International Immunopharmacology 72 (2019) 395–401

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Prognostic value of delta inflammatory biomarker-based nomograms in patients with inoperable locally advanced NSCLC

Meiying Guo[a], Wanlong Li[a,b], Butuo Li[a,c], Bing Zou[a,b], Shijiang Wang[a,b], Xue Meng[a,b], Xindong Sun[a,b], Jinming Yu[a,b,*], Linlin Wang[a,b,*]

[a] Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Shandong University, Jinan 250117, China
[b] Shandong Academy of Medical Sciences, Jinan 250001, China
[c] Department of Radiation Oncology and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin 300270, China

ARTICLE INFO

Keywords:
Locally advanced non-small cell lung cancer
Inflammatory biomarkers
Overall survival
Progression free survival
Nomogram

ABSTRACT

Objective: Inflammation plays critical roles in tumor growth and progression, and can be adversely affected by chemotherapy and radiotherapy. However, there have been few studies on the prognostic value of delta (Δ) inflammatory biomarkers before and after chemoradiotherapy in patients with locally advanced non-small cell lung cancer (LA-NSCLC).
Methods: In this study, pre/post-treatment and Δ inflammatory biomarkers of 370 patients who were diagnosed as having inoperable LA-NSCLC in Shandong Cancer Hospital between January 2005 and January 2016 were analyzed. Nomograms were then established for predicting prognosis.
Results: Median overall survival (OS) and progression free survival (PFS) for all patients were 28.1 (range 1.9–129.0) months and 11.1 (range 1.7–58.7) months, respectively. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) significantly increased and the lymphocyte-to-monocyte ratio (LMR) significantly decreased during the concurrent chemoradiotherapy course ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). Multivariate analysis revealed that pre-LMR, ΔNLR, and minimum absolute lymphocyte counts were independent predictors of OS ($P = 0.027$, $P = 0.012$, and $P = 0.015$, respectively) and post-LMR, post-NLR, and ΔNLR were independent predictors of PFS ($P = 0.014$, $P = 0.001$, and $P = 0.036$, respectively). Nomograms for OS and PFS were established by combining all significant inflammatory markers and clinicopathological characteristics. The concordance indexes for OS and PFS were 0.709 and 0.688, respectively.
Conclusion: Post-treatment and Δ inflammatory biomarkers may have more prognostic significance than baseline measurements of inflammatory biomarkers in LA-NSCLC patients. The proposed nomograms based on the dynamic inflammatory biomarkers and clinicopathological factors may be practical and widely available for evaluating the prognosis of patients with inoperable LA-NSCLC.

1. Introduction

Locally advanced non-small cell lung cancer (LA-NSCLC) accounts for approximately 40% of NSCLC cases at diagnosis, most of which are not suitable for surgery [1]. The standard care for patients with inoperable LA-NSCLC is concurrent platinum-based chemotherapy and radiotherapy [2]. However, the prognosis remains unsatisfactory, with a 5-year overall survival (OS) rate ranging between 15% and 25% [3]. The advent of immunotherapy has led to meaningful progress in improving the outcomes of cancer patients. Durvalumab, an anti-programmed death ligand 1 (PD-L1) antibody, has been reported to be effective in patients with LA-NSCLC after concurrent

Abbreviations: ALCmin, minimum absolute lymphocyte counts; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; CEA, carcinoembryonic antigen; CI, confidence intervals; HR, hazard ratio; KPS, karnofsky performance score; LA-NSCLC, locally advanced non-small cell lung cancer; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression free survival; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic

* Corresponding authors at: Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Shandong Academy of Medical Sciences, No. 440, Ji Yan Road, Jinan 250017, China.
E-mail addresses: sdyujinming@163.com (J. Yu), wanglinlinatjn@163.com (L. Wang).

https://doi.org/10.1016/j.intimp.2019.04.032
Received 5 March 2019; Received in revised form 16 April 2019; Accepted 16 April 2019
Available online 24 April 2019
1567-5769/

chemoradiotherapy (CCRT) and has been shown to significantly increase progression-free survival (PFS) [4]. Therefore, studying changes in immune status during CCRT of LA-NSCLC might be useful for identifying the subset group of patients who benefit from immunotherapy. The evaluation of inflammatory prognostic factors is also crucial for decision-making in routine clinical practice, and will ultimately improve patient outcomes.

Emerging evidence has indicated that systemic inflammation plays an integral role in both the development and progression of various cancers [5–7]. Increased systemic inflammation, as determined by measuring inflammatory cells, such as neutrophils, lymphocytes, platelets, and monocytes, and the ratios between them (i.e., neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], lymphocyte-to-monocyte ratio [LMR]), has been shown to correlate with prognosis in multiple malignancies [8–12]. For example, in lung cancer, elevated pretreatment NLR is associated with poor survival in patients with early stage [13] and advanced NSCLC [14], predicting resistance to first-line platinum-based chemotherapy [15]. Lymphocyte nadir is associated with 90% increased overall mortality risk in patients with stage III NSCLC [16]. Preoperative platelet count is a reliable marker of lymph node metastasis [17].

Nevertheless, most studies have correlated inflammatory biomarkers with survival outcomes in lung cancer to analyze the baseline parameters before treatment [18,19]. However, because immune status is not static, dynamic analyses may be more informative. Moreover, despite the fact that multiple studies have been conducted, inflammatory biomarkers are not applied in present clinical practice and their additive values regarding clinical prognostic markers remain unclear. A quantitative model, incorporating both clinicopathological and inflammatory variables, may be more essential and crucial for individualized risk assessment of death for LA-NSCLC patients.

Thus, in this study, we determined the prognostic significance of inflammatory biomarker changes before and after CCRT in patients with LA-NSCLC. In addition, we developed prognostic nomograms for PFS and OS based on these inflammatory markers and the clinicopathologic characteristics.

2. Materials and methods

2.1. Patients

This study was approved by the ethics committee of Shandong Cancer Hospital and Institute (Shandong, China). All patients signed informed consent forms and agreed to provide their blood samples and clinical data for research purposes. Between January 2005 and January 2016, 370 patients were retrospectively reviewed. The inclusion criteria were as follows: (1) age 18 years or older; (2) stage III NSCLC confirmed by histopathology and radiographic results based on the American Joint Committee on Cancer 7th edition TNM classification and staging system; (3) patients with neither prior therapy received CCRT nor operation after assessment by a multidisciplinary team; and (4) patients without autoimmune disease or active infection such as acute gastroenteritis, appendicitis, or cholecystitis.

2.2. Data collection and follow-up

Different types of information were acquired from the patients' medical records including imaging data, clinical information, and laboratory test results. Clinical information included age, gender, pathological type, Karnofsky Performance Score (KPS), smoking index, radiotherapy technique, and radiotherapy dose. Laboratory tests showed blood cell counts (lymphocyte, neutrophil, monocyte, and platelet counts), and pretreatment carcinoembryonic antigen (CEA) and hemoglobin levels. The ALCmin was defined as the minimum absolute lymphocyte count during treatment. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count, the PLR was defined as the absolute platelet count divided by the absolute lymphocyte count, and the LMR was calculated as the absolute lymphocyte count divided by the absolute monocyte count. Δ was defined as the changes in inflammatory biomarkers, which was calculated by the number of inflammatory biomarkers before CCRT minus those after CCRT.

After completion of the treatment, patients were followed every 3 months for the first 2–3 years, every 4–6 months for another 2 years, and thereafter annually. The follow-up evaluations consisted of a physical examination, complete blood count, blood biochemistry, tumor marker, thoracic computed tomography (CT) scans, abdomen B-ultrasound examination, and other examinations as needed. OS was calculated from the starting date of treatment to the date of death or censored at the date of last contact. PFS was calculated from the starting date of treatment to the date of diagnosing local recurrence/distant metastasis, or to the date of last follow-up.

2.3. Statistical analysis

The optimal cut-off value for all markers was assessed by a time-dependent receiver operating characteristic (ROC) curve analysis and analysis of the area under the curve. Survival curves were generated by the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazard regression model was used to detect the independence of related factors. Variables with $P < 0.15$ in univariate analyses were entered into multivariate analyses. Results of the Cox regression modeling are presented as hazard ratios (HRs) and associated 95% confidence intervals (CIs). Variables with $P < 0.05$ were considered statistically significant. Statistical evaluation was conducted with SPSS 23.0 (SPSS Inc., Chicago, IL).

A nomogram was established as a graphic representation of the prediction model and elaborated upon LRM coefficients by using the RMS package of R. The accuracy of the predictions was evaluated by Harrell's concordance index (c-index), which was calculated via a bootstrap method with 1000 resamples. The maximum value of the c-index is 1.0, indicating perfect discrimination, whereas 0.5 represents agreement by chance alone. Calibration curves were assessed graphically by plotting the observed rates against the nomogram predicted probabilities. The predictive accuracy of clinical features and the TNM stage was also investigated using the c-index. Related statistical analyses were conducted using R 3.4.4 software (Institute for Statistics and Mathematics, Vienna, Austria).

3. Results

3.1. Baseline characteristics of patients

The clinicopathological characteristics of the patients are shown in Table 1. Among them, male (84.3%) and squamous cell carcinoma (63.0%) accounted for the majority. Inflammatory biomarkers were measured before and after CCRT, and LMR was found to decrease significantly, whereas NLR and PLR increased significantly (all $P < 0.001$), demonstrating that the patients' inflammatory status worsened over time (Fig. 1).

3.2. Prognostic effects of inflammatory biomarkers

Using ROC curves, the optimal cut-offs of inflammatory biomarkers were determined according to the end-point of OS (Supplementary Fig. 1 and Supplementary Table 1). Patients were subsequently divided into two groups: the high group had values greater than or equal to optimal cut-offs and the low group had values less than optimal cut-offs.

The median OS and PFS for all patients were 28.1 (range, 1.9–129.0) months and 11.1 (range, 1.7–58.7) months, respectively. Clinicopathological characteristics combined with inflammatory biomarkers for the prediction of OS and PFS were further investigated by

Table 1
Baseline characteristics of patients with inoperable LA-NSCLC.

Characteristic	All patients(N = 370)	
	N	%
Age(years)		
< 60	186	50.3
≥60	184	49.7
Gender		
Male	312	84.3
Female	58	15.7
Histology subtype		
SCC	233	63.0
Non-SCC	137	37.0
T stage		
T1	39	10.5
T2	110	29.7
T3	89	24.1
T4	132	35.7
N stage		
N0	55	14.9
N1	37	10.0
N2	174	47.0
N3	104	28.1
Smoking index		
< 600	173	46.8
≥600	197	53.2
KPS		
≤80	209	56.5
> 80	161	43.5
Radiotherapy technique		
3D-CRT	185	50.0
IMRT	185	50.0
Radiotherapy dose(Gy)		
≤60	199	53.8
> 60	171	46.2
Pretreatment hemoglobin(g/L)		
≤130	171	46.2
> 130	199	53.8
Pretreatment CEA(ng/ml)		
≤4.4	144	38.9
> 4.4	226	61.1

univariate analysis with the Cox regression model. In univariate analysis, gender, N stage, smoking index, radiotherapy technique/dose, KPS, consolidation chemotherapy, pretreatment CEA, pre-NLR, pre-LMR, post-NLR, post-LMR, ΔNLR, and ALCmin were significantly associated with OS ($P < 0.05$); whereas age, N stage, radiotherapy dose, KPS, pretreatment CEA, post-NLR, post-PLR, post-LMR, ΔNLR, and ΔPLR were associated with PFS ($P < 0.05$) (Table 2). The variables with $P < 0.15$ were included in a multivariate Cox regression model, in which ΔNLR and N stage were verified to be independent prognostic factors for both OS and PFS. In addition, gender, consolidation chemotherapy, pre-LMR, and ALCmin were independent factors for OS ($P < 0.05$), and KPS, radiotherapy dose, post-NLR, and post-LMR were independent factors for PFS ($P < 0.05$) (Table 2).

Patients with pre-LMR < 2.38, ΔNLR < −2.24, and ALCmin < 0.335 had significantly worse OS ($P = 0.035$, $P = 0.001$, and $P = 0.002$, respectively). In addition, post-NLR ≥ 2.54, post-LMR < 1.16, and ΔNLR < −2.24 were factors statistically associated with a poor PFS ($P < 0.001$, $P = 0.006$, and $P = 0.011$, respectively; Fig. 2).

3.3. Nomogram development for predicting prognosis of LA-NSCLC patients

To predict the OS and PFS of LA-NSCLC patients treated with CCRT, two nomograms were established by Cox regression model analysis using independent factors of OS and PFS (Fig. 3A, B), which could predict the probability of death at 2 and 5 years and recurrence or metastasis at 1 and 2 years. Harrell's c-indexes for OS and PFS were 0.709 (95% CI: 0.613–0.805) and 0.688 (95% CI: 0.582–0.794), respectively. The calibration curves showed good agreement between the prediction by nomograms and actual observation (Fig. 4A, B). Moreover, the predictive performance of the combined model with clinical-TNM-inflammatory biomarkers was higher than the individual model alone and the clinical-TNM model (Fig. 5).

3.4. Subgroup analysis of inflammatory biomarkers according to consolidation chemotherapy

Consolidation chemotherapy (CCT) was administered in LA-NSCLC patients with good performance after CCRT in clinical practice. We further performed subgroup analysis of the inflammatory biomarkers according to whether CCT was administered. In patients with CCT, ALCmin was an independent prognostic factor for OS ($P < 0.05$), whereas ΔNLR was a prognostic factor for PFS ($P < 0.05$; Supplementary Table 2). In patients without CCT, ΔNLR was an independent prognostic factor for OS ($P < 0.05$), whereas post-NLR was a prognostic factor for PFS ($P < 0.05$; Supplementary Table 3).

To determine the subgroup that could benefit more from CCT, a forest plot of HRs for OS between the CCT and non-CCT groups was analyzed (Supplementary Fig. 2). The OS advantages of CCT were more significant for male patients (HR: 1.88; 95% CI, 1.40–2.51, $P < 0.001$), N2/3 stage (HR: 1.90; 95% CI, 1.27–2.83, $P = 0.002$; HR: 1.83; 95% CI, 1.09–3.07, $P = 0.022$), KPS ≤ 80 (HR: 1.94; 95% CI, 1.34–2.82, $P < 0.001$), post-NLR ≥ 2.54 (HR: 2.17; 95% CI, 1.51–3.11, $P < 0.001$), post-PLR ≥ 207 (HR: 2.44; 95% CI, 1.62–3.67, $P < 0.001$), post-LMR < 1.16 (HR: 2.54; 95% CI, 1.41–4.59, $P = 0.002$), ΔNLR < −2.24 (HR: 2.74; 95% CI, 1.59–4.71, $P < 0.001$), or ΔPLR < −93.7 (HR: 2.49; 95% CI, 1.55–4.02, $P < 0.001$; Supplementary Fig. 2).

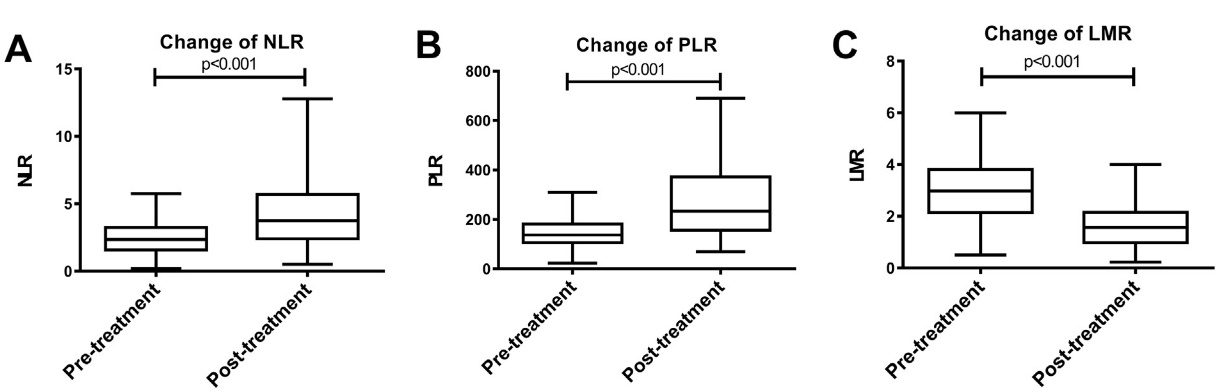

Fig. 1. Changes in inflammatory biomarkers before and after CCRT in patients with inoperable LA-NSCLC. (A) NLR was elevated after treatment ($P < 0.001$). (B) PLR was elevated after treatment ($P < 0.001$). (C) LMR decreased after treatment ($P < 0.001$).

Table 2
Univariate and multivariate survival analyses of OS and PFS in patients with inoperable LA-NSCLC.

	OS						PFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.994	0.759–1.302	0.967				0.746	0.566–0.983	0.037			
Gender	0.817	0.533–1.347	0.004	0.489	0.242–0.988	0.046	0.824	0.564–1.203	0.316			
Histology subtype	0.823	0.610–1.110	0.201				1.198	0.894–1.607	0.226			
T stage	1.103	0.964–1.263	0.152				0.989	0.861–1.137	0.881			
N stage	1.305	1.122–1.517	0.001	1.439	1.178–1.759	< 0.001	1.398	1.194–1.638	< 0.001	1.390	1.132–1.707	0.002
Smoking index	1.341	1.019–1.765	0.036				1.000	0.760–1.316	0.999			
Radiotherapy technique	1.432	1.088–1.885	0.010				1.047	0.793–1.383	0.745			
Radiotherapy dose	1.596	1.197–2.127	0.001				1.528	0.990–1.781	0.049	1.758	1.159–2.667	0.008
KPS	0.682	0.514–0.905	0.008				0.721	0.538–0.965	0.028	0.635	0.434–0.929	0.019
Consolidation chemotherapy	1.696	1.291–2.229	< 0.001	2.047	1.399–2.997	< 0.001	1.229	0.910–1.660	0.178			
Pretreatment hemoglobin	0.877	0.657–1.170	0.372				0.775	0.574–1.047	0.097			
Pretreatment CEA	1.450	1.042–2.017	0.027				1.610	1.135–2.284	0.008			
Pre-NLR	1.387	1.035–1.860	0.029				1.187	0.873–1.613	0.274			
Pre-PLR	1.253	0.919–1.708	0.154				0.897	0.643–1.251	0.521			
Pre-LMR	0.718	0.528–0.976	0.035	0.655	0.450–0.954	0.027	0.916	0.661–1.270	0.598			
Post-NLR	1.832	1.251–2.682	0.002				1.968	1.356–2.857	< 0.001	2.575	1.485–4.467	0.001
Post-PLR	1.382	0.998–1.914	0.052				1.416	1.034–1.938	0.030			
Post-LMR	0.616	0.444–0.854	0.004				0.605	0.423–0.865	0.006	1.814	1.129–2.914	0.014
△NLR	0.573	0.417–0.788	0.001	0.609	0.414–0.895	0.012	0.649	0.465–0.906	0.011	0.625	0.403–0.969	0.036
△PLR	0.806	0.588–1.105	0.180				0.716	0.521–0.984	0.040			
△LMR	1.216	0.885–1.672	0.228				1.031	0.747–1.425	0.851			
ALCmin	0.630	0.470–0.743	0.002	0.632	0.436–0.916	0.015	0.942	0.693–1.281	0.705			

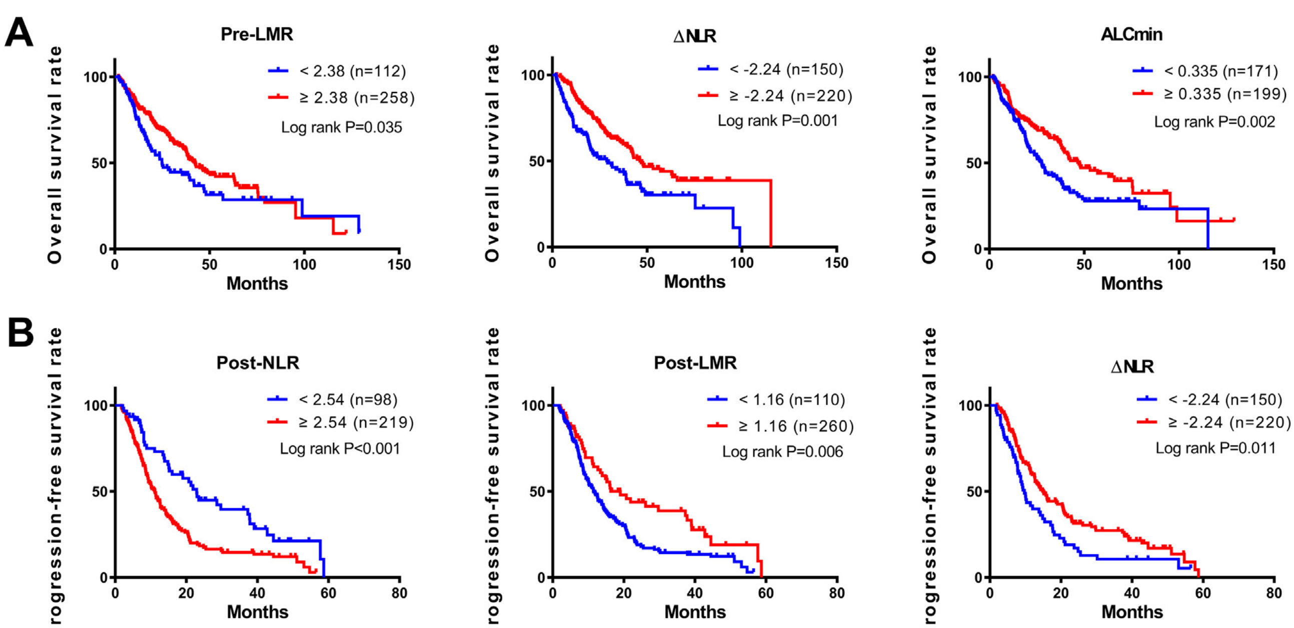

Fig. 2. Kaplan–Meier curves were used to show patients' outcomes among patients with different levels of inflammatory biomarkers. (A) Pre-LMR ≥ 2.38, ΔNLR ≥ −2.24, and ALCmin ≥ 0.335 were associated with favorable OS ($P = 0.035$, $P = 0.001$, and $P = 0.002$, respectively). (B) Post-NLR < 2.54, post-LMR ≥ 1.16, and ΔNLR ≥ −2.24 were associated with a good PFS ($P < 0.001$, $P = 0.006$, and $P = 0.011$, respectively).

4. Discussion

The treatment for inoperable LA-NSCLC is typically CCRT, yet the clinical progression and prognosis is heterogeneous. In addition, median survival time for patients with LA-NSCLC is still extremely poor, ranging from 12.6 to 29.3 months after diagnosis [20]. The development of novel prognostic factors and models will be of great significance for the better treatment stratification of these patients. In this study, we evaluated the prognostic value of dynamic inflammatory biomarkers in patients with LA-NSCLC, and developed two nomograms that predicted the OS and PFS based on inflammatory and clinicopathological variables.

Cancer progression is determined not only by the malignant behavior of tumors but also by the systemic inflammatory response, which was represented by the levels of several immune-associated cells [21,22]. Neutrophils, platelets, and monocytes have been proposed as important modulators favoring tumor invasion and metastasis [23–26]. In contrast, lymphocytes play a critical role in protective immunity by inhibiting tumor cell proliferation and migration [27,28]. Pretreatment NLR and PLR were found to be significant prognostic indicators of survival in patients with early stage and advanced NSCLC [13,14,29]. Moreover, LMR has been determined to be a useful predictor for

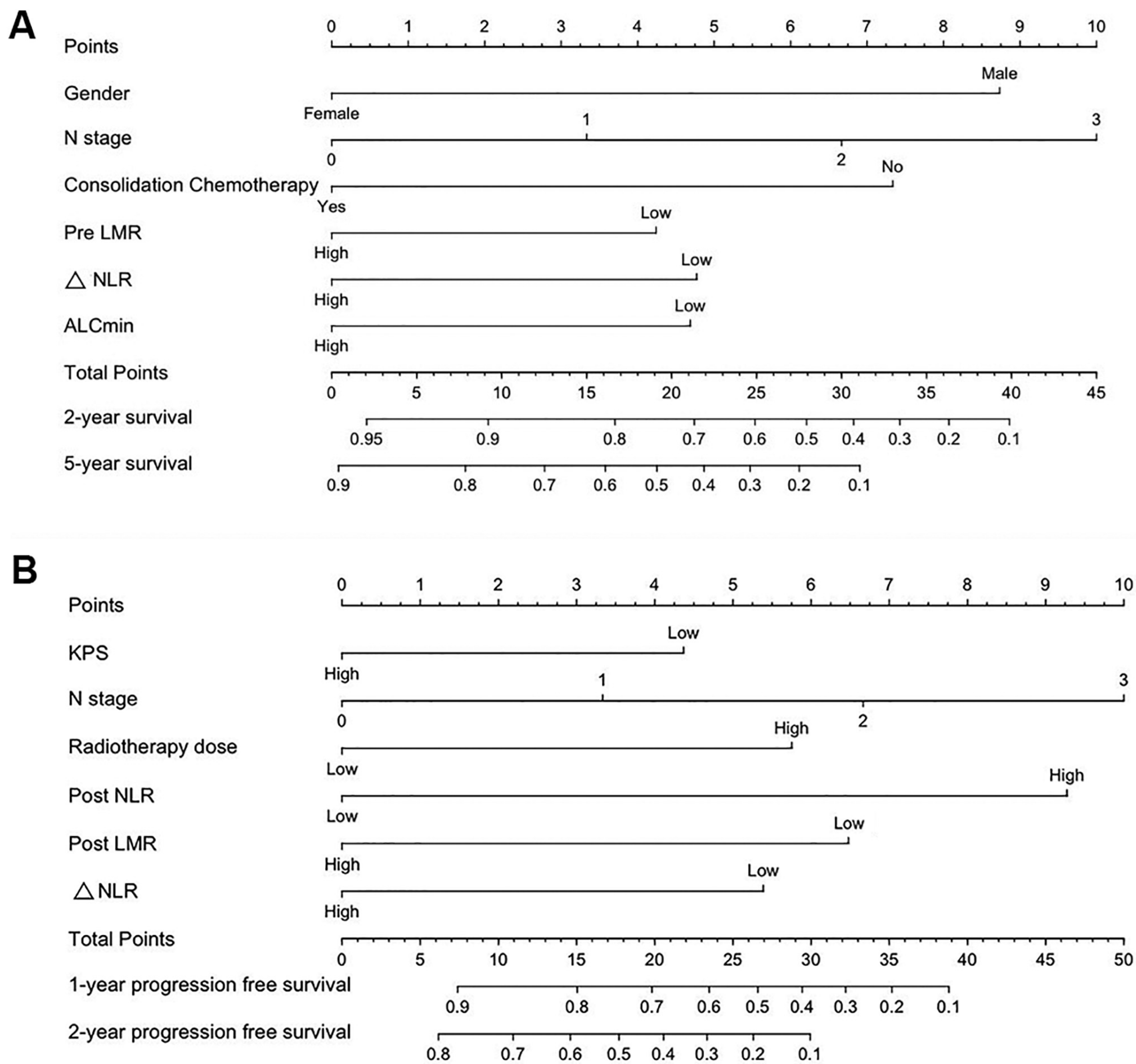

Fig. 3. Nomograms show the results of prognostic models using clinicopathological characteristics and inflammatory biomarkers to predict the OS and PFS of patients with inoperable LA-NSCLC. (A) Nomogram for 2- and 5-year OS. (B) Nomogram for 1- and 2-year PFS.

prognosis [12]. Cancer therapies including chemotherapy and radiotherapy are known to impact system immunity [30,31]. However, there is relatively limited information reflected by baseline evaluation compared with dynamic inflammatory markers, which may more precisely reveal the patient's actual inflammatory status during treatment.

In the 370 cases we studied, NLR and PLR significantly increased and LMR decreased during the treatment course, demonstrating damage to the immune system. Post-NLR, post-LMR, ΔNLR, and ALCmin were found to be superior in terms of prognostic ability. Nevertheless, pre-NLR and pre-LMR were associated with OS in univariate analysis but not in multivariate analysis, demonstrating that the dynamic evaluation of inflammatory status may more accurately predict a patient's prognosis. Besides, our study also indicated that patients with relatively small changes in inflammatory biomarkers after CCRT (i.e. those with higher tolerance to CCRT) showed favorable outcomes. The LA-NSCLC response to a PD-L1 inhibitor with good efficacy has been reported [4]. The observation of systemic inflammatory changes during CCRT might highlight the importance of evaluating the time point at which immunotherapies should be administered.

Inflammatory biomarkers are all easily evaluated in clinical settings, but are not all routinely used in practice. Nomogram is a simple graphical prediction model that has been confirmed to have better predictive ability than TNM staging alone [32–34]. In this study, the performance of a model combining clinical-TNM-inflammatory biomarkers was higher than that using an individual model alone and the clinical-TNM model, demonstrating that nomograms have better predictive capability when they incorporate integrated information. Although these models still need to be validated in more patients, our results are encouraging.

In addition to inflammatory biomarkers, other clinicopathological characteristics were found to be independent predictors of prognosis in our study. In agreement with the literature [35,36], we found that worse KPS was associated with a shorter PFS, and N2/3 stage was highly predictive of both a poor PFS and poor OS. Additionally, female sex was prognostic for a better OS [36,37]. Although the proportion of female patients was significantly less than that of male patients in our study, it was similar to the results of cancer statistics in China, which may reflect the low smoking rates of Chinese women [38]. Moreover, a

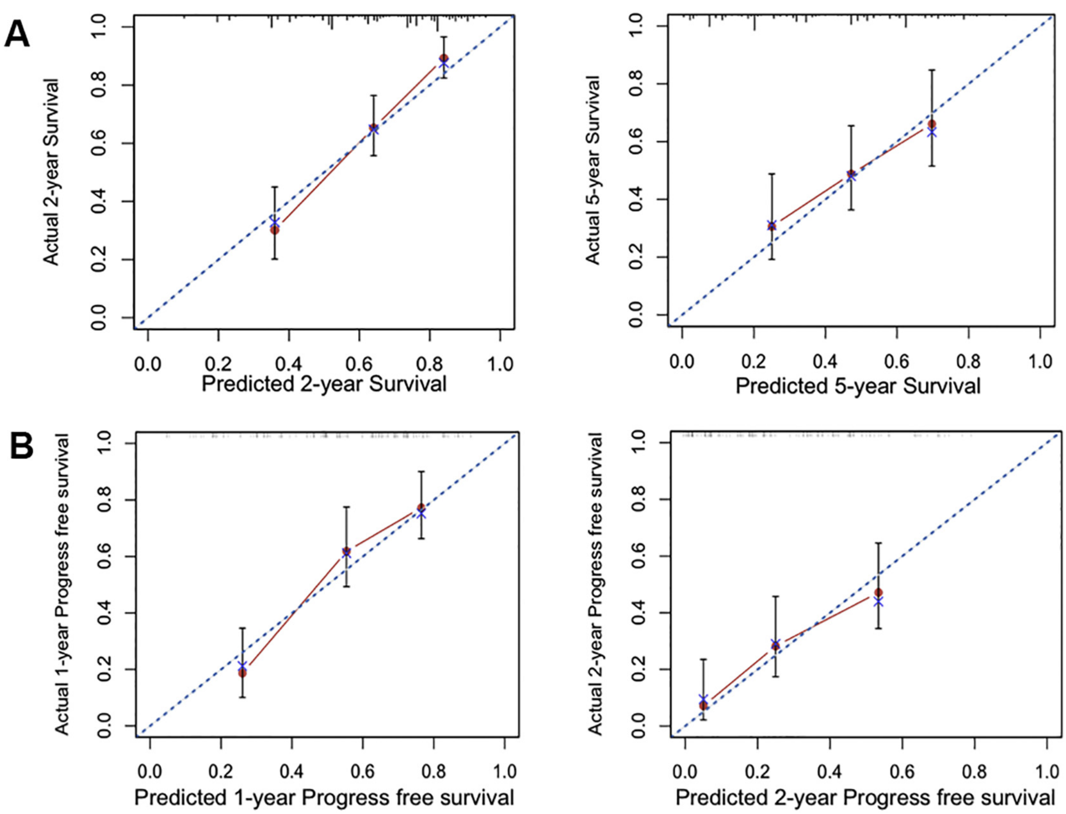

Fig. 4. Calibration plots of nomograms for predicting OS and PFS in patients with inoperable LA-NSCLC. (A) Calibration plots for predicting 2- and 5-year OS. (B) Calibration plots for predicting 1- and 2-year PFS. The x-axis is nomogram-predicted probability of survival and the y-axis is actual survival. The reference line is 45° and indicates perfect calibration.

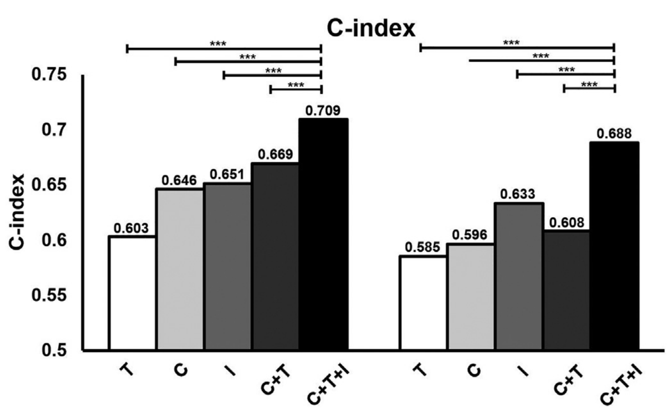

Fig. 5. Bar graphs represent the c-index of different prediction models for patients with inoperable LA-NSCLC. The Harrell's c-index for OS prediction was 0.709 (95% CI: 0.613–0.805). The predictive performance of the combined model with clinical-TNM-inflammatory biomarkers for OS was better than that of models with TNM stage (T), clinicopathological characteristics (C), inflammatory biomarkers (I), and clinical-TNM biomarkers (C + T) (all $P < 0.001$). The Harrell's c-index for PFS prediction was 0.688 (95% CI: 0.582–0.794). The predictive performance of the combined model with clinical-TNM-inflammatory biomarkers for PFS was also better than that of models with T, C, I, and C + T (all $P < 0.001$).

high radiotherapy dose (> 60 Gy) showed a lower PFS similar to RTOG0617 [39], but had no significant effect on OS, possibly due to patients having a lower tolerance for this treatment, leading to prolongation of radiotherapy and an associated increased risk of local control failure [40]. Nomograms that combine these inflammatory and clinicopathological characteristics may be of great help in guiding individualized treatment of patients with LA-NSCLC.

Although the effectiveness of CCT in LA-NSCLC is not completely understood, the survival benefit of CCT is reported to be better in Asian patients [1,41], especially Chinese patients [42]. According to our findings, CCT is an independent predictor of improved OS but not PFS. That may be associated with improved control in distant metastasis with CCT, which ultimately translates to better OS, whereas local control is more affected by radiotherapy. Furthermore, male sex, N2/3 stage, KPS ≤ 80, post-NLR ≥ 2.54, post-PLR ≥ 207, post-LMR < 1.16, and ΔNLR < −2.24 or ΔPLR < −93.7 may result in significant OS benefits, meaning that patients with a high risk of distant metastasis and weak immune status after CCRT are more suitable for CCT. It seems plausible that weak immune status after CCRT will favor tumor cell dissemination, metastasis, and colonization.

Although we successfully developed novel prediction models of prognosis according to clinicopathological factors and inflammatory biomarkers that may be widely available in the clinic, this study had several limitations. First, it was a retrospective study, and as such, was inevitably subject to bias. Secondly, our study was performed in a single central cohort; external validation should be performed in the future. Third, inflammatory biomarkers may be influenced by infection and steroid use. Although patients with active infections were excluded from this study, we have no data on whether latent infections were present, which should be ruled out in future prospective trials.

5. Conclusion

The findings of this study indicate that post-treatment and Δ inflammatory biomarkers are superior in predicting OS and PFS in LA-NSCLC patients. Nomograms based on dynamic inflammatory biomarkers and clinicopathological factors may be a more practical model for evaluating prognosis, and may offer individualized treatment for patients with inoperable LA-NSCLC.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.04.032.

Acknowledgements

This work was supported by the following grants: Natural Science Foundation of Shandong Province (Grant No. ZR2016HM41 and ZR2015HZ004), the Project of Postdoctoral Innovation of Shandong Province (2017M612283 and 201601006), the Project of Postdoctoral Science Foundation of China (Grant No. 2016M590640) and National Natural Science Foundation of China (Grant No. 81472812).

Disclosure statement

The authors have no conflicts to report.

References

[1] K. Tsujino, T. Kurata, S. Yamamoto, T. Kawaguchi, A. Kubo, S. Isa, Y. Hasegawa, S.H. Ou, M. Takada, M. Ando, Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature, J. Thorac. Oncol. 8 (9) (2013) 1181–1189.
[2] C.W. Jr, R. Paulus, C.J. Langer, R. Komaki, J.S. Lee, S. Hauser, B. Movsas, T. Wasserman, S.A. Rosenthal, E. Gore, Sequential vs concurrent chemoradiation for stage III non–small cell lung cancer: randomized phase III trial RTOG 9410, J. Natl. Cancer Inst. 103 (19) (2011) 1452–1460.
[3] N. Ramnath, T.J. Dilling, L.J. Harris, A.W. Kim, G.C. Michaud, A.A. Balekian, R. Diekemper, F.C. Detterbeck, D.A. Arenberg, Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5) (2013) E278–E313.
[4] S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M.W. De, Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, N. Engl. J. Med. 377 (20) (2017) 1919.
[5] J.V. Fernandes, R.N.O. Cobucci, C.A.N. Jatobá, J.M.G.D. Araújo, The role of the mediators of inflammation in cancer development, Pathol. Oncol. Res. 21 (3) (2015) 527–534.
[6] M.J. Proctor, D.S. Morrison, D. Talwar, S.M. Balmer, C.D. Fletcher, D.S.J. O'Reilly, A.K. Foulis, P.G. Horgan, D.C. Mcmillan, A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study, Eur. J. Cancer 47 (17) (2011) 2633–2641.
[7] R.M. Bremnes, K. Alshibli, T. Donnem, R. Sirera, S. Alsaad, S. Andersen, H. Stenvold, C. Camps, L.T. Busund, The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on non-small cell lung cancer, J. Thorac. Oncol. 6 (4) (2011) 824–833.
[8] C. D'Engremont, D. Vernerey, A.L. Pointet, G. Simone, F. Fein, B. Heyd, S. Koch, L. Vuitton, S. Kim, M. Jary, Additive value of pre-operative and one-month post-operative lymphocyte count for death-risk stratification in patients with resectable pancreatic cancer: a multicentric study, BMC Cancer 16 (1) (2016) 823.
[9] A. Kinoshita, H. Onoda, N. Imai, A. Iwaku, M. Oishi, N. Fushiya, K. Koike, H. Nishino, H. Tajiri, Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma, Br. J. Cancer 107 (6) (2012) 988–993.
[10] A.J. Templeton, M.G. McNamara, B. Seruga, F.E. Vera-Badillo, P. Aneja, A. Ocana, R. Leibowitz-Amit, G. Sonpavde, J.J. Knox, B. Tran, I.F. Tannock, E. Amir, Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis, J. Natl. Cancer Inst. 106 (6) (2014) dju124.
[11] G. Holgersson, S. Bergstrom, A. Hallqvist, P. Liv, J. Nilsson, L. Willen, J. Nyman, S. Ekman, R. Henriksson, M. Bergqvist, The prognostic value of pre-treatment thrombocytosis in two cohorts of patients with non-small cell lung cancer treated with curatively intended chemoradiotherapy, Neoplasma 64 (6) (2017) 909–915.
[12] C. Yuan, N. Li, X. Mao, Z. Liu, W. Ou, S.Y. Wang, Elevated pretreatment neutrophil/white blood cell ratio and monocyte/lymphocyte ratio predict poor survival in patients with curatively resected non-small cell lung cancer: results from a large cohort, Thorac. Cancer 8 (4) (2017) 350–358.
[13] N. Shaverdian, D. Veruttipong, J. Wang, D. Schaue, P. Kupelian, P. Lee, Pretreatment immune parameters predict for overall survival and toxicity in early-stage non–small-cell lung cancer patients treated with stereotactic body radiation therapy, Clin. Lung Cancer 17 (1) (2016) 39–46.
[14] G. Wu, Y. Yao, C. Bai, J. Zeng, D. Shi, X. Gu, X. Shi, Y. Song, Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients, Thorac. Cancer 6 (3) (2015) 275–287.
[15] Y. Yao, D. Yuan, H. Liu, X. Gu, Y. Song, Pretreatment neutrophil to lymphocyte ratio is associated with response to therapy and prognosis of advanced non-small cell lung cancer patients treated with first-line platinum-based chemotherapy, Cancer Immunol. Immunother. 62 (3) (2013) 471–479.
[16] K.H. Kang, J.T. Efird, N. Sharma, M. Yang, A. Dowlati, P. Linden, M. Machtay, T. Biswas, Prognostic potential of neutrophil-to-lymphocyte ratio and lymphocyte nadir in stage III non-small-cell lung cancer, Future Oncol. 13 (16) (2017) 1405–1414.
[17] H.B. Liu, X.L. Gu, X.Q. Ma, T.F. Lv, Y. Wu, Y.Y. Xiao, D.M. Yuan, Y.F. Li, Y. Song, Preoperative platelet count in predicting lymph node metastasis and prognosis in patients with non-small cell lung cancer, Neoplasma 60 (2) (2013) 203–208.
[18] K.A. Scilla, S.M. Bentzen, V.K. Lam, P. Mohindra, E.M. Nichols, M.A. Vyfhuis, N. Bhooshan, S.J. Feigenberg, M.J. Edelman, J.L. Feliciano, Neutrophil-lymphocyte ratio is a prognostic marker in patients with locally advanced (stage IIIA and IIIB) non-small cell lung cancer treated with combined modality therapy, Oncologist 22 (6) (2017) 737–742.
[19] Y.S. Tong, J. Tan, X.L. Zhou, Y.Q. Song, Y.J. Song, Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer, J. Transl. Med. 15 (1) (2017) 221.
[20] P. Goldstraw, R. Rami-Porta, H. Asamura, D. Ball, D.G. Beer, R. Beyruti, V. Bolejack, K. Chansky, J. Crowley, F. Detterbeck, The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer, J. Thorac. Oncol. 11 (1) (2016) 39–51.
[21] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (5) (2011) 646–674.
[22] K. Hattar, K. Franz, M. Ludwig, U. Sibelius, J. Wilhelm, J. Lohmeyer, R. Savai, F.S.B. Subtil, G. Dahlem, B. Eul, Interactions between neutrophils and non-small cell lung cancer cells: enhancement of tumor proliferation and inflammatory mediator synthesis, Cancer Immunol. Immunother. 63 (12) (2014) 1297–1306.
[23] M.R. Galdiero, C. Garlanda, S. Jaillon, G. Marone, A. Mantovani, Tumor associated macrophages and neutrophils in tumor progression, J. Cell. Physiol. 228 (7) (2013) 1404–1412.
[24] N.M. Bambace, C.E. Holmes, The platelet contribution to cancer progression, J. Thromb. Haemost. 9 (2) (2011) 237–249.
[25] M.Z. Wojtukiewicz, E. Sierko, D. Hempel, S.C. Tucker, K.V. Honn, Platelets and cancer angiogenesis nexus, Cancer Metastasis Rev. 36 (2) (2017) 1–14.
[26] F. Balkwill, A. Mantovani, Inflammation and cancer: back to Virchow? Lancet 357 (9255) (2001) 539–545.
[27] K.I. Alshibli, T. Donnem, S. Alsaad, M. Persson, R.M. Bremnes, L.T. Busund, Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer, Clin. Cancer Res. 14 (16) (2008) 5220–5227.
[28] K. Hiraoka, M. Miyamoto, Y. Cho, M. Suzuoki, T. Oshikiri, Y. Nakakubo, T. Itoh, T. Ohbuchi, S. Kondo, H. Katoh, Concurrent infiltration by CD8+ T cells and CD4+ T cells is a favourable prognostic factor in non-small-cell lung carcinoma, Br. J. Cancer 94 (2) (2006) 275–280.
[29] N.A. Cannon, J. Meyer, P. Iyengar, C. Ahn, K.D. Westover, H. Choy, R. Timmerman, Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors following stereotactic radiation therapy for early-stage non-small cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 90 (1) (2014) 280–285.
[30] M.T. Yazdi, M.S. Schinkelshoek, N.M. Loof, C. Taube, P.S. Hiemstra, M.J.P. Welters, S.H.V.D. Burg, Standard radiotherapy but not chemotherapy impairs systemic immunity in non-small cell lung cancer, Oncoimmunology 5 (12) (2016) e1255393.
[31] C. Tang, M.S. Lee, D. Gomez, L.B. Levy, Y. Zhuang, C. Lu, Z. Liao, R. Komaki, Effects of chemotherapy regimen and radiation modality on hematologic toxicities in patients receiving definitive platinum-based doublet chemoradiation for non-small cell lung cancer, Am. J. Clin. Oncol. 40 (6) (2017) 625–630.
[32] H. Chang, J. Gao, B.Q. Xu, S.P. Guo, R.B. Lu, G. Li, S.M. Huang, F. Han, Z.G. Liu, Y.L. Tao, Haemoglobin, neutrophil to lymphocyte ratio and platelet count improve prognosis prediction of the TNM staging system in nasopharyngeal carcinoma: development and validation in 3237 patients from a single institution, Clin. Oncol. 25 (11) (2013) 639–646.
[33] C. Oberije, D.D. Ruysscher, R. Houben, M.V.D. Heuvel, W. Uyterlinde, J.O. Deasy, J. Belderbos, A.M.C. Dingemans, A. Rimner, S. Din, A validated prediction model for overall survival from stage III non-small cell lung cancer: toward survival prediction for individual patients, Int. J. Radiat. Oncol. Biol. Phys. 92 (4) (2015) 935–944.
[34] C.N. Sternberg, Are nomograms better than currently available stage groupings for bladder cancer? J. Clin. Oncol. 24 (24) (2006) 3819–3820.
[35] M.J. Solan, M. Wernerwasik, Prognostic factors in non-small cell lung cancer, Semin. Surg. Oncol. 21 (2) (2003) 64–73.
[36] W. Liang, L. Zhang, G. Jiang, Q. Wang, L. Liu, D. Liu, Z. Wang, Z. Zhu, Q. Deng, X. Xiong, Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer, J. Clin. Oncol. 33 (8) (2015) 861–869.
[37] F. Blanchon, M. Grivaux, B. Asselain, F.X. Lebas, J.P. Orlando, J. Piquet, M. Zureik, 4-year mortality in patients with non-small-cell lung cancer: development and validation of a prognostic index, Lancet Oncol 7 (10) (2006) 829–836.
[38] W. Chen, R. Zheng, P.D. Baade, S. Zhang, H. Zeng, F. Bray, A. Jemal, X.Q. Yu, J. He, Cancer statistics in China, 2015, CA Cancer J. Clin. 66 (2) (2016) 115–132.
[39] J.D. Bradley, R. Paulus, R. Komaki, G. Masters, G. Blumenschein, S. Schild, J. Bogart, C. Hu, K. Forster, A. Magliocco, Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial ph, Lancet Oncol 16 (2) (2015) 187–199.
[40] M. M, H. C, K. R, S. WT, S. RS, L. CJ, B. RW, C. WJ, Effect of overall treatment time on outcomes after concurrent chemoradiation for locally advanced non-small-cell lung carcinoma: analysis of the Radiation Therapy Oncology Group (RTOG) experience, Int. J. Radiat. Oncol. Biol. Phys. 63 (3) (2005) 667–671.
[41] X. Wang, X. Ding, D. Kong, L. Zhang, Y. Guo, J. Ren, X. Hu, J. Yang, S. Gao, The effect of consolidation chemotherapy after concurrent chemoradiotherapy on the survival of patients with locally advanced non-small cell lung cancer: a meta-analysis, Int. J. Clin. Oncol. 22 (2) (2017) 1–8.
[42] L. Liu, N. Bi, Z. Ji, J. Li, J. Wang, X. Wang, Z. Hui, J. Lv, J. Liang, Z. Zhou, Consolidation chemotherapy may improve survival for patients with locally advanced non-small-cell lung cancer receiving concurrent chemoradiotherapy - retrospective analysis of 203 cases, BMC Cancer 15 (1) (2015) 1–9.