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ORIGINAL RESEARCH

Effect of Low-Dose Aspirin Use After Thermal Ablation in Patients with Hepatocellular Carcinoma: A Retrospective Study

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Purpose: To determine the effect of aspirin on hepatocellular carcinoma (HCC) recurrence and survival after thermal ablation.

Methods: A retrospective analysis was performed to evaluate the efficacy and safety of aspirin in combination with thermal ablation. The clinical data were collected for the enrolled patients. Progression-free survival (PFS), overall survival (OS), and adverse events were analyzed.

Results: A total of 174 patients with HCC were enrolled. The median PFS was 11.1 (95% confidence interval [CI]: 8.1−14.0) months for patients who took aspirin and 8.6 (95% CI: 5.5−11.8) months for patients who did not take aspirin. The median OS of patients in the aspirin group was 76.7 (95% CI: 58.1−95.3) months and that in the non-aspirin group was 53.5 (95% CI: 42.7−64.3) months. In patients with non-viral HCC, OS was significantly better for the aspirin group (P = 0.03) after ablation. The PFS of patients who underwent ablation alone in the aspirin group was obviously superior to that of patients in the non-aspirin group (P = 0.002). Stratified Cox regression analysis demonstrated that aspirin use after ablation might be a protective factor in specific HCC patient subgroups. The incidence of major adverse events did not significantly differ between the two groups.

Conclusion: Low-dose aspirin use was associated with better OS in patients with non-viral HCC after thermal ablation. In patients who received thermal ablation alone, the administration of low-dose aspirin could improve PFS. Aspirin use might be a protective factor in some patients after ablation.

Keywords: thermal ablation, aspirin, hepatocellular carcinoma, survival analysis, retrospective study

Introduction

Liver cancer is one of the most common malignant tumors. Hepatocellular carcinoma (HCC) accounts for the majority of liver cancers, and its incidence and mortality rates have been increasing over recent years.[1] The development of HCC is attributable to several causative factors and underlying liver disease, including hepatitis B virus infection, hepatitis C virus infection, alcoholic liver disease, and nonalcoholic steatohepatitis.[2] Thermal ablation has recently received considerable attention as a minimally invasive treatment for liver cancer. Both radiofrequency ablation (RFA) and microwave ablation (MWA) have been demonstrated to have survival benefits for HCC.[3] Moreover, combination therapy with transarterial chemoembolization (TACE) and ablation has also shown promising efficacy.[4,5] However, there are still substantial challenges in the management of HCC due to its high recurrence rates and the short survival period after ablation.

Aspirin, a nonsteroidal anti-inflammatory drug, is commonly used for the treatment of inflammatory diseases. Interestingly, long-term administration of aspirin has been observed to be associated with a low risk of cancer and

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favorable survival.[6,7] Several studies have explored the direct or indirect anticancer mechanisms of aspirin and have found that it might exert anticancer effects by inhibiting the activity of cyclooxygenase (COX), suppressing tumor cell-induced angiogenesis, and regulating glucose metabolism.[8–10] Our previous study found that low-dose aspirin administration during immune checkpoint inhibitor treatment is associated with better progression-free survival (PFS); this indicates that low-dose aspirin might play a potential adjuvant role in cancer management.[11] With regard to HCC, population-based studies have shown that aspirin use is associated with a reduced risk of HCC.[12,13] An updated systematic review and meta-analysis including approximately 2.5 million subjects, 822680 aspirin users, and 20626 HCC cases demonstrated a 30% reduced risk of HCC associated with aspirin use.[14] It was showed that aspirin significantly reduced the risk of HCC by 19% in Asia and by 33% in Europe and the U.S with no significant difference.[15] In a large-scale, long-term retrospective study, a 37% risk of HCC was reduced through aspirin therapy for high-risk patients with non-alcoholic fatty liver disease.[16] In addition, aspirin use was found to significantly decrease the risk of HCC recurrence after curative resection.[17] However, a cohort study demonstrated that while aspirin was beneficial in young individuals, males, or patients with viral hepatitis, it did not exert any protective effect in patients with liver cirrhosis.[18] Thus, the role of aspirin use in HCC remains controversial.

To date, only a few clinical studies have investigated the effect of aspirin in patients with liver cancer. In one such study, a matched-pair analysis demonstrated that using aspirin in combination with TACE might improve overall survival (OS) in patients with unresectable HCC.[19] Further, a retrospective study on 304 HCC patients that evaluated the efficacy of aspirin use after embolization suggested that aspirin use was associated with improved liver function and longer survival.[20] Aspirin use was also found to be beneficial in HCC patients receiving sorafenib and regorafenib treatment.[21] In addition, in animal models, the anti-inflammatory effect of aspirin effectively inhibits the proliferation, invasion, and metastasis of residual tumor cells after thermal ablation.[22] However, there is no clinical study on the association between aspirin use and the efficacy of liver tumor ablation. Thus, the role of aspirin as an adjuvant therapeutic agent for thermal ablation in HCC patients remains to be determined. In the present study, patients receiving thermal ablation treatment were included and followed up in order to investigate the effect of aspirin use on HCC after ablation.

Methods

Study Design

This was a retrospective study carried out in a major tertiary teaching hospital in Beijing. All procedures were performed according to the Declaration of Helsinki with the approval of the Ethics Committee at Beijing Ditan Hospital (KY2022-048). Informed consent was waived by the institutional review board of Beijing Ditan Hospital due to the retrospective nature of the study and anonymized data.

Patient Selection

The study population was sourced from inpatients treated with ablation therapy from July 2011 to June 2021. Inclusion criteria for the experimental group (aspirin group) were as follows: 1) diagnosed with HCC via histopathologic or imaging examination; 2) receiving thermal ablation treatment (RFA or MWA); 3) continuing to use low-dose aspirin (100 mg/day) for at least 1 month. Exclusion criteria for the experimental group: 1) with other active concomitant malignancies; 2) Child-Pugh grade C; 3) inadequate organ function; 4) incomplete medical records.

The patients in the control group (non-aspirin group) were randomly selected from inpatients who underwent thermal ablation therapy without aspirin administration during the same period based on the inclusion of the aspirin group. Inclusion criteria for the control group: 1) diagnosed with HCC via histopathologic or imaging examination; 2) receiving thermal ablation treatment (RFA or MWA) during the same period as the aspirin group (the time interval between the aspirin group patients and the control group patients receiving ablation therapy should be less than one week); 3) lack of aspirin use. Exclusion criteria were the same as those for the experimental group: 1) with other active concomitant malignancies; 2) Child-Pugh grade C; 3) inadequate organ function; 4) incomplete medical records. Numbers were assigned according to the order of admission to the patients who satisfied the study criteria. Then the random selection

was performed by the random-digit method, using computer-generated numbers. The control group was composed according to a ratio of 1:2 (aspirin group versus control group).

Ablation Procedure

Ablation procedures were performed as previously described.[23,24] Patients were under conscious analgesic sedation by intravenous administration of 0.5 mg atropine, 0.1 g pethidine hydrochloride, and 10 mg diazepam and application of local anesthesia (5 mL of 1% lidocaine). RFA and MWA were performed percutaneously under CT guidance. A 18-G puncture needle was used to lead the electrode/antenna to the target lesion. MWA was more frequently applied for large tumors adjacent to big vessels, and RFA was preferred to treat tumors with smaller size or near important tissues such as colon, heart or gallbladder. To ensure that the electrode/antenna was in the correct location, the angle and depth of each puncture were precisely calculated based on intraoperative CT scans. Ablative parameters and duration time were designed to induce a desired necrotic zone. After the procedure, the needle tract was ablated to prevent tumor dissemination and hemorrhage.

Data Collection

The electronic medical records were reviewed to collect the following clinical data: age, gender, etiology, cirrhosis, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, Child-Pugh classification, Barcelona Clinic Liver Cancer (BCLC) stage, ascites, tumor conditions (including tumor number, maximum tumor diameter, vascular invasion, and extrahepatic metastasis), treatment, medication, comorbidities, and laboratory tests (including blood routine, coagulation test, liver function, kidney function, alpha-fetoprotein [AFP] level, and C-reactive protein [CRP] level).

Follow-Up

All the patients were followed up until June 2023. The follow-up information came from in-clinic follow-up or telephone follow-up. The follow-up contents consisted of physical examination, laboratory test, radiographic report (contrast enhanced CT or MRI), and survival. The PFS and OS were assessed as the primary outcomes. Based on the Modified Response Evaluation Criteria In Solid Tumors (mRECIST), PFS was defined as the time from ablation to the earliest date of progressive disease (PD), death, or last follow-up.[25] OS was defined as the time from ablation to death or last follow-up. The secondary outcome was any adverse event due to treatment.

Statistical Analysis

SPSS 25.0 and R 4.1.1 were used to perform statistical analysis. Data were presented as mean ± standard deviation, median (interquartile range [IQR]), or number (%) as appropriate. Student's *t*-test was used to compare quantitative data, while Chi-square and Fisher's exact tests were used for qualitative data. For non-normal continuous variables, Mann–Whitney *U*-test was conducted. Survival curves were obtained using the Kaplan-Meier method, and the survival outcomes were compared using the Log rank test. Hazard ratio (HR) was estimated with stratified Cox regression analysis. P-value < 0.05 was considered statistical significant.

Results

Baseline Characteristics

A total of 58 patients with HCC who had taken aspirin prior to ablation were assigned to the aspirin group, and 116 patients who underwent ablation during the same period and had no history of taking aspirin were assigned to the control or non-aspirin group (Figure 1). Retrospective data were collected and analyzed for all 174 patients. Table 1 shows the baseline characteristics of the two groups. There was no significant difference in demographic features, tumor characteristics, laboratory test results, and treatments between the two groups. Of the 174 patients, 116 received combination therapy with TACE, including 37 patients in the aspirin group and 79 patients in the non-aspirin group. No significant

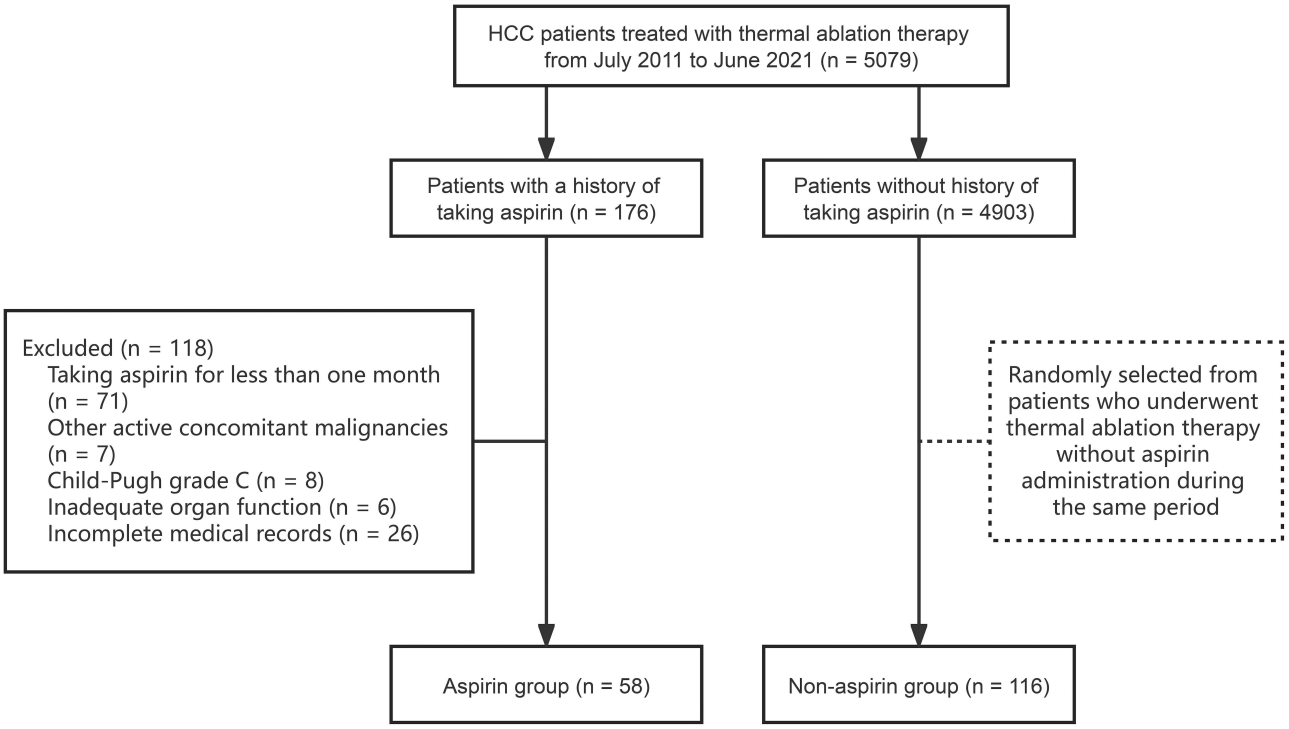

Figure 1 Patient selection flowchart.
Abbreviations: HCC, hepatocellular carcinoma.

difference in the complete ablation rate was found between the two groups (70.7% vs 59.5%, $P = 0.15$). The median follow-up time was 52.0 (IQR: 32.5−81.6) months for all the patients.

In the aspirin group, indications for aspirin administration were classified into four categories: presence of cardiovascular risk factors such as hypertension and dyslipidemia (n = 8), history of atherothrombotic disease (n = 23), postoperative treatment after cardiac surgery or percutaneous coronary intervention (PCI) (n = 19), and prevention of thrombosis (n = 8). In the aspirin group, 49 patients had taken aspirin consecutively over 3 months.

Table 1 Demographical Characteristics and Clinical Data of the Patients

Variables	Aspirin Group (n=58)	Non-Aspirin Group (n=116)	*P* value
Demographics			
Age (y, Mean ± SD)	63 ± 9	60 ± 9	0.08
Gender (Male/Female)	50/8	97/19	0.66
Etiology (HBV/HCV/HBV+HCV/Others)	42/3/1/12	96/13/0/7	> 0.05
Cirrhosis	47 (81.0%)	96 (82.8%)	0.78
ECOG PS (0/1)	29/29	70/46	0.19
Ascites	11 (19.0%)	35 (30.2%)	0.11
Child-Pugh class (A/B)	54/4	97/19	0.08
BCLC (0/A/B/C)	12/24/10/12	16/48/26/26	0.31

(*Continued*)

Table 1 (Continued).

Variables	Aspirin Group (n=58)	Non-Aspirin Group (n=116)	*P* value
Tumor			
Tumor number (Solitary/Multinodular)	38/20	64/52	0.19
Maximum tumor diameter (cm)	2.5 (1.7–4.0)	3.0 (2.0–4.5)	0.19
Vascular invasion	7 (12.1%)	18 (15.5%)	0.54
Extrahepatic metastasis	7 (12.1%)	13 (11.2%)	0.87
Laboratory test			
PLT (10~9/L)	131 (96–192)	116 (69–165)	0.10
INR (≤1.2/>1.2)	52/6	93/23	0.11
ALT (U/L)	27 (18–45)	26 (18–36)	0.18
AST (U/L)	29 (21–39)	28 (21–40)	0.78
TBIL (μmol/L)	13 (9–19)	14 (11–19)	0.21
ALB (g/L)	39 ± 4	39 ± 5	0.31
AFP (ng/mL)	7 (3–71)	11 (4–90)	0.50
CRP (mg/L)	2.4 (1.1–8.4)	2.7 (1.3–10.6)	0.70
Treatment			
Combination with TACE	37 (63.8%)	79 (68.1%)	0.57
Subsequent radiotherapy	5 (8.6%)	4 (3.4%)	0.28
Subsequent TKI	11 (19.0%)	27 (23.3%)	0.52
Subsequent immunotherapy	4 (6.9%)	7 (6.0%)	> 0.99

Abbreviations: SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; PLT, platelets; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; CRP, C-reactive protein; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitors.

Survival Analysis

Figure 2 depicts the Kaplan–Meier survival curves for comparing PFS and OS between the two groups. The median PFS were 11.1 (95% confidence interval [CI]: 8.1−14.0) months for patients who took aspirin and 8.6 (95% CI: 5.5−11.8) months for patients who did not take aspirin. The cumulative 6-month, 1-year, and 2-year PFS rates were 68.4%, 45.0%, and 28.7%, respectively, in the aspirin group and 66.3%, 44.0%, and 22.7%, respectively, in the non-aspirin group. The median OS of patients in the aspirin group was 76.7 (95% CI: 58.1−95.3) months and that in the non-aspirin group was 53.5 (95% CI: 42.7−64.3) months. The cumulative 1-, 3-, and 5-year OS rates were 94.6%, 76.4%, and 67.3%,

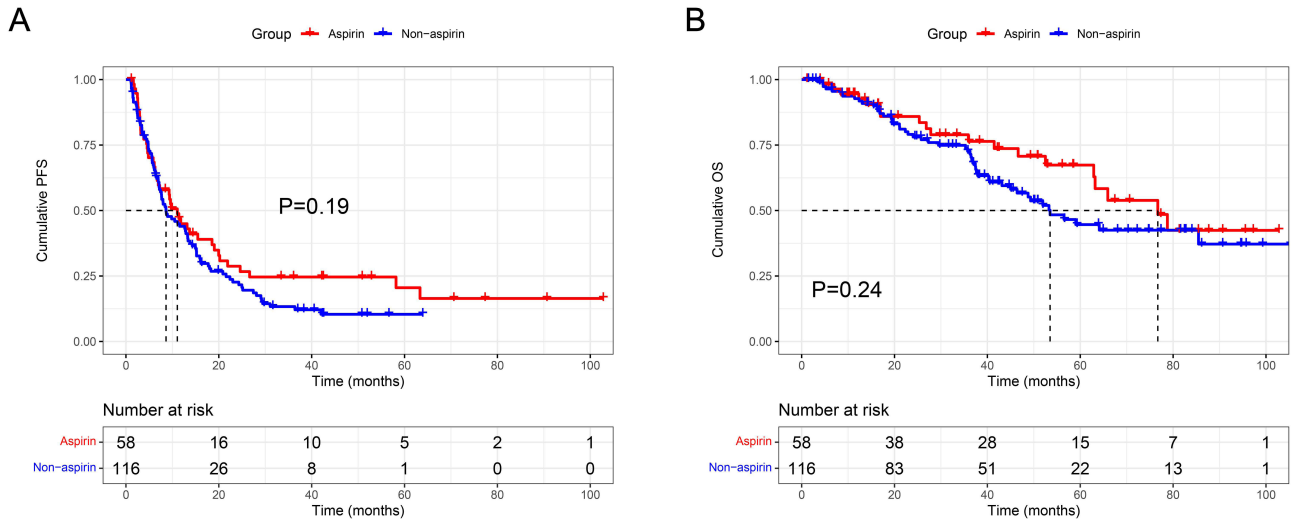

Figure 2 Comparison of PFS (**A**) and OS (**B**) between the two groups.
Abbreviations: PFS, progression-free survival; OS, overall survival.

respectively, in the aspirin group and 92.7%, 72.6%, and 44.6%, respectively, in the non-aspirin group. There was no statistically significant difference between the two groups in terms of PFS (P = 0.19) and OS (P = 0.24).

Subgroup Analysis

Subgroup analysis was performed for patients with HCC according to etiology and combination treatment. For patients with hepatitis B virus or hepatitis C virus infection, no significant difference in PFS and OS was found between the aspirin group and the non-aspirin group (Figure 3A, B, D and E; $P > 0.05$). In patients with non-viral HCC, OS was significantly better in the aspirin group (Figure 3F, P = 0.03) after ablation than in the non-aspirin group, while PFS was not significantly different (Figure 3C, P = 0.15). The PFS of patients who underwent only ablation in the aspirin group was obviously superior to that of patients who underwent only ablation in the non-aspirin group (Figure 4A, P = 0.002). However, there was no significant difference in OS (Figure 4C, P = 0.12). The difference in the PFS (Figure 4B, P = 0.45) and OS (Figure 4D, P = 0.88) of patients who received TACE + ablation did not reach statistical significance.

Stratified Cox Regression Analysis

The effect of aspirin in different populations with HCC was confirmed by stratified Cox regression analysis (Figures 5 and 6). The use of aspirin was identified as a significant protective factor for PFS in the following groups of patients: age ≤ 60 years (HR = 0.53, 95% CI = 0.29−0.95, P = 0.03), female gender (HR = 0.23, 95% CI = 0.06−0.80, P = 0.02), ECOG PS = 0 (HR = 0.50, 95% CI = 0.29−0.86, P = 0.01), ascites (HR = 0.34, 95% CI = 0.14−0.85, P = 0.02), and those receiving ablation alone (HR = 0.35, 95% CI = 0.18−0.69, P = 0.003). Aspirin had a similar protective effect in terms of OS in the following groups of patients: age ≤ 60 years (HR = 0.37, 95% CI = 0.14−0.97, P = 0.04), non-viral etiology (HR = 0.24, 95% CI = 0.06−0.98, P = 0.047), and BCLC stage B-C (HR = 0.41, 95% CI = 0.18−0.95, P = 0.04). It was shown that aspirin use was significantly associated with an increased risk of tumor progression and poor survival after ablation in patients with tumor diameter > 5 cm (HR > 1, P < 0.05).

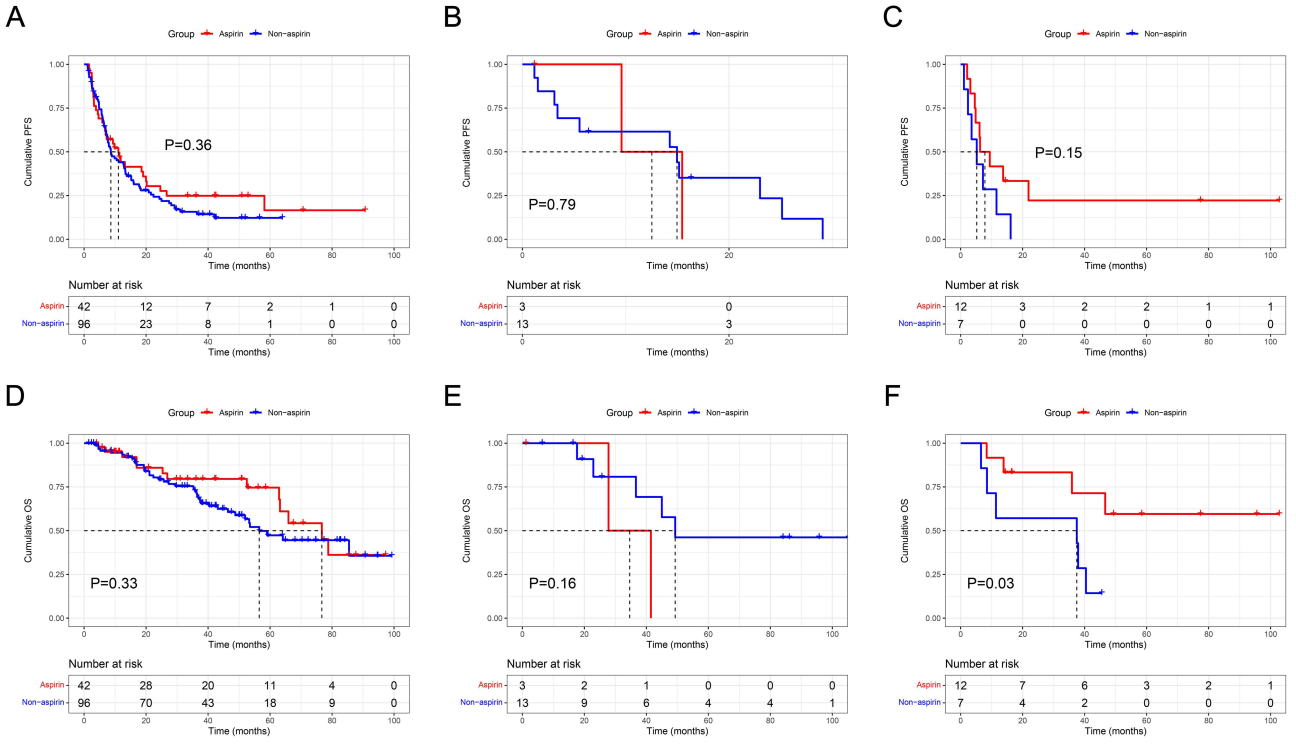

Figure 3 Comparison of PFS and OS in patients with different etiologies between the two groups. (**A**) PFS in HCC patients with hepatitis B virus infection, (**B**) PFS in HCC patients with hepatitis C virus infection, (**C**) PFS in patients with non-viral HCC, (**D**) OS in HCC patients with hepatitis B virus infection, (**E**) OS in HCC patients with hepatitis C virus infection, and (**F**) OS in patients with non-viral HCC.

Abbreviations: PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma.

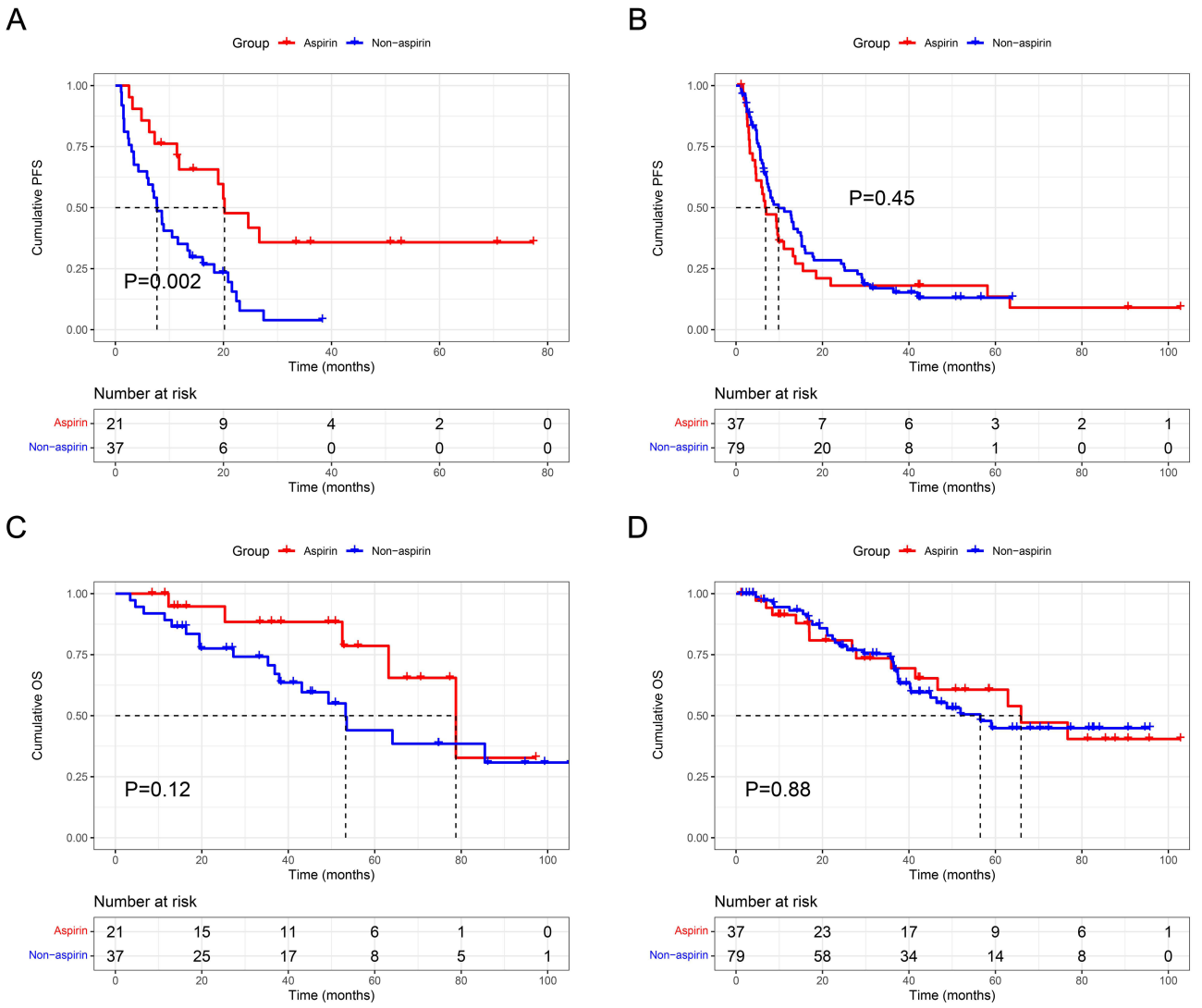

Figure 4 Comparison of PFS and OS in patients receiving ablation treatment with or without TACE between the two groups. (**A**) PFS in patients who underwent only ablation, (**B**) PFS in patients who received TACE + ablation, (**C**) OS in patients who underwent only ablation, and (**D**) OS in patients who received TACE + ablation.
Abbreviations: PFS, progression-free survival; OS, overall survival; TACE, transarterial chemoembolization.

Adverse Events

The incidence of the following major adverse events after ablation was compared between the two groups (Table 2): postoperative fever; pain in the liver region; gastrointestinal reactions; decrease in hemoglobin levels; decline in platelets (PLT); prolonged prothrombin time (PT); increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL); decline in albumin (ALB); abnormal renal function; elevated AFP; and increase in CRP levels. All adverse events were mild and could be alleviated or eliminated effectively after symptomatic treatment. The incidence of major adverse events was not significantly different between the two groups. In the aspirin group, tumor necrosis with local infection and encapsulated effusion in the lower right liver lobe were observed in one case each. In the non-aspirin group, postoperative increase in blood pressure, liver abscess, and intra-abdominal infection were observed in one case each, and two patients developed pulmonary inflammation. No treatment-related deaths occurred. During the follow-up period, 13.8% of the patients in the aspirin group and 12.1% in the non-aspirin group experienced gastrointestinal bleeding events, but there was no significant difference in its incidence. At the end of follow-up, a total of 69 (39.7%) patients died of end-stage liver disease or other serious complications, including 19 patients (32.8%) in the aspirin group and 50 patients (43.1%) in the non-aspirin group.

Variable	N	Aspirin	Non−aspirin	HR (95%CI)	P value
Age (y)					
<=60	79	23	56	0.53 (0.29−0.95)	0.03
>60	95	35	60	1.04 (0.65−1.66)	0.87
Gender					
Male	147	50	97	0.96 (0.65−1.41)	0.82
Female	27	8	19	0.23 (0.06−0.80)	0.02
Etiology					
HBV	138	42	96	0.82 (0.54−1.25)	0.36
HCV	16	3	13	1.23 (0.26−5.83)	0.79
Others	19	12	7	0.48 (0.17−1.34)	0.16
Cirrhosis					
No	31	11	20	1.21 (0.53−2.74)	0.66
Yes	143	47	96	0.72 (0.48−1.09)	0.12
ECOG					
0	99	29	70	0.50 (0.29−0.86)	0.01
1	75	29	46	1.33 (0.79−2.23)	0.28
Ascites					
No	128	47	81	0.99 (0.66−1.49)	0.97
Yes	46	11	35	0.34 (0.14−0.85)	0.02
Child−Pugh class					
A	151	54	97	0.88 (0.60−1.30)	0.53
B	23	4	19	0.30 (0.07−1.29)	0.11
BCLC					
0−A	100	36	64	0.97 (0.60−1.57)	0.90
B−C	74	22	52	0.65 (0.36−1.16)	0.14
Tumor number					
Solitary	102	38	64	0.83 (0.51−1.33)	0.43
Multinodular	72	20	52	0.90 (0.51−1.59)	0.71
Maximum tumor diameter (cm)					
<=5	129	48	81	0.90 (0.59−1.36)	0.61
>5	21	5	16	3.45 (1.07−11.17)	0.04
Vascular invasion					
No	149	51	98	0.89 (0.60−1.30)	0.53
Yes	25	7	18	0.29 (0.08−1.02)	0.054
Extrahepatic metastasis					
No	154	51	103	0.73 (0.49−1.07)	0.11
Yes	20	7	13	3.00 (0.96−9.34)	0.06
Combination with TACE					
No	58	21	37	0.35 (0.18−0.69)	0.003
Yes	116	37	79	1.18 (0.77−1.83)	0.45
Complete ablation					
No	64	17	47	1.33 (0.73−2.42)	0.35
Yes	110	41	69	0.81 (0.51−1.30)	0.39

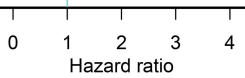

Figure 5 Stratified Cox regression analysis for PFS. P values less than 0.05 were marked in red font.
Abbreviations: PFS, progression-free survival; N, number; HR, hazard ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization.

Variable	N	Aspirin	Non−aspirin	HR (95%CI)	P value
Age (y)					
<=60	79	23	56	0.37 (0.14−0.97)	0.04
>60	95	35	60	1.08 (0.56−2.08)	0.82
Gender					
Male	147	50	97	0.78 (0.45−1.35)	0.38
Female	27	8	19	0.40 (0.05−3.24)	0.39
Etiology					
HBV	138	42	96	0.73 (0.39−1.38)	0.34
HCV	16	3	13	3.42 (0.56−20.71)	0.18
Others	19	12	7	0.24 (0.06−0.98)	0.047
Cirrhosis					
No	31	11	20	1.23 (0.40−3.78)	0.72
Yes	143	47	96	0.62 (0.34−1.14)	0.12
ECOG					
0	99	29	70	0.56 (0.27−1.18)	0.13
1	75	29	46	1.11 (0.50−2.48)	0.80
Ascites					
No	128	47	81	0.88 (0.46−1.66)	0.69
Yes	46	11	35	0.64 (0.24−1.71)	0.37
Child−Pugh class					
A	151	54	97	0.81 (0.46−1.42)	0.46
B	23	4	19	0.59 (0.08−4.55)	0.61
BCLC					
0−A	100	36	64	1.26 (0.61−2.61)	0.54
B−C	74	22	52	0.41 (0.18−0.95)	0.04
Tumor number					
Solitary	102	38	64	0.80 (0.39−1.63)	0.53
Multinodular	72	20	52	0.71 (0.32−1.57)	0.40
Maximum tumor diameter (cm)					
<=5	129	48	81	0.77 (0.40−1.49)	0.43
>5	21	5	16	4.39 (1.13−17.03)	0.03
Vascular invasion					
No	149	51	98	0.86 (0.48−1.56)	0.62
Yes	25	7	18	0.47 (0.13−1.69)	0.25
Extrahepatic metastasis					
No	154	51	103	0.81 (0.46−1.42)	0.46
Yes	20	7	13	0.52 (0.11−2.40)	0.40
Combination with TACE					
No	58	21	37	0.46 (0.17−1.25)	0.13
Yes	116	37	79	0.95 (0.51−1.79)	0.88
Complete ablation					
No	64	17	47	1.46 (0.68−3.12)	0.33
Yes	110	41	69	0.65 (0.31−1.39)	0.27

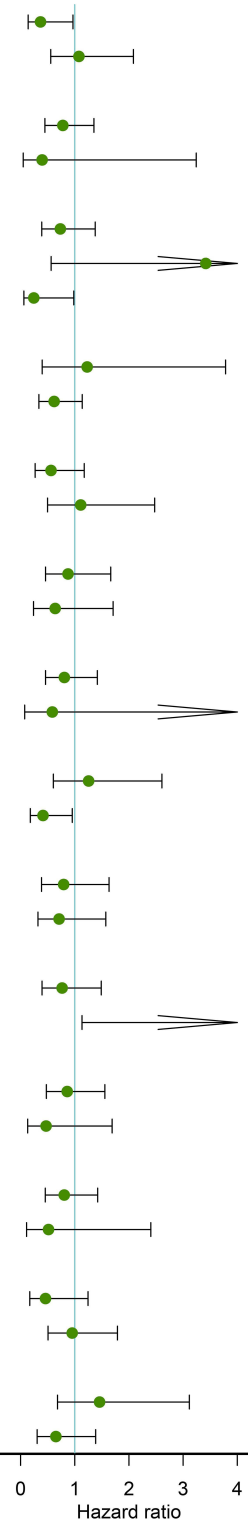

Figure 6 Stratified Cox regression analysis for OS. *P* values less than 0.05 were marked in red font.
Abbreviations: OS, overall survival; N, number; HR, hazard ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization.

Table 2 Adverse Events

Adverse Events	Aspirin Group	Non-Aspirin Group	*P* value
Postoperative fever	27.6%	22.1%	0.43
Pain in the liver region	20.7%	24.8%	0.55
Gastrointestinal reactions	20.7%	21.2%	0.93
Decrease of hemoglobin	13.8%	16.4%	0.66
Decline in PLT	19.0%	30.9%	0.10
Prolonged PT	28.3%	37.8%	0.28
Rise in ALT	56.9%	50.9%	0.46
Rise in AST	70.7%	66.1%	0.54
Rise in TBIL	22.4%	35.7%	0.08
Decline in ALB	48.3%	35.7%	0.11
Abnormal renal function	31.0%	38.7%	0.32
AFP elevation	16.0%	18.5%	0.71
Increased CRP level	50.0%	43.8%	0.64
Gastrointestinal bleeding	13.8%	12.1%	0.75

Abbreviations: PLT, platelets; PT, prothrombin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; CRP, C-reactive protein.

Discussion

With the development of minimally invasive technology, thermal ablation has become an important component of the management of liver cancer. It has been reported that HCC patients receiving ablation have a similar prognosis as those receiving resection, especially in cases of early-stage HCC.[26] The combined application of various technologies has also enabled the development of thermal ablation techniques for the treatment of liver cancer that go beyond early-stage cancers.[27,28] However, local tumor progression is the main factor influencing the survival benefit for patients after ablation.[29] Importantly, incomplete thermal ablation has been demonstrated to be associated with tumor progression in patients with HCC.[30] It has been suggested that insufficient radiofrequency ablation could promote residual HCC cell progression in vitro by enhancing autophagy via the HIF-1α/BNIP3 pathway.[31] Therefore, tremendous effort has been devoted to exploring potential drugs that can hinder local tumor progression.

As an antiplatelet drug, aspirin is now widely used for the prophylactic treatment of cardiovascular events. In addition, aspirin has been receiving an equal amount of attention for its anticancer effects. For example, the regular use of aspirin has been reported to reduce the risk of recurrence of colorectal adenomas in patients with a previous history of colorectal cancer or adenomas.[32] However, it is unclear whether this finding is applicable to liver cancer as well. Several studies have explored the association between COX-2 and HCC development, and COX-2 seems to be one of the most crucial targets via which aspirin exerts its anticancer effects.[33–35] As the level of COX-2 progressively increases from the normal liver to chronic hepatitis to cirrhosis, the risk of HCC recurrence also increases.[33] In addition, the antiangiogenic effect of aspirin also plays an important role in inhibiting tumor growth, invasion, and metastasis.[36] Aspirin was confirmed to modulate glucose uptake by targeting NF-κB or NF-κB/HIF1α signaling and eventually leading to the inhibition of hepatoma cell proliferation.[10] The above findings provide a theoretical basis for the application of aspirin in the treatment of liver cancer.

Here, we conducted a retrospective study to explore the effect of aspirin on disease progression and survival in HCC patients who underwent thermal ablation. In the survival analyses, we found that there were no differences in PFS and OS between patients in the aspirin group and patients in the non-aspirin group. A previous publication reported that aspirin had a significant chemopreventive effect in patients with viral hepatitis.[18] Considering that different etiologies

might trigger different oncogenic pathways, we performed subgroup analysis according to the etiologies of the patients. Our results revealed that aspirin use was significantly associated with better OS in patients with non-viral HCC after thermal ablation. Further, PFS tended to be higher in the aspirin group than in the non-aspirin group, although this finding was not significant (median PFS: 6.3 months vs 5.2 months, $P = 0.15$). Since individuals with non-viral HCC were not the major patient population in this study, it was difficult to identify the mechanism of action of aspirin in these patients. For tumors that cannot be completely removed by thermal ablation alone, combined treatment with TACE is undoubtedly the better treatment choice. Combined therapy contributes to better control of tumor progression and improvement of tumor clearance. The benefits of combined therapy have been extensively studied in the treatment of intermediate and advanced liver cancer.[37–39] In the present study, subgroup analysis was conducted based on whether the ablation was combined with TACE, and our results revealed that patients who underwent ablation alone in the aspirin group had better PFS than those in the non-aspirin group. For patients who received combination therapy, the interference of TACE might have confounded the role of aspirin. Stratified Cox regression analysis demonstrated that aspirin use might be a protective factor for some patients after ablation. However, these findings are limited by the small size of the patient groups after stratification, so the clinical implication of these findings is debatable and needs to be investigated further in the future.

An important complication of aspirin use is the risk of gastrointestinal bleeding. In order to overcome this risk, it was recommended that aspirin be continuously administered at a low dose (75–100 mg daily).[40,41] The aspirin dose used in our study was 100 mg per day, which meets this low dosage requirement. No significant correlation was shown between low-dose aspirin use and the risk of gastrointestinal bleeding in patients after thermal ablation. Only three patients in the aspirin group discontinued aspirin therapy because of gastrointestinal bleeding. Moreover, the incidence of major adverse events did not significantly differ between the two groups. The above results demonstrate that low-dose aspirin use was safe in patients with HCC.

One of the main limitations of this study is its retrospective study design, which might have led to a selection bias, loss to follow-up, and missing data. Additionally, propensity score matching was not employed because of the small sample size. We randomly selected patients who underwent thermal ablation during the same period as the control group to minimize the effects of artificial confounders. The administration of aspirin also meant that the patients already had some comorbidities. All of these confounders could have influenced the results of survival analysis. This study made no restrictions on tumor stages and treatment regimens and thus included some patients with extrahepatic metastasis in BCLC C stage. For these patients, ablation therapy was carried out as part of palliative or combination therapy, which might inevitably interfere with some of the analysis results.

Conclusion

Our findings suggest that low-dose aspirin use was significantly associated with better OS in patients with non-viral HCC after thermal ablation. For patients who received ablation alone, the administration of aspirin could have played a role in the suppression of tumor progression. Thus, aspirin use might be a protective factor for some HCC patients after ablation. Further prospective studies are warranted to confirm our conclusions.

Abbreviations

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; MWA, microwave ablation; TACE, transarterial chemoembolization; COX, cyclooxygenase; PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; CRP, C-reactive protein; mRECIST, Modified Response Evaluation Criteria In Solid Tumors; PD, progressive disease; IQR, interquartile range; HR, hazard ratio; PCI, percutaneous coronary intervention; CI, confidence interval; PLT, platelet; PT, prothrombin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Beijing Ditan Hospital of Capital Medical University (KY2022-048) and was conducted according to the Declaration of Helsinki. Informed consent was waived by the institutional review board of Beijing Ditan Hospital due to the retrospective nature of the study and anonymized data.

Author Contributions

All authors made significant contributions to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; agreed on the journal to which the article has been submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; and agreed to take responsibility and be accountable for the contents of the article.

Disclosure

The authors report no conflicts of interest in this work.

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