ORIGINAL ARTICLE

Peritoneal metastasis after emergency hepatectomy and delayed hepatectomy for spontaneous rupture of hepatocellular carcinoma

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Summary *Background and objectives:* Delayed hepatectomy is the preferred approach for spontaneous rupture of resectable hepatocellular carcinoma (HCC). However, delayed surgery for ruptured HCC may increase the risk of peritoneal metastasis.

Methods: A retrospective analysis was conducted on the pooled data obtained from 44 HCC patients with spontaneously ruptured hemorrhage, These patients were divided into emergency group and delayed group. Perioperative events, overall survival (OS) and disease-free survival (DFS) rates, and the incidence of recurrent and metastatic disease were compared between these two groups.

Results: Median survival time was 17.0 months in the emergency group *vs.* 28.0 months in the delayed group. In the emergency group, the 6-month, 1-year and 3-year OS rates were 58.8%, 57.6% and 11.5%. In the delayed hepatectomy group, the 6-month, 1-year and 3-year OS rates of were 84.3%, 77.5% and 37.8%. The incidence of peritoneal metastasis was higher in delayed group than in the emergency group, but the difference was not statistically significant (40.7% *vs.* 35.3%, $P > 0.05$).

Conclusion: Delayed hepatectomy warrants better short-term prognosis, compared with emergency hepatectomy, for HCC patients with spontaneously ruptured hemorrhage. Delayed hepatectomy does not increase the possibility of postoperative peritoneal metastasis.

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1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world and the third most lethal malignancy on a global scale,[1] and its incidence continuous to increase worldwide due to the increasing prevalence of hepatitis B virus infections.[2] Spontaneous rupture is a life-threatening complication of HCC, which has an incidence rate of 5—26% and a mortality rate of up to 25—75%, and approximately 6—10% of its mortality are due to primary liver cancers in China.[3,4] Spontaneous rupture may produce a spillage of tumor cells in the peritoneal surface with possible seeding and multiple nodule growth, A previous study reported that HCC was present in the parietal and peritoneal localizations in 14.3% of cases.[5,6] Most patients with HCC ruptures exhibit intrahepatic recurrence, and repeated hepatectomy and transarterial chemoembolization (TACE) can be used for treatment. Furthermore, some patients have extrahepatic metastases or recurrence, and suffer from peritoneal organs, or lung, bone and distant lymph node metastasis. However, there is presently no effective treatment, especially for peritoneal metastasis. Although peritoneal lavage to clean up the abdominal cavity and left 5-fluorouracil to the abdominal cavity at the end of the operation have been conventionally performed, high rates of peritoneal metastasis are still inevitable. The prognosis is poor, and factors that affect peritoneal metastasis after hepatectomy for patients with ruptured HCC remain unclear. It has been reported that transcatheter arterial embolization (TAE) is effective in achieving immediate hemostasis in cases that exhibit hepatic insufficiency and liver cirrhosis. Hepatectomy is an effective treatment for spontaneously ruptured HCC, in which long-term survival can be achieved in selected patients. Furthermore, several studies have demonstrated that 1- and 3-year survival rates of 60%—77% and 42%—54% were achieved, respectively.[7—10] Some studies[11] have shown that hepatectomy is a feasible intervention for spontaneous HCC ruptures, and that it should be performed when technically feasible either as an emergency or staged operation. However, the influence of the timing of surgery in patients with spontaneous rupture of resectable HCC on peritoneal metastasis remains disputed. A retrospective analysis was performed, in which the patients with spontaneous HCC ruptures underwent hepatectomy in our hospital. Survival, recurrence and peritoneal metastasis were compared in patients with spontaneous rupture of HCC after emergency and delayed hepatectomy, in order to clarify the influence of hepatectomy in patients with HCC ruptures and other factors on peritoneal metastasis.

2. Patients and methods

A total of 72 patients diagnosed with ruptured HCC at the Department of Hepatobiliary Surgery, the First Affiliated Hospital of Chongqing Medical University (Chongqing, China) from August 2011 to October 2016 were retrospectively reviewed. All treatments were approved by the Research Ethics Committee at The First Affiliated Hospital of Chongqing Medical University, and written informed consent was obtained from all patients who met the inclusive criteria before data collection and analysis. Among these patients, 44 patients underwent hepatectomy, others were only treated with conservative treatment or interventional therapy. These patients were evaluated based on their clinical symptoms and signs, laboratory tests and imaging studies. The most common symptoms of HCC rupture were acute abdominal pain and shock, accompanied by cough and constipation. A total of 44 patients were divided into two groups according to the timing of surgery. Emergency hepatectomy refers to the direct performance of surgery for patients with HCC rupture on day one, whereas delayed hepatectomy was defined as hemostasis by conservative treatment and TAE, followed by hepatectomy after seven days. Among these 44 patients, 17 patients underwent emergency hepatectomy and 27 patients underwent delayed hepatectomy. The clinicopathologic data of these patients, including demographics, liver function status, tumor characteristics, peritoneal metastasis and treatment outcomes, were reviewed and compared. Overall survival time and disease-free survival time were obtained by follow-up. Liver function status was evaluated using the Child-Pugh score system. HCC was stratified according to the BCLC staging classification.

Follow-up data was obtained by communicating with patients through telephone and medical records data. Follow-up was performed every 1—3 months in the first year after surgery, and every 3—6 months thereafter. Patients were monitored for recurrence and metastasis by recording their AFP levels, ultrasonography, contrast-enhanced CT, or MRI. The follow-up period was defined as the interval between the date of surgery and the date of patient death or deadline for follow-up. Disease-free survival was defined as the length of time after hepatectomy for ruptured HCC, during which a patient survives with no evidence of HCC.

Continuous variables are described as the median with range, and categorical variables are expressed as the number and percentage of subjects. Fisher exact test was conducted to evaluate differences in the frequencies of categorical variables between groups. $P < 0.05$ was considered statistically significant.

The Kaplan—Meier survival method was performed to evaluate differences in patient overall survival and disease-free survival between the two groups. Cox proportional hazard regression analysis was used to identify independent prognostic factors. Survival time and disease-free survival time started from the date of hepatic resection until death and the diagnosis of recurrence or closing date. The closing date of the present study was November 30, 2017. All statistical analyses were performed using statistical software SPSS 19.0 for Windows (SPSS, Chicago, IL, USA).

3. Results

The characteristics of the 44 patients with HCC ruptures, who underwent emergency or delayed hepatectomy, are presented in Table 1. Among these patients, 36 (81.8%) patients were male and eight (18.2%) patients were female. Furthermore, among these patients, 29 (65.9%) patients were HBsAg positive and 22 (50.0%) patients were associated with different extents of liver cirrhosis. According to

Table 1 Comparison of perioperative data of ruptured HCC patients between emergency hepatectomy and delayed hepatectomy.

Data	Emergency hepatectomy (*n* = 17)	Delayed hepatectomy (*n* = 27)	*P*-value
Age (year)	53.6 (26−73)	47.0 (18−70)	>0.05
Sex (M:F)	14:3	22:5	>0.05
Liver cirrhosis	8	14	
Child−Pugh A/B	14	25	>0.05
Child−Pugh C	3	2	
BCLC stage A/B/C	3/9/5	7/12/9	>0.05
AFP (μg/L)	5023.67 (16.47−30382.00)	10188.59 (1.04−106516.00)	>0.05
Operation time (minute)	247.13 (116.00−480.00)	263.42 (130.00−590.00)	>0.05
Intraoperative bleeding (ml)	956.67 (200.00−2100.00)	761.11 (50.00−3000.00)	>0.05
Intraoperative blood transfusion (ml)	973.30 (0.00−3800.00)	477.77 (0.00−300.00)	>0.05
Hospital stay (day)	18.33 ± 6.68	20.03 ± 5.87	>0.05
Abdominal metastasis	6	11	>0.05

Notes: AFP: α-fetoprotein; BCLC: Barcelona Clinic Liver Cancer.

Child−Pugh classification, preoperative liver function was categorized as Child−Pugh A/B in 39 patients and Child−Pugh C in five patients. There were no significant differences between these two groups in terms of intraoperative blood loss (956.67 [200.00−2100.00] ml *vs.* 761.11 [50.00−3000.00] ml, *P* > 0.05), intraoperative red blood cell transfusion (973.30 [0.00−3800.00] ml *vs.* 477.77 [0.00−300.00] ml, *P* > 0.05), hospital stay (18.33 ± 6.68 days *vs.* 20.03 ± 5.87 days, *P* > 0.05), and duration of the operation (247.13 [116.00−480.00] minutes *vs.* 263.42 [130.00−590.00] minutes, *P* > 0.05).

In the emergency group, median survival time was 17.0 months. Furthermore, the 6-month, 1-year and 3-year overall survival rate was 58.8%, 57.6% and 11.5%, respectively, while the 6-month, 1-year and 3-year disease-free survival rate was 52.9%, 41.9% and 8.4%, respectively. In the delayed group, the median survival time was 28.0 months. Furthermore, the 6-month, 1-year and 3-year overall survival rate was 84.3%, 77.5% and 37.8%, respectively, while the 6-month, 1-year and 3-year disease-free survival rate was 55.6%, 51.0% and 26.2%, respectively. The difference in overall survival and disease-free survival in the ruptured HCC between the emergency and delayed groups were not statistically significant (*P* = 0.231, *P* = 0.134) (Fig. 1). The overall survival rate of liver function Child-Pugh A/B patients after hepatectomy was obviously better than that of liver function Child-Pugh C patients (*P* < 0.05) (Fig. 2). However, for patients with Child-Pugh A/B, the difference in overall survival rates between the emergency and delayed groups were not statistically significant (*P* > 0.05) (Fig. 3).

In the emergency group, HCC recurrence and metastasis developed in 8/17 patients (47.1%), and the peritoneal
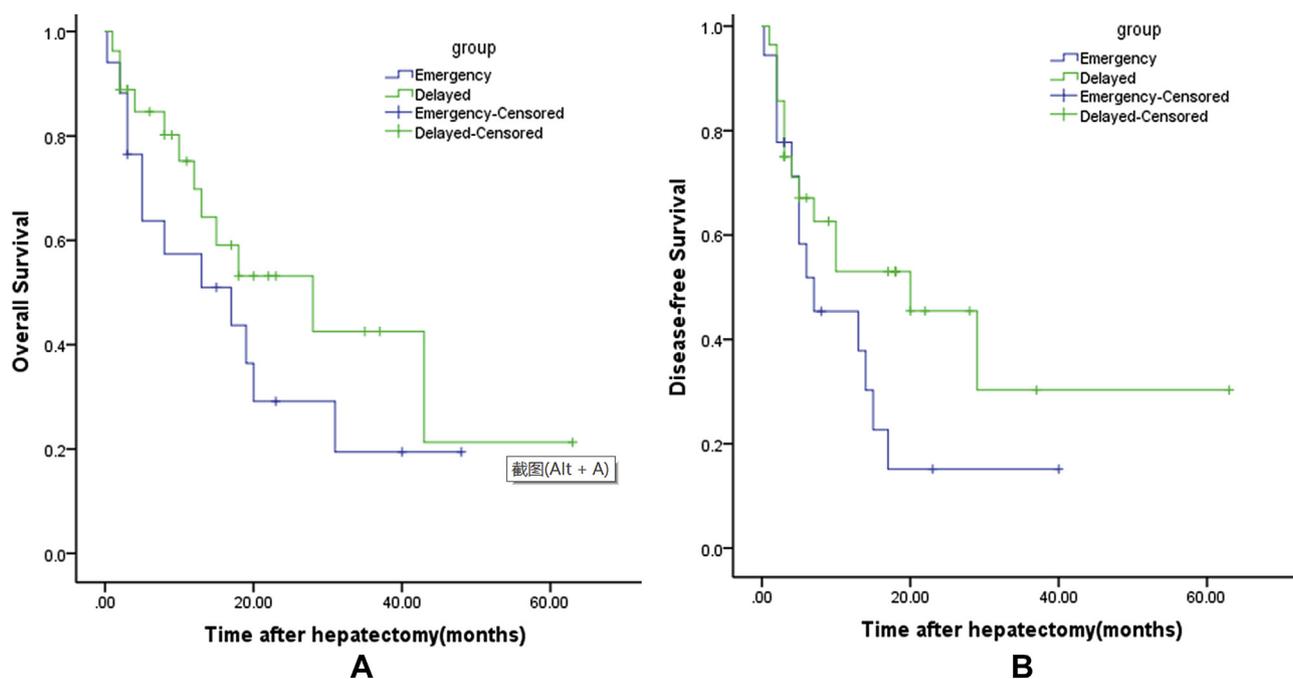

Figure 1 Overall survival (A) and disease-free survival (B) in the patients with HCC ruptures between emergency hepatectomy and staged hepatectomy.
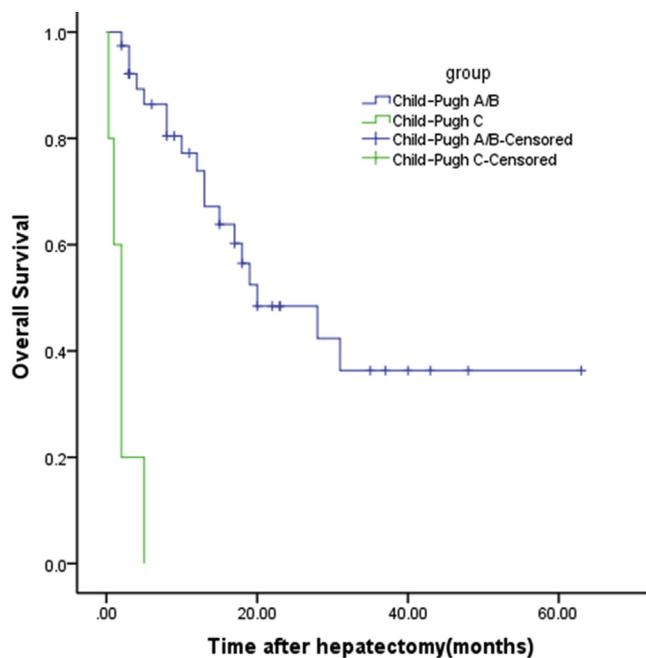
Figure 2 Overall survival in the patients with HCC ruptures underwent hepatectomy between liver function Child-Pugh A/B and Child-Pugh C.

metastasis rate was 35.3%. In the delayed group, HCC recurrence and metastasis developed in 13/27 patients (48.1%), and the peritoneal metastasis rate was 40.7%. There was no significant difference in recurrence and metastasis patterns between these two groups. Variables that might affect the peritoneal metastasis of ruptured HCC patients after hepatectomy were analyzed in the present
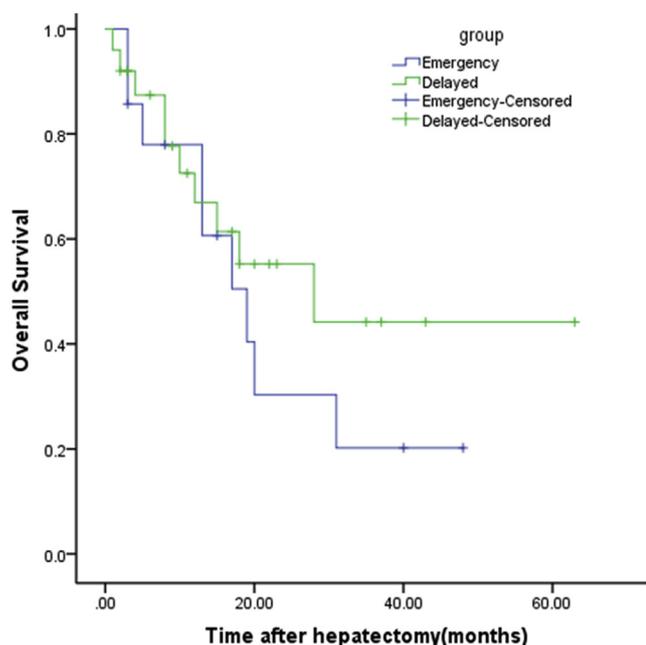

Figure 3 Overall survival in the patients with liver function Child-Pugh A/B between emergency hepatectomy and staged hepatectomy.

study (Table 2). In the univariate and multivariate analysis, it was found that a tumor size of >10 cm and an AFP of >10,000 μg/L were independent predictors of peritoneal metastasis ($P < 0.05$).

4. Discussion

The incidence of spontaneous rupture of HCC shows an obvious geographical difference in previously reported studies. Furthermore, 10%−15% of patients with HCC develop this complication, and approximately 12%−14% of patients with HCC develop tumor rupture bleeding in Asia, which is higher than that in Western countries.[3,12] Spontaneous rupture of HCC may be related to overgrowth of the tumor, necrosis, or coagulation disorders.[13] Some studies have shown that hypertension, liver cirrhosis, tumor diameter >5 cm, tumor protruding surface and tumor location are risk factors for the rupture and bleeding of HCC.[14,15] The tumor diameter of the patients in emergency and delayed groups was 8.64 ± 3.4 cm and 10.4 ± 4.9 cm, respectively. Furthermore, half of these patients have liver cirrhosis and most of them had cough, trauma and constipation when moving heavy objects, as well as other inducing factors, before the onset of the disease, which was followed by sudden abdominal pain, shock and other symptoms. Abdominal ultrasonography, CT examination and abdominal aspiration were helpful to the diagnosis.

The occurrence of HCC rupture is difficult to anticipate, and there are few therapeutic options. At present, surgical treatments such as hepatectomy and TAE are available. In particular, hepatectomy can not only induce hemostasis, but also remove tumors. However, various patient conditions often limit its use. TAE can effectively induce hemostasis in hemodynamically unstable patients. Furthermore, TAE has been increasingly used for ruptured HCCs, which is an effective, less invasive treatment for achieving immediate hemostasis, and most recent reports have cited a hemostasis success rate of >90%.[3,16,17] Successful hemostasis is expected to be an important factor for determining early mortality. Surgical treatment is the main treatment for the rupture and bleeding of HCC. It not only stops the bleeding, but also achieves the purpose of excision of the lesion. Its prognosis is much better than conservative treatment and hepatic artery embolization.[18,19] However, due to the number of patients with cirrhosis, liver dysfunction, increased postoperative mortality and complications, the timing of surgery is difficult to choose. Most studies have suggested that liver function Child-Pugh A or B patients can receive emergency hepatectomy, while Child-Pugh C patients are recommended for conservative treatment. After the recovery of the liver function, an elective operation was performed. If active bleeding occurs, TAE for emergency hemostasis can be initially performed.[20,21] With the improvement of surgical techniques and postoperative management, some studies have reported that emergency hepatectomy can obtain a better clinical prognosis, and has been recommended for patients with resectable HCC rupture and bleeding.[22,23] In the present study, five patients in the emergency group were hospitalized with shock and needed emergency surgery to hemostasis. Despite the overall volume of bleeding

Table 2 Univariate and multivariate analyses of variables associated with peritoneal metastasis in patients with spontaneous rupture of hepatocellular carcinoma.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Timing of surgery (emergency vs. delayed)	1.260 (0.359–4.428)	0.718	1.231 (0.205–7.384)	0.820
HBV (positive vs. negative)	0.917 (0.256–3.286)	0.894	0.036 (0.000–2.821)	0.135
Tumor size (>10 cm vs. ≤10 cm)	6.286 (1.598–24.727)	0.009	8.295 (1.190–57.834)	0.033
Tumor differentiation (high vs. middle vs. low)	2.444 (0.748–7.987)	0.139	2.548 (0.243–26.742)	0.436
Portal vein tumor thrombus (presence vs. absence)	1.400 (0.399–4.907)	0.599	0.847 (0.032–22.235)	0.921
Ascites (presence vs. absence)	1.067 (0.159–7.145)	0.947	0.045 (0.001–2.009)	0.109
Liver cirrhosis (presence vs. absence)	1.786 (0.523–6.100)	0.355	8.912 (0.060–1321.343)	0.391
Tumor nodule number (solitary vs. multiple)	1.714 (0.304–9.677)	0.542	1.816 (0.161–20.473)	0.629
AFP (≥10,000 vs. <10,000 μg/L)	9.000 (1.945–41.654)	0.005	21.821 (1.208–394.100)	0.037

Notes: AFP: α-fetoprotein; HBV: hepatitis B virus; HR: hazard ratio; CI: confidence interval.

rupture, the success rate of hemostasis was 100%. Zhong et al[24] compared the hemostatic effect of different methods in patients with HCC rupture, in which 79 patients underwent emergency hepatectomy, and the success rate of hemostasis was 95%, which was higher than TAE and the conservative treatment group. Although active bleeding, uncorrected coagulation function and other factors can lead to increased blood loss and transfusion volume during emergency hepatectomy, and even if the affect of the surgical field resulted in prolonging the operation time, emergency hepatectomy has a definite effect on hemostasis. In particular, emergency hepatectomy can save the life of patients with excessive bleeding.

Ou et al[25] analyzed the survival of 131 patients with HCC rupture and bleeding after hepatectomy. The 1-, 3- and 5-year overall survival rate of ruptured HCC patients with delayed hepatectomy was 82.8%, 55.2% and 41.4%, respectively, while the disease-free survival rate was 70.7%, 44.8% and 27.6%, respectively. The overall survival and disease-free survival of patients in the delayed group were longer than that of patients in the emergency group ($P = 0.034$, $P = 0.019$). Similar to the results of the above study, in the present study, for patients in the emergency group, median survival time was 17.0 month. The 6-month, 1-year and 3-year overall survival rate was 58.8%, 57.6% and 11.5%, respectively, while the 6-month, 1-year and 3-year disease-free survival rate was 52.9%, 41.9% and 8.4%, respectively. For patients in the staged group, median survival time was 28.0 months. The 6-month, 1-year and 3-year overall survival rate was 84.3%, 77.5% and 37.8%, respectively, while the 6-month, 1-year and 3-year disease-free survival rate was 55.6%, 51.0% and 26.2%, respectively. However, the difference in the overall survival and disease-free survival of patients with ruptured HCCs between the emergency and delayed groups were not statistically significant ($P = 0.231$, $P = 0.134$). This may be correlated to the small sample size or the short follow-up period.

Intrahepatic recurrence and peritoneal metastasis are common in patients with HCC after hepatectomy. Compared with the recurrence of intrahepatic lesions, peritoneal metastasis are mostly diffuse and difficult to deal with clinically, and its prognosis is extremely poor.[26] The present study shows that the timing of surgery did not affect the postoperative peritoneal metastasis.

Although the disease-free survival of patients in the staged group was low after six months, it did not increase the recurrence rate and incidence of peritoneal metastasis. Similar studies have shown that emergency hepatectomy and delayed hepatectomy have no significant effect on postoperative abdominal implantation metastasis.[27] Furthermore, there was no significant difference between these two groups, which may be correlated to the small sample size. In addition, since the postoperative peritoneal metastasis was mostly imaging diagnosis, the lack of pathological basis and postoperative follow-up time, as well as other factors, could have also affected these research results. Therefore, the above conclusions need to be verified through larger sample and long-term follow-up studies.

The present univariate and multivariate analysis revealed that a tumor diameter of >10 cm and an AFP of >10,000 μg/L are peritoneal metastasis risk factors in patients with ruptured HCCs. The peritoneal metastasis of liver cancer is caused by the metastasis of intrahepatic cancer cells to the greater omentum or abdominal wall colonization. Cancer cells can originate from the protruding surface, the rupture and hemorrhage of cancers, cancer cell exfoliation and diffusion in the intraperitoneal dissemination, and colonization caused by liver puncture or operation.[25] Zhou et al[28] considered that peritoneal lavage with aseptic distilled water for 15 min can effectively kill tumor cells and significantly reduce the incidence of abdominal implantation metastasis in patients with ruptured liver cancer. Therefore, the application of non-neoplasma touch technology in the operation was particularly important. The risk of peritoneal metastasis after the operation can be reduced, and the prognosis can be improved by isolating the cancer and rinsing the abdominal cavity repeatedly during the operation. At the same time, for patients with high risk, intraperitoneal fluorouracil chemotherapy is feasible. A study conducted by Chen[29] revealed that fluorouracil implants can significantly reduce the risk of peritoneal implantation metastasis after the rupture of HCC.

In conclusion, the present result demonstrates that emergency hepatectomy is not superior to delayed hepatectomy in terms of the incidence of intraperitoneal implantation metastasis. After the initial hemostasis, delayed hepatectomy can often allow patients to achieve a better

long-term survival rate, compared with emergency hepatectomy. Due to the small number of patients and short follow-up time, there may be bias in statistics. Therefore, the above conclusions needs to be further confirmed through long term follow-up studies with more large-scale samples.

Declaration

We declare that there is no conflict of interest in connection with the work submitted.

Disclosure statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that represents a conflict of interest in connection with the work submitted.

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