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Original Research Article

Nomogram for radiation-induced lymphopenia in patients receiving intensity-modulated radiotherapy based-chemoradiation therapy for newly diagnosed glioblastoma: A multi-institutional study

Nalee Kim [a], Joongyo Lee [b], Hyunju Shin [a], Jungwook Shin [c], Do-Hyun Nam [d], Jung-Il Lee [d], Ho Jun Seol [d], Doo-Sik Kong [d], Jung Won Choi [d], Kyuha Chong [d], Won Jae Lee [d], Jong Hee Chang [e,f], Seok-Gu Kang [e,f], Ju Hyung Moon [e,f], Jaeho Cho [g], Do Hoon Lim [a,*,1], Hong In Yoon [g,*,1]

[a] Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Republic of Korea
[b] Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University Health System, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD 20850, United States
[d] Department of Neurosurgery, Brain Tumor Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Republic of Korea
[e] Department of Neurosurgery, Severance Hospital, Yonsei University Health System, Yonsei University College of Medicine, Seoul, Republic of Korea
[f] Brain Tumor Center, Severance Hospital, Yonsei University Health System, Yonsei University College of Medicine, Seoul, Republic of Korea
[g] Department of Radiation Oncology, Heavy Ion Therapy Research Institute, Yonsei Cancer Center, Yonsei University Health System, Yonsei University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Purpose: Severe lymphopenia (SLP) has emerged as a significant prognostic factor in glioblastoma. Intensity-modulated radiation therapy (IMRT)-based radiation therapy (RT) is suggested to minimize the risk of SLP. This study aimed to evaluate SLP incidence based on multi-institutional database in patients with GBM treated with IMRT and develop a predictive nomogram.

Patients and methods: This retrospective study reviewed data from 348 patients treated with IMRT-based concurrent chemoradiation therapy (CCRT) at two major hospitals from 2016 to 2021. After multivariate regression analysis, a nomogram was developed and internally validated to predict SLP risk.

Results: During treatment course, 21.0% of patients developed SLP and SLP was associated with poor overall survival outcomes in patients with GBM. A newly developed nomogram, incorporating gender, pre-CCRT absolute lymphocyte count, and brain mean dose, demonstrated fair predictive accuracy (AUC 0.723).

Conclusions: This study provides the first nomogram for predicting SLP in patients with GBM treated with IMRT-based CCRT, with acceptable predictive accuracy. The findings underscore the need for dose optimization and radiation planning to minimize SLP risk. Further external validation is crucial for adopting this nomogram in clinical practice.

1. Introduction

Currently, maximal surgical resection followed by temozolomide (TMZ)-based concurrent chemoradiation therapy (CCRT) and adjuvant TMZ stands as the mainstay treatment for glioblastoma (GBM) [1]. Key clinicopathologic factors including age, extent of surgery, and methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter have been conceived as important prognostic factors [2–5]. Recently, the prognostic significance of severe lymphopenia (SLP) during treatment course has been increasingly recognized in GBM management [4,6–9]. While the significance of SLP is established in various solid tumors, a consensus on specific radiation dose constraints

* Corresponding authors at: Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea (D.H. Lim). Department of Radiation Oncology, Heavy Ion Therapy Research Institute, Yonsei Cancer Center, Yonsei University Health System, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea (H.I. Yoon).
E-mail addresses: dh8lim@skku.edu (D.H. Lim), yhi0225@yuhs.ac (H.I. Yoon).
[1] D.H. Lim and H.I. Yoon made equal contribution to the work as co-corresponding authors.

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to mitigate SLP remains to be undetermined [10].

Advance in radiation therapy (RT) technology have propelled the adoption of intensity-modulated radiation therapy (IMRT) in brain tumor management. IMRT provides an optimized RT planning by better dose distribution to the target volume and limiting radiation exposure to normal organs [11–14]. We previously found that IMRT significantly reduced the risk of SLP compared to the traditional 3-dimensional conformal radiation therapy (3D-CRT) in patients with GBM [6].

This study aimed to evaluate the incidence of SLP in patients with GBM treated using IMRT-based CCRT, utilizing real-world data from a multi-institutional database. Furthermore, we investigated the correlation between normal brain dose distribution and SLP and constructed a nomogram – a graphical tool representing a statistical predictive model – to individualize the prediction of SLP occurrence [15].

2. Materials and methods

2.1. Patient selection

We conducted a retrospective analysis of patient data from the Yonsei Cancer Center and Samsung Medical Center, two tertiary hospitals in the Republic of Korea. We reviewed the data of patients diagnosed with GBM isocitrate dehydrogenase (IDH) wild-type, CNS WHO grade 4, who underwent TMZ-based CCRT of 60 Gy in 30 fractions via IMRT, following surgical resection between January 2016 and June 2021. Exclusion criteria included patients treated with 3D-CRT based CCRT (N = 49), those receiving CCRT with escalated dose beyond 60 Gy (N = 37), those receiving whole-brain RT for leptomeningeal seeding (N = 21), and those with incomplete follow-up data (N = 13). A total of 348 patients were eligible for our analysis. This study was approved by the Institutional Review Boards of all the participating institutions (IRB no. 4–2022–0126, SMC 2022–07–008), and the protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of this study.

2.2. Treatment

Treatment strategy was established collaboratively by a multidisciplinary neuro-oncology team, including neurosurgeons, radiologists, radiation oncologists, and medical oncologists. Postoperative gadolinium-enhanced magnetic resonance imaging (MRI), performed within 48 h of surgery, determined the extent of resection, categorized into four groups: gross total resection (no visible contrast-enhanced residual tumor), subtotal resection (≥90 % of the tumor volume removed), partial resection (<90 % tumor volume removed), and biopsy (stereotactic biopsy). Additionally, the methylation status of MGMT promoter was assessed.

All patients received the adjuvant CCRT of 60 Gy in 30 fractions with concurrent TMZ (75 mg/m^2 daily), followed by six cycles of adjuvant TMZ (150–200 mg/m^2 for 5 days in each 28-day cycle) [1]. For RT, all patients underwent computed tomography (CT) simulations in a supine position with 2.5–3.0 mm slice thickness. Gross tumor volume included the resection cavity and residual contrast enhancing lesions on postoperative MRI. Clinical target volume (CTV) was delineated by adding 1.5–2.0 cm margin to gross tumor volume and including suspected tumor-infiltrating regions with high signal intensity on T2 fluid-attenuated inversion recovery sequences with modification based on anatomical barriers. Reduced-field clinical target volume (CTV-RF) was defined as the 0.5 cm extension from gross tumor volume. The planning target volume (PTV or PTV-RF) included an additional 3-mm margin around the CTV or CTV-RF. Either simultaneous boost or sequential boost was adopted based on institutional policy [3]. For selective patients with ventricular opening during surgical resection, whole-ventricle RT was applied as previously described.[16] For simultaneous boost, a total dose of 60 Gy to the PTV and 51 Gy to the PTV-RF was delivered over 30 fractions. In the case of sequential boost, a total dose of 50 Gy was administered to the PTV in 25 fractions, followed by a sequential 10 Gy boost in 5 fractions to the PTV-RF. Detailed information on the dose constraints for organs-at-risk is summarized in Supplementary Table 1. IMRT was executed using either volumetric-modulated arc therapy (Elekta AB; Elekta, Stockholm, Sweden or Varian Medical Systems, Palo Alto, CA, USA) or Tomotherapy (Hi-Art Tomotherapy; Accuray, Madison, WI, USA).

2.3. Lymphopenia

Patients were administered six TMZ cycles following CCRT until disease progression. We evaluated peripheral blood counts at five intervals: before surgery, before CCRT, and 1, 3, and 6 months after CCRT. Lymphopenia was assessed based on the Common Terminology Criteria for Adverse Events version 5.00, with absolute lymphocyte count (ALC)-based grades: grade 1 ($800 \leq ALC < 1000/\mu L$), grade 2 ($500 \leq ALC < 800/\mu L$), grade 3 ($200 \leq ALC < 500/\mu L$), and grade 4 ($ALC < 200/\mu L$). SLP was identified as a condition of grade 3 or higher lymphopenia after RT.

2.4. Statistical analysis

Patients who were lost to follow-up were censored. All patients were evaluated based on physical examination and MRI, 1 month after CCRT as well as every 3 months for the first 2 years and every 6 months thereafter. Overall survival (OS) was calculated from the start date of surgery to the date of death or the latest follow-up visit. OS was analyzed using the Kaplan–Meier method and compared using the log-rank test. Multivariable analysis was performed using Cox regression model, with $p < 0.05$ in the univariable analysis to identify the predictors of OS. The generalized estimating equation analysis was used to evaluate the temporal changes in peripheral blood counts over the follow-up period. Logistic regression analysis was performed to evaluate the predictive factors for SLP. The factors were selected with stepwise regression procedure and included in a multivariate analysis for SLP. In all analyses, a two-sided p value of < 0.05 was conceived statistically significant. A nomogram for predicting SLP probability was constructed based on the multivariate analysis of logistic regression model. Given the multicollinearity issue among dosmietric factors, we included factors with variation initiation factor < 10 and Akaike information criterion (AIC) to compare multivariate models to select the most discriminative dosimetric factors for SLP. The final nomogram was internally validated using 1,000 bootstrap simulations. Statistical performance of the nomogram was assessed using discrimination, measured by area under the receiver operating characteristic curve (AUC) and calibration, measured by calibration plot. Random forest regression analysis was performed to identify the importance among the variables included in the nomogram. All statistical analyses were performed using the Statistical Package for Social Sciences version 23.0 (IBM SPSS Statistics, Armonk, NY) and R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

3. Results

3.1. Baseline and treatments characteristics

Patient, tumor, and treatment characteristics of patients are summarized in Table 1. Median age was 58.2 years (IQR [Interquartile range], 50.5–63.5), and 199 (57.2 %) patients were male. Before and after surgery, 135 (38.8 %) and 101 (29.0 %) patients showed a poor performance status of KPS ≤ 70, respectively. Gross total resection was achieved in 245 (70.4 %) of the 332 surgically treated patients (95.4 %). In addition, MGMT promoter methylation was detected in 145 (41.7 %) patients. Regarding RT modality, 100 (28.7 %) and 248 (70.4 %) patients were treated with volumetric-modulated arc therapy and

Table 1
Patient, tumor, and treatment characteristics.

Characteristics		Total (N = 348)
Age		58.2 [50.5–63.5]
Sex	Male	199 (57.2)
	Female	149 (42.8)
Preoperative KPS		80.0 [70.0–90.0]
	≤70	135 (38.8)
Postoperative KPS		80.0 [70.0–90.0]
	≤70	101 (29.0)
MGMT promoter	Unmethylated	203 (58.3)
	Methylated	145 (41.7)
Extent of resection	Biopsy	16 (4.6)
	Partial resection	2 (0.6)
	Subtotal resection	85 (24.4)
	Gross total resection	245 (70.4)
Adjuvant temozolomide		5 [3–6]
RT Modality	VMAT	100 (28.7)
	TOMO	248 (71.3)
PTV, cc		511.7 [300.7–682.5]
PTV-RF, cc		138.6 [81.1–261.0]
Whole ventricle RT		95 (27.3)
Brain volume, cc		1430.0 [1318.2–1518.6]
Brain		
Dmean, Gy		34.3 [27.2–39.7]
Maximum brain dose, Gy		62.0 [61.5–63.1]
V5Gy, %		92.9 [86.1–98.4]
V10Gy, %		89.2 [78.5–96.5]
V15Gy, %		84.8 [67.8–94.5]
V20Gy, %		77.4 [56.5–90.4]
V30Gy, %		56.0 [38.7–74.7]

*Values are presented as the number of patients (%) or the median [interquartile range].
Abbreviations: KPS, Karnofsky performance status; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiation therapy; VMAT, volumetric-modulated arc therapy; TOMO, Tomotherapy; PTV, planning target volume; RF, Reduced-field; Dmean, Mean dose; VXXGy = volume receiving more than XX Gy.

Tomotherapy, respectively. The median PTV and PTV-RF were 511.7 cc (IQR, 300.7–682.5) and 138.6 cc (IQR, 81.1–261.0), respectively.

3.2. SLP

As shown in Supplementary Fig. 1 and Supplementary Table 2, the ALC values showed time-dependent changes (p = 0.020), while absolute neutrophil counts decreased after CCRT but remained similar during adjuvant TMZ (p = 0.120). Overall, 73 (21.0 %) patients developed SLP during the treatment course. There were no patients who had SLP before surgery. Patients with SLP showed significantly lower ALC at all time-points after CCRT than those without SLP (Fig. 1A, Supplementary Table 2). On the contrary, there was no difference in absolute neutrophil count according to SLP occurrence (Fig. 1B, Supplementary Table 2).

In patients who developed SLP, there was a higher proportion of females (65.8 % vs. 36.7 %, p < 0.001) and a greater frequency of whole ventricle RT compared to those who did not experience SLP (42.5 % vs. 23.3 %, p = 0.002, Supplementary Table 3). The IMRT modality, either volumetric-modulated arc therapy or Tomotherapy, showed no significant difference between the groups. Notably, patients with SLP had larger PTV or PTV-RF and showed higher brain radiation exposure than did those without SLP (all p < 0.005, Supplementary Table 3).

3.3. Prognostic factors for overall survival

With a median follow-up of 17.0 months (IQR, 10.0–24.0), the entire cohort exhibited a median OS of 23.4 months and a 1-year OS rate of 83.5 % (95 % confidence interval [CI] 79.4 %–87.7 %). Patients with SLP showed notably poorer OS than those without SLP (median: 17.0 vs. 24.0 months; 1-year OS: 68.0 % vs. 88.0 %, p = 0.015, Fig. 2). Cox multivariable regression analysis identified SLP as a significant negative factor affecting OS (hazard ratio 2.23, 95 % CI 1.52–3.28, p < 0.001), alongside male gender, old age, non-gross total resection, unmethylated MGMT promoter, and larger PTV (Table 2).

3.4. Predicting factors for SLP

A Pearson correlation matrix (Fig. 3) demonstrated correlations between SLP and various factors, including brain dose volumes from V5 to V30 Gy, PTV, and pre-CCRT ALC. Notably, the mean brain dose (Dmean) showed a slightly stronger association with SLP. Dmean is associated to varying degrees with all other volumes irradiated.

Subsequent multivariate analysis established female gender (odds ratio [OR] 3.00, 95 % CI 1.72–5.29, p < 0.001), and lower pre-CCRT ALC (OR 0.65, 95 % CI 0.42–0.96, p = 0.004) as independent predictors of SLP (Table 3). Multivariate logistic regression models incorporating different dosimetric factors were evaluated based on the AIC (Supplementary Table 4). The model that included brain Dmean was associated with the lowest AIC value. Finally, higher brain Dmean (OR 1.05, 95 % CI 1.03–1.12, p = 0.001) was associated with increased risk of SLP (Table 3). Other treatment modalities, including surgical extent

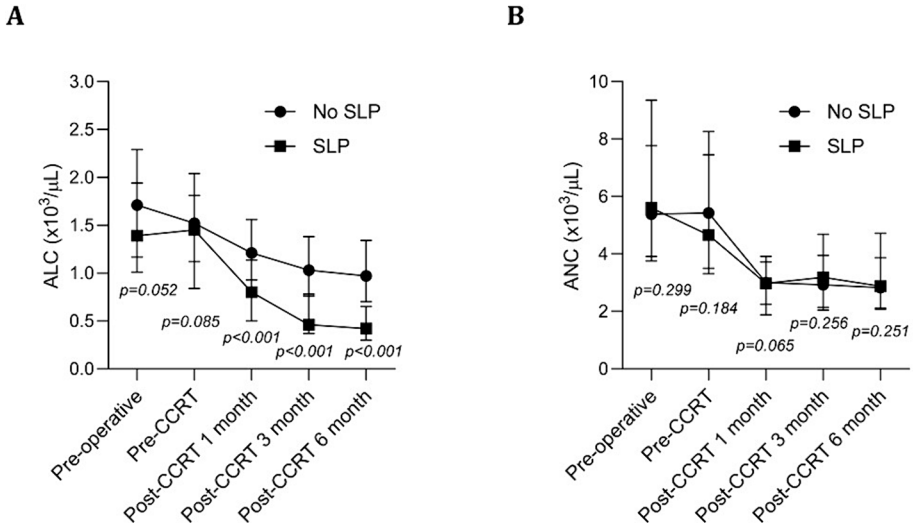

Fig. 1. Absolute lymphocyte count (ALC, A) and absolute neutrophil count (ANC, B) during and after concurrent chemoradiation therapy (CCRT), stratified by severe lymphopenia (SLP).

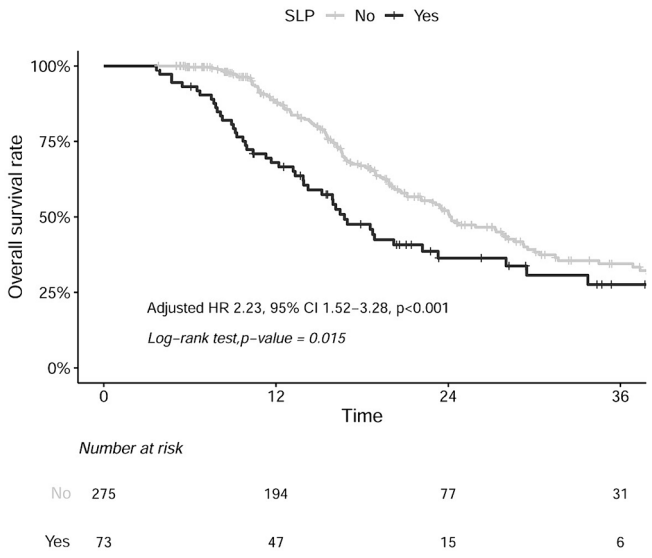

Fig. 2. Overall survival outcomes according to severe lymphopenia (SLP).

and cycles of adjuvant temozolomide, were not related to the development of SLP.

3.5. Nomogram

Given the multiple factors related to SLP risk, a nomogram for predicting SLP during treatment was developed (Fig. 4, https://github.com/ncidosimetry/lymphopenia-nomogram). The random forest regression analysis revealed that Brain Dmean had the highest relative importance, followed by pre-CCRT ALC and gender (Supplementary Table 5). The calibration plot revealed a good agreement between observed and predicted SLP probabilities. (Fig. 5A). The AUC was 0.723, indicating fair predictive accuracy of the model (Fig. 5B).

4. Discussion

In this study, we explored the prognostic influence of SLP on OS and the dosimetric determinants leading to SLP, ultimately developing a nomogram for individualized SLP prediction. We observed that SLP negatively influenced OS, even after adjustment for well-known prognosticators including age, extent of resection, and MGMT promoter methylation. To the best of our knowledge, this study provided the first nomogram for predicting SLP based on a large number of patients with GBM, treated with IMRT-based CCRT. The developed nomogram incorporating clinical and dosimetric factors accurately predicts the risk of SLP.

The prognostic impact of SLP has been well established across various solid tumors. For lung cancer, SLP during CCRT was significantly associated with dismal survival outcomes, particularly diminishing the survival benefits of maintenance immune checkpoint inhibitors [17–22]. Also, SLP is related to poor RT response in gastrointestinal cancers (esophagus, rectum, pancreas, etc.) [23–26]. Several studies have highlighted the negative impact of SLP in patients with GBM [4,6,9]. Byun et al. identified SLP as a negative prognostic factor in patients with GBM, treated with either 3D-CRT or IMRT [6]. We previously concluded that the adoption of IMRT and small PTV could mitigate the risk of SLP, possibly translating into better OS outcomes. In the current study, we observed a similar detrimental impact of SLP in patients with GBM, treated solely with IMRT. Our analysis identified the brain Dmean as a strong predictor of SLP. Utilizing our novel nomogram, clinicians can get help to anticipate the individualized risk of SLP during the RT planning stage.

During 30 fractions of CCRT to the brain, approximately 0.5 Gy and 2 Gy could be exposed to circulating blood cells and lymphocytes, respectively [27]. Based on the radiosensitivity of lymphocytes, brain RT may induce SLP. Various dose criteria have been proposed for SLP prediction, including brain V25Gy < 40 % or < 56 % as optimal cutoffs to prevent SLP occurrence within 3 months post-CCRT [28,29]. Our previous research indicated that V30 Gy > 30 % correlated with increased SLP incidence during treatment course [4]. Recently, a time-dependent computational framework for estimating the dose to circulating blood cells using a whole-body blood flow-based dose-volume histogram has been developed [30]. This system has shown a reliable correlation between the dose to circulating blood cells and the onset of SLP [18,31]. Importantly, it considers both beam-on time and spatio-temporal blood distribution, suggesting potential benefits of FLASH RT in preserving immune function and minimizing SLP [31]. In summary, better estimation tool for SLP prediction is needed to utilize the immune-preserving RT planning.

Large PTV is associated with increased radiation exposure to the normal brain tissue. Rudra et al. reported that limited-field CCRT, excluding T2 fluid-attenuated inversion recovery abnormalities, significantly preserved the ALC count at 3 months after CCRT (1100 vs. 900/uL, $p = 0.02$) [28]. Similarly, we previously reported an independent association between large PTV and increased SLP risk [6]. Recently, European Society for Radiotherapy and Oncology group revised their guidelines to reduce margin to the surgical cavity and residual abnormalities on contrast-enhanced T1 images from 2.0 cm to 1.5 cm [32]. Although PTV did not show statistical significance in SLP development in our analysis, adhering to this revised guideline to minimize PTV may

Table 2
Prognostic factors for overall survival.

		Univariable analysis			Multivariable analysis		
Variables	(ref. vs.)	HR	95 % CI	P-value	HR	95 % CI	P-value
Sex	(Male vs. Female)	0.60	0.44–0.81	0.001	0.50	0.36–0.71	<0.001
Age	Continuous	1.02	1.00–1.03	0.029	1.03	1.01–1.04	0.003
Preoperative KPS	(>70 vs. ≤ 70)	1.26	0.93–1.71	0.140			
Postoperative KPS	(>70 vs. ≤ 70)	1.25	0.92–1.71	0.159			
Extent of resection	(GTR vs. non-GTR)	1.36	1.08–1.58	0.043	1.43	1.03–1.98	0.033
MGMT promoter	(Unmethylated vs. Methylated)	0.52	0.38–0.71	<0.001	0.46	0.33–0.63	<0.001
RT modality	(VMAT vs. TOMO)	1.26	0.88–1.80	0.215			
PTV	Continuous (per 10 cc)	1.01	1.01–1.02	<0.001	1.01	1.01–1.02	0.001
PTV-RF	Continuous (per 10 cc)	1.01	1.00–1.02	0.065			
Whole ventricle RT	(No vs. Yes)	1.39	1.02–1.90	0.039	0.90	0.60–1.33	0.591
SLP	(No vs. Yes)	1.52	1.08–2.13	0.016	2.23	1.52–3.28	<0.001

* The foreparts of the parentheses were set as the reference groups.
Abbreviations: HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; GTR, gross total resection; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiation therapy; VMAT, volumetric-modulated arc therapy; TOMO, Tomotherapy; PTV, planning target volume; RF, Reduced-field; SLP, severe lymphopenia.

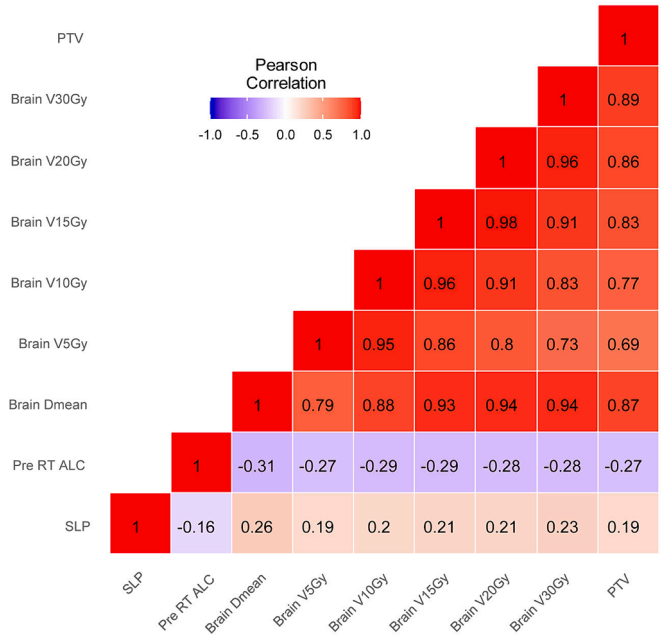

Fig. 3. Pearson correlation matrix showing associations of severe lymphopenia (SLP) with clinical factors.

reduce SLP risk through decreased brain Dmean. Furthermore, we recently reported that moderately hypofractionated CCRT with a total dose of 58.5 Gy in 25 fractions, as opposed to the standard 60 Gy in 30 fractions of CCRT, not only showed comparable survival outcomes, but also significantly reduced the risk of SLP [4]. In terms of RT modality, proton beam therapy has been observed to significantly lower the incidence of SLP, owing to the Bragg peak, to preserve the normal brain tissue from unintended radiation exposure. Mohan et al. reported that SLP occurred in only 14 % of patients treated with proton therapy, compared to 39 % following X-ray based RT [33]. Given Tomotherapy's helical beam delivery method, it is conceivable that the rates of SLP could differ from that observed in Volumetric-modulated arc therapy, which employs a modulated partial arc planning approach.[34] Nonetheless, we found no difference in the development of SLP between the two IMRT techniques.

Besides, sex differences in SLP risk have been repeatedly demonstrated in brain tumor [4,6,29,33]. Our study also found an elevated risk of SLP among females, potentially due to differences in cerebral perfusion. The increased cerebral blood flow and glucose metabolism in females compared to that in males may lead to greater radiation exposure of blood cells.

Although this study has its novelty to construct a nomogram for SLP risk prediction in IMRT-treated patients, it has some inherent limitations. Its retrospective design might encompass unrecognized biases. While this study primarily examined ALC, a more comprehensive analysis including tumor-infiltrating lymphocytes, CD8+, or CD4 + effector T-cells would better support minimizing radiation exposure to the normal brain tissue during RT planning process. Owing to the retrospective design of the study, weekly ALC and absolute neutrophil count measurements during CCRT could not be obtained. Also, further investigations based on orthotopic mouse model and modulating radiation exposure are needed to identify the impact of radiation exposure to brain and SLP.

Although this study presents a large database from multiple institutions using modern RT technology of IMRT, the nomogram requires further external validation for clinical endorsement.

In conclusion, we identified the prognostic significance of SLP in patients with GBM undergoing IMRT-based CCRT. Also, the developed nomogram, incorporating factors of gender, pre-CCRT ALC, and brain Dmean, showed acceptable predictive accuracy in this cohort. Further efforts to refine and validate this nomogram are essential to assist physicians in optimizing the lymphocyte-sparing RT techniques and targeting delineations and dose-fractionation for individualized treatment.

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CRediT authorship contribution statement

Nalee Kim: Conceptualization, Methodology, Formal analysis, Data

Table 3
Predictive factors for severe lymphopenia.

		Univariate analysis			Multivariate analysis		
Variables	(ref. vs.)	OR	95 % CI	p-value	OR	95 % CI	p-value
Sex	(Male vs. Female)	3.31	1.94–5.76	<0.001	3.00	1.72–5.29	<0.001
Age	Continuous	0.99	0.96–1.01	0.276			
Preoperative KPS	(>70 vs. ≤ 70)	0.91	0.53–1.54	0.722			
Postoperative KPS	(>70 vs. ≤ 70)	1.07	0.60–1.86	0.814			
Preoperative ALC	Continuous	0.59	0.41–0.83	0.004	0.75	0.50–1.05	0.133
Pre-CCRT ALC	Continuous	0.52	0.34–0.77	0.002	0.65	0.42–0.96	0.041
Extent of resection	(GTR vs. non-GTR)	0.87	0.48–1.53	0.643			
MGMT promoter	(Unmethylated vs. Methylated)	1.38	0.82–2.32	0.222			
Adjuvant temozolomide	Continuous	0.68	0.51–1.21	0.129			
RT modality	(VMAT vs. TOMO)	1.42	0.79–2.66	0.249			
PTV volume	Continuous (per 10 cc)	1.02	1.01–1.03	<0.001	1.01	0.98–1.04	0.428
PTV-RF volume	Continuous (per 10 cc)	1.02	1.00–1.03	0.013	0.98	0.96–1.01	0.204
Whole ventricle RT	(No vs. Yes)	2.43	1.41–4.18	0.001	1.68	0.68–4.17	0.263
Brain Dmean	Continuous	1.09	1.05–1.13	<0.001	1.07	1.03–1.12	0.001
Brain V5Gy	Continuous	1.07	1.03–1.11	<0.001			
Brain V10Gy	Continuous	1.05	1.02–1.08	<0.001			
Brain V15Gy	Continuous	1.04	1.02–1.06	<0.001			
Brain V20Gy	Continuous	1.03	1.02–1.05	<0.001			
Brain V30Gy	Continuous	1.03	1.02–1.04	<0.001			

* The foreparts of the parentheses were set as the reference groups.
Abbreviations: OR, odds ratio; CI, confidence interval; KPS, Karnofsky performance status; ALC, absolute lymphocyte count; GTR, gross total resection; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiation therapy; VMAT, volumetric-modulated arc therapy; TOMO, Tomotherapy; PTV, planning target volume; RF, Reduced-field; RT, radiation therapy; Dmean, mean dose; VXXGy, volume receiving more than XX Gy.

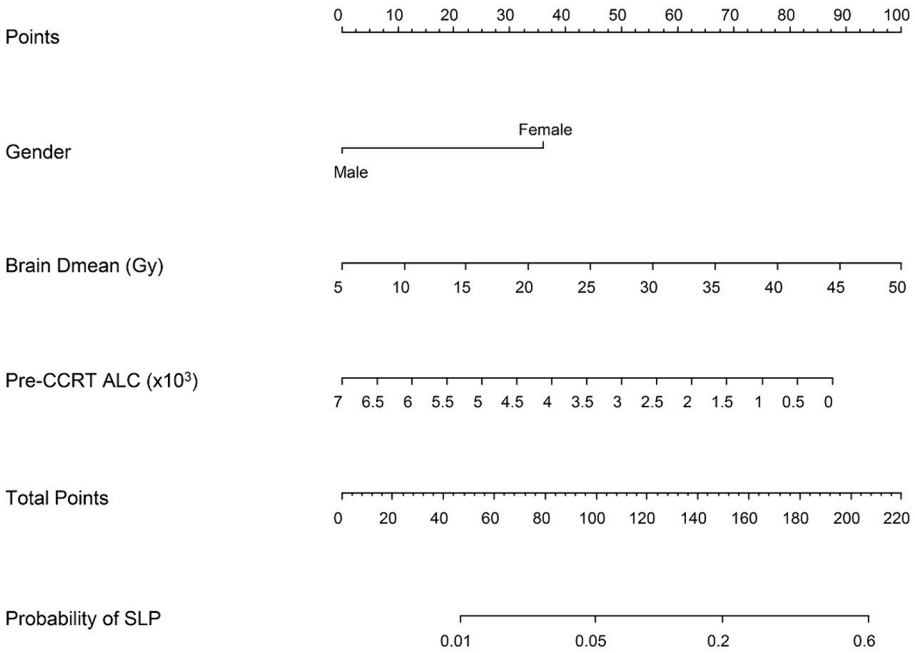

Fig. 4. Nomogram for probability of severe lymphopenia.

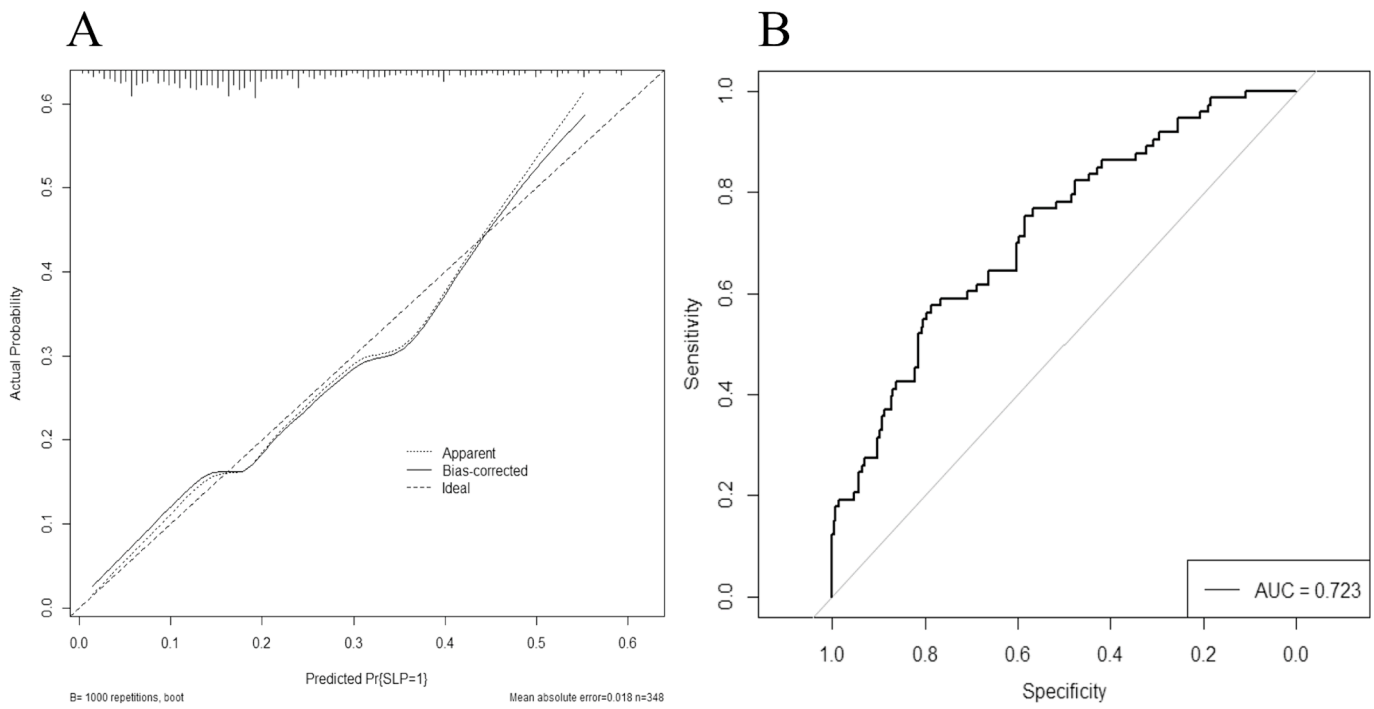

Fig. 5. Calibration plot (A) and receiver operating characteristic curve (B) for the nomogram predicting severe lymphopenia.

curation, Writing – original draft, Writing – review & editing, Visualization. **Joongyo Lee:** Investigation, Resources, Writing – review & editing. **Hyunju Shin:** Investigation, Resources, Writing – review & editing. **Jungwook Shin:** Investigation, Resources, Writing – review & editing. **Do-Hyun Nam:** Investigation, Resources, Writing – review & editing. **Jung-Il Lee:** Investigation, Resources, Writing – review & editing. **Ho Jun Seol:** Investigation, Resources, Writing – review & editing. **Doo-Sik Kong:** Investigation, Resources, Writing – review & editing. **Jung Won Choi:** Investigation, Resources, Writing – review & editing. **Kyuha Chong:** Investigation, Resources, Writing – review & editing, Data curation. **Won Jae Lee:** Investigation, Resources, Writing – review & editing, Data curation. **Jong Hee Chang:** Investigation, Resources, Writing – review & editing, Data curation. **Seok-Gu Kang:** Investigation, Resources, Writing – review & editing, Data curation. **Ju Hyung Moon:** Investigation, Resources, Writing – review & editing, Data curation. **Jaeho Cho:** Investigation, Resources, Writing – review & editing, Data curation. **Do Hoon Lim:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Hong In Yoon:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100799.

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