

TUMOR MICROENVIRONMENT INTERACTIONS IN PROSTATE CANCER PROGRESSION

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Introduction

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among men. One-third of tumors relapse within two years, progressing to a castration-resistant state. Emerging evidence suggests a role for the tumor microenvironment, with a strong association between inflammatory responses, tumorigenesis, and tumor progression. The relationship between tumors and inflammation is complex and involves multiple mechanisms. The tumor immunome, defined as the complete set of molecules and structures involved in the immune system—including immune receptors, antigens, cytokines, chemokines, immune cells, and genetic components such as MHC molecules—plays a role in every stage of prostate carcinogenesis. The blood immune-inflammatory composition is also characterized by changes in the levels of cytokines and chemokines, which are signaling molecules involved in immune responses. These molecules are often elevated and associated with worse prognosis and castration resistance. Systemic inflammatory responses can be assessed through various blood-based parameters, such as C-reactive protein, platelet count, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR) and SII (systemic immune inflammation index)=platelet count \times neutrophil count/lymphocyte count.

Aim of Study

This study investigates how inflammation affects the tumor microenvironment in prostate cancer, focusing on metastatic castration-resistant cases. In this study we examine immune cell infiltration, their density, and composition in both tumor and non-tumor areas. Moreover, it analyzes systemic inflammatory markers like C-reactive protein (CRP), platelet count, and blood cell ratios (NLR, LMR, PLR). By studying these factors this research aims to explore the relationship between immune cells in tumor tissue and systemic inflammation, helping to better understand immune effects in prostate cancer progression.

Results

Immune infiltration was slightly higher at the tumor margin than in the tumor bed and similar in non-tumor stroma, with lymphocytes as the main component. Macrophages were more common in the tumor bed, while neutrophils were prominent at the margin (Fig. 1a-f). Lymphocyte density negatively correlated with macrophages ($R_s=-0.599$, $p=0.018$) and neutrophils ($R_s=-0.779$, $p=0.005$). Neutrophil density at the invasive margin was linked to time to castration resistance ($R_s=0.615$, $p=0.044$). Macrophage density in the tumor bed correlated with NLR ($R_s=0.867$, $p=0.001$), SII ($R_s=0.752$, $p=0.008$), and cancer-related death ($R_s=0.610$, $p=0.046$). PRAD data linked immune cell levels to outcomes (Fig. 2). Analysis of RNAseq data confirmed abundant immune infiltration in castration-resistant prostate cancer (Fig. 3).

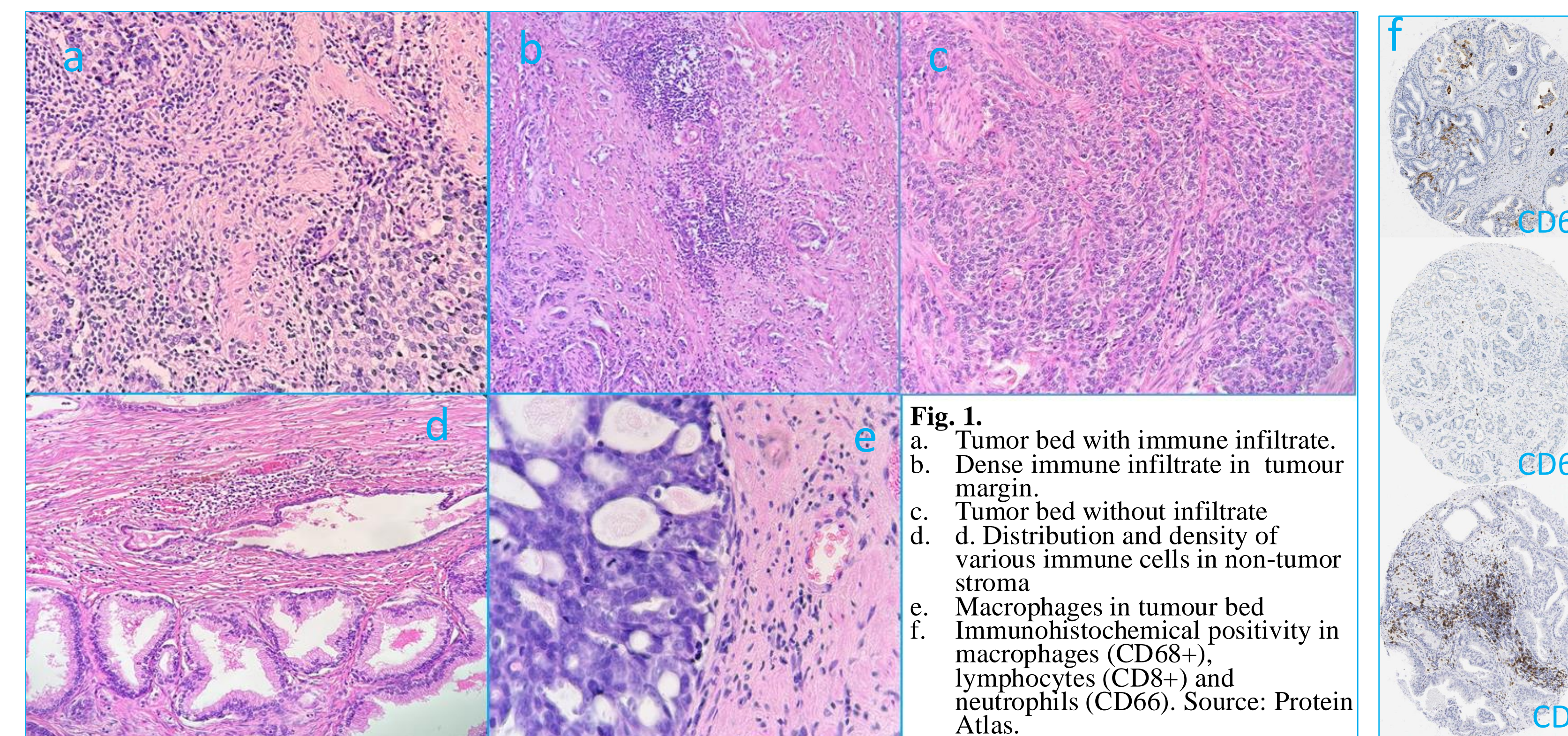


Fig. 1. Tumor bed with immune infiltrate. a. Tumor bed with immune infiltrate. b. Dense immune infiltrate in tumour margin. c. Tumor bed without infiltrate. d. Distribution and density of various immune cells in non-tumor stroma. e. Macrophages in tumour bed. f. Immunohistochemical positivity in macrophages (CD68+), lymphocytes (CD8+) and neutrophils (CD66). Source: Protein Atlas.

Methods

We retrospectively analyzed hematoxylin-eosin-stained prostatectomy/biopsy samples from metastatic castration-resistant prostate cancer cases. Tumor and non-tumor areas were assessed for immune infiltrates, including density (0-3 scale), distribution, and composition (lymphocytes, macrophages, neutrophils). Blood markers (C-reactive protein, platelet count, NLR, LMR, PLR) were collected from lab records. Correlation analysis examined relationships between tissue immune cells and systemic inflammatory markers. Web-based tools (TIMER2, ImmuCellAI, Protein Atlas) were used to further characterize the immune related prostate cancer outcomes.

Conclusions

We demonstrated, for the first time, a possible correlation between the tissue immunome and blood immune indices in castration-resistant prostate cancer cells, whereas, to date, these parameters have been studied independently.

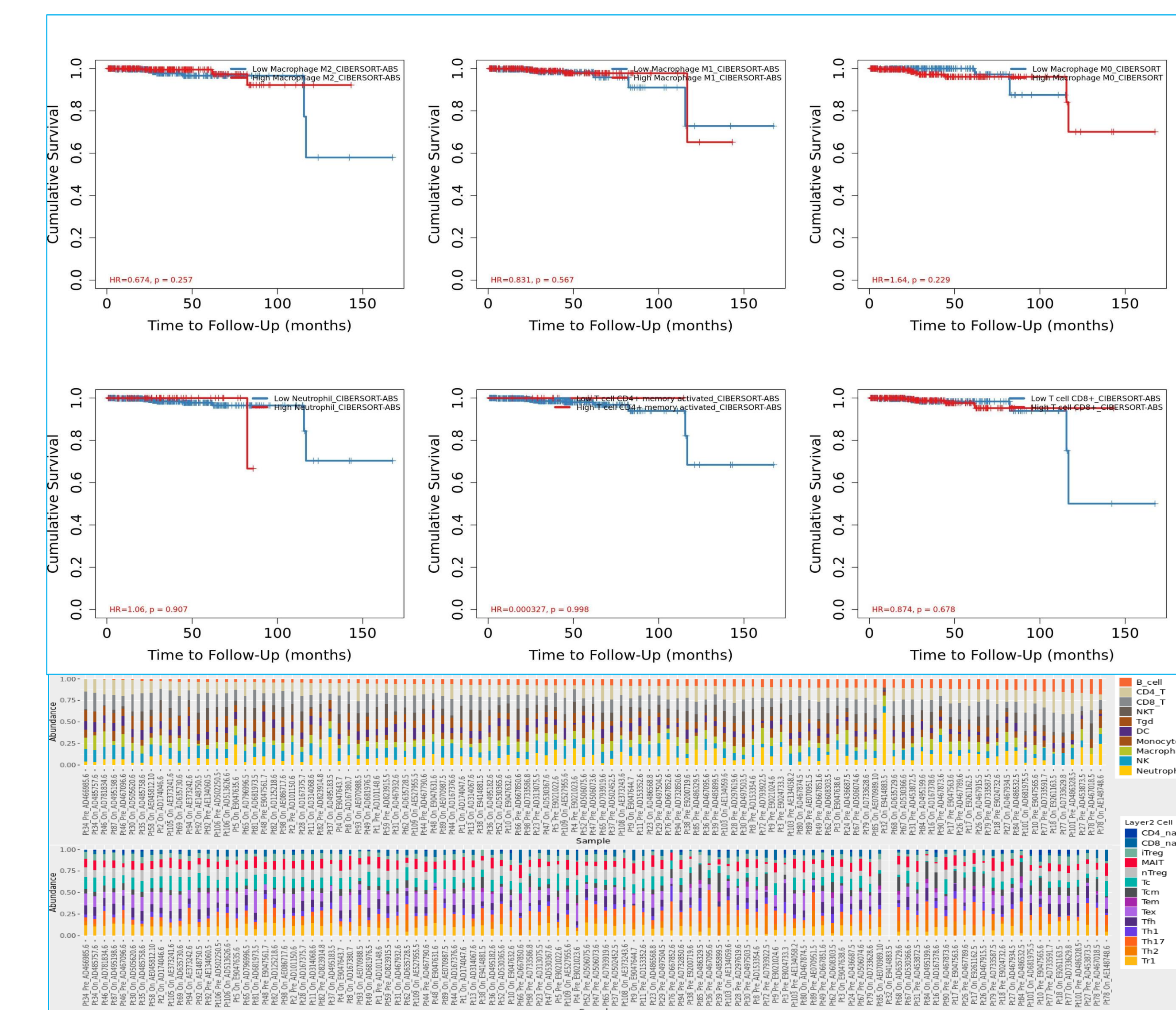


Fig. 2 Association of various immune cells with survival outcomes (overall survival - OS). No significant associations were found. Publicly available prostate adenocarcinoma (PRAD) data. N=498. Source: CIBERSORT.

The limitations of the study could be the tumor heterogeneity, the small sample size and the evaluation of only HE samples without detailed characterization of specific immune cell populations. Immunohistochemistry/multiplex immunofluorescence will be essential for further characterizing immune subpopulations in prostate cancer.

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