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Original paper

Bacterial infections and fever after hepatocellular carcinoma ablation therapy: Predictive role of procalcitonin

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Abstract

Aim of the study: Hepatocellular carcinoma (HCC) is a leading cause of mortality among patients with liver cirrhosis. According to the current practice guidelines, different ablations are used either as curative or palliative therapies. The current study aimed at determining bacterial infections as causes of fever and the predictive role of procalcitonin (PCT) among patients with HCC who had ablation therapy.

Material and methods: This cross sectional study was carried out on 100 patients with HCC during the period from November 2019 to December 2021. All patients were evaluated by full history taking, clinical examination, complete blood picture (CBC), liver biochemistry, coagulation profile, kidney function, C-reactive protein (CRP), serum PCT and blood cultures. All were done for all participants at the 4th day follow-up after the procedures of ablation. HCC was treated according to the guidelines.

Results: The frequency of fever after HCC ablation was 64% with variable intensities. Bacterial cultures were positive in 20 patients (20%). Twenty-four out of 100 patients had abnormally high PCT level. There was a highly statistically significant increase of PCT level in patients with a high CRP count and positive blood culture, $p < 0.05$. There was a statistically significant correlation between increased levels of PCT and levels of CRP, WBCs, albumin, AST, ALT, degree of fever, creatinine and BUN.

Conclusions: Bacterial infection accounts for 20% of fever among HCC patients after ablation therapy. PCT is 100% sensitive and specific for detection of the bacterial causes of fever among those patients.

Key words: procalcitonin, bacterial infection, hepatocellular carcinoma, ablation therapy.

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Introduction

Globally, the most frequently used ablation therapies for hepatocellular carcinoma (HCC) are percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation (MWA), and transarterial chemoembolization (TACE) [1]. These procedures have variable rates of major complications (4-7% in TACE and 2-3% in RFA) such as liver infarction, acute hepatic failure, intrahepatic biloma, hepatic abscess and cholecystitis [2], and general speaking these procedures are considered tolerable. However, most patients undergoing percutaneous ablation therapy experience temporary fever, abdominal pain and related constitutional symptoms defined as postablation syndrome [3].

The level of procalcitonin (PCT) rises in response to a pro-inflammatory stimulus, especially of bacterial origin. It is classified as an acute phase reactant. Serum levels of PCT may rise to the level of 100 µg/l in severe infection. It starts to rise 2-4 hours after catching the bacterial infection and has a half-life of 25 to 30 hours. The high PCT levels produced during infections are not followed by a parallel increase in calcitonin or a decrease in serum calcium level [4]. The predictive value

of PCT has been evaluated for patients with decompensated liver cirrhosis, and found superior to C-reactive protein (CRP), interleukin 6, and tumor necrosis factor α [5]. The current study aimed at determining bacterial infections as causes of fever and the predictive role of PCT among patients with HCC who had ablation therapy.

Material and methods

This cross sectional study was conducted at interventional ultrasonography units of the Tropical Medicine and the Radiology Departments, Zagazig University Hospitals, Egypt during the period between November 2019 and December 2021. A total of 100 naive HCC patients were included in this study as the research group.

Inclusion criteria

Patients in the current study are Egyptian cirrhotic patients with HCC aged 18 years and above, with a good mental state to understand the concept, benefits, risks, and steps of the study. Patients with HCC were candidates for ablation therapy per the current practice guidelines.

Exclusion criteria

Any major organ failure, history of fever, antibiotic use before the procedure or clinical and laboratory findings suggestive of infection or sepsis before the ablation.

Measures

All patients were subjected to: full history taking, full clinical examination, laboratory investigations: complete blood picture (CBC), liver biochemistry (bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total protein and albumin), coagulation profile (prothrombine time [PT], international normalized ratio [INR]), kidney functions tests (creatinine, blood urea), CRP, serum PCT level, and blood culture. Additional investigations were required case by case and when manifestations were suggestive of localization, e.g. urine analysis, chest X-ray, SARS-CoV-2 PCR, etc.

Serum PCT level: Was measured by ELISA. The cutoff value for the diagnosis of bacterial infection is 0.5 ng/ml. Samples were assayed immediately after sample collection. During the whole procedure serum samples require an appropriate dilution with Standard/Sample Diluent.

Blood culture: Was collected only once at the 4th day after ablation (short-term follow-up). Blood samples done for aerobic and non-aerobic bacterial infection from all patients regardless of development of fever and at the same time with collection of PCT value. Detection of the type of bacterial pathogen in the positive cases was not done because of financial and technical problems during the COVID-19 era.

HCC ablation: HCC was diagnosed with multiphase computed tomography (CT) with contrast imaging. Patients with HCC were treated case by case using PEI, RFA or TACE according to the Barcelona clinic liver cancer (BCLC) staging system. Microwave ablation was not used because it was not available in our institutions at the time of the study. All patients undergoing HCC ablation in the current study did not receive any prophylactic antibiotics before the procedure.

Fever: Was defined in the current study as increase in the body temperature to ≥ 37.8°C.

Statistical analysis

The collected data were computerized and statistically analyzed using the SPSS program version 20.0.

Qualitative data are presented as number and percentage and quantitative data are presented by mean ± SD or median (range). Continuous data were checked for normality using the Shapiro-Wilk test. The *t*-test was used to compare between two groups of normally distributed variables, while the Mann-Whitney *U* test was used for non-normally distributed variables. The chi-square test used for comparison between two qualitative variables. Significance was defined as $p < 0.05$.

Finally, receiver operating characteristic (ROC) curve analysis was performed to estimate the validity of PCT in predicting bacterial infection in HCC patients who developed fever after ablation therapy. The area under the curve (AUROC) was also calculated and the optimal cutoff value point was established at the point of maximum accuracy.

Ethical approved

The study was carried out in a manner consistent with the ethical principles of the Declaration of Helsinki, and it was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Zagazig University (approval no. 4863). Informed consent has been obtained from every participant.

Table 1. Distribution of the studied cases according to baseline characteristic

Variables	*n*	%
Gender		
Male	76	76
Female	24	24
Age (years)		
Min.-Max.	45.0-69.0	
Mean ±SD	56.42 ±5.59	
Median (IQR)	55.0 (52.0-61.0)	
Comorbidity		
No	46	46
Yes (diabetic)	54	54
CRP		
Normal (⩽ 5)	28	28
Abnormal (> 5)	72	72
Min.-Max.	0.50-300.0	
Mean ±SD	32.43 ±56.37	
Median (IQR)	17.0 (5.0-28.0)	
Blood culture		
No growth	80	80
Positive	20	20
Procedure		
Radiofrequency	54	54
Ethanol	28	28
TACE	18	18
Number of nodules		
Solitary	82	82
Multinodular	18	18
Cause of cirrhosis		
HCV	80	80
HBV	20	20
Child score		
Child A	82	82
Child B	18	18
Fever		
No	36	46
Yes	64	64
Degree		
Min.-Max.	37.0-40.0	
Mean ±SD	38.32 ±0.99	
Median (IQR)	38.50 (37.30-38.90)	

TACE – transarterial chemoembolization, CRP – C-reactive protein, HCV – hepatitis C virus, HBV – hepatitis B virus

Results

Patient characteristics

Hepatocellular carcinoma patients in the current study were aged between 45 and 69 years and the majority of them were males (76%). The majority of patients had a single liver mass (80%). Radiofrequency ablation was the most frequent ablation therapy, done in 54% of patients (Table 1). As expected, hepatitis C virus (HCV) was the leading cause of cirrhosis among our cohort (80%). Patients of the current study belongs to Child class A and B (none was Child C), and 54% of them had associated co-morbidities, mainly diabetes.

Short-term post-ablation follow-up

After ablation therapy by 4 days at short-term follow-up, patients were re-assessed for evaluation of ablation, detection of complications, detection of fever and any signs of infection. Laboratory parameters (CBC, liver biochemistry, PCT, CRP), and blood cultures were done for all patients at the date of the visit. CBC, liver functions and renal function results fall within the scope of figure for patients with Child A-B, as shown in Table 2. Out of the 100 patients recruited, 64 developed fever, which ranged from 38°C to 40°C, as shown in Table 1.

Markers of infection and predictive value of procalcitonin

Out of the 100 patients, 76 patients had normal PCT and 24 had an abnormally high PCT level as shown in Table 3, while CRP as shown in Table 1 was abnormally high (> 5) among 72 patients.

Blood cultures were positive only in 20% of patients. However, we did not identify the organisms from the blood cultures because of the financial and technical problems during the COVID-19 era. There was a highly statistically significant increase of PCT level in patients with a high CRP count and positive blood culture (Table 4). All patients with high PCT had abnormally high CRP > 5, while all patients positive for the blood culture had an abnormally high PCT level.

There was a statistically significant positive correlation between PCT level and levels of CRP, systemic WBC count, albumin, AST, ALT, degree of fever, creatinine and BUN, as shown in Table 5.

ROC curve for PCT accuracy in detection of bacterial infection identified a cutoff value more than 0.66 ng/ml with accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 100% (Table 6).

Table 2. Laboratory measures among studied group

Variable	Mean ±SD	Range
WBCs (×10^3)	7.5 ±5.2	3.8-25.4
Hemoglobin (gm/dl)	13.1 ±1.6	9.4-15
Platelets (×10^3)	203.6 ±58.8	101-290
Bilirubin (mg/dl)	1.5 ±0.47	1-2.7
Albumin (gm/dl)	3.8 ±0.42	3-4.5
AST (IU/l)	73.3 ±36.5	30-187
ALT (IU/l)	126.7 ±59.8	34-298
INR	1.2 ±0.29	1-1.9
Creatinine (mg/dl)	1.1 ±0.21	0.8-1.6
BUN (mg/dl)	20.2 ±3.5	10-26
Procalcitonin (ng/ml)	2.3 ±9.1	0.01-59
CRP (mg/dl)	32.4 ±56.4	0.5-300

Table 3. Distribution of the studied cases according to procalcitonin

Procalcitonin (ng/ml)	*n*	%
Normal (⩽ 0.5)	76	76
Abnormal (> 0.5)	24	24
Min.-Max.	0.01-59.0	
Mean ±SD	2.33 ±9.13	
Median (IQR)	0.10 (0.10-0.42)	

Discussion

In Egypt, HCC with the underlying chronic liver diseases are the most challenging health problems; HCC represents the fourth most common cancer nationally. Egypt ranks the 3rd and 15th most populous country in Africa and globally, respectively [6].

Table 4. Relation of procalcitonin to CRP and blood culture

Variables	Total (*N* = 100)		Procalcitonin				*p*
			Normal (*n* = 76)		Abnormal (*n* = 24)		
	n	%	*n*	%	*n*	%	
CRP							
Normal (⩽ 5)	28	28	28	36.8	0	0.0	< 0.001*
Abnormal (> 5)	72	72	48	63.2	24	100.0	
Min.-Max.	0.50-300.0		0.50-41.0		19.0-300.0		< 0.001*
Mean ±SD	32.43 ±56.37		12.96 ±10.03		94.08 ±90.18		
Median (IQR)	17.0 (5.0-28.0)		13.0 (2.80-18.0)		52.0 (32.5-150.0)		
Blood culture							
No growth	80	80.0	76	100.0	4	16.7	< 0.001*
Positive	20	20.0	0	0.0	20	83.3	

**Highly significant*

Table 5. Correlation between procalcitonin and different parameters

Variables	Procalcitonin	
	r_s	*p*
Age (years)	0.146	0.146
CRP	0.626	< 0.001*
WBCs	0.391	< 0.001*
Hemoglobin	–0.109	0.282
Platelets	0.140	0.164
Bilirubin	0.089	0.379
Albumin	0.251	0.012*
AST	0.223	0.027*
ALT	0.265	0.008*
INR	–0.056	0.579
Degree of fever	0.526	< 0.001*
Creatinine	0.617	< 0.001*
BUN	0.351	< 0.001*

**Significant*

This study aims to determine bacterial infections as causes of fever after PEI, RFA and TACE in the treatment of HCC. The age of the studied group ranged from 45 to 69 years old and the majority of them were males (76%), which agrees with local reports on the same topic by El Mahdy *et al.*, who noted an increased male-to-female ratio in HCC incidence due to the protective effect of female sex hormones against HCC development [7]. Protective roles of estrogens may include the inhibition of inflammatory responses, prevention of oxidative stress and inducing apoptotic cell death. Also, it is possibly related to some environmental exposures which are more common in males, for example, heavy alcohol use.

Focusing on the fever after HCC ablation therapy is not only related to the quality of life of patients post-procedurally or to the occurrence of complications [8], but also some recent reports link prolonged post-intervention fever with higher tumor recurrence rates

Table 6. Diagnostic accuracy of procalcitonin vs. CRP among the studied group in detection of bacterial infection

Variables	AUC	*p*-value	Cut off#	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP	0.965	< 0.001*	> 28	90.0	92.5	75.0	97.4	92.0
Procalcitonin	1.0	< 0.001*	> 0.66	100.0	100.0	100.0	100.0	100.0

*AUC – area under the curve, NPV – negative predictive value, PPV – positive predictive value; *Statistically significant at p ⩽ 0.05, #Cutoff was chosen according to Youden index*

at one year [9]. Furthermore, one recent report found that postoperative infection and its associated manifestations among patients receiving ultrasound-guided thermal ablation for HCC adversely affected tumor progression [10].

One question arises, why PCT was focused in HCC feverish patients post-ablation, and the answer can be inferred from our results, which showed significant increases in the level of PCT among our cohort, a result that agrees Tschaikowsky *et al*., who noted that PCT levels are known to increase dramatically in response to injury and inflammation, which are mainly associated with underlying bacterial infection. In the same instance the inflammation causes release of cytokines which act directly on the anterior hypothalamus and cause a release of prostaglandins, which mediate the febrile response [11].

Regarding development of fever after the procedure in the current study, there were 64 patients (64%) of the studied group who had fever; this disagrees with Chen *et al*., who recently reported that the frequency of post-RFA fever was 18.4% [12], while Siriwardana *et al*. reported a 25.2% rate of fever after TACE [13]. The differences are mainly related to assessment after a single intervention by Chen *et al*. and Siriwardana *et al*. in comparison to many percutaneous ablation therapies in our study or may be due to different antiseptic measures followed peri-procedurally, although they were followed during our interventions. In fact, the frequency of fever is expected to be higher and more intense with TACE than RFA and PEI, because fever in such circumstances is mainly due to tissue necrosis; that is more with TACE [12, 13], and the occurrence of high fever with RFA or PEI should sound the alarm to occurrence of complications, e.g. abscess formation [8].

The frequency of bacterial infection after HCC ablation was also investigated in the literature. Chen *et al*. [12] reported a rate of 4.8% positive blood cultures after RFA, while Zhang *et al*. [10] reported a positive culture rate of 34.7% (including blood and other body fluids) after RFA and microwave ablation. The differences in the figures between our study and other authors may be related to the nature of patients, type and number of ablation techniques investigated and source of the cultrate.

In this study there was a statistically significant increase of PCT level in patients with high CRP count, which agrees with Waterfield *et al*., who noted that both PCT and CRP are valuable markers in predicting bacterial infection even without an obvious source and they perform better than WBC count rise [14]. They also claimed that PCT appears more accurate at the beginning of infections, but overall CRP may be a convenient marker due to its sensitivity and feasibility. On the other hand, our results disagree with Sproston and Ashworth, who stated that the CRP levels are known to increase dramatically in response to injury and inflammation and also CRP is an acute phase reactant and is not necessarily associated with an underlying bacterial infection [15]. Our results showed the superiority of PCT over CRP in diagnosis of suspected bacterial infections; this was long ago demonstrated in a large meta-analysis conducted by Simon *et al*. [16].

The degree of agreement between PCT level and positivity of blood culture in the current study is 100%, and this agrees with Noviello and Huang, who stated that a positive blood culture is considered the gold standard for confirmation of bacteremia [17]. The major disadvantages of blood cultures are the lack of 100% sensitivity and the time it takes; it ranges from many hours to days. Given the urgency of treatment required for management of patients in sepsis, initially elevated PCT levels can fill the gap of delayed diagnosis and help early initiation of therapy [18]. Furthermore, PCT had shown a high specificity for bacterial causes of inflammation in patients, and its rapid elevation, which correlates with the severity of illness, makes it an ideal biomarker for bacterial infection [19-24].

Multivariate analysis revealed that PCT had a significant positive correlation with levels of CRP, WBCs, ALT, AST, degree of fever, creatinine and BUN as well as albumin levels. Soeters *et al*. highlighted that hypoalbuminemia is associated with the acquisition and severity of infection, especially bacterial infections, which are associated with subsequent increased PCT level, and also predicts infectious complications in non-infective disease. However, serum albumin levels are affected by other factors including the underlying liver cirrhosis, rendering it an unreliable marker if used alone. Furthermore, systemic inflammation in severe infection alters the function and kinetics of albumin, which in turn can increase the risk of a worse clinical outcome [25].

In the context of comparing the diagnostic accuracy of PCT and CRP in detection of bacterial infection in our cohort, the ROC curve revealed that PCT had higher sensitivity and specificity regarding prediction of bacterial infection with sensitivity of 100% and specificity of 100%, while CRP can predict bacterial infection with sensitivity of 90% and specificity of 92.5%, with significant area under the ROC curve for both of them; this agrees with many reports in the literature [19-24, 26-28], which emphasizes the superiority of PCT over CRP regarding presence of bacterial infection in terms of higher sensitivity and specificity. Combining both PCT and CRP would have synergistic predictive value.

This study had some limitations. First, it is a single center study with a small number of patients and a short duration of follow-up. Second, it lacked a comparative group. During the study period the peak of COVID-19 occurred, with limited possibilities of both hospital admissions and outpatient clinic visits. Third, there was a failure to identify the possible bacterial strains causing the fever, and this was related to limited resources during the pandemic. Hence the probability of contamination cannot be excluded, and this may explain the relatively high (20%) frequency of positive cultures. Fourth, the heterogeneity of ablation techniques applied; the frequency of fever may vary between percutaneous (PEI, RFA) and trans-arterial (TACE) ablation. Fifth, there was a lack of long-term follow-up to elucidate the impact of fever and bacterial infection peri-procedurally on the outcomes of HCC ablation.

In conclusion, most patients under ablation therapy for HCC develop fever. The etiology of fever may denote the underlying extensive necrosis of the tumor and healthy cells rather than an infectious etiology, which accounts for 20% in the current study. PCT seems to be a valuable predictor for bacterial infection and fever among these patients.

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Disclosure

The authors declare no conflict of interest.

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