Original Article

Expression of BAX and Bcl-2 Gene in Prostate Carcinoma and its Correlation with Gleason Score

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Abstract

Introduction: Prostate cancer is primarily a disease that occurs in the elderly age group amongst men above 65 years of age. The relationship between the Bcl-2 and Bax genes and the Gleason staging of prostate cancer has not been studied in depth, and there is a dearth of published Indian research on the subject. Hence, this study aims to comprehend how the apoptotic mechanism relates to prostate cancer. The aim of the study was to determine the proportion (expression) of Bcl-2 and BAX genes in prostate carcinoma (PCa) and to observe the correlation of Bcl-2 and BAX gene association with Gleason scoring in PCa. **Materials and Methods:** Transurethral resected prostatic Chips positive for PCa and paraffin blocks were evaluated for the study. H-score system was used based on the cytoplasmic staining into negative mild, moderate and strong cytoplasmic staining. **Results:** Fifty cases were analysed. There was a notable relationship between Gleason grade and tumour size, and levels of prostate-specific antigen (PSA) were in an increasing manner with Gleason's grade except at Grade 3, with the majority of cases falling into Gleason grade 5 (42%) and PSA levels falling into the range of 90–99 (28%), tumour size falling into the range of 3.1–6 cm (44%), T4 stage (34%) and metastasis (80%). **Conclusion:** This study concluded that PSA levels in cases of prostate cancer patients were showing an increasing trend with Gleason grade. This demonstrated a striking correlation between Gleason grade and H score BCL2, but not one that was particularly significant for the BAX gene.

Keywords: Carcinoma, gene, Gleason's score, mutation, prostate cancer

Introduction

Prostate carcinoma (PCa) has a diverse clinical behaviour from indolent tumours to aggressive lethal cancer. PCa is the second leading cause of cancer and the sixth cause of death amongst men worldwide.[1] Clinical prognostic factors which predict recurrence after treatment, include clinical stage, grade and pre-treatment serum levels of prostate-specific antigen (PSA). In 2020, there were 1.4 lacs new instances of prostate cancer identified worldwide, with an age-standardised rate (ASR) incidence of 31/1 lacs. Asia's South-central had the lowest ASR, whereas Northern Europe had the highest all-age incidence ASR (83).[2] Men over 65 years of age are more likely to develop prostate cancer than younger men. Since prostatic carcinoma is not amongst the most commonly reported diseases in India and there are not as many population-based cancer registries (PBCRs) amongst Indians, it is difficult to estimate the true frequency of the disease.[3] Karnataka's annual percentage change is 3.4%, according to a study that took into account PBCR between 2009 and 2011 in several Indian metropolises. Prostate cancer rose to the sixth spot in men's incidence rates amongst cancers in India in 2016 with a significant increase in the age-standardised incidence rate of 29.8% from 1990 to 2016 (4.8/100,000). PBCRs show a steady and rapid increase, disproving the notion that the incidence of prostate cancer is lower in India than in the West.[4] Prostate cancer has a variety of clinical behaviours, from slow-growing tumours to aggressive, fatal malignancies. Clinical prognostic factors that predict recurrence after therapy include clinical stage, grade and PSA blood levels before treatment (PSA).[5-8] Almost all tissues contain a mechanism for eliminating damaged cells through

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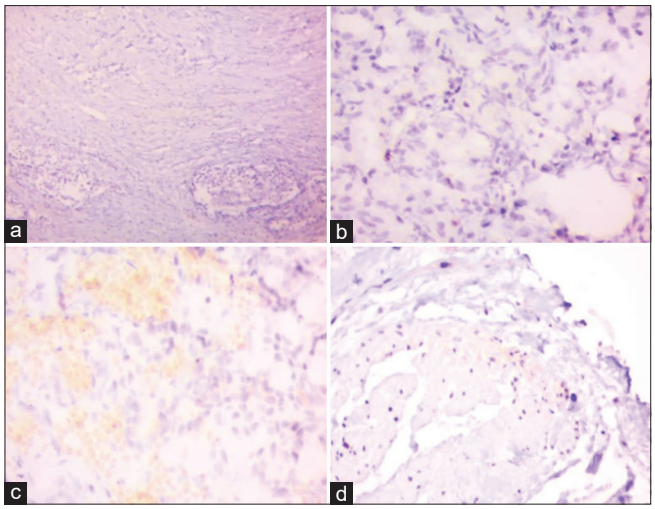

Figure 1: (a) Immunohistochemistry (IHC) staining –Bcl-2 (score 0- negative), (b) IHC staining –BAX (score 0- negative), (c) IHC staining –Bcl-2 (score 1- faint staining), (d) IHC staining –BAX (score 1- faint staining).

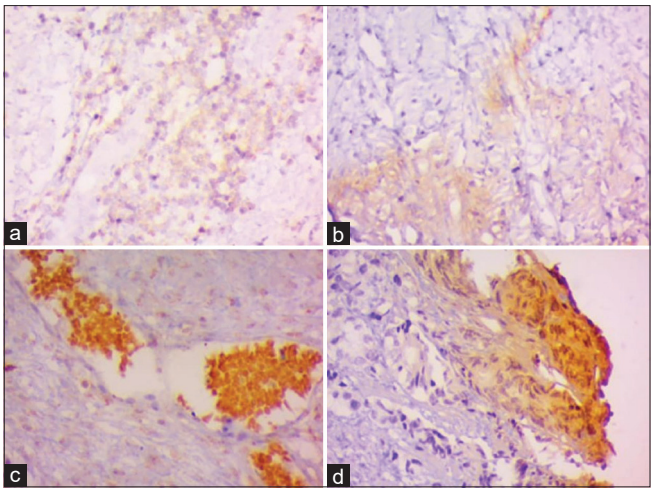

Figure 2: (a) Immunohistochemistry (IHC) staining –Bcl-2 (score 2- moderate staining), (b) IHC staining –BAX (score 2- moderate staining), (c) IHC staining –Bcl-2 (score 3- Strong staining), (d) IHC staining –BAX (score 3- strong staining).

a process known as apoptosis. Disruption of programmed cell death can lead to the accumulation of cells with defective genomes and, eventually, cancer.[9] Two examples of the genes that regulate apoptosis include the BCL2 gene family and the tumour suppressor gene p53. The Bcl-2 family of proteins includes both anti-apoptotic (such as Bcl-2 and Bcl-xL) and pro-apoptotic (such as BAX, BAK and BIM) proteins.[10] The Gleason grading system evaluated the prognosis of men with prostate cancer using tissue samples from a prostate biopsy. Prostate cancer accounts for 2.58% of all cancer incidences, according to a study done in Kolar.[11,12]

In the instance of prostate cancer, a Gleason score can be determined based on how the condition appears under a microscope.[13] This study aims to quantify the proportion (expression) of the Bcl-2 and BAX genes in prostate cancer and investigate the relationship between the Bcl-2 and BAX genes and prostate cancer Gleason scores.

Materials and Methods

The present study is an observational retrospective cross-sectional study done in the Department of Pathology conducted from September 2020 to October 2022. All transurethral resected prostatic chips positive for carcinoma prostate were confirmed by histopathological examination added in the study. Ethical clearance was obtained from the Institutional review board for the present study. Data regarding the demographic and clinical details, such as the study subject's age and stage of the disease, were collected from the medical record department of the institution. H and E slides were used for reviewing the histopathological types and the Gleason score of the tumour. Radiologic findings such as ultrasonography, magnetic resonance imaging (MRI) or computed tomography (CT) findings with respect to the stage of disease and size of the tumour were also evaluated. The study subjects with prostate all types of adenocarcinoma which were positive on biopsy were included in the study, whereas the study subjects who were diagnosed with metastatic adenocarcinoma of the prostate and subjects who had undergone radiation therapy and chemotherapy and subjects with recurrent lesions of the prostate were excluded from the study.

The immunostaining method for evaluating BAX and Bc1-2 was evaluated using multiple 4-micrometer thick sections of fixed formalin; paraffin-embedded tissues were then cut for immunohistochemical studies. A polymer-based (EnVision™) immunohistochemical method detects BAX and Bcl-2 genes. Reactive lymph node with follicular hyperplasia is used as a positive control, whereas immunostaining without adding antibodies is used as a negative control. Immunostained sections are examined under ×40 objective and ×10 eyepiece under a light microscope. BAX and Bcl-2 staining is evaluated as cytoplasmic. The protein expression was scored as mild, which states faint cytoplasmic stain, moderate, which states diffuse cytoplasmic stain and strong-which state diffuse intense cytoplasmic stain. When reporting, the percentage of malignant cells with positive staining is taken into account. H-score, which considers both intensity and the proportion of cells stained in each intensity, is used to quantify immunostaining [Figures 1 and 2].

H-score was calculated as follows:

(Percentage of cells stained at intensity 1 × 1) + (% of cells stained at intensity 2 × 2) + (% of cells stained at intensity 3 × 3). H-score between 0 and 300, in which 300 equals 100% of tumour cells stained strongly. H-score above 50 was considered to be positive for BAX and Bcl-2 expression. Two pathologists independently completed all the scoring; neither had access to any clinical information. Both pathologists made every decision based on the consensus. A third pathologist was consulted in case of any differences for a final

determination agreeable to all parties. The sample size for the present study was estimated using the proportion of BAX expression (P = 97.3) in prostate cancers, considering alpha error is 5%, and by substituting the values using the formula: $Z_{1-\alpha}{}^2$ p (1 − p)/d^2.

Where $Z_{1-\alpha}$ = Standard normal variant.

P = Expected proportion in population based on previous studies (97.3).

d = Absolute error of 5% (5).

Using the above values at 95% confidence level and the final estimated sample size is of 50, subjects with prostate cancer will be included in the study.

Statistical analysis

Descriptive statistics were prepared using SPSS 21.0 (Statistical Package for social sciences), Chicago, Illinois, USA (United states of America). Data were analysed using the Chi-square test and Yates correction. All statistical tests were performed at a 95% confidence interval. $P < 0.05$ was considered statistically significant. Pearson's correlation was done between the Gleason score with BAX/Bcl-2.

Results

The present study was conducted amongst 50 subjects who had adenocarcinoma of the prostate gland the median age of study subjects is 68 years old, and it is seen in the majority of older person's cancer. Table 1 shows the mean value of PSA in relation to Gleason grade. In the present study, 1 patient falls into Gleason Grade 1, whereas 10 of them fall into Grade 2, 7 of them into Grade 3, 8 of them fall into Grade 4 and 24 of them fall into Gleason Grade 5 (42%), The result shows that the mean value of PSA was in increasing manner with Gleason's grade except at 3rd Grade, and it was found to be statistically significant with a P = 0.001.

In the present study, the mean values of PSA were increasing with H-score Bcl-2 except for 3rd grade, which was not found to be statistically significant [Table 2]. In the present study, the mean value of H-score BAX was also increasing with the Gleason grade except for the 3rd grade, and it was also not found to be statistically significant [Table 3]. The present study found a moderate-positive correlation between Gleason grade and H-score and Bcl-2, which was found to be statistically significant (0.002). It was also found that there was a mild-positive correlation was found between Gleason grade and H-score and BAX, and it was also found to be statistically significant (0.016) [Table 4]. On evaluating the tumour size using MRI/CT scans, it was found to be there was a mild-positive correlation between tumour size and H-score of Bcl-2, and it was not found to be statistically significant, and there was no positive correlation between tumour size and H-score of BAX [Table 5].

Discussion

Clinical manifestations of prostate cancer can range from

Table 1: Gleason grade versus prostate-specific antigen levels

		PSA levels						
Gleason grade	*n*	Mean	SD	SE	95% CI for mean		*F*	*P*
					Lower bound	Upper bound		
One	1	7.000					6	0.001
Two	10	36.460	41.6897	13.1834	6.637	66.283		
Three	7	29.000	12.8841	4.8697	17.084	40.916		
Four	8	71.250	28.6942	10.1449	47.261	95.239		
Five	24	68.250	19.3351	3.9468	60.085	76.415		
Total	50	55.652	31.2261	4.4160	46.778	64.526		

F value is calculated utilizing Analysis of variance[ANOVA]. *n*: Number of patients, PSA: Prostate-specific antigen, SD: Standard deviation, SE: Standard error, CI: Confidence interval

Table 2: Gleason grade versus H score Bcl-2

		H-score Bcl-2						
Gleason grade	*n*	Mean	SD	SE	95% CI for mean		*F*	*P*
					Lower bound	Upper bound		
One	1	170.00					4	0.009
Two	10	170.00	36.818	11.643	143.66	196.34		
Three	7	152.14	31.867	12.044	122.67	181.61		
Four	8	176.25	39.619	14.007	143.13	209.37		
Five	24	201.67	30.024	6.129	188.99	214.34		
Total	50	183.70	37.044	5.239	173.17	194.23		

F value is calculated utilizing Analysis of variance[ANOVA]. *n*: Number of patients, SD: Standard deviation, SE: Standard error, CI: Confidence interval

Table 3: Gleason grade versus H-score BAX

	H-score BAX						
Gleason grade	*n*	Mean	SD	SE	95% CI for mean		*F*	*P*
					Lower bound	Upper bound		
One	1	75.00					2	0.160
Two	10	94.00	22.211	7.024	78.11	109.89		
Three	7	91.43	6.268	2.369	85.63	97.23		
Four	8	100.63	20.777	7.346	83.25	118.00		
Five	24	110.63	28.258	5.768	98.69	122.56		
Total	50	102.30	24.748	3.500	95.27	109.33		

F value is calculated utilizing Analysis of variance[ANOVA]. *n*: Number of patients, SD: Standard deviation, SE: Standard error, CI: Confidence interval

Table 4: Gleason grade versus H-score Bcl-2 and H-score BAX (correlation)

Correlation		
	Gleason grade	H-score BCL2
Gleason grade		
Pearson correlation	1	0.419**
Significance (two-tailed)		0.002
n	50	50
H-score BCL2		
Pearson correlation	0.419**	1
Significance (two-tailed)	0.002	
n	50	50

Correlations		
	Gleason grade	H-score BAX
Gleason grade		
Pearson correlation	1	0.340*
Significance (two-tailed)		0.016
n	50	50
H-score BAX		
Pearson correlation	0.340*	1
Significance (two-tailed)	0.016	
n	50	50

*Perason correlation is significant at 0.01 level, Correlation is significant at 0.01 level (two tailed test)

slow-growing tumours to deadly, aggressive diseases. Clinical prognostic factors that indicate recurrence after therapy include clinical stage, grade and PSA blood levels. Numerous studies show that the altered function of apoptosis in the development of cancer and the expression of specific apoptotic genes in tumours with high Gleason scores are related.[14-16] There is not much material available because most research on these relationships has been conducted outside India. Therefore, the current research aims to ascertain whether the expression of the genes BAX and Bcl-2 in prostate cancer correlates with Gleason ratings. Males under the age of 55 do, however, account for 10% of new diagnoses in the USA.[17] The likelihood of developing prostate cancer rises with age.

In the current research, most participants are between the ages of 61 and 70 (46%), and 71 and 80 (34%). This may be a result of the identification of early-onset prostate cancer, a condition that is becoming more widely known but underappreciated, as well as the contemporary screening techniques that are more widely used.[18] According to the available research, males under the age of 40 have experienced 30 documented cases of prostate cancer, with an incidence of 0.8%–1.1%.[18-20] In the current research, urinary retention was the most frequent symptom, followed by burning urination, hesitancy and dribbling. However, the early symptoms of bladder cancer can be irritable voiding symptoms (frequency, urgency and dysuria), bladder cancer patients usually present with painless haematuria (grossly apparent or microscopic). In the current research, metastasis affected most of the study population (80%). *T* indicates that despite the availability of reliable tests for early identification and efficient treatments for tumours so discovered, the diagnosis is usually delayed until the tumour has locally advanced or spread to other parts of the body. Because many malignancies would be latent and pose little threat to the host's life or health, doctors are reluctant to use these tests out of concern that treatment would result in unwarranted morbidity. According to a recent study from Keck Medicine of USC, men 45 and older are now more prone than they were 5 years ago to have metastatic prostate cancer. This result is consistent with warnings against routine yearly prostate cancer screenings.[21] Most of the study population in the current investigation had an H-score BAX of 50–100 (66%) and 100–150 (30%). Most of the study population in the current investigation had an H-score Bcl-2 of 151–200 (50%) and 201–250 (28%), respectively.

Gleason's grade versus prostate-specific antigen

With the exception of the third grade in the current study, men's PSA values increased in a gradational fashion, and the ANOVA test determined that this relationship was significant. The correlation between Gleason Grade and PSA levels was found to be exceptional and significant ($r = 0.54$). This suggests that PSA levels may rise until Grade 2, remain stable at Grade 3 (PSA levels of 29–37), and rise again in grades 4 and 5, with PSA levels varying from 68 to 72. Higher PSA levels indicate a worse prognosis for prostate cancer due to the moderate overall rise in PSA levels and rising Gleason's grade.

H-score BCL2 versus prostate-specific antigen

Anvari *et al.,* research[22] which demonstrated a strong correlation between Gleason Grade and H-score Bcl-2,

Table 5: Magnetic resonance imaging/computed tomography tumour size versus prostate-specific antigen levels and H-score BCL2

Correlation		
	MRI/CT tumour size	H-score BCL2
MRI/CT tumour size		
Pearson correlation	1	0.261
Significance (two-tailed)		0.068
n	50	50
H-score Bcl-2		
Pearson correlation	0.261	1
Significance (two-tailed)	0.068	
n	50	50
Correlation		
	MRI/CT tumour size	H score BAX
MRI/CT tumour size		
Pearson correlation	1	0.175
Significance (two-tailed)		0.225
n	50	50
H-score BAX		
Pearson correlation	0.175	1
Significance (two-tailed)	0.225	
n	50	50

Correlation is significant at 0.01 level(two tailed test),
MRI/CT: Magnetic resonance imaging/computed tomography

supports the findings of the current study that men's PSA values increased in a manner with H-score Bcl-2 except at the third grade, where it was not found to be significant.

Gleason grade versus tumour size

The correlation between Gleason Grade and tumour growth was astounding (r = 0.4). Gleason grade and tumour volume are correlated (r = 0.4). Friedersdorff *et al.*[23] compared to their research's analysis of the Prostate Health Index, which was not examined in our study, the Gleason score does not significantly correlate with tumour volume.

Gleason grade versus H-score Bcl-2

The correlation between Gleason Grade and H-score Bcl-2 was exceptional and significant (r = 0.42). According to Amirghofran *et al*.,[15] a strong correlation with the cell survival markers Ki-67 and Bcl-2 indicates that it contributes to tumour cell growth, consistent with the current study. In the 40 cancer cases that Alshahmi *et al.*[24] studied, Bcl-2 protein immunostaining was positive in 22/40 (55%) of the cases. According to their research, Bcl-2 immunostaining is more common in tumour samples and is linked to higher advanced Gleason scores, demonstrating that a rise in the ratio of this anti-apoptotic protein frequently occurs during prostate cancer growth which is supporting the present study. On the other hand, the research by Khor *et al*.[25] contradicts the present study's findings, which found no notable association between aberrant Bcl-2 expression and grading. Krajewska *et al*.[26] research, which supports our study, found that the anti-apoptotic protein Bcl-2 was expressed by 16 of 64 (25%) adenocarcinoma. This protein tends to be more prevalent in high-grade tumours (Gleason grade 8–10; 41%) and nodal metastases (38%) than in lower-grade (Gleason 2–7) tumours. A high association was found between Gleason Grade and H-score Bcl-2 by Anvari *et al*.[22]

Gleason grade versus H-score BAX

With the exception of the third grade, men's H score BAX values increased in the current research as the Gleason grade increased, but the ANOVA test did not find this to be statistically significant. Pearson's correlation revealed a weakly noteworthy link (r = 0.34) between the Gleason Grade and H-score BAX. An aberrant BAX expression and higher Gleason score were shown to have a marginally significant connection (P = 0.08) in a study by Khor *et al*.,[24] which supports the present study. Anvari *et al*.[22] showed no correlation between Gleason Grade and H-score BAX. BAX expression was highest in foci with peri neural invasion and was substantially higher in Gleason Grade 3 and 5 cancer than Gleason Grade 2 carcinoma in a Finland-based study by Tolonen *et al*.[27]

Gleason grade versus prostate-specific antigen

There was a remarkable relationship between Gleason Grade and PSA levels, and it was found to be significant (r = 0.54). A Japan-based study by Yoshino *et al*.[28] showed an indirect predictor of carcinoma prostate.

Tumour size versus prostate-specific antigen

There was a remarkable relationship between PSA levels and tumour size, which was found to be significant (r = 0.54). Wajsman Z.[29] which is almost similar to the present study.

Tumour size and H-score BCL2 and BAX

There was a mild remarkable relationship between tumour size and H-score and Bcl-2 and there was no significance found.

Limitations

This study's sample size (n = 50) is too small to draw conclusive conclusions. The study was conducted on a unicentric basis, so findings may differ if the study were conducted in a multicentric setting. Most cases had little evidence from follow-up because the patients did not show up for the additional treatment.

Conclusion

According to the study's findings, PSA levels in patients with prostate cancer showed an increasing tendency with Gleason grade and were significant on an ANOVA test. In addition, it revealed a strong link between Gleason grade and Bcl-2 H-score, but not one as strong for the BAX gene. Higher PSA levels show the severity and prognosis of prostate cancer as there is a moderate rise in PSA levels with increasing Gleason grade. Prostate cancers are more likely to express Bcl-2, which is more prevalent in tumour tissues and associated with a more excellent Gleason grade of the most advanced stage.

As far as we know, no Indian research has shown a connection between the BAX and Bcl-2 genes and the Gleason grade

in prostate cancer cases. This study is a pioneering effort to comprehend the pathogenesis of BAX and Bcl-2 in the development of PCa and its significance with increasing tumour grade and PSA levels with increasing tumour grade; as a result, it will be of the utmost use to clinicians in the future for targeted immunotherapy in long-term patient prognosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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