

# The Correlation of E-cadherin Expression with the Modified Gleason Score and the Grade Group of Prostatic Adenocarcinoma

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## Abstract

**Background:** E-cadherin is a cell adhesion molecule, its downregulation is associated with poorly differentiated tumors in many organs, and its loss is associated with adverse behavior of many tumors. **Objectives:** This study aims to find a correlation between E-cadherin status, the Grade Group, and the modified Gleason score in core biopsies obtained from prostatic carcinoma. **Materials and Methods:** This study is a retrospective and prospective cross-sectional study that was conducted on (50) paraffin blocks obtained from core biopsies of prostatic carcinoma. E-cadherin status was correlated with the Grade Group and the modified Gleason score. The E-cadherin staining pattern was also examined for its correlation with perineural invasion. Chi-square was used to determine the correlation between E-cadherin staining pattern on the one hand and the modified Gleason score, Grade Group, and perineural invasion on the other hand and  $P < 0.5\%$  was considered as significant. **Results:** Only six patients (12%) fall in Grade Group 1 and according to the modified Gleason score, most patients had high scores. Regarding E-cadherin expression, 24 cases (48%) had aberrant E-cadherin expression, while the rest 26 cases (52%) had a complete strong membranous expression. Statistically, there was a significant correlation between aberrant E-cadherin expression and increasing grade according to the modified Gleason score and Grade Group with  $P$  values of 0.032% and 0.022%, respectively. In 24 patients (48%), perineural invasion was detected half of them had aberrant E-cadherin expression which was statistically not significant when both the parameters (perineural invasion and aberrant E-cadherin expression) are tested against the modified Gleason score and the Grade Group ( $P = 0.71\%$ ). **Conclusion:** Aberrant E-cadherin expression is associated with increasing modified Gleason score and Grade Group but has no significant correlation with perineural invasion.

**Keywords:** E-cadherin, Grade Group, modified Gleason score, prostate

## INTRODUCTION

Epithelial mesenchymal transition (EMT) is the process by which epithelial cells gain more mesenchymal features, promoting tumor invasion and metastasis. EMT is also associated with chemoresistance in many cancers. The triggering event in EMT includes changes in intercellular adhesion molecules, and downregulation of epithelial markers among which E-cadherin is a key factor.<sup>[1,2]</sup>

E-cadherin is a membrane glycoprotein that functions to maintain epithelial cell–cell adhesion through  $\text{Ca}^{2+}$  binding site. Loss of E-cadherin leads to disaggregation of tumor cells from one another promoting invasiveness and metastasis.<sup>[3,4]</sup>

Prostate cancer is the most common cancer in men and the second most common cause of cancer-related deaths only after

lung cancer.<sup>[5]</sup> The incidence of prostate cancer increases with advanced age, in addition to the role of environmental and genetic factors. Screening with prostate-specific antigen (PSA) has also played some role in early diagnosis and treatment of prostate cancer, as it leads to diagnoses of clinically silent disease.<sup>[6,7]</sup>

Prostate cancer has been associated with variable outcomes. Many clinicopathological factors have been used to predict the

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outcome, including PSA level, Gleason scoring, tumor stage, and presence of lymph node involvement.<sup>[8]</sup>

Gleason grading system is a prognostic indicator that was introduced in the 1960s and modified in 2005, it depends on histological patterns for grading prostate cancer.<sup>[9,10]</sup>

Based on a pattern of glands, a Gleason score of 1–5 is given, the summation of the primary and the secondary patterns will give the Gleason grade. In 2014, the International Society of Urological Pathology introduced the Grade Grouping system, in which modified Gleason score 6 and below will be Grade Group I, 3 + 4 = 7 as Group II, 4 + 3 = 7 as Group III, 4 + 4 = 8 Group IV, and modified Gleason score 9 and 10 as Grade Group V.<sup>[11]</sup>

Downregulation of E-cadherin expression is found in poorly differentiated tumors of many organs.<sup>[12]</sup> The evidences of correlation between E-cadherin expression and various clinicopathological parameters of prostatic carcinoma are controversial. Some authors found no correlation between E-cadherin expression and age, serum PSA, tumor cell differentiation, and death from prostatic carcinoma,<sup>[13]</sup> while others found a negative impact of E-cadherin loss on the outcome with increased mortality from this tumor.<sup>[14]</sup>

The aim of this study is to find the correlation between E-cadherin expression and the pathological parameters gained from prostatic biopsies obtained for adenocarcinoma.

## MATERIALS AND METHODS

### Study design

This study is a retrospective and prospective cross sectional study that was conducted on (50) paraffin blocks obtained from core biopsies of prostatic carcinoma. Paraffin blocks were retrieved from PAR Hospital in Erbil city, Iraq.

The original slides were re-evaluated, the Grade Group and the modified Gleason score were obtained for each case. Then, a section was obtained and stained for E-cadherin according to the manufacturer's procedure. Positive and negative controls were run also. E-cadherin expression was considered as normal or aberrant staining.

E-cadherin expression was considered normal when there is a full membranous staining in more than 90% of cells examined in five different high-power fields; otherwise, it was assigned as aberrant.<sup>[15]</sup>

Then, the results were correlated to the Grade Group and the modified Gleason score. The E-cadherin staining pattern was also examined for its correlation with perineural invasion.

### Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The privacy of the patients was kept secure by using a code for each patient instead of names. The study protocol and the subject information were reviewed and approved by a local ethics committee (Directorate of Health in Duhok City).

## Statistical analysis

Chi-square was used to determine the correlation between E-cadherin staining pattern on the one hand and the modified Gleason score, Grade Group, and perineural invasion on the other hand and  $P < 0.5\%$  was considered as significant.

## RESULTS

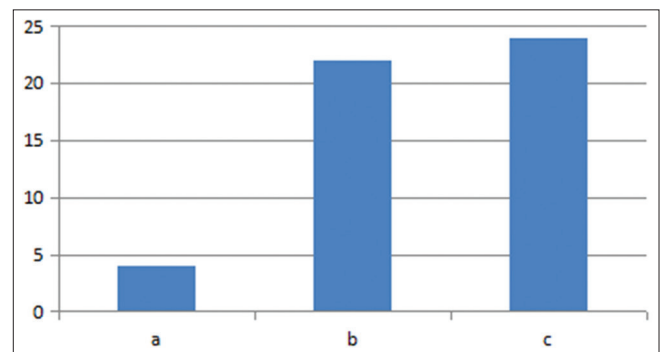
This study included 50 paraffin blocks obtained from core biopsies from patients who were proved to have prostatic adenocarcinoma. Of the included patients, 24 (48%) were in the seventh decade of life, and Figure 1 shows the age groups of the patients. Only six patients (12%) fall in Grade Group 1, and Figure 2 shows a microphotograph of prostatic adenocarcinoma belonging to the Grade Group 2 and Table 1 shows the Grade Group of all the patients, and according to the modified Gleason score, most patients had high score [Table 2] and Figure 3 shows a prostatic adenocarcinoma with a score of 5 + 4.

Regarding E-cadherin expression, 24 cases (48%) had aberrant E-cadherin expression [Figure 4], while the rest 26 cases (52%) had complete strong membranous expression [Figure 5]. Tables 3 and 4 show the correlation between E-cadherin expression and the modified Gleason score and the Grade Group, respectively. Statistically, there was a significant correlation between aberrant E-cadherin expression and increasing grade according to the modified Gleason score and Grade Group with  $P$  values of 0.032% and 0.022%, respectively.

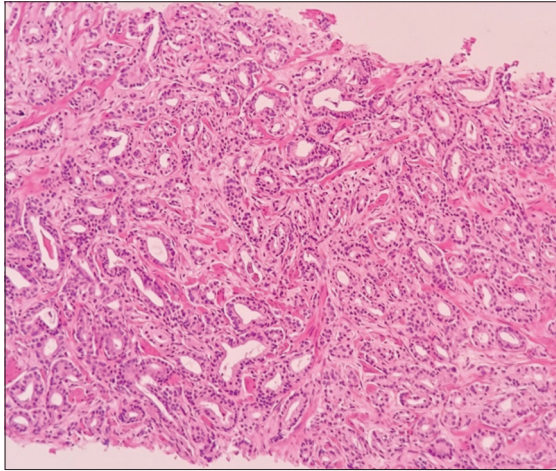
In 24 patients (48%), perineural invasion was detected [Figure 6], half of them had aberrant E-cadherin expression which was

**Table 1: The Grade Group of the enrolled patients**

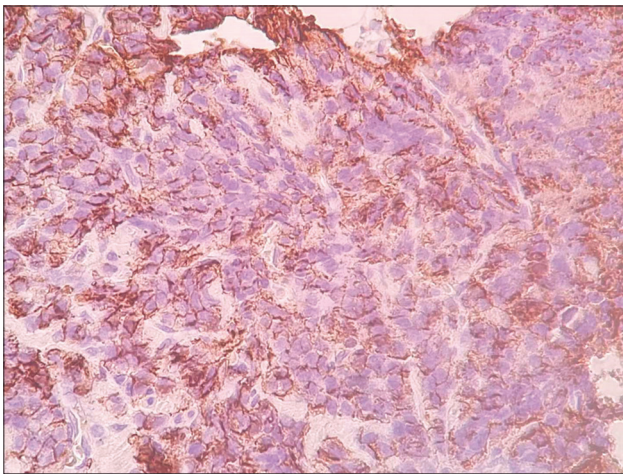
| Grade group   | n (%)    |
|---------------|----------|
| Grade Group 1 | 6 (12)   |
| Grade Group 2 | 8 (16)   |
| Grade Group 3 | 14 (28)  |
| Grade Group 4 | 12 (24)  |
| Grade Group 5 | 10 (20)  |
| Total         | 50 (100) |



**Figure 1:** The age of the included patients (a: 50–59 years, b: 60–69 years, c: ≥70 years)



**Figure 2:** Prostatic adenocarcinoma with Grade Group 2, most of the malignant glands are small and uniform with some larger glands and irregular outlines (H and E, ×100)



**Figure 4:** Aberrant E-Cadherin expression (×40)

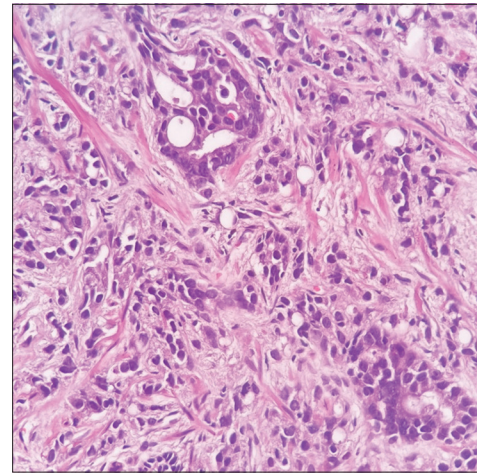
statistically not significant when both the parameters (perineural invasion and aberrant E-cadherin expression) are tested against the modified Gleason score and the Grade Group ( $P = 0.71\%$ ), while vascular invasion was detected in two patients (4%). The correlation between perineural invasion and the Grade Group and the modified Gleason score is shown in Table 5.

## DISCUSSION

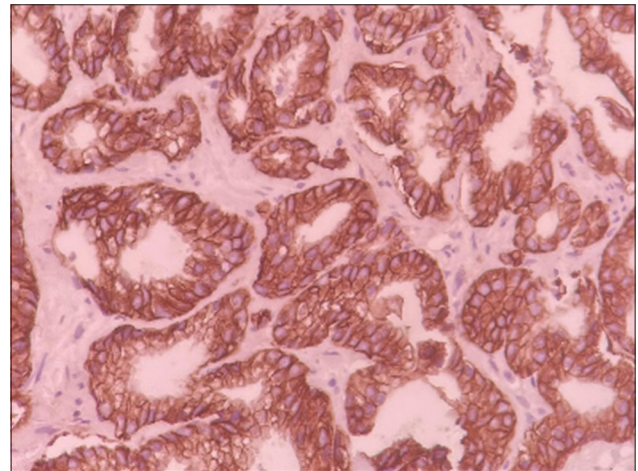
Cadherins are key factors in maintaining cell-to-cell contact, one member of this family is E-cadherin which plays the main role in cell adhesion. Downregulation of E-cadherin is associated with a transition from epithelial to mesenchymal phenotype, which is known as EMT.<sup>[16]</sup>

Aberrant E-cadherin expression is associated with aggressive tumors in many organs including the gastrointestinal tract and ovary.<sup>[17]</sup>

Many studies have shown a decrease in E-cadherin in diffuse-type gastric cancer and a shorter survival periods than



**Figure 3:** Prostatic adenocarcinoma with a score of 5 + 4, there is single-cell infiltration and cribriform glands (H and E, ×400)



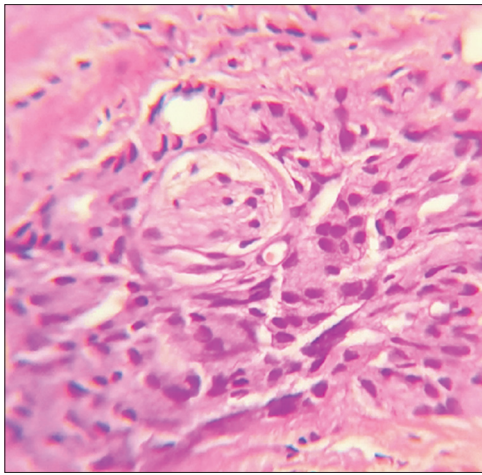
**Figure 5:** Complete diffuse strong membranous staining for E-Cadherin (×40)

**Table 2: The modified Gleason score of the included patients**

| Modified Gleason score | n (%)    |
|------------------------|----------|
| 3+3                    | 6 (12)   |
| 3+4                    | 8 (16)   |
| 4+3                    | 14 (28)  |
| 4+4                    | 11 (22)  |
| 3+5                    | 1 (2)    |
| 4+5                    | 8 (16)   |
| 5+4                    | 2 (4)    |
| Total                  | 50 (100) |

E-cadherin-positive cases,<sup>[18]</sup> while in breast cancer, most invasive and *in situ* lobular breast carcinomas are negative for E-cadherin, thus giving E-cadherin the role of a tumor suppressor.<sup>[19]</sup>

Aziza E. Abdelrahman *et al.* observed that most high-grade prostate cancer cases had heterogeneous E-cadherin expression, while majority of low-grade and benign prostatic



**Figure 6:** Prostatic adenocarcinoma with circumferential perineural invasion (H and E,  $\times 400$ )

hyperplasia (BPH) cases had a normal expression,<sup>[20]</sup> this goes in hand with the study conducted by Umbas *et al.*<sup>[21]</sup> In a study done by Sandy Figiel *et al.*, they found that more than half of cases with modified Gleason score 8 expressed E-cadherin aberrantly and that aberrant E-cadherin expression was associated with a shorter survival rate.<sup>[22]</sup>

In this study, it was found that there is a significant correlation between aberrant E-cadherin expression with increasing modified Gleason score ( $P = 0.032\%$ ) and Grade Group ( $P = 0.022\%$ ). Whether this aberrant expression is an independent prognostic factor or it is related to the grade of prostatic carcinoma, is a question that requires further studies.

To further emphasize the role of E-cadherin in prostate cancer progression, a group compared the expression of E-cadherin among prostatic hyperplasia cases, prostate carcinoma, and site of metastasis. They came up with similar results, as more than half of BPH cases had an intact expression, about half of cases with prostatic carcinoma expressed intact E-cadherin, while only a few metastatic cases had an intact expression.<sup>[23]</sup>

A prospective study of 103 cases on which EMT markers were tested revealed that E-cadherin was decreased in cancer cases when compared with BPH cases, but over a period of 3 years of follow-up, they failed to see any difference in disease-free survival between cases with normal and aberrant expression.<sup>[24]</sup>

However, Nabiha Missaoui *et al.* found that there was no correlation between E-cadherin expression and the clinicopathological parameters including patient age, tumor grade, and PSA level.<sup>[13]</sup> Koksai *et al.* also concluded that there was no correlation between E-cadherin expression and modified Gleason score.<sup>[25]</sup> Soler *et al.* reported that there was no significant correlation between E-cadherin and modified Gleason score. They attributed their results to the limited number of cases and stated that the expression of E-cadherin does not reflect the function of the protein.<sup>[26]</sup>

**Table 3: The correlation between E-cadherin expression with modified Gleason score ( $P=0.032$ )**

| Modified Gleason score | Normal E-cadherin expression, n (%) | Aberrant E-cadherin expression, n (%) |
|------------------------|-------------------------------------|---------------------------------------|
| 3+3                    | 5 (10)                              | 1 (2)                                 |
| 3+4                    | 6 (12)                              | 2 (4)                                 |
| 4+3                    | 7 (14)                              | 7 (14)                                |
| 3+5                    | 1 (2)                               | -                                     |
| 4+4                    | 5 (10)                              | 6 (12)                                |
| 4+5                    | 2 (4)                               | 6 (12)                                |
| 5+4                    | -                                   | 2 (4)                                 |
| Total                  | 26 (52)                             | 24 (48)                               |

**Table 4: The correlation between E-cadherin expression with Grade Group ( $P=0.022$ )**

| Grade group   | Normal E-cadherin expression, n (%) | Aberrant E-cadherin expression, n (%) |
|---------------|-------------------------------------|---------------------------------------|
| Grade Group 1 | 5 (10)                              | 1 (2)                                 |
| Grade Group 2 | 6 (12)                              | 2 (4)                                 |
| Grade Group 3 | 7 (14)                              | 7 (14)                                |
| Grade Group 4 | 6 (12)                              | 6 (12)                                |
| Grade Group 5 | 2 (4)                               | 8 (16)                                |
| Total         | 26 (52)                             | 24 (48)                               |

**Table 5: The correlation between E-cadherin expression with Grade Group and modified Gleason score in patients with perineural invasion ( $P=0.71$ )**

| Grade Group | Modified Gleason score | Aberrant E-cadherin expression, n (%) | Normal E-cadherin expression, n (%) |
|-------------|------------------------|---------------------------------------|-------------------------------------|
| 2           | 3+4                    | 2 (16.67)                             | 2 (16.67)                           |
| 3           | 4+3                    | 3 (25)                                | 4 (33.33)                           |
| 4           | 4+4                    | 3 (25)                                | 3 (25)                              |
|             | 3+5                    | 0                                     | 1 (8.33)                            |
| 5           | 4+5                    | 4 (33.33)                             | 2 (16.67)                           |
| Total       |                        | 12 (100)                              | 12 (100)                            |

These discrepant results between articles were related to differences in tissue processing, techniques of immunohistochemistry application, interpretation, and the scoring systems followed.<sup>[27]</sup>

In this study, half of the cases with aberrant E-cadherin expression had perineural invasion, but there was no significant correlation between them ( $P = 0.71\%$ ) and this is consistent with the study performed by Taghrid Bengallol *et al.* who also failed to detect a correlation between E-cadherin expression and perineural invasion.<sup>[27]</sup>

## CONCLUSION

Aberrant E-cadherin expression is associated with increasing modified Gleason score and Grade Group but has no significant correlation with perineural invasion.

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## Conflicts of interest

There are no conflicts of interest.

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