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OR 6251

Prognostic value of serum high-density lipoprotein cholesterol in patients with gallbladder cancer

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ABSTRACT

Objectives: the aim of this study was to evaluate the prognostic significance of preoperative serum lipid in patients with gallbladder cancer (GBC).

Methods: ninety-nine patients with GBC between October 2009 and December 2013 were reviewed in this retrospective study. Total serum cholesterol (TC), total triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein A (Apo-A), apolipoprotein B (Apo-B) and free fatty acids (FFA) were measured before surgery. The correlation of serum lipid levels with clinical data, including gender, age, tumor size, lymph nodes metastasis, tumor differentiation, distant metastasis and TNM stage were analyzed by univariate and multivariate survival analysis to evaluate independent prognostic factors.

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Results: compared with the normal HDL-C group (n = 57), the overall survival rate among GBC patients with low HDL-C levels (n = 42) was reduced ($p < 0.05$). However, there were no significant differences in overall survival for patients with different levels of TC, TG, Apo-A, Apo-B, LDL-C or FFA. The serum level of HDL-C was associated with TNM stage ($p < 0.05$) and distant metastasis ($p < 0.001$). The multivariate prognosis analysis showed that HDL-C and lymph nodes metastasis were independent prognostic factors ($p < 0.05$). A prognostic evaluation model based on HDL-C and lymph nodes metastasis was established.

Conclusion: preoperative serum HDL-C level was closely associated with distant metastasis of patients with GBC. HDL-C level may be a valuable prognostic factor for GBC patients. The combination of HDLC and lymph nodes metastasis can better predict the prognosis of GBC.

Key words: Gallbladder cancer. High density lipoprotein cholesterol. Serum lipid. Prognosis. Overall survival rate.

INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary tract malignancy and accounts for 80-85% of total biliary tract cancer cases (1). Epidemiological studies show that the incidence of GBC has obvious geographical and ethnic differences. Asia is a region with a high incidence of GBC, especially South Korea (2). According to one study, the incidence of GBC in China in 2014 was 2.37/100,000, which was higher than the world average (2.2/100,000), as well as the average incidence in developing countries (2.2/100,000) (3). More importantly, the burden of GBC is highest in China compared to other countries due to large population base (4). Early diagnosis of GBC is extremely difficult as clinical symptoms of GBC are similar to those of cholecystitis and cholelithiasis (5). At the same time, GBC is prone to lymph node and distant metastasis, thus the prognosis of GBC is very poor. This also means that the mean survival time of GBC is around six months, while the five-year survival rate is only 5% (2).

In view of this, many clinical and scientific studies have been performed to identify

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the corresponding markers that can accurately predict the prognosis of GBC. Unfortunately, no clear prognostic factors for GBC have been identified so far. Lee et al. (6) reported that CA 19.9 may be a survival predictor in patients with GBC. However, the criteria for inclusion of this study were only unresectable cases and not all patients diagnosed with GBC. Therefore, finding a reliable, easily accessible and economical prognostic indicator on a larger scale is of the upmost importance.

Many studies have reported the relationship between serum lipid levels and cancer prognosis (7-10). These studies have demonstrated that one or more of these lipids could be predictors of cancer prognosis. The serum lipids involved include total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), apolipoprotein A (Apo-A), apolipoprotein B (Apo-B) and free fatty acids (FFA). HDL-C has a favorable influence on the endothelial function and atherosclerosis prevention (11). However, its role in cancer, especially GBC, and its relationship with prognosis are still not fully understood.

The objective of this study was to evaluate the role of serum lipid levels as prognostic factors in GBC.

PATIENTS AND METHODS

Patients

A retrospective study of patients that underwent surgical treatment for GBC was performed at the Eastern Hepatobiliary Surgery Hospital, Shanghai (EHBH), between October 2009 and December 2013. A flow chart of the evaluated patients is shown in figure 1. The diagnosis of GBC is made based on imaging tests, mainly computed tomography (CT) scan and abdominal magnetic resonance imaging (MRI), although endoscopic ultrasound (EUS) may be performed in some cases. Radical resection of the gallbladder included cholecystectomy with a limited hepatic resection (non-anatomical 2-3 cm gallbladder bed resection or formal segment 4b + 5 resection) and regional lymphadenectomy. An enlarged lymphadenectomy or enlarged hepatectomy, choledochotomy plus cholangioenterostomy or adjacent organ resection may be performed if necessary. Palliative surgery included cholecystectomy with or without hepatic resection, cholangioenterostomy or only a

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lymph biopsy or abdominal nodule biopsy. GBC was confirmed in all patients using histological samples of surgical specimens. The study was approved by the Institutional Ethics Committee of the EHBH and all participants signed a written informed consent form. The exclusion criteria were as follows: a) the patients were not suitable for surgical treatment and lacked a histological diagnosis; b) a lack of serum lipid results; c) incomplete clinical and pathological data; d) no follow-up had been performed; e) the patients had other tumors; and f) the patient had received other treatments such as chemotherapy and radiotherapy after surgery. Patients who received other treatments after surgery were excluded due to the influence of other treatments such as chemotherapy on the prognosis of GBC (12).

Study grouping and data collection

Patients were divided into a low group and normal group based on recommended threshold levels of serum HDL-C and Apo-A. Similarly, the patients were divided into a high group and normal group based on recommended thresholds levels of serum TC, TG, Apo-B, LDL-C and FFA. The groups were defined as follows: high TC group (> 5.2 mmol/l) and normal TC group (≤ 5.2 mmol/l); high TG group (> 2.26 mmol/l) and normal TC group (≤ 2.26 mmol/l); low HDL-C group (< 0.91 mmol/l) and normal HDL-C group (≥ 0.91 mmol/l); high LDL-C group (> 3.1 mmol/l) and normal LDL-C group (≤ 3.1 mmol/l); low Apo-A group (< 120 mg/dl) and normal Apo-A group (≥ 120 mg/dl); high Apo-B group (> 114 mg/dl) and normal Apo-B group (≤ 114 mg/dl); and high FFA group (> 0.6 mmol/l) and normal FFA group (≤ 0.6 mmol/l). The clinical characteristic of the patients, including age, gender, histological grade, tumor size, lymph nodes, TNM stage and distant metastasis were evaluated. Surgical pathological and clinical results were evaluated according to the 2017 version of the eighth American Joint Committee on Cancer staging system.

Peripheral venous blood samples of patients with GBC were collected before surgery and used to determine the level of TC, TG, HDL-C, Apo-A, Apo-B, LDL-C and FFA.

Statistical analysis

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Measurement variables were expressed as the mean ± standard deviation (SD) and analyzed using the t test. Categorical variables were compared using the Chi-squared test or Fisher's exact test. The survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazard model was used for multivariate factor analysis. Bivariate correlation analysis was performed to determine the candidate variables before the multivariate factor analysis. The Cox model was also used to obtain the regression coefficient of the variable, which were named β1, β2, β3… βm, respectively. The formula of prognostic index (PI) was obtained as follows: PI = β1X1 + β2X2 + β3X3… + βmXm, where X represents the value of the variable. To verify the accuracy of the prediction ability of this prognosis model, the R software was used to calculate the concordance index (C-index) in a training set and validation set. All statistical analyses were performed using SPSS version 23, except the C-index, where the R software was used. A value of $p < 0.05$ was regarded as significantly different.

RESULTS

Characteristics of patients

Ninety-nine patients were included during the study period. The clinical characteristics of these patients are shown in table 1. The patients were aged between 23 and 77 years old, with an average age of 58.9 ± 10.0 years old, 63 were female and 36 were male. According to the degree of differentiation of the tumors, five were highly differentiated, 76 were moderately differentiated and 18 were poorly differentiated. There were 64 cases of lymph node metastasis and 20 cases of distant metastasis. With regard to TNM stage, one case was stage I, 16 cases were stage II, 49 cases stage III and 33 cases were stage IV.

The mean survival time of the 99 patients was 18.62 ± 2.408 months and the median survival time was eleven months. The mean follow-up time was 17.57 ± 10.464 months.

Univariate survival analysis

Firstly, the relationship between serum lipid levels and overall survival of GBC

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patients was analyzed. The univariate survival analysis showed that the levels of TC (p = 0.188), TG (p = 0.278), Apo-A (p = 0.455), Apo-B (p = 0.136) and FFA (p = 0.941) were not significantly associated with overall survival (Fig. 2). Interestingly, the one-year survival rate for normal HDL-C and low HDL-C groups were 56% *vs* 35%, the three-year survival rate was 0 *vs* 11% (only one patient survived) and the five-year survival rate were both 0. The mean survival time of the normal HDL-C group was 19.25 ± 1.912 months and the median survival time was 17 months, whereas the mean survival time of the low HDL-C group was 15.06 ± 2.925 months and the median survival time was nine months. The low HDL-C group had a poorer overall survival rate compared with the normal HDL-C group (Fig. 3), suggesting that HDL-C level was a potential prognostic indicator for GBC patients.

The relation between clinicopathological features and survival rate was subsequently analyzed. As shown in table 2, the degrees of lymph nodes metastasis (p = 0.034), TNM stage (p = 0.034) and distant metastasis (p = 0.001) were also significantly associated with the overall survival rate of GBC patients. Whereas age, gender, tumor size and histological grade were not associated with the survival rate.

The correlation between HDL-C level and other clinical characteristics

The relationships between serum HDL-C levels and the clinicopathological features of GBC are summarized in table 1. The statistical analysis showed that the HDL-C level was significantly related with TNM stage and distant metastasis (p = 0.023 and p = 0.001, respectively). However, there was no association between HDL-C level and other clinicopathological parameters, including age, gender, tumor size, histological grade or lymph nodes metastasis.

Bivariate correlation analysis

According to the univariate survival analysis, HDL-C level, TNM stage, distant metastasis and lymph nodes metastasis were significantly associated with the overall survival of GBC patients. Bivariate correlation analysis was further used to select candidate variables for multivariate prognosis analysis (Table 3). HDL-C and lymph nodes metastasis were strongly associated with distant metastasis and TNM staging

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(p = 0.001 and p < 0.001, respectively). In view of the convenience of obtaining HDL-C clinically, HDL-C was chosen as the variable instead of distant metastasis. Similarly, in order to confirm that lymph node metastasis only requires postoperative pathology, which is easier than that of TNM stage, HDL-C and lymph nodes metastasis were chosen as candidates for the multivariate survival analysis.

Multivariate survival analysis

As mentioned previously, HDL-C and lymph nodes metastasis were selected as candidates for the multivariate survival analysis. On the other hand, although there was no significant correlation between age and survival rate, age was also selected as a variable candidate as the p value did not exceed 0.1 (p = 0.055) (Table 1). The multivariate prognosis analysis showed that HDL-C and lymph node metastasis were independent prognostic factors for GBC patients. The risk of death among cases with low HDL-C levels was higher compared with GBC patients with normal HDL-C levels (hazard ratio [HR]: 1.847, CI: 1.100-3.101, p = 0.020). Similarly, the risk of death among GBC patients with lymph nodes metastasis was higher than those with no lymph nodes metastasis (HR: 2.008, CI: 1.123-3.589, p = 0.019).

A prognostic evaluation model based on HDL-C and lymph nodes metastasis

A prognostic evaluation model for GBC patients was established based on the two independent prognostic factors, HDL-C and lymph nodes metastasis. Firstly, the Cox regression model was used to obtain the regression coefficients of HDL-C and lymph nodes metastasis, which were 0.668 and 0.749, respectively. Based on this, the calculation formula of PI was simplified as follows: PI = 0.668*H + 0.749*L, where H represents the value of HDL-C, low HDL-C (< 0.91 mmol/l) was assigned a value of 2 and normal HDL-C (≥ 0.91 mmol/l) was assigned a value of 1 and L represents the value of lymph nodes metastasis. According to the 2017 version of the eighth American Committee on Cancer staging system, lymph nodes metastasis is classified as N0 (no lymph node metastasis), N1 (1-3 lymph node metastasis) and N2 (≥ 4 lymph node metastasis). Thus no lymph nodes metastasis was assigned a value of 0, 1-3 lymph nodes metastasis was assigned a value of 1 and ≥ 4 lymph nodes

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metastasis was assigned a value of 2. The PI values were then calculated for each patient. Based on the results, the 99 patients were divided into six groups as follows: PI 0.668 group (n = 18), PI 1.336 group (n = 17), PI 1.417 group (n = 35), PI 2.085 group (n = 24), PI 2.166 group (n = 4), and PI 2.834 group (n = 1). The Kaplan-Meier method was used for the survival analysis of each group and the log-rank test was used for a pairwise comparison of each group. The results indicated that there were no significant differences in overall survival between the PI 1.417 group and PI 0.668 group ($p = 0.248$) or the PI 1.417 group and PI 1.336 group ($p = 0.987$), or between the PI 2.085 group and PI 2.166 group ($p = 0.963$) and between the PI 2.085 group and the PI 2.834 group ($p = 0.125$). However, the overall survival rate of the PI 1.417 group was significantly different from that of the PI 2.085 group ($p = 0.011$). Therefore, patients with PI ≤ 1.417 were selected as the low-risk group and patients with PI > 1.417, as the high-risk group. Kaplan-Meier survival analysis was performed for these two groups and the results suggested a significant difference in survival rates between the two groups ($p < 0.001$) (Fig. 4).

To verify the accuracy of the prediction ability of this prognosis model, the R software was used to calculate the concordance index (C-index). The results showed that the training set (99 patients) had a C-index of 0.6997 (0.621052-0.778312). An additional 29 patients with pathologically confirmed GBC after surgery from our hospital, between March 2009 to November 2013, were selected as the validation set samples as there were no data on preoperative HDL-C level of GBC patients in the TCGA or SEER databases. These 29 patients had HDL-C data but did not have other complete serum lipid data (including TG or TC, LDL-C, Apo-A, Apo-B and FFA). According to the exclusion criteria, these 29 patients were not included in the initial 99 patient cohort. Among the 29 patients, 12 were in the low HDL-C group, 17 in the normal HDL-C group, eleven in the lymph nodes metastasis N0 group, seven in the N1 group, eleven in the N2 group, 15 in the low risk group of PI and 14 were in the high risk group of PI. The calculated C-index was 0.6788 (0.596771-0.760729), which was very close to the training set C-index (0.6997). These results confirmed that our prediction model had a good ability to predict the prognosis of patients with GBC.

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DISCUSSION

In the present study, the relationship between serum lipid levels and the prognosis of GBC was investigated and decreased HDL-C levels in the serum were associated with poor survival after surgery. This result is consistent with the effects of HDL-C in patients with most tumor types (7,13) but there are a few exceptions. For instance, Liu et al. (14) observed that overall survival of patients with nasopharyngeal carcinoma was shorter in patients with high pretreatment HDL-C levels. It is worth mentioning that according to the inclusion criteria of this study, the cases with distant transfer were excluded. Thus, the effect of HDL-C in this group was not elucidated. In contrast, this study highlighted that HDL-C levels were closely related to distant metastasis in GBC patients.

A mathematical prognostic evaluation model for calculating PI was established based on HDL-C and lymph node metastasis. The predictive accuracy of this model was tested with the C-index and the model was confirmed to have a good predictive ability for the prognosis of GBC. Furthermore, relying solely on lymph nodes metastasis to predict the prognosis of GBC is not sufficient. According to the results, the prognosis of patients in the PI 1.417 group (normal HDL-C level and lymph nodes metastasis N1) was significantly different from that in the PI 2.085 group (low HDL-C level and lymph nodes metastasis N1). Furthermore, the prognosis of the former group was significantly better than that of the latter, indicating that HDL-C levels play an important role in the GBC prognosis. The above results show that the established model can help to better predict prognosis. However, this model should be confirmed in further studies.

From previous studies, it was predicted that the role of HDL-C in GBC may be related to the N-myc downstream-regulated gene 1 (NDRG1). Human NDRG1, the inaugural member of the NDRG family, is a known metastasis suppressor in many cancers (15). The expression of NDRG1 has been associated with angiogenesis and low survival rates in cervical cancer (16), gastric cancer (17) and GBC (18). These studies indicated that NDRG1 was closely related to distant metastasis and was a poor prognosis factor for related cancers. On the other hand, Michael Hunter et al. (19) used yeast two-hybrid screening to explore the functions of NDRG1 in cellular trafficking. This

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study found that apolipoproteins A-I and A-II (Apo-AI and Apo-AII) were NDRG1-interacting partners, which are involved in lipid transport. Apo-AI and Apo-AII are the most important and abundant proteins in HDLs (20). In parallel, cancer cells need a continuous metabolic repertoire to expand and disseminate, especially lipid and cholesterol (21). Based on the above evidence, it was proposed that increased expression of the NDRG1 protein in GBC promotes interaction with Apo-AI and Apo-AII. This enhances the transport function and transports large amounts of cholesterol into tumors, resulting in a decrease in HDL-C levels in peripheral blood.

It is worth mentioning that this study had several limitations. Firstly, this is a retrospective analysis. Furthermore, in order to obtain the precise pathological evidence, patients who received surgical treatment were selected while those who could not be operated on were excluded. This inevitably led to bias. Secondly, the sample size used in this study was relatively small and our prognostic scoring model has not been verified in a wider external population. Thus, a larger sample size is needed to further verify the findings in this study.

In conclusion, the results in this study suggest that HDL-C may be a valuable prediction factor for GBC patients. The combination of HDLC and lymph node metastasis can better predict the prognosis of GBC. Although, further research is needed to confirm the reported results and identify relevant mechanisms to better guide the clinical judgment and treatment of GBC.

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Table 1. Baseline characteristics of low (< 0.91 mmol/l) and normal HDL-C (0.91-1.55 mmol/l) groups

Variable	*Total (%)*	*Low HDL-C group* n （%）	*Normal HDL-C group* n （%）	*p-value*
Age, years	58.9 ± 10.0	61.2 ± 9.4 (n = 42, 42.4%)	57.3 ± 10.2 (n = 57, 57.6%)	0.057
Gender				0.249
Male	36 (36.4%)	18 (42.9%)	18 (31.6%)	
female	63 (63.6%)	24 (57.1%)	39 (68.4%)	
Tumor size				0.584
< 5 cm	62 (62.6%)	25 (59.5%)	37 (64.9%)	
≥ 5 cm	37 (62.6%)	17 (40.5%)	20 (39.1%)	
Histological grade				0.848
High/moderate	81 (81.8%)	34 (81.0%)	47 (82.5%)	
Poor	18 (18.2%)	8 (19.0%)	10 (17.5%)	
Lymph nodes metastasis				0.226
Yes	64 (64.6%)	30 (71.4%)	34 (59.6%)	
No	35 (35.4%)	12 (28.6%)	23 (40.4%)	
TNM stage				0.023
I-II	17 (17.2%)	3 (7.1%)	14 (24.6%)	
III-IV	82 (82.8%)	39 (92.9%)	43 (75.4%)	
Distant metastasis				0.001
Yes	20 (20.2%)	15 (35.7%)	5 (8.8%)	
No	79 (79.8%)	27 (64.3%)	52 (91.2%)	

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Table 2. Log-rank test of clinicopathological features for the survival rate of GBC

Parameter	*Chi-squared*	*p-value*
Age (> 60 *vs* ≤ 60)	3.667	0.055
Gender	1.652	0.199
Tumor size (< 5 cm *vs* ≥ 5 cm)	0.023	0.880
Histological grade (high/moderate *vs* poor)	1.773	0.183
Lymph nodes metastasis (yes *vs* no)	4.500	0.034
TNM stage (I-II *vs* III-IV)	4.481	0.034
Distant metastasis (yes *vs* no)	11.545	0.001

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Table 3. Bivariate correlation analysis of age, HDL-C, TNM stage, distant metastasis and lymph nodes metastasis

	Age	*Lymph nodes metastasis*	*Distant metastasis*	*TNM stage*	*HDL-C*
Age	—	0.544	0.272	0.938	0.057
Lymph nodes metastasis	0.544	—	0.971	0.000*	0.365
Distant metastasis	0.272	0.971	—	0.711	0.001*
TNM stage	0.938	0.000*	0.711	—	0.340
HDL-C	0.057	0.365	0.001*	0.340	—

*Correlation is significant at the 0.01 level (2-tailed).

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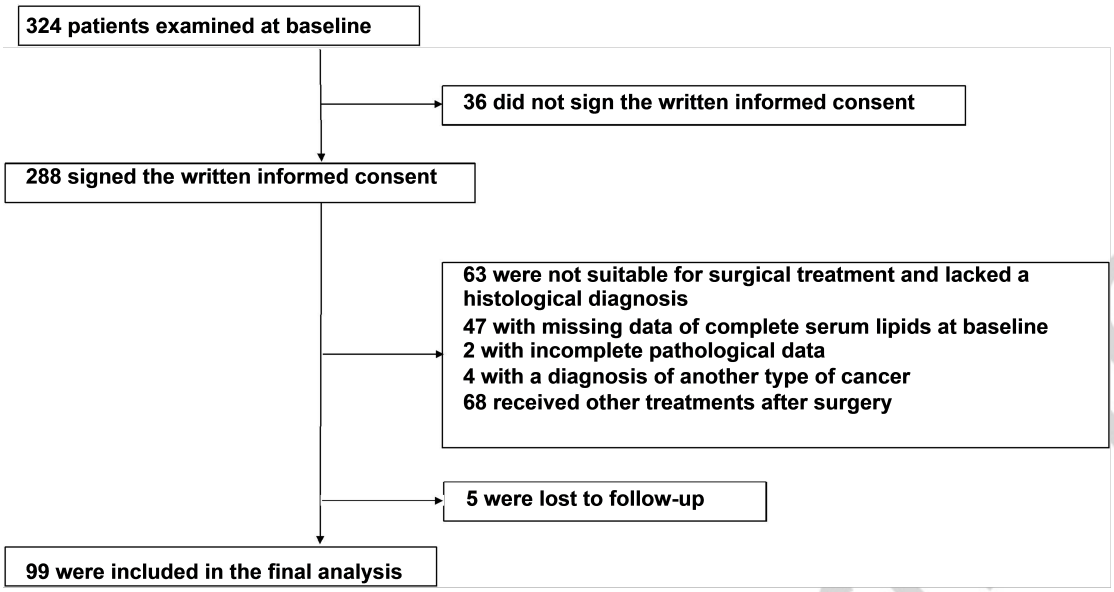

Fig. 1. Flow chart of 99 patients with GBC who were finally evaluated.

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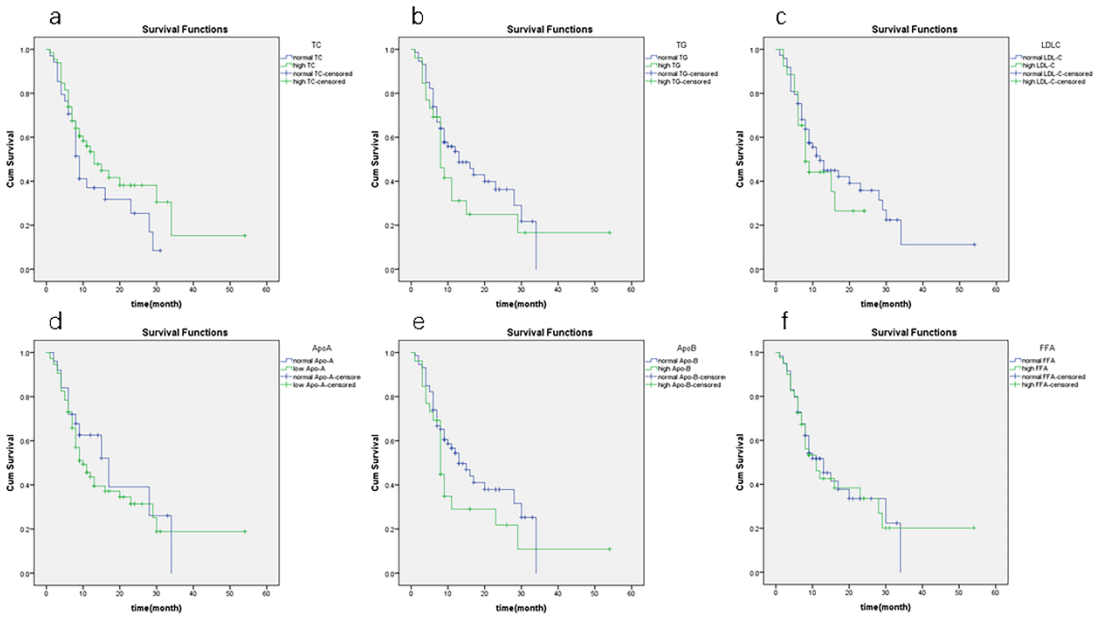

Fig. 2. Univariate survival analysis of GBC patients according to serum lipid levels: a) TC groups, p = 0.188; b) TG groups, p = 0.278; c) LDL-C groups, p = 0.37; d) Apo-A groups, p = 0.455; e) Apo-B groups, p = 0.136; and f) FFA groups, p = 0.941.

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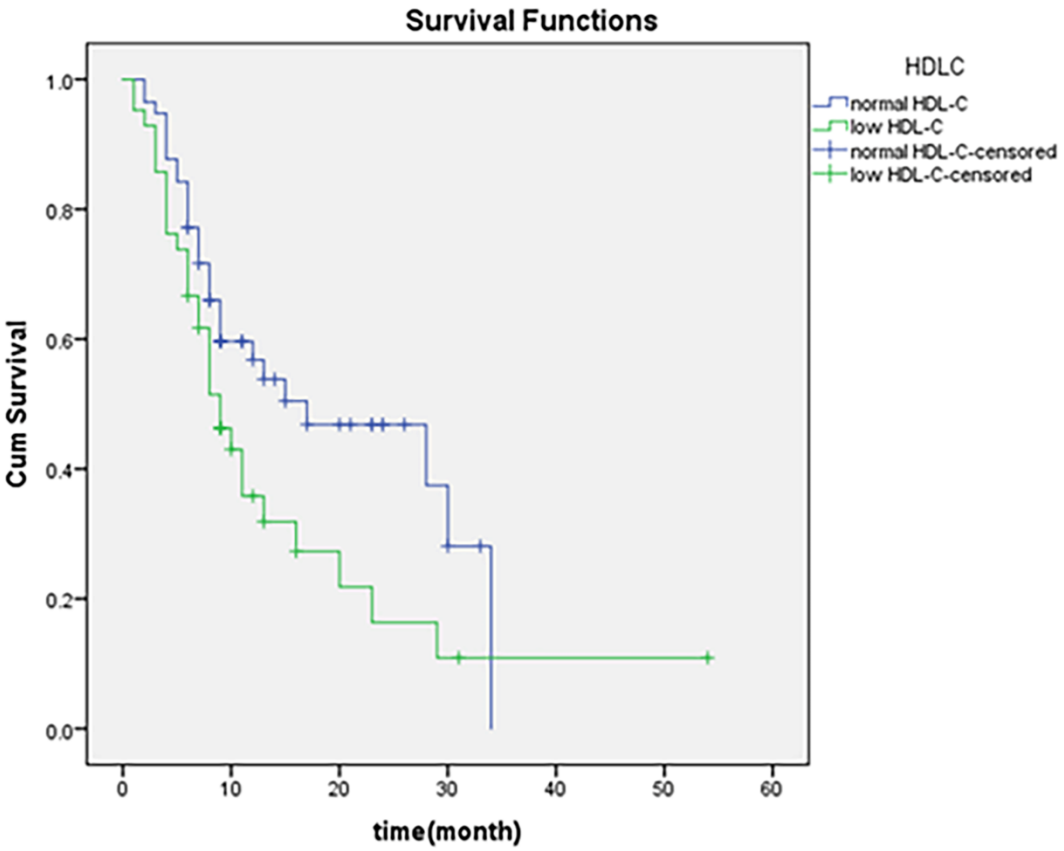

Fig. 3. Univariate survival analysis in the low HDL-C and normal HDL-C group. p = 0.042.

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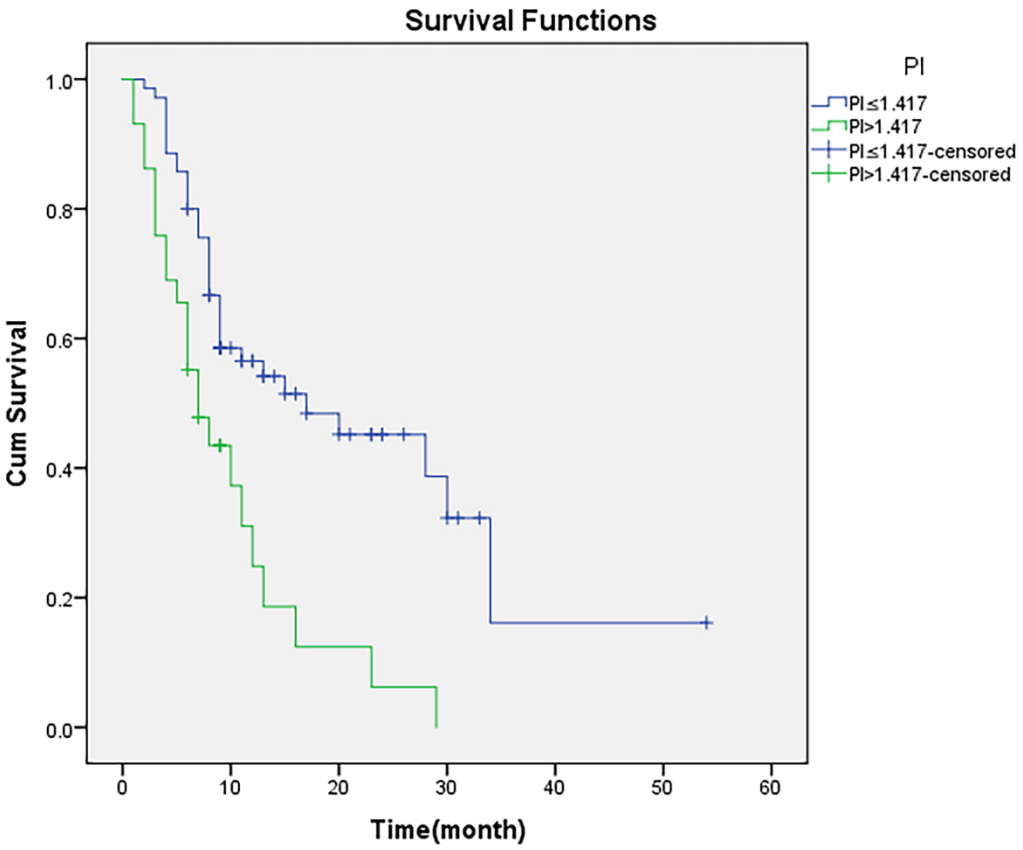

Fig. 4. The survival analysis in the prognostic evaluation model (PI ≤ 1.417 group *vs* PI > 1.417 group: $p < 0.001$). PI: prognostic index.

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