

# Prognostic value of fever grade combined with neutrophil percentage in hepatocellular carcinoma patients presenting fever as the initial manifestation

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**Background:** Hepatocellular carcinoma (HCC) patients with fever as the initial presentation are extremely rare. Our aim was to investigate the clinical characteristics and prognosis of patients with this disease.

**Patients and methods:** The clinical features were analyzed in a retrospective study of 63 HCC patients with fever as the first manifestation and 300 HCC patients without fever as the control group.

**Results:** HCC patients with fever had a higher neutrophil percentage, larger tumor size, worse tumor differentiation, advanced Barcelona Clinic Liver Cancer stage, and more hilar lymph node metastasis than HCC patients without fever (all  $P < 0.05$ ). Compared with HCC patients without fever, patients presenting with fever had shorter overall survival (OS, median: 13 months,  $P < 0.001$ ) and time to recurrence (TTR, median: 7.5 months,  $P < 0.001$ ). In addition, HCC patients with fever also had shorter OS and TTR than those without fever in all clinical subgroups with aggressive features (all  $P < 0.05$ ). Multivariate analysis showed that neutrophil percentage  $> 70\%$ , fever grade  $\geq 38.5^\circ\text{C}$ , tumor size  $> 5$  cm, and hilar lymph node metastasis were independent factors for OS and TTR. A positive correlation was observed between body temperature and serum neutrophil percentage ( $r = 0.527$ ,  $P < 0.001$ ). Patients with a fever grade  $\geq 38.5^\circ\text{C}$  had more incomplete encapsulation and larger tumor size, while those with a neutrophil percentage  $> 70\%$  presented with more incomplete encapsulation, vascular invasion, and worse tumor differentiation. Patients with a fever grade  $\geq 38.5^\circ\text{C}$  combined with a neutrophil percentage  $> 70\%$  had worse OS and TTR than other groups.

**Conclusion:** HCC patients presenting with fever have poorer prognosis than those without fever; however, their prognosis could be improved by timely surgical intervention. Patients with a neutrophil percentage  $> 70\%$  and a fever grade  $\geq 38.5^\circ\text{C}$  represent a rare HCC subgroup with an extremely dismal outcome and more aggressive clinical course.

**Keywords:** hepatocellular carcinoma, fever, neutrophils, prognosis, hepatectomy

## Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and its incidence has increased in recent years.<sup>1,2</sup> HCC patients with fever as the initial presentation are extremely rare and only a few cases have been reported.<sup>3,4</sup> These HCC patients present with symptoms that mimic liver abscess, as both share similar clinical symptoms and laboratory findings, which makes differential diagnosis a challenge.<sup>5,6</sup> Due to its rarity and diagnostic difficulties, most HCC patients with fever are already

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at an advanced stage at the time of diagnosis, and their prognosis is extremely dismal compared with those without fever, so they may represent a clinically distinct type of HCC.<sup>4</sup> Thus, it is necessary to clarify the clinical features of these patients and to explore the related risk factors influencing their prognosis in order to improve patient outcomes.

Although the reasons for fever may be varied, it has been reported that tumor progression is extremely rapid in HCC patients presenting with fever, with a mean survival of only 2.35–3.5 months.<sup>3,4</sup> Furthermore, these patients exhibit clinical characteristics that are distinct from other HCC patients. At this time, only limited experience based on a few cases has shown that surgical treatment might prolong the survival time of HCC patients with fever.<sup>5</sup> However, detailed analyses of a large cohort evaluating the prognosis of this HCC subgroup after surgery and the related predictive factors are not available.

In this study, the data of 363 cases were retrospectively analyzed, including 63 consecutive HCC patients presenting fever as the initial manifestation and 300 HCC patients without fever who underwent resection at our institute during the past 10 years. We evaluated the efficiency of surgical management of this HCC clinical subgroup as well as the prognostic factors influencing disease recurrence and survival after surgery.

## Patients and methods

### Patients

Between February 2004 and January 2013, 63 HCC patients with fever underwent curative hepatic resection at the Department of Surgery, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China. Ethical approval for this study and the use of human subjects was obtained from the research ethics committee of Zhongshan Hospital, consistent with the ethical guidelines of the 1975 Declaration of Helsinki, and written informed consent was obtained from all patients. The definitive pathological diagnosis of HCC was based on the World Health Organization criteria. Tumor differentiation was defined according to the Edmondson grading system.<sup>7</sup> Tumor stage was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging system.<sup>8</sup> Liver function was assessed by the Child-Pugh classification.

The enrollment criteria for all patients with fever in this study were as follows: 1) body temperature  $>38.0^{\circ}\text{C}$ ; 2) no prior anticancer treatment; 3) complete surgical resection, defined as resection of all tumor nodules with the cut surface being free of cancer by histologic examination;<sup>9</sup> 4) availability of suitable formalin-fixed, paraffin-embedded

tissues; and 5) availability of complete clinicopathologic and follow-up data. Patients with specific factors underlying the fever, such as extrahepatic infection, septicemia, and hepatolithiasis, were excluded. All patients underwent serological testing within 3 days before surgery to determine serum biochemistry. In addition, 300 HCC patients without fever were selected as the control group by random sampling stratified by age, sex, and year of diagnosis from the database within the same observational period.

### Follow-up and recurrence treatment

Survival data, including overall survival (OS) and time to recurrence (TTR), were collected until November 30, 2015. The median follow-up was 47 months. OS and TTR were defined as the interval between the date of surgery and death (or the last observation point taken), or any diagnosed relapse (intrahepatic recurrence and extrahepatic metastasis), respectively.<sup>10–12</sup> After surgery, one to three courses of prophylactic transcatheter arterial chemoembolization (doxorubicin, cisplatin, 5-fluorouracil, and iodized oil) were given to those patients with a high risk of recurrence, as evidenced by clinical features such as vascular invasion and microsatellite lesions.<sup>13</sup>

Patient follow-up was performed every 2 months during the first postoperative year and then at least every 3–4 months. Serum  $\alpha$ -fetoprotein (AFP) level, abdomen ultrasonography, and chest X-ray were performed to prospectively monitor recurrence every 1–6 months depending on the postoperative time. A computed tomography scan of the abdomen was performed every 6 months. A bone scan or magnetic resonance imaging was done if localized bone pain was reported. If recurrence was suspected, a computed tomography scan or magnetic resonance imaging was done immediately. Patients with an elevated serum AFP level and typical imaging appearance on computed tomography or magnetic resonance imaging were diagnosed with recurrence and received further treatment. Re-resection, radio frequency ablation, or percutaneous ethanol injection were considered if the recurrent tumor was localized. Transcatheter arterial chemoembolization was administered if the recurrent tumor was multiple or diffused. External radiotherapy was given if lymph node or bone metastasis was found; otherwise, symptomatic treatment was provided.<sup>14,15</sup>

### Statistical analysis

SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. A chi-square test, Fisher's exact test, and Student's *t*-test were used for comparisons between

the groups as appropriate. OS and recurrence rates were calculated by the Kaplan–Meier method. The differences in survival between the groups were compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazard regression model. All tests were two-tailed, and  $P$ -values  $<0.05$  were considered significant.

## Results

### Clinical characteristics of HCC patients presenting with fever and their prognosis

A total of 63 HCC patients presenting fever as the initial manifestation, including 56 males and seven females, were consecutively enrolled in this study. The median body temperature was  $38.5^{\circ}\text{C}$ , which was used as a cutoff for further analysis. Clinically, HCC patients with fever have symptoms that are similar to those associated with liver abscess, such as leukocytosis. In particular, neutrophil percentage in the peripheral blood increases in response to fever and is commonly used as an indicator for systemic inflammation from infectious or noninfectious causes. In addition, we found that the neutrophil percentage was higher in HCC patients with fever than in those without fever ( $70.1\% \pm 9.3\%$  vs  $57.9\% \pm 11.5\%$ ,  $P=0.001$ ; Figure 1A). Therefore, for patients with fever, a neutrophil percentage  $>70\%$  was used as cutoff for further study. The relationship between the neutrophil percentage and fever grade was further analyzed, and we found that body temperature and serum neutrophil percentage were positively correlated ( $r=0.527$ ,  $P=0.000$ ; Figure 1B).

Next, we compared the clinical characteristics of HCC patients with fever ( $n=63$ ) to those of HCC patients without fever ( $n=300$ ; Table 1). We found that HCC patients presenting with fever were more likely to have increased serum

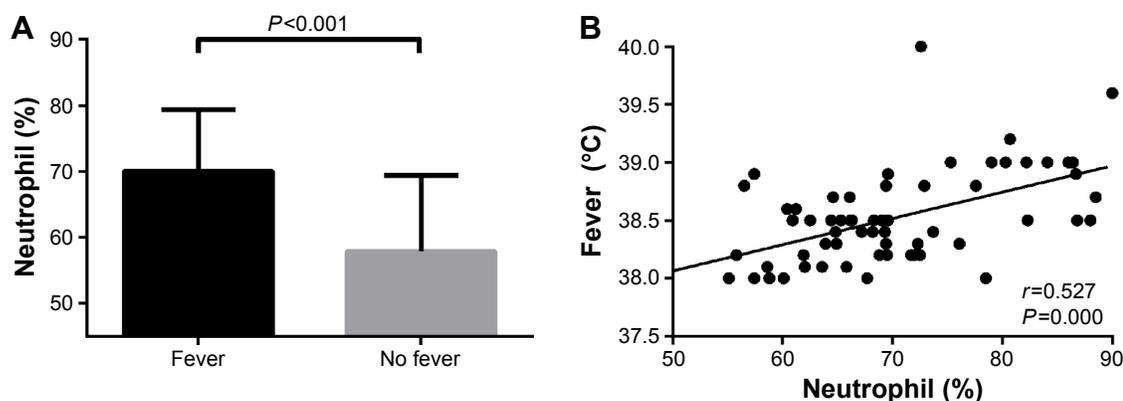
levels of  $\gamma$ -glutamyl transferase (GGT,  $P=0.000$ ), larger tumor size ( $P=0.000$ ), worse tumor differentiation ( $P=0.045$ ), more advanced BCLC stage ( $P=0.000$ ), and a higher likelihood of hilar lymph node metastasis ( $P=0.005$ ). There were no significant differences in other clinical characteristics between the two groups (Table 1).

The prognosis of HCC patients with fever was dismal. Kaplan–Meier analyses showed that HCC patients with fever had shorter OS (median: 13.0 months vs 58.3 months,  $P=0.000$ ) and TTR (7.5 months vs 40.5 months,  $P=0.000$ ) after operation compared with those without fever (Figure 2A and B). The 1-, 3-, 5-, and 7-year survival rates were 66.2%, 39.7%, 16.1%, and 16.1% in HCC patients with fever compared with 85.9%, 70.6%, 59.1%, and 56.9% in the control group, respectively. The 1-, 3-, 5-, and 7-year relapse rates were 55.8%, 77.2%, 85.8%, and 91.6% in HCC patients with fever, compared with 24.7%, 38.8%, 47%, and 56.7% in those without fever, respectively. Only three of 63 (4.8%) HCC patients with fever survived more than 5 years without tumor recurrence.

The OS and TTR between HCC patients with/without fever in different subgroups were further investigated using the Kaplan–Meier method (Table 2). The results showed that the prognosis for HCC with fever was worse than HCC without fever in all subgroups with aggressive features such as no tumor encapsulation, presence of vascular invasion, AFP  $>20$  ng/mL, GGT levels  $>54$  U/L, BCLC stage B + C, tumor size  $>5$  cm, and tumor differentiation III–IV (all  $P<0.05$ ).

### Factors affecting the prognosis of HCC patients presenting with fever

The prognostic factors of HCC patients with fever were further identified. Univariate analysis showed that tumor



**Figure 1** Neutrophil percentage and fever grade in HCC patients.

**Notes:** (A) Neutrophil percentage in peripheral blood is higher in HCC patients with fever than in those without fever ( $P<0.001$ , unpaired  $t$ -test, data shown as mean  $\pm$  SD). (B) Positive correlation between neutrophil percentage in peripheral blood and fever grade in HCC patients with fever ( $r=0.527$ ,  $P<0.001$ , Pearson correlation test).

**Abbreviation:** HCC, hepatocellular carcinoma.

**Table 1** Baseline characteristics of HCC patients with and without fever

Variables	HCC without fever (n=300)	HCC with fever (n=63)	P-value
Age, years			0.993
≤50	124	26	
>50	176	37	
Sex			0.203
Female	53	7	
Male	247	56	
GGT, U/L			0.000
≤54	154	8	
>54	146	55	
HBsAg			0.401
Negative	36	10	
Positive	264	53	
AFP, ng/mL			0.758
≤20	127	28	
>20	173	35	
Tumor size, cm			0.000
≤5	242	16	
>5	58	47	
Tumor encapsulation			0.240
Complete	153	27	
None	147	36	
Vascular invasion			0.784
Absence	210	43	
Present	90	20	
Tumor differentiation			0.045
I–II	223	39	
III–IV	77	24	
No of tumors			0.123
Single	272	53	
Multiple	28	10	
HLM <sup>a</sup>			0.005
No	295	57	
Yes	5	6	
Child-Pugh score			0.104 <sup>a</sup>
A	293	59	
B	7	4	
BCLC stage			0.000
0+A	210	9	
B+C	90	54	

**Notes:** <sup>a</sup>Fisher's exact tests; chi-square tests for all the other analyses.

**Abbreviations:** AFP,  $\alpha$ -fetoprotein; BCLC, Barcelona Clinic Liver Cancer; GGT,  $\gamma$ -glutamyl transferase; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HLM, hilar lymph node metastasis.

size >5 cm, lack of encapsulation, hilar lymph node metastasis, neutrophil percentage >70%, and fever grade  $\geq 38.5^{\circ}\text{C}$  were related to tumor recurrence of HCC patients with fever after operation. Multivariate analysis using a Cox regression model showed that the independent factors for tumor recurrence were tumor >5 cm ( $P=0.036$ , hazard ratio [HR]: 2.584, 95% confidence interval [95% CI]: 1.066–6.263), the presence of hilar lymph node metastasis ( $P=0.037$ , HR: 2.939, 95% CI: 1.069–8.081), neutrophil percentage >70% ( $P=0.026$ , HR: 2.204, 95% CI: 1.097–4.429),

and fever grade  $\geq 38.5^{\circ}\text{C}$  ( $P=0.025$ , HR: 2.059, 95% CI: 1.093–3.878; Table 3).

Univariate analysis showed that AFP >20 ng/mL, tumor size >5 cm, presence of hilar lymph node metastasis, lack of encapsulation, neutrophil percentage >70%, and fever grade  $\geq 38.5^{\circ}\text{C}$  were associated with shorter patient survival. Multivariate analysis showed that the independent factors for survival were the presence of hilar lymph node metastasis ( $P=0.004$ , HR: 6.140, 95% CI: 1.802–20.917), larger tumor size ( $P=0.022$ , HR: 3.610, 95% CI: 1.208–10.788), neutrophil percentage >70% ( $P=0.013$ , HR: 2.674, 95% CI: 1.232–5.804), and fever grade  $\geq 38.5^{\circ}\text{C}$  ( $P=0.012$ , HR: 2.922, 95% CI: 1.266–6.774; Table 3).

Next, we compared OS and TTR in the patients with fever according to neutrophil percentage >70% and fever grade  $\geq 38.5^{\circ}\text{C}$ . Patients with neutrophil percentage >70% had shorter OS (median: 6.8 months vs 16 months;  $P=0.000$ ) and TTR (median: 3.8 months vs 9 months;  $P=0.004$ ) than those with neutrophil percentage  $\leq 70\%$ . The 1-, 3-, and 5-year OS rates were 48.1%, 26.7%, and 0% in patients with neutrophil percentage >70% compared with 77.9%, 48.5%, and 25.1% in those with neutrophil percentage  $\leq 70\%$ , respectively. The 1-, 3-, and 5-year relapse rates were 78.2%, 88.4%, and 100% in patients with neutrophil percentage >70% compared with 41.6%, 70.8%, and 79.6% in those with  $\leq 70\%$ , respectively (Figure 2C and D).

Those with fever grade  $\geq 38.5^{\circ}\text{C}$  had shorter OS (median: 7 months vs 19.6 months,  $P=0.000$ ) and TTR (median: 5.6 months vs 12.1 months;  $P=0.000$ ) than those with fever grade <38.5°C. The 1-, 3-, and 5-year OS rates were 48%, 17.2%, and 6.5% in patients with fever grade  $\geq 38.5^{\circ}\text{C}$  compared with 88%, 68.3%, and 27.7% in those with fever grade <38.5°C, respectively. The 1-, 3-, and 5-year relapse rates were 75.7%, 90.9%, and 95.4% in patients with fever grade  $\geq 38.5^{\circ}\text{C}$  compared with 34.9%, 58.7%, and 73.4% in those with fever grade <38.5°C, respectively (Figure 2E and F).

## Prognostic significance of the combination of neutrophil percentage and fever grade in HCC patients presenting with fever

As the neutrophil percentage and fever grade were independent factors for survival in HCC patients presenting with fever, as well as the most easily available indices in clinical practice, the power of their combination for predicting patient outcome was further evaluated. Patients with fever were classified into three subgroups: group I (neutrophil percentage  $\leq 70\%$  and fever grade <38.5°C, n=22); group II (neutrophil percentage >70% and fever grade <38.5°C or

neutrophil percentage  $\leq 70\%$  and fever grade  $\geq 38.5^\circ\text{C}$ ,  $n=24$ ); and group III (neutrophil percentage  $>70\%$  and fever grade  $\geq 38.5^\circ\text{C}$ ,  $n=17$ ). Those in group III had the shortest OS (median: 5.1 months in group III vs 11.5 months in group II and 19.8 months in group I) and TTR (3 months in group III

vs 7.2 months in group II and 11.5 months in group I) compared with those in group I and II (all  $P<0.05$ , Figure 2G and H). Among the 17 patients in group III, only five patients survived for more than 1 year, and of those patients only two survived for more than 2 years after surgery. Furthermore,

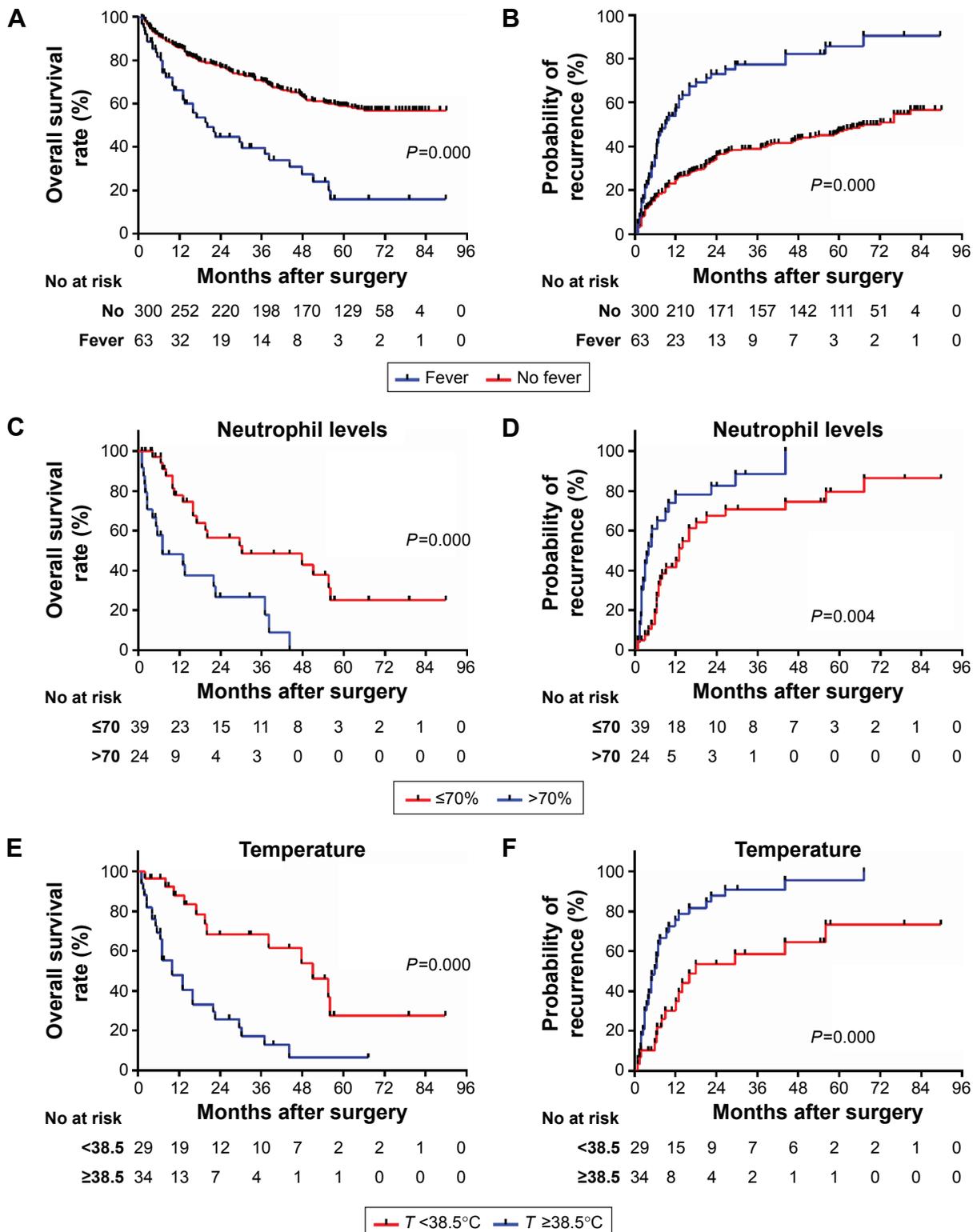
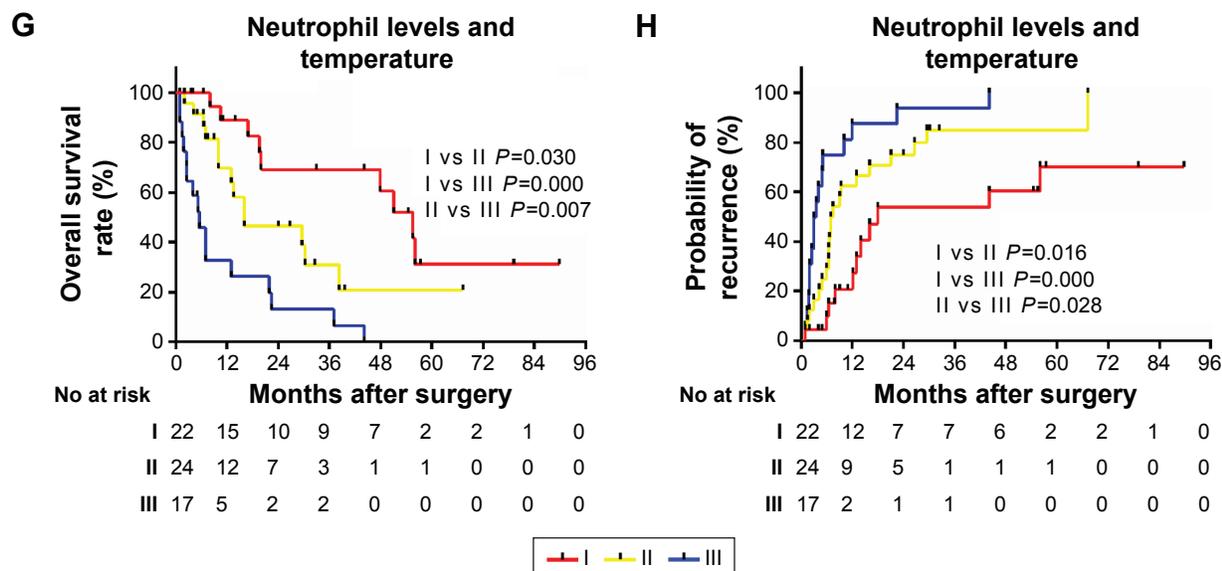


Figure 2 (Continued)



**Figure 2** Kaplan–Meier analysis.

**Notes:** (A, B) Kaplan–Meier analysis of OS rates and between patients with fever and without fever. (C, D) Kaplan–Meier analysis of OS and TTR in HCC patients with fever according to neutrophil levels, (E, F) body temperature, and (G, H) their combination. I: neutrophil percentage  $\leq 70\%$  and fever grade  $< 38.5^\circ\text{C}$ ; II: neutrophil percentage  $> 70\%$  and fever grade  $< 38.5^\circ\text{C}$  or neutrophil percentage  $\leq 70\%$  and fever grade  $\geq 38.5^\circ\text{C}$ ; III: neutrophil percentage  $> 70\%$  and fever grade  $\geq 38.5^\circ\text{C}$ .

**Abbreviations:** HCC, hepatocellular carcinoma; OS, overall survival; TTR, time to recurrence.

**Table 2** Kaplan–Meier analysis of survival between HCC patients with fever and without fever in different subgroups

Variable	TTR, <i>P</i> -value	OS, <i>P</i> -value
Age, years		
<50	0.000	0.002
$\geq 50$	0.000	0.000
Sex		
Female	0.256	0.194
Male	0.000	0.000
GGT, U/L		
$\leq 54$	0.866	0.029
$> 54$	0.009	0.000
HBsAg		
Negative	0.055	0.082
Positive	0.000	0.000
AFP, ng/mL		
$\leq 20$	0.001	0.007
$> 20$	0.000	0.000
Tumor size, cm		
$\leq 5$	0.576	0.646
$> 5$	0.000	0.009
Tumor encapsulation		
Complete	0.001	0.002
None	0.000	0.000
Vascular invasion		
Absence	0.000	0.000
Presence	0.007	0.002
Tumor differentiation		
I–II	0.000	0.000
III–IV	0.001	0.003
BCLC		
0+A	0.342	0.999
B+C	0.000	0.000

**Abbreviations:** AFP,  $\alpha$ -fetoprotein; BCLC, Barcelona Clinic Liver Cancer; GGT,  $\gamma$ -glutamyl transferase; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; OS, overall survival; TTR, time to recurrence.

14 of these patients had tumor recurrence within 1 year after surgery. In addition, multivariate analysis confirmed that group III was an independent prognosis indicator for both OS and TTR (all *P*-values  $< 0.05$ , Table 3).

## Correlation of neutrophil percentage and fever grade with clinicopathologic features

The clinical features of patients with fever according to neutrophil percentage  $> 70\%$  and fever grade  $\geq 38.5^\circ\text{C}$  were analyzed. Those with fever grade  $\geq 38.5^\circ\text{C}$  ( $n=34$ ) presented with more incomplete encapsulation ( $P=0.020$ ) and larger tumor size ( $P=0.007$ ) compared with those with fever  $< 38.5^\circ\text{C}$  ( $n=29$ ; Table 4). Patients with neutrophil percentage  $> 70\%$  ( $n=24$ ) presented with more incomplete encapsulation ( $P=0.000$ ), vascular invasion ( $P=0.015$ ), and worse tumor differentiation ( $P=0.039$ ) than those with neutrophil levels  $\leq 70\%$  ( $n=39$ ; Table 4).

Those with neutrophil percentage  $> 70\%$  combined with fever grade  $\geq 38.5^\circ\text{C}$  had the worst prognosis, and we found that these patients had more incomplete encapsulation ( $P=0.000$ ) and vascular invasion ( $P=0.028$ ) than any other combination (all *P*-values  $< 0.05$ ; Table 4).

## Discussion

HCC with fever is an uncommon subgroup that has different clinicopathologic features and poorer prognosis than HCC without fever.<sup>4</sup> Our study showed that HCC patients

**Table 3** Univariate and multivariate analysis of factors associated with TTR and OS<sup>a</sup>

Variables	TTR			OS		
	Univariate	Multivariate		Univariate	Multivariate	
	P-value	HR (95% CI)	P-value <sup>a</sup>	P-value	HR (95% CI)	P-value <sup>a</sup>
Age, ≤50 vs >50 years	0.949		NA	0.572		NA
Sex, female vs male	0.150		NA	0.232		NA
HBsAg, negative vs positive	0.166		NA	0.458		NA
GGT, ≤54 U/L vs >54 U/L	0.260		NA	0.142		NA
AFP, ≤20 ng/mL vs >20 ng/mL	0.085		NA	0.043	1.990 (0.970–4.083)	0.061
No of tumors, single vs multiple	0.072		NA	0.494		NA
Tumor size, ≤5 cm vs >5 cm	0.002	2.584 (1.066–6.263)	0.036	0.001	3.610 (1.208–10.788)	0.022
Encapsulation, complete vs none	0.018	0.878 (0.423–1.821)	0.726	0.019	0.645 (0.268–1.551)	0.327
Vascular invasion, no vs yes	0.410		NA	0.179		NA
Edmondson stage, I–II vs III–IV	0.264		NA	0.318		NA
HLM, no vs yes	0.012	2.939 (1.069–8.081)	0.037	0.005	6.140 (1.802–20.917)	0.004
Child-Pugh score, A vs B	0.911		NA	0.263		NA
BCLC stage, 0+A vs B+C	0.119		NA	0.051		NA
Neutrophil levels, ≤70% vs >70%	0.006	2.204 (1.097–4.429)	0.026	<0.001	2.674 (1.232–5.804)	0.013
Fever, <38.5°C vs ≥38.5°C	<0.001	2.059 (1.093–3.878)	0.025	<0.001	2.922 (1.266–6.774)	0.012
Combination						
I vs III	<0.001	2.218 (1.477–3.332)	<0.001	<0.001	2.483 (1.450–4.251)	<0.001
I, II vs III	<0.001	1.739 (1.268–2.385)	<0.001	<0.001	2.058 (1.455–2.912)	<0.001

**Notes:** I: neutrophil percentage ≤70% and fever grade <38.5°C; II: neutrophil percentage >70% and fever grade <38.5°C or neutrophil percentage ≤70% and fever grade ≥38.5°C; III: neutrophil percentage >70% and fever grade ≥38.5°C. <sup>a</sup>Multivariate analysis, Cox proportional hazards regression model. The clinicopathological variables were adopted for their prognostic significance by univariate analyses.

**Abbreviations:** AFP,  $\alpha$ -fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; GGT,  $\gamma$ -glutamyl transferase; HBsAg, hepatitis B surface antigen; HLM, hilar lymph node metastasis; HR, hazard ratio; NA, not applicable; OS, overall survival; TTR, time to recurrence.

with fever had a poor prognosis compared with those without fever. The median OS in patients with fever was only 13 months. However, this was higher than the median OS found in previous reports, which was only 2–3 months without surgery.<sup>3,5</sup> Thus, the longer survival time obtained in our study cohort may be due to timely surgical resection for these patients. Although surgical resection could improve the prognosis of this special subgroup of HCC, most of the patients presenting with fever died from tumor recurrence after surgery, and there were only three of 63 (4.8%) patients who survived for more than 5 years. Thus, a reasonable assessment of the prognosis of patients prior to surgery is necessary in order to tailor the most effective therapy according to characteristics of the individual tumors. Our data imply that the fever grade and neutrophil percentage could meet these requirements, as both show prognostic significance in predicting the clinical outcome for HCC patients presenting with fever and can be easily obtained before surgery.

We found that HCC patients with fever had a propensity for large tumor size, poor tumor differentiation, advanced tumor stage, and lymph node metastasis, which is indicative of the malignant nature of these patients. Furthermore, we found that even in the subgroups with malignant features, the OS and TTR of HCC with fever were worse than those of HCC without fever, suggesting that the worse prognosis

of patients with fever may be mainly caused by other factors. We found that the neutrophil percentage was higher in the HCC patients presenting with fever (70.1% vs 57.9%,  $P=0.001$ ) compared with those without fever. The cause of fever remains unclear. One explanation for neoplasm-associated fever and leukocytosis is the production of granulopoietin and pyrogens, including interleukin-1, interleukin-6, and tumor necrosis factor, by tumor cells.<sup>16–21</sup> These pyrogens have been associated with an increased incidence of neoplastic fever and with advanced stage in renal cell carcinomas and lymphomas.<sup>22–24</sup> These cytokines activate the anterior preoptic nuclei of the hypothalamus and raise the threshold of body temperature via prostaglandin E2.<sup>25</sup> In our study, patients with fever were characterized by large tumors, which have a risk of spontaneous liquefied necrosis within the tumor<sup>26</sup> and they may produce more humoral factors, contributing to fever and leukocytosis. In addition, patients with liquefied necrosis combined with fever and leukocytosis are often misdiagnosed as having liver abscess, which causes them to miss the best opportunity for resection and makes them more likely to be at an advanced stage at the time of eventual diagnosis.<sup>27–29</sup>

Host inflammatory conditions play important roles in tumor development and progression.<sup>30</sup> We found that the neutrophil percentage was higher in the HCC patients

**Table 4** Baseline of feverish patients according to neutrophil levels, fever grade, and their combination

Variables	Neutrophil level			Fever grade			Combination group		
	≤70% (n=39)	>70% (n=24)	P-value	<38.5°C (n=29)	≥38.5°C (n=34)	P-value	Groups I and II (n=46)	Group III (n=17)	P-value
Age, years			0.315			0.619			0.993
≤50	18	8		11	15		19	7	
>50	21	16		18	19		27	10	
Sex			1.000 <sup>a</sup>			0.694 <sup>a</sup>			1.000 <sup>a</sup>
Female	4	3		4	3		5	2	
Male	35	21		25	31		41	15	
HBsAg			0.485 <sup>a</sup>			0.492 <sup>a</sup>			1.000 <sup>a</sup>
Negative	5	5		6	4		7	3	
Positive	34	19		23	30		39	14	
AFP, ng/mL			0.384			0.651			0.751
≤20	19	9		12	16		21	7	
>20	20	15		17	18		25	10	
Tumor size, cm			0.065			0.007			0.195 <sup>a</sup>
≤5	13	3		12	4		14	2	
>5	26	21		17	30		32	15	
Tumor encapsulation			0.000			0.020			0.000
Complete	24	3		17	10		26	1	
None	15	21		12	24		20	16	
Vascular invasion			0.015			0.231			0.028
Absence	31	12		22	21		35	8	
Present	8	12		7	13		11	9	
Tumor differentiation			0.039			0.124			0.781
I–II	28	11		15	24		28	11	
III–IV	11	13		14	10		18	6	
No of tumors			0.294 <sup>a</sup>			0.092 <sup>a</sup>			0.715 <sup>a</sup>
Single	31	22		27	26		38	15	
Multiple	8	2		2	8		8	2	
HLM			1.000 <sup>a</sup>			0.678 <sup>a</sup>			0.657 <sup>a</sup>
No	35	22		27	30		42	15	
Yes	4	2		2	4		4	2	
Child-Pugh score			0.150 <sup>a</sup>			0.618 <sup>a</sup>			0.293 <sup>a</sup>
A	38	21		28	31		44	15	
B	1	3		1	3		2	2	
BCLC stage			0.135 <sup>a</sup>			0.280 <sup>a</sup>			0.423 <sup>a</sup>
0+A	8	1		6	3		8	1	
B+C	31	23		23	31		38	16	

**Notes:** Group I, neutrophil percentage ≤70% and fever grade <38.5°C; Group II, neutrophil percentage >70% and fever grade <38.5°C or neutrophil percentage ≤70% and fever grade ≥38.5°C; Group III, neutrophil percentage >70% and fever grade ≥38.5°C. <sup>a</sup>Fisher's exact tests; chi-square tests for all the other analyses.

**Abbreviations:** AFP,  $\alpha$ -fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B surface antigen; HLM, hilar lymph node metastasis.

presenting with fever compared with those without fever, which indicated the activation of an inflammatory state in these patients. More importantly, shorter OS and TTR were observed in patients with fever with a neutrophil percentage >70% than in those with a neutrophil percentage ≤70%. Neutrophils, which are the primary inflammatory cells, can enhance tumor cell survival, proliferation, and metastasis by secreting immunoreactive molecules, such as neutrophil elastase,  $\beta$ 2-integrins, oncostatin M, or hepatocyte growth factor.<sup>31–34</sup> Thus, the activation of an inflammatory state might contribute to the aggressive clinical course in HCC patients with fever.

We found that a neutrophil percentage >70% was an independent risk factor for the OS and TTR of HCC with fever, which confirmed that neutrophil-associated inflammation was involved in the poor prognosis of patients with fever. Meanwhile, we also found that body temperature was positively correlated with the neutrophil percentage, and fever grade ≥38.5°C was also an independent risk factor for OS and TTR of HCC with fever after resection. Because fever grade and leukocytosis are direct indices for host inflammatory status and are readily available in the clinic, we combined these two factors to predict the prognosis of HCC patients with fever undergoing resection. We found that the

median survival was only 5.1 months in patients presenting with fever grade  $\geq 38.5^{\circ}\text{C}$  combined with neutrophil percentage  $>70\%$ , and most of these patients (14/17) died from tumor recurrence even after tumor resection, which was similar to the survival of patients without surgery in previous reports (median survival: 2–3 months). Thus, it seems that surgical resection is not effective for these patients, and novel nonsurgical approaches need to be further explored in order to improve their prognosis, as they have aggressive disease and a rapidly deteriorating clinical course.

## Limitations

The limitations of this study are its relatively small cohort size, retrospective design, and procurement of data from a single study center. Additionally, C-reactive protein is not routinely measured in our daily practice, and we did not include C-reactive protein in this study. Finally, the precise mechanism of fever and leukocytosis in these HCC patients needs to be further explored.

## Conclusion

To our knowledge, this is the first report to demonstrate comprehensively the clinical characteristics of this rare clinical HCC subgroup with the largest sample size in the world. Our study indicates that HCC patients presenting with fever as the initial manifestation have a poorer prognosis than those without fever, while their prognosis would be improved by timely surgical intervention. Patients with a neutrophil percentage  $>70\%$  and a fever grade of  $\geq 38.5^{\circ}\text{C}$  have an extremely dismal outcome and more aggressive clinical course. Inflammatory processes and endogenous pyrogen-related cytokines may mediate the development and progression of cancer in these patients.

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## Disclosure

The authors report no conflicts of interest in this work.

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