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REVIEW

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Immune cell infiltration-based prognosis in prostate cancer: a review of current knowledge

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Abstract

Background Despite the widespread use of tumor immune cell infiltrates as prognostic biomarkers in many cancers, their use in prostate cancer remains relatively unexplored. More recently, many studies are validating the use of tumor-infiltrating lymphocytes, macrophages and neutrophils for predicting cancer progression for other cancers. This review aims to identify what tumor-infiltrating immune cells have prognostic value for prediction prostate cancer progression.

Main body of the abstract PubMed and Scopus were searched for eligible studies published from inception to May 31, 2023. Studies assessing tumor immune cell infiltrates were included. Twenty-six studies met the inclusion criteria. Infiltrating CD4+ and CD8+T cell lymphocytes were prognostic and were associated with improved prostate cancer outcomes. Increased infiltration of M1 and M2 macrophages was prognostic and associated with worsening prostate cancer outcomes. High levels of infiltrating mast cells prognostically improve prostate cancer outcomes. Evidence of increased infiltration of neutrophils, monocytes and dendritic cells are conflicting and will require further studies to validate their role in prostate cancer prognosis.

Short conclusion Despite the widespread use of tumor immune cell infiltrates for prediction outcome of many cancers, their use in prostate cancer is still limited. More evidence is required to help understand the landscape of immune cell infiltrates for predicting prostate cancer outcome.

Key points

1. Tumor-infiltrating immune cells are relevant for improving the clinical outcomes in prostate cancer.
2. Tumor-infiltrating immune cells affect the prostatic tumor microenvironment positively or negatively.
3. The prognosis of prostate cancer is dependent on which immune cells infiltrate the tumor.

Keywords Prostate cancer, Tumor immune cells, Infiltrating immune cells, Prognosis, Prediction

Background

In the year 2020, prostate cancer (PCa) was the 4th leading cancer accounting for 7.3% of global cancers and 3.8% of global cancer deaths. As a very common cancer in males, an estimated 1,414,259 cases of PCa were reported in the year 2020 with 375,304 deaths resulting from PCa (Ferlay et al. 2020, 2021). Though the 5-year survival rate

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of men diagnosed with PCa has been high (Noone et al. 1975), the incidence rate of PCa also remains high. From 2011 to 2015, the incidence rate of PCa was 85.7 and 580.7 cases per 100,000 persons older than 65 years for the world and the US populations, respectively (Noone et al. 1975). As far as the average life expectancy continues to rise, the incidence rate of the PCa will continue to rise.

PCa may initially be without any symptoms. Advanced stages of PCa are accompanied with symptoms such as back pain and urinary retention. Tumor node metastasis (TNM) classification of PCa can be complex. Screening for levels of prostate-specific antigen (PSA) and trans-rectal ultrasound scan are often used for screening for PCa mainly because of the lack of valuable predictive markers (Strasner and Karin 2015). Trans-rectal ultrasound, however, is not useful for staging and has less accuracy compared to pathological biopsies (Borley and Feneley 2009). Genetic markers have also been elusive (Taverna et al. 2013), making PSA the most used method for screening PCa, a method which is highly scrutinized. The introduction of the PSA screening was linked to a dramatic increase in the incidence of PCa from 1988 to 1992 (Brawley 2012; Potosky et al. 1995). Following the US Preventive Services Task Force (USPSTF) recommendations against PSA based screening (Hu et al. 2017; Moyer 2012), the incidence rate of PCa has been on the decline (Negoita et al. 2018). As a result, there has been a decline in the use of PSA testing with an accompanying increase in the burden of late-stage PCa. This implies that a greater proportion of men will be diagnosed with PCa at late stages of the diseases. Also, the previous decline in the mortality rate of PCA has since been leveling off (Negoita et al. 2018). This trend calls for identification and clinical validation of other diagnostic methods for PCa. At present, treatment options for PCa are limited to androgen deprivation therapy (ADT) and prostatectomy for which a subsequent proportion experience reoccurrence or PCa-related death (McLeod 2004).

Research is beginning to focus on alternative PCa treatment interventions and predictive markers. Several studies have found a link between tumor-infiltrating immune cells and cancer prognosis. This method is gaining popularity and possibly might be superior to conventional TNM. Research has shown immune infiltrating cells as relevant for improving clinical manifestations and cure rates in breast cancer (Adams et al. 2197; Manuel et al. 2012; Sui et al. 2020), colorectal cancer (Galon et al. 2006; Liu et al. 2022) and pancreatic ductal adenocarcinoma (Lohneis et al. 2017; Mahajan et al. 2018; Nejati et al. 2017; Tahkola et al. 2018; Wartenberg et al. 2018). The use of inflammatory biomarkers and tumor immune infiltrating cells has been studied in PCa and are proving to be superior to tradition TNM staging classifications (Bardan et al. 2014; Marzo et al. 2007; Elkahwaji 2013; Nakai and Nonomura 2013; Vasto et al. 2008). It is therefore necessary to systematically review the quality of evidence for using immune cell infiltrates for prostate cancer prognosis and predictions.

The aim of this systematic review was to summarize which immune cell infiltrates have been identified as having prognostic and predictive value for PCa progression and treatment.

Methods

This review was conducted following the 2020 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Page et al. 2021). A PRISMA checklist is provided in Additional file 2.

Search strategy

The electronic databases, PubMed (National Library of Medicine, National Center for Biotechnology Information) and Scopus, were searched for relevant studies up to May 31, 2023. Initial search strategy was to scope literature and identify synonyms of prostate cancer and immune cell infiltrates in relation to prostate cancer. Outcome of the initial search was then used to refine the final search strategy for a comprehensive scoping of literature in both databases. A complete list of all search terms is provided in the "Additional file 1: Appendix".

Literature search, using Medical Subject Heading (MeSH) and keywords, was limited to articles written in English language and about prostate cancer in humans. Titles, abstracts and text of each article were reviewed to identify studies investigating the role of tumor immune infiltrate cells in predicting the prognosis of prostate cancer. References within selected studies were also screened for relevance toward being included in this review.

Study selection

After reviewing titles, abstracts and full texts of articles returned by the search strategy, the following criteria were used to determine the eligibility of inclusion of each study in this review.

a. *Population* studies in which participants are males aged 18 years and above and diagnosed of prostate cancer.
b. *Intervention* studies documenting assessment of tumor immune cell infiltrate as prognostic biomarkers.
c. *Comparators* studies comparing the infiltration levels of different immune cells into the prostate in predicting PCa outcomes.

d. *Outcomes* patient survival indicated by measured outcomes such as disease-specific survival, overall survival, disease-free survival or disease outcome indicated by time to recurrence, time to biochemical failure.

Data extraction

For all studies included in this review, the main outcome was using immune cell infiltrates as a predictive tool for patient survival or predicting disease outcome. Data were extracted from all studies that met the inclusion criteria for this review. Publication year, author(s), study design, methods and key finding were among the key information extracted from the included studies.

Data synthesis

All immune cell infiltrates were grouped into classes such as lymphocytes and macrophages. The influence of these infiltrates on the disease outcome was examined based on the main findings from the studies in this review.

Ethical approval and consent

Ethical approval was not required for this systematic review as it did not directly involve any human subjects. It only summarizes data previously published by other studies assumed to have conducted under good ethical principles or granted ethical approval by an Institution Research Board (IRB). This review therefore does not contain any identifiable individual or personal data.

Results

This search produced 343 articles in total (Fig. 1). The title and abstract of all studies were screened. Following the screening, 264 studies were eliminated from this review. Eliminated studies applied prognostic predictors to other tissues/cancers not PCa or studied other biomarkers but not immune cell infiltrates for PCa prognosis. Seventy-nine studies passed the initial screening and were subject to full-text screening for relevance to this review. Ten duplicates were removed, 21 studies were excluded because they were not relevant to scope of this review. Another 21 studies were excluded because they were not related to the focus of this review. One commentary was also excluded. A total of 26 full-text studies were thus included in this review as shown in Table 1.

Characteristics of reviewed studies

All studies that were reviewed were published between 2007 and 2023. Ten (38%) of the studies (Liu et al. 2020, 2022; Davidsson et al. 2013; Feng et al. 2022; Fu et al. 2021; Glud et al. 2022; Meng et al. 2019; Wu et al. 2020a; Xie et al. 2023; Yang et al. 2022) in this review utilized a

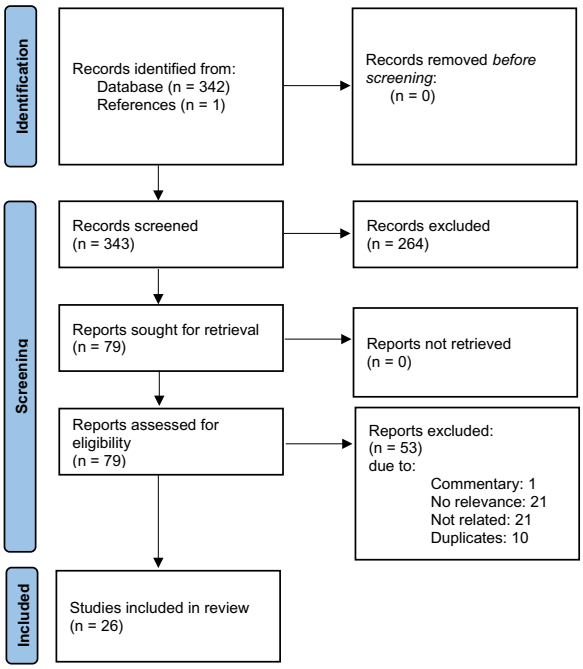

Fig. 1 PRISMA 2020 flow diagram showing process of study selection

case–control study design. Seven (27%) studies (Ma et al. 2021; Nardone et al. 2016; Rui et al. 2019; Watanabe et al. 2019; Zhang et al. 2019, 2020; Zhou et al. 2021) involved a retrospective analysis of patient data, and nine (35%) utilized a prospective approach (Andersen et al. 2021; Erlandsson et al. 2019; Nonomura et al. 2007, 2011; Shao et al. 2020; Sun et al. 2020; Yang et al. 2021; Zeigler-Johnson et al. 2016; Zhao et al. 2021).

Sources of data were mainly from public online databases including The Cancer Genome Atlas (TCGA), the gene expression omnibus (GEO) and from patients diagnosed with PCa. Twelve studies (Feng et al. 2022; Liu et al. 2020; Meng et al. 2019; Wu et al. 2020a; Xie et al. 2023; Yang et al. 2022; Ma et al. 2021; Rui et al. 2019; Zhang et al. 2019, 2020, 2022; Sun et al. 2020) utilized data from strictly online public databases. Four studies (Fu et al. 2021; Glud et al. 2022; Shao et al. 2020; Zhao et al. 2021) used a combination of data from online repositories in addition to data of patients diagnosed with PCa and ten studies (Davidsson et al. 2013; Nardone et al. 2016; Watanabe et al. 2019; Zhou et al. 2021; Andersen et al. 2021; Erlandsson et al. 2019; Nonomura et al. 2007, 2011; Yang et al. 2021; Zeigler-Johnson et al. 2016) used only data of patients diagnosed with PCa in a treatment facility.

Overall survival (OS) was the widely used outcome measure. Eight studies measured overall survival and how tumor immune infiltrates affect OS (Wu et al. 2020a; Yang et al. 2021, 2022; Nardone et al. 2016; Zhou et al.

Table 1 Characteristics of studies included in this review

References	Source of data	Study design	Sample size
Xie et al. (2023)	TCGA	Case–control	519
Glud et al. (2022)	Patients with Pca, Denmark; TCGA	Case–control	181
Fu et al. (2021)	TCGA; GEO; Pca patients, China	Case–control	427
Zhou et al. (2021)	Patients with Pca, China	Retrospective	239
Ma et al. (2021)	TCGA	Retrospective	495
Yang et al. (2021)	Patients with Pca, USA	Prospective	230
Liu et al. (2020)	TCGA	Case–control	550
Sun et al. (2020)	TCGA	Prospective	490
Wu et al. (2020a)	TCGA; GEO	Case–control	727
Shao et al. (2020)	TCGA; GEO; Pca patients, China	Prospective	882
Zhang et al. (2019)	TCGA; GEO	Retrospective	472
Watanabe et al. (2019)	Patients with Pca, Japan	Retrospective	75
Meng et al. (2019)	TCGA	Case–control	84
Nardone et al. (2016)	Patients with Pca, Italy	Retrospective	22
Zeigler-Johnson et al. (2016)	Patients with Pca, USA	Prospective	99
Davidsson et al. (2013)	Patients with Pca, Sweden	Case–control	735
Nonomura et al. (2011)	Prostate cancer patients, Japan	Prospective	71
Nonomura et al. (2007)	Patients with Pca, Japan	Prospective	104
Andersen et al. (2021)	Patients with Pca, Denmark	Prospective	902
Erlandsson et al. (2019)	Patients with PCa, Sweden	Prospective	592
Yang et al. (2022)	TCGA	Case–control	550
Feng et al. (2022)	TCGA	Case–control	550
Zhang et al. (2022)	TCGA	Case–control	219
Zhao et al. (2021)	Patients with Pca, USA; TCGA	Prospective	605
Zhang et al. (2020)	TCGA	Retrospective	487
Rui et al. (2019)	TCGA; GEO	Retrospective	372

PCa prostate cancer, *GEO* gene expression omnibus, *TCGA* The Cancer Genome Atlas, *USA* United States of America

2021; Erlandsson et al. 2019; Shao et al. 2020; Sun et al. 2020). Four studies (Feng et al. 2022; Xie et al. 2023; Nardone et al. 2016; Zhang et al. 2022) reported progression-free survival (PFS), same as recurrence-free survival (RFS) (Glud et al. 2022; Meng et al. 2019; Zhang et al. 2019; Nonomura et al. 2011) and biochemical recurrence (BR) (Liu et al. 2020; Zhang et al. 2020; Andersen et al. 2021; Shao et al. 2020). The characteristics of the included studies and the summary of findings are presented in Tables 1 and 2.

Immune cell infiltration biomarkers

T cells

Nineteen (19) studies (Davidsson et al. 2013; Feng et al. 2022; Fu et al. 2021; Glud et al. 2022; Liu et al. 2020; Wu et al. 2020a; Xie et al. 2023; Yang et al. 2022; Ma et al. 2021; Nardone et al. 2016; Rui et al. 2019; Watanabe et al. 2019; Zhang et al. 2020; Zhou et al. 2021; Andersen et al. 2021; Shao et al. 2020; Sun et al. 2020; Zeigler-Johnson et al. 2016; Zhao et al. 2021) assessed the effect of tumor-infiltrating lymphocytes (TILs) on PCa outcomes. The association between TILs and disease outcome measured by OS, DFS, RFS, PFS, CSS or BCF were assessed in all studies. The most common T cell assessed was CD8+. Nine studies (Fu et al. 2021; Glud et al. 2022; Liu et al. 2020; Wu et al. 2020a; Xie et al. 2023; Nardone et al. 2016; Zhou et al. 2021; Yang et al. 2021; Zeigler-Johnson et al. 2016) measured CD8+ as a prognostic biomarker for PCa. Eight of these studies (Fu et al. 2021; Glud et al. 2022; Liu et al. 2020; Xie et al. 2023; Nardone et al. 2016; Zhang et al. 2020; Zhou et al. 2021; Yang et al. 2021) reported an improved disease outcome with increased infiltration of CD8+. In the study by Zhou et al. (2021), Zeigler-Johnson et al. (2016) and Wu et al. (2020a) higher counts CD8+ was found to be associated with increased risk of BCF (PCa recurrence after prostatectomy), OS or CSS and OS, respectively (Wu et al. 2020a; Zhou et al. 2021; Zeigler-Johnson et al. 2016).

Five studies (Davidsson et al. 2013; Fu et al. 2021; Xie et al. 2023; Yang et al. 2022; Zhao et al. 2021) reported on the use of CD4+ as a prognostic biomarker for predicting PCa outcome. Three of these studies (Fu et al. 2021;

Table 2 Summary of findings of study included in review

Authors	Goal	Outcome(s) of interest	Summary of study
Xie et al.	Examine the relationship between risk signature and clinical parameters	Progression-free survival (PFS)	Strong positive correlation of risk scores with CD8+T cells and regulatory T cells (Tregs) infiltration Strong negative correlation was observed with follicular helper T cells and resting memory CD4+T cells
Glud et al.	Investigate the prostate-specific membrane antigen expression and CD8+T cells infiltration of PCa tumor	Recurrence-free survival (RFS)	CD8+T cell infiltrating score was elevated in metastatic prostate cancer tissue as compared with normal, adjacent normal, localized prostate cancer tissues ($p < 0.05$)
Fu et al.	To identify immune genes that exhibit a high correlation with prostate cancer recurrence	Cancer recurrence	Reduced infiltration by neutrophils, activated mast cells, CD4 memory-activated T cells and CD4 memory resting T cells results in increased rate of recurrence Increased influx of macrophages M2 and regulatory T cells (Tregs) increased risk of recurrence and a reduced rate of DFS ($p < 0.01$) The group classified as low-risk demonstrated elevated levels of immune cell infiltration, including CD8+T cells, CD4+T cells, macrophages, dendritic cells and neutrophils
Zhou et al.	The study examined the infiltration of CD8+and Foxp3+lymphocytes in 239 prostate cancer (PCa) tissues. It aimed to establish a new immune classification by considering the expression of B7-H3 and HHLA2, as well as the density of tumor-infiltrating T cells	Overall survival (OS) and cancer-specific survival (CSS)	The immune type IV, characterized by a high B7-H3 score and low levels of CD8+tumor-infiltrating lymphocytes (TILs), exhibited a more significant correlation with poor overall survival (OS) and cancer-specific survival (CSS) On the other hand, the immune type I, characterized by a low B7-H3 score and high levels of CD8+TILs, showed a significant correlation with improved overall survival (OS) and cancer-specific survival (CSS)
Ma et al.	Low versus high-level infiltration phenotype on PCa prognosis	Disease-free survival	The high-level cluster was associated with a shorter DFS when compared to the low-level cluster ($p = 0.020$). Myeloid-derived suppressor cells (MDSCs), Th1 cells, T helper cells, Tgd and plasmacytoid dendritic cells (pDC) demonstrated the highest prognostic value. Furthermore, the high-level cluster exhibited a higher abundance of these cells
Yang et al.	Significance of CD8+tumor Infiltration lymphocyte (TIL) in radical prostatectomy	Overall survival	High CD8+tumor-infiltrating lymphocyte (TIL) density is linked to improvement in a 5-year OS rates (98% vs. 91%; $p = 0.01$) and PCa-specific survival rates (99% vs. 95%; $p = 0.04$) compared to the low CD8+TIL density group Additionally, the high CD8+TIL density group demonstrated an increased 5-year biochemical recurrence-free survival (BRFS) and metastasis-free survival (MFS) rates
Liu et al.	Investigate the relationships between gene expression patterns and immune cell infiltration in prostate cancer	Biochemical recurrence	In the high-risk group, there were higher levels of infiltration observed for memory B cells, regulatory T cells, M2 macrophages and dendritic cells. On the other hand, in the low-score group, higher levels of infiltration were observed for activated mast cells, monocytes and CD8+T cells

Table 2 (continued)

Authors	Goal	Outcome(s) of interest	Summary of study
Sun et al.	Investigate the relationship between the tumor microenvironment and prostate cancer prognosis	Overall survival	Prostate cancer (PCa) tumors exhibiting higher immune scores demonstrate increased infiltration of macrophages, B cells, T cells and monocytes The group with lower immune scores exhibited a significantly decreased survival rate
Wu et al.	Patterns of immune cells infiltration and potential as prognostic biomarkers in the microenvironment of prostate cancer (PCa)	Overall survival	An increased presence of M1 macrophages and neutrophils in the tumor microenvironment was associated with a poor prognosis There was a consistent trend of reduced infiltration observed for T and mast cells in PCa tissues. Conversely, B and NK cell infiltration was increased significantly M2 macrophages, CD8+T cells, resting NK cells, memory B cells and activated dendritic cells showed a positive correlation with the malignancy of PCa Naive B cells, resting dendritic cells and activated NK cells demonstrated a negative correlation with the degree of malignancy
Shao et al.	Develop a gene signature for predicting PCa prognosis	Biochemical recurrence; overall survival	Patients with a low-risk score exhibited significantly longer overall survival (OS) compared with the high-risk score group ($p = 0.01$, 0.04, 0.02, respectively) The signature also indicated a higher likelihood of regulatory T cell (Treg) infiltration, as well as infiltration of both M1 and M2-polarized macrophages in patients with a high-risk score and prostate cancer (PCa) Furthermore, patients with a higher Gleason score demonstrated increased infiltration of M2-polarized macrophages
Zhang et al.	Evaluate tumor-infiltrating M2 macrophages (TIMMs) in localized PCa and explore its correlation with clinical parameters	Recurrence-free survival	Patients with high tumor-infiltrating immune microenvironment (TIMMs) experienced significantly poorer recurrence-free survival (RFS)
Watanabe et al.	Evaluate the infiltration of CCR4+ regulatory T cells (Tregs) in prostate cancer tissues; clarify the relationship between CCR4+ Treg infiltration and clinical outcomes (Gleason score, PSA, time to castration-resistant prostate cancer (CRPC))	Time of progression to castration-resistant prostate cancer; Gleason score; PSA levels; survival time	In biopsy specimens, 65.9% Tregs were positive for CCR4. The number of CCR4+Tregs positively correlated with clinical stage ($p < 0.001$) and Gleason score ($p = 0.006$). The poor prognosis group exhibited a significant increase in the total number of regulatory T cells (Tregs) and CCR4+Tregs compared to the good prognosis group ($p = 0.024$ and 0.01, respectively) Lower levels of CCR4+Tregs correlated to a significantly longer time to progression to castration-resistant prostate cancer (CRPC) (not reached vs 27.3 months; $p < 0.001$) and a higher median survival time (not reached vs. 69.0 months; $p = 0.014$)

Table 2 (continued)

Authors	Goal	Outcome(s) of interest	Summary of study
Meng et al.	Associations between TIICs and recurrence-free survival (RFS)	Recurrence-free survival	An increased proportion of M2 macrophages in prostate cancer (PCa) is linked to a poor prognosis, with a mean recurrence-free survival (RFS) of 819.11 days. Conversely, a lower proportion of M2 macrophages is associated with a more prolonged RFS, with a mean RFS of 992.65 days ($p = 0.025$)
Nardone et al.	Use tumor immune lymphocyte infiltration of tumor tissues for predicting prostate cancer outcome	Overall survival, post radiotherapy progression-free survival (PFS), biochemical progression-free survival (bPFS)	Higher peripheral stromal CD8 and lower PD-1 TIL scores correlated to a longer biochemical PFS Higher peripheral stromal CD8 and intratumoral CCR7 TIL scores correlated to a prolonged PFS and OS Lower peripheral stromal CD45 and peripheral stromal FoxP3 TIL scores correlated to a prolonged PFS and OS
Zeigler-Johnson et al.	Understanding prostatic inflammation by infiltrating lymphocytes and macrophages characterized by severity of the cancer	Time to biochemical failure	Regardless of obesity status, advanced tumor grade was significantly associated with higher CD68 cell counts ($p = 0.019$) In contrast, higher CD8 cell counts was linked to an increased biochemical failure
Davidsson et al.	Investigate the associoation between T helper cells, T cytotoxic cells, or CD4+ Treg cells and lethal prostate cancer	Cancer-specific mortality; All-cause mortality	Men who have a higher abundance of CD4+ regulatory T cells (Tregs) within their prostate tumor microenvironment face an increased risk of succumbing to the disease On the other hand, there was no observed association between T cytotoxic cells and lethal prostate cancer
Nonomura et al.	To access the use of prostate infiltrating tumor associate macrophages for prognosis after hormonal therapy	Recurrence-free survival	Tumor-associated macrophages (TAMs) count is positively correlated with higher serum PSA levels, higher Gleason score, advanced clinical stage and PSA failure Furthermore, patients with lower TAM counts have better recurrence-free survival compared to those with higher TAM counts ($p < 0.001$)
Nonomura et al.	Access the potential of mast cell accumulation around prostate cancer (PCa) as a prognostic factor	PSA-free survival	Elevated mast cell counts are significantly correlated with better prostate-specific antigen (PSA)-free survival compared to those with lower mast cell counts ($p < 0.001$)
Andersen et al.	Evaluate and characterize the potential of different immune cell as prognostic markers of prostate cancer	Biochemical recurrence	The presence of elevated levels of infiltrating regulatory T cells (Tregs), as well as M1 and M2 macrophages in the stroma and/or epithelium, was found to be significantly correlated with biochemical recurrence ($p < 0.05$)
Erlandsson et al.	Assess the prognostic value of M2 macrophages in a large cohort of prostate cancer patients	Overall survival	Men who exhibited a high abundance of M2 macrophages had approximately double the odds of experiencing prostate cancer-related mortality (odds ratio: 2.05; 95% confidence interval 1.46–2.88)
Yang et al.	Construct a prognostic model with the immune infiltration landscape for PCa status	Overall survival; Disease-free survival	Enrichment of neutrophils ($p = 0.024$), and M2 macrophages ($p = 0.007$) in high-risk group while the low-risk group exhibited a significant accumulation of CD4-activated memory T cells ($p = 0.017$)

Table 2 (continued)

Authors	Goal	Outcome(s) of interest	Summary of study
Feng et al.	Develop a predictive model for prostate cancer (PCa) progression using CIC (cancer-interacting cell)-related genes	Progression-free survival (PFS)	Tumor samples displayed elevated counts of myeloid dendritic cells, macrophages and T cells compared to the non-tumor samples Levels of mast cells, neutrophils, T helper type 1 (Th1) cells and NK cells were significantly decreased in patients with a high-risk score
Zhang et al.	The dysregulation of glycolytic enzymes and its impact on prostate cancer (PCa)	Progression-free survival	There was a significant negative association between higher risk scores and lower levels of NK cell infiltration, neutrophil cell infiltration and macrophage M2 cell infiltration. Conversely, higher risk scores were significantly positively correlated with increased levels of myeloid dendritic cell infiltration in PCa
Zhao et al.	Develop and validate an immune-related gene (IRG)-based signature to predict the prognosis of prostate adenocarcinoma (PRAD)	Biochemical failure	The high-risk group exhibited elevated infiltration levels of regulatory T cells and CD4+ memory-activated T cells compared to the low-risk group ($p < 0.05$) In contrast, the high-risk group displayed significantly reduced infiltration of neutrophils, monocytes and activated mast cells ($p < 0.05$) Higher infiltration levels of CD8+ T cells was mostly found in the high-risk group
Zhang et al.	To develop a predictive model for assessing the prognostic risk of patients	Disease-free survival: biochemical recurrence; cancer-specific death	There was a notable increase in the infiltration of M0, M1, M2 macrophages, naive B cells and plasma cells within the tumor microenvironment of the high-risk group A significantly higher infiltration of activated mast cells, CD8 T cells, resting dendritic cells, monocytes and activated dendritic cells in the low-risk group
Rui et al.	Assess the extent of prostate infiltration by immune cells and to examine the association between tumor recurrence and immune cells	Cancer recurrence	Th2 cells and Tcm cells exhibit a beneficially protective role in reducing prostate cancer recurrence (HR < 1) There is an inverse relationship between the extent of infiltration of Th2 cells and Tcm cells and the recurrence prostate cancer, with higher levels of infiltration associated with lower recurrence rates

Yang et al. 2022; Xie et al. 2017) reported improvement in disease outcome (cancer recurrence, OS and PFS) with increasing infiltration of CD4+ T cells. Contrarily, studies conducted by Zhao et al. (2021) and Davidsson et al. (2013) reported a worsening of PCa outcome with increased infiltration of CD4+ T cells.

Other cells such as Th1, Th2, CCR4+ Treg, CCR7+ Treg, Tgd, Tcm, CD3, CD8 CD68 and CD45 were also studied by some of the included studies (Feng et al. 2022; Ma et al. 2021; Nardone et al. 2016; Rui et al. 2019; Watanabe et al. 2019; Zeigler-Johnson et al. 2016). Ma et al. (2021) found significantly shorter DFS periods in patients with increased infiltration of Th1 and Tgd cells (Ma et al. 2021). In the study by Nardone et al. (2016), higher infiltration level of CD45+ and FOXP3+ into the peripheral stroma was found to correlate with prolonged PFS and OS. Higher infiltration levels of CD8+ into the peripheral stroma and higher intratumoral CCR7+ were also found to correlate with prolonged PFS and OS (Nardone et al. 2016).

Macrophages

Fourteen studies (Feng et al. 2022; Glud et al. 2022; Liu et al. 2020; Meng et al. 2019; Wu et al. 2020a; Yang et al. 2022; Zhang et al. 2019, 2020, 2022; Andersen et al. 2021; Erlandsson et al. 2019; Nonomura et al. 2011; Shao et al. 2020; Sun et al. 2020) evaluated the role of tumor-infiltrating macrophages on PCa prognosis. M2 macrophages were widely reported by ten (10) of these studies (Fu et al. 2021; Liu et al. 2020; Meng et al. 2019; Wu et al. 2020a; Yang et al. 2022; Zhang et al. 2019, 2022; Andersen et al. 2021; Erlandsson et al. 2019; Shao et al. 2020). All ten studies reported a poor prognosis with increased infiltration of M2 macrophages in patients. Four (4) studies (Wu et al. 2020a; Zhang et al. 2020; Andersen et al. 2021; Shao et al. 2020) reported the prognostic value of M1 macrophages for PCa. These four studies observed that increased infiltration of M1 macrophages is associated with poor disease outcomes. Only one (1) study (Zhang et al. 2020) investigated the role of M0 macrophages in prostate cancer prognosis and reported an increased infiltration of M0 macrophages into the prostate tissue of patients with high risk of cancer-specific death (CSD), disease-free survival (DFS) or biochemical recurrence (BR).

Neutrophils

Six studies (Feng et al. 2022; Fu et al. 2021; Wu et al. 2020a; Yang et al. 2022; Zhao et al. 2021; Zhang et al. 2022) accessed the role of infiltrating neutrophils in PCa prognosis. Four (Feng et al. 2022; Fu et al. 2021; Zhao et al. 2021; Zhang et al. 2022) of the six studies reported improved PCa outcomes with increased infiltration of neutrophils. On the contrast, the studies by Wu et al. (2020a,) and Yang et al. (2022) reported poorer prognosis with increased infiltration of tissue by neutrophils (Wu et al. 2020a; Yang et al. 2022).

Dendritic cells

Six studies (Feng et al. 2022; Fu et al. 2021; Liu et al. 2020; Wu et al. 2020; Zhang et al. 2020, 2022) reported on the role of infiltrating dendritic cells on the prognosis of PCa. Two studies (Fu et al. 2021; Zhang et al. 2020) reported improved PCa prognosis with increased infiltration of dendritic cells and three other studies (Liu et al. 2022; Feng et al. 2022; Zhang et al. 2022) also reported, contrastingly, poor prognosis with increased infiltration. The study by Wu et al. (2020a) reported improved prognosis with increased infiltration of resting dendritic cells and worsening prognosis with increased infiltration of activated dendritic cells (Zhao et al. 2021).

Mast cells

Seven (7) studies (Feng et al. 2022; Fu et al. 2021; Liu et al. 2020; Wu et al. 2020a; Zhang et al. 2020; Nonomura et al. 2011; Zhao et al. 2021) assessed the role of mast cells infiltration tumor on PCa outcomes such as OS, BF, BR and PFS. All seven studies reported improved prognosis or a reduction in the risk scores of PCa when there was higher infiltration of mast cells into the cancer tissue.

Monocytes

Four of the studies (Liu et al. 2020; Zhang et al. 2020; Sun et al. 2020; Zhao et al. 2021) included in this review assessed the role of monocytes on the PCa prognosis when they infiltrate the cancer tissue. Of the fours studies assessing monocytes for PCa prognosis, only one study (Sun et al. 2020) reported worsening prognosis (OS) with increased infiltration of monocytes. The remaining three studies (Liu et al. 2020; Zhang et al. 2020; Zhao et al. 2021) reported improvements of BR, BF, DSF, CSD with increased monocytes infiltrating the prostate tumor.

Other immune cells

Other immune cells such as natural killer (NK) cells and B cells were reported by a relatively few of the studies included in this review.

Three studies (Feng et al. 2022; Wu et al. 2020a; Zhang et al. 2022) assessed NK cells and three other studies assessed B cells. Of these, two (Feng et al. 2022; Zhang et al. 2022) reported favorable PCa prognosis with increased NK cells infiltration. The study by Wu et al. (2020a) also reported improved prognosis with infiltration of activated NK cells but worsened prognosis with reduction in NK cell infiltration (Wu et al. 2020a).

B cells were reported by all 3 studies (Liu et al. 2020; Wu et al. 2020a; Zhang et al. 2020) that assessed it to have a positive correlation with either the degree of malignancy or risk score and therefore resulting in a poorer prognosis (OS and BF).

Discussion

This systematic review sort to summarize which tumor-infiltrating immune cells have prognostic significance for the progression of prostate cancer. Twenty-six (26) studies were identified for this review. The results, mostly consistent but scanty, makes a case for considering tumor-infiltrating lymphocytes (T cells), macrophages and mast cells as prognostic biomarkers for predicting the outcome of prostate cancer. Overall, the results of this review are consistent with the findings of other cancer studies. The narrow scope of results limits the generalizability of findings to PCa.

CD4+ and CD8+ T cells

Findings of increased infiltration of CD4+ and CD8+ into prostate tissue are consistent with finding of other cancers (Galon et al. 2006; Tewari et al. 2013). Similar to T helper 1 (Th1), CD8+ cells have antitumor activity and therefore promote against the progression of cancer in a manner similar to T helper 1 (Th1) cells. It is this Th1-like activity of CD8+ and CD4+ that explains for the PCa outcomes (progression-free survival and overall survival). Cancer theory suggests that tumor cells may be eliminated by immune system of host, or remain in equilibrium (proliferation rate same as destruction rate) or escape the immune response altogether (Dunn et al. 2002). Due to the Th1 activity of T cells, CD8+ and CD4+, high levels of infiltration may help to reach partial removal or equilibrium in tumors producing an improvement in disease-free survival (DFS) (McGuigan et al. 2021). Overall, the findings of this review suggest that increased infiltration of prostate tissue by T cell lymphocytes (CD8+ and CD4+) was associated with improved survival outcomes. Majority of the studies in this review reported increased tumor infiltration with improved PCa outcomes such as OS. There seem to be a consensus among some studies indicating that infiltrating CD4+ and CD8+ into tumor tissues results in reduced cancer recurrence (Fu et al. 2021), improved RFS (Glud et al. 2022), improved PFS (Xie et al. 2023) and improved OS (Nardone et al. 2016; Yang et al. 2021). This points to the importance of CD4+ and CD8+ T cells as prognostic markers for PCa.

M1 and M2 macrophages

Without controversy, it appears that infiltration of macrophages into tumor tissues is associated with worsening prognosis. In hepatocellular carcinoma, triple negative breast cancer and follicular lymphoma, increased infiltration by macrophages is associated with poor overall survival. M2 macrophages promote tumor growth and invasion by angiogenesis. Therefore, increased infiltration of M2 macrophages should be associated with poor cancer outcomes. This supports the findings of Meng et al. (2019) who observed a reduced RFS for PCa patients with increased infiltration of M2 macrophages (Meng et al. 2019). This review has shown that infiltrating M2 and M1 macrophages into PCa tumors results in poor disease outcomes. Feng et al. (2022) have demonstrated a higher tumor infiltration density of macrophages than normal cells (Feng et al. 2022). M2 infiltration has been demonstrated by Erlandsson et al. (2019) to result in a two-fold increase in the odds of dying of PCa (Erlandsson et al. 2019). Studies have associated higher tumor density of macrophages with tumor cell proliferation, drug resistance, immune suppression and tumor vascularity (Komohara et al. 2014, 2015). By releasing growth factors such as epidermal growth factor (EGF) which promotes cancer cell proliferation, macrophages are able to induce cancer cell growth (Helm et al. 2014). Macrophages also produce extracellular matrix degrading enzymes and other proteases which disintegrate the extracellular matrix allowing cancer cells to escape (Gocheva et al. 2010). These are just a few of the mechanisms by which macrophages contribute to cancer progression and subsequently, poorer disease outcomes. The results of this review on both and M1 and M2 macrophages are convincing and points to strong evidence for the use of macrophage density in tumor cells as an early biomarker for PCa diagnosis and prognosis.

Neutrophils

Evidence suggest that tumor infiltration by neutrophils correlates with poor tumor prognosis (Masucci et al. 2019). As an independent prognostic factor, intratumoral neutrophil suggests short recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) (Masucci et al. 2019). The results of the studies by Wu et al. (2020a) and Yang et al. (2022) confirm this finding by reporting a worsened prognosis with increased infiltration of tumor by neutrophils (Wu et al. 2020a; Yang et al. 2022). Contrary to these findings, neutrophils are known to produce a number of antimicrobial mediators that have potential tumoricidal activity. They also recruit and activate immune cells that are able to elicit antitumor immune responses, release a range of cytokines, chemokines and proteases that play roles in T cell production (Zhang et al. 2016). This is the possible reason neutrophil infiltration is associated with improved cancer outcome as observed in other studies.

Evidence from this review corroborates the activities of neutrophils which suggest that increased infiltration of neutrophils into prostate tissue is associated with lower risks of biochemical failure (Zhao et al. 2021). Even though neutrophils infiltration is becoming an important predictor for cancer progression, more studies are required to validate its use for PCa as the current evidence are strongly contrasting.

Dendritic cells

Evidence from this review is highly conflicting on the role of dendritic cell in PCa prognosis. In this review, Fu et al. (2021) as well as Zhang et al. (2020) have demonstrated the favorable prognosis of PCa with higher infiltration of dendritic cells (Fu et al. 2021; Zhang et al. 2020) whiles the studies by Liu et al. (2020), Feng et al. (2022) and Zhang et al. (2022) point to unfavorable prognosis of PCa with increased dendritic cell infiltration in PCa (Feng et al. 2022; Liu et al. 2020; Zhang et al. 2022). This depicts the current state of evidence of the role of dendritic cells in cancer prognosis. Some research findings indicate an improved outcomes (decreased recurrence and improved survival) with increased dendritic cell density in the tumor tissue in general cancers (Goldman et al. 1998; Hillenbrand et al. 1999; Rocca et al. 2008; Reichert et al. 2001) but others also point to worsened outcome in breast cancer with increased infiltration of plasmacytoid dendritic cells (Sisirak et al. 2012; Treilleux et al. 2004). Tissue dendritic cells are made of different subsets of developmental and functional subsets that differentially regulate the function of T lymphocytes (Merad et al. 2013). There require more study of these cells to better appreciate their role in cancer prognosis (Szpor et al. 2021).

Mast cells

There is agreement between all studies included in this review that assessed the role of mast cell infiltration in PCa prognosis. All studies reported improved disease outcomes with mast cell infiltration. The similarity in findings of all seven studies points to the usability of mast cells as early diagnostic and prognostic markers for PCa. The role of mast cells in different cancers is poorly understood. Their infiltration appears to be beneficial in some cancers but not others, suggesting that their role (either tumor suppressing or promoting) is tumor-dependent (Varricchi et al. 2017). In metastatic renal cell carcinoma (mRCC), high mast cell density has been to shown to correlate with better OS (Yao et al. 2021). Similarly, increased mast cells levels correlate with tumor progression in gastric cancer (Lv et al. 2019), tumor aggression in pancreatic adenocarcinoma (Molderings et al. 1889) and hepatocellular adenocarcinoma (Terada and Matsunaga 2000). From this review, it appears that mast cells infiltration in PCa is associated with improved disease outcomes. This calls for further studies into the mechanism by which mast cells offer protection in prostate cancer.

Monocytes

In this review, it appears that higher levels of infiltrating monocytes into PCa tissues are associated with improvements of disease outcomes as demonstrated by Liu et al. (2020), Zhang et al. (2020) and Zhao et al. (2021). Even though it appears that monocytes infiltration is becoming an important predictor for cancer progression, more studies are required to validate its use for PCa. Considering that only a few studies have evaluated monocytes infiltration in prostate cancer, the finding of this review that monocyte infiltration can be beneficial for PCa prognosis is to be taken with caution. Studies of other cancers has shown that monocyte infiltration in colon cancer is associated with poor prognosis (Wu et al. 2020b) as demonstrated by Sun et al. (2020) who reported worsening of OS with increased infiltration of monocytes into prostate tumors (Sun et al. 2020). Since monocytes are precursors of macrophages, it is possible that they will have a similar effect on the tumor microenvironment as macrophages which has been shown to have a negative association with PCa prognosis.

Other immune cells

Other immune cells such as NK cells and B cells were reported by a relatively few studies. This makes generalizing their finding extremely risky. More studies would be needed to determine the pattern of infiltration of such cells and their impact of prognosis. It still worthy of notice that higher infiltration levels of B cells, according to 3 studies in this review, increase the risk of any adverse events occurring from PCa or even the malignancy of PCa (Liu et al. 2020; Wu et al. 2020a; Zhang et al. 2020). This is in contrast to the improved patient prognosis with infiltration of naïve B cells into neuroblastoma (Schaafsma et al. 2021).

Present evidence suggests that NK cell infiltration results in improved outcomes (Cózar et al. 2021; Nersesian et al. 2020) similar to what was reported by 3 studies in this review (Feng et al. 2022; Wu et al. 2020a; Zhang et al. 2022).

Conclusions

The result of this review shows the paucity of studies that have explored the use of tumor-infiltrating cells as prognostic biomarkers for prostate cancer. There appears to be a consensus regarding the infiltration of prostate tumors by lymphocytes, especially CD8+ and CD4+ cells; M1 and M2 macrophages; and mast cells

as potential prognostic biomarkers for prostate cancer. Increased infiltration of CD4+ and CD8+ in prostate tissue is associated with improved prostate cancer-specific survival, disease-free survival, biochemical failure and overall survival. Increased infiltration of M1 and M2 macrophages is be associated with a reduced recurrence-free survival and poor overall survival. The evidence supporting the use of neutrophils, monocytes and dendritic cells is lacking and conflicting. It is important that further work is conducted in this under-researched area to validate the clinical use of tumor-infiltrating immune cells for prostate cancer prognostics. Effective predictors and biomarkers with clinical applicability cannot be established until strong evidence is established.

Abbreviations

ADT	Androgen deprivation therapy
BF	Biochemical failure
BR	Biochemical recurrence
CSD	Cancer-specific death
CSS	Cancer-specific survival
DFS	Disease-free survival
EGF	Epidermal growth factor
GEO	Gene expression omnibus
IRB	Institutional review board
MeSH	Medical subject heading
mRCC	Metastatic renal cell carcinoma
NK	Natural killer
OS	Overall survival
PCa	Prostate cancer
PFS	Progression-free survival
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RFS	Recurrence-free survival
TCGA	The cancer genome atlas
TILS	Tumor-infiltrating lymphocytes
Th1	T helper 1
Th2	T helper 2
TNM	Tumor node metastasis

Supplementary Information

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Additional file 1. Table of search terms and search results.

Additional file 2. PRISMA 2020 checklist.

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