Research Square

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Levels of Pretreatment Blood Lipids are Prognostic Factors in Advanced NSCLC Patients Treated with Anlotinib

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Research

Keywords: triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), anlotinib, non-small cell lung cancer (NSCLC), prognostic factor, prediction model.

Posted Date: September 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-864724/v1

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Version of Record: A version of this preprint was published at Lipids in Health and Disease on November 20th, 2021. See the published version at https://doi.org/10.1186/s12944-021-01596-5.

Abstract

Background: Anlotinib, a small molecule for multi-target tyrosine kinase inhibition, is the third or further line of defense for treatment of non-small cell lung cancer (NSCLC). Results from an ALTER0303 phase III trial revealed that this drug confers significant survival benefits in patients. Although numerous inflammatory biomarkers play a vital role in treatment, none of them has focused on blood lipids before treatment. Here, we explored the relationship between blood lipids and efficacy of anlotinib, with a view of generating insights to guide future development of convenient and individualized treatment therapies.

Methods: We analyzed basal blood lipids, including triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), and high density lipoprotein (HDL), among other variables before treatment, in 137 patients with advanced NSCLC who received anlotinib as third or further-line treatment at the Ningbo Medical Center Lihuili Hospital, between July 2018 and December 2020. We selected the best cut off value for predicting treatment response, generated survival curves using the Kaplan–Meier method, then applied univariate and multivariate Cox regression analyses to assess predictors of survival.

Results: The entire study population recorded median progression-free survival (PFS) and overall survival (OS) of 4 (95% CI 3.142-4.858) and 8.3 (95% CI 6.843-9.757) months, respectively. We observed statistically significant differences across subgroup, between blood lipid indexes with different efficacies, except in the HDL subgroup. The low Disease control rate (DCR) was associated with significantly high TG, high TC and high LDL ($P = 0.000$). Results from multivariate analysis demonstrated that high TC and high LDL were independently associated with poor PFS or OS ($P \leq 0.003$). We used these results to establish a prediction model, and set high TC or high LDL as risk factors, respectively. The outcomes significant difference between 0 and ≥1 scores in PFS ($P = 0.000$) and OS ($P = 0.012$).

Conclusions: TC and LDL, before anlotinib therapy, were independent prognostic indicators for patients with advanced NSCLC who received this drug as a third or further-line of treatment. In addition, a risk score of 0 was attributed to a combination between low TC and low LDL, and these patients were exhibited excellent efficacy and survival rates.

Introduction

For decades, the rate of non-small cell lung cancer (NSCLC) has ranked highest among malignant tumors, with an overall 5-year survival rate of 20%.[1,2] Most patients are usually diagnosed an advanced stage, making its treatment a challenge. Generally, treatment of NSCLC is stage specific.[3,4] Patients with stage I or II are treated with complete surgical resection, when not contraindicated and mostly obtained good prognosis. However, those with stage III or advanced NSCLC are subjected to local or systemic treatment, including targeted therapy, radiotherapy, chemotherapy or immunotherapy, as these have shown excellent efficacy in patients who missed the opportunity for operation.[5–8] Recently, the targeted therapies based on important driving genes mutation have achieved tremendous survival benefits in patients with advanced NSCLC.[9–12] However, a large number of patients without gene mutation as well as those who became refractory to the targeted therapy, exhibit poor outcomes, necessitating development of optimum treatment options other than the existing above third-line. To date, discrepancies in the third line treatment methods recommended by the NCCN have limited success of curing NSCLC.[13] In China, researchers prefer using an antiangiogenic therapy, called anlotinib, as a third-line of treatment for advanced NSCLC.[15] In fact, results from phase II and III clinical trials have shown that the novel vascular-targeting agent (anlotinib) prolongs PFS patients in NSCLC for another 4 months relative to the placebo. Besides, the findings indicated that the drug confers an overall disease control rate (DCR) of 81%, while the overall response rate (ORR) was only 9.2%. Moreover, the shortest and longest response durations among patients who achieved DCR were 1.5 and at least 18 months, respectively.[14–17] Considering the huge differences in efficacy of anlotinib, we sought to identify biomarkers that regulate this phenomenon in order to improve prediction for the efficacy of anlotinib.

In advanced NSCLC, anlotinib is a small molecule multi-target tyrosine kinase inhibition of VEGFR1-3, FGFR1-4, and PDGFRα-β, among others.[18,19] It plays a crucial role as a third or further line of targeted therapy and has shown excellent efficacy in treating NSCLC during clinical trials. Anlotinib has also been associated with various adverse reactions, including hyperlipidemia among other symptoms.[15,17] Some previous studies have demonstrated that some elements such as CD31-labled activated circulating endothelial, levels of KLK5 and L1CAM, post-treatment hyperlipidemia, post-treatment hypertension status and pre-treatment ECOG scores, might be potential biomarkers for effectively predicting anlotinib in NSCLC patients.[19–22] To date, however, these genetic and cytological factors are expensive and inconvenient to obtain, and none of these evidences have described the potential association between blood lipids before treatment and efficacy of anlotinib in treatment of NSCLC. Therefore, we analyzed differences in basal lipids levels during patient survival as well as the effective ratio, and found that these can be a significant predictor to guide future individualized treatment.

Methods

Patient recruitment and selection criteria

We retrospectively reviewed data from advanced NSCLC patients, who received anlotinib as a third or further-line treatment at the Ningbo Medical Center Lihuili Hospital, between July 2018 and December 2020. Participants were included if they: (1) were pathologically diagnosed with stage IV NSCLC (recurrent or metastatic); (2) had a ECOG score of 3 or below; (3) had no history of heart disease, renal or liver failure, or other contraindications to targeted therapy; (4) underwent treatment with anlotinib as monotherapy more than 2 weeks after at least two previous lines of therapy for advanced disease; and (5) their treatment was assessed according to the RECIST 1.1 criteria. Conversely, participants were excluded if they; (1) exhibited no form of

hypolipidemic therapy prior to treatment; and (2) had a Body Mass Index (BMI) score higher than 30 at baseline. Finally, a total of 137 patients met the aforementioned criteria and were enrolled in the study.

Participant information

We collected each patient's basic information prior to anlotinib administration, including age, gender, and tumor stage among others. We also included patients whose baseline laboratory lipid information, namely TC, TG, LDL-C, and HDL-C, were available within 1 month prior to receiving anlotinib. The unit of measurement for lipids was mmol/L.

Statistical analysis

Categorical variables were compared using either a chi-square or Fisher's exact test. Overall survival (OS) was defined as the time from receiving anlotinib to death or final follow-up date, whereas progression-free survival (PFS) denoted the time from receiving anlotinib to progressive disease (PD) or death resulting from any cause. Both OS and PFS were calculated using the Kaplan–Meier method, and the resulting survival curves compared using the log rank test. Hazard ratios (HR) were estimated using the Cox regression analysis method. Overall response rate (ORR) was taken as the sum of partial response (PR) and complete response (CR), while disease control rate (DCR) was equal to the sum of ORR and stable disease (SD). Correlation between optimal treatment efficiency (%) and baseline lipid stratification was performed using the Chi square test, with multivariate analysis for the most significant variables performed using the Cox regression model. All statistical analyses were performed using packages implemented in R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS software (version 20.00, SPSS, Chicago, IL), with statistical significance set at $P < 0.05$.

Results

Patients' physical and clinical characteristics

A summary of physical and clinical characteristics of the 137 patients included in this study is shown in Table 1. Briefly, all patients' ECOG scores ranged from 0–3, and none of them had received treatment to either increase or decrease their blood lipid levels. The group's median age was 62 years old, while clinicopathological diagnosis revealed that all patients presented more than 4 stages. Squamous and non-squamous cell carcinoma accounted for 51.8 and 48.2%, respectively, and the median line of treatment using anlotinib was 3. The other three items alongside their median values are also listed in Table 1.

Table 1
Physical and clinicopathological characteristics of the 137 patients included in the present study

Patient characteristics	N = patients (%)
All	137
Age (years)	
< 65	83 (60.5%)
≥ 65	54 (39.5%)
Gender	
Male	99 (72.3%)
Female	38 (27.7%)
Histology	
squamous	71 (51.8%)
non-squamous	66 (48.2%)
PS (ECOG)	
0–1	95 (69.3%)
2–3	42 (30.7%)
Driver gene	
wild	108 (78.8%)
mutation	29 (21.2%)
Metastasis sites	
≤ 3	73 53.3%)
> 3	64 (46.7%)
Line(s) of treatment	
3	78 (56.9%)
> 3	59 (43.1%)

Optimal cut-off values for lipids

We generated ROC curves to determine the optimal cut-off values for the aforementioned blood lipids in all patients under this study. For TG, the optimal cut-off value for TG was 1.82 with an area under the curve (AUC) of 0.639 (95% CI: 0.527–0.751), that for TC was 4.77 with an AUC of 0.700 (95% CI: 0.606–0.795), whereas those for LDL and HDL were 2.965 (95% CI: 0.592–0.797) and 1.095 (95% CI: 0.431–0.654), respectively, with corresponding AUC values of 0.695 0.543. A summary of ROC curves is presented in Fig. 1.

Curative effect analysis

No patient from the analyzed cohort achieved CR (0%), thus the ORR (4%) was thought to be equal to the PR value (4%). SD took a majority of the response. We calculated the curative effect among different lipids groups layered based on their respective optimal cut-off values, and these are listed in Table 2. For TG, a total of 100 patients reached DCR, with the low group (TG < 1.82) comprising a significantly higher proportion (59.1%) relative to the high group (13.9%, $P = 0.000$). Conversely, the high group exhibited the highest proportion of PD (13.9%), which was significant different from those obtained in PR and SD ($P = 0.002$). Results from LDL corroborated those of TG and TC (Table 2). However, we observed no significant differences in the curative effect in the HDL group.

Table 2
Associations among the four lipids with treatment response

Response	n	%	TG			TC			LDL			HDL		
			< 1.82	≥ 1.82	*P* value	< 4.77	≥ 4.77	*P* value	< 2.965	≥ 2.965	*P* value	< 1.095	≥ 1.095	*P* value
CR	0	0												
PR	6	4	5 (3.6%)	1 (0.7%)	0.002	4 (2.9%)	2 (1.4%)	0.000	5 (3.6%)	1 (0.7%)	0.000	2 (1.4%)	4 (2.9%)	0.218
SD	94	68.6	76 (55.5%)	18 (13.1%)		67 (48.9%)	27 (19.7%)		73 (53.3%)	21 (15.3%)		52 (38%)	42 (30.1%)	
PD	37	27	19 (13.9%)	18 (13.1%)		8 (5.8%)	29 (21.2%)		12 (8.8%)	25 (18.2%)		15 (10.9%)	22 (16.1%)	
ORR	6	4												
DCR	100	72.6	81 (59.1%)	19 (13.9%)	0.000	71 (51.8%)	29 (21.2%)	0.000	78 (56.9%)	22 (16.1%)	0.000	54 (39.4%)	46 (33.6%)	0.162

Identification of prognostic factors of layered baseline lipids in the overall population

The study population had a median follow-up time of 16.3 months, and all patients exhibited recurrence. On the other hand, the entire population recorded median PFS and OS of 4 (95% CI 3.142–4.858) and 8.3 (95% CI 6.843–9.757) months, respectively. Results from univariate analyses revealed that TG and TC and LDL were all significant risk factors for PFS, while TC and LDL were risk factors for OS (Table 3). Incorporating the significant risk factors into multivariate analysis demonstrated that high TC and high LDL was independently associated with poor PFS (Table 4). For the results of TC in Fig. 2B and Fig. 3B, moreover, the high TC group showed shorter median PFS and OS rates, at 2 and 6 months, respectively, compared to those in the low group, namely 5.9 and 9.9 months, respectively (P_{PFS} = 0.000, P_{OS} = 0.003). Similarly, the high LDL group exhibited significantly shorter median PFS (Fig. 2C) and OS (Fig. 3C) compared with the low group (1.75 months *vs* 5 months, P_{PFS} = 0.000; 5.8 months *vs* 9.7 months, P_{OS} = 0.029). The high TG group exhibited significantly shorter median PFS (Fig. 2A) compared with the low group (2.0 months *vs* 5.0 months, P = 0.004) while there was no significant difference in OS between the high and low TG groups (Fig. 3A). Notably, we found no statistically significant differences in neither PFS (Fig. 2D) nor OS (Fig. 3D) between the high and low HDL groups (Table 4).

Table 3
Results of univariate analysis of factors associated with progression-free and overall survival rates

Variable (N = 137)	PFS			OS		
	HR	95%CI	Univariate (*P* value)	HR	95%CI	Univariate (*P* value)
Age (years)	1.057	0.756–1.505	0.713	0.897	0.508–1.324	0.564
< 65						
≥ 65						
Gender	1.162	0.797–1.694	0.435	1.067	0.697–1.634	0.764
Male						
Female						
Histology	1.198	0.855–1.679	0.294	1.165	0.799-1.700	0.428
squamous						
non-squamous						
PS (ECOG)	1.168	0.810–1.584	0.405	1.453	0.975–2.165	0.066
0–1						
2–3						
Driver gene	1.002	0.663–1.515	0.993	1.147	0.726–1.811	0.557
wild						
mutation						
Metastasis sites	0.932	0.667–1.316	0.707	0.997	0.685–1.453	0.989
≤ 3						
> 3						
Line(s) of treatment	1.063	0.758–1.494	0.725	0.768	0.523–1.127	0.178
3						
≥ 3						
TG	1.689	1.152–2.475	0.007	1.431	0.949–2.159	0.088
< 1.82						
≥ 1.82						
TC	2.647	1.655–3.777	0.000	1.773	1.213–2.592	0.003
< 4.77						
≥ 4.77						
LDL	3.056	2.091–4.495	0.000	1.532	1.040–2.257	0.031
< 2.965						
≥ 2.965						
HDL	1.085	0.773–1.522	0.637	0.910	0.623–1.328	0.624
< 1.095						
≥ 1.095						

Table 4
Results of multivariate analysis of significant factors associated with progression-free survival

Variable (N = 137)	PFS		
	HR	95%CI	Multivariate (*P* value)
TC	1.841	1.187–2.857	0.006
< 4.77			
≥ 4.77			
LDL	2.133	1.336–3.406	0.002
< 2.965			
≥ 2.965			

The prediction model by TC and LDL value

We incorporated the significant factors, namely baseline TC and LDL values, into multivariate analysis to identify independent prognostic factors using. The high value was equivalent to a risk factor, and for the presence of each a risk factor, the patients' risk score was raised by 1. Based on this, we found that patient's scores ranged from 0 (extremely favorable) to 2 score (extremely unfavorable). Results indicated that scores of 0, 1 and 2 were significantly associated with PFS (*P* = 0.000, 95%CI 3.142–4.858) and OS (*P* = 0.017, 95%CI 6.843–9.757). Specifically, 0 score was associated with superior survival rates while relative to 1 and 2 (Table 5). However, the survival rates showed a cross connection among the three group (Fig. 4A, 4B). Additionally, in grouped comparison, 0 score exhibited no significant differences with score 1 in mPFS (*P* = 0.198). Therefore, we combined scores 1 and 2 groups into a high score group (≥ 1 score), then re-calculated the survival between 0 score and ≥ 1 score group. Results revealed significant differences in PFS and OS between the two groups as well as the survival curve (Fig. 4C **and D**).

Table 5
Median progression-free survival (mPFS) and median overall survival (mOS) for different scores in patients stratified according to presence of different independent prognostic factors obtained from multivariate analysis (TC and LDL)

Prognosis	Score			95%CI	*P* value
	0(n = 75)	1(n = 19)	2(n = 43)		
mPFS (months)	5.8	4.8	1.5	3.142–4.858	0.000
mOS (months)	9.9	7.9	5.6	6.843–9.757	0.017

Note: The unit of measurement for lipids is mmol/L. A score of 0 represents low TC (< 4.77) and low LDL (< 2.965) at baseline; a score of 1 denotes low TC (< 4.77) and high LDL (≥ 2.965) or low LDL (< 2.965) and high TC (≥ 4.77) at baseline; whereas 2 represents high TC (≥ 4.77) and high LDL (≥ 2.965) at baseline.

Discussion

Angiogenesis occupies an absolute position in tumorigenesis and development, paving way for restraining of tumor growth by blocking of the process.[23, 24] Particularly, VEGFs and VEGFRs are key family members of regulators of angiogenesis, whose combination reportedly promotes angiogenesis behavior.[25–27] Anlotinib, an oral multi-targeted tyrosine kinase receptor inhibitor, has been shown to actively regulate anti-angiogenesis and selectively inhibit VEGFR (2/3), PDGFR (α/β), and FGFR (1–4), as well as other targets.[17–19] Numerous studies have demonstrated the role of VEGFs in lipid and lipoprotein metabolism. Particularly, VEGF-A is significantly upregulated during occurrence of heart and blood vessel diseases,[28, 29] whereas VEGF-B is basically homologous with VEGF-A.[30] In the past, VEGF-C/D were thought to be associated with lymphangiogenesis, with several studies demonstrating that VEGF-D further plays a crucial role in lipid metabolism via its endothelial cell receptors VEGFR-2/3.[31, 32] Furthermore, immunohistochemical results have confirmed that VEGF-A, VEGF-D, VEGFR-1 and VEGFR-2 are elevated in hyperlipidemic rabbits.[33] Despite VEGFA-D and VEGFR1-4 belonging to the same receptor family, their functions in blood lipids are complicated and contradictory while their regulation is controlled by unknown factors. A part from that, extremely abundant cancer cells were known to exhibit intense lipid and cholesterol and cholesterol attraction, which are satisfied by increasing food intake or external carbohydrates, lipoelasticity or lipid synthesis[33– 35]. Importantly, this aberrant lipid metabolism not only influences the primary tumor, but also affects exogenous lipid production by the tumor microenvironment thereby predisposing body tissues to malignancy.[36, 37] Based on these findings, it is evident that lipid metabolism processes are often upregulated in cancer.

Results of the present study showed that high levels baseline lipids, mainly TC and LDL, shorten survival rates of patients and affects efficacy of anlotinib therapy. Specifically, the present study population exhibited median OS and PFS times of 8.3 and 3.1 months, respectively, which were slightly shorter

than the corresponding 5 (PFS) and 9.6 (OS) months from ALTER0303.[15] This may be attributed to the fact that the patients included in our research were all diagnosed at stage 4 and were treated with anlotinib as a third or further line, relative to those in ALTER0303 who were at stage 3 or using anlotinib as a second-line therapy. Previous studies have shown that several factors, such as ECOG scores before treatment, hyperlipidemia and hypertension status after treatment, respectively, played some predictive roles in prognosis of anlotinib therapy mainly due to occurrence of adverse reactions.[19, 20] However, we found no study that combined basal lipids with prognosis. In the present study, there was no significant difference in survival analysis among different ECOG scores, the reason might be that in order to eliminate data skew, we divided ECOG score 0–1 into a group and 2–3 into another resulted from the lack of score 0 patients, but the other researchers arranged ECOG score 0 into a group appreciably and 1–2 into another because there was no score 3 in their data. We initially analyzed efficacy of anlotinib therapy with different basal lipids level, and results from multivariate analysis demonstrated that high TC and LDL were independent predictors for poor PFS. Moreover, survival data also confirmed that the high basal TC and LDL might result in poor efficacy in curing NSCLS patients treated with anlotinib. Our retrospective study enrolled patients with comparatively advanced status, which may have led to very poor natural prognosis. In addition, the different treatments of posterior line may have influenced the overall survival rates to a varying degree. Based on the reason for the divergence of the multivariate analysis registering as three factors in PFS but just one factor in OS, we established a scoring system with scores ranging from 0 to 2, and comprising basal TC and LDL. During this process, we expected that a high value would represent a high risk and anticipated the significant difference according this model. Although we observed significant differences in PFS (P = 0.000) and OS (P = 0.017) among the 3 groups, the PFS curve with scores of 0 and 1 was so close together that it generated a negative result between them (P = 0.198) during stratified analysis. Considering that the small sample size might have led to the lack of score 1 patients, we reconsidered a high score group (≥ 1 score) comprising both 1 and 2 score groups, and found statistically significant difference in PFS (P = 0.000) between 0 and ≥ 1 scores, as well as in OS (P = 0.012).

Based on the calculated results, we hypothesized that the basal TC and LDL accounts could be potential predictors for choosing anlotinib to treat NSCLC. However, the study had some limitations. Firstly, all patients recruited herein were at an advanced NSCLC stage, suggesting that many uncertain factors may have impacted the observed results. In addition, their diet and nutritional status at that time might also have influenced the recorded lipid indexes. Secondly, it is possible that the subsequent therapy after anlotinib, which involved radiochemotherapy and immunotherapy, may have potentially affected prognosis. Lastly, our sample size was relatively small and may have resulting in a minimal PR and 1 score group, thereby introducing potential bias. And the lack of validation analysis with independent data sets would led to the necessity of high level validation of prediction models in future.

Conclusion

In summary, basal TC and LDL are excellent biomarkers for evaluating patient response to anlotinib treatment during treatment of advanced NSCLC. Patients with high levels of baseline TC and LDL, prior to anlotinib therapy, exhibit both inferior curative efficacy and survival rates than those in the low group. Taken together, the findings indicate that changes in blood lipids during anlotinib treatment are potential prognostic factors for NSCLC.

Ethics statement

The study was approved by the Ningbo Medical Center Lihuili Hospital ethics committee. The authors obtained the necessary rights to use patient information for the purpose of the research. The research is a retrospective review, patient names or other identifiers pertinent to patient privacy were anonymized or confidentially maintained.

Declarations

Ethics statement

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Author contributions

Tian Chen and Mengqiu Tang contributed to the conception and design of the study. Chao Song and Mengqiu Tang wrote the article together. Gaofeng Liang, Xiaoyu Xu and Chen Wang contributed to thacquisition and analysis of the data. Zhanchun Zhang and Tian Chen participated in revising of the article.

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Figures

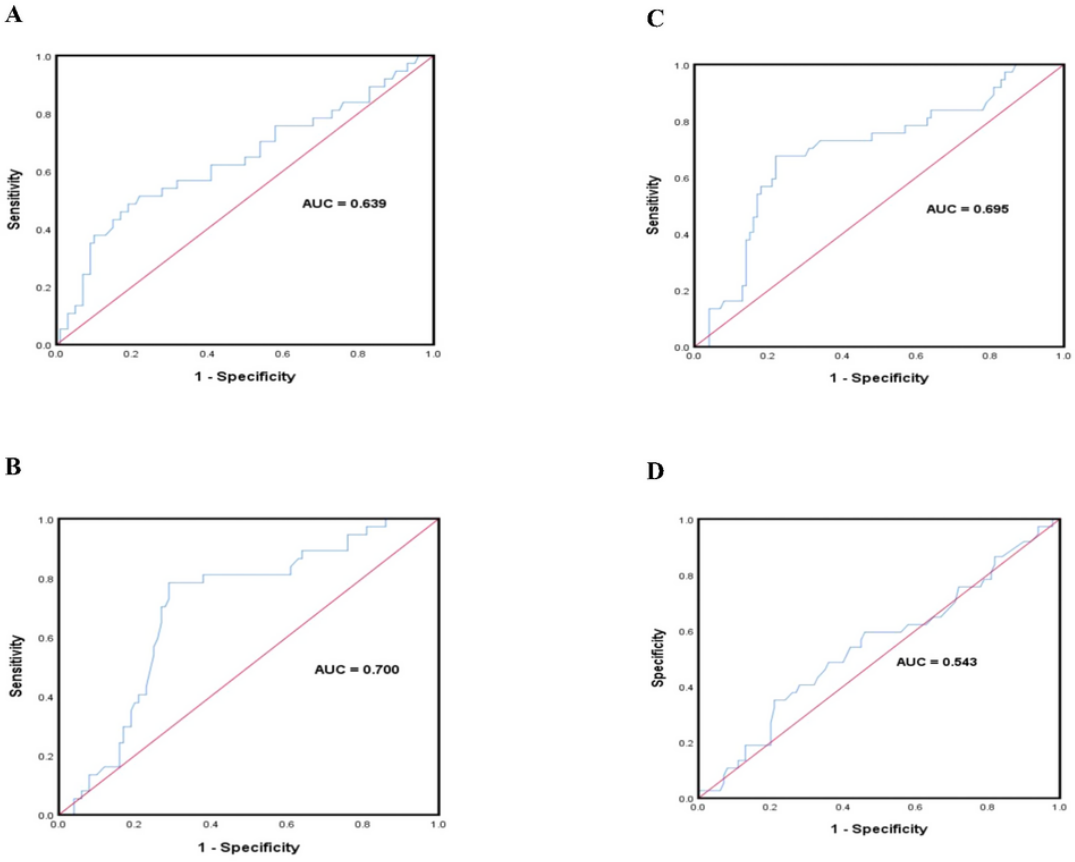

Figure 1

Receiver operating curves showing response to treatment and optimum cut-off values for TG (A), TC (B), LDL (C), HDL (D).

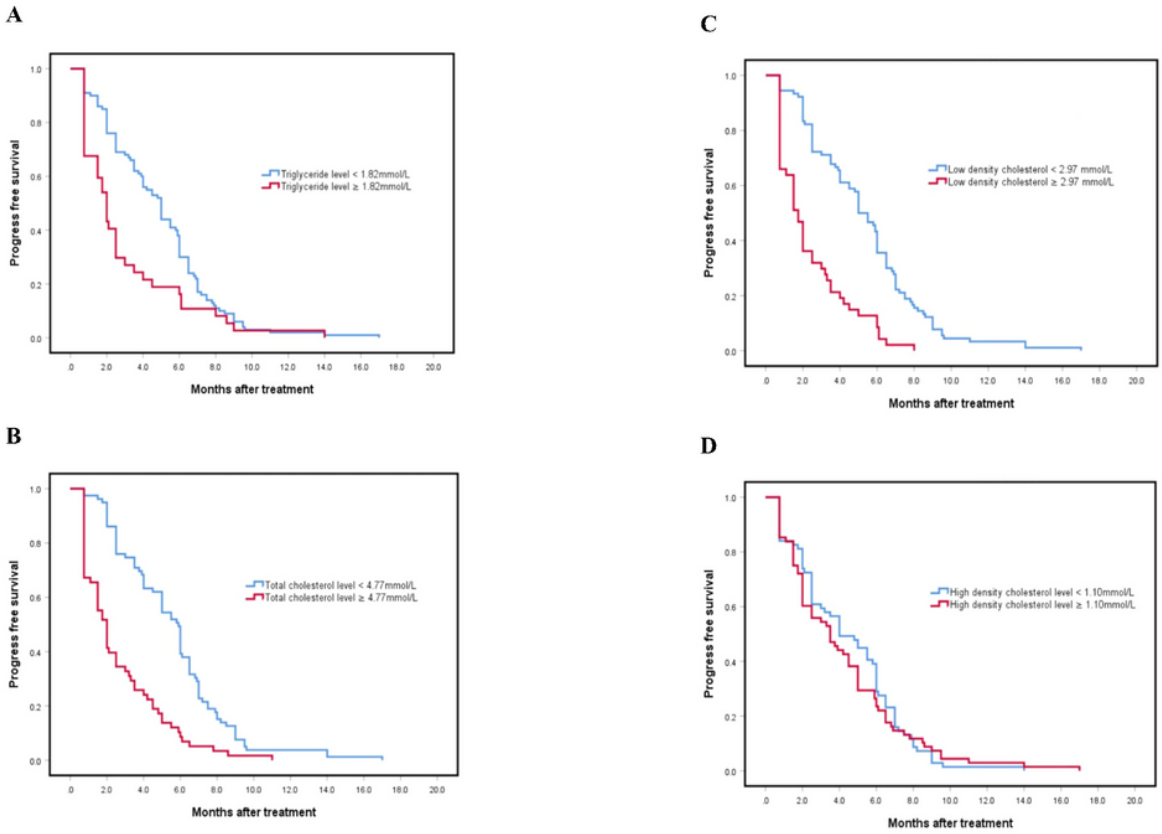

Figure 2

Relationship between TG, TC, LDL and HDL with progression-free survival rates (PA = 0.004, PB = 0.000, PC =0.000, PD=0.619).

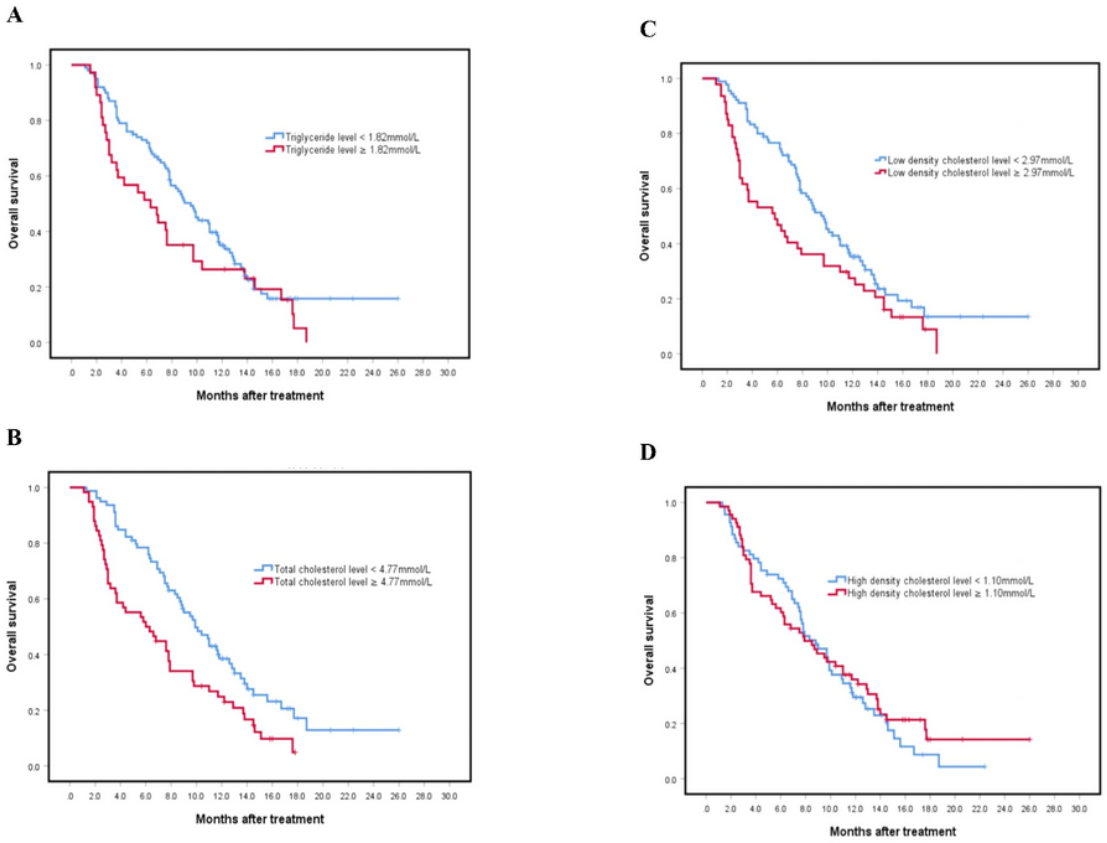

Figure 3

Relationship between TG, TC, LDL and HDL with overall survival rates (PA = 0.084, PB = 0.003, PC = 0.029, PD = 0.622).

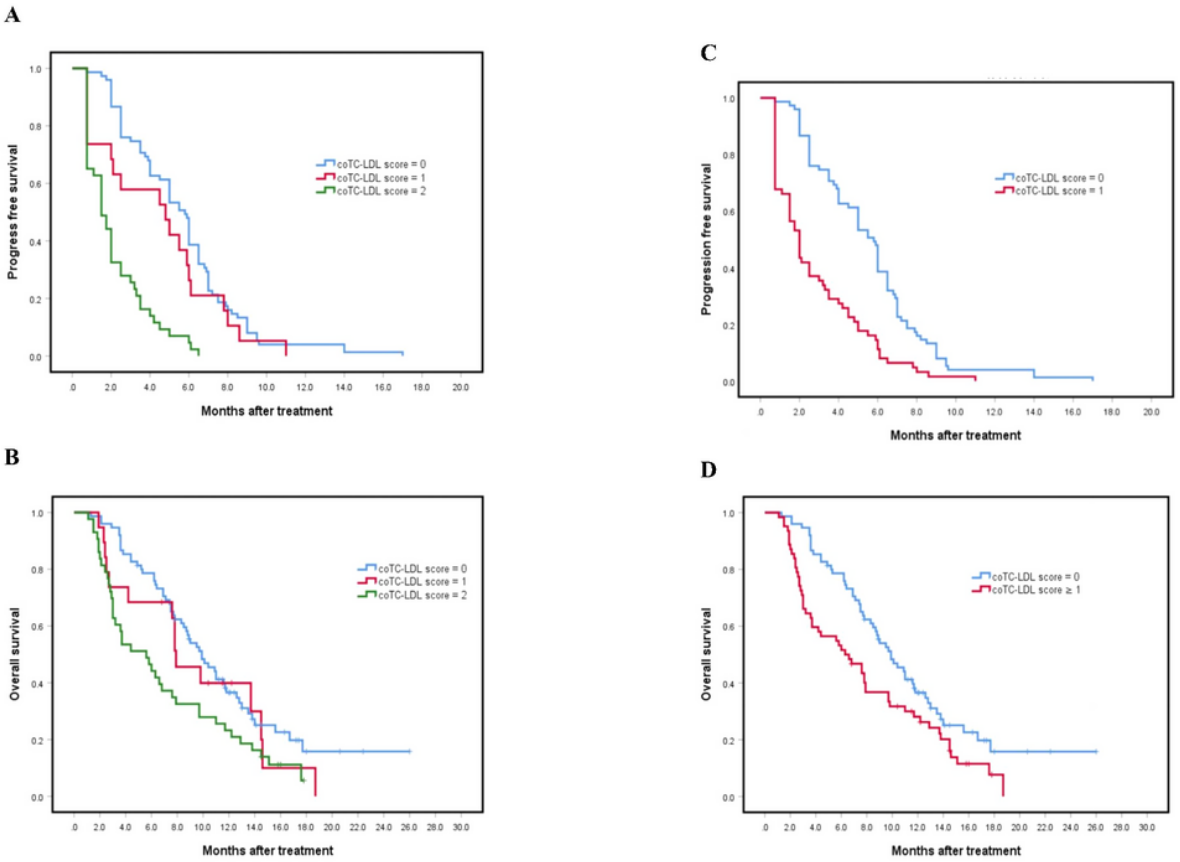

Figure 4

Relationship between scoring groups with PFS and OS (PA = 0.000, PB = 0.017, PC = 0.000, PD = 0.012)