# Right Atrial Tumour Thrombus in Advanced Hepatocellular Carcinoma: Surgical Techniques and Prognosis

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## ABSTRACT

Hepatocellular carcinoma (HCC) with right atrium (RA) tumour thrombus is a rare condition but the treatment always poses challenges. Debates remain with regard to the use of cardiopulmonary bypass (CPB) in the surgical procedures. The aim of the present review was to summarise the surgical procedures of RA tumour thrombus removal and to discuss the pertinent indications. Twenty-three articles involving 35 patients were collected and recruited into this study. Surgical operation for HCC was performed in 29 (82.9%) patients and non-surgical operation in 6 (17.1%) patients. RA tumour thrombus removal was performed with the aid of CPB in 25 (71.4%), venovenous bypass in 3 (8.6%), and without CPB in 7 (20%) patients. After tumour thrombus removal, RA or vessel wall reconstruction with a graft was required in 7 (20%) patients. The overall median survival time of this patient cohort was 30.8 months. The median survival time of patients who received a hepatectomy was 30.5 months, in comparison to 6.0 months for those who did not receive a hepatectomy. Aggressive surgical treatment prolongs survival of selective patients with HCC with RA tumour thrombus. CPB is helpful for complete removal of the tumour thrombus from the RA. In patients with tumour thrombus invading the RA or vessel walls, a graft repair is warranted.

**Key Words:** *Hepatocellular carcinoma, Inferior vena cava, Right atrium, Tumour thrombus.*

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## INTRODUCTION

Hepatocellular carcinoma (HCC) with tumour thrombus extending to the inferior vena cava (IVC) and right atrium (RA) is rare, accounting for about 4% of the patients.[1] Owing to the pertinent adverse events, such as right heart failure, pulmonary embolism, pulmonary metastases, Budd-Chiari syndrome, and sudden death, this condition often has a dismal prognosis.[1,2] If left untreated, the median survival of patients was only 2–5 months.[1] The advanced HCC is usually considered inoperable or at least unable to be managed with the conventional technique of subtotal liver resection due to intrahepatic and distant metastases.[3] It could be an indication of liver transplantation, but the results were also disappointing.[4] Recently, there was proof that tumour downgrading (transarterial chemoembolisation with subsequent external beam radiotherapy) followed by living donor liver transplantation was successfully performed in a 35-year-old male patient with HCC with tumour thrombus extension to the left and middle hepatic veins, IVC and RA, offered the best chance of survival. There was no recurrence of HCC happening to the patient at 1-year follow-up.[3]

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Radical resection of HCC can prolong patient survival; however, early recurrence in the remnant liver or distant metastases remains a problem after surgical operation.[5] The poor outcomes made some surgeons believe that surgical treatment was useless and thus was contraindicated for HCC with IVC/RA tumour thrombus. Nevertheless, some others achieved significant benefits in patient survival by surgical treatment of advanced HCC with IVC/RA tumour thrombus was clearly demonstrated.[6] In general, the treatment of choice for advanced HCC with IVC/RA tumour thrombus is challenging, and there have been different judgments on the outcomes. In spite of continuous reports of attempts of aggressive surgical treatments, prognoses seemed to be heterogeneous depending on patient conditions. So far, there have been scanty reports describing the surgical indications and techniques of RA tumour thrombus removal. This article aims to summarise the surgical procedures of RA tumour thrombus removal and to discuss the pertinent indications.

## METHODOLOGY

The MEDLINE, EMBASE, and Cochrane databases were comprehensively retrieved for studies published between January 2000 and December 2021. The search terms and keywords included hepatocellular carcinoma, hepatectomy, tumour thrombus, right atrium, total hepatic vascular exclusion, cardiopulmonary bypass, and cardiac surgical procedures. Additional studies were also sought by reviewing the reference lists of the recruited publications and conference abstracts. A careful

retrieval was made to try to seek randomised controlled trials that described HCC with tumour thrombus extending to the IVC and RA. Retrospective studies, case series and case reports on HCC with RA tumour thrombus were also included. The exclusion criteria were RA tumour thrombus not treated surgically, RA tumour thrombus caused by other carcinomas, and details of surgical treatment of HCC with RA tumour thrombus not being available (Figure 1).

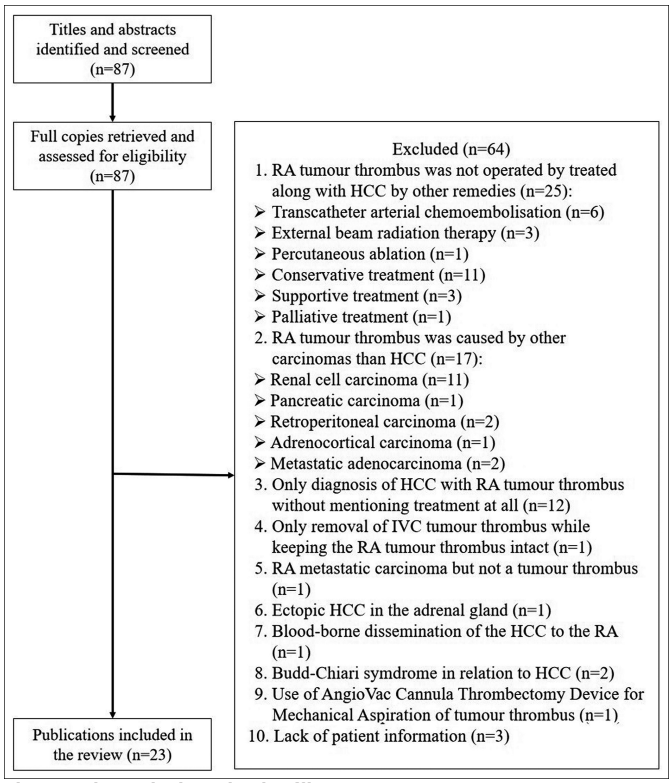


**Figure 1: The exclusion criteria of literature.**
**HCC: Hepatocellular carcinoma; RA: Right atrium; IVC: Inferior vena cava.**

The data independently extracted from each study were the study population, demographics, clinical manifestations, therapeutic strategies, procedures performed, effectiveness, and patient outcomes. Data extraction was carried out by tabulating all the necessary information from each report. This process was replicated three times by three different reviewers to avoid omissions and ensure the integrity and credibility of the data. Publication bias might affect the cumulative evidence, and the bias might come from the case reports and case series. Three reviewers independently reviewed titles, abstracts and the text as needed to determine whether studies met inclusion criteria. Conflicts between reviewers were resolved by re-review and analysis. When there was heterogeneity, the effect of each study on the overall effect was explored by removing each study individually. As a result, a total of 64 articles were excluded and 23 articles were recruited.

IBM SPSS statistics 22 software was used for the statistical analysis. The measurement data were expressed as mean ±standard deviation and median (range), while categorical data were given as numbers and percentages. The categorical variables were compared by chi-square or Fisher exact test with continuity correction. The value of $p<0.05$ was considered statistically significant. The heterogeneity was determined by an $I^2$ method, and $I^2>50\%$ with $p<0.1$ was considered a significant heterogeneity. A RevMan version 5.5.1.0 was used to draw a forest plot.

## RESULTS

All 23 articles involving 35 patients were collected and recruited into this study.[5–27] These articles included three retrospective studies,[6,21,27] 3 case series[13,25,26] and 17 case reports.[5,7–12,14–20,22–24] A forest plot of procedural survival and recurrence was shown in Figure 2.

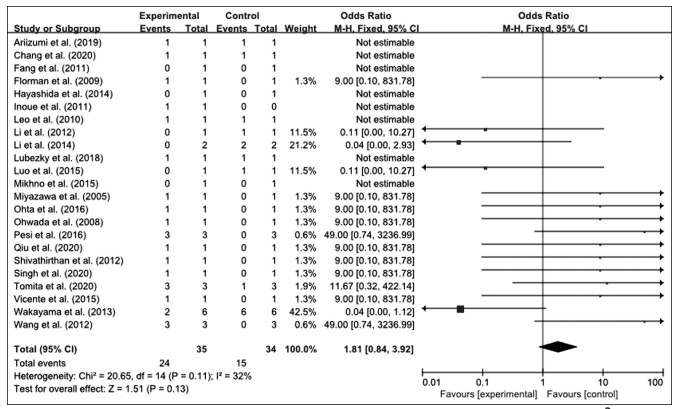


**Figure 2: A forest plot of procedural survival and recurrence ($I^2$=32%, p=0.11).**

Gender was reported for 32 patients, while the gender of the remaining 3 patients was unknown: there were 26 (81.3%) male and 6 (18.8%) female patients. Patients were at the age of 61.7 ±11.3 (range, 35–77; median, 65) years (n=32).

The onset symptoms were reported for 11 patients, with 3 (27.3%) patients being asymptomatic[11,14,15] and 8 (72.7%) patients being symptomatic. There were 16 documented symptoms for the 8 symptomatic patients: leg oedema (n=4),[5,7,9,13] dyspnoea (n=3),[5,9,17] abdominal pain (n=2),[7,13] abdominal distension (n=2),[5,16] cyanosis (n=1),[5] cold sweating (n=1),[5] night sweats (n=1),[10] tachypnoea (n=1),[5] and weight loss (n=1).[10]

All 35 patients were diagnosed with HCC with RA tumour thrombus. There were 3 (8.6%) recurrent HCCs[19,23,25] and 32 (91.4%) primary HCCs. The aetiology of HCC was reported for 15 patients: hepatitis C (n=7),[12,16,19,20,23–25] hepatitis B (n=5),[10,13–15] hepatitic disorder (n=2)[9,11], and alcoholic liver disease (n=1).[25] Preoperative liver functional results are shown in Table I.

The diagnostic precedence of HCC and RA tumour thrombus was reported for 22 patients: HCC and RA tumour thrombus were diagnosed simultaneously in 18 (81.8%) patients,[5,8,10–17,19,20,22–24,26] HCC diagnosed ahead of RA tumour thrombus in 3 (13.6%) patients (in 2 of which the HCC was diagnosed 8 and 11 years earlier, and RA tumour thrombus actually developed years later),[25] and RA tumour thrombus diagnosed first in 1 (4.5%) patient, in whom the pathology of the excised RA mass revealing a metastatic HCC prompted screening of the primary lesion.[9]

**Table I: Preoperative liver functional results**

| Indicator | n (normal/abnormal) | Mean ±SD | Range | Median |
|---|---|---|---|---|
| Alanine aminotransferase (ALT) (U/L)[5,9,11–15,20] | 8 (3/5) | 95.9 ±107.6 | 11–397 | 80 |
| Aspartate aminotransferase (AST) (U/L)[5,7,9,11-15,20,21] | 13 (4/9) | 126.6 ±177.8 | 19–593 | 60 |
| Albumin (g/dL)*[7,9,11–14,20,21] | 11 | 3.8 ±5.9 | 2.7–5.1 | 3.6 |
| Prothrombin time activity (%)[7,11,12,21] | 6 (3/3) | 78.2 ±5.9 | 74–88 | 75 |
| D-dimer (μg/mL)[5,7] | 2 (0/2) | 11.6 ±1.9 | 10.2–12.9 | 66 |
| α-fetoprotein (ng/mL)**[5,7,9–11,15,16,19,20,24,25] | 16 (6/10) | 10,026.5 ±23,185.4 | 15–85,492 | 912 |
| Fibrin degradation product (μg/mL)[5,7] | 2 (0/2) | 13.8 ±1.7 | 12.6–15 | 13.8 |
| Indocyanine green retention rate at 15 min (%)[7,11,12,21,27] | 7 (0/7) | 18.9 ±4.5 | 12–23.5 | 22.3 |

** In one of the patients, the albumin level was extremely small as to 0.0042 g/dL,[15] which was excluded from the statistics. ** The α-fetoprotein values were reported for 19 patients at the time of admission. It was reported as normal in 3 patients.[13,14] The α-fetoprotein values were extremely low in 3 patients,[21] which was excluded from the statistics.*

There were 54 diagnostic techniques that were used for the diagnosis of HCC and (or) RA tumour thrombus in 22 patients: computed tomography (n=18, 33.3%),[5,7,8,10–16,19–24] transthoracic echocardiography (n=12, 22.2%),[5,6,9,11,13,14,19,20,23,24] magnetic resonance imaging (n=8, 14.8%),[11,13,14,16,17,21] ultrasonography of the abdomen (n=7, 13.0%),[9,12,13,20,21] transoesophageal echocardiography (n=6, 11.1%),[7–10,15,20] hepatic angiogram (n=1, 1.9%),[20] IVC gram (n=1, 1.9%),[23] and positron emission tomography (PET)/computed tomography (CT) (n=1, 1.9%).[19]

A Child-Pugh class was reported for 13 patients: Class A, 12 (92.3%) patients[7,16,21,24,25,27] and Class B, 1 (7.7%) patient.[25] The locations of HCCs in the liver were described for 22 patients: it was in the right lobe in 12 (54.5%),[7–9,13,14,17–19,21–23,26] in the left lobe in 9 (40.9%),[5,10–13,20,21,24] and in both lobes in 2 (9.1%) patients.[15,16] The dimension of HCC was 103.2 ±50.2 (range, 49–210; median, 90) mm (n=11).[7,9–11,13–15,20,22,24]

The procedures of hepatectomy and RA tumour thrombus removal during the surgical operations were described for 27 patients: a one-stage operation with hepatectomy first in 20 (74.1%),[8,10–14,21–24,26,27] a one-stage operation with RA tumour thrombus removal first in 4 (14.8%)[7,15,19,20] (in one of them resection of metastatic HCC in the diaphragm was performed after RA tumour thrombus removal)[19], and an RA tumour thrombus removal only with no hepatectomy in 3 (11.1%) patients.[5,9,16] The surgical approach for hepatectomy was reported for 19 patients with laparotomy being the most common. Surgical operation for HCC was performed in 29 (82.9%) patients, including hepatectomy in 9 (31.0%),[7,12,13,15,21,22,24] lobectomy in 8 (27.6%),[17,20,27] hepatic parenchymal transection in 3 (10.3%),[8,10,26] extended segmentectomy in 2 (6.9%),[18,23] and extended hepatectomy,[11] segmentectomy,[13] sectionectomy (3.7%)[25] and diaphragmatic tumour removal in 1 (3.4%) patient each,[19] and hepatectomy unspecified in 3 (10.3%) patients.[6] The treatments of choice of HCCs in the remaining 6 patients were: postoperative transarterial chemoembolisation (TACE) in 2 (33.3%),[5,12] and microwave ablation,[16] microwave ablation plus TACE,[18] radiofrequency ablation[25] and preoperative TACE, percutaneous ethanol injection therapy, and radiofrequency ablation[25] in 1 (16.7%) patient each.

The tumour thrombus in RA was located in the lower part of RA just above the orifice of IVC in 4 (11.4%) patients.[6,9,23] In 25 patients, the tumour thrombus extended to the hepatic veins and (or) IVC: it extended to the IVC in 22 (88%),[9,11,13–17,19,20,22–26] right hepatic vein in 7 (28%),[14,17,21,26,27] left hepatic vein in 6 (24%),[11,16,20,24,27] left middle hepatic vein in 2 (8%),[21] left portal vein in 3 (12%),[10,21] middle hepatic vein in 3 (12%),[15,27] middle portal vein in 1 (4%)[10], and hepatic vein (unspecified) in 1 (4%) patient.[13] In addition, metastatic HCC was in the diaphragm in 3 patients[25] and in the right lung in 1 patient.[11] The dimension of RA tumour thrombus was 64.6 ±34.9 (range, 30–140; median, 57.5) mm (n=8).[7,9–11,21,23] RA tumour thrombus caused tricuspid regurgitation and stenosis in 1 (2.9%) patient.[9]

The surgical approach for RA tumour thrombus removal was described for 17 patients: a median sternotomy in 16 (94.1%)[11,12,15,16,19,21,22,24,27] and a partial sternotomy 1 (5.9%) patient.[7] The intrathoracic incisions for RA tumour thrombus removal were reported for 23 patients, and the manoeuvres were most commonly performed under direct vision via an RA incision.

An RA/IVC/hepatic vein thrombectomy was performed in all patients. The operation was performed on an urgent basis in 2 patients.[5,9] After tumour thrombus removal, RA/IVC/hepatic vein reconstruction with a graft was required in 7 (20%) patients: RA wall was reconstructed by using an artificial graft or a pericardial patch in 2 (28.6%) patients,[27] reconstruction of the hepatic vein in 2 (28.6%) patients (with polytetrafluoroethylene ringed graft[21] and interposed polytetrafluoroethylene ringed graft[12] in one patient each), IVC defect patch repair in 3 (42.8%) patients (with polytetrafluoroethylene,[11] with autologous pericardial tube graft,[22] and with horse pericardium patch[23] in one patient, each).

RA tumour thrombus removal was performed with the aid of cardiopulmonary bypass (CPB) in 25 (71.4%), a venovenous bypass in 3 (8.6%), and without CPB in 7 (20%) patients. In addition, CPB techniques also included hypothermic circulatory arrest (HCA) in 6 (17.1%),[5,12,17,21] a beating heart in 2 (5.7%)[19,22], and (right) femoral vein cannulation in 5 (14.3%) patients.[5,7,11,19,20]

The indications for HCA were a huge tumour thrombus,[5] a preserved liver function that could be tolerable to HCA,[12] and the concern about the advantages of reduced blood loss and better and thorough thrombus removal with lesser ischaemic damage.[21] CPB with a beating heart was aimed to avoid ischaemic damage and intraoperative hypotension.[19]

Among the 4 patients with an RA tumour thrombus in the lower part of RA just above the orifice of IVC, one patient was operated on under CPB[9], and 3 were on total hepatic vascular exclusion (THVE).[6,23]

The CPB time was 51.5 ±31.8 (range, 32.2–123; median, 42) min (n=7). The HCA times were reported in 2 patients, and both were 14 min.[12,21] A THVE was applied in 20 patients.[6,7,10,11,14,19,20,23–27] The THVE time was 20.0 ±6.0 (range, 12–30; median, 20) min (n=10).[10,11,14,19,20,23–25] The operation time was 8.4 ±3.0 (range, 3–13.4; median, 9) hours (n=15).[6,7,10,11,14,15,19–23,25,27] Blood loss was 3,199.6 ±2,422.0 (range, 800–8,200; median, 2,474) mL (n=15).[6,7,11,14,15,19–21,23,25,27]

The surgical specimens of HCC were pathologically investigated in 16 patients: 9 (56.3%) were moderately differentiated,[11,14,15,21,23–25] 2 (12.5%) were moderately to poorly differentiated[7,12], and 5 (31.2%) were poorly differentiated.[10,19,20,25] A positive surgical margin was found in 4 patients,[19,25] which was in the diaphragm in 3 patients[25] and in both the surgical stump of the diaphragm and in the IVC in 1 patient.[19] A negative surgical margin was reported for 3 patients.[10,11,15]

Patients' hospital stay after the operation was 20.3 ±10.1 (range, 10–43; median, 16.1) days (n=20)[6,7,11,13,15,16,18–27]. Postoperative α-fetoprotein was reported for 3 patients with a mean of 226.0 ±302.7 (range, 16–573; median, 89) ng/mL (n=3).[25] Patients were on a follow-up of 16.1 ±19.0 (range, 1.3–98; median, 6) months (n=20).[5–13,15,16,18–22,24–27]

Postoperative metastasis occurred in 18 (51.4%) patients. The metastatic sites were reported in 17 patients: in the lung in 6 (35.3%),[7,12,15,27] in the remnant liver in 3 (17.6%),[13,25] and in the parasternal site,[25] diaphragm,[8] right thoracic cavity and vertebral body,[19] right posterior lobe and portal vein,[16] lung and bone,[25] lung and adrenal gland,[27] lymph node,[27] and brain,[27] in 1 (5.9%) patient, each. The time of metastasis was 7.6 ±5.3 (range 1–17; median, 6) months (n=8) after operation.

The prognoses of 31 patients were known. At the end of follow-up, 13 (41.9%) patients were still alive,[7,8,10–12,18–20,22–24,26,27] whereas, 18 (58.1%) died[5,9,13–17,21,25,27] ($\chi^2$=1.6, p=0.310). A Kaplan-Meier survival analysis showed that the overall median survival time of this patient cohort was 30.8 months. The median survival time of patients receiving a hepatectomy was 30.5 months, in comparison to 6.0 months for those without receiving a hepatectomy.

## DISCUSSION

From a technical point of view, the RA tumour thrombus can be removed under THVE, CPB, or both. When tumour thrombus extends just inside the IVC, the thrombus can be extracted by placing a Satinsky clamp longitudinally at the cavotomy site, even without the use of THVE.[6]

THVE is usually necessary in thrombectomy for IVC tumour thrombus. A THVE by clamping the infrahepatic IVC, the hepatic artery, and the portal vein may support the open surgery for tumour thrombus only involving the suprahepatic or retrohepatic IVC or tumour thrombus only slightly extending to RA.[26] Thrombectomies performed under THVE by reducing the liver caudally help moving the tumour thrombus inferiorly, and THVE could be achieved by looping the IVC just below the confluence into the RA without the use of CPB.[6] THVE can decrease operative bleeding while removing the tumour thrombus inside the IVC.[16] CPB preserves intraoperative circulation, although CPB has potential risks of coagulation dysfunction, transient immunosuppression, and tumour dissemination.[19] HCA also has the advantage of reducing operative bleeding and liver damage.[17]

THVE is usually indicated for tumour thrombi extending into the IVC above the diaphragm or just extending into the RA, which can be reduced manually but carries a risk of incomplete resection.[28] For patients with tumour thrombus into the supradiaphragmatic IVC, access can be made via laparotomy by dividing the diaphragm without the median sternotomy or thoracotomy. After liver mobilisation and subsequent dissection between the liver and the diaphragm, the liver could be reduced caudally and the tumour thrombus moved inferiorly. THVE could be applied at the level of the IVC just below the confluence into the RA. In this way, thrombectomy could be performed under THVE without the use of CPB.[6] Shivathirthan *et al*.[23] also applied a technique of caudal traction of the mobilised liver, and facilitating retracting the tumour thrombus caudally. THVE with RA clamping just above the IVC orifice may sometimes bring about complications including dysarrhythmias and conduction system injury.[23] Shivathirthan *et al*.[23] summarised the indications of use of THVE as tumour thrombus slightly protruding the RA with no involvement of the tricuspid valve or right ventricle; with no invasion of the right atrial wall; and caudal traction of the mobilised liver helping the retraction of the tumour thrombus.

An alternative technique is use of normothermic CPB usually combined with THVE. The use of CPB with HCA in cirrhotic patients was restrained for fear of intraoperative bleeding, possible cerebral damage, and preoperative hepatic failure.[21] Shivathirthan *et al*. recommended CPB with cardiac arrest was used, when tumour thrombus invades the RA wall or extends into the RA.[23] Otherwise, tumour thrombus removal could be performed on CPB with a beating heart. Ohwada *et*

*al*. suggested HCA time should be kept within 40 min for completing RA tumour thrombus removal.[20] However, HCA time >40 min is required in some complicated cases or for simultaneous liver tumour resection, and combined techniques, such as THVE, descending aorta clamping, or occlusion balloon catheter insertion should be considered.

The use of CPB depended on the extension of tumour thrombus into the RA. CPB was mandatory for removing tumour thrombus extending fully into the RA, while THVE is enough when tumour thrombus was slightly protruded into the RA.[6] Shivathirthan *et al*. proposed that the use of CPB depended on whether the tumour thrombus invaded the IVC or RA wall.[23] Wang *et al*. reported that the patients with surgical treatment of advanced HCC had 1-, 3- and 5-year survival of 68.0%, 22.5%, and 13.5%, respectively, and a median survival time of 19 months, with the longest survival of 105 months.[6] The present study revealed a median survival of 30.8 months, much longer than that reported in the literature. This might be attributed to the high selectivity of patients with a low preoperative metastatic rate (3/35, 8.6%).

From the present study, the indications for surgical radical removal of the tumour thrombus were patient with: well-preserved liver function without distant metastasis;[14] asymptomatic sudden elevation of liver function tests;[15] the tumour was not invading the RA wall and that the patient had well-preserved heart function;[19] prevention of sudden death due to tumour thrombosis;[25] and the symptomatic patient had a risk of sudden death due to tumour thrombus in the RA.[7]

In short, CPB was necessary for tumour thrombus extending into the RA, and THVE without CPB was enough for those IVC or RA was not invaded by tumour thrombus. Preoperative tumour downgrading is helpful for easy tumour thrombectomy by stabilising tumour thrombus, reducing tumour size, facilitating tumour removal, and preventing tumour fragmentation.[23]

A small patient population of this cohort and incomplete information of some patients constituted the main drawbacks of this study. As a result, there showed no significant difference in the median survival between patients with the use of CPB and those without the use of CBP. In addition, the roles that a beating heart and HCA played in the surgical treatment were unable to be evaluated.

## CONCLUSION

Aggressive surgical treatment prolongs the survival of selective patients HCC with RA tumour thrombus. CPB is helpful for the complete removal of the tumour thrombus from the RA. In patients with tumour thrombus invading the RA or vessel walls, a graft repair is warranted.

**COMPETING INTERESTS:**

The author declared that he has no competing interests.

**AUTHOR'S CONTRIBUTION:**

SMY: Substantial contribution to the conception and design of the work; and the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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