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Review

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# Hepatic resection for hepatocellular carcinoma

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## Abstract

Hepatic resection has become the standard treatment of primary liver cancer. Indications for hepatic resection in patients with hepatocellular carcinoma (HCC) vary greatly between Japan and other countries because the clinical practice guidelines for HCC defined by the Japan Society of Hepatology differ from the EASL-EORTC clinical practice guidelines. Hepatic resection is not recommended as a treatment for the patients at Barcelona Clinic Liver Cancer (BCLC) stage B. Otherwise, there are many surgeons/clinicians who believe that not all HCC patients at BCLC stage B should be excluded from an indication for hepatectomy because many reports showed good prognosis after hepatic resection for HCC patients over BCLC stage B. The survival rate is expected to increase with better outcomes of hepatectomy in the future. This paper has described indications for hepatectomy for patients with HCC through comparison of domestic guidelines with overseas guidelines, focusing on their differences.

**Keywords**: Hepatic resection, hepatocellular carcinoma, guidelines

## INTRODUCTION

Indications for surgical resection in patients with hepatocellular carcinoma (HCC) vary greatly between Japan and other countries. This is because many Japanese medical institutions decide on the indication based on the clinical practice guidelines for HCC defined by the Japan Society of Hepatology[1], which differs from the EASL-EORTC clinical practice guidelines[2] in terms of the HCC stage, and the hepatic reserve as an indication for hepatectomy. This paper compares both guidelines in terms of surgical resection for hepatocellular carcinoma.

## EVALUATION OF PREOPERATIVE HEPATIC RESERVE

Liver carcinoma is often caused by viral hepatitis, alcoholic hepatitis, or non-alcoholic steatohepatitis (NASH), and when hepatectomy is performed it is necessary to pay attention to postoperative decrease in residual liver function as well as curability of the cancer.

The Child-Pugh score[3] is used worldwide to assess preoperative hepatic reserve. The EASL-EORTC clinical practice guidelines[2] usually exclude Child-Pugh B and C patients and even Child-Pugh A patients with increased portal blood pressure or high levels of bilirubin from indications for hepatectomy. The Japanese guidelines also recommend a treatment decision based on the Child-Pugh score, and hepatectomy in Child-Pugh A and B patients and liver transplant in Child-Pugh C patients have shown favorable results[4,5]. Importantly, an indication for liver transplant in Child-Pugh C patients is because liver transplants performed in Japan are usually living-donor liver transplantation due to the scarcity of brain-dead donors, and patients undergoing liver transplantation have developed liver cancer mostly caused by decompensated cirrhosis.

The evaluation scale often used in Japan for hepatectomy is assessment of liver damage under the general rules for the clinical and pathological study of primary liver cancer calculated by an indocyanine green retention rate after 15 min (ICG15), ascites, serum bilirubin level, serum albumin level, and prothrombin activity[6]. Actually, many reports showed that the ICG load test was a significant predictor of postoperative death[7,8], and the Makuuchi criteria[9] for safe hepatic resection, which are used as a reference for hepatectomy in many institutions, also base the advisability of hepatectomy on bilirubin level, ICG15, and ascites as well as the resectable limits. There was little mortality in patients undergoing hepatectomy in compliance with these criteria. Based on what was mentioned above, the ICG load test is considered likely to be important for decision-making concerning indications for hepatectomy.

Some reports showed that technetium-99m-galactosyl human serum albumin (99mTc-GSA) liver scintigraphy was more useful than ICG15 retention rate in the assessment of histological hepatic damage[10,11] and more effective in the prediction of complications and operative death in patients with hepatic disorders[12]. However, 99mTc-GSA scintigraphy using nuclides is performed only at a limited number of institutions and is not common worldwide.

## INDICATIONS FOR HEPATECTOMY

Indicators for surgery other than hepatic reserve include tumor diameter, the number of tumors, presence of vascular invasion and extrahepatic metastasis. Looking at the stage classification, the EASL-EORTC-guidelines[2] recommend hepatectomy as a treatment option for HCC patients at Barcelona Clinic Liver Cancer (BCLC) stage 0 or BCLC stage A and with normal portal blood pressure and bilirubin level. Transarterial chemoembolization (TACE) is recommended as a treatment for the patients at BCLC stage B [Figure 1]. However, studies showed the 5-year survival rate and perioperative mortality rate in HCC patients at BCLC stage B and undergoing hepatectomy were 30% to 57% and 2.6% to 5.4% respectively[13-16], and the prognosis of the patients with solitary hepatocellular carcinoma and undergoing hepatectomy was much more favorable than those undergoing TACE. There are many surgeons/clinicians who believe that not all HCC patients at BCLC stage B should be excluded from an indication for hepatectomy.

In terms of the number of HCC tumors, a better prognosis was reported in patients with a solitary tumor than in patients with multiple tumors[17]. Hepatectomy was more useful than local ethanol injection treatment in patients with liver damage A or B under the general rules for the clinical and pathological study of primary liver cancer. The treatment plan may change depending on if the HCC tumor size is larger or smaller than 3 cm. Hasegawa *et al.*[18] reported that hepatectomy showed more favorable outcomes than radiofrequency ablation (RFA) in patients with a solitary tumor smaller than 3 cm. As written above, hepatectomy is recommended as the first treatment option for patients with solitary HCC, and RFA is reported for patients with HCC smaller than 3 cm as the second treatment option equivalent to hepatectomy [Figure 2].

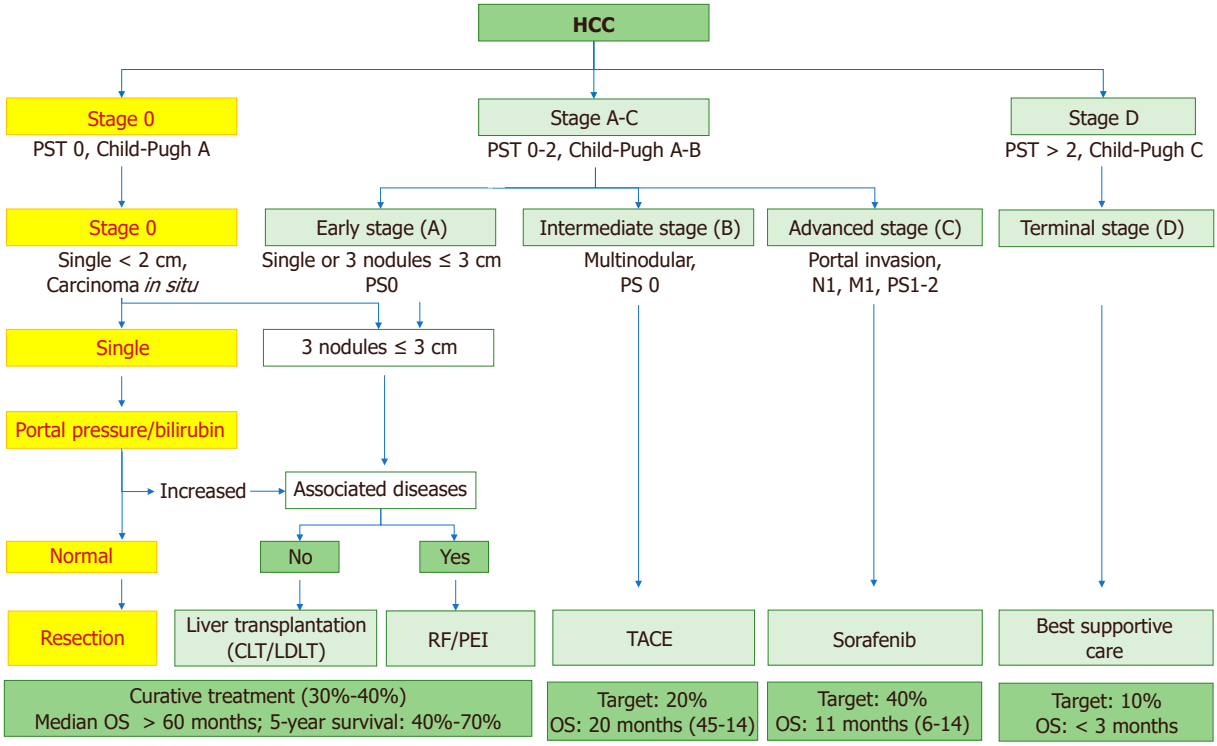


**Figure 1.** Updated BCLC staging system and treatment strategy: EASL-EORTC Clinical Practice Guidelines[2]. HCC: hepatocellular carcinoma; PST: performance status; CLT: cadaveric liver transplantation; LDLT: living donor liver transplantation; RF: radiofrequency; PEI: percutaneous ethanol injection; TACE: transcatheter arterial chemoembolization; OS: overall survival

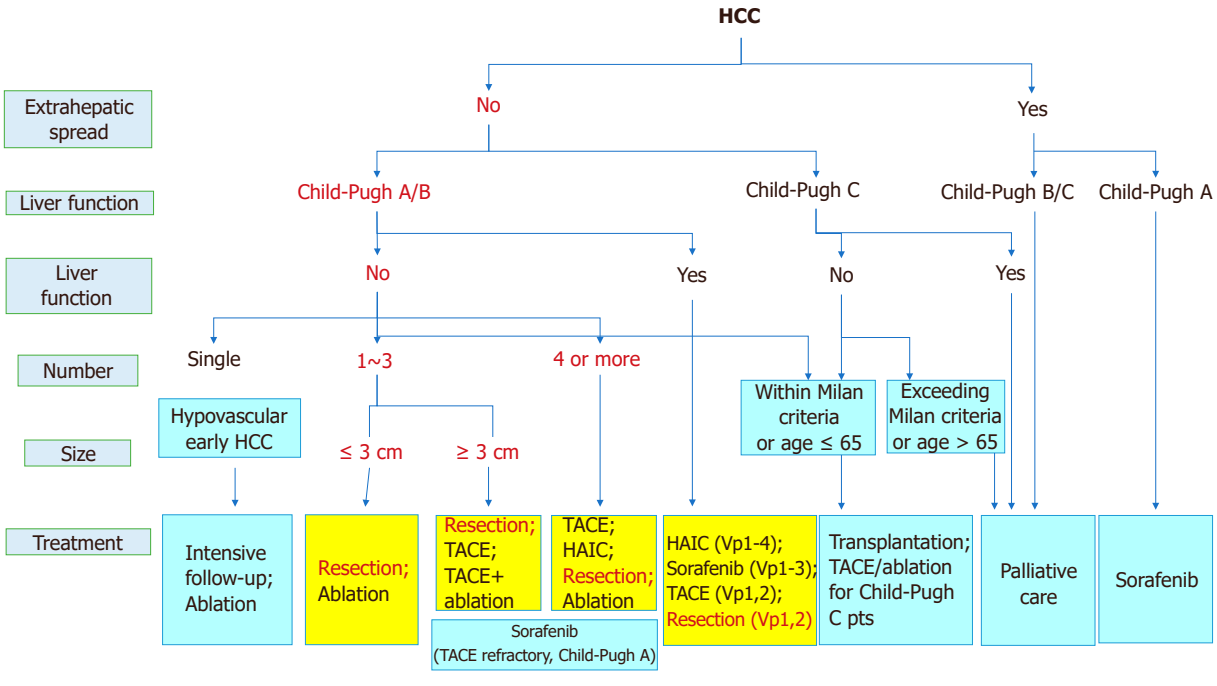


**Figure 2.** JSH-LCSGJ consensus-based treatment algorithm for hepatocellular carcinoma (HCC) revised in 2014[1]. TACE: transcatheter arterial chemoembolization; HAIC: hepatic arterial infusion chemotherapy; JSH: Japan Society of Hepatology; LCSGJ: Liver Cancer Study Group of Japan

Hepatectomy or RFA is recommended for the patients with 2 or 3 tumors 3 cm or smaller, based on the data examined by Hasegawa *et al.*[18]. Huang *et al.*[19] compared hepatectomy and RFA for HCC patients under the Milan criteria and showed a better survival rate in patients undergoing hepatectomy. However, since the patient characteristics in their study were very different from those in Japan, a randomized controlled trial (SURF trial, UMIN000001795) comparing hepatectomy and RFA in Japanese HCC patients under the Milan criteria has been conducted in Japan. The trial has not reported a high level of evidence for surgical resection and RFA in HCC patients with 4 or more tumors, and recommends transcatheter embolization/chemoembolization (TAE/TACE) as the first treatment option and hepatic arterial infusion chemotherapy and molecular targeted drug therapy as the second treatment option for those patients.

### Indications for hepatectomy (vascular invasion)

The indications for surgery for HCC with vascular invasion are described here. The 5-year survival rate for HCC patients with portal vein invasion and undergoing hepatectomy was found to be 1% to 38%, which showed a survival benefit[20,21]. Kokudo *et al.*[21] reported that the prognoses of patients with Child-Pugh score A and undergoing hepatectomy were strongly favorable and that hepatectomy was effective in patients with localized invasion in the first branch of the portal vein. TACE, molecular targeted drug therapy, and hepatic arterial infusion chemotherapy for HCC patients with vascular invasion were also reported[22-24], but a consensus on these treatments has not yet been reached in Japan. Therefore, hepatectomy, embolization therapy, hepatic arterial infusion chemotherapy, and molecular targeted drug therapy are recommended equally at present in Japan as treatments for HCC patients with vascular invasion.

The AASLD[25] guidelines suggest that adults with Child-Pugh class A cirrhosis and resectable T1 or T2 HCC undergo resection rather than radiofrequency ablation. These patients are indicated for resection. Most studies define patients with resectable HCC as those: (A) with one to three unilobar lesions, with an upper size limit of 5 cm for single lesions and 3 cm for more than one lesion; (B) without radiographic evidence of extrahepatic disease of macrovascular invasion; and (C) occurring in the setting of minimal or no portal hypertension and in the absence of synthetic dysfunction. It is different from Japanese guidelines. The Chinese guidelines[26] similarly define general surgical indication for cases with less than three tumors. But, it is different from AASLD guidelines at the point about including resection of portal vein tumor thrombus (PVTT) and concomitant splenectomy for cases with portal hypertension.

In Europe and the US, the use of molecular targeted drug therapy is recommended for HCC patients with vascular invasion at BCLC stage C.

## HEPATECTOMY PROCEDURE

Since HCC is known to spread through veins into the liver, systematic removal of the tumor-bearing portal territory is advisable, if possible. Some recent literature has reported that patients undergoing systematic resection had better prognoses than those undergoing nonsystematic resection (segmental resection)[27-31]. However, many patients develop HCC in the background of chronic liver diseases, and some of them may not undergo systematic resection at present due to poor hepatic reserve. Therefore, the indication for surgery and the surgical procedure are often determined upon consideration of the balance between tumor conditions and liver function conditions. While systemic resection is anatomic resection of the tumor-bearing portal territory with consideration to HCC development through the portal vein, nonsystematic resection is resection of the tumor with some surgical margin regardless of the anatomy of the vessels. Some studies have reported that a comparison of surgical outcomes between systematic resection and nonsystematic resection showed no significant difference in cumulative survival rate and relapse-free survival rate[32-34]. It is recommended in Japan to choose either a small range of systematic resection or nonsystematic resection as

reductive surgery, depending on hepatic function, for patients with small HCC (5 cm or smaller) and major resection of at least 2 segments for patients with large HCC.

The procedure for resection of the right hepatic vein at its root with preservation of the inferior right vein[35], the procedure for systematic resection of the HCC-bearing portal territory with dye infusion under ultrasound guidance[36], and the procedure for systematic resection of the identified tumor-bearing territory with transection of Glisson's sheath[37,38] are reported as the surgical procedures preserving the liver parenchyma. The procedure for resection of segment 3 and 4 with preservation of segment 2[39] is also included.

The surgical procedure for HCC in the caudate lobe generally removes the ventral liver parenchyma also, which has raised the question of impaired hepatic functions. Surgical procedures such as dorsal resection of the caudate lobe isolated and identified using the counterstaining technique[40,41] and isolated resection of the caudate lobe after parenchymal transection along the middle hepatic vein[42] currently have been designed.

Reports on laparoscopic hepatectomy for HCC are increasing lately. It is reported that laparoscopic hepatectomy is superior to open hepatectomy due to the magnifying effect of the area being operated on and allows less hemorrhage from the hepatic veins due to the hemorrhagic reduction effect of the pneumoperitoneum[43-45]. It is also reported that laparoscopic hepatectomy has a lower incidence of complications such as ascites than open hepatectomy[46-48]. Laparoscopic hepatectomy for HCC has been reported to have long-term outcomes equivalent to those of open hepatectomy and superior to radiofrequency ablation in local control for small HCC located at the liver surface. In Japan, laparoscopic hepatectomy is currently recommended based on the judgments of the International Consensus Conference on Laparoscopic Liver Resection that laparoscopic hepatectomy could be performed on patients with hepatic reserve sufficient to undergo open hepatectomy and is advisable for partial resection or lateral segmental resection for solitary tumor with a maximum diameter no more than 5 cm located in the anterior inferior segments (segments 2 to 6)[49]. In Europe and the US, some reports have described laparoscopic hepatectomy but have not made a clear recommendation for it. In any case, it is considered that laparoscopic hepatectomy should be done by a team with well-experienced surgeons and only at a well-equipped medical institution providing adequate intensive care during the perioperative period due to insufficient accumulation of evidence about safety in laparoscopic hepatectomy.

## PROGNOSIS OF PATIENTS UNDERGOING HEPATECTOMY

The studies have reported that there was no significant difference in postoperative relapse rate between patients with resection margin of at least 1 cm and patients with resection margin of less than 1 cm[50-52] and comparison of the prognosis in patients with resection margin of at least 5 mm and less than 5 mm also showed no significant difference in survival rate[53,54]. Based on these results, a minimum distance of resection margin is allowed for hepatectomy for HCC in Japan. In contrast, Hu *et al.*[55] reported that the prognosis was favorable in patients with Milan criteria-compliant HCC with resection margin of at least 1 cm. Another study showed that patients with a resection margin of at least 2 cm had a more favorable prognosis than patients with a margin of 1 cm[56]. It is thought that the distance of the resection margin may affect prognosis.

Well-known predictors of poor prognosis after hepatectomy also include tumor diameter of at least 5 cm, multiple tumors, no capsular formation, positive vascular invasion, impaired liver function, TNM classification stage 3 or 4, and AFP level of at least 32 ng/mL[57,58]. Some research has indicated that tumor size is not a prognostic predicator[59,60].

Tumor markers such as PIVKA-II and AFP are reported as predictors of recurrence after hepatectomy for HCC. HCC patients with a thrombus in the main portal vein or the first branch of the portal vein are considered

**Table 1. The result of hepatic resection for HCC**

| Author | HCC characteristics | 1-year OS (%) | 3-year OS (%) | 5-year OS (%) |
|---|---|---|---|---|
| Garancini *et al*.[65] | BCLC A/B | 95/83.3 | 61.1/50 | 46.2/41.2 |
| Wu *et al*.[66] | BCLC 0-A | 95.9 | 85.3 | 67.6 |
| Jiang *et al*.[67] | BCLC A, multifocal | 96 | 71.7 | 36.3 |
| Li *et al*.[68] | BCLC A or B, ruptured | 66.3 | 23.4 | 10.1 |
| Xu *et al*.[69] | BCLC B or C | 81.4 | 48.5 | 28.2 |
| Wang *et al*.[70] | Small tumors | 92.6 | 83.3 | 73 |
| Shrager *et al*.[71] | Large HCC (> 10 cm) | 57 | 30 | 19 |
| Lee *et al*.[72] | Large HCC (> 10 cm) | 66 | 44 | 31 |
| Shah *et al*.[73] | Large HCC | 69 | 63 | 54 |
| Pandey *et al*.[74] | Large HCC | 63 | 35 | 28.6 |
| Ng *et al*.[75] | Large or multinodular | 74 | 50 | 39 |
| Roayaie *et al*.[76] | Macroscopic vascular invasion | 52 | 22 | 14 |
| Pawilk *et al*.[20] | Portal or hepatic vein invasion | 45 | 17 | 10 |
| Ban *et al*.[77] | Portal vein thrombosis | 70 | 37 | 22 |
| Vitale *et al*.[78] | BCLC-C | 55 | 44 | 0 |

HCC: hepatocellular carcinoma; OS: overall survival; BCLC: Barcelona Clinic Liver Cancer

to have a poor prognosis. The Glasgow Prognostic Score (GPS) is one of the important predictors and is believed to make the prognoses of HCC patients clearer[61]. In addition, some studies have shown that the preoperative neutrophil-lymph node ratio (NLR) is a predictor of poor prognosis[62]. Sarcopenia is also considered to be a predictor of poor prognosis[63]. Japanese study showed that patients with non-B non-C HCC had a better prognosis and a lower risk of recurrence than those with hepatitis C virus (HCV)-related HCC[64].

We investigated the outcomes of HCC after hepatic resection[65-78]. There are no significant difference mortality of HCC patients between BCLC A and B [Table 1]. Garancini said that surgical treatment of HCC in BCLC stage B should not be considered contraindicated for such patients. HCC patients with vascular invasions had higher mortality rate than single large HCC. We should pay attention to vascular invasions more than tumor size for good surgical prognosis.

At last, we showed outcomes of hepatic resection in Japan. The Liver Cancer Study Group of Japan determined that the cumulative survival rate[64] at all HCC stages was 90.2% at 1 year, 81.3% at 2 years, and 56.8% at 5 years. Looking at the 5-year survival rate by tumor diameter, survival rate was 73.9% in patients with tumor size of less than 2 cm ($n$ = 4168), 63.1% in patients with tumor size of 2 to 3 cm ($n$ = 7212), 59.7% in patients with tumor size of 3 to 5 cm ($n$ = 6022), and 52.4% in patients with tumor size of 5 to 10 cm ($n$ = 3869). The 5-year survival rate of patients with tumor size of 10 cm and bigger was 45.4%. Thus, patients with increasing tumor size have a worse prognosis. Looking at survival rate by the number of tumors, while the 1-year survival rate and the 5-year survival rate were 90% and 50% to 60% respectively in patients with one or two tumors, the 5-year survival rate declined to 37% in patients with more than three tumors [Table 2]. Looking at the 5-year survival rate by stage, survival rate was 82.8%, 70%, 52%, 31%, and 26.8% in patients at stage I, II, III, IVA, and IVB, respectively. However, the 5-year survival rate has been increasing steadily in recent years. While it was 12.5% in the 1980s, it steadily increased to 44% in the 2000s.

The incision criteria are different in each guideline. But, expansion of criteria for resection is progressing. The survival rate of HCC after hepatic resection is expected to increase with better outcomes of hepatectomy in the future.

## CONCLUSION

This paper has described indications for hepatectomy for patients with HCC through comparison of domestic guidelines with overseas guidelines, focusing on their differences.

**Table 2. Cumulative survival rates (%) of hepatocellular carcinoma patients in Japan[61] treated with hepatic resection**

| Years | | Number | Cumulative survival rates (%) | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 | 3 | 5 | 7 | 10 |
| Tumor number | 1 | 16,531 | 93.7 | 80.8 | 67.0 | 54.7 | 39.0 |
| | 2 | 3494 | 90.0 | 71.0 | 54.8 | 40.4 | 27.2 |
| | ≥ 3 | 2717 | 81.1 | 55.8 | 37.9 | 28.1 | 20.4 |
| Portal vein invasion | Vp0 | 19,075 | 94.4 | 80.5 | 65.5 | 52.4 | 36.8 |
| | Vp1 | 1908 | 84.9 | 62.4 | 48.2 | 39.0 | 28.9 |
| | Vp2 | 714 | 69.1 | 42.2 | 29.2 | 22.5 | 17.3 |
| | ≥ Vp3 | 852 | 59.8 | 34.3 | 25.0 | 20.5 | 15.6 |
| TNM stage by LCSGJ | I | 2339 | 97.8 | 90.0 | 74.3 | 61.4 | 42.5 |
| | II | 9755 | 94.1 | 78.0 | 62.5 | 50.1 | 35.5 |
| | III | 3902 | 85.6 | 61.8 | 43.5 | 33.5 | 23.3 |
| | IVA | 1208 | 69.4 | 38.9 | 25.9 | 20.3 | 15.4 |
| | IVB | 2118 | 56.5 | 28.0 | 18.7 | 14.5 | 14.5 |

LCSGJ: Liver Cancer Study Group of Japan

## DECLARATIONS

### Authors' contributions

Mainly edited the manuscript: Yamaguchi S, Kosaka T
Qualified the manuscript: Eguchi S
Read and approved the manuscript: Yamaguchi S, Kosaka T, Eguchi S

### Availability of data and materials

Not applicable.

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None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



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