The Predictive Value of Tumor Volume, Inflammatory Biomarkers, and Their Dynamic Changes on Early Tumor Response for Elderly Patients With Esophageal Squamous Cell Carcinoma Underwent Radiotherapy

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Research article

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Abstract

Background: To investigate the tumor volume, pre-treatment inflammatory biomarkers (pre-IBs), and their dynamic changes on early tumor response (ETR) in elderly patients (≥70 years) with esophageal squamous cell carcinoma (ESCC) underwent radiotherapy.

Methods: The ETR was assessed according to RECIST 1.1 at 1 month after radiotherapy. The tumor volume ((gross tumor volume (GTV) at the initial treatment planning (GTVi), and GTV at shrinking irradiation field planning (GTVs)), IBs (neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), and lymphocyte/monocyte (LMR)) which also included during treatment IBs (dur-IBs), and clinical variables were collected and analyzed from 197 patients received radiotherapy at our institution between 2015 and 2020. The tumor volume change rate (TVCR) and dynamic changes of IBs (delta-IBs) were defined as follows: TVCR=(1-GTVs/GTVi)×100%, delta-IBs=1-dur-IBs/pre-IBs. A nomogram based on logistic regression analysis were then established for predicting ETR.

Results: GTVi and pre-LMR significantly decreased, pre-NLR, and pre-PLR significantly increased during radiotherapy or chemoradiotherapy (all P<0.001). Multivariate analysis indicated that TVCR [OR, 0.197; 95%CI, 0.093-0.414; P<0.001], pre-NLR [OR, 2.568; 95%CI, 1.031-6.394; P=0.043], and delta-NLR [OR, 2.831; 95%CI, 1.126-7.119; P=0.027] were statistically significant with ETR. And c-index of the nomogram established by combining all independent predictors for ETR was 0.769 [95%CI, 0.161–0.302].

Conclusion: TVCR, Pre-NLR, and delta-NLR were significant with ETR in elderly patients with ESCC who underwent radiotherapy. And the developed nomogram with superior prediction ability for ETR could assist in patients counseling and guide to make individual treatments and follow-up strategies.

Highlights

- To our knowledge and limited literature searches, this was the first report that describes the prognostic significance of early tumor response combined with tumor volume, inflammatory biomarkers and their dynamic changes in elderly ESCC patients underwent radiotherapy.
- TVCR, Pre-NLR, and delta-NLR were significant with ETR in elderly patients with ESCC who underwent radiotherapy.
- The c-index of the nomogram established by combining all independent predictors for early tumor response was 0.769.

Background

According to the Cancer statistics in China of 2015, esophageal cancer (EC) is the 3rd most common incident cancer and the 4th leading cause of cancer death, and 90% of its pathological type is esophageal squamous cell carcinoma (ESCC) [1]. And the incidence of EC patients has been increasing annually in China, particularly with population aging combined with population and the improvement of

the social security system, the elderly patients have accounted for 50% of the EC cases [2–4]. And most elderly patients are accompanied by other basic diseases, poor physical and physiological conditions, and sometimes show accompanied by malnutrition, electrolyte disorder, and dysfunction of the heart, liver, and kidney, which are not considered suitable for operation [5]. So, radiotherapy, or chemoradiotherapy (CRT) become the main treatment for elderly EC patients, and it is reported that about 70% of EC patients need radiotherapy at different stages of tumor treatment [6]. However, local recurrence and distant metastasis are the main causes of treatment failure, and the risk of perforation and bleeding caused by radiotherapy in the short term after recurrence is high, and the effect of second-line chemotherapy is poor [7, 8]. Even if the elderly EC patients have the same clinical stage, and they are also given the same treatment as young patients, but the curative effect could be very different [9].

So, it is necessary to predict the early tumor response (ETR) of radiotherapy for elderly EC patients to optimize the individual treatment strategy, increase radiosensitizer appropriately, and follow-up promptly to improve the local control rate and the survival rate.

The earlier effective treatment is detected, the greater the benefit to elderly patients in clinical practice. Tumor volume is the most intuitive manifestation of the therapeutic effect, and with the improvement of radiotherapy technology, we can routinely evaluate tumor volume during radiotherapy. Some studies have also reported that tumor volume is a potential predictor for EC patients [10–12]. Moreover, the interaction between inflammatory cells and tumor cells can change the dynamic balance of tumor tissue to influence the therapeutic effect [13, 14]. Now, more and more studies investigate the relationship between inflammatory biomarkers (IBs) and the prognosis of patients with EC [15–18]. Additionally, cancer-related inflammation is a key determinant of disease progression, and patient survival, especially the host response in the form of systemic inflammation has been shown to independently predict prognosis [19–21].

Whether tumor volume or IBs is constantly changing during treatment, the tumor volume change rate (TVCR) and dynamic changes of IBs (delta-IBs) may be more valuable in reflecting the real-time response to radiotherapy and be more accurate for predicting ETR. Most of these prognostic biomarkers in previous studies were collected at the pre-treatment and did not involve the response of the tumor to radiotherapy during treatment [10–12,15–18]. Meanwhile, elderly patients are often excluded or at least underrepresented in randomized trials. Now, we must recognize that elderly cancer patients do not necessarily have a short life as life expectancy keeps on increasing. They could be adjusted treatment strategy and monitored if the early tumor response could be predicted. Hence, this study aimed to investigate tumor volume, IBs, and their dynamic changes on ETR in elderly ESCC patients (≥ 70 years) who underwent radiotherapy.

Methods

Patients

We performed a retrospective analysis of 197 ESCC patients aged ≥ 70 years who were underwent radiotherapy with or without chemotherapy in Shandong Cancer Hospital between 12/2015 and 02/2020. Inclusion criteria include the following: (1) new diagnosed ESCC and confirmed by histopathology; (2) receipt of 50-64Gy radiotherapy with or without chemotherapy, and a repeated computed tomography scan was performed before and follow 40Gy for shrinking irradiation field; (3) availability of complete blood cell counts (CBCs), and radiology date (include esophagography, enhanced computed tomography, radiotherapy planning evaluation system and imaging data) before and during treatment; (4) the local focus could not be resected; (5) Karnofsky performance status ≧ 70; (6) no history of malignant tumors, no intolerable serious medical diseases, no distant metastasis, no active esophageal bleeding; (7) no autoimmune, blood, and infectious diseases or fever. All patients in this study were restaged according to the American Joint Committee of Cancer 7th edition TNM classification and staging system. For the clinical and treatment characteristics of the patients see Table 1.

Table 1
Clinical characteristics of elderly patients with ESCC.

	Total	Response	Non-response
Characteristics.	**N = 197 (%)**	**N = 126 (%)**	**N = 71(%)**
Gender			
Male	127 (64.5)	74 (58.7)	53 (74.6)
Female	70 (35.5)	52 (41.3)	18 (25.4)
Location			
Cervical	19 (9.6)	15 (11.9)	4 (5.6)
Upper Thoracic	38 (19.3)	20 (15.9)	18 (25.4)
Middle Thoracic	64 (32.5)	42 (33.3)	22 (31.0)
Lower Thoracic	76 (38.6)	49 (38.9)	27 (38.0)
cT-stage			
T2	27 (13.2)	16 (12.7)	11 (15.5)
T3	142 (72.1)	88 (69.8)	54 (76.1)
T4	28 (14.2)	22 (17.5)	6 (8.5)
cN-stage			
N0	62 (31.5)	44 (34.9)	18 (25.4)
N1	94 (47.7)	53 (42.1)	41 (57.7)
N2	37 (18.8)	28 (22.2)	9 (12.7)
N3	4 (2.0)	1 (0.8)	3 (4.2)
TNM stage			
IIA/IIB	66 (33.5)	42 (33.3)	24 (33.8)
IIIA/IIIB	99 (50.3)	61 (48.4)	38 (53.5)
IVA	32 (16.2)	23 (18.3)	9 (12.7)
Treatment modality			
Radiotherapy	140 (71.1)	89 (70.6)	51 (71.8)
Chemoradiotherapy			
Concurrent	57 (28.9)	37 (29.4)	20 (28.2)

	Total	Response	Non-response
Chemotherapy			
No	140 (71.1)	89 (70.6)	51 (71.8)
PF regimen	43 (21.8)	25 (19.8)	18 (25.4)
TP regimen	14 (7.1)	12 (9.5)	2(2.8)
Radiation dose (Gy)			
< 60	103 (52.3)	66 (52.4)	37 (52.1)
≥ 60	94 (47.7)	60 (47.6)	34 (47.9)

Abbreviation: PF regimen, cisplatin + fluorouracil; TP regimen, paclitaxel + cisplatin; clinical T stage, N stage, TNM stage, Clinical cancer stage according to the American Joint Committee of Cancer seventh edition TNM classification and staging system.

Treatment characteristics

All patients were underwent 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy. Radiotherapy alone or concurrent chemoradiotherapy was performed according to the clinical stage and the physical condition of patients. All radiotherapy plans were generated in the Eclipse system (Varian Medical Systems, Palo Alto, CA, Version 13.5.35), and delivered with 6 MV photons beams. The prescribed doses of radiotherapy were 50-64Gy at 2.0Gy per fraction once daily and five fractions per week. Plans were normalized to 95% of the plan tumor volume received 100% of the prescribed dose. The dose of all organs at risk (OARs) was controlled below the safe range. The chemotherapy regimen has mainly consisted of two platinum-based regimens. One was cisplatin with fluorouracil, one was cisplatin with paclitaxel.

The delineation of target volumes, OARs, and doses of chemotherapy regimens followed the guidelines of the Chinese Society of Clinical Oncology and the National Comprehensive Cancer Network for EC.

Response evaluation

All patients performed esophagography and enhanced computed tomography before and at 1 month after radiotherapy. The imaging data were analyzed and the ETR of all patients were assessed by an imaging deputy chief physician and a radiotherapy deputy chief physician according to Response Evaluation Criteria in Solid Tumor 1.1 (RECIST 1.1) without knowledge of the results of TVCR and IBs studies. Patients with an outcome of complete response (CR) or partial response (PR) were subsequently classified as responders, while those who had an outcome of stable disease (SD) or progressive disease (PD) were defined as non-responders.

TVCR and delta-IBs calculation

IBs included neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), and lymphocyte/monocyte (LMR) in this study. The CBCs were collected at different time points. The first time point was before the start of radiotherapy which we defined as pre-IBs. The second was when preparing shrinking irradiation field planning which we defined as dur-IBs. The gross tumor volume (GTV) defined on radiotherapy planning refers to the range of tumor lesions with certain shapes and sizes displayed by existing auxiliary examination methods including computed tomography and esophagography, and its stereoscopic imaging reflects the actual shape of the tumor. And we defined GTV including the primary tumor and involved lymph nodes at initial treatment planning as GTVi, at shrinking irradiation field planning as GTVs. All GTVi and GTVs were extracted from the Varian treatment planning system.

The TVCR and delta-IBs were calculated as follows:

TVCR = (1 − GTVs / GTVi)×100%

Delta-IBs = 1 − Dur-IBs ÷ Pre-IBs

Statistical analysis

Converting continuous variables into binary variables by using receiver operating characteristic (ROC). The difference between pre-treatment and during treatment of tumor volume and IBs were compared using Wilcoxon's sign rank test. Univariate logistic regression analysis was performed to estimate the odds ratio (OR) and confidence interval (CI) to evaluate the effect of independent variables on ETR. To avoid omitting indicators that might be of clinical significance, factors that had $P < 0.1$ in univariate analyses were subjected to multivariate analysis. Scatter plot and Spearman's rank correlation coefficient (r) values were performed in the same kind of parameters. A significant difference was considered if a P-value was < 0.05 in 2-sided. And Statistical evaluation was conducted with IBM SPSS Statistics 25.0 software (SPSS Inc., Chicago, IL). A nomogram for possible prognostic factors associated with ETR was established by R 3.4.4 software (Institute for Statistics and Mathematics, Vienna, Austria), and the predictive accuracy was evaluated by the concordance index (c-index).

Results

Clinical parameters of the patients

The median age and radiation doses were 76 years (range, 70–84 years) and 60 Gy (range, 50–64 Gy), respectively. And the clinical characteristics of 197 elderly patients with stage II to IVA ESCC who received radiotherapy were summarized in Table 1. There was a significant decrease in GTVi compared to GTVs, with GTVi decreasing by a mean of 15.29 (range − 29.38 to 258.4; P < 0.001), as well as pre-LMR decreasing by a mean of 1.722 (range − 6.845 to 7.774; P < 0.001), while there was a significant increase in pre-NLR compared to dur-NLR, with pre-NLR increasing by a mean of 3.697 (range − 10.54 to 36.08; P < 0.001), as well as pre-PLR increasing by a median of 152.9 (range − 194.5 to 848.4; P < 0.001) (Fig. 1a-d).

At 1 month after radiotherapy, 126 patients (64.0%) were assessable for responders, and 71 patients (36.0%) were assessable for non-responders.

Univariate and multivariate analyses for ETR

In univariate analysis, gender [OR, 0.483; 95%CI, 0.254–0.918; $P = 0.026$], TVCR [OR, 0.221; 95%CI, 0.113–0.422; $P < 0.001$], pre-NLR [OR, 3.839; 95%CI, 2.080–7.088; $P < 0.001$], delta-NLR [OR, 2.839; 95%CI, 1.410–5.717; $P = 0.003$], pre-PLR [OR, 3.064; 95%CI, 1.521–6.173; $P = 0.002$], delta-PLR [OR, 2.693; 95%CI, 1.308–5.542; $P = 0.007$], pre-LMR [OR, 0.428; 95%CI, 0.236–0.777; $P = 0.005$], and dur-LMR [OR, 0.496; 95%CI, 0.270–0.913; $P = 0.024$] were significantly associated with ETR (Table 2). The variables with $P < 0.1$ in univariate analysis were subjected to multivariate analysis. And we found that TVCR [OR, 0.197; 95%CI, 0.093–0.414; $P < 0.001$], pre-NLR [OR, 2.568; 95%CI, 1.031–6.394; $P = 0.043$], and delta-NLR [OR, 2.831; 95%CI, 1.126–7.119; $P = 0.027$] were independently associated with ETR in multivariate analysis (Fig. 2).

Table 2
Univariate analysis of clinical, tumor volume, and inflammatory parameters in predicting the early tumor response of elderly ESCC patients.

Parameters	*P* value	OR	95% CI
Clinical parameters			
Gender (Male vs. Female)	0.026	0.483	0.254–0.918
Location (Cervical vs. Thoracic)	0.162	2.264	0.721–7.105
cT-stage (T2 vs. T3 & T4)	0.585	0.793	0.346–1.819
cN-stage (N0 vs. N+)	0.167	1.580	0.826–3.021
TNM stage (II vs. III & IVA)	0.947	0.979	0.529–1.812
Treatment modality (RT vs. CRT)	0.859	1.060	0.557–2.018
Radiation dose (< 60 vs. ≥ 60), Gy	0.971	1.011	0.565–1.809
Tumor volume			
Initial GTV (< 63.3 vs. ≥63.3), cm^3	0.122	0.630	0.351–1.132
Shrinking GTV (< 56.6 vs. ≥56.6), cm^3	0.545	1.197	0.669–2.143
TVCR (< 6.24% vs. ≥6.24%)	< 0.001	0.221	0.113–0.432
Inflammatory parameters			
NLR			
Pre-NLR (< 2.764 vs. ≥2.764)	< 0.001	3.839	2.080–7.088
Dur-NLR (< 6.539 vs. ≥6.539)	0.213	1.463	0.804–2.664
Delta-NLR (<-1.728 vs. ≥-1.728)	0.003	2.839	1.410–5.717
PLR			
Pre-PLR (< 209.2 vs. ≥209.2)	0.002	3.064	1.521–6.173
Dur-PLR (< 203.1 vs. ≥203.1)	0.296	1.424	0.734–2.764
Delta-PLR (<-0.1778 vs. ≥-0.1778)	0.007	2.693	1.308–5.542
LMR			
Pre-LMR (< 3.219 vs. ≥3.219)	0.005	0.428	0.236–0.777
Dur-LMR (< 1.246 vs. ≥1.246)	0.024	0.496	0.270–0.913
Delta-LMR (< 0.6444 vs. ≥0.6444)	0.136	0.611	0.320–1.168

Spearman correlation coefficient in TVCR and delta-IBs

Further correlation studies indicated that delta-NLR was positively correlated with delta-PLR ($r = 0.696$, $P < 0.001$) (Fig. 3d). And the delta-LMR was negatively correlated with delta-NLR ($r=-0.654$, $P < 0.001$) (Fig. 3e), as well as delta-PLR ($r=-0.612$, $P < 0.001$) (Fig. 3f).

Nomogram for predicting prognosis of ETR

The nomogram was established by multivariate logistic regression according to all significantly independent factors for ETR in elderly ESCC patients (Fig. 4a). And Fig. 4a also shown that the TVCR had the best predictive value for ETR, then pre-NLR, delta-NLR in this study. The calibration curve of the nomogram for ETR demonstrated good agreement between nomogram prediction and actual observation (Fig. 4b). And the C-index for the prediction nomogram was 0.769 (95%CI, 0.698–0.839) by internal bootstrapping validation.

Discussion

Nowadays, there is still no established standardized treatment strategy for elderly EC patients due to their special characteristics. Although considerations which include age, functional status, risk of treatment-related morbidities, life expectancy, and personal preference should be taken into account when making treatment decisions, the prognosis of elderly patients with EC is still poorer than young non-elderly patients [5]. Furthermore, RECIST 1.1 which has been widely used in the clinic to evaluate tumor's response to anticancer therapy still has some limitations. First, its main evaluation criteria are to measure changes in the longest diameter of assessable lesions, while ignoring short diameter and tumor volume; secondly, the one-dimensional measurement based on morphological changes ignores molecular changes and cannot effectively reflect the biological changes in tumors, which may lead to inaccurate prediction of treatment responses; thirdly, the evaluation of efficacy by RECIST 1.1 criteria is usually carried out one or three months after treatment, which may delay the detection of disease progression and recurrence [22]. Hence, it is necessary to explore new biomarkers to predict the ETR of elderly ESCC patients. Tumor volume can be easily gotten from the Varian treatment planning system, and IBs have the advantages of economy, simple detection, and easy to be accepted by the majority of patients. Based on those, we investigated the tumor volume, pre-IBs, and their dynamic changes on ETR in newly diagnosed elderly ESCC patients (≥ 70 years) who underwent radiotherapy. And our present study found that TVCR, pre-NLR, and delta-NLR were significantly associated with ETR in elderly ESCC patients. Furthermore, the developed nomogram based on all independent predictors had a better prediction ability for ETR.

Generally speaking, the bigger tumor volume is, the great tumor burden is. As far as EC is concerned, *Boggs et al* thought that the greater the tumor volume load, the lower the survival time of patients, and tumor volume is an independent prognostic factor affecting the survival of patients [10]. *Chen et al* retrospectively analyzed the clinical data of 187 patients after radiotherapy and found that the survival time of patients with higher GTV ($> 39.41 cm^3$) which was based on the radiation therapy planning system was significantly lower than that of the comparison group ($GTV < 39.41 cm^3$) [11]. Furthermore, *Créhange*

et al have also retrospectively analyzed the tumor volume of 148 patients with EC underwent radiotherapy and found that overall survival (OS) of patients with tumor volume ≥ 100cm^3 which was calculated by assimilation as the sum of two pairs of truncated cones was significantly lower than that of patients with tumor volume < 100cm^3 (P = 0.041) [12]. The tumor volume in the present study was automatically calculated by the radiotherapy planning system, and neither GTVi nor GTVs was associated with ETR. One reason was that all the ESCC patients were elderly which had dull sensation, late appearance of self-feeling symptoms, and late medical treatment so that most of the tumor volume were larger than non-elderly patients when diagnosed. Another was that esophagus was a hollow organ, the hollow tissue would affect the accuracy of the automatic drawing of tumor tissue. However, it did not mean that tumor volume had no predictive value in elderly ESCC patients. It seemed to be more valuable to quantify tumor volume change during treatment from the aspect of disease regression. *Jobbour et al* had reported that tumor volume reduction during CRT could predict post-CRT survival in NSCLC [23]. *Yang et al* also found that volume reduction rate was an outcome predictor for head-and-neck cancer patients treated with radiotherapy [24]. Interestingly, NSCLC patients with pronounced volume regression had worse locoregional tumor control and overall survival in *Brinkv et al* study [25]. However, elderly ESCC patients who were bigger TVCR (≥ 6.24%) had better ETR in this study which might suggest that TVCR might be a more sensitive indicator than tumor volume. Moreover, there was a significant decrease between GTVi and GTVs which indicated that radiotherapy was an effective treatment for elderly ESCC patients. Currently, radiotherapy physicians still manually delineate and calculate tumor volumes by computer systems and therapeutic planning systems, while many factors such as doctors' clinical knowledge, experience, energy, and status determine that there are some differences in drawing quality between different doctors and different patients [26]. There is no doubt that these also affect target delineation and calculation of tumor volume. It is possible to solve these problems with artificial intelligence (AI) at the age of precision medicine. *Lin et al* have used AI technology to automatically draw nasopharyngeal tumors on magnetic resonance images, which provided a solution for accurate and efficient delineation of radiotherapy targets [27]. *Choi et al* have confirmed the plausibility of deep learning-based automatic segmentation for clinical implementations in breast cancer [28]. So, the prospect of precision medicine based on radiotherapy for tumors will be promising with the development of AI.

Apart from tumor volume, some studies also found that inflammatory response is closely associated with tumor prognosis [19, 29]. The inflammatory response can participate in and promote the malignant transformation, migration, and diffusion of tumor cells by up-regulating cytokines, producing inflammatory mediators, inhibiting apoptosis, promoting angiogenesis, and inducing DNA mutation [14,30–31]. Lymphocytes, neutrophils, platelets, and monocytes have always been considered to play an important role in immune balance and inflammatory response. Lymphocytes are considered to be tumor suppressor cells, which can induce tumor cell death and inhibit tumor progression [32]. An abnormal increase of neutrophils may lead to tumor proliferation, increased potential of local invasion and metastasis, tumor vascularization, and help tumor cells escape immune surveillance [33]. Platelets can cooperatively activate tumor cells and are essential for early metastasis of cancer [34]. Monocytes may be

involved in tumor growth and promote tumor progression and metastasis [35]. Furthermore, the complex IBs which include NLR, PLR, and LMR can reflect the dynamic relationship between anti-tumor and promoting tumor. Our present study found there was a significant increase in pre-NLR during radiotherapy, as well as in pre-PLR, and a significant decrease in pre-LMR. This association between changes of IBs and radiotherapy at different time points could at least be partly explained. Besides immunity gradually decreases with age, larger tumor volume ($P < 0.0001$), concurrent chemotherapy ($P < 0.0001$), and stage III disease ($P = 0.05$) would lead to a lower count of lymphocytes [36].

The predictive value of NLR in EC has been confirmed in many studies. *Yoo et al* have conducted a retrospective study on 138 locally advanced EC patients who received concurrent CRT, and found that high pre-NLR group the progression-free survival (PFS) time and OS time were significantly shorter in the high pre-NLR group (NLR ≥ 2.0) were significantly associated with decreased PFS and OS (all $P < 0.05$) [15]. *Zhou et al* have also analyzed 517 locally advanced EC patients who received CRT and pointed out that pre-NLR > 5 was an independent predictor of PFS and overall OS (all $P < 0.001$). Similar to these results, pre-NLR was an independent predictor for ETR in elder ESCC patients who underwent radiotherapy in this study [16]. Additionally, delta-NLR was also significant associated with ETR, and elderly ESCC patients who were with low delta-NLR (<-1.728) would get better ETR which might suggest that delta-IBs were also predictors for them. *Choil et al* have found that changes in NLR after neoadjuvant treatment showed a statistically significant correlation with advanced breast cancer patients' survival [37]. *Templeton et al* reported that early decline of NLR was associated with favorable outcomes, whereas an increase was associated with worse outcomes for metastatic renal cell carcinoma with targeted therapy [38]. Whether pre-NLR or delta-NLR, these studies did not specifically analyze the elderly patients. This was the first significant study that analyzed the predictive value of pre-NLR and delta-NLR in elderly ESCC patients. In therapy, delta-NLR should be better reflect the sensitivity of the tumor to treatment. However, pre-NLR had a better predictive value than delta-NLR in this study which might be that pre-NLR was better able to reflect the state of the body's original response.

Recently, many scholars have studied the prognostic value of PLR and LMR in cancer patients, but their role in ESCC is still controversial. *Xie et al* found that PLR had the predictive ability for ESCC patients with different stages, which was an independent predictor for stage I ~ II, but not for stage III ~ IV [17]. While *Jun et al* thought that there was no significant correlation between PLR and postoperative survival time by analyzing the clinical data of patients with ESCC [39]. Another study also reported that a low LMR (< 4) was a significant and independent predictor of poor survival in non-elderly EC patients who received curative thoracoscopic esophagectomy [18]. But our present study found that PLR and LMR were not significant with ETR in multivariate analyses for elderly ESCC patients. The reason might be that radiotherapy might result in part of necrosis and death of cancer cells as well as the surrounding tissues, which in turn cause an inflammatory response similar to the wound healing response. Interestingly, there was a correlation between delta-NLR and delta-LMR, as well as delta-PLR, while only delta-NLR was significantly associated with ETR in this study.

We have confirmed that the IBs and TVCR were significant with early tumor response in ESCC patients who underwent radiotherapy or CRT by different retrospective studies [40–41]. However, we did not analyze the tumor volume and IBs on ETR in elderly ESCC patients. To our knowledge and limited literature searches, this was the first report that describes the prognostic significance of ETR combined with tumor volume, IBs, and their dynamic changes in elderly ESCC patients who underwent radiotherapy. But several limitations would be addressed here. First, this was a retrospective, single-center, and small population study that was entire of elderly ESCC patients, which might limit the universality of the results. Second, oncology does not have a specific age threshold for elderly patients with cancer. And we defined the elderly as the patient whose age ≥ 70 years. Last, there is no consensus on the exact cut-off value for IBs, and various methods including ROC and median values have been used to determine the optimal segregation points. Consequently, larger, multicenter, and prospectively designed clinical trials are required to confirm these initial results.

Conclusions

In summary, our study confirmed that TVCR, pre-NLR, and delta-NLR before and during RT were associated with ETR in elderly ESCC patients. Moreover, TVCR had the best predictive value, suggesting that pre-NLR may be an important factor predicting the ETR. And the developed nomogram with superior prediction ability for ETR could assist in patients counseling and guide to make individual treatments and follow-up strategies for elderly ESCC patients.

Abbreviations

CI, confidence interval; CBCs, complete blood cell counts; CR, complete response; CRT, chemoradiotherapy; Delta-, dynamic changes of; Dur-, during treatment; EC, esophageal cancer; ETR, early tumor response; ESCC, esophageal squamous cell carcinoma; GTV, gross tumor volume; GTVi, GTV at the initial treatment planning; GTVs, GTV at shrinking irradiation field planning; IBs, inflammatory biomarkers; LMR, lymphocyte/monocyte; NLR, neutrophil/lymphocyte; OARs, organs at risk; OR, odds ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PLR, platelet/lymphocyte; PR, partial response; Pre-, pre-treatment; RECIST 1.1, Response Evaluation Criteria in Solid Tumor 1.1; ROC, receiver operating characteristic; SD, stable disease; TVCR, tumor volume change rate;

Declarations

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Authors' Contributions

SL, and CL, guarantor of integrity of the entire study, data analysis, manuscript preparation; LW, DX, and ZL, literature research; CL, and XM, study concepts and design, manuscript editing. All authors

contributed to manuscript revision, read and approved the submitted version.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The ethics committee of Shandong Cancer Hospital and Institute approved the study. Also, administrative permissions to access the patients' clinical data used in our research were granted by the ethical review board. And written informed consent was waived because of its retrospective design.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

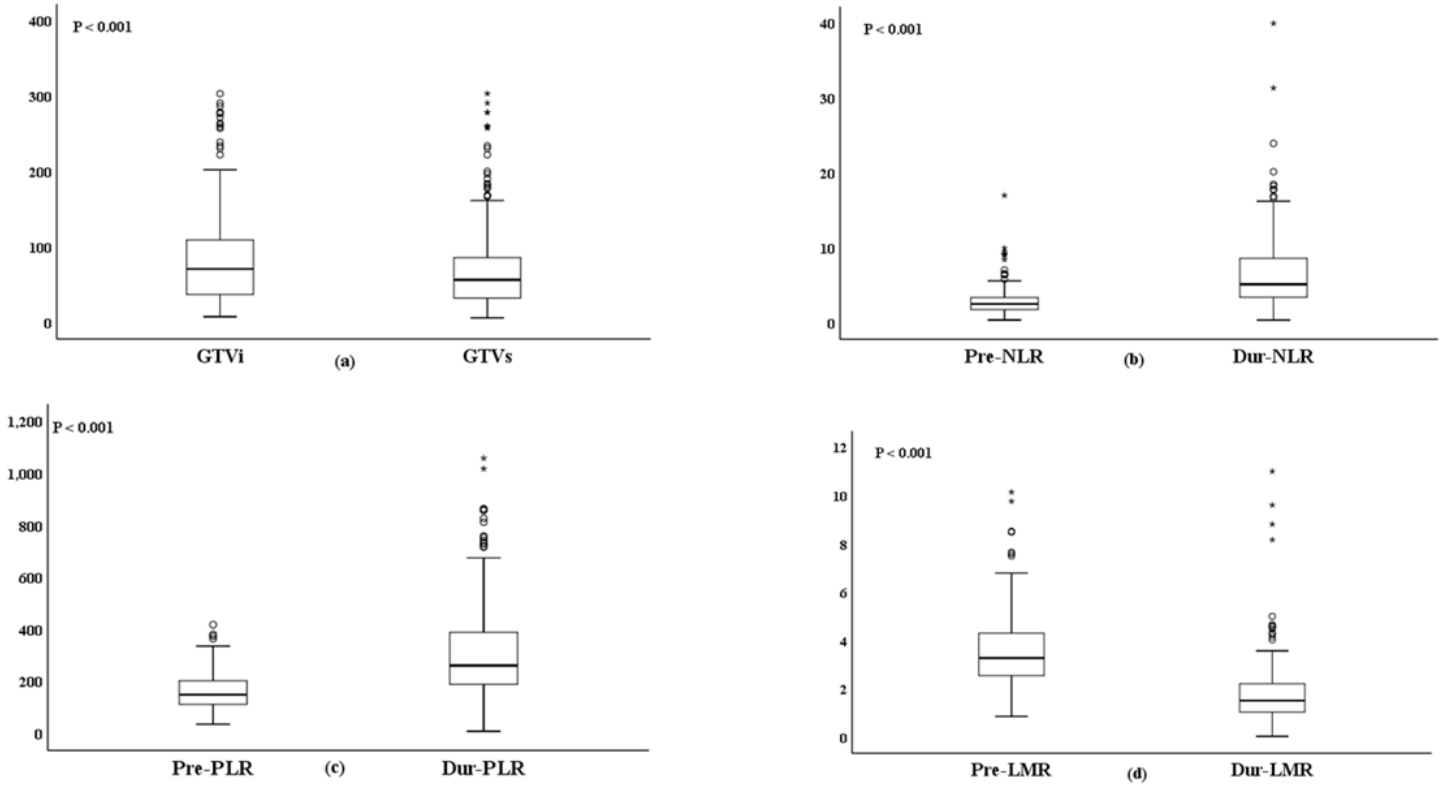

Figure 1

Boxplot of GTV (a), pre/dur-NLR (b), pre/dur-PLR (c), and pre/dur-LMR (d). Wilcoxon's signed rank test, all $P < 0.001$.

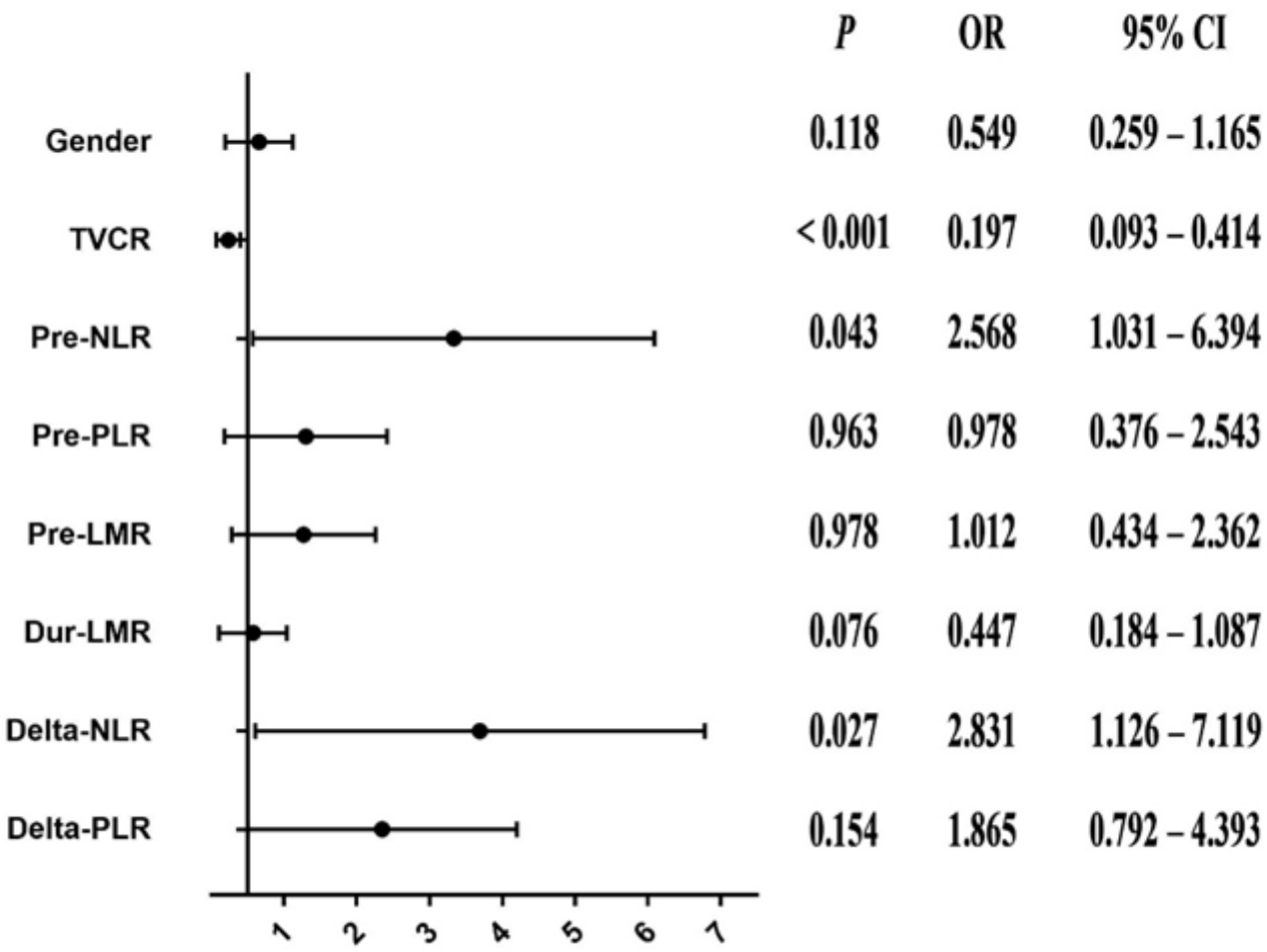

Figure 2

The forest plot of the multivariate analysis of clinical, TVCR, and inflammatory parameters in predicting the early tumor response in elderly patients with ESCC.

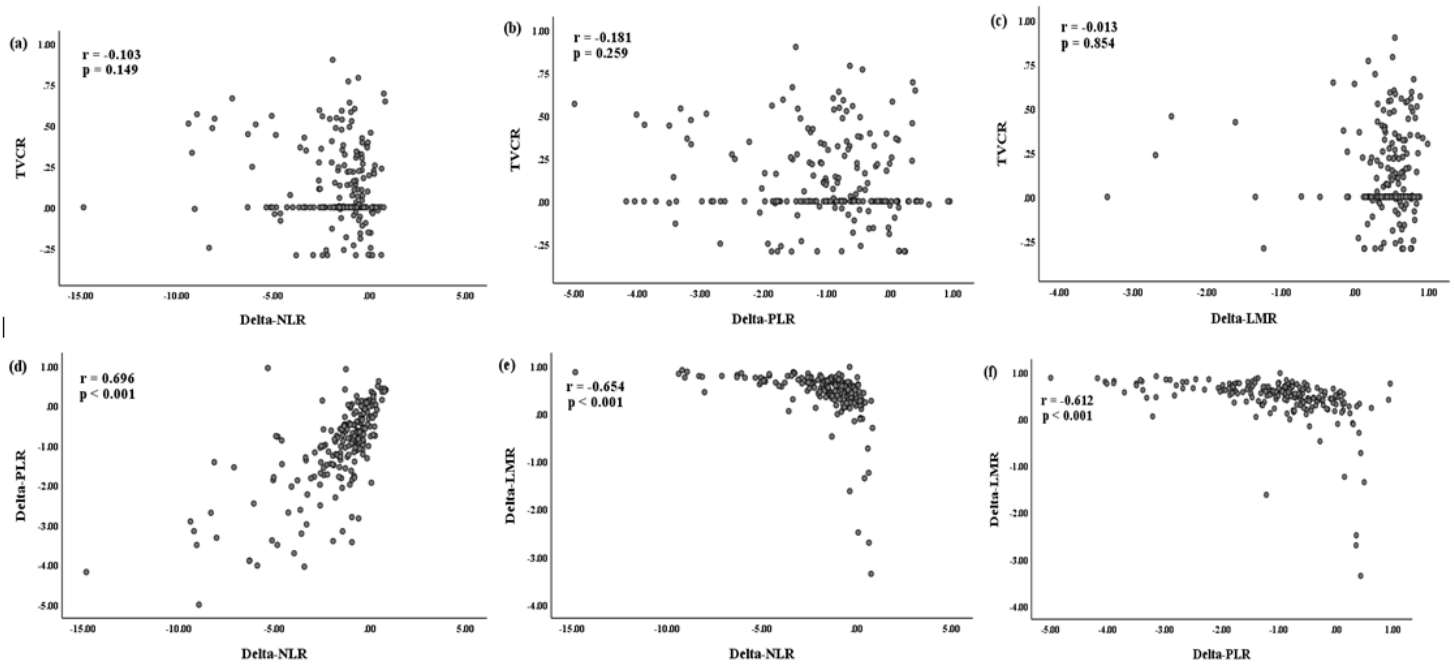

Figure 3

Scatter plot and Spearman's rank correlation coefficient (r) in the delta-IBs and TVCR.

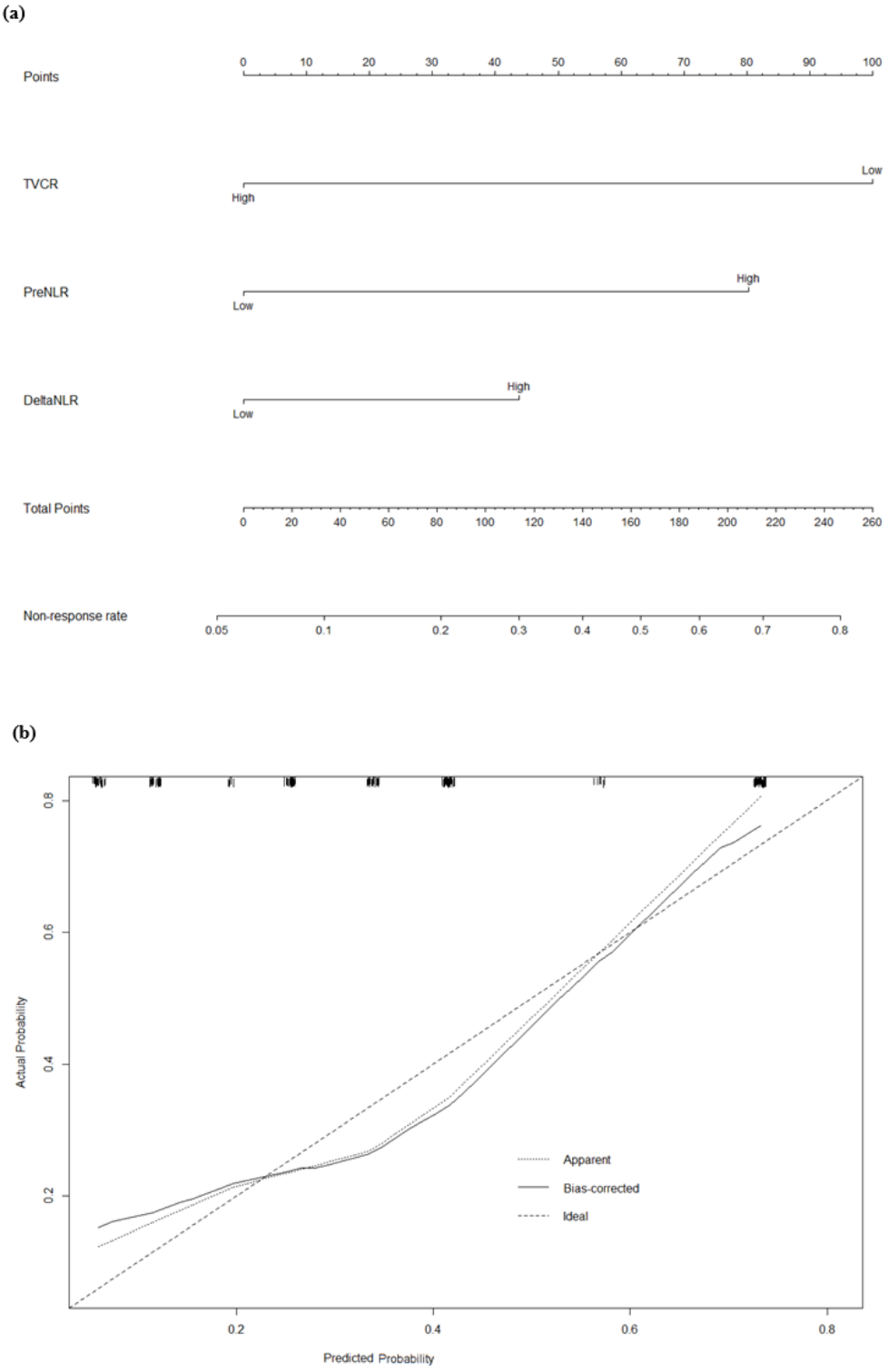

Figure 4

Prediction Nomogram for early tumor response (ETR). (a) Nomogram predicts ETR prediction based on TVCR, pre-NLR, and delta-NLR in elderly patients with ESCC. The nomogram is used by totaling the points identified at the top of the scale for each independent factor. This total point score is then identified on the total points scale to determine the probability of risk prediction. (b) The calibration curve of the nomogram for ETR, and the c-index for ETR prediction was 0.769.