OncoTargets and Therapy

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ORIGINAL RESEARCH

Preoperative apolipoprotein B/apolipoprotein A1 ratio: a novel prognostic factor for gastric cancer

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Background: The correlations between lipid profile (lipid molecules and their derivative indexes) and clinical outcome have been widely testified in many carcinomas, but its prognostic value remains unknown in gastric cancer (GC). Our purpose in the study was to comprehensively evaluate the clinical significance of lipid profile in GC.

Methods: We retrospectively collected clinical information of 1,201 GC patients who received surgery at Sun Yat-sen University Cancer Center from 2005 to 2010. Kaplan–Meier analysis and Cox proportional hazards regression model were performed to determine its prognostic significance.

Results: Lipid profile including cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), LDL-C/HDL-C ratio, and ApoB/ApoA1 ratio were analyzed. For the first time, we found ApoB/ApoA1 ratio showed the biggest prognostic potency among all lipid-related variables and could act as an independent prognostic factor in GC. Patients with a high ApoB/ApoA1 ratio (≥1) had a shorter overall survival (hazard ratio: 1.373, 95% confidence interval: 1.123–1.68; P=0.002).

Conclusion: Preoperative serum ApoB/ApoA1 ratio might be used as a novel prognostic indicator of GC.

Keywords: ApoB/ApoA1 ratio, gastric cancer, prognosis, marker, overall survival

Introduction

Gastric cancer (GC) is one of the most commonly diagnosed malignancies and ranks as the third and second leading cause of cancer-related mortality both in the world and in China, respectively.[1,2] Recently, although we have made great progress in clinical treatments, like laparoscopic radical gastrectomy and neoadjuvant chemotherapy/radiotherapy, the clinical outcome of GC still remains unsatisfactory with an estimated 5-year survival rate of 53%.[3,4] To date, numerous prognostic factors based on serum/tissue biochemical markers were validated to guide clinical treatment and to predict prognosis in GC, for instance, HER2 status for instructing Herceptin therapy and microRNA signature for forecasting patient survival.[5,6]

A lipid profile including lipid molecules (cholesterol [CHO], triglycerides [TG], high-density lipoprotein-cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], apolipoprotein A1 [ApoA1], apolipoprotein B [ApoB]) and their derivative indexes (LDL-C/HDL-C ratio and ApoB/ApoA1 ratio) has been considered to be related with several carcinomas. Hong et al[7] reported that preoperative serum lipid profile was related to outcome of nonmetastatic colorectal cancer. A study conducted by Zhao et al[8] Found that HDL-C level was lower in prostate cancer patients compared with the normal population. However, the relationship between lipid profile and

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http://dx.doi.org/10.2147/OTT.S156690

clinical outcome in GC still remains unknown and needs to be elucidated.

In this study, we aimed to comprehensively investigate the prognostic value of lipid molecules and their derivative indexes in GC.

Methods

Patient selection

In this study, we reviewed a total of 1,201 stage I–IV GC patients who received surgery at Sun Yat-sen University Cancer Center from May 13, 2005 to September 15, 2010. This research was authorized by the Ethics Committee of the Sun Yat-sen University Cancer Center, and every patient signed the informed consent. The inclusion criteria of patients included the following: 1) pathologically diagnosed GC based on the 8th Tumor–Node–Metastasis (TNM) staging system; 2) no neoadjuvant chemotherapy or radiotherapy before operation; 3) detailed and complete follow-up data. The clinicopathological factors in our study were age, sex, tumor size, tumor location, blood type, TNM stage, differentiation, preoperative lipid molecules (CHO, TG, HDL-C, LDL-C, ApoA1, and ApoB), and survival status.

Patient follow-up

Postoperative follow-up was implemented every 3 months for the 1st and 2nd years, every half a year for the 3th–5th years, and annually until death or final follow-up. Overall survival (OS) was defined as the interval from surgery to the date of death or end of follow-up. Altogether, 1,201 GC patients received regular follow-up, and the last scheduled follow-up date was March 28, 2017.

Lipid profile

Lipid profile included lipid molecules (mentioned earlier) and their derivative indexes, including LDL-C/HDL-C ratio and ApoB/ApoA1 ratio. Briefly, LDL-C/HDL-C ratio was defined as dividing preoperative serum LDL-C concentration by serum HDL-C concentration, and ApoB/ApoA1 ratio was acquired by dividing ApoB level with ApoA1 level. We next used x-tile,[9] a statistical software based on Kaplan–Meier analysis, to determine the cut-off value of each lipid profile factor. The cut-off values were 1.9 mM, 4.1 mM, 1.2 mM, 3.1 mM, 1.4 mM, 1 mM, 2.9, and 1 for TG, CHO, HDL-C, LDL-C, ApoA1, ApoB, LDL-C/HDL-C ratio, and ApoB/ApoA1 ratio, respectively.

Statistical analysis

Survival curves was plotted by Kaplan–Meier method, and the differences were calculated by log-rank test. Univariate and multivariate Cox regression model was used to evaluate clinical significance of clinicopathological parameters and lipid profile. One-sample K–S test was conducted to determine normality of ApoB, ApoA1, LDL-C, HDL-C, ApoB/ApoA1 ratio, and LDL-C/HDL-C ratio. Spearman's rank correlation analysis was to evaluate the following correlations: ApoB versus LDL-C, ApoA1 versus HDL-C, and LDL-C/HDL-C ratio versus ApoB/ApoA1 ratio. *P*-value (two-sided) <0.05 was considered as statistically significant. Statistical analyses were conducted using SPSS software (version 22; SPSS Inc. Chicago, IL, USA). The Akaike information criterion (AIC) provides an objective method of determining the performance of indicated prognostic model. The AIC is calculated as follows: $AIC=-2l+n$ (l refers to log-likelihood and n is the number of parameters in the model). The model with the lowest AIC indicates the best prognostic potency.

Results

Patient characteristics

Characteristics of the 1,201 GC patients are presented in Table 1. The median age of the patients was 58 years (range: 19 to 86). In total, 831 (69.2%) of the patients were male and 370 (30.8%) were female. Five hundred and seventy (47.4%) of the tumors were found in lower third of the stomach, 583 patients (48.5%) were diagnosed with upper third tumors, and the rest, 49 (3.9%), of the tumors were located in full third of stomach. Tumor size was distributed as <5 cm (659, 54.9%) and ≥ 5 cm (542, 45.1%). According the 4th edition of World Health Organization classification for digestive tumors,[10] 204 (17%) of the tumors were classified as well/moderate and 997 (83%) were poor/others. Clinical staging was done using the 8th Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM staging system,[11] and the number of patients in stage I, II, III, and IV were 184 (15.3%), 252 (21%), 659 (54.9%), and 106 (8.8%), respectively. Furthermore, the ABO blood type distribution was as follows: A (335, 27.9%), B (284, 23.6%), O (497, 41.4%), and AB (85, 7.1%). As regards lipid profile, the distributions were as follows: TG <1.9 mM (1056, 87.9%) versus TG ≥ 1.9 mM (145, 12.1%); CHO <4.1 mM (229, 19.1%) versus CHO ≥ 4.1 mM (972, 80.9%); HDL-C <1.2 mM (735, 61.2%) versus HDL-C ≥ 1.2 mM (466, 38.8%); LDL-C <3.1 mM (579, 48.2%) versus LDL-C ≥ 3.1 mM (622, 51.8%); ApoA1 <1.4 mM (955, 79.5%) versus ApoA1 ≥ 1.4 mM (246, 20.5%); ApoB <1 mM

Table 1 Characteristics of the 1,201 GC patients

Characteristics	Patients	%
Age (years)		
<60	675	56.2
≥60	526	43.8
Sex		
Male	831	69.2
Female	370	30.8
Tumor location		
Lower third	570	47.4
Upper third	583	48.5
Full third	48	4
Tumor size (cm)		
<5	659	54.9
≥5	542	45.1
Differentiation		
Well/moderate	204	17
Poor/others	997	83
TNM stage		
I	184	15.3
II	252	21
III	659	54.9
IV	106	8.8
Blood type		
A	335	27.9
B	284	23.6
O	497	41.4
AB	85	7.1
TG (mM)		
<1.9	1056	87.9
≥1.9	145	12.1
CHO (mM)		
<4.1	229	19.1
≥4.1	972	80.9
HDL-C (mM)		
<1.2	735	61.2
≥1.2	466	38.8
LDL-C (mM)		
<3.1	579	48.2
≥3.1	622	51.8
ApoA1 (mM)		
<1.4	955	79.5
≥1.4	246	20.5
ApoB (mM)		
<1	721	60
≥1	480	40
LDL-C/HDL-C ratio		
<2.9	670	55.8
≥2.9	531	44.2
ApoB/ApoA1 ratio		
<1	947	78.9
≥1	254	21.1

Abbreviations: ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; CHO, cholesterol; GC, gastric cancer; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; TNM, tumor–node–metastasis.

(721, 60%) versus ApoB ≥1 mM (480, 40%); LDL-C/HDL-C ratio <2.9 (670, 55.8%) versus LDL-C/HDL-C ratio ≥2.9 (531, 44.2%); and ApoB/ApoA1 ratio <1 (947, 78.9%) versus ApoB/ApoA1 ratio ≥1 (254, 21.1%).

Correlations between ApoB, ApoA1, and ApoB/ApoA1 ratio and LDL-C, HDL-C, and LDL-C/HDL-C ratio

Among all lipid profile molecules, ApoB and ApoA1 account for the major components of LDL-C and HDL-C, respectively.[12,13] Likewise, a Swedish research published in *Lancet* showed that ApoB/ApoA1 ratio was superior to LDL-C/HDL-C ratio in predicting the risk of coronary disease.[14] Thus, we first analyzed the correlations between the above factors. One-sample K–S test showed that the above factors (ApoA1, ApoB, LDL-C, HDL-C, LDL-C/HDL-C ratio, and ApoB/ApoA1) lacked normality (Figure 1A–C). Therefore, Spearman's rank correlation instead of Pearson's linear correlation was used for further analysis. As shown in Figure 1A–C, a significant correlation was found in ApoB concentration versus LDL-C concentration (r=0.829; 95% confidence interval [CI]: 0.805–0.852; P<0.001), ApoA1 concentration versus HDL-C concentration (r=0.710; 95% CI: 0.677–0.741; P<0.001), and ApoB/ApoA1 ratio versus LDL-C/HDL-C ratio (r=0.788; 95% CI: 0.762–0.813; P<0.001), indicating the good representative capacity of ApoA1, ApoB, and ApoB/ApoA1 ratio.

Univariate and multivariate Cox regression analysis of prognostic factors

Univariate Cox proportional hazard model was used to find out the prognostic factors in all candidate variables including clincopathological parameters (including age, sex, tumor size, tumor location, blood type, TNM stage, and differentiation) and the aforementioned lipid profile. As can be seen in Table 2 (left panel), age, tumor location, differentiation, TNM stage, TG, ApoA1, ApoB, LDL-C/HDL-C ratio, and ApoB/ApoA1 ratio were significantly related with clinical outcome of GC patients.

In order to determine the independent prognostic factors, the significant variables from univariate analysis were further subjected to multivariate regression analyses. As shown in Table 2 (right panel), age ≥60 years (hazard ratio [HR]: 1.363, 95% CI: 1.146–1.620, P<0.001), upper and full third location of tumor (HR: 1.43, 95% CI: 1.18–1.72, P<0.001; HR: 2.7, 95% CI: 1.89–3.85, P<0.001, respectively), poor/other differentiations of tumor (HR: 1.75, 95% CI: 1.34–2.28, P<0.001),

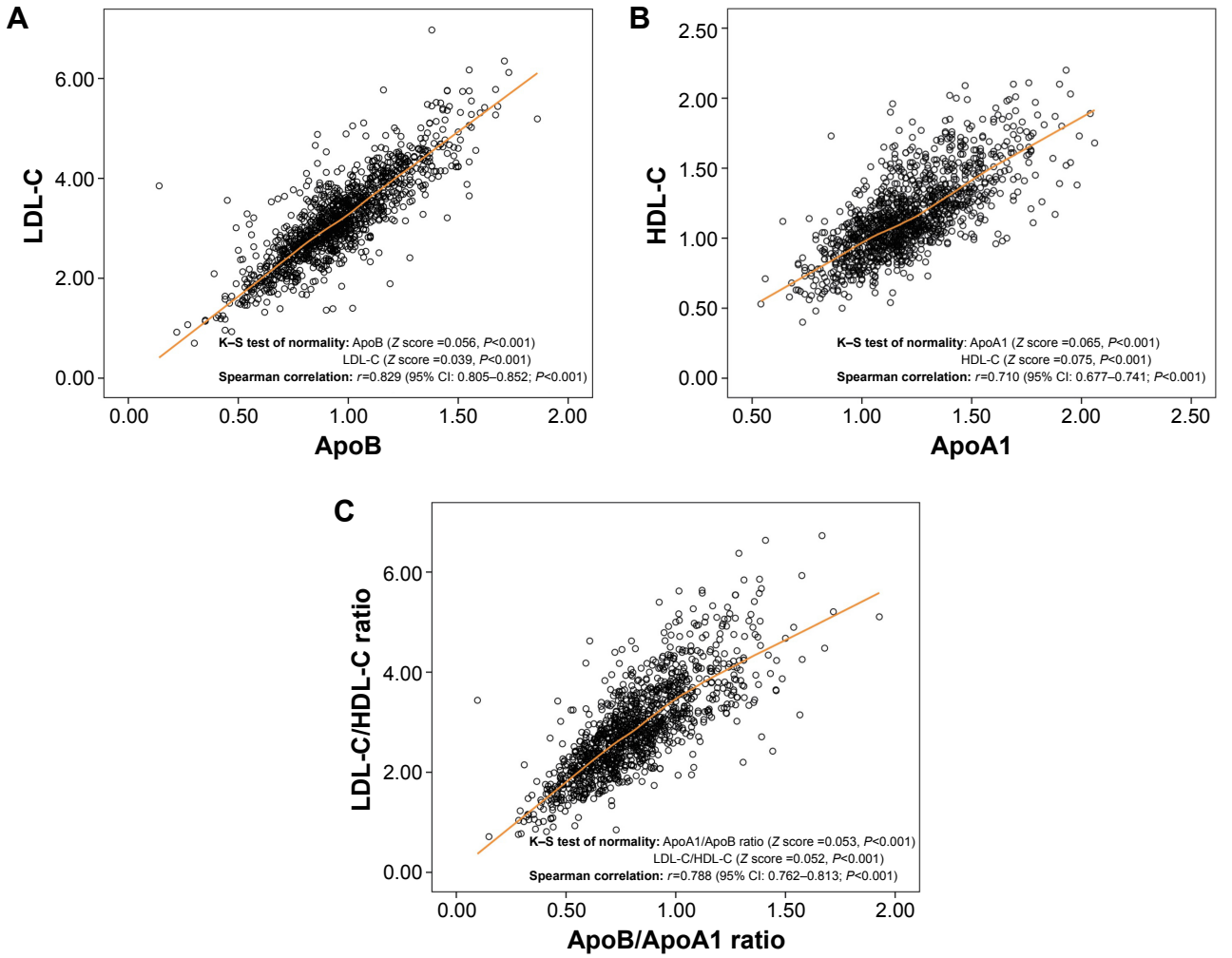

Figure 1 ApoB, ApoA1, and ApoB/ApoA1 ratio were correlated with LDL-C, HDL-C, and LDL-C/HDL-C ratio, respectively.
Notes: (**A**) Spearman's rank correlation analysis between ApoB and LDL-C (r=0.829, P<0.001). (**B**) Spearman's rank correlation analysis between ApoA1 and HDL-C (r=0.71, P<0.001). (**C**) Spearman's rank correlation analysis between ApoB/ApoA1 ratio and LDL-C/HDL-C ratio (r=0.788, P<0.001).
Abbreviations: ApoA1, apolipoprotein A1, Apo B, apolipoprotein B; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

TNM stage II, III, or IV (HR: 2.481, 95% CI: 1.365–4.51, P=0.003; HR: 10.66, 95% CI: 6.23–18.45, P<0.001; HR: 29.75, 95% CI: 16.74–52.87, P<0.001, respectively), and high ApoB/ApoA1 ratio (HR: 1.373, 95% CI: 1.123–1.68, P=0.002) were correlated with poorer OS of GC patients.

Furthermore, prognostic performance test also confirmed the conclusion that ApoB/ApoA1 ratio was an independent prognostic factor for GC among the lipid profile tests. As displayed in Table 3, the AIC value of the basal model, which incorporated significant clinicopathological parameters according to univariate analysis (age, tumor location, differentiation, and TNM stage), was 6,671.6. Among all lipid profile factors, when adding ApoB/ApoA1 ratio into the model, the AIC value presented the maximum reduction (from 6,671.6 to 6,664.8), indicating a better prediction accuracy of the model.

Association between ApoB/ApoA1 ratio and prognosis of GC patients

In order to further investigate the prognostic role of ApoB/ApoA1 ratio in GC, we used Kaplan–Meier analysis to draw survival curves and used the log-rank test to compare different groups. As shown in Figure 2A, GC patients with high ApoB/ApoA1 ratio (mean OS: 291 weeks) had a significantly poorer survival than those with low ApoB/ApoA1 ratio (mean OS: 361 weeks), and 5-year survival rate was 43.1% versus 55.8% (high ApoB/ApoA1 ratio versus low). However, when stratified by TNM stage and differentiation, this prognostic significance varied greatly among subgroups. The results showed that the prognostic value of ApoB/ApoA1 ratio was also apparent in stage III–IV patients (P<0.001, Figure 2C) and those with poor/other differentiations of tumor (P<0.001; Figure 2E).

Table 2 Univariate and multivariate Cox proportional hazard model of GC with overall survival

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
<60 (ref)	1	**<0.001**	1	<0.001
≥60	1.408 (1.188–1.668)		1.363 (1.146–1.620)	
Sex				
Male (ref)	1	0.994		
Female	0.999 (0.831–1.202)			
Blood type				
A (ref)	1			
B	1.002 (0.79–1.271)	0.989		
O	1.010 (0.819–1.245)	0.928		
AB	1.143 (0.806–1.622)	0.454		
Tumor location				
Lower third (ref)	1		1	
Upper third	1.691 (1.414–2.023)	**<0.001**	1.43 (1.18–1.72)	**<0.001**
Full third	4.556 (3.203–6.48)	**<0.001**	2.7 (1.89–3.85)	**<0.001**
Tumor size (cm)				
<5 (ref)	1	**<0.001**		
≥5	1.86 (1.567–2.207)			
Differentiation				
Well/moderate (ref)	1	**<0.001**	1	**<0.001**
Poor/others	1.808 (1.393–2.348)		1.75 (1.34–2.28)	
TNM stage				
I (ref)	1		1	
II	2.832 (1.562–5.137)	**<0.001**	2.481 (1.365–4.51)	**0.003**
III	12.636 (7.409–21.552)	**<0.001**	10.66 (6.23–18.45)	**<0.001**
IV	35.023 (19.784–61.999)	**<0.001**	29.75 (16.74–52.87)	**<0.001**
TG (mM)				
<1.9	1	**0.005**		
≥1.9	0.656 (0.488–0.882)			
CHO (mM)				
<4.1	1	0.09		
≥4.1	0.834 (0.676–1.029)			
HDL-C (mM)				
<1.2	1	0.13		
≥1.2	0.873 (0.731–1.041)			
LDL-C (mM)				
<3.1	1	0.366		
≥3.1	1.082 (0.912–1.283)			
ApoA1 (mM)				
<1.4	1	**0.004**		
≥1.4	0.717 (0.572–0.9)			
ApoB (mM)				
<1	1	**0.042**		
≥1	1.194 (1.006–1.417)			
LDL-C/HDL-C ratio				
<2.9	1	**0.044**		
≥2.9	1.191 (1.005–1.411)			
ApoB/ApoA1 ratio				
<1	1	**0.001**	1	**0.002**
≥1	1.382 (1.133–1.685)		1.373 (1.123–1.68)	

Note: The bold values denote statistical significance ($P<0.05$).

Abbreviations: ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; CHO, cholesterol; CI, confidence interval; GC, gastric cancer; HDL-C, high-density lipoprotein-cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; TNM, tumor–node–metastasis.

Table 3 Prognostic value of ApoB/ApoA1 ratio on OS in GC

Model	AIC
Basal model[a]	6,671.6
Basal model plus TG	6,672.2
Basal model plus CHO	6,673.0
Basal model plus HDL-C	6,673.6
Basal model plus LDL-C	6,672.2
Basal model plus ApoA1	6,672.4
Basal model plus ApoB	6,669.2
Basal model plus LDL-C/HDL-C ratio	6,672.0
Basal model plus ApoB/ApoA1 ratio	6,664.8

Notes: [a]Basal model, a Cox regression model including the following variables: age, tumor location, differentiation, tumor size, and TNM stage.

Abbreviations: AIC, Akaike information criteria; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; CHO, cholesterol; GC, gastric cancer; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; OS, overall survival; TG, triglycerides; TNM, tumor–node–metastasis.

However, OS was not significant in those with stage I–II (P=0.782; Figure 2B) and well/moderate differentiation (P=0.812; Figure 2D).

Correlation between ApoB/ApoA1 ratio and clinicopathological characteristics

The association between ApoB/ApoA1 ratio and clinicopathological characteristics is summarized in Table 4. As is shown, ApoB/ApoA1 ratio was significantly correlated with sex (P=0.005), differentiation (P=0.044), and blood type (P=0.041). However, there was no statistically significant correlation between ApoB/ApoA1 ratio and age, tumor location, and TNM stage.

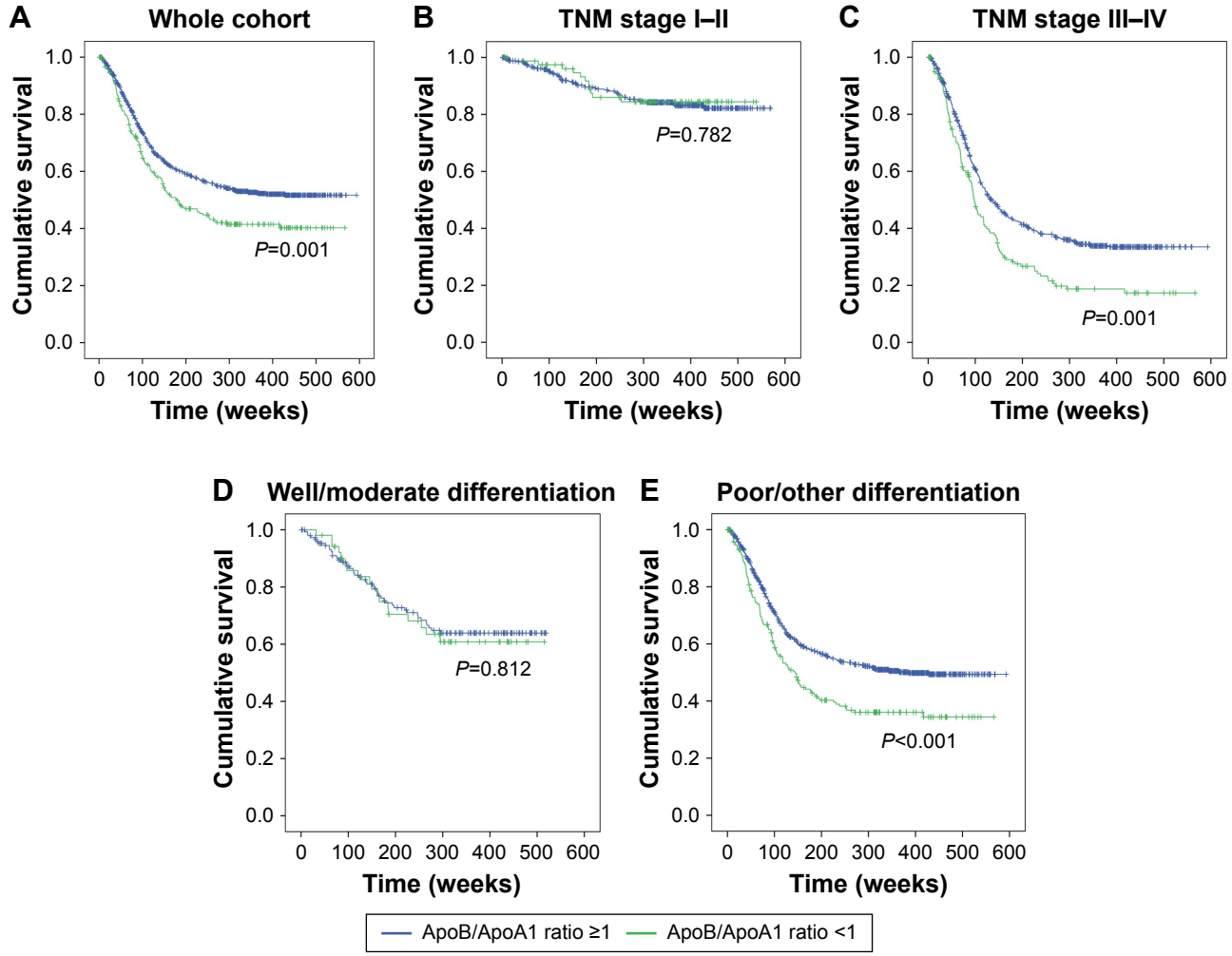

Figure 2 Kaplan–Meier curves of OS for GC patients with low versus high ApoB/ApoA1 ratio.

Notes: (**A**) Comparison of OSs in the whole cohort of patients with low versus high ApoB/ApoA1 ratio (P=0.001). (**B**) Comparison of OSs in the stage I–II patients with low versus high ApoB/ApoA1 ratio (P=0.782). (**C**) Comparison of OSs in the stage III–IV patients with low versus high ApoB/ApoA1 ratio (P<0.001). (**D**) Comparison of OSs in the patients of well/moderate differentiation with low versus high ApoB/ApoA1 ratio (P=0.812). (**E**) Comparison of OSs in the patients of poor/other differentiations with low versus high ApoB/ApoA1 ratio (P<0.001).

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; GC, gastric cancer; OS, overall survival; TNM, tumor–node–metastasis.

Table 4 Relationship between ApoB/ApoA1 ratio and clinicopathological characteristics in the 1,201 GC patients

Characteristics	ApoB/ApoA1 ratio <1	ApoB/ApoA1 ratio ≥1	*P*-value
Age (years)			0.058
<60	551	406	
≥60	124	120	
Sex			**0.005**
Male	644	187	
Female	313	57	
Tumor location			0.091
Lower third	479	104	
Upper third	439	131	
Full third	39	9	
Tumor size (cm)			0.321
<5	532	127	
≥5	425	117	
Differentiation			**0.044**
Well/moderate	152	52	
Poor/others	805	192	
TNM stage			0.166
I	151	33	
II	204	48	
III	526	133	
IV	76	30	
Blood type			**0.041**
A	250	85	
B	237	47	
O	402	95	
AB	68	17	

Note: The bold value denotes statistical significance ($P<0.05$).
Abbreviations: ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; GC, gastric cancer; TNM, tumor–node–metastasis.

Discussion

In this study, we created a new prognostic index for GC, ApoB/ApoA1 ratio, by dividing preoperative ApoB concentration with ApoA1 concentration.

Recently, abnormal lipid metabolism has been validated to be a vital metabolic reprogramming process in cancer cell.[15] An American research group found that increased unsaturated lipid is a metabolic biomarker in ovarian cancer stem cells and could serve as a cancer stem cell-specific target.[16] Pascual et al[17] reported that blocking fatty acid receptor CD36 could inhibit metastasis of human oral cancer in a mouse model. These findings suggest that lipid metabolism is related to cancer formation and development and might be developed as an anticancer target. As a result, their end products, the lipid molecules, also present abnormal expression in cancer patients. Besides, numerous studies have validated the prognostic role of lipid molecules and their derivative indexes in many carcinomas.[7,8]

As for GC, an article written by Liu et al[18] showed that canonical lipid markers (HDL-C, LDL-C, CHO, and TG) do not present prognostic significance in GC, and this result is consistent with our findings (Table 2). Generally, ApoA1 and ApoB were also included as part of the routine lipid test panel before treatment in our hospital. Also, LDL-C/HDL-C ratio and ApoB/ApoA1 ratio show significant diagnostic ability in many diseases.[19–21] Thus, in our research, we incorporated ApoA1, ApoB, ApoB/ApoA1 ratio, and LDL-C/HDL-C ratio for analysis, as well as the aforesaid traditional markers. Eventually, we found that ApoB/ApoA1 could act as an independent prognostic marker in GC among all lipid molecules and their derivate indexes.

Our research has some inadequacies. First, our data were retrospectively collected from a single cancer center. Second, due to information bias, we could not acquire the exact time of tumor recurrence/progression, and hence chose OS as the primary outcome. Third, the underlying mechanism of lipid metabolism in the carcinogenesis and cancer development of GC needs further investigation.

Conclusion

We found for the first time that ApoB/ApoA1 ratio could serve as a prognostic factor in GC. To generalize the utilization of ApoB/ApoA1 ratio, validation by a prospective multicenter study is required.

Acknowledgment

This study was supported by a grant from the National Natural Science Foundation of China (grant number 81302144).

Disclosure

The authors report no conflicts of interest in this work.

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