Research Square

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Time-specific lymphocyte kinetics predict prognosis for patients with locally advanced cervical adenocarcinoma undergoing definitive radiotherapy: insights from a retrospective cohort study

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Abstract

Background

Lymphocytes are the foundation of anti-cancer immune response and effective immunotherapy, yet they are unavoidably compromised during radiotherapy (RT). This results in unsatisfactory treatment efficacy for cervical adenocarcinoma, which is a radio-resistant subtype of cervical cancer. In this study, we systematically evaluated the prognostic value of peripheral lymphocyte counts measured before, during and after RT for cervical adenocarcinoma (ADC) patients.

Methods

A single center, retrospective study was conducted. Longitudinal lymphocytes counts were collected for 193 patients with locally advanced ADC, beginning 1 week before the initiation of definitive RT and continuing up to 6 months post-RT. Survival analyses were performed to evaluate and compare the prognostic significance of lymphocyte counts across different time points. RNA-sequencing data of tumor tissues was analyzed to explore the underlying mechanism.

Results

Patients with high lymphocyte counts exhibited better overall survival (OS) and progression free survival (PFS) at most time points assessed. The maximal survival advantage was observed during the 1st week of RT. Among patients who didn't undergo surgery following RT, during the 1st week of RT the low lymphocyte group had a hazard ratio (HR) of 2.45 (95% CI: 1.09–5.5) for OS and 2.21 (95% CI: 1.21–4.04) for PFS, as determined by the multivariate COX regression. Analyses with limited samples suggested that lymphocyte counts 3–6 months post-RT might also be prognostic. No correlation was observed between patients' peripheral lymphocyte counts and levels of tumor infiltrating immune cells.

Conclusions

Low lymphocyte counts during and post-RT, particularly in the 1st week of RT, are associated with poor prognosis for ADC patients, illustrating the clinical value of mitigating the impact of RT on lymphocytes in the early stage of RT.

Background

Cervical cancer, which accounts for 6.24% of all cancer cases among women[1], remains a significant healthcare issue today, particularly in developing countries[2]. While squamous cell carcinoma (SCC) is the major histological type, the incidence of cervical adenocarcinoma (ADC), which arises from the

glandular epithelial cells of cervix, accounts for up to 25% of cervical malignancies, and is still rising[3]. Concurrent chemo-radiotherapy is the standard first-line treatment of locally advanced cervical carcinoma (LACC) (2018 FIGO stages IB3, IIA2-IVA), for both ADC and SCC[4]. However, the treatment efficacy for LACC is still not satisfying, with a 5-year OS rate around 65–70%[2,5]. ADC patients have higher incidence of recurrence and metastasis compared to SCC patients[6], posing a big challenge for their clinical management.

The association between lymphocyte (Lym) count and prognosis of solid tumor patients has received extensive attention[7–9]. With the wide application of immunotherapy (IT), this association has become more clinically meaningful, as various subsets of Lym are key regulators and effectors of human's anti-tumor immune response[9,10]. Without enough functionally normal Lym, IT drugs such as immune checkpoint inhibitors would lose its foundation. For cervical cancer, the association between Lym count and prognosis has also been established. Low Lym counts before, during or after radiotherapy (RT) were all found to be associated with shorter survival[11–17]. However, most patients enrolled in these studies were SCC patients, with the effects of Lym counts on the prognosis of ADC patients remains unknown. Furthermore, the varying effects of Lym counts at different time points were not thoroughly investigated. This is of clinical significance, since Lym counts undergo drastic change during RT, given that radiation unavoidably kills Lym.

In this study, we make use of a retrospective cohort of ADC patients in our hospital to systematically and dynamically study the impact of Lym counts on the prognosis of ADC patients who underwent definitive RT. We found that there might be vital time windows where the total Lym counts matter more than that at other time points, which imply for opportunity to optimize the current definitive RT regimen, particularly in the context of combined RT and IT.

Methods

Patient Selection

ADC patients were selected from our ongoing retrospective cohort of the ATTRACT study (evaluation of the treatment response and prognosis of cervical adenocarcinoma after radiotherapy)[18], which was approved by the Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH) (IRB number: K6420), registered on http://clinicaltrials.gov (register number was NCT06741046, registered on 16/12/2024).

The inclusion criterion of this study: 1) Diagnosis of ADC confirmed with pathological exam; 2) FIGO stage (restaged according to the 2018 classification): IB3, IIA2 to IVA; 3) Received definitive radiotherapy (including both external beam radiotherapy (EBRT) and brachytherapy); 4) CBC results available for at least one time point before, during or after RT (within 6 months post-RT). Exclusion criterion: patients didn't complete the entire course of definitive radiotherapy for any reason.

Clinical Data collection

Patients' clinical characteristics were collected from the electronic health record system, including their demographic characteristics (age, HPV status, etc), tumor features (FIGO stage, histology, grade, etc), and treatment details (chemotherapy regimen, radiotherapy regimen, maintenance therapy post-RT, whether they undergo surgery or not, whether they undergo immune-therapy or not). Patients' total Lym counts were obtained from their CBC results within one week before the initiation of RT, throughout the entire course of RT, and up to 6 months following the completion of RT. Patients' averaged Lym counts were calculated for the week before RT, for each week during RT and each month post-RT (for the period of 3rd to 6th months post-RT, one average Lym count was calculated). Patients' survival status was obtained by periodical telephone follow-up, and patients' tumor progression status were obtained via regular telephone follow-up as well as their electronic health record in the hospital. Patients' overall survival (OS) was defined as the duration from diagnosis to the date of death or last follow-up, progression free survival (PFS) was defined as the duration from treatment to the date of first sign of progression indicated by radiological examination (CT, MRI or PET-CT).

RNA-seq data collection and analyses of TME

To explore the association between the Lym count in the peripheral blood and the levels of different types of tumor infiltrating immune cells (TIIC) in the tumor tissue, we used the RNA-seq data of surgically resected tumor tissues of 23 ADC patients (technical details were available in a previously published paper[19]: doi 10.3389/fimmu.2025.1563593) to infer TIIC. These patients underwent surgery directly and didn't undergo RT. TIIC levels were inferred using four different bioinformatic tools (Quantiseq[20], TIMER[21], MCPcounter[22], Consensus^{TME}[23]). Quantiseq and TIMER are deconvolution-based algorithms, while MCPcounter is based on the enrichment scores of marker genes. Consensus^{TME} integrates the results of multiple algorithms. The ESTIMATE[24] algorithm was used to calculate the overall immune scores of tumors. All the algorithms were implemented using the R package "tigeR[25]". Regarding the Lym counts of these 23 ADC patients, their most recent Lym counts measured before surgery (mostly 1 day before they underwent surgery) were collected.

Statistical analysis

OS and PFS were selected as the end point of survival analysis. OS was defined as the period of time from the start date of RT to the date of death, PFS was defined from the start date of RT to the date of first radiographically confirmed progression or recurrence of tumor. Survival analysis was carried out using the Kaplan-Meier (KM) analysis and the multivariate COX regression. For the KM analysis, differences in survival between groups was compared using the log-rank test. For the multivariate COX regression, covariates were empirically selected, and the significance of variables were tested using the Wald test. We used two-sided P-value < 0.05 as the significance threshold for all statistical tests. All analyses were carried out in R (version 4.5.3).

Results

193 patients diagnosed with ADC and underwent definitive RT were included in this study. The median follow-up time was 28.37 months (interquartile range: 10.43–48.1 months). Supplementary Table 1 presents the clinical characteristics of these patients. Most patients had FIGO stage II (84, 43.5%) or III (95, 49.2%) diseases. 87 patients (45.1%) underwent surgery after definitive RT. 64 patients (33.2%) took maintenance therapy (chemotherapy or/and IT).

Figure 1 illustrates the dynamic change of Lym counts of all patients, from 1 week prior to RT to 6 months post-RT. Before the initiation of RT, 113 in 153 patients had a Lym count larger than 0.8×10^9/L (the lower limit of the normal range of Lym count according PUMCH standard). After the initiation of RT, patients' Lym counts dropped quickly. During the 5th week after RT initiation, the averaged Lym count of all patients with available CBC results was 0.42×10^9/L. After the completion of RT, patients' Lym gradually increased, yet within 6 months post-RT, the Lym counts were still much lower than that before RT.

Kaplan-Meier (KM) analysis and multivariate COX regression were performed using patients' Lym counts measured at all different time points. Figure 2A compares the progression free survival (PFS) of patients in the groups of high and low Lym during the 1st week of RT (groups were defined using the median Lym counts of all patients as the cut-off: 1.06×10^9/L). Patients with high Lym counts had longer PFS (Log-rank test, P = 0.082, n = 150 patients). Multivariate COX regression identified the Lym group (high V.S. low) as a significant independent predictor of PFS (HR = 1.64, 95% CI: 1.02–2.63, P = 0.042, n = 150), together with FIGO stage and having surgery after RT. Among patients who didn't undergo surgery following RT, the Lym group remained significant in both univariate and multivariate analyses, with a HR of 2.21 (95% CI: 1.21-4) in the COX regression model (Fig. 2C-D). The high Lym group was also significantly associated with overall survival (OS) (Fig. 3). Particularly, among patients who didn't undergo surgery following RT, the HR of the high Lym group was 2.45 (95%CI: 1.09–5.5).

Figure 4 compares the HR of the Lym group (high V.S. low) at different time points, as estimated by multivariate COX regression. The HR of the Lym group within the 1st week after RT initiation was greater than that of other time points during RT in most cases. For time points post-RT (especially within the 3rd and 4th to 6th months post-RT), the HR of the Lym group was large, yet the estimates carried considerable uncertainty owing to the limited sample size. When using 0.8×10^9/L as the cut-off to define high and low Lym groups, similar results were obtained (Supplementary Fig. 1). Figure 5 presents a comparison of the AUROC (area under the receiver operating characteristics curve) for the absolute Lym count (modelled as a continuous variable) at different time points in predicting patients' OS and PFS, revealing patterns like those observed for the HR of the Lym group (Fig. 4).

To explore the relationship between peripheral Lym counts and TIIC, we compared the estimated TIIC levels of patients in the high and low Lym groups (defined using the median of Lym). We found no

consistent significant differences in TIIC levels across the results given by different algorithms (Supplementary Fig. 2).

Discussion

Multiple studies have found the association between Lym counts in the peripheral blood of SCC patients and their prognosis. ADC exhibits a lower incidence, reduced sensitivity to RT[26] and a poorer prognosis than SCC[27]. Furthermore, ADC remains comparatively understudied, underscoring the urgent need for further investigation and the optimization of its therapeutic regimen. Building on the standard concurrent chemo-radiotherapy backbone, IT is now recommended for stage IIIA-IVA cervical cancer patients (2014 FIGO classification) in the 2026 NCCN guidelines supported by level I evidence[28]. This paradigm shift has also prompted further investigations into its efficacy across diverse histological subtypes, including SCC, ADC and adeno-squamous carcinoma[29–31].Researchers have discovered that lymphopenia caused by RT, especially conventional fractionated RT, to a large extent weakened the effect of IT[32,33]. Despite these scientific discoveries and theoretical deductions, no study up to now has paid specific attention to the association between Lym count and prognosis of ADC, which was undoubtfully a research gap to be filled. In addition, most relevant studies only analyzed Lym counts at one or two time points, resulting in the loss of key information.

In this study, we comprehensively and dynamically analyzed the association between Lym counts and clinical outcomes of ADC patients. We found that low level of Lym during the 1st week of RT was associated with worse prognosis. More importantly, the effect size of Lym count group during the 1st week of RT in survival analyses was larger than that of other time points during RT. Besides, low level of Lym during 4th -6th months post-RT may also be associated with worse prognosis. Exploratory analysis indicated that Lym counts in the peripheral blood is not parallel to the counts of TIIC in the primary tumor tissue.

It is well recognized that RT can activate the immune system of human to combat cancer via various mechanisms. One of the most important mechanisms is the induction of immunogenic cell death of tumor cells, releasing tumor antigen and promoting the infiltration of effector Lym into the tumor microenvironment (TME). Studies have found that it generally takes 3–7 days for the activation and trafficking of T-cells since the exposure to tumor antigen[34,35]. This probably means that the 1st week during RT is a critical time window for the launch or escalation of anti-tumor response. Therefore, Lym count might be an indicator of the intensity of immune response in this period. In the future, in-depth study could be carried out using advanced technique, such as single-cell analysis of tumor biopsy during RT, to dissect the relevant biological processes in the TME.

Post-RT Lym counts might also be associated with the prognosis of ADC patients. The underlying mechanism might be related to the immunological surveillance function of humans' immune system[36], as a higher Lym count post-RT probably means a better ability of the immune system to spot and

eradicate micro-metastasis[37].Increasing evidence suggest that the anti-tumor response extends beyond the local primary tumor, encompassing a complex systemic interplay involving not only TME but also peripheral lymphoid tissues and the blood circulation[38]. These insights suggest the feasibilities and values of monitoring and analyzing peripheral biomarkers in accessing patient's anti-tumor immune status.Results of this study have important clinical implications. The most important one is that measures should be taken to reduce the impact of RT on Lym, especially during the 1st week after initiating RT. This might be achieved by postponing the radiation to pelvic lymphatic drainage area relative to radiation to cervix, such as brachytherapy. This strategy has already been explored by other researchers using animal models, and experiment results illustrated improved survival and higher level of tumor infiltrating Lym[39]. In theory, this strategy should be more clinically meaningful in the context of combined RT and IT. In recent years, consensus has been reached about the important immune modulation functions of RT, implying that more emphasis should be put on evaluating and modulating the impact of RT on patients' immune system in the pursuit of overall improved tumor control. In summary, this study for the first time systematically and longitudinally evaluated the association between Lym counts and the prognosis of ADC patients, suggesting that the Lym count is worth taking into consideration in making clinical decisions.

This study has several limitations. First, the study is a single-center retrospective study, therefore the conclusions derived require further validation; Second, a proportion of patients had no available CBC results for many time points (especially during the post-RT period), which reduced the effective sample size; Third, only 18 patients received IT, which disenabled us in evaluating the association of Lym count and clinical outcomes specifically in this sub-group. Future studies should pay more attention to patients receiving combined RT and IT, for whom the Lym count should be more influential.

Overall, this study found that the low Lym count of ADC patients during the 1st week after RT initiation and several months post-RT is significantly associated with worse prognosis, which may present a viable direction for further therapeutic optimization.

Conclusion

Low lymphocyte counts measured at multiple time points during the peri-RT period are associated worse prognosis for locally advanced ADC patients who received definitive RT, in particular during the 1st week of RT. However, peripheral lymphocyte counts may not be associated with the levels of TIICs, suggesting other underlying biological mechanisms remain to be explored. Overall, findings in this study prompt taking active measures to protect ADC patients' peripheral lymphocytes from RT to improve their clinical outcome.

Abbreviations

SCC: Squamous Cell Carcinoma

ADC: Cervical Adenocarcinoma

LACC: Locally Advanced Cervical Carcinoma

Lym: Lymphocyte

IT: Immunotherapy

RT: Radiotherapy

EBRT: External Beam Radiotherapy

OS: Overall Survival

PFS: Progression Free Survival

TIIC: Tumor Infiltrating Immune Cells

KM: Kaplan-Meier

AUROC: Area Under the Receiver Operating Characteristics Curve

TME: Tumor Microenvironment

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Peking Union Medical College Hospital: K6420. Written informed consents were acquired from every participant.

Consent for publication

Not applicable

Availability of Data and Materials

The patients' lymphocyte counts and their clinical outcomes analyzed during the current study are not publicly available due to the inclusion of confidential information, but are available from the corresponding author on reasonable request. The RNA-seq data of the tumor specimen analyzed in this study are available in the GEO dataset (GSE291865).

Competing interests

The authors declared that there are no conflicts of interests.

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Authors' contribution

YZ: Conceptualization, Formal Analysis, Methodology, Validation, Visualization, Writing-original draft, Funding acquisition. GW: Conceptualization, Formal Analysis, Investigation, Validation, Visualization, Writing-original draft. YQ: Conceptualization, Formal Analysis, Investigation, Validation, Visualization, Writing-original draft. ZW: Data curation, Validation, Investigation. XY: Data curation, Methodology. JZ: Data curation, Resources. ZG: Conceptualization, Investigation. JY: Conceptualization, Resources, Supervision, Writing-review & editing. FZ: Conceptualization, Project administration, Supervision, Writing-review & editing.

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Figures

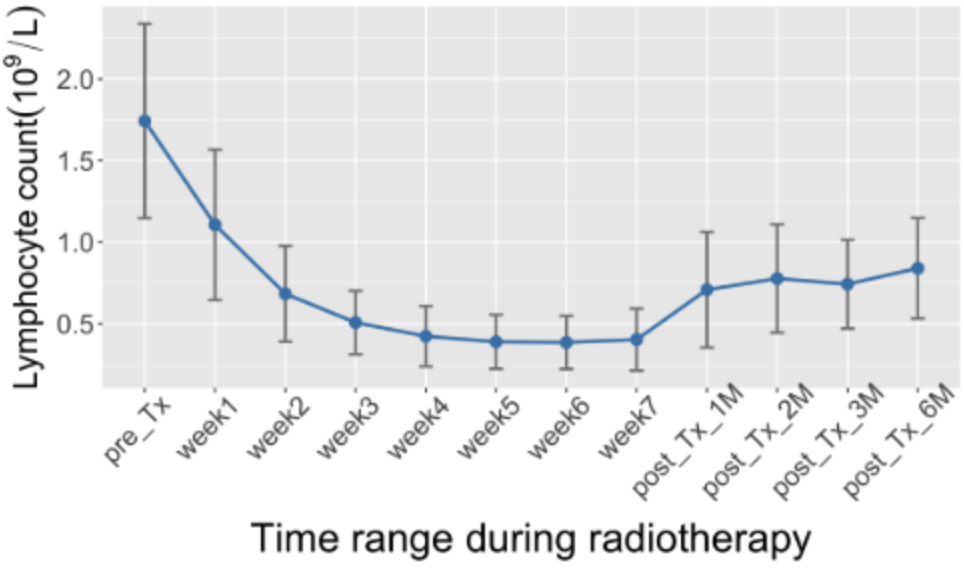


Figure 1

Change of Lym count before, during and after RT for ADC patients. Means of Lym counts are presented with points, and standard deviations (SD) are presented with error bars. **pre_Tx**: before radiotherapy (RT); **week n**: the n^{th} week during RT; **post_Tx_1M**: the 1 month after the completion of the entire RT course;

post_Tx_2M: the 2nd month after RT; **post_Tx_3M**: the 3rd month after RT; **post_Tx_6M**: the 4th to 6th months after RT.

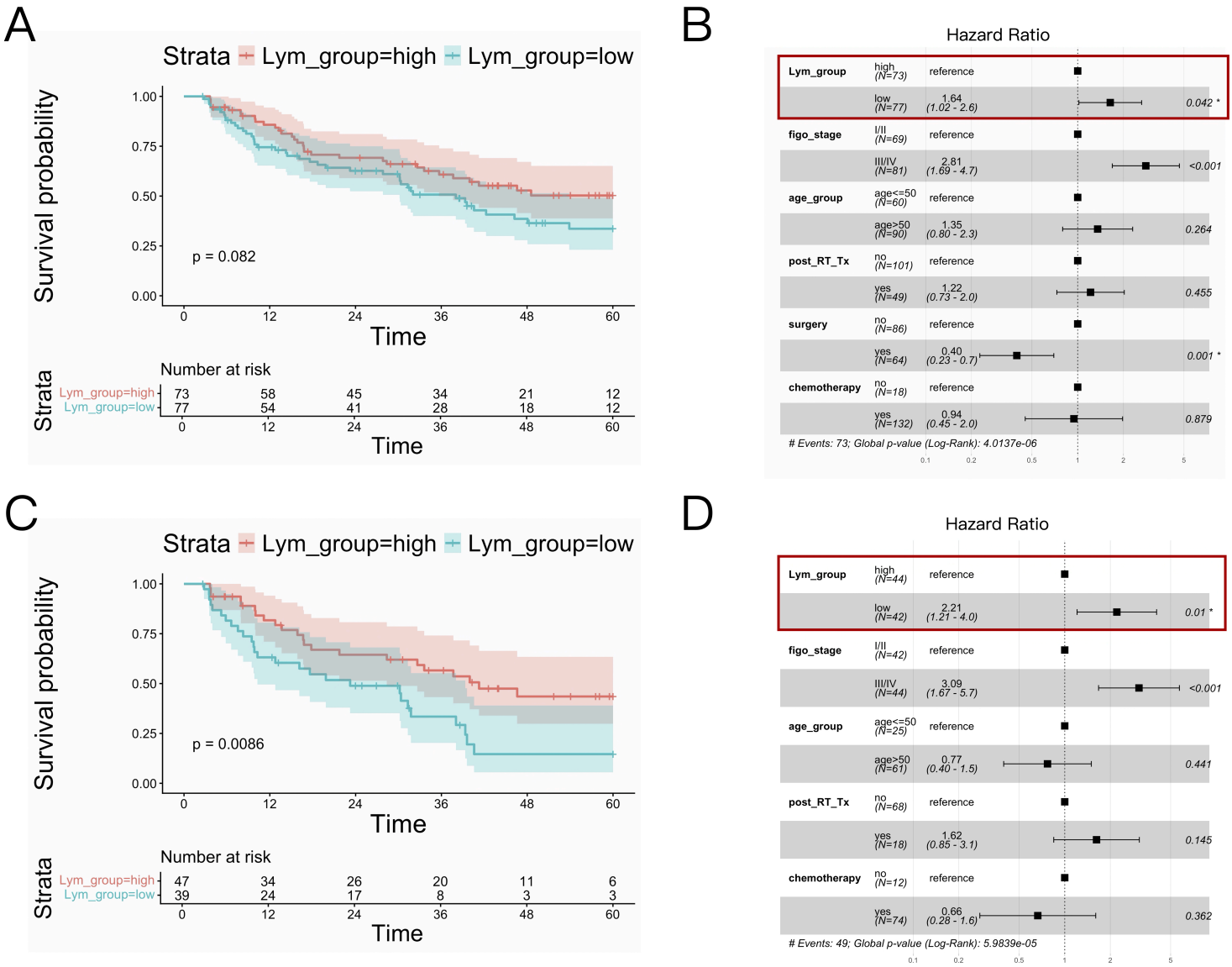


Figure 2

The association of averaged Lym count during the 1st week of RT and PFS. A, KM analysis result for patients in the high and low Lym groups (defined using the median of Lym of all patients); B, multivariate COX regression result for PFS and patients' Lym groups; C, KM analysis for patients who didn't undertake surgery after RT; D, multivariate COX regression result for patients who didn't undertake surgery after RT.

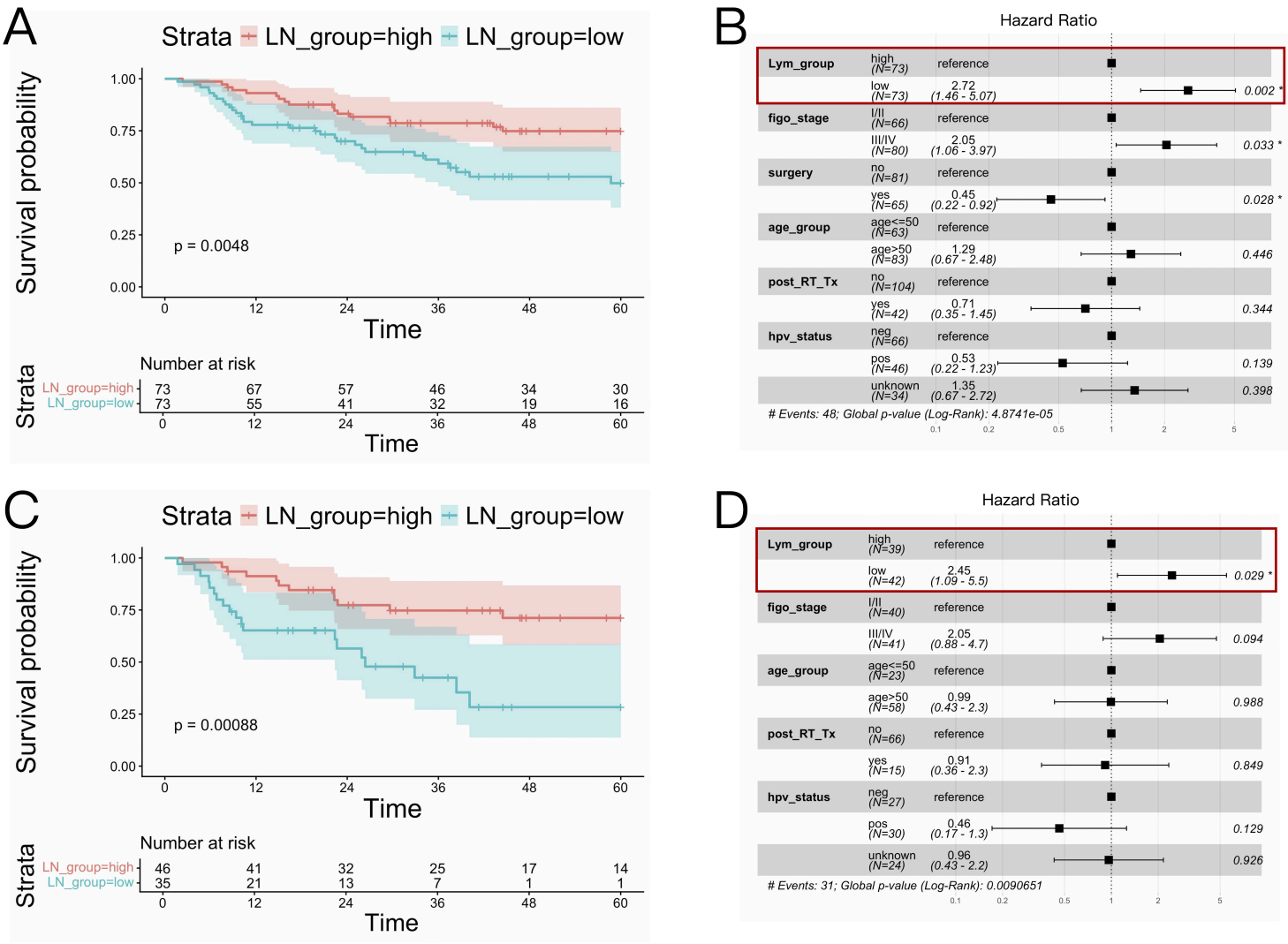


Figure 3

The association between averaged Lym count during the 1st week of RT and OS. A, KM analysis result for patients in the high and low Lym groups (defined using the median of Lym of all patients); B, multivariate COX regression for OS and patients' Lym groups; C, KM analysis for patients who didn't undertake surgery after RT; D, multivariate COX regression for patients who didn't undertake surgery after RT.

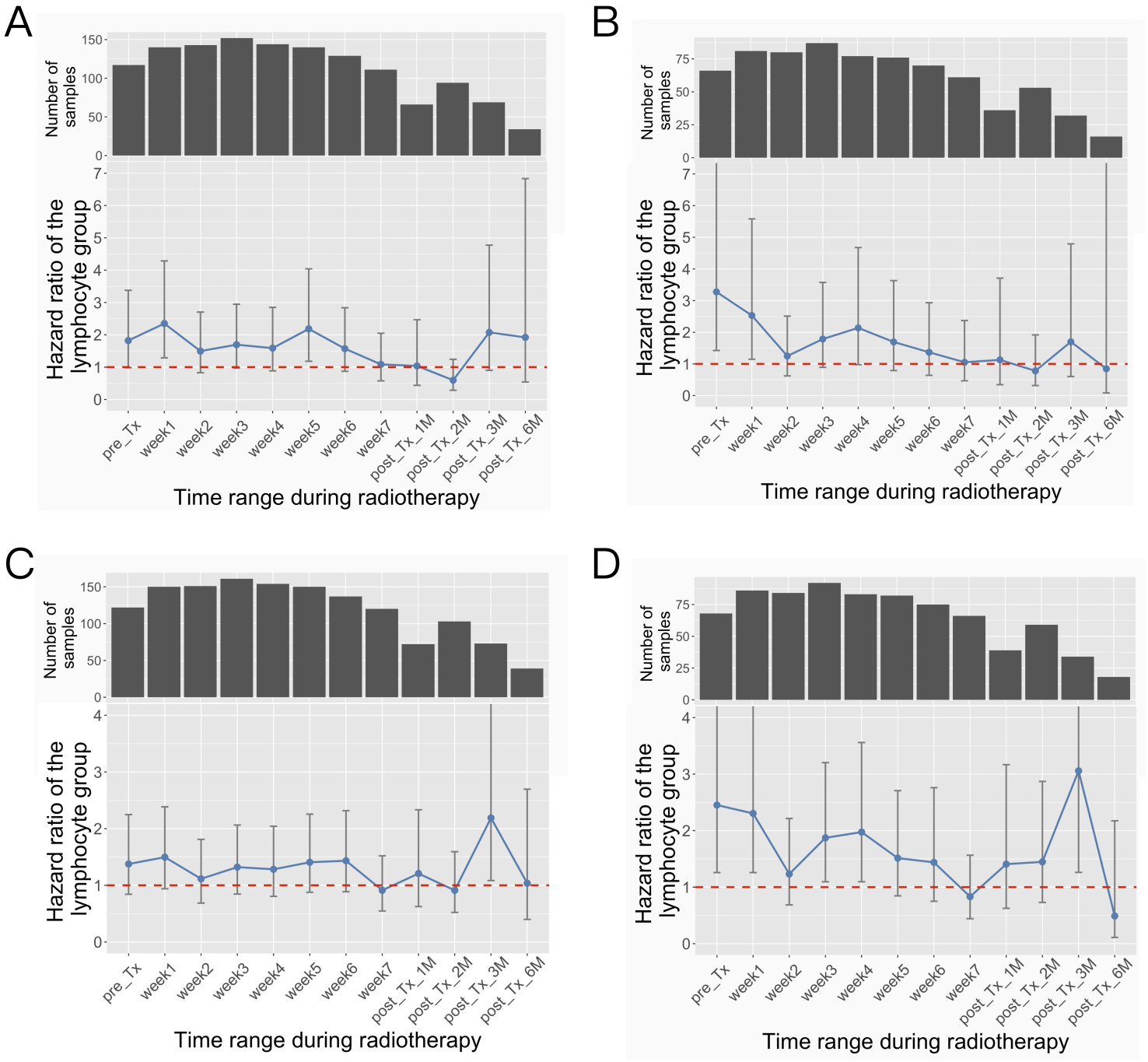


Figure 4

Hazard Ratios (HR) for Lym groups at different time point estimated by multivariate COX regression. The bar plot at the top of each panel displays the number of patients included in the analyses at different time points. The point plots with 95% CI (confidence interval) present the HR of Lym group estimated by COX regression. A, all patients included in the analysis, with OS as the end point; B, patients who didn't undertake surgery after RT included, with OS as the endpoint; C, all patients included, with PFS as the end point; D, patients who didn't undertake surgery included, with PFS as the end point.

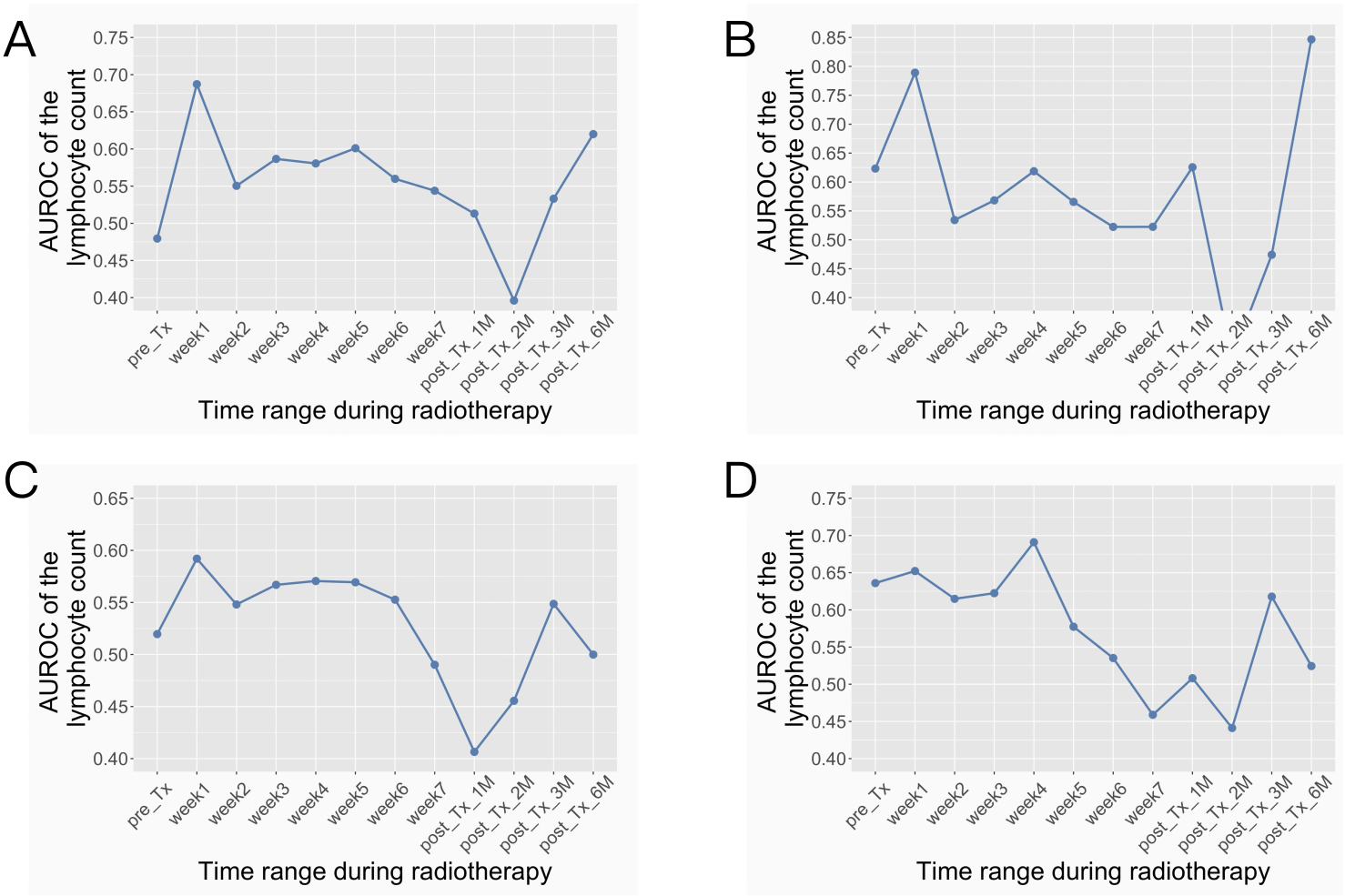


Figure 5

The AUROC of using patients' absolute Lym counts to predict patients' clinical outcome. A, all patients included in the analysis, with OS as the end point. B, patients who didn't undertake surgery after RT included, with OS as the endpoint. C, all patients included, with PFS as the end point. D, patients who didn't undertake surgery included, with PFS as the end point.

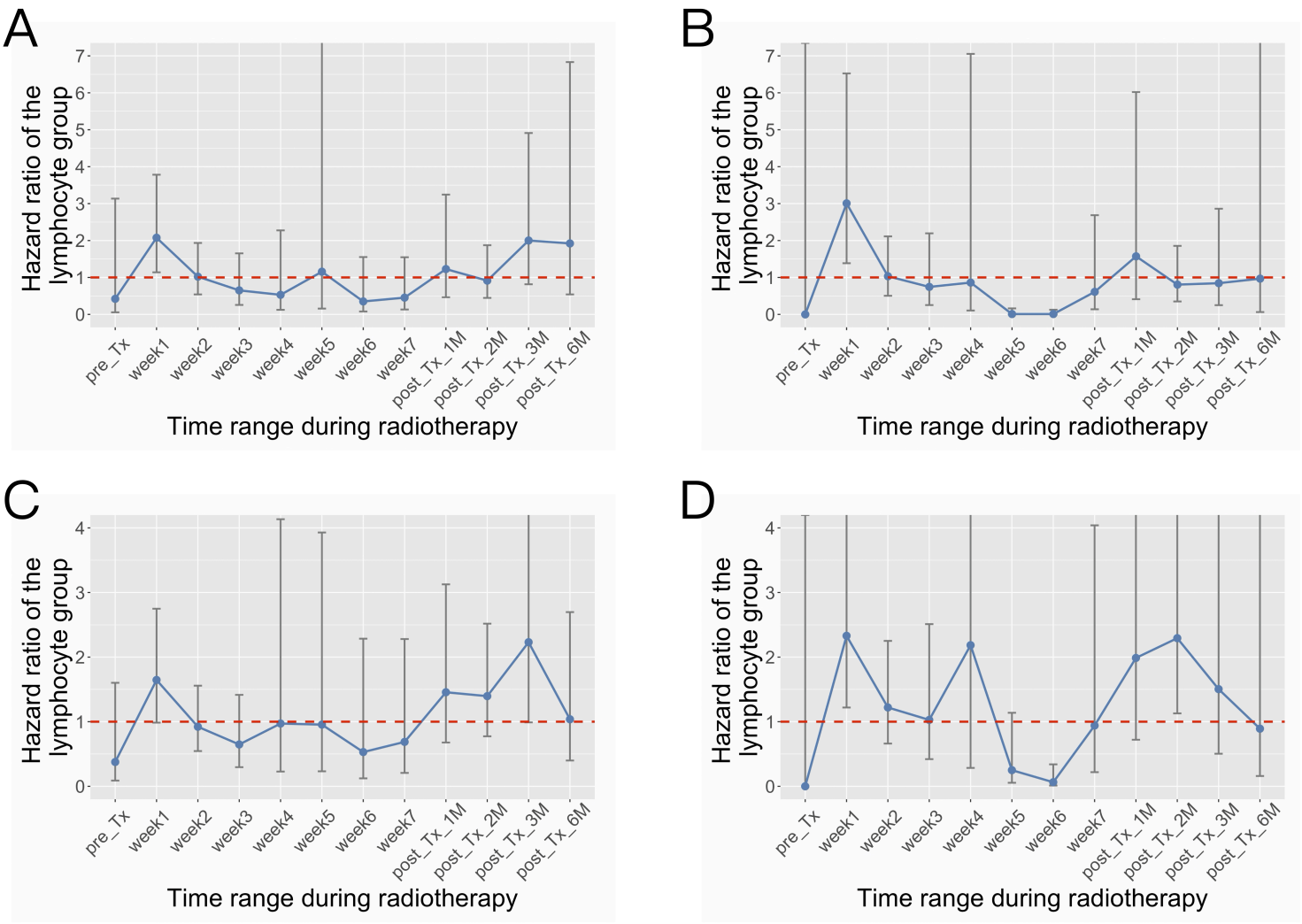


Figure 6

The AUROC of using patients' absolute Lym counts to predict patients' clinical outcome. A, all patients included in the analysis, with OS as the end point. B, patients who didn't undertake surgery after RT included, with OS as the endpoint. C, all patients included, with PFS as the end point. D, patients who didn't undertake surgery included, with PFS as the end point.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigureTables.docx