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Evaluation of Glutathione peroxidase activity and Angiotensin II as monitoring biomarkers of long-term therapy in Iraqi patients with prostate cancer

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ABSTRACT

Introduction: Prostate cancer is the second most common cancer in men worldwide. The current therapeutic approaches include the use of hormonal manipulation, particularly agents like Goserelin acetate and Bicalutamide.

Objective: The present study sought to explore the combination of Goserelin acetate and Bicalutamide therapy on aldosterone, angiotensin II, glutathione, and glutathione peroxidase activity in prostate cancer patients, before treatment and after three years of therapy.

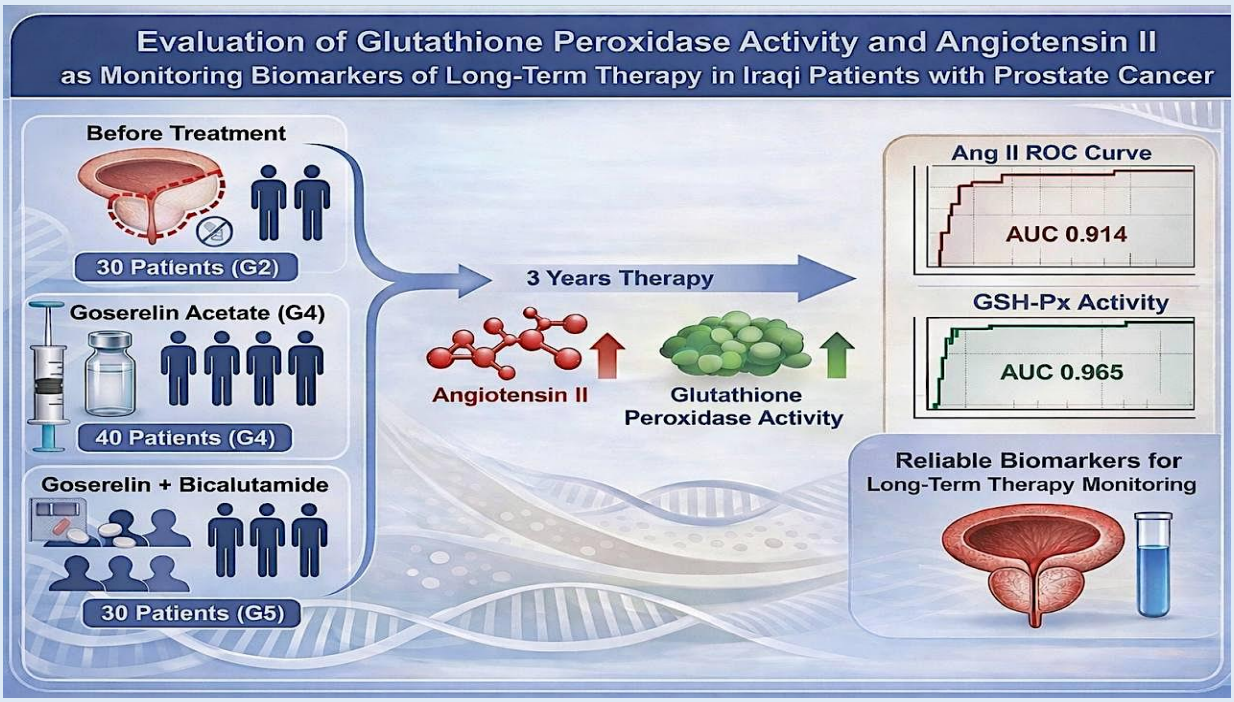
Methods: A total of 100 participants were collected, including 30 prostate cancer patients before treatment (G_2), 40 participants were collected after treatment with Goserelin acetate as monotherapy (G_4), and 30 participants with Goserelin acetate and Bicalutamide as combine therapy (G_5).

Results: The results showed significantly in all parameters when compared to newly diagnosed except GSH in monotherapy. Notably, ROC curve analysis demonstrated an excellent discriminative ability, with an AUC of 0.914 for G_4 and 1.000 for G_5 in Ang II hormone, also in GSH-Px enzyme activity was 1.000 for group G_4 and 0.968 for group G_5. This highlighting Ang II and GSH-Px activity as a highly sensitive and specific monitoring biomarker for long-term treatment response assessment.

Conclusion: This study highlights a strong association between alterations in steroid hormones and prostate cancer progression under combination hormonal therapy, suggesting their potential role as biomarkers for monitoring therapeutic efficacy.

Novelty of the Study: This study provides the first comparative evaluation of Glutathione peroxidase activity and Angiotensin II as monitoring biomarkers of long-term therapy in Iraqi patients with prostate cancer.

Keywords: Aldosterone, Angiotensin II, Glutathione peroxidase activity, Goserelin acetate, Bicalutamide.



Graphical abstract: Evaluation of glutathione peroxidase activity and angiotensin ii as monitoring biomarkers of long-term therapy in Iraqi patients with prostate cancer.

INTRODUCTION

Cancer is one of the epidemic diseases, which is still a major health problem worldwide despite the big development in treatment and diagnostic methods [1], while the second most frequent malignancy cause of death worldwide is prostate cancer (PCa) [2], it constitutes a major cause of urological morbidity among Iraqi males [3]. It is an initial treatment, and the synthesis of androgens can be inhibited for prostate cancer [4]. Goserelin acetate (Zoladex) and Bicalutamide inhibiter for androgen production. Therefore, suppressive therapy is also needed for other tissues that produce androgens. The removal of the prostate, known as a prostatectomy, can be done either laparoscopically or openly. Urinary incontinence and erectile dysfunction are potential adverse effects following prostatectomy; anastomotic strictures raise the risk [5]. Goserelin acetate is a type of hormone (endocrine) therapy [6]. It is a synthetic decapeptide analogue of Luteinizing Hormone Releasing Hormone (LHRH), a pituitary hormone that controls the

release of other hormones [7]. However, it is used for the management of locally confined stage carcinoma of the prostate [8].

The primary androgen in male adults' bloodstreams and its dynamic metabolite, dihydrotestosterone, is testosterone [9]. It has a distinctive four ring C18 steroid structure and is mostly produced by Leydig cells in the interstitium of the testis between the seminiferous tubules [10]. Gonadotropin-Releasing Hormone (GnRH) is a hormone that affects the pituitary gland and is released by the hypothalamus, a part of the brain [11]. The pituitary gland releases Luteinizing Hormone (LH) in response to stimulation from GnRH and LH activates Leydig cells by binding to receptors on Leydig cells after passing from the circulation to the testes, which leads to the production of testosterone by Leydig cells as a result of binding [12], Goserelin acetate injection targeted binding to prevent testosterone production [13].

Angiotensin II (Ang II) is an octapeptide that induces vasoconstriction and elevates blood pressure within a complex regulatory and counterregulatory framework [14]. Angiotensin II stimulates Aldosterone (ALD) production [15]. The Renin-angiotensin-aldosterone system (RAAS) contributes a regulatory role in hemodynamic stability [16].

Glutathione Peroxidase (GSH-PX) (EC.1.11.1.9) are studied for their important role in removing harmful Reactive Oxygen Species (ROS) by breaking down hydrogen peroxide (H_2O_2) or lipid peroxides to protect cells from damage. It is an 85 KDa protein that reduces H_2O_2 to molecular oxygen and water by using monomeric Glutathione (GSH) as an electron donor is the major part of the antioxidant defense mechanism [17-19]. Glutathione is a tri-peptide containing three amino acid residues including glutamate, cysteine, and glycine It is turned to GSSG by GSH-Px and the specific role of GSH in prevention of cancer became clear by the definition of major role of this compound in conjugation with carcinogens during detoxification [20,21]. Show Figure 1. The present study aimed to investigate the potential of these steroid hormones as predictive biomarkers for monitoring treatment efficacy.

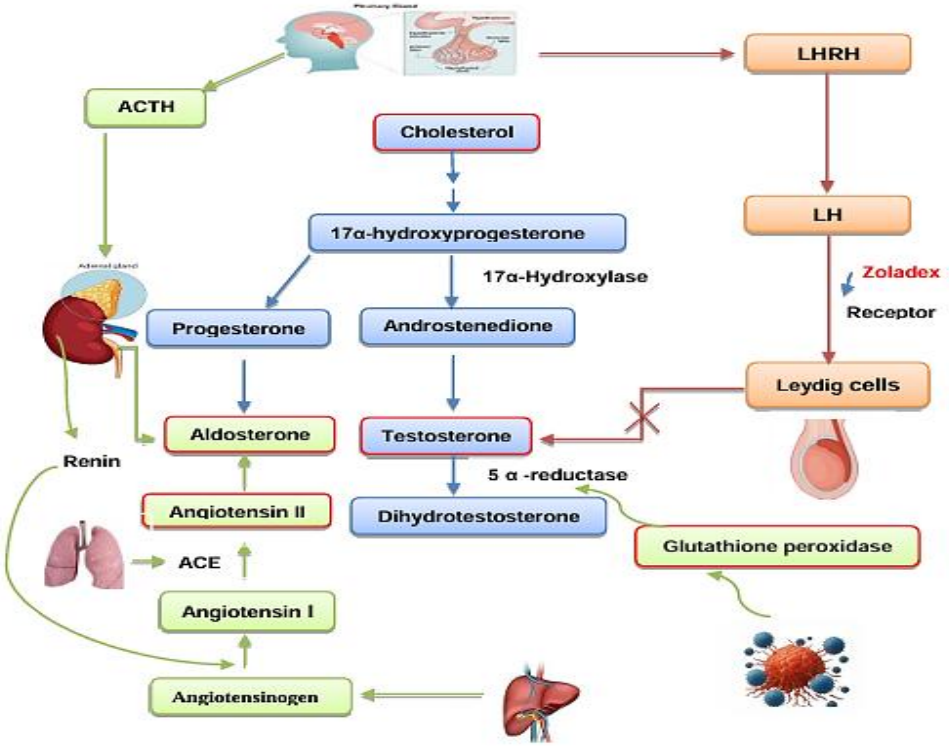


Figure 1. Effects of Goserelin acetate in testosterone production pathway (ACE: Angiotensin converting enzyme).

MATERIALS AND METHODS:

Materials (patients and samples): The experiment was conducted using100 participants that were divided into three groups:

- Group 2 (G_2): 30 PCa patients newly diagnosed.
- Group 4 (G_4): 40 PCa patients treated with goserelin acetate (3.6 mg) as monotherapy after 12 months.
- Group 5 (G_5): 30 PCa patients treated with goserelin acetate (3.6 mg) with Bicalutamide as combine therapy after 3 years.

Patient samples for Group 2, Group 4, and Group 5 were collected from Al-Amal National Hospital for Oncology. For each patient, 5 mL of venous blood was drawn and centrifuged to separate the serum. The study included patients diagnosed with stage II prostate cancer presenting with advance PCa. All participants were non-smokers and had undergone voluntary prostatectomy. Exclusion criteria included patients with chronic diseases such as cardiovascular disorders, diabetes mellitus, hypertension, or any other concurrent malignancies. Patients with metastatic prostate cancer or those receiving triple therapy (including prednisolone, chemotherapy, or radiotherapy) were also excluded. Basic diagnostic tests and medical history reviews were conducted to confirm eligibility.

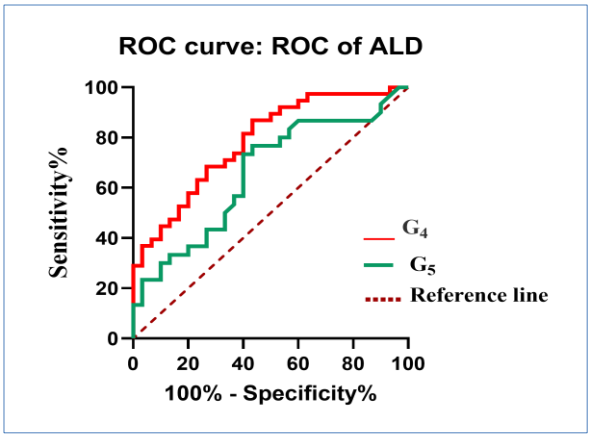
Methods (steroids assay, antioxidant detection): Serum levels of ALD, and Ang II were quantified using enzyme-linked immunosorbent assay (ELISA) kits (ELK-Biotechnology, China). The assay sensitivities were 9.41 pg/mL for ALD levels and 8.95 pg/mL for Ang II levels, with detection ranges of 31.25–2000 pg/mL and 31.25–2000 pg/mL, respectively. It is worth mentioning the catalogue numbers were ELK9313 and ELK1399; for human ALD and Ang II, respectively. Reduced glutathione (GSH) concentrations (µ mol/L) were determined using enzymatic colorimetric methods, while GSH-Px activity (U/L) (was measured following the two-step ELK-Biotechnology protocol, consisting of an enzymatic reaction followed by a chromogen reaction. The concentrations of GSH (µ mol/L) were calculated using standard calibration curves.

Statistical analysis: The mean±SD was applied for all GSH in G_4 had a moderate ability to discriminate. The statistical significance of the mean value differences was investigated using the one-way ANOVA test and ROC curve, have been used. The Statistical Package for the Social Sciences (prism, version 10.4.2 (633)) was utilized for all analysis, Microsoft Excel 2016 and curve expert 1.4. Statistical significance is indicated as follows **p≤0.001 and *p≤0.05 significant and p>0.05 as no significant. The normality distribution was assessed using the Gaussian distribution test and the Shapiro- Wilk normality test. It is worth mentioning terms of SD= standard deviation, CI= confidence interval, AUC= area under the curve, SE= standard error, and ROC = Receiver operator curve.

Findings and Results: The results in this research show, ALD levels (pg/mL) were considerably higher in G_4 and G_5 than in G_2, as Table 1 demonstrates. Compared to G_5 (mean difference = 0.1756, p = 0.0225), the increase in G_4 was more noticeable (mean difference = 0.2515, p = 0.0004). With a higher AUC in G_4 (0.7842) than in G_5 (0.6561).

Table 1: Comparison between G_2, G_4 and G_5 groups in ALD levels (pg/mL) with ROC curve.

Groups / Items	G_4 (pg/mL)	G_5 (pg/mL)
Mean± SD	1.883±0.2192	1.959±0.3159
95%CI	1.811-1.955	1.841-2.077
Mean Diff vs. G_2	0.2515	0.1756
p-value	0.0004	0.0225
Significance	***	*
AUC	0.7842	0.6561
SE	0.05482	0.07131
Cut off value	< 1.973	< 2.115

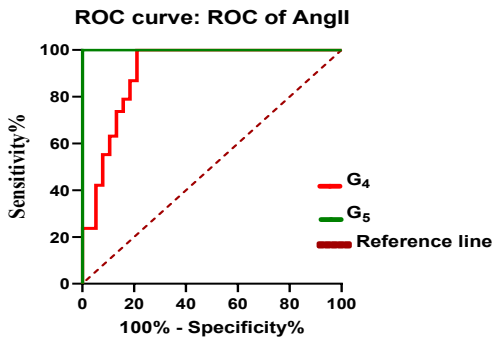


❖ Mean± SD for G_2 (2.135±0.2644) and 95%CI (2.036-2.233).

However, G_2 group results mean ± SD value of Ang II was 127.9 ± 55, with a 95%CI of 109.8–146. Angiotensin II levels, on the other hand, were significantly lower in G_4 (52.89 ± 3.775) and G_5 (513.1 ± 129.6), with respective 95% CIs of 51.65–54.13 and 464.7–561.5. The average deviations from G_2 were -94.84 for G_5 and -460.3 for G_4. There was a strong correlation between treatment status and Ang II levels, as evidenced by the highly statistically significant changes in both groups ($p < 0.001$). Outstanding discriminative ability, especially in G_5, was indicated by the AUC, which was 0.9141 for G_4 and 1.000 for G_5. For G_4 and G_5, the SE was 0.03409 and 0.00, respectively. The ideal cutoff values were found to be < 63.68 for G_5 and > 275.0 for G_4. Interestingly, the G_5 curve shows perfect classification performance (AUC = 1.000). See Table 2.

Table 2: Comparison between G_2, G_4 and G_5 groups in Angiotensin II levels (pg/mL) with ROC curve.

Groups / Items	G_4 (pg/mL)	G_5 (pg/mL)
Mean± SD	52.89 ±3.775	513.1±129.6
95%CI	51.65-54.13	464.7-561.5
Mean Diff vs. G_2	-460.3	-94.84
p-value	<0.001	<0.001
Significance	***	***
AUC	0.9141	1.000
SE	0.03409	0.00
Cut off value	> 275.0	< 63.68

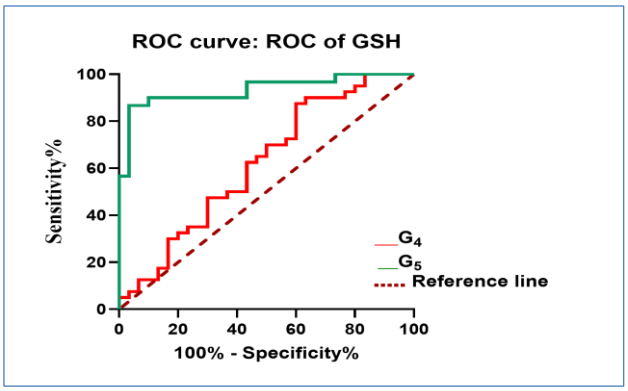


On the other hand, the 95% CI for G_2 was 41.70–47.18, and the mean ±SD was 44.44 ± 7.337 in glutathione levels. The mean ±SD of GSH level in G_4 group was 47.53 ± 7.174 (95% CI: 45.24–49.83), which no statistically significantly from G_2 ($p = 0.1015$). The mean value of G_5, on the other hand, was significantly lower at 31.97 ± 5.033 (95% CI: 30.09–33.85), and the difference was highly significant ($p < 0.001$). Glutathione level in G_4 group had a moderate ability to discriminate (AUC = 0.6146; SE = 0.06974), according to ROC curve analysis, in G_5 the AUC = 0.9350 and SE = 0.03309. For G_4 and G_5, the ideal cutoff values were found to be > 40.10 and < 34.52,

respectively. Glutathione levels in G_4 had a moderate ability to discriminate (AUC = 0.6146; SE = 0.06974), according to ROC curve analysis, in G_5 the AUC = 0.9350; SE = 0.03309). For G_4 and G_5, the ideal cutoff values were found to be > 40.10 and < 34.52, respectively. The ROC curve figure also shows that the G_4 curve is located closer to the reference line, indicating limited accuracy, while the G_5 curve is positioned significantly above the reference line, indicating high sensitivity and specificity. These results collectively imply that GSH has limited significance in G_4 but strong monitoring and discriminative value in G_5. Noted Table 3. In glutathione peroxidase activity, G_2 showed a mean ± SD of 120.5 ± 28.51, with a 95%CI was 109.9 -131.2. However, GSH-Px activity was significantly decreased in the two treated groups. Mean ± SD was 24.60 ± 4.824 (95% CI: 23.05-26.14) and 82.98 ± 10.14 respectively in G_4 and G_5. It should be noted that the decreases in both G_4 and G_5 were significantly significant with respect to those of G_2 ($p < 0.001$), indicating a clear effect of therapy on antioxidant enzymes' activities. The AUC was 1.000 in G_4 and 0.9683 in G_5.

Table 3: Comparison between G_2, G_4 and G_5 groups in GSH (µmol/L) levels with ROC curve.

Groups / Items	G_4 (µmol/L)	G_5 (µmol/L)
Mean± SD	47.53±7.174	31.97±5.033
95%CI	45.24-49.83	30.09-33.85
p-value	0.1015	<0.001
Significance	ns	***
AUC	0.6146	0.9350
SE	0.06974	0.03309
Cut off value	> 40.10	< 34.52

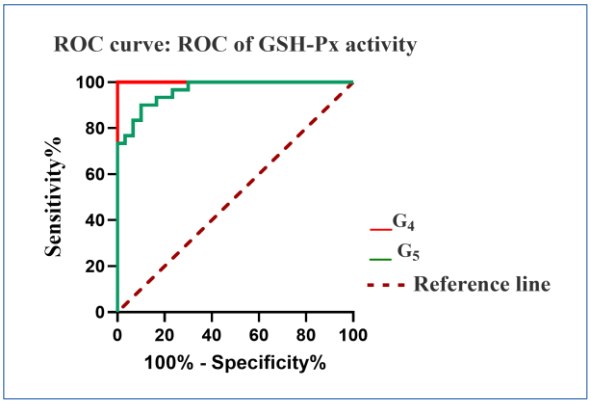


❖ Mean± SD for G_2 (44.44±7.337) and 95%CI (41.70-47.18).

The cut-off values were established as < 61.77 and <98.77 for G_4 and G_5, respectively. The ROC curves are well away from the reference line and appear to perform extremely well in both measures, especially G_4. These results indicate that the activity of GSH-Px enzyme was a good discriminator between groups and may be considered as an indicator to evaluate the effect of treatment. See Table 4.

Table 4: Comparison between G_2, G_4, and G_5 groups in GSH-Px enzyme activity (U/L) with ROC curve.

Groups / Items	G_4 (U/L)	G_5 (U/L)
Mean± SD	24.60±4.824	82.98±10.14
95%CI	23.05-26.14	79.20-86.77
p-value	<0.001	<0.001
Significance	***	***
AUC	1.000	0.9683
SE	0.000	0.01785
Cut off value	< 61.77	< 93.77



❖ Mean± SD for G_2 (120.5±28.51) and 95%CI (109.9-131.2).

The rise in chronic illnesses, including cancer, over the past century has posed a serious threat to the health systems of citizens in developing nations. Cancer is a serious health issue in many nations, as seen by rising rates of occurrence, death, and substantial treatment expenses for people of all ages and genders [22]. In current study, evaluated the long-term biochemical effects of hormonal therapy in PCa patients by comparing newly diagnosed patients with patients treated for three years with goserelin acetate as well as with goserelin acetate combined with bicalutamide. The analysis focused on hormonal regulation, oxidative stress, and antioxidant defense systems, supported by ROC curve statistical analysis to assess discriminative performance. In ALD hormone, the results demonstrated a significant reduction in ALD levels in both G_4 and G_5 groups compared to G_2. The decrease was more pronounced in G_4 group, indicating a stronger suppressive effect on ALD secretion depending on long-term ADT. On the other hand, ROC further confirmed the clinical relevance of ALD, where G_4 exhibited a higher AUC value (0.784) than G_5 (0.656), suggesting that ALD is a moderately accurate biomarker for distinguishing untreated patients from those receiving goserelin acetate. The present study suggested this reduction in ALD may reflect improved hormonal regulation and reduced tumor-associated endocrine dysregulation after therapy, that agreement with Pawlonka [23,24], which indicate that the environment can influence the local concentration of RAAS, which may, in turn, determine aldosterone levels [25]. On the other hand, the results showed Ang II levels marked and contrasting changes between treatment groups. A significant decrease was observed in G_4, indicating effective suppression of the RAS, which is known to contribute to PCa progression through angiogenesis and cellular proliferation. Conversely, Ang II levels were significantly elevated in G_5. Also, that due to irregulate aldosterone secretion by potassium and Adrenocorticotropic hormone (ACTH). Activating local RAAS also causes a rise in ang II [26]. Food protein-derived antihypertensive peptides have attracted substantial attention as a safer alternative for drugs. The regulation of the RAS is an essential aspect underlying the mechanisms of antihypertensive peptides. Most of the identified antihypertensive peptides exhibit the ACE inhibitory effect [27]. The current study suggested, the unexpected increase which may reflect the modulation of RAS activity induced by combined anti-androgen therapy. Notably, ROC curve analysis demonstrated an excellent discriminative ability, with an AUC of 0.914 for G_4 and 1.000 for G_5. This highlighting Ang II as a highly sensitive and specific biomarker for long-term treatment response assessment. When compared to untreated patients, GSH-Px enzyme activity dramatically dropped in both treated groups, with the G_4 group experiencing a more noticeable decline. According to this research, long-term androgen deprivation seriously compromises the defense mechanisms of antioxidant enzymes. It's interesting to note that G_5 comparatively higher enzyme activity than that of group G_4 might point to a partial compensatory response brought on by the combination therapy. With an AUC of 1.000 for group G_4 and 0.968 for group G_5, the ROC curve analysis demonstrated exceptional diagnostic performance, demonstrating that GSH-Px enzyme activity is among the most trustworthy biomarkers for evaluating therapeutic effect. Notably, ROC curve analysis demonstrated an excellent discriminative ability, with an AUC of 0.914 for G_4 and 1.000 for G_5. This highlighting Ang II as a highly sensitive and specific biomarker for long- term treatment response assessment. However, ALD in G_4 exhibited a higher AUC value (0.784) than G_5 (0.656).

Ethical Considerations: The study received ethical approval from the Ethical Committee at the Faculty of Science, University of Baghdad (Approval date: March 21, 2025; Reference No.: CSEC/0325/0048).

CONCLUSIONS

According to the results, these parameters may serve as valuable biomarkers for monitoring treatment efficacy in prostate cancer patients, potentially aiding in the control of tumor progression during the course of therapy. Continued evaluation of these markers could contribute to more personalized and adaptive treatment strategies. This method improves patient outcomes and highlights the significance of incorporating biomarker analysis into standard clinical practice. As research advances, more knowledge may result in advance therapeutic interventions customized for unique patient profiles.

List of Abbreviations: PCa: prostate cancer; LHRH: Luteinizing Hormone Releasing Hormone; GnRH: Gonadotropin-Releasing Hormone; LH: Luteinizing Hormone; Ang II: Angiotensin II; ALD: Aldosterone; RAAS: Renin-angiotensin-aldosterone system; GSH-PX: Glutathione Peroxidase; ROS: Reactive Oxygen Species; H_2O_2: hydrogen peroxide; GSH: Glutathione; SD: standard deviation; ACE: Angiotensin converting enzyme; G_2: Group 2; G_4: Group 4; G_5: Group 5. ACTH: Adrenocorticotropic hormone

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Transparency of Data: Following the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

Author Contribution: All authors contributed equally to the main contributor to this paper. All authors read and approved the final paper.

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