Int J Clin Exp Pathol 2024;17(2):39-46
www.ijcep.com /ISSN:1936-2625/IJCEP0154545

Original Article

Survivin expression is associated with lymph node metastasis and short survival in patients with colorectal adenocarcinoma

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Received November 21, 2023; Accepted January 16, 2024; Epub February 15, 2024; Published February 28, 2024

Abstract: Background: Survivin, a protein belonging to the Inhibitor of apoptosis (IAP) family, is the smallest member in terms of size. It works by preventing programmed cell death and regulating the advancement of the cell cycle. Being a part of the group of inhibitors associated with apoptosis, survivin is connected to increased aggression and negative prognosis in different malignancies, including colorectal cancer (CRC). Materials and methods: Pathology tissue blocks of 209 primary tumors, and 44 adenomas, were used in this study, as well as an anti-Survivin antibody. A semiquantitative method was used to score the Survivin expression based on an evaluation of the percentage and intensity of nuclear expression. Result: Survivin expression was identified in 127 (60.8%) CRC samples and in 14 adenomas (31.8%). There was an association between positive Survivin immunostaining and lymph node metastasis (*P*: 0.001), lymphovascular invasion (*P*: 0.020), and short overall survival (Log-rank 4.012, P=0.045) and disease-free survival probabilities (Log Rank 4.921, P=0.027). There was no association between Survivin expression and age, gender, tumor location, size, stage, margin status, and tumor recurrence. Conclusion: Survivin immune expression is associated with worse prognoses in CRC patients. Survivin can be a potential disease biomarker and could be used in management plans for CRC patients.

Keywords: Survivin, metastasis, survival rate, colorectal carcinoma, tissue microarray

Introduction

Survivin, a member of the inhibitor of apoptosis protein family (IAPs), plays a crucial role in regulating apoptosis and T-cell responses for anti-tumor immunity. Being a unique protein with distinct functional characteristics, it displays divergent roles such as controlling cell growth and apoptosis. Survivin displays a unique expression pattern characterized by being highly expressed during embryonal development while being absent in the majority of normal, fully differentiated tissues. However, it becomes upregulated in various types of carcinomas. The presence of Survivin in tumors is not only associated with the prevention of cell death and decreased apoptosis, but it is also linked to resistance towards chemotherapy and the aggressive nature of tumors [1]. Consequently, scientists have been actively researching distinctive biomarkers that could potentially be utilized for diagnosing and tracking carcinoma progression, specifically colon cancer. Colorectal cancer (CRC) ranks as the third most prevalent form of cancer globally and is the fourth leading cause of cancer-associated death [2]. As a result, scientists have been diligently seeking out distinctive biomarkers that could potentially be utilized for diagnosing and monitoring the treatment of patients with CRC. Nevertheless, there have been no discoveries of such indices thus far. Several qualifying stages are required for neoplastic biomarkers that could potentially have clinical implications in CRC patients. Therefore, specific molecular targets like vascular endothelial growth factor (VEGF), human epidermal growth factor receptors (EGFR), and others have been discovered. These targets are either currently being utilized in cancer treatment or are being investigated in

https://doi.org/10.62347/ZCUD7995

clinical trials [3]. Survivin, which contains a conserved domain called baculoviral IAP repeat (BIR), is one of the IAP family members that has been extensively studied. In terms of its functionality, survivin plays a dual role. Firstly, it functions as an antagonist of apoptotic cell death by obstructing caspases in conjunction with X-linked inhibitor of apoptosis protein (XIAP). Secondly, it operates as a regulator of mitosis [4]. A noteworthy observation is that the formation of a survivin-XIAP complex stimulates tumor cell invasion and metastasis. This process is facilitated through the interaction of the complex with TGF-beta activated kinase 1 binding protein 1 (TAB1)/TGF-beta activated kinase 1 (TAK1), leading to the activation of Nuclear Factor kappaB (NF-kB). Furthermore, the activation of cell motility kinases, such as Focal Adhesion Kinase (FAK), contributes to this mechanism [5]. As mentioned above that survivin is expressed in proliferating foetal tissues but not in most adult tissues under normal physiological circumstances. Survivin has been identified as one of the 40 genes that were found to be expressed at higher levels in cancer tissues compared to normal cells, through analyses of human transcriptomes. Over the past few decades, numerous studies have consistently supported the idea that survivin is upregulated in several prevalent human neoplasms including non-small cell lung cancer, gastric cancer, liver cancer, and CRC. These studies further suggest that the expression of survivin is linked to a less favourable prognosis [6, 7]. Review of the literature has indicated that over expression of survivin in CRC could potentially act as a predictive factor; however, the direct correlation between survivin expression levels and pathological factors of tumorigenesis, as well as patient survival, is still a matter of debate. Therefore, we present a thorough meta-analysis study to evaluate the importance of survivin expression through micro-array tissue examination as a prognostic and pathological marker in CRC.

Materials and methods

Tissue microarray

The construction of the tissue microarray was performed according to the procedures outlined in previous studies [8, 9]. This study involved examining pathology slides of primary colorectal cancer, adenomas, and normal colonic mucosa tissue that were stained with haematoxylin and eosin. Specific regions of interest were identified and designated. Areas with tumor necrosis, poorly fixed preservation, crushing artefacts, stromal tissue with no tumor cells, or autolysis changes were excluded from the study. Two cores of the desired tissue were obtained from donor paraffin blocks that matched the selected sections. These cores were then transferred to recipient blocks using a tissue microarray machine called TMA Master 1.14 SP3, manufactured by 3D Histech Ltd., located in Budapest, Hungary. Sections measuring 4 micrometres in thickness were cut from the tissue microarray (TMA) blocks without any staining and were used for immunohistochemistry examinations.

Immunohistochemistry

The Anti-Survivin Rabbit Polyclonal antibody (ab24479; Abcam) was used to carry out immunocytochemistry. The ideal dilution of the antibody is used to ensure compatibility with VENTANA detection kits. An automated immunostainer, specifically the Ventana Benchmark XT by Ventana Inc. in Tucson, AZ, was utilized for the immunohistochemistry procedure. The positive control was utilized according to the instructions provided by the manufacturer. The negative controls were treated without the addition of the primary antibody.

Evaluation of survivin immunostaining

The promotion of cell proliferation is likely linked to the presence of Survivin in the nuclear pool. In this research, the staining intensity of Survivin in the nucleus was evaluated through a semi-quantitative approach. The staining was assessed on a scale from 0 to 3, with 0 representing a negative result, 1 indicating weak staining, 2 denoting moderate staining, and 3 signifying strong staining. The calculation for the percentage of cells with positive staining was determined using the following scale: 0 indicated no staining, 1 represented 1-10% staining, 2 indicated 10-50% staining, and 3 indicated staining exceeding 50%. By combining the intensity score with the percentage score, a final score ranging from 1 to 6 was obtained. The overall score was separated into two categories: a group for negative expressions (scores 0-2) and a group for positive expressions (scores 3-6).

Table 1. Clinicopathological parameters of cases (*n*=209)

Parameter	Range	Number (%)
Age	<60 years	112 (53.6%)
	≥60 years	97 (46.4%)
Sex	Male	113 (54.1%)
	Female	96 (45.9%)
Tumor location	Right colon	55 (26.3%)
	Left colon	131 (62.7%)
	Rectum	23 (11%)
Tumor size	<5 cm	93 (44.5%)
	≥5 cm	116 (55.5%)
Grade	Well-differentiated	43 (20.6%)
	Moderately-differentiated	137 (65.5%)
	Poorly-differentiated	29 (13.9%)
Primary tumor	T1	3 (1.4%)
	T2	33 (15.8%)
	T3	155 (74.2%)
	T4	18 (8.6%)
Nodal metastasis	Negative	118 (56.5%)
	Positive	86 (41.1%)
	Cannot be assessed	5 (2.4%)
Distant metastasis	Positive	60 (28.7%)
	Negative	149 (71.3%)
Lymphovascular invasion	Positive	50 (23.9%)
	Negative	159 (76.1%)
Margin status	Involved	11 (5.3%)
	Free	198 (94.7%)
Recurrence	Recurrence	66 (31.6%)
	No recurrence	143 (68.4%)

Statistical analysis

The chi-squared test was employed to examine the disparities between two sets of variables. The Kaplan-Meier method was utilized to measure the overall survival (OS) and disease-free survival (DFS) values, with comparison being conducted using the log-rank (Mantel-Cox) test. DFS was determined by measuring the duration between the point of diagnosis and the occurrence of recurrent illness (or the latest instance of being disease-free). The SPSS® (IMB NY, USA) software package, version 20 was utilized to conduct statistical analyses. A significance level of P<0.05 was deemed as statistically significant.

Results

The clinicopathological features of the cases are summarized in **Table 1**. Survivin expression was identified in 127 (60.8%) of CRC samples and in 14 adenomas (31.8%) (**Figure 1**), while totally negative in normal colonic mucosa (**Table 3**). There is a statistically significant difference in Survivin expression between CRC and adenomas (P=0.00044). There was an association between positive Survivin immunostaining and nodal metastasis (P=0.001) lymphovascular invasion (P=0.02), and overall survival (P=0.045). Positive Survivin immunostaining was identified in 58.1% and 72.4% of well-differentiated and poorly differentiated tumors, respectively, but there was no statistically significant association with tumor grade (P=0.381). Furthermore, Survivin expression was not associated with age, gender, tumor location, tumor size, tumor stage, distant metastasis, or margin status (**Table 2**). In the survival analysis, patients with Survivin positive tumors tended to have short OS (Log rank 4.012, P=0.045) and DFS (Log Rank 4.921, P=0.027).

Discussion

Survivin overexpression is observed at an early stage of colonic adenocarcinoma tumorigenesis. It appears to escalate throughout the normal sequence of mucosa-adenoma-carcinoma and correlates with the gradual reduction of tumor differentiation. Survivin overexpression exhibits a direct correlation with the upregulation of other anti-apoptotic proteins (TACE and MCL1) and shows a tendency towards an opposite correlation with the proapoptotic BAX gene. This activation is believed to promote cell proliferation and could potentially be used to categorize patients with precursor lesions like adenomas. Furthermore, our findings indicate that survivin remains elevated throughout all stages of the disease, including the presence of lymph node metastases. This suggests that there is potential to target survivin in patients with advanced disease. Published studies indicated that the presence of Survivin is significantly linked to the progression from low-grade to high-grade dysplasia [10]. The data provided offer support

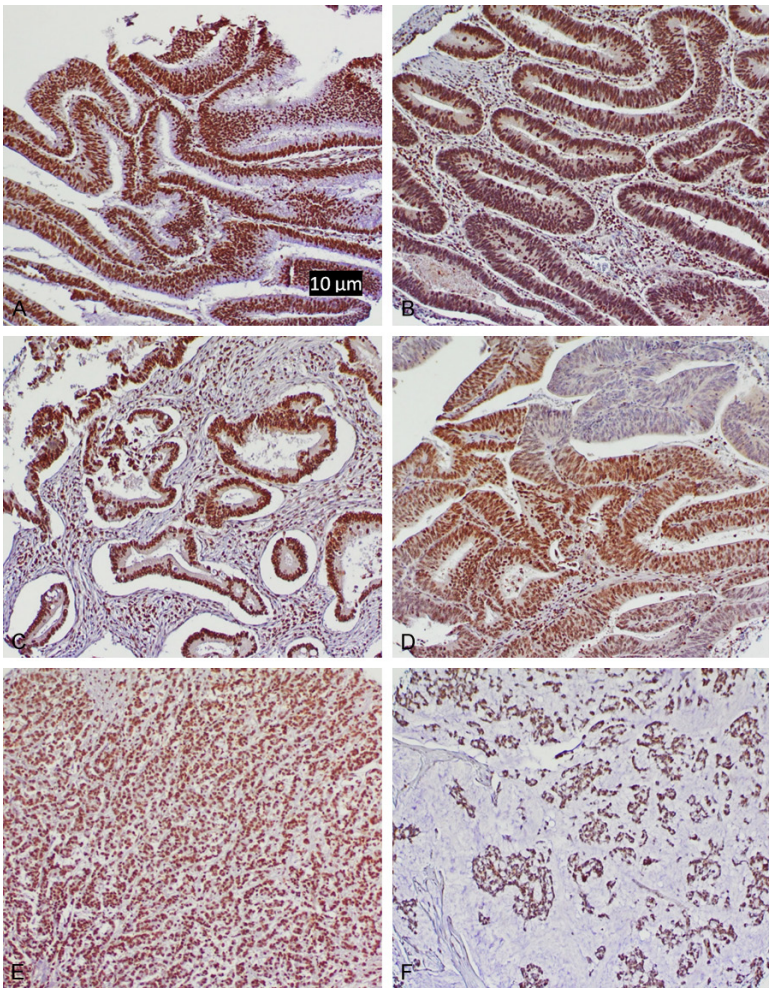

Figure 1. Histopathologic Images of Survivin immunostaining. A. Tubulovillous Adenoma with Several Survivin-Positive Epithelial Cells (400×). B. Well differentiated adenocarcinoma showing strong expression of survivin in the tumour cells (400×). C and D. A moderately differentiated adenocarcinoma showing noticeable expression of the survivin protein in a significant number of the tumour cells (400×). E. Most of the tumour cells in a poorly differentiated adenocarcinoma display a significant presence of survivin staining (400×). F. Mucinous adenocarcinoma displays a remarkable strong presence of survivin immunostaining (400×).

for the idea that the overexpression of survivin is an initial occurrence in the development of colorectal cancer. As a result, it could potentially have a prognostic indicator when assessing colon adenomas. Survivin expression, despite being consistently overexpressed in invasive cancer, does not show any correlation between tumor stage and overall survival. As a result, the prognostic value of survivin expression in assessing colonic adenocarcinomas seems to be limited.

Survivin is observed to have high expression levels during fetal development, however, it is barely detectable in mature tissues. Survivin has been identified as one of the significantly upregulated proteins in carcinomas in comparison to normal tissue, according to an examination of 3.5 million transcriptomes [11]. In a previous study involving 230 patients, tissue microarray revealed that survivin expression was not detected in any of the normal samples [12]. However, it is found to be expressed in only a limited number of normal adult tissue types, such as basal epithelial cells in the colon [13]. A meta-analysis was performed in one study to assess the relationship between survivin expression and clinicopathological parameters or overall survival in CRC patients, using data from 15 relevant studies [14]. It is worth noting that they discovered a correlation between survivin expression and both vascular/lymphatic invasion and the presence of lymph node metastases. The heterogeneity observed when comparing nodal status with survivin overexpression may be attributed to the limited number of studies that have examined the relationship between survivin expression and pathology parameters such as vascular vessel invasion and lymph node metastasis. Alternatively, the differences in heterogeneity could also be attributed to variations in the extent of lymph nodes dissections performed during surgery across the studies. Therefore, the studies did not provide any information regarding the quantity of lymph nodes retrieved through lymph node sampling. The results obtained by Mehrotra and colleagues [15], provide support for the idea that the increased expression of survivin is associated with both blood vessel invasion and lymph node metastasis. Their study demonstrated that survivin not only promotes tumor cell invasiveness but also aids in the development of metastases when

Table 2. Distribution of survivin immunoexpression in relation to clinicopathological parameters

Parameter		Survivin Immunostaining		*p* value
		Negative	Positive	
Age	<60 years	46 (41.1%)	66 (58.9%)	0.329*
	≥60 years	36 (37.1%)	61 (62.9%)	
Sex	Male	39 (34.5%)	74 (65.5%)	0.085*
	Female	43 (44.8%)	53 (55.2%)	
Tumor location	Right colon	22 (40%)	33 (60%)	0.991*
	Left colon	51 (38.9%)	80 (61.1%)	
	Rectum	9 (39.1%)	14 (60.9%)	
Tumor size	<5 cm	32 (34.4%)	61 (65.6%)	0.128*
	≥5 cm	50 (43.1%)	66 (56.9%)	
Grade	Well-differentiated	18 (41.9%)	25 (58.1%)	0.381*
	Moderately-differentiated	56 (40.9%)	81 (59.1%)	
	Poorly-differentiated	8 (27.6%)	21 (72.4%)	
Primary tumor	T1	1 (33.3%)	2 (66.7%)	0.078*
	T2	15 (45.5%)	18 (54.5%)	
	T3	64 (41.3%)	91 (58.7%)	
	T4	2 (11.1%)	16 (88.9%)	
Nodal metastasis	Positive	21 (24.4%)	65 (75.6%)	0.001*
	Negative	59 (50%)	59 (50%)	
	Unknown	2 (40%)	3 (60%)	
Distant metastasis	Positive	22 (36.7%)	38 (63.3%)	0.374*
	Negative	60 (40.3%)	89 (59.7%)	
Lymphovascular invasion	Positive	13 (26%)	37 (74%)	0.02*
	Negative	69 (43.4%)	90 (56.6%)	
Margin status	Involved	6 (54.5%)	5 (45.5%)	0.224*
	Free	76 (38.4%)	122 (61.6%)	
Recurrence	Recurrence	29 (43.9%)	37 (56.1%)	0.213*
	No recurrence	53 (37.1%)	90 (62.9%)	

*Chi Square Test.

Table 3. Categories of survivin immunostaining in colorectal cancer and adenomas

Tissue Sampled Examined	Immunostaining Results		*p* value
	positive immunostaining	Negative immunostaining	
Primary tumor (*n*=209)	127 (60.8%)	82 (39.2%)	
Adenomas	14 (31.8%)	35 (68.2%)	0.00044 ●

●The chi-square test.

interacting with XIAP. Hence, it is enticing to hypothesize that tumors that exhibit both survivin and XIAP may possess a significant inclination towards invasiveness and the ability to metastasize. Jakubowska and colleagues [16], found that 84.2% of CRC patients had positive expression of survivin. The results obtained in this study align with the observations documented in the research conducted by Kalliakmanis et al. [17] and Choi and Chang [18]. These studies reported a positive presence of survivin in 88.3% and 83.3% of colorectal cancer cases, respectively. The functions of Survivin vary depending on where it is located. When found in the nucleus, this protein is responsible for regulating cell growth. On the other hand, when it is distributed to the cytoplasm, it plays a crucial role in determining the tumor viability [19]. The cell cycle progression is directly influenced by the location of nuclear

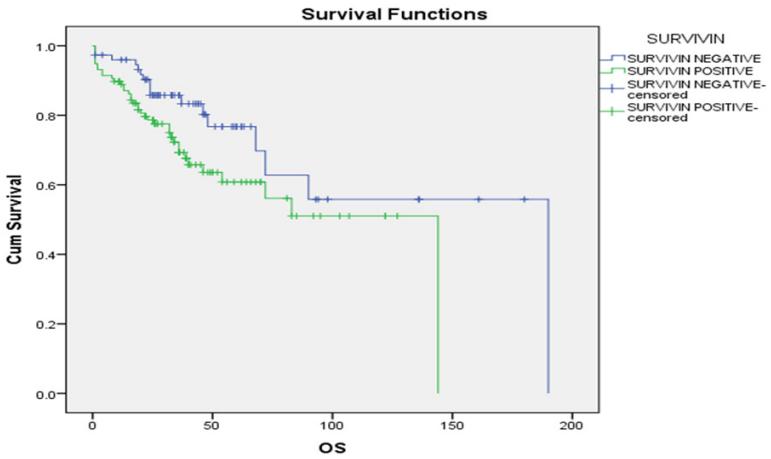

Figure 2. Overall survival curve (Kaplan Meier) in relation to Survivin immunoexpression in colorectal cancer patients. There is an association between positive Survivin immunostaining and overall survival (Log-rank 4.012, P=0.045).

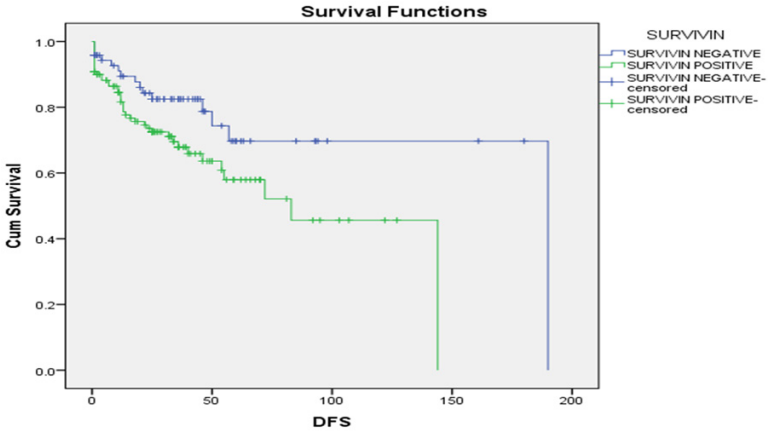

Figure 3. Disease-free survival curve (Kaplan Meier) in relation to Survivin immunoexpression in colorectal cancer patients. There is an association between positive Survivin immunostaining and disease-free survival (Log Rank 4.921, P=0.027).

survivin. The nuclear overexpression of survivin has been shown to enhance cellular overgrowth activity and promote transition of cells into S phase of the cell cycle. Consequently, this leads to a decrease in the proportion of cells in the G0/G1 phase [20]. The presence of nuclear survivin expression in CRC cells suggests that the tumor is actively undergoing mitotic activity and raises the likelihood of developing metastatic foci in distant organs. In a one study, a higher occurrence of survivin expressed as a positive feature was observed in the cell cytoplasm (81%) when compared to its presence in the cell nucleus (63%) among the patients diagnosed with CRC [16]. Ponnelle et al. [21] supported the finding that survivin expression was more prevalent in the cytoplasm (41%) rather than in the nucleus (39%) of colon adenocarcinoma cells. However, the data contradicts the findings of Shintani et al. [22] and Qi et al. [23] studies, which reported a higher occurrence of positive survivin expression in the nucleus compared to the cytoplasm of cancer cells.

Our findings indicated a notable association between survivin, and tumor aggressiveness as well as the invasiveness of tumor cells. This association extended to lymphovascular invasion short overall survival, and disease-free survival rate (**Figures 2** and **3**). Since lymphatic invasion is a high-risk factor for positive lymph node metastasis; Chu et al. [24] and Xiaoyuan et al. [25] found that there was a direct relationship between higher levels of survivin expression and the occurrence of lymph node metastasis. The presence of lymph node involvement in CRC patients is linked to an unfavorable prognosis because it raises the chances of distant organs metastasis. Li et al. [26] found that there was a correlation between survivin overexpression and the occurrence of distant organ metastases as well as disease relapse among the patients with CRC. Additionally, Lee et al. [27] demonstrated a strong connection between the presence of survivin and both the primary tumor as well as distant metastasis, and advanced tumor stage. Additionally, a study revealed that the mRNA expression of survivin was markedly higher in the malignant cells when compared to the marginal tissues, providing further evidence for this observation. Furthermore, it was observed that the expression of survivin was noticeably higher in the tumoral tissues of CRC patients who had lymph node metastasis, as compared to those who

did not have positive lymph nodes. This finding indicates that survivin may have an influential role in promoting the growth of CRC cancer cells, as well as facilitating the spread of cancer cells to lymph nodes [28]. Our findings were confirmed by the current in-depth analysis, which showed that there is a direct association between the presence of survivin overexpression among patients with CRC, distant metastases, and overall survival.

Conclusion

To sum up, the analysis of survivin through immunohistochemistry in CRC patients' tissues indicated a significant impact of protein localization on cancer cells. The overexpression of survivin in malignant cells can lead to an unfavourable response, potentially enhancing their ability to grow and multiply. The higher occurrence of tumor survivin proliferation is highly associated with an increased probability of developing metastasis in the lymph nodes. Further detailed studies are needed to assess survivin expression, as it holds the potential for assisting in the future diagnosis of CRC. Nevertheless, we believe that survivin expression in patients with CRC can be effectively used in clinical applications.

Disclosure of conflict of interest

None.

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