Original Article

Prognostic nomogram integrated baseline serum lipids for patients with non-esophageal squamous cell carcinoma

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Background: Serum lipids have been documented as prognostic biomarkers in several types of cancer, however the prognostic value of serum lipids in non-esophageal squamous cell carcinoma (non-ESCC) is not clear. The purpose of this study was to investigate the prognostic roles of serum lipids in non-ESCC and to establish a novel effective nomogram for overall survival (OS) and disease-free survival (DFS) in patients with non-ESCC.

Methods: We retrospectively analyzed the prognostic values of pretreatment serum lipids, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoproteinA-I (ApoAI), and apolipoprotein B (ApoB) and three lipid derivatives: atherogenic index [AI: (TC–HDL-C)/HDL-C], THR (TG/HDL-C) and LHR (LDL-C/HDL-C) in non-ESCC patients. Prognostic factors predictive of OS and DFS were determined by univariate and cox hazards analysis, and prognostic nomograms were established. The predictive power of independent prognostic factors was compared adopting time-dependent ROC. Comparisons between the nomograms and traditional TNM staging systems were evaluated using the C-index and decision curve analysis.

Results: A total of 180 non-ESCC patients were recruited in this prospective study between January 2006 and December 2016. Four (cancer type, TNM stage, TC, and TG) and five (cancer type, TNM stage, TC, TG, and LDL-C) independent prognostic factors were chosen to generate the nomogram for OS and DFS, respectively. Our results showed that the area under curves (AUCs) of cancer type and TG were higher than TNM stage for OS. For DFS, however, AUCs of cancer type, TG and LDL-C were higher than the TNM stage. The C-index of the nomogram for predicting the OS was 0.69, which was significantly higher than that of TNM stage (0.58, P=0.005). In addition, for DFS, the C-index of the nomogram was significantly higher than that of the TNM stage (0.70 *vs.* 0.60, P=0.001). Furthermore, decision curve analysis showed that the predictive accuracy of the prognostic nomogram for OS and DFS were both higher than the TNM stage.

Conclusions: Our study demonstrated that pretreatment of serum lipids based on the prognostic nomogram could be applied to predict the OS and DFS in non-ESCC patients.

Keywords: Lipids; non-esophageal squamous cell carcinoma (non-ESCC); nomogram; prognosis

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Introduction

Esophageal cancer (EC) is one of common causes of cancer death worldwide (1). EC is the 5th leading cancer in incidence and is ranked 4th for cancer-related mortality in China (2). The prognosis of EC is extremely poor because of the inability to detect the disease at an early stage (3). The predominant histological subtype of EC is esophageal squamous cell carcinoma (ESCC), which accounts for more than 90% of all cases in China (4). Non-esophageal squamous cell carcinoma (non-ESCC) is a rare subtype of EC, which is a rare disease. In addition, studies investigating the prognostic risk factors of non-ESCC are limited. Therefore, studying the prognosis for non-ESCC patients becomes a health problem that needs prompt solutions.

The serum lipid profile including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoproteinA-I (ApoAI), and apolipoprotein B (ApoB). Lipids, as key components of the cellular membrane, as well as the metabolites of organisms, play important roles in processes, including cellular energy storage, structural composition, and signal transduction (5,6). In previous studies, it has been shown that an abnormal lipid metabolism was strongly associated with an increased risk of several types of cancer risk (7-10).

Nomograms have been used as reliable and pragmatic prediction tools to obtain individual risk by integrating some important factors for estimating prognosis in the outcomes of cancers. In addition, nomograms have been proven to provide more precise prediction compared with traditional TNM staging systems (11). In this study, we adopted nomograms to investigate the prognostic values of the serum lipid profile on overall survival (OS) and disease-free survival (DFS) in patients with non-ESCC, In addition, we further visualized it as nomogram for more convenient clinical practice, and then compared the prediction accuracy between prognostic nomograms and traditional TNM staging systems.

Methods

Patients and study design

Here, we performed a retrospective study of non-ESCC patients. Patients were collected at the Sun Yat-sen University Cancer Center (SYSUCC), Guangzhou, China. between January 2006 and December 2016. This study was approved by the Clinical Research Ethics Committee of the Sun SYSUCC, and all patients provided written informed consent at the first visit to our center. Patients included in the analysis met the following criteria: (I) non-ESCC diagnosis confirmed by histopathology, no malignancies except for non-ESCC; (II) patients who did not undergo anti-tumor therapy; (III) no cardiovascular disease, diabetes, and chronic hepatitis; (IV) data were collected one week before treatment.

Clinical information was collected from medical charts and records before treatment at the SYSUCC. Patients were classified according to 7th edition of the AJCC TNM staging guidelines. Clinical characteristics included gender, age, family history, alcohol consumption history, cancer location, histological type, TNM stage, and treatment. The prognostic markers included TC, TG, HDL-C, LDL-C, APOAI, APOB, AI, THR, LHR, and body mass index (BMI). The AI was calculated by the following formula: (TC-HDL-C)/HDL-C (12). The definition of THR was the ratio of TC to HDL-C, and LHR was the ratio of LDL-C to HDL-C.

Clinical outcome assessment and patient follow-up

The patients were followed up via clinic visits and telephone interviews. OS was calculated from the date of the first non-ESCC diagnosis to the date of death due to cancer or by patient censoring on the date of the last follow-up. DFS was defined as the date of the first non-ESCC diagnosis to the date of the first relapse at any site, death due to cancer, or the date of the last follow-up visit. All patients were followed up until death or April 2018 (end of follow-up).

Statistics

Categorical variables were classified based on clinical findings. AI and BMI were transformed into categorical variables based on routine cut-off values in the clinical application. The best cut-off values of other continuous variables were determined by X-tile (13). OS and DFS were estimated by the Kaplan-Meier survival analysis and were compared by using the log-rank test. Variables with a P value of ≤ 0.1 in univariate analysis were subjected to Cox proportional analysis. The predictive accuracy of the independent prognostic factors was evaluated adopting time-dependent receiving operative characteristics (ROC) curve. According to the results of Cox proportional analysis, prognostic nomogram for predicting OS and DFS were established and the predictive accuracy was measured by

Harrell's concordance index (C-index). The larger the C-index, the more accurate prognostic prediction (14), and validated using 1,000 bootstrap re-samplings. Comparisons between the prognostic nomogram and traditional TNM staging systems were evaluated using the C-index and decision curve analysis (15). Statistical analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA) and R 3.4.4 software (Institute of Statistics and Mathematics, Vienna, Austria). P values of <0.05 were considered statistically significant.

Results

Characteristics of all patients

According to our selection criteria, a total of 180 patients were included in the retrospective study. One hundred and forty (77.8%) patients were male, and 40 (22.2%) were female; the median age was 56.3 (range, 24–80) years. The median follow-up for OS and DFS was 18 and 15 months respectively. Baseline characteristics of non-ESCC patients and subgroups were shown in *Table 1*.

The prognostic factors impact on outcomes of non-ESCC

The results of univariate analysis and multivariate Cox hazards analysis were presented in *Table 2*. For OS, the univariate analysis demonstrated that age, cancer type, TNM stage, TC, TG, HDL-C, LDL-C, APOB, AI, THR, and LHR were associated with OS ($P \leq 0.1$). In addition, multivariate Cox proportional analysis showed that cancer type [hazard ratio (HR) =0.62; 95% confidence interval (CI): 0.48–0.79; P<0.001], TNM stage (HR =2.00; 95% CI: 1.29–3.08; P=0.002), TC (HR =3.15; 95% CI: 1.63–6.10; P=0.001), and TG (HR =0.49; 95% CI: 0.29–0.83; P=0.009) were significant independent prognostic factors in non-ESCC patients. For DFS, the univariate analysis showed that cancer type, TNM stage, TC, TG, HDL-C, LDL-C, APOB, AI, THR, and LHR were associated with OS ($P \leq 0.1$). But the multivariate analysis showed that only cancer type (HR =0.67; 95% CI: 0.53–0.85; P=0.001), TNM stage (HR =2.23, 95% CI: 1.47–3.39; P<0.001), TC (HR =3.22, 95% CI: 1.71–6.06; P<0.001), TG (HR =0.48, 95% CI: 0.29–0.79; P=0.004), and LDL-C (HR =0.53, 95% CI: 0.28–0.99; P=0.045) were significantly independently associated with DFS. A forest plot was created to shows the hazard ratios and 95% confidence intervals for DFS and OS according to the Cox proportional hazards regression analysis (*Figure 1*). In line with these findings, the Kaplan-Meier curves for OS and DFS according to cancer type, TNM stage, TC, TG and LDL-C levels were significantly different, as confirmed by the log-rank test (*Figure 2*). Furthermore, the results of time-dependent ROC curve for OS showed that AUCs of cancer type and TG were higher than TNM stage (*Figure 3A*). For DFS, data showed that the AUCs of cancer type, TG, and LDL-C were higher than the TNM stage (*Figure 3B*).

Prognostic nomograms for prediction of OS and DFS

The resulting variables from the Cox proportional analysis were used to build the prognostic nomograms for OS and DFS (*Figure 4*). The prognostic factors of nomogram for OS included four risk factors, including cancer type, TNM, TC, and TG. In addition, the nomogram for DFS included five risk factors (cancer type, TNM, TC, TG, and LDL-C). Each prognostic factor within the nomogram was assigned a point. By sum of the total points from all variables combined with the location at the total point scale allowed us to obtain the probabilities of the outcomes by drawing a vertical line towards the axis labeled "1-, 3- and 5-Year Overall Survival/Disease-Free Survival Probability".

Comparison of predictive accuracy for OS and DFS between nomogram and staging systems

As shown in *Table 3*, our prognostic nomograms displayed better accuracy than TNM stage in predicting both OS and DFS in non-ESCC patients. The C-index of the nomograms for OS was 0.69 (95% CI: 0.64–0.74), which was significantly higher than that of the TNM stage (0.58; 95% CI: 0.53–0.64; P=0.005). For DFS, the C-index of the nomograms was 0.70 (95% CI: 0.64–0.75), which was also significantly higher than that of the TNM stage (0.60; 95% CI: 0.55–0.65; P=0.001). In addition, decision curve analysis showed that both the predictive accuracy of prognostic nomograms for OS and DFS were better than the TNM stage (*Figure 5*).

Discussion

In our study, we investigated the prognostic values of serum lipids and clinical characteristics in non-ESCC patients. Based on the results of Cox hazards analysis, we established nomograms predicting OS and DFS in non-ESCC patients, which showed better predictive accuracy than traditional

Table 1 Main clinical characteristics and parameter in 180 patients with non-ESCC

Characteristics	No. (%)
Gender (n)	
Male	140 (77.8)
Female	40 (22.2)
Age	
≤54 years	57 (31.7)
>54 years	123 (68.3)
Alcohol (n)	
No	125 (69.4)
Yes	55 (30.6)
Family history	
No	140 (77.8)
Yes	40 (22.2)
Stage	
I and II	89 (49.4)
III and IV	91 (50.6)
Treatment	
Surgery only	93 (51.7)
Chemotherapy and/or radiotherapy	40 (22.2)
Surgery and chemotherapy and radiotherapy	47 (26.1)
Location	
Upper	15 (8.3)
Middle	108 (60.0)
Lower	57 (31.7)
Dead	
No	56 (31.1)
Yes	124 (68.9)
Tests	
TC (mmol/L)	
≤6.12	153 (83.6)
>6.12	27 (16.4)
TG (mmol/L)	
≤1.04	81 (44.3)
>1.04	99 (55.7)
HDL-C (mmol/L)	
≤0.95	45 (24.6)
>0.95	135 (75.4)
LDL-C (mmol/L)	
≤3.58	110 (60.1)
>3.58	70 (39.9)
APOAI (g/L)	
≤1.39	145 (79.2)
>1.39	35 (20.8)
APOB (g/L)	
≤0.92	59 (32.2)
>0.92	121 (67.8)
AI	
<4	119 (66.1)
≥4	61 (33.9)
THR	
≤1.10	108 (60.0)
>1.10	72 (40.0)
LHR	
≤3.15	107 (59.4)
>3.15	73 (40.6)
BMI status (kg/m^2)	
<18.5	23 (12.8)
18.5–22.9	81 (45.0)
≥23.0	76 (42.2)

Non-ESCC, non-esophageal squamous cell carcinoma; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOAI, apolipoproteinA-I; APOB, apolipoprotein B; AI, the ratio of TC minus HDL-C to HDL-C; THR, the ratio of TC to HDL-C; LHR, the ratio of LDL-C to HDL-C; BMI, body mass index.

Table 2 Univariate and multivariate cox hazards analysis for OS and DFS in 180 patients with non-ESCC

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value*	HR	95% CI	P value*
OS						
Gender (male *vs.* female)	1.30	0.83–2.04	0.260			
Age (≤54 *vs.* >54)	1.64	1.04–2.60	0.033	1.44	0.89–2.31	0.137
Location (upper *vs.* middle *vs.* lower)	1.11	0.80–1.55	0.542			
Cancer type (SC *vs.* AC *vs.* others)	0.73	0.58–0.92	0.008	0.62	0.48–0.79	0.000
TNM stage (III–IV *vs.* I–II)	1.59	1.07–2.36	0.023	2.00	1.29–3.08	0.002
Alcohol history (yes *vs.* no)	0.79	0.50–1.24	0.300			
Treatment (SUR *vs.* CR *vs.* SUR + CR)	0.97	0.73–1.29	0.819			
TC (≤6.12 *vs.* >6.12)	1.63	0.97–2.73	0.063	3.15	1.63–6.10	0.001
TG (≤1.04 *vs.* >1.04)	0.55	0.37–0.82	0.003	0.49	0.29–0.83	0.009
HDL-C (≤0.95 *vs.* >0.95)	1.76	1.07–2.91	0.027	1.57	0.77–3.21	0.212
LDL-C (≤3.58 *vs.* >3.58)	0.62	0.41–0.94	0.026	0.60	0.31–1.17	0.133
APOAI (≤1.39 *vs.* >1.39)	0.85	0.51–1.41	0.528			
APOB (≤0.92 *vs.* >0.92)	0.54	0.36–0.81	0.003	0.72	0.43–1.21	0.218
AI (<4 *vs.* ≥4)	0.64	0.41–0.99	0.044	1.08	0.47–2.51	0.851
THR (≤1.10 *vs.* >1.10)	0.64	0.42–0.96	0.033	1.75	3.64–0.84	0.136
LHR (≤3.15 *vs.* >3.15)	0.53	0.35–0.81	0.003	0.65	0.31–1.36	0.252
BMI (<18.5 *vs.* 18.5–22.9 *vs.* ≥23.0)	0.94	0.71–1.25	0.662			
DFS						
Gender (male *vs.* female)	1.14	0.74–1.76	0.559			
Age (≤54 *vs.* >54)	1.30	0.86–1.97	0.210			
Location (upper *vs.* middle *vs.* lower)	1.12	0.82–1.54	0.483			
Cancer type (SC *vs.* AC *vs.* Others)	0.81	0.65–1.00	0.054	0.67	0.53–0.85	0.001
TNM stage (III–IV *vs.* I–II)	1.72	1.18–2.50	0.005	2.23	1.47–3.39	0.000
Alcohol history (yes *vs.* no)	0.88	0.58–1.34	0.551			
Treatment (SUR *vs.* CR *vs.* SUR + CR)	0.88	0.67–1.16	0.373			
TC (≤6.12 *vs.* >6.12)	1.56	0.96–2.54	0.073	3.22	1.71–6.06	0.000
TG (≤1.04 *vs.* >1.04)	0.51	0.35–0.74	0.000	0.48	0.29–0.79	0.004
HDL-C (≤0.95 *vs.* >0.95)	1.82	1.13–2.92	0.014	1.81	0.93–3.54	0.082
LDL-C (≤3.58 *vs.* >3.58)	0.64	0.43–0.95	0.038	0.53	0.28–0.99	0.045
APOAI (≤1.39 *vs.* >1.39)	1.02	0.64–1.61	0.941			
APOB (≤0.92 *vs.* >0.92)	0.59	0.41–0.87	0.008	0.86	0.52–1.40	0.537
AI (<4 *vs.* ≥4)	0.62	0.41–0.94	0.025	0.95	0.44–2.04	0.894
THR (≤1.10 *vs.* >1.10)	0.60	0.41–0.89	0.012	1.73	0.87–3.44	0.118
LHR (≤3.15 *vs.* >3.15)	0.54	0.36–0.81	0.002	0.74	0.38–1.43	0.364
BMI (<18.5 *vs.* 18.5–22.9 *vs.* ≥23.0)	1.02	0.78–1.34	0.874			

*, Cox hazard regression model. Non-ESCC, non-esophageal squamous cell carcinoma; OS, overall survival; DFS, disease-free-survival; HR, hazard ratio; 95% CI, 95% confidence interval; SC, small cell carcinoma; AC, adenocarcinoma; SUR, surgery only; CR, chemotherapy and/or radiotherapy; SUR + CR, surgery and chemotherapy and/or radiotherapy; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOAI, apolipoprotein A-I; APOB, apolipoprotein B; AI, atherogenic index; THR, the ratio of TC to HDL-C; LHR, the ratio of LDL-C to HDL-C.

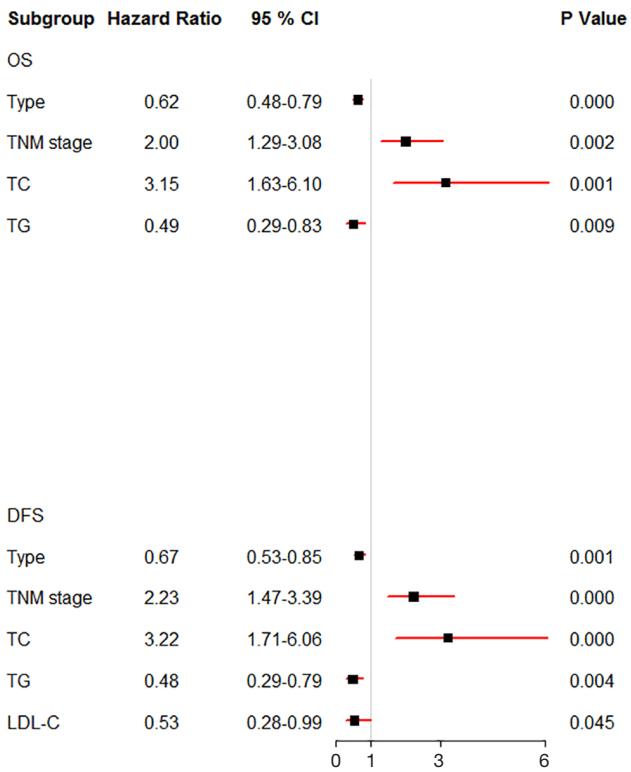

Figure 1 Forest plot showed the hazard ratio and 95% confidence interval for OS and DFS according to the Cox proportional hazards regression analysis. CI, confidence interval; OS, overall survival; DFS, disease-free survival; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

TNM staging systems. By doing this, we could assess the prognosis risk of each patient, and provided individual tailored post-treatment. To our knowledge, this study was the first retrospective analysis to investigate the prognostic roles of pretreatment of serum lipids in non-ESCC patients.

The TNM stage was the most common tool used in prognostic and guiding treatment options of many cancers. However, this system had some controversies, because it was only based on the anatomical extent of cancers, which was not adequate for prognosis without taking into account other prognostic biomarkers (16,17). Moreover, in this study, we integrated TNM stage with baseline serum lipids to predict both OS and DFS in non-ESCC patients, which displayed better accuracy compared to the TNM stage.

Lipids were components of biological membranes, and played several important roles in energy storage and cellular signalling. Abnormal lipid metabolism can affect cell growth, proliferation, differentiation, and motility (18). Fatty acid synthase (FASN) played a crucial role in epithelial-mesenchymal transition (EMT), which had been shown to be closely related to cancer development and metastasis (19). In several studies, high expression of FASN had reported in breast cancer, prostate cancer, ovarian cancer, and colorectal cancer (20-22). In the present study, we confirmed that the serum lipids of TC, TG, and LDL-C were significantly associated with the mortality of non-ESCC patients. These results were similar with previous reports. Cholesterol played an important role in cellular structure and function, especially in the synthesis of steroid hormones, and an abnormal cholesterol biosynthesis might contribute to tumor growth and progression (23). Cholesterol had been shown to modulate several proteins implicated in key cellular signaling pathways to alter the cytoskeleton, cell polarity, and angiogenesis, thereby leading to malignant transformation (24-28). Several studies had reported that serum TC levels were related with the prognosis in lung cancer, breast cancer, prostate cancer, and colorectal cancer (29,30). Our results showed that non-ESCC patients with high preoperative serum TC levels

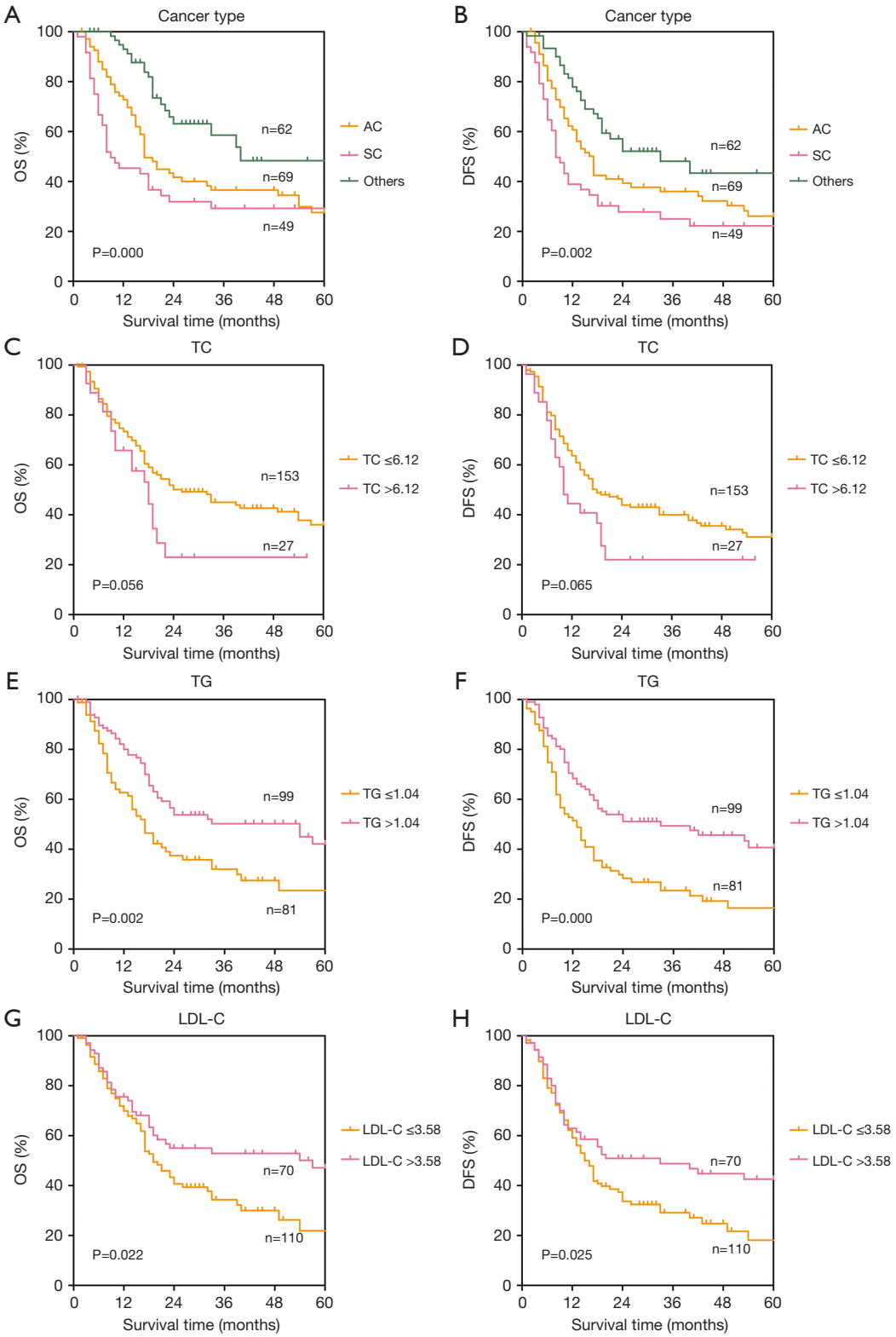

Figure 2 Kaplan-Meier curves for OS and DFS. OS, overall survival; DFS, disease-free survival; AC, adenocarcinoma; SC, small cell carcinoma; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

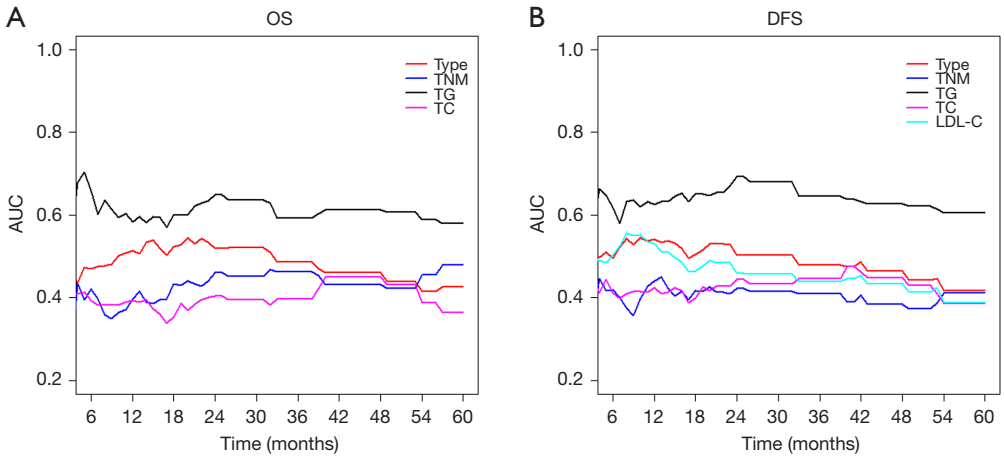

Figure 3 Time-dependent ROC curve for OS and DFS. ROC, receiving operative characteristics; OS, overall survival; DFS, disease-free survival; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

(TC >6.12 mmol/L) had a shorter DFS and OS than the non-ESCC patients with serum TC levels ≤6.12 mmol/L). TG acted as an energy source for neoplastic cells, which could promote cell proliferation and tumor growth (31,32). Moreover, several studies reported that the levels of serum TG were associated with lung cancer, thyroid cancer, rectal cancer, breast cancer, non-Hodgkin's lymphoma, and prostate cancer (9,33). Both DFS and OS of patients with TG levels ≤1.04 mmol/L were significantly shorter than the patients with TG >1.04 mmol/L. LDL and the LDL receptor (LDLR) were prognostic indexes for survival in patients with small cell lung cancer (34). Ox-LDL receptor 1 (OLR1) could activate nuclear factor-κB (NF-κB) target genes, leading to proliferation, migration, and inhibition of apoptosis and *de novo* lipogenesis genes (35). In our study, we found that LDL-C was an independent prognostic factor for DFS in non-ESCC patients. However, for OS, this phenomenon was not observed. Other prognostic factors, such as HDL-C, APOAI, APOB, AI, THR, and LHR were not independent prognostic factor based on the multivariate analysis, which maybe the because of the difference in tumor types, research population, and cut-off values leading to different results.

This study had several limitations. First, this study was a retrospective analysis, so there may be a potential source for selection bias. Second, this was a single-center study of a limited number of patients. Third, this study only focused on the prognostic values of serum lipids, other prognostic factors, such as inflammation-based prognostic markers (36-38), molecular biomarkers (39-41), and coagulation (42,43) were not included. Thus, future validation of our findings in a larger population across multiple centers was warranted.

Conclusions

Overall, we established predictive nomograms based on the pretreatment of serum lipids for OS and DFS in non-ESCC patients, which showed that the predictive accuracy was better than traditional TNM staging system. It could as practical tools for individualized prognostication in clinical medicine.

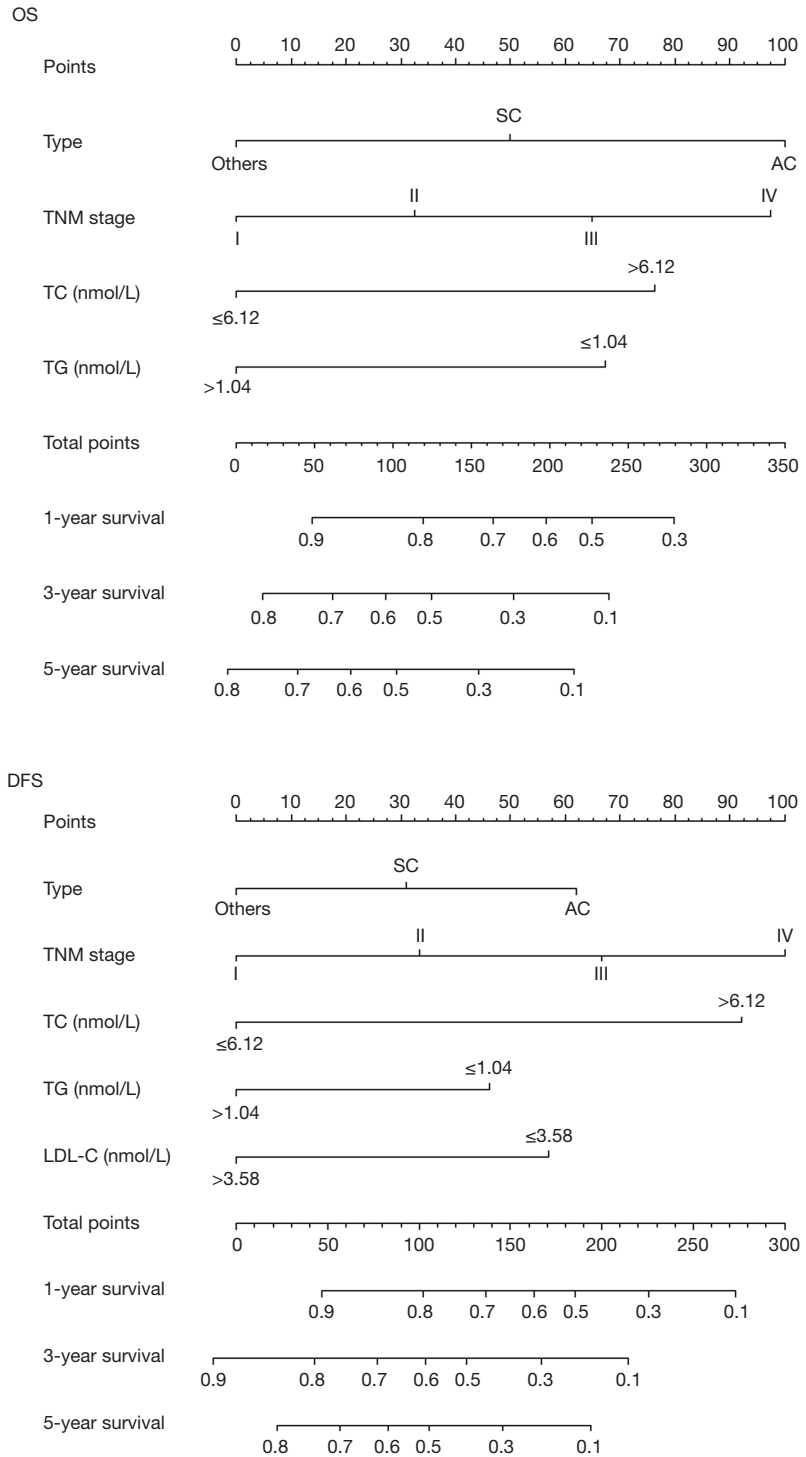

Figure 4 Prognostic nomograms for OS and DFS. OS, overall survival; DFS, disease-free survival; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

Table 3 The C-index of prognostic nomograms and TNM stage for prediction of OS and DFS

Model for survival prediction	C-index (95% CI)	P
Nomogram (OS)*	0.69 (0.64–0.74)	–
Nomogram (DFS)#	0.70 (0.64–0.75)	–
TNM stage (OS)	0.58 (0.53–0.64)	–
TNM stage (DFS)	0.60 (0.55–0.65)	–
Nomogram (OS) *vs.* TNM stage (OS)		0.005
Nomogram (DFS) *vs.* TNM stage (DFS)		0.001

*, nomogram (OS), including four risk factors (cancer type, TNM, TC and TG); #, nomogram (DFS), including five risk factors (cancer type, TNM, TC, TG and LDL-C). OS, overall survival; DFS, disease-free-survival; C-index, concordance index; CI, confidence interval.

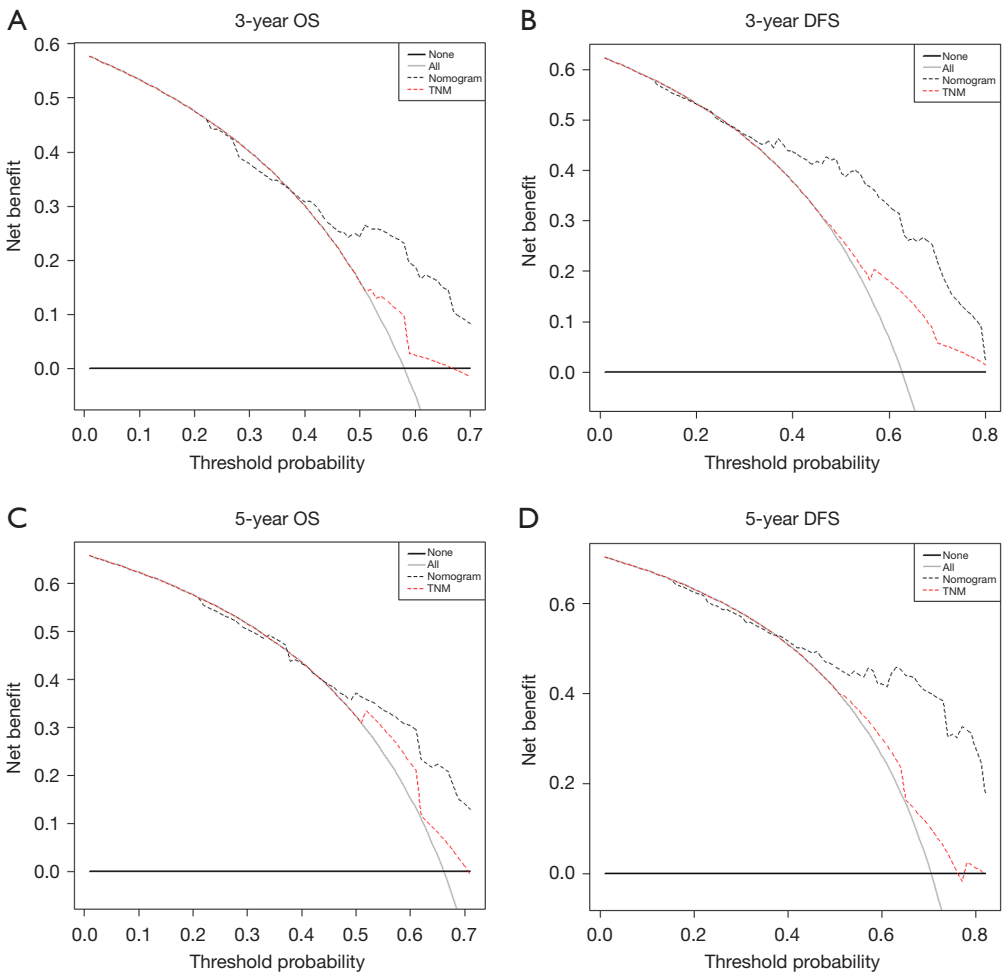

Figure 5 Decision curve analysis the predictive accuracy of prognostic nomograms for OS and DFS. OS, overall survival; DFS, disease-free survival.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The ethics of study was approved by the Clinical Research Ethics Committee of the Sun Yat-sen University Cancer Center (No. GZR2015-015) and written informed consent was obtained from all patients.

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