancer in 2020 was as high as 600000, and the number of athletic patients who died due to this disease was 540000. The clinical incidence of this disease ranks among the top 8 of all malignant tumors. The incidence and mortality of esophageal cancer in China are extremely high, and the cure rate of the disease is extremely low, which makes it as a malignant tumor that poses a serious threat to the health of Chinese residents. EMSO guidelines clearly has pointed out that surgery is the first choice for early esophageal cancer, while radiotherapy alone or concurrent chemo radio therapy can be carried out for those who refuse surgery and cannot tolerate the surgery (Wang et al., 2022).

Nevertheless, owing to the absence of concrete clinical manifestations in the initial stages of the disease and the relatively weak awareness of the national regular health examination, the disease of most athletic patients has developed to the middle and late stage at the time of treatment and the best opportunity for surgical treatment is lost. Radiotherapy and systemic chemotherapy are the main measures for the treatment of advanced esophageal cancer, which can prolong the survival time of athletic patients (Yang et al., 2021).

However, with the extension of chemotherapy treatment time, the drug resistance of athletic patients to related drugs of chemotherapy can be gradually improved, which will improve the metastasis rate and recurrence rate of the disease and affect the overall prognosis of the disease. Chemotherapy is the application of cytotoxic chemotherapeutic drugs to kill tumor cells in order to improve and control the disease. However, these drugs have a strong cytotoxicity and poor selectivity, which may produce different degrees of inhibition and damage to the immune system during the treatment process.

Therefore, the traditional concept in clinical practice believes that there is an antagonistic relationship between chemotherapy and immunotherapy, which cannot be used in combination (Lee et al., 2021). This study aims to

analyze the efficacy and safety of programmed death molecule (PD-1) inhibitors in the clinical treatment of athletic patients with advanced esophageal cancer. The details are summarized as follows.

2. Data and Methods

2.1 Data

Seventy-four athletic patients who were operated in our hospital ranging from August 2019 to August 2021 suffering from advanced esophageal cancer were enrolled as the observation subjects of this study. The clinical data of the athletic patients were retrospectively analyzed, and the athletic patients were grouped based on the therapeutic regimen.

And 37 athletic patients were included in the controlling and observing groups, respectively. There was no obvious discrepancy between the data and information submitted by the athletic patients in each group, P>0.05, as illustrated in Table 1, Figure 1 and Figure 2.

Table 1: Comparing the clinical data of patients with advanced esophageal cancer in the two groups

Group	N	Male / female (n)	Mean age (years)	Pathological differentiation (n)			Primary site (n)		
				HIGH DIFFERENTIATION	MIDDLE DIFFERENTIATION	POOR DIFFERENTIATION	UPPER THORACIC SEGMENT	MID THORACIC SEGMENT	LOWER THORACIC SEGMENT
Control group	37	22/15	65.00 ± 2.61	11	16	10	9	16	12
Observation group	37	24/13	64.81 ± 2.59	8	17	12	5	19	13
X^2/t		0.230	0.263	0.637	0.055	0.259	1.410	0.488	0.060
P		0.2	0.793	0.425	0.815	0.611	0.235	0.485	0.806

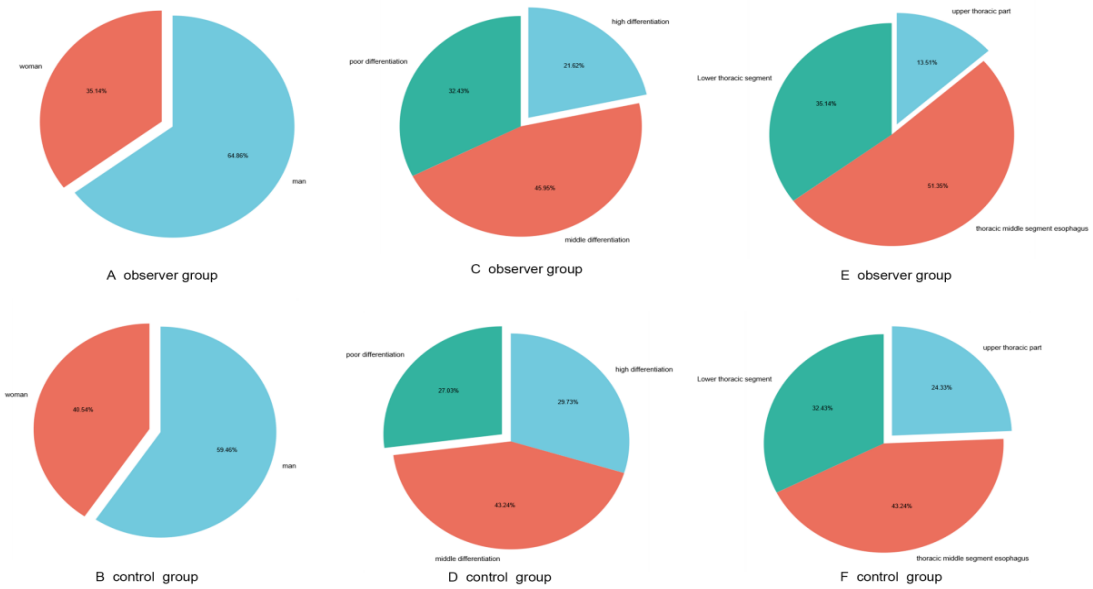

Figure 1: Comparison of clinical data of two groups of patients with advanced esophageal cancer

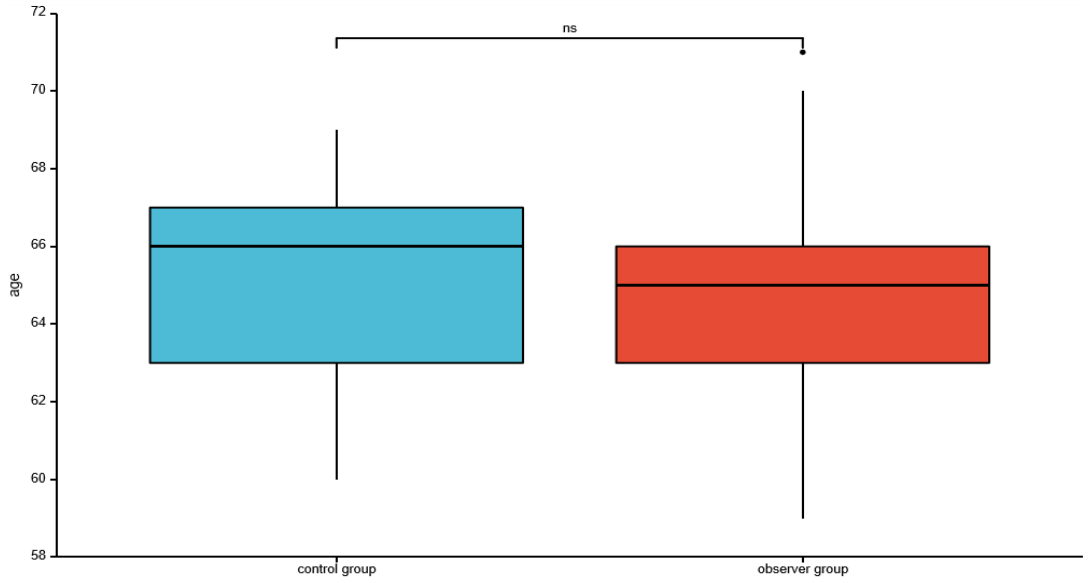

Figure 2: Patient age profile

Inclusion criteria: (1) Patients with esophageal malignant tumor were diagnosed by histopathology; (2) First-line (athletic patients with newly treated advanced esophageal cancer, unable to accept radical surgery, relapse after half a year of radical chemo radio therapy, etc.) receiving chemo radio therapy and immunotherapy; (3) Athletic Patients with complete clinical medical records; (4) Patients with ECOG score of 0 or 1; (5) Athletic Patients with good organ function and no contraindications to chemotherapy.

Exclusion criteria: (1) Athletic Patients with esophageal perforation or contraindications to radiotherapy and chemotherapy; (2) Athletic Patients with distant metastasis and uncontrollable medical diseases; (3) Patients with

autoimmune diseases; (4) Patients with a history of anti-PD-1 or PD-L1-related treatment; (5) Athletic Patients with other malignant tumors; (6) Patients with gastrointestinal bleeding or bleeding tendency.

2.2 Methods

The control group: All athletic patients were treated with single agent chemotherapy. Docetaxel was dissolved into an appropriate amount of sodium chloride injection with a concentration of 0.9%, which was fully diluted and then injected intravenously for the athletic patients, with a dose of 75mg/m^2, every 21 days as a cycle, and it was used on the first day of each cycle.

Nedaplatin was dissolved into sodium chloride injection (500ml) with a concentration of 0.9%, and it was fully diluted and then injected intravenously for the athletic patients with a dose of 75mg/m^2. The treatment lasted for 21 days as a cycle and the patients were treated on the first day of the treatment cycle. The patients were treated with dexamethasone tablets one day before chemotherapy, twice a day, 8mg each time, and the patients were treated for three consecutive days.

The observation group: The patients in this group were treated with chemotherapy and combined with PD-1 inhibitors, and the following drugs could be selected: The dose of Pembrolizumab was 200mg, or the dose of Nivolumab was 200mg or 300mg, or the dose of Camrelizumab was 200mg, or the dose of Sintilimab was 200mg, and athletic patients were injected intravenously and the treatment cycle was 21 days.

After completing 2-3 cycles of medication treatment, an evaluation of curative effects would be carried out, and the next course of treatment would be carried out for those whose condition had not progressed. All athletic patients received antiemetic, liver protection and other treatments during the treatment period. The doctor adjusted the actual dosage of drugs according to the athletic patients' body surface area, the incidence of adverse reactions and physical fitness score.

2.3 Observation indicators

1) The duration of survival, including progression-free survival and general survival, of athletic patients with terminal esophageal cancer in the two groups were tallied.

2)The clinical efficacy of the athletic patients in both groups was analyzed. All patients were followed up for once every 1 to 3 months after treatment. Before and after treatment, the tumor control status of patients was evaluated by chest CT. If necessary, MRI and CT examinations of the head or

abdomen were carried out for athletic patients to evaluate their conditions. This study evaluated the clinical efficacy of short-term clinical outcomes based on criteria for assessing the efficacy of the solid tumors.

All lesions disappeared completely after treatment, and the shortest diameter of pathological lymph nodes was less than 1cm (returned to normal state), and the state was maintained for at least 1 month as complete remission; the sum of the maximum diameters of measurable lesions was decreased by 30% or above compared with that before treatment, and the state was maintained for at least 1 month as partial remission; the athletic patients' conditions were stable when the conditions were between partial remission and progression after treatment.

After treatment, the total maximum diameter of lesions was increased by 20% or more than that before treatment, and new lesions appeared as progress. The total remission rate and partial remission rate were summed as the objective effective rate, and complete remission rate, partial remission rate and stability rate were summed as the total control rate (Lee et al., 2021).

3) The incidence of adverse reactions during therapy in athletic patients between groups was recorded. The treatment-related adverse reactions included nausea, vomiting, fatigue, fever, abdominal pain, reduced white blood cell count, reduced platelet count, elevated bilirubin levels; immune-related adverse reactions include skin mucosal reaction, endocrine damage, hematotoxicity, immune pneumonia, immune myocarditis and nephritis.

4) The ratio of neutrophil count to lymphocyte count and neutrophil count / (white blood cell count- neutrophil count) of the two groups were counted, that is, NLR index level and dNLR index level. The test data of blood routine of the patients mostly recently to the treatment and after treatment were collected to calculate NLR value and DNLR value.

5) The athletic patients' quality of living was analyzed. Post treatment, quality of living evaluation form of athletic patients with cancer (FACT-G) was used to evaluate, including emotional, physiological, functional and social items, involving 27 items. The full score of the scale was 108. The upper the mark, the greater the quality of living of the athletic patient.

2.4 Statistical process

In this paper, spss20.0 was used to conduct standardized statistical processing, the measurement between groups was expressed in the form of ($\overline{x} \pm s$), and the results were obtained by t-test; the expression form of the count between groups was "%", and the results were obtained by chi square test. If there was a significant difference between the data, the expression

form was P < 0.05.

3. Results

3.1 Comparing survival periods between groups

Based on the data in Table 2 and Figure 3, both progression-free survival time and general survival time in the observing group were clearly prolonged than those in the controlling group, P < 0.05.

Table 2: Comparing the survival duration of patients with terminal esophageal cancer in the two groups (n=37, months)

Group	Progression-free survival time	Overall survival time
Control group	5.05 ± 0.23	8.48 ± 0.65
Observation group	7.84 ± 0.55	10.24 ± 1.11
T	27.477	9.723
P	0.001	0.001

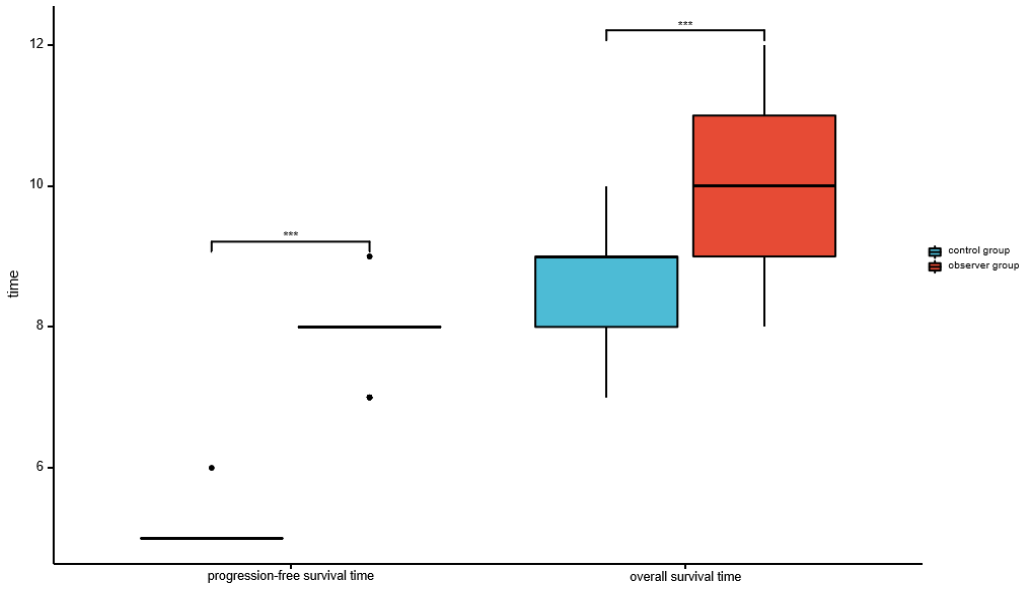

Figure 3: Comparison of survival time between two groups of patients with advanced esophageal cancer

3.2 Comparison of clinical efficacy between groups

According to the data in Table 3 and Figure 4, the objective effective rate and total control rate of the observing group was clearly superior to the controlling group, it seems that the observation group outperformed the control group in terms of both objective effective rate and total control rate, and this difference is statistically significant (P < 0.05).

Table 3: Comparison of clinical efficacy of two groups of patients with advanced esophageal cancer [n (%)]

Group	N	Complete remission	Partial remission	Stable	Progression	Objective efficiency rate	Total control rate
Control group	37	4 (10.81)	9 (24.32)	10 (27.03)	14 (37.84)	13 (35.14)	23 (62.16)
Observation group	37	8 (21.62)	14 (37.84)	11 (29.73)	4 (10.81)	22 (59.46)	33 (89.19)
X^2		1.591	1.577	0067	7.341	4.391	7.341
P		0.207	0.209	0.797	0.003	0.036	0.007

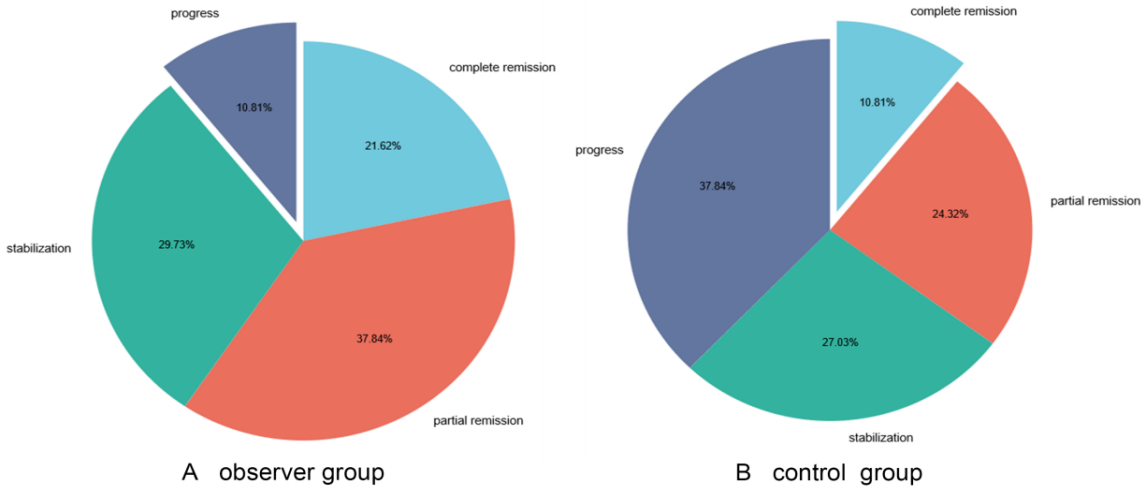

Figure 4: Comparison of clinical efficacy of two groups of patients with advanced esophageal cancer

3.3 Comparison of the incidence of treatment-related adverse reactions between groups

According to the data in Table 4 and Figure 5, there was no meaningful discrepancy in the occurrence of treatment-related adverse reactions in the observed and controlling groups, P>0.05. There was no significant difference in the occurrence of treatment-related adverse reactions between the observed and control groups, and this conclusion is supported by a statistical test with a p-value greater than 0.05.

Table 4: Comparing therapy related negative reactions in two groups of patients with advanced esophageal cancer [n (%)]

Group	N	Nausea	Vomiting	Fatigue	Fever	Abdominal pain	Decreased white blood cell count	Decreased platelet count	Increased blood bilirubin levels
Control group	37	12 (32.43)	8 (21.62)	8 (21.62)	3 (8.11)	6 (16.22)	4 (10.81)	5 (13.51)	6 (16.22)
Observation group	37	8 (21.62)	10 (27.03)	9 (24.32)	2 (5.41)	5 (13.51)	4 (10.81)	7 (18.92)	8 (21.62)
X^2		1.096	0.294	0.076	0.215	0.107	0.001	0.398	0.352
P		0.295	0.588	0.782	0.643	0.744	1.000	0.528	0.553

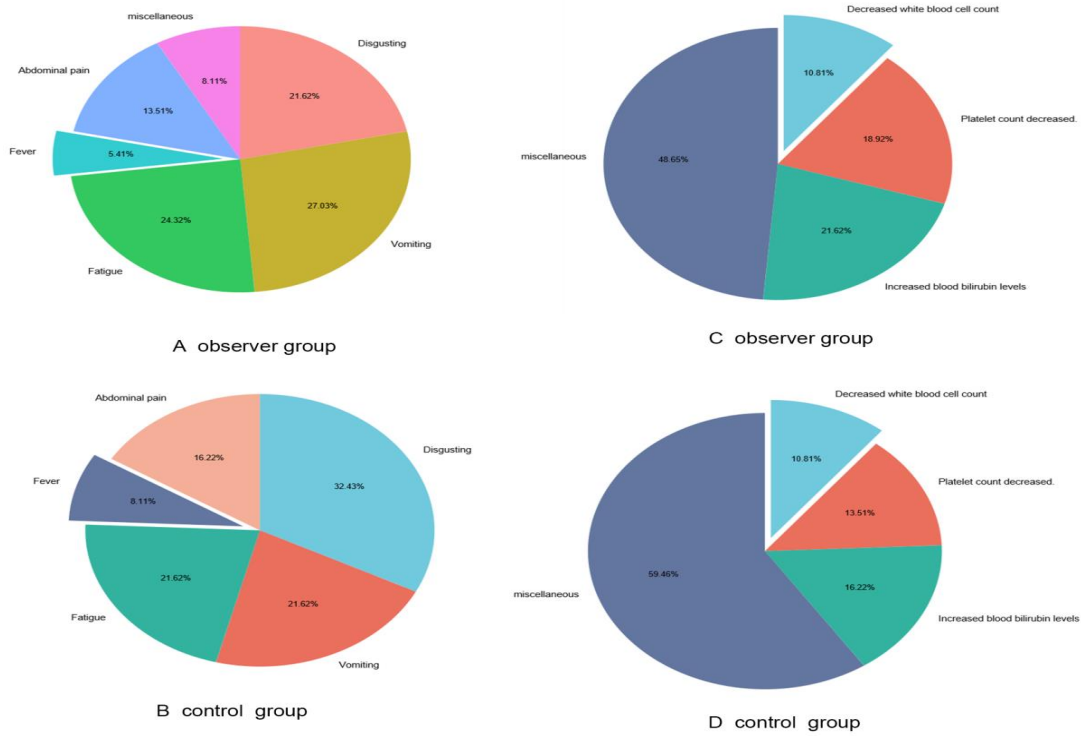

Figure 5: Comparison of treatment-related adverse reactions between the two groups of patients with advanced esophageal cancer

3.4 The comparing of the occurrence of immune-related negative reactions among groups

According to the data in Table 5 and Figure 6, there was no clear discrepancy in the occurrence rate of immune-related undesired reactions between the observing group and the controlling group, P>0.05.

Table 5: Comparing the occurrence rate of immune-related undesired reactions among the two groups [n (%)]

Group	N	Mucocutaneous reaction	Endocrine damage	Hematotoxicity	Immune pneumonia	Autoimmune myocarditis	Nephritis
Control group	37	5 (13.51)	6 (16.22)	11 (29.73)	1 (2.70)	2 (5.41)	2 (5.41)
Observation group	37	3 (8.11)	2 (5.41)	13 (35.14)	3 (8.11)	0 (0.00)	0 (0.00)
X^2		0.561	2.242	0.247	1.057	2.056	2.056
P		0.454	0.134	0.619	0.304	0.152	0.152

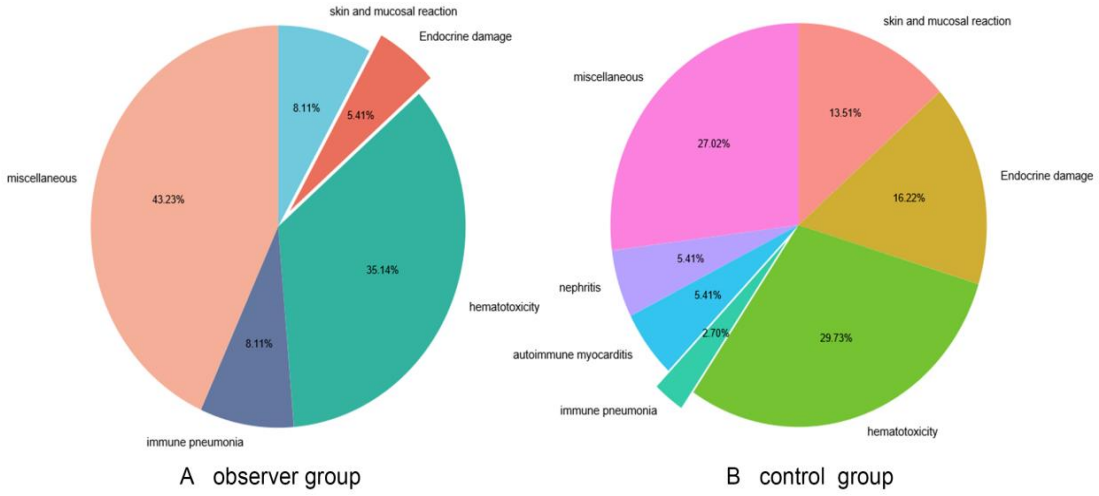

Figure 6: Comparison of the incidence of immune-related adverse reactions between the two groups

3.5 Comparison of the changes in NRL and dNLR values between groups

According to the data in Table 6 and Figure 7, before treatment, there was no obvious discrepancy between NRL and DNLR in the observing groups, P>0.05; after treatment, the levels of all indexes in the observing groups decreased, and all of them were dominated by the observing group, P<0.05.

Table 6: Comparison of the improvement of NRL and dNLR values between the two groups (n=37)

Group	Nrl		Dnlr	
	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT
Control group	2.58 ± 0.29	2.06 ± 0.15	1.82 ± 0.45	1.75 ± 0.26
Observation group	2.61 ± 0.33	1.76 ± 0.08	1.79 ± 0.38	1.38 ± 0.11
T	0.415	10.734	0.310	7.972
P	0.679	0.001	0.758	0.001

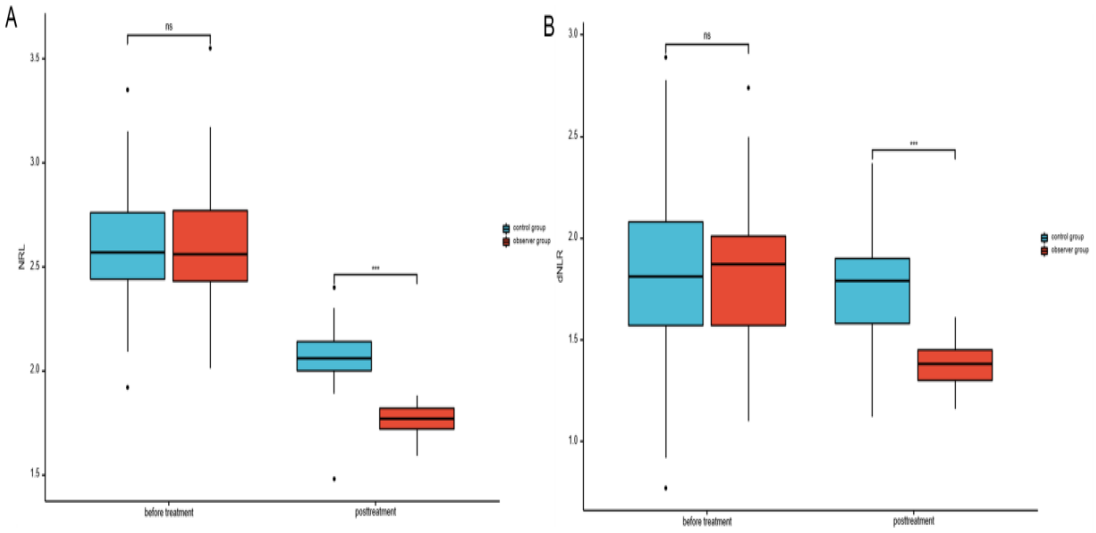

Figure 7: Comparison of the improvement of NRL and dNLR values between the two groups

3.6 Comparison of quality of life between groups

According to the data in Table 7 and Figure 8, the scores of each item and the overall score of the quality of living scale in the observing group was clearly superior to that in the controlling group, P<0.05.

Table 7: Comparing the quality of living of two groups of patients with advanced esophageal carcinoma (n=37, points)

Group	N	Emotion	Physiology	Function	Society	Total score
Control group	37	18.43 ± 2.24	16.84 ± 1.74	18.35 ± 2.07	15.97 ± 1.86	69.62 ± 7.95
Observation group	37	22.94 ± 1.20	24.16 ± 2.03	23.62 ± 3.16	20.51 ± 2.29	91.35 ± 8.63
X^2		10.880	16.571	8.426	9.435	11.226
P		0.001	0.001	0.001	0.001	0.001

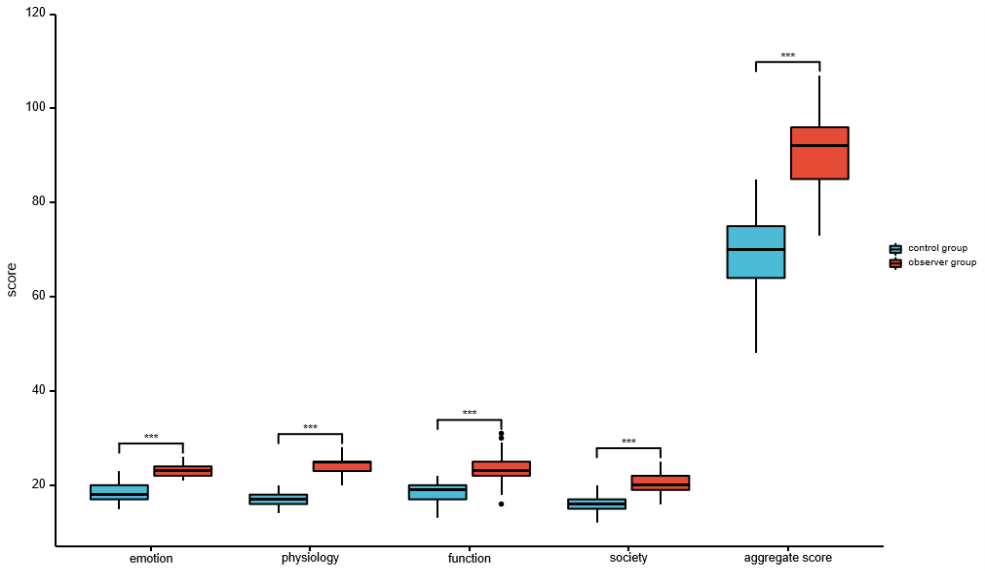

Figure 8: Patients' quality of life

4. Discussion

The number of athletic patients with esophageal cancer in China (including new cases and death cases) accounts for more than 50% of the world. Compared with other malignant tumors, the disease features a high morbidity and low cure rate (Soeratram et al., 2022). The clinical characteristics of patients with different esophageal cancers are different, and with the progression of the disease, patients can have many comorbidities. In addition, patients' nutritional status, psychological status, physical strength and other different conditions are also different, which all can have a certain impact on the conditions and prognosis (Parikh et al., 2019).

In clinical practice, most athletic patients with esophageal cancer are hospitalized due to the symptoms such as eating obstruction or burning sensation after the sternum, and the symptoms of most patients are mild or even not obvious. In the process of disease development, athletic patients may have anemia due to poor nutritional status and chronic gastrointestinal bleeding. Patients with advanced esophageal cancer have a high risk of esophagotracheal fistula, which can induce cough, fever and other manifestations (Ishikawa et al., 2021). In clinical practice, most athletic patients with esophageal cancer have progressed to locally advanced stage at the time of diagnosis, and even some them have distant metastasis of cancer cells, which cannot be treated by radical surgery, and advocate the implementation of integrated treatment on the basis of chemotherapy and radiotherapy (Chen et al., 2021; Daiko et al., 2020).

The cure rate of advanced esophageal cancer is extremely low. At this stage, it is advocated to carry out systemic treatment for athletic patients, with the goal of reducing symptoms such as malignant dysphagia, improving the

quality of life of athletic patients and prolonging their survival time (Han et al., 2020). Clinical meta-analysis has shown that (Hirano & Kato, 2019) the application of palliative systemic chemotherapy for patients with advanced esophageal cancer has an ideal effect in improving the conditions and quality of life of athletic patients. Esophageal cancer can be divided into squamous cell carcinoma and adenocarcinoma.

There are certain differences in the response of squamous cell carcinoma and adenocarcinoma to immunotherapy and targeted therapy. Trastuzumab is one of the drugs that targets human epidermal growth factor receptor 2. Compared with Ramucirumab, which targets vascular endothelial growth factor, trastuzumab is more suitable for the treatment of adenocarcinoma (Li & Zuo, 2019; Wang et al., 2019).

Immunotherapy of immune checkpoint inhibitors can achieve the ideal efficacy for the treatment of squamous cell carcinoma, but if the expression level of programmed cell death ligand 1 (PD-L1) in athletic patients is low or even no PD-L1 overexpression, the clinical efficacy is unknown. Immunotherapy relies on the combination of PD-1 receptor and ligand to reactivate toxic T lymphocytes in the tumor microenvironment, so as to achieve the purpose of inhibiting the tumors. Relevant clinical studies have pointed out that (Fukuoka et al., 2019) PD-1 immunosuppressant applied in the clinical treatment of esophageal cancer can play an ideal effect of anti-tumor activity, with higher safety. It can be applied in the second-line treatment of athletic patients with metastatic esophageal squamous cell carcinoma and advanced esophageal squamous cell carcinoma, and combined with chemotherapy treatment can obtain ideal clinical efficacy.

Relevant clinical studies have shown that (Sihag et al., 2021) the second-line treatment of pembrolizumab applied in the clinical treatment of patients with esophageal cancer has better efficacy than systemic chemotherapy with docetaxel, paclitaxel and other drugs alone. The results of this study revealed that the progression-free duration of survival and overall survival were clearly prolonged in the observed group than in the controlling group, and the objective remission rate and overall control rate were clearly superior in the observed group than in the controlling group. There was no remarkable discrepancy in the occurrence rates of treatment-related negative reactions and immune-related adverse reactions among the observed and controlling groups. It is suggested that in the clinical treatment of athletic patients with advanced esophageal cancer, the application of PD-1 inhibitors can obtain ideal clinical efficacy, and it has high safety.

Esophageal cancer can promote protein binding to PD-1, which can block the autoimmune system to kill cancer cells. Immune checkpoint inhibitors can inhibit PD-1 on lymphocytes, which can prevent the combination

of protein and PD-1, and improve the ability of the athletic patient's autoimmune system to kill cancer cells. Although it can kill tumor cells, the immune system also has an attack on its own normal cells, promoting the incidence of adverse reactions of the immune system. Immune-related adverse reactions include skin system, gastrointestinal system, liver and endocrine system and other rare inflammatory events, although tumor necrosis factor- α (TNF- α) antagonists and glucocorticoids have good curative effects on the adverse reactions of the immune system, there are still a few patients who may have serious toxic reactions or fulminant toxic reactions during the treatment process, which may even pose a threat to their life safety (Sato et al., 2021; Smyth et al., 2021).

In order to ensure the clinical efficacy of patients and the safety of treatment plan, it is necessary to closely monitor the clinical performance of patients during the treatment process and timely implement the corresponding measures. In this study, patients in both groups had immune pneumonia, and the reason may be related to the patients themselves that they may be complicated with immune system related diseases. Therefore, the relevant inspection work must be implemented before the application of PD-1 inhibitors in the treatment of patients with advanced esophageal cancer to reduce the risk of immune-related adverse reactions.

With the gradual deepening of clinical research, it has been found that inflammation is generally involved in the process of tumor proliferation, invasion and metastasis. At present, no clinical research or guidelines have clearly pointed out the association between NLR, dNLR and prognosis of malignancy patients. Relevant clinical studies have demonstrated that (Schoemmel et al., 2021) high NLR levels adversely affect the prognosis of patients with gastric cancer, intestinal cancer and pancreatic cancer. Some studies have also pointed out that (Pouw et al., 2021) NLR may be related to the rate of survival of esophageal cancer patients. According to the outcome of this study, the NLR and dNLR in the observed group were obviously below those in the controlling group after the therapy, indicating that the application of PD-1 inhibitors in the clinical treatment of advanced esophageal cancer patients could improve the patients' condition and delay the progression of the disease.

In this study, the scores of all items and general scores of the observed group were obviously superior to those of the controlling group, indicating that the application of PD-1 inhibitors in the treatment of patients with advanced esophageal cancer can clearly enhance the quality of living of patients. The reason is that the combination of PD-1 inhibitor treatment and chemotherapy treatment can achieve a synergistic effect. Because chemotherapy treatment, especially low-dose drug treatment, can promote tumor cell immunogenicity, enhance antigen processing and presentation, eliminate immunosuppressive

related Treg cell forms and stimulate specific anti-tumor immune response; at the same time, cytokines and immune cells can promote the sensitivity of tumor cells to relevant chemotherapeutic drugs, so as to improve the treatment effects, control the progression of disease and improve the quality of life of patients.

In a word, PD-1 inhibitors applied in the clinical treatment of patients with advanced esophageal cancer have the advantages of high efficacy and safety. However, this article is a study that belongs to a single center retrospective analysis, so the results obtained may have certain limitations. And there are some problems such as short follow-up time, small sample size, etc., so the research results are not universal, and it is necessary to carry out large sample size and prospective control studies in the future.

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