

# THE PROGNOSTIC IMPLICATIONS OF PERIOPERATIVE SERUM CHOLESTEROL LEVELS IN PATIENTS WITH GASTRIC CANCER

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## Introduction

Evaluation of nutritional status is essential in patients with GC, and nutrition is greatly involved in the maintenance of immune function and continuity of adjuvant chemotherapy

T-Chol is rarely used as a postoperative nutritional index, and the significance of the changes in perioperative T-Chol levels has not been clarified.

In the present study, we investigated the clinical significance of changes in perioperative T-Chol levels by measuring the preoperative and postoperative T-Chol levels in patients with GC who underwent gastrectomy.

## Materials and methods

This retrospective study enrolled 212 patients with pathological stage II/III GC who underwent gastrectomy between January 2004 and February 2020. (Table 1)

To define elevated T-Chol levels, we reviewed the preoperative serum T-Chol just before surgery and postoperative serum T-Chol a month after surgery in patients with GC who underwent gastrectomy.

Based on the perioperative serum T-Chol results, we categorized the patients into two groups, the increased and decreased T-Chol groups.

## Results

Patients with increased serum T-Chol levels had significantly lower preoperative serum albumin levels ( $p < 0.001$ ).

The increasing group tended to have low serum T-Chol levels before surgery (Fig. 1), suggesting that patients with increased serum T-Chol levels may have a poor nutritional status before surgery. (Table 2)

Regarding the recurrence pattern, no significant difference was found between the increasing and decreasing serum T-Chol levels in patients with GC ( $p = 0.977$ ). (Table 2)

Patients with increased serum T-Chol levels after gastrectomy had significantly lower overall and recurrence-free survival rates than those with decreasing T-Chol levels. (Fig. 2)

Increased T-Chol ( $p = 0.040$ ), pathological stage ( $p < 0.001$ ), and the administration of adjuvant chemotherapy ( $p = 0.006$ ) were independent predictors of recurrence-free survival of patients with GC. (Table 3)

These patients had early recurrence, and as a result, had a poor prognosis. Hematogenous recurrence occurred in 4 of the 10 patients. (Supplemental Table)

Supplemental Table. Clinicopathological features of patients with the highest rate of increased serum T-Chol levels after surgery

Rate of increase	Preoperative T-cho	Postoperative T-cho	Age	Gender	pStage <sup>a</sup>	Adjuvant chemotherapy	Recurrence type	Years after surgery
1.71	100	171	84	male	IIIA	absent	Hematogenous	0.8
1.69	95	161	67	male	II	absent	Lymphatic	1.6
1.63	109	151	74	male	IIIA	present	Peritoneal	1.5
1.61	109	176	56	male	II	present	No Recurrence	6.8
1.54	102	157	79	female	II	absent	No Recurrence	4.7
1.52	112	170	76	female	II	present	No Recurrence	7.9
1.42	119	169	60	male	IIIA	present	Lymphatic	6.7
1.42	142	201	80	male	II	absent	Hematogenous	0.6
1.40	107	150	67	female	IIIB	present	Peritoneal	1.5
1.35	101	136	85	female	IIIA	absent	Hematogenous	1.1

## Discussion

Patients with GC with increased serum T-Chol levels after surgery tended to have low Alb levels before surgery, suggesting that many of these patients had a poor nutritional status before surgery.

Prolonged fasting leads to low triiodothyronine levels, resulting in reduced LDL receptors on the cell membrane. Thus, serum T-Chol level is increasing.

*Kobayashi M, Sano R, Oikawa S, Abe R, Fujii Y, Goto Y and Yamauchi Y: Lipids Metabolism during 10-days-fasting of Psychosomatic Patients. Journal of Atherosclerosis and Thrombosis, 1986, 14: 1155-1160.*

→ T-Chol levels may reflect nutritional status, so the poor nutritional status might make prognoses worse with GC patients.

The LDL receptor is overexpressed in certain types of cancer cells. The LDL receptor has a pro-tumorigenic effect mediated by the enhancement of cell growth or migration.

*Gallagher EJ, Zelenko Z, Neel BA, Antoniou IM, Rajan L, Kase N, LeRoith D. Elevated tumor LDLR expression accelerates LDL cholesterol-mediated breast cancer growth in mouse models of hyperlipidemia. Oncogene 2017, 36: 6462-6471.*

Excess lipids stored in organelles called lipid droplets (LD) are a key resource for fueling the energy-intensive process of metastasis in pancreatic cancer.

*Rozeveld CN, Johnson KM, Zhang L, Razidlo GL. KRAS Controls Pancreatic Cancer Cell Lipid Metabolism and Invasive Potential through the Lipase HSL. Cancer Res 2020, 80: 4932-4945.*

→ Cholesterol may reflect an important index of tumor progression in GC.

Increased serum T-Chol levels suppress the anti-tumor immune response by deactivating regulatory T cell-controlled expression of genes such as sterol regulatory element binding proteins (SREBPs).

*Perry C, Beier UH. Cancer aided by greasy traitors. Nature 2021, 591: 204-206.*

## Conclusion

In the present study, we demonstrated that patients with GC whose serum T-Chol levels increased dramatically after gastrectomy had early recurrence and poor prognosis, suggesting that meticulous surveillance is needed.

Table 1 Clinicopathological characteristics of patients in the present study

Age (years) (mean±SD)	68.9±11.7
Gender, male / female	139 / 73
Type of procedure	
Total gastrectomy	106 (50.0)
Distal gastrectomy	92 (43.4)
Proximal gastrectomy	2 (0.9)
Others	12 (5.7)
pT stage, pT1-3 / pT4n	128 / 84
pN stage, pN0 / pN1n	44 / 168
lymphatic invasion, negative / positive	23 / 189
venous invasion, negative / positive	45 / 167
Tumor size (mm) (mean±SD)	61.7±33.2
Histological type, differentiated / undifferentiated	120 / 92
pStage, II / III	107 / 105
Macroscopic appearance, localize / diffuse	79 / 133
Adjuvant chemotherapy, present / absent	115 / 97

Table 2. Clinicopathological characteristics of transition of T-Chol value in patients with gastric cancer

	decreasing T-Chol	increasing T-Chol	p value
Age, < 69 / 69 ≤	79 / 94	15 / 24	0.592
Gender, male / female	112 / 61	27 / 12	0.710
Post operative body weight, increasing / decreasing	6 / 125	3 / 28	0.375
Preoperative Alb, high / low	100 / 73	8 / 31	< 0.001
Postoperative lymphocyte, increasing / decreasing	92 / 81	26 / 13	0.154
Type of procedure, Total gastrectomy / Others	91 / 82	15 / 24	0.156
pT stage, pT1-3 / pT4	107 / 66	21 / 18	0.370
Lymphatic invasion, negative / positive	22 / 151	1 / 38	0.086
Venous invasion, negative / positive	35 / 138	10 / 29	0.516
Tumor size (mm), ≤ 50 / 50 <	82 / 91	12 / 27	0.074
Histological type, differentiated / undifferentiated	99 / 74	21 / 18	0.723
pStage, II / III	88 / 85	19 / 20	0.860
Macroscopic appearance, localize / diffuse	65 / 108	14 / 25	1.000
Adjuvant chemotherapy, present / absent	97 / 76	18 / 21	0.289
Recurrence type			
Lymphatic	23	8	0.977
Hematogenous	15	4	
Peritoneal	22	9	
Others	2	1	

Fig. 1

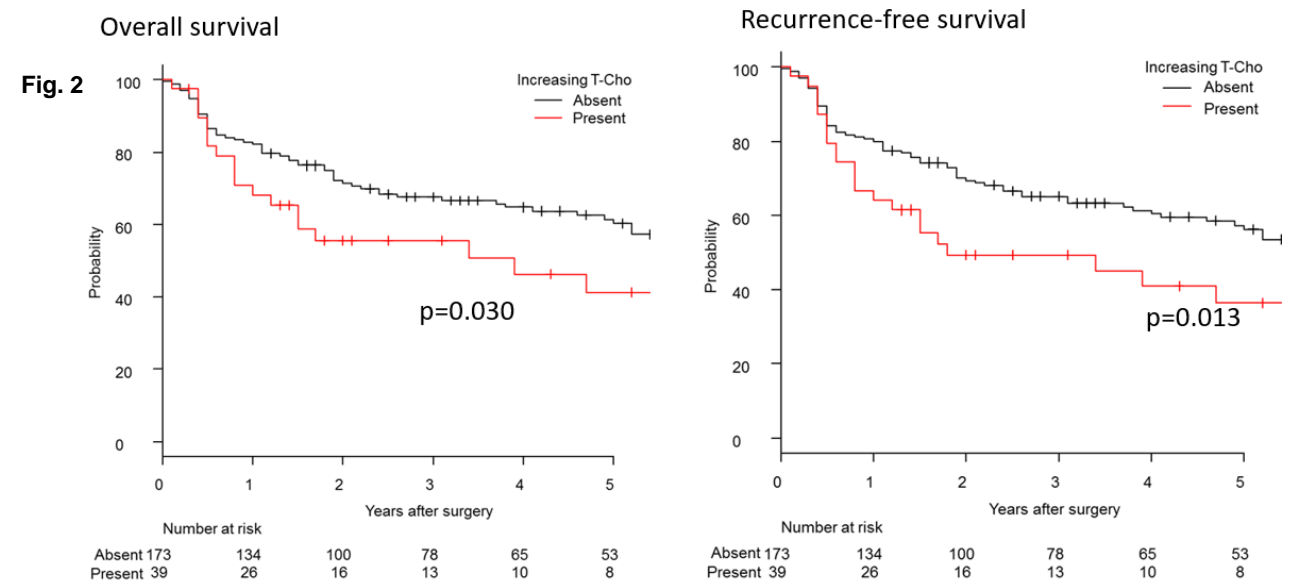
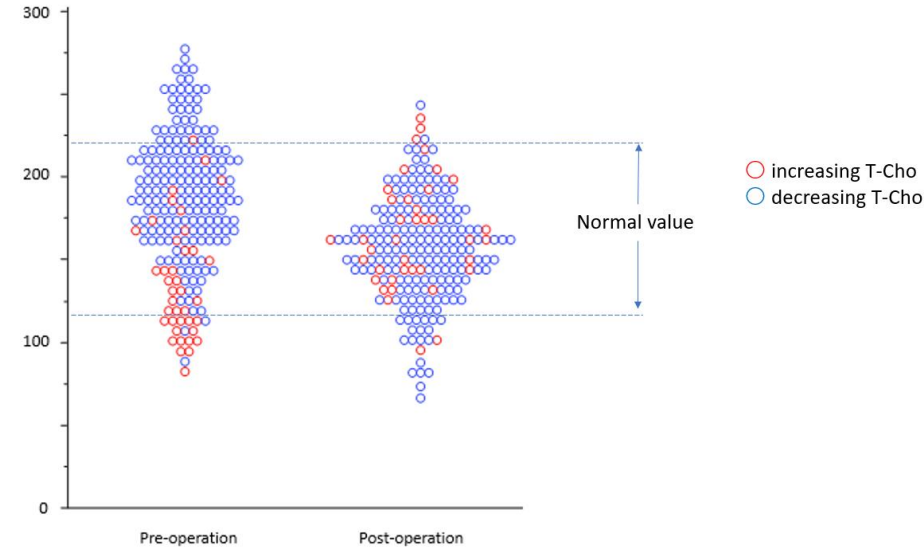


Table 3. Cox proportional hazard model for 5-year recurrence free survival in patients with gastric cancer

Variable	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age, 69 < vs ≤ 69	1.54 (1.02-2.33)	0.039	1.41 (0.90-2.21)	0.133
Gender, female vs male	1.23 (0.79-1.91)	0.369	-	-
Postoperative Lymphocyte, decreasing vs increasing	1.26 (0.82-1.91)	0.288	-	-
Preoperative Alb, low vs high	1.84 (1.22-2.78)	0.004	1.39 (0.86-2.24)	0.178
Type of procedure, total vs others	1.46 (0.97-2.12)	0.072	-	-
Lymphatic invasion, positive vs negative	2.28 (0.92-5.61)	0.074	-	-
Venous invasion, positive vs negative	2.17 (1.20-3.90)	0.010	1.48 (0.80-2.75)	0.210
Tumor size (mm), 50 < vs ≤ 50	1.32 (0.87-2.00)	0.192	-	-
Pathological type, differentiated vs undifferentiated	1.16 (0.77-1.76)	0.469	-	-
pStage <sup>a</sup> , III vs II	3.46 (2.19-5.44)	< 0.001	4.28 (2.65-6.91)	< 0.001
Macroscopic appearance, diffuse vs localize	1.01 (0.67-1.54)	0.952	-	-
Adjuvant chemotherapy, absent vs present	1.67 (1.11-2.51)	0.015	1.86 (1.20-2.88)	0.006
Transition of T-Chol value, increase vs decrease	1.78 (1.11-2.83)	0.016	1.70 (1.02-2.81)	0.040