Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 08, 2023

Original Research Article

TO STUDY THE EXPRESSION OF SURVIVIN IN COLORECTAL NEOPLASIA

[1]Dr Shilpa Bhimalli, [2]Dr Sachin Gj, , [3]Dr Ravindra Nidoni, [3]Dr Shruthi Bhimalli

[1]Assistant Professor, Dept. Pathology, VTSM Peripheral Cancer Centre (Branch of Kidwai Cancer Institute, Bangalore
[2]Assistant Professor, Department, Cardiology, Jaideva Institute of Cardiology
[3]Consultant Liver Transplant and HPB Surgeon, Sparsh Hospital
[3]Consultant in Cataract, Cornea and Refractive Surgery Department, Anugraha Eye Hospital, Vijayapur

Corresponding Author: Dr Shilpa Bhimalli

Article History: **Received:** 13.08.2023 **Revised:**21.08.2023 **Accepted:** 30.08.2023

Abstract

To live is to incur the risk of cancer". Never has a disease instilled fearin the minds of common man and spiked the interests of researchers as cancer, both eagerly looking for a cure to this dreadful disease that not only causes mortality but also emotional and mental agony and suffering Colorectal cancers account for over nine percent of newly diagnosed cancers, with around million new cases and 600,000 associated deaths worldwide, responsible for almost 10% of all cancer deaths[1]. But colorectal carcinoma is unequal in geographic distribution. It is mainly a disease of developed countries with a western culture with a comparatively lower incidence in Asian and African countries including India however recent studies have shown an increase in incidence in these regions

KEYWORDS: Colon, Carcinoma, rectal

Introduction

"To live is to incur the risk of cancer". Never has a disease instilled fearin the minds of common man and spiked the interests of researchers as cancer, both eagerly looking for a cure to this dreadful disease that not only causes mortality but also emotional and mental agony and suffering. Cancers figure among the leading causes of morbidity and mortality worldwide with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 [1].

Colorectal cancer is the second most commonly diagnosed malignancy among women, the third most commonly diagnosed malignancy among men and the fourth most common cause of cancer mortality worldwide[1]. Colorectal cancers account for over nine percent of newly diagnosed cancers, with around 12 million new cases and 600,000 associated deaths worldwide, responsible for almost 10% of all cancer deaths[1]. But colorectal carcinoma is unequal in geographic distribution. It is mainly a disease of developed countries with a western culture with a comparatively lower incidence in Asian and African countries including India however recent studies have shown an increase in incidence in these regions[2].

It is an important public health problem with many proven screening tests and a higher chance of long disease free survival or cure when identified and treated in its early stages. Unfortunately most patients present at an advanced stage due to its clinical nature.

Apoptosis is a tightly regulated pathway of cell death where the cells destined to die activate intrinsic enzymes called caspases which degrade the cells own nuclear DNA and cytoplasmic proteins[3]. Apoptosis normally takes place both during development and in adults and also helps in removal of senescent and potentially harmful cells.

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Dysregulation of apoptosis by either of the two mechanisms – down regulation of proapoptotic elements and upregulation or over expression of antiapoptotic elements, confers an increased longevity upon the cell and as a consequence indirectly leads to accumulation of oncogenic mutations in a cell which should have been eliminated by apoptosis. This finally leads to the emergence of a malignant clone. Many malignancies have been shown to have dysregulated apoptosis best exemplified by over expression of bcl2, an anti- apoptotic protein in follicular lymphoma and p53 gene mutations which render the neoplastic cells resistant to intrinsic pathway of apoptosis[4,5]. So dysregulation of apoptosis plays a critical role in cancer emergence, survivaland growth of the tumor.

Dysregulated apoptosis has also shown to be involved in tumorresistance to anticancer therapy. Thus targeting apoptotic pathways will induce tumor apoptosis, reduce resistance to anticancer therapies and sensitizes cancer cells to apoptosis induction by other therapies.
There are three important antiapoptotic family of proteins which include FLICE-inhibitory proteins (FLIPs), Bcl-2 family and Inhibitors of Apoptosis Proteins (IAPs). The Inhibitors of Apoptosis (IAP) family of proteins are a group of proteins which inhibit the intrinsic pathway of apoptosis[6]. Common to all the members of this family is the presence of Baculovirus IAP repeats (BIR) in one to three copies. Survivin, the smallest member of the IAP family is a bifunctional regulator of apoptosis and cellular proliferation[7]. It is normally expressed during embryonic development, nearly undetectable in healthy adult tissue and is re expressed in most cancers including colorectal cancers[7].

MATERIAL AND METHODS

It was carried out on specimens obtained from patients with confirmed histopathological diagnosis of colorectal adenomas and adenocarcinomas. The study was VTSM Peripheral Cancer Centre (Branch Of Kidwai Cancer Institute ,Bangalore

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INCLUSION CRITERIA:

Patients with colorectal adenomas and adenocarcinomas.

EXCLUSION CRITERIA:

Chemotherapy and/or radiotherapy prior to sampling. Recurrent and metastatic adenocarcinomas.
Cancer types other than adenocarcinomas.

RESULTS:

A total of 90 participants were included in the analysis. The proportion of participants below 40 years were 10.0% and the proportion of participants above 40 years were 90.0%.The proportion of males constituted 60% of the study subjects. The remaining 40% of the participants were females respectively.

Table 1: Descriptive analysis of age groups in study group (N=90)

Age groups	**Frequency**	**Percentage**
<40 years	9	10.0
>40 years	81	90.0
II.Gender		

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Male	54	60
Female	36	40

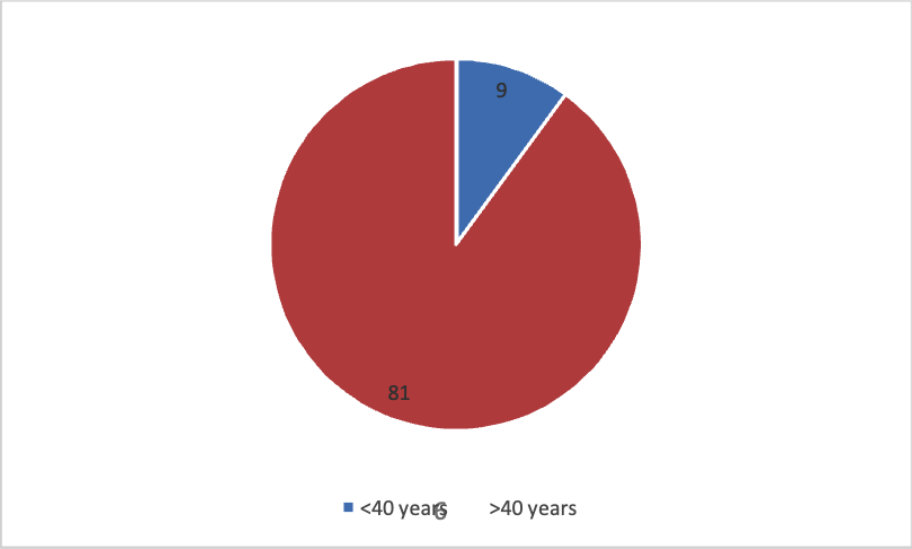

Chart 1 : Pie chart for age groups in study group (N=90)

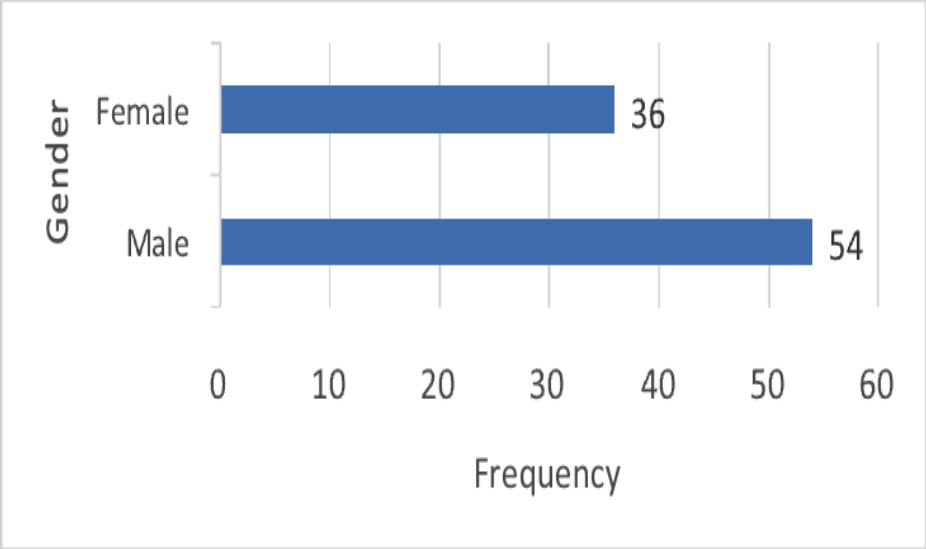

Chart 1:Bar chart for gender in study group(N=90)

Table 2: Descriptive analysis of final diagnosis in study group (N=90)

Final diagnosis	Frequency	Percentage
Normal	30	33.3
Adenoma	30	33.3
Adenocarcinoma	30	33.3

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The number of participants who were normal was 30(33.3%) and 30(33.3%) had adenoma in study population. The proportion of subjects with adenocarcinoma was 30(33.3%) in the study population. (Table 3)

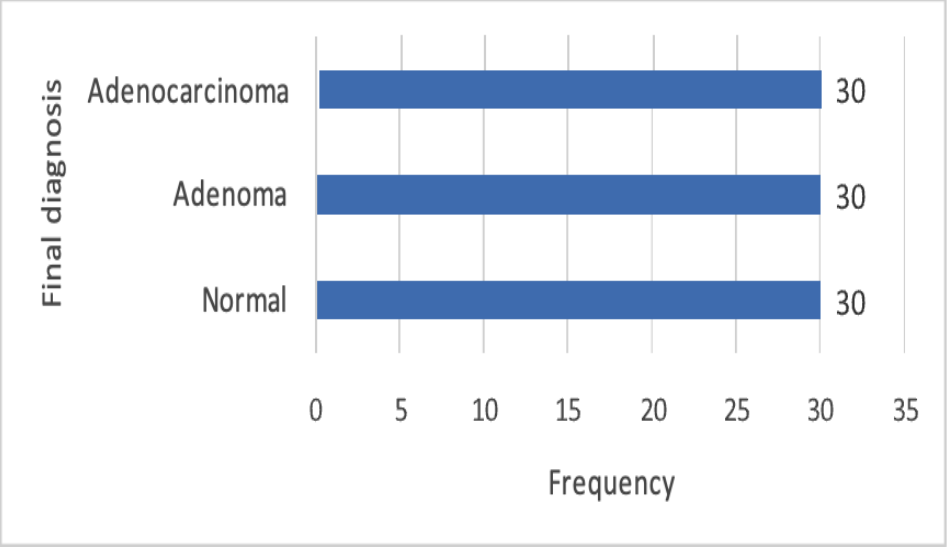

Chart 2: Bar chart of final diagnosis distribution in study group (N=90)

Table 3:Descriptive analysis of tumor site in study group (N=60)

Tumor site	Frequency	Percentage
Rectum	23	38.3
Right hemicolon	15	25.0
Left hemicolon	10	16.6
Sigmoid colon	12	20.0

The number of participants who had tumor in the rectum was 23 (38.3%). Tumor was present in right hemicolon in 15 (25.0%) people. The proportion of subject with tumor location in left hemicolon and sigmoid colon were 16.6% and 20.0% respectively in study population. (Table 4)

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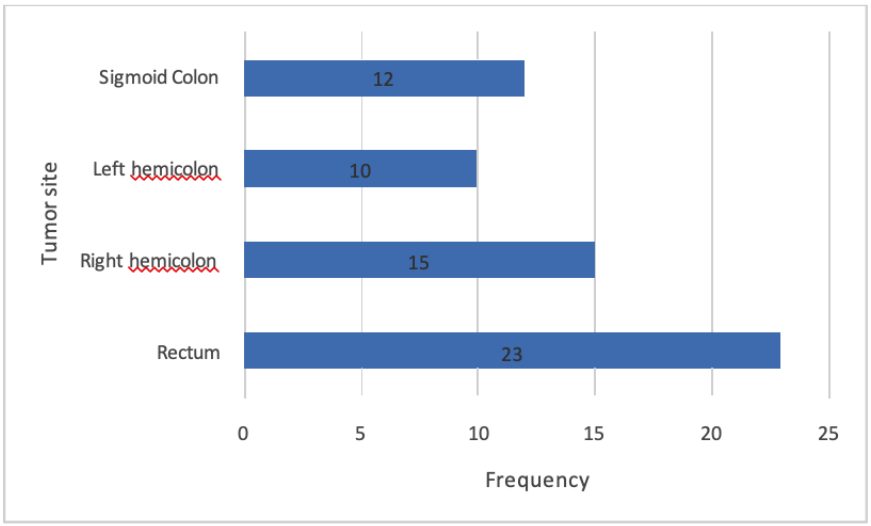

Chart 3: Bar chart for tumor site in study group (N=60)

Table 4: Descriptive analysis of carcinoma grade, stage and tumor stage instudy group (N=30)

Parameter	Frequency	Percentage
Carcinoma Grade		
1	10	33.3
2	12	40.0
3	8	26.6
II.Stage		
I	13	43.3
II A	4	13.3

Out of 30 subjects with adenocarcinoma, the grade of carcinoma was 1, 2 and 3 in 33.3%, 40% and 26.6% of the participants respectively. Tumor stage was stage 1 in 43.3% of participants, 8 participants had stage II malignancy and the remaining 9 participants had stage III malignancy. Majority of the participants belonged to T2 and T3 stage.

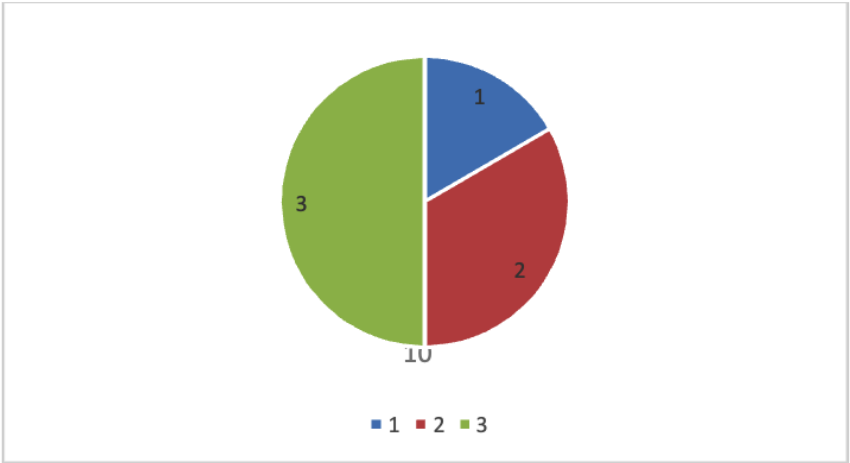

Chart 4: Pie chart of carcinoma grade distribution in study group (N=30)

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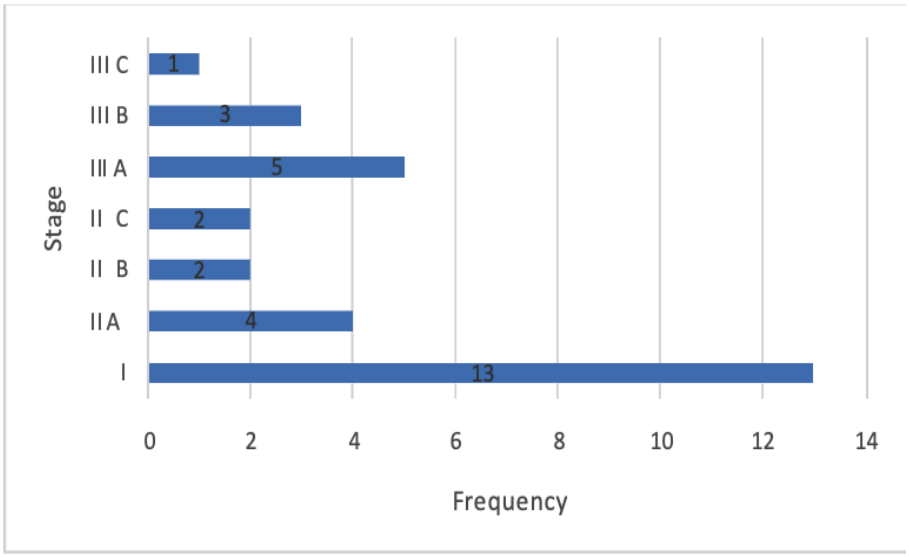

Chart 4: Bar chart of stage distribution in study group (N=30)

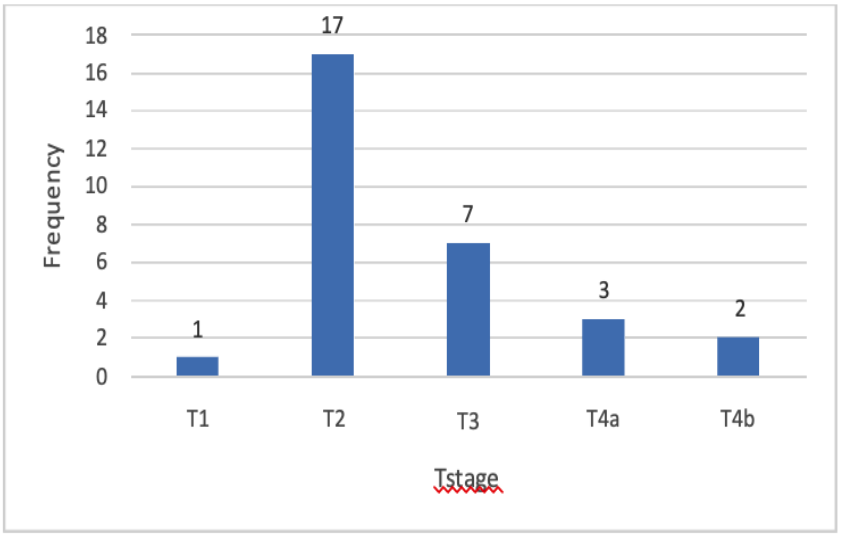

Chart 5: Bar chart of tumor stage distribution in study group (N=30)

DISCUSSION

The present study includes 90 cases which is comprised of 30 samples of normal colorectal epithelium, 30 cases of colorectal adenomas and 30 casesof colorectal adenocarcinomas.

The age group of patients included in the study varied from less than 20 years to more than 70 years with most of the patients being above 40 years of age. 60 percentage of the patients were males and 40 % were females. In most of the patients, the tumor was located in the rectum (38.3%), followed by right hemicolon (25%), left hemicolon (16.6%) and sigmoid colon (20%).

Out of the 30 adenocarcinomas that were studied, 10 were well differentiated, 12 were moderately differentiated and 8 were poorly differentiated. AJCC staging was used. 13 were stage I, 8 were stage II and 9 belonged to stage 3. Of the 8 stage II tumors, 4 belonged to stage IIA, 2 belonged to stage IIB and 2 belonged to stage IIC. 5 of the stage III tumors were of

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stage IIIA, 3 were of stage IIIB and 1 was of stage IIIC.

In the present study 9 out of 90 patients (10%) were below 40 years of age and 81 out of 90 (90%) were above 40 years of age. The mean differences of survivin expression between those below 40 years and those above 40 years was -6.62, which was statistically not significant.
Hai-Yan Tan et al in 2005 observed in his study that comparison of survivin expression with age of the patient was statistically not significant [8].
Alfred King-Yin et al and Woong Na et al found that no correlation existedbetween survivin expression and patient's age [9].
The study conducted by Ren Chong Xi and colleagues in 2011 also showed no significant correlation between survivin expression and age [10].
In the present study, 54 patients (60%) were male and 36 (40%) were female. Statistical analysis showed that the difference between mean expression between males and females was statistically not significant.
Hai-Yan Tan and colleagues in their study conducted during 2005 found no significant correlation between survivin expression by the tumor and gender[8].
In 2009 a study was conducted by Woong Na et al which showed that survivin expression by colorectal neoplasia did not correlate with the gender [11].
Similarly Ren Chong Xi and colleagues in their 2011 study concluded that no correlation existed between gender and survivin expression by colorectal adenomas and carcinomas [10]

In the present study, Survivin expression was minimal to absent in normal colonic mucosa, gradually increased in adenomas from low grade dysplasia to high grade dysplasia and was maximally expressed in adenocarcinomas. The differences in mean survivin expression between normal mucosa and adenomas and between adenomas and adenocarcinomas was statistically significant (P value less than 0.001).

This observation of minimal to absent survivin expression in normal colonic epithelium and its significantly higher expression in adenomas and adenocarcinomas makes survivin a potentially exploitable target of anti-cancer therapy with maximal targeting of the tumor and minimal damage to the normal epithelium. Also the significant increase observed in survivin expression from normal mucosa to adenoma to adenocarcinoma suggests that survivin has an important role in colorectal tumorigenesis and malignant transformation of adenomas (the adenoma-carcinoma sequence).

This result of the present study correlates with that of Hiroshi Kawasaki et al who in their 2001 study of colorectal neoplasia which included 43 hyperplastic polyps, 171 adenomas with low grade dysplasia, 42 adenomas with high grade dysplasia and 60 carcinomas concluded that the immunoreactivity of Survivin significantly increased from hyperplastic polyps to adenomas with low grade dysplasia and adenomas with high grade dysplasia and carcinomas which showed that survivin played an important role in the malignant transformation of adenomas [12].

CONCLUSION

The aim of the present study was to examine the expression of Survivin,a novel member of the Inhibitor of apoptosis family of proteins, in colorectal neoplasia, its role in the transition sequence from normal to adenocarcinomaand its association with various clinico-pathological characters of adenocarcinomas.

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