Predictive Value of Procalcitonin for Bacterial Infection after Hepatocellular Carcinoma Ablation Therapy

Mostafa H. Elshamy[1], Hanaa H. Elsaid[2], Abeer H. Abdelkader[1], * Reham A.Abdelkhalek [1]
[1] Tropical Medicine Department, [2]Clinical pathology Department, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Reham A AbdelKhalik
E mail: Reham.aidy@gmail.com

Abstract:
Background: The most globally used primary treatments for un-resectable hepatocellular carcinoma (HCC) are trans-arterial chemoembolization (TACE), percutaneous ethanol injection (PET) and radiofrequency ablation (RFA)
Objectives: determine the role of procalcitonin to predict bacterial infection and correspondingly the usefulness of antibiotic use in HCC patients who develop fever after TACE, PET or RFA.
Patients and methods: This cross section study conducted at Interventional ultrasound unit Tropical Medicine Department and Radiology Department, Zagazig University Hospitals at period of time from November 2019 to December 2021.
Full history taking, clinical examination, CBC, liver biochemistry (S. bilirubin, ALT, AST, total protein and S. albumin), coagulation profile (PT, INR), kidney function (S. creatinine, blood urea), C-reactive protein (CRP), serum procalcitonine and blood culture was done for all participant at 4 days follow up after the procedures.
Results: 24 of 100 patients had abnormal procalcitonin level. There is highly statistically significant increase of procalcitonin level in patients with high CRP count and positive blood culture, $P<0.05$. There is statistically significant increased level of procalcitonin with positive correlation between procalcitonin level and levels of CRP, WBCs, Albumin, AST, ALT, Degree of fever, Creatinine and BUN. There is no statistically significant difference of blood culture results in relation to the child score of the patients.
Conclusion: bacterial infection mostly not the causative agent of fever in HCC patient after ablation therapy, it may be due to underlying extensive necrosis of the tumor and healthy cells.
Keywords: Procalcitonin; Bacterial Infection; Hepatocellular Carcinoma; Ablation Therapy.

Tob Regul Sci. ™ 2022;8(1): 2228-2237
DOI: doi.org/10.18001/TRS.8.1.168

Introduction

The most globally used primary treatments for unresectable hepatocellular carcinoma (HCC) are transarterial chemoembolization (TACE), percutaneous ethanol injection (PET) and radiofrequency ablation (RFA) **(1).** These procedures have low rate 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) so they are generally well tolerated. However, most of 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 a response to a pro-inflammatory stimulus, especially of bacterial origin. It is classed as an acute phase reactant. Serum levels of procalcitonin may rise to the level of 100 µg/L in severe infection. It starts to rise 2-4 hours after catching bacterial infection and has a half-life of 25 to 30 hours. the high procalcitonin levels produced during infections are not followed by a parallel increase in calcitonin or a decrease in serum calcium level **(4).**

In patients with decompensated liver cirrhosis, PCT showed the best diagnostic value relative to C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α **(5).**

Patients and Methods

This cross section study conducted at Interventional ultrasound unit at Tropical Medicine Department and Radiology Department, 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.

Inclusion Criteria:

HCC patients aged above 18 years who candidate for ablation therapy and agree for enrolment in the study.

Exclusion Criteria:

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

All patients will be subjected to the following:

Full history taking, Full clinical examination, Laboratory investigation: Complete blood picture(CBC), liver biochemistry (S. bilirubin, ALT, AST, total protein and S. albumin), coagulation profile (PT, INR), kidney functions tests (S. creatinine ,blood urea) and **C-reactive protein (CRP).**

Serum Procalcitonin level: measured by ELISA. cutoff value of 0.5 ng/mL for the diagnosis of bacterial infection. Samples should be assayed immediately after collection. During the whole procedure. Serum samples require an appropriate dilution with Standard/Sample Diluent.

Blood culture: collection of blood sample was done at 4 days short time follow up after the procedures. Blood Samples done for aerobic and non-aerobic bacterial infection from all patients regardless development of fever and at the same time with of collection of procalcitonin value. No detection of the type of bacterial pathogen done in the positive case because it was not the scope of this study and will increase the cost.

Statistical analysis: The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 20.0

Qualitative data represented as number and percentage and quantitative data represented by mean ± SD or median (range). Continuous data were checked for normality by using Shapiro Walk test. T-test was used to compare between two groups of normally distributed variables while Mann Whitney U test was used for non- normally distributed variables. Chi square test used for comparison between two qualitative variables. Significance was defined as $P < 0.05$

Finally, Receiver operating characteristic (ROC) curve was done to estimate the validity of the procalcitonin in predicting bacterial infection in HCC patients who developed fever after ablation therapy. Area Under Curve (AUROC) was also calculated 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 faculty of medicine, Zagazig University (approval no.4863). Informed consent has been obtained from every participant.

Results:

HCC patients came to intervention unit at Tropical medicine department and radiological department at the periods from November 2019 to December 2021

This study include100 HCC patients who are suitable for ablation therapy either percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) or trans-arterial chemoembolization (TACE) and agreed to be enrolled in this study

Their age range from 45- 69 years and the majority of them were male (76%). The majority of patients had single liver mass 80%. Radiofrequency ablation was the most ablation therapy done in 54% of patients. (Table 1)

After ablation therapy by 4 days at short time follow up of these patients for evaluation of ablation, detection of complication, detection of fever and any signs of infection. Laboratory parameters (CBC, liver biochemistry, procalcitonin, CRP), blood culture was done for all patients.

CBC, liver functions and renal function results near the normal value. (Table 2)

64 of 100 patients develop fever range from 38-40 degree. 76 patients of the studied cases had normal procalcitonin and 24 had abnormal procalcitonin level. (Table 3) Blood culture was positive in 20% of patients with no detection of type of bacteria. There was highly statistically significant increase of procalcitonin level in patients with high CRP count and positive blood culture. (Table 4)

There was statistically significant increased level of procalcitonin with positive correlation between procalcitonin level and levels of CRP, WBCs, Albumin, AST, ALT, Degree of fever, Creatinine and BUN. (Table 5)

ROC curve for procalcitonin in detection of bacterial infection is at cutoff value more than 0.66 ng/mL with accuracy 100%, PPV, NPV also 100%. (Table 6).

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

	No.	%
SEX		
Male	76	76.0
Female	24	24.0
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	46.0
Yes (diabetic)	54	54.0
CRP		
Normal (≤5)	28	28.0
Abnormal (>5)	72	72.0
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	80.0
Positive	20	20.0
Procedure		

Radiofrequency	54	54.0
Ethanol	28	28.0
TACE	18	18.0
Number of nodules		
Solitary	82	82.0
Multi nodular	18	18.0
Cause of cirrhosis		
HCV	80	80.0
HBV	20	20.0
Child score		
Child A	82	82.0
Child B	18	18.0
Fever		
No	36	46.0
Yes	64	64.0
Degree		
Min. – Max.	37.0 – 40.0	
Mean ± SD.	38.32 ± 0.99	
Median (IQR)	38.50(37.30 – 38.90)	

Table 2. Laboratory measures among studied group:

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

Table 3. Distribution of the studied cases according to Procalcitonin

Procalcitonin	No.	%
Normal (≤0.5)	76	76.0
Abnormal (>0.5)	24	24.0
Min. – Max.	0.01 – 59.0	
Mean ± SD.	2.33 ± 9.13	
Median (IQR)	0.10 (0.10 – 0.42)	

Table 4. Relation between procalcitonin with CRP and blood culture

	Total (n = 100)		Procalcitonin				Test of Sig.	p
			Normal (n = 76)		Abnormal (n = 24)			
	No.	%	No.	%	No.	%		
CRP								
Normal (≤5)	28	28.0	28	36.8	0	0.0	χ^2= 12.281*	<0.001*
Abnormal (>5)	72	72.0	48	63.2	24	100.0		
Min. – Max.	0.50 – 300.0		0.50 – 41.0		19.0 – 300.0		U= 80.0*	<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	χ^2= 79.167*	<0.001*
Positive	20	20.0	0	0.0	20	83.3		

Table 5. Correlation between procalcitonin and different parameters

	Procalcitonin	
	r_s	p
Age (years)	0.146	0.146
CRP	0.626	<0.001*
WBCs	0.391	<0.001*
HB	-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	0.526	<0.001*
Creatinine	0.617	<0.001*
BUN	0.351	<0.001*

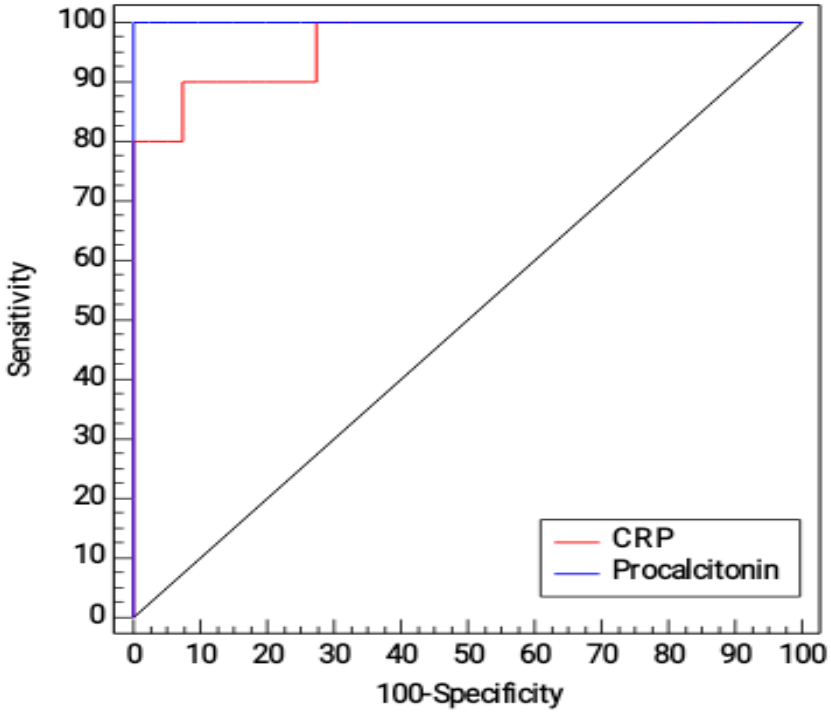

Table 6. ROC curve for detection of Bacterial Infection by procalcitonin & CRP among the studied group:

	AUC	p	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 a Curve
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at p ≤ 0.05 #Cut off was choose according to Youden index

Discussion

In Egypt, HCC is the most challenging health problem; it represents the fourth common cancer. Egypt ranks the third and 15th most populous country in Africa and worldwide, respectively **(6)**.

This study aims to determine the role of procalcitonin to predict bacterial infection and the usefulness of antibiotic use in HCC patients who develop fever after TACE, PEI or RFA at Interventional ultrasound unit Tropical Medicine Department and Radiology Department, Zagazig University Hospitals through screening of 100 patients who diagnosed by Multiphase computerized tomography (CT) with contrast imaging and proved to have HCC candidate for percutaneous ablation therapy.

the age of studied group range from 45 to 69 years old and the majority of them were males 76%, this agree with **El Mahdy et al., (7)** who denoted increased male-to-female ratio in HCC incidence due to the protective effect of female sex hormones against HCC development. protective role 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 more common at males, for example, heavy alcohol use.

Regarding development of fever after the procedure there were 64 patients (64%) of the studied group had fever this disagree with **Nault et al., (8)** who denoted that the frequency of post-RFA fever was 18.4% only most probably due to assessment after only RFA not including the other procedures of percutaneous ablation therapy or may due to stricter antiseptic measures during the procedure.

In this work there was statistically significant increase of procalcitonin level in patients with high CRP count, this agree with **Waterfield et al., (9)** who denoted that Both PCT and CRP are valuable markers in predicting bacterial infection even without obvious source and they perform better than WBCs count rise. That study also showed that PCT appears more accurate at the beginning of infections, but overall CRP may be a convenient marker for its sensitivity and feasibility. This disagree with **Sproston and Ashworth., (10)** who signified that the C-reactive protein levels are known to increase dramatically in response to injury and inflammation and also CRP is an acute phase reactant and not necessary to be associated with underlying bacterial infection. In our work also, there was highly statistically significant increase of procalcitonin level in patients with positive blood culture this agree with **Noviello and Huang .,(11)** who designated that a positive blood culture is considered the gold standard for confirmation of bacteremia, but its results take hours to days .Given the urgency of treatment required for management of patients in sepsis , an initially elevated PCT level can help to confirm an early diagnosis .Furthermore, PCT had shown a high specificity for bacterial causes of inflammation in patients and its rapid elevation which correlate with the severity of illness make it an ideal biomarker for bacterial infection.

Our study also showed that there was statistically significant increased level of procalcitonin among feverish group and this agree with **Tschaikowsky et al., (12)** who signified that procalcitonin levels are known to increase dramatically in response to injury and inflammation which mainly associated with underlying bacterial infection. In the same instance the inflammation cause release of cytokines which act directly on the anterior hypothalamus and cause a release of prostaglandins, which mediate the febrile response.

Multivariate analysis in our study revealed that procalcitonin had significant positive correlation with levels of CRP, WBCs, ALT, AST, Degree of fever, Creatinine and BUN as well as Albumin. **Soeters et al., (13)** highlighted that hypoalbuminemia is associated with the acquisition and severity of infection especially bacterial infections which associated with subsequent increased procalcitonin level and also predicts infectious complications in non-infective disease. Furthermore, systemic inflammation in severe infection alters the function and kinetics of albumin, which in turn can increase the risk of worse clinical outcome.

In our study , regarding validity of detection of bacterial infection by procalcitonin & CRP among the studied group , the ROC curve revealed that procalcitonin providing higher sensitivity and specificity regarding prediction of bacterial infection presence with sensitivity of 100% and specificity 100 % ,while CRP can predict bacterial infection with sensitivity of 90% and specificity 92.5 % with significant area under the ROC curve for both of them , this agree with **Zhao et al., (14)** who signify the higher sensitivity and specificity of procalcitonin regarding presence of bacterial infection with less sensitivity and specificity of CRP when compared to procalcitonin , Also this study highlighted the synergistic role of combination assay of PCT and CRP levels which was associated with best detection with highest sensitivity and specificity.

Limitation of the study: This study is one center study and had short duration follow up.

Conclusion:

Most patients who develop fever after percutaneous ablation therapy for HCC, the etiology of fever denote the underlying extensive necrosis of the tumor and healthy cells while infectious complications are not common.

Recommendation: Further study on large sample of patients with long duration follow up.

Declarations:

Consent for Publication: I confirm that all authors accept the manuscript for submission

Funding: No fund

Conflicts of Interest: The authors declare no conflicts of interest regarding the publication of this paper.

References

1. **Fitzmorris P, Shoreibah M, Anand B., et al (2015):** Management of hepatocellular carcinoma. Journal of Cancer Research and Clinical Oncology, vol. 141, no. 5, pp. 861–876.
2. **Park, JG.; Park, SY.; Tak, WY., et al.(2017).** Early complications after percutaneous radiofrequency ablation for hepatocellular carcinoma Clin. Radiol. 2017, 72, e9–e15.

3. **Filippousis P, Sotiropoulou E, Manataki A, et al, (2011):** "Radiofrequency ablation of subcapsular hepatocellular carcinoma: single center experience," European Journal of Radiology, vol. 77, no. 2,pp. 299–304.
4. **Vijayan AL, Ravindran S, Saikant R., et. (2017).** "Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy". Journal of Intensive Care. 5: 51. doi:10.1186/s40560-017-0246-8. PMC 5543591. PMID 28794881.
5. **S. Connert, W. Stremmel, and C. Elsing (2003):** "Procalcitonin is a valid marker of infection in decompensated cirrhosis," Zeitschrift für Gastroenterologie, vol. 41, no. 2, pp. 165–170.
6. **Abd-Elsalam S, Elwan N, Soliman H et al. (2018):** Epidemiology of liver cancer in Nile delta over a decade: A single-center study. South Asian J Cancer. 2018;7:24–26.
7. **El Mahdy T, Abd Elfatah E, Mohamed M., et al. (2016):** Relation between sex hormones and hepatocellular carcinoma. *Andrologia.* ;48:948–55
8. **Nault J.C, Sutter O, Nahon P., et al. (2018):** Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations. *J. Hepatol.* 68:783–797.
9. **Waterfield T, Maney JA, Hanna M et al. (2006**): Point-of-care testing for procalcitonin in identifying bacterial infections : a diagnostic accuracy study. BMC Pediatr. 2018;18(1):1–6. doi: 10.1186/s12887-017-0974-x
10. **Sproston R and Ashworth J (2018):** Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018 Apr 13;9:754.
11. **Noviello S and Huang DB.(2019**). The basics and the advancements in diagnosis of bacterial lower respiratory tract infections. Volume 40 - Issue 7 - p 639-642.
12. **Tschaikowsky K, Braun GG, Troeger MR., et al. (2020**): Predictive value of procalcitonin, interleukin-6, and C-reactive protein for survival in postoperative patients with severe sepsis. *J Crit Care*. 2011;26(1):54–64. doi:10.1016/j.jcrc.2020.04.011
13. **Soeters P.B., Wolfe R.R., Shenkin A (2019**). Hypoalbuminemia: Pathogenesis and Clinical Significance. J. Parenter. Enter. Nutr. 2019;43:181–193. doi: 10.1002/jpen.1451.
14. **Zhao J, Zhang S , Dong X., et al. (2017).** "Serum procalcitonin levels as a diagnostic marker for septic arthritis: A meta-analysis". The American Journal of Emergency Medicine. 35 (8): 1166–1171.