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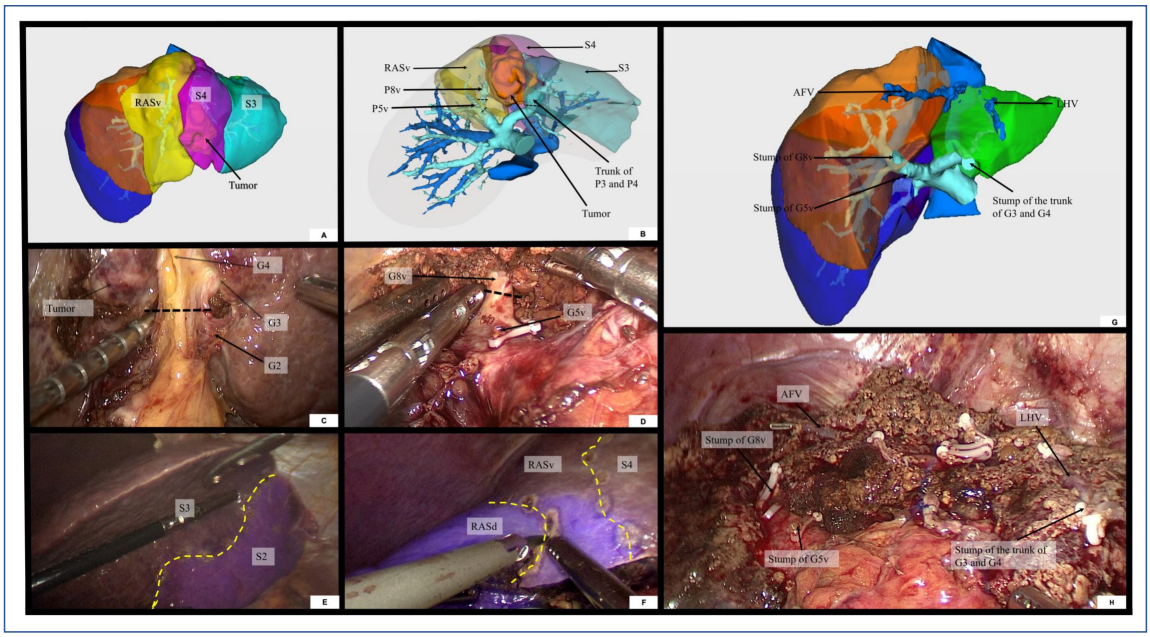

Key steps of laparoscopic anatomic hepatectomy navigated by ICG fluorescence staining guided by 3D virtual imaging combined with intraoperative ultrasound (Pages 315-323)

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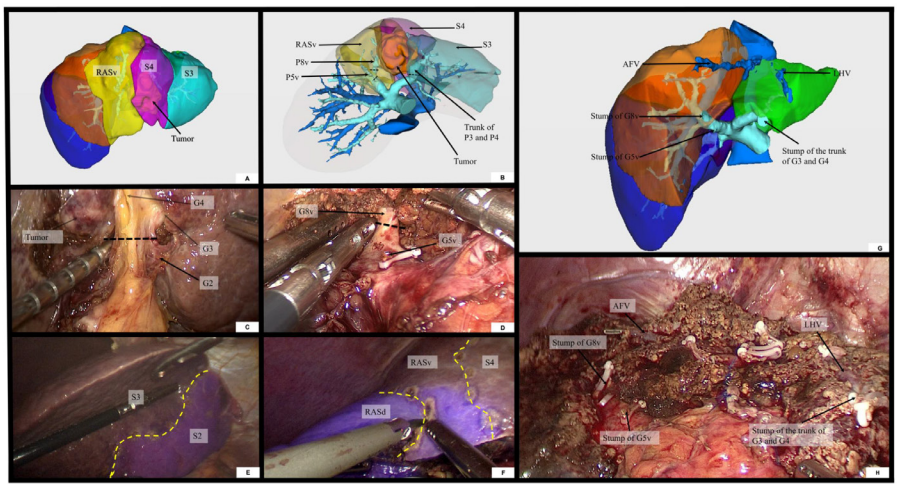

Key steps of laparoscopic anatomic hepatectomy navigated by ICG fluorescence staining guided by 3D virtual imaging combined with intraoperative ultrasound. (A) Establish a 3D virtual image based on the patient's preoperative CT scan, and determine the tumour-bearing liver segment by calculating the portal vein territory of each hepatic segment or subsegment. **(B)** Formulate a detailed surgical plan with the tumor-bearing portal territories as the resection area. **(C,D,E,F)** Transvenous injection of ICG after confirmation and clamping of the target portal vein under intraoperative ultrasound guidance, followed by anatomical liver segment resection under ICG fluorescence navigation. **(G,H)** The transection after laparoscopic anatomic hepatectomy is basically consistent with the transection on the 3D image after virtual hepatectomy. (Pages 315-323)

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EDITORIAL
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Surgery for postoperative intrahepatic recurrence after curative resection for hepatocellular carcinoma: Repeat hepatectomy versus salvage liver transplantation

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Abstract: Liver resection (LR) remains a cornerstone curative option for patients with hepatocellular carcinoma (HCC), and yet the high rate of postoperative intrahepatic recurrence poses a significant clinical challenge. Despite numerous attempts, no adjuvant therapy has shown definitive efficacy in preventing recurrence. In this context, salvage liver transplantation (SLT) and repeat hepatectomy (RH) have emerged as key curative strategies for recurrent disease. While SLT is associated with the most favorable survival outcomes, limited donor availability, particularly in Eastern countries, often necessitates the use of RH, which can also offer promising results. These evolving treatment strategies underscore the urgent need for improved risk stratification, optimized surgical decision-making, and innovative approaches to managing recurrent HCC.

***Keywords*:** hepatocellular carcinoma, salvage liver transplantation, repeat hepatectomy

1. Introduction

Hepatocellular carcinoma (HCC) is rated as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide (*1*). The widely accepted and recommended first-line curative treatments for HCC are liver resection (LR), liver transplantation (LT), and local ablation (*e.g*., radiofrequency ablation (RFA) and microwave ablation) (*2*). However, the recurrence rate after curative LR remains high. The curative treatment modalities for intrahepatic recurrent HCC include salvage liver transplantation (SLT), repeat hepatectomy (RH), and RFA (*3*). The surgeries recommended for postoperative intrahepatic recurrence include RH and SLT (*4*). However, the choice of surgery to treat intrahepatic recurrence of HCC needs to be further investigated.

The current review covers recent studies dealing with surgery to treat postoperative intrahepatic recurrence of HCC.

2. Salvage liver transplantation and salvage living donor liver transplantation

Starzl *et al*. reported the first LT in 1963 (*5*). Since then, improvements in surgical techniques and perioperative patient care for LT have resulted in LT becoming a common and routine surgery. A study by Mazzaferro *et al*. resulted in LT becoming a standard treatment for HCC (*6*). Over the past few years, salvage liver transplantation (SLT) has been recommended for treating recurrent HCC following primary LR to improve the survival rates of patients with HCC. SLT was initially proposed by Majno *et al*. (*7*) and involves the curative resection or ablation of the primary tumor, followed by transplantation in the event of recurrence.

With advances in surgical technology, SLT has become widespread because of its effectiveness (*8,9*). SLT is thought to be comparable to primary liver transplantation and is associated with a decent long-term survival rate (*10*). The long-term survival rate for SLT is superior compared to RH or other salvage therapies for HCC recurrence (*11-13*).

The indications for SLT differ among studies, particularly with regard to the acceptable extent of recurrent HCC lesions (*14-16*). The definition of "transplantability criteria in SLT," referring to the standards identifying those patients who would get the maximum benefit from transplantation for HCC recurrence following hepatectomy, remains controversial (*17*). Most of the studies agree that the Milan criteria are suitable for deciding the transplantability criteria in SLT (*18*).

The scarcity of cadaveric donors has prompted Eastern countries to opt for living donor liver

Table 1. Summary of studies comparing salvage liver transplantation and repeat hepatectomy for treating hepatocellular carcinoma patients with postoperative intrahepatic recurrence

First author	Year	Country/region	Number of patients	Type of treatment	5-year survival *3-year survival ** 5-year disease-specific survival
Yamashita Y (*20*)	2015	Japan	*n* = 13	SLDLT	75%
			n = 146	RH	61%
Ali MA (*31*)	2016	Taiwan	*n* = 25	SLT	80%
			n = 31	RH	60%
Lim C (*32*)	2017	Japan and France	*n* = 77	SLT	71%
			n = 314	RH	71%
Fang JZ (*33*)	2020	China	*n* = 46	SLT	77%
			n = 78	RH	56%
Kim JM (*34*)	2020	South Korea	*n* = 21	SLDLT	81%*
			n = 45	RH	60%*
Yoon YI (*35*)	2022	South Korea	*n* = 84	sLDLT	87%**
			n = 163	RH	56%**
Yang L (*36*)	2025	China	*n* = 77	SLT	76%
			n = 401	RH	58%

Abbreviations: SLT: salvage liver transplantation; SLDLT: salvage living donor liver transplantation; RH: repeat hepatectomy.

transplantation (LDLT) (*19*). Reports on salvage LDLT (sLDLT) for recurrent HCC are scarce. Yamashita *et al*. (*20*) reported 13 patients undergoing sLDLT for recurrence and concluded that in patients with grade B liver damage, sLDLT is superior to RH.

3. Repeat hepatectomy

Several treatment centers currently recommend RH as the first line of therapy for recurrent HCC because it is safe and has survival rates that are comparable to the first hepatectomy (*21*). Currently, there are no uniform guidelines on the indications for RH; however, according to the Japanese HCC guidelines, the basic principles are similar to those in primary cases (*22*).

A study by Nagasue *et al*. in 1986 was the first to report on the performance of RH for recurrent HCC in nine patients (*23*). That study indicated that RH is a possible and meaningful therapeutic approach for treating patients with recurrent HCC in the remnant liver. Later, several studies reported the technical feasibility of RH for treating intrahepatic HCC recurrence (*24-27*). Mise *et al*. (*28*) reported that RH was successful even in patients who had had recurrence three or more times. However, the surgical procedure for repeat LR is challenging and is associated with complications. The more times that a hepatectomy is performed, the more challenging the resection becomes.

Laparoscopic or robotic hepatectomy is being increasingly preferred as it is a minimally invasive method of treating HCC. Compared to open LR, minimally invasive liver surgery is associated with lesser intraoperative bleeding and a shorter hospital stay (*29*). RH is more feasible after laparoscopic resection because of the minimal adhesions (*30*). Therefore, the number of patients undergoing RH is expected to increase considering the increase in the number of patients with primary HCC undergoing minimally invasive hepatectomy.

Currently, there is no consensus on whether RH is superior to other methods used to treat recurrent HCC. The prognosis for RH compared to other treatments might not be valid due to selection bias. Patients for whom RH is not recommended might have poor liver function, or tumor recurrence might be too severe. Prospective randomized studies that prove the superiority of RH over other alternative treatments for recurrent HCC need to be conducted.

4. Comparative study of SLT and RH

Table 1 shows previous studies recommending SLT and RH for intrahepatic recurrent HCC (*20,31-36*). Most of the studies are from Eastern countries, where RH is a commonly performed procedure. The 5-year survival rates have been reported in most studies, and the 5-year survival rates for patients undergoing SLT or SLDLT (71–87%) are generally superior to those for patients undergoing RH (56–71%). Although the postoperative complication rate was not considered, SLT is considered to be the best treatment for intrahepatic recurrent HCC. Of course, one needs to understood that the condition of the patients in the two groups differs; that said, the disease-free survival associated with SLT is better even after propensity score matching (*32,35,36*).

In conclusion, the current article conducted an overview of the reported surgeries for treatment of postoperative intrahepatic recurrence of HCC. Results indicated that SLT yields the best survival outcomes when the tumor conditions are reasonable and the donor pool is sufficient. RH is frequently performed as the second-best treatment option in Eastern countries and is associated with an acceptable survival outcome.

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ORIGINAL ARTICLE
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Characteristics of home-visit nursing stations and psychiatric home-visit nursing service users requiring frequent visits and support coordination in Japan

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Abstract: This study examined the characteristics of service users requiring frequent visits (≥ 3 times/week) and support coordination from home-visit nursing stations and psychiatric home-visit nursing in Japan. Psychiatric home-visit nursing is vital for individuals with mental disorders, but its implementation has lagged behind physical home-visit nursing because of Japan's historical emphasis on institutional psychiatric care. A questionnaire survey was conducted from October 2024 to January 2025, involving 56 home-visit nursing stations with 224 service users. Home-visit nursing stations into four types and users into three care patterns: persistent frequent visits without support coordination, support coordination without persistent frequent visits, and both. In total, 15.6% of users received home visits ≥ 3 times/week, with significant variation by facility type. Frequent visits were associated with schizophrenia, long-term service use, comorbid physical conditions, and low levels of functioning (Global Assessment of Functioning [GAF], mean score, 41.9). Those needing frequent visits and coordination had the lowest GAF scores and highest rates of hallucinations, impulsivity, and self-harm. The primary reasons for support coordination and frequent visits included psychiatric symptom fluctuations, changes in self-care, and family-related issues. The finding show that frequent psychiatric home-visit nursing is associated with diverse and complex care needs requiring tailored coordination and resource allocation, highlighting the importance of structured, individualized care planning and the need to document visit rationales and assessment methods. This is the first Japanese study detailing the profiles of high-need psychiatric home-visit nursing users, offering foundational data for future policy and practice development.

***Keywords*:** home-visit nursing, community psychiatric care, community outreach services, Global Assessment of Functioning, medical insurance system, Japan

1. Introduction

In Japan, psychiatric home-visit nursing is an important element of community psychiatric care that helps people with mental disorders to continue to live in the community. The services are provided by nurses and occupational therapists in the user's home and contain include physical and mental status assessments, symptom management, psychological care, lifestyle support, and user empowerment. Under the Japanese universal health insurance system, the fee for psychiatric home-visit nursing is covered by medical insurance. The two main service providers are psychiatric medical facilities and home-visit nursing stations. The two systems differ, and in recent years, the provision of care from home-visit nursing stations has been increasing in response to growing service needs (*1*). Services provided by visiting nursing stations are conducted based on psychiatric home care instructions issued by the attending psychiatrist (*2*). The frequency of home-visit nursing is determined by the home-visit nursing service provider based on the patient's care plan.

The implementation of psychiatric home-visit nursing has been delayed compared with the provision of home-visit nursing covered by medical insurance for users with physical illnesses. This situation has arisen because of

the characteristics of psychiatric care in Japan, where inpatient treatment in medical institutions has been the mainstay for people with mental disorders (*2,3*). In recent years, the policy of promoting community care for people with mental health conditions has meant that numerical targets and measures related to psychiatric nurse visits have been included in regional medical plans formulated by prefectures on the basis of the Medical Service Act. However, according to a survey conducted in 2023, in 14 out of 47 prefectures, such information was limited to numerical targets for psychiatric nurse visits (*4*).

Visits from home-visit nursing stations to patients in their homes, following a written home-visit nursing care instruction from a psychiatrist and provided under the basic psychiatric home-visit nursing care fee, can occur up to three times per week (or five times per week for up to 3 months after discharge from hospital and for up to 14 consecutive days under special instructions). The frequency of home-visit nursing care is determined through consultation with the user on the basis of their living conditions, medical condition, treatment status (including medications and physical illness), self-care ability (*i.e.*, whether it is sufficient to support the continuation of community life), use of social resources, and relationships with family and neighbors. Other social resources in the community may also be necessary. The appropriateness of the current frequency of home-visit nursing care is a matter of debate, and there is a need to clarify the background characteristics of users and to develop data that can serve as a basis for improving the system.

The purpose of this study was to determine the background characteristics and medical status of patients who use psychiatric home-visit nursing care services three or more times per week, and to characterize the home-visit nursing stations providing these services. The presence or absence of support coordination was also analyzed, as well as the relationship between the attributes of the various providers of home-visit nursing care and the frequency with which they were used.

2. Materials and Methods

2.1. Participants

A questionnaire survey was administered to 56 home-visit nursing stations nationwide providing psychiatric home-visit nursing care. The inclusion criteria were among the service users who use psychiatric home-visit nursing at the survey partner facilities, those who satisfy either or both of the following: *i*) Users who have had a support coordination (including the change of frequency of visits) during the past year, or *ii*) Users who have used home-visit nursing at least three times a week for at least one month in the past year. Data from those who opted out of the survey through disclosure were not included.

The questionnaire was developed based on administrative indicators used in Japan, as well as on discussions between the researchers about the items needed for this study. It consisted of two parts: a facility questionnaire and a user questionnaire. The facility questionnaire was filled out by facility managers, and the user questionnaire was filled out by home care nurses. The user form was filled out by the charge nurse on the basis of the information in the charts of patients who had an increased or decreased frequency of visits, or who had been visited frequently for > 1 month in the past year. "Frequent visits" was defined as three or more visits per week. The survey was conducted from October 2024 to January 2025.

2.2. Questionnaire contents

The facility questionnaire covered the function of the home-visit nursing station and the characteristics of its users. Regarding the function of the home-visit nursing station, the respondents were asked about the number of staff, the total number of users, and the number of users receiving psychiatric home-visit nursing care. Regarding the characteristics of home-visit nursing station users, we obtained data on their psychiatric diagnosis (International Classification of Diseases, 10th revision (ICD-10) category), age (in 10-year increments), Global Assessment of Functioning (GAF) score (in 10-point increments), and frequency of visits (less than once per month, once every 2 weeks, once per week, twice per week, three times per week, more than three times per week).

The user form asked about the target users' basic characteristics (gender, age, diagnosis), psychiatric symptoms, presence of complications, reasons for support coordination and frequent visits, and the services used.

2.3. Analysis

Home-visit nursing agencies that provide psychiatric services are diverse, in terms of their time of establishment, size, and the roles they play in the community; therefore, they were categorized into four types in this study (Table 1). Data on the functions of the home-visit nursing stations and the characteristics of their users were acquired *via* the facility questionnaire and descriptive statistics were calculated. The data are presented according to the classification of facility types outlined in Table 1.

After tabulating the data, three patterns of care use were distinguished: Pattern 1: persistent (> 1 month) frequent visits without support coordination, Pattern 2: support coordination without persistent (> 1 month) frequent visits, Pattern 3: both support coordination and persistent (> 1 month) frequent visits (Table 2).

SPSS software (IBM Corp., Armonk, NY, USA) was

Table 1. The four types of home-visit nursing stations

Types	Home-visit nursing stations
Specialized/Independent	Stand-alone offices (including those with multiple offices) that primarily provide psychiatric home-visit nursing services.
Medical Institution-Affiliated	Facilities that have medical institutions, welfare services for persons with disabilities, *etc.* within the corporation.
Regional Cooperation	Facilities that primarily implement long-term care insurance, *etc*., and provide psychiatric home-visit nursing care in cooperation with relevant community organizations.
Specialized/Nationwide Expansion	Facilities operating multiple home health care agencies nationwide.

Table 2. Use patterns of the different types of home-visit nursing stations (*n* = 224)

Types	Number of offices	Number of cases	Pattern 1	Pattern 2	Pattern 3
Specialized/Independent	12	52	30 (57.7%)	14 (26.9%)	8 (15.4%)
Medical Institution-Affiliated	5	23	5 (21.7%)	10 (43.5%)	8 (34.8%)
Regional Cooperation	5	9	4 (44.4%)	3 (33.3%)	2 (22.2%)
Specialized/Nationwide Expansion	34	140	64 (45.7%)	27 (19.3%)	49 (35.0%)
Total	56	224	103 (46.0%)	54 (24.1%)	67 (29.9%)

Pattern 1: Users who received persistent (> 1 month) frequent (≥ 3 days per week) visits without support coordination, Pattern 2: Users who received support coordination without persistent (> 1 month) frequent visits, Pattern 3: Users who received both support coordination and persistent (> 1 month) frequent visits.

used for the analysis. The significance level was set at 5%. Descriptive analyses of the data from a publicly available mental health and welfare database were conducted to estimate the frequency of psychiatric home-visit nursing.

2.4. Ethics

Home care nurses and administrators were informed about the study in writing, and consent was deemed to have been given upon the completion and return of the questionnaire. Users eligible for the medical record survey received a written explanation of the study and had the opportunity to opt out. The questionnaires were assigned identification numbers and administered such that participants could not be identified (ethics approval number: NCGM-S-004521-00).

3. Results

3.1. Characteristics of home-visit nursing stations by facility type

Fifty-six completed facility forms were analyzed in terms of the number of users, number of visits, and frequency of visits per facility.

The average number of users per facility was 128.0, and on average 109.2 of them were charged for basic psychiatric home-visit nursing care. The total number of users was highest for the "regional cooperation" type, whereas the number of psychiatric home-visit nursing users was highest for the "specialized/independent" type and the "medical institution-affiliated" type. The average total number of visits per month was 676.9, and the average total number of visits for psychiatric care was 546.6.

Overall, the most common visitation frequency was once per week (39.3%), followed by twice per week (22.6%). In total, 15.6% of users received home visits three or more times per week. The "specialized/independent", "regional cooperation", and "specialized/nationwide expansion" types had large proportions of weekly users, whereas the "medical institution-affiliated" type had the largest proportion of users (42.8%) who used the facility once per month or less. In addition, 19.5% of the users of the specialized/nationwide expansion type services received three or more visits per week, compared with < 10% for all other facility types (Table 3).

3.2. Differences in user characteristics between care patterns

User characteristics were compared between care patterns (Table 4). Overall, 53.1% of users were female. There was no statistically significant difference in sex ratio between care patterns. The most common diagnoses were schizophrenia/delusional disorder (48.2%) and mood disorder (depression/bipolar) (28.6%). Pattern 2 had the smallest percentage of users with schizophrenia/delusional disorder (37.0%), and larger percentage of mood disorder (35.2%), and developmental disorder (13.0%). A large proportion of Pattern 1 and 3 users had received home-visit nursing care services for > 3 years, and 39.8% of Pattern 1 and 29.8% of Pattern 3 users

Table 3. User frequency data for the different types of home-visit nursing stations

Numbers	Average number of users per establishment (%)				
	Total (56 offices)	Specialized/ Independent (12 offices)	Medical Institution-Affiliated (4 offices)	Regional Cooperation (5 offices)	Specialized/Nationwide Expansion (35 offices)
Number of users per office	128.0	156.3	185.3	191.0	102.7
Number of visits per office					
Total number of visits	676.9	633.3	457.0	1,053.2	663.3
Number of psychiatric home-visit nurses	546.6	588.3	450.8	161.4	598.3
Number of users by frequency of visits per office (% of total)					
Less than once a month	11.1 (11.3)	15.6 (10.5)	79.0 (42.8)	6.2 (15.5)	4.3 (4.4)
Once every two weeks	11.0 (11.2)	21.3 (14.3)	49.3 (26.7)	7.4 (18.5)	7.0 (7.2)
Once a week	38.5 (39.3)	74.2 (49.8)	47.8 (25.9)	18.8 (47.0)	40.3 (41.2)
Twice a week	22.1 (22.6)	24.8 (16.7)	5.5 (3.0)	6.6 (16.5)	27.0 (27.7)
3 times a week	14.3 (14.6)	12.1 (8.1)	3.0 (1.6)	1.0 (2.5)	17.9 (18.3)
More than 4 times a week	1.0 (1.0)	0.9 (0.6)	0.0 (0.0)	0.0 (0.0)	1.1 (1.2)

Table 4. Characteristics of home-visit care users by care pattern

Characteristics	Total (n = 224)	Pattern 1 (n = 103)	Pattern 2 (n = 54)	Pattern 3 (n = 67)	χ^2/F	p
	n (%)/Mean(SD)	n (%)/Mean(SD)	n (%)/Mean(SD)	n (%)/Mean(SD)		
Sex						
Male	97 (43.3)	50 (48.5)	20 (37.0)	27 (40.3)	1.621	0.445
Female	119 (53.1)	51 (49.5)	29 (53.7)	39 (58.2)		
Diagnosis						
Schizophrenia	108 (48.2)	54 (52.4)	20 (37.0)	34 (50.7)	36.841	0.000
Mood disorders	64 (28.6)	29 (28.2)	19 (35.2)	16 (23.9)	0.964	0.617
Anxiety disorders	12 (5.4)	7 (6.8)	3 (5.6)	2 (3.0)	-	
Developmental disorders	18 (8.0)	8 (7.8)	7 (13.0)	3 (4.5)	-	
Intellectual disorders	23 (10.3)	11 (10.7)	5 (9.3)	7 (10.4)	-	
Substance use disorders	13 (5.8)	6 (5.8)	2 (3.7)	5 (7.5)	-	
Others	38 (17.0)	16 (15.6)	9 (16.7)	13 (19.4)	-	
Years of service use					5.221	0.073
< 1 year	29 (12.9)	12 (11.7)	6 (11.1)	11 (16.4)		
1 – 3 years	58 (25.9)	19 (18.4)	21 (38.9)	18 (26.9)		
3 – 5 years	48 (21.4)	25 (24.3)	7 (13.0)	16 (23.9)		
Over 5 years	75 (33.5)	41 (39.8)	14 (25.9)	20 (29.8)		
Psychiatric Symptoms						
Anxiety	114 (50.9)	62 (60.2)	22 (40.7)	30 (44.8)	36.841	0.000
Depression	93 (41.5)	46 (44.7)	23 (42.6)	24 (35.8)	7.841	0.020
Hallucination/Delusion	77 (34.4)	35 (34.0)	16 (29.6)	26 (38.8)	13.057	0.001
Impulsivity	47 (21.0)	23 (22.3)	7 (13.0)	17 (25.4)	10.522	0.005
Confusion	26 (11.6)	11 (10.7)	8 (14.8)	7 (10.4)	0.104	0.950
Verbal violence	24 (10.7)	17 (16.5)	2 (3.7)	5 (7.5)	-	
Excited	24 (10.7)	15 (14.6)	2 (3.7)	7 (10.4)	-	
Self-harm	22 (9.8)	10 (9.7)	4 (7.4)	8 (11.9)	-	
Physical Complications	120 (53.6)	56 (54.4)	26 (48.1)	38 (56.7)	3.645	0.698
Services used						
In-home care (home help)	79 (35.3)	40 (38.8)	12 (22.2)	27 (40.3)		
Support for continuous employment (Type B)	53 (23.7)	24 (23.3)	12 (22.2)	17 (25.4)		
Psychiatric day care	16 (7.1)	8 (7.8)	2 (3.7)	6 (9.0)		
Home-visit nursing care	17 (7.6)	11 (10.7)	2 (3.7)	4 (6.0)		
Visits and consultation by public health nurses	24 (10.7)	10 (9.7)	4 (7.4)	10 (14.9)		
GAF score	41.9	40.8 (116.8)	44.1 (186.6)	38.3 (105.6)	3.04	< 0.05

Pattern 1: Users who received persistent (> 1 month) frequent (≥ 3 days per week) visits without support coordination, Pattern 2: Users who received support coordination without persistent (> 1 month) frequent visits, Pattern 3: Users who received both support coordination and persistent (> 1 month) frequent visits. Cases where the χ^2 test was not appropriate because the expected frequency was ≤ 5 are indicated by "-".

had used them for > 5 years (χ^2 = 5.22, p = 0.073). In total, 53.6% of users had physical comorbidities, with the highest proportion among Pattern 3 users, although the difference between patterns was not statistically significant. Current psychiatric symptoms included anxiety (50.9%), depression (41.5%), and delusions/hallucinations (34.4%). Psychiatric symptoms were most common among Pattern 1 users, especially anxiety (60.2%), verbal abusiveness (16.5%), and excitement (14.6%). Pattern 2 users were the most likely to experience confusion (14.8%) and Pattern 3 users were the most likely to experience hallucinations/delusions (38.8%), self-harm (11.9%), and impulsivity (25.4%) The overall mean GAF score was 41.9 (SD = 24.2), with Pattern 3 users (38.3; SD = 105.6) having the lowest mean GAF score (F = 3.04, p < 0.05).

3.3. Reasons for adjustment of support and frequency of visits

The most common reason overall for support coordination was a "change in psychiatric symptoms" (74.4%). In Pattern 3, the most common reasons were a "change in psychiatric symptoms" (79.1%), "change in self-care level" (50.7%), "need for medication" (41.8%), "change in physical condition" (29.9%), and "change in family situation" (28.4%). The most common reasons for frequent visits were "unstable mental symptoms" (90.6%), "need for physical care" (27.6%), and "need for family support" (19.4%). All of these reasons were cited more frequently by Pattern 1 than Pattern 3 users (Table 5).

4. Discussion

Previous studies in the Japanese context have examined the characteristics of frequent home-visit nursing for the elderly (*5*). Regarding psychiatric home -visit nursing, qualitative studies have been conducted on care content and other aspects (*6,7*) evaluations of specific intervention methods (*8*), and investigations into the proportion and trends of psychiatric home-visit nursing care provision (*4,9*), psychiatric care of general home visiting nurses (*10,11*) as well as studies investigating the overall evaluation of these services among all users (*12*), Some studies have also addressed the issue of violence experienced by psychiatric home-visit nurses (*13,14*). However, no research has investigated the profiles of high-need psychiatric home-visiting nursing users in relation to visit frequency in the Japanese context.

In the 2022 survey, the average number of visits for patients receiving home-visit nursing care from home-visit nursing stations based on basic psychiatric home-visit nursing care expenses was 5.7 times per month (*15*), and the re-analysis of the June 30th survey (630 surveys, National Center of Neurology and Psychiatry) on mental health welfare (*16*) conducted using ChatGPT showed that the number of visits per week was 1.4 times. Compared to these surveys, the target population for this study was high-care-volume cases (three or more visits per week) with support coordination. Compared with the 2022 survey (*15*), a higher proportion of users in this study had physical symptoms (53.6% *vs.* 49.3%), and the mean GAF score was lower (41.9 *vs.* 50.3).

The Pattern 1 users in this study (continuous care,

Table 5. Reasons for frequent visits/support coordination

Reasons	Total (n = 224)	Pattern 1 (n = 103)	Pattern 2 (n = 54)	Pattern 3 (n = 67)
Reason for support coordination	n (%)	n (%)	n (%)	n (%)
Changes in psychiatric symptoms	90 (74.4)		37 (68.5)	53 (79.1)
Changes in self-care levels	51 (42.1)		17 (31.5)	34 (50.7)
Need for medication assistance	43 (35.5)		15 (27.8)	28 (41.8)
Changes in physical symptoms	31 (25.6)		11 (20.4)	20 (29.9)
Changes in support	34 (28.1)		18 (33.3)	16 (23.9)
Change in family situation	30 (24.8)		11 (20.4)	19 (28.4)
Changes in relationships with neighborhood	11 (9.1)		3 (5.6)	8 (11.9)
Coordination toward the end of home-visit nursing care	2 (1.7)		2 (3.7)	0 (0.0)
Support Coordination				
Increase/decrease in frequency of visits	109 (90.1)		51 (94.4)	58 (86.6)
Telephone support and phone calls	33 (27.3)		13 (24.1)	20 (29.9)
Coordination of medical visits and hospitalization	18 (14.9)		7 (13.0)	11 (16.4)
Coordination of services	21 (17.4)		12 (22.2)	9 (13.4)
Information sharing with stakeholders and families	49 (40.5)		21 (38.9)	28 (41.8)
Reasons for frequent visits				
Unstable psychiatric symptoms	154 (90.6)	94 (91.3)		60 (89.6)
Physical care needed	47 (27.6)	34 (33.0)		13 (19.4)
Need support for family members	33 (19.4)	23 (22.3)		10 (14.9)
Difficulty in using other services	30 (17.6)	18 (17.5)		12 (17.9)
Other	30 (17.6)	22 (21.4)		8 (11.9)

Pattern 1: Users who received persistent (> 1 month) frequent (≥ 3 days per week) visits without support coordination, Pattern 2: Users who received support coordination without persistent (> 1 month) frequent visits, Pattern 3: Users who received both support coordination and persistent (> 1 month) frequent visits.

three or more visits per week) often needed physical care and family support, and many of them had been using the home-visit care service for ≥ 5 years. Pattern 2 users (support coordination and frequent visits) were characterized by a wide range of psychiatric problems, including risk of self-harm and harming others persisting over a long period of time, and received a wide range of care types, including physical care and family support, with frequent visits providing support with symptoms and daily life. Pattern 2 users (support coordination, infrequent visits) had a higher likelihood of mood and developmental disorders, and most of them had been using home-visit nursing station services for < 3 years. Support adjustment in Pattern 2 users was often attributed to changes in physical condition or life circumstances. Pattern 3 users (support adjustment and continuous use of home-visit nursing care three or more times per week) had lower GAF scores, and many of them had symptoms such as hallucinations, delusions, impulsivity, and self-injury. The most common reasons for support adjustment were changes in symptoms, medication support, and self-care. Pattern 3 users were characterized by fluctuating psychiatric symptoms and self-care, and when symptoms worsened, frequent visits and cooperation with a wide range of support sources were used to adjust care and allow the continuation of community life. Many Pattern 3 patients were receiving support from local public health nurses, and some of them needed support coordination. Pattern 1 users were characterized by serious disease requiring continuous and diverse support, and Pattern 3 users by changes in family situation necessitating support. Pattern 1 users continued to receive frequent visits for > 1 year after support adjustment.

In a previous study, 89.9% of care service users received up to three visits per week from a home-visit nursing agency (36.7% received one visit per week). The same study found little relationship between the GAF score and frequency of visits (*17*).

In conclusion, this study is the first to detail patients receiving psychiatric home-visit nursing at least three times per week, and it is clear that a variety of characteristics and factors are associated with such frequent visits, including the patient's level of functioning. It is necessary to verify the long-term effects of frequent home visits from nurses on such patients. Frequent home-visit nursing care requires medical resources, and, for service transparency, it is essential to clarify the role of home-visit nursing in allowing patients like those in this study to continue living in the community. Clearly recording the decisions and rationale regarding the number of visits is also necessary to implement appropriate care plans.

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Rising cognitive behavioral therapy claims among Japanese youth despite population decline: A retrospective study using the National Database of Health Insurance Claims (FY 2014–2022)

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Abstract: Cognitive behavioral therapy (CBT) is reimbursed under the national insurance system of Japan, although predominantly for adults. Recent mental health crises among children and adolescents have prompted policy reforms to expand access to CBT. This study aimed to assess trends in CBT insurance claims among Japanese youth (0–19 years) from fiscal year 2014–2022 using national claims data. Outpatient psychotherapy and CBT claims from the National Database of Health Insurance Claims (NDB) were analyzed and stratified by age group. Linear regression was applied to assess trends. The number of CBT claims for youth increased markedly from 691 (1.5%) in 2014 to 4,497 (12.8%) in 2022, with significant upward trends for ages 5–9, 10–14, and 15–19 (all $p < 0.05$). Claims for adults declined during the same period. The use of CBT among children and adolescents in Japan has grown substantially, but most protocols remain adult-oriented. These results highlight the need for child-specific CBT programs and broader provider eligibility. A key limitation is that the data lacked disorder-specific information, which restricts analysis of treatment indications.

Keywords: adolescents, CBT, NDB, psychotherapy, youth

1. Introduction

Cognitive Behavioral Therapy (CBT) is a well-established, evidence-based intervention; however, its widespread implementation remains limited by persistent barriers to access (*1-3*). The need for broader dissemination is supported by clinical trials demonstrating its efficacy across a range of conditions, including subthreshold depression and other forms of psychological distress (*4,5*). As a scalable intervention, CBT holds promise for addressing workforce shortages and facilitating the integration of empirically supported treatments into pediatric mental health services (*6*).

The reimbursement of CBT is a key policy in Japanese mental health problems, but most patients have been adults. CBT was first promoted in fiscal year (FY) 2010 by the Ministry of Health, Labour and Welfare (MHLW) to improve treatment of depression and reduce risk of suicide. In Japan, training for CBT and its implementation are predominantly centered around adults.

Recent trends indicate a marked increase in incidence and prevalence of neurodevelopmental disorders among Japanese youth, including autism spectrum disorder and attention-deficit/hyperactivity disorder, as confirmed by a recent nationwide study using the National Database of Health Insurance Claims (NDB) (*7-9*). In FY 2024, there were 524 deaths from suicide under the age of 18, the highest number ever recorded in Japan. These mental health challenges among children and adolescents have prompted policy initiatives to expand access to children's mental health services (*10*).

A previous study highlighted significant regional

disparities in availability of child and adolescent mental health professionals in Japan, revealing a marked imbalance in distribution of specialists, particularly between rural and urban areas (*6*). Rural regions suffer from a severe shortage of child psychiatry specialists, with a 4.7-fold difference in student-to-specialist ratios compared to urban areas. Rural areas also have the greatest need for additional support regarding access to mental health resources (*i.e.*, specialists, mental health facilities) and rates of truancy, bullying, suicide, and child abuse. Aside from reflecting individual and familial challenges, these findings also expose systemic gaps in terms of early intervention and sustained mental health support (*10*).

From a health policy perspective, the MHLW has enacted progressive reimbursement reforms to encourage early intervention and psychosocial treatment. Initially, CBT was reimbursed only when facilitated by physicians, but subsequent amendments in 2016 and 2018 allowed nurses to deliver certain components under physician supervision, aiming to alleviate the shortage of specialized providers. In March 2021, a refined point system was introduced with a strict limit of 16 sessions per series as well.

Mental health challenges among children and adolescents in Japan, including an increase in school absenteeism, suicide rates under the age of 18, and neurodevelopmental disorders, have prompted major policy initiatives aimed at expanding access to mental health care. Randomized controlled trials in the United States and Europe have demonstrated that interventions tailored to children and adolescents, such as Trauma-Focused CBT (TF-CBT) and the Unified Protocol for Children (UP-C), can significantly reduce symptoms and improve functional gains compared to standard adult-oriented protocols.

Although research on CBT for children and adolescents in Japan has steadily increased in recent years, access to these evidence-based interventions remains uneven across regions. In many clinical settings, CBT protocols originally designed for adults with depression are routinely applied to younger populations without formal adaptations, primarily due to lack of standardized youth-specific manuals within the national reimbursement framework. Nonetheless, recent implementation studies indicate that culturally tailored CBT programs for Japanese youth are both feasible and increasingly undergoing pilot testing (*11*).

These programs have expanded particularly in school settings, utilizing simplified materials and familiar cultural references (*11*). For example, one study reported that 60.9% of participating children no longer met diagnostic criteria for anxiety disorders after treatment, and trauma-focused CBT was associated with improvements in PTSD symptoms and social functioning (*12,13*). Additional evidence supports CBT's effectiveness in educational settings: a group-based intervention for upper elementary students reduced depressive symptoms and improved social skills, while more recent trials of transdiagnostic CBT protocols customized for adolescents have shown promise for broader applicability (*14,15*).

Nevertheless, CBT services for children remain limited in availability throughout Japan. Persistent regional disparities and structural barriers — such as insufficient clinical training, partial insurance coverage, and inadequate dissemination — continue to impede access. To explore this gap between research and real-world practice, the present study analyzes national trends in insurance claims for CBT among children and adolescents aged 0–19, with a focus on age- and region-specific patterns.

This study evaluated the impact of recent insurance reforms on annual CBT claim counts among children and adolescents (0–19 years), focusing on age-specific trends.

2. Methods

2.1. Japan national insurance system for CBT

In 2010, CBT was first made eligible for coverage under the national insurance system when delivered by physicians; however, services provided by nurses were not reimbursed at that time. In 2016, to reduce physician burden, reimbursement was allowed when part of the conversation is conducted by a full-time nurse with a certain level of knowledge and experience under the direction of a physician. Subsequent revisions to the reimbursement policy have primarily focused on addressing adult depression. A comprehensive overview of these insurance code modifications related to CBT reimbursement is presented in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=107*). In this study, each CBT claim corresponds to a single reimbursed session under the Japanese national insurance system. As a peculiarity of the Japanese CBT insurance medical system, all CBT claims still require physician involvement, either directly or *via* supervision of a nurse. Psychologists cannot claim insurance reimbursement for cognitive behavioral therapy in Japan.

2.2. Data source

This study examined how these policy changes have affected outpatient psychotherapy use among children and adolescents nationwide. Publicly available data from FY 2014–2022 was analyzed to determine whether the reforms correlated with increased access to psychotherapy and to elucidate any emerging trends or gaps, particularly among younger age groups. The classification of psychotherapy categories (general psychotherapy, CBT, psychoanalysis, psychosomatic

therapy, and group therapy) followed the official medical fee schedule as defined in the Japanese Health Insurance Claims Manual issued by the MHLW.

2.3. Study population and outcome measures

This study focused on outpatient psychotherapy claims that included additional charges for child/adolescent services. Data regarding total annual claims (for all ages and those aged 0–19 years) in FY 2016–2022 was collected from all forms of psychotherapy and specifically from CBT. To analyze differences in utilization, patients were divided into several age groups (0–4, 5–9, 10–14, and 15–19 years). The primary outcome measure was the annual number of psychotherapy claims (including CBT) per 100,000 individuals in these age groups. Using population estimates from the Basic Resident Register, the annual CBT claim rates per 100,000 population were also calculated for each age group (Ministry of Internal Affairs and Communications, 2024).

2.4. Statistical analysis

Descriptive analyses were conducted to determine the proportion of individuals aged 0–19 who received psychotherapy, specifically CBT, for each fiscal year. To assess temporal trends in utilization, the ordinary least squares linear regression was applied to annual counts (FY 2014–2022 for overall trends; FY 2016–2022 for additional fees). A proportion analysis was conducted, calculating the fraction of psychotherapy/CBT claims for children/adolescents (0–19 years) relative to the total for all ages per year. An age-stratified trend analysis involved fitted simple linear regression models, using fiscal year as the independent variable to estimate the annual change (slope β), *p*-value, and coefficient of determination (R^2) for each subgroup.

We addressed reviewer concerns about the limited data points and model assumptions by applying logistic transformation to proportion data and re-examining age-stratified trends in CBT claims *via* ordinary least squares (OLS) regression. The annual number of CBT claims was initially standardized as a proportion of the highest value observed across all years for each age group. The logit transformation was subsequently applied: $\text{logit}(p) = \log((p + 1e{-}5) / (1 - p + 1e{-}5))$, where ε was set to 1e−5 to prevent undefined results. Regression models were evaluated for each age group (0–4, 5–9, 10–14, 15–19 years), providing results for slope (β), 95% confidence intervals, *p*-values, and R^2. The Benjamini–Hochberg false discovery rate correction was used to account for multiple testing.

A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed using PRISM for Mac (GraphPad Software, Boston, USA) and complemented with standard statistical software for confirmatory checks.

2.5. Ethics

Because the data was publicly available and anonymized in the NDB Open Data system, no ethical approval was required. This approach complies with the Japanese guidelines regarding secondary use of de-identified administrative data.

This study adhered to the ethical principles of secondary use of anonymized data as outlined in the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" issued by the Ministry of Education, Culture, Sports, Science and Technology and the MHLW.

3. Results

3.1. Declining birthrate in Japan

According to the national census data, the total population of Japan decreased from 127.10 million in FY 2014 to 122.49 million in FY 2022. Similarly, the population under 19 years old fell from 22.54 million in FY 2015 to 20.65 million in FY 2022 (a reduction of 1.89 million), clearly demonstrating the ongoing demographic decline in Japan.

3.2. Distribution of psychiatric claims among children and adolescents

The total outpatient psychotherapy claims (including general psychotherapy, CBT, psychoanalysis, psychosomatic therapy, and group therapy) increased from 59.5 million in FY 2014 to 69.4 million in FY 2022 (+16.5%) (Table 1), indicating a rising demand, increased public awareness, and expanded access to evidence-based psychiatric services. Among individuals aged 0–19 years, claims increased from 2,604,906 in FY 2015 to 4,365,557 in FY 2022 (+67.6%). The most notable year-on-year increase occurred between FY 2020 and FY 2021, during the COVID-19 pandemic.

3.3. Annual psychotherapy and CBT trends

Table 2 presents the total number of outpatient psychotherapy claims from FY 2014 to 2022. From FY 2014 to 2022, the proportion of younger patients (0–19 years) with outpatient psychotherapy claims increased from 4.1% to 6.3% for all types of psychotherapy and from 1.5% to 12.8% for CBT specifically. During the same period, the proportion of CBT among all psychotherapy claims increased from 4.3% in FY 2014 to 23.2% in FY 2022. Figure 1 shows a rising rate toward younger recipients of CBT during this period. Table 2 shows that CBT's share of all psychotherapy claims declined slightly from approximately 0.075% in

FY2014 to 0.051% in FY2022, while for patients aged 0–19 it increased from nearly 0% to 0.007%, reflecting a demographic shift in service utilization across age groups. During the same period, the proportion of CBT among all psychotherapy claims increased from 4.3% in FY 2014 to 23.2% in FY 2022. Figure 2 shows CBT claims per 100,000 population by the 0- 19 age group, which accounts for demographic shifts over time and highlights utilization trends.

Table 1. Yearly trends in the number of outpatient psychotherapy claims

Fiscal year	Number of claims		%
	All Ages	0–19 years	
2014	46,277,930.00	4,642,656.00	10.03%
2015	47,741,947.00	5,085,490.00	10.65%
2016	48,252,633.00	5,404,208.00	11.20%
2017	48,963,364.00	5,916,930.00	12.08%
2018	51,440,193.00	6,292,346.00	12.23%
2019	52,899,920.00	6,680,150.00	12.63%
2020	51,785,332.00	6,982,524.00	13.48%
2021	54,995,840.00	8,032,054.00	14.60%
2022	56,344,049.00	8,386,488.00	14.88%

3.4. Age-stratified analyses and linear regression results

Table 3 describes the number of CBT claims stratified per age group (0–4, 5–9, 10–14, and 15–19 years) from FY 2014 to 2022 alongside the linear regression results (slope, p-value, R^2).

A simple linear regression using the fiscal year as the independent variable yielded the following slopes (β) and statistical indices. For the 0–4 years subgroup, there was no significant change in claims (β = –1.65; 95% CI: –5.1 to 1.8; p = 0.272; R^2 = 0.17). Significant upward trends were seen with both the 5–9 years subgroup (β = +64.28; 95% CI: 32.4 to 96.2; p = 0.0033; R^2 = 0.73) and 10–14 years subgroup (β = +147.22;

Table 2. Annual psychotherapy and cognitive behavioral therapy usage in Japan (FY 2014–FY 2022)

Fiscal Year	All Psychotherapy			Cognitive Behavioral Therapy			Population
	All Ages	0–19 years	%	All Ages	0–19 years	%	0–19 years
2014	59,488,413	2,423,135	4.07%	44,888	691	1.54%	22,770,002
2015	61,191,289	2,604,906	4.26%	42,216	2,518	5.96%	22,541,461
2016	61,839,713	2,810,594	4.54%	44,660	630	1.41%	22,383,548
2017	63,418,056	3,054,238	4.82%	43,422	680	1.57%	22,175,187
2018	64,805,124	3,269,494	5.05%	38,923	2,445	6.28%	21,954,522
2019	66,198,805	3,461,649	5.23%	37,384	2,918	7.81%	21,692,242
2020	64,549,221	3,614,392	5.60%	35,470	3,003	8.47%	21,405,309
2021	68,141,614	4,170,348	6.12%	37,562	4,125	10.98%	21,037,894
2022	69,439,156	4,365,557	6.29%	35,231	4,497	12.76%	20,655,250

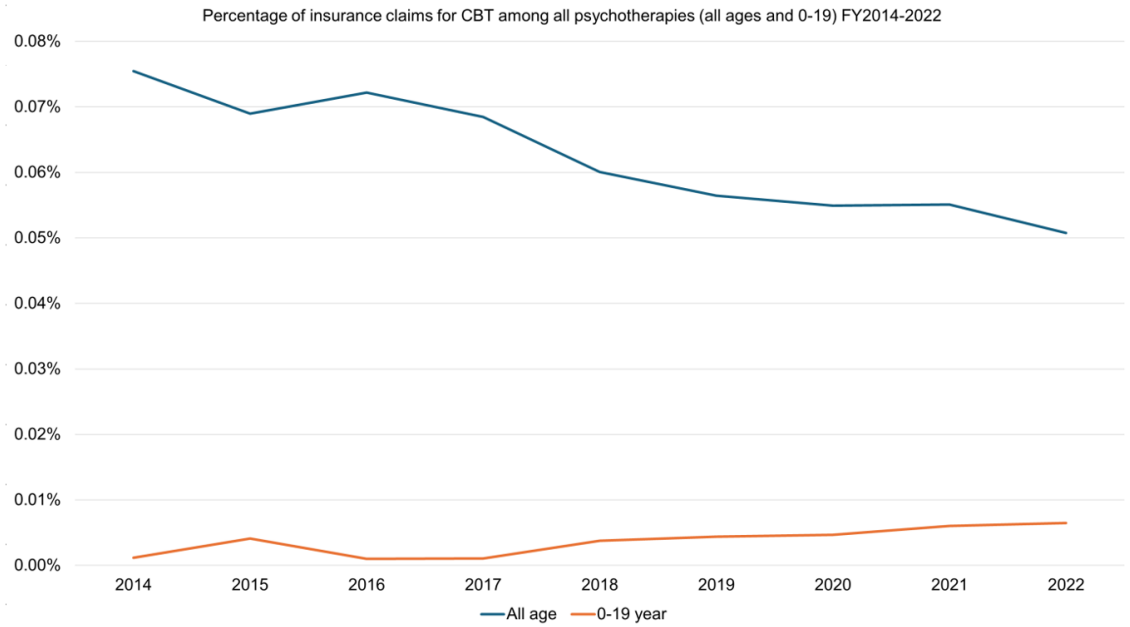

Figure 1. Trends in the share of CBT claims among all psychotherapy claims (FY 2014–2022). CBT's share of all psychotherapy claims fell from about 0.075% in FY2014 to 0.051% in FY2022, while for patients aged 0–19 it climbed from nearly 0% to 0.007% over the same period.

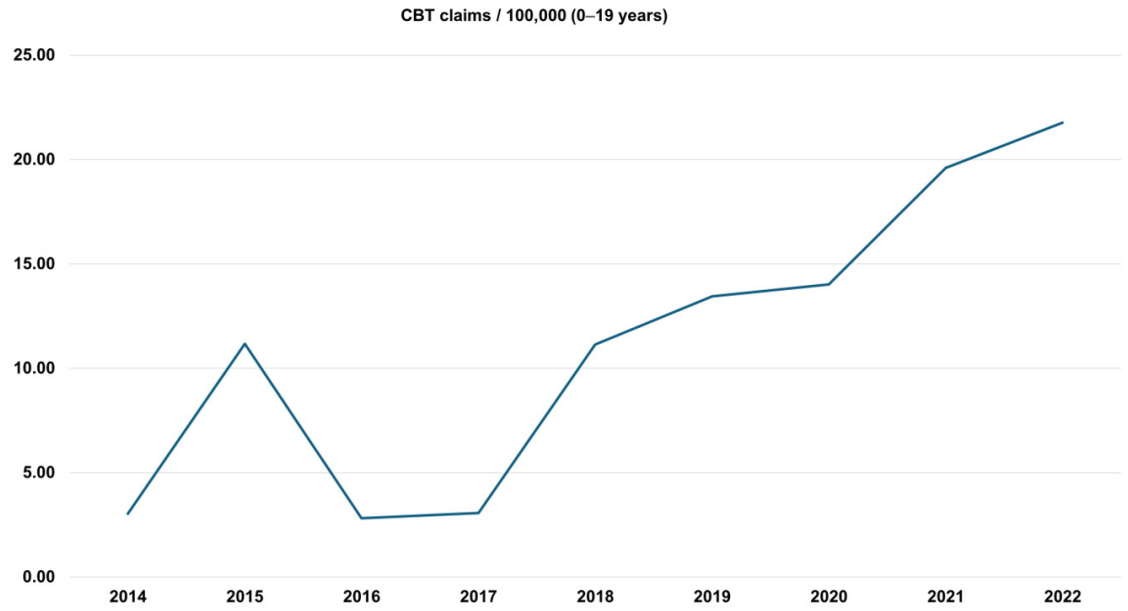

Figure 2. Trends in CBT claims per 100,000 population among individuals aged 0–19 years, FY 2014–2022.

95% CI: 102.5 to 191.9; p = 0.00089; R^2 = 0.81). For the 15–19 years subgroup, there was substantial growth with moderate model fit (β = +240.63; 95% CI: 65.4 to 415.8; p = 0.0177; R^2 = 0.58). Overall, marked and consistent growth was seen among Japanese youth aged 0–19 years (β = +530.66; 95% CI: 360.5 to 700.8; p = 0.00014; R^2 = 0.85).

These results suggest that the primary drivers of increased CBT utilization among youth are in seen in those aged 5–9, 10–14, and 15–19 years. However, the negligible CBT utilization in the 0–4 years age bracket likely reflects the developmental unsuitability of standard adult CBT manuals for toddlers, who predominantly require play-based and parent-mediated interventions tailored to their cognitive level.

Table 3 provides a summary of the findings from the logit-transformed regression analyses. Upward trends statistically most significant and robust were observed in the 10–14 and 15–19 year age brackets, with p-values adjusted to less than 0.01, followed by the 5–9 year age group, where the adjusted p-value was less than 0.05. No significant trend was observed in the 0–4 year age group. These results confirm the initial patterns of behavior while resolving the shortfalls of employing raw count-based OLS regression.

4. Discussion

4.1. Trends and systemic barriers in CBT provision for children and adolescents in Japan

This study revealed a substantial and consistent increase in CBT claims among children and adolescents (0–19 years) in Japan from FY 2014 to FY 2022. In contrast, CBT claims among adults showed a declining trend during the same period, resulting in a relative shift in service provision toward younger age groups.

The NDB data from FY 2014 to 2022 revealed that CBT claims were decreasing for all ages but increasing for children (0–19 years). Notably, the CBT protocols covered by reimbursement are all intended for adults. In Japan, the protocols specified in the reimbursement are not always followed for children and adolescents. The CBT claims for young patients are likely not based on protocols such as TF-CBT or UP-C, which have demonstrated higher levels of empirical support for youth. TF-CBT has shown efficacy in randomized controlled trials, while UP-C has yielded promising results in quasi-experimental studies (*12,14*).

CBT is widely acknowledged as an effective therapeutic modality for various mental health problems. Unfortunately, systemic and administrative factors have historically limited its accessibility in Japan. For instance, only physicians (or in certain cases, nurses working jointly with physicians) could formally bill for CBT under national insurance. Psychologists were largely unable to claim insurance reimbursement directly, despite being key providers of psychotherapeutic interventions in many countries. Consequently, psychologists often had to operate under a physician's supervision for billing, hindering the growth and dissemination of CBT. Furthermore, the commonly imposed 16-session limit has traditionally restricted treatment duration for patients requiring more extensive care, such as those with chronic conditions or severe symptoms that require continued support. This is particularly problematic in cases involving children and adolescents, who benefit from more developmentally

Table 3. Number of cognitive behavioral therapy (CBT) claims by age subgroup (FY 2014–2022)

Age group	All Psychotherapy									Cognitive Behavioral Therapy				
	2014	2015	2016	2017	2018	2019	2020	2021	2022	Slope (β)	95% CI Lower	95% CI Upper	*p*-value	R^2
0–4 years	0	33	0	0	0	0	0	0	0	-0.35	-1.06	0.35	0.27	0.17
5–9 years	0	127	0	0	61	121	286	479	527	1.20	0.16	2.23	0.03	0.52
10–14 years	150	352	65	76	398	645	949	1,140	1,183	0.39	0.14	0.64	0.01	0.66
15–19 years	541	2,006	565	604	1,986	2,152	1,768	2,506	2,787	0.79	0.17	1.41	0.02	0.57
Overall (0–19 years)	691	2,518	630	680	2,445	2,918	3,003	4,125	4,497	0.82	0.48	1.17	0.004	0.77

Remark: A minus sign (−) is preferred over a hyphen (-) for indicating negative values.

attuned interventions that may not necessarily fit into a short-term treatment protocol. In particular, play-based techniques, collaboration with parents and schools, and other adaptations require flexibility that can be undermined by the limit on the number of sessions.

Although our findings demonstrated a steady rise in CBT claims among youth, the absence of diagnostic information in the NDB dataset limited our ability to determine which conditions (*e.g.*, anxiety disorders, depression, or neurodevelopmental disorders) were associated with the increase. This lack of granularity posed challenges in interpreting whether CBT services had been equitably distributed across diagnostic categories or whether certain populations had remained underserved. To address these gaps, future research could utilize linked datasets that combine insurance claims with electronic health records, or implement provider-level surveys that document clinical indications for CBT. Such efforts would support a more targeted allocation of training resources and assist policymakers in refining CBT training program and guidelines within child and adolescent mental health services.

4.2. New system for child and adolescent support claims

Although the overall number of claims increased in FY 2016 due to less strict criteria for CBT claims, the number of claims for the 0–19 age group decreased from the previous year. However, this could be attributed more to new additions to the Child and Adolescent Additions introduced in FY 2016 rather than with the CBT claim requirements. After 2016, the MHLW revised reimbursement policies to improve access to psychiatric care for children and adolescents in response to increasing concerns over developmental disorders, school absenteeism, and suicide among youth. From FY 2016 to 2021, several additional reimbursement fee categories were gradually implemented for outpatient psychotherapy.

Psychologists were allowed to bill for services provided to minors, and higher reimbursement rates were offered without the 16-session restriction. These changes helped alleviate long-standing obstacles regarding children's mental health in Japan. Psychologists can now deliver therapy more freely, and patients who need protracted care can receive it for up to two years on a weekly basis. Many clinicians, such as psychiatrists, nurses, psychologists, and social workers, can treat children with mental illness using various types of psychotherapy, including CBT. In Japan, where child and adolescent psychiatric resources remain limited, digital delivery — *via* apps or online platforms — holds promise not only for expanding access to CBT for youth, but also for training child psychiatrists and other medical professionals to deliver CBT (*16-19*).

Further reforms that allow psychologists to claim reimbursement independently across all age groups could possibly help increase access to CBT and reduce treatment gaps, especially in underserved regions. This robust upward trajectory highlights an increasing demand for CBT, underscoring the urgent need for accelerated CBT workforce training. Additionally, pilot digital CBT initiatives should be established in low-resource prefectures to ensure equitable access. Concurrently, development of interdisciplinary CBT training curricula, leveraging skills of psychiatrists, psychologists, nurses, and social workers, can facilitate upscaling of high-quality CBT services for children and adolescents.

Therefore, Policy recommendations include *i*) expanding insurance eligibility to allow independent claims by licensed psychologists, *ii*) establishing regional CBT training hubs, and *iii*) piloting child-specific CBT protocols (*e.g*., TF-CBT, UP-C) within the national reimbursement system.

4.3. Limitation

Since this study analyzed absolute claim counts without reference to population denominators, changes in the underlying population size were unaccounted for. Future research should analyze per capita rates to provide a more nuanced understanding of service utilization trends.

The NDB Open Data lacks disorder-specific information, outcome measures, and granular age breakdowns, limiting analysis of indications for CBT, treatment effects, and age-specific needs. Lack of disorder-specific data makes it impossible to ascertain which diseases CBT is typically being utilized for (*e.g.*, depression, anxiety, OCD, or PTSD) and which populations might be most in need of expanded services. This lack of diagnostic granularity also restricts our ability to determine whether CBT utilization was primarily for depression, anxiety, developmental disorders, or other indications.

The NDB Open Data also lacks direct outcome measures, precluding large-scale evaluations of short- and long-term responsiveness to CBT. Researchers cannot gauge symptom trajectories, relapse rates, or functional improvements, thereby hindering any robust assessment of therapy effectiveness.

Although the database organizes claims data in various ways, it does not allow sufficiently granular age breakdowns at certain analytic levels. This shortcoming hinders the investigation of how younger children, older children, and adolescents differ in their use of/need for specialized CBT approaches.

Prior to the Child and Adolescent Support Add-on, psychologists were generally unable to bill directly for CBT, and a 16-session limit was often applied under standard codes. This new add-on addresses several of these issues, and future work is needed to determine whether similar reforms would also be applicable to adults or other psychotherapeutic interventions.

Although prefecture-level CBT claim data are unavailable, previous studies have identified regional disparities in access to child mental health services. Digital CBT and mobile delivery models should be explored to address access gaps in underserved areas.

5. Conclusion

Based on the NDB Open data, the use of CBT in Japan has been increasing, especially among the youth, from FY 2014 to 2022. This increase is unrelated to the FY 2022 Child and Adolescent Support Add-on, which is beyond the study period. Future analyses should assess the long-term effects of this reform on CBT access across all ages.

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Risk factors for and a prediction nomogram of physical frailty in older patients hospitalized with acute calculous cholecystitis

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Abstract: Frailty increases the risk of complications and delays recovery in older patients with acute calculous cholecystitis (ACC). Early identification is crucial to improving outcomes. Subjects were 386 older inpatients with ACC at two hospitals who were randomly divided into a training set (n = 270) and validation set (n = 116). Patients were categorized into frail and non-frail groups. Binary logistic regression identified significant predictors, and a nomogram was developed. The incidence of frailty was 27% (n = 73). Smoking, a sleep disorder, impaired ADL, and malnutrition were independent predictors for frailty ($p < 0.05$). The nomogram showed good discrimination (AUC = 0.752), with a sensitivity of 82.6% and a specificity of 67.4%. Calibration was acceptable (Hosmer–Lemeshow χ^2 = 4.407, p = 0.732), and decision curve analysis demonstrated clinical utility. The developed nomogram reliably predicts the risk of frailty in older patients with ACC and may facilitate targeted early interventions in clinical practice.

***Keywords*:** physical frailty, acute calculous cholecystitis, elderly, influencing factors, prediction model

1. Introduction

Acute calculous cholecystitis (ACC) is one of the most common surgical acute abdominal conditions. With changes in lifestyle and dietary habits, the incidence of ACC has been increasing. ACC is highly prevalent in China, where it is closely linked to the widespread occurrence of gallstones and the prevalence of gallbladder stones among adults is estimated to be 4.2% to 21.7% (*1*). A study conducted in Liaoning Province reported that the annual prevalence of gallbladder stones increased from 1.59% in 2016 to 2.52% in 2020 (*2*). However, the exact etiology and pathogenesis of gallbladder stones remain unclear. They are generally believed to be associated with multiple factors, including genetic predisposition, metabolic abnormalities, biliary cholesterol supersaturation, impaired gallbladder motility, mucin hypersecretion, intestinal microbiota imbalance, dietary habits, and lifestyle (*3-5*). Due to the rapid progression of ACC, delayed treatment can lead to serious complications, including cholangitis, biliary peritonitis, and septic shock, which may be life-threatening (*6*). Thus, health management of older patients with ACC remains a considerable challenge for medical professionals.

The main treatment options for ACC include conservative management, surgical intervention, and cholecystostomy. Currently, laparoscopic cholecystectomy (LC) is considered to be the treatment of choice for ACC (*7*). It offers several advantages, including minimal surgical trauma, faster recovery, and shorter hospitalization (*8*). The evaluation of pros and cons for surgery in elderly suffering from ACC is more complex than in young people; in addition, old age is not a contraindication for surgery; but better identification of frailty could help lead to the best clinical decision by the surgeon (*9*). Although clinical guidelines emphasize the importance of preoperative frailty assessment in patients with ACC, only a limited number of studies have evaluated the role of frailty in preoperative risk assessment among patients with ACC (*10*), and they have provided evidence for the association between frailty and postoperative outcomes in patients with ACC. Thus, there is a need to identify preoperative clinical variables for older patients with ACC undergoing LC, with a particular focus on frailty.

Frailty is a geriatric syndrome characterized by a

multisystem physiological decline, increased vulnerability to stressors, and adverse clinical outcomes, such as disability, hospitalization, and mortality (*11-13*). The development of physical frailty in older patients is the result of a combination of multiple factors. By using internationally developed screening tools (*14*), potential factors influencing physical frailty can be identified. A review identified as many as 34 factors influencing frailty, encompassing physiological, psychological, social, and lifestyle domains (*15*). However, the development of physical frailty is reversible (*16*), thereby necessitating the development of a convenient and rapid early warning tool, which would improve the management of physical frailty in older patients with ACC, allow early identification of risk factors for physical frailty, and facilitate the adoption of effective intervention measures to prevent, delay, or reverse the progression of frailty.

Currently, research on physical frailty has paid insufficient attention to hospitalized older adults, and specific assessments of patients with ACC are still lacking. Nomogram models are extensively utilized in clinical research to aid clinical decision-making and generate a numerical probability of clinical events to assess patients' frailty (*17*). Although various frailty assessment tools and predictive models have been developed for elderly patients undergoing surgery or hospitalization, there are no existing models of the ACC population specifically.

Given the unique pathophysiological characteristics, surgical considerations, and recovery patterns in older patients with ACC, our study addresses this issue by establishing a tailored nomogram that integrates geriatric, nutritional, and functional domains. This model represents an innovative effort to facilitate the early identification of frailty in patients with ACC and to optimize clinical decision-making.

2. Patients and Methods

2.1. Study design

This was a retrospective cohort study. Convenience sampling was used to select inpatients at two hospitals (the First Hospital Affiliated with Chongqing Medical University and Peking University International Hospital) in China. Subjects were patients with ACC who were 65 years of age or older who were seen from December 2023 to April 2025. Prior to conducting the study, approval was received from the Ethics Committee of the School of Medicine, Hamamatsu University (No. 25-124), the First Hospital Affiliated with Chongqing Medical University (No. 2023-337) and the Peking University International Hospital (No. 2023-KY-0085-01). Subjects' data were processed and electronically stored in accordance with the ethical principles of the Declaration of Helsinki for medical research involving human subjects.

2.2. Quality control measures

i) Controlling selection bias: During the factor extraction phase, close communication with experts was maintained to develop a detailed, scientifically sound, and feasible research protocol. Subjects were selected strictly based on predefined inclusion and exclusion criteria.

ii) Standardizing research implementation: Prior to the study, all research team members underwent standardized training and assessments. Uniform instructions were used throughout the study. Informed consent was obtained from patients and their families. Investigators accompanied subjects throughout the process, answered questions in real time, and ensured timely collection and thorough verification of the authenticity and completeness of questionnaires.

iii) Controlling information bias: A double data entry method was used to ensure the accuracy of data input. Two researchers independently entered, verified, and analyzed the clinical data to maintain data reliability and consistency.

2.3. Subjects

The inclusion criteria for this study were as follows: *i*) patients with ACC who were 65 years of age and older, *ii*) using the diagnostic criteria for ACC as defined by the Tokyo Guidelines (TG18) (*18*), and *iii*) patients who were conscious and provided written informed consent.

The exclusion criteria were as follows: *i*) patients who have been clearly diagnosed with dementia or mental illness, *ii*) patients who could not assist in completing the survey, and *iii*) those with any known severe vision or auditory problems or who were unable to complete the questionnaire. Informed consent was obtained from all patients.

2.4. Sample size

Researchers were trained on the standard use of research tools before conducting the study. Subjects signed the informed consent form, completed the questionnaire individually, and submitted it immediately. When subjects were unable to complete the questionnaire on their own, the researchers assisted them by asking questions. After the questionnaires were collected, they were immediately checked for any omissions, which were corrected on the spot. Data were stored and analyzed anonymously. Based on the method of calculating the sample size for logistic regression (*19*), the sample size should be at least 5 to 10 times the number of independent variables, so the required sample size for modeling would be 138 to 276 patients. In this study, considering a potential loss to follow-up of approximately 40%, we initially planned to recruit 276 subjects but ultimately enrolled 392 individuals.

2.5. Instruments and measurements

Data collected included the demographics of the subjects, such as age, sex, body mass index (BMI), marital status, place of residence (rural/urban), level of education, annual income including tax, alcohol and smoking status, sleep disorder, exercise habits, and living alone, and clinical data such as multimorbidity and polypharmacy, nutritional status (assessed using the Nutritional Risk Screening 2002) (*20*), functional independence (assessed using the Barthel Index) (*21*), depressive state (assessed using the Patient Health Questionnaire-9 [PHQ-9]) (*22*), and frailty measures (Fried's Frailty Phenotype) (*11*). Postoperative data collected included operating time, duration of hospitalization, and postoperative complications. All data were recorded and managed using Microsoft Excel.

2.5.1. Fried's Frailty Phenotype (Fried's FP)

Specially trained nurses assessed frailty status based on functional status at the time of admission using Fried's FP (*13*). Fried's FP test is an easy-to-use and intuitive tool that demonstrates minor variations in performance across different healthcare professionals, countries, and source of data. Fried's FP is a multi-dimensional screening tool consisting of five domains: *i*) weight loss (shrinking): Unintentional weight loss: In the past year, unexpected weight loss > 4.5 kg or > 5% (excluding diet and exercise); *ii*) slow walking speed (slowness): This was assessed by recording the time required to walk 4.6 m; *iii*) grip strength (weakness): This was assessed using the mean of three consecutive measures of the dominant hand, and the cut-of points were adjusted for sex and BMI; *iv*) fatigue (poor endurance/energy): This was assessed with two questions from the Center for Epidemiological Studies–Depression. Elderly individuals were asked how many days a week "I feel I need to work hard to do everything" and "I feel I cannot continue my life," and any answer of more than 3 days a week was assigned 1 point; and *v*) low physical activity: Men exercising less than 383 kcal per week (about 2.5 hours / week) or women exercising less than 270 kcal per week (about 2 hours / week) according to the Minda Leisure Activity Questionnaire. The scores were summed, with a score of ≥ 3 classified as frail.

2.5.2. Nutritional Risk Screening 2002 (NRS 2002)

This scale is a nutritional risk-screening tool developed by Kondrup *et al.* (*20*) in 2002 that includes three items: disease severity score, nutritional impairment score, and age score. With a total score of 0 to 7, "3" is considered nutritional risk and "4" no nutritional risk. This scale is the most widely used and clinically validated nutritional risk screening tool and has been recommended by several nutritional associations.

2.5.3. Barthel Index (BI)

The BI is an ordinal scale used to measure functional disability while performing ten daily activities (*21*). It is a validated 10-item instrument that measures a patient's independence in performing the main activities of daily living (ADL), including bathing, dressing, toileting, transferring, continence, and feeding. Functional status is defined as "independent" if the subject does not require any assistance from another person for any ADL. The subject is considered "partially dependent" if they require some assistance from another person for ADL and "totally dependent" if they require assistance for all ADL. Scores range from 0-100, with a total score of 100 indicating the highest level of independence.

2.5.4. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (*22*) was used as a self-administered screening tool to assess the severity of depressive symptoms. Unlike other depression scales, the PHQ-9 includes nine items that assess symptoms of Major Depressive Disorder (MDD), as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The questionnaire assessed how often the subjects had been disturbed by any of the nine items during the immediately preceding two weeks. Each item on the PHQ-9 is scored on a scale of 0 to 3 (0 = not at all, 1 = several days, 2 = more than a week, 3 = nearly every day). The PHQ-9 total score ranges from 0 to 27 (scores of 0-4 indicate normal or no depressive symptoms; 5-9 indicate mild depression; 10-14 indicate moderate depression; 15-19 indicate moderately severe depression; and ≥ 20 indicate severe depression).

2.6. Statistical analyses

Statistical analyses were performed using the software IBM SPSS Statistics 29.0 and R version 4.5.0. Frailty was analyzed as a categorical variable. Descriptive statistics of the baseline demographic and clinical variables were calculated using the mean (standard deviation) or percentage (%). The Shapiro-Wilk test was used to assess normal distribution. The Mann–Whitney *U* test and chi-square tests were used to compare continuous and categorical variables, respectively. Ordinal logistic regression was used for categorical variables to predict variables affecting frailty. The area under the receiver operating characteristic (ROC) curve and the area under the curve (AUC) of the ROC were used to evaluate the model's discriminative ability; the Hosmer-Lemeshow test and calibration curve were used to evaluate the model's goodness of fit; and decision curve analysis (DCA) was used to evaluate the clinical benefit of the model. The significance level was set at $\alpha = 0.05$, and statistical significance was defined as a p-value < 0.05.

3. Results

3.1. Subject characteristics and the prevalence of frailty

A total of 392 elderly patients with ACC were interviewed, and six were excluded due to incomplete clinical data. Ultimately, 386 elderly patients with ACC were included. Of these, 270 served as the training set, while 116 served as the validation set. The prevalence of frailty in the two sets was 27% and 21.6%, respectively. The mean (± standard deviation) patient age in the training set was 71.86 ± 6.03 years. For the validation set, the average age was 70.18 years. The subjects' basic characteristics and univariate analysis data are shown in Table 1.

3.2. Related variables

Table 1. Univariate analysis of physical frailty in older patients with acute calculous cholecystitis

Variable	Training set			*p*-value	Validation set			*p*-value
	Total *n* = 270	Non-frail *n* = 197 (73%)	Frail *n* = 73 (27%)		Total *n* = 116	Non-frail *n* = 91 (78.4%)	Frail *n* = 25 (21.6%)	
Age (years, x ± s)	71.86 ± 6.03	71.85 ± 5.24	72.89 ± 7.80	0.102	70.18 ± 5.9	70.24 ± 6.35	69.96 ± 4.0	0.148
65 ≤ age < 70	33 (12.2%)	20 (60.6%)	13 (39.4%)		68 (58.6%)	57 (83.8%)	11 (16.2%)	
70 ≤ age < 80	116 (43%)	99 (85.3%)	17 (14.7%)		37 (31.9%)	25 (67.6%)	12 (32.4%)	
Age ≥ 80	121 (44.8%)	78 (64.5%)	43 (35.5%)		11 (9.5%)	9 (81.8%)	2 (18.2%)	
Sex (*n*, %)				0.273				0.316
Male	148 (54.8%)	104 (70.3%)	44 (29.7%)		64 (55.2%)	48 (75%)	16 (25%)	
Female	122 (45.2%)	93 (76.2%)	29 (23.8%)		52 (44.8%)	43 (82.7%)	9 (17.3%)	
BMI	22.64 ± 3.47	22.78 ± 3.36	22.26 ± 3.73	0.295	23.13 ± 3.54	22.94 ± 3.6	23.82 ± 3.27	0.358
Marital status (*n*, %)				0.158				0.583
Married	218 (80.7%)	155 (71.1%)	63 (28.9%)		98 (84.5%)	76 (77.6%)	22 (22.4%)	
Unmarried, divorced, or widowed	52 (19.3%)	42 (80.8%)	10 (19.2%)		18 (15.5%)	15 (83.3%)	3 (16.7%)	
Level of education (*n*, %)				0.063				0.138
No post-secondary	230 (85.2%)	163 (70.9%)	67 (29.1%)		106 (91.4%)	85 (80.2%)	21 (19.8%)	
Bachelor degree or above	40 (14.8%)	34 (85%)	6 (15%)		10 (8.6%)	6 (60%)	4 (40%)	
Place of residence (*n*, %)				0.643				0.327
Rural	83 (30.7%)	59 (71.1%)	24 (28.9%)		69 (59.5%)	52 (75.4%)	17 (24.6%)	
Urban	187 (69.3%)	138 (73.8%)	49 (26.2%)		47 (40.5%)	39 (83%)	8 (17%)	
Annual income including tax (*n*, %)				0.227				0.953
< 50,000	154 (57%)	108 (70.1%)	46 (29.9%)		69 (59.5%)	54 (78.3%)	15 (21.7%)	
≥ 50,000	116 (43%)	89 (76.7%)	27 (23.3%)		47 (40.5%)	37 (78.7%)	10 (21.3%)	
Smoking status (*n*, %)				< 0.001				0.003
Quit/non-smoker	217 (80.4%)	168 (77.4)	49 (22.6%)		32 (27.6%)	31 (96.9%)	1 (3.1%)	
Current smoker	53 (19.6%)	29 (54.7%)	24 (45.3%)		84 (72.4%)	60 (71.4%)	24 (28.6%)	
Alcohol status (*n*, %)				0.425				0.169
Quit/non-drinker	233 (86.3%)	168 (72.1%)	65 (27.9%)		102 (87.9%)	82 (80.4%)	20 (19.6%)	
Current drinker	37 (13.7%)	29 (78.4%)	8 (21.6%)		14 (12.1%)	9 (64.3%)	5 (35.7%)	
Exercise habits (*n*, %)				0.002				0.004
No	93 (34.4%)	57 (61.3%)	36 (38.7%)		63 (54.3%)	43 (68.3%)	20 (31.7%)	
Yes	177 (65.6%)	140 (79.1%)	37 (20.9%)		53 (45.7%)	48 (90.6%)	5 (9.4%)	
Multimorbidity (*n*, %)				0.048				0.026
0–1	134 (49.6%)	105 (78.4%)	29 (21.6%)		60 (51.7%)	52 (86.7%)	8 (13.3%)	
≥ 2	136 (50.4%)	92 (67.6%)	44 (32.4%)		56 (48.3%)	39 (69.6%)	17 (30.4%)	
Sleep disorder (*n*, %)				< 0.001				0.015
No	177 (65.6%)	141 (79.7%)	36 (20.3%)		37 (31.9%)	24 (64.9%)	13 (35.1%)	
Yes	93 (34.4%)	56 (60.2%)	37 (39.8%)		79 (68.1%)	67 (84.8%)	12 (15.2%)	
Polypharmacy (*n*, %)				0.024				< 0.001
0–3	232 (85.9%)	175 (75.4%)	57 (24.6%)		59 (50.9%)	50 (84.7%)	9 (15.3%)	
≥ 4	38 (14.1%)	22 (57.9%)	16 (42.1%)		57 (49.1%)	32 (56.1%)	25 (43.9%)	
Depressive state (*n*, %)				0.021				< 0.001
No	181 (67%)	140 (77.3%)	41 (22.7%)		66 (56.9%)	59 (89.4%)	7 (10.6%)	
Yes	89 (33%)	57 (64%)	32 (36%)		50 (43.1%)	32 (64.0%)	18 (36%)	
ADL (*n*, %)				< 0.001				0.025
Dependent	65 (24.1%)	34 (52.3%)	31 (41.7%)		93 (80.2%)	69 (74.2%)	24 (25.8%)	
Independent	205 (75.9%)	163 (79.5)	42 (20.5%)		23 (19.8%)	22 (95.7%)	1 (4.3%)	
Living alone (*n*, %)				0.111				0.186
No	220 (81.5%)	156 (70.9%)	64 (29.1%)		98 (84.5%)	79 (80.6%)	19 (19.4%)	
Yes	50 (18.5%)	41 (82%)	9 (18%)		18 (15.5%)	12 (66.7%)	6 (33.3%)	
Malnutrition (*n*, %)				< 0.001				0.010
No	186 (68.9%)	148 (79.6%)	38 (20.4%)		68 (58.6%)	59 (86.8%)	9 (13.2%)	
Yes	84 (31.1%)	49 (58.3%)	35 (41.7%)		48 (41.4%)	32 (66.7%)	16 (33.3%)	

Data are expressed as the mean ± standard deviation or median (interquartile range) unless indicated otherwise; statistical significance was defined as a *p*-value < 0.05. BMI: body mass index; ADL: activities of daily living.

Table 2. Logistic regression analysis of physical frailty in older patients with acute calculous cholecystitis for development of a predictive model

Variable	Group	*B*	SE	Wald χ^2	*p*-value	OR	95% CI	
							Lower limit	Upper limit
Smoking status	Quit/non-smoker				Reference			
	Current smoker	0.985	0.36	7.501	0.006	2.678	1.323	5.42
Exercise habits	No				Reference			
	Yes	-0.508	0.349	2.126	0.145	0.602	0.304	1.191
Multimorbidity	0–1				Reference			
	≥ 2	0.324	0.358	0.817	0.366	1.383	0.685	2.791
Sleep disorder	No				Reference			
	Yes	0.575	0.329	3.058	0.08	1.778	0.933	3.389
Polypharmacy	0–3				Reference			
	≥ 4	0.683	0.426	2.572	0.109	1.981	0.859	4.566
Depressive state	No				Reference			
	Yes	0.104	0.373	0.078	0.078	1.11	0.534	2.306
ADL	Dependent				Reference			
	Independent	-1.067	0.368	8.422	0.004	0.344	0.167	0.707
Malnutrition	No				Reference			
	Yes	0.985	0.379	6.756	0.009	2.677	1.274	5.626

Statistical significance was defined as a p-value < 0.05. SE: standard error; OR: odds ratio; CI: confidence interval; ADL: activities of daily living.

In the modeling group, univariate analysis revealed that smoking status, exercise habits, multimorbidity, sleep disorder, polypharmacy, depressive state, ADL, and malnutrition were significant influencing factors (p < 0.05), as shown in Table 1.

3.3. Logistic regression of patients with ACC

Logistic regression analysis was performed using physical frailty (no = 0, yes = 1) as the dependent variable and variables with statistical significance in univariate analysis as independent variables. The results of the multivariate regression analysis indicated that smoking status, ADL, and malnutrition were independent factors influencing physical frailty in older patients with ACC (p < 0.05), as shown in Table 2.

3.4. Development of an individualized prediction model

Figure 1 shows the constructed nomogram using the software R. In practical application, healthcare professionals first locate the corresponding scores for each predictive indicator on the first row (Points) of the nomogram based on the patient's specific condition, they sum the scores and draw a vertical line intersecting the last row of the nomogram from the marked total score (Total Points). At this intersection point, the value represents the patient's probable risk of physical frailty.

3.5. Validation and evaluation of the predictive model

The prediction model achieved an AUC of 0.752 (95% CI: 0.685–0.812) in the training set with a specificity of 67.1% and a sensitivity of 73.6%, as shown in Figure 2A. The Hosmer- Lemeshow-show test yielded a χ^2 value of 4.407 and a p-value of 0.732 as shown in Figure 3A. The DCA curve did not intersect with the two extreme curves, implying that the net return rate of the nomogram prediction model is higher than that intervention and non-intervention, underscoring the model's clinical applicability, as shown in Figure 4A. Collectively, these results indicate that the nomogram model is suitable for predicting the risk of frailty in older patients who were hospitalized for ACC.

For external validation, 116 patients with ACC were used. The AUC of the model was 0.873 (95% CI: 0.778–0.968) and is shown in Figure 2B. The results of the Hosmer–Lemeshow test were χ^2 = 14.379 and p = 0.0724. The accuracy and specificity of the model were 68% and 97.8%, respectively, indicating that the model performed well in its predictive efficacy in the external validation set. Both the calibration curve (Figure 3B) and DCA (Figure 4B) further affirmed the model's discriminating ability and clinical utility.

4. Discussion

4.1. An elevated risk of physical frailty in older patients with ACC

Presently, there are few studies on physical frailty in hospitalized patients with ACC, and there is no risk prediction model for physical frailty in patients with ACC. In our study population, the prevalence of physical frailty among hospitalized elderly patients with ACC was found to be 27.0%, indicating a high level of physical frailty in this population. Physical frailty can affect the quality of life of older people, leading to postoperative complications, readmission, and even death (*23-25*). Therefore, an urgent task is to develop a risk prediction model for early identification of physical frailty in elderly individuals with ACC and timely intervention.

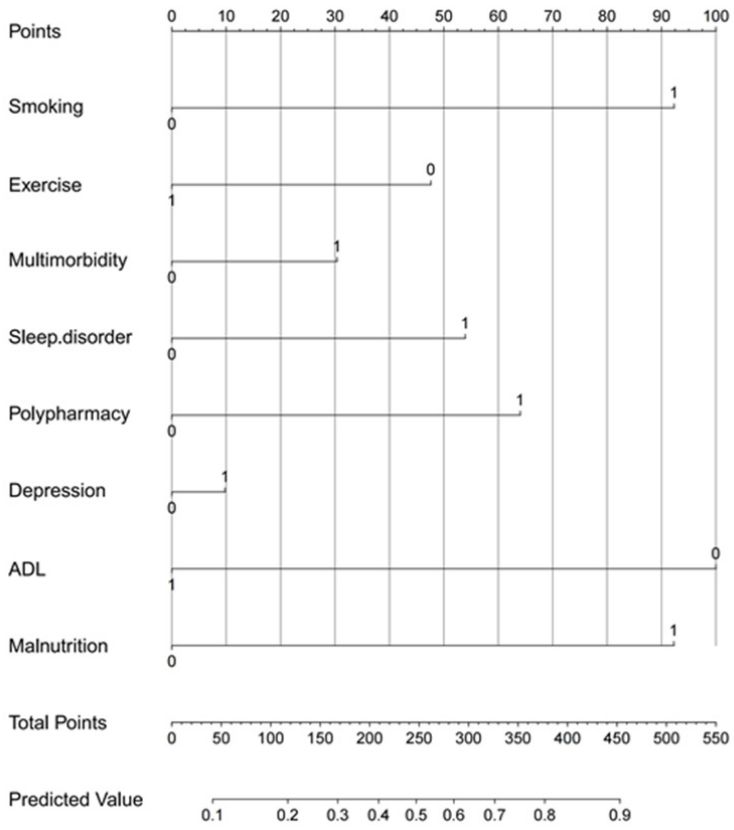

Figure 1. Nomogram to predict the risk of physical frailty in older patients with acute calculous cholecystitis. This nomogram includes smoking, exercise, multimorbidity, sleep disorder, polypharmacy, depression, sleep disorders, ADL, and malnutrition. The horizontal scale labeled "Points" reflects the impact of each variable. A line was drawn up to the points axis for each variable. The total score was calculated by summing all of the variables. Then, the probability of non-frailty and frailty was determined by drawing a line down from the total points axis to the horizontal axis "Risk of non-frailty" and "Risk of frailty" below.

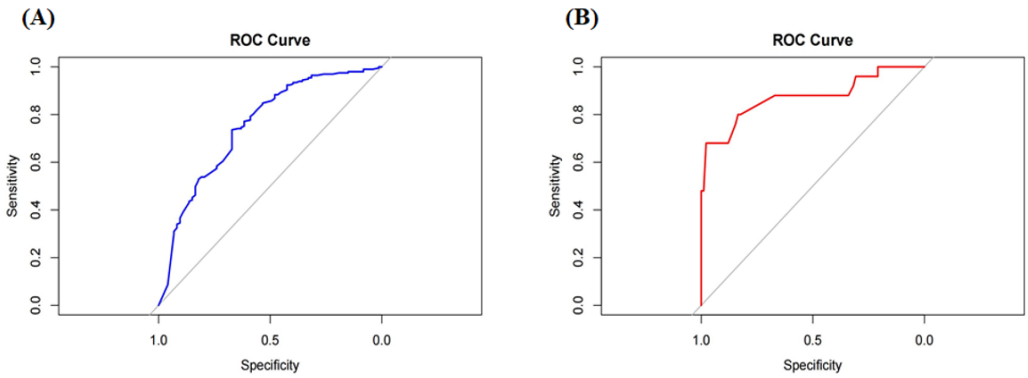

Figure 2. The receiver operator characteristic (ROC) curve for the model to predict the risk of frailty. (A) Training set; **(B)** Validation set.

In addition, Li *et al*. (*26*) reported that the incidence of frailty among hospitalized patients with hemodialysis was approximately 34.7%, which is about 10% higher than the risk of frailty observed in our study. Ramos *et al*. (*27*) also used the Frailty Phenotype (FP) in a study of patients undergoing asymptomatic aortic stenosis, and they reported that the prevalence of frailty was high as 59.6%. Additionally, Goh *et al*. (*28*) used the Clinical Frailty Scale (CFS) to evaluate the frailty status of 233 elderly patients undergoing emergency laparotomy and found a 26.0% incidence of frailty risk. These data suggest that greater attention should be paid to the risk of frailty in older adults with diseases. Early screening and identification of high-risk individuals are essential,

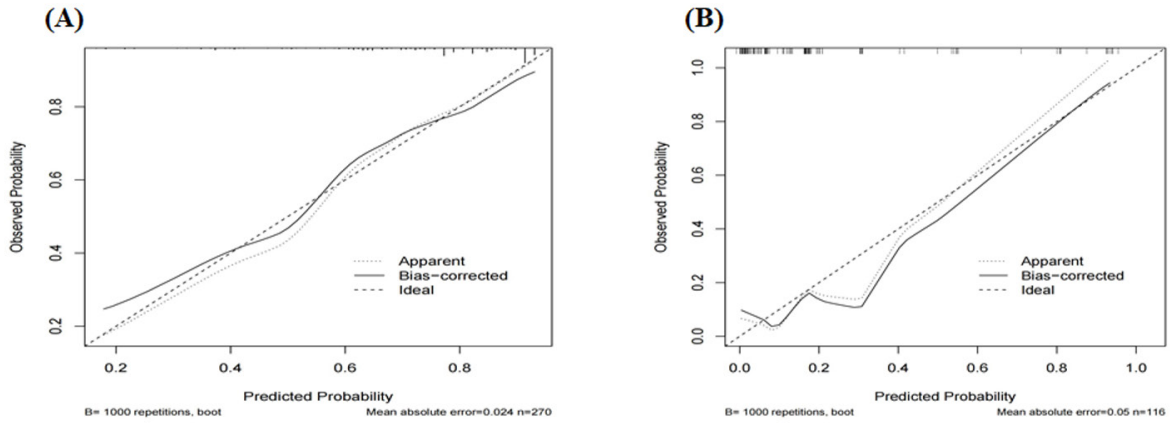

Figure 3. Calibration curve for the frailty risk model in training and validation sets of older patients with acute calculous cholecystitis. (A) Calibration curves for the training group show that the apparent curve closely matches the ideal curve, indicating predictive probability. **(B)** Calibration curves for the test group also show that the apparent curve aligns well with the ideal curve, confirming the model's strong predictive performance. Note: The X-axis represents the predicted possible risk of physical frailty in patients with ACC. The Y-axis represents the actual diagnosed ACC. The dashed line represents the original performance, and the solid dashed line represents the performance during internal validation by Bootstrapping (*B* =1,000 repetitions).

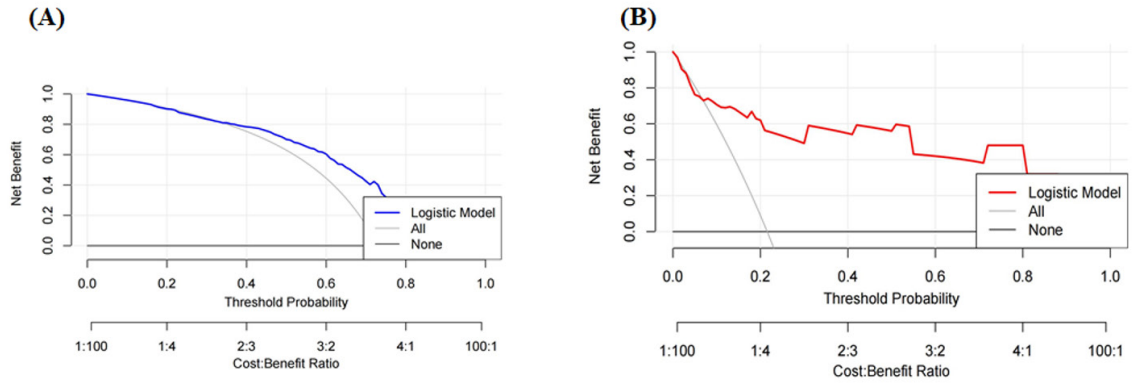

Figure 4. Decision curve analysis (DCA) of the nomogram to predict frailty risk in training and validation sets.

Table 3. Comparison of existing models to predict frailty and our ACC-specific model

Name of model	Applicable population	Predictive factors	Method of prediction	Applicability to ACC
Clinical Frailty Scale (CFS)	General elderly	Functional status	Clinical scoring	Not disease-specific
Frailty Index (FI)	General elderly	> 30 variables (deficit accumulation)	Continuous index	Complex and non-specific
Hospital Frailty Risk Score	Inpatients	ICD code-based	Risk stratification	Not personalized; lacks functional data
This study's nomogram	Elderly patients with ACC	Smoking, ADL, malnutrition, sleep disorder	Logistic regression + nomogram	High specificity and tailored to ACC

ACC: acute calculous cholecystitis; ADL: activities of daily living.

along with timely and effective interventions to prevent or delay the onset and progression of frailty.

As shown in Table 3, compared to existing frailty models such as the CFS, Frailty Index (FI), and general nomograms developed for surgical patients, our model features several innovations. First, it is the first frailty prediction model specifically designed for elderly patients with ACC, incorporating clinical variables closely related to their perioperative status. Second, it integrates modifiable and multidimensional risk factors

such as impaired ADL, malnutrition, smoking, and sleep disorders — factors that are both clinically relevant and targetable for intervention. Third, the model exhibits strong external validation performance (AUC = 0.873), underscoring its predictive reliability. A comparative summary is provided in Figure 2B.

4.2. Analysis of risk factors for physical frailty

This study established a model encompassing smoking status, exercise habits, multimorbidity, sleep disorder, polypharmacy, depressive state, sleep disorders, ADL, and malnutrition to forecast the risk of frailty in older patients with ACC. The results of this study indicate that impaired ADL increases the risk of physical frailty in older patients with ACC. Previous research has demonstrated a bidirectional relationship between ADL and frailty (*29,30*), wherein frailty may lead to functional decline and increased dependence in ADL, while limitations in ADL may in turn exacerbate frailty by reducing physical activity and social engagement. This reciprocal dynamic underscores the importance of early identification and intervention for older adults exhibiting even minor impairments in ADL. From a clinical perspective, healthcare providers should not only encourage patients to maintain regular physical activity within their functional capacity but also promote engagement in cognitively stimulating and socially interactive activities. A comprehensive, multidimensional approach to rehabilitation may help mitigate the progression of frailty and thus preserve independence.

A depressive state, characterized by persistent low mood and diminished interest, is a prevalent psychological concern among the elderly (*31*). Although our study did not find a statistically significant association between depressive symptoms and physical frailty, several previous studies have reported a strong link between the two (*32,33*). Depression may contribute to reduced appetite, poor nutritional intake, and decreased physical activity, all of which are recognized contributors to the onset and progression of frailty. These observations underscore the importance of incorporating mental health assessments and timely psychological support into comprehensive geriatric care. Moreover, although regular physical exercise has been widely acknowledged as a protective factor against frailty (*18*), this association was not confirmed in our study. A possible explanation lies in the clinical context of our subjects, many of whom were in the active treatment phase of their illness, potentially limiting their engagement in physical activity. Therefore, interpretation of such findings requires consideration of the subjects' functional status and disease stage, and future longitudinal studies are warranted to further clarify these associations.

A study has indicated that smoking is a significant risk factor for increased physical frailty (*34*), a finding that aligns with the results of our study. Chronic tobacco use is known to impair cardiopulmonary function, reduce exercise capacity, and exacerbate systemic inflammation, all of which may contribute to decreased physical performance and an accelerated decline in functional reserve among older adults. This cumulative physiological burden promotes the development and progression of frailty. Given that smoking is a modifiable behavioral risk factor, incorporating smoking cessation into comprehensive frailty prevention and intervention strategies has substantial clinical value. Smoking cessation interventions, including counseling, nicotine replacement therapy, and behavioral strategies, have been shown to improve not only cardiopulmonary function but also physical performance and quality of life in older adults (*35*). Incorporating structured cessation programs into perioperative care pathways could thus directly contribute to a reduced risk of frailty. Cessation programs tailored to the elderly population may not only delay the onset of frailty but also contribute to improved overall health outcomes and a reduction in long-term healthcare resource utilization.

This study found that sleep disorders are significant risk factors for physical frailty in older patients with ACC. A recent systematic review analyzing 13 cross-sectional and 4 longitudinal studies found that insomnia symptoms, both short and long sleep durations, and perceived poor sleep quality were independently associated with physical frailty (*36*). Mounting evidence confirms the significant role of sleep quality in the development and progression of frailty. From a clinical standpoint, routine screening for sleep disturbances should be integrated into geriatric assessments. Moreover, comprehensive interventions — including behavioral strategies and psychological support — may not only alleviate sleep-related symptoms but also mitigate negative emotional states, thereby improving sleep quality and potentially slowing the trajectory of physical decline. Future studies should explore individualized, multifactorial interventions to optimize sleep health as a key component in frailty prevention.

Although multimorbidity, polypharmacy, and exercise habits were not significantly associated with physical frailty in our multivariate analysis, they remain clinically important factors that should not be disregarded. Numerous studies have consistently reported strong associations between these variables and frailty. For instance, a Japanese cohort study found that individuals taking five or more medications had nearly twice the odds of being frail (adjusted OR: 1.89, 95% CI: 1.40–2.57), particularly presenting with components such as weight loss, weakness, and slowness (*37*). Similarly, a multicenter cohort study in China demonstrated that polypharmacy among hospitalized patients age 65 and older was a significant predictor of frailty progression over a two-year period (*38*). In addition, a hospital-based study in Nepal revealed that the presence of comorbidities increased the risk of frailty by more

than threefold (*39*). These findings suggest a complex interplay wherein multimorbidity necessitates the use of multiple medications, which may lead to adverse drug reactions, reduced physiological resilience, and ultimately increased frailty. From a clinical perspective, this underscores the importance of implementing structured medication reviews and targeted deprescribing protocols as part of routine frailty management. Even in the absence of significant associations in a given study, the underlying biological plausibility and consistent evidence from prior research highlight the need for continued vigilance in managing these factors to prevent the exacerbation of frailty in older adults.

Given that our study population consisted of hospitalized older adults, opportunities for regular physical activity were inherently limited. Nevertheless, the influence of exercise on the development and progression of frailty should not be underestimated. Emerging evidence suggests that the type, mode, intensity, and duration of physical activity significantly affect both the onset and potential reversal of frailty. A community-based study in Taiwan reported that engaging in 31–60 minutes of daily exercise reduced the risk of frailty by 59%, while exercising for more than 60 minutes led to a 69% risk reduction (*40*). Conversely, another study has noted that high-frequency exercise, including intensive resistance training, may be associated with more severe frailty in certain populations (*41*). These findings underscore the necessity of individualized exercise programs that account for an older adult's baseline physical capacity, comorbidities, and recovery stage. From a clinical perspective, tailoring exercise interventions to meet functional needs and avoid overexertion is critical to maximizing benefit and minimizing harm. Thus, incorporating structured yet adaptable physical activity programs into frailty management protocols may offer a safe and effective strategy to improve outcomes in older adults.

Malnutrition has been widely recognized as a critical and modifiable risk factor for physical frailty among older adults. Numerous studies have demonstrated a strong association between malnutrition and frailty, particularly among inpatients or surgical patients. For instance, a recent systematic review reported that older adults at risk of malnutrition were 2.5 to 4 times more likely to be frail compared to well-nourished individuals (*30*). This relationship is often bidirectional: frailty may lead to reduced appetite and food intake due to fatigue, depression, or swallowing difficulties, while malnutrition accelerates sarcopenia and worsens the severity of frailty (*42*). In the present study, malnutrition, assessed with the NRS-2002, was identified as an independent risk factor for frailty in elderly patients with ACC. This finding corroborates previous findings and highlights the importance of routine nutritional assessment and intervention in frailty prevention strategies. Early identification of nutritional risk followed by individualized dietary counseling, oral nutritional supplements, and, when appropriate, enteral nutrition support may mitigate the progression of frailty and improve postoperative outcomes. Given that nutritional interventions are relatively low-cost and easily implementable, integrating structured nutritional screening into routine care — particularly in high-risk populations such as elderly patients with ACC — should be a clinical priority.

Although a depressive state, polypharmacy, and lack of exercise were not statistically significant in the multivariate model, they were retained in the final predictive nomogram based on their established clinical relevance and corroboration in previous studies. Even in the absence of statistical significance, the inclusion of these variables enhances the clinical interpretability and comprehensiveness of the model, aligning with the goal of early identification and prevention. This approach is also consistent with previous nomogram studies that emphasize clinical plausibility over strict statistical thresholds when selecting predictive variables (*43,44*). The model we propose represents an interdisciplinary framework that integrates physical, psychological, and lifestyle-related dimensions in understanding frailty. While each domain may be analyzed independently, in real-world clinical settings, these factors interact in complex and tightly interwoven ways to influence overall health outcomes. Moreover, this predictive model equips clinical healthcare professionals with a practical tool for assessment of the risk of frailty. After brief training, they can use this model to forecast the risk of frailty in patients with ACC. This proactive approach facilitates early risk identification, enabling timely interventions. Such early actions can mitigate deteriorations in patients' frailty status during therapeutic procedures.

4.3. Limitations

The limitations of this study are as follows: First, in this study, the variables included in the model were not limited to those identified in the multivariate analysis. To develop a comprehensive predictive model, we also incorporated psychological factors that displayed significance in univariate analysis. Future research should conduct multicenter studies with larger sample sizes to enhance the reliability of the findings. Second, the predictive factors involved in this study were limited and primarily based on self-reported data. Future research should include more objective measurement predictors to identify risk factors for physical frailty more comprehensively and objectively. Third, the nomogram developed in this study was mainly based on data from elderly patients with ACC in two Chinese cities, and its generalizability may be influenced by patients' demographic characteristics, disease presentation, and regional differences in medical practice; the model requires external validation in other regions. Fourth,

age is a risk factor for physical frailty, and there may be differences in risk factors between different age groups (older and young people). Future research should explore and predict physical frailty in cancer patients across different age groups. Fifth, this study provides an initial nomogram tool to predict physical frailty in elderly patients with ACC. To enhance its practicality and convenience, future research could consider developing a dynamic nomogram or an online calculator to establish a predictive platform that facilitates the screening, prevention, and management of physical frailty in elderly patients with ACC.

4.4. Clinical implications and prospects for application

This frailty prediction model has potential for broad clinical applicability, particularly in preoperative evaluation and emergency triage of elderly patients with ACC. Since frailty is a crucial determinant of postoperative outcomes and treatment tolerance, the model may assist surgeons and geriatricians in stratifying surgical risk, guiding perioperative decision-making, and tailoring individualized care plans. For example, patients identified as high-risk can receive early interventions such as nutritional supplementation, physiotherapy, or closer postoperative monitoring.

Moreover, the simplicity of the model and the limited number of predictors facilitate its integration into electronic medical record (EMR) systems, allowing automated alerts about the risk of frailty during hospitalization. With further validation, this model also has the potential to be developed into a mobile app or web-based calculator for bedside or outpatient use by clinicians, enhancing its efficiency and accessibility in busy hospital settings. These future directions would greatly enhance the real-time utility of the model in both acute care and routine management.

An important point worth noting, however, is that several predictors in the model — such as smoking status, sleep quality, and depressive symptoms — are based on self-reported information. While self-reported data can be subject to recall bias or subjective misinterpretation, many of these variables (*e.g.*, ADL, PHQ-9, NRS2002) have been widely validated and are commonly used in clinical assessments. Nevertheless, the reliability of the model in real-world use may vary depending on the accuracy of patient-reported inputs. To address this limitation, future work should focus on developing standardized data collection interfaces, possibly incorporating patient-reported outcome measures (PROMs) *via* EMRs or apps, and conducting prospective studies to evaluate the model's real-time performance across diverse clinical settings.

5. Conclusions

Older patients with ACC are at a higher risk of frailty. This risk is intricately associated with various factors. By identifying high-risk individuals and implementing tailored interventions to alleviate frailty, the exacerbation of disease symptoms can be mitigated in patients with ACC. Moreover, this nomogram should be validated and widely used across diverse populations and healthcare settings in the future.

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Study on sufficient blood vessel ligation and bowel mobilization in laparoscopic surgery for ascending colon cancer

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Abstract: Although well established, laparoscopic surgery for ascending colon cancer is a difficult procedure due to the presence of many blood vessels requiring treatment and the need for sufficient mobilization to extract the right colon through a small laparotomy. This is the first study to investigate the adequacy of vascular ligation and bowel mobilization for laparoscopic resection of ascending colon cancer and extracorporeal reconstruction. This retrospective study included 103 consecutive patients who underwent laparoscopic colectomy for ascending colon cancer from 2015 to 2022 at the Center Hospital of the National Center for Global Health and Medicine. We analyzed correlations between clinicopathological factors and vessels ligation or the mobilization range. The strongest factor correlated with vascular ligation was the distance from the Bauhin valve to the distal edge of the tumor (Length B). These lengths were significantly longer in the vascular ligated group (the right colic artery (RCA): 81 mm; the accessory right colic vein (ARCV): 85 mm; right branch of the middle colic artery (MCA-rt): 106.5 mm) than in the nonligated group (50 mm, 43 mm, 50 mm, $p < 0.01$). Mobilization range was not correlated with tumor location or size. According to the result, we developed practical indicators to assist during laparoscopic surgery: *i*) To omit the RCA ligation, Length B should be shorter than approximately 5 cm; *ii*) If Length B exceeds approximately 8 cm, both the RCA and ARCV should be ligated; and *iii*) If Length B exceeds approximately 10 cm, the MCA-rt should be ligated.

***Keywords*:** right hemicolectomy, extracorporeal anastomosis, complete mesocolic excision

1. Introduction

Currently, colon cancer surgery is generally performed laparoscopically in Japan (*1*). Since 2022, the number of robot-assisted laparoscopic surgeries for colorectal cancer has increased following approval under the National Health Insurance (*2*). We have since performed both laparoscopic and robotic surgeries, but primarily laparoscopic surgery for ascending colon cancer from 2015 to 2022.

We perform laparoscopic colon cancer resections using the complete mesocolic excision and central vascular ligation (CME–CVL) technique (*3-7*). Although well established, laparoscopic CME–CVL of the right colon is a difficult procedure due to the many blood vessels requiring treatment, including the ileocolic artery/vein (ICA/V), right colic artery (RCA), accessory right colic vein (ARCV), and right branch of the middle colic artery (MCA-rt), all of which exhibit considerable anatomical variations (*8,9*). Identification of the gastrocolic trunk of Henle and its tributaries requires detailed anatomical knowledge and meticulous dissection to vessel injury. Bleeding in this area can be difficult to control and may require conversion to an open procedure. After vascular ligation, the right colon is mobilized and extracted through a small laparotomy in the umbilicus. The specimen is then excised and anastomosed extracorporeally. In this process, tension on the mesocolon during extraction can cause bleeding, particularly from the mesocolon and the gastrocolic trunk of Henle. Moreover, the bowel must be sufficiently pulled out to allow extracorporeal reconstruction.

The number of vascular ligations and mobilization range in laparoscopic colectomy for ascending colon cancer can vary depending on whether it is near the Bauhin valve or the hepatic flexure. While these should be minimized to facilitate laparoscopic manipulation, they must be sufficient to permit extracorporeal resection and reconstruction. This is a major concern when performing laparoscopic surgery, but to our knowledge, no studies have examined this issue. This is the first study to investigate extent of vascular ligation and bowel mobilization for laparoscopic resection and extracorporeal reconstruction of ascending colon cancer

and to establish practical intraoperative indicators.

2. Patients and Methods

2.1. Patients

This was a retrospective study including all consecutive patients who underwent laparoscopic colectomy for ascending colon cancer with D2 or D3 lymph node dissection and extracorporeal reconstruction from January 2015 to December 2022 at the Center Hospital of the National Center for Global Health and Medicine. We obtained data from medical records retrospectively.

2.2. Ethics declarations

This procedure was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its amendments or comparable ethical standards. The ethical review committee of the National Center for Global Health and Medicine approved the study protocol (NCGM-S-004511-01).

Study participation was announced on the website of the hospital, and patients could know they were included in the study, such that reluctant patients could reach the researcher to express their refusal.

2.3. Surgical technique

All surgical procedures were performed laparoscopically, using either standard right hemicolectomy or ileocecal resection with the CME–CVL technique (*3*). With five-port placement, a medial-to-lateral approach was used to dissect the right colon. First, the mesentery of the terminal ileum near the ileocolic vessels was incised sharply. Through this window, the mesenteric fascia of the ascending colon was separated from the retroperitoneum, identifying the duodenum and pancreas. Second, the ileocolic vessels were ligated at their origins with hemostatic clips, as they commonly include the ICA, RCA, MCA, and ARCV for identification (Figure 1). Using a lateral approach, mobilization of the distal ileum and right hemi-colon was performed. Mobilization began at the ileocecal region and continued to either the hepatic flexure (H-Fx) or mid-transverse colon (Mid-T), along with omentum dissection. The surgeons chose to use between the medial-to-lateral approach and the lateral-to-medial approach, therefore, in some cases, procedures were performed in reverse order. Following mobilization, extracorporeal tumor resection and reconstruction were performed. The midline umbilical incision was extended to approximately 4 cm, and the specimen including the tumor was extracted. In most cases, functional end-to-end ileocolic anastomosis using a linear stapler was performed. In some cases, end-to-side anastomosis using a circular stapler was performed.

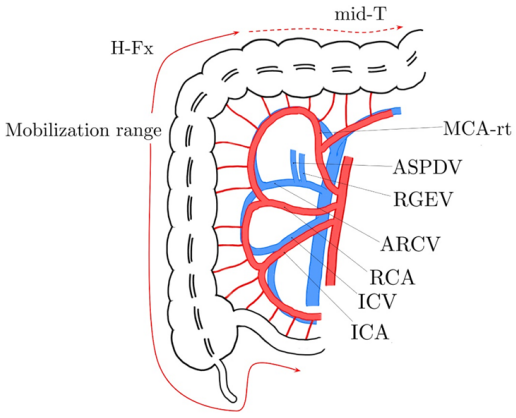

Figure 1. Common vascular anatomy of ascending colon. Range of mobilization: Mid-T: toward middle of transverse colon, H-Fx: toward hepatic flexure. MCA-rt: Right branch of middle colic artery; RGEV: Right gastroepiploic vein; ASPDV: Anterior superior pancreaticoduodenal vein; ARCV: Accessary right colic vein; RCA: Right colic artery; ICA/ICV: Ileocolic artery/Ileocolic vein.

According to Japanese colorectal cancer guidelines (*10*), the bowel was resected approximately 10 cm from the tumor, as lymph node spread rarely extends beyond this point.

2.4. Tissue measurements

Specimens were stretched and pinned on boards and fixed in formalin immediately after the operation. Pathologists and surgeons measured tissues on formalin-fixed specimens (Figure 2). They measured the distances from the Bauhin valve to the tumor (Length A), to the distal edge of the tumor (Length B), the distal margin of the specimen (Length C), and the tumor size along the intestinal axis (Length D).

2.5. Outcomes

Primary endpoints were the ligation of three arteries and mobilization range. Secondary endpoints were blood loss, operation time, postoperative complications and hospital stay.

2.6. Statistical analysis

Clinicopathological factors, including measured lengths, were compared between the ligated and nonligated groups of each vessel. Similarly, factors were compared between two groups with different mobilization ranges (H-Fx *vs*. Mid-T).

In the subset of 67 cases with RCA, we analyzed the correlation between vascular ligation and short-term outcomes, including operative time, blood loss, postoperative complications (Clavien–Dindo Grade II or higher), and postoperative hospital stay, to evaluate surgical safety.

Categorical and continuous variables were analyzed

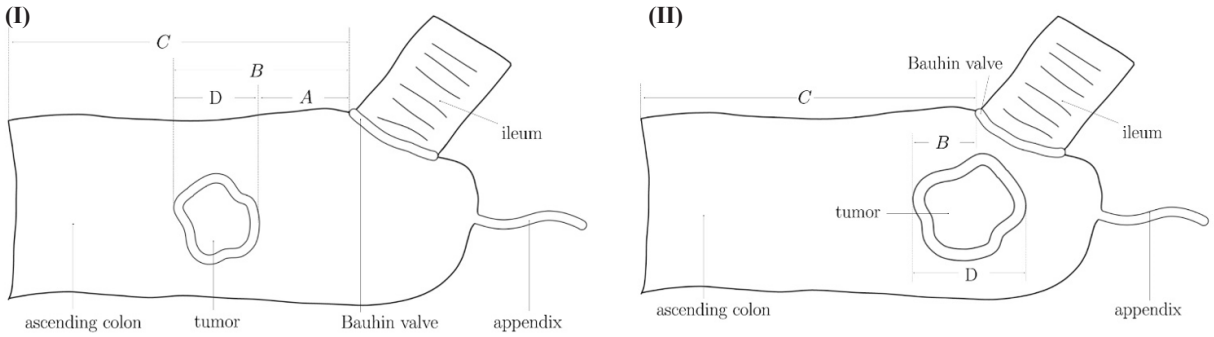

Figure 2. Measurement of formalin-fixed specimen. (I) when the tumor was located on the distal side of Bauhin valve; **(II)** when proximal edge of the tumor was on the cecal side of Bauhin valve. Length A: the distance from Bauhin valve to tumor; Length B: the distance from Bauhin valve to distal edge of tumor; Length C: the distance from Bauhin valve to distal margin of the specimen; Length D: tumor diameter along intestinal axis.

using Fisher's exact test and the Mann–Whitney *U* test, respectively. A p-value < 0.05 was considered statistically significant. All analyses were performed using JMP-Pro 15.1.0 from SAS (Cary, NC, U.S.A.).

3. Results

This study included 103 cases. Table 1 shows clinical characteristics of the patients. Median body mass index (BMI) was 22.6 kg/m^2, with three cases having a BMI > 30 kg/m^2, and the maximum recorded BMI was 33.3 kg/m^2. Anastomosis methods used were functional end-to-end anastomosis (FEEA) in 72 cases, end-to-side stapled anastomosis in 29 cases, and hand-sewn end-to-end anastomosis in two cases. Comparison among subgroups is summarized in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=108*).

Regarding surgical findings, feeding arteries of the tumors, which were ligated during lymph node dissection, included the ICA, RCA, and MCA-rt in 71, 18, and 5 cases, respectively. The ICA and RCA, ICA and MCA-rt, and RCA and MCA-rt were the feeding arteries in six, three, and three cases, respectively. The RCA was identified in 67 cases (65.0%), of which 46 (68.7%) were ligated. The ARCV and MCA-rt were ligated in 53 (51.5%) and 26 cases (25.2%), respectively. In one case, the MCA was ligated at its root, which was classified in the right-branch ligated group. The range of colon mobilization was to the H-Fx and Mid-T in 38 (36.9%) and 65 cases (63.1%), respectively. No case required conversion to laparotomy, and all procedures were completed laparoscopically. No serious complications, such as fatalities or reoperation, occurred during or after surgery. However, five and two cases had Clavien–Dindo Grade II and IIIa complications, respectively.

Table 1 shows the pathological findings as well. The median tumor diameter along the intestinal axis (Length D) was 30 mm. The median of Length A and Length B was 30 and 61 mm, respectively. Length B was equal to Length A + D when the tumor was located on the anal side of the Bauhin valve, but when the proximal edge of the tumor was on the cecal side of the Bauhin valve, Length A was recorded as 0 and Length B was shorter than Length A + D. The median distance from the Bauhin valve to distal margin of the specimen (Length C) was 160 mm (Figure 2).

Table 2 shows the analysis results regarding right colic vessel ligation. The strongest factor correlated with vascular ligation was Length B. For each of the three vessels, values of Length B were significantly longer in the ligated group (RCA: 81 mm, ARCV: 85 mm, and MCA-rt: 106.5 mm) compared with the nonligated group (RCA: 50 mm, ARCV: 43 mm, and MCA-rt: 50 mm; p < 0.01). Accordingly, Length C was significantly longer in the ligated group than in the nonligated group for each vessel (RCA: 200 *vs.* 135 mm, p < 0.01; ARCV: 200 *vs.* 135 mm, p < 0.01; MCA-rt: 205 *vs.* 150 mm, p < 0.01). Length A was also significantly correlated with ARCV and MCA-rt ligation (ARCV: 45 *vs.* 20 mm, p < 0.01; MCA-rt: 75 *vs.* 20 mm, p < 0.01). Length D correlated only with the RCA ligation (37.5 *vs.* 30.0 mm; p = 0.05).

Operative time was significantly longer in the RCA- and ARCV-ligated groups (227 and 233 minutes, respectively) compared to nonligated groups (195 minutes; p = 0.03, 207.5 minutes; p = 0.04, respectively). Intraoperative blood loss was significantly greater in the MCA-ligated group (72.5 mL) than in the nonligated group (36 mL; p = 0.03).

Although body size factors were generally not strongly correlated with vascular ligation, the ARCV-ligated group had a significantly higher BMI (23.3 kg/m^2) than the nonligated group (22.1 kg/m^2, p = 0.02). The BMI of the MCA-rt-ligated group (23.6 kg/m^2) also tended to be higher than that of the nonligated group (22.5 kg/m^2, p = 0.06).

Table 3 presents analysis of the mobilization range. No correlation was found between tumor location or size and mobilization range. However, Length C was significantly longer in the group with mobilization to the Mid-T colon compared with the H-Fx group (170 *vs.* 138 mm, p < 0.01). Operative time was also significantly

Table 1. Patient characteristics

Characteristic	Value
Age (year)	74 (43–91)
Gender (*n*)	Male: 57 Female: 46
Body height (cm)	160 (136–181)
Body weight (kg)	56.3 (35.0–93.5)
BMI (kg/m/m)	22.6 (15.9–33.3)
Surgical procedure (*n*)	Ileo-cecal resection: 36, Right hemicolectomy: 67
Lymph node dissection (*n*)	D2: 16 D3: 87
Anastomosis method (*n*)	FEEA: 72 End-to-side stapled anastomosis: 29 Hand-sewn end-to-end anastomosis: 2
Tumor feeding artery (*n*)	ICA: 69 RCA: 17 MCA-rt: 5 ICA + RCA: 6 ICA + MCA-rt: 3 RCA + MCA-rt: 3
RCA ligation: yes / no (*n*)	46 (68.7%) / 21 (31.3%)
ARCV ligation: yes / no (*n*)	53 (51.5%) / 50 (48.5%)
MCA-rt ligation: yes / no (*n*)	26 (25.2%) / 77 (74.8%)
Range of mobilization (*n*)	H-Fx: 38 (36.9%) Mid-T: 65 (63.1%)
Operating time (min)	225 (112–394)
Blood loss (mL)	40 (0–590)
Postoperative complications (> C–D Grade II**) (*n*)	7 (6.8%) (Grade II: 5, Grade IIIa: 2)
Postoperative hospital stay (days)	8 (5–46)
Tumor depth (*n*)	M: 3, SM: 24, MP: 13, SS: 48, SE: 14, SI: 1
Lymph node metastasis (*n*)	Positive: 39 Negative: 64
Length A (mm): Bauhin valve to tumor	30 (0–180)
Length B (mm): Bauhin valve to the distal edge of the tumor	61 (12–212)
Length C (mm): Bauhin valve to distal margin of the specimen	160 (35–290)
Length D (mm): Tumor size along the intestinal axis	30 (0–130)

103 cases were included. Medians are indicated with range in parentheses unless otherwise indicated. *RCA existed in 67 cases. **Postoperative complications classified Clavien-Dindo Grade or more serious were counted. FEEA: functional end-to-end anastomosis. ICA: ileocolic artery. RCA: right colic artery. ARCV: accessory right colic vein. MCA-rt: right branch of the middle colic artery. H-Fx: hepatic flexure. Mid-T: middle of transverse colon. C-D: Clavien-Dindo. Tumor depth: M: mucosa, SM: submucosa, MP: muscularis propria, SS; subserosa, SE: serosa exposed, SI: serosal invasion.

Table 2. Analysis of operative parameters according to right-colic vessels ligation

Outcome	RCA ligation			ARCV ligation			MCA-rt ligation		
	Yes (n = 46)	No (n = 21)	p vaule	Yes (n = 53)	No (n = 50)	p vaule	Yes (n = 26)	No (n = 77)	p vaule
Length A (mm): Bauhin valve to tumor	45 (0–86.3)	30 (0–37.5)	0.06	45 (13–85)	20 (0–30)	< 0.01*	75 (22.5–112.5)	20 (0–47.5)	0.06
Length B (mm): Bauhin valve to distal edge of the tumor	81 (53–130)	50 (37.5–68.5)	< 0.01*	85 (57.5–130)	43 (30–63.5)	< 0.01*	106.5 (64.5–143.8)	50 (35–80)	< 0.01*
Length C (mm): Bauhin valve to distal margin of the specimen	200 (143.8–230)	135 (115–157.5)	< 0.01*	200 (152.2–225.0)	135 (115–160)	< 0.01*	205 (165–205)	150 (120.0–182.5)	< 0.01*
Length D (mm): Tumor size along the intestinal axis	37.5 (25–50)	30 (17.5–40.0)	0.05*	32 (22–50)	30 (17.5–45.0)	0.20	30 (18–50.3)	30 (20–45)	0.05*
Operation time (min)	227 (204.3–250.8)	195 (166–232.5)	0.03*	233 (199–254)	207.5 (174.5–242)	0.04*	233.5 (199.5–265.75)	222 (186.5–243.5)	0.03*
Blood loss (mL)	54 (17.3–125.5)	30 (9.5–81.5)	0.26	60 (16.5–146.5)	34.5 (10.5–72.0)	0.05	72.5 (37.5–123)	36 (11.5–102.0)	0.26
Postoperative complications frequency (> C–D GradeII) (% (n))	10.9% (5)	0% (0)	0.17	9.4% (5)	4.0% (2)	0.44	11.5% (3)	5.2% (4)	0.17
Postoperative hospital stay (days)	9 (8–12)	9 (8–11)	0.84	9 (8–11)	8 (7-9.25)	0.07	8 (8–11)	8 (7–10)	0.84
Body height (cm)	155.6 (149.5–164.6)	160 (152.3–171.3)	0.15	157.5 (151.1–164.9)	162.2 (153.3–168.1)	0.08	161 (151.29–164.9)	159.5 (153.0–167.25)	0.15
Body weight (kg)	55.8 (50.4–62.8)	55 (50.6–62.9)	0.99	56.3 (50.4–67.2)	56.7 (49.3–63.9)	0.46	58.1 (49.7–71.9)	56 (50.25–64.75)	0.99
BMI (kg/m/m)	22.6 (20.4–24.2)	21.4 (19.5–24.3)	0.21	23.3 (20.7–24.9)	22.1 (19.3–23.9)	0.02*	23.6 (20.3–27.0)	22.5 (19.7–24.0)	0.21

Values are medians indicated with interquartile range in parentheses. Postoperative complications are indicated with its frequency and count in parentheses. *p value < 0.05 was considered significant. RCA: right colic artery. ARCV: accessory right colic vein. MCA-rt: right branch of middle colic artery. C–D: Clavien-Dindo.

Table 3. Analysis of operative parameters according to mobilization range

Outcome	Range of mobilization		
	H-Fx (n = 38)	Mid-T (n = 65)	p vaule
Length A (mm): Bauhin valve to tumor	25 (0–45)	35 (0–70)	0.25
Length B (mm): Bauhin valve to distal edge of the tumor	50 (35.0–82.5)	75 (36.5–107.5)	0.12
Length C (mm): Bauhin valve to distal margin of the specimen	138 (118.8–166.3)	170 (135–215)	< 0.01*
Length D (mm): Tumor size along the intestinal axis	29 (15.3–46.3)	30 (22–46)	0.48
Anastomosis methods (%)	FEEA 94.7%, E-to-S 5.3%	FEEA 55.4%, E-to-S 41.5%, hand 3.1%	< 0.01*
Operation time (min)	194.5 (167.0–222.8)	233 (202.5–256.0)	< 0.01*
Blood loss (mL)	37 (14.3–61.3)	60 (14.5-148.5)	0.10
Postoperative complications frequency (> C–D GradeII) (% (n))	7.9% (3)	6.2% (4)	0.71
Postoperative hospital stay (days)	8 (7–10)	9 (7.5–11.0)	0.33
Body height (cm)	157 (151.0–170.5)	161 (153.1–165.6)	0.76
Body weight (kg)	56.3 (48.4–65.3)	56.3 (51.1–65.7)	0.72
BMI (kg/m/m)	22.1 (19.5–24.2)	22.6 (20.0–24.3)	0.65

Values are medians indicated with interquartile range in parentheses unless otherwise indicated. Postoperative complications are indicated with its frequency and count in parentheses. *p value < 0.05 was considered significant. Range of mobilization; Mid-T: toward middle of transverse colon, H-Fx: toward hepatic flexure. FEEA: functional end-to-end anastomosis. E-to-S: end-to-side stapled anastomosis. Hand: hand-sewn end-to-end anastomosis. C–D: Clavien-Dindo.

longer in the Mid-T colon group than in the H-Fx group (233.0 *vs.* 194.5 min, $p < 0.01$). FEEA was significantly more frequent in the H-Fx group (n = 36; 97.7%) than in the Mid-T group (n = 36; 55.4%, $p < 0.01$). Factors related to body size were not correlated with mobilization range.

Table 4 shows evaluation of vascular treatment and surgical safety. Vascular ligation was performed in the following order: ICA/V, RCA, ARCV, and MCA-rt. The ICA/V was ligated in all cases. RCA was present in 67 cases, and this analysis was restricted to these cases. Operative time was significantly longer when the RCA (227 *vs.* 195 min, $p = 0.03$) or ARCV (228.0 *vs.* 202.5 min, $p = 0.03$) was ligated. Although ligation of the RCA or ARCV did not affect blood loss, MCA-rt ligation tended to increase the amount of bleeding (72.5 *vs.* 35.0 mL, $p = 0.08$). While ARCV or MCA-rt ligation did not affect the frequency of postoperative complications, all five postoperative complication cases occurred in the RCA-ligated group ($p = 0.17$). However, the ligation of these vessels did not impact postoperative hospital stay.

4. Discussion

This is the first study to investigate sufficient vascular ligation and bowel mobilization for laparoscopic resection and extracorporeal reconstruction of ascending colon cancer. We searched PubMed by June 2025 using the phrases "ascending colon cancer", "laparoscopic surgery", "vascular ligation", and "mobilization", and no previous research on this issue was found.

Right-sided colon resection can be performed using several approaches, with the two main approaches being the medial-to-lateral approach and the lateral-to-medial approaches. However, the conventional medial-to-lateral approach in laparoscopic right colectomy has been standardized (*11-13*). Due to anatomical complexity and vascular variation, dissection and vascular ligation around the duodenum and pancreas make it difficult to safely proceed (*14-16*). In our cohort, choice of the approach was left to the discretion of the surgeon based on intraoperative findings.

As expected, our analysis showed a correlation between the vascular ligation and Length A and B. Notably, Length C was significantly longer in the vascular ligated group. Surprisingly, only minimal correlation was found with tumor size or patient body size. Surgeons may be able to predict the need for vascular ligation based primarily on tumor location, focusing on distance from the Bauhin valve to the tumor and to the distal edge of the tumor, regardless of body size. Additionally, we conducted multivariate analyses (data not shown); neither Lengths A and B nor BMI were found to be statistically significant factors.

From the results of these analyses, we propose the following practical intraoperative indicators for determining the necessity of vascular ligation: *i*) To omit the RCA ligation, the distance from the Bauhin valve to the distal edge of the tumor should be less than approximately 5 cm; *ii*) If this distance is greater than approximately 8 cm, both the RCA and ARCV should be ligated; *iii*) If the distance exceeds approximately 10 cm, the MCA-rt should be ligated.

Regarding mobilization range, contrary to expectations, no correlation was observed with tumor characteristics or body size. As expected, Length C and operative time were significantly longer in the mobilization range of the Mid-T group. Additionally, the range of bowel mobilization was correlated with the anastomosis technique ($p < 0.01$). This result was attributed to surgery timing. Before 2018, most cases involved mobilization toward the center of the transverse colon, using the end-to-side anastomosis technique. The first 40 cases were affected by this bias. Therefore, due

Table 4. Surgical safety according to extent of vascular ligation

Outcome	RCA ligation			ARCV ligation			MCA-rt ligation		
	Yes (n = 46)	No (n = 21)	p vaule	Yes (n = 41)	No (n = 26)	p vaule	Yes (n = 16)	No (n = 51)	p vaule
Operation time (min)	227 (204.3–250.8)	195 (166.0–232.5)	0.03*	228 (201.5–254.0)	202.5 (168.5–231.3)	0.03*	229 (199.8–262.5)	222 (188–242)	0.24
Blood loss (mL)	54 (17.3–125.5)	30 (9.5–81.5)	0.26	50 (14.5–134.5)	38 (19.3–94.0)	0.56	72.5 (52.0–136.5)	35 (12–104)	0.08
Postoperative complications frequency (> C–D GradeII) (% (n))	10.9% (5)	0% (0)	0.17	7.3% (3)	7.7% (2)	1.00	6.3% (1)	7.8% (4)	1.00
Postoperative hospital stay (days)	9 (8–12)	9 (8–11)	0.84	9 (8.0–11.5)	9 (8–12)	0.84	8 (8-11)	9 (8–12)	0.68

Values are medians indicated with interquartile range in parentheses unless otherwise indicated. Postoperative complications are indicated with its frequency and count in parentheses. *p value < 0.05 was considered significant. RCA: right colic artery. ARCV: accessory right colic vein. MCA-rt: right branch of middle colic artery. C–D: Clavien-Dindo.

to this historic influence, our study could not provide reliable indicators for the required mobilization range.

Postoperative complications of Clavien–Dindo Grade II or higher were observed in seven cases (6.7%). There were no reoperations or fatal complications. Two cases had Grade IIIa complications: one developed a subcutaneous abscess due to anastomotic leakage, which required drainage, and another required long tube insertion for small bowel obstruction. Five cases experienced Grade II complications: one case of anastomotic leakage was treated conservatively with antibiotics, two cases of urinary tract infection required antibiotics, and two cases required postoperative blood transfusion. Although no significant correlation was found between postoperative complications and vascular ligation or mobilization range, it is noteworthy that all complications were observed in the RCA-ligated group only.

In five of the 103 cases, additional vascular ligation or mobilization was required during extracorporeal specimen extraction (data shown in Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=108*). These cases are important examples of minimal need for procedures and are considered very important cases in this study. In two cases, the ARCV had to be ligated through a small laparotomy due to excessive tension. In these cases, of course, the ARCV were not ligated laparoscopically. In one of these cases, Lengths A, B, and C were 70, 88, and 210 mm, respectively — values greater than the median distances in our ARCV-ligated group, which were not aligned with our indicator *ii*) above, suggesting that ARCV should have been ligated laparoscopically in advance. In the other case, these distances were 0, 30, and 90 mm, respectively — within the expected range of the ARCV nonligated group and aligned with our indicator *ii*). Although this patient was thin with a BMI of 16 kg/m^2, the depth of the tumor was serosal invasion (SI); it invaded the retroperitoneum, and the retroperitoneal tissue was also resected along with the tumor, which may have affected the additional ligation of the ARCV, as it was necessary to remove a large tissue mass. This was the only case in our study with a tumor invading depth with SI, indicating that the case was influenced by factors that could not be captured by this limited analysis alone.

In two other cases, the ARCV or anterior superior pancreatico-duodenal vein (ASPDV) was damaged and caused bleeding during extracorporeal extraction, requiring additional laparoscopic manipulation to achieve hemostasis. In one case, the ARCV had not been ligated, and Length A (25 mm) and Length B (60 mm) were shorter than the median distances observed in our ARCV ligation group and aligned with our indicator *ii*). In this case, obesity may have contributed to the patient being at risk of damaging the ARCV, as body weight was 93.5 kg (the highest value in this study) and BMI was 31.2 kg/m^2. However, the ASPDV was damaged in another

case, where the ARCV was ligated, the tumor depth was submucosa (SM), the size was 24 mm, and the BMI was 23.0 kg/m^2. Those parameters indicated that the patient had no obvious risk factor. This operation may have had some technical problems.

In one case, additional mobilization was required. Mobilization had been conducted toward the H-Fx, but it was insufficient to pull the intestine out of the abdomen at the time of pulling out the intestine through the small laparotomy. Length C was 108 mm, which was not longer than the median length of the group, considering the range of mobilization to the H-Fx. FEEA reconstruction was performed in this case, and the BMI was 24.1. Although not a significant factor in this analysis, the large tumor size of 70 mm may have influenced the insufficient mobilization range.

Based on these cases requiring additional procedures, there may be influences from factors that could not be derived from the analysis results of this study alone.

Currently, colectomy is performed using the da Vinci Xi robotic surgical system (Intuitive Surgical California, USA). In laparoscopic colectomy, intracorporeal anastomosis is technically more difficult than extracorporeal anastomosis, increasing the operative time (*17,18*). Although risk of intra-abdominal contamination with bowel content and tumor cells is a concern, intracorporeal anastomosis helps avoid traction of the bowel and the mesentery through the small laparotomy for resection and reconstruction (*19*). In addition to traditional laparoscopy, this robotic system features a surgeon-guided, stable camera platform, providing superior 3D views, seven degrees of freedom instrumentation, tremor filtering, and individualized ergonomics. Because intracorporeal anastomosis is easier with robotic surgery (*20*) and requires less bowel mobilization, we usually choose this method for robotic colectomy. According to the lower necessity of mobilization to extract the colon or conduct the extracorporeal anastomosis, robotic surgery with intracorporeal anastomosis is expected to have different suggested lengths for each vessel ligation. In the future, we plan to analyze the vascular ligation and mobilization range required when performing intracorporeal anastomosis in robot-assisted surgery and compare the results with those of this study. To evaluate the necessity of mobilization, more detailed description like the distance from the distal margin might be required rather than the mobilization range as described in this study, because robotic surgery enables more customized minimum mobilization for each case.

This study has several limitations, including being a nonrandomized retrospective study and the small number of patients included from a single institution. Each ligation group had small cases, as the results should be read cautiously. Our retrospective study design limited the information we could obtain and analyze. The lengths of the specimens were all measured after formalin fixation. Specimens were known to shrink after removal and then after formalin fixation (*21*), so their lengths might have been different from the length on any preoperative or intraoperative measurement. This difference might make the study result difficult to utilize in clinical settings. Hopefully, future studies will show more clinically applicable indicators.

5. Conclusion

In this retrospective single-institute study, we explored sufficient blood vessel ligation and bowel mobilization in laparoscopic surgery for ascending colon cancer with extracorporeal anastomosis. As a result, the distance from the Bauhin valve to the distal edge of the tumor was identified as a strong factor for vascular ligation. The following indicators may be useful in determining whether vascular ligation is necessary: *i*) To omit the RCA ligation, the distance from the Bauhin valve to the distal edge of the tumor should be shorter than approximately 5 cm; *ii*) If the distance from the Bauhin valve to the distal edge of the tumor exceeds approximately 8 cm, both the RCA and ARCV should be ligated; and *iii*) If the distance from the Bauhin valve to the distal edge of the tumor exceeds approximately 10 cm, the MCA-rt should be ligated.

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An evaluation of the effectiveness of 3D virtual imaging combined with intraoperative ultrasonography to guide liver staining in anatomic segmental hepatectomy

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Abstract: Identification of a tumor-bearing portal territory using indocyanine green (ICG) fluorescence imaging (IGFI) facilitates precise laparoscopic anatomic hepatectomy (LAH). However, it is technically challenging to perform a transhepatic portal injection of ICG or to clamp the target portal pedicle and inject ICG during LAH. Herein, we aimed to investigate the feasibility and efficacy of portal territory identification using IGFI under the combined guidance of three-dimensional (3D) virtual imaging and intraoperative ultrasound (IOUS) in LAH. We enrolled patients eligible for LAH in the current study between June 2020 and April 2023. All patients had preoperative surgical planning based on 3D virtual imaging in which the boundaries of the tumor-bearing portal territory were displayed and the predicted remnant liver volumes (PRLVs) were calculated. We then conducted ICG fluorescence liver-segment staining and LAH under the combined guidance of 3D virtual imaging and IOUS. Actual remnant liver volumes (ARLVs) were calculated using 3D virtual imaging after surgery. Of the 73 patients who achieved a valid demarcation by IGFI, 14 (19.2%) underwent hemi-hepatectomy, while 19 (26%) and 40 (54.8%) underwent sectionectomy and segmentectomy, respectively. The IGFI-identified intraoperative hepatic segment boundaries were highly matched with the boundaries of the tumor-bearing portal territory in the 3D virtual images in 72 (98.6%) patients, and we observed that the ARLVs and PRLVs were also robustly correlated ($r^2 = 0.8734$, $p < 0.0001$). In summary, 3D virtual imaging and IOUS contribute significantly to the staining and identification of a tumor-bearing portal territory and the accurate implementation of LAH.

***Keywords*:** 3D virtual imaging, Intraoperative ultrasonography, Laparoscopic anatomic hepatectomy, Indocyanine green fluorescence imaging

1. Introduction

Anatomic hepatectomy is defined as the complete removal of an anatomically and relatively independent hepatic segment or subsegment, or a combination of hepatic segments (*1*). Anatomic hepatectomy removes the lesion along with the hepatic segments of the tumor-bearing portal branch, playing an especially significant role in eradicating possible intrahepatic micrometastases; this then achieves surgical margin safety, reduces intraoperative bleeding and the incidence of perioperative biliary complications, and attenuates the risk of postoperative liver failure (*2,3*). Therefore, anatomic hepatectomy is valuable in the treatment of liver malignancies such as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and liver metastases from colon cancer (*4-6*). It is acknowledged that the identification of the tumor-bearing portal territory is essential for the precise execution of anatomic hepatectomy (*7*). Traditionally, identification of the portal territory is based on superficial markings produced by the staining of the portal branch as guided by intraoperative ultrasound (IOUS) (*8*), or by interruption of the portal pedicle that serves the segment(s) (*9*). These techniques do not offer a readily durable line of demarcation on the hepatic surface, and they often fail to stain liver segments and subsegments. In addition, the techniques do not provide clear, effective guidance with respect to

the direction of liver parenchyma dissection (*10*).

Indocyanine green (ICG) fluorescence imaging (IGFI) has been adopted widely, particularly during laparoscopic hepatectomy, in order to visualize hepatic segments by transhepatic injection of ICG into tumor-bearing or tumor-free portal branches under IOUS guidance (*i.e.*, positive staining or counterstaining), or by intravenous administration of ICG after clamping the target portal pedicle (*i.e.*, negative staining) (*11*). This technique enables the clear and persistent visualization of portal territory at the liver surface and within the hepatic parenchyma relative to conventional dye injection techniques. However, in laparoscopic hepatectomy, IOUS-guided precise puncture of the target portal branch or clamping the segmental portal pedicle remains technically challenging. For successful performance of these operations, it is crucial to establish the anatomic relationship between the tumor and the neighboring structures preoperatively and to conduct detailed preoperative planning. With the development of modern digital imaging techniques, three-dimensional (3D) virtual imaging modalities have been gradually introduced to visualize intrahepatic structures and to facilitate preoperative planning of liver resection (*12,13*). 3D virtual imaging technology provides a more intuitive, clear, and multi-angle view of the size, location, and shape of the tumor and the course of the intrahepatic vessels — as well as their spatial relationships — with significant advantages over conventional preoperative assessments. In addition, 3D virtual imaging not only enables the display and quantification of the perfusion territory of each portal branch (thus contributing to individualized hepatic segmentation, virtual hepatectomy (VH), and determination of the number of tumor-bearing portals and their specific orientations) but also allows slicing of the 3D virtual images in any plane and displaying the anatomic structures such as blood vessels and tumors on the cut surface (*14*). The cut surface in a specific plane can then be used to simulate IOUS images for quick and accurate intraoperative identification of the target portal branch. Thus, the combination of 3D virtual imaging and IOUS techniques may facilitate the puncture or clamping of target portal branches and also expedite the success of IGFI staining of the target liver segment during laparoscopic anatomic hepatectomy (LAH).

In this study, we described our experience with the co-application of 3D virtual imaging and IOUS techniques in LAH for ICG fluorescence liver-segment staining.

2. Materials and Methods

2.1. Materials

We enrolled a total of 821 patients with hepatic malignancies who underwent laparoscopic hepatectomy from June 2020 to April 2023 at the Second Affiliated Hospital of Nanchang University and from June 2022 to April 2023 at Mianyang Central Hospital. Of the 821 patients, 73 patients underwent VH preoperatively using 3D virtual imaging software, and then, they underwent LAH with tumor-bearing portal territory identification using IGFI. We analyzed 60 men and 13 women, with a median age of 62 (interquartile range, 48–68) years. Of these, 67 were diagnosed with HCC, five with ICC, and one with both HCC and ICC (Table 1 presents details of the baseline characteristics of all patients). We obtained written informed consent from all patients prior to hepatectomy. This study received the approval of Research Ethics Commission of the Second Affiliated Hospital of Nanchang University (No. 2021050) and was conducted in accordance with the Declaration of Helsinki.

2.2. Acquisition and processing of 3D virtual images

Computed tomography (CT) data were obtained using a 256-slice helical CT scanner (Brilliance iCT, Philips Medical Systems, Haifa, Israel); and the scan data requirements were arterial, portal, and delayed-phase CT images and a slice thickness of 1 mm. The 3D virtual image was reconstructed based on the preoperative CT scan data by employing CT image postprocessing software (Xudong Digital Medical Imaging Technology Co., Shenzhen, China) as follows:

i) We first imported the digital imaging and communications in medicine (DICOM) image data from the thin-layer CT scans. *ii*) The hepatic artery, hepatic vein, and portal images on two-dimensional (2D) CT images were then automatically segmented by adopting the threshold analysis algorithm, and the 3D virtual image of the intrahepatic vasculature was automatically reconstructed. *iii*) Multiple seed points were selected in the target region of the 2D image, and a region-growing algorithm and a periodic iteration-segmentation method

Table 1. Summary of characteristics of patients

Variables	Values
Age, median [IQR], years	62 [48–68]
Male, *n* (%)	60 (82.2)
Background liver	
Normal liver, *n* (%)	18 (24.7)
Chronic hepatitis, *n* (%)	55 (75.3)
Preoperative diagnosis	
HCC, *n* (%)	67 (91.8)
ICC, *n* (%)	5 (6.8)
cHCC-ICC, *n* (%)	1 (1.4)
Child-Pugh class	
A, *n* (%)	73 (100)
Tumor size, median [IQR], mm	44 [35.5–60.5]
Tumor number	
Single, *n* (%)	61 (83.6)
Multiple (≤ 3), *n* (%)	12 (16.4)

HCC: hepatocellular carcinoma, ICC: intrahepatic cholangiocarcinoma, cHCC-ICC: combined hepatocellular-hepatocellular, IQR: interquartile range.

were automatically applied to segment and reconstruct the 3D virtual images of the liver and tumor. *iv*) Finally, we calculated the territories of all tertiary portals and a portion of the quaternary portals around the tumor. The algorithm for the calculation of the portal territory was based on the Voronoi tessellation, which is bordered by a line equidistant from the surrounding vessels (*15*).

Surgeons can identify the tumor-bearing portal branch and the spatial-location relationship of the tumor with nearby portal territories through 3D virtual imaging software. We conducted VH by subtracting the tumor-bearing portal territory from the entire liver; and we calculated the predicted remnant liver volumes (PRLVs) after VH. PRLV-to-standard liver volume (SLV) ratio was calculated to ensure that the residual liver volume ratio was > 40%, and the SLV was subsequently calculated based on the Urata formula (*16*). Hepatectomy terminology was determined in accordance with the 2000 Terminology Committee of the International Hepato-Pancreato-Biliary Association (*17*), and morbidity was established in accordance with the 2009 Clavien–Dindo classification of surgical complications (*18*).

Preoperative identification of tumor-bearing portal branches by 3D virtual image software provides an anatomic basis for searching for the target portal branch. However, as the IOUS image is a 2D image, difficulties remain in accurately locating the target portal branch by directly matching it with the 3D virtual image. Thus, the 3D virtual image is cut according to the possible placement directions and angles of the IOUS. In our case, the IOUS images were also simulated using cut surfaces of 3D virtual images to reduce the difficulty of target portal branch identification under IOUS and to improve the success rate of portal puncture. The target portal branch was then identified when an IOUS image matched the simulated image. When negative staining was planned, the surgeon executed 3D virtual imaging to plan access to the target portal branch in order to reduce the difficulty of dissecting or clamping the laparoscopic tumor-bearing portal branch.

2.3. ICG fluorescence imaging system

IGF images were acquired using a fluorescence laparoscopy system (IMAGE1 S, Karl Storz SE & Co. KG, Tuttlingen, Germany). This system enables the acquisition of color images under white illumination, monochrome fluorescence images under near-infrared illumination, and fused images of pseudocolor (green) fluorescence images with white-light color images. In addition, surgeons were able to select the imaging mode displayed on the screen at any time with a button switch.

2.4. Administration of ICG for the identification of the portal territory

The IGFI technique for identifying the tumor-bearing portal territory described above was appropriately selected according to the preoperative 3D virtual image. The IOUS was used to find the target portal vein branches from the first hepatic portal towards the tumour. The target portal vein branch is identified when an image similar to the section image of the preoperative 3D visualisation image is found on the ultrasound monitor. For transhepatic portal injection of ICG, 5–10 mL of ICG (0.025 mg/mL) was injected into the portal branch under IOUS guidance without clamping the Glisson pedicle at the hepatic hilum.

For intravenous injection of ICG, 5–10 mL of ICG (0.25 mg/mL) was injected after tumor-bearing portal branch occlusion or ligation. We observed fluorescence images on the surface of the liver after ICG administration and on the cut surface of the liver when the liver parenchyma was dissected, and we recorded them by applying a fluorescence laparoscopy system.

Compared with other methods, negative staining is more likely to be applied for hemi-hepatectomy, lobectomy, or left-sided segmentectomy because the origin of the secondary branches of the Glisson pedicle is principally located outside the liver or close to the surface of the liver near the hilum (*9*), allowing it to be clamped without or with only a slight dissection of the liver parenchyma. In contrast, positive staining or counterstaining tends to be used in resections, wherein the hilar separation is considered difficult due to technical reasons or in right-sided hepatic segmental resections, as a majority of the tumor-bearing portal branches are deep within the liver. In addition, a combination of these techniques may be used in complex cases. In the following sections, we describe representative cases with technical details.

2.5. Positive staining technique (Case 1)

We planned LAH for a 4.9-cm-diameter HCC, and the functional reserve was normal with a Child-Pugh class of A. The preoperative 3D virtual image showed that the HCC was located at segment VIII (S8), but the portal vein trunk of S8 was very short and divided into ventral (P8v) and dorsal (P8d) branches after entering the S8 segment (Figure 1, A and B). In this situation, as direct injection of P8 tended to cause ICG reflux resulting in staining failure, we decided on P8v and P8d injections. The IOUS images of punctures at P8v and P8d were simulated preoperatively using 3D virtual imaging technology (Figure 1, C and D), and we rapidly found IOUS images that matched the simulated images intraoperatively and identified the target portal branches (Figure 1, E and F). P8v and P8d were thus successfully punctured and subsequently injected with ICG diluted with sterile water. The S8 was ultimately completely removed (Figure 1, G and H).

2.6. Counterstaining technique (Case 2)

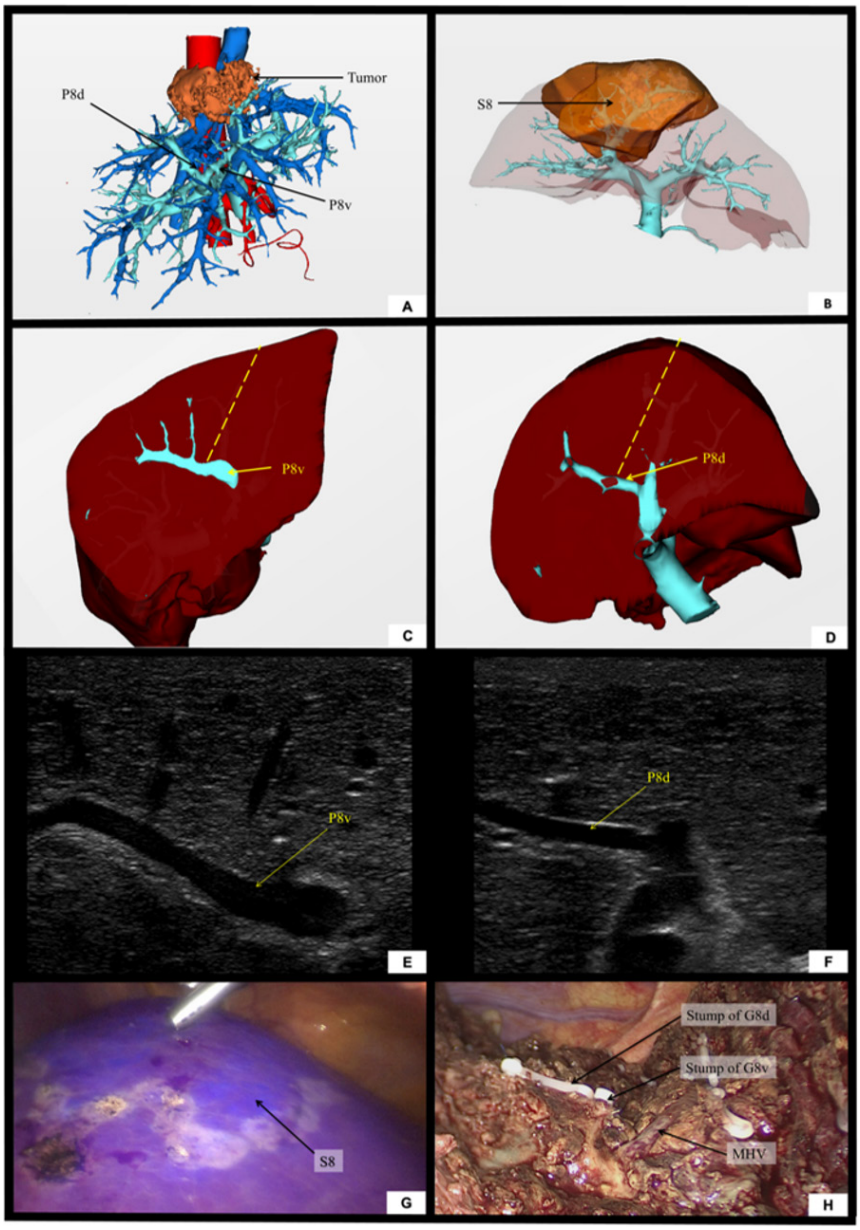

Figure 1. Positive staining. (A) 3D image shows that the tumor was located at segment VIII (S8), with P8 divided into the dorsal branch (P8d) and ventral branch (P8v). **(B)** 3D image shows the perfusion territory of P8. **(C, D)** IOUS images during the puncture of P8v and P8d were simulated using 3D visualization technology. **(E, F)** IOUS images during the puncture of P8v and P8d. **(G)** ICG fluorescence imaging clearly shows S8 as fluorescing. **(H)** Cut surface of the liver after S8 resection using positive staining. A portion of the MHV is visible in the cut surface. IOUS, intraoperative ultrasound; ICG, indocyanine green; MHV, middle hepatic vein.

When the tumor-bearing portal branch is obstructed by a portal cancer thrombus, the tumor-bearing portal territory can be identified by counterstaining, as first introduced by Takayama *et al.* in 1991 (*19*); this could alternatively be applied when the tumor-bearing portal is too thin and difficult to puncture. In our case, the tumor-bearing portal territory showed a fluorescence-deficient region, and the nearby tumor-free portal territory was displayed as a fluorescent area upon fluoroscopic laparoscopy after portal injection of ICG. LAH was planned for an HCC with a diameter of 8.7 cm. The 3D virtual image depicted the tumor as located at segment V (S5) and the ventral subsegments of segment VI (S6v); several small portal branches also flowed into S5, and the portal branching into the ventral side of S6 was thin (Figure 2, A and B). Since this situation increased the difficulty of portal puncture, we planned to puncture the portal branches flowing to segment VIII (S8) and the dorsum of S6 (S6d). We then simulated the IOUS images of the punctures at P8 and P6d preoperatively using 3D visualization technology (Figure 2, C and D). P6d and P8 were then successfully identified and punctured under IOUS guidance (Figure 2, E and F), and the tumor-bearing portal territory appeared as a fluorescence-deficient region. A complete resection of the S6v and S5 was thus achieved, whereas the territory supplied by the P6d was

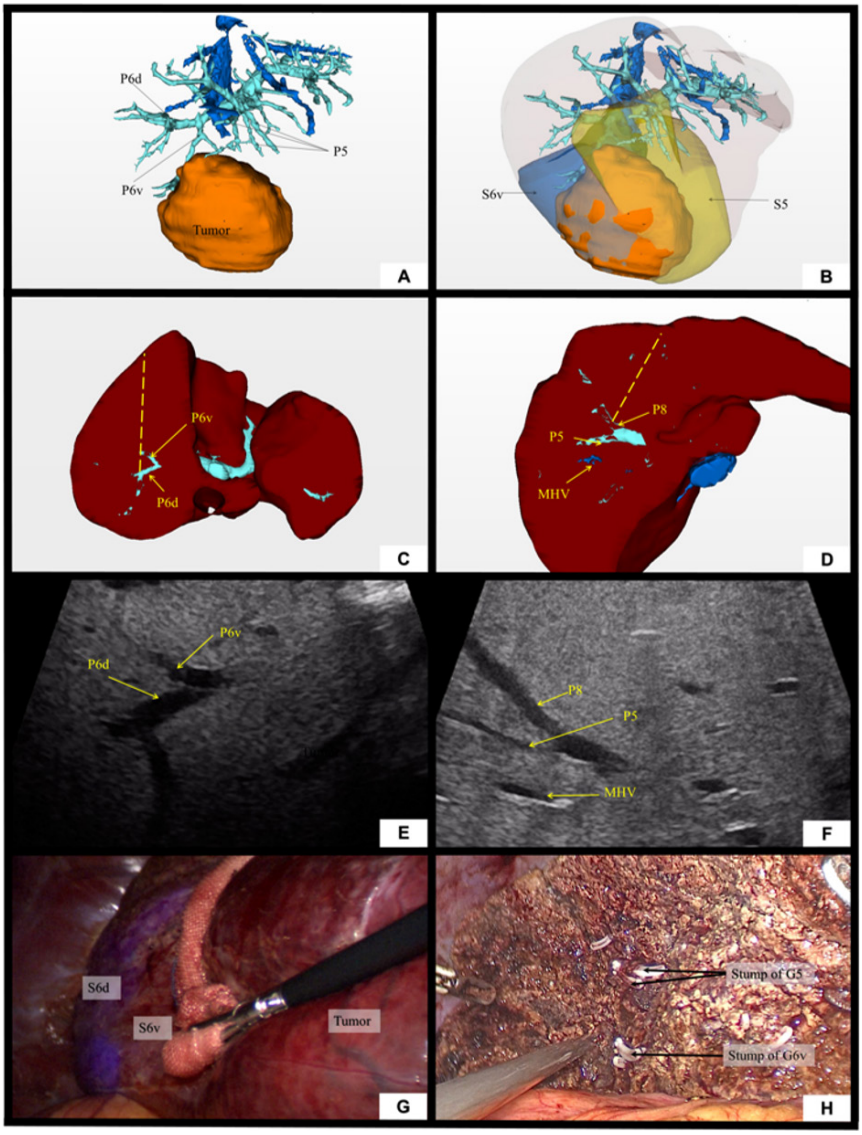

Figure 2. Counterstaining. (A,B) 3D image shows that the tumor was located in the perfusion territory supplied by the ventral branch of P6 (P6v) and P5. **(C,D)** IOUS images during the puncture of P8 and the dorsal branch of P6 (P6d) were simulated using 3D visualization technology. **(E,F)** IOUS images during the puncture of P8 and P6d. **(G)** ICG fluorescence imaging clearly shows the perfusion territory of the P6d as fluorescing, while the perfusion territory of the P6v was identified as defects in fluorescence. **(H)** Cut surface of the liver after resection of the tumor-bearing portal perfusion territory. The disconnected sections of P5 and P6v are visible in the cut surface. IOUS, intraoperative ultrasound; ICG, indocyanine green; MHV, middle hepatic vein.

unaffected (Figure 2, G and H).

2.7. Negative staining technique (Case 3)

When the tumor-bearing portal branch is temporarily clamped shut, the tumor-bearing portal territory can be recognized as a fluorescence defect *via* intravenous ICG injection (*11*). We planned LAH for a 3.8-cm-diameter HCC and ascertained from the 3D virtual image that the tumor was located at segment III (S3), segment IV (S4), and the ventral segment of the right anterior section (RASv) (Figure 3, A and B). Following the clamping of the Glisson pedicle of S3, S4, and RASv (G3, G4, G5v, and G8v) and the intravenous injection of ICG, the tumor-bearing portal territory appeared fluorescence-deficient, while the remaining areas exhibited fluorescence (Figure 3, C–F). After the resection line was marked by electrocautery, we performed LAH (Figure 3H).

2.8. Hepatectomy

We determined an effective and sustained demarcation between the prospectively removed hepatic territory and the remaining hepatic territory following ICG fluorescent liver-segment staining. Inflow was intermittently occluded using the Pringle maneuver, and the liver parenchyma was dissected using the forceps clamp-crushing technique. The orientation of the cut relative to the liver parenchyma was adjusted through manipulation under real-time guidance of IGFI. A drainage tube was subsequently placed at the hepatic transection site to monitor postoperative bleeding and bile leakage.

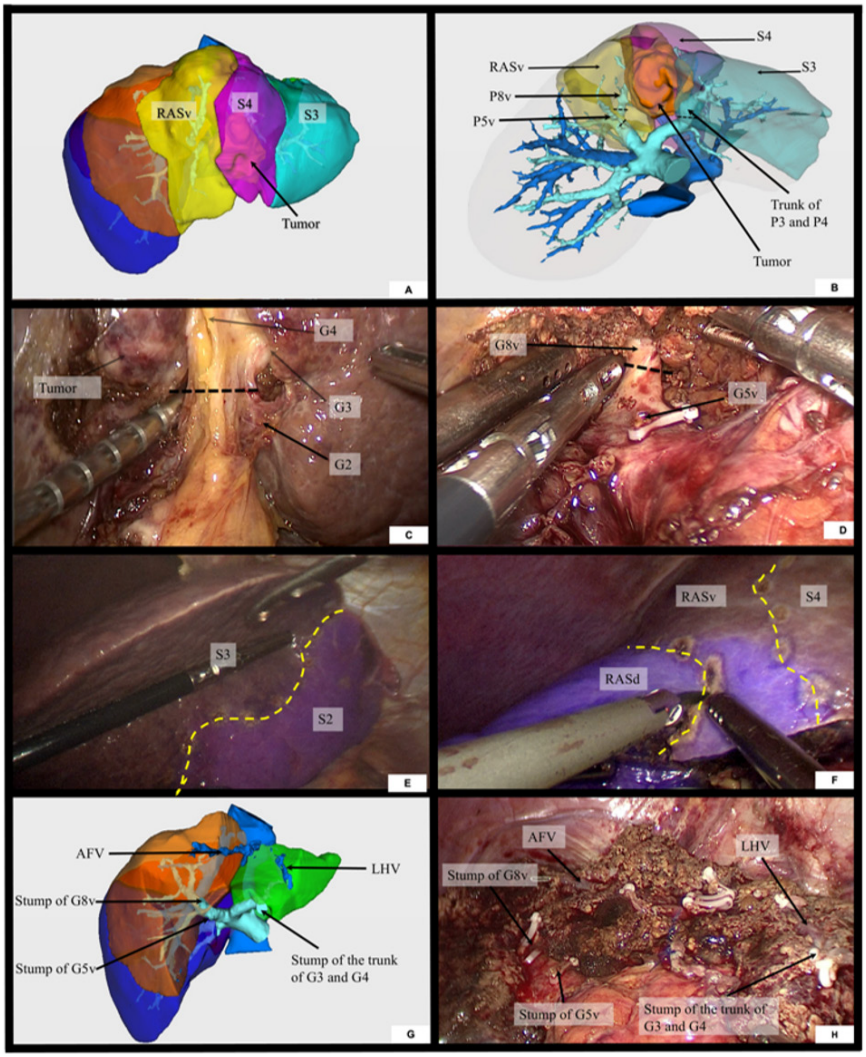

Figure 3. Negative staining. (A) 3D image shows that the tumor was located in the S3, S4, and RASv. **(B)** Access for dissection and clamping of P5v, P8v, and the trunk of G3 and G4 using 3D visualization technology. **(C)** Clamping of the trunk of G3 and G4. **(D)** Clamping of P5v and P8v. **(E,F)** After intravenous injection of ICG, S3, S4, and RASv showed fluorescence-deficient areas, and the demarcation lines on the liver surface highly resembled the boundaries on the 3D images. **(G,H)** The transection after LAH exhibited strong similarity to the transection on the 3D image after VH. ICG, indocyanine green; RAS, right anterior section; AFV, anterior fissure vein; LHV, left hepatic vein.

2.9. Follow-up

Biochemical indicators such as blood count and liver function were regularly evaluated after surgery, and an abdominal CT examination was performed approximately 3 days postoperatively to assess postoperative complications. Based on the patient's CT data, the 3D virtual image of the postoperative liver was reconstructed, and the actual remnant liver volumes (ARLVs) were calculated. ARLV and PRLV were then compared to assess the consistency of LAH versus VH.

2.10. Statistical analysis

We used proportions to summarize the distribution of categorical variables. For continuous variables, we calculated and used medians and interquartile ranges. The correlation analysis between ARLV and PRLV was conducted using Pearson's method. All statistical analyses were performed by adopting the Statistical Package for Social Sciences software, version 25.0 (IBM, Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant.

3. Results

Of the 73 patients who demonstrated a valid demarcation by IGFI, 14 (19.2%) underwent hemi-hepatectomy, while 19 (26%) and 40 (54.8%) underwent sectionectomy and segmentectomy, respectively. The tumor-bearing portal territory was identified through positive staining in 22 cases, counterstaining in one case, positive staining with counterstaining in two cases, and negative staining in 48 cases. The ICG fluorescence boundaries that represented the tumor-bearing portal territory versus the normal liver could be clearly observed intraoperatively in all patients. The intraoperative IGFI-identified hepatic segment boundaries matched the boundaries of the tumor-bearing

Table 2. Summary of characteristics of patients

Characteristics	Values
Total number	73
Fluorescence staining technique	
Positive staining technique, *n* (%)	22 (30.1)
Counter staining technique, *n* (%)	1 (1.4)
Positive staining with Counter staining technique, *n* (%)	2 (2.7)
Negative staining technique, *n* (%)	48 (65.8)
Surgical procedure	
Mono-segmentectomya[a], *n* (%)	30 (41.1)
Combined-segmentectomya, *n* (%)	10 (13.7)
Sectionectomy, *n* (%)	19 (26)
Hemi-hepatectomy, *n* (%)	14 (19.2)
Operation time, median [IQR], min	355 [225–457]
Estimated blood loss, median [IQR], mL	200 [100–400]
Transfusion	
Concentrated red blood cell, median (range), U	0 (0–4)
Fresh frozen plasma, median (range), mL	0 (0–600)
Postoperative length of stay, median [IQR], day	9 [7–11]

[a] Including the removal of portal vein territory smaller than Couinaud segment. IQR: interquartile range.

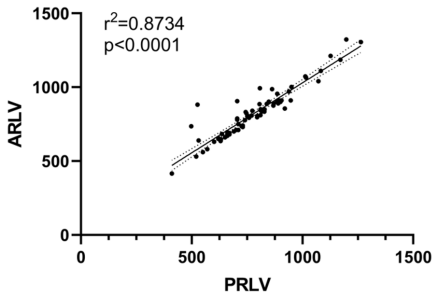

Figure 4. ARLV showed a strong correlation with the PRLV (r^2 = 0.8734, p < 0.001). ARLV, predicted remnant liver volume; PRLV, actual remnant liver volumes.

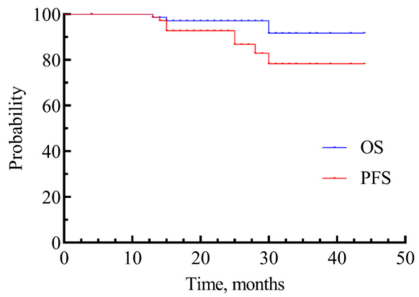

Figure 5. Kaplan-Meier curves for OS and PFS in all patients. OS, overall survival; PFS, progression-free survival.

portal territory detected by 3D visualization in 72 (98.6%) patients. Of the 22 cases in which portal injection was performed, hepatic tissues from one case (4.5%) did not stain as expected, and the stained area did not adequately cover the liver segment to be removed. We determined the target liver-segment boundaries intraoperatively by preoperative 3D virtual images combined with IOUS. LAH was ultimately completed in all cases, except for three cases in whom the conversion to laparotomy was abrogated due to massive intraoperative bleeding (Table 2 summarizes the intraoperative and postoperative results of 3D visualization-guiding ICG fluoroscopic staining for LAH).

None of the patients experienced intraoperative adverse incidents associated with ICG or fluoroscopic staining procedures. The median operative time was 355 min (interquartile range, 225–457 min), and the median estimated blood loss was 200 mL (interquartile range, 100–400 mL). All patients were discharged without major complications, and all pathologic results showed a negative resection margin. The median postoperative length of stay was 9 days (interquartile range, 7–11 days). As shown in Figure 4, ARLV and PRLV exhibited a robust correlation (r^2 = 0.8734, p < 0.0001) (Figure 4).

The median follow-up time for all patients was 22 months (interquartile range, 16–29.5 months). Survival rates at 1, 2, and 3 years were 98.6%, 97.1%, and 91.7%, respectively, while PFS rates at 1, 2, and 3 years were 98.6%, 92.8%, and 78.3%, respectively (Figure 5).

4. Discussion

Identification of portal territory by portal injection of dye under IOUS guidance constitutes an essential method for performing anatomic hepatectomy (*8*). By using this technique, the stained area is visualized on the surface of the liver. However, the intersubsegmental plane is impossible to follow when the liver parenchyma is divided, as conventional dyes fade immediately after injection (*20*). The other method widely used for anatomic hepatectomy is the Glisson pedicle approach described by Takasaki *et al*. (*9*). After the Glisson pedicle of the target liver segment is dissected and clamped, hepatic segment boundaries can be identified by the hepatic surface ischemia line. However, similar to portal staining, the Glisson pedicle approach also fails to identify the intersegmental plane during parenchymal dissection. The application of the IGFI technique can resolve these issues. Unlike conventional dye, ICG does not fade rapidly after injection and is retained by the liver for several hours (*21*). Thus, the IGFI technique enables the identification of intersegmental planes during parenchymal transection and real-time navigation in anatomic hepatectomy.

The accurate identification of target portal branches by IOUS guidance is critical for successful staining, and the preoperative clarification of the anatomic relationship between HCC and the surrounding portal vein branches is vital for the accurate identification and puncture of the target portal branch under IOUS guidance. Nevertheless, the type and number of tertiary portal vein branches in each patient vary. In 33–70% of cases, an individual Couinaud segment is supplied by two or more third-order portal vein branches (*22,23*), and a tumor may also have two or more tumor-bearing portal vein branches. This situation greatly complicates identification of the

tumor-bearing portal vein branch under IOUS guidance. Traditional 2D imaging data do not objectively reflect the complicated anatomic structure of the liver and the detailed morphologic characteristics of a lesion. Thus, accurate preoperative identification of the portal vein branch of the hepatic segment and the tumor-bearing portal vein branch using traditional 2D imaging data is quite difficult.

Using 3D virtual imaging, surgeons can observe the size, location, and morphology of the tumor and the intrahepatic vascular anatomy from different angles. This modality also allows individual segmentation of the liver by calculating the portal territory, determining the liver segment where the tumor is located, identifying the tumor-bearing portal branch, and performing surgical planning by virtual hepatectomy. Thus, 3D virtual imaging provides an anatomic basis for finding the target portal branch intraoperatively. We herein determined the locations of tumors and the identification of tumor-bearing portal branches in each patient by applying 3D virtual imaging technology. However, the IOUS image is 2D and cannot be directly matched with the 3D virtual image so as to precisely identify the target portal vein. Therefore, we simulated the IOUS image by transecting the 3D virtual image to assist surgeons in accurately identifying the target portal vein branch under IOUS (Figure 1, C and D). We were able to generate an ultrasonographic image that matched the simulated image when performing IOUS so as to quickly identify the target portal branch and perform the puncture (Figure 1, E and F). As a result, we achieved a 96% staining success rate in cases where we injected ICG into the hepatic portal vein. Therefore, preoperative, 3D virtual image-based surgical planning and simulated IOUS imaging contribute to the success of IOUS-guided portal vein injection and the precise execution of anatomic hepatectomy. The application of IOUS in laparoscopic surgery is limited by the position and angle of the trocar, and the utilization of the puncture needle is limited by the abdominal wall and the inflexibility of instruments. Therefore, the identification and puncture of the portal vein under IOUS in laparoscopic hepatectomy are more technically challenging. We recommend that these factors be taken into account when planning intraoperative IOUS-guided portal puncture *via* 3D virtual imaging preoperatively. After a successful puncture, the speed of the dye injection needs to be controlled, because rapid injection tends to cause dye reflux and staining failure.

Compared with other methods, negative staining is easier to perform in LAH. It does not require a puncture of the target portal branch but is performed by the intravenous injection of ICG after clamping the segmental portal pedicle. However, the Glisson approach is also invasive and technically demanding, particularly when the origin of the tumor-bearing portal branch is located within the liver parenchyma. 3D virtual imaging allows surgeons to understand the course of the tumor-bearing portal branch preoperatively and plan access to this portal branch, thus contributing to a reduction in the difficulty of dissection and the clamping of the target Glisson pedicle (Figure 3, C and D). Negative staining is often applied in anatomic hemi-hepatectomies and lobectomies, and such extensive hepatectomies reflect a potential to result in insufficient remnant liver volume. Since postoperative liver failure and morbidity are known to be influenced by remnant liver volume (*24*), accurate preoperative assessment of the remaining liver volume is crucial for the safe performance of anatomic hepatectomy. The PRLV was calculated after VH, facilitating preoperative assessment and reducing the incidence of postoperative liver failure and mortality. We also calculated the ARLVs postoperatively and uncovered a significant correlation between ARLVs and PRLVs. Our data therefore supported our contention that 3D virtual imaging technology enabled accurate prediction of the anatomic hepatectomy plan and indirectly demonstrated that the intraoperative volume of the resected liver was also approximately the same as the volume of the tumor-bearing portal territory in the 3D virtual images.

There were some limitations to this study. First, we had no control group, and it was thus impossible to depict differences in clinical outcomes. Additional studies are also required with respect to evaluating the differences in operative time, blood loss, disease-free survival, and mortality rates for anatomic hepatectomy with or without 3D virtual imaging and IOUS guidance. Second, the 3D virtual images could not be navigated in real time during LAH. Thus, although preoperatively created 3D virtual images and simulated IOUS images can provide a reference for liver surgeons during LAH, they cannot be matched with IOUS images and surgical views in real time. The position of the intraoperative ultrasound needs to be adjusted several times until the ultrasound image matches the preoperative simulated image. We posit that the technically complete integration of 3D visualization software with IOUS and laparoscopic systems for the real-time navigation of 3D visualization software during surgery will facilitate LAH with increased precision.

In conclusion, 3D virtual imaging and IOUS contribute significantly to the staining and identification of tumor-bearing portal territories and the accurate implementation of LAH. It enables surgeons to quickly and accurately locate and puncture or block the target portal vein during surgery, precisely identify the tumor-bearing portal territory, and perform laparoscopic anatomic liver resection.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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BRIEF REPORT
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Hepatic venous plexuses on the right border of the caudate lobe against the right liver in a liver cast

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Abstract: Identifying the right border of the caudate lobe against the right liver is clinically important; however, this remains challenging. As the paracaval portion (PC) of the caudate lobe is adjacent to segment 8 of the right liver, we dissected a liver cast made from epoxy resin and colored dye to define the right border of the PC against segment 8. On the right border of the PC, two major venous plexuses appearing as bouquet-shaped branches joined the inferior vena cava and the middle hepatic vein, forming short hepatic veins, whereas the venous plexuses in segment 8 joined the right hepatic and the vein inferior vena cava. These venous plexuses in PC and segment 8 created a zigzag boundary plane, which coincided with the boundary found between the caudate lobe and the right liver. Moreover, no longitudinal venous branch was found between the PC and segment 8 in the liver cast.

***Keywords*:** liver cast, caudate lobe, paracaval portion

1. Introduction

The caudate lobe is located deep in the liver and is a clinically important segment. The resection of liver tumors in the caudate lobe remains challenging in the era of laparoscopic (*1*) or robotic hepatectomy (*2*), and concomitant resection of the caudate lobe is required in the curative treatment of perihilar cholangiocarcinoma (*3*). The resection of the paracaval portion (PC) of the caudate lobe is among high-level hepatectomies according to the criteria defined by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (*4,5*).

Although the left border of the caudate lobe is easily detected as the Spiegel lobe, identifying its right border remains challenging. This has been a great concern for liver surgeons when performing isolated resection of the caudate lobe. Takayama attempted to find the right border of the caudate lobe using a counter-staining technique, *i.e.*, injecting dye into the posterior portal vein (*6*); however, this is an indirect and uncertain identification method.

We have previously demonstrated the distribution of the PC of the liver on hepatic casts (*7-11*) and defined portal branches of the caudate lobe as dorsal branches from the main trunk or 1st order branch of the portal vein. The caudate lobe was divided into the following three portions according to portal segmentation: *i*) Spiegel; *ii*) PC; and *iii*) caudate process (*7-9*). In the present paper, we describe for the first time the venous plexuses on the right border of the caudate lobe in a liver cast.

2. Materials and Methods

A liver cast was made after injecting colored epoxy resin into the portal vein (blue), hepatic artery (red) and the bile duct (yellow). The present study examined three subjects. The specimens were fixed in water to preserve the natural hepatic shapes, as they would be in the body. Liver tissue was corroded completely using potassium hydroxide.

After fixation, we dissected the liver cast using a pair of forceps with fine tips and extracted the small Glissonean and venous branches, gently piece by piece (Figure 1). The right portal vein was divided at the proximal site of bifurcation of the anterior and posterior portal branches (Figure 2). After meticulous dissection, the portal and hepatic venous branches in the PC of the caudate lobe and segment 8 of the liver were observed.

The present study was approved by the National Center for Global Health and Medicine Research Ethics Committee/Institutional Review Board (approval number: NCGM-G-004020-00).

3. Results and Discussion

The Glissonean and hepatic venous branches in the PC were completely dissected from those in segment 8 (Figure 3). The PC of the caudate lobe was surrounded by the triangle made from the inferior vena cava (IVC), middle hepatic vein (MHV), and right branch of the portal vein (Figure 4).

Each venous branch was approximately 100μm in size, and numerous tiny papillary branches created two bouquet-shaped venous plexuses (Figure 4). The two major venous plexuses joined the MHV and IVC, respectively. On the opposite side of the right liver, the other two major venous plexuses were found in segment

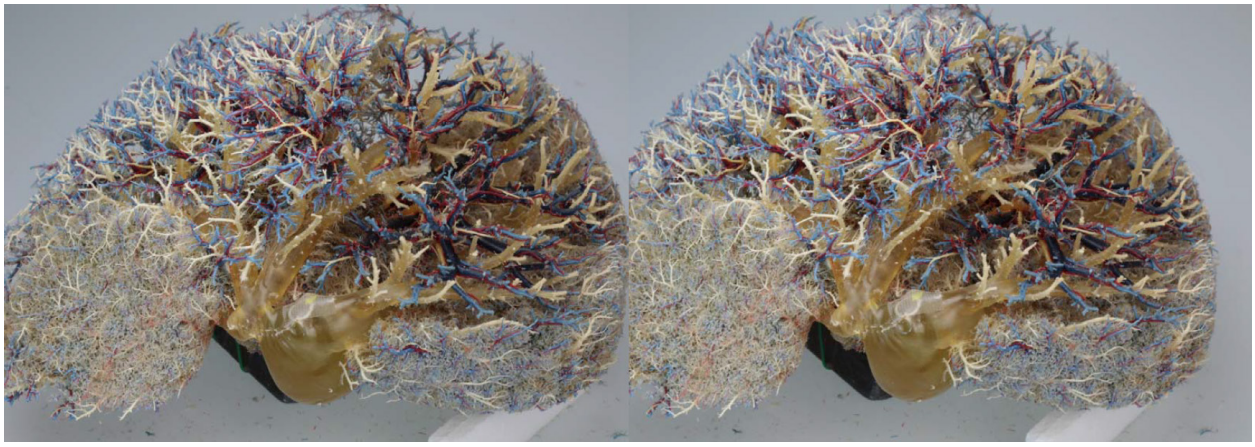

Figure 1. Cranial view of the liver cast from a ventral position.

Figure 2. Cranial view of the liver cast focusing on the root of the middle (white asterisk) and right (yellow asterisk) hepatic veins. The paracaval portion of the caudate lobe is located behind the middle hepatic vein.

Figure 3. Caudal view of the liver cast after dividing the right liver. The right liver is connected to the inferior vena cava through the venous plexuses in segment 8 (black arrowhead).

8 of the right liver (Figure 5). They joined the right hepatic vein (RHV) and IVC, respectively. The boundary between the caudate lobe and right liver coincided with the boundary between these venous plexuses in the PC and segment 8 of the liver, creating a zigzag boundary plane (Figure 6). No longitudinal intersegmental vein was observed between the PC and segment 8. These venous plexuses were found in the remaining two liver casts and no longitudinal intersegmental vein was noted between the PC and segment 8 in these two liver casts.

In the present case study, the two venous plexuses found in the PC of the liver joined the IVC as short hepatic veins and MHV. The venous plexuses in segment 8 joined the IVC and RHV, respectively. Additionally, we found that the border between the caudate lobe and right liver coincided with the boundary between the venous plexuses in the PC and segment 8, creating a zigzag irregular boundary plane. No thick longitudinal vein was noted between the PC and segment 8 of the liver, as previously shown by Maki *et al.* (*12*). In addition, these meticulous venous plexuses can never be detected on a recent CT scan or three-dimensional tomographic scans.

There have been several arguments about the right border of the caudate lobe of the liver. Kogure *et al*. advocated that the caudate process hepatic vein (CPHV) entering the IVC ran in the segmental plane between the caudate process and right liver (*13*). However, liver surgeons do not recognize the CPHA as the intersegmental vein between the caudate process and right liver. Maki *et al*. reported that the paracaval vein ran just along the boundary between the PC and right liver in 30 out of 63 (48%) participants based on analysis of the three-dimensional (3D) CT images (*12*). The paracaval vein was a branch of the RHV; however, no sagittal branch was found in the present cast. This difference will be caused by the difference of the methods of the study between liver casts and 3D-CT. On liver casts, very tiny hepatic venous branches can be seen inside the liver, while these tiny branches cannot be detected without dissecting and cutting other branches. On the other hand, on 3D-CT analysis, most thick venous branches were

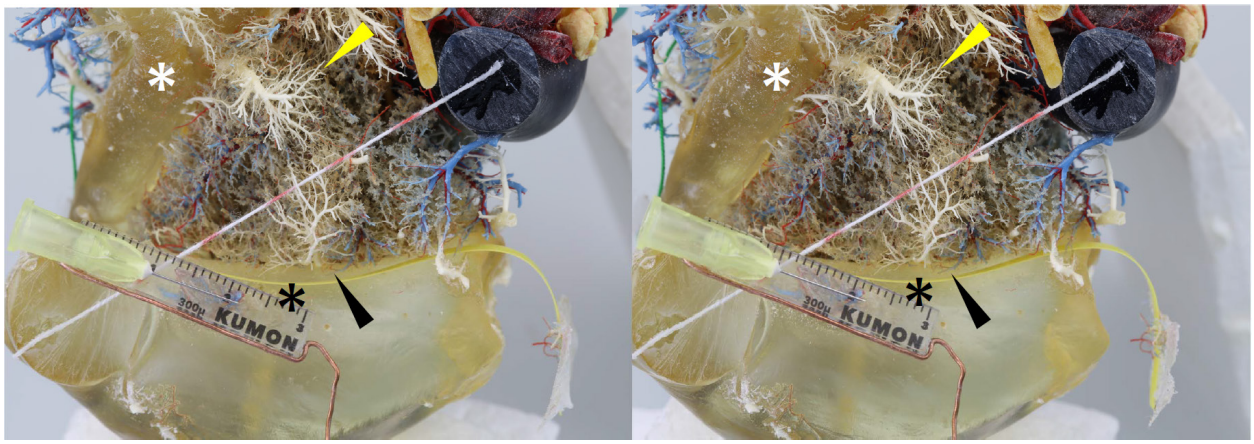

Figure 4. The right border of the paracaval portion of the caudate lobe. One venous plexus (yellow arrowhead) joins the middle hepatic vein (white asterisk), whereas another venous plexus (black arrowhead) joins the inferior vena cava (black asterisk).

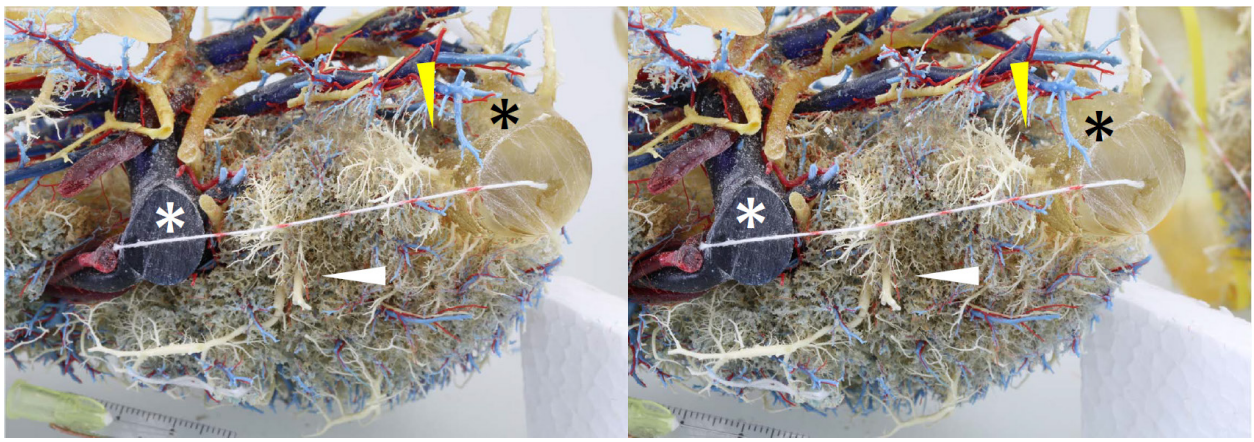

Figure 5. The left border of the right liver. Two venous plexuses are seen: one plexus (yellow arrowhead) joins the right hepatic vein (black asterisk) and another plexus (white arrowhead) joins the inferior vena cava that has been divided on the root of the short hepatic vein.

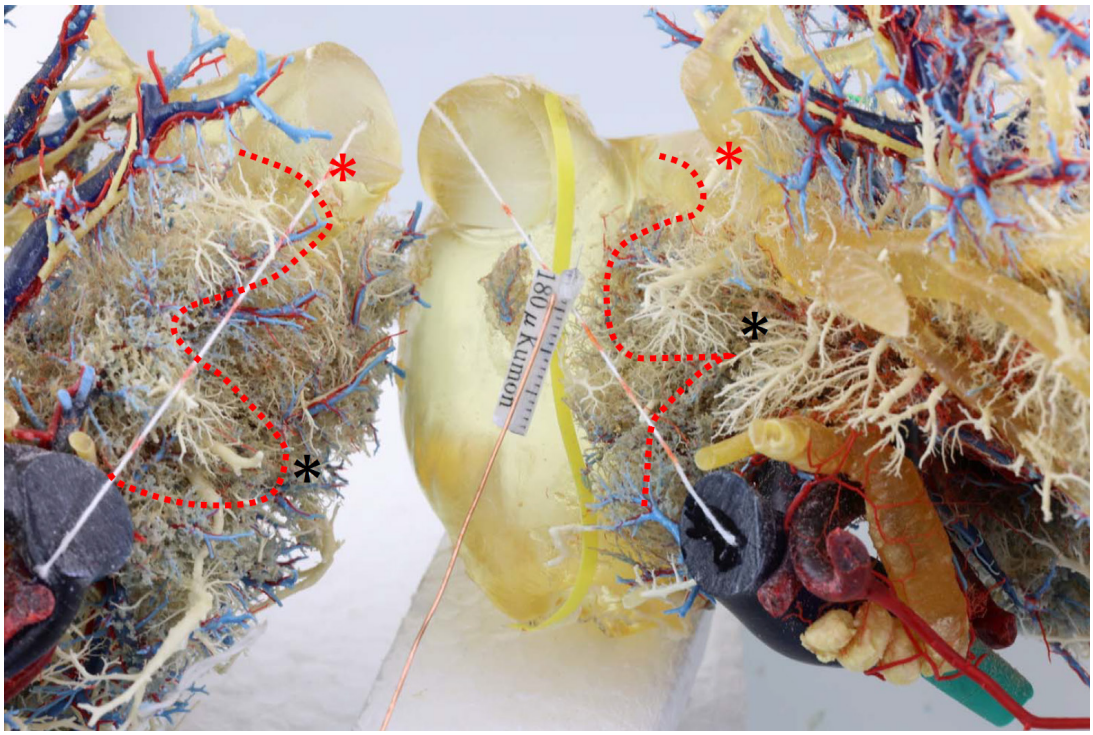

Figure 6. Caudal view of the cast after dividing the right liver and the boundary between the right liver and paracaval portion of the caudate lobe. The red dotted line shows the boundary between segment 8 in the right liver and paracaval portion in the caudate lobe. The red and black asterisks show the spots between the two livers that were connected to each other.

visualized, while the tiny venous plexus will never be shown. Each method has advantages and disadvantages to demonstrate all of the hepatic venous branches.

Takayama *et al.* clinically demonstrated the right border of the caudate lobe by injecting a dye into the posterior portal branch, as a counter-staining method (*6*). This appears to be a very clever method of visualizing the right border of the caudate lobe; however, there is a possibility that the non-stained area includes proximal branches of the posterior section. Thus, the caudate area defined by using this method was larger than that decided by using the Kumon's definition. We previously injected indocyanine green solution into the portal venous branch in PC, and found the boundary of the PC of the caudate lobe using fluorescent images using right hemihepatectomy (*14*). This will be a definite but technically demanding method to identify the boundary.

In the present cast, venous drainage of the caudate lobe joined the IVC or MHV as a venous plexus, *i.e.*, tiny venous capillary branches creating bouquet-shaped branches. This venous system can never be visualized using a 3D CT. Gadžijev's atlas also showed these venous branches in his atlas book (*15*), but they were not as clear as the present photos. In addition, he did not mention the right boundary of the caudate lobe in association with the venous plexus. Although we have examined a very small number of samples, we predict that the main venous drainage of the PC will be toward the IVC or MHV, and there will be no thick hepatic venous branch, dividing the PC and segment 8 or 7 of the liver, as previously reported (*12,13*).

The drawback of the present study is that the findings are clearly obtained from only one hepatic cast. However, dissecting the other two casts, we also found the venous plexuses, but no longitudinal venous branches were found between the PC and segment 8. This may be attributed to the fact that quality of these casts was not sufficient for visualizing the venous plexuses. In future studies, we will further increase the number of casts examined for proper investigation.

In conclusion, bouquet-shaped venous plexuses were found at the right border of the caudate lobe and left border of the right liver. These venous plexuses will never appear on the current 3D-CT and can be found only in a study using liver casts.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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BRIEF REPORT
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Knowledge gaps in antimicrobial stewardship in a Japanese hospital: A cross-sectional study highlighting the need for role-specific education for nurses and administrative staff

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Abstract: Knowledge gaps pertaining to antimicrobial stewardship (AMS) among different hospital professions can hinder program effectiveness. This study aimed to identify and comparatively analyze AMS knowledge levels at a Japanese hospital. We conducted a cross-sectional, internet-based survey of all hospital employees (n = 2,703) to assess their knowledge of the antimicrobial stewardship team (AST) and programs (ASPs). The survey response rate was 48.4% (1,307 of 2,703). Significantly lower proportions of nurses and administrative staff than medical doctors and pharmacists knew about the AST and ASPs ($p < 0.001$). Critically, a significantly lower proportion of nurses (62.5%) than medical doctors (97.4%) ($p < 0.001$) was aware of the importance of sample collection for bacterial cultivation before antibiotic administration. These findings reveal significant role-specific knowledge gaps and strongly suggest that educational interventions targeting nurses and administrative staff are needed for promoting hospital-wide ASPs and ensuring their effective implementation.

Keywords: antimicrobial resistance, antimicrobial stewardship programs, antimicrobial stewardship team, questionnaire, awareness

1. Introduction

Antimicrobial resistance (AMR) is a significant global threat (*1*). To combat this, antimicrobial stewardship programs (ASPs) are crucial for ensuring the appropriate use of antimicrobials (*2*). In Japan, the establishment of multidisciplinary antimicrobial stewardship teams (ASTs) has been widely promoted since the 2018 Revision of Medical Fees (*3*).

The Infectious Diseases Society of America (Arlington, VA, USA) and the Society for Healthcare Epidemiology's (Arlington, VA, USA) guideline "Developing an Institutional Program to Enhance Antimicrobial Stewardship" states that antimicrobial stewardship (AMS) should be conducted in collaboration with various occupations (*2*). For instance, nurses are involved in many aspects of infectious disease care, from specimen collection to antimicrobial administration (*4*), while administrative staff, though not directly involved in treatment, generate essential data for program evaluation. Therefore, successful AMS implementation requires all hospital staff to understand their specific roles and the importance of stewardship.

However, previous studies have primarily focused on medical doctors and pharmacists, with limited reports focusing on nurses (*5*-*8*) and virtually none focusing on administrative staff. Therefore, this study aimed to investigate and compare knowledge levels regarding AMS, ASTs, and ASPs across these different professions. We hypothesized that knowledge levels would be significantly lower among nurses and administrative staff than among medical doctors and pharmacists and that a significant awareness gap would exist between doctors and nurses regarding the critical AMS practice of obtaining culture samples before antibiotic administration.

2. Materials and Methods

2.1. Study sample and data collection

A cross-sectional, internet-based survey was conducted at a university hospital in Tokyo, Japan. The AST at the

participating institution was established in 2018 and has since implemented multifaceted ASPs.

The AST's clinical support activities are primarily directed at medical doctors and include: *i*) prospective audit and feedback for patients on broad-spectrum antimicrobials; *ii*) infectious disease management support for patients with positive blood or cerebrospinal fluid cultures or patients with detected multidrug-resistant organisms; *iii*) regular multidisciplinary conferences with departments such as hematology, cardiovascular surgery, and emergency medicine; and *iv*) monitoring of renal function and dose adjustment support for antimicrobials requiring therapeutic drug monitoring. These ongoing activities are supplemented by educational outreach for all staff.

All 2,703 hospital employees were invited to participate between November 1 and December 31, 2023. Recruitment was conducted *via* internal announcements, and the questionnaire was administered using Microsoft Forms. Responses with identical timestamps and duplicate questionnaires from the same individual were excluded. This study was approved by the Ethics Committee of the Tokyo Medical University (approval number: T2023-0073) and conformed to the provisions of the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained electronically from all participants *via* the first page of the online survey.

2.2. Measurements

2.2.1. Knowledge of AST and ASPs

The participants were asked about their knowledge level of the AST and adherence to ASPs by the AST with regard to the following aspects: prospective audit and feedback on antibiotic use, feedback on antibiotic use to departments, feedback on sample collection for bacterial cultivation before antibiotic use, and support for sample collection. All five items were answered using a "yes or no" format. For medical doctors and nurses, an additional survey item was included regarding their awareness of sample collection before antimicrobial therapy. The participants responded using a four-point Likert scale: 1 = "strongly aware", 2 = "somewhat aware", 3 = "not very aware", 4 = "not at all aware", or 5 = "no antibiotic administration". In this study, participants who responded with "strongly aware" or "somewhat aware" were defined as being aware of the importance of sample collection for bacterial cultivation before administering antibiotics, whereas participants who responded with "not very aware" or "not at all aware" were defined as being unaware.

To ensure content validity, the draft questionnaire was reviewed by a panel of in-house experts, including an infectious disease specialist, a certified nurse in infection control, and a Board Certified Infection Control Pharmacy Specialist. The questionnaire was then finalized based on their feedback to improve the clarity and relevance of the items. The translated questionnaire is provided in the Supplemental Material (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=109*).

2.2.2. Other measurements

All participants reported their job categories (*i.e.*, medical doctor, nurse, pharmacist, administrative staff, or other); department (medical doctor: internal medicine, surgery, junior resident, or other; nurse: inpatient, outpatient, or other; pharmacist: central, inpatient, or other; administrative staff: involved in the medical billing department or other); and years of experience (*i.e.*, < 2 years, < 5 years, < 10 years, and > 10 years).

2.3. Statistical analysis

The proportion of "yes" responses to questions on the knowledge of the AST and ASPs was calculated for each occupation. Differences between medical occupations were compared using the chi-square test. If significant differences were observed, we conducted post-hoc tests with Bonferroni correction to examine the differences. The proportions of medical doctors and nurses who were aware of the importance of sample collection for bacterial cultivation before antibiotic administration were calculated. For this analysis, the participants who responded with "no administration of antibiotics" were excluded. The proportions were compared using the chi-square test. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29 (IBM Japan, Tokyo, Japan). Statistical significance was defined as a two-sided p-value of < 0.05.

3. Results and Discussion

In total, 2,703 individuals were invited to participate in the study, of whom 1,308 responded. The response rate was 48.4%. The proportions of respondents for each occupation were as follows: 21.3% (163/764) were medical doctors, 68.0% (777/1,143) were nurses, 77.3% (58/75) were pharmacists, 39.8% (128/322) were administrative staff, and 45.4% (181/399) were other. One medical doctor was excluded from the analysis because of duplication. Therefore, the final analysis set comprised 1,307 participants. Table 1 outlines the characteristics of the participants in the analysis set. Nurses constituted the largest proportion of the sample (59.4%). Of these, 71.4% worked in inpatient settings. Administrative staff accounted for 9.8% of the sample, followed by medical doctors (12.5%), pharmacists (4.5%), and others (13.8%).

This study revealed a significant knowledge gap regarding the AST and ASPs among different hospital

professions. This finding is consistent with previous international reports, such as a study from South Africa that also identified differing levels of knowledge among doctors, pharmacists, and nurses (*9*). As illustrated in Figure 1, significant differences were observed among professions in their knowledge of both the AST (Figure 1A) and ASPs (Figure 1B) (all $p < 0.001$). Post-hoc tests revealed that the knowledge levels of nurses and administrative staff were significantly lower than those of medical doctors and pharmacists (all $p < 0.001$). This study also assessed pharmacists, whose knowledge of AMS was found to be comparable to that of medical doctors. This may reflect the specific context in Japan, where, according to national policy, pharmacists are often positioned at the center of a given AST (*10*), which may have contributed to their higher level of AMS knowledge.

Additionally, this study investigated the knowledge levels of the administrative staff. The results showed that the administrative staff had low knowledge levels of AST. This finding, while perhaps unsurprising, likely reflects the structure of our institution's ASPs and may highlight a common dynamic in many institutions where educational interventions for administrative staff are less intensive than those targeted to clinical professionals. Nevertheless, the Infectious Diseases Society of America (Arlington, VA, USA) guidelines for AMS state that all hospital staff should receive education about AMS

Table 1. Participants' characteristics

	Total		Medical doctor		Nurse		Pharmacist		Administrative staff		Other	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Occupation	1,307	(100)	163	(12.5)	777	(59.4)	58	(4.4)	128	(9.8)	181	(13.8)
Department: Medical doctor												
Internal medicine			61	(37.4)								
Surgery			48	(29.4)								
Junior resident			27	(16.6)								
Other			27	(16.6)								
Department: Nurse												
Inpatient					555	(71.4)						
Outpatient					187	(24.1)						
Other					35	(4.5)						
Department: Pharmacist												
Central							25	(43.1)				
Inpatient							22	(37.9)				
Other							11	(19.0)				
Department: Administrative staff												
Medical billing department									42	(32.8)		
Other									86	(67.2)		
Experience												
Less than 2 years	227	(17.4)	27	(16.6)	137	(18.0)	4	(7.0)	27	(21.1)	32	(17.7)
Less than 5 years	442	(33.8)	16	(9.8)	356	(46.0)	6	(10.0)	27	(21.1)	37	(20.4)
Less than 10 years	215	(16.4)	30	(18.4)	128	(16.0)	14	(24.0)	18	(14.1)	25	(13.8)
More than 10 years	423	(32.4)	90	(55.2)	156	(20.0)	34	(59.0)	56	(43.8)	87	(48.1)

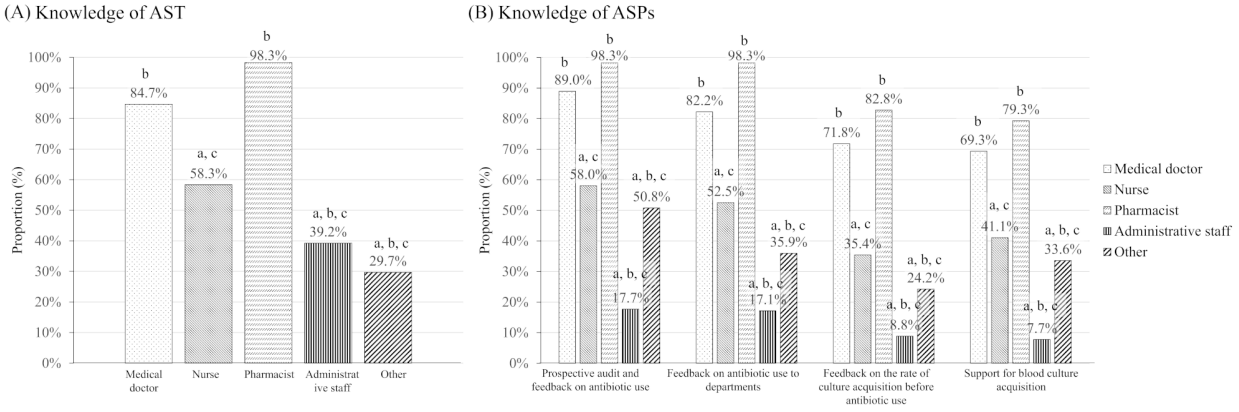

Figure 1. Proportions of respondents with knowledge of the antimicrobial stewardship team (AST) and antimicrobial stewardship programs (ASPs), based on occupation. (A) Knowledge of AST; **(B)** Knowledge of ASPs. [a]$p < 0.001$ versus medical doctors. [b]$p < 0.001$ versus nurses. [c]$p < 0.001$ versus pharmacists. AST: antimicrobial stewardship team; ASP: antimicrobial stewardship program.

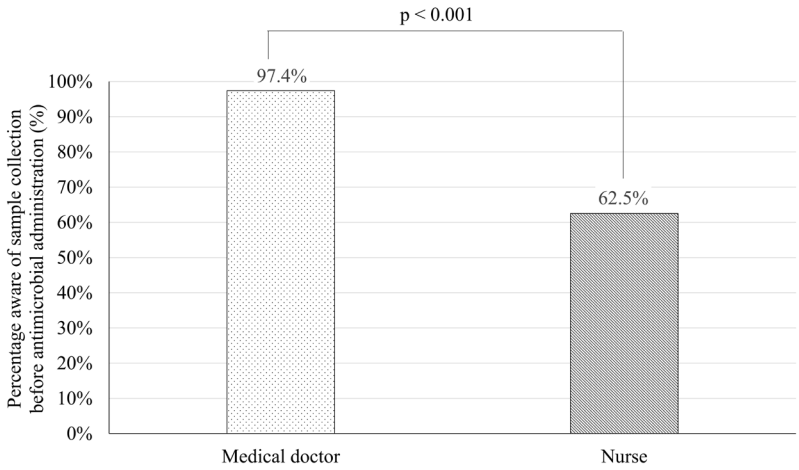

Figure 2. Proportions of medical doctors and nurses who were aware of sample collection for bacterial cultivation before antimicrobial administration.

(*11*). In Japan, administrative data are crucial for evaluating ASPs; for instance, Diagnosis Procedure Combination (DPC) data are widely used to assess antimicrobial consumption and the appropriateness of sample collection (*12*). The administrative department generates these essential data; therefore, the reliance on administrative data underscores why an understanding of AMS principles is important for ensuring data accuracy and, consequently, robust stewardship evaluation. The results of this study suggest that enhancing knowledge levels among administrative staff is important for supporting the accurate utilization of such data by ASTs in Japan, a consideration that may extend to any healthcare system reliant on administrative data for stewardship monitoring.

A critical finding of our study was the disparity in awareness regarding the collection of samples for bacterial cultivation before antibiotic administration. The proportion of nurses who were aware of this crucial practice was significantly lower than that of medical doctors (62.5% *vs.* 97.4%, respectively; $p < 0.001$) (Figure 2). A large-scale, multi-professional survey in South Africa reported a similar, albeit smaller, disparity in antimicrobial knowledge among medical doctors (68.71%), pharmacists (68.59%), and nurses (65.94%) (*12*). In stark contrast, the gap of over 30 percentage points observed between doctors and nurses in our study is particularly pronounced, highlighting the urgent need for targeted educational interventions for nurses at our institution. This knowledge gap is a significant concern because nurses are responsible for important tasks related to AMS, such as administering antibiotics and collecting samples for bacterial cultivation (*4*). Obtaining blood cultures after antibiotic administration significantly reduces the sensitivity of the results (*13,14*). Our results suggest that a lack of knowledge about AMS among nurses, which represents a potential gap between theoretical education and its application in clinical practice, may contribute to suboptimal practices of obtaining samples for bacterial cultivation. This gap is particularly concerning because previous studies (*5-8*) report that many nurses feel anxious about the lack of AMS education and desire further education on antibiotics, thereby highlighting the need for educational models that better integrate AMS principles into routine clinical workflows.

A strength of this study is its comprehensive inclusion of all hospital staff categories, particularly administrative staff, who are often overlooked in such surveys. However, our study has several important limitations. First, as this was a single-center study, the external validity of our results is limited. The observed knowledge gaps likely reflect the specific context of our institution's ASP, and hospitals with different operational models or educational strategies may yield different results. Therefore, caution is required when generalizing these findings. Second, although we adapted certain questionnaire items from previous studies (*8*) and assessed content validity through an expert review, the survey instrument did not undergo formal psychometric validation, which could have affected the precision of our measurements. Third, the low response rate could have introduced a selection bias, as staff with a greater interest in ASPs may have been more likely to participate, potentially leading to an overestimation of the overall knowledge level. Despite these limitations, to the best of our knowledge, this study is the first to examine AST knowledge among medical professionals and administrative staff in Japan. The results of this study provide useful information for future ASPs.

In conclusion, this study revealed significant role-specific knowledge gaps in AMS, particularly among nurses and administrative staff. These findings strongly suggest that educational interventions targeting these specific professions are essential for promoting hospital-wide ASPs and ensuring their effective implementation.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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CORRESPONDENCE

Discontinuation of biosimilar infliximab in Japanese patients with rheumatoid arthritis achieving sustained clinical remission or low disease activity during the IFX-SIRIUS STUDY I (the IFX-SIRIUS STUDY II): A clinical, ultrasound, and biomarker-based effectiveness after discontinuation and reinitiation of biosimilar infliximab

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Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting synovial joints. Biosimilar disease-modifying anti-rheumatic drugs offer cost-effective alternatives to originator biologics for RA treatment but remain expensive for long-term use. This prospective study investigated the clinical benefit of discontinuing CT-P13, a biosimilar of infliximab, in RA patients maintaining clinical remission or low disease activity. Five patients were enrolled from the IFX-SIRIUS STUDY I. CT-P13 was discontinued for 48 weeks, with evaluation using clinical indices, musculoskeletal ultrasound (MSUS), and serum biomarkers. Two patients experienced clinical relapse at weeks 5 and 36. The patient who relapsed at week 36 was re-administered CT-P13 and showed improved clinical outcomes without adverse events. Patients with non-clinical relapse showed no changes in disease activity scores or MSUS scores, with no notable alterations in serum cytokine levels. Over 50% of the patients maintained non-clinical relapse after CT-P13 discontinuation, and relapsed patients improved after re-administration without adverse events. This study was registered in the Japan Registry of Clinical Trials (*https://jrct.mhlw.go.jp*) on April 20, 2020, as jRCTs071200007.

Keywords: rheumatoid arthritis, biosimilar, infliximab CT-P13, musculoskeletal ultrasound, biomarker, drug discontinuation

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects the synovial joints (*1*). The uncontrolled disease activity of RA may lead to joint destruction and deformity, thus impairing patients' quality of life. Therefore, tight control of disease activity using a treat-to-target strategy is recommended to prevent joint destruction (*2*). Advancements in RA treatment, including the use of biological originator disease-modifying anti-rheumatic drugs (bDMARDs) and biosimilar DMARDs (bsDMARDs), have improved clinical outcomes, enabling the achievement of low disease activity or clinical remission in patients with RA.

We conducted the IFX-SIRIUS STUDY I (jRCTs071190030) to evaluate the efficacy and safety of switching from originator infliximab (IFX) to CT-P13, a biosimilar of originator IFX in patients with RA achieving clinical remission (*3*). The study showed that clinical relapse following the switch to CT-P13 was infrequent, with only two of 18 patients experiencing relapse within 24 weeks. Patients who completed the 24-week study period showed minimal alterations in musculoskeletal ultrasound (MSUS) scores, cytokine/

chemokine levels, and clinical indices. Switching from bDMARDs to bsDMARDs is expected to reduce patients' economic burden and improve medical insurance finances. However, continuing bsDMARDs remains costly. Notably, several reports have shown the clinical benefits of discontinuing bDMARD in patients with RA (*4-6*). Thus, we expected that patients with RA would be able to maintain good outcomes after discontinuing CT-P13. However, there is no evidence of an optimal approach for discontinuing bsDMARDs such as CT-P13.

Hence, in this study, we aimed to investigate the clinical benefit of discontinuing CT-P13 in patients with RA, maintaining clinical remission or low disease activity by treating with CT-P13 during the IFX-SIRIUS STUDY I. In addition, we aimed to evaluate the disease activity using clinical disease activity indices and MSUS to accurately assess inflammation at the joint level, continuing from the IFX-SIRIUS STUDY I and evaluate the effectiveness and safety of CT-P13 retreatment in patients with RA who experienced clinical relapse.

2. Study design

This prospective, open-label, interventional, single-arm clinical trial was conducted at 19 centers across Japan (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=105*). The study was registered in the Japan Registry of Clinical Trials as jRCTs071200007, and approved by the certified review board of Nagasaki University (CRB20-003). Written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki (*7*), the Clinical Trials Act (since February 2019), the Act on the Protection of Personal Information and related regulatory notifications, and this clinical study protocol. The study protocol has been previously published (*8*), where the detailed methodology is described. Accordingly, only the principal methods are outlined in this section.

2.1. Participants

The inclusion criteria were: *i*) treatment with CT-P13 and non-clinical relapse during IFX-SIRIUS STUDY I, and *ii*) ability to give written informed consent and comply with study requirements. Key exclusion criteria included: *i*) history of infusion reaction to CT-P13 requiring medication, and *ii*) glucocorticoid or conventional synthetic DMARD dose changes after IFX-SIRIUS STUDY I.

2.2. Intervention

The patients discontinued intravenous CT-P13 throughout the study period. In cases of clinical relapse, CT-P13 was re-administered at 3 mg/kg at 0, 2, and 6 weeks, followed by maintenance doses every 8 weeks. All patients continued the same doses of methotrexate and oral glucocorticoids received before CT-P13 discontinuation. Clinical relapse was defined as: *i*) ΔDisease Activity Score-28 (DAS28)-erythrocyte sedimentation rate (ESR) ≥ 1.2 or DAS28-ESR ≥ 3.2, and *ii*) increased DAS28-ESR due to RA disease activity rather than other factors.

2.3. Outcome measurements

The study visits were conducted at baseline and 12, 24, 36, and 48 weeks after CT-P13 discontinuation (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=105*). Clinical disease activity was evaluated using DAS28-ESR and DAS28-C reactive protein (CRP) values. Patient functional assessment was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI). MSUS imaging was performed at baseline, week 48, and clinical relapse using a multifrequency linear transducer (12–24 MHz). Joint synovitis was assessed at 22 joints using grayscale (GS) and power Doppler (PD) scores (0–3 scale). We also assessed GLOESS. X-ray images of bilateral hands and feet were evaluated using the van der Heijde-modified total Sharp score (vdH-mTSS) method. Serum concentrations of rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (ACPA), and matrix metalloproteinase-3 (MMP-3) were measured using standard assays. Multiplex cytokine/chemokine bead assays were performed using MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel to measure 41 cytokines and chemokines. Serum interleukin-6 and tumor necrosis factor-α levels were measured using specific ELISA kits.

2.4. Study endpoints

The primary endpoint was the proportion of patients experiencing clinical relapse between baseline and week 48. Secondary endpoints included changes in total PD and GS scores, GLOESS, DAS28 values, vdH-mTSS, HAQ-DI scores, and serum biomarker levels from baseline to various time points. Safety endpoint was the occurrence of adverse events.

2.5. Statistical analysis

The primary analysis was planned to estimate the 95% confidence interval of the proportion of patients with clinical relapse using Wilson's score interval (*9*). However, statistical estimations were excluded due to small sample size (five patients), and individual data points were presented instead. The graphs were created using GraphPad Prism (version 9.5.1; GraphPad Software, La Jolla, CA).

3. Patients' characteristics

In IFX-SIRUS STUDY I, 16 patients completed the study period without clinical relapse. In contrast, five patients were included in this study between April 20, 2020 and December 31, 2023. These five cases were enrolled from three participating institutions. Supplemental Table S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=105*) shows the baseline patient characteristics.

The patients (three females and two males) were 74, 73, 63, 51, and 49 years old. All patients tested positive for RF and ACPA. The dosage and interval of CT-P13 were 6 mg/kg every 8 weeks in 2 cases and 3 mg/kg every 8, 12, or 14 weeks in the other cases. The methotrexate dose at baseline was 6 mg/week in one case, 8 mg/week in three cases, and 10 mg/week in one case. One patient received prednisolone at a dose of 5 mg/day. No case involved the concomitant use of csDMARDs other than methotrexate. None of the patients had a history of treatment with bDMARDs, except for the originator IFX and CT-P13. One patient had a history of treatment with the JAK inhibitor, tofacitinib.

4. The endpoints

The primary endpoints showed that of the five patients in the study, two experienced clinical relapses by week 48. One patient (Case 4) relapsed at week 5, leading to discontinuation of the study, while another patient (Case 5) relapsed at week 36 and was subsequently re-administered CT-P13.

Table 1 presents the longitudinal clinical and laboratory data, including DAS28-ESR, DAS28-CRP, HAQ-DI, the total GS and PD scores, GLOESS, and vdH-mTSS during the study period. Figure 1 illustrates the actual values of DAS28-ESR for each participant. Patients who achieved non-clinical relapse showed no changes in DAS28 values and MSUS scores during the study period. In one case of relapse (Case 4, relapse at week 5), DAS28-ESR increased from 1.25 at baseline to 4.35 at relapse, and GLOESS increased from 3 at baseline to 8 at relapse. In the other case (Case 5, relapse at week 36), DAS28-ESR increased from 2.85 at week 24 to 4.14 at relapse and improved to 2.38 at week 48 after re-administering CT-P13. In addition, the HAQ-DI value improved from 0.5 at relapse to 0.125 at week 48 after the re-administration of CT-P13. However, Case 5 showed almost no change in MSUS score at relapse. In addition, no changes were observed in vdH-mTSS during the study period. Supplemental Table S3 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=106*) shows the levels of multiple cytokine arrays and ELISA during the study period. The results revealed that neither clinical relapse nor non-relapse cases exhibited notable alterations in any cytokine level. During the study period, no adverse events occurred in the safety analysis.

In this study, of the patients with RA who maintained clinical remission or low disease activity during IFX-SIRIUS STUDY I, we observed non-clinical relapses in three cases, while two patients experienced clinical relapse after discontinuing CT-P13. Of the two patients who experienced a relapse, the one who was re-administered CT-P13 had improved clinical disease activity indices and patient-reported outcomes, including DAS28-ESR, DAS28-CRP, and HAQ-DI values without any adverse events after re-administration of CT-P13.

The introduction of bDMARDs in clinical practice has dramatically improved the outcomes of patients with RA. However, the currently available bDMARDs are expensive, and this has led to restricted treatment access in patients with RA. Switching from originator infliximab to CT-P13 plays an important role in cost savings and health gains for patients with RA. However, the long-term continuation of CT-P13 remains costly.

Notably, several studies have demonstrated the clinical impact of discontinuing bDMARDs in patients with RA. In particular, the majority of these studies have focused on TNF inhibitors (*4,5,10-15*). The previous prospective studies have shown that among patients with RA with remission or low disease activity, the proportion of those who maintained non-clinical relapse 1 year after discontinuing TNF inhibitors varied widely, ranging from as low as 13% (*12*) to as high as 62% (*5*). In this study, although the number of cases was limited to five, over 50% (three cases) showed non-clinical relapse during the 52-week study period. In addition, among the two relapsed cases, one patient who was re-administered CT-P13 showed improvement in disease activity without adverse events, including infusion reactions.

The strength of this study was that it prospectively evaluated the therapeutic effectiveness of CT-P13 using clinical disease activity indices and standardized MSUS findings, which accurately and objectively evaluated disease activity at the joint level and the serum levels of multiple biomarkers, such as cytokines and chemokines.

Residual synovitis, such as the PD score detected using MSUS, is a risk factor for relapse in patients with RA who maintain clinical remission (*16*). In addition, some reports have suggested that a positive PD score in patients with RA with clinical remission is associated with an increased risk of relapse following discontinuation of bDMARDs (*17,18*). In this study, the total PD score at the time of CT-P13 discontinuation was zero in all cases, indicating that only the PD score might be insufficient to predict relapse. However, the PD score remained zero throughout the study period after CT-P13 discontinuation in non-clinical relapsed cases, indicating non-clinical relapse and the absence of synovitis progression, as evaluated by MSUS during the study period.

The association between serum cytokine levels

Table 1. Longitudinal clinical, laboratory data, the musculoskeletal ultrasound score and vdH-mTSS

Subject numbers	Visit	DAS28-ESR	DAS28-CRP	HAQ-DI	Patient global VAS	SJC (28 joints)	TJC (28 joints)	ESR (mm/H)	CRP (mg/dL)	Total GS score	Total PD score	GLOESS	vdH-mTSS
Case 1	Baseline	2.16	1.49	0.375	0	0	0	22	0.332	10	0	10	48.5
	Week 12	2.84	2.33	0.375	5	0	0	52	3.6				
	Week 24	2.48	1.93	0.25	1	0	0	34	1.34				
	Week 36	2.43	1.7	0.25	0	0	0	32	0.683				
	Week 48	2.64	1.89	0.375	8	0	0	37	0.878	9	0	9	49
Case 2	Baseline	0.77	0.98	0	0	0	0	3	0.005	0	0	0	12
	Week 12	1.25	0.99	0	0	0	0	6	0.008				
	Week 24	1.13	0.99	0	0	0	0	5	0.009				
	Week 36	0.97	0.99	0	0	0	0	4	0.009				
	Week 48	1.13	1	0	0	0	0	5	0.011	0	0	0	12
Case 3	Baseline	2.56	1.54	0.375	7	2	0	19	0.028	1	0	1	35
	Week 12	2.23	1.3	0.25	5	0	0	22	0.114				
	Week 24	2.22	1.09	0.375	0	0	0	24	0.042				
	Week 36	2.37	1.25	0.375	3	0	0	28	0.097				
	Week 48	2.44	1.33	0.125	0	1	0	22	0.027	1	0	1	35
Case 4	Baseline	1.25	1.34	0	0	0	0	6	0.19	3	0	3	11.5
	Week 5 (relapse)	4.35	3.84	0.25	20	3	5	28	0.988	7	2	8	N/A
Case 5	Baseline	1.68	1.25	0.25	10	0	0	9	0.05	0	0	0	82
	Week 12	1.85	1.27	0	0	0	0	14	0.135				
	Week 24	2.85	2.63	0.25	10	0	5	8	0.116				
	Week 36 (relapse)	4.14	3.62	0.5	20	3	8	13	0.14	1	0	1	N/A
	Week 48	2.38	1.8	0.125	10	0	1	11	0.046	0	0	0	82

CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; GLOESS, Global OMERACT-EULAR Synovitis Score; GS, gray scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; N/A, not available; PD, power Doppler; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale; vdH-mTSS, van der Heijde-modified total Sharp score

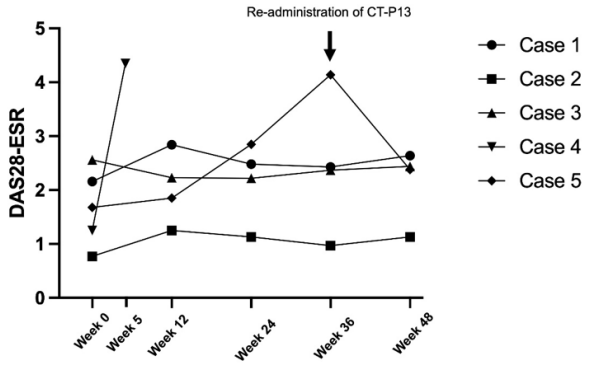

Figure 1. Longitudinal changes in the DAS28-ESR for each participant.

and relapse following discontinuation of bDMARDs in patients with RA has been investigated in several studies. One study demonstrated that certain serum cytokines, including IL-34, CCL1, IL-1β, IL-2, and IL-19, can predict relapse in patients with RA after discontinuation of bDMARDs (*19*). In addition, another study has revealed that a combination of 12 biomarkers, including VCAM-1, EGF, VEGF, and IL-6, may predict relapse after discontinuation of bDMARDs (*20*). In this study, no noticeable changes in serum cytokine levels were observed during the study period. Given the limited number of cases, further research is required to elucidate the relationship between relapse after CT-P13 discontinuation and serum cytokine levels.

This study had some limitations. First, the sample size was small; only five patients were evaluated. Thus, the planned analyses involving statistical estimation could not be evaluated. Second, we also aimed to identify the predictive factors for clinical relapse after discontinuing CT-P13. However, with only two relapse cases, it was not possible to explore predictive factors following the discontinuation of CT-P13. To overcome these limitations, it is essential to enroll and analyze a larger number of cases. However, this study provides a prospective evaluation of therapeutic change by incorporating clinical disease activity indices, MSUS, and multiple biomarkers. As a result, the findings offer substantial clinical value.

In conclusion, we revealed that over 50% of patients with RA who achieved clinical remission or low disease activity maintained non-clinical relapse after discontinuing CT-P13. In addition, one patient who experienced relapse showed improved disease activity without any adverse events after the re-administration of CT-P13. Future research should focus on investigating the long-term effects and predicting relapse after discontinuation of biosimilars using a larger sample size.

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Elevated risk of severe COVID-19 outcomes among underweight patients in Japan: A national registry-based study

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Abstract: We conducted a study to determine the impact of body mass index (BMI) (underweight, normal weight, and overweight) on the severity of COVID-19 across different periods of variant predominance using a large-scale data registry of hospitalized COVID-19 patients in Japan (COVIREGI-JP), involving 46,291 Japanese patients aged 20–89 years. Severity was classified based on the most intensive treatment received throughout the hospitalization. Multiple logistic models were used to assess the risk of severe disease, and adjusted odds ratios (ORs) for BMI < 18.5, 18.5–20, and ≥ 25 relative to BMI of 20.1–24.9 were calculated by sex and age group. The risk of severe COVID-19 and death was high among those with BMI < 18.5 [OR (95% CI): 1.88 (1.52–2.33), 1.59 (1.22–2.07)] as well as those with BMI ≥ 25 [1.38 (1.20–1.60), 1.87 (1.50–2.34)] for both men and women, respectively. The risk was extremely high among those with BMI < 18.5 when the Omicron variant was predominant [2.41 (1.66–3.49) for men, 2.96 (1.77–4.97) for women]. An important point to note is that being underweight as well as obesity increased the risk of severe COVID-19 and death. More attention should be paid to underweight individuals when predicting COVID-19 risk.

***Keywords*:** COVID-19, infectious disease, BMI, obesity, lean

1. Introduction

Numerous studies have examined possible associations between body mass index (BMI) and COVID-19 severity, hospitalization, and death. Most studies have reported obesity as a risk factor for all three (*1-9*). Because of the small number of people studied, the risk for each BMI category by sex and age has not been established. In Europe and the US, the number of thin people (BMI < 18.5) is quite low, so there have also been only limited studies on the severity of COVID-19 and death in underweight individuals (*10-12*). To the best of our knowledge, no studies have analyzed the severity of COVID-19 among underweight individuals by variant. In Japan, the prevalence of people with BMI < 18.5 is higher, and there is a tendency toward increased numbers of people in the lower normal weight range (18.5 ≤ BMI ≤ 20.0) among older adults ≥ 65 years of age (*13*).

Therefore, we conducted the present study to evaluate associations between being underweight and COVID-19 severity and death by sex and age, by SARS-CoV-2 variant (Omicron or not), and by the four categories of underweight, lower normal weight, normal weight, and overweight (including obesity).

2. Study design

2.1. Data source and ethical approval

This study was approved by the ethics review board (NCGM-S-004352-02) of the Japan Institute for Health Security (JIHS, formerly NCGM: National Center for Global Health and Medicine). Informed consent was

waived due to the retrospective nature of the study. This research was conducted in accordance with the Declaration of Helsinki.

This study used data from COVIREGI-JP, a large-scale registry of hospitalized COVID-19 patients in Japan, which contains data on patients' characteristics and clinical course during hospitalization (*e.g.,* admission and discharge dates, treatments and dates, and survival or death). Prior to beginning this work, we informed the registry on the JIHS' website (the primary investigator's affiliation), provided a webinar for journalists, a press release, *etc.*, and asked hospitals to participate in COVIREGI-JP and voluntarily register patients' information. A total of 531 hospitals was involved with this registry system. The details have been reported elsewhere (*14-16*).

The inclusion criteria for enrollment were: *i*) a positive SARS-CoV-2 test (*14*); and *ii*) inpatient treatment at a healthcare facility. If a patient had a history of multiple COVID-19 hospitalizations and met the aforementioned inclusion criteria, each admission was included separately in the registry. However, those data were excluded from the current analysis. This was because multiple hospitalization data for a particular patient could not be linked and therefore the most intensive treatment during hospitalization, which was the outcome criterion for the present study, could not be identified. The purpose here was to avoid the inclusion of duplicate data. Non-Japanese citizens were also excluded to minimize any potential effects of ethnicity.

2.2. Patients

There were 75,148 patients registered in the COVIREGI-JP who were hospitalized between January 26, 2020 and December 14, 2022 and who were discharged or dead by December 15, 2022. We defined the non-Omicron and Omicron variant–predominant periods (referred to as the non-Omicron and Omicron periods) as the periods before and after December 1, 2021, respectively. Patients were excluded from the analysis in the following order: non-Japanese citizens (n = 10,473), sex missing (n = 22), outside of the age range of 20-89 years (n = 8,080), transferred from another hospital (n = 5,615), transferred to another hospital (n = 4,891), still hospitalized (n = 1,470), treatment details missing (n = 383), and admission and/or discharge dates missing (n = 177). Finally, therefore, the analysis included 46,291 patients aged 20–89 years (26,467 men and 19,824 women).

2.3. Definition of disease grades

We graded the severity of COVID-19 based on the most intensive treatment received throughout the hospitalization, as shown in the header of Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*), as follows: grade 0 (no oxygen, *i.e.,* patients were never given supplemental oxygen); grade 1 (patients were given a nasal cannula or oxygen mask); grade 2 [patients were given high-flow oxygen or non-invasive positive pressure ventilation (NIPPV)]; grade 3 [invasive mechanical ventilation (IMV)]; grade 4 [extracorporeal membrane oxygenation (ECMO)]; and grade 5 (death during hospitalization regardless of treatment). We considered pooled grades 3, 4 and 5 as "severe" for these analyses, but grade 5 (death) was also analyzed separately.

2.4. Statistical analysis

The frequency distributions of COVID-19 grades and other categorical data are shown as percentages. Continuous variables were summarized as the mean and standard deviation (SD). The BMI categories of patients with severe grade 3/4/5 (IMV/ECMO/death) and separately grade 5 (death) were compared to those with grade 0 (no oxygen, reference group) using multiple logistic regression and expressed as the odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, date of admission, smoking, and comorbidities. There were too many types of comorbidities (25 diseases), so the comorbidities to adjust for were selected using a stepwise procedure with $p < 0.10$ for entry and removal. Grades 1 and 2 were excluded from the primary analysis in order to focus on the risk of severe grades (3 and above) by comparing them to grade 0. The inclusion of grade 2 could obscure the association between BMI and the severity of COVID-19, so the ORs for grade 2/3/4/5 were also calculated for sensitivity analyses, with grade 0 as the reference group. The entire observation period was divided into 2-month intervals and the date of admission was categorized by interval and coded as a dummy variable for statistical adjustment. The separated analysis was conducted by the Omicron period and the non-Omicron period. A two-sided p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. The key findings of this study

3.1. Characteristics of patients

The mean duration of hospitalization, including the day of admission, was 13.5 days (range: 1 to 762) for patients admitted to hospital because of a positive test for SARS-CoV-2.

The ages, smoking status, BMI, and prevalence of comorbidities in these COVID-19 patients are shown in Table 1. The mean age was 55.7 years for men and 57.2 years for women. The mean BMI was 24.9 kg/m^2 for men and 23.1 kg/m^2 for women. The frequency of the BMI categories — underweight, lower normal weight,

Table 1. Characteristics and comorbidities of the COVID-19 patients registered in Japan

Items	Men (*n* = 26,467)		Women (*n* = 19,824)	
	n	%	*n*	%
Age (20–89 years)				
Mean ± standard deviation	55.7 ± 18.4		57.2 ± 20.7	
Smoking history*				
Currently smoking (until shortly before the onset of symptoms)	5,963	22.5% (25.6%)	1,866	9.4% (11.1%)
Former smoking	8,403	31.7% (36.1%)	2,120	10.7% (12.6%)
Never smoking	8,887	33.6% (38.2%)	12,796	64.5% (76.2%)
Unknown	3,214	12.1%	3,042	15.3%
BMI (kg/m^2)*				
Mean ± standard deviation	24.9 ± 5.8		23.1 ± 4.7	
< 18.5 (underweight)	1,152	4.4% (5.0%)	2,087	10.5% (12.4%)
18.5–20.0 (lower normal weight)	1,426	5.4% (6.2%)	2,383	12.0% (14.1%)
20.1–24.9 (normal weight)	10,713	40.5% (46.7%)	7,781	39.3% (46.1%)
≥ 25 (overweight/obesity)	9,638	36.4% (42.0%)	4,625	23.3% (27.4%)
unknown	3,538	13.4%	2,948	14.9%
Comorbidities				
Myocardial infarction	676	2.6%	170	0.9%
Congestive heart failure	796	3.0%	515	2.6%
Peripheral vascular disease	521	2.0%	260	1.3%
Cerebrovascular disorders	1,820	6.9%	1,124	5.7%
Hemiplegia	245	1.2%	654	1.4%
Dementia	1,098	4.1%	1,703	8.6%
COPD	945	3.6%	167	0.8%
Chronic lung diseases other than COPD	496	1.9%	229	1.2%
Bronchial asthma	1,253	4.7%	1,449	7.3%
Mild liver disease	340	1.7%	1,239	2.7%
Moderate to severe liver dysfunction	61	0.3%	193	0.4%
Peptic ulcer	250	0.9%	141	0.7%
Hypertension	8,534	32.2%	5,559	28.0%
Hyperlipidemia	4,061	15.3%	2,942	14.8%
Mild diabetes	4,525	17.1%	2,209	11.1%
Severe diabetes	763	2.9%	256	1.3%
Diabetes mellitus (mild and severe)	5,288	20.0%	2,465	12.4%
Obesity	2,281	8.6%	1,044	5.3%
Moderate to severe renal dysfunction	701	2.6%	304	1.5%
Maintenance hemodialysis before hospitalization	377	1.4%	159	0.8%
Solid cancers	1,224	4.6%	717	3.6%
Leukemia	98	0.4%	74	0.4%
Lymphoma	224	0.8%	160	0.8%
Metastatic solid cancers	401	1.5%	200	1.0%
Connective tissue disease	237	0.9%	497	2.5%
HIV infection	105	0.4%	1	0.0%

*Percentage values in parentheses are for excluding the "unknown" category.

normal weight, overweight, and "unknown" — were 4.4%, 5.4%, 40.5%, 36.4%, and 13.4%, respectively for men and 10.5%, 12.0%, 39.3%, 23.3%, and 14.9% for women. Many patients had hypertension (32.2% of men and 28.0% of women), hyperlipidemia (15.3% of men and 14.8% of women), diabetes (20.0% of men and 12.4% of women), and obesity (8.6% of men and 5.3% of women) as comorbidities (Table 1).

3.2. Lower weight patients have an extremely high risk of death

The risks of grade 3/4/5 (IMV/ECMO/death) and grade 5 (death) were mostly higher in men than in women (except for the very small number of deaths in the 40-49-year-old group) and increased with age for both sexes (Figure 1, Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). The risks of grade 3/4/5 and grade 5 were higher in the elderly group than in the younger group.

ORs and 95% CIs by BMI (relative to BMI 20.1–24.9 kg/m^2) by grade, with grade 0 as the

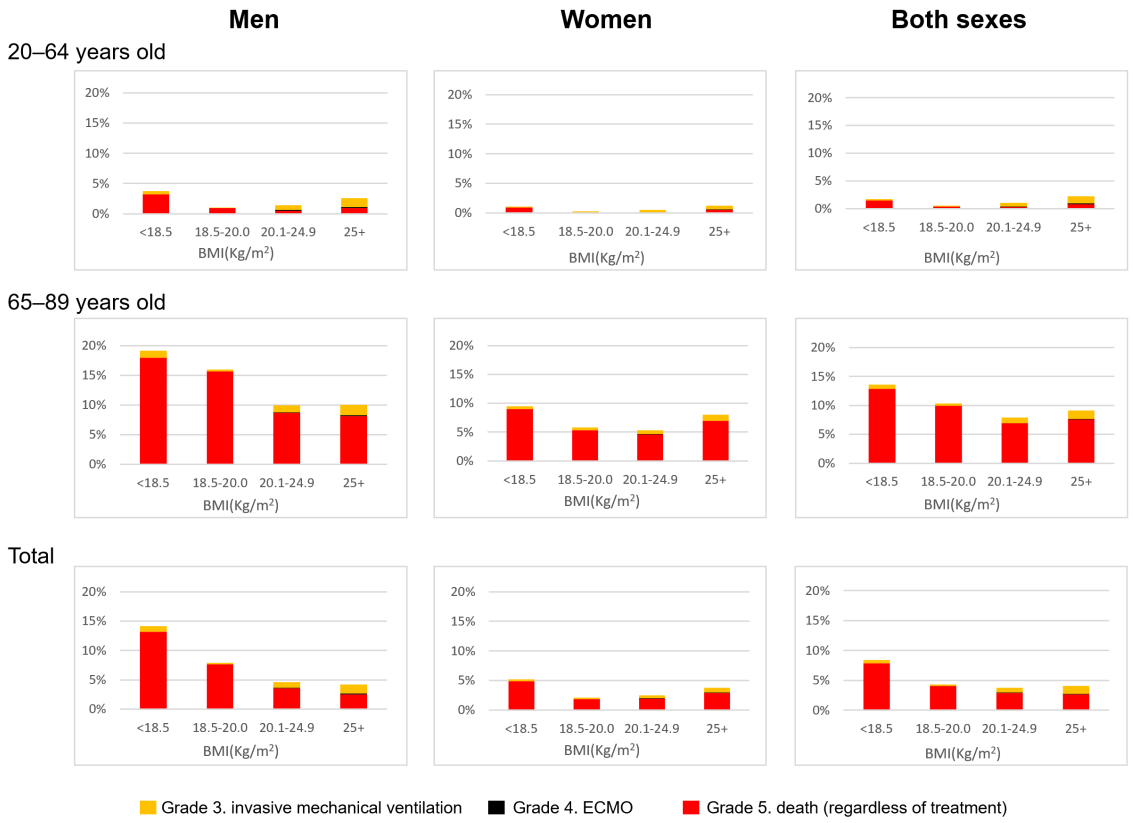

Figure 1. The frequency of each grade by sex and age groups among COVID-19 patients registered in Japan.

reference group, for the entire period are shown in Figure 2A and Supplemental Table S2-A (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). Patients with BMI < 18.5 and ≥ 25 had a significantly increased risk of grade 3/4/5 COVID-19 and death in all age groups. In the younger group (20–64 years), the risk of death increased particularly when the BMI was < 18.5 (OR 4.84 for men, 8.50 for women, and 5.75 for both). In older adults (65–89 years), BMI < 18.5 was associated with a significantly increased risk of grade 3/4/5 and death. For the risk of COVID-19 severity and death, the proportion of patients in the lower normal weight range (18.5 ≤ BMI ≤ 20.0) was significantly higher in men, and for those overweight (BMI ≥ 25) it was significantly higher in women.

3.3. The risk remained elevated even during the Omicron period, when general severity was declining

An analysis was conducted separately for the time when the Omicron variant was preponderant, and for the period when other variants were. The strength of the association between BMI and severity of and death from COVID-19 differed between these two periods. For the non-Omicron period, the trend differed slightly according to age (Figure 2B, 2C, and Supplemental Table S2-B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). Young people with BMI < 18.5 and ≥ 25 had an increased risk of grade 3/4/5 and death, whereas older men with BMI < 18.5 had an increased risk of grade 3/4/5 and death [OR (95% CI): 1.54 (1.15–2.06), 1.61 (1.19–2.18)], and older women with BMI ≥ 25 had a significantly increased risk [2.10 (1.60–2.76), 2.13 (1.58–2.85)].

In the period when Omicron was predominant, no younger women with 20.1 ≤ BMI ≤ 24.9 died (Figure 2B and 2C, and Supplemental Table S2-C, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*), but patients with BMI < 18.5 had a significantly increased risk of grade 3/4/5 and death among both sexes [OR (95% CI): 2.61 (1.94-3.51)]. However, there was no significantly increased risk of grade 3/4/5 and death for patients with BMI ≥ 25.

4. Discussion

This study examined body size and the risk of severe COVID-19 and death. To the best of our knowledge, this is the first study showing that the risk of COVID-19 severity grade 3/4/5 and death significantly increased in underweight individuals with a BMI < 18.5, and especially among younger people, regardless of the variant period.

A U-shaped association was observed between BMI and COVID-19 severity for whole period (Figure 2A and Supplemental Table S2-A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). Comparing the period dominated by the

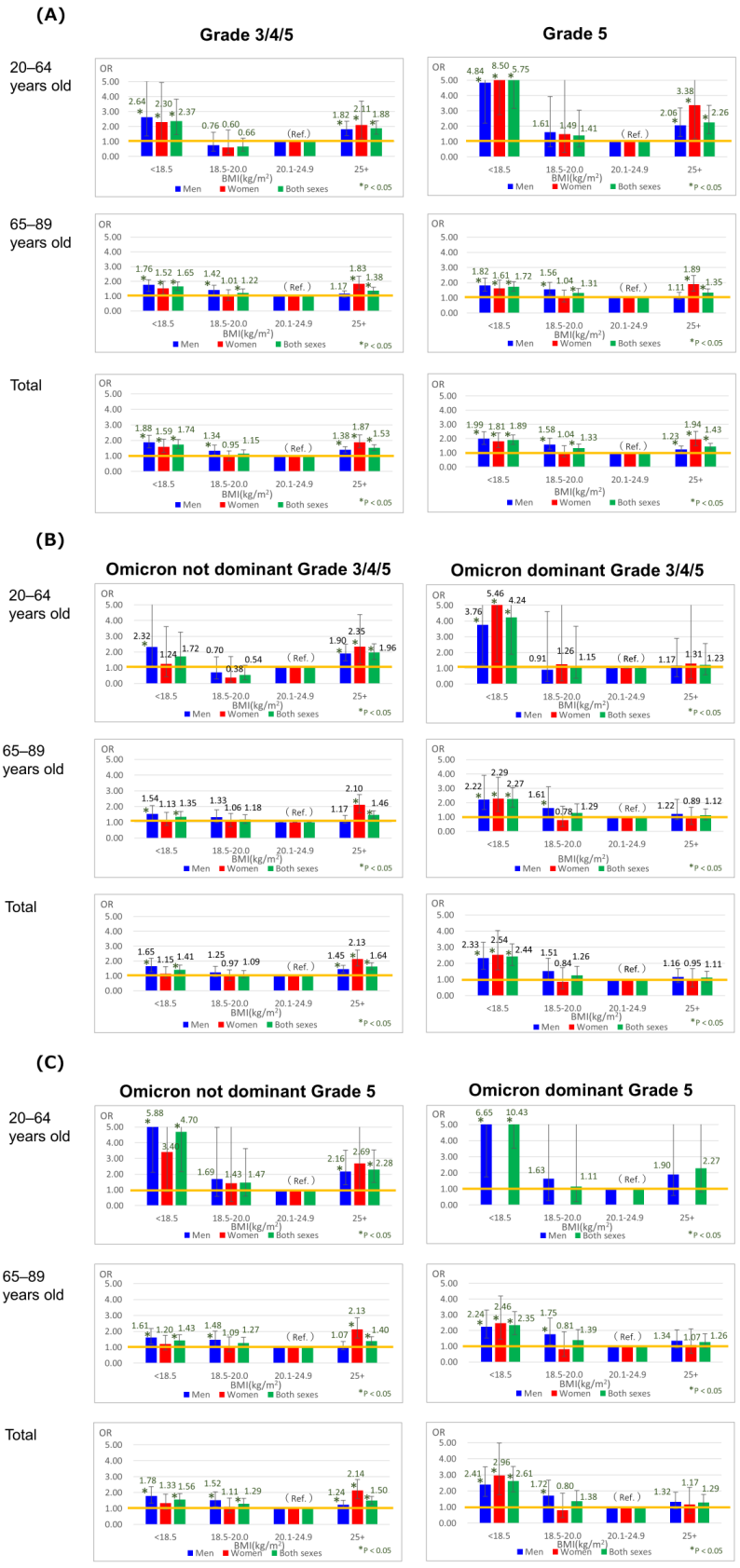

Figure 2. (A) Association between BMI and grades of COVID-19 severity; **(B)** Association between BMI and grades of COVID-19 severity by SARS-CoV-2 variant (Omicron or not); **(C)** Association between BMI and death of COVID-19 by SARS-CoV-2 variant (Omicron or not). Odds ratio (OR) and 95% confidence interval (CI) for each grade (using "Grade 0" as a reference) according to BMI by a multiple logistic regression model; 10-year dummy variables were used to adjust for age, and dummy variables for 2-month intervals were used to adjust for date of admission. ORs (95% CIs) in bold indicate statistical significance at $p < 0.05$. Comorbidities were selected by a stepwise procedure using $p < 0.10$ for entry and removal. None of the comorbidities was selected for adjustment.

Omicron variant with that of other prevalent variants revealed a slightly different trend. Notably, during the Omicron period, overweight individuals did not have a significantly increased risk of COVID-19 severity and death. In contrast, during the period when other variants were dominant, overweight individuals had a significantly higher risk of COVID-19 severity. This analysis was also performed separately for older and younger patients.

Although many studies have examined the relationship between BMI and COVID-19 severity and death, only a handful of studies have separately analyzed the impact of being underweight with BMI < 18.5 (*10-12*). However, no studies have analyzed COVID-19 severity and death among individuals with a BMI < 18.5 grouped by age and variant. Reasons for this may include the small number of people in the overall analysis and the fact that the number of people with BMI < 18.5 was too small for some ethnic groups to be analyzed (*13*). Moreover, no studies have examined whether different SARS-CoV-2 variants influenced the association between BMI and COVID-19 severity and death. Therefore, the present study determined the risk of severe disease and death in 49,291 subjects from a large national registry dataset, which was analyzed by age group (20–64 and 65–89 years) and BMI < 18.5. In addition, the effect of viral variant-specific differences on pathogenesis was also analyzed.

In the present study, underweight people had a significantly increased risk of death. The mechanism responsible for this is not clear, but it is thought to be influenced by a frail constitution. Another possibility is that the system that prioritized the elderly and obese resulted in differences in vaccination status, which prevented an increase in the risk of severe illness and death during the period when Omicron was predominant. However, there was no significant association between BMI status and vaccination coverage (data not shown).

The present study had several limitations. Patients with a history of two or more COVID-19 hospitalizations were excluded because the most intensive treatment was not identifiable, and duplicate data needed to be avoided. That said, a strength of this study is that we were able to perform a variant-specific analysis of COVID-19 and evaluate the risk of severe illness and death for patients with a BMI < 18.5, and especially for lower normal weight individuals with BMI of 18.5–20.0 among the elderly. Since the analysis was performed on hospitalized patients, the status of care was known, and the analysis could be performed using worst-case data during hospitalization.

It is important to note the tendency toward underweight and lower normal weight in the elderly as well as obesity. We found that the strength of the association between body size and COVID-19 differed between the period when the Omicron variant predominated and the period when other variants were dominant. We suggest that more attention should be given to underweight individuals and those with lower normal weight in predicting the risk of COVID-19 severity and mortality. Prevention and treatment of COVID-19 has been a priority for overweight and elderly people. Underweight people should also be prioritized regardless of age in the future.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Comments			
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2. Main manuscript
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4. Acknowledgments
5. References
6. Tables
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