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Running Title: An Early Predictor of Liver Cancer

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The Value of King's Score as a Predictor of Risk of Hepatocellular Carcinoma among Egyptian Patients with Hepatitis C Virus-Related Cirrhosis

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Abstract

Background: Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the second leading cause of cancer-related deaths worldwide. Egypt is one of the African countries with a high incidence of HCC. The process of carcinogenesis in the liver, particularly in post-hepatitic necrosis, is related to the severity of liver damage and fibrosis. The present study aimed to investigate the utility of King's score to identify patients at higher risk of developing HCC among patients with hepatitis C virus-related cirrhosis.
Method: 58 patients were included in this retrospective case-control study. They were divided into two groups; group I included 29 patients diagnosed with HCC and group II comprised 29 patients without HCC. King's score was calculated for all the patients based on their pararmeters at the time of diagnosis and their records of one year prior to the diagnosis.
Results: King's score was significantly higher in group I, not only at the time of diagnosis (95.4±45.2 vs 24.23±7.4 P<0.001), but also when calculated from the patients' records a year before the diagnosis (70.4±41.8 vs 17.46±8.2 P<0.001).
Conclusion: King's score can diagnose higher risk of developing HCC up to one year before the appearance of focal lesion.

Keywords: Liver neoplasms, Carcinoma, Hepatocellular, Retrospective study, Case-control study, Carcinogensis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the second leading cause of cancer-related deaths worldwide. Egypt is known to be one of the African countries with a high incidence of HCC.[1] The prevalence of hepatocellular carcinoma worldwide is as high as that of chronic viral hepatitis.[2] According to the guidelines of several professional societies, patients with cirrhosis should be screened with alpha-fetoprotein testing and abdominal ultrasound every six months.[3]
King's score was initially introduced by Cross et al.[4] in King's college, after which it was named. It is calculated through a formula that involves age of the patient, AST level, INR, and platelet count. It is similar to APRI score with addition of age and INR. It was introduced and validated

as a non-invasive predictive test of liver fibrosis and cirrhosis.[4] The score was later used to predict the recurrence of HCC after resection and to predict the outcomes of intervention.[5]

The current study was conducted to determine the ability of the King's score to identify patients at higher risk of HCC among Egyptian patients with hepatitis C virus (HCV)-related cirrhosis.

Patients and Methods

The present study was a retrospective cohort study conducted in Tropical Medicine Department between May 2015 and May 2017. This study included 58 patients with HCV-related cirrhosis diagnosed with a combination of clinical, radiological, and laboratory evidence. They were divided into two groups according to the presence of HCC diagnosed with ultrasound and confirmed with alpha fetoprotein and triphasic CT. The two groups comprised group I (patient group), including 29 patients with HCV-related cirrhosis recently diagnosed with HCC and group II (control group), including 29 patients with HCV-related cirrhosis without HCC. The study was reviewed and approved by IRB of the Faculty of Medicine, Zagazig University.

The exclusion criteria were as follows: patients<18 years, those who did not give informed consent to participate in the study, those with incomplete past laboratory data, any causes of cirrhosis other than HCV, coexistent hematologic disease, previous treatment for HCC, hepatic tumors other than HCC, and extrahepatic spread.

The patients were subjected to the following at the time of diagnosis; complete history taking, thorough clinical examination, routine laboratory investigations, including complete blood count and liver, and kidney function tests, coagulation profile, alpha fetoprotein, and viral markers.

The participants were also subjected to radiological evaluation via pelvi-abdominal ultrasound to confirm the diagnosis of cirrhosis and detect focal lesions and triphasic CT to confirm diagnosis of HCC. The state of liver decompensation was assessed utilizing Child-Pugh score.[6] HCC was staged according to the BCLC staging and the subjects were assigned to a suitable management protocol accordingly.[7]

Medical records of the patients were collected from the patients' database of Tropical Medicine Department. Their records were evaluated at two stages: at the time of diagnosis and one year prior to diagnosis. The King's score was calculated in these two stages according to the following formula: age (years) x AST (IU/l) x INR / platelets (10^9/l) [5]

Statistical method

The data were analyzed using SPSS epi info version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous Quantitative variables were expressed as the mean ± SD and categorical qualitative variables were expressed as number and percentage. Numerical data were checked for normal distribution using Shapiro Walk test. Simple t-test was employed to compare the two groups concerning the normally of data distribution while Mann-Whitney U test was utilized for non-normally distributed data. The categorical data were compared with Chi-square test or Fisher's exact test when appropriate. The clinical performance of king's score was tested via receiver operator characteristic (ROC) curve.

Results

Table 1 represents the demographic, clinical, and sonographic data of both groups at time of diagnosis. It shows that there were no significant differences between the studied groups in any of the demographic or clinical data, except for the frequency of encephalopathy. Hepatic encephalopathy was more frequent in group I at the time of diagnosis (72.4% vs 37.9% *P*=0.008*)*. Table 1 also shows that there were no significant differences between the studied groups concerning

liver, spleen sizes or portal vein diameter, ascites or Child score.

Table 2 depicts the radiological criteria of hepatocellular carcinoma found in group I. Based on this table, the majority of the patients (75.9%) had a single lesion at the time of diagnosis. It also shows that the majority of them had tumors exceeding 3 cm in size (89.6%). The right lobe was the most common site for focal lesions and in a minority of the patients, masses were observed in both lobes. Table 2 also indicates that the majority of the patients (55.1%) were in stage B (intermediate stage) at the time of diagnosis. They were assigned for TACE and RFA according to the recommendations of BCLC.

Table 3 summarizes the laboratory investigations of both groups at the time of diagnosis. As could be seen, group I had significantly lower albumin level and platelet count compared to group II (2.79 ± 0.33 vs 3.05±0.5 P=0.003 and 128.65 ± 32.34 vs 179.55 ± 52.27 P=0.04). Table 3 also shows that group I had significantly higher INR and AST level (1.90 ± 0.44 vs 1.10 ± 0.15 P<0.001and 115.58 ± 36.83 vs 67.54 ± 8.31 P<0.001). Alpha fetoprotein was also significantly higher in group I (374.16 ± 282.77 vs 26.30 ± 11.22 P<0.001).

Table 4 represents a summary of the laboratory parameters of the patients dating 1 year before the diagnosis. It shows that the parameters that showed significant differences between the studied groups included platelet count, AST, and INR. AST and INR were significantly higher in group I (102.06 ± 25.38 IU and 1.70 ± 0.48 vs 65.93 ± 8.31 IU and 0.87 ± 0.14 in succession P<0.001). The platelet count was significantly lower in group I (158.65 ± 32.34 vs 189.55 ±60.27 x103 cells/µL P=0.045).

King's score

The comparison of King's score between the studied groups showed that King's score was significantly higher in group I, not only at the time of diagnosis (95.4±45.2 vs 24.23±7.4 P<0.001 table 2), but also in the values calculated from the patients' records one year before diagnosis (70.4±41.8 vs 17.46± 7.8 P<0.001 Table 4).

Figure 1 demonstrates that King's score rose significantly with time in group I from 70.4±41.8, one year before diagnosis to 95.4±45.2 year IU/10^9 plt, at the time of diagnosis (P<0.001). The comparison of King's score in group II showed that it also rose significantly from 17.46±7.8 one year before the study to 24.23 ±7.4 year.IU/10^9plt at time of the study (P=0.0013).

Blotting ROC curve for King's score values shows that it could be a diagnostic marker for HCC. At a cut off value of 37.3 year.IU/10^9plt, it could diagnose HCC with a sensitivity of 82.8% and specificity of 100% (AUC=0.95 P<0.001) (Table 5).

The King's score can identify the patients at higher risk of developing HCC one year before diagnosis with a specificity of 24% and sensitivity of 96.6% at a cut off value of 32.2 year.IU/109plt (AUC=0.521 P=0.785)(Table 5).

Discussion

The data collected from this study suggested that King's score is not only useful as a marker for diagnosis of hepatocellular carcinoma, but also a sensitive marker for early prediction of higher risk of hepatic carcinogenesis even one year before the appearance of the suspicious focal lesions in the liver. This study also found that AST, as a marker of the necro-inflammatory changes in the liver, in patients with chronic HCV infection could be a sensitive marker for carcinogensis. Platelet count was also found to be associated with the deterioration of liver functions and to hepatocellular carcinoma. The ongoing process of inflammation and necrosis, which takes place in the liver as a result of chronic hepatitis C virus infection, is the main risk factor of carcinogenesis in the liver. This justifies the relation between liver cancer and necroinflammatory markers.

Hepatocellular carcinoma is the most serious sequel of liver cirrhosis. The follow-up of cirrhotic patients is meant to

early detect small focal lesions and manage them while it is still possible. The cirrhotic patients should perform ultrasound examination and alpha fetoprotein measurement biannually to screen hepatocellular carcinoma. To date, several studies have questioned the cost effectiveness of this expensive screening tests and claimed that stratification of the risk could help decrease the costs and save the test to the high risk patients.[8] There is a need for a simple cost effective test to identify the patients with a higher risk of HCC to assign those patients at higher risk to a tighter follow-up schedule that includes more frequent sonographic evaluation for early detection of small lesions while they are still curable.

The inflammatory and platelet-based markers were not only proved to be valid for diagnosis of cirrhosis in chronic viral hepatitis, but also to be good markers for prediction of early and late recurrence of hepatocellular carcinoma following resection.[9]

In our study, we tried to investigate the value of King's score not only as a diagnostic marker of HCC, but also as an early predictor of the high risk of HCC one year before the appearance of focal lesions. We used a retrospective design, including two groups of patients; group I consisted of patients recently diagnosed with HCC and group II comprised cirrhotic patients without HCC. The two groups had no significant differences concerning any of the demographic, clinical, and sonographic data.

For note, a large percentage of patients were at stage B of the disease, which is considered as the intermediate stage once the resection of the tumor is no longer an option. This indicates the importance of frequent follow-up in patients with chronic HCV to help discovering hepatocellular carcinoma at an earlier stage of the disease, which opens a way for further curative treatment options.

Among all the laboratory data recorded for the two groups of the patients one year before diagnosis platelet count, AST and INR were significantly different between the two groups at the time of diagnosis and one year prior to diagnosis. Group I always had lower platelet count, higher AST, and INR than group II. This agrees with Pang et al,[5,10] stating that thrombocytopenia could predict the recurrence of HCC after resection. Another study by Pang et al.[5] also confirmed that platelet count can be a cheap predictor of survival among patients with HCC; however, the study could not provide a cut off value. This finding also agrees with the study by Liu et al.[9] who found that the pro-inflammatory markers, like AST, can predict early and late recurrence of HCC after resection.[9]

These three parameters along with the patient's age formulate the King's score. In our study, King's score was significantly higher in group I than that in group II throughout the period of the follow-up from one year before to the time of diagnosis. This agrees with Mobarak et al. [11] who suggested that King's score had a fair predictive value to the development of HCC.[11]

Studying the clinical performance of King's score as a predictor of HCC revealed that at a cut off value of 32.22, King's score can predict the risk of HCC appearance within one year with a sensitivity of 96% and specificity of 24%. After the appearance of HCC, King's score could work as a diagnostic marker with a cut off value of 37 and it can diagnose HCC with a sensitivity 82.2% and specificity of 100%. This clinical performance, as a diagnostic marker, approaches that recorded for AFP.

This study included a small number of patients with just one cause of liver cirrhosis, which is HCV; this may have affected the results. Further wider scale studies that include a larger sample size with different causes of liver cirrhosis could yield more trusted results. The retrospective design was also used to avoid very long periods of follow-up that may

lead to loss of patients; however, a prospective cohort design will be more accurate and will lead to further reliable results.

Based on this study, the calculation of King's score is recommended for all patients with chronic HCV infection, specifically those with evidence of liver cirrhosis. This will help the health care providers find the patients at higher risk of hepatocellular carcinogenesis and hence, assign them to a more frequent schedule of follow-up with ultrasonographic examination and alpha fetoprotein level measurement for early detection of small tumors.

King's score is recommended to be routinely calculated for all patients with HCV-related cirrhosis. Patients with King's score exceeding 32 should be assigned for a more frequent follow-up schedule for early detection of focal lesion. We could recommend further studies on the use of King's score to predict high risk for hepatic carcinogenesis over larger number of patients with prospective design over longer periods of follow-up. We also suggest further research on the ability of King's score to predict the appearance of HCC in HCV patients following antiviral treatment.

Conclusion

King's score can identify patients at higher risk of HCC among Egyptian patients with HCV-related cirrhosis in a period up to one year before the appearance of focal lesion. It can also act as a diagnostic marker of HCC with clinical performance, which is comparable to that of AFP.

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Conflict of Interest

None declared.

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Table 1. Comparison between the studied groups concerning the demographic, clinical, and sonographic data at the time of diagnosis

Demographic data		Group (I) (N=29)		Group (II) (N=29)		X^2	*P*-value (Sig.)
		No.	%	No.	%		
Gender	Male	24	82.8	19	65.5	2.248	0.13(NS)
	Female	5	17.2	10	34.5		
Age (years)	Mean ± SD	56.86 ± 5.73		58.55 ± 6.74		T=1.028	0.3(NS)
Jaundice		21	72.4	17	58.6	1.2	0.26(NS)
History of hematemesis/ melena		15	51.7	15	51.7	0.00	1(NS)
Encephalopathy		21	72.4	11	37.9	6.9	0.008(S)
Lowe limb edema		15	51.7	13	44.8	0.2	0.5(NS)
Ascites	No	15	51.7	15	51	3.7	0.2(NS)
	Mild	4	17.2	9	31		
	Moderate	7	24	3	10		
	Tense	3	6.8	2	6		
Child's score	A	15	51.7	14	48.3	2.9	0.2(NS)
	B	7	24.1	12	41.4		
	C	7	24.1	3	10.3		
Liver size	Normal	2	6.9	2	6.9	0.7	0.6(NS)
	Shrunken	20	68.9	17	58.6		
	Enlarged	7	24.1	10	34.4		
Spleen	Normal	0	0	1	0.6	fisher	1(NS)
	Enlarged	29	100	28	99.4		
Portal vein	<16 cm	22	75.9	16	55.1	2.7	0.09(NS)
	16 cm +	7	24.1	13	44.8		

Table 2. Radiological criteria and staging of HCC in group I at the time of diagnosis

	N=29 N (%)
Number of focal lesions	
Single lesion	22(75.9%)
<3 lesions	5(17.2%)
>3 lesions	2(6.9%)
Size of largest focal lesion	
<3cm	3(10.3%)
<5cm	13(44.8%)
>5cm	13(44.8%)
Site of focal lesion	
Left lobe	3(10.3%)
Right lobe	20(68.9%)
Both	6 (20.7%)
Tumor staging according to BCLC	
Stage 0	1
Stage A (early)	3(10.3%)
Stage B (intermediate)	16(55.1%)
Stage C (advanced)	2(6.9%)
Stage D (end stage)	5(17.2%)

Table 3. Comparison between the studied groups concerning the laboratory data at the time of diagnosis

Laboratory findings	Group I (N=29)	Group II (N=29)	T Test and MW test	p-value (Sig.)
WBC ($x10^3/\mu L$)	4.81 ± 0.68	4.65 ± 0.36	T=1.6	0.11(NS)
Hemoglobin (g/dl)	10.26 ± 0.92	10.61 ± 0.61	T=1.7	0.09(NS)
Plt ($x10^3/\mu L$)	128.65 ± 32.34	179.55 ± 52.27	Z=2	0.04(S)
Albumin (g/dl)	2.79 ± 0.33	3.05 ± 0.53	T=3	0.003(S)
Bilirubin (mg/dl)	1.69 ± 0.91	1.65 ± 1.11	Z=1.4	0.15(NS)
AST (IU/L)	115.58 ± 36.83	67.54 ± 8.31	Z=5.6	<0.001(HS)
ALT (IU/L)	104.72 ± 35.83	100.51 ± 11.29	Z=0.4	0.6(NS)
INR	1.90 ± 0.44	1.10 ± 0.15	T=9.2	<0.001(HS)
AFP (ng/ml)	374.16 ± 282.77	26.30 ± 11.22	Z=6.2	<0.001(HS)
King score ($year.IU/10^9 plt$)	95.43 ± 45.52	24.23±7.4	Z= 5.9	<0.001(HS)

WBC; white blood cells, Plt; platelet, AST; aspartate transaminase, ALT; alanine transaminase, INR; international normalizing ratio, AFP; alpha fetoprotein NS; non-significant, S; significant, HS; highly significant

Table 4. Comparison between the laboratory data of the studied groups one year before diagnosis

Laboratory findings	Group I (N=29)	Group II (N=29)	T Test and MW test	*P*-value (Sig.)
WBC ($x10^3/\mu L$)	5.45 ± 1.02	5.08 ± 0.60	T= 0.654	0.35(NS)
Hemoglobin (g/dl)	10.41 ± 1.04	10.57 ± 0.58	T= 0.732	0.47(NS)
Plt ($x10^3/\mu L$)	158.65 ± 32.34	189.55 ±60.27	Z= 2.007	0.045(S)
Albumin (g/dl)	2.83 ± 0.35	2.86 ± 0.69	Z= 0.523	0.6(NS)
Bilirubin (mg/dl)	1.70 ± 0.80	1.81 ± 1.32	Z=0.616	0.54(NS)
AST (IU/L)	102.06 ± 25.38	65.93 ± 8.31	T=4.147	<0.001**(HS)**
ALT (IU/L)	100.48 ± 29.22	100.27 ± 19.45	Z=0.647	0.518(NS)
INR	1.70 ± 0.48	0.87 ± 0.14	Z= 6.412	<0.001**(HS)**
AFP (ng/ml)	32.12 ± 17.15	25.54 ± 15.94	Z= 0.272	0.786(NS)
King score (year.IU/10^9plt)	70.79 ± 41.88	17.46 ± 7.81	Z= 4.4	<0.001(HS)

WBC; white blood cells, Plt; platelet, AST; aspartate transaminase, ALT; alanine transaminase, INR; international normalizing ratio, AFP; alpha fetoprotein, NS; non-significant, S; significant, HS; highly significant

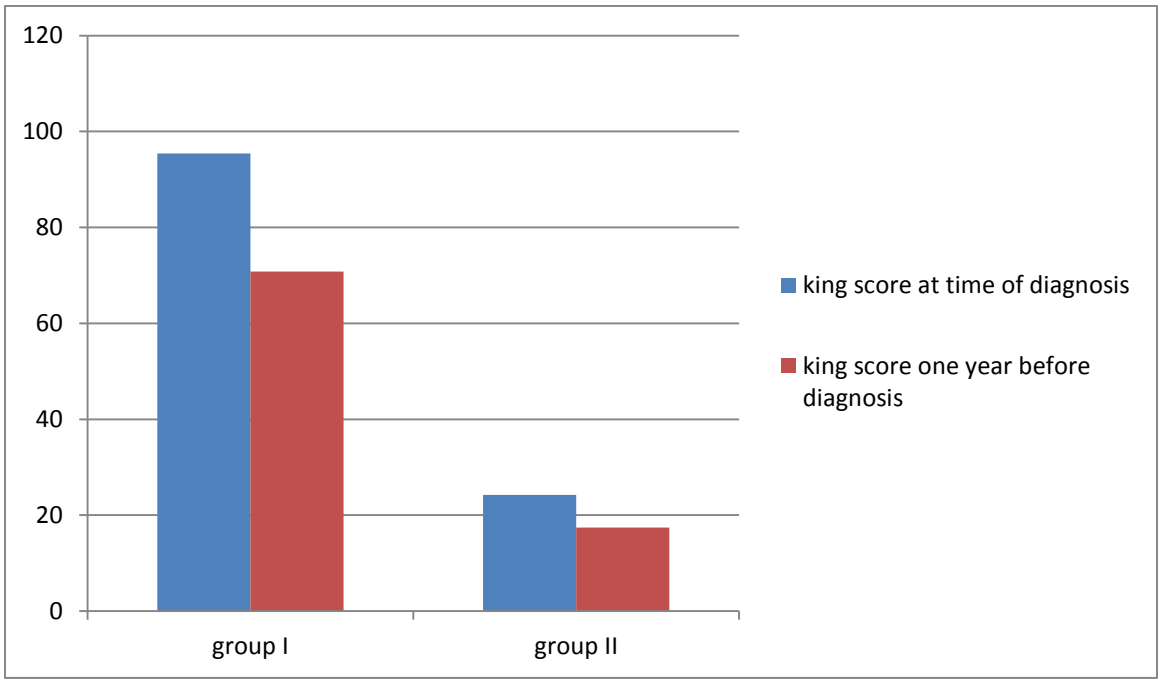

Figure 1. This figure shows the comparison of King's score (KS) in both groups at the time of diagnosis and one year before the diagnosis.