

Review Article

Hepato-pancreatoduodenectomy for hilar cholangiocarcinoma: a case report and literature review

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Abstract: Background: Hepato-pancreatoduodenectomy (HPD) is the only way to achieve R0 resection for some advanced hilar cholangiocarcinoma (HCC). However, early experiences with HPD were associated with high mortality, leading to the limitation of HPD in the treatment of HCC. Case presentation: we present the case of a 62-year-old man with HCC (Bismuth IV) that achieved R0 resection by HPD which including the resection of the whole extrahepatic biliary system with the adjacent liver and pancreatoduodenum. And there was no mortality and only transient liver dysfunction happened postoperatively. Conclusions: Radical resection for HCC should not only be applied for early HCC, like Bismuth I or II, but also some advanced HCC patients. With the improvements in surgical techniques and perioperative patient care, we believe that HPD can be performed with low mortality and offers a better probability of long-term survival in patients with HCC (especially advanced HCC).

Keywords: Hepatopancreatoduodenectomy, Hilar cholangiocarcinoma, radical resection, survival outcome

Introduction

Hilar cholangiocarcinoma (HCC), also known as Klatskin tumor, or proximal cholangiocarcinoma, is a bile duct epithelial carcinoma occurring at the hepatic bile duct, the right and left bile duct or the confluence of the right and left hepatic bile ducts [1]. The reports revealed the incidence of HCC is about 0.01%~0.02% and accounts for 58%~75% of all bile duct carcinomas. The nature course of HCC is only 6 to 12 months [1, 2]. At present, surgical resection is considered the only possible cure for this disease because of the current lack of effective adjuvant treatment. But as the special anatomic characteristics of the hepatic hilum and highly invasive character of the tumor, the curative resection rate is less than 50%.

Moreover, some reports displayed that the 5-year survival rate of all the HCC is about 10% and about 30%-60% of curative resection HCC patients [3-6]. But the mortality of radical resection is very high, especially during the 1990s, which is about 30% [6-10]. But over the

last two decades, with the improvements in surgical techniques and perioperative patient care, the mortality rate after HPD has gradually decreased [4, 6, 11]. So, we report this case of a 62-year-old man who was diagnosed as HCC (Bismuth IV) achieved R0 resection successfully and we reviewed the literature of HCC treated by HPD.

Case

History and examination

A 62-year-old man presented at our hospital with a history of mild jaundice of skin and sclera. And computed tomography (CT) showed hilar space occupying. Laboratory tests showed increased total hyperbilirubinemia level (TB, 220 mmol/L). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels were with normal ranges.

Tumor markers, only cancer antigen 19-9 (CA 19-9) increased mildly. Others, like alpha fetoprotein (AFP), cancer antigen 15-3 (CA 15-3)



Figure 1. Images obtained on admission. Magnetic resonance imaging showing the tumor invasion of the common bile duct and the confluence of right and left hepatic bile duct and adjacent hepatic bile duct.

and cancer antigen 12-5 (CA 12-5) were within normal ranges. A magnetic resonance imaging (MRI) showed that a material mass, about 2.5 cm, occupied in the hepatic portal, and left and right hepatic duct cannot conjunct, and the extra hepatic bile duct cannot show on the image (**Figure 1**). This clinical evidence revealed that the diagnosis is most likely to be tumor of hepatic portal. And the initial diagnosis was HCC (Bismuth IV). We decided to perform surgery which includes the resection of middle and caudate lobe of liver.

Surgery

The patient was placed in the supine position under general anesthesia.

Laparotomy is performed by a right subcostal incision with the midline upward extension. By gross inspection, there is no peritoneal seeding, hepatic metastasis or periaortic node metastasis. Firstly, dissect the hilar vasculatures carefully and preserve those feeding the left liver. And we found that we need to resect and reconstruct these vasculatures to achieve curative intended resection because of local vascular invasion. Then, the caudate lobe liver and adjacent right liver are resected. After that, the patency of the left common bile duct was explored and the hepaticoplasty was completed. Thirdly, pancreatoduodenectomy is completed and cholangioenterostomy and enteroenterostomy are finished (**Figure 2**). Finally, the HPD which includes middle lobe and caudate

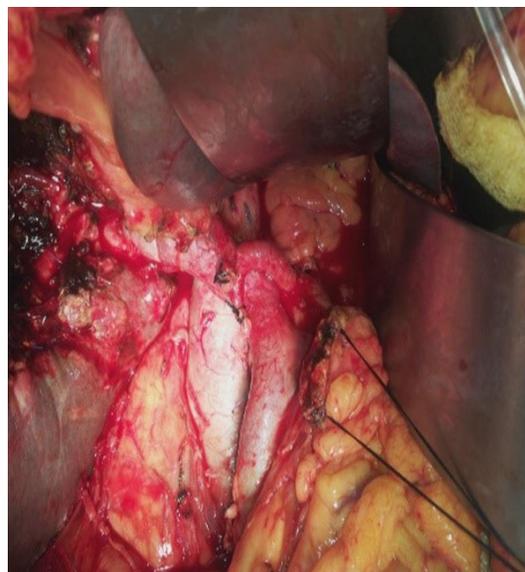


Figure 2. Surgical outcome of hepatoduodenectomy. The pancreatic transection from the neck is completed. The pancreatic vasculatures between the uncinate process and the superior mesenteric are divided.

lobe liver and the whole extra hepatic bile system and pancreatoduodenum was performed. This whole procedure lasted for about 14 hours and the total blood loss was about 1500 ml. The patient's vital signs were stable. But taking into account the long operation, the patient was sent into Intensive Care Unit (ICU) ward and returned to the general ward the next day for the stable vital signs. There was no severe morbidity but transient liver dysfunction. Finally, the patient's postoperative condition was stable and discharged seven days later.

Histology

Staining of the resected specimen with hematoxylin and eosin revealed adenocarcinoma of hilar bile duct, medium differentiation. And there is no lymph node metastasis or vascular invasion. And the pathology report confirmed that the negative margin was achieved.

Results of literature review

In order to prove if HPD can improve the long-term survival of HCC, we reviewed the literature of HPD for HCC. Due to both the low number of comparative studies eligible for the inclusion in the review and the high inter-studies heterogeneity, it was unavailable to conduct a meta-

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Table 1. Characteristics of the studies included in this review

Author	Sample size (n)			Type of study	Study results
	Total	Included	Excluded		
Tsukada, K 1994 (14)	7	5	2 GC	Retrospective	HPD may be appropriate in patients with advanced GC But for CC, further evaluation was needed
Nimura, Y 1997 (2)	37	17	20 GC	Retrospective	Survival benefit and postoperative morbidity were unexpected after HPD
Yoshimi, F 2001 (12)	37	13	24 PD	Retrospective	HPD should be tried for diffuse bile duct cancer
Hirono, S 2006 (17)	11	6	5 GC	Retrospective	HPD offers a chance of long survival for CC
Miwa, S 2007 (29)	26	17	9 GC	Retrospective	Low mortality and long-term survival justified performing HPD for advanced CC
Wakai, T 2008 (39)	28	14	3 middle CC; 11 GC	Retrospective	HPD provides survival benefits for some patients with locally advanced biliary carcinoma
Hermming, A.W 2010 (15)	40	13	9 GC; 11 others	Retrospective	HPD can be performed safely
Kaneoka, Y 2010 (13)	75	9	37 distal CC; 29 KT with Hx	Retrospective	HPD improves survival of patients with CC compared with standard surgeries
Lim C.S, 2012 (40)	23	13	10 GC	Retrospective	HPD can offer R0 resection and long-term survival for CC patients
Ebata, T 2012 (37)	85	59	26 distal CC	Retrospective	HPD can be performed with low mortality and offers a better probability of long-term survival
Sakamoto, Y 2013 (41)	19	14	5 GC	Retrospective	HPD can be an acceptable option for widespread bile duct cancer
Mizuno, T 2015 (20)	6	6	-	Retrospective	HPD offered a favorable overall survival
Total	394	186	208		

HPD, hepatopancreatoduodenectomy; HCC, hilarcholeangiocarcinoma.

Table 2. Main outcomes of interest

Study	Classification I-III/IV (n)	Operative Time (min)	Blood loss (ml)	RO (%)	Mortality (%)	Morbidity (%)	Hospital stay (days)	Survival (%) 1-year/5-year	Differentiation (n) Well/others	Differentiation (n) Well/others
Tsukada, K 1994 (9)	-	820 (674-957) ^b	1984 (1850-4985) ^b	-	40	100	48 (42-65) ^b	100/0	-	-
Nimura, Y 1997 (2)	-	-	-	-	11.8	76.5	-	33.3/0	-	-
Yoshimi, F 2001 (7)	2/11	686±105 ^a	3700±1500 ^a	53.8	7.7	69.2	34±12 ^a	50/16.7	8/5	-
Hirono, S 2006 (13, 34)	3/3	722 (616-849) ^b	4595 (2200-8400) ^b	-	16.7	100	-	40/0	-	-
Miwa, S 2007 (34)	-	-	-	64.7	0	47	-	94.1/52.9	-	-
Wakai, T 2008 (38)	9/14	654 (335-957) ^b	1875 (500-5066) ^b	64.3	14.3	85.7	-	42.9/14.3	-	-
Hermming, A.W 2010 (10)	-	300 (180-450) ^b	700 (150-2500) ^b	-	0	-	14 (7-42) ^b	100/23	-	-
Kaneoka, Y 2010 (8)	11/3	550±30 ^a	1354±53 ^a	64.3	0	57.1	-	85.7/50	5/9	-
Lim, C.S, 2012 (39)	-	-	-	76.9	-	91.3	-	76.9/32.3	-	-
Ebata, T 2012 (36)	-	762±141 ^a	2696±1970 ^a	72.9	2.4	78	-	81.9/37	13/46	-
Sakamoto, Y 2013 (40)	11/2	810 (492-1362) ^b	2300 (900-7760) ^b	57.1	-	92.9	-	85.7/42.9	6/8	-
Mizuno, T 2015 (17)	4/2	929 (753-1171) ^b	2568 (1185-6692) ^b	33.3	16.7	83.3	-	80/60	-	-

^aMean ± standard deviation; ^bMedian.

analysis of the data to compare HPD with pancreatoduodenectomy (PD) or hepatectomy (Hx). Then a descriptive analysis reporting a summary of data on the outcomes of interest was performed using the un-weighted mean and range of average values (min-max). Both baseline patients' information and outcomes data were extracted from the included studies and reported as mean, median or simple counts. After the methodological quality assessment of included comparative studies by using the

modified grading system of the SIGN, two of the three studies are of good quality.

As a result, we included twelve studies representing 394 bile duct carcinoma patients including 186 HCC patients (**Table 1**). There were three comparative studies comparing HPD with PD and hepatectomy (Hx) (**Table 3**). The other 9 studies were case reports. And none of these studies was RTC (randomized controlled trial). In total, eleven studies report-

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Table 3. Benefits of HPD for HCC in comparison with PD or Hx

	Kaneoka, Y 2010 (8)		Yoshimi, F 2001 (7)		Nimura, Y 1997 (2)	
	HPD	Hx	HPD	PD	HPD	Hx
Patients (n)	9	29	13	24	17	89
Mortality (%)	0	10.3	0	0	11.8	0
Morbidity (%)	57.1	34.5	69.2	62.5	76	-
RO (%)	64.3	58.6	53.8	87.5	-	-
Stage (n) 0-III/IV	11/3	22/7	2/11	10/14	-	-
Differentiation Well/mod+por (n)	5/9	9/20	8/5	11/13		
Operative time (min)	550±30 ^a	429±21 ^a	686±105 ^a	411±58 ^a	-	-
Blood loss (ml)	1354±153 ^a	1096±107 ^a	3700±1500 ^a	1400±700 ^a	-	-
Hospital stay (days)	44 ^b	32 ^b	34±13 ^a	24±13 ^a	-	-
5-year survival rate (%)	50	34.6	15.4	41.7	0	29.2

HPD, hepatopancreatoduodenectomy; PD, pancreatoduodenectomy; Hx, hepatectomy; HCC, hilar cholangiocarcinoma. ^aMean ± standard deviation; ^bMedian.

ed postoperative mortality. The overall mortality rate was 5.6% (ranging from 0% to 40%). Also, there were eleven studies reported postoperative morbidity and the overall morbidity rate was 66.8% (47-100%) (Table 2). All twelve studies reported long-term outcomes. 1-year survival rate ranged from 33.3% reported by Nimura Y to 100% reported by Tsukada K and Hermming A.W. The other nine studies reported 1-year survival was 40%, 42.9%, 50%, 76.9%, 80%, 81.9%, 85.7% (two studies), 94.1%. The mean 1-year survival rate was about 80%. 5-year survival rate for twelve studies was: 0% (three studies), 14.3%, 16.7%, 23%, 32.3%, 37%, 42.9%, 50%, 52.9% and 60%. The mean 5-year survival rate was 31.7% (Table 2).

Additionally, the study by Ebata in 2012 reported 85 cholangiocarcinoma patients with 59 HCC patients underwent HPD. The survival analysis showed that the overall survival rate for the 85 patients was 79.7% at 1 year, 48.5% at 3 years, 37.4% at 5 years, and 32.1% at 10 years after surgery, with a median survival time (MST) of 31.2 months. There were six patients with HCC survived for more than 5 years after HPD and one survived more than 10 years. And in this study, authors compared overall survival of 85 cholangiocarcinoma patients after HPD with 179 patients with unresectable tumor. The survival outcome after HPD (3-, 5-year survival rate, 48.5% and 37.4%) was much better than unresectable tumor (3-, 5-year survival rate, 2.9% and 0%) (P<0.01). The most recent study by Mizuno T in 2015 reported the 5-year sur-

vival rate was 60% with 80% morbidity rate and 33.3% mortality rate.

Of three comparative studies, Nimura et al. [31] reported the comparison of HPD and hepatectomy for HCC in 1997. Although there was no detail data for comparing hepatectomy group and unresected tumors group, survival analysis of three groups showed that the 1-year and 2-year survival rate for HPD, Hx and unresectable tumors group were 30%, 83%, 23% and 20%, 45%, 0% respectively. A better 3-year survival outcome showed in Hx group compared with HPD and unresectable groups (3-year survival, Hx vs HPD vs Unresectable group = 45% vs 0% vs 0%, P<0.05) (Tables 2 and 3). However, whether there was any difference of tumor stage among different groups or not, they did not mention it. So, the result was controversial.

In 2001, Yoshimi et al. [32] compared HPD with PD for extrahepatic bile duct cancer. There was no significant difference of patients' number, tumor stage, and preoperative management between two groups. That's to say, two groups were comparable. The postoperative outcomes showed that operative time and blood loss were significantly less in PD group compared with HPD group (mean 411 vs 686 min, P = 0.0000; mean 1400 vs 3700 ml, P = 0.0000). The mortality was both 0% in two group and morbidity was similar (69.2% vs 62.5%, P>0.05). The RO rate in HPD group was smaller than PD group (53.8% vs 87.5%, P>0.05) and

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hospital stay in HPD was more than PD group (mean 34 vs 24 days, $P>0.05$). And the cumulative survival rates for PD group patients were little higher than HPD group though there was no significant difference (1-year and 3-year, 76.3% vs 48% and 41.5% vs 32%, $P>0.05$) (Tables 2 and 3).

Another comparative study by Kaneoka Y in 2010 compared the effects of HPD (14 patients) with PD (32 patients) and Hx (29 patients) on cholangiocarcinoma. Three groups were preoperatively comparable. Median survival time and 5-year survival per group were as follows: 24 months and 31% in the Hx group, 51 months and 49% in the PD group, and 63 months and 50% in the HPD group (Hx vs PD, $P<0.05$). And the authors concluded that HPD improved survival of patients undergoing surgery for widespread cases. As they included perihilar and distal cholangiocarcinoma patients which not all of were needed for our review, we extracted the data about HCC and analyzed separately. The results as follows: 29 patients underwent Hx and 14 patients underwent HPD. The long-term survival in HPD group were obviously better compared with Hx group (5-year, 50% vs 32%, $P>0.05$) without any significant difference. The mortality can morbidity rate for two groups were: HPD vs Hx, 0% vs 10% and 34% vs 57%, $P>0.05$. And the R0 rate was 59% for Hx group and 64% for HPD group with no significant difference ($P>0.05$) [33].

Discussion

Hilar cholangiocarcinoma (HCC) is considered to be one of the most challenging problems in Department of hepatobiliary surgery. Firstly, its special anatomy leads to being difficult to detect it early. The current diagnosis mainly depends on imaging, tumor markers and pathological examination. Secondly, accurate preoperative assessment is essential because it's the key to the choice of treatment and surgical options. Lastly, high quality of surgical techniques is essential for radical resection of HCC [1, 3, 7, 8, 11-15]. So, early reports about HCC reported low resectable and survival rate. Although someone tried HPD for HCC to get radical resection, high mortality and morbidity led to the doubt of HPD. In recent years, with improvements in surgical techniques and perioperative patient care, the mortality and morbidity rate after HPD has gradually decreased

[3, 8, 15-17]. So, many surgeons began to re-evaluate the value of HPD for HCC.

Additionally, the clinical pathological characteristic of HCC was described as high differentiation and slow growing tumor in the past. But in recent years, it was proved not true though observing the histological differentiation characteristics and half were poorly differentiated adenocarcinoma [7, 13, 18, 19]. Its prognosis is closely related with the pathological type and the papillary adenocarcinoma with the best prognosis accounted for only about 10% of all. Even well differentiated adenocarcinoma showed common local or beyond bile duct serosa invasion [14, 20, 21]. Studies reported that once the tumor broke through the serosa layer, 81.4% specimens had peripheral lymphatic metastasis and the vascular invasion rate increased greatly. Also, some researches displayed that 30-40% HCC patients were found to have liver parenchyma invasion or liver metastasis while operation. Neurological and hepatic parenchyma invasion are risk factors for postoperative recurrence of HCC patients [2, 3, 14, 17, 21-24]. So, we thought it's better to cut the liver bile duct before the resection of liver to ensure adequate margin (intraoperative ultrasound guidance). Most related studies results encouraged to perform radically surgical resection but pay enough attention to detect bile duct margins and expand biliary resection because of the submucosal spread characteristics of cholangiocarcinoma, especially papillary type which can spread up to 3 cm in the submucosa. It is difficult to determine the accurate extent of surgical resection. For mass-forming cholangiocarcinoma which was characterized by local infiltration, if there is no lymph node metastasis, most studies results encouraged to appropriately expand the extent of surgery to avoid residual tumor [24-32].

At present, related researches showed that the resection rate of HCC is 10-85%, and only half of resectable patients who assessed preoperatively can achieve radical resection which still include 20% pathological positive margin. Overall 5-year survival rate is about 10% and 5-year survival rate of radical resection patients is about 30-60% [3, 9, 13, 14, 23, 24, 27, 33, 34]. But the current domestic situation is that the resection rate for HCC combined liver is very low. Although the rate of surgical resection has increased from 10% to the current 54.3%-

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83.3%, the radical resection rate is only 28.2-37.6% and the 5-year survival rate after radical resection is 13.4-25.8%. There still exists a gap in comparison with other countries [3, 13-15, 17, 24, 35]. Currently, surgical resection is considered as a definitive surgery for such HCC patients to achieve R0 resection to improve long-term survival [15, 32, 36, 37].

As HCC is characterized by submucosal diffuse invasion, hepatopancreatoduodenectomy (HPD) is more and more considered as the only way to achieve R0 resection for some advanced HCC. However, HPD is more challenging than standard radical resection of HCC and there are some contrary opinions about this operation because of the high mortality and morbidity rate of HPD. Especially in the reports before 2000s, the mortality and morbidity of HPD for HCC were very high, For example, 40% mortality and 100% morbidity after HPD for HCC patients were reported by Tsukada K in 1994 and 11.8% mortality and 76.5% morbidity were reported by Nimura Y in 1997 (**Table 2**). With the development of surgical techniques, the mortality after HPD decreased obviously (ranging from 40% in 1994 to 0% in 2010 and 16.7% in 2015). Although the morbidity is still high, more and more survival benefits were achieved with the improvement of surgical development.

As for the long-term effectiveness of HPD on HCC, our system review results supported the above options. Our result in **Table 2** showed that 5-year survival rates increased from 0% in 1994 to 50% in 2010. Especially, study in 2012 by Ebata reported survival rate for 85 cholangiocarcinoma patients underwent HPD was 79.7% at 1 year, 48.5% at 3 years, 37.4% at 5 years, and 32.1% at 10 years after surgery. There were even six patients with HCC survived for more than 5 years after HPD and one patient survived more than 10 years. Additionally, survival rate for 53 patients after R0 resection was 54.3% at 3 year and 46.6% at 5 year. The most recent study by Mizuno T in 2015 reported the 5-year survival rate was 60% with 80% morbidity rate and 33.3% mortality rate. The above results indicated an increasing survival outcome for HPD on HCC with characteristic of submucosal diffuse invasion because the HPD, instead of standard radical resection, was the only way to R0 and had more hoping to achieve better long-term survival.

In order to comprehensively evaluate HPD on HCC, we systematically review the comparative effectiveness of HPD with Hx and PD. Firstly, the comparative study by Nimura Y et al. in 1997 compared survival results of HPD with Hx for HCC and unresectable tumor (1-year, 30%, 83%, 23%). Survival outcomes of HPD group were obviously better than unresectable tumors though there was no significant difference. Moreover, survival rates of Hx group were significantly higher than HPD group. But it was closely related to stage of tumor which was definitely later in Hx group. So, this result could not exactly explain that the survival benefits of Hx group were better than HPD group. But for some unresectable cholangiocarcinoma patients, if not taking HPD, palliative treatments like bile drainage can make them survival days or months instead of years. So, with acceptable mortality and morbidity, improving long-term survival for several months by HPD can be meaningful for unresectable tumor patients using standard radical resection method.

In the same way, Yoshimi, F et al. compared HPD with PD for HCC in 2001. There was no significant difference between the cumulative rates of the PD group and HPD group. And R0 resection rate of PD group was higher than HPD group (87.5% vs 53.8%, $P = 0.04$) which can be explained with the different tumor stage and invasion as mentioned above. What's surprising is that Kaneoka Y et al. compared the effects of HPD (14 patients) with PD (32 patients) and Hx (29 patients) on cholangiocarcinoma in 2010. But for HCC patients, only HPD compared with Hx. Although the operative time and blood loss of HPD group were more than Hx group (mean, 500 min vs 429 min and 1354 ml vs 1096 ml, $P < 0.05$), the mortality and morbidity were similar (0% vs 10% and 57% vs 34%, $P > 0.05$). And long-term survival increased obviously in HPD group (5-year survival rate, 50% and median, 24 months) compared with Hx group (5-year survival rate, 31% and median, 63 months) ($P > 0.05$). The improvement of survival must be related to R0 resection rate (HPD vs Hx = 64% vs 59%, $P > 0.05$). From this, we lead to conclusion that, with the improvement of surgical techniques, HPD can improve the survival benefits for HCC with tendency of spreading in the submucosa compared with Hx only. HPD, was the only way to achieve R0 for HCC with characteristic of submucosal diffuse

invasion. Otherwise, this kind of patient had to accept to be belonged to unrescetable cases using alleviative method and had a relative shorter survival time.

At present, the high morbidity and risk of HPD have a close relationship to surgical extent and development of surgical techniques [37, 38]. At the beginning, the morbidity of PD was very high and surgeons thought PD as a difficult and high-risk surgery at that time. With decades of improvement, the morbidity of PD has decreased greatly. In view of this, we have reasons to believe that HPD could be expertly applied with low morbidity rate in the future.

Summary

This review is the largest sample of literature review of HPD for HCC. Although the total sample is still small and there is not enough complete data for a meta-analysis, our descriptive analysis for reported studies showed that mortality of HPD has decreased greatly and long-term survival rate has obviously improved with still high morbidity rate. As the biological characteristic of spreading in the submucosa of HCC, HPD can achieve higher rate of R0 resection than hepatectomy only and offer survival benefits for some patients. But lager sample study is needed to further evaluate the exact effect of long-term survival. More related literature and detail data for meta-analysis or RCT can help to determine the value of HPD.

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Disclosure of conflict of interest

None.

Authors' contribution

Qin Yang and Hui Mao contributed to the data acquisition and analysis and drafted the manuscript. Wen-Jie Ma, Jun-Ke Wang and Hai-Jie Hu contributed to data acquisition. Anuj Shrestha was involved in the revision of the manuscript. Fu-Yu Li contributed to the study design and revision of the manuscript. All authors have

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