

Soluble programmed death ligand-1 (sPD-L1) is elevated in aggressive prostate cancer disease among African men

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Abstract

Background

The programmed death 1 (PD1)/programmed death-ligand 1 (PDL1) targeted immunotherapies have become a new mode of treatment for several tumours; however, there is limited evidence on the expression and prognostic value of PD1/PDL1 in prostate cancer, especially in African men.

Methods

The plasma concentrations of PD-L1/PD1 were assessed using Enzyme-Linked Immunosorbent Assay in patients with prostate cancer and normal healthy controls at the Uganda Cancer Institute. The association between plasma PD-L1/PD1 concentration levels and PSA levels, Gleason scores, age, and Body mass index were determined.

Results

We found significant differences in the median plasma concentrations of PD-L1 and PD-1 immune checkpoint molecules between Prostate cancer cases and normal healthy controls of (0.285 vs 0.035) p -value 0.001 and (0.596 vs 0.355) p -value 0.017, respectively. We found no significant association between age, plasma PSA levels, BMI and Gleason scores, and PD-1 among patients with prostate cancer and controls. However, elevated levels of PD-L1 were significantly associated with raised Gleason scores among patients with prostate cancer with a p -value of <0.001 .

Conclusions

Elevated PD-L1 levels were statistically significantly linked to high Gleason scores. These results may guide clinicians in assessing the prognosis of patients individually and selecting suitable patients that will make favorable candidates for anti-PD-L1 immunotherapy.

Background

Prostate cancer is the second most frequently diagnosed cancer in men worldwide, accounting for approximately 15% of all new cancer diagnoses in men (1). In 2020, the Global Cancer Observatory (Globocan) report indicated an annual worldwide incidence of 1.4 million prostate cancer cases, with approximately 375,304 deaths (2). Reports indicate that men of African ancestry suffer disproportionately from prostate cancer at a rate almost twice as high as men of European origin, irrespective of new treatment modalities (3–5).

The mainstay therapy for advanced prostate cancer remains androgen deprivation therapy (ADT)(6). Among patients with metastatic prostate cancer, various treatment options for metastatic castration-resistant prostate cancer (mCRPC) such as hormonal therapy, chemotherapy, and radiopharmaceuticals have shown significantly increased overall survival (OS). Still, these ultimately develop resistance (7, 8).

In the last decade, the introduction of immunotherapy which works through the augmentation of immune responses against cancers has yielded promising results and considerably changed the treatment landscape owing to its efficacy and minimal side effects (9, 10). Thus, immune checkpoint inhibitors have emerged as a complementary treatment arm in cancer clinical care and research (11, 12). The co-inhibitory receptor programmed death1 (PD-1) is expressed on activated T cells and B cells. Upon binding to its ligands PD-L1, which is expressed on macrophages, dendritic cells and some tumour cells, T cell activation is downregulated by inhibiting CD28 signaling (13). Besides being expressed on cell membranes, several extracellular (soluble) forms of PD-L1, including spliced variants and proteolytic cleavage forms, have been reported in various types of cancer(14). Soluble PD-L1 can bind to PD1 on T cells and suppress anti-tumour immunity, thus facilitating tumour growth. Blocking the PD1/PD-L1 interaction using immune checkpoint inhibitors have been shown to reduce tumour growth and increase overall survival of patients. (15).

Anti-PD1 antibody immunotherapy (e.g.nivolumab) and anti-PD-L1 antibody (e.g., atezolizumab) have demonstrated improved response rates and overall survival among patients with melanoma and renal cell carcinoma, respectively(16, 17).

The ongoing clinical trials show that immunotherapy might provide a promising approach for the future treatment of prostate cancer (18). Studies indicate that PD-L1 expression is up-regulated in prostate cancer tissues compared to paired benign prostate tissues. Similarly, high levels of PD-L1 expression have been shown to have a positive correlation with high Gleason scores and androgen receptor expression in patients with aggressive primary prostate cancer (19–21).

This study assessed the circulating levels of immune checkpoint molecules, PD-1 and PD-L1, among prostate cancer patients and normal healthy controls and their association with age, BMI, plasma PSA, and Gleason scores at the Uganda Cancer Institute.

Methods

Study population

This was a case-control study in which 86 men, 57 prostate cancer patients on androgen deprivation therapy, and 29 normal healthy controls were recruited from January 2020 to June 2020 at the Uganda Cancer Institute, Kampala, Uganda. All study participants were aged 40 years and above. Controls were men aged 40 years and above with no history of prostate cancer and with a PSA of less than 4ng/ml. The cases were men with a histological diagnosis of Prostate cancer and on androgen deprivation therapy.

Study procedures

A pre-designed questionnaire was used to obtain demographic data and the medical history of study participants. Six (6) mls of blood in an ethylenediaminetetraacetate (EDTA) anti-coagulated tube was collected by a trained study nurse from each study participant. Blood samples were transported within one hour to the laboratory for processing. This study obtained ethical approval from the School of Biomedical Sciences Higher Degrees Research and Ethics Committee (REF: SBS-HDREC- 779) and the Uganda National Council for Science and Technology (UNCST). All study participants provided written informed consent before enrolment into the study.

Plasma collection and Immunoassays

Separation of platelet-poor plasma

All laboratory procedures and tests were carried out in the Translational Research laboratory at the Infectious Diseases Institute, Makerere University, Kampala, Uganda. On reception in the laboratory, whole blood samples were immediately centrifuged at 6⁰C at a speed of 1000g for 10 minutes. The supernatant was collected in a sterile falcon tube and centrifuged again at 1600g for 10 minutes at 6⁰C. The resulting supernatant was then separated into two aliquots and stored at -80⁰C for later use to perform the Immunoassays.

ELISA Immunoassays

Plasma levels of immune checkpoint regulators were measured in pg. /ml and commercially procured control samples for each analyte were assayed in parallel to ensure good results. Stored plasma samples were retrieved and thawed at 4-8 ⁰C. Immunoassays were performed in duplicates using Human checkpoint markers PD-1 and PD-L1 Quantikine ELISA Kits (R&D Systems), following the manufacturer's instructions.

Statistical analysis

Categorical variables (demographic and clinical factors) were summarized as absolute

numbers and proportions. Continuous variables (plasma concentration of cytokines) were summarized as medians and interquartile ranges. Mann-Whitney U-test was used to compare continuous variables and Fisher's exact test for comparing categorical variables. The association of immune checkpoint molecules with different ages, Gleason score, PSA, and BMI was explored using conditional linear regression. All analyses were performed using STATA16.

Results

Clinico-demographic factors in Prostate cancer patients and controls

The median age was 70 years in cases and 59 years in the control group. The median BMI was 20.84 in the cases and 19.45 in the control group. The majority of the participants, 49.43% for cases and 68.97% for controls were in the normal BMI range of 18.5-24.9. The median PSA was 33.01ng/ml and 1.8ng/ml among cases and controls, respectively. Among the cases, the majority (31.58%) had a PSA of > 100ng/ml. 43.86% of the prostate cancer patients had advanced prostate cancer with Gleason scores of 8-10. Full description of clinical and demographics characteristics in table 1.

Table 1; Clinical characteristics of Prostate cancer patients and controls

Plasma levels of immune checkpoint molecules

The median concentrations of the PD-1 and PD-L1 were generally higher in cases than in controls. We found significant differences in the plasma concentrations of PD-L1 and PD-1 immune checkpoint molecules between Prostate cancer cases and normal healthy controls with *p-values* of 0.001 and 0.017, respectively, as seen in **Figure 1**. We found high levels of PD-L1 were significantly associated with raised Gleason scores among patients with prostate cancer with a *p-value* of <0.001 (Table 3).

However, the study found no significant association between age, plasma PSA levels, BMI and Gleason scores, and PD-1 checkpoint molecule among patients with prostate cancer and controls.

Figure 1; Median concentrations of immune checkpoint molecules in prostate cancer patients and controls.

Table 2; Median plasma concentrations of immune checkpoint molecules in Prostate cancer patients and controls.

Table 3: Association between immune checkpoint molecules and age, BMI, PSA, and Gleason score among Prostate cancer patients and controls.

Discussion

This was the first study to assess the association between soluble PD-1/PD-L1 levels and prostate cancer clinical characteristics in African populations. This study evaluated the circulating concentrations of immune checkpoint molecules PD-1 and PD-L1 and their association with PSA levels, Gleason scores, age, and BMI among patients with Prostate cancer and controls at the Uganda Cancer Institute. Consistent with previous studies, our results suggest a significant association between PD-L1 levels and high Gleason scores, prognostic of aggressive tumour behavior in prostate cancer (20, 22–24)

This finding further suggests that the PD-1/PD-L1 pathway activation supports the evasion of the anti-tumour immune response, driving tumour pathogenesis. The probability of anti-tumour immune response to anti-PD-1/anti-PD-L1 antibody therapy is associated with the expression of PD-L1 on the tumour cell surface (24–27)

Different mechanisms by which PD-L1-expressing cells evade T-cell immunity have been hypothesized, namely: inducing (1) apoptosis, (2) T cell energy, or (3) functional exhaustion of T-cells, (4) forming a molecular shield to keep lysis off tumour cells, (5) increasing production of the immunosuppressive cytokine IL-10, and (6) facilitating Treg cell-mediated suppression(28)(29). Increased expression of PD-L1 on tumour cells has previously been described for several malignancies, including glioblastoma, pancreatic, ovarian, breast, renal, head, and neck, esophageal, and non-small cell lung cancer. PD-L1 expression has also been associated with poor prognosis and adverse Clinico-pathological characteristics (21, 30, 31). A study by *Gevensleben et al., 2016* provided early evidence of abundant expression of PD-L1 in primary prostate cancer as a common occurrence and is a negative predictor for BCR-free survival (23, 32). Similarly, *Heng Li et al. 2019 and colleagues* looked at the expression of PD-1/PD-L1 in a retrospective cohort of men with prostate cancer who received adjuvant hormonal therapy (AHT) after radical prostatectomy (RP). They found moderate to high PD-L1 expression in 49.6% of primary prostate cancers after radical prostatectomy. In addition, PD-L1 expression was significantly associated with reduced biochemical recurrence-free survival (33).

Topalian et al. 2012 and colleagues carried out an immune-histochemical assessment of PD-L1 in pretreatment cancer specimens from 42 patients. They revealed that objective response to treatment was seen exclusively in (36%) PD-L1-positive tumours (34). *Bishop et al. 2015* and colleagues recently reported that CRPC patients resistant to enzalutamide showed elevated levels of PD-L1 in blood. The authors further concluded that PD-L1 expression on tumour cells might be a possible mechanism of non-AR-driven resistance to enzalutamide (22).

There is a need for predictive biomarkers that can identify patients who will benefit most from anti-PD-1/PD-L1 immunotherapy. Our study and many others provide evidence of PD-L1 expression as a promising predictive biomarker for patients likely to benefit from therapeutic blockade of PD-1/PD-L1 immunotherapies (35, 36). Based on our results, we provided credible evidence that Prostate cancer patients with higher Gleason scores were more likely to have higher levels of PD-L1 expression with statistical significance.

These patients are more likely to benefit from blocking the PD-1/PD-L1 pathway.

Conclusion

In conclusion, our study confirms that circulating levels of PD-L1 are significant independent prognostic factors in patients with prostate cancer. In addition, PD-L1 overexpression was statistically significantly linked to high Gleason scores. These results may guide clinicians in assessing the prognosis of patients individually or by selecting suitable patients that will be favorable candidates to receive anti-PD-1/PD-L1 immunotherapy. We recommend extensive prospective cohort studies to validate these findings further.

Abbreviations

PD-1

Programmed cell death - 1

PD-L1

Programmed cell death ligand -1

PSA

Prostate-specific antigen

ADT

Androgen Deprivation Therapy

ELISA

Enzyme-Linked Immunosorbent Assay

EDTA

Ethylene Diamine Tetra Acetate

BMI

Body Mass Index

Declarations

Authors' contributions

PK, OJS, and NN contributed to the conceptualization of the manuscript. CN and MA contributed to the running of the laboratory assays. PK and KS collected, cleaned, analyzed data and drafted manuscript. HK, SK, MJ, SJR, KS and JO read and reviewed the manuscript information and data. All authors read and approved the final version of the manuscript.

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interests.

Research involving Human participants and/or Animals and Ethical Approval

This study obtained ethical approval from the School of Biomedical Sciences Higher Degrees Research and Ethics Committee (REF: SBS-HDREC- 779) and the Uganda National Council for Science and Technology.

Informed consent

All study participants provided written informed consent before enrolment into the study.

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Availability of data and materials

All data files used in this manuscript article [and its supplementary information files] are available via fig share <https://doi.org/10.6084/m9.figshare.14904870.v1>

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Tables

Table 1; Clinical characteristics of Prostate cancer patients and controls

| Clinical characteristics | Cases n(57) | Controls n(29) |
|---------------------------------|-----------------------|-----------------------|
| Age | | |
| Median(IQR) | 70 (44-89) | 59 (44-82) |
| <40yrs | 1 (1.75%) | 0 (0.00%) |
| 41-65yrs | 17 (29.82%) | 18 (62.07%) |
| 66-75yrs | 26 (45.61%) | 6 (20.69%) |
| >75yrs | 13 (22.81%) | 5(17.24%) |
| BMI (kg/m2) | | |
| Median(IQR) | 20.84 (16.03-27.61) | 19.45 (17.22-22.46) |
| <18.5 | 8 (14.04%) | 9 (31.03%) |
| 18.5-24.9 | 43 (49.43%) | 20 (68.97%) |
| 25-29.9 | 6 (10.53%) | 0 (0.00%) |
| 30 and above | 0 (0.00%) | 0 (0.00%) |
| Gleason Score | | |
| Median(IQR) | 7 (6-10) | - |
| 6 (3+3) | 13 (22.8%) | - |
| 7 (3+4)or (4+3) | 19 (33.33%) | - |
| 8(4+4) | 10 (17.54%) | - |
| 9 (4+5) | 9 (15.79%) | - |
| 10 (5+5) | 6 (10.53%) | - |
| Plasma PSA (ng/ml) | | |
| Median (IQR) | 33.01 (0.024 - 10000) | 1.8 (0.134-4.00) |
| ≤ 4 | 16 (28.07%) | 29 (100%) |
| 5-20 | 9 (15.79%) | 0 (0.00%) |
| 20-100 | 14 (24.56%) | 0 (0.00%) |
| >100 | 18 (31.58%) | 0 (0.00%) |

Table 2. Plasma levels of PD-1 and PD-L1 between cases and controls

| Immune check point marker | Cases Median (IQR) | Controls Median (IQR) | p-value |
|----------------------------------|-------------------------------|----------------------------------|----------------|
| PD-1 (pg./ml) | 0.596 (0.319 - 0.842) | 0.355 (0.245-0.616) | 0.0170 |
| PD-L1 (pg./ml) | 0.285(0.250 -0.340) | 0.035(0.029-0.045) | 0.0101 |

Table 3: Association between immune checkpoint molecules and age, BMI, PSA, and Gleason score among Prostate cancer patients and controls.

| Participants | Immune Checkpoint Molecules | Age <i>p</i> -value correlation co-efficient (r) | BMI <i>p</i> -value correlation co-efficient (r) | PSA <i>p</i> -value correlation co-efficient (r) | Gleason score <i>p</i> -value correlation co-efficient (r) |
|---------------------------------|-----------------------------|--|--|--|--|
| Cases (N=57) Controls (N=29) | | | | | |
| Cases | sPD-1 | 0.800 (-0.0222) | 0.697 (0.0396) | 0.758 (0.0180) | 0.278 (0.1425) |
| | sPD-L1 | 0.492 (-0.0106) | 0.247 (-0.1863) | 0.485 (0.0657) | 0.014 (0.3165) |
| Controls | sPD-1 | 0.397 (-0.0465) | 0.087 (0.3003) | 0.819 (-0.0538) | N/A |
| | sPD-L1 | 0.039 (-0.2776) | 0.056 (0.2327) | 0.606stata (-0.0556) | N/A |

Figures

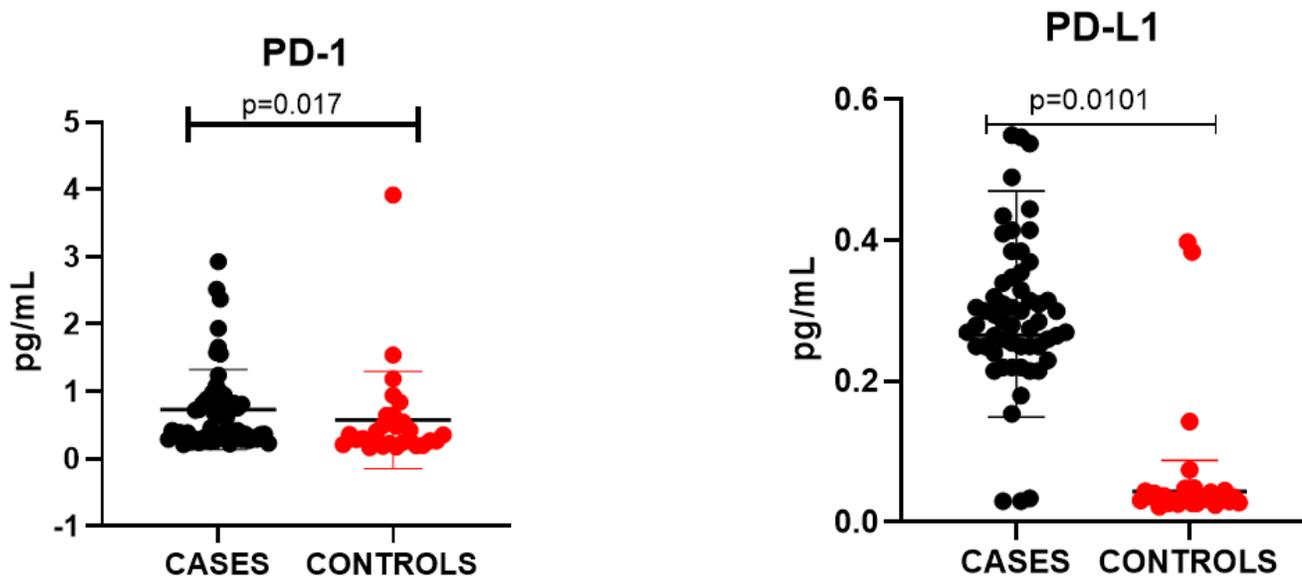


Figure 1

Median concentrations of immune checkpoint molecules in prostate cancer patients and controls.

Supplementary Files

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