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Association of Ki-67 Expression and the Aggressiveness of Hepatocellular Carcinoma

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Abstract

Background: Ki-67 is a nuclear proliferative marker. It is therefore widely used as a cell proliferation marker to grade tumors.

Aim of Study: The aim of the current study was to assess the possible association between Ki-67 and the aggressiveness of hepatocellular carcinoma.

Material and Methods: This study was conducted at Pathology Department in National Liver Institute, Menoufia University. A total of 114 cases were included. TMA was performed for tumor blocks and stained with antibody against Ki-67.

Results: The percentage of Ki-67 expression ranged between 1 and 95% with a mean ± SD of 56.72±40.53 and a median of 80. As regard Ki-67 expression, large tumor size group were significantly associated with increased expression of Ki-67 (p=0.049). On the other hand, older age group (>60 years) and large tumor size group (>5cm) were significantly associated with increased percentage of Ki-67 expression (p=0.035 and 0.015) respectively.

Conclusion: Ki-67 expression is associated with aggressive hepatocellular carcinoma, so it could change the type of therapy for these tumors.

Key Words: *Ki-67 – Hepatocellular carcinoma – Aggressiveness – TMA – Expression.*

Introduction

HEPATOCELLULAR Carcinoma (HCC) is the sixth most common malignancy and is the leading cause of mortality in patients with cirrhosis **[1,2]**. An estimated half million new cases are diagnosed each year world-wide with disease burden highest in developing countries (85% of all cases) **[3,4]**.

The average age of diagnosis is 65 years with a shift in the last decade toward diagnosis at an earlier age **[1,4]**. This trend is especially seen in developing countries and has implications for treatment **[1,4]**.

Chronic HBV and HCV infections are the major risk factors for the development of HCC through a multistep pathway that involves viral and non-viral dependent pathophysiological steps **[5]**. Inflammation, necrosis, fibrosis, and ongoing regeneration characterize the cirrhotic liver and contribute to HCC development especially in patients with Hepatitis C Virus (HCV) **[6]**.

Ki-67 is a nuclear DNA-binding protein with two human isoforms that have predicted molecular weights of 320kDa and 359kDa **[7,8]**. It is a cell proliferation antigen that is constitutively expressed in cycling mammalian cells **[9]**. A detailed cell cycle analysis showed that the Ki-67 antigen is expressed in cells at G1, S and G2-M phases but not in G0 phase of the cell cycle **[10]**.

The dynamic localization of Ki-67 has led to suggestions that it could coordinate nucleolar disassembly and reassembly at either side of mitosis **[11]**. Indeed, Ki-67 is required to localize nucleolar granular components to mitotic chromosomes, so it may play a role in nucleolar segregation between daughter cells **[12]**.

Studies showed that the proliferative activity of a wide variety of tumors may be of prognostic value with respect to survival of the patient. Current methods of assessing the proliferation and growth of tumors including immunohistochemical staining of Ki-67 **[13]**.

Immunostaining of Ki-67 is a quick, simple and sensitive technique for the estimation of proliferative activity of tumors and it serves as one of the major factors related to tumor proliferation

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that can be assessed with Immunohistochemistry (IHC) [14].

Material and Methods

This retrospective study was carried out on 114 liver biopsies obtained from patients who underwent partial or total hepatectomy for HCC.

Paraffin embedded blocks of those specimens were retrieved from the Archive of Pathology Department, National Liver Institute, Menoufia University, in the period between 2010 and 2017.

Clinical data were retrieved from medical files preserved at the Archive of Surgery Department and Oncology Unit, National Liver Institute, Menoufia University.

All patients included in the study were completely evaluated by clinical, laboratory and radiological data collected from patients' medical records:

Clinical data included patient age and gender.

Laboratory investigations included virology state and alpha fetoprotein level.

Radiological data included number, size (in greatest dimension) and site of focal lesions.

Hi stop athological evaluation included histopathological type, tumor grade, degree of differentiation, adjacent liver and pathologic stage (According to AJCC staging system, 7th edition).

Tissue microarray construction (TMA):

Hematoxylin and Eosin (H & E) stained slides were used to identify viable and representative areas of each sample that is circled with a pilot pen.

Tissue cores with a diameter of 1.5 micron from predefined regions of each specimen in the donor paraffin block were punched manually using a tissue array needle set we utilized the TMA needles with a simple handheld holder with a great success without the need to use the expensive tissue arrayer instrument [15], and arrayed in triplicate on a recipient paraffin block, into a ready-made hole, guided by a defined x-y position. A control normal tissue is placed in a strategic regions throughout the blocks or asymmetrically at one end of the block.

Tissue Microarray (TMA) construction map is created, indicating the position and origin of each core in the tissue microarray. The map is then used to set up the actual construction of the array. The TMA is divided into different rows designated by capital letters. These quadrants are further separated in a checkerboard order by letters and numbers [16].

Immunohistochemical staining:

About 4 micron thick sections of these tissue array blocks were cut and mounted on positive charged slides and used for immunohistochemical staining by Ki-67 which was a concentrated rabbit monoclonal antibody (Mab-Mib-1-YLEM, Dako Cytomation, Glostrup, Denmark). The primary antibody was added at a 1:50 dilution. The detection Kit was Invitrogen (Cell marque, USA). In this system, two reagents were utilized; the biotinlated secondary anti-immunoglobulin which is a purified goat polyvalent anti-mouse IgG capable of binding to the primary antibody and the streptvidin-biotin enzyme complex.

Positive controls for the reaction were performed with specific paraffin embedded sections of lymph node and negative controls were made by substituting the primary antibody with non-immune serum.

Finally, the reaction can be visualized by appropriate substrate/chromogen (Diaminobenzidine, DAB) reagent.

Interpretation of Ki-67:

It was evaluated as regard positivity of expression and percentage of expression. The immunoreactivity for Ki-67 was seen as nuclear staining of malignant hepatocytes, where non-tumor liver tissue showed negativity. The assessment of ki-67 was based on nuclear staining pattern. At least 10 fields in each tumor section were evaluated at medium power (200X) to determine the proportion of tumor cells of the entire fields of the sections. The positivity of each staining was also described by means of a Positivity Index (PI), which indicates the percentage of positive cells among 1000 arbitrarily selected tumor cells in a given tissue section. Percentage of positivity was expressed as range, mean and median.

Statistical analysis:

The data were collected, tabulated and statistically analyzed using the statistical package for the social science program for windows (Version 22; SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (X ± SD) and analyzed by applying Mann-Whitney test (U) for comparison between two groups not normally distributed. Qualitative data were expressed as number and percentage (no & %) and

analyzed by applying chi-square test (χ^2) and 2 X 2 table, if one cell has expected number less than 5 fisher's exact test was applied.

Results

The main clinicopathological characteristics of the patients are shown in (Table 1).

Table (1): Distribution of the studied cases according to clinicopathological parameters. (n=114).

Variables	No.	%
Gender:		
Male	94	82.5
Female	20	17.5
Age (years):		
≤60	86	75.4
>60	28	24.6
Range	35.0-75.0	
Mean ± SD	56.25±7.36	
Median	57.0	
HBV (+ve)	3	2.6
HCV (+ve)	99	86.8
Virology (+ve)	102	89.5
AFP (ng/ml):		
<400	76	66.7
≥400	18	15.8
Censor	20	17.5
Range	1.0-14500.0	
Mean ± SD.	683.97±2278.24	
Median	31.5	
Number of focal lesions:		
Single	83	72.8
Multiple	31	27.2
Size (cm):		
≤5	80	70.2
>5	34	29.8
Range	1.0-17.0	
Mean ± SD	5.14±3.10	
Median	4.0	
Stage (AJCC):		
T1	45	39.5
T2	58	50.9
T3	11	9.6
Type:		
Classic	105	92.1
Clear cell	9	7.9
Grade:		
Low grade	78	68.4
High grade	36	31.6
Differentiation:		
Well differentiated	3	2.6
Moderately differentiated	106	93.0
Poorly differentiated	5	4.4
Adjacent liver:		
Non cirrhotic	21	18.4
Cirrhotic	93	81.6

AFP : Alpha Fetoprotein.
No : Number.
SD : Standard Deviation.

Immunohistochemical results of Ki-67 in studied cases (Table 2):

Ki-67 immune positive cells were identified by brownish nuclear staining of malignant cells in comparison to negative staining of adjacent non-tumorous tissue Figs. (1,2).

Table (2): Immunohistochemical results of Ki-67 in studied cases (n=114).

Ki-67	No.	%
Expression:		
Negative	23	20.2
Positive	91	79.8
Percentage (%):		
Range	1.0-95.0	
Mean ± SD	42.06±31.35	
Median	40.0	

No: Number.
SD: Standard Deviation.

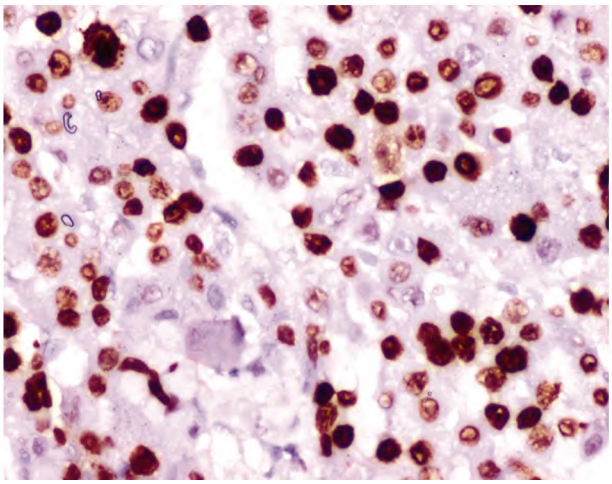

Fig. (1): A case of hepatocellular carcinoma showing positive nuclear Ki-67 expression (IHC X400).

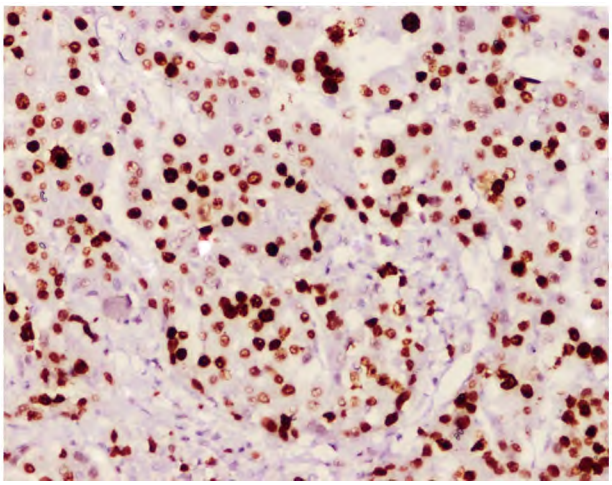

Fig. (2): A case of hepatocellular carcinoma showing high nuclear Ki-67 expression (IHC X200).

Table (3): Association between Ki-67 (expression) and clinicopathological parameters in total sample (n=114).

Variables	Ki-67 (expression) Negative (n=23)		Positive (n=91)		Test of sig.	*p*-value
	No.	%	No.	%		
Gender:						
Male	18	19.1	76	80.9	χ^2=	FE$_p$=
Female	5	25.0	15	75.0	0.351	0.548
Age (years):						
≤60	19	22.1	67	77.9	χ^2=	0.371
>60	4	14.3	24	85.7	0.799	
Range	35.0-64.0		36.0-75.0		*t*=	0.859
Mean ± SD	56.0±6.42		56.31±7.62		0.178	
Median	57.0		57.0			
HBV:						
Negative	23	20.7	88	79.3	χ^2=	FE$_p$=
Positive	0	0.0	3	100.0	0.799	1.000
HCV:						
Negative	1	6.7	14	93.3	χ^2=	FE$_p$=
Positive	22	22.2	77	77.8	1.957	0.298
Virology:						
Negative	1	8.3	11	91.7	χ^2=	FE$_p$=
Positive	22	21.6	80	78.4	1.168	0.454
AFP (ng/ml):						
<400	17	22.4	59	77.6	χ^2=	MC$_p$=
≥400	5	27.8	13	72.2	3.917	0.128
Censor	1	5.0	19	95.0		
Range	1.20-4000.0		1.0-14500.0		U=	0.869
Mean ± SD	317.46±847.30		795.96±2555.77		773.50	
Median	37.5		27.0			
Number:						
Single	17	20.5	66	79.5	χ^2=	0.894
Multiple	6	19.4	25	80.6	0.018	
Size (cm):						
≤5	20	25.0	60	75.0	χ^2=	0.049*
>5	3	8.8	31	91.2	3.877*	
Range	1.0-14.0		1.0-17.0		U=	0.106
Mean ± SD	4.26±2.58		5.36±3.19		820.50	
Median	4.0		4.0			
Stage (AJCC):						
T1	12	26.7	33	73.3	χ^2=	0.312
T2	10	17.2	48	82.8	2.327	
T3	1	9.1	10	90.9		
Type:						
Classic	20	19.0	85	81.0	χ^2=	FE$_p$=
Clear cell	3	33.3	6	66.7	1.050	0.383
Grade:						
Low grade	16	20.5	62	79.5	χ^2=	0.895
High grade	7	19.4	29	80.6	0.017	
Differentiation:						
Well	1	33.3	2	66.7	χ^2=	MC$_p$=
Moderate	21	19.8	85	80.2	0.955	0.784
Poor	1	20.0	4	80.0		
Adjacent liver:						
Non cirrhotic	2	9.5	19	90.5	χ^2=	FE$_p$=
Cirrhotic	21	22.6	72	77.4	1.813	0.237

χ^2 : Chi square test. FE : Fisher Exact. MC : Monte Carlo. U : Mann Whitney test. *t* : Student *t*-test.
No : Number. SD : Standard Deviation. * : Statistically significant. AFP : Alpha Fetoprotein.

Table (4): Association between Ki-67 percentage of expression and clinicopathological parameters in total sample (n=114).

Clinicopathological parameters	No	Ki-67 (percentage %) Range	Mean ± SD	Median	Test of sig.	*p*-value
Age (years):						
•≤60	86	2.0-95.0	38.31±30.12	40.0	U=	0.035*
• >60	28	1.0-95.0	53.57±32.79	50.0	885.50	
Gender:						
•Male	94	2.0-95.0	42.70±31.51	40.0	U=	0.648
• Female	20	1.0-90.0	39.05±31.20	45.0	879.0	
HBV:						
• Negative	111	1.0-95.0	42.16±31.65	40.0	U=	0.979
• Positive	3	20.0-60.0	38.33±20.21	35.0	165.0	
HCV:						
• Negative	15	2.0-90.0	42.80±25.04	50.0	U=	0.721
• Positive	99	1.0-95.0	41.95±32.31	40.0	700.0	
Virology:						
• Negative	12	2.0-90.0	43.92±26.77	50.0	U=	0.684
• Positive	102	1.0-95.0	41.84±31.95	40.0	568.0	
AFP (ng/ml):						
• <400	76	1.0-95.0	44.32±32.74	50.0	K=	0.442
•≥400	18	2.0-95.0	33.06±31.26	20.0	1.633	
• Censor	20	2.0-90.0	41.60±25.33	42.50		
Number:						
• Single	83	1.0-95.0	39.88±31.44	40.0	U=	0.292
• Multiple	31	2.0-95.0	47.90±30.86	50.0	1121.5	
Size (cm):						
•≤5	80	1.0-95.0	37.10±29.82	40.0	U=	0.015*
• >5	34	2.0-95.0	53.74±32.19	50.0	968.50	
Stage (AJCC):						
• T1	45	1.0-95.0	33.26±26.83	25.0	K=	0.054
• T2	58	2.0-95.0	46.56±33.72	47.0	5.767	
• T3	11	2.0-95.0	54.27±28.68	50.0		
Type:						
• Classic	105	1.0-95.0	43.34±31.46	50.0	U=	0.093
• Clear cell	9	2.0-80.0	27.11±27.25	20.0	313.0	
Grade:						
• Low grade	78	1.0-95.0	43.51±29.94	50.0	U=	0.488
• High grade	36	2.0-95.0	38.92±34.44	20.0	1290.5	
Differentiation:						
• Well differentiated	3	5.0-60.0	38.33±29.29	50.0	K= 0.162	0.922
• Moderately differentiated	106	1.0-95.0	42.0±31.24	40.0		
• Poorly differentiated	5	8.0-95.0	45.60±40.97	20.0		
Adjacent liver:						
• Non-cirrhotic	21	2.0-95.0	47.33±30.70	5.0	U=	0.342
• Cirrhotic	93	1.0-95.0	40.87±31.53	40.0	847.0	

K : K for Kruskal Wallis test. U : Mann Whitney test. SD : Standard Deviation. * : Statistically significant. AFP : Alpha Fetoprotein. No : Number.
#: Excluded from the association due to small number of case (n=1).

Ki-67 was expressed in 91 cases of the studied group with a percentage of 79.8%.

The percentage of Ki-67 expression ranged between 1 and 95 with a mean ± SD of 56.72±40.53 and a median of 80.

Association between Ki-67 expression and different clinicopathological parameters (Table 3). There was statistically significant association between large tumor size (>5cm) and positive Ki-67 expression (p-value=0.049). Also, there was statistically significant association between high percentage of expression and old age group (>60 years) (p-value=0.035) and advanced tumor stage (T3) (p-value=0.054).

Correlation between Ki-67 percentage of expression and different clinicopathological parameters (Tables 4,5):

There was direct correlation between Ki-67 percentage of expression and both age and size of the tumor (p-value=0.035 and 0.021) respectively.

Table (5): Correlation between Ki-67 percentage of expression and different clinicopathological parameters in total sample (n=114).

Clinicopathological parameters	Ki-67 (percentage %)	
	r_s	p-value
Age (years)	0.198	0.035*
AFP	–0.118	0.257
Size (cm)	0.217	0.021*

r_s : Spearman coefficient. AFP : Alpha Fetoprotein.
* : Statistically significant.

Discussion

Hepatocellular Carcinoma (HCC) is the sixth most common malignancy and is the leading cause of mortality in patients with cirrhosis **[1,2]**. Ki-67 is a direct substrate of the cyclin-dependent kinase CDK1 and is hyperphosphorylated in mitosis **[7,8]**. Studies showed that the proliferative activity of a wide variety of tumors may be of prognostic value with respect to survival of the patient. Current methods to assess the proliferation and growth of tumors includes immunohistochemical staining of Ki-67 **[9]**.

In hepatocellular carcinoma, Ki-67 has been used as a useful proliferative marker in several studies **[17]**.

Besides, there have been already studies demonstrating that Ki-67 was strongly associated with the aggressiveness of tumor, including prostatic cancer **[13]**. In addition, several meta-analyses concluded that high Ki-67 could predict poor prognosis in patients with cervical cancer, gliomas, lymphoma, breast cancer, and lung cancer **[13,18-22]**. It was reported that Ki-67 could be an independent marker for worse prognosis in patients with liver cancer, those results were contradictory **[13,23-27]**.

In the present study, the expressions of the proliferative marker Ki-67 114 cases. Ki-67 was expressed in 91 cases 0f the studied group with a percentage of 79.8%.

The percentage of Ki-67 expression ranged between 1 and 95% with a mean ± SD of 56.72± 40.53 and a median of 80. Ki-67 was highly expressed and significantly related to large tumor size, older age and advanced tumor stage.

The present study matched with a meta-analysis provided evidence that high Ki-67 was closely associated with large tumor size **[7]**. However, this meta-analysis showed close association between Ki-67 and histological grade, number of tumor nodes, the status of metastasis, cirrhosis and vein invasion in HCC patients in contrast to the results in the present study **[7]**.

Other studies showed that the expression of Ki-67 has been found to correlate with the histological stages of hepatocellular carcinoma in agreement to the present study **[13,18,20]** and tumor progression **[13,22]**.

Mohamed et al., and others **[5,28,29]** found that the expressions of the proliferative marker Ki-67 was highly expressed and significantly related to the tumor grade, portal invasion and intra-hepatic metastasis. None of these results matched with our study. This discrepancy in results could be due to the difference in the sensitivity of the monoclonal antibodies used.

Ng et al., **[22]** in their study found strong association between Ki-67 expression and tumor cellular differentiation. We failed to find a significant correlation between Ki-67 expression and other pathologic features, such as tumor invasiveness in terms of venous permeation and direct liver invasion. These results were comparable to Ng et al., results **[22]**. In contrast, tumor size in their study **[22]** had no correlation to Ki-67 expression.

Conclusion:

Ki-67 expression is associated with aggressiveness of HCC as it I associated with poor prognostic parameters such as older age, larger tumor size and higher tumor stage (T3).

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الإرتباط بين التعبير عن كاى ٦٧ وعدوانية سرطان الخلايا الكبدية

الخلفية: كاى ٦٧ هو دليل تكاثر نووى ولذلك يستخدم على نطاق واسع كدليل تكاثر خلوى لتحديد درجة الأورام.

الهدف من الدراسة: هو تقييم الإرتباط المحتمل ما بين كاى ٦٧ وعدوانية سرطان الخلايا الكبدية.

الأدوات وطرق الفحص: أجريت هذه الدراسة بقسم علم الأمراض بمعهد الكبد القومى، جامعة المنوفية على مجمل ١١٤ حالة. تم عمل تقنية التقطيع النسيجى المصفوف الصغير على بلوكات الورم وتم إستخدام الصبغات المناعية وصباغة الأنسجة بمضاد كاى ٦٧.

النتائج: نسبة التعبير عن كاى ٦٧ تتراوح ما بين ١ إلى ٩٥٪ ومتوسط ٨٠ إرتبطت الأورام ذات الحجم الكبير بزيادة التعبير عن كاى ٦٧ وكذلك إرتبطت نسبة التعبير المئوية عن كاى ٦٧ بالورم نو الحجم الأكبر والمرضى ذوى الأعمار الأطول.

الخلاصة: التعبير عن كاى ٦٧ يرتبط بعدوانية سرطان الخلايا الكبدية ومن ثم يمكن تغيير نوعية العلاج لهذه الأورام.