



HAL
open science

Impact of circulating lymphocyte kinetics following radiotherapy on patient survival: A model-based meta-analysis

Thao-Nguyen Pham, Julie Coupey, Juliette Thariat, Samuel Valable

► **To cite this version:**

Thao-Nguyen Pham, Julie Coupey, Juliette Thariat, Samuel Valable. Impact of circulating lymphocyte kinetics following radiotherapy on patient survival: A model-based meta-analysis. *Computers in Biology and Medicine*, 2025, 186, pp.109702. <10.1016/j.compbimed.2025.109702>. <hal-04913185>

HAL Id: hal-04913185

<https://normandie-univ.hal.science/hal-04913185v1>

Submitted on 27 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.


L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License



Impact of circulating lymphocyte kinetics following radiotherapy on patient survival: A model-based meta-analysis

Thao-Nguyen Pham^{a,b,c}, Julie Coupey^a, Juliette Thariat^{b,c,1} , Samuel Valable^{a,1,*}

^a Université de Caen Normandie, CNRS, Normandie Université, ISTCT UMR6030, GIP CYCERON, F-14000, Caen, France

^b Laboratoire de Physique Corpusculaire UMR6534 IN2P3/ENSICAEN, France - Normandie Université, France

^c Department of Radiation Oncology, Centre François Baclesse, Caen, Normandy, France

ARTICLE INFO

Keywords:

Radiation-induced lymphopenia
Model-based meta-analysis
Parametric survival model
Causal relationship
Radiotherapy

ABSTRACT

Introduction: Radiation-induced lymphopenia (RIL) has been shown to adversely affect the prognosis of cancer patients undergoing radiotherapy (RT). This model-based meta-analysis investigated the prognostic significance of lymphocyte counts both early and late after RT and examined the dose–response relationship between post-RT lymphocyte levels and patient survival.

Methods: A literature search of published articles on the effect of RIL on cancer prognosis was conducted using the PubMed and Cochrane databases. A survival model was developed, incorporating absolute lymphocyte count (ALC) thresholds during (1 month after RT initiation, nadir) and 6 months after RT (recovery) as covariates to estimate progression-free survival (PFS) and overall survival (OS). This survival model, with the lymphocyte count cutoff as a covariate, was then used to simulate the benefit of increased PFS and OS in populations without lymphopenia or severe lymphopenia compared to the total population.

Results: A total of 35 studies met the inclusion criteria for survival analysis. Our survival model revealed an increase in survival in the subgroup without lymphopenia compared to the total population. The subgroup without lymphopenia 1 month after RT initiation showed a 10.28 % and 3.92 % increase in 24-month PFS and OS, respectively. The subgroup without lymphopenia at 6 months showed a 5.82 % and 2.78 % increase in 24-month PFS and OS, respectively.

Conclusion: This study highlights the critical role of lymphocyte nadir and recovery following RT in patient prognosis and strengthens the evidence for a causal relationship between RIL and patient outcomes. Expanding the dataset and including randomized controlled trials would provide a more comprehensive understanding of monitoring or knowledge of ALC profiles following RT.

1. Introduction

The immune system plays a critical role in both the development and elimination of malignant tumors [1]. Radiotherapy (RT) has traditionally been considered as a local treatment. However, recent evidence highlights its broader impact on the immune system through the abscopal effect, i.e., an immune response beyond the irradiated area [2]. The perception of RT as a purely local treatment has changed dramatically in recent years, and it is now widely accepted that RT can induce a systemic immune response, providing a strong rationale for combining RT with immunotherapy [2–5].

Lymphocytes are a type of white blood cell that play a central role in

the immune system's ability to recognize and eliminate cancer cells [6]. Despite its efficacy, RT can induce lymphopenia, referred to as radiation-induced lymphopenia (RIL), which is characterized by a decrease in the number of lymphocytes [7–9]. This common side effect has significant clinical consequences, with severe lymphopenia being correlated with poorer prognosis, as evidenced by a reduction in survival in various cancers [7,8].

Recently, attention has shifted from simply documenting lymphopenia to examining the dynamic nature of lymphocyte counts during and after RT. However, the majority of existing studies have focused primarily on the severity of lymphopenia during or immediately after RT [10]. Most studies addressing the prognostic value of RIL have only

* Corresponding author.

E-mail address: samuel.valable@cnrs.fr (S. Valable).

¹ Authors equally contributed.

partially investigated the longitudinal dynamics of lymphocyte changes after RT by analyzing acute RIL during RT [10]. Yet, few studies have addressed the relationship between the dynamics of lymphocyte recovery after RIL and prognosis. Emerging evidence suggests that lymphocyte counts late after RT may have a greater prognostic impact than the initial decline observed early after treatment in several types of cancer, including oropharyngeal cancer, non-small cell lung cancer, esophageal cancer, and pancreatic cancer [11–14]. Therefore, a longitudinal approach is essential to study acute lymphopenia both during treatment and recovery, if any, after the lymphopenia nadir. Additionally, the dose–response relationship (i.e., biological gradient) between increasing lymphocyte counts after treatment and improved survival outcomes remains understudied.

A systematic review and meta-analysis demonstrated a significant adverse prognostic association between lymphopenia and overall survival (OS) in patients receiving RT for solid tumors [10]. However, the existing literature on the correlation between lymphocyte counts and cancer outcomes lacks a clear gradient relationship. Most studies compared outcomes between lymphopenia and non-lymphopenia groups, but used different thresholds to define lymphopenia. With more accurate predictive models now being available [15–17], establishing a survival relationship based on lymphocyte counts is essential to fully leverage the potential benefits of controlling RIL. In addition, the prognostic impact of lymphocyte recovery beyond the acute phase of treatment has yet to be fully addressed on a meta-level.

To fill these knowledge gaps and deepen our understanding of how RIL impacts prognosis, this study employed a model-based meta-analytic approach [18]. This method allowed us to quantitatively assess the relationship between both early and late post-RT absolute lymphocyte counts (ALC) and patient survival, going beyond binary group comparisons and modeling lymphocyte count as a continuous variable. By incorporating longitudinal data and exploring the dose–response relationship, we aimed to provide a model framework for how lymphocyte counts after RT and their recovery influence patient outcomes.

2. Materials and methods

2.1. Literature search

2.1.1. Search strategy

A literature search of published articles on the effect of RIL on cancer prognosis was performed using the PubMed and Cochrane online databases, employing keywords such as “radiation-induced lymphopenia”, “tumor control”, and “radiotherapy effect”. The relevant references identified were manually screened for further inclusion. The search was updated in January 2024.

2.1.2. Exclusion criteria

Studies using single-dose irradiation and those involving non-solid tumors or radiation exposure for reasons other than cancer treatment were excluded. Letters, case reports, studies with a sample size of less than 10, and non-English language articles were also excluded.

2.1.3. Inclusion criteria

Survival data were stratified by time in correlation with lymphocyte nadir or lymphopenia grade during or after RT. Clinical trials and retrospective reports on longitudinal progression-free survival (PFS) and OS in clinical practice were included.

2.1.4. Data extraction

For each study, the following information was extracted: (1) publication characteristics, title, authors, and year of publication; (2) patient population characteristics, demographics, dosing regimen, cancer type, RT type, and concomitant treatment; (3) clinical outcome measures and longitudinal PFS and OS data; (4) covariates relevant to PFS and OS; (5) ALC cutoff for stratified survival data. The reported survival rates over

time were derived from the Kaplan–Meier curve.

2.2. Survival modeling using model-based meta-analysis

Model-based meta-analysis (MBMA) integrates data from multiple studies using a modeling approach to explore relationships, predict outcomes, and account for variability across studies. A longitudinal MBMA was performed to separately quantify the probability of PFS and OS based on pooled data from our established meta-database. The analysis was performed with a nonlinear model using the nlme package in R [19].

2.2.1. Selection of covariates

Study type, tumor type, and time since treatment initiation were used to select covariates relevant to PFS and OS after RT using stepwise covariate selection.

2.2.2. Model development

We initially used parametric survival models to address the limitations of the Kaplan–Meier curve, which allowed for the prediction and inclusion of covariates such as lymphocyte concentration during and after RT. We began by remodeling the data extracted from the Kaplan–Meier curve using parametric survival models. Since these models assume an underlying distribution of the data, we first tested different probability distributions to identify the most suitable model for OS and PFS.

As a starting point, the probability of OS and PFS, $S(t)$, was tested using three parametric survival models as the basic structural model: (1) the exponential model, which assumes a constant hazard rate over time (eq. (1)); (2) the log-logistic model, in which the hazard initially increases (early increase in deaths/progression) and then levels off (eq. (2)); (3) the Weibull model, which captures various hazard patterns, including increasing, decreasing, or constant hazard rates, depending on the estimated shape parameter k (eq. (3)). The baseline hazard ratio was allowed to vary between studies to capture the diversity of survival outcomes across different experimental conditions.

$$S(t) = \exp(-\lambda t) \quad (\text{eq. 1})$$

$$S(t) = \frac{1}{1 + (\lambda t)^k} \quad (\text{eq. 2})$$

$$S(t) = \exp(-(\lambda t)^k) \quad (\text{eq. 3})$$

where $S(t)$ is the survival rate, λ is the scale parameter, t is the time since RT initiation, and k is the shape parameter. The residual sum of squares (RSS) and Akaike information criterion (AIC) were used as selection criteria. Fisher’s exact test was used to compare the RSS between the models.

Fivefold cross-validation was performed and the mean square error was calculated for each model.

2.2.3. Effect of lymphocyte count cutoff on survival curve

A lymphocyte cutoff of 1 month (nadir) or 6 months (recovery) after RT initiation was identified as a relevant factor affecting the hazard ratio within the survival model.

$$\lambda = f(\text{Lym} > \text{Lym}_{\text{cutoff}}) = \lambda_0 + a * \text{Lym}_{\text{cutoff}} \quad (\text{eq. 4})$$

where $\text{Lym}_{\text{cutoff}}$ is the lymphocyte cutoff 1 month (nadir) or 6 months (recovery) after RT initiation and a is the parameter denoting the linear relationship between the lymphocyte cutoff 1 month (nadir) or 6 months (recovery) after RT initiation and the scale parameter. A $\text{Lym}_{\text{cutoff}}$ value of 0 was defined as the $\text{Lym}_{\text{cutoff}}$ value of the entire population in each study, without stratification by lymphopenia status.

After including the lymphocyte count cutoff in the survival model,

the models (exponential model, log-logistic model, and Weibull model, respectively) become:

$$S(t) = \exp\left(-\left(\lambda_0 + a^*Lym_{cutoff}\right)t\right)$$

$$S(t) = \frac{1}{1 + \left(\left(\lambda_0 + a^*Lym_{cutoff}\right)t\right)^k}$$

$$S(t) = \exp\left(-\left(\left(\lambda_0 + a^*Lym_{cutoff}\right)t\right)^k\right)$$

where $S(t)$ is the survival rate, λ is the scale parameter, t is the time since RT initiation, k is the shape parameter, Lym_{cutoff} is the lymphocyte cutoff 1 month (nadir) or 6 months (recovery) after RT initiation, and a is the parameter denoting the linear relationship between the lymphocyte cutoff 1 month (nadir) or 6 months (recovery) after RT initiation and the scale parameter.

Different studies reported different cutoffs, which could be either the median lymphocyte nadir of the specific dataset or the threshold for defining lymphopenia according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 classification [20] (Grade 1 as 1000 cells/ μ L, Grade 2 as 800 cells/ μ L, Grade 3 as 500 cells/ μ L, and Grade 4 as 200 cells/ μ L).

This model was then compared to the basic model without the lymphocyte cutoff as a covariate. The AIC was used as the performance metric and selection criterion.

2.2.4. Simulation

The survival model, with the effect of the lymphocyte count cutoff as a covariate, was then used to simulate the benefit of increasing PFS and OS in the population without lymphopenia or severe lymphopenia compared to the total population. Lymphopenia was defined as an ALC of <1000 cells/ μ L of blood, and severe lymphopenia was defined as an ALC of <500 cells/ μ L of blood, according to the CTCAE version 5.0 classification [20].

The difference in survival between the population without lymphopenia or severe lymphopenia and the total population was calculated for each study as follows:

$$\Delta S(t, \text{no lymphopenia}) = S(t, Lym_1) - S(t, Lym_0)$$

$$\Delta S(t, \text{no severe lymphopenia}) = S(t, Lym_{0.5}) - S(t, Lym_0)$$

where $\Delta S(t, \text{no lymphopenia})$ and $\Delta S(t, \text{no severe lymphopenia})$ are the differences in PFS or OS of the population without lymphopenia or severe lymphopenia compared to the total population. $S(t, Lym_1)$, $S(t, Lym_{0.5})$, and $S(t, Lym_0)$ are the PFS or OS of the population without lymphopenia (total lymphocyte count >1000 cells/ μ L), without severe lymphopenia (total lymphocyte count >500 cells/ μ L), and the total population, respectively, at time t after RT initiation.

A one-sided t -test (or nonparametric Wilcoxon test when sample size was <5) was used to compare ΔS with 0 under the null hypothesis that patient survival was independent of lymphopenia status.

2.3. Heterogeneity and sensitivity analysis

2.3.1. Heterogeneity analysis

To assess the variability in parameter estimation across the included studies, we performed a heterogeneity analysis. In this analysis, we estimated a separate value of parameter a ((cells/ μ L)⁻¹, denoting the impact of lymphocyte counts on survival in eq.4) for each individual study, rather than assuming a single common effect. The degree of heterogeneity was quantified using the I^2 statistic, which represents the proportion of the total variation in a parameter that is due to differences between studies rather than random chance. By calculating I^2 , we were

able to determine whether the differences observed in parameter a across studies were meaningful or merely due to random variation. In addition to I^2 , we also calculated the Q-statistic and its associated p-value to formally test the null hypothesis that all studies share a common parameter estimation. If the p-value from the Q-test is less than 0.05, it indicates a significant heterogeneity across studies.

2.3.2. Sensitivity analysis

To evaluate the robustness of our findings and the influence of individual studies on the overall estimates of parameter a ((cells/ μ L)⁻¹, denoting the impact of lymphocyte counts on survival in eq.4), we performed a leave-one-out sensitivity analysis. We iteratively removed one study at a time from the meta-dataset and re-estimated parameter a using the remaining studies. If the exclusion of a particular study results in a significant change in the value or direction of the parameter estimate, this suggests that the study may be an influential outlier.

2.4. Data availability

The data generated in this study are available in the manuscript and supplementary files.

3. Results

3.1. Literature search results

The results of the literature search are shown in Fig. 1. A total of 35 studies met the inclusion criteria for survival analysis, including six studies on glioblastoma [21–26], one on nasopharyngeal cancer [27], three on oropharyngeal cancer [13,28,29], seven on esophageal cancer [11,30–35], eight on non-small cell lung cancer [12,36–42], one on hepatocarcinoma [43], two on pancreatic cancer [14,44], four on cervical cancer [38,45–47], one on rectal cancer [48], and two on prophylactic cranial irradiation in small cell lung cancer [49,50]. A summary of study characteristics is provided in Table S1.

Among the selected studies, 18 and 29 examined the association between lymphopenia either during or within 1 month after RT initiation and PFS and OS, respectively. These studies investigated the impact of lymphopenia during RT on prognosis. Additionally, three and four studies explored the connection between lymphopenia occurring 6 months after RT initiation and PFS and OS, respectively, focusing on the long-term recovery phase after treatment. The assessment of lymphopenia at these two time points was modeled separately.

3.2. Model structure selection

As a first step, we identified the optimal survival model structure to represent the PFS and OS of the collected data. The log-logistic model showed the best performance among the PFS models, with the lowest RSS and AIC values. The RSS of the log-logistic model was significantly lower than that of the exponential model according to Fisher's test ($p = 0.01$), but not significantly lower than that of the Weibull model (Table S2). A log-logistic model was used for further analysis of PFS rate.

According to the survival model, the exponential model had the lowest AIC. The RSS of the exponential model was not significantly greater than that of the Weibull model ($p = 0.63$). The exponential model was selected for further analysis of the OS rate due to its simplicity, with only one parameter for estimation.

The selected model also achieved the lowest mean square error following cross-validation, confirming the choice of the model structure (Table S3).

3.3. Parametric survival modeling with the absolute lymphocyte count nadir following radiotherapy as a covariate

In this section, our goal was to evaluate parametric survival models

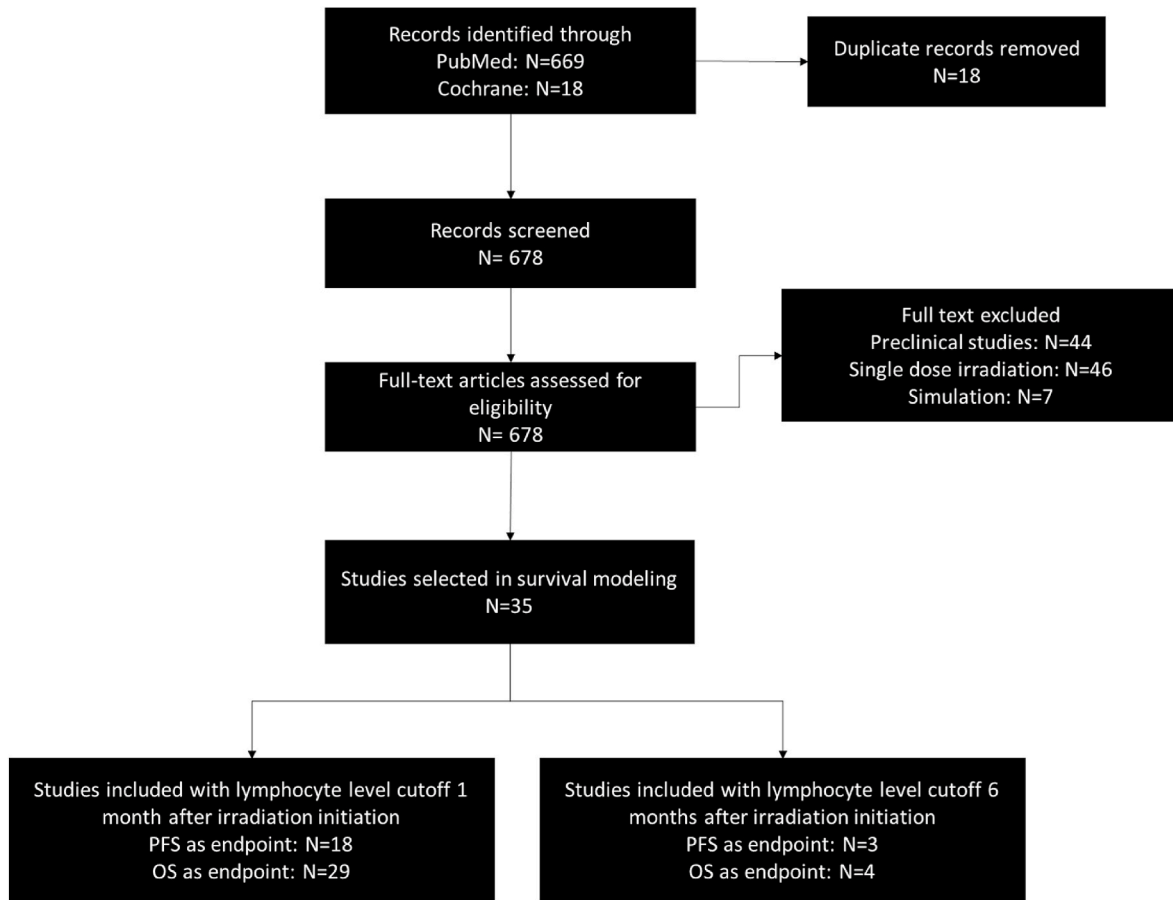


Fig. 1. Literature search strategy flowchart.

that account for the early effects of RIL (ALC nadir during RT). A total of 474 time points from 18 studies were used to fit the PFS data with the log-logistic model, considering a lymphocyte cutoff of 1 month after RT initiation as a covariate. The model with the lymphocyte cutoff 1 month after RT initiation as a covariate did not perform better than the basic model (AIC of 2570.51 vs. 2568.90, Fig. 2A1). However, when the parameter λ_0 was estimated separately for each study, the new model with lymphocyte nadir implementation achieved a lower AIC of 2154.02 (Fig. 2A1). The parameter estimation for this model is presented in Table S4. Model fitting is illustrated in Fig. 2A2. The decrease in PFS over time followed the log-logistic model, with the curve shifting to the left for the subpopulation with lymphopenia (ALC <1000 cells/ μ L for lymphopenia and ALC <500 cells/ μ L for severe lymphopenia), indicating a lower PFS over time (Fig. 2A2). The model indicated that PFS at 6, 12, 24, and 36 months after RT increased with increasing ALC (1 month after RT initiation) (Fig. 2A3).

A total of 772 observations from 29 studies were used to fit the OS data with the exponential model, considering the lymphocyte cutoff 1 month after RT initiation as a covariate. The model with the lymphocyte cutoff 1 month after RT initiation as a covariate performed better than the basic model (AIC of 4297.51 vs. 4304.90, Fig. 2B1). When the parameter λ_0 was estimated separately for each study, the new model with lymphocyte nadir implementation achieved a lower AIC of 3753.00 (Fig. 2B1). The parameter estimation for this model is presented in Table S4. Model fitting is illustrated in Fig. 2B2. The decrease in OS over time followed the exponential model, with the curve shifting to the left for the subpopulation with lymphopenia (ALC <1000 cells/ μ L for lymphopenia and ALC <500 cells/ μ L for severe lymphopenia), indicating a lower OS over time (Fig. 2B2). The model indicated that OS at 6, 12, 24, and 36 months after RT increased with increasing ALC (1 month after RT

initiation) (Fig. 2B3).

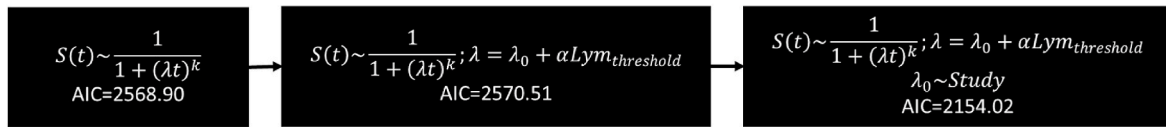
3.4. Parametric survival modeling with the absolute lymphocyte count 6 months following radiotherapy as a covariate

We further assessed parametric survival models that considered the late effects of RIL (recovery of ALC, 6 months after RT). A total of 63 time points from three studies were used to fit the PFS data with the log-logistic model. The model with the lymphocyte cutoff 6 months after RT initiation as a covariate did not perform better than the basic model (AIC of 454.34 vs. 338.58, Fig. 3A1). However, when the parameter λ_0 was estimated separately for each study, the new model with implementation of the lymphocyte nadir lower limit achieved a lower AIC of 284.46 (Fig. 3A1). The parameter estimation for this model is presented in Table S5. Model fitting is shown in Fig. 3A2. The decrease in PFS over time followed the log-logistic model, with the curve shifting to the left for the subpopulation with lymphopenia (ALC <1000 cells/ μ L for lymphopenia and ALC <500 cells/ μ L for severe lymphopenia), indicating a lower PFS over time (Fig. 3A2). The model indicated that PFS at 6, 12, 24, and 36 months after RT increased with increasing lymphocyte counts 6 months after RT initiation (Fig. 3A3).

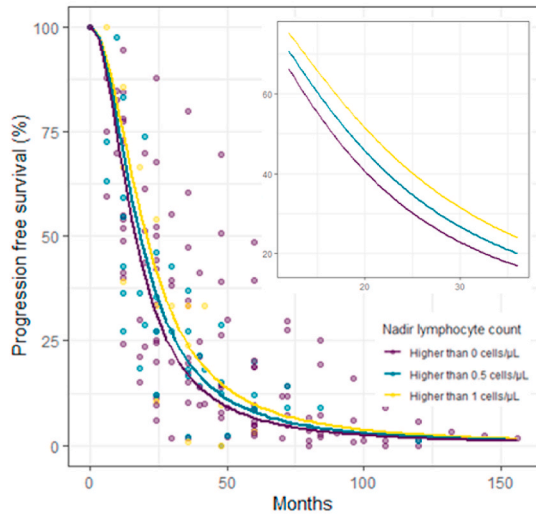
A total of 81 time points from four studies were used to fit the OS data with the exponential model, considering the lymphocyte cutoff 6 months after RT initiation as a covariate. The model with the lymphocyte cutoff 6 months after RT initiation as a covariate did not perform better than the basic model (AIC of 454.24 vs. 452.36, Fig. 3B1). When the parameter λ_0 was estimated separately for each study, the new model with implementation of the lymphocyte nadir lower limit achieved a lower AIC of 389.34 (Fig. 3B1). The parameter estimation for this model is presented in Table S5. Model fitting is shown in Fig. 3B2.

A.1

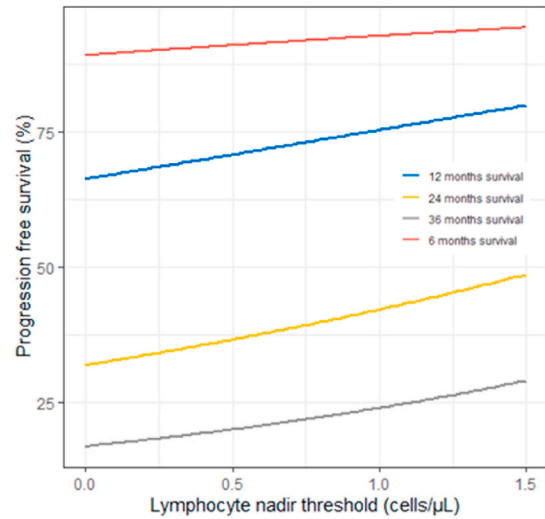
$n_{obs} = 474, n_{study} = 18$



A.2

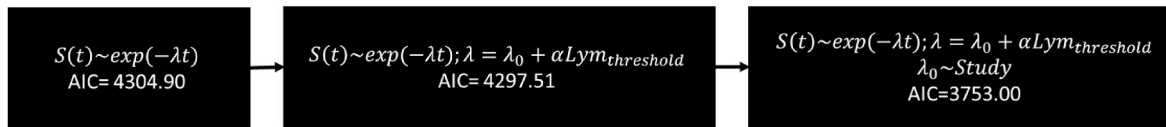


A.3

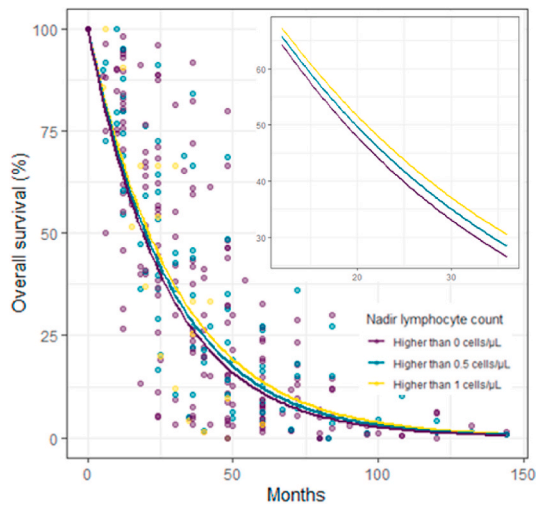


B.1

$n_{obs} = 772, n_{study} = 29$



B.2



B.3

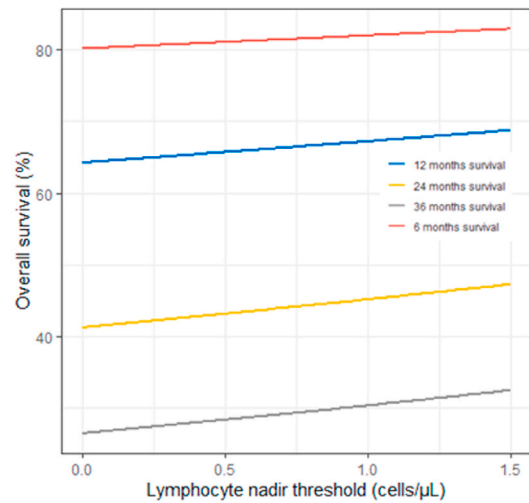
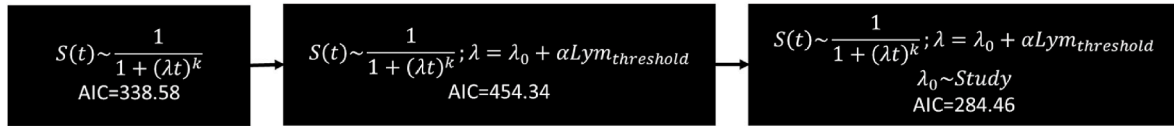


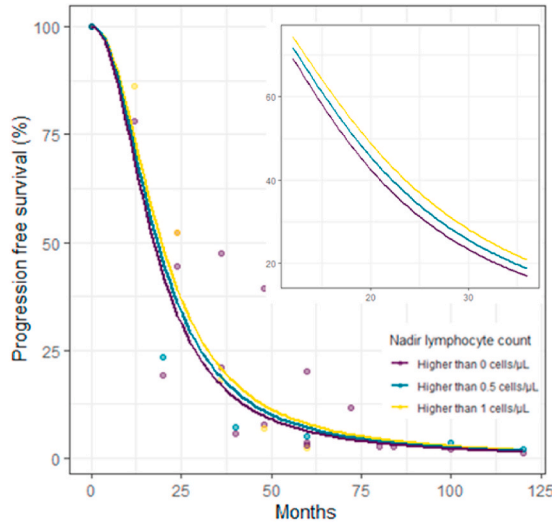
Fig. 2. Survival model with lymphocyte cutoff 1 month after radiotherapy initiation as a covariate of progression-free survival (A) or overall survival (B) as a function of months after treatment (A.1, B.1), Akaike information criterion of the model with or without the effect of lymphocyte cutoff 1 month after radiotherapy initiation; (A.2, B.2) simulated survival curve of the total population (purple), the population without severe lymphopenia 1 month after treatment initiation (blue), and the population without lymphopenia 1 month after treatment initiation (yellow); (A.3, B.3) survival rate as a function of lymphocyte cutoff 1 month after radiotherapy initiation at 6 (red), 12 (blue), 24 (yellow), and 36 (gray) months after treatment initiation. In panels A.2 and B.2, the dots represent data from the literature, and the curve represents the survival curve simulated from the parametric survival model. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

A.1

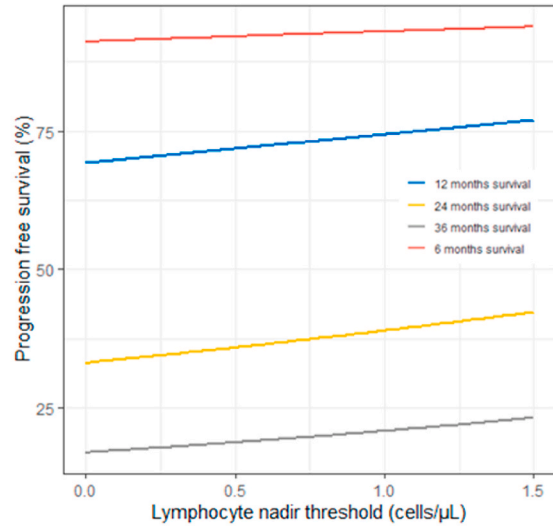
$n_{obs} = 63, n_{study} = 3$



A.2

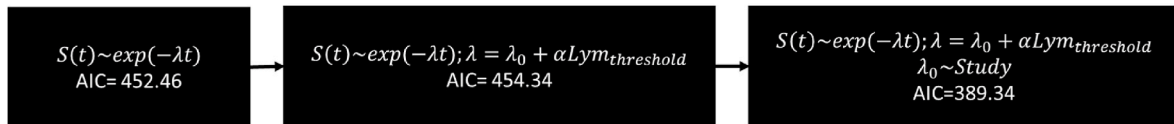


A.3

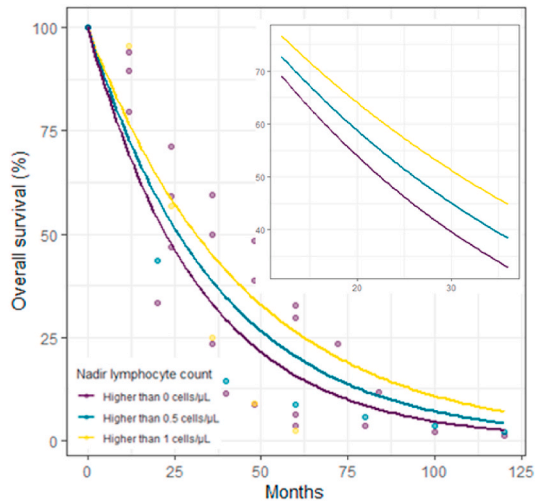


B.1

$n_{obs} = 81, n_{study} = 4$



B.2



B.3

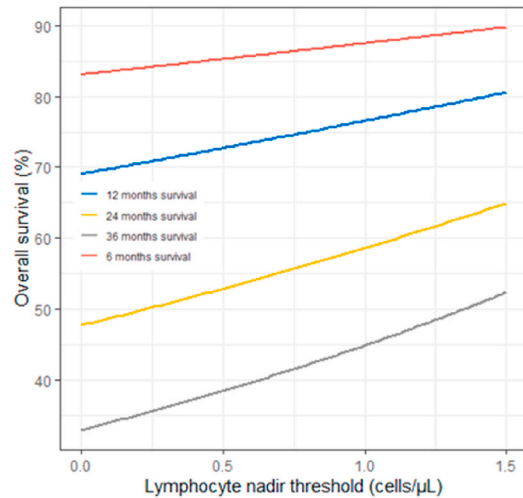


Fig. 3. Survival model with lymphocyte cutoff 6 months after radiotherapy initiation as a covariate of progression-free survival (A) or overall survival (B) as a function of months after treatment (A.1, B.1), Akaike information criterion of the model with or without the effect of lymphocyte cutoff 1 month after radiotherapy initiation; (A.2, B.2) simulated survival curve of the total population (purple), the population without severe lymphopenia 1 month after treatment initiation (blue), and the population without lymphopenia 1 month after treatment initiation (yellow); (A.3, B.3) survival rate as a function of lymphocyte cutoff 1 month after radiotherapy initiation at 6 (red), 12 (blue), 24 (yellow), and 36 (gray) months after treatment initiation. In panels A.2 and B.2, the dots represent data from the literature, and the curve represents the survival curve simulated from the parametric survival model. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The decrease in OS over time followed the exponential model, with the curve shifting to the left for the subpopulation with lymphopenia (ALC <1000 cells/ μ L for lymphopenia and ALC <500 cells/ μ L for severe lymphopenia), indicating a lower OS over time (Fig. 3B2). The model indicated that OS at 6, 12, 24, and 36 months after RT increased with increasing lymphocyte counts 6 months after RT initiation (Fig. 3B3).

3.5. Simulation of survival rate according to different absolute lymphocyte counts following radiotherapy

Using simulations from 18 studies (for PFS) or 29 studies (for OS), we investigated the increase in survival when considering RIL (ALC <1000 cells/ μ L for lymphopenia and ALC <500 cells/ μ L for severe lymphopenia) early after RT. The increase in survival of the population without lymphopenia 1 month after RT compared with that of the total population is summarized in Fig. 4A. The PFS of the subpopulation without lymphopenia 1 month after RT initiation was 3.18 %, 7.63 %, 11.15 %, and 10.98 % greater on average than that of the total population at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided t -test, compared to 0). Compared to the total population, the subpopulation without severe lymphopenia achieved OS rates that were 1.66 %, 3.87 %, 5.37 %, and 5.04 % greater on average at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided t -test, compared to 0). The OS of the subpopulation without lymphopenia at 1 month after RT initiation was 1.85 %, 3.08 %, 4.37 %, and 4.78 % greater than that of the total population at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided t -test, compared to 0). Compared to the total population, the subpopulation without severe lymphopenia achieved OS rates that were 0.92 %, 1.52 %, 2.13 %, and 2.31 % greater at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided t -test, compared to 0).

In addition, we explored the increase in survival when considering RIL early after RT using simulations from three studies (for PFS) or four studies (for OS) (Fig. 4B). The PFS of the subpopulation without lymphopenia at 6 months after RT was 1.79 %, 4.26 %, 6.46 %, and 6.19 % greater on average than that of the total population at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided Wilcoxon test, compared to 0). Compared to the total population, the subpopulation without severe lymphopenia achieved 0.87 %, 2.15 %, 3.16 %, and 2.91 % greater OS rates at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided Wilcoxon test, compared to 0). The percentages of patients without lymphopenia at 6 months after RT initiation were 4.40 %, 7.58 %, 11.48 %, and 13.34 % greater on average than those of the total population at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided t -test, compared to 0). Compared to the total population, the subpopulation without severe lymphopenia achieved 2.17 %, 3.69 %, 5.45 %, and 6.15 % greater OS rates on average at 6, 12, 24, and 36 months after RT initiation, respectively ($p < 0.01$ according to one-sided Wilcoxon test, compared to 0).

Finally, our analysis aimed to compare the timing of lymphopenia and its impact on PFS and OS. The data indicated that PFS at 6 and 12 months was significantly greater in patients with early lymphopenia (at 1 month) than in those with late lymphopenia (at 6 months post-RT) (Fig. 4C; $p < 0.05$ according to nonparametric Wilcoxon test). However, this difference in PFS did not persist at 24 months post-RT. Conversely, the increase in OS was significantly greater in patients who experienced late lymphopenia (at 6 months) than in those who experienced early lymphopenia (at 1 month post-RT) (Fig. 4D; $p < 0.01$ according to nonparametric Wilcoxon test).

3.6. Heterogeneity and sensitivity analysis

Heterogeneity analysis revealed no significant variability between studies in estimating the impact of lymphopenia at nadir or 6 months

post-RT on PFS and OS, with $I^2 = 0$ for both outcomes (Figs. S1–S2). This indicates that the observed variation in effect size across studies is likely attributable to random chance rather than meaningful differences in study characteristics.

For sensitivity analysis, a leave-one-out approach was employed to examine the stability of parameter estimates for both PFS and OS at 1 and 6 months post-RT (Figs. S3–4). For PFS at 1 month, the leave-one-out parameter estimates ranged from a maximum of -0.006 to a minimum of -0.01 (Fig. S3), with a pooled parameter estimate of -0.01 . Exclusion of individual studies had minimal effect on the parameter estimates. In the most extreme case, when the study by Ghosh et al. (2023) was excluded, the parameter estimate was reduced by approximately 1.6 times. At 6 months after RT, the parameter estimates for PFS ranged from -0.003 to -0.03 , with a pooled estimate of -0.006 (Fig. S4). Excluding the study by Zhao et al. (2022) resulted in a fivefold reduction in the parameter estimate.

For OS, the leave-one-out sensitivity analysis at 1 month yielded parameter estimates ranging from -0.002 to -0.005 , with a pooled estimate of -0.003 (Fig. S3). Similar to PFS, the exclusion of most individual studies had little impact on the overall parameter estimate. At 6 months, parameter estimates for OS ranged from -0.005 to -0.01 (Fig. S4), with a pooled estimate of -0.006 . Exclusion of individual studies had minimal impact on the parameter estimates for OS. In the most extreme case, the parameter estimate was reduced by approximately 1.6-fold after excluding the Zhao et al. (2022) study in both the 1-month and 6-month models.

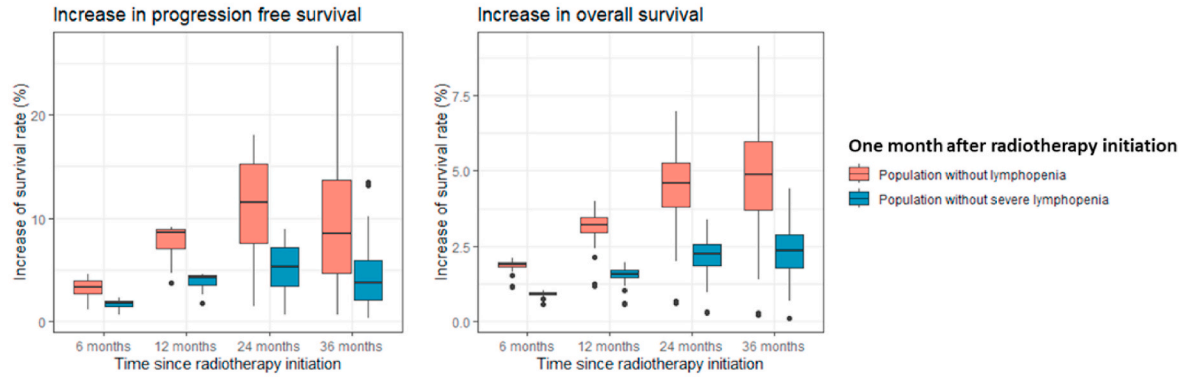
4. Discussion

This study investigated the impact of patient lymphocyte counts following RT on patient survival. Lymphopenia early after treatment (1 month after RT initiation) was strongly associated with short-term PFS improvement, while late lymphopenia (6 months after RT) had a more significant impact on long-term OS.

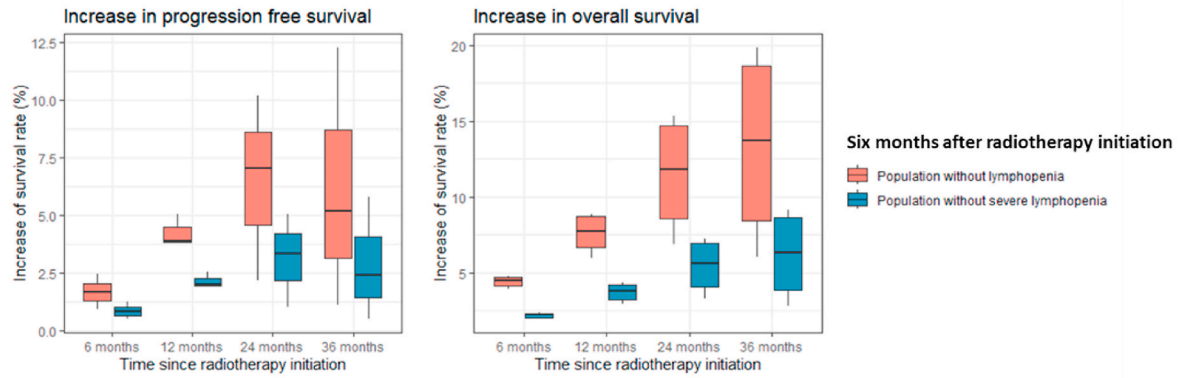
Our MBMA demonstrated a concentration-dependent relationship between increasing lymphocyte counts after RT and improved survival outcomes. This approach strengthens the causal link between lymphocyte recovery and prognosis, moving beyond simple binary distinctions (lymphopenia vs. non-lymphopenia). The impact of RIL on prognosis from most current studies has been viewed as a binary outcome—the presence or absence of lymphopenia. This raised the question of whether the poor prognosis is the result of RIL or whether both phenomena are the result of tumor progression. In fact, the progression of multiple tumor lineages has been shown to result in a lymphopenic environment in the circulating blood beyond the tumor microenvironment. Lymphopenia has been observed in more than 20 % of patients with advanced disease and in only 3 % of those with localized disease across several tumor types, including pancreas cancer, melanoma, non-Hodgkin's lymphoma, breast cancer, sarcoma, and glioblastoma [51–54]. Biological gradients are one of the criteria used to strengthen causal inference, as proposed by Hill [55], and have been widely used in causal inference in epidemiology. By incorporating the concentration-dependent relationship, this study strengthens the causal relationship between RIL and prognosis.

In addition, our results demonstrated that the benefit of lymphocyte recovery on OS becomes more pronounced at this later stage. Patients with higher lymphocyte counts at 6 months had significantly longer OS than the total population. This underscores the importance of monitoring lymphocyte counts over an extended period of time, rather than focusing solely on early nadir counts. Low ALCs during chemoradiotherapy are a strong predictor of poor outcomes and pathologic response rates in several types of cancer [10]. However, RIL is temporary and the ALC may recover after treatment completion [32,56]. Currently, little is known about how ALC recovery contributes to prognosis [32]. Various associations between ALC recovery and patient prognosis have been reported. Deng et al. reported that lymphocyte

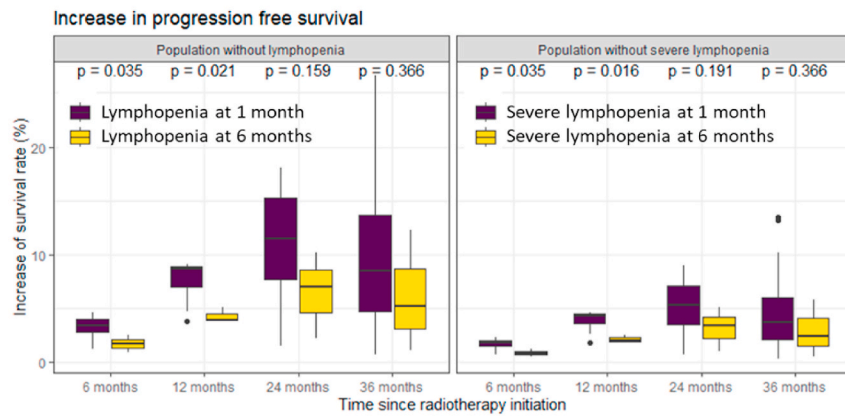
A.



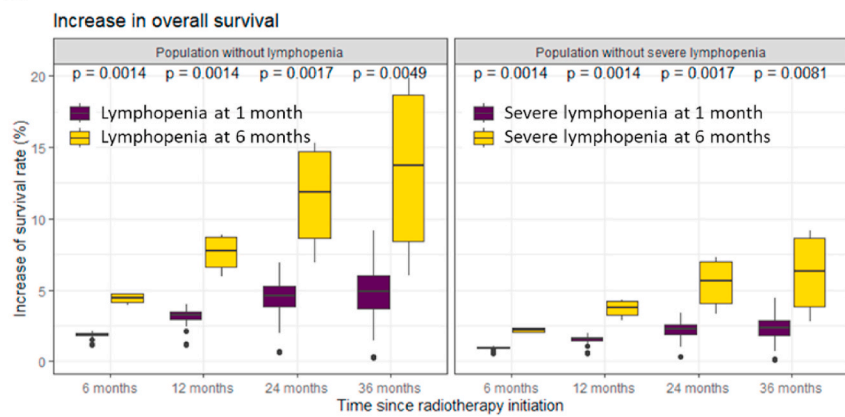
B.



C.



D.



(caption on next page)

Fig. 4. Increased survival in the population without lymphopenia compared to the total population. (A, B) Increase in progression-free survival (left) and overall survival (right) in the population without lymphopenia (red) or with severe lymphopenia (blue) at 1 month (A) or 6 months (B) after radiotherapy initiation compared to the total population. (C, D) Comparison of the increase in progression-free survival (C) and overall survival (D) between the population without lymphopenia (left) or severe lymphopenia (right) at 1 month (purple) or 6 months (yellow) after radiotherapy initiation.

Legend: The increase in survival of the population without lymphopenia (absolute lymphocyte count [ALC] ≥ 1000 cells/ μL of blood) or severe lymphopenia (ALC ≥ 500 cells/ μL of blood) was calculated as the survival of the total population (%) minus the survival of the population without lymphopenia (ALC ≥ 1000 cells/ μL of blood) or severe lymphopenia (ALC ≥ 500 cells/ μL of blood) (%) for each study. The p-values in panels C and D are the results of the nonparametric Wilcoxon test, which compared the increase in survival in the population with lymphopenia (ALC < 1000 cells/ μL of blood) or severe lymphopenia (ALC < 500 cells/ μL of blood) at 1 month or 6 months after radiotherapy initiation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

recovery was not associated with prognosis in esophageal cancer patients [32]. In contrast, Tseng et al. showed that esophageal cancer patients with inadequate lymphocyte recovery had worse survival outcomes, while also demonstrating the potential of this recovery index to differentiate prognosis in patients with a G1–3 ALC nadir during chemoradiotherapy, which had previously been overlooked [11]. This finding is also consistent with the study by Lee et al. in advanced pancreatic cancer patients [14], where recovery from severe lymphopenia was significantly associated with superior OS and PFS in patients with locally advanced pancreatic cancer. This discrepancy may be due differences in the definition of lymphocyte recovery, which was defined as a lymphocyte count above varying thresholds across studies. Therefore, the use of the ALC as a continuous covariate in a parametric survival function is necessary to strengthen the argument of the relationship between ALC recovery and treatment prognosis. This finding supports the idea of monitoring and controlling ALC not only during but also after RT. Limiting the dose to primary lymphoid organs such as the bone marrow has been shown to improve RIL recovery [4,6,11], thus potentially improving treatment prognosis. In addition, the evidence presented bolsters the idea of using RIL recovery as a valuable prognostic factor for RT.

Time-to-event survival estimates are typically derived from observed patient data using the Kaplan-Meier method, a non-parametric approach widely regarded as the gold standard for survival analyses [57]. However, survival estimates generated using regression models may offer greater precision, particularly in situations where the number of patients in certain strata is limited [57]. Unlike Kaplan-Meier estimation, parametric survival models allow for a more detailed representation of the survival function, as they rely on underlying distributional assumptions. This approach also facilitates the interpolation of survival estimates at unreported time points [58]. Among the usual parametric models of survival and failure-time data, the exponential and Weibull distributions are the most commonly used. The exponential model assumes a constant hazard rate over time, while the Weibull model allows for a monotonic hazard rate that can increase or decrease over time [58,59]. The exponential model was selected to analyze OS in this study because it assumes a constant hazard rate over time. This approach was appropriate given the observed pattern of hazard reduction associated with changes in lymphopenia. For PFS, the log-logistic model was found to provide the best fit for the data. Unlike the exponential model, the log-logistic model captures a hazard function that initially increases to a peak and then decreases, a pattern often observed in cancer survival models. This pattern reflects the typical trajectory of cancer treatment effects, where the initial response to treatment is followed by a reduction in hazard at a later time point as patients recover [60,61]. Similar to OS, the hazard for PFS was found to decrease as lymphopenia status improved, reinforcing the potential role of lymphocyte recovery as a prognostic indicator.

This study presents a model-based framework for analyzing survival data, focusing on the longitudinal impact of lymphocytes on survival. Unlike traditional meta-analyses, which only compare primary endpoints at the end of the study, MBMAs have significant potential to provide robust information [62]. This method integrates trial data from multiple sources and quantifies the effects of different trial populations and treatments. Our survival models for PFS and OS, which linked lymphopenia status 1 month after treatment to survival, demonstrated

strong sensitivity and robustness in capturing the effects of early lymphocyte changes. In contrast, models that attempted to link late lymphopenia (6 months post-treatment) to survival outcomes showed poor sensitivity due to the limited availability of data at this time point. While current data are insufficient to draw firm conclusions about the impact of late lymphopenia, the model provides a basis for future analysis when more comprehensive data become available. The use of MBMA in survival analysis of RIL has several practical implications for clinical practice. By tracking lymphocyte recovery over time, clinicians could be able to identify patients at higher risk for poor outcomes, allowing for timely adjustments to treatment protocols. Enhancing lymphocyte counts through strategies such as controlled clinical trials could provide valuable insights into effective interventions to boost lymphocyte recovery. Additionally, the ability to predict poor survival outcomes associated with RIL highlights the importance of exploring potential therapies to restore lymphocyte levels. For example, interleukine-7, a cytokine known to stimulate lymphocyte production, may be a promising candidate for future therapeutic development [63–65]. Another critical consideration is the synergistic effect of other treatments, such as chemotherapy, which may exacerbate lymphopenia [66,67]. This highlights the need for combined treatment protocols that mitigate the risk of lymphopenia while maintaining therapeutic efficacy.

Nevertheless, this study has several limitations. First, the generalizability of our findings is limited by the heterogeneity between studies and the observational nature of the data, which may be biased. Our study may have omitted some sources of variability, including differences in the characteristics of the study populations. The observed relationship between RIL and survival could be influenced by other factors (e.g., concomitant treatments, disease progression, or demographic characteristics such as age). Research examining the impact of late RIL on survival after RT is limited and has only focused on certain types of tumors. Therefore, it would be necessary to expand the dataset and conduct a randomized controlled clinical trial to draw a more precise conclusion. Finally, using only two time points for lymphocyte concentration limits the understanding of the causal relationship between RIL and patient prognosis. Again, for a more robust conclusion, an expansion of the dataset is needed and a randomized controlled clinical trial with an increase in the number of follow-up time points after RT should be conducted.

5. Conclusion

In conclusion, this study highlights the critical role played by lymphocyte nadir and recovery following RT in patient prognosis. Our MBMA revealed a gradient effect in which both early (1 month) and late (6 months) lymphocyte counts influenced survival. Furthermore, the model-based approach has the advantage of capturing the continuous influence of lymphocyte levels, providing valuable insights for future research. This approach goes beyond traditional binary comparisons and strengthens the causal link between RIL and patient outcomes. However, limitations such as observational data and limited research on late RIL require further investigation. To validate these findings, future research should prioritize large-scale randomized controlled trials that account for variability in study populations and treatment protocols. By expanding the dataset and incorporating randomized controlled trials,

we can build a more comprehensive understanding of the impact of RIL and guide the development of effective strategies to improve patient outcomes after RT. Additionally, future work should include subgroup analyses by cancer type to improve generalizability and sensitivity analyses to assess the robustness of the conclusions.

CRediT authorship contribution statement

Thao-Nguyen Pham: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julie Coupey:** Writing – review & editing, Conceptualization. **Juliette Thariat:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Samuel Valable:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Ethics statement

Non-applicable.

Declaration of competing interest

The authors declare no potential conflicts of interest.

Acknowledgments

This project received financial support from the CNRS through the 80|Prime program, the Ligue Contre le Cancer, and the French Region of Normandy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.compbiomed.2025.109702>.

References

- F. Chen, J.-Y. Jin, T.S.K. Hui, H. Jing, H. Zhang, Y. Nong, et al., Radiation induced lymphopenia is associated with the effective dose to the circulating immune cells in breast cancer, *Front. Oncol.* 12 (2022) 768956, <https://doi.org/10.3389/fonc.2022.768956>.
- Z. Zhang, X. Liu, D. Chen, J. Yu, Radiotherapy combined with immunotherapy: the dawn of cancer treatment, *Signal Transduct. Targeted Ther.* 7 (2022) 258, <https://doi.org/10.1038/s41392-022-01102-y>.
- S. Demaria, C. Guha, J. Schoenfeld, Z. Morris, A. Monjazeb, A. Sikora, et al., Radiation dose and fraction in immunotherapy: one-size regimen does not fit all settings, so how does one choose? *J Immunother Cancer* 9 (2021) e002038 <https://doi.org/10.1136/jitc-2020-002038>.
- T.-N. Pham, J. Coupey, M. Rousseau, J. Thariat, S. Valable, Revealing the effect of X-ray or proton brain irradiation on systemic inflammation and leukocyte subpopulation interplay in rodents, *J. Leukoc. Biol.* 116 (2024) 1530–1543, <https://doi.org/10.1093/jleuko/qiae156>.
- T.-N. Pham, J. Coupey, J. Thariat, S. Valable, Bayesian networks in modeling leukocyte interplay following brain irradiation: a comprehensive framework, *Comput. Methods Progr. Biomed.* 257 (2024) 108421, <https://doi.org/10.1016/j.cmpb.2024.108421>.
- T.-N. Pham, J. Coupey, S.M. Candéias, V. Ivanova, S. Valable, J. Thariat, Beyond lymphopenia, unraveling radiation-induced leukocyte subpopulation kinetics and mechanisms through modeling approaches, *J. Exp. Clin. Cancer Res.* 42 (2023) 50, <https://doi.org/10.1186/s13046-023-02621-4>.
- C. Terrones-Campos, B. Ledergerber, I.R. Vogelius, L. Specht, M. Helleberg, J. Lundgren, Lymphocyte count kinetics, factors associated with the end-of-radiation-therapy lymphocyte count, and risk of infection in patients with solid malignant tumors treated with curative-intent radiation therapy, *Int. J. Radiat. Oncol. Biol. Phys.* 105 (2019) 812–823, <https://doi.org/10.1016/j.ijrobp.2019.07.013>.
- S. Yovino, L. Kleinberg, S.A. Grossman, M. Narayanan, E. Ford, The etiology of treatment-related lymphopenia in patients with malignant gliomas: modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells, *Cancer Invest.* 31 (2013) 140–144, <https://doi.org/10.3109/07357907.2012.762780>.
- T.-N. Pham, J. Coupey, J. Toutain, S.M. Candéias, G. Simonin, M. Rousseau, et al., Early effects of different brain radiotherapy modalities on circulating leukocyte subpopulations in rodents, *Int. J. Radiat. Biol.* 100 (2024) 744–755, <https://doi.org/10.1080/09553002.2024.2324471>.
- P.J.J. Damen, T.E. Kroese, R. Van Hillegersberg, E. Schuit, M. Peters, J.J. C. Verhoeff, et al., The influence of severe radiation-induced lymphopenia on overall survival in solid tumors: a systematic review and meta-analysis, *Int. J. Radiat. Oncol. Biol. Phys.* 111 (2021) 936–948, <https://doi.org/10.1016/j.ijrobp.2021.07.1695>.
- I. Tseng, D. Ai, Y. Chen, H. Zhu, F. Li, Y. Xu, et al., Lymphocyte recovery from radiation-induced lymphopenia in locally advanced esophageal squamous cell carcinoma: correlations with prognosis and lymphocyte-related organs, *Radiat. Oncol.* 18 (2023) 172, <https://doi.org/10.1186/s13014-023-02354-w>.
- Q. Zhao, T. Li, S. Du, J. He, Z. Zeng, Shortened radiation time promotes recovery from radiation-induced lymphopenia in early-stage non-small cell lung cancer patients treated with stereotactic body radiation therapy, *Technol. Cancer Res. Treat.* 21 (2022) 153303382211122, <https://doi.org/10.1177/15330338221112287>.
- A.J. Lin, M. Gang, Y.J. Rao, J. Campian, M. Daly, H. Gay, et al., Association of posttreatment lymphopenia and elevated neutrophil-to-lymphocyte ratio with poor clinical outcomes in patients with human papillomavirus-negative oropharyngeal cancers, *JAMA Otolaryngol Head Neck Surg* 145 (2019) 413, <https://doi.org/10.1001/jamaoto.2019.0034>.
- B.M. Lee, H.K. Byun, J. Seong, Significance of lymphocyte recovery from treatment-related lymphopenia in locally advanced pancreatic cancer, *Radiother. Oncol.* 151 (2020) 82–87, <https://doi.org/10.1016/j.radonc.2020.07.026>.
- M. García-Cardosa, R. Meiriño, F.A. Calvo, E. Antolín, B. Aguilar, M. Vidorreta, et al., FLIP: a novel method for patient-specific dose quantification in circulating blood in large vessels during proton or photon external beam radiotherapy treatments, *Phys. Med. Biol.* 69 (2024) 225017, <https://doi.org/10.1088/1361-6560/ad8ea5>.
- B. Maayah, A. Moussaoui, S. Bushnaq, O. Abu Arqub, The multistep Laplace optimized decomposition method for solving fractional-order coronavirus disease model (COVID-19) via the Caputo fractional approach, *Demonstr. Math.* 55 (2022) 963–977, <https://doi.org/10.1515/dema-2022-0183>.
- B. Maayah, O. Abu Arqub, S. Alnabulsi, H. Alsulami, Numerical solutions and geometric attractors of a fractional model of the cancer-immune based on the Atangana-Baleanu-Caputo derivative and the reproducing kernel scheme, *Chin. J. Phys.* 80 (2022) 463–483, <https://doi.org/10.1016/j.cjph.2022.10.002>.
- P. Chan, K. Peskov, X. Song, Applications of model-based meta-analysis in drug development, *Pharm. Res. (N. Y.)* 39 (2022) 1761–1777, <https://doi.org/10.1007/s11095-022-03201-5>.
- J. Pinheiro, D. Bates, R Core Team, *Nlme: Linear and Nonlinear Mixed Effects Models*, 2023.
- Health UD of, Services H, others, *Common Terminology Criteria for Adverse Events Version 5 (CTCAEv5)*, 2017. No Title.
- R. Mohan, A.Y. Liu, P.D. Brown, A. Mahajan, J. Dinh, C. Chung, et al., Proton therapy reduces the likelihood of high-grade radiation-induced lymphopenia in glioblastoma patients: phase II randomized study of protons vs photons, *Neuro Oncol.* 23 (2021) 284–294, <https://doi.org/10.1093/neuonc/noaa182>.
- S. Rudra, C. Hui, Y.J. Rao, P. Samson, A.J. Lin, X. Chang, et al., Effect of radiation treatment volume reduction on lymphopenia in patients receiving chemoradiotherapy for glioblastoma, *Int. J. Radiat. Oncol. Biol. Phys.* 101 (2018) 217–225, <https://doi.org/10.1016/j.ijrobp.2018.01.069>.
- S. Ghosh, J. Huang, M. Inkman, J. Zhang, S. Thotala, E. Tikhonova, et al., Radiation-induced circulating myeloid-derived suppressor cells induce systemic lymphopenia after chemoradiotherapy in patients with glioblastoma, *Sci. Transl. Med.* 15 (2023) eabn6758, <https://doi.org/10.1126/scitranslmed.abn6758>.
- H.K. Byun, N. Kim, H.I. Yoon, S.-G. Kang, S.H. Kim, J. Cho, et al., Clinical predictors of radiation-induced lymphopenia in patients receiving chemoradiation for glioblastoma: clinical usefulness of intensity-modulated radiotherapy in the immuno-oncology era, *Radiat. Oncol.* 14 (2019) 51, <https://doi.org/10.1186/s13014-019-1256-6>.
- J. Xi, B. Hassan, R.G.N. Katumba, K. Khaddour, A. Govindan, J. Luo, et al., The predictive value of absolute lymphocyte counts on tumor progression and pseudoprogression in patients with glioblastoma, *BMC Cancer* 21 (2021) 285, <https://doi.org/10.1186/s12885-021-08004-2>.
- E. Le Rhum, F.B. Oppong, M. Vanlancker, R. Stupp, B. Nabors, O. Chinot, et al., Prognostic significance of therapy-induced myelosuppression in newly diagnosed glioblastoma, *Neuro Oncol.* 24 (2022) 1533–1545, <https://doi.org/10.1093/neuonc/noac070>.
- L.-T. Liu, Q.-Y. Chen, L.-Q. Tang, S.-S. Guo, L. Guo, H.-Y. Mo, et al., The prognostic value of treatment-related lymphopenia in nasopharyngeal carcinoma patients, *Cancer Res Treat* 50 (2018) 19–29, <https://doi.org/10.4143/crt.2016.595>.
- S.P. Ng, H. Bahig, A. Jethanandani, C. Pollard, J. Berends, E.M. Sturgis, et al., Lymphopenia during radiotherapy in patients with oropharyngeal cancer, *Radiother. Oncol.* 145 (2020) 95–100, <https://doi.org/10.1016/j.radonc.2019.12.023>.
- G.L. Jensen, P. Blanchard, G.B. Gunn, A.S. Garden, C. David Fuller, E.M. Sturgis, et al., Prognostic impact of leukocyte counts before and during radiotherapy for oropharyngeal cancer, *Clinical and Translational Radiation Oncology* 7 (2017) 28–35, <https://doi.org/10.1016/j.ctro.2017.09.008>.
- R. Davuluri, W. Jiang, P. Fang, C. Xu, R. Komaki, D.R. Gomez, et al., Lymphocyte nadir and esophageal cancer survival outcomes after chemoradiation therapy, *Int. J. Radiat. Oncol. Biol. Phys.* 99 (2017) 128–135, <https://doi.org/10.1016/j.ijrobp.2017.05.037>.

- [31] Y. Shiraishi, P. Fang, C. Xu, J. Song, S. Krishnan, E.J. Koay, et al., Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: a propensity matched analysis of the relative risk of proton versus photon-based radiation therapy, *Radiother. Oncol.* 128 (2018) 154–160, <https://doi.org/10.1016/j.radonc.2017.11.028>.
- [32] W. Deng, C. Xu, A. Liu, P.S.N. Van Rossum, W. Deng, Z. Liao, et al., The relationship of lymphocyte recovery and prognosis of esophageal cancer patients with severe radiation-induced lymphopenia after chemoradiation therapy, *Radiother. Oncol.* 133 (2019) 9–15, <https://doi.org/10.1016/j.radonc.2018.12.002>.
- [33] X. Wang, Z. Zhao, P. Wang, X. Geng, L. Zhu, M. Li, Low lymphocyte count is associated with radiotherapy parameters and affects the outcomes of esophageal squamous cell carcinoma patients, *Front. Oncol.* 10 (2020) 997, <https://doi.org/10.3389/fonc.2020.00997>.
- [34] H. Xu, M. Lin, Y. Hu, L. Zhang, Q. Li, J. Zhu, et al., Lymphopenia during definitive chemoradiotherapy in esophageal squamous cell carcinoma: association with dosimetric parameters and patient outcomes, *Oncol.* 26 (2021) e425–e434, <https://doi.org/10.1002/onco.13533>.
- [35] X. Cheng, B. Chen, S. Wang, J. Zhang, J. Zhu, M. Liu, et al., Association between lymphopenia and survival outcomes in esophageal carcinoma patients receiving combined immunotherapy and chemoradiotherapy, *Oncol.* 28 (2023) e606–e616, <https://doi.org/10.1093/oncolo/oyad094>.
- [36] Q. Zhao, G. Chen, L. Ye, S. Shi, S. Du, Z. Zeng, et al., Treatment-duration is related to changes in peripheral lymphocyte counts during definitive radiotherapy for unresectable stage III NSCLC, *Radiat. Oncol.* 14 (2019) 86, <https://doi.org/10.1186/s13014-019-1287-z>.
- [37] N. Kim, J. Myoung Noh, W. Lee, B. Park, H. Park, J. Young Park, et al., Proton beam therapy reduces the risk of severe radiation-induced lymphopenia during chemoradiotherapy for locally advanced non-small cell lung cancer: a comparative analysis of proton versus photon therapy, *Radiother. Oncol.* 156 (2021) 166–173, <https://doi.org/10.1016/j.radonc.2020.12.019>.
- [38] Y. Cho, Y. Kim, I. Chamseddine, W.H. Lee, H.R. Kim, L.J. Lee, et al., Lymphocyte dynamics during and after chemo-radiation correlate to dose and outcome in stage III NSCLC patients undergoing maintenance immunotherapy, *Radiother. Oncol.* 168 (2022) 1–7, <https://doi.org/10.1016/j.radonc.2022.01.007>.
- [39] X. Xie, S.H. Lin, J.W. Welsh, X. Wei, H. Jin, R. Mohan, et al., Radiation-induced lymphopenia during chemoradiation therapy for non-small cell lung cancer is linked with age, lung V5, and XRCC1 rs25487 genotypes in lymphocytes, *Radiother. Oncol.* 154 (2021) 187–193, <https://doi.org/10.1016/j.radonc.2020.09.002>.
- [40] W. Jing, T. Xu, L. Wu, P.B. Lopez, C. Grassberger, S.G. Ellsworth, et al., Severe radiation-induced lymphopenia attenuates the benefit of durvalumab after concurrent chemoradiotherapy for NSCLC, *JTO Clinical and Research Reports* 3 (2022) 100391, <https://doi.org/10.1016/j.jtocrr.2022.100391>.
- [41] M. Nakamura, H. Ishikawa, K. Ohnishi, Y. Mori, K. Baba, K. Nakazawa, et al., Effects of lymphopenia on survival in proton therapy with chemotherapy for non-small cell lung cancer, *J. Radiat. Res.* 64 (2023) 438–447, <https://doi.org/10.1093/jrr/rrac084>.
- [42] Y. Li, X. Fan, Q. Yu, H. Zhai, M. Mo, J. Sun, et al., Proton and carbon ion radiation therapy decreased severe lymphopenia by reducing thoracic vertebra and aortic doses in non-small cell lung cancer versus intensity modulated radiation therapy, *Int. J. Radiat. Oncol. Biol. Phys.* 116 (2023) 579–589, <https://doi.org/10.1016/j.ijrobp.2022.12.030>.
- [43] B. De, S.P. Ng, A.Y. Liu, S. Avila, R. Tao, E.B. Holliday, et al., Radiation-associated lymphopenia and outcomes of patients with unresectable hepatocellular carcinoma treated with radiotherapy, *JHC* 8 (2021) 57–69, <https://doi.org/10.2147/JHC.S282062>.
- [44] A.T. Wild, J.M. Herman, A.S. Dholakia, S. Moningi, Y. Lu, L.M. Rosati, et al., Lymphocyte-sparing effect of stereotactic body radiation therapy in patients with unresectable pancreatic cancer, *Int. J. Radiat. Oncol. Biol. Phys.* 94 (2016) 571–579, <https://doi.org/10.1016/j.ijrobp.2015.11.026>.
- [45] E.S. Wu, T. Oduyebo, L.P. Cobb, D. Cholakian, X. Kong, A.N. Fader, et al., Lymphopenia and its association with survival in patients with locally advanced cervical cancer, *Gynecol. Oncol.* 140 (2016) 76–82, <https://doi.org/10.1016/j.ygyno.2015.11.013>.
- [46] L. Yang, Z. Xu, L. Ma, Q. Liu, A.T.Y. Chang, Q. Wang, et al., Early onset of severe lymphopenia during definitive radiotherapy correlates with mean body dose and predicts poor survival in cervical cancer, *Colorado Bus. Mag.* 34 (2022) 149–159, <https://doi.org/10.3233/CBM-210292>.
- [47] Z. Xu, L. Yang, H. Yu, L. Guo, A machine learning model for grade 4 lymphopenia prediction during pelvic radiotherapy in patients with cervical cancer, *Front. Oncol.* 12 (2022) 905222, <https://doi.org/10.3389/fonc.2022.905222>.
- [48] H. Liu, H. Wang, J. Wu, Y. Wang, L. Zhao, G. Li, et al., Lymphocyte nadir predicts tumor response and survival in locally advanced rectal cancer after neoadjuvant chemoradiotherapy: immunologic relevance, *Radiother. Oncol.* 131 (2019) 52–59, <https://doi.org/10.1016/j.radonc.2018.12.001>.
- [49] X. Fan, L. Yang, W. Qin, B. Zou, B. Fan, S. Wang, et al., Prophylactic cranial irradiation-related lymphopenia affects survival in patients with limited-stage small cell lung cancer, *Heliyon* 9 (2023) e16483, <https://doi.org/10.1016/j.heliyon.2023.e16483>.
- [50] Y. Lin, Y. Kang, Y. Wu, Y. Chen, Y. Hu, Lymphocytopenia and survival after whole-brain radiotherapy in patients with small-cell lung cancer, *Thoracic Cancer* 14 (2023) 1268–1275, <https://doi.org/10.1111/1759-7714.14868>.
- [51] C. Borg, I. Ray-Coquard, I. Philip, G. Clapisson, N. Bendriss-Vermare, C. Menétrier-Caux, et al., CD4 lymphopenia as a risk factor for febrile neutropenia and early death after cytotoxic chemotherapy in adult patients with cancer, *Cancer* 101 (2004) 2675–2680, <https://doi.org/10.1002/cncr.20688>.
- [52] J. Péron, C. Cropet, O. Tredan, T. Bachelot, G. Clapisson, et al., CD4 lymphopenia to identify end-of-life metastatic cancer patients, *Eur. J. Cancer* 49 (2013) 1080–1089, <https://doi.org/10.1016/j.ejca.2012.11.003>.
- [53] O. Tredan, M. Manuel, G. Clapisson, T. Bachelot, S. Chabaud, C. Bardin-Courageot, et al., Patients with metastatic breast cancer leading to CD4+ T cell lymphopenia have poor outcome, *Eur. J. Cancer* 49 (2013) 1673–1682, <https://doi.org/10.1016/j.ejca.2012.11.028>.
- [54] P. Chongsathidkiet, C. Jackson, S. Koyama, F. Loebel, X. Cui, S.H. Farber, et al., Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors, *Nat. Med.* 24 (2018) 1459–1468, <https://doi.org/10.1038/s41591-018-0135-2>.
- [55] A.B. Hill, The environment and disease: association or causation? *Proc. Roy. Soc. Med.* 58 (1965) 295–300, <https://doi.org/10.1177/003591576505800503>.
- [56] S.G. Ellsworth, A. Yalamanchali, H. Zhang, S.A. Grossman, R. Hobbs, J.-Y. Jin, Comprehensive analysis of the kinetics of radiation-induced lymphocyte loss in patients treated with external beam radiation therapy, *Radiat. Res.* 193 (2019) 73, <https://doi.org/10.1667/RR15367.1>.
- [57] M. May, J. Sterne, M. Egger, Parametric survival models may be more accurate than Kaplan-Meier estimates, *BMJ* 326 (2003) 822, <https://doi.org/10.1136/bmj.326.7393.822>.
- [58] F. Emmert-Streib, M. Dehmer, Introduction to survival analysis in practice, *MAKE* 1 (2019) 1013–1038, <https://doi.org/10.3390/make1030058>.
- [59] S. Bennett, Log-logistic regression models for survival data, *Appl. Statist.* 32 (1983) 165, <https://doi.org/10.2307/2347295>.
- [60] A.O. Langlands, S.J. Pocock, G.R. Kerr, S.M. Gore, Long-term survival of patients with breast cancer: a study of the curability of the disease, *BMJ* 2 (1979) 1247–1251, <https://doi.org/10.1136/bmj.2.6200.1247>.
- [61] P. Borges, Estimating the turning point of the log-logistic hazard function in the presence of long-term survivors with an application for uterine cervical cancer data, *J. Appl. Stat.* 48 (2021) 203–213, <https://doi.org/10.1080/02664763.2020.1720627>.
- [62] J.W. Mandema, M. Gibbs, R.A. Boyd, D.R. Wada, M. Pfister, Model-based meta-analysis for comparative efficacy and safety: application in drug development and beyond, *Clin. Pharmacol. Ther.* 90 (2011) 766–769, <https://doi.org/10.1038/clpt.2011.242>.
- [63] F. Ponchel, R.J. Cuthbert, V. Goëb, IL-7 and lymphopenia, *Clin. Chim. Acta* 412 (2011) 7–16, <https://doi.org/10.1016/j.cca.2010.09.002>.
- [64] H.K. Byun, K.-J. Kim, S.C. Han, J. Seong, Effect of interleukin-7 on radiation-induced lymphopenia and its antitumor effects in a mouse model, *Int. J. Radiat. Oncol. Biol. Phys.* 109 (2021) 1559–1569, <https://doi.org/10.1016/j.ijrobp.2020.12.004>.
- [65] T. Daix, A. Mathonnet, S. Brakenridge, P.-F. Dequin, J.-P. Mira, F. Berbillé, et al., Intravenously administered interleukin-7 to reverse lymphopenia in patients with septic shock: a double-blind, randomized, placebo-controlled trial, *Ann. Intensive Care* 13 (2023) 17, <https://doi.org/10.1186/s13613-023-01109-w>.
- [66] V.M. Patil, G.K. Singh, V. Noronha, A. Joshi, N. Menon, S.G. Lashkar, et al., Lymphopenia during chemoradiation-foe or friend, *Ecancermedicalscience* 14 (2020) 1109, <https://doi.org/10.3332/ecancer.2020.1109>.
- [67] C. Ménétrier-Caux, I. Ray-Coquard, J.-Y. Blay, C. Caux, Lymphopenia in cancer patients and its effects on response to immunotherapy: an opportunity for combination with cytokines? *J Immunother Cancer* 7 (2019) 85, <https://doi.org/10.1186/s40425-019-0549-5>.