Efficacy and Safety of IL-2 injection for the treatment of childhood solid tumors or lymphoma with malignant pleural effusion, ascites and pericardial effusion

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Research Article

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Abstract

Background Currently, no available coherent management protocol exists for pediatric cancers associated with pleural effusion, ascites, and pericardial effusion. This study aimed to retrospectively present our experience in treating pediatric cancer patients with pleural effusion, ascites, and pericardial effusion using interleukin-2 (IL-2) and dexamethasone (DEX) intracavitary injections.

Methods Between January 1st, 2008 and December 31st, 2020, medical reports of patients diagnosed with solid tumors or lymphoma were checked to identify those with concurrent > 2 cm pleural effusion and/or ascites and/or pericardial effusion. Patients diagnosed with effusions and treated with IL-2 were identified as being in the effusion group. Meanwhile, patients with the same primary tumors and effusions but did not receive interleukin 2 injection were reviewed and classified as the control group.

Results Forty patients with solid tumors and Sixty-six patients with lymphoma were further diagnosed with pleural effusion, ascites, or pericardial effusion. A total of eighty-five patients received IL-2 injection while the remaining twenty-one did not. When lymphoma and solid tumor patients were combined, the Kaplan Meier analysis revealed a significant difference between the two groups, with $p<0.01$ for event free survival (EFS) and $p<0.01$ for overall survival (OS), both of which had $p<0.01$. Hazard ratio was found to be 0.344 for OS and 0.352 for EFS.

Conclusions This retrospective study illustrates that thoracic, intraperitoneal, or pericardial injection of DEX plus IL-2 can be an effective and safe treatment for pediatric cancers with pleural effusion, ascites, and pericardial effusion.

Introduction

Malignant pleural effusion, ascites, and pericardial effusion are common complications of most pediatric cancers, including 50% of patients with lymphomas and 50% with other tumors (like all kinds of sarcomas, neuroblastoma (NB), and hepatoblastoma (HB))[1-3]. Malignant pleural effusion and pericardial effusion can cause breathlessness and are sometimes life-threatening. Moreover, hemorrhagic pleural effusion or ascites from a ruptured tumor may increase metastasis risk. As shown in a report from Children's Oncology Group (COG) protocol AHOD0031, pleural effusion is an independent risk factor for the relapse of Hodgkin lymphoma[3]. However, no coherent management protocol is currently found for pleural effusion, ascites, and pericardial effusion. It seems that pleural effusion, ascites, and pericardial effusion can only be resolved with systemic chemotherapy, which can not only immediately relieve the discomfort of children but also increase metastasis risk. This study retrospectively presents our twelve-year's experience in treating pleural effusion, ascites, and pericardial effusion with interleukin-2 (IL-2) and dexamethasone (DEX) intracavitary injections among pediatric cancer patients.

Methods

This work was a single-center, retrospective cohort study. The ethics committee of our hospital approved our study protocols. Medical records from patients confirmed with solid tumors or lymphoma between January 1st, 2008 and December 31st, 2020, were reviewed to identify patients diagnosed with >2 cm pleural effusion, and/or more than grade 1 ascites, and/or more than small pericardial effusion. For pleural effusion, small effusion (SE) is described as any effusion measuring 2–3 cm in size. Moderate effusion (ME) is any effusion >3 cm in size that reached the mid-thoracic level on computer tomography (CT) image. Large effusion (LE) is any effusion that extends from the lung base to the apex and displaces heart and mediastinum toward the opposite side[3]. For ascites, grade 1 (G1) is mild ascites only detectable by ultrasound, grade 2 (G2) is moderate ascites evident by moderate symmetrical distension of abdomen, grade 3 (G3) is large or gross ascites with marked abdominal distension[4]. For pericardial effusion, total effusion (sum of the anterior and posterior) is categorized as small (S, 1 to 9 mm), moderate (M, 10 to 19 mm), or large (L, 20 mm or more) [5]

Patients diagnosed with effusions who received IL-2 injection were classified as effusion group. Meanwhile, patients with the same primary tumors with effusions who did not obtain IL-2 injection were reviewed and classified as a control group. To diagnose solid tumors or lymphoma, a fine needle biopsy or open biopsy was performed routinely.

The following patient data were extracted, including age, gender, tumor type, tumor stage, clinical manifestations of pleural effusion, ascites and pericardial effusion, therapeutic regimens of pleural effusion, ascites, and pericardial effusion, treatment response, and patient outcome. The Institutional Review Boards approved the collection of patients' clinical records. All data were anonymous, and informed consent was waived due to retrospective observational nature of this study. For patients whose disease was measurable by CT or magnetic resonance imaging (MRI), their responses were assessed according to revised-RECIST criteria. Complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) were recorded accordingly[6].

Statistical analysis

The primary outcome was event-free survival (EFS) and overall survival (OS) rates. EFS was defined as the interval between diagnosis and disease progression, relapse, or death, and OS was defined as the interval between diagnosis and death from any cause or last contact. The Kaplan and Meier approach was used to estimate patient survival times. Kaplan Meier analysis was used to describe the time from IL-2 exposure to follow-up, and the log-rank test was used to compare findings between effusion and control groups. P <0.05 was considered as significance difference. GraphPad Prism 8.0 was used for all statistical analyses and images.

Results

Patients

Between January 1st, 2008 and December 31st, 2020, 372 patients were diagnosed with solid tumors, while 416 were diagnosed with lymphoma. Among them, forty patients with solid tumors and sixty-six patients with lymphoma were further diagnosed with pleural effusion, ascites, or pericardial effusion. A total of eighty-five patients received IL-2 injection while the remaining twenty-one patients did not. Indeed, twenty-one patients were diagnosed at early stage of this retrospective study. IL-2 injection was not routinely used to treat effusions at the time.

Among eighty-five patients in the effusion group, twenty-one had stage III diseases (including T cell lymphoblastic lymphoma, B cell lymphoblastic lymphoma, primitive neuroectodermal tumor (PNET), HB, and pediatric pneumoblastoma (PPB) in twelve, three, two, and two cases, respectively), while the remaining sixty-four had stage IV diseases (including T cell lymphoblastic lymphoma, B cell lymphoblastic lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma (BL), anaplastic large cell lymphoma (ALCL), rhabdomyosarcoma (RMS), NB, Ewing's, HB, PNET, and PPB in twenty-four, six, six, three, two, seven, four, four, four, three, and one case, respectively). Meanwhile, fifty-eight patients only had pleural effusion (including bilateral pleural effusions in twenty-nine patients), while fifteen only had ascites. The remaining twelve cases had concurrent pleural effusion, ascites, and pericardial effusion. Moreover, the remaining twelve patients all had bilateral pleural effusions.

Accordingly, for patients without IL-2 injection, 1 had stage II disease (HB in one), and one had stage IVs disease (NB in one). Nine cases had stage III diseases (including T cell lymphoblastic lymphoma in three cases, B cell lymphoblastic lymphoma in one, Ewing's in two, PNET in one, and HB in two), while the remaining ten patients had stage IV diseases (including T cell lymphoblastic lymphoma in two cases, B cell lymphoblastic lymphoma in one, DLBCL in two, ALCL in one, RMS in three, and PNET in one). Meanwhile, eleven patients only had pleural effusion (including bilateral pleural effusions in seven patients), while six only had ascites. The remaining four cases had concurrent pleural effusion, ascites, or pericardial effusion, all of which had bilateral pleural effusions. The detailed characteristics of one hundred and six patients are presented in Table 1.

Table 1. The detailed characteristics of 106 patients

	Effusion group		Control group	
	Solid tumor	Lymphoma	Solid tumor	Lymphoma
Age(mean±se)	5.42±3.97	8.02±3.43	4.96±3.7	9.8±2.39
Gender				
Male	15	32	6	6
Female	14	24	5	4
stage				
II			1	
III	4	15	5	4
IV	24	44	4	6
IVs			1	
Histology				
RMS	7		3	
NB	4		1	
PPB	3			
Ewing's sarcoma	4		2	
HB	6		3	
PNET	5		2	
T cell lymphoblastic lymphoma		36		5
B cell lymphoblastic lymphoma		9		2
DLBCL		6		2
BL		3		
ALCL		2		1

Note: RMS, rhabdomyosarcoma; NB, neuroblastoma; PPB, pediatric pneumoblastoma; HB, hepatoblastoma; PNET, primitive neuroectodermal tumor; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt's lymphoma; ALCL, anaplastic large cell lymphoma

Dyspnea, cough, and discomfort were the most frequently reported symptoms of pleural and pericardial effusions, whereas abdominal distension, abdominal pain, and edema were the most widely recognized symptoms of ascites.

Treatment

While all patients in the effusion group were diagnosed with a malignant tumor and pleural effusion, ascites, or pericardial effusion, IL-2 injection therapy may be administered without a pathological diagnosis as long as malignant lesions associated with pleural, abdominal, or pericardial effusion were

identified on imaging. We obtained written informed consent from patients' parents or legal guardians before starting the therapy. First, patients performed thoracic, abdominal cavity, or pericardial cavity puncture with the indwelling of a drainage tube, and pathology was simultaneously obtained if permitted.

In patients with unilateral pleural effusion, no more than 600 mL fluid was drained on the first day and no more than 1000 mL each day; for patients with bilateral pleural effusions, the total drainage volume was the same. Ascites should not exceed 1000 mL each time, and pericardial effusion should not exceed 100 mL each time. In the presence of multi-cavity effusions, the drained effusion amount should be reduced as appropriate, and static electricity of hydration solution should be applied simultaneously.

After discharge, 0.9% sodium chloride injection (0.9%NaCl, maximum 100 mL) combined with IL-2 (5.0-10.0×106 IU/m2, maximum dose 10.0×106 IU) and DEX (5 mg) was injected via the drainage tube. The injection was administered every other day, and the total number of injections was not strictly limited, which was stopped when ultrasound confirmed that the effusion was no more than 2 cm or disappeared. For patients with bilateral pleural effusions or multi-cavity effusions, the maximum total doses of IL-2 and DEX were maintained at 10.0×106 IU and 5 mg, respectively, which should be divided according to 0.9%NaCl volume. It should be noted that 0.9%NaCl volume should not exceed 50 mL during unilateral thoracic injection and should not exceed 20 mL during pericardial cavity injection. Besides, the injection time should be more than 1 hour. It was advisable to use an injection pump to pump the fluid at a uniform rate. No strict requirement was found for the intraperitoneal injection rate or the fluid amount. After injection, the drainage tube was closed until the following day, and the child was instructed to change the position as much as possible to ensure the wider distribution of IL-2.

Chemotherapy might be initiated during IL-2 therapy. All patients in the control group were treated according to pathology diagnosis without IL-2 therapy.

Response

A total of four hundred and eighty one injections were administered for eight-five patients. The average number of injections into the pericardial cavity was two, while that into pleural and intraperitoneal cavities were three to four. Only one patient with T cell lymphoblastic lymphoma received the maximum seven pleural injections.

Among the eighty-five patients, half had bloody drainage fluid, and tumor exfoliated cells were detected in the drainage fluid from thirty-one patients. The injections generally had limited toxicity, and only eleven patients developed a moderate fever on the first day of injection. No patient developed respiratory distress related to IL-2 injection therapy. Simultaneously, no allergic reaction or catheter-related infection occurred.

Outcome

In this study, patients with solid tumors were mainly treated according to the protocols from COG or International Society of Pediatric Oncology group (SIOP)[7-13], whereas those with lymphoma were

mainly treated in line with BFM protocols[14-17]. All patients in the effusion group achieved CR of effusions from IL-2 injection therapy, even though one patient received seven injections altogether. No recurrence of pleural effusion, ascites, or pericardial effusion was noticed.

Among patients in the effusion group with lymphoma, four died of disease progression, and two had relapsed disease (including three with T cell lymphoblastic lymphoma, one with DLBCL, one with BL, and one with ALCL). One of the two patients with relapsed disease died, while the other with ALCL achieved SD after crizotinib treatment[18]. The five-year EFS and five-year OS for patients with lymphoma were 89.3%±31.2% (95%CI, 80.9% to 97.6%) and 91.1%±28.8% (95%CI, 83.4% to 98.8%), respectively. Among patients in the control group with lymphoma, two died of disease progression, and two had relapsed disease (including one with T cell lymphoblastic lymphoma, two with DLBCL, and one with ALCL). Both patients with relapsed disease died. The five-year EFS and five-year OS for patients with lymphoma were 60%±51.6% (95%CI, 23.1% to 96.9%). The Kaplan Meier analysis demonstrated significant differences between the two groups with both of which $p<0.01$. When we calculated the hazard ratio (HR), we found that it was 0.191 for EFS and 0.161 for OS (Figure 1).

For patients in the effusion group with solid tumors, four died due to disease progression, and eight got relapsed diseases (including three with RMS, one with NB, three with PPB, one with Ewing's sarcoma, one with HB, and one with PNET). Seven of the eight patients with relapsed disease died, while the other with HB achieved secondary CR after irinotecan treatment[19]. The five-year EFS and five-year OS were 62.1% ±49.4% (95%CI, 43.3% to 80.9%) and 65.5%±48.4% (95%CI, 47.1% to 83.9%), respectively. For patients in the control group, among patients with solid tumors, two died due to disease progression, and four got relapsed diseases (including three with RMS, one with NB, one with Ewing's sarcoma, and one with PNET). Three patients with relapsed disease died, while the other with NB achieved PR after irinotecan treatment and alive with tumor. The five-year EFS and five-year OS were 45.5%±52.2% (95%CI, 10.4% to 80.5%) and 54.5%±52.2% (95%CI, 19.5% to 89.6%), respectively. The Kaplan Meier analysis showed no statistical difference between the two groups with both of which $p>0.05$ (Figure 2).

However, when lymphoma and solid tumor patients were combined, the Kaplan Meier analysis revealed a significant difference between the two groups, with $p<0.01$ for EFS and OS. HR=0.344 between OS and 0.352 between EFS (Figure 3).

The mean effusion control time (<2m pleural effusion, or disappearance of ascites or pericardial injection) for the effusion group was 5.76±1.95 days (95%CI, 5.34 to 6.19 days), while for the control group was 18.3±5.25 days (95%CI, 15.94 to 20.72 days), which had statistical difference ($p<0.01$).

Discussion

Several reports exist on the small size of pediatric patients with pleural effusion or ascites[2, 20, 21]. However, no existing study has been conducted to investigate the role of IL-2 in pediatric cancer patients with malignant pleural effusion, ascetics, and pericardial effusion. It has been well recognized that IL-2 plays a vital role in activating and maintaining specific and nonspecific immune responses[22]. IL-2 can

induce activated natural killer cells and enhance antibody-dependent cellular cytotoxicity[23]. As such, IL-2 injection is applied in treating adult tumors[24, 25].

Remarkably, we found that DEX administration combined with IL-2 via thoracic, intraperitoneal, or pericardial injection quickly resolved the fluid and immediately relieved the discomfort of patients. Moreover, no recurrence of pleural effusion, ascites, or pericardial effusion was observed in our patients. These results suggested that IL-2 played a particular role in treating pleural effusion, ascites, and pericardial effusion. Initially, we administered IL-2 without obtaining a pathological diagnosis to save the patient's life when imaging examination revealed a potentially malignant tumor associated with pleural effusion, ascites, or pericardial effusion, especially in critically ill children. Our treatment is effective, as all symptoms, including chest pain and dyspnea, improved to varying degrees in affected children. The mean effusion control time for the effusion group was 5.76±1.95 days vs. 18.3±5.25 days for the control group, which significantly differed. Although tumor-exfoliated cells were only detected in thirty-one patients, there was no misdiagnosis, and this procedure has become our regular treatment model.

Pleural effusion, ascites, and pericardial effusion are the possible signs of tumor spread, indicating the contamination of pleural space or abdominal cavity; thus, they are often considered negative prognostic factors[3, 21]. However, as reported in the study on NB patients from St. Jude Children's Research Hospital, no difference is found in the survival related to a pleural effusion[2].

Our retrospective study included many tumors, so it was difficult to determine the tumor prognosis from survival. However, the five-year EFS and five-year OS for patients in the effusion group with lymphoma were 89.3%±31.2% (95%CI, 80.9% to 97.6%) and 91.1%±28.8% (95%CI, 83.4% to 98.8%) while those for patients in the control group with lymphoma were 60%±51.6% (95%CI, 23.1% to 96.9%). There was a statistical difference, and HR was <1, indicating that IL-2 therapy is a protective factor for survival. The NHL-BFM90 study reports a 90% EFS rate for patients with T-cell lymphoblastic lymphoma and a 93.9% three-year EFS for those with mature B cell lymphoma. In our study, the five-year EFS in the effusion group was 89.3%±31.2%, comparable to those reported in other studies but not in the control group. As such, our study showed that with the appropriate treatment, pleural effusion, ascites, and pericardial effusion were not poor prognostic factors.

The five-year EFS and five-year OS for patients in the effusion group with solid tumors were 62.1%±49.4% (95%CI, 43.3% to 80.9%) and 65.5%±48.4% (95%CI, 47.1% to 83.9%), vs. in the control group, where the five-year EFS and five-year OS were 45.5%±52.2% (95%CI, 10.4% to 80.5%) and 54.5%±52.2% (95%CI, 19.5% to 89.6%). Nowadays, the 5-year OS for patients with pediatric solid tumors ranges from 50% to 80%[9, 26, 27]. Our five-year OS was slightly lower than the average level, which might be because the three children diagnosed with type III PPB died. Furthermore, despite the lack of a statistically significant difference between the two groups (p=0.593), it is obvious that interleukin-2 therapy has a beneficial effect; at least, it does not reduce survival. Moreover, when all patients were combined, a statistically significant difference between the two groups was observed. The reason might be that the number of patients in the solid tumor group was relatively small.

It is known that IL-2 administration is associated with numerous side effects, and there is evidence that increased doses of IL-2 lead to increased toxicity[28]. Several dosage regimens, including high intravenous doses (720,000 or 600,000 international units/kg), have been applied for obtaining the maximum therapeutic benefit[24]. At our hospital, the recommended dosage of IL-2 is 1 million IU/ m2/ time (maximum dose 10.0×106 IU). Our study suggested that IL-2 injection following this dose was well tolerated and highly safe. The possible mechanism of IL-2 in treating adult pleural effusion is that IL-2 increases the numbers of CD3+ T cells and NK cells in the pleural space and enhances the immune response, thus reducing the incidence of pleural effusion. However, the mechanism of IL-2 in treating pediatric cancers remains unknown. Most pediatric cancers arise from embryonal cells that are distinctly different from epithelial cells, and the immune response itself is also markedly different between adults and children. Consequently, the low mutational burden and relative lack of neoantigen expression are among the defining traits of pediatric cancers, which have limited their immune targeting susceptibility[29].

To sum up, this retrospective research demonstrates that thoracic, intraperitoneal injection or pericardial injection of DEX plus IL-2 is an effective and highly safe treatment for pediatric cancers with pleural effusion, ascites, and pericardial effusion. However, further randomized trials are warranted to provide more real evidence to evaluate the efficacy of IL-2 in treating pediatric patients.

List Of Abbreviations

IL-2	interleukin-2
DEX	dexamethasone
EFS	event free survival
OS	overall survival
NB	neuroblastoma
HB	hepatoblastoma
COG	Children’s Oncology Group
SE	small effusion
ME	moderate effusion
CT	computer tomography
LE	large effusion
G1	grade 1

G2	grade 2
G3	grade 3
S	small
M	moderate
L	large
MRI	magnetic resonance imaging
CR	complete response
PR	partial response
PD	progressive disease
SD	stable disease
PNET	primitive neuroectodermal tumor
PPB	pediatric pneumoblastoma
DLBCL	diffuse large B-cell lymphoma
BL	Burkitt's lymphoma
ALCL	anaplastic large cell lymphoma
RMS	rhabdomyosarcoma
NaCl	sodium chloride injection
SIOP	Society of Pediatric Oncology group

Declarations

Ethics approval and consent to participate Approved by the Ethical Institution of the first hospital of Jilin university. Because of its retrospective manner, informed consent was waived by the Ethical Institution of the first hospital of Jilin university

Statement: All methods were carried out in accordance with relevant guidelines and regulations.

Consent to Participate This is a retrospective study, informed consent was waived by the Ethical Institution of the first hospital of Jilin university. However, when we performed the IL-2 injection, we obtained written informed consent from patients' parents or legal guardians before starting the therapy.

informed consent was obtained by each patients or their parents.

Consent for publication: Not applicable

Availability of data and materials Patient's data were available in medical records room of the first hospital of Jilin university. The datasets generated and/or analysed during the current study are not publicly available due to they are files in medical records room in our hospital, but are available from the corresponding author on reasonable request.

Competing interests The authors indicated no potential conflicts of interest.

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Authors' contributions

1)YTZ: Dr. Z made substantial contributions to design of the work; drafted the manuscript; agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

2)XDZ: Dr. Z made substantial contributions to design of the work; drafted the manuscript; all authors have read and approved the manuscript; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

3)YLG: Dr. G made substantial contributions to the design of the work revised the manuscript critically; all authors have read and approved the manuscript.; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

4)JC: Dr. C made substantial contributions to design of the work; drafted the manuscript; agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

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Figures

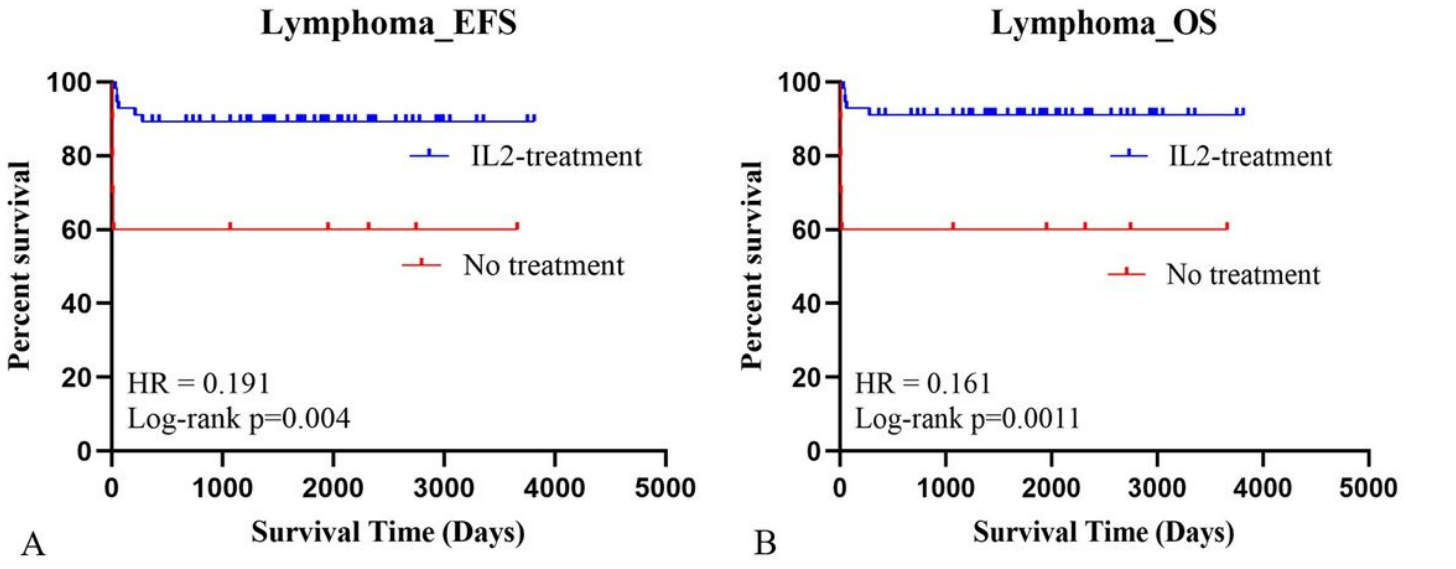

Figure 1

A: The Kaplan Meier analysis demonstrated significant differences between the effusion group and control group for lymphoma patients in EFS (p<0.01). The hazard ratio was 0.191 for EFS. A: The Kaplan Meier analysis demonstrated significant differences between the effusion group and control group for lymphoma patients in OS (p<0.01). The hazard ratio was 0.161 for OS.

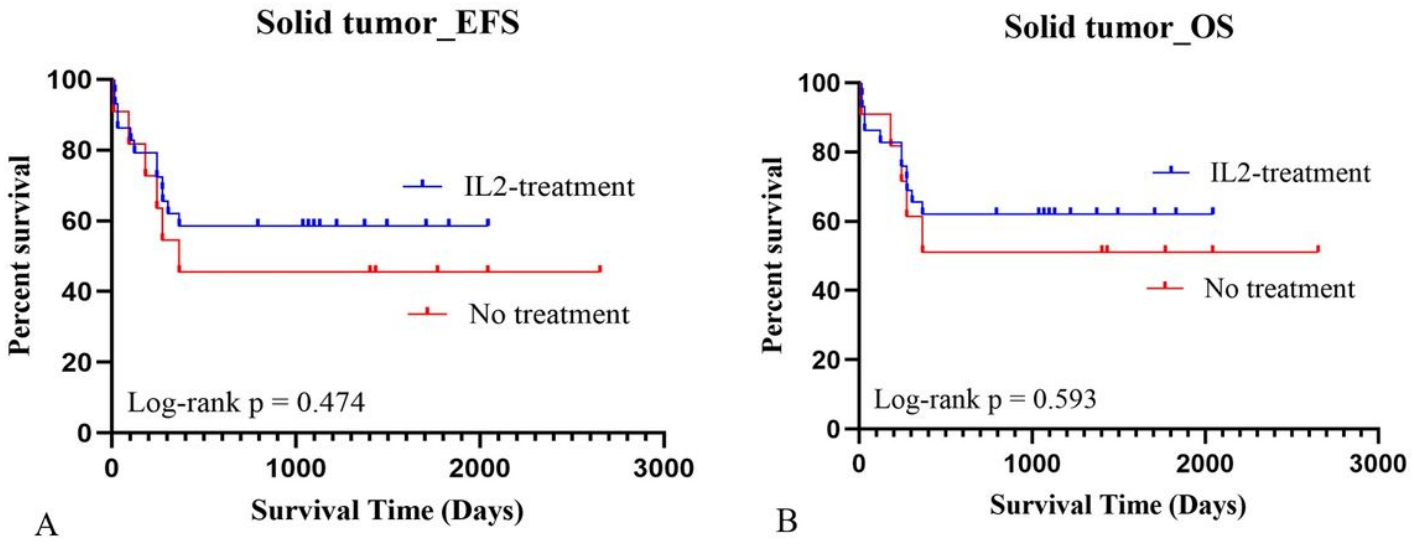

Figure 2

A: The Kaplan Meier analysis demonstrated no differences between the effusion group and control group for solid tumor patients in EFS (p>0.05). A: The Kaplan Meier analysis demonstrated no differences between the effusion group and control group for solid tumor patients in OS (p>0.05).

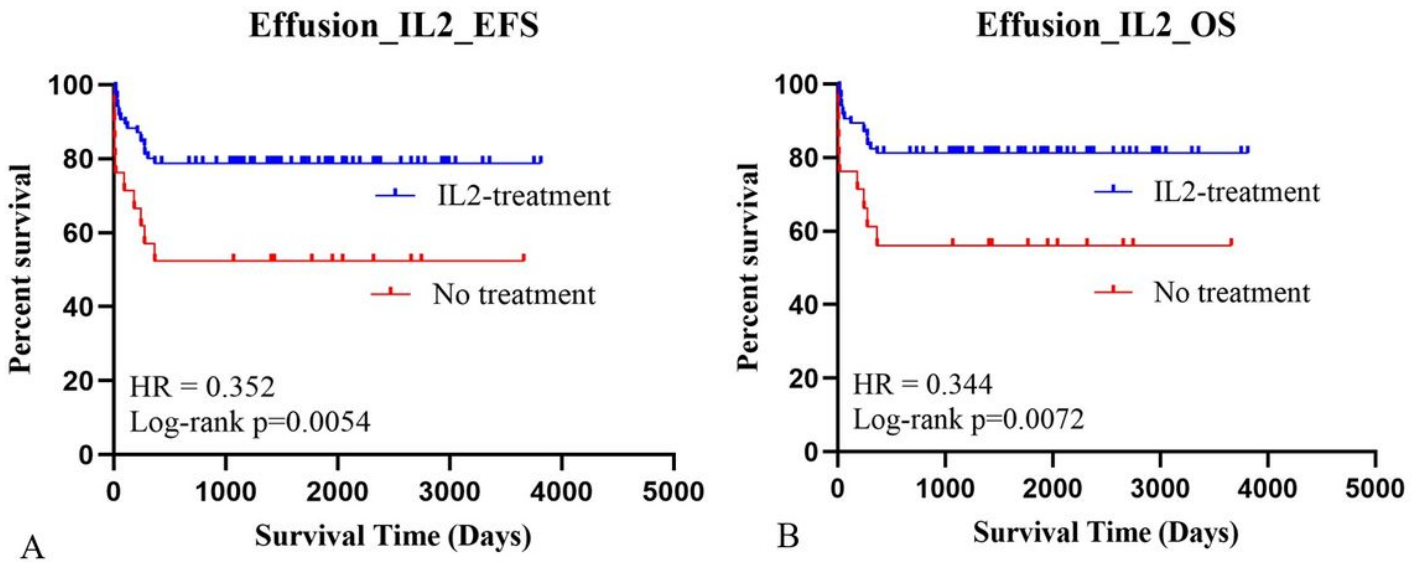

Figure 3

A: The Kaplan Meier analysis demonstrated significant differences between the effusion group and control group for pediatric cancer patients in EFS ($p<0.01$). The hazard ratio was 0.352 for EFS. A: The Kaplan Meier analysis demonstrated significant differences between the effusion group and control group for pediatric cancer patients in OS ($p<0.01$). The hazard ratio was 0.344 for OS.