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ORIGINAL SCIENTIFIC REPORT

Perioperative Allogeneic Blood Transfusion Does not Influence Patient Survival After Hepatectomy for Hepatocellular Carcinoma: A Propensity Score Matching Analysis

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Abstract

Background Whether perioperative allogeneic blood transfusion (PABT) negatively influences patient survival after hepatectomy (HR) for hepatocellular carcinoma (HCC) remains controversial.

Methods Five hundred two patients who underwent HR for initial HCC between 1994 and 2015 were enrolled in this study. All patients were divided into two groups: the PABT group and the non-PABT group. Differences of clinicopathological factors, overall survival (OS), recurrence-free survival (RFS), and the recurrence pattern between the two groups were evaluated. Using propensity score matching for tumor-related factors, liver functions, and surgical factors (total 11 factors), the survival impact of PABT was also analyzed.

Results In the entire cohort, 78 patients (15.5%) received PABT such as red cell concentrate, fresh-frozen plasma, or platelets. OS (5-year OS: 55% vs. 76%; $p = 0.0005$) and RFS (2-year RFS: 47% vs. 56%; $p = 0.0131$) were significantly worse in the PABT group. The extrahepatic recurrence happened more frequently in the PABT group (15% vs. 5.4%; $p = 0.0039$). There were many significant clinicopathological differences between the two groups: more advanced tumor stage (tumor diameter, stage III or IV, microvascular invasion), worse liver functions (albumin, indocyanine green retention rate at 15 min), and more surgical stress (blood loss, operation time) in the PABT group. After propensity score matching, 43 pairs of patients were extracted. In this matched cohort, the survival curves of the PABT and non-PABT groups almost completely overlapped both in OS (5-year OS: 62% vs. 62%; $p = 0.4384$) and in RFS (2-year RFS: 49% vs. 47%; $p = 0.8195$). The significant difference of the extrahepatic recurrence rate disappeared in the matched cohort ($p = 0.5789$).

Conclusion Using propensity score matching, we found that PABT does not influence patient survival after HR for HCC.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and second leading cause of cancer-related death worldwide [1]. With appropriate patient selection, hepatectomy (HR) is currently the primary treatment of choice for HCC [2, 3]. During recent decades, hepatic surgeons have focused on improving surgical techniques and managements of HR for HCC, resulting in greatly improved perioperative outcomes [4], and the perioperative allogeneic blood transfusion (PABT) rate has decreased

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from 62 to 22% in the last decade [5]. However, PABT including red cell concentrate (RCC), fresh-frozen plasma (FFP), or platelets is still necessary when excessive intra-operative bleeding occurs or in patients with liver cirrhosis who show decreased platelet count or prothrombin activity.

Many studies have reported on the negative effects of PABT on patient survival after HR for HCC [6–12]. Two recent meta-analyses [13, 14] revealed that PABT was associated with adverse clinical outcomes for patients with HCC undergoing HR, including overall survival (OS) and recurrence-free survival (RFS); therefore, the authors concluded that surgeons should avoid PABT during HR whenever possible. However, these studies were retrospective, and patient backgrounds were not adjusted. There may thus be a high possibility that worse oncologic outcomes are not necessarily due to PABT itself, but rather to other tumor-related factors, liver functions, and surgical factors associated with PABT.

Addressing this hypothesis, four papers have reported survival impact of PABT for HCC using a propensity score matching analysis [15–18]. Three [15–17] denied a survival impact of PABT for HCC; however, Wada et al. [18] reported that PABT was still a poor prognostic factor in OS even after performing propensity score matching. In addition, survival curves of OS and RFS after propensity score matching of the non-PABT group were still higher than those of the PABT group, and the p values were close to 0.05 in both Yang et al.'s [15] and Peng et al.'s reports [17]. Therefore, the survival impact of PABT for HCC remains controversial.

We present here a retrospective analysis of the survival impact of PABT including RCC, FFP, or platelets for HCC using 11 propensity scores matching associated with tumor-related factors, liver functions such as indocyanine green retention rate at 15 min (ICGR15), and surgical factors including blood loss.

Patients and methods

Patients

Five hundred two patients with initial HCC who underwent HR at the Department of Gastroenterological Surgery, Kumamoto University Hospital, between 1994 and 2015, were enrolled. The medical records of these 502 patients were followed up through December 2018. The median follow-up period in this series was 53 months. This study was approved by the Human Ethics Review Committee of the Graduate School of Medicine, Kumamoto University (No. 1291).

Definitions of perioperative blood transfusion

PABT was defined as the transfusion of RCC, FFP, or platelets during HR. During HR, blood transfusion of RCC and/or FFP was given when patients were hemodynamically unstable or when their hemoglobin level was below 8 mg/dl or prothrombin activity was bellow 40%. Platelets were transfused when intraoperative coagulation of blood seemed severe because of a low platelet count of $< 10 \times 10^4/\mu l$.

Surgical techniques and follow-up methods

In almost all HRs, intermittent Pringle's maneuvers consisting of clamping the portal triad for 15 min and then releasing the clamp for 5-min intervals were applied. The CUSA system (Valleylab, Boulder, CO, USA) was mainly used to transect the liver parenchyma. Eighty-seven patients (17%) underwent a laparoscopic hepatic resection [19]. Complications were evaluated by Clavien's classification, and those with a score of Grade II or more were defined as positive [20]. Pathological diagnoses such as microvascular invasion (MVI) were performed by two or three certificated experts according to the general rules of the Liver Cancer Study Group of Japan [21].

After discharge, all patients were examined every 3 month for recurrence by computed tomography (CT) or magnetic resonance imaging (MRI), and tumor markers such as α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP). When recurrence was suspected, we treated the recurrent HCC by repeat HR [22], radiofrequency ablation (RFA) or lipiodolization [23].

Statistics

Continuous variables are summarized as the means ± standard deviations (SDs) and were compared using Student's t test. Categorical variables were compared using the Chi-square test. Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. A propensity score method was applied to minimize the influence of confounders on the selection bias, and propensity scores were generated by a logistic regression model [24, 25]. The tumor-related factors, liver functions, and surgical factors (total 11 factors) entered in the propensity model included tumor diameter, the number of tumors, MVI, stage [21], AFP, DCP, total bilirubin (T-bil), albumin (Alb), ICGR15, blood loss, and operation time. One-to-one matching between the groups was performed using a caliper width of 0.2. All analyses were performed with JMP Pro 13.0 (SAS Institute, Cary, NC, USA). p values bellow 0.05 were considered significant.

Results

Comparisons of clinicopathological variables and patient survival of the entire cohort

Seventy-eight patients (15.5%) received PABT. PABT consisted of six patterns as follows: RCC + FFP + platelets in 2 patients, RCC + FFP in 34 patients, FFP + platelets in 3 patients, RCC in 9 patients, FFP in 13 patients and platelets in 17 patients. The entire cohort was divided into two groups: the PABT group ($n = 78$) and the non-PABT group ($n = 424$). Table 1 summarizes comparisons of clinicopathological variables between the two groups. Platelets (8.8 ± 1.3 vs. $9.5 \pm 1.6 \times 10^4$/μl; $p < 0.0001$) were significantly lower in the PABT group. In the PABT group, liver functions were significantly worse such as PT (80.6 ± 14.9 vs. 84.8 ± 11.4%; $p = 0.0034$), Alb (3.8 ± 0.5 vs. 4.0 ± 0.4 g/dl; $p < 0.0001$), and ICGR15 (16.8 ± 13.2 vs. 12.5 ± 7.6%; $p = 0.0001$). Tumor-related factors were significantly more advanced in the PABT group such as tumor diameter (5.4 ± 4.0 vs. 4.1 ± 3.1 cm; $p = 0.0018$), the positive rate of MVI (54 vs. 35%; $p = 0.0011$), and stage III or IV (55 vs. 32%; $p = 0.0009$). As for surgical stress, in the PABT group, operation time was significantly longer (488 ± 117 vs. 388 ± 104 min; $p < 0.0001$) and blood loss was significantly greater (1618 ± 1147 vs. 436 ± 376 g; $p < 0.0001$). Morbidity in the PABT group was significantly higher than in the non-PABT group (37 vs. 15%; $p < 0.0001$).

The OS of the PABT group was significantly worse than that of the non-PABT group ($p = 0.0005$; Fig. 1a). The 5-year OS rate of the PABT group was 55% and that of the non-PABT group was 76%. The RFS of the PABT group was also significantly worse than that of the non-PABT group ($p = 0.0131$; Fig. 1b). The 2-year RFS rate of the PABT group was 47% and that of the non-PABT group was 56%. The extrahepatic recurrence happened more frequently in the PABT group than in the non-PABT group (12 (15%) vs. 23 (5.4%); $p = 0.0039$).

Comparisons of clinicopathological variables and patient survival of the propensity score-matched cohort

Propensity score matching of the two groups using 11 factors related to liver functions, tumor-related factors and

Table 1 Comparisons of clinicopathological factors of all patients

Variables	PABT (−) ($n = 424$)	PABT (+) ($n = 78$)	p value
Age (years)	66 ± 10	66 ± 9	0.6027
Male/female	331/93	61/17	0.9782
HBs-Ag (+) (%)	108 (26%)	26 (33%)	0.1569
HCV-Ab (+) (%)	203 (48%)	37 (47%)	0.9428
Hb (g/dl)	12.3 ± 2.9	12.1 ± 2.4	0.1356
PT (%)	84.8 ± 11.4	80.6 ± 14.9	0.0034
Platelets (10^4/μl)	9.5 ± 1.6	8.8 ± 1.3	<.0001
T-bil (mg/dl)	0.8 ± 0.3	0.8 ± 0.4	0.9759
Alb (g/dl)	4.0 ± 0.4	3.8 ± 0.5	<.0001
ICG15R (%)	12.5 ± 7.6	16.8 ± 13.2	0.0001
Child A/B	411/13	73/5	0.1778
Operation time (min)	388 ± 104	488 ± 117	<.0001
Bleeding (g)	436 ± 376	1618 ± 1147	<.0001
Major HR (%)	112 (26.4)	26 (33%)	0.2161
Morbidity (%)	65 (15%)	29 (37%)	<.0001
Tumor diameter (cm)	4.1 ± 3.1	5.4 ± 4.0	0.0018
The number of tumor	2 ± 1	2 ± 1	0.2867
MVI (+) (%)	148 (35%)	42 (54%)	0.0011
Stage III/IV (%)	135 (32%)	43 (55%)	0.0009
AFP (ng/ml)	4098 ± 24,397	6169 ± 32257	0.5166
DCP (mAU/ml)	3638 ± 15,749	4554 ± 11,735	0.6269

HBS-Ag, hepatitis B virus surface antigen; HCV-Ab, hepatitis C antibody; Hb, hemoglobin; PT, prothrombin time; T-bil, total bilirubin; Alb, albumin; ICGR15, indocyanin green retention rate at 15 min; HR, hepatectomy; MVI, microvascular invasion; AFP, alfa-fetoprotein; DCP, des-gamma carboxyprothrombin

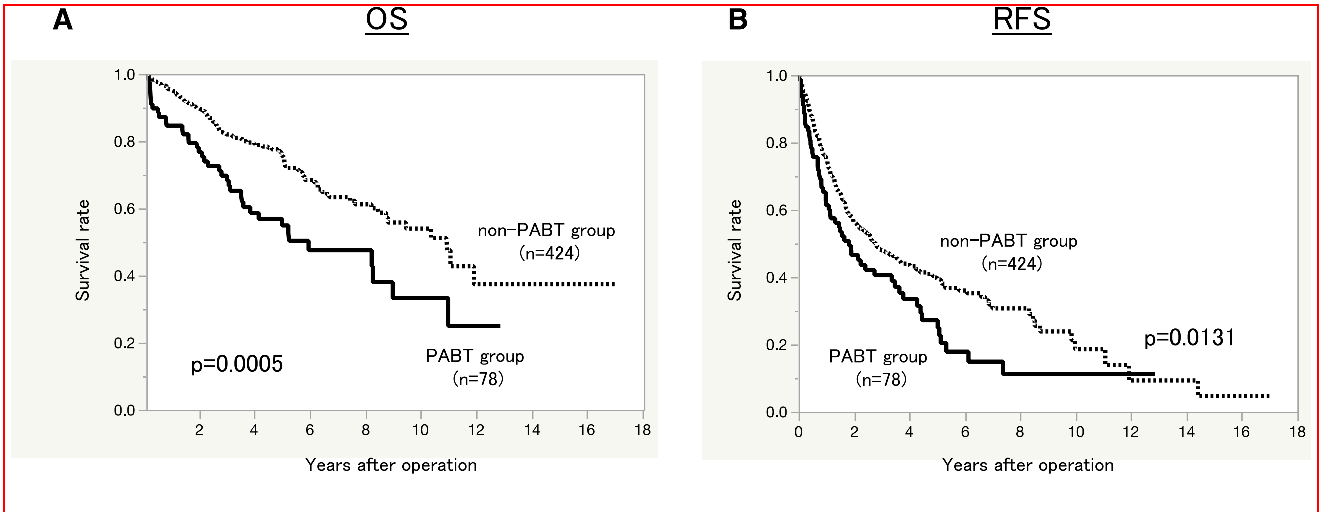

Fig. 1 Overall survival (**a**) and recurrence-free survival (**b**) curves after HR for HCC of the PABT group ($n = 424$) and the non-PABT group ($n = 78$) in the entire cohort

surgical stress created 43 pairs of patients. PABT consisted of 5 patterns as follows: RCC + FFP in 9 patients, FFP + platelets in 2 patients, RCC in 8 patients, FFP in 10 patients and platelets in 14 patients. In this matched cohort, comparisons of clinicopathological variables between the PABT group ($n = 43$) and the non-PABT group ($n = 43$) are summarized in Table 2. Significant differences disappeared in all variables including PT, platelets and morbidity between the two groups.

In this matched cohort, OS and RFS curves of the two groups were almost completely overlapped (Fig. 2), and the significant differences in OS and RFS in the entire cohort disappeared in this matched cohort (OS: $p = 0.4384$; RFS: $p = 0.8195$). The 5-year OS rate of the PABT group was 62% and that of the non-PABT group was also 62%. The 2-year RFS rate of the PABT group was 49% and that of the non-PABT group was 46%. In the matched cohort, the significant difference of the rate of extrahepatic recurrence which was found in the entire cohort disappeared (4 (9.3%) vs. 3 (6.9%); $p = 0.5789$).

Discussion

Recently reported PABT rates of HR for HCC from high-volume centers of HR have ranged from 14 to 42% [4, 5, 26, 27]. Aloia et al. [28] reported the U.S. nationwide PABT rate of HR for HCC performed between 2005 and 2007 to be 28.7%. These PABT rates were only for RCC; therefore, we consider that our PABT rate, which includes RCC, FFP or platelets, of 15.5% is extremely low. In addition, in our institution, HR for HCC is often performed in patients with cirrhosis or portal hypertension who tend to be hemorrhagic [29, 30].

The reason why PABT can cause worse clinical outcomes remains uncertain; however, the mechanism underlying its adverse effects has generally been assumed to be immune suppression. Some investigators have reported that allogeneic blood transfusion (ABT) suppresses host immunity via a functional reduction in T lymphocytes, natural killer cells, macrophages or monocytes, or increased numbers of suppressor T cells [31–33]. In recent years, increasing number of studies have demonstrated that several lymphocyte surface markers such as CD2 and CD4 are significantly changed after ABT, and these markers are closely associated with tumor proliferation, apoptosis, and progression [34, 35]. In addition, soluble HLA class I and soluble Fas-ligand released by leukocytes present in blood products were reported to inhibit the activity of NK cells and cytotoxic T cells [36, 37]. It has also been speculated that the infusion of growth factors such as vascular endothelial growth factor and transforming growth factor β, as well as an enhanced inflammatory response as a result of the exposure of the recipient immune system to donor microparticles, could stimulate the spread and proliferation of cancer cells [38]. Almost all reports concerning the clinical effects of PABT of HR for HCC have been limited to RCC transfusion; however, from the above considerations of possible mechanisms of clinical effects of ABT, PABT should not be limited to RCC but should extend to include FFP and platelets. On the other hand, Procter et al. [39] reported that depletion of extracellular arginine might be the mechanism of the immunosuppressive effect of packed red blood cells.

Two recent meta-analyses [13, 14] including 5635 and 7241 patients revealed that PABT was associated with adverse clinical outcomes of HR for HCC including OS, RFS, and morbidity rate; however, there were several

Table 2 Comparisons of clinicopathological factors of propensity score-matched patients

Variables	PABT (−) (n = 43)	PABT (+) (n = 43)	p value
Age (years)	64 ± 10	66 ± 10	0.2969
Male/female	40/3	38/5	0.3158
HBs-Ag (+) (%)	16 (37%)	16 (37%)	1.0000
HCV-Ab (+) (%)	18 (42%)	19 (44%)	0.8276
Hb (g/dl)	12.1 ± 3.1	11.7 ± 2.8	0.0653
PT (%)	82.6 ± 9.2	81.9 ± 8.7	0.1389
Platelets (10^4/μl)	9.5 ± 1.1	8.9 ± 1.4	0.0788
T-bil (mg/dl)	0.9 ± 0.3	0.9 ± 0.4	0.5152
Alb (g/dl)	3.9 ± 0.5	3.9 ± 0.5	0.9828
ICG15R (%)	13.8 ± 7.1	16.2 ± 12.0	0.2655
Child A/B	43/0	43/0	1.0000
Operation time (min)	466 ± 86	469 ± 101	0.9136
Bleeding (g)	1000 ± 514	1006 ± 576	0.9532
Major HR (%)	15 (35%)	12 (28%)	0.6426
Morbidity (%)	11 (26%)	15 (35%)	0.3469
Tumor diameter (cm)	4.3 ± 2.7	4.4 ± 2.9	0.7704
The number of tumor	2 ± 1	2 ± 2	0.7721
MVI (+) (%)	14 (33%)	18 (42%)	0.3717
Stage III/IV	22 (51%)	20 (47%)	0.6661
AFP (ng/ml)	751 ± 3259	6368 ± 3517	0.3001
DCP (mAU/ml)	2597 ± 8535	3571 ± 11,245	0.6522

HBS-Ag, hepatitis B virus surface antigen; HCV-Ab, hepatitis C antibody; Hb, hemoglobin; PT, prothrombin time; T-bil, total bilirubin; Alb, albumin; ICGR15, indocyanin green retention rate at 15 min; HR, hepatectomy; MVI, microvascular invasion; AFP, alfa-fetoprotein; DCP, des-gamma carboxyprothrombin

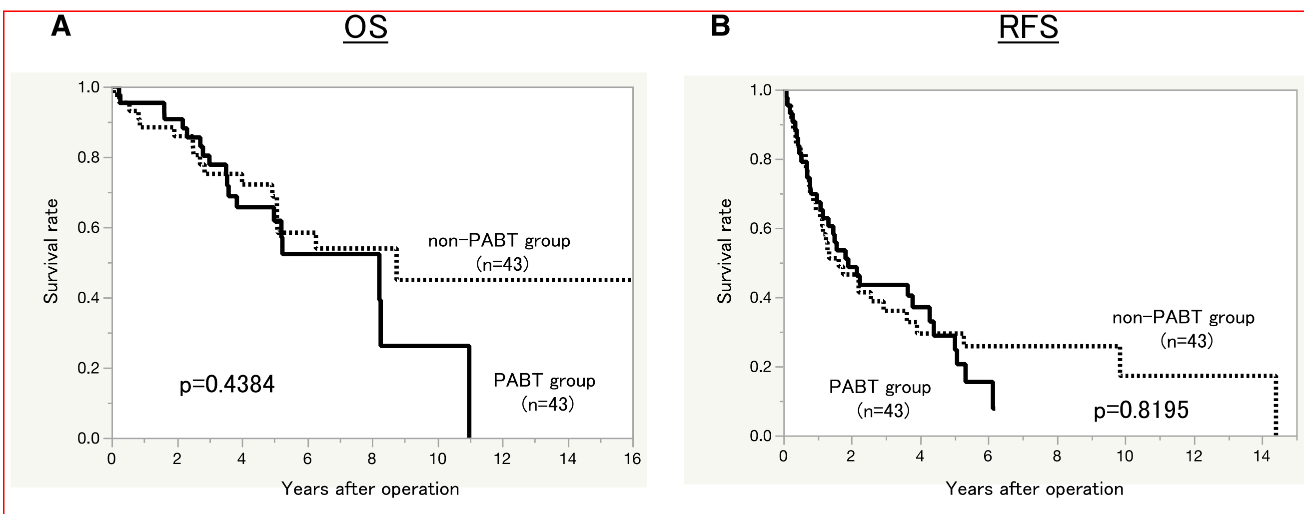

Fig. 2 Overall survival (**a**) and recurrence-free survival (**b**) curves after HR for HCC of the PABT group (n = 43) and the non-PABT group (n = 43) in the matched cohort

limitations in these meta-analyses. Most included studies were retrospective cohort studies, and many confounding factors such as tumor-related factors, liver functions, and surgical stress, which would strongly affect short- and long-term surgical results, cannot be eliminated. It is easy to forecast that the PABT group has advanced tumor stage, worse liver functions, and larger surgical stress; therefore, in these situations, propensity score matching analysis would be a promising procedure to evaluate the oncological effects of PABT itself in HR for HCC.

Four papers with propensity score matching have reported the clinical effects of PABT in HR for HCC [15–18]. These studies included more patients than ours (234, 60, 89, and 74), and three of the four [15–17] found no survival impact of PABT for HCC, as has our present study. However, the survival curves of OS and RFS after propensity score matching of the non-PABT group were still higher than those of the PABT group, and the p values were close to 0.05 in both Yang et al.'s [15] and Peng et al.'s papers [17]. On the contrary, in our analyses, the OS and RFS curves of the PABT and non-PABT groups almost completely overlapped (Fig. 2). We anticipate that this complete disappearance of survival impact of PABT in our matched cohort is due to the successful matching of confounding factors such as MVI, ICGR15, and blood loss. We have emphasized that not tumor size but MVI is the strongest predictor for poor survival after HR or living-donor liver transplantation for HCC [2, 40, 41], and ICGR15 value is regarded as the most important parameter to estimate liver function during HR for HCC in Asian countries [42]. In addition, this is the first report which revealed the disappearance of PABT influence to the recurrence pattern of HCC after HR by propensity score matching. In the entire cohort, the extrahepatic recurrence happened more frequently in the PABT group ($p = 0.0039$); however, this significant difference disappeared in the matched cohort ($p = 0.5789$).

Katz et al. [43] reported that not PABT but increased blood loss during HR for HCC was an independent poor prognostic factor. However, blood loss is difficult to match between the PABT group and non-PABT group. In our matched cohort, not statistically significant, hemoglobin (11.7 ± 2.8 vs. 12.1 ± 3.1 g/dl; $p = 0.0658$) and platelets (8.9 ± 1.4 vs. $9.5 \pm 1.1 \text{x} 10^4/\mu l$; $p = 0.0788$) were lower in the PABT group. The indication of PABT did not change in the matched cohort with the same extent of blood loss; therefore, the PABT group included more patients who are likely to need RBC or platelets transfusions.

Of course, surgeons should reduce blood loss during HR for HCC and avoid unnecessary PABT to protect patients from the risks of infection or allergic reactions [44, 45]; however, according to our and other propensity score matching analyses of the clinical effects of PABT during HR for HCC, surgeons should not hesitate to perform PABT to maintain patient safety in situations of unstable hemodynamics or hemorrhagic tendency. Aging populations are increasing in developing countries, and HR for HCC patients with heart or renal comorbidities is also likely to increase; therefore, hesitation to use PABT for fear of oncological disadvantage should be excluded during HR for HCC.

This study has several limitations. First, this is a retrospective single-institution cohort study and not a randomized control trial. However, for the research question at hand, it is nearly impossible and ethically questionable to perform a randomized trial. Furthermore, it would be challenging, and even impossible, to recruit patients for such a trial. A second limitation lies in the small patient population. The PABT group consists of 78 patients because of our low transfusion rate, and matching many confounding factors such as MVI, ICGR15, and blood loss necessarily restricted the patient population to 43 pairs. This small cohort itself would influence the survival comparisons. In addition, the complete adjustment of clinicopathological variables between the PABT and non-PABT groups even using propensity score patching would be impossible.

In conclusion, the present study using propensity score matching revealed that PABT does not influence patient survival after HR for HCC.

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