

Original Article



Adverse Effects of Ligation of an Aberrant Left Hepatic Artery Arising from the Left Gastric Artery during Radical Gastrectomy for Gastric Cancer: a Propensity Score Matching Analysis

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ABSTRACT

Purpose: No consensus exists on whether to preserve or ligate an aberrant left hepatic artery (ALHA), which is the most commonly encountered hepatic arterial variation during gastric surgery. Therefore, we aimed to evaluate the clinical effects of ALHA ligation by analyzing the perioperative outcomes.

Materials and Methods: We retrospectively reviewed the data of 5,310 patients who underwent subtotal/total gastrectomy for gastric cancer. Patients in whom the ALHA was ligated (n=486) were categorized into 2 groups according to peak aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels: moderate-to-severe (MS) elevation (≥ 5 times the upper limit of normal [ULN]; MS group, n=42) and no-to-mild (NM) elevation (< 5 times the ULN; NM group, n=444). The groups were matched 1:3 using propensity score-matching analysis to minimize confounding factors that can affect the perioperative outcomes.


Results: The mean operation time (P=0.646) and blood loss amount (P=0.937) were similar between the 2 groups. The length of hospital stay was longer in the MS group (13.0 vs. 7.8 days, P=0.022). No postoperative mortality occurred. The incidence of grade \geq IIIa postoperative complications (19.0% vs. 5.1%, P=0.001), especially pulmonary complications (11.9% vs. 2.5%, P=0.003), was significantly higher in the MS group. This group also showed a higher Comprehensive Complication Index (29.0 vs. 13.9, P<0.001).

Conclusions: Among patients with a ligated ALHA, those with peak AST/ALT ≥ 5 times the ULN showed worse perioperative outcomes in terms of hospital stay and severity of complications. More precise perioperative decision-making tools are needed to better determine whether to preserve or ligate an ALHA.

Keywords: Gastric cancer; Gastrectomy; Hepatic artery; Postoperative complications; Liver dysfunction

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Author Contributions

Conceptualization: L.S., S.T.; Data curation: L.S., S.J.H., C.S.; Formal analysis: L.S., S.J.H., C.S.; Investigation: L.S., S.T.; Methodology: L.S., S.T.; Project administration: S.T.; Resources: S.T., C.M., K.Y.M., K.H.I., H.W.J.; Supervision: S.T.; Writing - original draft: L.S., S.T.; Writing - review & editing: L.S., S.T.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. Although adjuvant treatment has improved the survival of patients, surgical resection remains the mainstay of treatment for gastric cancer. Curative surgery for gastric cancer involves gastric resection with negative margins and adequate lymph node dissection [2]. For complete lymph node dissection, it is essential to clear the soft tissue around the blood vessels and to ligate the vessels at their origin [3].

During gastric cancer surgery, the most commonly encountered vascular variation is an aberrant left hepatic artery (ALHA) arising from the left gastric artery (LGA), with a reported incidence ranging from 6.5% to 34% [4-10]. When the LGA is ligated in radical gastrectomy, patients with an ALHA occasionally experience liver dysfunction because the ALHA supplies arterial blood to a part or the entirety of the left lobe of the liver. Because most patients with a ligated ALHA show only mild and transient liver dysfunction, previous studies have reported that ligating the ALHA seems to be safe [11-13]. However, the consequences of sacrificing an ALHA are not well known, and the decision to perform ALHA ligation remains controversial. To date, no consensus exists on whether an ALHA should be ligated or preserved during gastric cancer surgery.

In this study, we hypothesized that the severity of liver dysfunction after ALHA ligation would affect the perioperative outcomes, including postoperative complications, even with a careful selection of patients in whom the ALHA can be safely ligated. The present study was designed to determine the impact of ALHA ligation on short-term postoperative outcomes in patients undergoing gastrectomy for gastric cancer.

MATERIALS AND METHODS

Study design

We retrospectively reviewed a prospective database of patients (n=5,310) who underwent subtotal or total gastrectomy for gastric cancer between January 2015 and December 2019. Eight patients had no records concerning the presence of an ALHA and were excluded, whereas an ALHA was identified in 936 patients (17.6%) during gastric cancer surgery. If the ALHA was determined to be a replaced type based on preoperative computed tomography (CT) evaluation, it was usually preserved. However, the ALHA was sacrificed if it was deemed to be an accessory type or in patients with advanced tumors. The ALHA was preserved in 318 patients (34.0%) and ligated in 618 patients (66.0%). Among the 618 patients with a ligated ALHA, we excluded 26 patients with M1 gastric cancer; 22 patients who underwent preoperative chemotherapy or radiotherapy; 1 patient with noncurative resection; 35 patients with preoperative liver disease, such as liver cirrhosis or hepatitis; 25 patients with preoperative elevated levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT); and 23 patients with combined resection of the liver and gallbladder. The remaining 486 patients were finally included in this study.

To evaluate the liver function after surgery, we routinely measured the AST and ALT levels on postoperative days (PODs) 0, 1, 2, 3, and 5. According to the American College of Gastroenterology guidelines [14], we categorized patients into the following 2 groups: (i) moderate-to-severe (MS) elevation group with postoperative peak AST or ALT levels ≥ 5

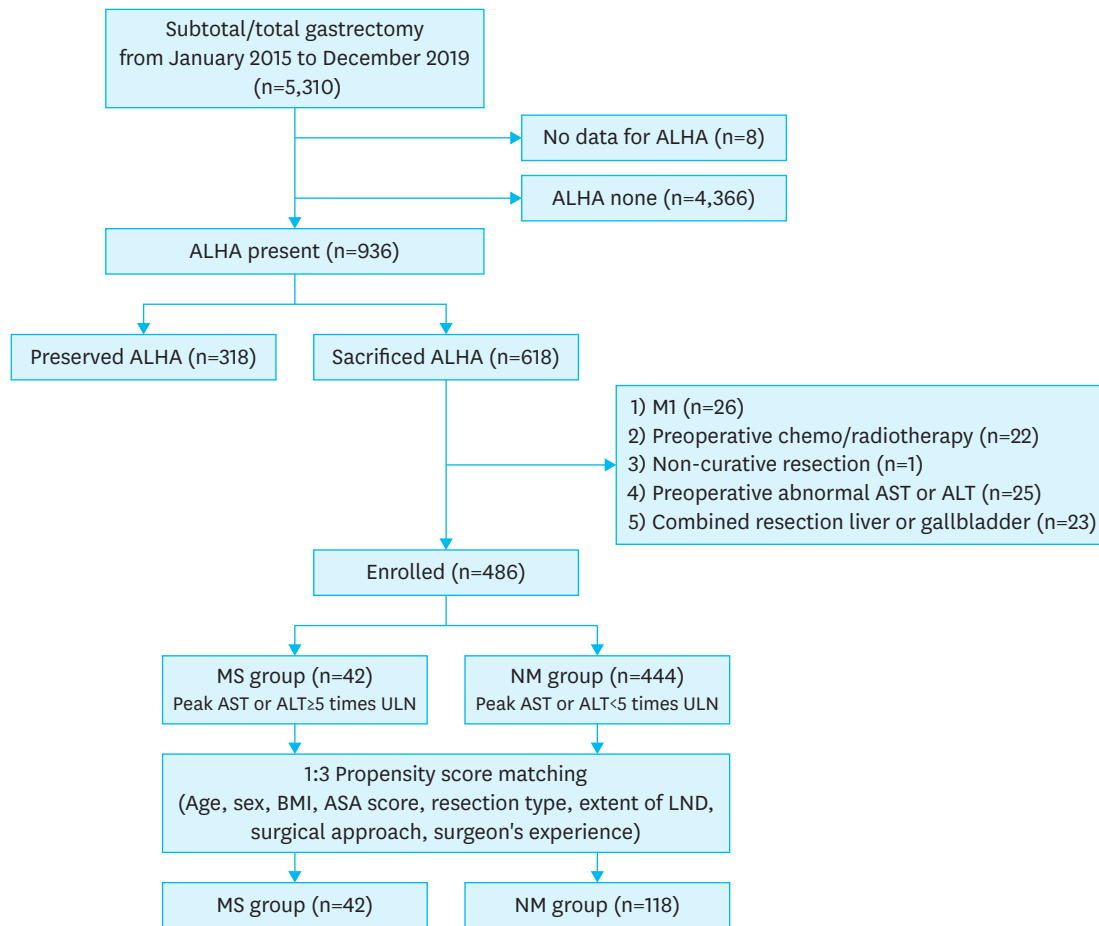


Fig. 1. Flow diagram of the study.

ALHA = aberrant left hepatic artery; ALT = alanine aminotransferase; ASA = American Society of Anesthesiologists; AST = aspartate aminotransferase; BMI = body mass index; LND = lymph node dissection; MS = moderate-to-severe elevation of liver enzymes; NM = no-to-mild elevation of liver enzymes; ULN = upper limit of normal.

times the upper limit of normal (ULN) (n=42) and (ii) no-to-mild (NM) elevation group with postoperative peak AST or ALT levels <5 times the ULN (n=444) (**Fig. 1**).

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (approval No. 4-2020-0653). The requirement for informed consent for the use of patient data was waived owing to the retrospective study design.

Perioperative management

The standard clinical pathway for patients undergoing radical gastrectomy for gastric cancer at our hospital was applied. Antibiotics were injected 15 minutes before skin incision. Postoperative antibiotics were not routinely used but were injected in patients who had bowel content spillage during surgery or inflammatory symptoms and signs after POD 3. We used patient-controlled anesthesia for postoperative pain control and nonsteroidal anti-inflammatory drugs for additional pain control. Intravenous antiemetics were injected only on the day of surgery. We considered using liver-protective agents for patients with elevated AST or ALT levels. Because of the lack of a consensus on the severity of liver enzyme elevation that would indicate the need for using liver-protective agents, the cutoff value differed among surgeons. Water intake was allowed on POD 2, liquid diet on POD 3, and soft diet from POD

4. Until POD 3, crystalloid solution was typically used for fluid replacement in patients who had a normal recovery course. Discharge was recommended on POD 5, depending on the patient's readiness.

Surgical outcomes

We retrospectively reviewed the CT images of the patients and determined the anatomical variations of the celiac trunk based on Adachi's classification, which divides the branching variations of the celiac trunk into 6 types [15,16]. In addition, we collected and analyzed perioperative data to evaluate surgical outcomes, including postoperative complications. Postoperative complications were defined as any adverse events that required additional pharmacologic, interventional, or surgical management within 30 days of surgery. All postoperative complications were graded according to the Clavien-Dindo classification [17]. We calculated the Comprehensive Complication Index (CCI) as the sum of all complications weighted for their severity, which was determined using the Clavien-Dindo classification [18].

Propensity score matching (PSM)

PSM analysis was used to minimize the possible influence of confounding factors on the surgical outcomes. The propensity score for each patient was calculated on the basis of age, sex, body mass index, American Society of Anesthesiologists score, type of resection, extent of lymph node dissection, surgical approach, and surgeon experience. Patients in the MS (n=42) and NM (n=118) groups were matched 1:3 using the nearest propensity score on the logit scale (caliper of 0.1) and analyzed to compare surgical outcomes. After PSM, imbalance was defined as an absolute standardized mean difference of >0.20.

Statistical analysis

Categorical variables were analyzed using the χ^2 and Fisher's exact tests, and continuous variables were analyzed using Student's t-test. All tests were 2-sided, and statistical significance was set at $P < 0.05$. Statistical analyses were performed using IBM SPSS Statistics software for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

RESULTS

Patient demographics

Table 1 lists the patients' demographic characteristics. Before PSM, total gastrectomy (MS, 47.6% vs. NM, 25.9%, $P=0.003$) and D2 lymph node dissection (MS, 71.4% vs. NM, 47.5%, $P=0.003$) were more frequent in the MS group than in the NM group. After PSM, the matched groups showed no significant differences in terms of patient demographics. Moreover, no significant difference was observed in the celiac trunk variations based on Adachi's classification ($P=0.524$).

Perioperative and pathologic outcomes

Table 2 shows the perioperative and pathologic outcomes in both groups. The surgical approach did not significantly differ between the 2 groups ($P=0.915$). We categorized surgeons as seniors and juniors based on a surgical experience cutoff of 100 gastrectomy cases. No difference in surgeon experience was noted between the 2 groups ($P > 0.999$). The mean operation time (MS, 194.1 minutes vs. NM, 189.6 minutes, $P=0.646$) and blood loss amount (MS, 164.6 mL vs. NM, 173.1 mL, $P=0.937$) did not differ between the groups. The mean length of hospital stay was significantly longer in the MS group than in the NM group

Aberrant Left Hepatic Artery Ligation

Table 1. Patient demographics

Variables	Before matching			Standardized difference	After matching			Standardized difference
	MS group (n=42)	NM group (n=444)	P-value		MS group (n=42)	NM group (n=118)	P-value	
Age (yr)	61.8±11.6	59.4±12.6	0.241	0.196	61.8±11.6	63.6±12.6	0.420	0.148
Sex			0.473	0.117			>0.999	0.024
Male	28 (66.7)	271 (61.0)			28 (66.7)	80 (67.8)		
Female	14 (33.3)	173 (39.0)			14 (33.3)	38 (32.2)		
BMI (kg/m ²)	23.7±3.4	23.5±3.1	0.686	0.063	23.7±3.4	23.5±2.7	0.683	0.070
ASA score			0.425	0.253			0.970	0.076
1	5 (11.9)	87 (19.6)			5 (11.9)	12 (10.2)		
2	22 (52.4)	238 (53.6)			22 (52.4)	63 (53.4)		
3	14 (33.3)	111 (25.0)			14 (33.3)	41 (34.7)		
4	1 (2.4)	8 (1.8)			1 (2.4)	2 (1.7)		
Type of resection			0.003	0.462			0.587	0.123
Subtotal	22 (52.4)	329 (74.1)			22 (52.4)	69 (58.5)		
Total	20 (47.6)	115 (25.9)			20 (47.6)	49 (41.5)		
Extent of LN dissection			0.003	0.502			0.570	0.115
D1+	12 (28.6)	233 (52.5)			12 (28.6)	40 (33.9)		
D2	30 (71.4)	211 (47.5)			30 (71.4)	78 (66.1)		
Adachi's classification			0.254	0.372			0.524	0.318
Type I	40 (95.2)	416 (93.7)			40 (95.2)	112 (94.9)		
Type II	0	11 (2.5)			0	2 (1.7)		
Type III	0	1 (0.2)			0	1 (0.8)		
Type IV	1 (2.4)	9 (2.0)			1 (2.4)	3 (2.5)		
Type V	0	6 (1.4)			0	0		
Type VI	1 (2.4)	0			1 (2.4)	0		
Other	0	1 (0.2)			0	0		

Values in parentheses are percentages. Values are presented as mean±standard deviation.

ASA = American Society of Anesthesiologists; BMI = body mass index; LN = lymph node; MS = moderate-to-severe elevation of liver enzymes; NM = no-to-mild elevation of liver enzymes.

Table 2. Perioperative and pathologic outcomes

Variables	Before matching			Standardized difference	After matching			Standardized difference
	MS group (n=42)	NM group (n=444)	P-value		MS group (n=42)	NM group (n=118)	P-value	
Surgical approach			0.145	0.318			0.915	0.080
Open	20 (47.6)	147 (33.1)			20 (47.6)	58 (49.2)		
Laparoscopic	15 (35.7)	183 (41.2)			15 (35.7)	38 (32.2)		
Robotic	7 (16.7)	114 (25.7)			7 (16.7)	22 (18.6)		
Surgeon's experience level			0.494	0.132			>0.999	0.007
Senior	38 (90.5)	383 (86.3)			38 (90.5)	107 (90.7)		
Junior	4 (9.5)	61 (13.7)			4 (9.5)	11 (9.3)		
Operation time (min)	194.1±58.3	180.2±60.9	0.156	0.234	194.1±58.3	189.6±53.7	0.646	0.081
Blood loss (mL)	164.6±188.3	119.2±142.0	0.135	0.272	164.6±188.3	162.1±173.1	0.937	0.014
LOS (days)	13.0±13.9	7.3±4.0	0.011	0.559	13.0±13.9	7.8±4.0	0.022	0.505
T stage			0.012	0.510			0.248	0.359
1	17 (40.5)	285 (64.2)			17 (40.5)	61 (51.7)		
2	4 (9.5)	35 (7.9)			4 (9.5)	16 (13.6)		
3	11 (26.2)	55 (12.4)			11 (26.2)	16 (13.6)		
4a	10 (23.8)	69 (15.5)			10 (23.8)	25 (21.2)		
N stage			0.274	0.359			0.201	0.463
0	26 (61.9)	307 (69.1)			26 (61.9)	75 (63.6)		
1	7 (16.7)	42 (9.5)			7 (16.7)	10 (8.5)		
2	5 (11.9)	30 (6.8)			5 (11.9)	8 (6.8)		
3a	1 (2.4)	32 (7.2)			1 (2.4)	13 (11.0)		
3b	3 (7.1)	33 (7.4)			3 (7.1)	12 (10.2)		

Values in parentheses are percentages. Values are presented as mean±standard deviation.

LOS = length of hospital stay; MS = moderate-to-severe elevation of liver enzymes; NM = no-to-mild elevation of liver enzymes.

(MS, 13.0 days vs. NM, 7.8 days; P=0.022). No significant difference was observed in the pathologic T (P=0.248) and N (P=0.201) stages between the groups after matching.

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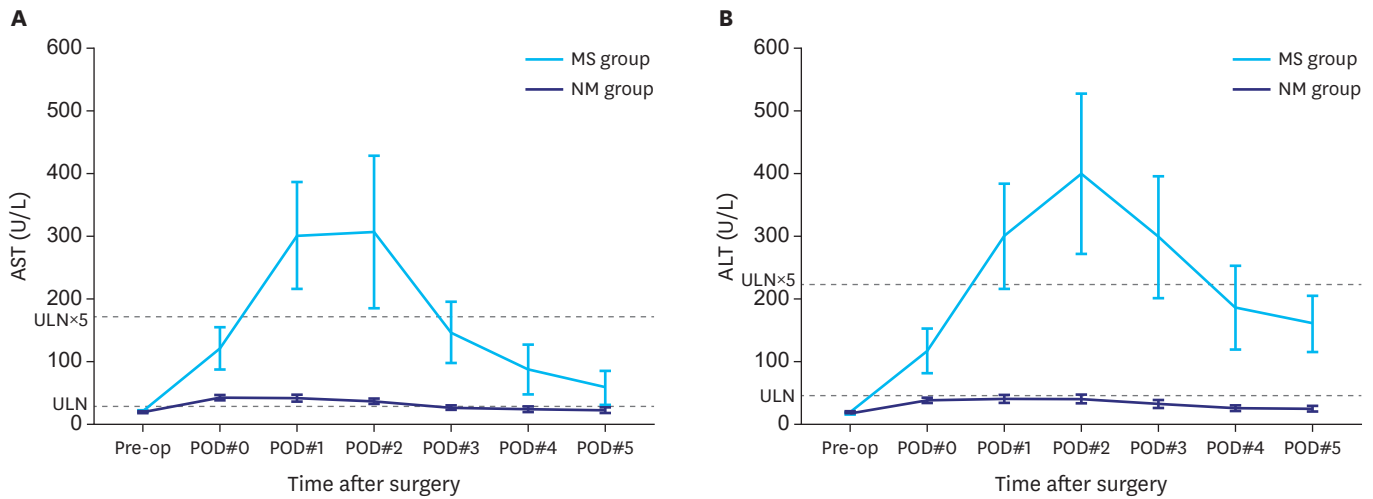


Fig. 2. Perioperative serial changes of the mean (95% confidence interval) AST (A) and ALT (B) levels in the MS (n=42) and NM (n=118) groups after matching. ALT = alanine aminotransferase; AST = aspartate aminotransferase; MS = moderate-to-severe elevation of liver enzymes; NM = no-to-mild elevation of liver enzymes; POD = postoperative day; ULN = upper limit of normal.

Perioperative liver function

Fig. 2 shows the serial changes in the mean AST and ALT levels in the 2 groups after matching. The mean AST and ALT levels in the MS group were the highest on POD 2 and decreased to <math>< 5</math> times the ULN on POD 5. The mean AST and ALT levels in the NM group decreased to less than the ULN on POD 5. No liver-related fatal complications, such as liver abscess or liver failure, were recorded.

Postoperative complications

The incidence of postoperative complications of grade \geq IIIa, based on the Clavien-Dindo classification, was higher in the MS group than in the NM group (MS, 19.0% vs. NM, 5.1%; $P=0.001$) (**Table 3**). When we analyzed all grade \geq IIIa postoperative complications, the incidence of pulmonary complications was higher in the MS group than in the NM group (11.9% vs. 2.5%, $P=0.003$). Moreover, the incidence of bleeding was higher in the MS group, although the statistical difference was marginal (MS, 4.8% vs. NM, 0%; $P=0.068$). The mean CCI was higher in the MS group than in the NM group (MS, 29.0 vs. NM, 13.9; $P<0.001$).

Table 3. Postoperative complications (within 30 days of surgery)

Variables	Before matching			Standardized difference	After matching			Standardized difference
	MS group (n=42)	NM group (n=444)	P-value		MS group (n=42)	NM group (n=118)	P-value	
Complication			0.008	0.390			0.001	0.439
None or \leq GII	34 (81.0)	416 (93.7)			34 (81.0)	112 (94.9)		
\geq GIIIa	8 (19.0)	28 (6.3)			8 (19.0)	6 (5.1)		
All complications \geq GIIIa								
Leakage	4 (9.5)	8 (1.8)	0.014	0.246	4 (9.5)	4 (3.4)	0.208	0.169
Anastomotic stenosis	0	2 (0.5)	>0.999	0.095	0	0		
Bleeding	2 (4.8)	2 (0.5)	0.039	0.273	2 (4.8)	0	0.068	0.316
Fluid collection	0	4 (0.9)	>0.999	0.135	0	1 (0.8)	>0.999	0.131
Intestinal obstruction	1 (2.4)	2 (0.5)	0.238	0.164	1 (2.4)	0	0.262	0.221
Cardiac	1 (2.4)	2 (0.5)	0.238	0.164	1 (2.4)	0	0.262	0.221
Pulmonary	5 (11.9)	11 (2.5)	0.008	0.371	5 (11.9)	3 (2.5)	0.003	0.368
CVA	0	2 (0.5)	>0.999	0.095	0	0		
CCI	29.0 \pm 12.6	18.1 \pm 10.9	<0.001	1.122	29.0 \pm 12.6	13.9 \pm 12.1	<0.001	1.056

Values in parentheses are percentages. Values are presented as mean \pm standard deviation.

CCI = Comprehensive Complication Index; CVA = cerebrovascular accident; G = grade of complication based on the Clavien-Dindo classification; MS = moderate-to-severe elevation of liver enzymes; NM = no-to-mild elevation of liver enzymes.

DISCUSSION

In this study, the incidence of ALHA was 17.0%. Among the enrolled patients in whom the ALHA was ligated during gastric cancer surgery, 8.6% were found to have elevated AST or ALT levels (≥ 5 times the ULN) within 5 days after surgery. These patients had longer hospital stay, higher incidence of grade \geq IIIa postoperative complications (particularly pulmonary complications), and higher CCI.

No consensus exists on whether it is safe to ligate an ALHA during gastric cancer surgery, owing to a lack of robust and consistent evidence. With respect to oncologic safety, discontinuation of the ALHA blood flow cannot be avoided because the LGA needs to be ligated at its origin for complete lymph node dissection [3]. However, one previous study showed equivalent results in terms of the number of retrieved lymph nodes between routine ALHA preservation and ALHA ligation [9]. Considering the liver damage that can occur after ligating an ALHA, it is desirable to preserve a replaced ALHA, which supplies total arterial flow to the left lobe of the liver. Some lethal post-ALHA ligation complications have been reported, such as necrosis or abscess in the left liver lobe, cholangitis, and liver failure [19,20]. Considering oncologic safety and postoperative liver function, we generally preserved the ALHA when it was suspected to be a replaced type and sacrificed the ALHA if it was judged to be an accessory type or if the cancer was in the advanced stages.

In our study, we found that most patients with a ligated ALHA had normal or mildly elevated postoperative liver enzyme levels. Moreover, patients with peak AST or ALT levels ≥ 5 times the ULN showed a rapid decrease in liver enzyme levels, which decreased to < 5 times the ULN during hospitalization. It has been shown that collateral arterial flow from the hepatic or phrenic arteries can reduce persistent liver ischemia [21]. Previous studies have also reported that most patients show mild and transient elevation of liver enzyme levels that normalize within 2 weeks after ALHA ligation [11,13,22]. In terms of postoperative liver function, sacrificing the ALHA seems to be a safe option during gastric cancer surgery.

However, the postoperative outcomes of patients with peak AST or ALT levels ≥ 5 times the ULN after ALHA ligation were worse than those of patients with normal or mildly elevated liver enzyme levels, even when surgeons carefully selected patients in whom the ALHA can be safely ligated. The CCI is generally known to reflect all types of postoperative complications and correlates with overall postoperative costs [23]. A higher CCI is associated with a poor prognosis in patients with gastric cancer [24,25]. Thus, the results of our study imply an increased economic burden for some patients undergoing ALHA ligation, owing to a considerably longer hospital stay and increased incidence and severity of postoperative complications. Therefore, among patients who underwent ALHA ligation, those with peak AST or ALT levels ≥ 5 times the ULN should have had their ALHA preserved. Our results reflect the real-world setting in which careful patient selection for ALHA ligation did not meet our expected outcomes, as the proportion of patients with peak AST or ALT levels ≥ 5 times the ULN remained high.

Liver enzyme elevation after ALHA ligation has been found to be affected by the extent of the feeding area supplied by the ALHA [11]. To date, no effective and noninvasive method has been developed to identify the feeding area of the ALHA. Surgeons usually rely on preoperative imaging findings in distinguishing between the replaced and accessory types of ALHA by assessing the arterial configuration of the right liver lobe. Measuring the diameter

of the ALHA or LGA on preoperative abdominal CT has also been suggested to help in decision making, because the ALHA or LGA diameter has been reported to be associated with postoperative liver dysfunction after ALHA ligation [26]. However, imaging studies have limited ability to evaluate the collateral arterial blood supply. Moreover, ALHA imaging studies have low accuracy and tend to be given less importance by radiologists. Among patients with ALHA ligation in our study, only 20.8% (101/486) had documented information about the ALHA, whereas the preoperative CT findings of 74.3% (361/486) of the patients do not mention the ALHA. Moreover, 4.9% (24/486) of the patients had records indicating the absence of a hepatic vascular anomaly. The development of an effective perioperative tool is needed to distinguish between patients requiring ALHA preservation and those in whom the ALHA can be safely ligated.

Our study was performed at a high-volume center for gastric cancer and reflects the real-world setting. We used PSM analysis to minimize the influence of confounding factors that could affect postoperative outcomes, especially concerning the type of resection and the extent of lymph node dissection. Nevertheless, our study had several limitations. A potential selection bias exists owing to the retrospective nature of this study. It was difficult to determine the precise reason for ligating the ALHA. As a result, we could not distinguish whether the ALHA was sacrificed because it was deemed an accessory type or whether it was simply not preserved. Moreover, as there is no consensus about the surgical strategy for an ALHA, it is possible that different surgeons made different decisions about preserving or ligating the ALHA in similar patient situations. Recently, our institution initiated a prospective study on the development of a decision-making tool based on a near-infrared system for determining whether to preserve or ligate the ALHA. The results of this study suggest the possibility of an effective tool that can identify patients in whom ALHA ligation can result in severe liver damage. Another limitation was the lack of a consensus on the severity of liver enzyme elevation that would indicate the need for using liver-protective agents. Future studies on the ALHA should consider the use of liver-protective agents. Moreover, our study does not explain the precise mechanism by which grade \geq IIIa postoperative complications, particularly pulmonary complications, tended to occur more often in patients with deteriorated liver function. However, a recent study suggested that high-mobility group box chromosomal protein 1 (HMGB1), a proinflammatory cytokine, could have a role. HMGB1 has been found to be involved in the initiation of an inflammatory response following ischemia in the liver and is associated with acute lung injury, including lung edema [27]. Further investigation into the inflammatory response associated with liver ischemia is necessary to elucidate the mechanism.

In conclusion, among patients with a ligated ALHA, 8.6% presented with MS liver enzyme elevation. These patients showed poorer short-term postoperative outcomes, in terms of the length of hospital stay and the incidence and severity of postoperative complications, than patients with NM liver enzyme elevation. Therefore, more precise perioperative decision tools need to be developed to determine the indications for either preserving or ligating the ALHA.

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