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Gamma-glutamyl transferase to aspartate aminotransferase ratio (GSR) predicts prognoses in patients with colorectal cancer with liver metastasis after microwave ablation

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Abstract

Background Microwave ablation (MWA) is widely used to eliminate colorectal liver metastases (CRLM). However, the risk of tumor recurrence is difficult to predict due to lack of reliable clinical and biological markers. Elevation of gamma-glutamyl transferase (GGT) and aspartate transaminase (AST) provides signals for liver inflammation and cancer progression. The present study evaluated the association between pre-ablation GGT to AST ratio index (GSR) and hepatic recurrence in patients with CRLM after MWA.

Methods A retrospectively analyzed 192 CRLM patients who underwent MWA from January 2013 to December 2017. Pre-ablation GSR was classified into high (≤ 2.34) or low (> 2.34) using the upper quartile value. The prognostic value of GSR and other risk factors for liver progression-free survival (LPFS) and cancer-specific survival (CSS) were evaluated by univariate and multivariate analyses.

Results High GSR was significantly associated with males ($P=0.041$), the presence of cholelithiasis ($P=0.012$), but not pre-ablation chemotherapy ($P=0.355$), which caused significantly increased levels of GGT ($P=0.015$) and AST ($P=0.008$). GSR showed a significant association with LPFS and CSS through univariate analysis ($P=0.002$ and 0.006) and multivariate analysis ($P=0.043$ and 0.037). The subgroup analysis demonstrated no interaction between GSR and all variables except for distribution in the sub-analysis of LPFS.

Conclusions Our findings suggest that the pre-ablation GSR can be considered as a promising prognostic indicator for poor prognosis of patients with CRLM underwent MWA.

Trial registration Not applicable.

Keywords Colorectal cancer, Liver metastasis, Microwave ablation, Gamma-glutamyl transpeptidase, Aspartate aminotransferase

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Background

Colorectal liver metastases (CRLM) are a major challenge in clinical oncology and a leading cause of mortality in patients with advanced colorectal cancer (CRC) [1]. The liver is the primary site of metastatic spread, and most patients with CRC eventually succumb to hepatic involvement [2]. Several randomized controlled trials have shown that ablative interventions, especially microwave ablation (MWA), can be effectively integrated with systemic and surgical therapies [3–6]. This multimodal approach significantly improves the prognosis.

Despite the growing interest in MWA for CRLM, biomarkers specifically tailored for MWA remain poorly developed. Although previous studies have investigated the prognostic factors of liver metastases, such as the clinical risk score (CRS) and tumor burden score (TBS) [7, 8], and clinical biomarkers such as carcinoembryonic antigen (CEA) and gamma-glutamyl transferase (GGT) [9, 10], these indicators have been mainly developed for post-hepatectomy prediction. Some studies have suggested that circulating markers, including alpha-fetoprotein, prothrombin time activity, and albumin-bilirubin, could also be used for predicting ablation outcomes [11–13]. However, it's important to note that these investigations primarily focused on hepatocellular carcinoma (HCC), and there is currently no definitive evidence supporting the applicability of these peripheral blood biomarkers in the context of CRLM.

Circulating GGT and Aspartate aminotransferase (AST) are two well-known clinical parameters of hepatic injury, both of which are predominantly present in the liver, but are also found in other organs, such as the heart, kidney, and muscle [14, 15]. Meanwhile, the levels of serum liver GGT and AST are strongly environmentally and genetically correlated with each other [16] and share genetic variances [17]. In terms of cellular biology, GGT is a membrane-bound enzyme involved in numerous cellular processes, including amino acid transfer and glutathione (GSH) metabolism, which plays a crucial role in the antioxidant system [14]. Emerging evidence has shown that serum GGT levels serve as an indicator of oxidative stress [18]. AST, which is cytoplasmic or mitochondrial, catalyzes the transfer of amino groups to generate products involved in gluconeogenesis and amino acid metabolism [19]. Increased levels of GGT and AST are commonly observed in metabolic dysfunction-associated fatty liver disease (MAFLD), alcoholic liver disease, hepatitis infection, and drug toxicity [19–21].

However, GGT is more significant in biliary injury, cholestatic liver disease, and tumor progression than AST, as evidenced by the strong correlation between serum levels of GGT and various cancers, such as primary CRC and CRLM [22–24]. Mechanistically, the main reason for the increase in GGT in liver tumors is the production of high levels of reactive oxygen species to combat tumor cells [25]. Additionally, the tumor microenvironment may contain factors, such as inflammatory mediators, that can also stimulate the expression of GGT [26]. To minimize the non-tumor impact of GGT, we introduce the new parameter GGT/AST ratio (GSR) to CRLM.

The excellent diagnostic significance of the GSR in biliary obstruction and HCC has indicated that this division by AST likely specifies and strengthens the clinical value of GGT [27, 28]. Thus, we aim to explore whether the GSR can predict the progression of CRLM and serve as a simple and cost-effective clinical marker.

Methods

Patient enrollment and baseline information

We retrospectively analyzed data from 306 patients diagnosed with CRC who underwent hepatic metastasis ablation at the Sixth Affiliated Hospital of Sun Yat-sen University between January 2013 and December 2017. In adherence to the retrospective nature of this study, written informed consent was obtained from all patients, and the Clinical Research Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University approved the research protocol.

In types of liver malignancies, GGT was correlated with tumor burdens, but not AST. But some tumors GGT's increasea not related to tumor characteristics. Consistent with our study, GGT didn't reflect the tumor burden. Chemotherapy induced hepatic toxicity increased GGT, but not GSR. It is know that, increased GGT or AST because of biliary obstruction.

The inclusion and exclusion criteria, diagnostic procedures, and treatment modalities corresponded to those explicated comprehensively within our prior study [29, 30], supplemented by additional cases. Specifically, inclusion criteria for the study were as follows: 1) patients diagnosed with CRC confirmed by pathological examination; 2) patients with liver-limited metastases and no major vascular invasion confirmed by contrast-enhanced computed tomography (CECT), contrast-enhanced magnetic resonance imaging (CEMRI), or positron emission tomography-computed tomography (PET-CT); 3) number of CRLM ≤ 9, and size of CRLM ≤ 5 cm. Exclusion criteria included: 1) patients with Child–Pugh class C or severe coagulation disorders (platelet count $< 50 \times 10^3$/μl, prothrombin time > 20 s); 2) patients with poor performance status (ECOG PS > 2); 3) patients with extrahepatic metastases prior to ablation ($N = 74$); 4) Patients with lesions that could not be completely ablated due to proximity to major biliary structures or adherence to the gastrointestinal tract after the initial ablation ($N = 7$);

5) patients with unresectable primary lesions ($N=7$). (Fig. 1). The final cohort encompassed 192 eligible cases. For these patients, comprehensive demographic data, laboratory results, imaging findings, therapy protocols, and follow-up records were systematically collected. Additionally, a series of routine tests, including complete blood counts, serum biochemical indices, and tumor markers, were performed within one week before the MWA to ensure a thorough evaluation of each case.

The decision to employ MWA was made after comprehensive discussions by a multi-disciplinary team (MDT). Each patient's treatment plan was carefully deliberated by the MDT, and upon reaching a consensus, the proposed strategy was communicated to the patient, from whom written informed consent was then obtained. Post-MWA, routine chemotherapy was administered as per the MDT's collective decision, tailored to each patient's individual clinical scenario.

Microwave ablation procedure

The preparatory phase for MWA involved the early execution of enhanced ultrasound to ascertain the lesions' precise location, number, and size. Patients were required to provide informed consent, supplemented by administering 50 mg of pethidine hydrochloride intramuscularly roughly 30 min before the procedure, with an additional 50 mg administered as needed throughout ablation. Our institution utilized a 2450-MHz MWA system (KY2000; Nanjing Kangyou Biological Energy Co. Ltd, Nanjing, China), encompassing a microwave generator with a power output spanning 1–100 W, a flexible coaxial cable, and a cooling shaft antenna (KY-2450-b; Nanjing Kangyou Biological Energy Co. Ltd., Nanjing, China). The procedures were conducted under real-time ultrasound guidance (LOGIQ E9; GE Healthcare, Milwaukee, WI, USA).

Local anesthetic drug was administered using 2% lidocaine prior to puncture, with a 24-G needle measuring 10 cm utilized to ensure the deposition of lidocaine within the hepatic capsule. The antenna, guided by ultrasound, was subsequently inserted at the center of the largest section, extending 5 mm beyond the lesion's deep edge. The energy output was tailored within the range of 45–60 W, delivered for 5–15 min to guarantee

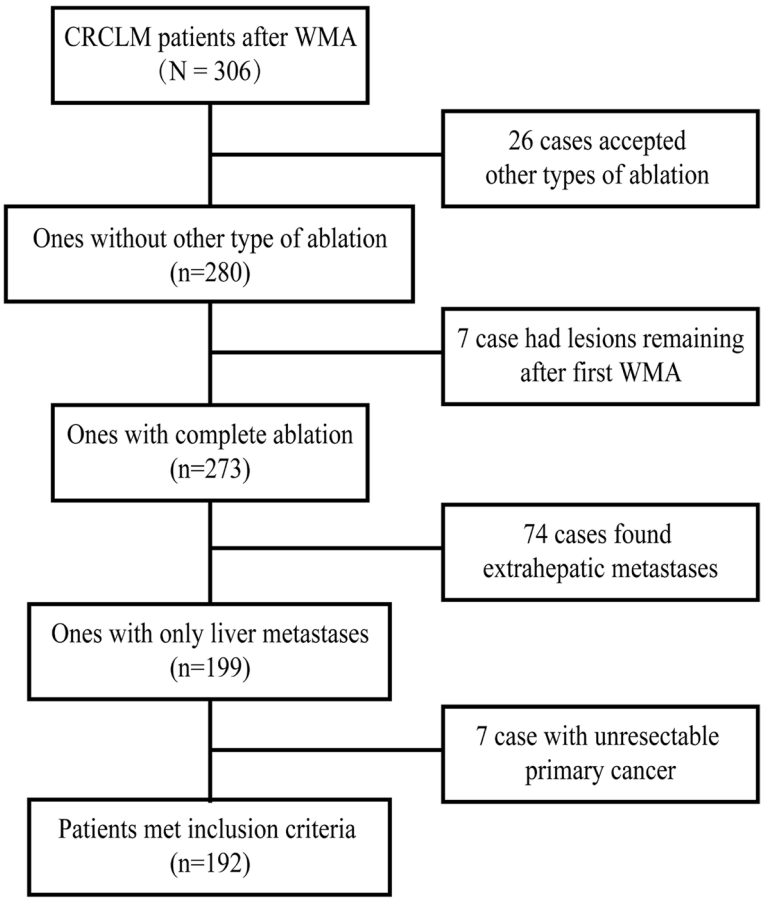

Fig. 1 Procedure of colorectal cancer liver metastases patients' disposition for retrospective analysis

comprehensive lesion ablation, alongside a margin of at least 5 mm encompassing the surrounding liver parenchyma. After the ablation of the needle tract, the procedure was concluded.

Follow-up protocol

Patients were recommended to undergo serological and imaging assessments every three months. Furthermore, a recurrent multidisciplinary evaluation was conducted to explore further treatment strategies for patients exhibiting local or systemic disease progression. Liver progression-free survival (LPFS) was defined as the temporal interval spanning ablation to hepatic progression or worsening. Likewise, cancer-specific survival (CSS) was computed from ablation to the point of the patient's last follow-up or death from cancer.

Statistical analysis

The normal ranges recommended by our institutional testing equipment and the threshold values for serum GGT and AST were established at 60 U/L and 40 U/L, respectively. The GSR was delineated as GGT/AST, with the upper quartile value of 2.34 constituting the demarcation. Baseline data from the patient pool was categorized into two groups to facilitate comparative analysis. The Pearson chi-square and Fisher's exact tests were used to check differences within categorical variables. As for non-normally distributed continuous variables and categorical variables, the Mann–Whitney U test was employed to explore discrepancies between the two cohorts. Employing the Kaplan–Meier methodology, estimations were conducted for LPFS and CSS, and the disparities in survival were subjected to the log-rank test. Univariate and multivariate analyses were affected by utilizing the Cox proportional hazard regression model, wherein factors manifesting a P value below 0.1, concurrently demonstrated clinical significance, were inducted into the multivariate analysis. A two-tailed P value below 0.05 denoted statistical significance. The statistical software employed encompassed SPSS version 22.0 (IBM SPSS, Chicago, IL, USA) and R (version 4.2.3).

Results

Correlations among liver enzymes and clinicopathological parameters

Our investigation revealed a robust positive correlation between GSR and GGT levels ($r=0.77$, $P<0.001$, Supplementary Fig. 1). Notably, this correlation persisted across both high and low GSR groups, affirming the consistency of this association (both $P<0.05$). Conversely, no statistically significant correlation emerged between GSR and AST levels (all $P>0.05$), emphasizing the specificity of GSR as an indicator linked to GGT.

The normality status of GGT and AST levels exhibited no discernible associations with demographic factors, such as age and sex (both $P>0.05$, Table 1). Similarly, prevalent liver and gallbladder diseases, including cholelithiasis and hepatic steatosis, showed no significant impact on GGT and AST levels. Furthermore, no correlations were identified with primary tumors' clinical staging and pathological subtyping.

The administration of pre-ablation chemotherapy correlated with a notable elevation in GGT ($P=0.015$) and AST ($P=0.008$) levels. The distribution of liver metastases and prior hepatic resection were also associated with increased GGT levels ($P<0.05$). Interestingly, GSR exhibited a positive correlation with GGT levels yet remained resilient to the influence of pre-ablation chemotherapy and hepatectomy (both $P>0.05$). In patients with cholelithiasis, GSR levels increased significantly ($P=0.012$).

Follow-up and survival analysis

The follow-up period concluded in August 2023, revealing median durations of CSS and LPFS measuring 94.2 and 14.1 months, respectively. Among the 192 CRLM patients, 74 (38.5%) died of tumor-related complications, while 113 (58.9%) experienced hepatic recurrence. Notably, three-year CSS and LPFS rates were registered at 22.9% and 56.8%, respectively.

Furthermore, both elevated GGT and GSR levels were associated with inferior LPFS ($P=0.003$ and 0.002, respectively, Fig. 2A and C). However, exclusively elevated GSR correlated with CSS ($P=0.006$, Fig. 2B), while GGT demonstrated no connection with patient CSS ($P=0.540$, Fig. 2D). Several other factors contributed to hepatic recurrence, including lymph node metastasis of the primary lesion, the quantity and distribution of liver metastases, elevated CEA levels, and prior hepatic resection (all $P<0.05$, Table 2). In addition to GSR, the differentiation grade of the primary tumor and CA19-9 levels displayed strong correlations with patient CSS ($P=0.006$ and 0.002, respectively).

To mitigate the impact of confounding variables, a multivariate Cox regression analysis was conducted, incorporating factors with P values below 0.1. Consequently, GSR stood out as a robust independent risk factor for both LPFS ($P=0.043$, HR, 95% CI: 1.84, 1.02–3.31, Table 2) and CSS ($P=0.037$, HR, 95% CI: 1.70, 1.03–2.81, Table 2). Additionally, lymph node metastasis of the primary lesion and pre-ablation surgery maintained their associations with LPFS ($P=0.003$ and 0.004, Table 2). Furthermore, elevated CA19-9 and poorly differentiated tumors emerged as independent risk factors for unfavorable CSS (both $P<0.05$, Table 2).

Subsequently, the prognostic value of GSR across distinct subgroups was examined, accompanied by assessing

Table 1 Baseline characteristics of GGT, AST and GSR groups

	n%/M [P_{25}, P_{75}]	GGT(U/L)			AST(U/L)			GSR		
Characteristics	***N* = 192**	**≤ 60**	**> 60**	***P***	**≤ 40**	**> 40**	***P***	**≤ 2.34**	**> 2.34**	***P***
Patient characteristics		148(77)	44(23)		172(90)	20(10)		144(75)	48(25)	
Age (years)				0.534			0.225			0.866
≤ 60	110(57)	83(56)	27(61)		96(56)	14(70)		82(57)	28(58)	
> 60	82(43)	65(44)	17(39)		76(44)	6(30)		62(43)	20(42)	
Sex				0.105			0.826			**0.041**
Male	129(67)	95(64)	34(77)		116(67)	13(65)		91(63)	38(79)	
Female	63(33)	53(36)	10(23)		56(33)	7(35)		53(37)	10(21)	
HBsAg				0.240			0.780			0.345
Negative	164(85)	124(84)	40(91)		146(85)	18(90)		121(84)	43(90)	
Positive	28(15)	24(16)	4(9)		26(15)	2(10)		23(16)	5(10)	
Hepatic steatosis				1.000			0.383			0.366
Absent	176(92)	136(92)	40(91)		156(91)	20(100)		134(93)	42(88)	
Present	16(8)	12(8)	4(9)		16(9)	0(0)		10(7)	6(12)	
Diabetes mellitus				0.127			0.738			0.465
Absent	166(87)	131(89)	35(80)		149(87)	17(85)		126(88)	40(83)	
Present	26(13)	17(11)	9(20)		23(13)	3(15)		18(12)	8(17)	
Cholelithiasis				0.060			0.745			**0.012**
Absent	165(86)	131(89)	34(77)		147(85)	18(90)		129(90)	36(75)	
Present	27(14)	17(11)	10(23)		25(15)	2(10)		15(10)	12(25)	
Primary tumor characteristics										
Location of primary tumors				0.731			0.059			0.317
Colon	96(50)	73(49)	23(52)		82(48)	14(70)		75(52)	21(44)	
Rectum	96(50)	75(501)	21(48)		90(52)	6(30)		69(48)	27(66)	
Pathological type				0.352			0.450			0.091
High differentiation	45(23)	38(26)	7(16)		42(24)	3(15)		38(27)	7(15)	
Mild differentiation	132(69)	98(66)	34(78)		116(67)	16(80)		96(67)	36(75)	
Low differentiation	8(4)	7(5)	1(2)		8(5)	0(0)		5(3)	3(6)	
Other	4(2)	3(2)	1(2)		3(2)	1(5)		3(2)	1(2)	
Missing	3(2)	2(1)	1(2)		3(2)	0(0)		2(1)	1(2)	
T stage				0.237			0.424			0.109
T2	16(8)	13(10)	3(7)		15(9)	1(5)		13(9)	3(6)	
T3	158(82)	125(84)	33(75)		142(83)	16(80)		122(86)	36(75)	
T4	13(7)	8(5)	5(11)		11(6)	2(10)		7(5)	6(13)	
Missing	5(3)	2(1)	3(7)		4(2)	1(5)		0(0)	3(6)	
Lymph node metastasis				0.719			0.230			0.120
Negative	73(38)	56(39)	17(39)		68(40)	5(25)		51(35)	22(46)	
Positive	114(59)	90(60)	24(55)		100(58)	14(70)		91(64)	23(48)	
Missing	5(3)	2(1)	3(6)		4(2)	1(5)		2(1)	3(6)	
Liver metastasis characteristics										
Presentation				0.689			0.083			0.255
Metachronous	39(20)	31(21)	8(18)		38(22)	1(5)		32(22)	7(15)	
Synchronous	153(80)	117(79)	36(82)		134(78)	19(95)		112(78)	41(85)	
Number				0.119			0.187			0.868
Solitary	94(49)	77(52)	17(39)		87(51)	7(35)		71(49)	23(48)	
Multiple	98(51)	71(48)	27(61)		85(49)	13(65)		73(51)	25(52)	
Maximum size (mm)				0.541			0.133			0.772
≤ 30	182(95)	139(94)	43(98)		90(52)	14(70)		136(94)	46(96)	
> 30	10(5)	9(6)	1(2)		82(48)	6(30)		8(6)	2(4)	

Table 1 (continued)

Characteristics	n%/M [P_{25}, P_{75}]	GGT(U/L)			AST(U/L)			GSR		
	N = 192	≤60	>60	*P*	≤40	>40	*P*	≤2.34	>2.34	*P*
Distribution				**0.014**			0.367			0.220
Unilobar	141(73)	115(78)	26(59)		128(74)	13(65)		109(76)	32(67)	
Bilobar	51(27)	33(22)	18(41)		44(26)	7(35)		24(24)	16(33)	
Pre-ablation treatment										
Pre-ablation chemotherapy				**0.015**			**0.008**			0.355
No	83(43)	71(48)	12(27)		80(48)	3(15)		65(45)	18(37)	
Yes	109(57)	77(52)	32(73)		92(52)	17(85)		79(55)	30(63)	
Pre-ablation hepatectomy				**0.022**			0.622			0.141
No	161(84)	129(87)	32(73)		145(84)	16(80)		124(86)	37(77)	
Yes	31(16)	19(13)	12(27)		27(16)	4(20)		20(14)	11(23)	

GGT Gamma-glutamyl transpeptidase, *AST* Aspartate aminotransferase, *GSR* Gamma-glutamyl transferase to aspartate aminotransferase ratio index, *HBsAg* hepatitis B surface antigen

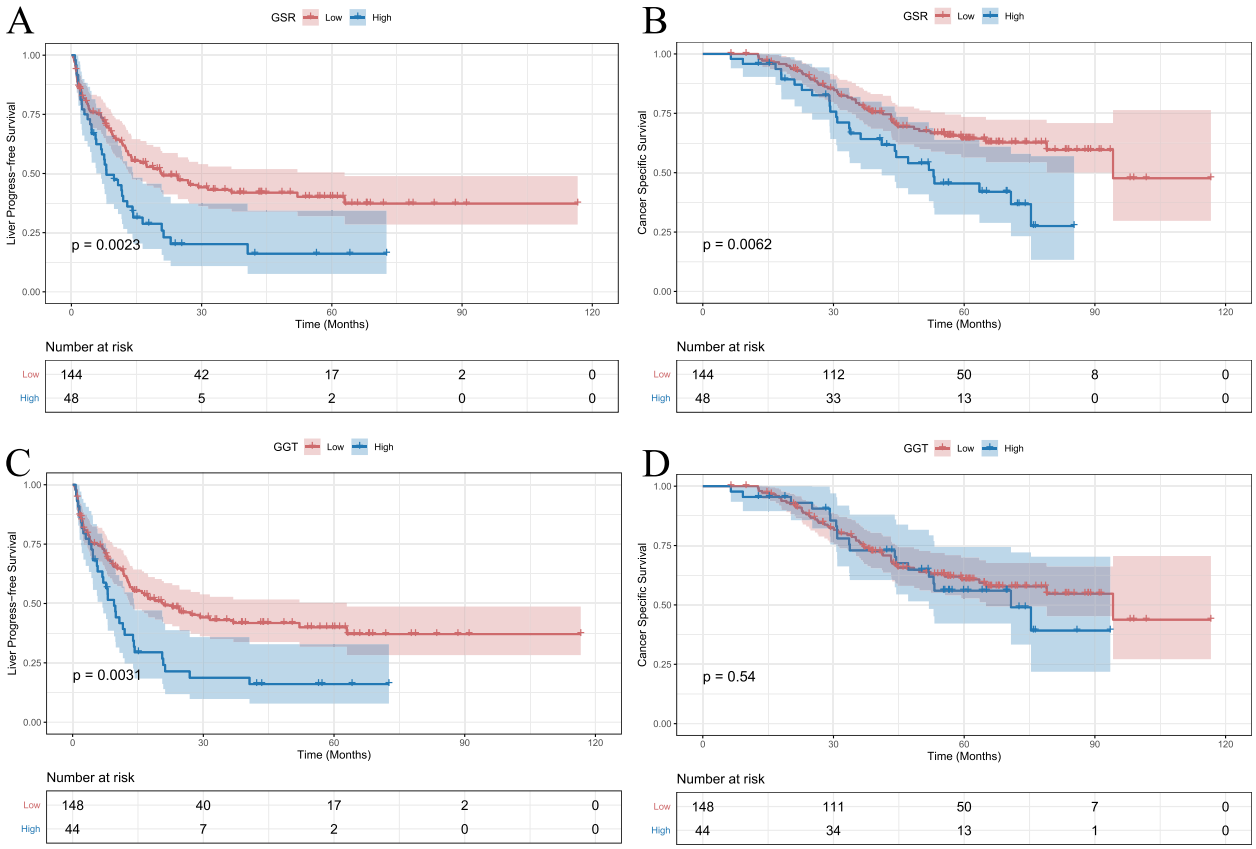

Fig. 2 Analysis of the Kaplan–Meier method for prognostic value of GSR in LPFS and CSS of CRLM after MWA. **A**, **B** Higher GSR predicted worse LPFS (**A**) and CSS (**B**) with MWA in CRLM patients ($P = 0.002$ and 0.006). **C**, **D** GGT was associated with CRLM patients' LPFS treated with MWA ($P = 0.003$), but not associated with CSS ($P = 0.540$)

interactions between GSR and diverse variables (Fig. 3 and Supplementary Fig. 2). Among the subgroups, only the distribution of liver metastases unveiled an interactive effect with GSR concerning LPFS ($P = 0.025$, Fig. 3).

Discussion

In this study, we aimed to investigate the prognostic value of GSR, a new index based on the ratio of GGT to AST, in patients with CRLM undergoing MWA. Our

Table 2 Univariate and multivariate analysis of factors of LPFS and CSS

Factors	LPFS						CCS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Patient characteristics												
Age (> 60 years)	0.88	(0.62, 1.24)	0.449				1.27	(0.81, 2.01)	0.301			
Sex (male vs female)	0.75	(0.52, 1.08)	0.122				0.98	(0.60, 1.58)	0.922			
HBsAg (+)	1.13	(0.71, 1.80)	0.622				0.97	(0.51, 1.85)	0.937			
Hepatic steatosis	1.04	(0.53, 2.05)	0.917				1.30	(0.60, 2.84)	0.511			
Diabetes mellitus	1.04	(0.63, 1.71)	0.882				0.80	(0.40, 1.60)	0.522			
Cholelithiasis	0.78	(0.47, 1.28)	0.318				1.01	(0.53, 1.93)	0.969			
Primary tumor characteristics												
Location (colon vs rectum)	0.84	(0.60, 1.17)	0.295				1.12	(0.71, 1.77)	0.628			
Pathological type	1.39	(0.98, 1.98)	0.066	1.48	(0.98, 2.26)	0.063	2.00	(1.21, 3.28)	**0.006**	1.89	(1.13, 3.14)	**0.015**
T stage	1.54	(0.96, 2.47)	0.074	1.26	(0.74, 2.13)	0.400	1.51	(0.81, 2.79)	0.191			
Lymph node metastasis	1.70	(1.16, 2.40)	**0.006**	1.86	(1.23, 2.83)	**0.003**	1.37	(0.85, 2.21)	0.195			
Liver metastasis characteristics												
Presentation (metachronous vs synchronous)	1.26	(0.82, 1.93)	0.297				1.40	(0.74, 2.65)	0.307			
Number (solitary vs multiple)	1.57	(1.12, 2.20)	**0.009**	1.53	(0.98, 2.38)	0.060	1.16	(0.73, 1.83)	0.526			
Size (> 30 mm)	2.00	(0.97, 4.12)	0.059	2.00	(0.50, 0.83)	0.123	2.04	(0.82, 5.09)	0.126			
Bilobar diseases	1.52	(1.05, 2.20)	**0.025**	1.19	(0.75, 1.87)	0.459	1.17	(0.70, 1.94)	0.542			
Serum biochemical indices												
Elevated CEA (> 5 ng/mL)	1.47	(1.04, 2.06)	**0.029**	1.50	(0.98, 2.31)	0.065	1.13	(0.72, 1.79)	0.594			
Elevated CA19-9 (> 37 kU/L)	1.36	(0.87, 2.12)	0.179				2.26	(1.36, 3.75)	**0.002**	2.23	(1.13, 3.14)	**0.003**
Elevated GGT (> 60 U/L)	1.76	(1.21, 2.55)	**0.003**	1.00	(0.54, 1.85)	0.989	1.18	(0.70, 1.96)	0.544			
Elevated AST (> 40 U/L)	1.33	(0.81, 2.18)	0.266				0.69	(0.30, 1.60)	0.387			
Higher GSR (> 2.34)	1.80	(1.24, 2.60)	**0.002**	1.84	(1.02, 3.31)	**0.043**	1.93	(1.20, 3.13)	**0.006**	1.70	(1.03, 2.81)	**0.037**
Pre-ablation treatment												
Pre-ablation chemotherapy	1.05	(0.72, 1.52)	0.817				0.94	(0.59, 1.49)	0.795			
Pre-ablation hepatectomy	1.75	(1.12, 2.73)	**0.014**	2.06	(1.26, 3.37)	**0.004**	1.13	(0.64, 2.00)	0.677			

LPFS Liver progression-free survival, *CSS* Cancer-specific survival, *HR* Hazard ratio, *CI* Confidence interval, *HBsAg* Hepatitis B surface antigen, *KRAS* Kirsten rat sarcoma viral oncogene, *GGT* Gamma-glutamyl transpeptidase, *AST* Aspartate aminotransferase, *GSR* Gamma-glutamyl transferase to aspartate aminotransferase ratio index

main findings were that high GSR was associated with male and the presence of cholelithiasis but not with pre-ablation chemotherapy, which increased GGT and AST levels. In addition, high GSR was an independent predictor of poorer LPFS and CSS in patients with CRLM after MWA.

GGT and AST are well-established markers of liver function and liver injury, and previous studies have shown that their levels were not only related to liver injury but also influenced by liver tumors and their activity. [14, 31]. It is not surprising that CRLM patients have increased serum GGT and AST levels, as there is liver occupancy and hepatic toxicity from chemotherapy. One study found that increased serum GGT levels were strongly correlated with advanced tumor burden and chemotherapy in CRLM patients [22]. Although it has been widely reported that GGT is capable of predicting poor prognosis in CRLM patients, most studies have not addressed the correlation between GGT levels and tumor burden [23, 32]. Consistent with previous studies, our findings indicate that GGT is significantly increased in patients with chemotherapy and adversely affects prognosis under MWA. However, GGT levels do not show an association with tumor burden in the liver. Similarly, Seebacher et al. observed that GGT is an independent parameter for survival in patients with endometrial cancer but is not correlated with tumor stage [24]. Taken together, the prognostic classification ability of GGT should not be fully explained by tumor stage. These results suggest that GGT might be associated with systemic changes of the disease, such as inflammation and hepatotoxicity, rather than with the local neoplastic transformation [33]. The elevation of GGT and AST levels after chemotherapy indicates that these two factors

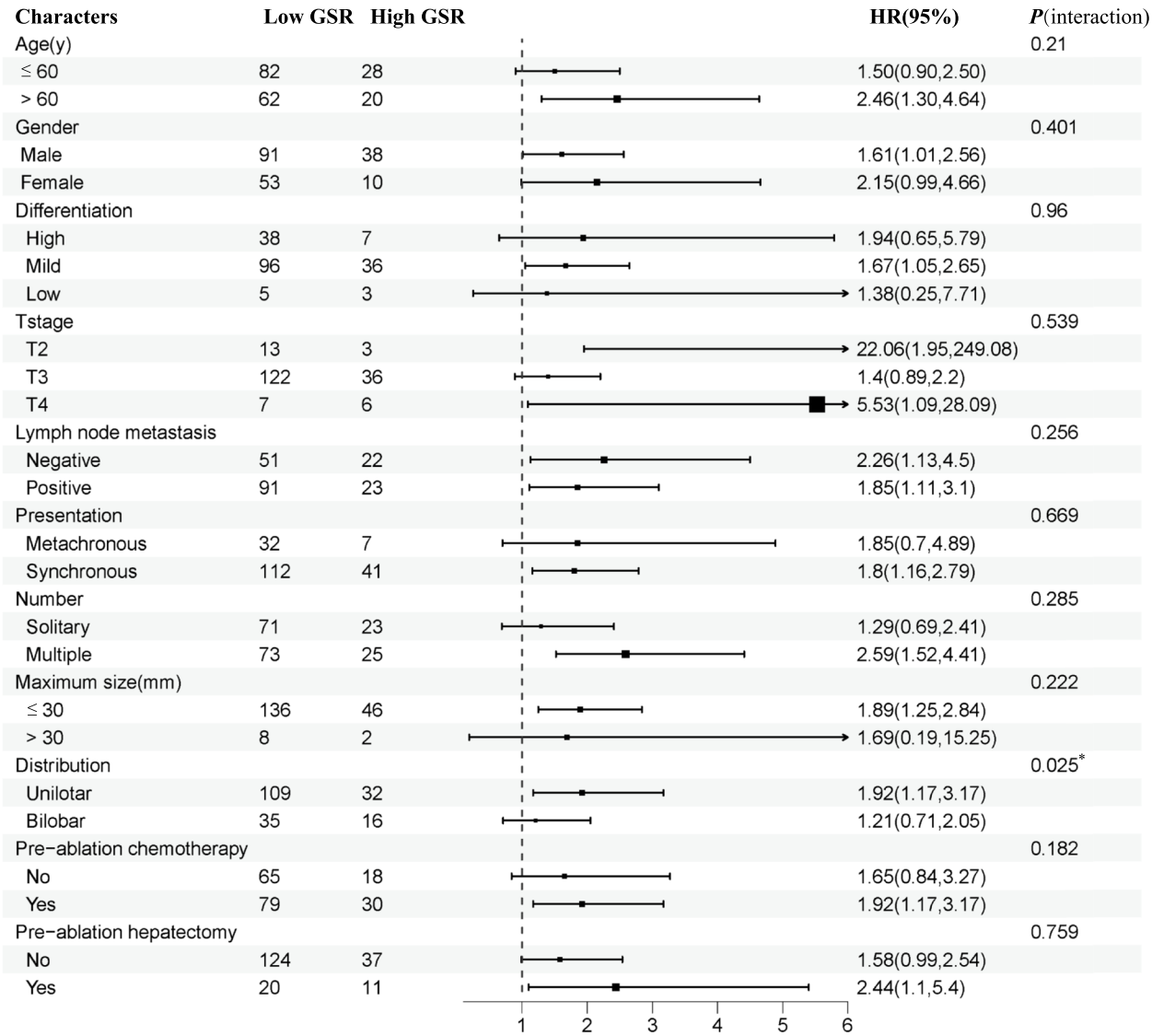

Fig. 3 The forest graph of LPFS in CRLM patients showed that there were no interact effect between subgroups expect of distribution of metastasis (interaction $P = 0.025$)

reflect drug-induced hepatotoxicity as well as cancer activity. To account for the non-tumor-related significance of GGT, the pre-ablation GGT levels were adjusted for AST levels.

However, no association between GSR and tumor stage was identified in this cohort. Unlike GGT or AST alone, the GSR was not affected by chemotherapy but was significantly correlated with cholelithiasis, which represents changes that promote tumor growth, such as inflammation [34], changes in bile flow [35], and alterations in metabolic hormone levels [36]. The strong correlation between GSR and cholelithiasis is consistent with an early finding that extrahepatic biliary atresia (EHBA) exhibited higher GSR than intrahepatic disease (IHD) [37]. This suggests that GSR is correlated with extrahepatic biliary abnormalities. Increasing evidence has recognized cholelithiasis as a condition linked to the development of multiple cancers, such as cholangiocarcinoma [38], hepatocellular carcinoma [39], colorectal cancer [40], breast cancer [41], prostate cancer [42], and kidney cancer [42]. Furthermore, research has identified cholelithiasis as an independent prognostic factor for recurrent unresectable intrahepatic cholangiocarcinoma patients who underwent MWA [43]. These findings suggest that cholelithiasis might partly support GSR as a potential risk factor for CRLM under MWA.

To the best of our knowledge, there is scarce published evidence exploring the role of the GSR in tumor biology. A recent study found that liver cancer increases serum GSR levels when compared to patients with chronic hepatitis B virus (HBV) infection [44]. Another HCC study highlighted that the GSR is a more effective biomarker than AFP for the early diagnosis of HBV-related HCC [28]. The importance of the GSR for the diagnosis of HCC was also identified by Ekmen et al. [45]. Although no correlation between the GSR and tumor parameters was found in these studies, nor in our present data, an increased GSR could reflect more active tumorigenesis based on the aforementioned studies. The potential of the GSR as a tumor parameter prompted us to investigate its prognostic significance in the CRLM cohort. As anticipated, our results demonstrated that an elevated GSR is associated with a higher risk of death and recurrence in patients with CRLM who underwent MWA. However, GGT alone is not an independent factor for CSS and LPFS. Therefore, adjustment by AST improved the prognostic predictive value of GGT.

Furthermore, in the subgroup analysis of LPFS, there was a significant interaction between the distribution of liver metastases and GSR. This implies that the distribution of liver metastases may alter the prognostic effect of GSR because patients with bilateral or multiple liver metastases may have higher tumor burden and lower ablation efficacy compared with those with single liver metastases [46]. Therefore, GSR may be a useful biomarker for risk stratification of patients with CRLM and for guiding the optimal treatment strategy.

However, our study has some limitations. First, our study was retrospective and observational, which may introduce selection bias and residual confounding. Second, our study was conducted in a single center, which may limit the external validity and reproducibility of our results. Third, our study did not explore the biological mechanisms and pathways of GSR in CRLM, which may require further experimental and molecular studies.

Conclusions

In conclusion, our study demonstrated that GSR, an index derived from the ratio of GGT to AST, is associated with LPFS and CSS in CRLM patients and may be a potential convenient and economical biomarker.

Abbreviations

GSR	Gamma-glutamyl transferase to aspartate aminotransferase ratio
MWA	Microwave ablation
CRLM	Colorectal liver metastases
HCC	Hepatocellular carcinoma
GGT	Gamma-glutamyl transferase
AST	Aspartate transaminase
LPFS	Liver progression-free survival
CSS	Cancer-specific survival
CRC	Colorectal cancer
CRS	Clinical Risk Score
TBS	Tumor Burden Score
CEA	Carcinoembryonic antigen
HBsAg	Hepatitis B surface antigen
HR	Hazard ratio
CI	Confidence interval
KRAS	Kirsten rat sarcoma viral oncogene

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03419-0.

Supplementary Material 1: Supplementary Fig. 1. The association of GGT, AST, and GSR with prognosis in patients with CRLM after MWA. The correlation coefficients (Corr.) and significance levels (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$) are shown for each pair of variables.

Supplementary Material 2: Supplementary Fig. 2. The forest graph of CSS in CRLM patients showed that there were no interact effect between all subgroups.

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Authors' contributions

MH, ZC and SQ contributed equally in this study. Conceptualization and design: MH, GL and PH; data curation: MH, ZC, SQ, JZ, YH, SP, JH, JL, ZC; formal analysis: SP, PH; original draft: MH; review & editing: ZC, SQ, YL and MA; supervision and validation: MH and GL. All authors read and approved the submitted version.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the protocol and the Declaration of Helsinki. The full protocol and informed consent form were approved by the Institutional Review Board of Sun Yat-sen University. All participants provided written consent before study entry.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Li J, Liu G, Xie X, Zhang D, Zheng R, Yang H, et al. Outcomes Following Different Thermal Ablation Strategies in Patients with Unresectable Colorectal Liver Metastases. Radiology. 2023;308:e223135.
2. Tropea A, Biondi A, Corsaro A, Donati M, Basile F, Gruttadauria S. Combined microwave thermal ablation and liver resection for single step treatment of otherwise unresectable colorectal liver metastases; a monoistitutional experiences. Eur Rev Med Pharmacol Sci. 2014;18(2 Suppl):6–10.
3. Stattner S, Primavesi F, Yip VS, Jones RP, Ofner D, Malik HZ, et al. Evolution of surgical microwave ablation for the treatment of colorectal cancer liver metastasis: review of the literature and a single centre experience. Surg Today. 2015;45:407–15.
4. Ruers T, Van Coevorden F, Punt CJA, Pierie J-PEN, Borel-Rinkes I, Ledermann JA, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst. 2017;109:djx015.
5. Eng OS, Tsang AT, Moore D, Chen C, Narayanan S, Gannon CJ, et al. Outcomes of microwave ablation for colorectal cancer liver metastases: a single center experience. J Surg Oncol. 2015;111:410–3.
6. Wang J, Liang P, Yu J, Yu MA, Liu F, Cheng Z, et al. Clinical outcome of ultrasound-guided percutaneous microwave ablation on colorectal liver metastases. Oncol Lett. 2014;8:323–6.
7. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230:309–18 discussion 318–21.
8. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A, et al. The Tumor Burden Score: A New, "Metro-ticket" Prognostic Tool For Colorectal Liver Metastases Based on Tumor Size and Number of Tumors. Ann Surg. 2018;267:132–41.
9. Cheung YS, Chan HL, Wong J, Lee KF, Poon TC, Wong N, et al. Elevated perioperative transaminase level predicts intrahepatic recurrence in hepatitis B-related hepatocellular carcinoma after curative hepatectomy. Asian J Surg. 2008;31:41–9.
10. Matias M, Casa-Nova M, Faria M, Pires R, Tato-Costa J, Ribeiro L, et al. Prognostic Factors after Liver Resection for Colorectal Liver Metastasis. Acta Med Port. 2015;28:357–69.
11. Huang J, Cui W, Xie X, Lin K, Jin D, Xie X, et al. A novel prognostic model based on AFP, tumor burden score and albumin-bilirubin grade for patients with hepatocellular carcinoma undergoing radiofrequency ablation. Int J Hyperthermia. 2023;40:2256498.
12. Zhang J, Guo G, Li T, Guo C, Han Y, Zhou X. Long-term survival analysis of ultrasound-guided percutaneous microwave ablation for hepatocellular carcinoma conforming to the milan criteria: Primary versus recurrent HCC. Int J Hyperthermia. 2024;41:2318829.
13. Tang X, Wang Q, Jin R, Hu C. A novel nomogram to predict prognosis in elderly early-stage hepatocellular carcinoma patients after ablation therapy. J Hepatocell Carcinoma. 2024;11:901–11.
14. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci. 2001;38:263–355.
15. Kalas MA, Chavez L, Leon M, Taweesedt PT, Surani S. Abnormal liver enzymes: A review for clinicians. World J Hepatol. 2021;13:1688–98.
16. Whitfield JB, Zhu G, Nestler JE, Heath AC, Martin NG. Genetic covariation between serum gamma-glutamyltransferase activity and cardiovascular risk factors. Clin Chem. 2002;48:1426–31.
17. Rahmioglu N, Andrew T, Cherkas L, Surdulescu G, Swaminathan R, Spector T, et al. Epidemiology and genetic epidemiology of the liver function test proteins. PLoS ONE. 2009;4:e4435.
18. Lee D-H, Blomhoff R, Jacobs DR. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Radic Res. 2004;38:535–9.
19. Sookoian S, Pirola CJ. Alanine and aspartate aminotransferase and glutamine-cycling pathway: Their roles in pathogenesis of metabolic syndrome. World J Gastroenterol. 2012;18:3775–81.
20. Badmus OO, Hillhouse SA, Anderson CD, Hinds TD, Stec DE. Molecular mechanisms of metabolic associated fatty liver disease (MAFLD): Functional analysis of lipid metabolism pathways. Clin Sci (Lond). 2022;136:1347–66.
21. Desjardin M, Bonhomme B, Le Bail B, Evrard S, Brouste V, Desolneux G, et al. Hepatotoxicities Induced by Neoadjuvant Chemotherapy in Colorectal Cancer Liver Metastases: Distinguishing the True From the False. Clin Med Insights-Oncol. 2019;13:1179554918825450.
22. Xiao B, Peng J, Tang J, Deng Y, Zhao Y, Wu X, et al. Serum Gamma Glutamyl transferase is a predictor of recurrence after R0 hepatectomy for patients with colorectal cancer liver metastases. Ther Adv Med Oncol. 2020;12:1758835920947971.
23. He WZ, Guo GF, Yin CX, Jiang C, Wang F, Qiu HJ, et al. Gamma-glutamyl transpeptidase level is a novel adverse prognostic indicator in human metastatic colorectal cancer. Colorectal Dis. 2013;15:e443–52.
24. Seebacher V, Polterauer S, Grimm C, Rahhal J, Hofstetter G, Bauer E-M, et al. Prognostic significance of gamma-glutamyltransferase in patients with endometrial cancer: A multi-centre trial. Br J Cancer. 2012;106:1551–5.
25. Corti A, Belcastro E, Dominici S, Maellaro E, Pompella A. The dark side of gamma-glutamyltransferase (GGT): Pathogenic effects of an 'antioxidant' enzyme. Free Radical Biol Med. 2020;160:807–19.
26. Reuter S, Schnekenburger M, Cristofanon S, Buck I, Teiten M-H, Daubeuf S, et al. Tumor necrosis factor alpha induces gamma-glutamyltransferase expression via nuclear factor-kappaB in cooperation with Sp1. Biochem Pharmacol. 2009;77:397–411.
27. Tang K-S, Huang L-T, Huang Y-H, Lai C-Y, Wu C-H, Wang S-M, et al. Gamma-glutamyl transferase in the diagnosis of biliary atresia. Acta Paediatr Taiwan. 2007;48:196–200.
28. Wang Q, Chen Q, Zhang X, Lu XL, Du Q, Zhu T, et al. Diagnostic value of gamma-glutamyltransferase/aspartate aminotransferase ratio, protein induced by vitamin K absence or antagonist II, and alpha-fetoprotein in hepatitis B virus-related hepatocellular carcinoma. World J Gastroenterol. 2019;25:5515–29.
29. Peng S, Huang P, Yu H, Wen Y, Luo Y, Wang X, et al. Prognostic value of carcinoembryonic antigen level in patients with colorectal cancer liver metastasis treated with percutaneous microwave ablation under ultrasound guidance. Medicine. 2018;97:e0044.
30. Qin S, Hu H, Cui R, Lin J, Liu Y, Wang Y, et al. A prognostic nomogram for intrahepatic progression-free survival in patients with colorectal liver metastases after ultrasound-guided percutaneous microwave ablation. Int J Hyperthermia. 2022;39:144–54.
31. Murata J, Ricciardi-Castagnoli P, Dessous L'Eglise Mange P, Martin F, Juillerat-Jeanneret L. Microglial cells induce cytotoxic effects toward colon carcinoma cells: measurement of tumor cytotoxicity with a gamma-glutamyl transpeptidase assay. Int J Cancer. 1997;70:169–74.

32. Gong Z, Zhang X, Geng Q, Li W, Huang M, Chen Z, et al. AKP and GGT level can provide an early prediction of first-line treatment efficacy in colorectal cancer patients with hepatic metastases. Biomark Med. 2021;15:697–713.
33. Mitrić A, Castellano I. Targeting gamma-glutamyl transpeptidase: A pleiotropic enzyme involved in glutathione metabolism and in the control of redox homeostasis. Free Radic Biol Med. 2023;208:672–83.
34. Di Ciaula A, Wang DQ-H, Portincasa P. Cholesterol cholelithiasis: Part of a systemic metabolic disease, prone to primary prevention. Expert Rev Gastroenterol Hepatol. 2019;13:157–71.
35. Castro J, Amigo L, Miquel JF, Gälman C, Crovari F, Raddatz A, et al. Increased activity of hepatic microsomal triglyceride transfer protein and bile acid synthesis in gallstone disease. Hepatology. 2007;45:1261–6.
36. Wang HH, Liu M, Clegg DJ, Portincasa P, Wang DQ-H. New insights into the molecular mechanisms underlying effects of estrogen on cholesterol gallstone formation. Biochim Biophys Acta. 2009;1791:1037–47.
37. Manolaki AG, Larcher VF, Mowat AP, Barrett JJ, Portmann B, Howard ER. The prelaparotomy diagnosis of extrahepatic biliary atresia. Arch Dis Child. 1983;58:591–4.
38. Chen L, Fan Z, Sun X, Qiu W, Mu W, Chai K, et al. Examination on the risk factors of cholangiocarcinoma: A mendelian randomization study. Front Pharmacol. 2022;13: 900424.
39. Guo L, Mao J, Li Y, Jiao Z, Guo J, Zhang J, et al. Cholelithiasis, cholecystectomy and risk of hepatocellular carcinoma: A meta-analysis. J Cancer Res Ther. 2014;10:834–8.
40. Pan S-Y, Zhou C-B, Deng J-W, Zhou Y-L, Liu Z-H, Fang J-Y. The effects of pks+ escherichia coli and bile acid in colorectal tumorigenesis among people with cholelithiasis or cholecystectomy. J Gastroenterol Hepatol. 2024;39:868–79.
41. Peng J, Li L, Ning H, Li X. Association between cholelithiasis, cholecystectomy, and risk of breast and gynecological cancers: Evidence from meta-analysis and mendelian randomization study. Ann Hum Genet. 2024. https://doi.org/10.1111/ahg.12573.
42. Li Y-D, Ren Z-J, Gao L, Ma J-H, Gou Y-Q, Tan W, et al. Cholelithiasis increased prostate cancer risk: Evidence from a case-control study and a meta-analysis. BMC Urol. 2022;22:160.
43. Ge Y, Jeong S, Luo G-J, Ren Y-B, Zhang B-H, Zhang Y-J, et al. Transarterial chemoembolization versus percutaneous microwave coagulation therapy for recurrent unresectable intrahepatic cholangiocarcinoma: Development of a prognostic nomogram. Hepatobiliary Pancreat Dis Int. 2020;19:138–46.
44. Qiu S, Jin L, Yang D, Zhang D. Clinical application value of hepatitis B virus basal core promoter 1762/1764 and GGTII and GGT in patients with HBV-DNA-positive primary liver cancer. Medicine (Baltimore). 2023;102:e35699.
45. Ekmen N, Akalin Ç, Akyildiz M. Predictive value of protein induced by absence of vitamin K absence or antagonist II, alpha-fetoprotein and gamma-glutamyltransferase/aspartate aminotransferase ratio for the diagnosis of hepatocellular carcinoma in transplantation candidates. Eur J Gastroenterol Hepatol. 2021;32:294–9.
46. Schmidt BC, Leiderer MT, Amin T, Viol F, Huber S, Henes FO, et al. Does gamma-glutamyltransferase correlate with liver tumor burden in neuroendocrine tumors? Endocrine. 2023. https://doi.org/10.1007/s12020-023-03545-x.

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