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Meta-Analysis

A Meta-Analysis on the Prognostic and Predictive Role of Stem-like CD8+ T Cells in Cancer Immunotherapy: Correlating Clinical Outcomes

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Abstract

Background: Stem-like CD8+ T cells, marked by TCF1 and PD-1, possess self-renewal and effector differentiation abilities, crucial for cancer immunotherapy. Despite tumor microenvironment constraints, their abundance often correlates with favourable outcomes.

Aim: To assess the prognostic and predictive relevance of stem-like CD8+ T cells in patients receiving immunotherapy for cancer.

Methodology: 721 publications from PubMed, Embase, Scopus, and Web of Science (2015–2025) were evaluated in accordance with PRISMA 2020 guidelines. 8 studies were included in the meta-analysis. Two independent reviewers conducted data extraction. Pooled hazard ratios (HRs) and confidence intervals (CIs) were calculated using RevMan software, and the I^2 statistic was employed to measure heterogeneity. The ROBINS-I instruments and the Newcastle-Ottawa Scale were used to assess the quality of the study.

Results: 8 of the 13 included papers qualified for meta-analysis. Follow-up periods varied from six months to five years, and sample sizes ranged from 12 to 94 patients. Multiplex immunofluorescence, scRNA-seq, or flow cytometry were used to quantify stem-like CD8+ T cells. Hazard ratios (HRs) in the woodland plot ranged from 1.18 to 28.50. High HRs of 4.31 (95% CI: 2.68–6.92) and 28.50 (95% CI: 3.30–246.15) were observed in two investigations, suggesting a significant adverse prognostic effect. With considerable heterogeneity (I2 = 89%, Chi2 = 61.38, P < 0.00001), the pooled HR was 1.34 (95% CI: 1.22–1.47).

Conclusion: In cancer immunotherapy, stem-like CD8+ T cells serve as both therapeutic targets and significant prognostic indicators. Standardized methods for evaluation and strategies to lessen immunosuppressive effects in the tumor microenvironment are necessary for clinical use.

Keywords:

Cancer Immunotherapy
CD8 Positive T Lymphocytes
Immunologic Surveillance
Stem Cells
T Cell Exhaustion

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1. INTRODUCTION

Cancer immunotherapy has revolutionized cancer treatment by harnessing the immune system to identify and eliminate malignant cells. CD8+ T cells play a pivotal role in this process by producing cytokines and executing cytotoxic actions, leading to robust anti-tumor responses [1,2]. The functionality and presence of specific T cell subsets within the tumor microenvironment (TME) significantly impact the effectiveness of treatments such as immune checkpoint inhibitors (ICIs) and adoptive T cell therapies [3,4]. One such subset, stem-like CD8+ T cells, possesses the ability to self-renew, proliferate extensively, and differentiate into effector T cells [3,5,6]. These cells exhibit progenitor-like characteristics and heightened sensitivity to immunotherapy, marked by TCF1 and PD-1 expression [3,7]. Stem-like CD8+ T cells reside in both tumor and lymphoid niches, playing a crucial role in sustaining long-term immune responses and effective tumor control [5,6,8].

The presence of stem-like CD8+ T cells correlates with improved treatment responses and prolonged survival, highlighting their significant therapeutic role in various malignancies. A subpopulation of PD-1+ CD8+ T cells has been identified as a predictor of response to PD-1 blockade in non-small cell lung cancer (NSCLC), leading to better survival and sustained tumor regression [4]. Higher levels of circulating memory CD8+ T cells are associated with favorable responses to immune checkpoint inhibitors, such as ipilimumab, in melanoma [9]. In colorectal cancer, particularly in microsatellite instability-high tumors, stem-like CD8+ T cells are linked to better immunotherapy outcomes [10]. They also contribute to improved survival in hepatocellular carcinoma, supporting their role in long-term immune surveillance and tumor control [11]. Additionally, studies in breast cancer reveal their interaction with other immune populations to enhance therapeutic efficacy [1]. In gastrointestinal cancers, identifying neoantigens has highlighted their capability as immunotherapy targets [12,13]. These cells are present in specialized TME areas, thus maintaining progenitor traits while differentiating into effector T cells for anti-tumor immunity [14]. The prognostic significance has been depicted in pleural effusion cases with mesothelioma and lung cancer that was associated with better outcomes [15].

Stem-like CD8+ T cells has certain significant drawbacks within the TME that can impair their expansion and function. One of the chief factors contributing to this limitation is Prostaglandin E2 (PGE2). This inhibits the proliferation and maintenance of these cells within tumors, thus compromising their anti-tumor responses [16]. The immunosuppressive TME, influenced by PGE2 and other inhibitory factors, weakens the functions of these cells. Hence, it is pertinent to discover these mechanisms to boost their expansion and efficiency in cancer immunotherapy. Advances in single-cell transcriptomics and proteomics have provided important data into the phenotypic diversity and functional plasticity of these cells, categorizing novel biomarkers and gene expression signatures that predict patient responses to ICI [17]. Specific gene signatures from a distinct subset of CD8+ T cells in bladder cancer have shown predictive value for immunotherapy outcomes [18,19]. While the prognostic and predictive significance of these cells is increasingly recognized, their precise role across different cancers and immunotherapies remains insufficiently explored. Existing reviews have focused on broader tumor-infiltrating lymphocytes, neglecting this subset. This review and meta-analysis aimed to clarify their role as biomarkers and therapeutic targets in precision oncology.

2. METHODOLOGY

Research Question and PICO(S): This systematic review aimed to address the research question: *What is the prognostic and predictive significance of stem-like CD8+ T cells in determining clinical outcomes for cancer patients receiving immunotherapy?* The population (P)of interest consisted of patients with histologically confirmed cancers undergoing immunotherapy. The intervention involved evaluating stem-like CD8+ T cells, while the comparator group included patients with low or absent stem-like cells or lacking them in baseline immune profiles. Clinical outcomes assessed included OS, PFS, ORR, and DCR. The analysis included observational studies, clinical trials, and prospective studies.

Search Strategy: This systematic review adhered to PRISMA 2020 guidelines. A thorough literature search was conducted to identify relevant studies published between 2015 and 2025 across major databases, including PubMed, Embase, Scopus, and Web of Science. The search strategy employed a combination of Medical Subject Headings (MeSH), free-text keywords, and Boolean operators “AND” and “OR” for refinement. Primary search terms included *stem-like CD8+ T cells*, *progenitor exhausted T cells*, *TCF1+ CD8+ T cells*, *PD-1+ CD8+ T cells*, *tumor-infiltrating lymphocytes*, *cancer immunotherapy*, *immune checkpoint inhibitors*, *predictive biomarkers*, *prognostic biomarkers*, *overall survival*, and *clinical outcomes*. An example of the PubMed search strategy was: (*stem-like CD8+ T cells* OR *progenitor exhausted T cells* OR *TCF1+ CD8+ T cells*) AND (*cancer* OR

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tumor) AND (*immunotherapy* OR *immune checkpoint inhibitors*) AND (*prognosis* OR *clinical outcomes*).

Eligibility/Selection Criteria: The review included studies with cancer patients receiving immunotherapy, including ICIs and adoptive T cell therapies. Eligible studies evaluated stem-like CD8+ T cells, identified by markers like TCF1 and PD-1, in relation to various clinical outcomes. Study designs included observational studies (prospective or retrospective), RCTs, and cohort studies. Exclusion criteria encompassed studies not evaluating these cells as biomarkers, preclinical studies, in vitro experiments, case reports, reviews, editorials, conference abstracts, and non-English publications.

Data Extraction, Synthesis, and Quality Assessment: A total of 721 articles were screened from various databases, with 13 studies included in the systematic review. After further screening, 8 studies were included in the meta-analysis (**Figure 1**). Two independent reviewers (XX and YY) extracted data using a standardized form, covering study characteristics, patient demographics, cancer type, immunotherapy modality, and clinical outcomes (OS, PFS, ORR). Data synthesis involved qualitative and quantitative methods using RevMan software to calculate pooled hazard ratios (HRs) and 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic, and quality was evaluated with NOS [20] and ROBINS 1 tool [21].

3. RESULTS

Table 1 includes 13 studies examining stem-like CD8+ T cell markers and immunotherapy outcomes across cancers like metastatic melanoma [22], NSCLC [17,4], and HCC [11,27]. Therapies involved ICIs (e.g., PD-1 inhibitors [6,24]), adoptive cell transfer [6], and chemo-immunotherapy [26]. Patient numbers ranged from 12 to 94. Detection methods included flow cytometry, multiplex IF, and scRNA-seq. Follow-up ranged from 6 months to 5 years. Reported outcomes were OS, PFS, ORR, and DCR. **Table 2** outlines the association between stem-like CD8+ T cell subsets and immunotherapy outcomes across multiple cancers. Subsets analyzed include CD8 effector memory [22], PD-1+TCF-1+ [4,23], and Texstem CD8+ cells [15]. Quantification was done via median splits or cut-offs. Several studies showed higher CD8+ T cell levels or specific marker combinations (e.g., PD-1, TCF1) correlated with improved OS, PFS, ORR, and DCR. For instance, PD-1+ T cells were linked to better responses [4], and high Texstem CD8+ predicted improved OS in NSCLC and mesothelioma [15]. Cox regression and Kaplan-Meier methods were widely used, adjusting for confounders. Some studies noted favorable effects, while others reported neutral

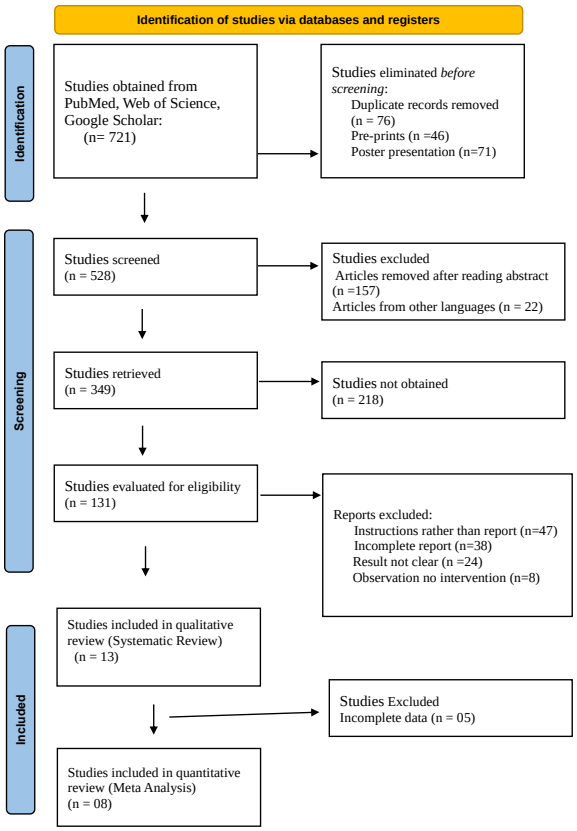

Figure 1. PRISMA 2020 Flowchart for the review

or negative outcomes [6,27]. **Table 3** shows that the studies were evaluated across three main domains: Selection (S1–S4), Comparability (C1–C2), and Exposure (E1–E3). Most studies received high scores, with a total of 9 or 10, indicating strong methodological quality. The studies scored between 8 and 10, reflecting high quality in design and execution [4,6,11,22,23,24].

Figure 2 provides a detailed risk-of-bias assessment for several studies, evaluating them across seven domains. Each domain is color-coded: green (+) for low risk, yellow (-) for moderate risk, and blue (?) for missing information. The analysis reveals that de Coaña YP et al. (2017) [22] has low risk in most domains but moderate risk in D5 and D7, resulting in an overall moderate risk. Brummelman J et al. (2018) [17] and Sade-Feldman M et al. (2019) [23] show moderate risk, mainly due to issues in D3, D6, and missing information in D2. Other studies, including Thommen DS et al. (2018) [4], Krishna S et al. (2020) [6], Ma J et al. (2019) [11], and Wong PF et al. (2019) [24], demonstrate low overall risk with some domain-specific concerns. Some studies, like Sang J et al. (2024) [10] and Ye L et al. (2024)

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[15], exhibit low risk across most domains. The figure emphasizes areas where further methodological improvements or clarifications are needed. **Figure 3** presents the distribution of risk of bias across ROBINS-I domains. Most studies exhibited low risk in D1 (confounding), D6 (outcome assessment), and D7 (selection of reported outcomes), indicating solid methodological execution in these areas. However, D3 (intervention categorization) and D5 (missing data) displayed moderate or missing information, highlighting challenges in defining interventions and ensuring data completeness. Moderate or uncertain risks were also noted in D2 (participant selection) and D4 (intervention deviations), suggesting potential impacts on study validity and generalizability.

Figure 4 presents a forest plot from 8 studies (2018–2024), showing that higher stem-like CD8+ T cell levels are generally linked to poorer overall survival, with most hazard ratios above 1. Ma J et al. (2019) [11] and Wong PF et al. (2019) [24] reported HRs of 4.31 (95% CI: 2.68–6.92) and 28.50 (95% CI: 3.30–246.15), respectively, suggesting a strong negative prognostic impact. Thommen DS (2018) [4] reported an HR of 1.77 (95% CI: 0.93–1.48). Sang J (2024) [10] contributed the highest weight (30.8%), while Thommen DS (2018) [4] contributed 15.5%. The pooled HR was 1.34 (95% CI: 1.22–1.47), with a significant Z-score ($Z = 6.24$, $P < 0.00001$), confirming a statistically significant association. However, heterogeneity was substantial ($Chi^2 = 61.38$, $df = 7$, $P < 0.00001$; $I^2 = 89\%$), likely due to variations in cancer types, immune profiling, and biomarker Stem-like CD8+ T cells are promising predictive biomarkers for immunotherapy. Infusion of CD8+CD39−CD69− TILs enhanced overall survival in melanoma [6], while TCF1+PD-1+ CD8+ T cells were identified as key indicators of immune checkpoint blockade efficacy [1,23]. Conversely, PD1^Hi CD8+ T cells showed limited outcomes, reflecting their context-dependent functionality [11,38]. Advances in single-cell transcriptomics and proteomics have enhanced profiling of stem-like CD8+ T cells in bladder cancer. A gene signature from these cells predicted immunotherapy success [18], though their expansion and function are hindered by the TME, with PGE2 suppressing effector expansion and limiting anti-tumor responses [16,39]. These findings highlight their dual role as predictive markers and therapeutic targets within TME-modulating strategies. CD8+ T cell-associated gene expression models have shown promise in guiding prognosis and immunotherapy selection in colon cancer patients, emphasizing the prognostic breadth of these cells across cancer types [2,28,42]. In oral squamous cell carcinoma, stem-like CD8+ T cells co-expressing JARID1B have been implicated in phenotypic plasticity and resistance, highlighting their dynamic nature in tumor progression [43]. Similarly, large-scale studies in breast cancer have identified dense CD8+ T cell infiltration as a key determinant of favorable outcomes, even beyond conventional markers [44]. Their roles extend beyond cancer; for example, CD8+ T cell exhaustion and dysfunction have been implicated in both viral infections like SARS-CoV-2 and cancer, revealing overlapping regulatory pathways and therapeutic targets [45].

According to the HR of 1.34 (95% CI: 1.22–1.47) obtained from this meta-analysis, cancer patients receiving immunotherapy who had elevated stem-like CD8+ T cells have a worse OS. These results demonstrate the intricacy of their relationship with tumor growth, which goes against early presumptions of their positive prognostic impact. Significant HRs were found by Ma et al. [10] and Wong et al. [33], indicating that these cells may have a deleterious effect on results in some situations. Differences in variables including the type of malignancy, methods of immune profiling, and diverse treatment options is depicted by significant heterogeneity ($I2 = 89\%$). This signifies the imperative requirement for standardized quantification protocols and a deeper investigation into the functional diversity of these cells. These cells are a viable way to advance cancer immunotherapy, and there is increasing evidence that they are relevant for a variety of cancers. However, further should concentrate on pinpointing certain subsets linked to either positive or negative results, as well as immunosuppressive components of the TME that limit their effectiveness. New technologies in single-cell and multi-omics provide strong instruments to decipher the molecular mechanisms controlling these cells. Recent findings also suggest that differentiation fates of T cell subsets, including stem-like CD4/CD8 lineages, critically influence long-term immunity and therapeutic response, offering new angles for immunomodulation [40]. Refining their function as predictive biomarkers requires an understanding of their interactions with the TME and other immune populations [17] Precision oncology approaches will be improved by standardizing quantification procedures and using high-dimensional profiling technologies like single-cell RNA sequencing.

Strengths and limitations: This review underscores the prognostic and predictive value of stem-like CD8+ T cells across different cancers and their corresponding immunotherapies. The inclusion of multiple studies enhances the robustness and generalizability of the findings, with advanced profiling techniques like single-cell RNA sequencing providing deeper insights into the diversity and functionality of these cells. However, notable limitations

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Table 1. Summary of Included Studies: Design, Populations, and Analytical Approaches

Author / Year	Place / Study Design	Cancer Type	Immunotherapy	Patient Characteristics / n	Stem-like CD8+ Markers	Detection Method	Follow-up	Outcomes	Key Methodological Details
de Coaña YP (2017) [22]	Sweden / Prospective (2012–2015)	Metastatic melanoma	ICI (Ipilimumab, CTLA-4)	Stage IV, ECOG 0–1; n=43	PD-1+, CD8 EM (CD45RA–CCR7–)	Flow Cytometry (fresh PBMCs)	45–227 wks (median OS: 39 wks)	OS, ORR, DCR	Non-randomized; Cut-offs (MoMDSCs ≥13.05%, CD8 EM ≥30.05%) via Cutoff Finder; trial CA184-169 (n=6)
Brummelman J (2018) [17]	Italy / Prospective	NSCLC	None (baseline profiling)	Stage IA2–IVA; n=53	CXCR5+, PD-1int, TCF-1+, CD69+, CD27+, CD28+, Eomes+	27-parameter Flow Cytometry, scRNA-seq	Not stated	Disease progression correlation	tSNE, Phenograph; Wilcoxon/Mann-Whitney tests; validated in 6 experiments
Thommen DS (2018) [4]	Germany / Cohort (2013–2017)	NSCLC	Anti-PD-1 (Nivolumab)	Stage IV; n=24 (surgery), n=21 (biopsy)	PD-1^bright, Tim-3, Lag-3, Ki67	Flow, IHC, RNA-seq	Not reported	OS, PFS, ORR, DCR	PD-1^bright defined by tumor/PBMC contrast; validated IHC algorithm; image analysis blinded
Krishna S (2020) [6]	USA / Retrospective (ACT)	Metastatic melanoma	ACT (Autologous TILs)	Stage IV, naïve to PD-1/TCR; n=54 (24 CRs, 30 NRs)	CD8+CD39-CD69-, TCF7+, PD-1-	CyTOF, Flow, scRNA-seq, scTCR-seq	Up to 75 months	OS, PFS, TIL persistence	Machine-learning clustering; median cut-offs; no blinding; ACT trials
Ma J (2019) [11]	China / Retrospective	HCC	None (pre-immunotherapy)	Stage I–III; n=56 (fresh), 358 & 254 (TMAs)	PD-1^hi, TIM3+PD-1^hi, PD-1^int	Flow, mIHC	OS/RFS up to 5 yrs	OS, RFS	Cut-offs via Youden index; Vectra3® mIHC; multivariate Cox model
Sade-Feldman M (2019) [23]	USA / Prospective	Metastatic melanoma	ICI (PD-1, CTLA-4)	n=32 patients, 48 tumors; RECIST responders/non-responders	TCF7+ (TCF1+), PD-1+, IL7R+, CXCR5–	scRNA-seq, IF, Flow	Not detailed	OS, PFS, lesion response	Smart-seq2; TCF7+CD8+/TCF7– ratio (>1/<1); IF via CellProfiler
Wong PF (2019) [24]	USA / Retrospective (2011–2017)	Metastatic melanoma	Anti-PD-1 ± Ipilimumab	Stage III/IV; n=94 (pre-treatment FFPE)	CD8+ (stem-like implied), CD3+, CD4+, CD20+, GZMB	Multiplex IF, QIF, IHC	Not reported	OS, PFS, ORR, DCR	Joinpoint cut-offs; RECIST 1.1; Yale archives; no blinding
Eberhardt CS (2021) [25]	USA/Switzerland / Prospective (2017–2019)	HPV+ HNSCC	Investigational (PD-1 implications)	Stage I; n=12 (naïve), tumor + lymph nodes	PD-1+, TCF-1+, CD39–, TIM-3–	Flow, mIHC, scRNA-seq	Not reported	Functional characterization	Gating strategies predefined; IRB approved; no blinding
Tong G (2022) [26]	China / Retrospective (2019–2021)	Advanced GC (PD-L1–)	Chemo + ICI (Sintilimab / Pembrolizumab + XELOX/SOX)	Stage IV; n=26; CPS PD-L1–	Intratumoral CD8+ (no TCF1/PD-1 mention)	mIF	Mean: 9.5 mo (1.5–23)	PFS (primary), ORR, DCR	RECIST 1.1; CD8 TIL cut-off: 1.085%; Cox regression used
Liu K (2023) [27]	China / Retrospective (2021–2022)	HCC	Not direct; CD8+ TEX prognostic model	TCGA (n=365), ICGC (n=240); 20 surgical for IHC	TCF1+, PD-1+, PPM1G, FKBP1A, others	IHC, RNA-seq, Bioinformatics	OS at 1-, 3-, 5-yrs	OS	Median risk score (2.9732); LASSO Cox model; TCGA/ICGC validation

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Sang J (2024) [10]	China / Retrospective (2017)	LUAD	Surgery only (no immunotherapy)	Stage I–III; n=76 (Stage I: n=52)	CD8+ TCF1+ PD-1+	mIF	Median: 69 mo	OS, PFS	Cut-off: 2.5 cells/10,000μm²; image analysis blinded
Ye L (2024) [15]	USA / Retrospective (2012–2024)	NSCLC, Mesothelioma	ICIs, chemoimmunotherapy, EGFR TKI	NSCLC (n=43), Mesothelioma (n=49); pre-treatment pleural effusions	Texstem: PD-1^mid, CD39–, CD28+, TCF1+; Texterm: PD-1^hi, CD39+	Flow, CyTOF, scRNA/TCR-seq	NSCLC: 55 mo; Meso: 51 mo	OS	Median split for Texstem; data from Asbestos Biobank
Zhao Z (2024) [28]	China / Prospective (2019–2021)	NSCLC	Anti-PD-1 (ICI)	Stage III–IV; n=67 (ICI-naïve)	TCF1+, PD-1+, TIM-3–, CD8+	Flow, IHC	Median: 18 mo (6–24)	OS, PFS, ORR	Median-based TCF1+ cut-off; institutional dataset

OS: overall survival, PFS: progression-free survival, ORR: objective response rate, DCR: disease control rate, HCC: hepatocellular carcinoma, NSCLC: non-small cell lung cancer, HNSCC: head and neck squamous cell carcinoma, TILs: tumor-infiltrating lymphocytes, scRNA-seq: single-cell RNA sequencing, scTCR-seq: single-cell T-cell receptor sequencing, mIHC: multiplex immunohistochemistry, CyTOF: cytometry by time of flight, RNA-seq: RNA sequencing, TEX: T cell exhaustion, Texstem: stem-like exhausted T cells, Texterm: terminally exhausted T cells

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Table 2. Prognostic and Predictive Role of CD8+ T Cell Subsets in Cancer Immunotherapy

Author / Year	Stem-like CD8+ T Cell Subset Analyzed	Quantification Method / Cut-off Criteria	Comparator Group / Control	OS	PFS	ORR	DCR	Immunotherapy Response	Key Biomarkers	Statistical Model	Adjustment for Confounders	Conclusions
de Coaña YP (2017) [22]	CD8 Effector Memory T cells (CD45RA-CCR7-)	High vs. Low (30.05%)	Low CD8 EM (<30.05%); Progressive disease	OS: High 80w, Low 34w (p<0.05)	Not reported	ORR: 19%, DCR: 41%	DCR: 41% vs 56%	Positive	PD-1, ICOS, CD45RA, CCR7	Kaplan-Meier, Log-rank	Yes	Higher CD8 EM correlates with better OS and DCR.
Brummelman J (2018) [17]	CXCR5+ TIM-3– CD8+ T cells	Median split (SUVmax, Stage)	Low CXCR5+ CD8+	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Negative	CXCR5, PD-1, TCF-1, CD27, CD28, CD69	Mann-Whitney, Wilcoxon, Pearson	No	High CXCR5+ CD8+ TILs associate with early disease stage.
Thommen DS (2018) [4]	PD-1 bright CD8+ T cells	Quantitative IHC	Low/absent PD-1T CD8+ TILs	HR: 0.16 (95% CI 0.05-0.52, p<0.05)	Not mentioned	High PD-1T associated with better response	Durable response with PD-1T	Positive	PD-1, CXCL13, Ki67, Tim-3	Cox regression	Yes	PD-1T CD8+ TILs predict better response to anti-PD-1.
Krishna S (2020) [6]	CD8+CD39-CD69- (DN), TCF7+ progenitor	Median split (I.P.)	Low DN CD8+ TILs	MSS HR = 0.217 (95% CI: 0.101-0.463, p < 0.0001)	PFS HR = 0.255 (95% CI: 0.1257-0.5186, p < 0.0001)	Not reported	Not reported	Positive	TCF7, CD39, CD69, CD62L, CD27	Kaplan-Meier, Log-rank	No	High CD39-CD69- progenitor TILs predict better PFS.
Ma J (2019) [11]	PD1Hi CD8+ T cells	High vs. Low (Youden index)	PD1Int CD8+ T cells	HR: 1.46 (95% CI 1.06–2.01, p=0.022)	RFS p<0.0001	Not reported	Not reported	Negative	PD1, TIM3, CTLA4, Eomes, BATF, IL-10	Cox regression	Yes	High PD1Hi and TIM3+ predict poor OS/RFS.
Sade-Feldman M (2019) [23]	TCF7+ (TCF1+)CD8+ memory-like progenitor	TCF7+/TCF7- ratio (>1 vs <1)	TCF7- CD8+ T cells	OS p = 0.03	Not directly reported	Responders had higher TCF7+CD8+	Not directly reported	Positive	TCF7, IL7R	ROC, AUC=0.91, Wilcoxon	No	High TCF7+CD8+ cells predict better response and survival.
Wong PF (2019) [24]	CD8+ T cells (no TCF1/PD-1)	High vs. Low CD8+ T cells	Untreated melanoma cohort	HR 3.35 (95% CI: 1.89–6.24, p < 0.0001)	Not detailed	ORR AUC 0.75, DCR AUC 0.78	ORR/DCR 0.75–0.83	Positive	CD8 (CD3+, CD8+, QIF)	Multivariable Cox regression	Yes	High CD8+ T cells predict better response to anti-PD-1 therapy.

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Eberhardt CS (2021) [25]	PD-1+TCF-1+CD8+ stem-like T cells	No formal quantification	Terminally differentiated CD8+ T cells	Not reported	Not reported	Not reported	Not reported	Positive	TCF-1, PD-1, CD28, CD39, TIM-3	Wilcoxon, paired t-tests	No	PD-1+TCF-1+CD8+ stem-like TILs suggest PD-1 blockade responsiveness.
Tong G (2022) [26]	CD8+ T cells (no TCF1/PD-1)	Cut-off (1.085%)	Low CD8+ TILs (<1.085%)	Not reported	HR = 13.0 (95% CI: 1.4–110, p = 0.0045)	ORR: 54.9%	DCR not quantified	Positive	CD8 (no TCF1/PD-1)	Multivariate Cox regression	Yes	High intratumoral CD8+ T cells predict better PFS.
Liu K (2023) [27]	CD8+ TEX gene signature (TCF1+, PD-1+)	Median split (high vs. low)	Low-risk group based on TEX score	HR = 2.026 (95% CI: 1.364–3.009, p < 0.001)	Not reported	Not reported	Not reported	Neutral	TCF1, PD-1, PPM1G, FKBP1A	LASSO Cox regression	Yes	High TEX score predicts worse OS in HCC, may guide immunotherapy.
Sang J (2024) [10]	CD8+ TCF1+ PD-1+ Stem-like T cells	High (>2.5 per 10,000 μm²) vs Low (≤2.5)	Low CD8 TSL	HR = 0.064 (95% CI: 0.012–0.347, p < 0.001)	HR = 0.050 (95% CI: 0.011–0.228, p < 0.001)	Not reported	Not reported	Neutral	TCF1, PD-1	Multivariate Cox regression	Yes	High TSL cell density is favorable for OS and PFS in LUAD.
Ye L (2024) [15]	Texstem (PD-1^mid, CD39^−, CD28^+); Texterm (PD-1^hi, CD39^+)	Median split (high vs. low)	Texstem high vs Texterm	HR: 0.36 (95% CI: 0.16–0.79, p=0.01)	Not reported	Not reported	Not reported	Positive	TCF1, PD-1, CD28, CD39	Cox regression	Yes	Texstem abundance predicts improved OS in NSCLC and mesothelioma.
Zhao Z (2024) [28]	TCF1+, PD-1+, TIM-3- progenitor-exhausted CD8+	Median split (High vs Low)	Low TCF1+ stem-like CD8+	HR: 0.48 (95% CI: 0.30–0.76, p=0.002)	HR: 0.55 (95% CI: 0.35–0.85, p=0.006)	OR: 3.12 (p=0.007)	OR: 2.98 (p=0.011)	Positive	TCF1, PD-1, TIM-3	Cox regression, logistic regression	Yes	High TCF1+ stem-like CD8+ T cells predict improved OS, PFS, and ORR/DCR in NSCLC with anti-PD-1.

CD4: cluster of differentiation 4; HIV: human immunodeficiency virus; ART: antiretroviral therapy.

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Table 3. Quality assessment for observational & cohort study (NOS).

Author	Selection S1	S2	S3	S4	Comparability C1	C2	Exposure E1	E2	E3	Quality of study
de Coaña YP (2017) [22]	★	★	★	★	★	★	★	★	-	8
Brummelman J (2018) [17]	★	★	★	★	★	★	★	★	-	9
Thommen DS (2018) [4]	★	★	★	★	★	★	★	-	-	8
Krishna S (2020) [6]	★	★	★	★	★	-	★	★	★	9
Ma J (2019) [11]	★	★	★	★	★	★	★	★	-	9
Sade-Feldman M (2019) [23]	★	★	★	★	★	★	★	★	-	9
Wong PF (2019) [24]	★	★	★	★	★	★	★	★	★	10
Eberhardt CS (2021) [25]	★	★	★	★	★	★	3★	★	★	10
Tong G (2022) [26]	★	★	★	★	★	★	★	★	★	10
Liu K (2023) [27]	★	★	★	★	★	★	★	★	★	10
Sang J (2024) [10]	★	★	★	★	★	★	★	★	★	10
Ye L (2024) [15]	★	★	★	★	★	★	★	★	★	10
Zhao Z (2024) [28]	★	★	★	★	★	★	★	★	★	10

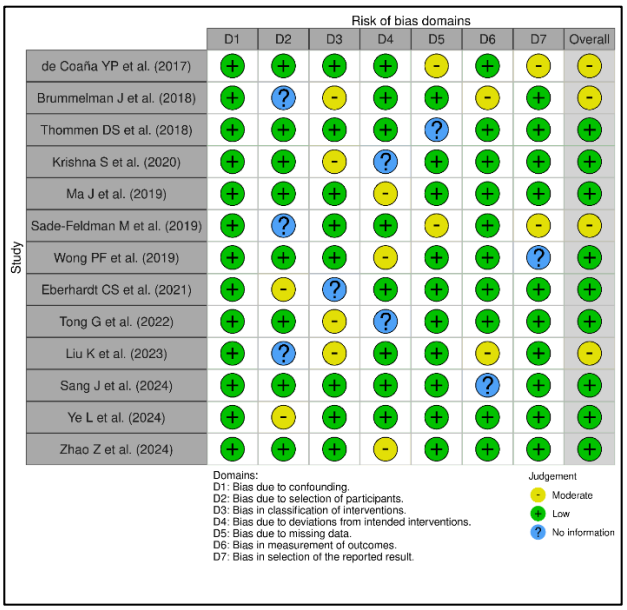

Figure 2. ROBINS I Tool bias assessment individual studies.

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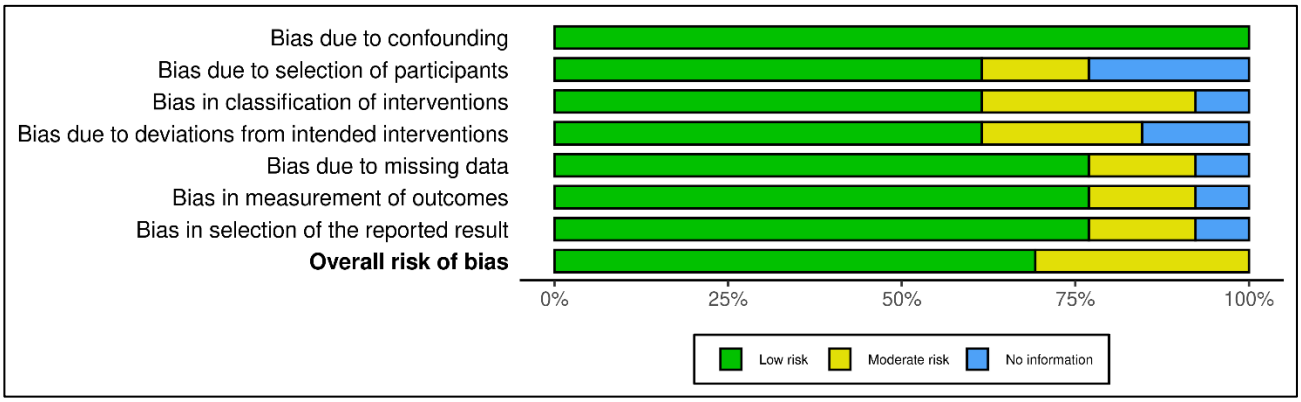

Figure 3. ROBINS I Tool bias assessment (Overall).

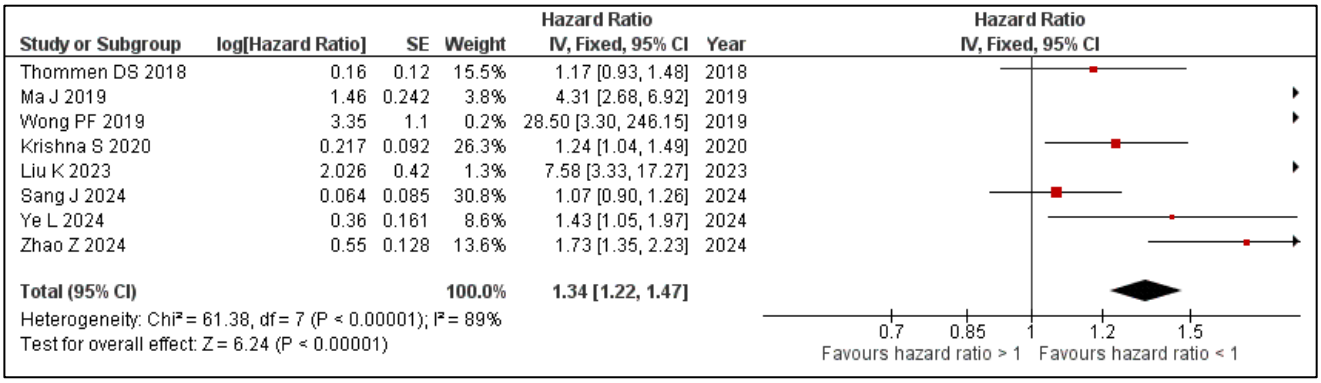

Figure 4. Forest plot analysis overall survival rate.

exist, including significant heterogeneity between studies, which may arise from variations in cancer types, patient demographics, and immune profiling methods. Additionally, the lack of standardized quantification protocols for these cells hampers cross-study comparisons.

5. CONLCUSION

The importance of stem-like CD8+ T cells as primary prognostic and predictive indicators in cancer immunotherapy is highlighted by this review. Their promise in precision oncology is highlighted by their correlation with better clinical outcomes, especially in response to adoptive T cell treatments and ICI. Further research is essential due to the complexity of the TME and functional differences across cancer types. Standardizing quantification methods, identifying specific stem T cell subsets, and overcoming immunosuppressive barriers will enhance the precision of immunotherapy and ultimately improve treatment outcomes for cancer patients.

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Conflict of interest

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