Original Article

Expression of anti - Apoptotic survivin in odontogenic keratocyst, adenomatoid odontogenic tumor and ameloblastoma

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Abstract

Background: The process of odontogenesis is complex involving epithelial–mesenchymal interactions, along with the molecular signalling pathways triggering the initiating process. The triggering factors and cells precisely involved in the pathogenesis of odontogenic cysts and tumors are unknown. There is a vast array of biomarkers used to stain different sites, thereby helpful in diagnosing and evaluating the prognosis of these cysts and tumors. In the following study, Anti Apoptotic survivin expression patterns were assessed quantitatively in 48 samples (12 each) of Reduced Enamel Epithelium, Adenomatoid Odontogenic Tumor, Odontogenic Keratocyst and Ameloblastoma.

Aim: The Aim of this study is to assess the anti-apoptotic survivin expression in Reduced Enamel Epithelium, Adenomatoid odontogenic tumour, Odontogenic Keratocyst and Ameloblastoma.

Materials and Methods: The present study is carried out with 12 samples in each group. Routine hematoxylin and eosin staining was performed for confirmatory diagnosis. Later Immunohistochemistry was performed using survivin antibody. Survivin protein expression was analyzed using the parameters like location, intensity, percentage of cells positivity with survivin protein and extent of staining. With the help of Olympus BX 43 microscope, with ProgRes microscope camera, the 48 slides obtained were examined. The region of interest was selected in each slide and number of cells positively stained was counted. Data was analyzed using SPSS software version 23. Descriptive for scale data, results were analysed by using ANOVA with Chi-square test for intergroup comparison.

Results: The results showed significant P value <0.05. Expression of survivin was highest in Ameloblastoma, followed by Odontogenic keratocyst, Adenomatoid odontogenic tumor, and Reduced Enamel Epithelium.

Conclusion: Survivin was involved in the inhibition of apoptosis as well as the detailed understanding of the biological behaviour of odontogenic cysts and tumours, thereby increasing therapeutic approaches.

Keywords: Adenomatoid odontogenic tumor, anti-apoptotic survivin, immunohistochemistry, odontogenic keratocyst

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INTRODUCTION

Odontogenic cysts and tumours are epithelial-lined pathologic cavities surrounded by fibrous connective tissue that develop from odontogenic tissues in the maxilla and mandible tooth-bearing areas. They are caused by the proliferation of odontogenic epithelial rests and cystic degeneration.[1] Traditional histology is still the gold standard for diagnosing these diseases, while immunohistochemistry (IHC) and molecular methods are yet to gain traction.[2] The first signs of tooth development appear during the sixth week of pregnancy. At this stage, the oral epithelium thickens along the eventual dental arches. The primitive oral cavity or stomodeum is lined by oral ectoderm or primitive oral epithelium.[3] Each of these down-growths from the dental lamina is referred to as an enamel organ. There are several types of neural crest cells, each of which differentiates into its own component later on. They specifically form the mesenchymal section of the growing tooth.[4,5] Broca made the first attempt to identify odontogenic cysts (OCs) and odontogenic tumours (OTs) in 1868 and several works have been published since then.[6] Jens J. Pindborg and Ivor R.H. Kramer of the University of Copenhagen edited the first version of the "histological categorization of OTs, jaw cysts, and associated lesions" in 1971. In terms of prevalence and location, OCs and OTs are poorly understood.[5,7]

Keratocystic odontogenic tumours (KCOT) form from odontogenic epithelial cells and dental lamina remnants and oral epithelium basal cell expansions. Epithelial cells in KCOT appear to have a distinct proliferation potential compared to epithelial cells in other odontogenic diseases.[8] As per the majority of reports, Adenomatoid Odontogenic Tumor (AOT) frequently manifests as a slow-growing, painless mass affecting the anterior maxilla, with three clinical subtypes that all have the same histology: follicular type (73%), extra-follicular variant (24%), and peripheral (3%).[9]

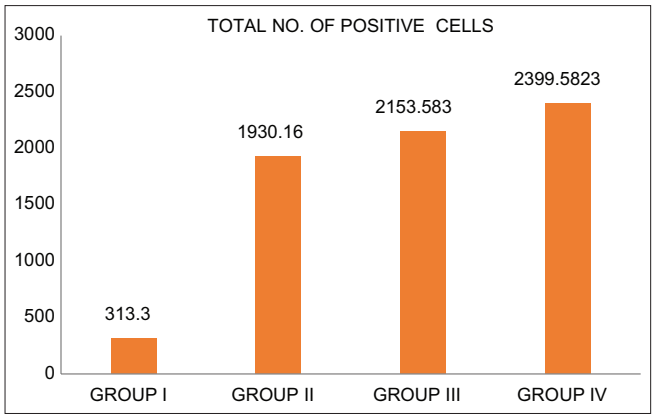
Ambrosini *et al*. discovered survivin in 1997 as an antiapoptotic protein involved in foetal development that is overexpressed in malignant tissues. This 16.5 kDa protein belongs to the inhibitor of apoptosis protein (IAP) family, which regulates the cell cycle and suppresses apoptosis.[9] It has antiapoptotic and promitotic functions and is involved in Bax inhibition.[10] Survivin is involved in the development and progression of several cancers. Survivin is encoded by the BIRC5 gene, which can be found on chromosome 17's long arm.[11] Several studies have shown that oncogenic mutations alter apoptosis, resulting in tumour development, progression, or metastasis. Survivin belongs to two protein families that regulate apoptosis in mammalian cells: bcl-2 and IAPs.[12] As a result, because survivin targets cancer cells while leaving normal cells alone, it is an appropriate target for cancer therapy.[13,14] Survivin is also thought to play a role in tumour cell resistance to radiation and chemotherapeutic treatments and high levels of expression are associated with a higher risk of tumour recurrence. The present study examines antiapoptotic survivin expression in Reduced Enamel Epithelium, Adenomatoid Odontogenic Tumor, Odontogenic Keratocyst, and Ameloblastomas using IHC.

MATERIALS AND METHODS

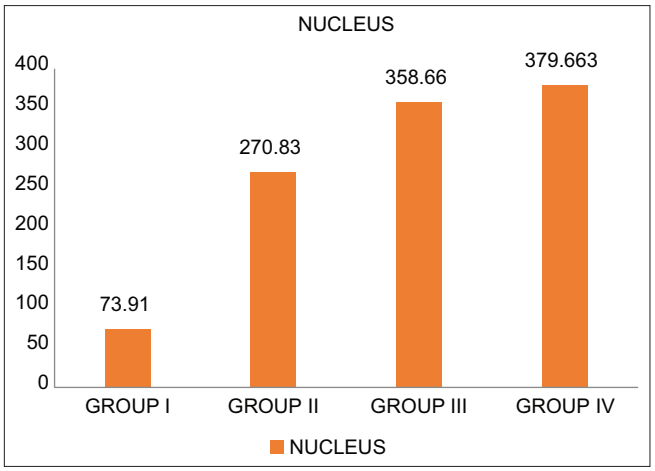
The present study was conducted using formalin-fixed, paraffin-embedded blocks of 12 cases of reduced enamel epithelium as the control group. Histopathologically diagnosed cases of 12 Adenomatoid Odontogenic tumours, 12 Odontogenic keratocysts, and 12 Ameloblastomas. They were taken from the archives of G. Pulla Reddy Dental College and Hospital, Department of Oral and Maxillofacial Pathology, Kurnool. (Approved by the ethical committee on 11/12/2019 at G. Pulla Reddy Dental College and Hospital, Kurnool, Andhra Pradesh).

METHODOLOGY

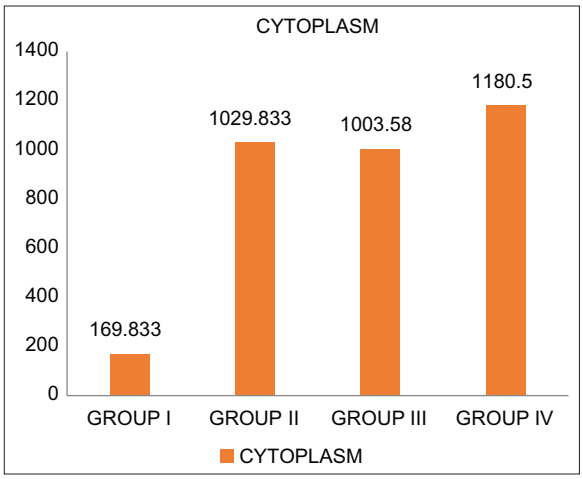
From the archival material, serial sections of 3 microns thick were cut and carefully fixed on the prepared slide (Poly-L-Lysine-coated microslides) using a rotary microtome. All the specimens were routinely processed with alcohol, xylene, and other chemicals before being embedded in paraffin. All the reagents used throughout the procedure are evenly distributed on the glass slides by covering the entire tissue section without any air bubble. Before the experiment, all reagents should be brought to room temperature procedure. The sections of group I, II, III, and IV were first stained with hematoxylin and eosin examination to reconfirm the diagnosis. Later, other sections of all the four groups were subjected for immunohistochemical analysis using survivin antibody. All the obtained 48 slides were examined under BX43 microscope by Olympus manufacturers, with ProgRes microscope camera ProgRes CapturePro microscope camera software from Jenoptic solutions software under urgery for impaction ×40. Five areas were randomly selected from each case and 200 cells in each area were analyzed to count the percentage of positive cells at 40x magnification. A total of 15 images were obtained. The total cell count per 100 cells was intended to measure in each image [Figure 1a-i]. Cell counting was carried out using software named QuPath Version 0.1.2. (developed by University of Edinburgh). The image properties were automatically detected by the software, as a HDAB stained slide. All the images were analyzed. The Region of Interest



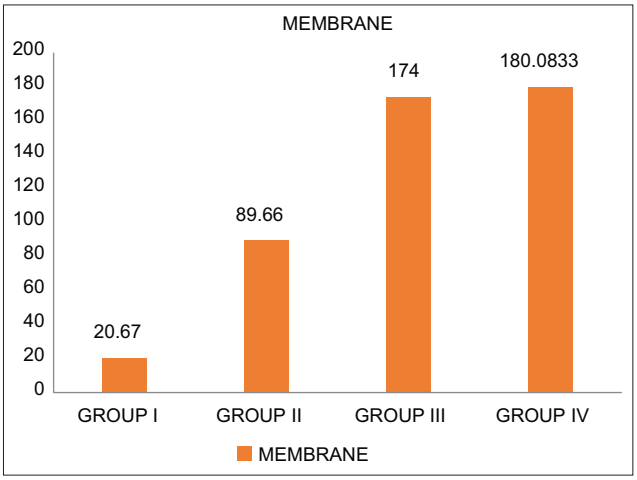
Graph 1: Bar chart showing percentage of cells positive for Survivin in groups, odontogenic keratocyst, adenomatoid odontogenic tumor and ameloblastoma



Graph 2: Bar chart showing percentage of nuclues for Survivin in groups, odontogenic keratocyst, adenomatoid odontogenic tumor and ameloblastoma



Graph 3: Bar chart showing percentage of cytoplasm for Survivin in groups, odontogenic keratocyst, adenomatoid odontogenic tumor and ameloblastoma



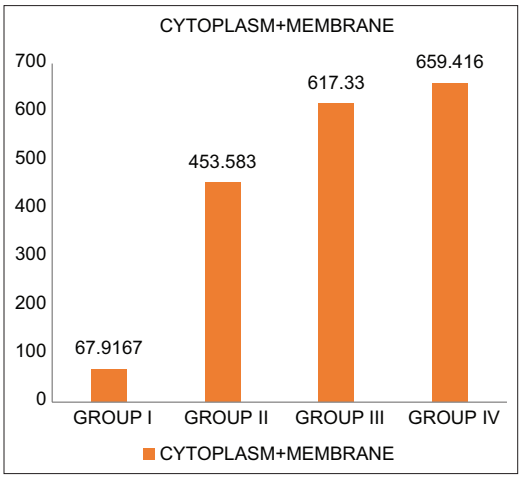
Graph 4: Bar chart showing percentage of membrane for Survivin in groups, odontogenic keratocyst, adenomatoid odontogenic tumor and ameloblastoma

(ROI) was selected in the image and the number of cells selected was taken as standard, that is, 100 cells. The number of cells stained positive and the number of cells stained negative were calculated.

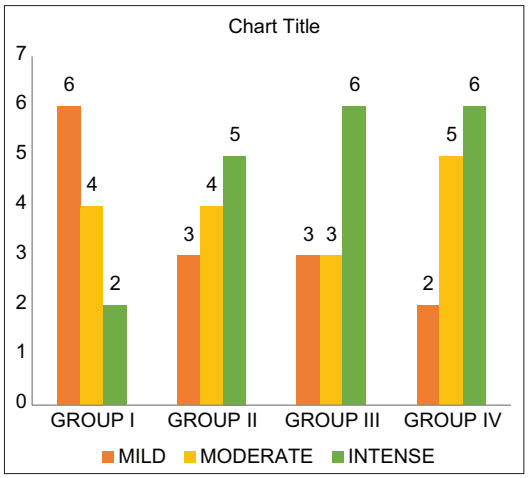
RESULTS

Data were analyzed using SPSS software version 23. Descriptive for scale data, one way analysis of variance is performed and *post hoc* Tukey's test is done for intergroup comparison. Routine hematoxylin and eosin staining was performed for confirmatory diagnosis. Later, IHC was performed using survivin antibody. Survivin protein expression was analyzed using the parameters like location, intensity, percentage of cells positivity with survivin protein, and extent of staining in Group I, Group II, Group III, and Group IV. The criteria used for intensity, location, and percentage of cells positivity with survivin expression are mentioned below. Criteria used for location are Nucleus, Cytoplasm, Membrane, and Cytoplasm + Membrane. Criteria taken for percentage of positive cells with survivin expression are the mean values. Criteria used for intensity are 0-none, 1-mild, 2-moderate, and 3-intense. In the present study, comparison of survivin expression with respect to location, intensity, and percentage of cells positively stained was assessed in REE, AOT, OKC, and Ameloblastoma.

The present study showed the percentage of cells positivity with survivin expression in all study groups. In Group I, mean of 313.3, in Group II mean of 1930.16, in Group III mean of 2153.583, and in Group IV mean of positive cells 2399.5823 as shown in Graph 1. Highest number of positive cells were seen in Group IV followed by III, II, and I. Survivin expression showed statistical significance in Ameloblastoma ($P = .00657$) as shown in Table 1.



Graph 5: Bar chart showing percentage of CYTOPLASM+MEMBRANE for Survivin in groups, odontogenic keratocyst, adenomatoid odontogenic tumor and ameloblastoma



Graph 6: Bar chart representing comparison of Survivin expression between in groups, odontogenic keratocyst, adenomatoid odontogenic tumor and ameloblastoma and Reduced Enamel Epithelium

Table 1: Demonstrates the total number of positive cells between various study groups

Total Number of Positive Cells	Mean	Standard Deviation	*t*	*P*
Group I (*n*=12)	313.3	210.5	5.945	0.3603
Group II (*n*=12)	1930.16	1263.6	0.934	0.3343
Group III (*n*=12)	2153.583	732.5	0.387	0.6069
Group IV (*n*=12)	2399.5823	846.5	0.581	0.00657

Table 2: Demonstrates the nuclear expression between various study groups

Sample	Mean	Standard Deviation	*t*	*P*
Group I (*n*=12)	73.91	58.30	4.422	0.9876
Group II (*n*=12)	270.83	182.07	1.250	0.2243
Group III (*n*=12)	358.66	152.87	0.25	0.8008
Group IV (*n*=12)	379.663	240.35	0.675	0.00219

Table 3: Demonstrates the cytoplasmic expression between various study groups

Sample	Mean	Standard Deviation	*t*	*P*
Group 1 (*n*=12)	169.833	150.30	6.22523	0.3873
Group II (*n*=12)	1029.833	840.95	0.5220	0.3664
Group III (*n*=12)	1003.58	434.89	-0.8820	0.6069
Group IV (*n*=12)	1180.50	541.94	0.5675	0.00213

Table 4: Demonstrates the membrane expression between various study groups

Sample	Mean	Standard Deviation	*t*	*P*
Group 1 (*n*=12)	20.67	20.98	7.225	0.7612
Group II (*n*=12)	89.66	65.32	1.96	0.9040
Group III (*n*=12)	174	93.32	0.12	0.0622
Group IV (*n*=12)	180.0833	2.98	1.987	0.000542

The present study showed the percentage of nuclear positivity with survivin expression in all study groups. In Group I 73.91, Group II 270.83, Group III 358.66, and Group IV 379.663 mean of positive cells as shown in Graph 2. Highest number of positive cells with nuclear expression were seen in Group IV followed by III, II, and I. Survivin showed statistical significance in Ameloblastoma ($P = 0.00219$) as shown in Table 2.

The present study showed the percentage of cytoplasmic positivity with survivin expression in all study groups. In Group I 169.833, in Group II 1029.833, in Group III 1003.58, and in Group IV 1180.50 mean of positive cells cells as shown in Graph 3. Highest number of positive cells with cytoplasmic expression were seen in Group IV followed by II, III, and I. Survivin showed statistical significance in Ameloblastoma ($P = .00213$) as shown in Table 3.

The percentage of membrane positivity with survivin expression in Group I 20.67, Group II 89.66, Group III 174, and Group IV 180.0833 mean of positive cells with membrane expression as shown in Graph 4. Highest number of positive cells were seen in Group IV followed by III, II, and I. Survivin showed statistical significance in Ameloblastoma ($P = .000542$) as shown in Table 4.

The percentage of cytoplasm+membrane positivity with survivin expression in Group I 67.9167, in Group II 453.583, in Group III 617.33, and in Group IV 659.416 mean of positive cells with cytoplasm+ membrane as shown in Graph 5. Highest number of positive cells with cytoplasm+membrane expression was seen in Group IV followed by III, II, and I. Survivin showed statistical significance in Ameloblastoma ($P = .00101$) as shown in Table 5.

Table 6 shows the intensity variation of survivin staining between various groups. In Group I, 0 (0%) cases showed no staining, mild staining was seen in 6 (50%), moderate staining was seen only in 4 (33%), and intense staining was

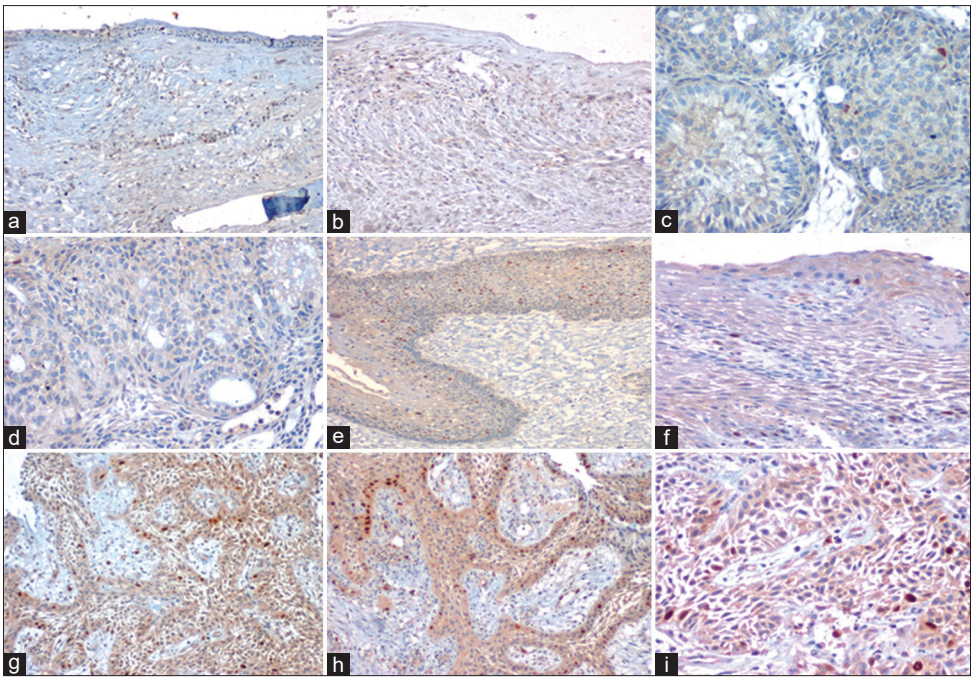


Figure 1: (a) Photomicrograph of Reduced Enamel Epithelium showing Mild Staining. (10X) (b) Photomicrograph of Reduced Enamel Epithelium showing Moderate Staining. (10X) (c) Photomicrograph of Adenomatoid Odontogenic tumor showing Intense Staining. (40X)(d) Photomicrograph of Adenomatoid Odontogenic tumor showing Moderate Staining. (40X) (e) Photomicrograph of Odontogenic Keratocyst showing Moderate Staining. (10X) (f) Photomicrograph of Odontogenic Keratocyst showing Intense Staining. (40X) (g) Photomicrograph of AMELOBLASTOMA showing Cytoplasmic, Nuclear, Cytoplasm + Membrane staining. (10X)(h) Photomicrograph of AMELOBLASTOMA showing Moderate staining. (10X) (i) Photomicrograph of AMELOBLASTOMA showing Intense staining. (40X)

Table 5: Demonstrates the cytoplasm+membrane expression between various study groups

Sample	Mean	Standard Deviation	*t*	*P*
Group 1 (*n*=12)	67.9167	68.80	3.786	0.8650
Group II (*n*=12)	453.583	396.01	1.06	0.8256
Group III (*n*=12)	617.33	536.72	0.43	0.2967
Group IV (*n*=12)	659.416	373.43	0.67	0.00101

Table 6: Demonstrates the intensity variation between various study groups

Grading	Group I (*n*=12)	Group II (*n*=12)	Group III (*n*=12)	Group IV (*n*=12)	*P*
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Mild	6 (50%)	3 (25%)	3 (25%)	2 (17%)	
Moderate	4 (33%)	4 (33%)	3 (25%)	5 (42%)	0.00005987
Intense	2 (17%)	5 (42%)	6 (50%)	6 (50%)	

Table 7: Demonstrates the statistical values for difference between REE, AOT, OKC & ameloblastoma

	Group I & IV	Group II & IV	Group III & IV
Chi-square test value	2.057	2.0112	2.034
P	0.3501576	0.394412	0.367865

seen in 2 (17%) cases. In Group II, 0 (0%) cases showed no staining, 3 (25%) showed mild staining, 4 (33%) showed moderate staining, and 6 (42%) showed intense staining. In Group III, 0 (0%) cases showed no staining, 3 (25%) showed mild staining, 3 (25%) showed moderate staining, and 6 (50%) showed intense staining. In Group IV, 0 (0%) showed no staining, 2 (17%) showed mild staining, 5 (42%) showed moderate staining, and 6 (50%) showed intense staining. Graph 6 shows comparison of statistical significance between the study groups as ($P = .00005987$).

Table 7 showed the statistical values for difference between REE, AOT, OKC and AMELOBLASTOMA.

DISCUSSION

Tumours and cysts that develop from tooth-forming tissues or their remnants and become entrapped within the jaw bones or adjacent soft tissues are known as odontogenic tumours and cysts. In the etiopathogenesis of these tumours, no definitive cause or stimulus has been identified.[15] Some of these events are designed to stimulate the release of certain substances within tumour cells, which help to maintain viability and survival.[16,17] This study was designed to investigate the immunohistochemical profile of three proteins involved in cell proliferation, cell response to proliferative stimuli, and apoptosis inhibition in the odontogenic epithelium of REE, AOT, OKC, and Ameloblastoma based on reports found in the literature. The epithelium associated with OCs and OTs comes from one of the sources listed below.[18]

(1) The reduced enamel epithelium of the crown of the teeth.

(2) Malassez epithelial rests, which are traces of the Hertwig's root sheath.
(3) Serres epithelial rests, which are traces of the dental lamina.
(4) The tooth germ, which includes the enamel organ, dental papilla, and dental sac.[19]

As per current literature, the following are potential sources for the development of an odontogenic tumour: prefunctional dental lamina, postfunctional dental lamina, basal cell layer of the gingival epithelium, dental papilla, dental follicle, and periodontal ligament.[20] Several genetic and molecular changes appear to favour tumour development and progression. Apoptosis control and cell cycle regulation are thought to be inextricably linked processes.[17] Although the exact etiology and pathogenesis of odontogenic tumours are unknown, recent studies have revealed several molecular alterations in the formation of odontogenic tumours. In health and disease, IHC is an important application for determining the distribution of monoclonal and polyclonal antibodies in the tissue of interest.

Apoptosis, or the genetically determined removal of cells, is now recognized as a distinct and important method of "planned" cell death. The IAPs is a group of proteins that regulate apoptosis and play an important role in antitumor immunity by regulating T cell responses. Several researchers have looked for survivin in various types of neoplastic and preneoplastic lesions throughout the body. As a result, survivin is an excellent cancer therapy target because it specifically targets cancer cells while leaving healthy cells alone. Survivin is also thought to be involved in tumour cells, radiation resistance, and chemotherapeutic resistance. Survivin may also have a role in cancer cells, radiation resistance, and chemotherapeutic treatment resistance. Overexpression of survivin has been linked to aggressive behaviour in OCs and OTs.[21] A comparison of the staining intensities of different panel markers between OCs and OTs confirms and supports the fact that these two lesions differ significantly in terms of clinical characteristics and biological behaviour. As a result, the IHC analysis used in this study may be useful in distinguishing between OCs and OTs.

In the present study, 48 selected cases, in which Group I (REE), Group II (AOT), Group III (OKC), and Group IV (Ameloblastoma) each of 12 cases. IHC was performed using the survivin antibody. In AOT, 0 (0%) cases showed no staining, mild staining was seen in 3 (25%), moderate staining was seen in 4 (33%), and intense staining was seen in 5 (42%) cases. Nuclear, cytoplasmic, and membrane expression of survivin seen in our study. Our study results showed intense staining and the high percentage of cells positivity with survivin expression in group IV followed by group III, II, and I and showed statistical significance between the groups ($P = .00005987$). The findings of our study were correlated with those of S.M. ElSheikh *et al*.[9] who used an immunohistochemical technique to examine the expression of survivin in AOT specimens and tooth germ specimens as a control. The reaction was mostly found in duct-like structures and whorled pattern spindle cells. Furthermore, two ameloblastoma patterns were discovered: an antiapoptotic proliferating area in the outer layer (periphery) that morphologically resembles preameloblasts or ameloblast like–cell, and a proapoptotic differentiating region in the inner layer (center). This explains the AOT cases' positive response to survivin. In cell proliferation and differentiation, survivin expression is linked to AOT. Similarly, Rogelio Gonzalez-Gonzalez *et al*.[22] investigated survivin expression in relation to Bcl-2, Bax, and Ki-67 expression in ameloblastomas and the results revealed that survivin expression, in addition to Bcl-2 and Bax expression, is related to the behaviour of ameloblastomas. Hiroyuki Kumamoto *et al*. investigated the role of survivin and X chromosome–linked IAP (XIAP) expressions in ameloblastomas, survivin reactivity was found in many peripheral columnar or cuboidal cells and some central polyhedral cells, in ameloblastomas suggesting that are related to the aggressive behaviour.[23] M Andric *et al*.[24] investigated survivin expression in odontogenic keratocysts and periapical cysts. Survivin was discovered in the lining of parakeratinized squamous epithelial Odontogenic Keratocyst (OKC) walls. The base layer cells had the most intense immunostaining. Survivin may play a role in OKC's violent behaviour, as per the researchers. I Brajic *et al*.[23] investigated the expression of survivin, cyclin D1, and p21hras in KCOT before and after decompression and pericoronal follicles. Survivin was found to have nuclear expression in the epithelial cells of the KCOT's basal, suprabasal, and lower superficial layers. Survivin expression was found in the cytoplasm of epithelial cells in pericoronal follicles. Zulfin Shaikh *et al*.[17] conducted a study to evaluate the expression of p53 and survivin, which are involved in cell cycle progression and apoptosis inhibition, in Ameloblastoma and AOT, in which survivin expression was predominantly cytoplasmic in both peripheral and central stellate reticulum-like cells, with only focal nuclear expression in peripheral ameloblast-like cells. In the case of AOT, p53 and survivin expression was primarily cytoplasmic, with only a few cells displaying nuclear staining. Survivin's predominant cytoplasmic staining suggests that it functions as an antiapoptotic

rather than a cell division regulator in these tumours. L Lo Muzio *et al*.[25] conducted a study to look into the potential expression and impact of survivin in primary oral SCC specimens and healthy oral mucosa specimens. Normal oral mucosa samples revealed positivity was found only in the basal and parabasal layers and was regarded as negative for expression of survivin. These findings reiterate the importance of deregulation of apoptosis as a critical pathogenetic component of tumour progression and identify survivin as a potential novel molecular marker of aggressive neoplasia. Ayhan Ozcan, *et al*.[26] investigated the expressions of survivin, E-cadherin, CD138, and CD38 and their possible diagnostic uses in cystic ameloblastomas, radicular cysts, DCs, KCOTs. In all cases, CAs and KCOTs had diffuse 3 and strong nuclear survivin expression, cytoplasmic staining in epithelial and stromal cells. The staining was highest in the basal cell layer in these situations, demonstrating a role in the aggressiveness and etiology of malignant tumours back up these findings. Agnieszka Bargenda *et al*.[27] conducted a study in chronic kidney disease in children and found increased amounts of survivin in patient urine samples that did not match its serum level, implying that this molecule is expressed in renal tissue as a protective factor against progressive damage and recommending survivin as a diagnostic marker in CKD follow-up. Olga Kanicka et al. examined the expression of survivin, Ki67, and Bcl 2 in sinonasal inverted papillomas, sinonasal squamous cell carcinoma, and nasal chronic sinusitis as a control in their study. Survivin immunostaining was observed in 14 of 20 (70%) sinonasal Inverted Papillomas (IPs) and 10 of 12 (83.4%) Sinonasal Squamous Cell Carcinomas (SNCs). Their findings could point to a link between survivin, Ki67, and Bcl 2, which could play a role in sinonasal carcinogenesis.[28]

CONCLUSION

From our study, it is concluded that high percentage of cells stained positively with survivin expression and intense staining was seen in Ameloblastoma, followed by Odontogenic keratocyst, Adenomatoid odontogenic tumor, and reduced enamel epithelium. Absence of staining was not seen in all the groups. This comparison showed statistical significance between the groups ($P = .00005987$). In our study, no observations on extent criteria were made. Survivin's predominant cytoplasmic staining suggests that it functions as an antiapoptotic in OCs and OTs rather than in cell division. The higher the survivin expression, the worse the prognosis, and the lower the survivin expression, the better the prognosis. Survivin expression may play a role in odontogenic epithelial oncogenesis because it contributes to biological properties such as cell survival, proliferation, differentiation, and tissue structuring and cellular regulation during tooth development. As a result of the above findings, survivin was involved in the inhibition of apoptosis and the detailed understanding of the biological behaviour of odontogenic cysts and tumours, thereby increasing therapeutic approaches.

"Further studies have to be conducted using large sample size and molecular diagnostic tools and methods to elicit genetic profile for better understanding of the mechanisms involved in tumorigenesis and behaviour of these OCs and OTs".

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Conflicts of interest
There are no conflicts of interest.

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