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ORIGINAL ARTICLE

Surgical Resection and Prognostic Analysis of 142 Cases of Hilar Cholangiocarcinoma

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Abstract Surgical resection for hilar cholangiocarcinoma is the only curative option, but low resectability rate and poor survival outcomes remain a challenge. This study was to assess the surgical resection for hilar cholangiocarcinoma and analyze the prognostic factors influencing postoperative survival. One hundred forty-two patients with hilar cholangiocarcinoma who underwent surgical resection between January 2006 and December 2014 were analyzed retrospectively based on clinicopathological and demographic data. Univariate and multivariate analysis against outcome were employed to identify potential factors affecting prognosis. Ninety-five patients were performed with R0 resection with median survival time of 22 months; whereas, 47 patients underwent non-R0 resection (R1 = 20, R2 = 27) with that of 10 months. Of these 95 patients, 19 underwent concomitant with vascular resection and reconstruction and 2 patients underwent pancreaticoduodenectomy. 64.8% patients (n = 92) underwent combined with hepatectomy. The one-year, three-year, and five-year survival rates after R0 resection were 76.3, 27.8, 11.3%, respectively, which was significantly better than that after non-curative resection (P = 0.000). Multivariate analysis revealed that non-curative resection (RR: 2.414, 95% CI 1.586–3.676, P = 0.000), pathological differentiation (P = 0.015) and preoperative serum total bilirubin above 10 mg/dL (RR: 1.844, 95% CI 1.235–2.752, P = 0.003) were independent prognostic factors. Aggressive curative resection remains to be the optimal option for hilar cholangiocarcinoma. Non-curative resection, pathological differentiation, and preoperative serum total bilirubin above 10 mg/ dL were associated with dismal prognosis.

Introduction

Hilar cholangiocarcinoma (HCCA) comprising approximately 50% of all malignant bile duct tumors, is an intractable cancer [1], which requires a high level of expertise in hepatobiliary surgery due to the deep anatomical location of tumor [2, 3]. In addition, curative resection for HCCA is a complex procedure involving hepatectomy, lymphadenectomy, vascular resection and reconstruction, even pancreaticoduodenectomy (PD) [4, 5]. Consequently, curative resection is a challenging surgery and carries with a considerable risk of mortality and severe postoperative morbidity [6, 7]. Undoubtedly, curative resection offers HCCA patients the only potential chance for long-term survival, but the rates of mortality and morbidity require further improvement [8]. Meanwhile, many definitive prognostic factors affecting the postoperative survival have not been identified and accepted by surgeons [9–13], despite majority investigations have focused on this field. Therefore, the aims of this study were to assess the surgical management for HCCA and analyze potential factors influencing postoperative prognosis.

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Materials and Methods

Patients

Between January 2006 and December 2014, 216 patients with a presumed diagnosis of HCCA were admitted to the Department of Hepatobiliary, Sun-Yat-Sen Memorial Hospital, Sun-Yat-Sen University. With the approval of local institutional review board, we reviewed the medical records of all potential candidates for surgery. Seventy-four patients without any surgical interventions were excluded due to multiple metastasis, severe preoperative malnutrition, compromised liver function or severe involvement of contralateral major vessels. Therefore, curative-intent laparotomy was conducted in the remaining 142 patients. Consequently, 95 patients underwent curative resection (R0 resection) and 47 patients were performed with palliative resection (R1 = 20, R2 = 27). All the 142 patients were enrolled into this study.

Preoperative Evaluation and Management

To comprehensively evaluate disease lesion and assess surgical resectability, the laboratory and imaging examinations were carried out for all candidates. The lesion location, proximal and distal extension of tumor as well as vascular involvement extent were evaluated by ultrasonography, multidetector row computed tomography (MDCT), and magnetic resonance cholangiopancreatography (MRCP). Patients who were scheduled to accept major hepatectomy with preoperative serum total bilirubin over 11.70 mg/dL (200 μmol/L) were suggested with biliary drainage prior to surgery. None of patients underwent portal vein embolization (PVE). Percutaneous transhepatic cholangial drainage (PTCD) under ultrasound guidance was performed for 33 patients and 4 patients underwent endoscopic nasobiliary drainage (ENBD). When the surgical approach of extended hepatectomy was established preoperatively, three dimensional computed tomography (3-D CT) volumetry was applied to calculate the remnant liver in order to avoid hepatic failure postoperatively. Definitive surgery arrangement was carried out when preoperative serum total bilirubin level decreased to below 11.70 mg/dL (200 μmol/L), whereas those without biliary drainage were performed with surgery within 7 days.

Surgical Procedures

Surgical resections consisting of hemihepatectomy, extended hemihepatectomy, central hepatectomy, and external bile duct resection with or without caudate lobectomy were carried out on individuals referring to Bismuth-Corlette classification with imaging information. Locoregional lymphadenectomy including nodes at the hepatoduodenal ligament and upper part of the retropancreatic, and celiac nodes was routinely carried out. Upon the completion of the tumor resection, the biliary tract reconstruction was reestablished by Roux-en-Y bilioenteric anastomosis.

Vascular resection and reconstruction was carried out only when vessels adhered to and could not be freed from tumor entity during skeletonization of the hepatoduodenal ligament, regardless of whether the macrovascular invasion was detected preoperatively by MDCT [14]. Meanwhile, the end-to-end anastomosis model or vascular prothesis was employed to reestablish vascular continuity.

Pathologic verification was performed for all resected specimens. R0 resection was of microscopically tumor-free and a microscopically positive margin was defined as R1 resection. R2 resection meant grossly positive margins. According to the predominant pathologic grade of differentiation, tumor was mainly classified as three types: well-differentiated, moderately differentiated, and poorly differentiated adenocarcinoma. Apart from these, perineural invasion, lymph nodal metastasis, vascular invasion including hepatic artery, portal vein, and tumor thrombi were also assessed.

Definition of Mortality and Morbidity

Mortality was defined as any postoperative death occurring in-hospital stay. Major complications were regarded as having a grade of III–IV according to Clavien-Dindo classification [15].

Statistics

Continuous variables were expressed as median and range. The category variables were expressed as numbers. Cumulative survival time counted from the month of surgery was calculated with the Kaplan-Meier method and difference in survival curves was compared through log-rank test. A Student's t test (two-tailed) or Mann–Whitney U tests and χ^2 test or Fisher's exact test were used to analyze continuous or categorical variables, respectively. A multivariate Cox proportional hazards regression analysis (enter method) was performed to identify variables with P values less than 0.05 in the univariate analysis. P values less than 0.05 was considered to be significant. The statistical analyses were performed with SPSS 17.0.

Results

Demographic and Clinicopathological Features of Patients

The current study population consisted of 84 male and 58 female patients with a mean age of 59.5 years (range, 28–82 years). According to Bismuth-Corlette classification, 16

(11.27%) patients were with type I, 15 (10.56%) with type II, 17 (11.97%) with type IIIA, 38 (26.76%) with IIIB, and 56 (39.44%) with IV. Clinicopathological and demographic features of these candidates showed no significant difference factors between these with R0 resection and those with non-curative resection, except for perineural invasion ($P = 0.000$) (Table 1).

Operative Variables

In the whole cohort, 95 patients were performed with R0 resection, while the remaining 47 underwent non-curative resection including R1 resection ($n = 20$) and R2 resection ($n = 27$). A total of 92 patients (92/142, 64.8%) underwent combined with hepatectomy. Meanwhile, 34 out of these 92 (37.0%) patients underwent caudate lobectomy. Consequently, the R0 resection rate of those who underwent combined with hepatectomy was 75% (69/92). In addition, another 2 patients with type I lesion were conducted with PD. The details of surgical procedures of candidates who underwent surgery were depicted in Table 2.

Vascular resection and reconstruction was carried out in 19 patients including right hepatic artery alone ($n = 6$), portal bifurcation plus right hepatic artery ($n = 3$), and portal bifurcation alone ($n = 10$). The portal vein reconstruction was by model of end-to-end anastomosis ($n = 12$) and vascular prothesis ($n = 1$) between the residual trunk and corresponding branch, and the hepatic arterial reconstruction were based on fashion of end-to-end ($n = 4$) or with gastroduodenal artery anastomosis ($n = 2$).

Postoperative Hospital Stay and Survival

The median postoperative hospital stay was 23 days (range 13–119 days) with curative resection and 14 days (8-105 days) with non-curative resection. The cumulative overall 1-year, 3-year, and 5-year survival rates were 76.3, 27.8, and 11.3%, respectively, in curative resection group vs 36.4, 10.8, and 0% in non-resection group ($P = 0.000$). Median survival time after curative resection was 22 and 10 months after non-curative resection.

Mortality and Morbidity

The perioperative overall mortality rate in this study was 7.0% (10/142). Mortality occurred to 10 patients consisting of 4 in curative resection group and 6 in non-curative resection group. The main causes of mortality included hepatic failure resulting in multiple organ failure ($n = 6$), pneumonia causing respiratory failure ($n = 2$), postoperative gastrointestinal hemorrhage ($n = 1$), and anastomosis site leakage ($n = 1$). A total of 83 patients suffered from postoperative complications with the overall morbidity rate of 58.5%. Meanwhile, 27.5% patients

(39/83) encountered major complications (grade III to IV). Bile leakage was the most frequent complication and observed in 38 patients. Relaparotomy was required in 6 patients due to intra-abdominal bleeding ($n = 4$) and bilioenteric anastomosis bleeding ($n = 2$) within 7 days postoperatively. The details of postoperative complications were summarized in Table 3.

Statistic Analysis

Univariate analysis suggested CA19–9, preoperative serum total bilirubin, marginal status, pathological differentiation, and lymph nodes status were significant predictors for poor survival (Table 4). Meanwhile, Cox multivariate analysis disclosed that non-curative resection (RR: 2.414, 95% CI 1.586–3. 676, $P = 0.000$), pathological differentiation ($P = 0.015$), serum total bilirubin ≥10 mg/dL (RR: 1.844, 95% CI 1.235–2.752, $P = 0.003$) were independent prognostic factors (Fig. 1).

Discussion

Surgical resection has been recognized as an only potential curative option for HCCA [1, 2]. Despite close proximity to hilum vital structures and longitudinal extension of HCCA make curative resection a challenge, an improvement in postoperative survival has been reported with the advances of surgical techniques. The recent literature reviews of high-volume center of HCCA treated surgically indicate the median survival time is 16–40 months with 5-year survival rate of 11–40%, and perioperative mortality rate is around 10% with morbidity rate of approximate 42–75% [2, 4, 9, 13, 16, 17]. In the present study, combined hepatectomy including caudate lobectomy was conducted in 64.8% patients (92/142), and 13.39% patients (19/142) underwent concomitant vascular resection and reconstruction. Besides that, it was noted that 66.20% patients (94/142) who underwent surgical resection were with type III (IIIA or IIIB) or type IV lesion. Consequently, the one-year, three-year, and five-year survival rates in curative resection group were 76.3, 27.8, and 11.3%, respectively, and overall morbidity rate was 58.3% with perioperative mortality of 7.0%. Despite our results was not enough favorable but acceptable, at least, which was compatible with that reported in previous published series.

It is an incontrovertible fact combined hepatectomy or extended hepatectomy have markedly increased the resectable rate of HCCA [6, 18, 19]. It has been increased from traditionally 30% to currently 49.2–95% [2, 9, 13]. Simultaneously, the median survival of HCCA has also been dramatically ameliorated. KY. Paik et al. [20] reported 5-year survival rate was 64.2% without any in-hospital death of 16 patients who underwent right trisectionectomy with caudate lobectomy. In the study of Shimizu et al. [21], the R0 rate was

Table 1 Demographic and clinicopathological features of 142 HCCA patients

	Curative resection group	Palliative resection group (R1/R2)	*P* value
Number of patients	95	47	
Age	59.92 (28–82)	59.11 (32–76)	0.681
Gender	M = 57, F = 38	M = 27, F = 20	0.771
Mean serum total bilirubin	219.05 (5.7–712.7)	207.9(9.6–647.5)	0.504
CEA	6.87 (0.4–202.9)	16.3(0.5–352.9)	0.176
CA19-9	2376.3 (0–100,000)	5820.5(0–100,000)	0.228
ALB	37.95 (17.9–47.2)	37.78(28.2–45.8)	0.531
PTCD	26	11	0.688
Bismuth-Corlette classification:			0.122
I	9	7	
II	8	7	
IIIA	9	8	
IIIB	31	7	
IV	38	18	
Pathological differentiation:			0.500
Well	33	16	
Moderate	34	13	
Poor	28	18	
Perineural invasion	51	10	0.000
Lymph nodes metastases	47	22	0.765
Hepatitis virus infection	12	4	0.465
No.12 lymph nodes invasion[a]	39	16	0.420
Tumor thrombi	19	4	0.080

[a] Lymph nodes at hepatoduodenal ligament

Table 2 Sugical procedures of 142 HCCA patients

Bismuth-Corlette classification:	I	II	IIIA	IIIB	IV
Numbers	16	15	17	38	56
Margin status:					
R0	9	8	9	31	38
R1	3	4	6	1	6
R2	4	3	2	6	12
Surgical procedures:					
External bile duct resection	12	13	3	5	9
External bile duct resection with S4b	2	1	2	2	2
Right hemihepatectomy	0	0	9	0	13
Right hemihepatectomy with S1	0	0	1	0	0
Extended right hemihepatectomy	0	0	2	0	5
Extended right hemihepatectomy with S1	0	0	0	0	4
Left hemihepatectomy	0	0	0	11	9
Left hemihepatectomy with S1	0	1	0	15	7
Extended left hemihepatectomy with S1	0	0	0	3	3
Central hepatectomy	0	0	0	2	4
Pancreaticoduodenectomy	2	0	0	0	0

63.6% for patients who underwent left-side hepatectomy and 5-year survival was 36.7% with median survival of 24.4 months. In addition, patients with type IV lesion were previously considered not suitable for surgery, which was documented by the American Joint Committee on Cancer (AJCC) cancer staging manual (7th, edition). However, a study of combined extended hepatectomy for those who with type IV from Jang et al. [22] indicated that median survival time was 16 months in curative resection group and 12 months in palliative resection group (*P* = 0.006). Consistent with the previous literatures, R0 resection rate of those who underwent combined with hepatectomy was 75% (69/92) in this series, which was higher than the overall curative resection rate of 66.9% (95/142). Furthermore, 67.86% (38/56) patients with type IV underwent curative resection with median survival time of 23 months, which was significantly better than that of 7 months with non-curative resection (*P* = 0.000). Although combined hepatectomy did not develop impacts on postoperative survival in our study (*P* = 0.302), we believed that combined hepatectomy was essential to obtain higher R0 resection rate and benefit selected HCCA patients.

For another, combined with vascular resection and reconstruction has also made contribution to improvement resectability of HCCA currently, though it was regarded as a

Table 3 Postoperative complications of 142 HCCA patients

	No. of patients with curative resection $n = 95$	No. of patients with palliative resection $n = 47$	Total $n = 142$
Morbidity[a]			
Grade IVa			
Hepatic encephalopathy	1	0	1
Hepatic or renal insufficiency	4	3	7
ARDS	2	0	2
Grade IIIb			
Intra-abdominal abscess	0	0	0
Liver abscess	0	6	6
Bilioenteric anastomosis bleeding	2	0	2
Intra-abdominal bleeding	3	1	4
Grade IIIa			
Intra-abdominal abscess	2	0	2
Gastrointestinal bleeding	9	1	10
Pleural effusion	13	4	17
Ascites	20	2	22
Liver abscess	0	1	1
Grade II			
Bile leakage	38	11	49
Pneumonia	15	0	15
Pulmonary abscess	1	0	1
Intra-abdomonial infection	21	5	26
Sepsis	8	2	10
Wound infection	3	2	5
Grade I	19	9	28
No. of complications:	161	47	20
No. of patients with complications	63	20	83
No. of patients with major complications	29	10	39

Table 3 (continued)

	No. of patients with curative resection $n = 95$	No. of patients with palliative resection $n = 47$	Total $n = 142$
Postoperative hospital stays (day)	23	14	

[a] According to Clavein-Dindo classification

common surgical contraindication previously [23, 24]. The 5 year survival rate of combined with portal vein resection and reconstruction for HCCA in series of over 10 cases reported ranges from 9.9% to 25% with mortality of 9.6%–40% [25, 26]. In the current series, the median survival time for 19 patients who underwent combined with vascular resection and reconstruction was 17 months with one-year, three-year survival rates of 78.8%, 21.3% respectively. And the mortality was 5.26% (1/19). Although these outcomes was inferior to results in recent literatures, compared with median survival of advanced cholangiocarcinoma without any interventional procedures, combined with vascular resection and reconstruction offered advanced HCCA patients chance for acceptable survival benefits to some extent [27, 28].

As we all know, postoperative liver failure is the fatal complication of aggressive hepatic surgery, which makes the significance of preoperative biliary drainage under controversial debate to certain extent. Although zero mortality rate after R0 resection for HCCA has been achieved by Sano et al. with preoperative biliary drainage routinely applied [13], multivariate analysis of their study also revealed preoperative cholangitis was associated with postoperative mortality and morbidity. In this study, patients who were scheduled to undergo major hepatectomy with preoperative serum total bilirubin over 11.70 mg/dL (200 μmol/L) were suggested with biliary drainage prior to surgery. Consequently, patients with preoperative serum total bilirubin below 10 mg/dL obtained apparent survival benefits than those with that above 10 mg/dL (20 vs 14 months, $P = 0.003$). Additionally, preoperative biliary drainage trends to result in bile duct infections, even delay treatment [29]. Therefore, to obtain the better outcomes of surgery, preoperative biliary drainage should be a selective procedure which is depended on preoperative definitive serum total bilirubin level and scheduled surgical policy.

Although many investigations published have established various clinicopathologic factors focusing on affecting prognosis of HCCA [9–13, 23], the most consistently reported and well-recognized independently determinant factors is surgical margin status. Hepatitis and tumor thrombi regarded as potential prognostic factors were seldom discussed. To our knowledge, only a few studies have described the role of hepatitis

Table 4 Univariate and multivariate analysis of prognostic factors of survival outcome of 142 HCCA patients

Factors	No.of patients	Univariate analysis			Multivariate analysis	
		Median survival (month)	χ^2 value	P value	RR (95% CI)	P value
Age			0.975	0.332		
<60	72	20				
≥60	70	15				
Agender			0.521	0.471		
Male	84	17				
Female	58	14				
TBIL			5.436	0.020		0.003
<10 mg/dL	79	20			Reference	
≥10 mg/dL	63	14			1.844, 95% CI (1.235–2.752)	
CEA level			3.634	0.057		
<15 ng/ml	134	17				
≥15 ng/ml	8	8				
CA-199 level			4.748	0.029		0.459
<200 U/ml	67	20			Reference	
≥200 U/ml	75	13			1.174, 95% CI (0.768–1.793)	
ALB level			0.292	0.589		
<35 g/L	25	18				
≥35 g/L	117	16				
PTCD			0.763	0.382		
Present	37	14				
Absent	105	17				
Bismuth-Corlette classification			2.993	0.559		
I	16	20				
II	15	12				
IIIA	17	15				
IIIB	38	17				
IV	56	18				
Hepatitis virus infection			0.398	0.528		
Present	16	16				
absent	126	20				
Resection margin			21.858	0.000		0.000
R0	95	22			Reference	
R1/R2	47	10			2.268, 95% CI (1.493–3.444)	
Combined hepatectomy			0.302	0.583		
Yes	92	17				
No	50	16				
Combined caudate lobectomy			1.121	0.271		
Present	34	22				
Absent	108	15				
Combined vascular reconstruction			0.123	0.726		
Present	19	17				
Absent	123	16				

Table 4 (continued)

Factors	No.of patients	Univariate analysis			Multivariate analysis	
		Median survival (month)	χ^2 value	P value	RR (95% CI)	P value
Postoperative chemotherapy			1.331	0.249		
Yes	54	20				
No	88	14				
Pathologic differentiation			11.301	0.004		0.015
Well	49	24			Reference	
Moderate	47	14			1.139, 95% CI (0.785–2.217)	
Poor	46	12			2.405, 95% CI (1.250–3.345)	
Perineural invasion			1.187	0.276		
Present	63	18				
Absent	79	15				
Tumor thrombi			0.776	0.378		
Present	19	16				
Absent	123	17				
Lymph node metastases			4.501	0.034		0.247
Present	69	20			1.280, 95% CI (0.843–1.945)	
Absent	73	15			Reference	
No.12 lymph node invasion			3.578	0.059		
Present	90	17				
Absent	52	14				

virus infection for HCCA. In the study of Abdel Wahab M et al. [30], the median survival of patients with HCV infection was shorter than that of non-hepatitis virus infection patients ($P = 0.005$) and multivariate analysis confirmed that it was an independent prognostic factor. On the contrary, we failed to note that viral infection such as HBVor HCV has negative effect on postoperative prognosis of HCCA (16 vs 20 months, $P = 0.528$). Perhaps, the low morbidity of hepatitis (16/142) in this study was accounted for this discrepancy. Of course, the significance of hepatitis viral infection has remained uncertain
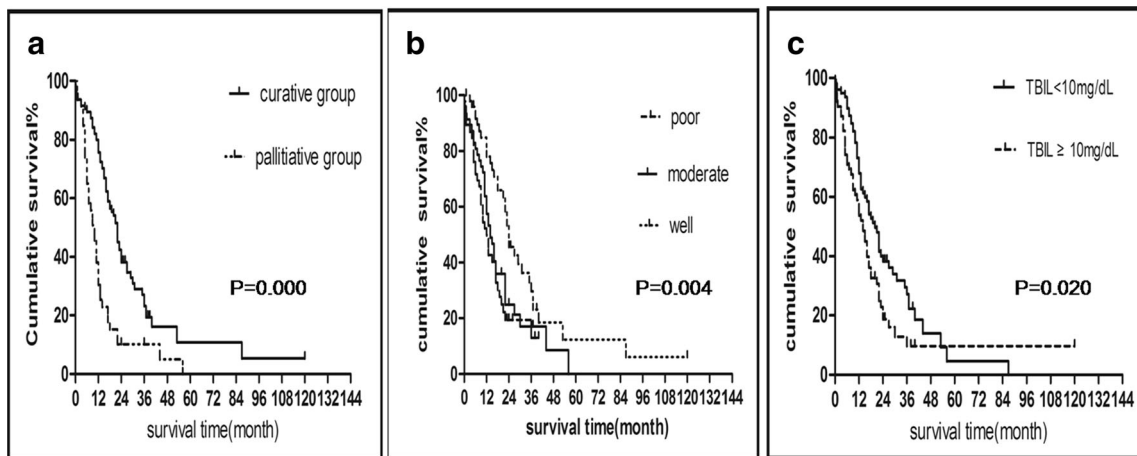

Fig. 1 Overall survival rates according to the status of resection margin ($P = 0.000$), preoperative serum total bilirubin level ($P = 0.020$), and pathological differentiations ($P = 0.004$). Cox multivariate analysis revealed that non-curative resection (RR: 2.414, 95% CI 1.586–3.676, $P = 0.000$), preoperative serum total bilirubin above 10 mg/dL (RR: 1.844, 95%CI 1.235–2.752, $P = 0.003$) and pathological differentiation ($P = 0.015$) were independent prognostic risk factors for poor survival

and should be further explored. As for tumor thrombi, few reports concerned can be traced in recent literatures. In this study, the pathological examination revealed 19 patients with tumor thrombi invasion. As a result, the median survival time with pathological tumor thrombi invasion was 16 months, comparing with 17 months in absence of tumor thrombi invasion ($P = 0.378$). With the limitation of small sample, we could not confirm that whether the poor survival was associated with tumor thrombi invasion. Even so, tumor thrombi as an interesting factor deserves further exploration.

There are some limitations in this retrospective study. First, our relatively small study cohort resulting in influencing factors was not perceived as statistically reasonable or convincing. Second, in light of the retrospective nature of most published series including the current one, more valid data about surgical approach for HCCA should be provided by the future multicenter prospective studies. Last but not the least, the significance of postoperative adjuvant chemotherapy remains to be elaborated by randomized controlled trials, though our study did not demonstrate effects of adjuvant chemotherapy due to the small sample.

In summary, curative resection as a single curative therapy has benefited HCCA patients with acceptable mortality and morbidity. Combined hepatectomy with vascular resection and reconstruction have improved the resectability rate and survival outcomes. The further refinements of aggressive surgical techniques and improvement of therapeutic strategy would benefit more advanced HCCA patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from individual participants included in the study.

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