Research Article

Digestive Surgery

Dig Surg 2020;37:275–281
DOI: 10.1159/000503100

Received: April 19, 2019
Accepted: August 29, 2019
Published online: November 13, 2019

A Preoperative Scoring System to Predict Carcinoma in Patients with Gallbladder Polyps

Shinji Onda[a] Yasuro Futagawa[b] Takeshi Gocho[a] Hiroaki Shiba[a]
Yuichi Ishida[a] Tomoyoshi Okamoto[b] Katsuhiko Yanaga[a]

[a]Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan; [b]Department of Surgery, The Jikei University Daisan Hospital, Tokyo, Japan

Keywords
Gallbladder polyps · Gallbladder carcinoma · Preoperative diagnosis · Laparoscopic cholecystectomy

Abstract
Introduction: A preoperative scoring system to predict carcinoma in patients with gallbladder polyps (GBPs). ***Methods:*** Preoperative parameters of patients with GBPs who underwent cholecystectomies were used to construct a scoring system to ascertain the risk of malignancy (reference group). The scoring system developed from this approach was applied to the validation group. ***Results:*** In the reference group, 11.5% of patients had carcinomas, in whom the median age was 68 years and the polyp size was 16.9 mm. According to the univariate analysis, the significant factors for carcinoma were age ≥65 years, the presence of gallstones, polyp size ≥13 mm, solitary polyp, and sessile polyp. Age ≥65 years and polyp size ≥13 mm were significant factors according to the multivariate analysis. From these results, we developed a preoperative scoring system to predict carcinoma. The patients were divided into 1 of 2 groups: low-risk and high-risk and their malignancy rates were 4.1 and 61.1% respectively ($p < 0.001$). In the validation group, the malignancy rate was higher for those in the high-risk group ($p = 0.016$). ***Conclusions:*** The proposed preoperative scoring system based on simple clinical variables appears to be useful for predicting malignancy in patients with GBPs.

Introduction

The prevalence of gallbladder polyps (GBPs) is approximately 5% in the adult population [1–3]. Patients with GBPs are typically asymptomatic; however, the detection of GBPs has been increasing due to the increased usage of abdominal imaging. The differential diagnosis of GBPs is difficult, particularly in terms of discerning whether the polyp is benign or malignant, using imaging modalities such as ultrasonography, computed tomography (CT), magnetic resonance imaging, and endoscopic ultrasonography (EUS). The biological nature of GBPs is difficult to define before surgery, and the lack of randomized controlled trials make the surgeon's decision to perform surgery a challenge. Thus, there has not yet been a universally accepted consensus regarding an indication for surgery. Previous studies have reported that the clinical factors that predict malignant GBPs include size, number, polyp shape, and patient age [4–11]. Clinical practice

karger@karger.com
www.karger.com/dsu

Shinji Onda
Department of Surgery
The Jikei University School of Medicine
3-25-8, Nishishimbashi, Minato-ku, Tokyo 105-8461 (Japan)
E-Mail s-onda@jikei.ac.jp

guidelines in Japan for the management of biliary tract cancers comprising sessile GBPs with a diameter equal to or greater than 10 mm with rapid growth indicate cholecystectomy for prophylactic treatment; and for patients with a high likelihood of gallbladder cancer, open cholecystectomy (OC) is recommended [12]. However, the incidence of carcinoma is not high in the patients who undergo cholecystectomy according to the guidelines; thus, the patients with GBPs at low-risk for malignancy can safely undergo laparoscopic cholecystectomy (LC). It is, therefore, necessary to develop a scoring system that can accurately predict the possibility of malignancy among patients with GBPs who undergo cholecystectomy.

This study was designed to assess the predictive values of clinical features and ultrasound findings in making differential diagnoses of polypoid lesions of the gallbladder and to construct a scoring system to predict carcinoma.

Materials and Methods

Patients and Methods

We retrospectively analyzed consecutive patients who were preoperatively diagnosed with GBPs and who underwent cholecystectomies at the Jikei University Hospital from May 2009 to November 2014 (reference group). The study protocol was approved by the Ethics Committee of the Jikei University School of Medicine (27-177[8062]). Our surgical indications for GBPs were based primarily on the 2007 guidelines for the management of biliary tract cancers, as follows: polyp with a size larger than 10 mm; polyp with a rapid increase of size; and sessile polyp. In addition to the guidelines, the presence of a color signal in the polyp as determined by Doppler ultrasound was also included. Clinical and laboratory parameters were collected from each patient retrospectively from their medical records, including age, sex, body mass index, and the presence of diabetes mellitus, hypertension, and dyslipidemia.

Preoperative abdominal ultrasonography was performed for all patients to evaluate the size of the polyps, the complications from gallstones, and the texture of the liver, as well as the presence of a color signal in the polyp by Doppler ultrasonography. EUS was performed to analyze the following findings: polyp size, echo level, internal echo pattern, number and shape of polyps, and surface pattern. In patients with multiple polyps, the size of the largest polyp was measured.

In patients who underwent both ultrasonography and EUS, the size of the polyp was obtained from the ultrasonography. The number of polyps was categorized as either *solitary* or *multiple*, and the shape of the polyp was classified as *pedunculated* or *sessile*. Size increase of polyp was defined as diameter increase ≥2 mm by ultrasonography for at least 3 months of follow-up. Contrast-enhanced CT was performed to evaluate the tumor enhancement, and magnetic resonance imaging or drip infusion cholangiography CT was performed for preoperative evaluation of the biliary anatomy.

All patients were informed about the guidelines, which recommend OC for polypoid lesions highly suspicious for malignancy of the gallbladder, and of the possible risks of laparoscopic surgery. LC or OC was performed after informing all the patients about risks associated with laparoscopy and written informed consent was obtained from each patient. These surgeries were carefully performed to prevent perforation of the gallbladder. Intraoperative perforation of the gallbladder was confirmed by surgical notes or videos, and the incidence of gallbladder perforation and its outcome was evaluated. The pathological diagnosis was classified as carcinoma, adenoma, cholesterol polyp, hyperplastic polyp, fibrous polyp, or cholesterolosis. Patients diagnosed with early-stage carcinoma, defined as T1 or less, without lymph node metastasis were followed up by clinical examination, tumor markers, and imaging studies, whereas those patients with pathologically proven advanced carcinoma underwent additional curative surgery and chemotherapy.

The preoperative clinical data and EUS findings were compared between patients with gallbladder carcinoma and those with benign polyps.

Validation

According to the results of the univariate and multivariate analyses from the reference group, we developed a preoperative scoring system to predict carcinoma in patients with GBPs. We constructed a scoring system that the significant parameters from univariate analysis were assigned 1 point and the significant parameters from multivariate analysis were weighted assigned 2 points to each. The total scores were calculated by the sum of the assigned points. The patients were categorized into one of the following 2 risk groups according to their risk scores: low-risk and high-risk. The cut-off value was determined from the receiver operating characteristic (ROC) curve. The malignancy rates of the low-risk and high-risk groups were compared.

The established scoring system was then applied to another cohort composed of 72 patients with GBPs who underwent cholecystectomies from 2 hospitals of the Jikei University School of Medicine: 41 consecutive patients from the Jikei University Hospital from December 2014 to October 2017, and 31 consecutive patients from the Jikei University Daisan Hospital from January 2014 to October 2017.

Statistical Analysis

The continuous variables are presented as the mean ± SD or as medians with ranges, and the categorical variables are summarized as frequencies and percentages. The univariate analysis was performed using Fisher's exact test or Welch's *t* test, as appropriate. A multivariate analysis was performed to identify significant predictive variables. An ROC curve analysis was performed for the correlation analysis. The results were considered statistically significant when p values were <0.05. The statistical analyses were performed using SPSS version 20 (IBM Co., Armonk, NY, USA).

Results

Patients' Clinical and Imaging Characteristics

We performed 141 cholecystectomies for patients who were preoperatively diagnosed with GBPs at the Jikei University Hospital from May 2009 to November 2014. Two patients were excluded from this study because of incomplete data and the remaining 139 patients were included in this study (reference group). Patients included in this study

Table 1. Comparison of the demographic, laboratory, and imaging findings between benign polyp group and malignant polyp group

	Malignant (n = 16)	Benign (n = 123)	p value
Age, years, median (range)	68 (35–88)	50 (16–81)	0.003
Age ≥65 years, n (%)	9 (56.3)	16 (13.0)	<0.001
Gender, male, n (%)	9 (56.3)	75 (61.0)	0.789
BMI, kg/m^2, mean ± SD	24.5±2.80	23.2±3.80	0.114
Hypertension, n (%)	7 (43.8)	31 (25.2)	0.139
Diabetes mellitus, n (%)	3 (18.8)	9 (7.3)	0.144
Total cholesterol, mg/dL, mean ± SD	198±34.5	208±36.1	0.303
LDL-cholesterol, mg/dL, mean ± SD	109±28.3	122±31.3	0.176
Triglyceride, mg/dL, mean ± SD	191±170	137±87.0	0.228
Cholinesterase, IU/L, mean ± SD	363±82.8	342±78.8	0.353
Gallstones, n (%)	7 (43.8)	23 (18.7)	0.046
Fatty liver, n (%)			
Yes	7 (43.8)	40 (32.5)	0.393
No	8 (50.0)	78 (63.4)	
Unevaluated	1 (6.3)	5 (4.1)	
Polyp size, mm, mean ± SD	16.9±7.47	10.4±4.23	0.004
Polyp size, mm, n (%)			
1–9	2 (12.5)	37 (30.1)	0.235
10–14	6 (37.5)	78 (63.4)	0.059
≥15	8 (50.0)	8 (6.5)	<0.001
Size increase of polyp, n (%)	4/5 (80.0)	76/78 (97.4)	0.172
US Doppler positive, n (%)			
Yes	6 (37.5)	48 (39.0)	1.000
No	8 (50.0)	60 (48.8)	
Unevaluated	2 (12.5)	15 (12.2)	
CT enhancement, n (%)			
Yes	8 (50.0)	45 (36.6)	1.000
No	0	5 (4.1)	
Unevaluated	8 (50.0)	73 (59.3)	
Solitary polyp, n (%)	9 (56.3)	31 (25.2)	0.017
Sessile polyp, n (%)	6 (37.5)	17 (13.8)	0.028

BMI, body mass index; LDL, low-density lipoprotein; CT, computed tomography.

were aged 16–88 years (median 51 years), 55 of whom were women. In the reference group, the pathological diagnosis consisted of carcinoma in 16 (11.5%; T1-stage was in 11 and T2-stage was in 5 patients), adenoma in 11 (7.9%), cholesterol polyp in 91 (65.5%), hyperplastic polyp in 12 (8.6%), cholesterolosis in 2 (1.4%), and fibrous polyp in 1 (0.7%). Three patients had both a cholesterol polyp and a hyperplastic polyp (2.2%). Another 3 patients had mucosa hyperplasia, fatty tissue, and benign unclassified mucosal polyp. The mean polyp size was 11.2 ± 4.25 mm.

LC was performed for 130 patients (94%), one of whom was converted to open procedure due to severe adhesion. Primary OC was performed on 9 patients (6%).

The comparisons of clinical and laboratory features between the carcinoma group and the benign group are shown in Table 1; the comparison of the EUS findings is shown in Table 2. In the univariate analysis, significant predictive clinical and imaging variables for malignant

Table 2. Comparison of EUS findings between benign group and malignant group

	Benign (n = 31)	Malignant (n = 6)	p value
Polyp size, mm, mean ± SD	9.9±2.87	17.7±7.06	0.043
Echo level, n (%)			
Hyperechoic	16 (51.6)	2 (33.3)	0.660
Hypo or isoechoic	15 (48.4)	4 (66.7)	
Internal echo pattern, n (%)			
Homogeneous	23 (74.2)	4 (66.7)	0.653
Heterogeneous	8 (25.8)	2 (33.3)	
Surface, n (%)			
Smooth	5 (16.1)	1 (16.7)	1.000
Lobulated	26 (83.9)	5 (83.3)	

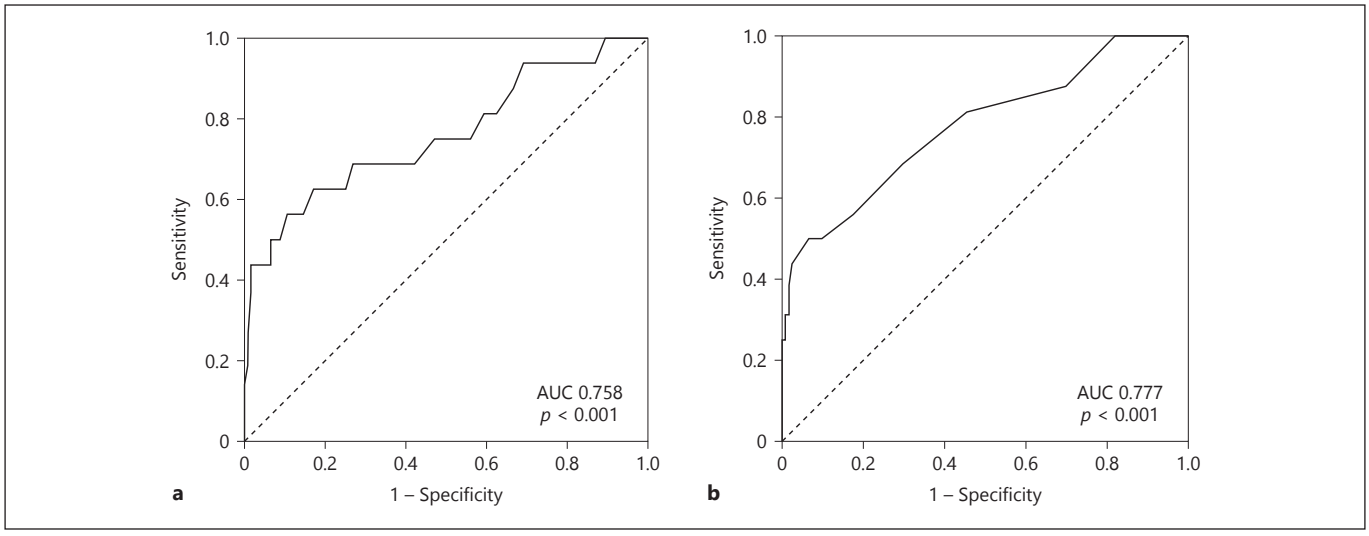

Fig. 1. ROC analysis for predicting gallbladder carcinoma. **a** Age; (**b**) polyp size. AUC, area under the ROC curve.

Table 3. Results of the multivariate analysis for the factors that were significantly associated with carcinoma of the gallbladder on univariate analysis

	OR	95% CI	*p* value
Carcinoma			
Age ≥65 years	5.98	1.73–20.7	0.005
Polyp size ≥13 mm	4.21	1.14–15.6	0.032
Solitary polyp	1.99	0.54–7.26	0.300
Gallstones	3.22	0.89–11.6	0.075
Sessile polyp	2.90	0.75–11.3	0.124

polyps consisted of age (median 68 vs. 50 years; $p = 0.003$), age older than 65 years ($p < 0.001$), the presence of gallstones ($p = 0.046$), polyp size by ultrasonography (mean 16.9 ± 7.47 vs. 10.4 ± 4.23 mm; $p = 0.004$), solitary polyp ($p = 0.017$), and sessile polyp ($p = 0.028$; Table 1). ROC curve analysis identified the following cut-off values as significant predictors of malignancy: 65 years of age (sensitivity = 56%; specificity = 87%; area under the ROC curve [AUC] 0.758; $p < 0.001$); 13 mm for polyp diameter (sensitivity = 56%; specificity = 82%; AUC 0.777; $p < 0.001$; Fig. 1). In the multivariate analysis, significant predictive variables for malignant polyps were age older than 65 years ($p = 0.005$) and polyp size over 13 mm ($p = 0.032$, Table 3).

Preoperative Predictive Scoring System

According to the results of the univariate and multivariate analyses, we developed a preoperative scoring system to predict the presence of gallbladder cancer in patients with GBPs. The total scores could easily be calculated by the sum of the following 5 variables: total score = (age older than 65 years: 2) + (polyp size over 13 mm: 2) + (presence of gallstones: 1) + (solitary polyp: 1) + (sessile polyp: 1). Thus, the theoretical minimum and maximum total scores were 0 and 7 respectively. The patients were categorized into one of the following 2 risk groups according to their risk scores: low-risk (score 0–3; $n = 121$) and high-risk (score 4–7; $n = 18$). According to the ROC curve analysis, we defined the optimal cut-off value of the total score 4 (sensitivity = 69%; specificity = 94%; AUC 0.777; $p < 0.001$; Fig. 2). The malignancy rates of the low-risk and high-risk groups were 4.1 and 61.1%, respectively, and were statistically significant ($p < 0.001$, Table 4).

Application of the Scoring System to the Validation Group

Of the 72 patients in the validation group, 6 had carcinoma (8.3%). According to the reference study, of these 72 patients, 64 had been classified as low risk (score 0–3) and 8 had been classified as high risk (score 4–7). The malignancy rates of the low-risk and high-risk groups were 4.7 and 37.5%, respectively, and were statistically significant ($p = 0.016$, Table 4).

Intraoperative Perforation of the Gallbladder

In the reference group, an intraoperative perforation of the gallbladder was observed in 14 of 130 (11%) LC patients, including 11 of 119 (9%) with benign polyps and 3 of 11 (27%) with malignant polyps, compared with 1 of 9

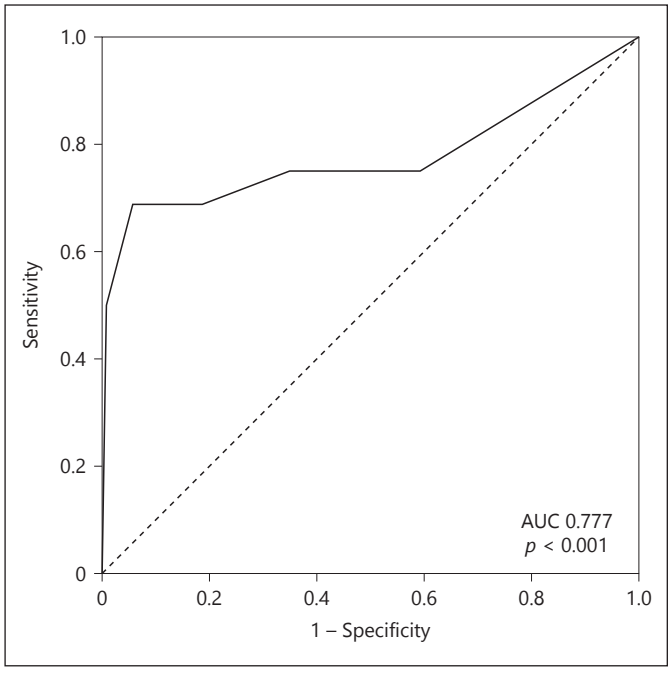

Fig. 2. ROC analysis for the risk scores for predicting gallbladder carcinoma. AUC, area under the ROC curve.

Table 4. Comparison between the 2 risk groups of the incidence and relative risk of carcinoma

Risk score	Reference group		Validation group	
	number of patients	carcinoma, *n* (%)	number of patients	carcinoma, *n* (%)
Low risk (0–3)	121	5 (4.1)	64	3 (4.7)
0	54	4	25	1
1	30	0	14	0
2	21	1	16	2
3	16	0	9	0
High risk (4–7)	18	11 (61.1)	8	3 (37.5)
4	9	3	6	1
5	5	4	1	1
6	4	4	1	1
7	0	0	0	0

Total risk score = (over 65 years old = 2) + (polyp size over 13 mm = 2) + (presence of gallstone = 1) + (solitary polyp = 1) + (sessile polyp = 1).

(11%) OC patients consisting of 1 of 4 (25%) with benign polyps and none of the 5 with malignant polyps. One of the 3 patients with malignant lesions who had undergone LC developed peritoneal recurrence after 15 months, despite vigorous intraoperative saline and water irrigation. The intraoperative gallbladder perforation rate was not significantly different between the LC and OC patients ($p = 1.000$).

Discussion

We have shown that older age, the presence of gallstones, large polyp size, solitary polyp, and sessile polyp were significant predictive factors for gallbladder carcinoma, and we developed a scoring system based on these 5 parameters. This scoring system is novel and simple to understand and easy to preoperatively calculate for clinical practice and can help determine the strategy for treating GBPs, including operative approaches. For low-risk patients, LC might be selected, and for high-risk patients, OC or radical cholecystectomy should be considered. Furthermore, unnecessary examinations for low-risk patients, such as EUS and enhanced CT, could be reduced.

In the current study, age ≥65 years and polyp size larger than 13 mm were the significant predictive variables for malignancy according to the multivariate analysis; however, many other studies have reported several predictive values for gallbladder malignancy, such as older age, large size, solitary lesion, sessile lesion, and presence of gallstones [4–11].

Many studies have found that older age is a significant predictive factor that increases the likelihood of malignancy [4, 5, 9, 11], particularly an age older than 50–65 years. In a systematic review, specific data examining polyp size and malignancy were found in 20 studies, in which malignant GBPs ≥1 cm, <1 cm, and <5 mm constituted 8.5, 1.2, and 0% of GBPs, respectively [13]. The majority of studies advocated that GBP size larger than 10 mm might be the most reliable predictor of malignant neoplasm [4, 5, 10]. Results of the current study revealed a larger size criterion than the previously advocated 10 mm because most polyp sizes in this study were larger than 10 mm. On the other hand, another study reported an incidence of adenomas/carcinomas in polyp sizes <5 mm [14]; thus, smaller polyps do not rule out the possibility of carcinoma.

We believe that it is not enough to predict the risk of malignancy with just the 2 parameters of patient age and polyp size. Therefore, we constructed a scoring system that included all 5 parameters based on the results of the univariate analysis. In addition, because older age and larger polyp size are the most powerful predictors for malignancy, age older than 65 years and polyp size larger than 13 mm were weighted double in the scoring system by assigning 2 points to each. Our study showed that the sensitivity and specificity of the scoring system were higher than that of

the polyp size. The proposed scoring system provides useful information to predict gallbladder cancer risk, and similar results were obtained in the validation study.

It is not always necessary to differentiate adenoma from adenocarcinoma preoperatively because adenomas have been shown to have malignant potential and both of these lesions should be resected. The theory of an adenoma-carcinoma sequence of gallbladder cancer has been supported by a histological observation [15], in which 1,605 cholecystectomy specimens were reviewed, of which, 18 adenomas and 79 adenocarcinomas were found with evidence of transformation from adenoma to invasive cancer that was histologically traceable. On the other hand, other authors believe that gallbladder carcinoma arises in situ from flat and dysplastic epithelium and that the actual risk of adenoma progressing to carcinoma is uncertain [16].

In several studies, improved accuracy of EUS for differentiating between GBPs has been reported, and a scoring system based on the EUS cancer screening has been reported to be useful for differentiating between neoplastic and non-neoplastic GBPs [17–19]. In the current study, however, EUS was not routinely performed and its findings were not significant predictive factors for malignancy, perhaps due to the relatively small sample size. We do not believe that routine use of EUS is financially practical, and it can be skipped for patients at low-risk for malignancy.

Early gallbladder carcinoma can be safely treated with cholecystectomy alone, but when an LC is planned, the surgical procedure should be carefully performed to prevent gallbladder perforation. Spillage of bile into the peritoneal cavity can lead to peritoneal dissemination or port-site metastasis [20]. In our study, LC was performed in 94% of patients with GBPs, even though the guidelines stated that OC was recommended for patients at high risk of malignancy. We believed that because there was insufficient available evidence of risk factors for malignancy in GBPs patients. Consequently, in our study, the intraoperative perforation rate of the gallbladder was not significantly different between the patients undergoing LC and OC. According to our results, LC can be safely performed in patients with GBPs except for lesions that are highly suspicious for malignancy. In patients with high risk score, OC is recommended to avoid possible recurrence.

This study has some limitations, including its retrospective design and the small number of enrolled patients. The patients enrolled were those who underwent cholecystectomy due to the possibility of malignancy; thus, many patients thought to have benign polyps who did not undergo surgery were excluded from this study. This selection bias could have had an effect on the scoring system.

Conclusion

The proposed preoperative scoring system based on simple clinical variables appears to be useful for predicting malignancy in patients with GBPs.

Acknowledgment

The authors would like to thank Enago (www.enago.com) for the English language review.

Statement of Ethics

The study protocol was approved by the Ethics Committee of the Jikei University School of Medicine (27-177[8062]), and the written informed consent was obtained from each patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding source to declare.

Author Contributions

S.O.: conception and design of the study, analysis and interpretation of data, collection and assembly of data, drafting of the article. Y.F.: collection of data and revision of the article. T.G., H.S., Y.I., and T.O.: collection of data. K.Y.: collection of data, critical revision of the article.

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