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RESEARCH ARTICLE

ASPARTATE AMINOTRANSFERASE TO PLATELET RATIO INDEX VERSUS NEUTROPHIL TO LYMPHOCYTE RATIO FOR PREDICTION OF POST RADIOFREQUENCY ABLATION RECURRENCE OF HEPATOCELLULAR CARCINOMA.

Mohammad M. Sallam , Emad Hamed Fawzy and Hany Mohamed Elsadek .
Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt.

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Abstract

Background & Aims: Tumor recurrence after curative radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) is common. The burden of frequent post- ablation investigations especially triphasic computerized tomography (TCT) is high. We investigated whether post ablation measurement of aspartate aminotransferase to platelet ratio index (APRI) and neutrophil to lymphocyte ratio (NLR) as simple and cheap biomarkers can precisely predict HCC recurrence and which of them is more valuable.
Methods: In this retrospective study, the demographic, clinical, laboratory and imaging data of 42 HCC patients treated with RFA were statistically analyzed. Patients were classified into two groups; those with HCC recurrence (group I) and those without (group II). In order to test the value of baseline NLR versus that of APRI in predicting tumor recurrence and compare both to alfa fetoprotein (AFP), we used receiver operating curve (ROC) statistics.
Results: Mean values of AST, Platelets count, APRI, NLR and AFP showed significant correlation with HCC recurrence. Using logistic regression analysis, NLR was the only independent risk factor predicting HCC recurrence. NLR had the highest sensitivity and specificity for prediction of HCC recurrence (90.9 % and 85%) followed by that of AFP (86.4 % and 75%), and lastly by that of APRI (72.7% and 70%).
Conclusion: NLR is a promising, simple and cheap surrogate marker for prediction of HCC recurrence after radiofrequency ablation, and is far more significant than APRI.
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Introduction:-

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide (**1**).HCC is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis (**2**).The incidence of HCC is highest in Asia and Africa, where the endemic high prevalence of hepatitis B (HBV) and hepatitis C (HCV) strongly predisposes to the development of chronic liver disease and subsequent development of HCC (**3**). Radiofrequency ablation (RFA) became a main modality of loco-regional therapy for HCC, because of its

Corresponding Author:- Mohammad M. Sallam.
Address:- Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt.

effectiveness and safety for small HCC (<5.0 cm), with a 3-year survival rate of 62–77%, a low treatment complication rate of 8–9%, and a low treatment mortality rate of 0–0.5% (**4-6**).
A number of factors, such as number and size of tumor nodules, increased levels of serum tumor markers, hepatitis C virus (HCV), HBV infections, diabetes mellitus and hyperglycemia,were reported to be related to HCC recurrence after RFA **(7,8).**

Despite the established role of alfa fetoprotein (AFP) in HCC diagnosis , it is of low significant value in prediction of HCC recurrence (**9,10**).

Aspartate aminotransferase(AST)-to-platelet ratio index (APRI) is a simple and feasible test validated in assessing the stage of fibrosis and in predicting prognosis for patients with chronic hepatitis (**11,12).**APRI shows reliable discriminative ability for predicting not only overall survival of HCC patients, but also tumor recurrence **(13).**APRI was also found to be a prognostic biomarker in small HCC patients after RFA therapy and surgical resection (**14,15)**.

Some studies demonstrated that background liver inflammation and fibrosis play important roles both in the process of hepatocarcinogenesis and in recurrence after resection surgery **(16,17)**. Moreover, there are increasing evidences that the presence of systemic inflammation correlates with poorer cancer-specific survival in certain cancers **(18-20).**Various markers of systemic inflammatory response, including cytokines, C-reactive protein (CRP), and absolute blood neutrophil or lymphocyte count as well as their ratio such as neutrophil-to-lymphocyte ratio (NLR) have been investigated for their prognostic roles in certain cancer populations (**21,22).**Patients with elevated NLR have a relative lymphocytopenia and neutrophilic leucocytosis which denote that the balance is tipped in favor of protumor inflammatory response and is associated with poor oncologic outcome **(23).**Significant elevation of NLR increases the risk of HCC recurrence and recipient death in patients undergoing transplantation for HCC (**24).**
Several studies indicate that serum AFP level, AST level, AST-to-alanine aminotransferase (ALT) ratio, APRI and NLR have been associated with HCC recurrence and poor survival **(11,12,25-27).**

We conducted this study to compare the value of NLR and APRI for prediction of post RFA recurrence of HCC.

Patients and Methods:-

This retrospective study had been carried out in Internal Medicine Department, Gastroenterology Unit, Faculty of Medicine, Zagazig University, from Aug. 2014 to Aug. 2016. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration and its later amendments.

Inclusion criteria : Patients with single focal lesion ≤5 cm or up to three lesions each ≤3 cm of HCC who received curative RFA.

Exclusion criteria included portal vein thrombosis, extra hepatic metastasis, class C liver cirrhosis (according to Child-Turcotte-Pugh score) **(28,29)**. Also, we excluded patients with hematological disorders, active infection, heart failure, renal impairment (serum creatinine > 1.5 mg/dl), pregnancy or history of drug abuse or ongoing chemotherapy intake and those who lost follow up.

Out of 50 HCC patients who underwent curative RFA, 42 patients who met our inclusion and exclusion criteria were selected and enrolled in the study. The studied 42 patients were divided into two groups; group I (recurrence group) including 22 patients with post-ablation recurrence of HCC, and group II (recurrence free group) including 20 patients without recurrence. Diagnosis of recurrence was made by radiologic evidence using triphasic CT (TCT).

All studied patients underwent baseline (one month after curative RFA) clinical examination, imaging studies including chest x ray, pelviabdominal ultrasonography and TCT, as well as laboratory investigations including complete blood count (CBC), liver function tests, kidney function tests, coagulation profile and serum AFP level, in addition to calculation of APRI and NLR. All participants were subjected to follow up reevaluation of AFP, APRI and NLR every 3 months for 2 years. And TCT every 6-12 months.

Statistical Analysis:-

The quantitative variables were expressed as means ± standard deviation (SD) and the categorical variables as count numbers and proportions. Statistical analysis was performed with SPSS package version 19 (SPSS Inc., Chicago, IL) using the suitable test e.g. ANOVA, qui square, Pearson's correlation and logistic regression analysis. The result was

considered significant if the $P \leq 0.05$. In order to test the predictive accuracy (sensitivity and specificity) of various markers in predicting tumor recurrence, we used receiver operating curve (ROC) statistics.

Results:-

Table (1) showed comparison between group I and group II regarding demographic, clinical and laboratory parameters. There were significant differences between the two groups regarding the investigated tumor markers; APRI, NLR and AFP. HCC recurrence showed a significant positive correlation with each of AST, APRI, NLR and AFP, and a significant negative correlation with platelets count (table 2).

Using logistic regression analysis model, high NLR was the independent risk factor (p= 0.002) for prediction of HCC recurrence(table 3). In order to test the predicting accuracy (sensitivity and specificity) of NLR in predicting tumor recurrence as compared to APRI and AFP, we used ROC curve statistics (table 4). NLR had the highest sensitivity and specificity (90.9 % and 85%) followed by AFP (86.4 % and 75%), and lastly by APRI (72.7% and 70%) (table 4, fig.1, fig. 2, fig. 3).

Table 1:- Demographic, clinical and laboratory parameters of all participants.

Parameters	**All patients** (n=42)	**Group I** (n=22)	**Group II** (n=20)	**P**
Age (mean±SD, years)	60.24 ± 10.30	58.14 ± 9.61	62.55 ± 10.78	NS
Male Gender(n,%)	26, 61.90	15, 68.20	11 ± 55.00	NS
Lesion(s) number (mean±SD)	1.29 ± 0.64	1.32 ± 0.72	1.25 ± 0.55	NS
Lesion(s) size (mean±SD, cm)	3.25 ± 1.19	3.38±1.19	3.12 ± 1.05	NS
Possible HCC etiology				
HCV infection (n, %)	30, 71.40	17, 77.30	13± 65.00	NS
HBV infection (n, %)	10, 23.80	5, 22.70	5 ± 25.00	NS
Non-viral (n, %)	4, 9.50	2, 9.10	2 ± 10.00	NS
Cirrhosis (n, %)	39, 92.90	20. 90.90	19 ± 95.00	NS
Child's Class				
A (n, %)	35, 83,30	19, 86.40	16 ± 80.00	NS
B (n, %)	7, 16.70	3, 13.40	4 ± 20.00	NS
Antiviral therapy (n, %)	15, 35.70	7, 31.80	8 ± 20.00	NS
AST(mean±SD, IU)	1.66 ± 0.72	1.86 ± 0.80	1.43 ± 0.56	NS
Platelet count (mean±SD, $x10^9$/L)	112.79 ± 64.59	95.27± 45.34	132.05±77.36	NS
APRI (mean±SD)	1.82 ± 0.98	2.12 ± 0.74	1.49 ± 1.12	0.036
NLR (mean±SD)	1.78 ± 0.97	2.37 ± 0.82	1.13 ± 0.67	<0.001
AFP (mean±SD, ng/ml)	3818 ± 6053	6107 ± 6655	1300 ± 4168	0.008

NS: non significant.

Table 2:- Correlation between different clinicopathologic parameters and tumor recurrence.

Parameter	**r**	**P**
Age	- 0.217	NS
Sex	0.136	NS
Lesion(s) number	0.054	NS
Lesion(s) size	0.118	NS
HCC etiology	- 0.031	NS
Cirrhosis	- 0.079	NS
Child's Class	- 0.085	NS
Antiviral therapy	- 0.085	NS
AST	0.299	0.027
Platelet count	- 0.288	0.032
APRI	0.325	0.018
NLR	0.648	<0.001
AFP	0.401	0.004

NS: non significant.

Table 3:- Independent risk factor(s) predicting tumor recurrence using logistic regression analysis.

Predicting factor	**P**	**95% Confidence Interval for B**	
		Lower bound	Upper bound
AST	NS	- 0.125	0.524
Platelet count	NS	- 0.007	0.002
APRI	NS	- 0.499	0.060
NLR	0.002	0.121	0.519
AFP	NS	0.000	0.000

NS: non significant.

Table 4:- Comparison between sensitivity and specificity of APRI, NLR and AFP in predicting tumor recurrence using ROC curve statistics

Predictor	**Cut-off value**	**Area under the curve (AUC)**	**95.0% Confidence Interval (CI)**		**P**	**Sensitivity**	**Specificity**
			Lower bound	Upper bound			
APRI	1.66	0.744	0.581	0.907	0.007	72.7 %	70.0 %
NLR	1.55	0.903	0.801	1.000	< 0.001	90.9 %	85.0 %
AFP (ng/ml)	210	0.864	0.745	0.982	< 0.001	86.4 %	75.0 %

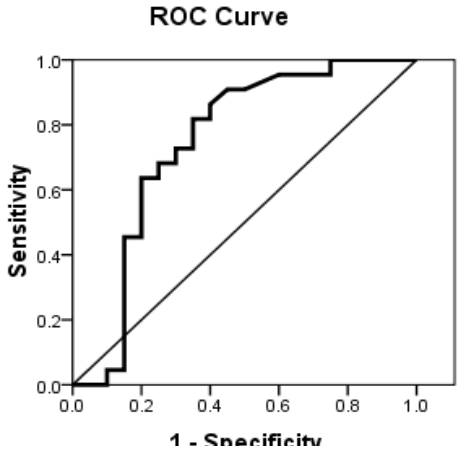

Figure 1:- ROC Curve for APRI sensitivity and specificity in predicting tumor recurrence

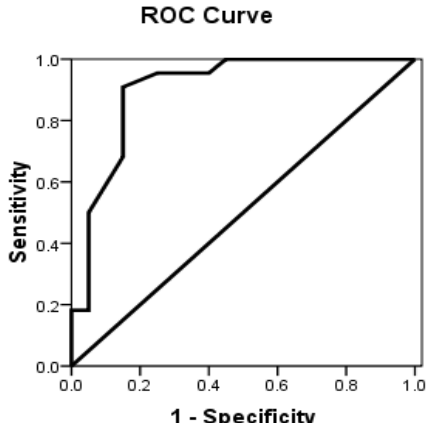

Figure 2:- ROC Curve for NLR sensitivity and specificity in predicting tumor recurrence

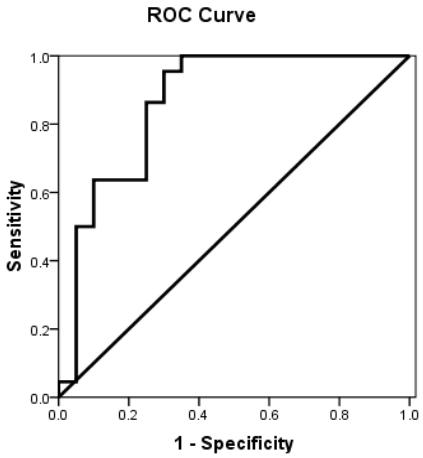

Figure 3:- ROC Curve for AFP sensitivity and specificity in predicting tumor recurrence

Discussion:-

The burden of HCC has been increasing in Egypt with a doubling in the incidence rate in the past 10 years **(30).**Several studies investigated predictors for prognosis and survival for patients of HCC after RFA but only few studies investigated the predictors of tumor recurrence after radiofrequency **(31,32).**

This study was conducted for evaluation of the postoperative NLR and APRI as predictors of post RFA recurrence of HCC. Both markers were compared together and to AFP. The mean values of the investigated markers (APRI, NLR and AFP) were significantly higher in the recurrence group than in the recurrence free group (2.12±0.74 versus 1.49±1.12,*P*=0.036; 2.37±0.82 versus1.13±0.67, *P*<0.001 and 6107±6655 versus1300±4168,*P*=0.008, respectively).

In the current study, five parameters (AST, PLT, APRI, NLR and AFP) showed significant correlation with HCC recurrence (*P* values were: 0.027,0.032, 0.018,<0.001 and 0.004, respectively).

In this study, APRI showed a significant positive correlation to HCC recurrence (r = 0.325, *P* = 0.018). Similarly, APRI was validated in several previous studies as a simple, noninvasive way to assess the degree of liver fibrosis in patients with chronic hepatitis B or C and also had a reliable discriminative ability for predicting overall survival and HCC recurrence **(14,33,34).**

In our study, NLR showed a highly significant positive correlation to HCC recurrence (r = 0.648, *P*< 0.001).By using logistic regression analysis model, the only independent risk factor for prediction of tumor recurrence among the above five parameters was NLR (*P*=0.002).

It is widely accepted that inflammatory process plays a significant role in several stages of tumor development and progression.The tumor increases the inflammatory process, which in turn predisposes to tumor progression, via inhibition of apoptosis and promotion of angiogenesis **(21,22)**.*Wu and colleagues* reported that hepatic inflammatory activity was associated with early HCC recurrence **(16).**

NLR, a biomarker of tumor inflammation and host immunity, was associated with increased mortality in cancer **(35).**In agreement with the results of our study *Chen et al.***(36) ,** *Dan et al.***(37)** and *Tajiriet al.***(38)** reported that high postoperative NLR is associated with high recurrence rate of HCC after RFA.

The association between the high level of NLR and the increased numbers of HCC recurrence in our study and in previous studies may be attributed to the fact that host's immune response to tumors depends on lymphocytes, whereas patients with a large NLR have relative lymphocytopenia, which results in the attenuation of lymphocyte-mediated antitumor immune responses in these patients **(36).** Another explanation is that the patients with a large NLR usually have an enhanced neutrophil response, which could promote the production of pro-angiogenic factors,

including vascular endothelial growth factor, interleukin-8, and matrix metalloproteinase. These pro-angiogenic factors may promote tumor growth and recurrence **(39).**

The comparison between sensitivity and specificity of APRI, NLR and AFP in predicting tumor recurrence, in our study, using ROC curve statistics revealed that NLR attained the highest level of sensitivity and specificity(90.9 % and 85%) with Cut-off value **(**1.55) compared to AFP (86.4 % and 75%) and APRI (72.7% and 70%).

In contrary to our results, in their study on 98 post RFA HCC patients**,** *Chung et al.***(40)** reported that APRI was significantly higher in the recurrence group than in the recurrence free group (2.3±1.8 vs. 1.3±1.4, *P*=0.018), while there was no significant difference between the two studied groups regarding NLR.The difference between our results and that of *Chung et al.* may be attributed to the different etiologic background of HCC as in our current study the main etiology of HCC was chronic HCV infection (77.3%) while in study of *Chung et al.*,the main etiology was chronic HBV infection (55.6%).

Conclusion:-

From the aforementioned findings, we can speculate that NLR is more valuable than APRI in predicting HCC recurrence after RFA .NLR is a promising surrogate marker in predicting post RFA HCC recurrence .Further studies are needed to validate the clinical relevance of NLR in follow up of HCC patients.

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