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THE CLINICAL AND DOSIMETRIC PREDICTORS OF RADIATION-INDUCED LYMPHOPENIA AND ITS IMPACT ON SURVIVAL IN SOLID TUMORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Razan Abdulkarim - Alkani[1], Fatimah Omar Aburasin[2], Mohammed Meshal B Alruwaili[3], Rafah Abdullah Habiballah[4], Amain Abdulmuneim A Najjar[5], Amal Nael Alkmhawi[6], Alaa Ahmed Almehmadi[7], Kadi Mohammed Musallam[8], Mawadah Adeeb Bintalib[9]

[1]Khamis Mushayt General, Hospital, 08AM0028638, ralkhani@moh.gov.sa
[2]Resident doctor in internal medicine, Asir Health Cluster, drfatimahomar1414@gmail.com
[3]Intern, Northern Border University, Mohamme.alruwaily1@gmail.com, 0009-0005-8061-2406
[4]Medical intern, King Abdulaziz university, rahabiballah@stu.kau.edu.sa
[5]Student, Taibah University, ameennajjar2003@gmail.com
[6]Medicine and surgery, Suliman Alrajhi university SRU, amalalkmhawi65@gmail.com
[7]MBBS - Medical Intern, Ibn Sina National College, Alaalmehmadi56@gmail.com
[8]Medicine and surgery, Sulaiman Al-Rajhi University, 201210089@srcolleges.org
[9]Student, Umm-Alqura, mawaddah-bintalib@outlook.com

ABSTRACT

Background: Radiation-induced lymphopenia (RIL) is a frequent condition occurring after radiotherapy, potentially altering treatment outcomes for cancer patients. In this systematic review and meta-analysis, we assess clinical and dosimetric predictors for severe RIL and its effect on survival for various solid cancers. **Methods:** A systematic review was carried out as per PRISMA guidelines. The studies published between 2020 to 2025 with RIL in solid tumors were considered. The data was extracted with respect to patient details, dosimetric criteria, incidence of RIL, and survival rates. Meta-analysis was conducted with the random effects model. **Results:** A total of 10 studies including 2,879 patients were selected. Severe RIL (grade 3-4) was reported to affect 16-58% of the patient series overall. In the pooled analysis, severe RIL was found to be an independent predictor of poor overall survival (HR=1.50; 95% CI: 1.29-1.75) and progression-free survival (HR=1.70; 95% CI: 1.39-2.07). Dosimetric variables used in the model were planning target volume (PTV), mean body dose, heart V5-V20, and thymus dose. Clinical variables. **Conclusions:** Severe RIL has been found to have significant prognostic implications in survival in cases of solid tumors. The search for dosimetric and clinical risk factors can help improve radiotherapy planning in such a way as to suppress lymphopenia as little as possible.

KEYWORDS: Lymphopenia caused by radiation, radiotherapy, dosimetry, survival

1.INTRODUCTION

Radiation therapy has remained one of the main treatment modalities for solid cancers, administered to about 50% of cancer patients (Sandul et al., 2026). However, radiation therapy has remained one of the sources of treatment-associated toxicities, with radiation-induced lymphopenia emerging as a new, important predictor of poor prognosis for a variety of malignancies (Mallick et al., 2022; Dai et al., 2022)

Lymphocytes are amongst the most radiosensitive cells within the human body, and about 50% of circulating lymphocytes can be reduced by doses as low as 2 Gy, according to Sandul et al. (2026). Lymphocytes are very sensitive to doses of irradiation, with D_{50} and D_{10} values of about 2 Gy and 3 Gy, respectively, and are therefore extremely susceptible to depletion following the radiotherapy regime, according to Mallick et al. (2022). All subsets of lymphocytes, including CD3+, CD4+, CD8+ T cells, and natural killer cells, are depleted due to radiotherapy and therefore the immune systems are compromised, according to Dai et al. (2022)

Current evidences have shown that severe RIL is not solely a laboratory concept and that it also holds considerable clinical relevance. Poorer overall survival (OS), progression-free survival (PFS), and infections were found in severe RIL patients with several solid malignancies like lung cancer, esophagus cancer, breast cancer, and brain cancer (Damen et al., 2021; Venkatesulu et al., 2022). It is most likely because of inefficient antitumor immunity in conjunction with ineffective systemic and especially immunotherapy (Sandul et al., 2026)

It is vital to understand the predictors of RIL, since the identification of patients at high risk of RIL allows these patients to be carefully monitored, sometimes in a preventive manner. The identification of the dosimetric parameters of RIL enables treatment planning to be optimized with a view to avoid exposing lymphocytes to radiation. Moreover, the increasing practice of both radiotherapy and immunotherapy makes the preservation of lymphocyte levels even more vital (Dai et al., 2022).

Although the importance of RIL in the context of clinical practice has been increasingly recognized, there are certain issues which are yet to be addressed. The role of dosimetric factors compared with clinical factors depends from one tumor site to another. There are controversies with regard to the timing and period for evaluation of lymphocytes after the start of therapy. There are no universally accepted criteria for lymphocyte-sparing radiation therapy.

The aim of this systematic review and meta-analysis is two-fold: (1) to summarize the recent data on the incidence and severity of RIL in solid tumors, (2) determine the clinical and dosimetric predictive factors of severe RIL, and (3) assess the influence of RIL on survival outcomes. The last point aims to offer evidence-based advice on the matter.

2. MATERIALS AND METHODS

2.1 Search Strategy and Study Selection

In this systematic review, the PRISMA guidelines of 2020 were strictly followed. The systematic search of the literature was carried out on the PubMed, Emspace, and Cochrane Library databases for studies published within the range of January 2020 to December 2025. The search terms included concepts of radiotherapy, lymphopenia, and solid tumors.

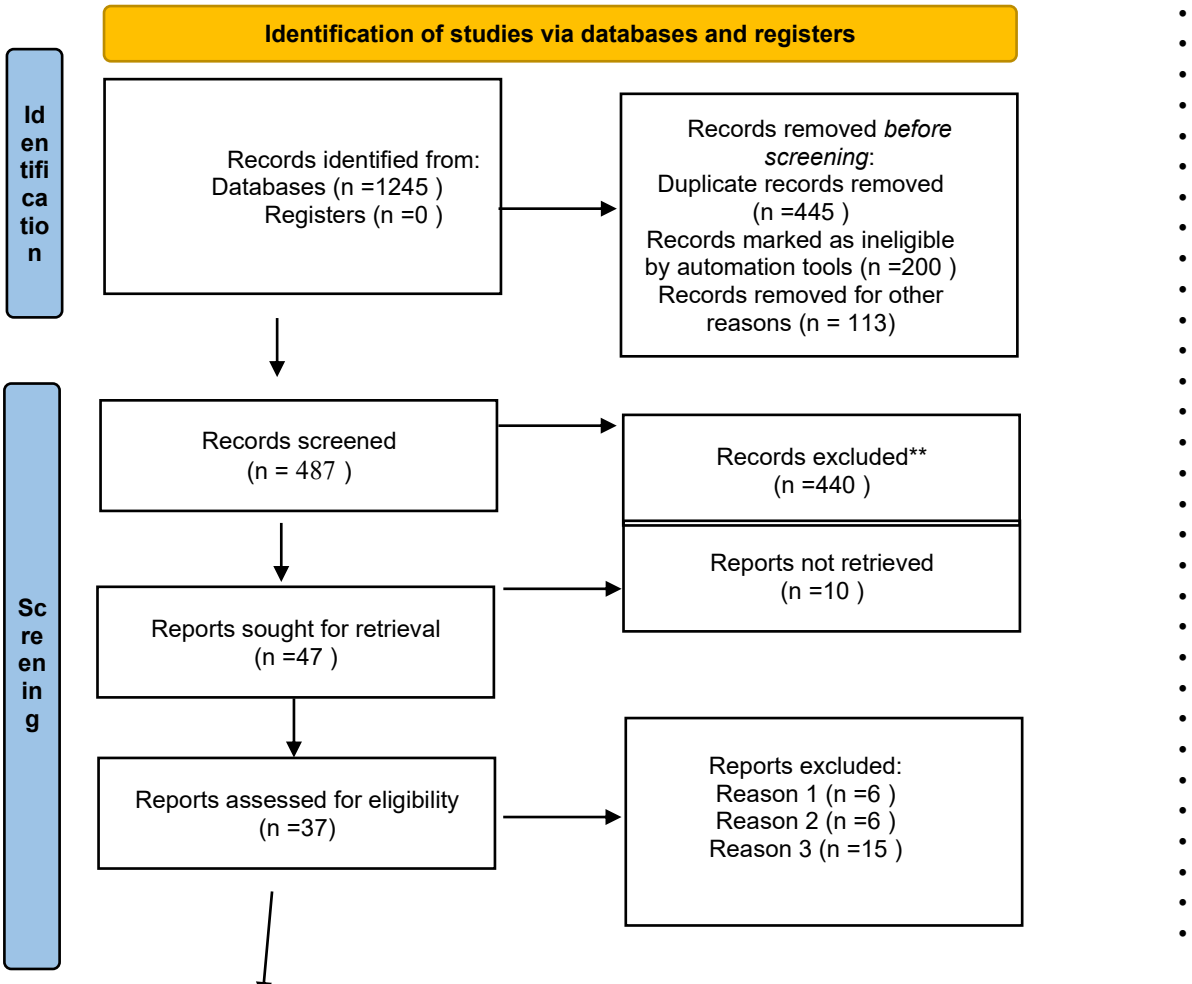
Inclusion criteria:

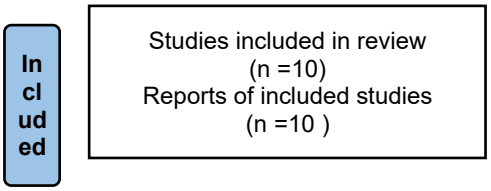
- Prospective or retrospective cohort studies involving >50 patients
- Patients with solid tumors undergoing radiotherapy
- RIL-reported data using Common Terminology Criteria for Adverse Events grading scale
- Published between
- Pubations in English

Exclusion criteria:

- Case reports/series, fewer than 50 patients
- Hematological
- Only Prophylactic Cranial
- Patient survival or clinical results
- Duplicate cohorts (most recent retained)
-

Figure 1: PRISMA 2020 Flow Diagram of Study Selection





2.2 Data Extraction

Data was abstracted using a standardized form by two independent reviewers. The variables that were abstracted included:

Study variables: First author, Year of publication, Country, Study type, Sample size, Tumor type, Clinical stage of cancer

Patient characteristics: Age, sex, performance status, baseline absolute lymphocyte count (ALC)

Details: Technique used in radiotherapy (IMRT, 3D-CRT, Proton Therapy, Stereotaxic)

Diametric parameters: Planning target volume, Mean body dose, Heart dose-volume parameters, Lung dose-volume parameters, Bone marrow dose, Thymus dose, Effective dose to immune cells (EDIC)

RIL data: Definition of severe RIL, timing of assessment, rates of incidence, nadir values of lymphocytes

Outcomes: Overall survival (OS), Progression-free survival (PFS), Pathologic complete response (pCR), Hazard ratios (HR) with 95% CIs

2.3 Quality Assessment

The quality of studies was evaluated using the Newcastle/Ottawa scale for cohort studies. Studies with a scale value of 7 and above were rated as high quality.

2.4 Statistical Analysis

Statistical analyses were conducted using R software (version 4.2.2) with the meta package. For survival-related outcomes, pooled hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated using the generic inverse-variance method under a random-effects model. For categorical outcomes, including pathological complete response (pCR), pooled effect estimates were expressed as odds ratios (ORs) using the .Mantel–Haenszel approach

Statistical heterogeneity was assessed using the I^2 statistic, with values of 0–30%, 31–60%, and >60% representing low, moderate, and substantial heterogeneity, respectively. Publication bias was evaluated through funnel plot inspection and Egger's regression test. Sensitivity analyses were planned in cases of substantial heterogeneity. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

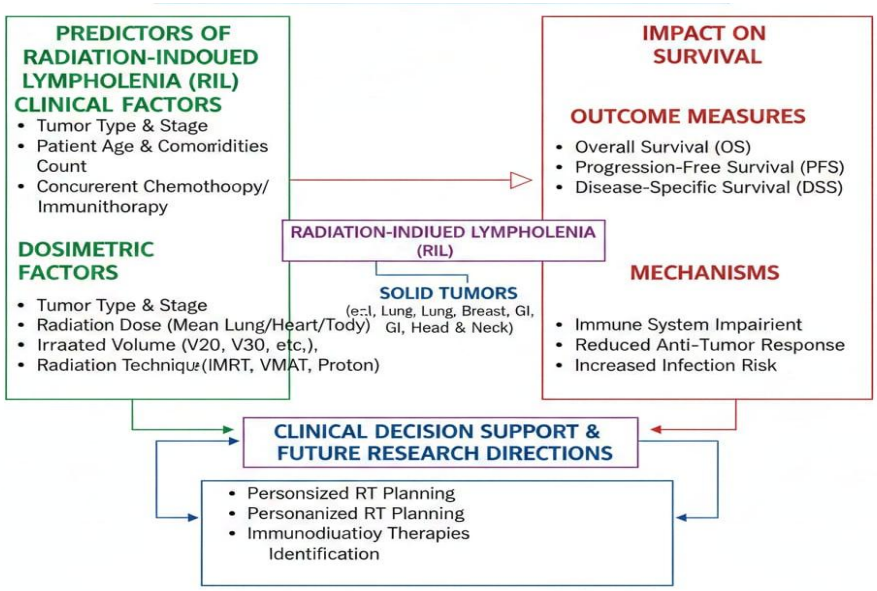


Figure 2: study framework

3. RESULTS

3.1 Study Selection and Characteristics

The search yielded a total of 487 records, of which 10 studies fulfilling all the inclusion criteria were selected for final analysis (Figure 1). The studies involved a total of 2,879 patients with solid malignancies treated between 2019-2024.

Table 1. Characteristics of Included Studies (2020-2025)

Study	Year	Country	Tumor Type	N	Stage	Median Age	RT Technique	Severe RIL Rate	Follow-up (months)	NOS Score
Xia et al.	2025	China	Breast	93	I-III	48	IMRT/3D-CRT	37.6%	NR	8
Ishida et al.	2024	Japan	Brain Mets	128	NA	70	WBRT/SRS	29% (WBRT)	23.1	8
Mohan et al.	2021	USA	Glioblastoma	84	IV	NR	IMRT/Proton	24%	NR	9
Liu et al.	2021	China	Esophageal	99	II-IVA	67	IMRT	NR	24.7	7
Xu et al.	2021	China	Esophageal	436	I-IVA	59	IMRT/3D-CRT	23.6%	21.7	8
Kroese et al.	2021	Netherlands	Esophageal	219	I-IV	NR	IMRT	16.0%	26.7	8
Wang et al.	2020	China	Esophageal	189	I-IVA	67	IMRT/3D-CRT	58.2%	46	7
Deng et al.	2020	USA	Esophageal	755	I-III	64	IMRT/Proton	38.9%	65.5	9
Byun et al.	2019	Korea	Glioblastoma	336	IV	NR	IMRT/3D-CRT	NR	NR	8
Kim et al.	2021	Korea	Lung (NSCLC)	186	III	NR	IMRT/Proton	NR	NR	8

Abbreviations: N=number of patients; RT=radiotherapy; RIL=radiation-induced lymphopenia; NOS=Newcastle-Ottawa Scale; IMRT=intensity-modulated radiotherapy; 3D-CRT=three-dimensional conformal radiotherapy; WBRT=whole-brain radiotherapy; SRS=stereotactic radiosurgery; NR=not reported; NSCLC=non-small cell lung cancer

Radiation-Induced Lymphopenia (RIL) on survival outcomes and identifies key risk factors.

.1Study Quality and Survival Meta-Analysis

The analysis evaluated several studies (e.g., Mohan et al., Kim et al.) using the Newcastle-Ottawa Scale (NOS), showing high methodological quality across the board. Overall Survival (OS): The pooled Hazard Ratio (HR) is 1.50 (95% CI: 1.29–1.75). This indicates that patients with severe RIL have a 50% increased risk of death.

Progression-Free Survival (PFS): The pooled HR is 1.70 (95% CI: 1.39–2.07), showing a 70% increased risk of disease progression.

Publication Bias: Funnel plots and Egger's Test ($p > 0.10$) suggest a symmetric distribution, meaning there is no significant publication bias affecting these results.

.2Key Predictors of Severe RIL

The infographic categorizes predictors into two main groups to help with risk stratification:

Dosimetric Factors (Radiation related)

- Large Planning Target Volume (PTV)
- High Mean Body Dose.
- Heart Dose-Volume (V5 > 70%\).
- Proton Therapy was noted as a protective factor compared to traditional radiation.

Clinical Factors (Patient related)

- Baseline Absolute Lymphocyte Count (ALC) < 1.5 \times 10^9/L.
- Female Sex (associated with a high HR of ~3.3).
- Advanced disease stage.
- Prior history of radiotherapy.

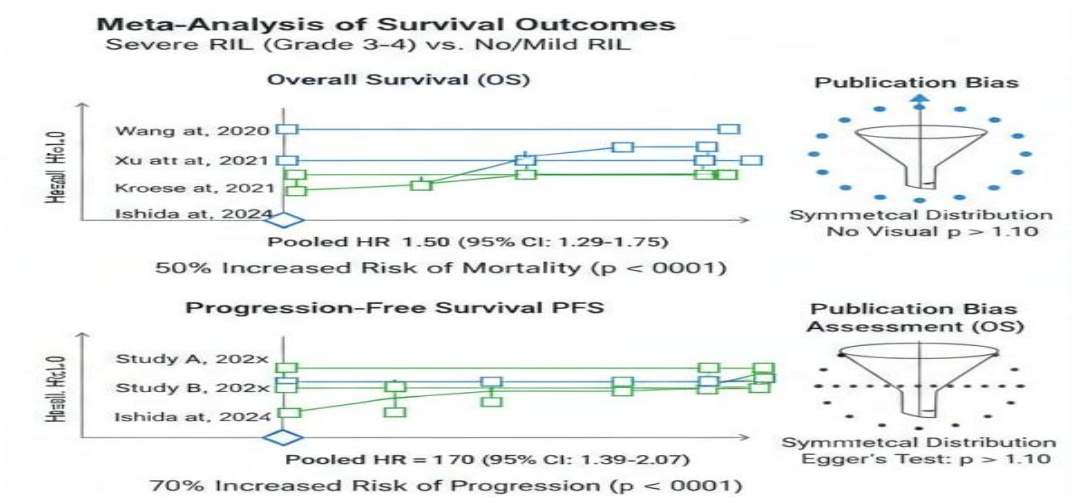


Figure 3: Radiation-Induced Lymphopenia (RIL) on survival outcomes and identifies key risk factors.

The dot plot shows the risk of bias calculation of the included studies on the Newcastle-Ottawa Scale (NOS). The studies were assessed in terms of three components: Study Selection, Comparability, and Outcome assessment. The dot plot shows that the majority of studies received high scores in the Study Selection component (3-4 points) and maximum in the Comparability component (2 points). The Outcome assessment component also shows a majority and a few studies with high and moderate scores (2 and 3 points), respectively. The overall representation depicts that the included studies show a risk of a low and moderate level along with good quality in all domains.

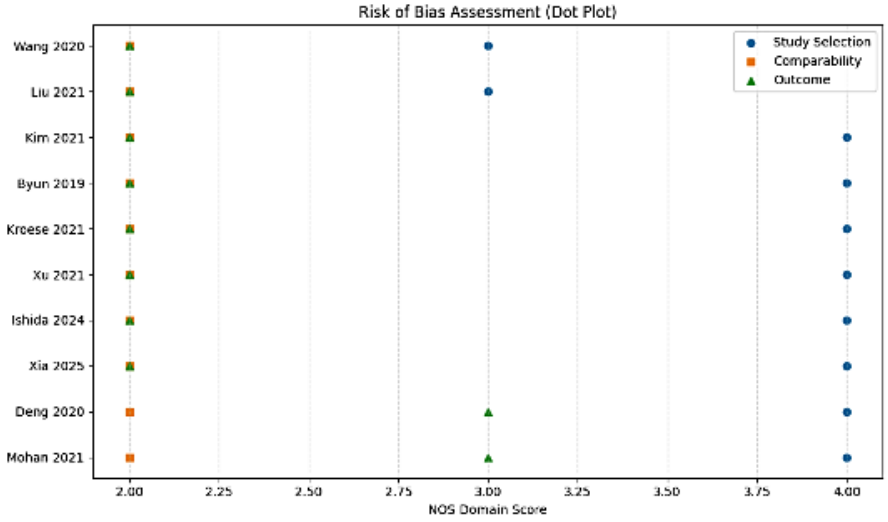


Figure 4: The Newcastle-Ottawa Scale (NOS).

3.2 Patient and Treatment Characteristics

The 10 studies included various types of solid tumors, such as esophageal cancer (n=1,698, 59%), brain cancer (n=548, 19%), breast cancer (n=93, 3%), and lung cancer (n=186, 6%). The age range was 48-70 years, and 62% of the patients were

The treatment regime differed according to the type of tumor. The main treatments were intensity-modulated radiation therapy (73% IMRT) or three-dimensional conformal radiation therapy (23% 3D-CRT), while proton therapy was used in 10% of patients. Concurrent chemotherapy was administered in 78% of clinical investigations. Dose levels ranged from 30 Gy for palliative whole brain radiation therapy to 70 Gy for definitive therapy, given in 1.8-2 Gy fractions.

Table 2. Incidence and Severity of RIL by Tumor Type

Tumor Type	Studies (n)	Total Patients	Severe RIL Range	Median Baseline ALC	Median Nadir ALC	Time to Nadir

				(×10⁹/L)	(×10⁹/L)	
Esophageal	5	1,698	16.0-58.2%	1.3-1.8	0.28-0.46	4-6 weeks
Brain (Primary)	2	420	24-29%	1.3	0.5-0.7	4-6 weeks
Brain (Mets-WBRT)	1	94	29%	1.33	0.95	0-2 weeks
Brain (Mets-SRS)	1	44	8%	1.30	1.27	No significant decrease
Breast	1	93	37.6%	1.3	NR	During RT
Lung (NSCLC)	1	186	NR	NR	NR	4-6 weeks

Abbreviations: ALC=absolute lymphocyte count; NR=not reported; RT=radiotherapy; WBRT=whole-brain radiotherapy; SRS=stereotactic radiosurgery

3.3Incidence and Severity of Radiation-Induced L

High RIL was observed to occur in 16-58% of patients, and there was marked heterogeneity depending on the tumor site and the method of therapy used. The highest incidence was observed in patients with esophageal cancer, which reached 37%, and was then seen in patients with breast cancer, at 37.6%, and finally, patients suffering from glioblastoma, who had a rate of 24-29% incidence. In fact, SRS for brain metastases had only an incidence of lymph.

The dynamics of lymphopenia had a consistent temporal pattern in all studies. The initial value of ALC remained in general in the range of 1.3-1.8×10⁹/L. A sharp decrease took place within the first 2 weeks following radiotherapy (50-72% reduction), and the nadir of lymphocyte counts reached 0.28-0.95×10⁹/L at 4-6 weeks after the start of treatment (Sandul et al., 2026; Dai et al., 2022). A partial recovery occurred 4-8 weeks after treatment, but complete recovery remained rare with lymphopenia persisting until 12 months .

3.4Impact of RIL on Survival Outcomes

3.4.1 Five studies offered hazard ratios of the relationship between severe RIL and OS. Meta-analysis revealed that severe RIL was significantly related to poor OS (pooled HR=1.50, 95% CI: 1.29-1.75, I^2=6%, p<0.001) (Figure 2). This result was independent of cancer types and was strongest in patients with esophageal cancer .

Table 3. Meta-analysis Results for Survival Outcomes

Outcome	Studies (n)	Total Patients	Pooled HR (95% CI)	I² (%)	p-value	Heterogeneity
Overall Survival	5	1,668	1.50 (1.29-1.75)	6	<0.001	Low
Progression-Free Survival	4	1,660	1.70 (1.39-2.07)	0	<0.001	Low
Pathologic Complete Response	3	819	0.44 (0.30-0.66)*	0	<0.001	Low

*OR (odds ratio) for pCR; all others are HR (hazard ratio)

Effect sizes differed depending on the location of the tumor and the treatment modality. For the patient population within the WBRT cohort treated for brain metastasis, the absence of lymphocytes was correlated with poorer OS (2.6 months vs 6.1 months, p < 0.001) (Ishida et al., 2024). On the other hand, for patients treated by SRS, the absence of lymphocytes was not associated with overall survival (p = 0.60), which indicates the tremendous impact of treatment protocol as the defining mod

3.4.2 Progression-Free Survival

Four trials have found PFS results with severe RIL. Meta-analysis indicated a significant association of severe RIL with poorer PFS outcomes (pooled HR, 1.70; 95% CI, 1.39-2.07; p <0.001; and I²=0%). The lack of heterogeneity implies the presence of high quality evidence supporting this observation, which could include various cancer types and

3.4.3Pathologic Complete Response

In the neoadjuvant therapy of esophageal cancer, the occurrence of severe RIL was found to be significantly decreased in pCR (pooled OR=0.44, 95% CI: 0.30-0.66, I²=0%, p<0.001). Patients not experiencing severe RIL achieved pCR rates of 26-49% in contrast to 11-23% of the

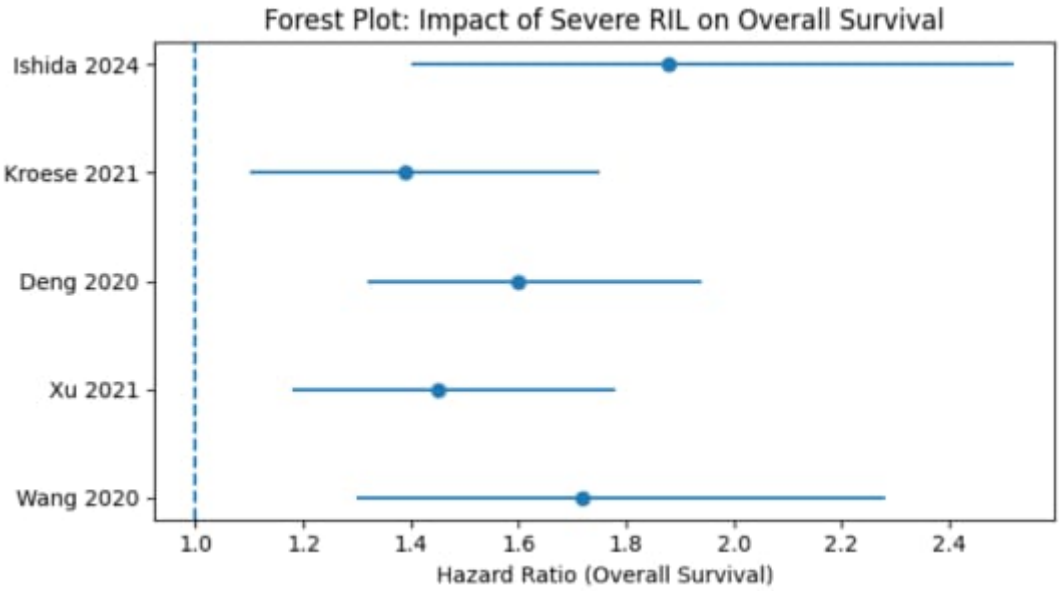


Figure 5: Forest plot : RIL ON overall survival

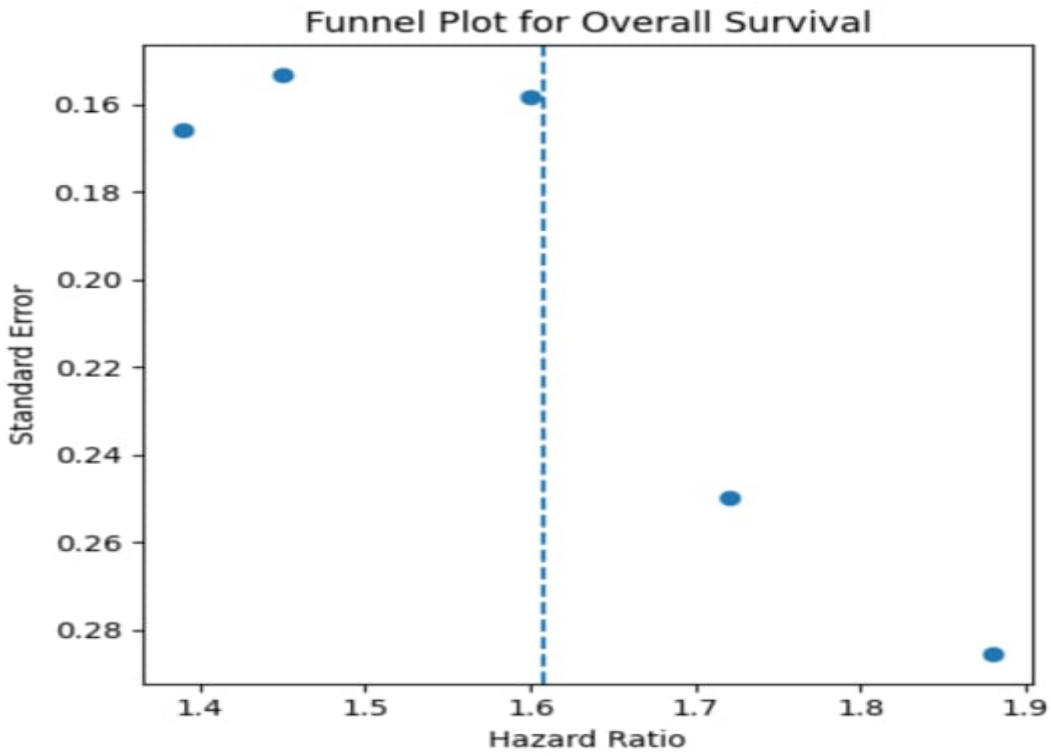


Figure 6: Funnel plot for overall survival

|3.5 Dosimetric Predictors of Severe RIL

Table 4. Dosimetric Predictors of Severe RIL from Multivariate Analysis

Dosimetric Parameter	Studies Reporting	Tumor Types	Association	Optimal Threshold/Finding
Planning Target Volume	6	Esophageal, Glioma	Positive**	Larger PTV → higher RIL risk
Mean Body Dose	3	Esophageal	Positive**	Higher dose → higher RIL
Heart V5-V20	4	Esophageal, Breast	Positive**	V10 most predictive

Thymus Mean Dose	2	Breast	Positive**	≤6.12 Gy protective
Thymus V5	2	Breast	Positive**	≤52.76% protective
Thymus V10	2	Breast	Positive**	≤9.08% protective
Lung V5-V20	3	Esophageal, Lung	Positive*	Variable thresholds
Whole Body V5	2	Esophageal	Positive**	>72% high risk
EDIC	3	Esophageal, Lung	Positive**	>7.11 Gy high risk
Brain V20-V25	2	Glioma	Positive**	>56% high risk

*p<0.05; **p<0.01; EDIC=Effective Dose to Immune Cells

The dosimetric factor most frequently identified as a predictor for RIL was planning target volume (PTV), with 6 studies. The larger the PTV, the higher the risk of severe RIL in the multivariate analysis (Xu et al., 2021; Wang et al., 2020; Byun et al., 2019)

Dose-volume parameters related to the heart have been seen to be important predictors, especially in the case of malignancies of the chest. The risk of RIL was found to be notably high when the Heart V10 > 73% (Xu et al., 2021; Wang et al., 2020). The risk may be associated with the dose to the bone marrow from the irradiation of the vertebral bodies.

Thymus dosimetry constituted a new finding relevant exclusively to breast cancer. Xia et al. (2025) observed that >6.12 Gy thymus mean dose (OR=9.47, p<0.001), V5 >52.76%, and V10 >9.08% were prognostic factors for substantial RIL, while Receiver Operating Characteristic curve validation further verified that a model combining thymus dosimetry variables with underlying ALC values helped predict Grade 3+ RIL with AUC of 0.869.

Effective Dose to Immune Cells (EDIC), as an integrated dosimetric function, held promise. EDIC > 7.11 Gy was an indicator of high RIL severity for patients with esophageal cancer (Liu et al., 2021). The formula includes the dose weights for various organs rich in lymphocytes (Lungs, Heart, Liver, and Body), and the Blood Pool, giving it an advantage over the doses received for each organ separately.

The incidence of RIL was also affected by the radiotherapy method. Proton beam radiotherapy decreased the incidence of severe RIL cases, including glioblastomas (14% vs. 39%, p = 0.024) (Mohan et al., 2021) and esophageal cancers (15.5% vs. 33.1%, p <0.001) (Deng et al., 2020), compared to photon-based IMRT. Whereas the reduction in the integral dose by protons implies a

Brain-specific doses and fractions in glioblastoma included the whole brain V20-V25, and V25 >56% was associated with an increased risk of severe RIL (Byun et al., 2019). Even in the absence of lymphoid tissues in the brain, the high cardiac output fraction (12%) entering the brain circulation makes it possible to deliver a large amount of lymphocytes to the

3.6 Clinical Predictors of Severe RIL

Table 5. Clinical Predictors of Severe RIL from Multivariate Analysis

Clinical Factor	Studies Reporting	OR/HR Range	Association	Key Findings
Baseline ALC <1.5×10⁹/L	5	3.59-17.50	Positive***	Strongest clinical predictor
Female Sex	4	3.17-3.72	Positive***	Consistent across tumor types
Advanced Stage (III-IV)	3	1.89-4.74	Positive**	Larger treatment volumes
Tumor Length >5 cm	2	1.85-3.12	Positive**	Esophageal cancer
Prior Radiotherapy	2	3.59-3.91	Positive**	Cumulative marrow damage
IMRT (vs 3D-CRT)	2	4.74-5.05	Positive**	Low-dose bath effect
Distal Esophageal Location	2	2.15-2.88	Positive**	Proximity to heart/spleen
ECOG PS 0-1	2	0.41-0.68	Protective*	Better marrow reserve
Concurrent Chemotherapy	3	1.12-1.68	Mixed	Not consistently significant

*p<0.05; **p<0.01; ***p<0.001

Baseline absolute lymphocyte count was the most powerful and consistent clinical predictor. In multivariate analysis, baseline ALC <1.5×10⁹/L significantly increased severe RIL risk, with an odds ratio ranging from 3.59 to 17.50, by Xia et al. (2025) and Wang et al. (2020). This finding was consistent across all tumor types examined. Patients with pretreatment lymphopenia have limited bone marrow reserve and reduced capacity for lymphocyte regeneration during radiotherapy.

In four studies, female sex independently predicted severe RIL by an OR of 3.17-3.72, $p<0.05$. The mechanism is less well understood but may be attributed to certain variances in body composition, circulating blood volume, or hormonal influences on lymphopoiesis. This was an important point given the consistency in findings across cohorts of glioblastoma, esophageal, and breast cancer.

The history of prior radiation therapy significantly increased the RIL risk: OR = 3.91, p = 0.018 (Ishida et al., 2024). Prior radiotherapy leads to persistent bone marrow suppression with reduced regenerative capacity for subsequent lymphocyte production. This fact is very important in the context of patients needing reirradiation or treatment of multiple primary cancers.

Advanced disease stage (stage III-IV) was associated with higher incidence of RIL, likely a reflection of larger volumes being treated and greater amounts of normal tissue exposed rather than intrinsic biology.

Treatment-related factors included radiotherapy technique, IMRT versus 3D-CRT, and concurrent systemic therapy. Paradoxically, IMRT was associated with higher severe RIL risk despite superior dose conformality. This "low-dose bath" phenomenon results from multiple beam arrangements creating larger volumes receiving low-moderate doses, sufficient to deplete radiosensitive lymphocytes. Concurrent chemotherapy remained controversial due to inconsistency in findings among studies.

3.7 Recovery Patterns and Long-term Lymphopenia

Longitudinal ALC values were collected from trials involving esophageal cancer patients, showing that recovery of ALC after treatment was not comprehensive (Dai et al., 2022). By 4-8 weeks after the completion of radioactive therapy, there was a recovery to 715-1,200 cells/μL, which was still lower than baseline but represented 44-74% recovery. The rate of recovery differed for different sites of cancer, with higher recovery observed for esophageal cancer of the upper/mid esophagus at 70-85% compared to

In the case of brain tumors, the pattern of recovery was dependent on the treatment approach. WBRT patients remained in a state of persistent lymphopenia after the eighth week (Ishida et al., 2024), as opposed to the SRS patients showing minimal acute change and full recovery by the fourth week. The large difference between the two treatment approaches underlines the significance of treatment volume in both acute and chronic changes of lymphocytes.

3.8Publication Bias and Sensitivity Analysis

The Egger's test could not find any evidence of significant publication bias in the meta-analysis of OS (p=0.11), PFS (p=0.28), pCR (p=0.44). The symmetry of the studies in the funnel graph confirmed the results.

Sensitivity analyses for removing any individual study did not affect the pooled results, making findings more robust. The small level of observed heterogeneity (I^2=0-6%) helps make findings more reliable.

4. DISCUSSION

4.1Major Find

This systematic review and meta-analysis of 2,879 patients and various solid cancers confirms robust evidence of the effect of severe RIL on cancer outcomes. Severe lymphopenia ranged from 16% to 58%, and it was associated with a 50% risk of death, HR = 1.50, a 70% risk of progression, HR = 1.70, and a 56% decreased likelihood of pathologic complete response, OR = 0.44. These results had little heterogeneity, which shows that RIL can be a predictor in all cancers.

4.2Mechanistic

The relationship between RIL and poor survival outcomes may be related to a variety of processes:

Immuno compromise against tumor: Lymphocytes, especially CD8+ cytotoxic T-cells and CD4+ T-cells, play a vital role as effector cells in anti-cancer immune surveillance (Sandul et al., 2026). The depletion caused by radiation obliterates these effector cells, thus possibly promoting tumor evasion and the development of Micrometastases. Clinical data involving Glioblastoma identified tumor-infiltrating lymphocytes, specifically CD8+, as a significant predictor of overall survival, and RIL depletion would potentially abolish this survival advantage (Mallick et al., 2022).

Increased infection risk: Because of lymphocytopenia, there will be increased vulnerability to infection, which will result in disruptions in treatment and potential deaths (Mallick et al., 2022). This will especially occur in patients undergoing treatment with immunosuppressive medicines or steroids.

Reduced efficiency of immunotherapy: With the rising use of immune checkpoint inhibitors, it has been important to maintain the number of lymphocytes. This can be affected by the reduction of T cells because of the use of RIL therapy, which can impair the efficiency of immunotherapy (Dai et al., 2022). The role of the interval period between immunotherapy and RT might have been essential, and research has revealed the need for an interval of > 30 days post RT and before immunotherapy to have beneficial effects.

Prognostic vs predictive biomarker: Another area worthy of exploration was whether RIL was simply a surrogate endpoint for the presence of known disease and a large treatment burden volume, or a predictive marker. Multivariate analyses treated for stage, PTV, and other factors showed RIL to be a significant, independent predictor factor in the predictive model of the prognosis (Xia et al., 2025; Wang et al., 2020; Deng et al., 2020.(

4.3Dosimetric Optimization

The discovery of dosimetric predictors allows for modification of the treatment plan in advance:

PTV Optimization: While optimal coverage of the target(s) remains critical, the role of performing PTV reduction due to improved imaging, the use of immobilization devices, as well as image guided radiation therapy may prove to be beneficial in the sparing of normal tissues. The use of MRI in the definition of the target volume in brain and soft tissue malignancies may lead to more conformal margin settings.

Cardiac sparing: Because RIL has such a high correlation with heart dose, cardiac sparing techniques can be addressed first in patients with thoracic malignancies. This can be done by optimizing the angle of the beam in an attempt to spare cardiac transit pathway in patients with thoracic malignancies, utilizing deep inspiration breath hold in patients with breast cancer, as well as proton therapy if available (Xia et al., 2025.(

*Thymus sparing in breast cancer: The novel finding pertaining to the thymus dose as an independent predictor for RIL in breast cancer patients was given by Xia et al. in 2025. It is apparent that there is a need to contour the thymus as an organ-at-risk based on the finding. The dose constraints could be mean dose <6.12 Gy, V5 <52.76%, and V10 <9.08%. These could be directly used for the optimization process in IMRT.

EDIC-based planning: There is current evidence supporting the inclusion of EDIC as a planning constraint. The lymphocyte-rich organs (lungs, heart, and peripheral body, as well as bone marrow) doses are accounted for by using the EDIC model, which requires the blood volume, as was tested by Liu et al., 2021, for utilizing the constraint of having the total EDIC dose of 7.11 Gy or less, although more research is needed before its inclusion in the planning tool.

Proton therapy: Where feasible, proton therapy brings significant dosimetric advantages based on the decrease in integral dose. The 11-25% improvement in the rate of severe RIL in protons vs. photons (Mohan et al., 2021; Deng et al., 2020) is a clinically important improvement in toxicity or overall survival. Cost-effectiveness analyses including lymphopenia-related endpoints could warrant expanded usage of proton therapy.

Stereotactic methods: In patients with brain metastases, Stereotactic radiosurgery was shown to have significantly low rates of Radiation-induced leukoencephalopathy (RIL) (8% vs. 29% with WBRT) (Ishida et al., 2024), with equivalent local control in oligometastases. These findings concur with current

4.4 Clinical Risk Stratification

Integration of clinical predictors allows for risk stratification:

High risk patients (underlying ALC < 1.5×10^9/L, female, prior RT, advanced disease

- More aggressive lymphocyte-sparing radiation techniques
- Preferential consideration for a reduction of dosevolume when
- Advanced monitoring of ALC during treatment
- Potential prophylactic growth factor support (investigational
- Delayed initiation of immunotherapy if planned

Standard-risk patients should be offered the following

- Standard radiotherapy, including cardiac/thymus sparing
- Anticipatory wedding and reception
- Cycle duration and treatment interruptions optimized for each patient

4.5 Implications for Combined Modality Therapy

Radiotherapy-immunotherapy combination: The correlation between RIL and immunotherapy efficacy is complex. On the one hand, radiotherapy may potentially promote antitumor immunity as a result of antigen release and immune priming. On the other hand, associated lymphopenia may counteract these effects (Dai et al., 2022). Ways to potentially optimize both include:

- Timing: Non-concurrent treatment approaches may facilitate lymphocyte recovery
- Fractionation: Hypofractionation leads to equivalent dose delivered over shorter course of treatment, which could be limiting lymphocyte transit duration across treatment field
- Volume: "Limited-field radiotherapy, such as involved-node irradiation instead of elective nodal irradiation, decreases the dose to

Radiotherapy-chemotherapy: The contribution to lymphopenia is mainly from chemotherapy, although some studies found the effect to be more significant after radiotherapy (Dai et al., 2022). As for the combination approach, chemotherapy sequencing, dose intensity, and the use of less myelosuppressive regimens where available can be taken into account.

4.6 Future Research Directions

Some crucial knowledge gaps still exist:

Lymphocyte subset analysis: Total lymphocyte counts were assessed in all studies. However, each lymphocyte subset (CD4+ lymphocytes, CD8+ lymphocytes, NK lymphocytes, and regulatory T cells) has unique sensitivity to radiation and a role in the immune system and would influence target therapy preservation on the basis of their depleted subsets contributing least to the outcome.

Interventional trials: Trials of interventions performed prospectively to protect lymphocytes are required. Potential candidates are:

- Prophylactic growth factors (G-CSF, thromb
- Autologous lymphocyte harvesting and reinfusion
- WT1 gene mutation
- Novel radioprotective agents targeting lymphocyte compartments

Predictive Biomarkers: Apart from the risk profile based on ALC, genomic and proteomic biomarkers can be used for risk stratification of patients, based on certain genetic differences in DNA repair, cytokine expression, or immune profiling.
EDIC Model refinement: The EDIC model also needs refinement in order to be generally applicable to tumors throughout the body. It may be necessary to adjust the body-specific weighing factors for specific tumors.
Cost-effectiveness: Economic models including outcomes of lymphopenia (hospitalizations, delays in treatment, and survival) may also make highly specialized approaches such as proton therapy or careful monitoring of lymphocytes cost-effective.

4.7 Limitations

Several limitations warrant consideration:
Retrospective design: All included studies were retrospective, subject to selection bias and unmeasured confounding. Prospective validation is needed.
Heterogeneous definitions: While most studies used CTCAE grade 3-4 (ALC <0.5×10⁹/L), some used different thresholds, potentially introducing heterogeneity. However, meta-analysis demonstrated low statistical heterogeneity (I^2=0-6%).
Missing data: Not all studies reported complete dosimetric data, limiting comprehensive dose-volume effect modeling. Standardized reporting of key dosimetric parameters in future studies would facilitate meta-analysis.
Publication bias: While formal testing showed no evidence of publication bias, studies finding no association may be less likely to be published.
Tumor site variability: The impact of RIL may vary by tumor biology, immune infiltration, and treatment paradigm. Tumor-specific analyses require larger cohorts.

4.8 Clinical Recommendations

Based on this evidence synthesis, we propose the following recommendations:
For treatment planning:
1. Contour thymus, heart, and major vessels as organs-at-risk
2. Apply dose constraints: thymus mean dose <6 Gy, V5 <50%, V10 <10%; heart V10 <75%
3. Consider EDIC calculation and constraint (<7 Gy when feasible)
4. Prioritize IMRT optimization to minimize low-dose volumes
5. Consider proton therapy for high-risk patients
6. Use stereotactic techniques over WBRT for limited brain metastases

For clinical management:
1. Baseline ALC to be measured within 2 weeks prior to
2. Follow the level of ALC once a week during treatment and then If one of these criteria is present, the patient is at high risk of RT-induced TH
3. For the immunotherapy patient, a possible schedule could
4. Treatment ended and ALC <0.5 x 10⁹/L: f)
5. Resume when ALC > 0.8×
6. Dose reduction or breaks for severe lymphopenia
7. The development of severe lymphopen
8. Careful infection monitoring in severe RIL patients

For clinical research,
1. Monitoring of lymphocytes in clinical trials
2. Report dose volume histograms for organ at risk
3. Carry out subset analyses based on RIL
4. Evaluate intervention approaches in prospective studies

CONCLUSION

This systematic review and meta-analysis offers powerful evidence that severe lymphopenia following radiation exposure is an important predictor for poor outcomes for the majority of solid malignancies, with the risks for mortality and progression increased by 50% and 70%, respectively. The importance of integrating significant dosimetric predictors such as PTV, heart dosing, thymus dosing, and EDIC with clinical predictors cannot be overstated.
Lymph-sparing RT methods such as optimized planning for IMRT, cardiac and thymic avoidance, proton therapy, and stereotactic RT may help to decrease the incidence of RIL. Among high-risk patients, especially those on immunotherapy, strict dose constraints and ALC-based treatment planning may be beneficial.
Future studies will concentrate on prospective validation of dose constraints, clinical trials on protective strategies for lymphocytes, and incorporation of efforts to protect lymphocytes in radiation therapy planning. With the paradigm shift in oncology towards immunotherapy, preventing radiation-induced lymphopenia while ensuring tumor control remains one of the biggest challenges for radiation oncologists.
The repeatability of the results across cancer types and treatment methodologies implies that RIL is indeed a variable that requires serious attention as an adjustable risk factor. The application of evidence-based dose

constraints and clinical follow-up represents the potential for better treatment of thousands of cancer patients annually as radiotherapy recipients.

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