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Original Research

Survivin Expression in Renal Cell Carcinoma and Its Correlation with Clinicopathological Parameters

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Abstract

Objective: The aim of the current study is to cast further light on the issues related to prognostication of renal cell carcinoma (RCC), assessing the expression of survivin in a subset of primary RCC and determine its relation to different clinicopathological features and disease free survival.

Methods: The present series consisted of tissue samples obtained from 37 Libyan patients with stage I, II, III, or IV RCC. Survivin expression in these tumors was assessed by immunohistochemistry using an automated staining system. Different grading systems were tested for expression of survivin.

Results: Expression of survivin was significantly associated with venous invasion (tumor thrombus) (p= 0.042), larger tumor size (p= 0.051), higher primary T classification (p= 0.013), advanced tumor stage (p= 0.033), and borderline association (p= 0.068) with tumor location. In univariate (Kaplan-Meier) survival analysis, survivin expression showed a borderline association (p= 0.089) with disease-free survival (DFS). However, there was no significant correlation between survivin expression and gender, age, histological grade, distance metastasis, lymph node involvement, perinephric fat and capsular invasion, status at end point and recurrence.

Conclusion: Survivin expression in RCC may identify patients at risk of a more aggressive disease and a worse prognosis, further investigations, on a larger and more heterogeneous population, should be carried out to validate and extend our results.

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for more than 90% of all renal malignancies. The incidence rates of RCC vary among different populations, with higher rates in Europeans and lower rates in Asians [1]. RCC encompasses 4 specific subtypes, but most (> 80%) of renal cell tumors are classified as clear cell RCC (ccRCC), and this subtype is responsible for the majority of deaths caused by the disease [2]. Once metastatic disease develops, the 5 year survival rate for patients with ccRCC drops from 60% to <5% [3]. And because a large proportion of patients with clinically localized disease will subsequently develop metastases, there is a need to identify biomarkers in primary tumor tissue that not only predict RCC aggressiveness but also serve as potential therapeutic targets [4].

Renal tumorigenesis is a complex and a multistep process determined by environmental and genetic factors. Thus, it is essential to identify novel molecular markers underlying the development of RCC and predicting its prognosis, which will help us to explore additional prognostic factors to identify RCC patients at high risk of tumor progression and develop more effective therapeutic strategies.

Apoptosis (programmed cell death) has been proposed to play a role not only in cancer onset and progression but also in sustaining decreased tumor cell sensitivity to chemotherapy [5, 6], which still represents one of the main prognostic indicators in these neoplasia [7]. Recently, novel proteins which suppress apoptosis through caspase-dependent and caspase-independent mechanisms have been characterized, and named

inhibitors of apoptosis (IAPs). In humans, six members of the IAP family have been described: HIAP1, HIAP2, XIAP, NIAP, livin, and survivin [8].

Survivin is a member of IAP family, which participates in the complex network regulating programmed cell death and also cell division [9]. It seems over-expressed in a variety of human tumors, including breast, colon, pancreas, prostatic carcinoma, neuroblastoma, melanoma and non- Hodgkin's Lymphomas [10]. Most of the previous studies found a positive correlation between survivin expression and prognosis of the disease [11].

In the present study, we examined the expression of survivin in 37 RCCs using immunohistochemistry (IHC), and correlated the results with the established clinicopathological factors of the disease.

PATIENTS AND METHODS

Clinicopathological features and follow up data

The records of all newly diagnosed Renal cell carcinoma cases in the period from January 2003 to January 2012 based on availability of representative paraffin blocks were retrieved from the files of the Histopathology Department, Benghazi University, 37 Libyan patients (23male, 14 female) were diagnosed with RCC. For each patient, we obtained the following information: Age, gender, diagnosis, grade and stage. We then reviewed the patient files and hospital information systems to obtain more information about type of initial surgical procedure, the anatomic site of tumor at initial presentation and date of initial diagnosis. One pathologist confirmed all histological diagnoses and the following histopathological features were recorded including primary tumor (T1, T2, T3 or T4), tumor type (clear cell RCC, papillary RCC and chromophobe RCC), tumor grade (well, moderately or poorly differentiated), lymphovascular permeation, capsular and perinephric fat invasion and number of lymph nodes examined.

All the patients were followed up until death or when last seen alive at their clinical visit (October 2012) with the follow-up-time range (9-119 month). The duration of follow-up and the outcomes at the end of follow-up were determined for each patient from hospital and clinic charts.

The clinical and histopathologic data of each patient were collected and entered into a computer database according to the criteria of tumour–node–metastasis (TNM) classification of the International Union against Cancer [12]. The histological grade of tumors was determined according to the Fuhrman grading system. The key clinicopathological data of the patients are summarized in Table 1.

Survivin Immunostaining

Formalin-fixed, paraffin-embedded primary renal cell carcinoma tissue was obtained from 37 patients. Sections were cut serially at 5µm for immunohistochemical (IHC) analysis. IHC analysis was done using an automated system (BenchMark XT, Ventana Medical System, Inc. Tucson, Arizona, USA). This fully automated processing of code-labeled slides included baking of the slides, solvent free deparaffinization, antigen retrieval in a cell conditioning buffer CCI (Mild: 36 minutes conditioning, and standard: 60 minutes conditioning), incubation with Rabbit monoclonal anti-Survivin antibody, 2.0ml ready-to-use from Spring Bioscience (clone: SP79, Catalog No: M3794, 6920 Koll Center Parkway, CA 94566, USA), Dilution 1: 50 for 32 minutes, at 37ºC. Application of I-View™ DAB Detection Kit (Lot no. B05860AZ), which, includes: I-View DAB HRP, I-View DAB Inhibitor, I-View DAB Biotin, I-View DAB H2O2, and I-View DAB Copper. Counterstaining with haematoxylin II (C00758) was done for 4 minutes, and post-counterstaining with blueing reagent (B11129) was done for 4 minutes as well. After staining, the sections was dehydrated in ethanol, cleared in xylene, and covered with Mountex and cover slips.

Evaluation of Survivin staining

Survivin staining was evaluated using regular light microscope at the magnification of x40, blinded by the information on tumor grade, stage or clinical outcome. Nuclear and cytoplasmic staining were evaluated separately. Three different grading (A, B and C) systems were applied to assess the patterns of survivin expression in tumor cells. In system A, the staining was graded into four categories: {0} no expression (no detectable staining), {1} weak staining, {2} moderate staining, and {3} strong staining intensity. In system B, staining was graded in two categories: {1} no/weak expression and {2} moderate/strong expression. Finally, in system C, Survivin expression was categorized simply as negative or positive. All three systems were statistically tested, and the negative/positive grading “C” seemed to provide the most meaningful correlates of survivin with the clinically relevant data. In calculating the staining indexes, cytoplasmic and nuclear index, the intensity of staining and the fraction of positively stained cells were taken into account using the following formula:

$$\mathbf{I} = 0 \times f0 + 1 \times f1 + 2 \times f2 + 3 \times f3$$

Where **“I”** is the staining index, and f0–f3 are the fractions of the cells showing a defined level of staining intensity (from 0 to 3). Theoretically, the index could vary between 0 and 3 [13, 14].

Table 1. Clinicopathological characteristics of the patients with RCC.

Characteristic	No. of patients (%)
Gender	
Male	23 (62)
Female	14 (38)
Age (yrs)	
< 55 years	20 (54)
> 55 years	17 (46)
Primary tumor status	
T1	14 (38)
T2	15 (40)
T3	8 (22)
T4	0 (0)
LN involvement[(1)]	
No	15 (83)
Yes	3 (17)
Metastasis[(2)]	
No	22 (76)
Yes	7 (24)
Stage[(3)]	
I	15 (43)
II	11 (31)
III	4 (12)
IV	5 (14)
Histological grade[(4)]	
G 1	2 (5)
G 2	26 (70)
G 3	8 (22)
G 4	1(3)
Localization	
Right Kidney	18 (49)
Left Kidney	19 (51)
Tumor Thrombus	
Yes	7 (19)
No	30 (81)
Primary tumor size	
<5cm	9 (24)
>5cm	28 (76)
Histological subtypes	
Clear cell RCC	28 (76)
Papillary RCC	2 (5)
Chromophobe RCC	7 (19)
Perinephric fat invasion[(5)]	
No	34 (94)
Yes	2 (6)
Capsular invasion	
No	33 (89)
Yes	4 (11)
Recurrence during the follow-up	
Yes	11 (30)
No	26 (70)
Status at the end of follow-up	
Alive	15 (65)
Died	8 (35)
Missed	14 (38)
Respond to treatment	
No	12 (32)
Yes	25 (68)

(1) There were no data about the number of the lymph nodes in some cases, because lymphadenectomies were performed in different centers in addition to Benghazi.
(2) In 8 cases, distance metastasis cannot be assessed (Mx), because of lacking the data about them.
(3) There were 2 dropped cases in our series during follow-up.
(4) In G4, there was only one case, which was a sarcomatoid RCC. It was excluded.
(5) In one case, perinephric fat invasion cannot be assessed, because no perinephric fat tissue was observed.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics (IBM Company, NY, USA) and STATA (StataCorp., Texas, USA) software packages (IBM PASW Statistics for Windows, version 18.0.3 and STATA/SE 11.1). Frequency tables were analysed using the Chi-square test, with likelihood ratio (LR) or Fischer's exact test being used to assess the significance of the correlation between the categorical variables. Odds Ratios and their 95% Confidence Intervals (95% CI) were calculated where appropriate, using the exact method. Difference in the means of continuous variables was analyzed using non-parametric tests (Mamm-Whitney or Kruskal-Wallis) and multiple independent samples, respectively. Analysis of variance (ANOVA) was only used deriving the mean values (and their 95% CI) of each individual stratum. Univariate survival analysis for the outcome measure (DSS, DFS) was based on Kaplan-Meier method, with log-rank (Mantel-Cox) comparison test. To assess the value of survivin as an independent predictor, multivariate survival analysis was performed, using the Cox proportional hazards regression model controlling for the confounding by the following variables: age, sex, tumor localization, T, grade, (for DFS), and recurrence as additional variable (for DSS). In all tests, the values $p<0.05$ were regarded statistically significant.

RESULTS

Description of Survivin expression pattern

The intracellular localization of survivin in tumor cells was predominantly nuclear and only weakly cytoplasmic, so we have included in the statistical analysis the nuclear and cytoplasmic percentage of immunostaining. Examples of the staining patterns of survivin are illustrated in Figures 1-4. Of the 37 tumors, 9 (24%) were considered negative (staining intensity 0) (Figure 4), whereas 28 (76%) were considered positive (Figures 1-3).

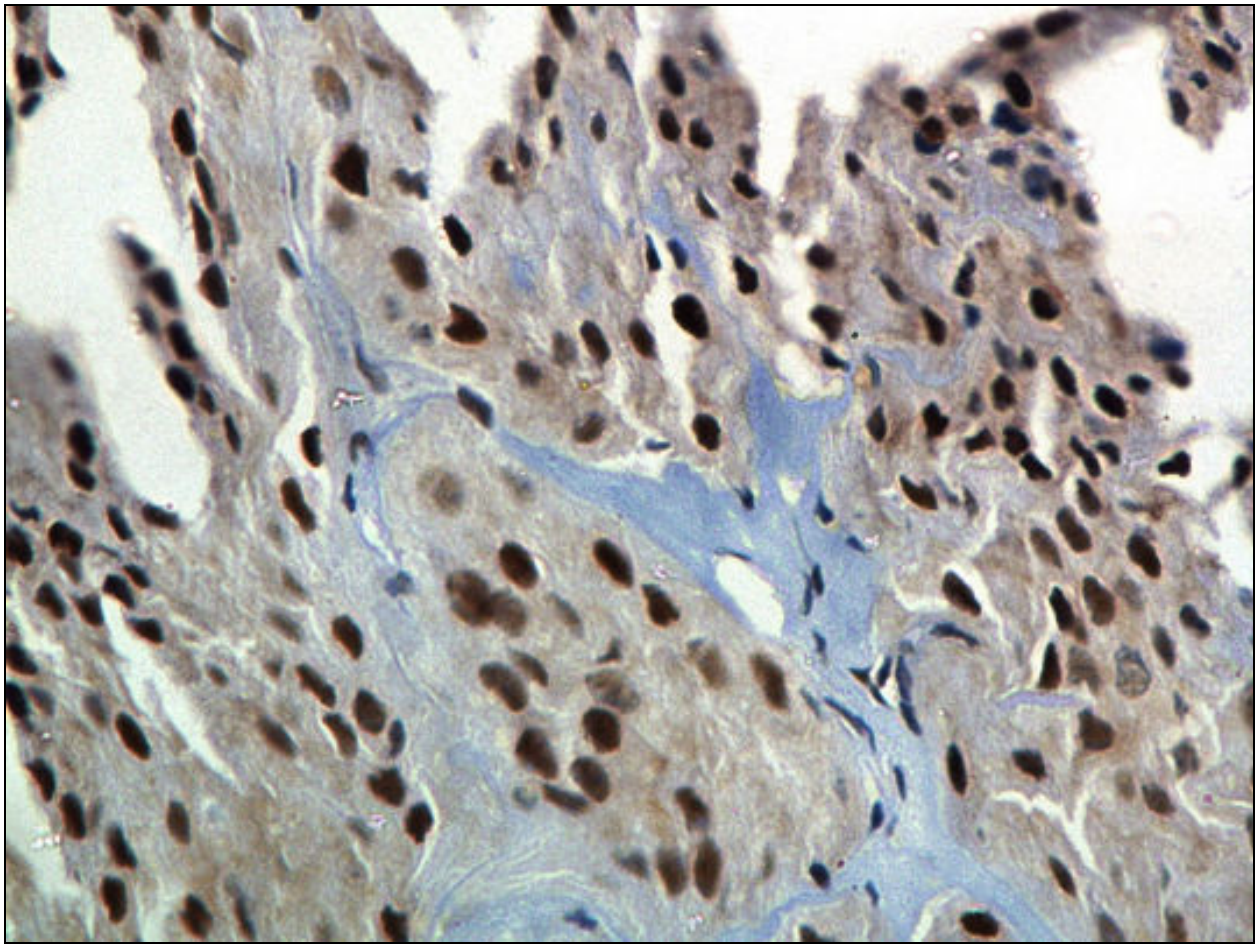

Figure 1. Strong nuclear survivin expression in RCC (IHC, x400)

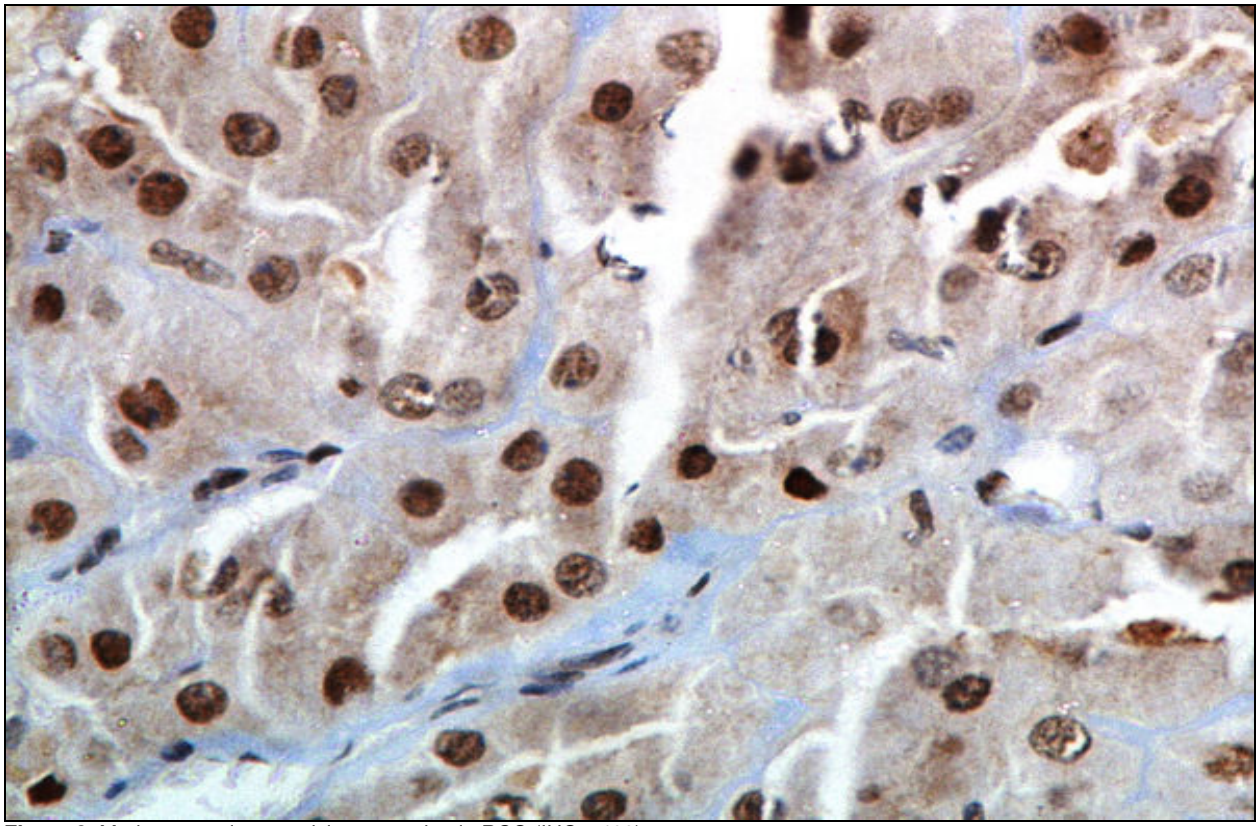

Figure 2. Moderate nuclear survivin expression in RCC (IHC, x400)

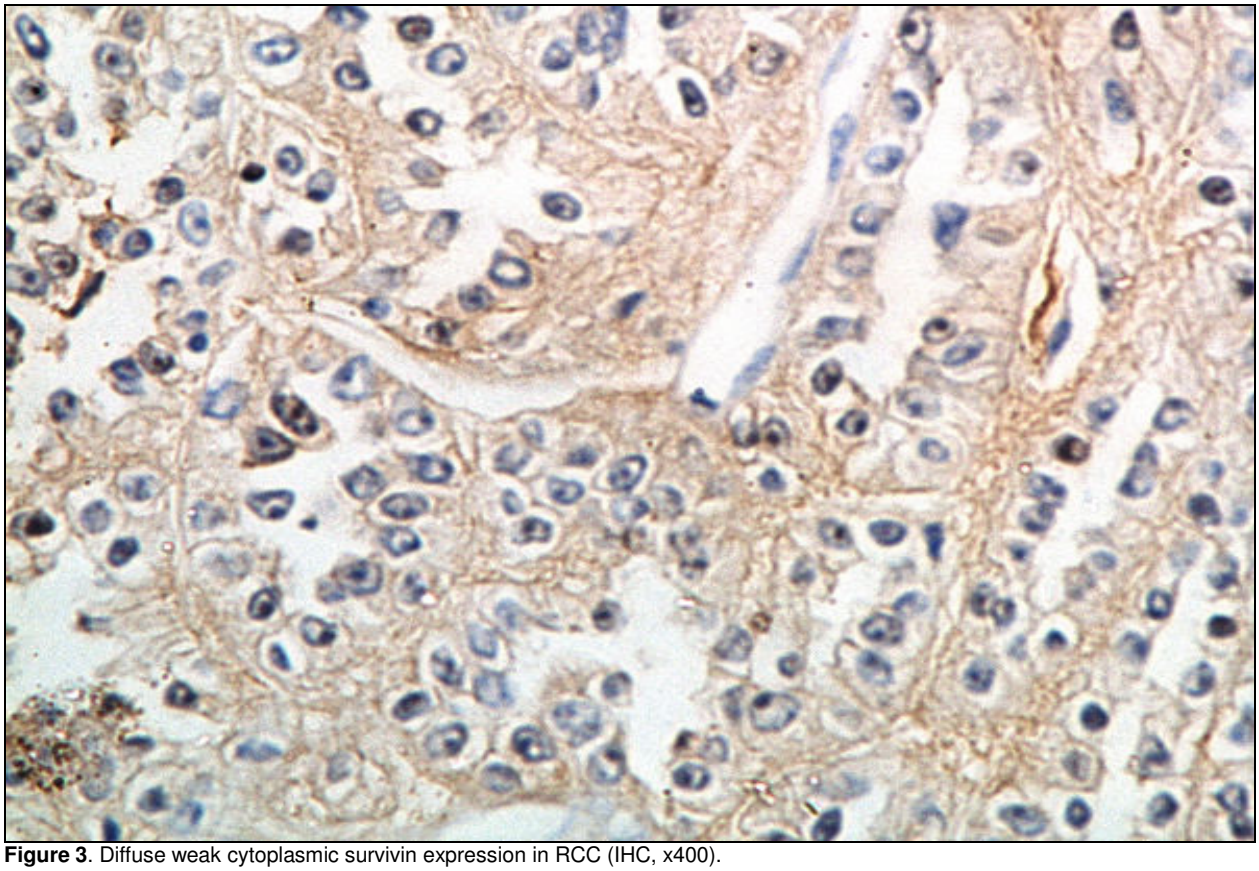

Figure 3. Diffuse weak cytoplasmic survivin expression in RCC (IHC, x400).

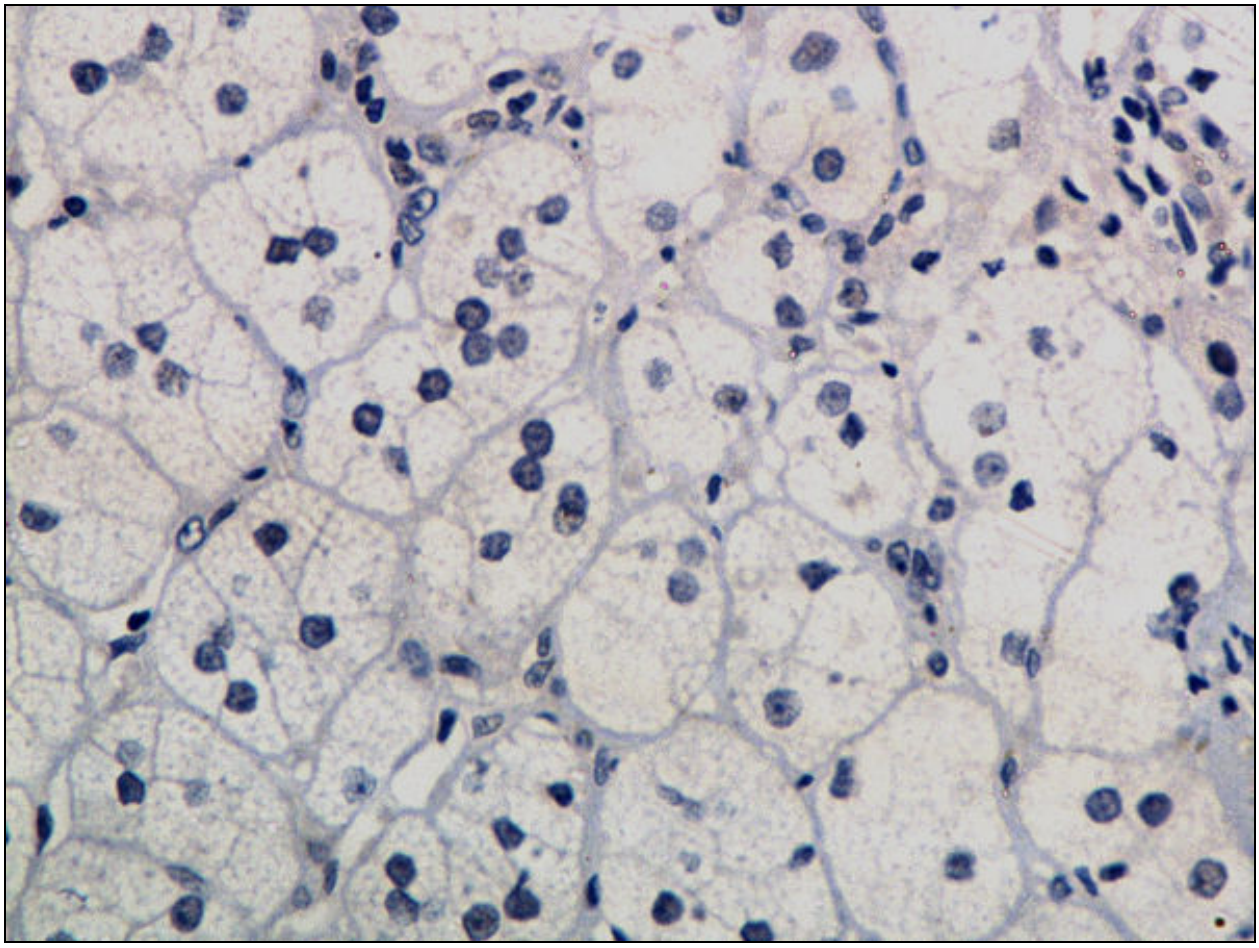

Figure 4. Negative survivin expression in RCC (IHC, x400)

Survivin expression correlates with the clinicopathological features

The distribution of survivin expression in tumor samples in relation to clinic-pathological characteristics is presented in (Table 2 and 3). Using different cut- off points [mean, median, and 3- teir score (0 vs 1, 2, 3), (0, 1 vs 2, 3) and (0, 1, 2, 3)]. The present study revealed that a significant correlation between survivin expression and venous invasion (tumor thrombus), patients who had tumors with high survivin expression were more likely to have tumor thrombus (p= 0.042), larger tumor size (> 5 cm) (p<0.051), advanced tumor stage (p= 0.033). Survivin expression associated significantly with primary tumor classification (pT1, pT2 vs pT3; p= 0.013). Survivin expression showed a borderline association (p= 0.068) with tumor location as it is expressed more in tumors arising in the right kidney in comparison with those originate from the left kidney.

On the other hand, early tumor recurrence (relapse), gender, age, distance metastasis, lymph node involvement, perinephric and capsular invasion, tumor grade and status at end point as well as response to treatment had no significant relationship with expression of survivin.

Survival analysis

In the Kaplan–Meier survival analysis (at median as cut-off point) there was a borderline (p= 0.08) difference in DFS between patients who have survivin expression above median and those with survivin expression below median (Figure 5). Interestingly , at 2- years follow- up, 85% of the patients with tumors expressing survivin below median showed longer disease free survival in comparison with only 57% of patients with tumors expressing survivin above median.

Table 2. Correlation between survivin expression and clinico-pathological features of RCC.

Features	Number of cases (%)	Survivin Expression		p-value
		Negative (0)	Positive (1 ,2, 3)	
Gender				0.267
Male	23 (62)	7 (30)	16 (70)	
Female	14 (38)	2 (14)	12 (86)	
Age group (years)				1.000
< 55	20 (54)	5 (25)	15 (75)	
> 55	17 (46)	4 (24)	13 (76)	
Lymph node involvement[(1)]				1.000
Yes	3 (17)	1 (33)	2 (67)	
No	15 (83)	5 (33)	10 (67)	
Distant metastasis[(2)]				0.484
Yes	7 (24)	1 (14)	6 (86)	
No	22 (76)	6 (27)	16 (73)	
Tumor Stage[(3)]				0.833
I	15 (43)	5 (33)	10 (67)	
II	11 (31)	2 (18)	9 (82)	
III	4 (12)	1 (25)	3 (75)	
IV	5 (14)	1 (20)	4 (80)	
Tumor grade[(4)]				0.734
G1	2 (6)	0 (0)	2 (100)	
G2	26 (72)	6 (23)	20 (77)	
G3	8 (22)	2 (25)	6 (75)	
Tumor location				0.068
Right Kidney	18 (49)	2 (11)	16 (89)	
Left Kidney	19 (51)	7 (37)	12 (63)	
Primary tumor size				0.051
< 5cm	9 (24)	4 (44)	5 (56)	
> 5cm	28 (76)	9 (32)	19 (68)	
Tumor Thrombus				0.771
Yes	7 (19)	2 (29)	5 (71)	
No	30 (81)	7 (23)	23 (77)	
Primary tumor classification				0.864
pT1	14 (38)	4 (29)	10 (71)	
pT2	15 (40)	3 (20)	12 (80)	
pT3	8 (22)	2 (25)	6 (75)	
Recurrence				0.832
No	26 (70)	18 (69)	8 (31)	
Yes	11 (30)	8 (73)	3 (27)	

(1) There were no data about the number of the lymph nodes in some cases, because lymphadenectomies were performed in different centers in addition to Benghazi.
(2) In 8 cases, distance metastasis cannot be assessed (Mx), because of lacking the data about them.
(3) There were 2 dropped cases in our series during follow-up.
(4) In G4, there was only one case, which was a sarcomatoid RCC. It was excluded.

Table 3. Correlation between survivin expression and clinicopathological features of RCC

Features	Number of cases (%)	Survivin Expression		p-value
		Median (< 0.20)	Median (> 0.20)	
Gender				0.623
Male	23 (62)	15 (65)	8 (35)	
Female	14 (38)	8 (57)	6 (43)	
Age group (years)				0.699
< 55	20 (54)	13 (65)	7 (35)	
> 55	17 (46)	10 (59)	7 (41)	
Lymph node involvement[1]				0.245
Yes	3 (17)	1 (33)	2 (67)	
No	15 (83)	11 (73)	4 (27)	
Distant metastasis[2]				0.667
Yes	7 (24)	3 (43)	4 (57)	
No	22 (76)	13 (59)	9 (41)	
Tumor Stage[3]				0.033
I	15 (43)	8 (53)	7 (47)	
II	11 (31)	11(100)	0 (0)	
III	4 (12)	1 (25)	3 (75)	
IV	5 (14)	1 (20)	4 (80)	
Tumor grade[4]				0.429
G1	2 (6)	2 (100)	0 (0)	
G2	26 (72)	16 (62)	10 (38)	
G3	8 (22)	4 (50)	4 (50)	
Tumor location				0.898
Right Kidney	18 (49)	11 (61)	7 (39)	
Left Kidney	19 (51)	12 (63)	7 (37)	
Primary tumor size				0.079
< 5cm	9 (24)	2 (22)	7 (78)	
> 5cm	28 (76)	18 (64)	10 (36)	
Tumor thrombus				0.042
Yes	7 (19)	2 (29)	5 (71)	
No	30 (81)	21 (70)	9 (30)	
Primary tumor classification				0.013
pT1	14 (38)	8 (57)	6 (43)	
pT2	15 (40)	13 (87)	2 (13)	
pT3	8 (22)	2 (25)	6 (75)	
Recurrence				0.534
No	26 (70)	17 (65)	9 (35)	
Yes	11 (30)	6 (55)	5 (45)	

[1] There were no data about the number of the lymph nodes in some cases, because lymphadenectomies were performed in different centers in addition to Benghazi.
[2] In 8 cases, distance metastasis cannot be assessed (Mx), because of lacking the data about them.
[3] There were 2 dropped cases in our series during follow-up.
[4] In G4, there was only one case, which was a sarcomatoid RCC. It was excluded.

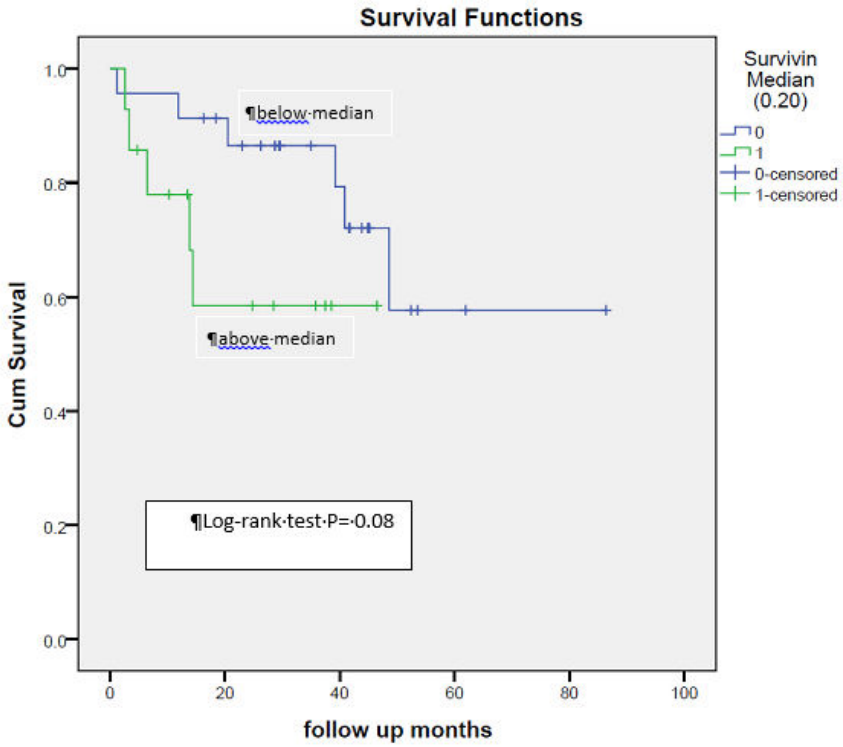

Figure 5. Survivin expression (median according to < 0.20 and > 0.20) as determinant of disease-free survival in univariate (Kaplan–Meier) analysis.

DISCUSSION

Up to now, the molecular mechanisms underlying the development of RCC are still poorly understood. Therefore, it is crucial to exploit molecular markers that can accurately represent biological features of tumors and predict the outcome, which will help us to perform tailored therapy for individual cases. As a unique inhibitor of apoptosis protein, survivin reduces the susceptibility of tumor cells to apoptotic stimuli and thereby promotes tumor cell survival during tumor development and progression [15].

Survivin seems to aid tumor progression and survival by a different mechanism (i.e., inhibition of apoptosis) [16], it is thought to promote tumor progression by rendering cells refractory to programmed death [17] .It is expressed during fetal development but not within adult tissues [18]. Most strikingly, survivin was found in the most common human cancers, suggesting that cancer cells return to a fetal pattern of survivin expression. Re-expression of survivin may enhance cell viability and enable the neoplastic cell to overcome the cytotoxic effects of chemotherapeutic agents [19, 20]. To date, a number of studies have attempted to evaluate the associations of the survivin and DFS. In accordance with our observations, a clinical setting, recently reported that survivin is linked with poor cancer-specific survival when expressed at high levels in ccRCC [21]. Survivin also promotes and stabilizes mitotic microtubules necessary for cell development and proliferation [22].

Lei and coworkers [23] have demonstrated that the expression of survivin was elevated both in RCC cell lines and in tumor tissues. It has been proposed that expression level of survivin was a biomarker to predict RCC progression and prognosis [24]. Increased survivin expression is an unfavorable prognostic marker associated with decreased overall survival in many malignancies, including renal, colon, and breast cancer [25, 26]. In the present data we have found that increased survivin expression associated with shorter disease-free survival of RCC patients.

Several studies have reported that elevated expression of survivin was associated with advanced tumor stage and grade, and patients with high survivin levels had a significantly shorter overall survival time than those with low survivin levels [27, 28, 29]. In the current study, we observed that the survivin expression was associated significantly (p=0.033) with advanced tumor stage, in addition, it was associated with tumor thrombus, larger tumor size, higher primary T-classification, tumor location and shorter disease-free survival of RCC patients, these findings are in agreement with previous observations demonstrated by Parker et al [21], who reported that high survivin

expression in RCC was associated significantly with tumor thrombus, larger tumor size, advanced tumor stage, higher grade, tumor necrosis, lymph node involvement and distance metastases as compared with patients who had tumors with low survivin expression.

Data from other investigators on survivin expression and RCC aggressiveness are limited, possibly; due to differences in evaluation methods. In a previously published study, researchers have evaluated survivin mRNA expression in 57 RCCs (47 were ccRCC) using quantitative RT- PCR and found no association of survivin expression and primary tumor classification [20]. However, conclusions from that investigation were limited by the lack of data on protein expression.

Furthermore, many researchers studied other members of the IAP family and concluded similar results, Ramp et al [30] reported that expression of XIAP, one of the IAPs, was associated with both tumor grade and stage in conventional RCC.

Survivin was expressed in all histologic RCC types in our study. Nevertheless, we did not analyze the statistical significance of the histologic subtype because only limited numbers of subtypes other than clear cell RCC were included in our study.

In conclusion, even if based on a limited number of cases, the present study suggests that survivin expression in RCC may identify patients at risk of a more aggressive disease and a worse prognosis. Furthermore, survivin expression does not correlate with the emergence of early recurrence (relapse), although its expression seems to be associated with the stage of tumors. Admittedly, further studies on a larger cohorts and more heterogeneous population are warranted to validate and extend our results, and may anticipate the proper selection for adjuvant therapy in such malignancies.

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