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Original Article

Metabolic syndrome associated with adverse pathological features in patients with colorectal adenocarcinoma

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Abstract: Previous studies suggested a link between metabolic syndrome (MetS) and colorectal cancer (CRC). It is unclear whether MetS influences the prognosis of CRC via increasing the risk of adverse pathologic features. We aimed to assess the association between MetS and pathological features of CRC, especially in different gender. This retrospective cohort study included 2232 consecutive colorectal adenocarcinoma patients underwent radical colectomy in a single medical institution. Patients were divided into subgroups of MetS and non-MetS according to the criteria of China Diabetes Society. Data were collected for pathological subtypes, histological grade, invasion depth, lymph node (LN) status, and tumor-node-metastasis (TNM) stage. Logistic regression analysis indicated that MetS was significantly correlated with mucinous adenocarcinoma (MAC) (OR=3.56, 95% CI: 1.94-6.52, P<0.001), signet-ring cell carcinoma (SRCC) (OR=6.58, 95% CI: 1.50-28.92, P=0.013), high grade (OR=1.95, 95% CI: 1.29-2.97, P=0.002), positive LN status (OR=1.80, 95% CI: 1.28-2.53, P=0.001), and high TNM stage (OR=1.69, 95% CI: 1.20-2.37, P=0.002) in women, while MetS was significantly correlated with SRCC (OR=4.74, 95% CI: 1.4-16.04, P=0.012) and high grade (OR=1.58, 95% CI: 1.12-2.26, P=0.012) in men. Multivariately, hyperglycemia was significantly correlated with SRCC, high grade, positive LN, and high TNM stage in men (P<0.05), but not in women. Hyperglycemia was only significantly correlated with MAC in female (OR=2.56, 95% CI: 1.34-1.88, P=0.004). Low high-density lipoprotein cholesterol (HDL-C) was significantly correlated with positive LN (OR=1.76, 95% CI: 1.30-2.38, P<0.001) and high TNM stage (OR=1.85, 95% CI: 1.36-2.50, P<0.001) in women, but not in men. The finding of the present study suggested that the presence of MetS and/or low HDL-C in women predicted risk of MAC, LN metastasis of CRC and high TNM stage, while the presence of hyperglycemia in men predicted risk of high histological grade, LN metastasis, and high TNM stage. Improvement of MetS and HDL-C status in women or hyperglycemia in men may favor the prognosis of CRC patients complicated with MetS.

Keywords: Colorectal cancer, colorectal adenocarcinoma, metabolic syndrome, hyperglycemia, HDL-C, high-density lipoprotein cholesterol, signet-ring cell carcinoma, mucinous carcinoma, diabetes, pathological feature

Introduction

Metabolic syndrome (MetS) comprises combination of factors including central obesity, elevated fasting glucose, hypertension and dyslipidemia [reduced high-density lipoprotein cholesterol (HDL-C) and/or elevated triglyceride (TG)] [1]. MetS is one of the most prevalent comorbidities of colorectal cancer (CRC). Epidemiological evidence shows a positive correlation between MetS and the risk of many kinds of cancers including CRC [2, 3]. The prognosis of CRC is worse in patients with MetS than in those without MetS [4].

Adenocarcinoma accounts for >90% of CRC cases. Colorectal adenocarcinoma can be further divided into mucinous carcinoma and non-mucinous adenocarcinoma (or classic adenocarcinoma) according to mucin content in tumor tissue. Classic colorectal adenocarcinoma is composed of irregularly distributed tubular structures in desmoplastic stroma. Mucinous carcinoma can be further divided into two subtypes including mucinous adenocarcinoma (MAC) and signet-ring cell carcinoma (SRCC). Most mucinous carcinomas are more aggressive than classic adenocarcinomas [5, 6].

As a component of MetS, diabetes was shown to be associated with worse histopathological features of CRC [7]. Given the close relationship between diabetes and MetS, we hypothesized that MetS status might influence the prognosis via increasing the risk of adverse pathological features of CRC. We performed the retrospective cohort study to determine whether MetS and its components were associated with adverse pathological features of CRC, especially for patients of different genders.

Patients and methods

Patients

The retrospective cohort study included 2232 consecutive primary colorectal adenocarcinoma patients who underwent radical colectomy between January 2011 and December 2018 in Zhejiang Provincial People's Hospital.

Patients were excluded in this study including: (1) Patients with missing clinical data to determine MetS status and/or tumor-node-metastasis (TNM) stage (n=124); (2) Patients were treated with preoperative chemotherapy and radiotherapy (n=38), because preoperative treatment may change the pathological features such as TNM stage of CRC. Other histopathological types of CRC including neuroendocrine carcinoma, squamous carcinoma, undifferentiated carcinoma were not enrolled in this study due to their rarity in radical resected specimens of CRC.

Medical records including gender, age, blood pressure, body weight, height, preoperative levels of fasting blood glucose, blood TG, and blood HDL-C, were collected. Pathological parameters of the CRC were collected from the pathological reports of the patients, which included pathological subtypes, histological grade, invasion depth, tumor location, lymph node status, and TNM stage. The pathological sections and clinical data were reviewed for accuracy of pathological features and TNM stage. If a few patients have more than 2 locations and/or histologic subtypes, only the more aggressive one was adopted for the study.

Ethics

This study was reviewed and approved by the Ethics Committee of Zhejiang Provincial People's Hospital (KY2019012). The retrospective analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent and the need for informed consent was waived by the Ethics Committee.

Diagnostic criteria for MetS

MetS was diagnosed in the presence of any 3 or more of the following 4 factors according the criteria of China Diabetes Society (CDS) [1]: (1) central obesity: body mass index (BMI) ≥ 25.0 kg/m^2; (2) hyperglycemia: fasting plasma glucose ≥ 6.10 mmol/L or already diagnosed as type 2 diabetes (T2D) and receiving hypoglycemic drug treatment; (3) hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or already diagnosed as hypertension and receive antihypertensive drug administration; and (4) dyslipidemia: hypertriglyceridemia (fasting plasma TG ≥ 1.7 mmol/L) and/or reduced blood levels of HDL-C: fasting plasma HDL-C <0.9 mmol/L for males or <1.0 mmol/L for females).

Pathological subtypes

According to World Health Organization (WHO) definition and previous reports [8, 9], CRC was further divided into four subtypes: (1) Classic adenocarcinoma (well, moderately or poorly-differentiated adenocarcinoma); (2) MAC (>50% of the tumor is composed of pools of extracellular mucin that contain malignant epithelium); (3) SRCC (tumor cells with abundant intracytoplasmic mucin and >50% of the tumor cells have prominent intracytoplasmic mucin); and (4) AC with components (adenocarcinoma with presence but <50% of MAC and/or SRCC).

Histological grade

According WHO definition, CRC was divided into 3 grades based on the extent of well-formed glands [8], which included well-differentiated (>95% glands), moderately differentiated (50-95% glands), and poorly differentiated (<50% glands). To reduce interobserver's variability in evaluation of histological grade, classic adenocarcinoma and AC with components was simply divided into low grade (well-differentiated and/or moderately-differentiated adenocarcinoma) and high grade (poorly-differentiated adenocar-

cinoma) [10], while MAC, SRCC were not further graded.

Invasion depth

According to American Joint Cancer Committee (AJCC) (8th edition) [11], T stages were divided into Tis, T1, T2, T3, and T4 stage. In this study, invasion depth was further divided into deep invasion and non-depth invasion. Deep invasion was defined as pT-stage ≥ 3, which included T3 (penetration through the muscularis propria) and T4 stage [involvement of the serosal surface (visceral peritoneum) or directly invade adjacent organs or structures]. Non-deep invasion was defined as pT-stage ≤2, which included Tis (invasion of lamina propria without penetration through the muscularis mucosa), T1 (invasion of submucosa), and T2 (penetration through the submucosa into but not through the muscularis propria). High-grade intraepithelial neoplasia was not assigned to Tis category, because these lesions lack potential for tumor spread.

TNM stage

Tumor stage was recorded according to TNM staging of AJCC (8th edition) [11]. Stages were further classified into low stage and high stage in this study: Low stage included 0, I, IIA, IIB and IIC (T4bN0M0), while high stage included IIIA (T1~2N1M0), IIIB, IIIC, IVA, IVB and IVC.

Statistical analysis

Continuous variables such as age were expressed as mean ± standard deviation (SD) and analyzed by *T*-test. Categorical data were expressed as frequency and percentage, which were further analyzed by χ^2 test. Multinomial logistic regression analysis were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for risks of developing non-classic adenocarcinoma in association with MetS or its individual component (classic adenocarcinoma as references). Univariate or multivariate binary logistic regression models were used to determine ORs and 95% CIs of high grade, deep invasion, positive lymph node status, and high TNM stage in association with MetS or its components.

Statistical analysis was performed with SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Two-sided $P \leq 0.05$ was considered significant.

Results

Baseline characteristics

As showed in **Table 1**, the average age was 63.7 ± 12.8 years old (18-95 years old). There were 1345 (60.3%) men. About 416 patients (18.6%) were MetS. Data were available for BMI in 2105 patients, while levels of fasting blood glucose, TG, and HDL-C were collected in all 2232 patients.

Association between MetS and pathological features of CRC

As showed in **Table 2**, for women, the ratios of histological subtypes for classic AC, MAC, SRCC, and AC with components were 83.1%, 4.2%, 0.7%, 12.0% in non-MetS group, while the ratios were 72.9%, 12.4%, 2.3%, 12.4% in MetS group. For men, the ratios of for classic AC, MAC, SRCC, and AC with components were 83.6%, 4.6%, 0.6%, 11.1% in non-MetS group, while the ratios were 80.8%, 4.2%, 2.1%, 13.0% in MetS group. The ratios of high grade, positive LN, and high TNM stage were 28.5%, 57.6%, and 57.6% in MetS groups for women, which were remarkably higher than those of non-MetS groups (the ratios were 17.2%, 43.7%, and 45.5% in non-MetS groups, respectively).

As showed in **Table 3**, logistic regression (adjusted by age) analysis indicated that MetS was remarkably associated with increased risk of MAC (OR=2.0, 95% CI: 1.30-3.08, P=0.002) and SRCC (OR=5.70, 95% CI: 2.24-14.49, P<0.001) in all patients. MetS was significantly correlated with increased risk of MAC (OR=3.56, 95% CI: 1.94-6.52, P<0.001), SRCC (OR=6.58, 95% CI: 1.50-28.92, P=0.013), high grade (OR=1.95, 95% CI: 1.29-2.97, P=0.002), deep invasion (OR=1.84, 95% CI: 1.20-2.84, P=0.006), positive LN (OR=1.80, 95% CI: 1.28-2.53, P=0.001), and high TNM stage (OR=1.69, 95% CI: 1.20-2.37, P=0.002) in female, while MetS was only significantly correlated with increased risk of SRCC (OR=4.74, 95% CI: 1.4-16.04, P=0.012) and high grade (OR=1.58, 95% CI: 1.12-2.26, P=0.012) in male.

Association between individual component of MetS and pathological features of CRC

Multivariately, hyperglycemia was significantly correlated with increased risk of SRCC (OR=

Table 1. Baseline characteristics (Overall and across metabolic syndrome status)

Variables	Overall	Non-MetS	Mets	*P*
Age (Mean ± SD)	63.7 ± 12.8	63.1 ± 13.1	66.2 ± 11.1	<0.001
Male				
No	887	710	177	0.194
Yes	1345	1106	239	
BMI ≥ 25 kg/m^2				
No	1655	1519	136	<0.001
Yes	450	213	237	
Hypertension				
No	1149	1117	32	<0.001
Yes	1083	699	384	
Hyperglycemia (FPG ≥ 6.1 mmol/L or treatment)				
No	1622	1543	79	<0.001
Yes	610	273	337	
Hypertriglyceridemia				
No	1764	1526	238	<0.001
Yes	468	290	178	
Low HDL-C				
No	1499	1344	155	<0.001
Yes	733	472	261	
Tumor location				
Right	531	406	125	0.008
Transverse	83	66	17	
Left	154	126	28	
Rectosigmoid	1464	1218	246	

BMI: body mass index; FPG: fasting plasma glucose.

Table 2. Distribution of pathological features (Overall and across both sex) in patients with colorectal cancer according to metabolic syndrome status

Factors	Female			Male			Overall		
	Non-MetS (%)	MetS (%)	*P*	Non-MetS (%)	MetS (%)	*P*	Non-MetS (%)	MetS (%)	*P*
Histology									
Classic AC	590 (83.1)	129 (72.9)	<0.001	925 (83.6)	193 (80.8)	0.136	1515 (83.4)	322 (77.4)	0.001
MAC	30 (4.2)	22 (12.4)		51 (4.6)	10 (4.2)		81 (4.5)	32 (7.7)	
SRCC	5 (0.7)	4 (2.2)		7 (0.6)	5 (2.1)		12 (0.7)	9 (2.2)	
Components	85 (12.0)	22 (12.4)		123 (11.1)	31 (13.0)		208 (11.5)	53 (12.7)	
High grade									
No	559 (82.8)	108 (71.5)	0.002	886 (84.5)	174 (77.7)	0.012	1445 (83.9)	282 (75.2)	<0.001
Yes	116 (17.2)	43 (28.5)		162 (15.5)	50 (22.3)		278 (16.1)	93 (24.8)	
Deep Invasion									
No	194 (27.3)	30 (16.9)	0.004	257 (23.2)	63 (26.4)	0.304	451 (24.8)	93 (22.4)	0.288
Yes	516 (72.7)	147 (83.1)		849 (76.8)	176 (73.6)		1365 (75.2)	323 (77.6)	
Positive LN									
No	400 (56.3)	75 (42.4)	0.001	630 (57.0)	130 (54.4)	0.468	1030 (56.7)	205 (49.3)	0.006
Yes	310 (43.7)	102 (57.6)		476 (43.0)	109 (45.6)		786 (43.3)	211 (50.7)	
High TNM stage									
No	387 (54.5)	75 (42.4)	0.004	609 (55.1)	129 (54.0)	0.759	996 (54.8)	204 (49.0)	0.032
Yes	323 (45.5)	102 (57.6)		497 (44.9)	110 (46.0)		820 (45.2)	212 (51.0)	
Right colon									

No	492 (69.3)	105 (59.3)	0.011	852 (77.0)	169 (70.7)	0.038	1344 (74.0)	274 (65.9)	0.001
Yes	218 (30.7)	72 (40.7)		254 (23.0)	70 (29.3)		472 (26.0)	142 (34.1)	

Statistics: X^2 test. Mucinous AC: mucinous adenocarcinoma; SRCC: signet-ring cell carcinoma; Components: adenocarcinoma with mucinous carcinoma components; LN: lymph node; Right colon: including cecum, ascending colon, transverse colon.

Table 3. Association between metabolic syndrome and adverse pathological features in patients with colorectal cancer

Factors	Variable	Female		Male		Overall	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Histology							
Mucinous AC	MetS	3.56 (1.94-6.52)	<0.001	0.98 (0.49-1.98)	0.962	2.00 (1.30-3.08)	0.002
SRCC	MetS	6.58 (1.50-28.92)	0.013	4.74 (1.40-16.04)	0.012	5.70 (2.24-14.49)	<0.001
Components	MetS	1.17 (0.71-1.95)	0.537	1.22 (0.80-1.87)	0.353	1.24 (0.89-1.71)	0.202
High grade	MetS	1.95 (1.29-2.97)	0.002	1.58 (1.12-2.26)	0.012	1.74 (1.33-2.28)	<0.001
Deep invasion	MetS	1.84 (1.20-2.84)	0.006	0.85 (0.62-1.17)	0.307	1.15 (0.89-1.48)	0.296
Positive LN	MetS	1.80 (1.28-2.53)	0.001	1.12 (0.85-1.49)	0.430	1.38 (1.12-1.71)	0.003
High TNM stage	MetS	1.69 (1.20-2.37)	0.002	1.06 (0.80-1.40)	0.711	1.30 (1.05-1.61)	0.017

Statistics: Logistic regression with age as covariate. Mucinous AC: mucinous adenocarcinoma; SRCC: signet-ring cell carcinoma; Components: adenocarcinoma with mucinous carcinoma components; LN: lymph node.

Table 4. Association between components of metabolic syndrome and histological subtypes in patients with colorectal cancer

Factors	MetS components	Female		Male		Overall	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Subtypes							
Mucinous AC	Triglycerides ≥ 1.7 mmol/L	1.16 (0.60-2.26)	0.654	0.81 (0.42-1.57)	0.529	1.04 (0.65-1.64)	0.879
	BMI ≥ 25 kg/m^2	1.10 (0.54-2.22)	0.799	0.91 (0.47-1.74)	0.767	0.99 (0.62-1.59)	0.968
	Hypertension	0.70 (0.36-1.36)	0.295	0.54 (0.30-0.97)	0.040	0.61 (0.40-0.94)	0.026
	Low HDL-C	3.06 (1.66-5.66)	<0.001	1.38 (0.80-2.40)	0.250	2.0 (1.34-2.98)	0.001
	Glycemia ≥ 6.1 mmol/L	2.56 (1.34-1.88)	0.004	1.79 (0.99-3.23)	0.052	0.46 (0.30-0.70)	<0.001
SRCC	Triglycerides ≥ 1.7 mmol/L	0.42 (0.05-3.71)	0.437	0.67 (0.13-3.43)	0.628	0.55 (0.15-1.96)	0.352
	BMI ≥ 25 kg/m^2	1.92 (0.41-8.99)	0.405	0.87 (0.20-3.77)	0.856	1.25 (0.44-3.54)	0.677
	Hypertension	0.89 (0.17-4.76)	0.896	0.49 (0.11-2.18)	0.350	0.72 (0.24-2.15)	0.558
	Low HDL-C	1.80 (0.42-7.65)	0.427	8.36 (1.72-40.54)	0.008	3.88 (1.42-10.58)	0.008
	Glycemia ≥ 6.1 mmol/L	4.02 (0.83-19.52)	0.085	9.01 (2.02-40.21)	0.004	5.75 (2.01-16.41)	0.001
Components	Triglycerides ≥ 1.7 mmol/L	1.12 (0.66-1.88)	0.679	0.74 (0.46-1.18)	0.205	0.90 (0.64-1.28)	0.569
	BMI ≥ 25 kg/m^2	0.53 (0.28-1.02)	0.058	0.94 (0.61-1.46)	0.788	0.78 (0.54-1.12)	0.176
	Hypertension	0.84 (0.52-1.35)	0.464	0.92 (0.63-1.35)	0.681	0.89 (0.66-1.19)	0.429
	Low HDL-C	1.25 (0.79-1.99)	0.341	1.58 (1.09-2.30)	0.016	1.45 (1.09-1.94)	0.012
	Glycemia ≥ 6.1 mmol/L	1.25 (0.75-2.08)	0.383	1.39 (0.92-2.08)	0.117	1.33 (0.97-1.82)	0.079

Statistics: Multivariate logistic regression. Mucinous AC: mucinous adenocarcinoma; SRCC: signet-ring cell carcinoma; Components: adenocarcinoma with mucinous carcinoma components; LN: lymph node.

9.01, 95% CI: 2.02-40.21, P=0.004), high grade (OR=1.78, 95% CI: 1.27-2.48, P=0.001), positive LN (OR=1.37, 95% CI: 1.06--1.78, P=0.017), and high TNM stage (OR=1.37, 95% CI: 1.06-1.78, P=0.016) in male, while hyperglycemia was only significantly correlated with increased risk of MAC (OR=2.56, 95% CI: 1.34-1.88, P=0.004) in female (**Tables 4**, **5**).

Low HDL-C was significantly correlated with increased risk of MAC (OR=3.06, 95% CI: 1.66-5.66, P<0.001), deep invasion (OR=1.70, 95% CI: 1.20-2.43, P=0.003), positive LN (OR=1.76, 95% CI: 1.30-2.38, P<0.001), and high TNM stage (OR=1.85, 95% CI: 1.36-2.50, P<0.001) in female, while low HDL-C was significantly correlated with increased risk of SRCC (OR=8.36,

Table 5. Association between components of metabolic syndrome and adverse pathological features in patients with colorectal cancer

Factors	MetS components	Female		Male		Overall	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Hige Grade	Triglycerides ≥ 1.7 mmol/L	0.96 (0.62-1.50)	0.866	1.20 (0.83-1.72)	0.338	1.09 (0.83-1.45)	0.532
	BMI ≥ 25 kg/m^2	1.0 (0.63-1.59)	0.990	0.89 (0.61-1.30)	0.554	0.92 (0.69-1.24)	0.599
	Hypertension	1.15 (0.79-1.67)	0.467	0.86 (0.63-1.18)	0.356	0.96 (0.76-1.22)	0.739
	Low HDL-C	1.35 (0.92-1.99)	0.126	1.21 (0.87-1.68)	0.255	1.25 (0.98-1.61)	0.074
	Glycemia ≥ 6.1 mmol/L	1.25 (0.82-1.90)	0.297	1.78 (1.27-2.48)	0.001	1.55 (1.20-2.02)	0.001
Deep Invasion	Triglycerides ≥ 1.7 mmol/L	0.64 (0.44-0.92)	0.017	0.73 (0.54-1.0)	0.048	0.69 (0.55-0.88)	0.003
	BMI ≥ 25 kg/m^2	1.0 (0.67-1.50)	0.986	0.84 (0.62-1.15)	0.276	0.91 (0.71-1.17)	0.458
	Hypertension	0.97 (0.70-1.34)	0.845	0.95 (0.73-1.24)	0.717	0.97 (0.79-1.19)	0.758
	Low HDL-C	1.70 (1.20-2.43)	0.003	2.0 (1.47-2.71)	<0.001	1.86 (1.48-2.35)	<0.001
	Glycemia ≥ 6.1 mmol/L	1.28 (0.87-1.86)	0.207	0.88 (0.65-1.19)	0.401	1.02 (0.80-1.28)	0.896
Positive LN	Triglycerides ≥ 1.7 mmol/L	0.53 (0.37-0.75)	<0.001	0.79 (0.58-1.02)	0.066	0.67 (0.54-0.83)	<0.001
	BMI ≥ 25 kg/m^2	0.96 (0.67-1.37)	0.822	0.94 (0.72-1.24)	0.671	0.94 (0.76-1.17)	0.594
	Hypertension	1.25 (0.94-1.67)	0.131	0.87 (0.69-1.09)	0.220	0.99 (0.83-1.18)	0.892
	Low HDL-C	1.76 (1.30-2.38)	<0.001	1.20 (0.94-1.53)	0.144	1.39 (1.15-1.67)	0.001
	Glycemia ≥ 6.1 mmol/L	1.10 (0.80-1.53)	0.554	1.37 (1.06-1.78)	0.017	1.27 (1.04-1.56)	0.020
High TNM stage	Triglycerides ≥ 1.7 mmol/L	0.53 (0.38-0.76)	<0.001	0.84 (0.63-1.11)	0.212	0.71 (0.57-0.88)	0.002
	BMI ≥ 25 kg/m^2	0.89 (0.62-1.27)	0.524	0.86 (0.66-1.13)	0.284	0.87 (0.70-1.08)	0.197
	Hypertension	1.24 (0.93-1.66)	0.138	0.84 (0.67-1.05)	0.126	0.96 (0.81-1.15)	0.688
	Low HDL	1.85 (1.36-2.50)	<0.001	1.25 (0.98-1.59)	0.070	1.45 (1.20-1.74)	<0.001
	Glycemia ≥ 6.1 mmol/L	1.06 (0.77-1.48)	0.713	1.37 (1.06-1.78)	0.016	1.25 (1.03-1.54)	0.028

Statistics: Multivariate logistic regression. LN: lymph node.

95% CI: 1.72-40.54, P=0.008), AC with components (OR=1.58, 95% CI: 1.09-2.30, P=0.016), and deep invasion (OR=2.0, 95% CI: 1.47-2.71, P<0.001) in male (**Tables 4**, **5**).

The results also showed that hypertriglyceridemia was negatively associated with deep invasion (OR=0.64, 95% CI: 0.44-0.92, P=0.017), positive lymph node status (OR=0.53, 95% CI: 0.37-0.75, P<0.001), and high TNM stage (OR=0.53, 95% CI: 0.38-0.76, P<0.001) in women (**Table 5**), while hypertriglyceridemia was only negatively associated with deeper invasion (OR=0.73, 95% CI: 0.54-1.0, P=0.048) in men (**Table 5**).

In addition, hypertension was negatively associated with increased risk of MAC (OR=0.54, 95% CI: 0.30-0.97, P=0.040) in men (**Table 4**), but not in women (P>0.05). High BMI was not significantly associated with the assessed pathological features of CRC (P>0.05).

Discussion

MetS and its components are related to pathological features of many kinds of cancer, such as prostate cancer, ovarian cancer, and bladder cancer [12-14]. MetS predicted risk of poor differentiation and LN metastasis in ovarian cancer [13]. The presence of MetS was associated with increased risk of higher T stage and histological grade in bladder cancer [14]. Our present study suggested that the presence of MetS predicted risk of more aggressive subtypes (SRCC and MAC), high grade, lymph node metastasis, and high TNM stage for all patients, while the presence of MetS in female predicted risk of MAC, SRCC, high grade, positive LN, and high TNM stage. However, the presence of MetS in male only predicted the risk of SRCC and high grade. In a recent report, MetS was positively associated with cancer mortality in women, but not in men. Meanwhile, MetS was associated with a high risk of colorectal cancer death in women [3]. Our results support the notion that MetS predicted risk of adverse pathological features and poor prognosis of CRC in women.

SRCC is extremely rare and even more aggressive than MAC [15, 16]. Molecular features of colorectal mucinous carcinoma are different from those of classic adenocarcinoma [17]. Compared with classic adenocarcinoma, colorectal SRCC shows decreased intracellular adhesion molecules, high frequency of RAS or

RAF mutation, stable microsatellite instability/CpG island methylation phenotype, and high frequency of loss of heterozygosity [18]. The aggressive behavior of SRCC was supposed to be associated with the above specific molecular features. Moreover, MAC is also different from SRCC in biological behavior. Colorectal MAC with absence of signet-ring cell component had a favorable effect on survival of the patients [19].

To further clarify the relationship between MetS and pathological features in CRC, multivariate logistic regression model including all components of MetS and age was used in the present study. The results demonstrated that hyperglycemia predicted risk of MAC, SRCC, positive LN status, and high TNM stage in all patients. However, hyperglycemia predicted risk of high grade, positive LN status and high TNM stage in men, but not in women. Hyperglycemia is characteristic of diabetes or pre-diabetes. Pre-diabetes is characterized by elevated blood glucose levels but not enough to diagnose as diabetes. Previous research suggested that colon cancer risk is increased in pre-diabetic men, but not in women [20]. Diabetes was reported to be significantly associated with increased risk of colorectal SRCC and AC with components [7]. Long term antidiabetic medications can significantly prolong the survival and improve the prognosis of CRC [21].

The present results also demonstrated that low HDL-C predicted risk of MAC, SRCC, positive LN status, and high TNM stage in all patients (**Tables 4**, **5**). Moreover, low HDL-C predicted positive LN status and high TNM stage in women, but not in men. It has been reported that low HDL-C is correlated with poor differentiation in some cancers such as prostate and gastric cancer [12, 22]. Low HDL-C also showed to be associated with the development of CRC [23]. It is well known that HDL transports cholesterol from cells to the liver. In addition, HDL has anti-inflammatory and antioxidant properties [24]. Our present results suggested that the presence of low HDL-C might predict adverse pathological features and poor prognosis of CRC in women. Whether low HDL-C was a causal factor for adverse pathological features still needs further investigation.

The molecular mechanism for the association between MetS or its components and pathological features is poorly understood. KRAS mutation in CRC has been linked to aggressive histological features and behavior [25]. Growing evidences suggested that hyperglycemia is likely to be a causal factor for CRC development and prognosis. At first, high glucose triggers nucleotide imbalance through O-GlcNAcylation of key enzymes and induces KRAS mutation in pancreatic cells [26]. Secondly, hyperglycemic condition can modify phosphorylation of the tumor suppressor TET2 by AMPK and regulate TET2 stability, so as to contribute to the oncogenic status [27]. Third, hyperglycemia promotes epithelial-mesenchymal-transition (EMT) and stem cell properties in pancreatic ductal epithelial cells [28]. Whether these mechanisms were associated with the effects of hyperglycemia on pathological features of CRC and prognosis needs further investigation.

Our present study also showed that hypertriglyceridemia was negatively associated with deep invasion, positive lymph node status, and high TNM stage in women, while hypertriglyceridemia was only negatively associated with deeper invasion in men. It is reported that patients with diabetes with hyperlipidemia have more well-differentiated tumors, compared with patients with only diabetes [7]. Recently, a negative correlation between hypertriglyceridemia and positive lymph node status has been described in prostate cancer [12]. The association and molecular mechanism linking hypertriglyceridemia and CRC need further investigation.

Interestingly, hypertension was shown to be negatively associated with risk of MAC for men and all subjects in the present study, the reason still needs further investigation.

Future research is needed to clarify the molecular mechanisms linking MetS and its individual components with pathogenesis and pathological features of MetS-related cancer including CRC.

This retrospective cohort study had some limitations. It was a single center clinical study and there were only 21 cases of SRCC due to the rarity of the disease. BMI values of 127 patients were unavailable, which might have led to selection bias. The present study was based on the CDS criteria for diagnosis of MetS, and the conclusions should be interpreted with caution, especially if other criteria are adopted.

In summary, MetS and its individual components are differently associated with adverse pathological features of CRC in men and women. The presence of MetS and low HDL-C in women predicted risk of MAC, LN metastasis, and high TNM stage of CRC, while the presence of hyperglycemia in men predicted risk of high histological grade, LN metastasis, and high TNM stage. Improvement of MetS and HDL-C status in women or hyperglycemia in men may improve the prognosis of CRC patient complicated with MetS.

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Disclosure of conflict of interest

None.

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References

[1] Metabolic syndrome study cooperation group of Chinese diabetes and society. Suggestions about metabolic syndrome of Chinese diabetes society. Chin J Diab 2004; 12: 156-161.

[2] Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, Panagiotakos DB and Giugliano D. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. Endocrine 2013; 44: 634-647.

[3] Watanabe J, Kakehi E, Kotani K, Kayaba K, Nakamura Y and Ishikawa S. Metabolic syndrome is a risk factor for cancer mortality in the general Japanese population: the Jichi medical school cohort study. Diabetol Metab Syndr 2019; 11: 3.

[4] Shen Z, Ye Y, Bin L, Yin M, Yang X, Jiang K and Wang S. Metabolic syndrome is an important factor for the evolution of prognosis of colorectal cancer: survival, recurrence, and liver metastasis. Am J Surg 2010; 200: 59-63.

[5] Bagante F, Spolverato G, Beal E, Merath K, Chen Q, Akgul O, Anders RA and Pawlik TM. Impact of histological subtype on the prognosis of patients undergoing surgery for colon cancer. J Surg Oncol 2018; 117: 1355-1363.

[6] Kermanshahi TR, Magge D, Choudry H, Ramalingam L, Zhu B, Pingpank J, Ahrendt S, Holtzman M, Zeh H, Bartlett D, Zureikat A and Pai RK. Mucinous and signet ring cell differentiation affect patterns of metastasis in colorectal carcinoma and influence survival. Int J Surg Pathol 2017; 25: 108-117.

[7] Sharma A, Ng H, Kumar A, Teli K, Randhawa J, Record J and Maroules M. Colorectal cancer: histopathologic differences in tumor characteristics between patients with and without diabetes. Clin Colorectal Cancer 2014; 13: 54-61.

[8] In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th edition. IARC: Lyon, France; 2010.

[9] Vallam KC, Desouza A, Bal M, Patil P, Engineer R and Saklani A. Adenocarcinoma of the rectum-A composite of three different subtypes with varying outcomes? Clin Colorectal Cancer 2016; 15: e47-52.

[10] Fletcher C. Diagnostic histopathology of tumors. 4th edition. Philadelphia: Elsevier Saunders; 2012. pp. 452-460.

[11] Amin M, Greene F and Edge S. AJCC cancer staging manual. 8th edition. New York: Springer; 2017. pp. 251-274.

[12] Lebdai S, Mathieu R, Leger J, Haillot O, Vincendeau S, Rioux-Leclercq N, Fournier G, Perrouin-Verbe MA, Doucet L, Azzouzi AR, Rigaud J, Renaudin K, Charles T, Bruyere F and Fromont G. Metabolic syndrome and low high-density lipoprotein cholesterol are associated with adverse pathological features in patients with prostate cancer treated by radical prostatectomy. Urol Oncol 2018; 36: 80, e17-e24..

[13] Chen Y, Zhang L, Liu W and Wang K. Case-control study of metabolic syndrome and ovarian cancer in Chinese population. Nutr Metab (Lond) 2017; 14: 21.

[14] Sha N, Xu H, Chen T, Tian DW, Xie WQ, Xie LG, Zhang Y, Xing C, Liu XT, Shen ZH, Wu ZL, Hu HL and Wu CL. The evaluation of the association between the metabolic syndrome and tumor grade and stage of bladder cancer in a Chinese population. Onco Targets Ther 2016; 9: 1175-1179.

[15] Kong X, Zhang X, Huang Y, Tang L, Peng Q and Li J. Characteristics and prognostic factors of colorectal mucinous adenocarcinoma with signet ring cells. Cancer Manag Res 2017; 9: 573-580.

[16] Pozos-Ochoa LI, Lino-Silva LS, Leon-Takahashi AM and Salcedo-Hernandez RA. Prognosis of signet ring cell carcinoma of the colon and rectum and their distinction of mucinous adeno-

carcinoma with signet ring cells. A comparative study. Pathol Oncol Res 2018; 24: 609-616.
[17] Nam JY, Oh BY, Hong HK, Bae JS, Kim TW, Ha SY, Park D, Lee WY, Kim HC, Yun SH, Park YA, Joung JG, Park WY and Cho YB. Molecular characterization of colorectal signet-ring cell carcinoma using whole-exome and RNA sequencing. Transl Oncol 2018; 11: 836-844.
[18] Tajiri K, Sudou T, Fujita F, Hisaka T, Kinugasa T and Akagi Y. Clinicopathological and corresponding genetic features of colorectal signet ring cell carcinoma. Anticancer Res 2017; 37: 3817-3823.
[19] Sung CO, Seo JW, Kim KM, Do IG, Kim SW and Park CK. Clinical significance of signet-ring cells in colorectal mucinous adenocarcinoma. Mod Pathol 2008; 21: 1533-1541.
[20] Onitilo AA, Berg RL, Engel JM, Glurich I, Stankowski RV, Williams G and Doi SA. Increased risk of colon cancer in men in the prediabetes phase. PLoS One 2013; 8: e70426.
[21] Peng F, Hu D, Lin X, Liang B, Chen Y, Zhang H, Xia Y, Lin J, Zheng X and Niu W. Impact of long-term antihypertensive and antidiabetic medications on the prognosis of post-surgical colorectal cancer: the Fujian prospective investigation of cancer (FIESTA) study. Aging (Albany NY) 2018; 10: 1166-1181.
[22] Guo E, Chen L, Xie Q, Chen J, Tang Z and Wu Y. Serum HDL-C as a potential biomarker for nodal stages in gastric cancer. Ann Surg Oncol 2007; 14: 2528-2534.
[23] Choi YJ, Lee DH, Han KD, Shin CM and Kim N. Abdominal obesity, glucose intolerance and decreased high-density lipoprotein cholesterol as components of the metabolic syndrome are associated with the development of colorectal cancer. Eur J Epidemiol 2018; 33: 1077-1085.
[24] Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V and Fruchart JC. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med 2007; 357: 1301-1310.
[25] Jang S, Hong M, Shin MK, Kim BC, Shin HS, Yu E, Hong SM, Kim J, Chun SM, Kim TI, Choi KC, Ko YW and Kim JW. KRAS and PIK3CA mutations in colorectal adenocarcinomas correlate with aggressive histological features and behavior. Hum Pathol 2017; 65: 21-30.
[26] Hu CM, Tien SC, Hsieh PK, Jeng YM, Chang MC, Chang YT, Chen YJ, Lee EYP and Lee WH. High glucose triggers nucleotide imbalance through O-GlcNAcylation of key enzymes and induces KRAS mutation in pancreatic cells. Cell Metab 2019; 29: 1334-1349, e10.
[27] Wu D, Hu D, Chen H, Shi G, Fetahu IS, Wu F, Rabidou K, Fang R, Tan L, Xu S, Liu H, Argueta C, Zhang L, Mao F, Yan G, Chen J, Dong Z, Lv R, Xu Y, Wang M, Ye Y, Zhang S, Duquette D, Geng S, Yin C, Lian CG, Murphy GF, Adler GK, Garg R, Lynch L, Yang P, Li Y, Lan F, Fan J, Shi Y and Shi YG. Glucose-regulated phosphorylation of TET2 by AMPK reveals a pathway linking diabetes to cancer. Nature 2018; 559: 637-641.
[28] Rahn S, Zimmermann V, Viol F, Knaack H, Stemmer K, Peters L, Lenk L, Ungefroren H, Saur D, Schafer H, Helm O and Sebens S. Diabetes as risk factor for pancreatic cancer: hyperglycemia promotes epithelial-mesenchymal-transition and stem cell properties in pancreatic ductal epithelial cells. Cancer Lett 2018; 415: 129-150.