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Prognostic biomarkers of penile squamous cell carcinoma: A systematic review

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202620002

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 February 2026 and was last updated on 2 February 2026.

INTRODUCTION

Review question / Objective This systematic review targets to answer the following question: Which tissue-based biomarkers can be found in penile squamous cell carcinoma and how do they correlate with prognostic outcome measures. In order to answer the review question, studies investigating human tissue samples from male patients with verified cases of penile squamous cell carcinoma (PSCC) and the expression of tissue-based biomarkers or molecular alterations are collected. Animal/xenograft, other specimen type than tissue and wrong tumor entities are excluded. The collected studies will be compared for the presence, absence and different levels of biomarker expression/genetic alteration. The expression of biomarkers/genetic alterations will be compared to the reported prognostic outcome measure. Studies will be selected if a survival outcome (e.g., overall survival, disease-specific survival, cancer-specific survival, disease-free survival, progression-free survival, metastasis-free survival) and its association with biomarker expression has been assessed. Studies not reporting individual or original data and publications that were not peer reviewed are excluded.

Rationale Penile squamous cell carcinoma is a rare but aggressive malignancy with high mortality in advanced stages. There are frequent studies that have been evaluating the prognostic relevance of certain, single biomarkers as e.g. HPV or p53 in PSCC. However, to the best of our knowledge, there is no up-to-date systematic review reporting on a wide range of studied biomarkers and their association with prognostic outcomes. In order to guide future research and identify possible therapeutic targets, this systematic review tries to

lay the foundation by identifying tissue-based biomarkers that might correlate with prognosis in this cancer entity.

Condition being studied The disease of interest is penile squamous cell carcinoma (PSCC). The systematic review will be addressing the following factors of interest: Biomarker expression and their correlation with predefined outcome measures.

METHODS

Search strategy A systematic literature search of the databases PubMed, Cochrane, OVIMEDLINE, Scopus and Web of Science was conducted. All databases were searched independently and blinded to each other. The databases were searched on 12.6.2025 (PubMed) and on 19.6.2025 (Cochrane, OVIMEDLINE, Web of Science and Scopus). Studies published until 12.6.25 (PubMed) and 19.6.25 (Cochrane, OVIMEDLINE, Web of Science and Scopus) will be sought. There were no other methods to identify studies.

Finalized search queries:

1. PUBMED:
A systematic search was conducted in the PubMed database on June 12th, 2025 using Python (Biopython and pandas packages) and a custom-built script designed for automated literature retrieval and export. The script is publicly available at: [GitHub link].

Search query:
("penile neoplasm*" OR "penile cancer*" OR "PSCC" OR "penile squamous cell carcinoma*" OR "Penile Neoplasms"[Mesh]) AND (biomarker* OR "Biomarkers, Tumor"[Mesh] OR immunohistochemistry OR IHC OR microenvironment* OR "immune checkpoint*" OR "microsatellite instabilit*" OR "tumor mutational burden*" OR "gene expression*" OR sequencing OR "tissue array analysis" OR "in situ hybridization" OR "Reverse Transcriptase Polymerase Chain Reaction" OR "single-cell analysis" OR microRNA)

The search combined terms related to penile cancer and biomarkers or molecular characterization techniques. All records retrieved from this search were automatically extracted and exported as an Excel file using the Python script. The resulting dataset was subsequently used for downstream processes, including title and abstract screening, data extraction, and study categorization.

2. OVID MEDLINE
OVID MEDLINE was searched on June 19th, 2025 (at https://ovidsp-dc1-ovid-com.libproxy.helsinki.fi/ovid-new-a/ovidweb.cgi), using the search "((penile neoplasm* or penile cancer* or PSCC or penile squamous cell carcinoma*).ti,ab. or exp Penile Neoplasms/) and (biomarker*.ti,ab. or exp Biomarkers, Tumor/ or immunohistochemistry.ti,ab. or IHC.ti,ab. or microenvironment*.ti,ab. or "immune checkpoint*".ti,ab. or "microsatellite instabilit*".ti,ab. or "tumor mutational burden*".ti,ab. or "gene expression*".ti,ab. or sequencing.ti,ab. or "tissue array analysis".ti,ab. or "in situ hybridization".ti,ab. or "Reverse Transcriptase Polymerase Chain Reaction".ti,ab. or "single-cell analysis".ti,ab. or microRNA.ti,ab.)" The complete reference for all results was exported as an excel sheet.

3. COCHRANE
A systematic search was conducted in the Cochrane Library on June 19th, 2025. The following search strategy was applied using the Advanced Search interface:

Search queries:

Line #1: "penile cancer" OR "penile neoplasm" OR "penile squamous cell carcinoma" OR PSCC

Line #2: biomarker OR immunohistochemistry OR IHC OR microenvironment OR "immune checkpoint" OR "microsatellite instability" OR "tumor mutational burden" OR "gene expression" OR sequencing OR "tissue array analysis" OR "in situ hybridization" OR "reverse transcriptase polymerase chain reaction" OR "single-cell analysis" OR microRNA

Line #3: #1 AND #2

The search combined terms related to penile cancer and biomarkers or molecular characterization techniques. All records retrieved from this search were screened for relevance based on titles and abstracts. Eligible studies were selected for further analysis and categorization.

4. SCOPUS:
A systematic search was conducted in the Scopus database on June 19, 2025, using the Helsinki University Library proxy access. The following search strategy was applied to identify relevant studies on penile cancer biomarkers:

Search string:

(TITLE-ABS-KEY("penile neoplasm" OR "penile cancer" OR PSCC OR "penile squamous cell carcinoma")) AND (TITLE-ABS-KEY(biomarker OR immunohistochemistry OR IHC OR microenvironment OR "immune checkpoint" OR "microsatellite instability" OR "tumor mutational burden" OR "gene expression" OR sequencing OR "tissue array analysis" OR "in situ hybridization" OR "reverse transcriptase polymerase chain reaction" OR "single-cell analysis" OR microRNA))

This search targeted articles where the terms appeared in the title, abstract, or author keywords. The search was conducted via the following Scopus URL:

https://www-scopus-com.libproxy.helsinki.fi/results/results.uri?sort=plf-f&src=s&sid=83e6212bf59c60a433350f48c39c0009&sot=a&sdt=a&sl=443&s=TITLE-ABS-KEYpenile+neoplasm+OR+penile+cancer+OR+PSCC+OR+penile+squamous+cell+carcinoma+AND+TITLE-ABS-KEYbiomarker+OR+immunohistochemistry+OR+IHC+OR+microenvironment+OR+immune+checkpoint+OR+microsatellite+instability+OR+tumor+mutational+burden+OR+gene+expression+OR+sequencing+OR+tissue+array+analysis+OR+in+situ+hybridization+OR+reverse+transcriptase+polymerase+chain+reaction+OR+single-cell+analysis+OR+microRNA&origin=searchadvanced&editSaveSearch=&txGid=cde21f1d2629bb288a29d0c0d063f93b&sessionSearchId=83e6212bf59c60a433350f48c39c0009&limit=10

The search results were exported in CSV format, including all available metadata fields for subsequent screening and data extraction.

5. Web of Science
A systematic search was conducted in the Web of Science Core Collection database on June 19th, 2025. The following search strategy was applied:

Search query:
TS=("penile neoplasm" OR "penile cancer" OR "PSCC" OR "penile squamous cell carcinoma") AND TS=(biomarker OR immunohistochemistry OR IHC OR microenvironment OR "immune checkpoint" OR "microsatellite instability" OR "tumor mutational burden" OR "gene expression" OR sequencing OR "tissue array analysis" OR "in situ hybridization" OR "reverse transcriptase polymerase chain reaction" OR "single-cell analysis" OR microRNA)

The search combined terms related to penile cancer and biomarkers or molecular characterization techniques. All records retrieved from this search were selected and exported as an Excel file for further downstream analyses, including title and abstract screening, data extraction, and categorization.

Participant or population Patients with penile squamous cell carcinoma.

Intervention The selected articles identify and evaluate tissue-based biomarker expression and/or molecular alteration in PSCC. Studies not investigating this were excluded.

Comparator Different levels of biomarker expression and the presence/absence of genetic alteration will be compared. If the data allows for a meta-analysis, this will be performed. Further information on a potential meta-analysis is provided in section 22.

Study designs to be included Eligible studies include original research published in English in a peer-reviewed journal. Studies not reporting individual or original data e.g., reviews, editorials or letters or articles that were not peer reviewed e.g., conference abstracts, book chapters, author manuscripts and case reports, are excluded.

Eligibility criteria Only published studies will be sought. The review will only include studies published in English and there are no search date restrictions. Studies for which the full text is not accessible through our institutional subscriptions are excluded. In addition to the already mentioned criteria in the PICO section, the following inclusion criteria were applied:

Inclusion criteria:
- The article was published In English in a peer-reviewed journal and the study type is original research.
- Sample/patient number > 2
- Investigated samples are PSCC samples
- The study used human tissue samples
- Biomarker expression or genetic alteration has been studied
- Prognostic outcome has been studied (e.g. OS (overall survival), DSS (disease-specific survival), CSS (cancer-specific survival), DFS (disease-free survival), PFS (progression-free survival) and MFS (metastasis-free survival))

Exclusion criteria:
- Studies not reporting individual or original data (e.g. reviews, editorials, reports, letters)

- Publications that were not peer reviewed (e.g. conference abstracts, book chapters, author manuscripts)
- No PSCC studied
- Sample/patient number < 2
- Animal/Xenograft study
- HPV/p16 studied as the only biomarker
- No full text available
- Prognosis of the biomarker not studied
- Prognostic data not shown
- No biomarkers studied.

Information sources For this systematic review Pubmed, Ovid Medline, Cochrane, Scopus and Web of Science were screened with the earlier mentioned search strategies.

Main outcome(s) The most relevant outcomes for this systematic review are the biomarker expression in the tissue-based sample (biomarker name; HR, CI univariate/multivariate analysis, p-values, analysis method) and the survival outcome measures (e.g. overall survival (OS), disease-specific survival (DSS), cancer-specific survival (CSS), disease-free survival (DFS), progression-free survival (PFS), metastasis-free survival (MFS).

Additional outcome(s) Not applicable.

Data management Two reviewers applied eligibility criteria and selected studies for inclusion in the systematic review. Two people independently screened records for inclusion and were blinded to each other's' decisions. Any disagreements between individual judgements were resolved by discussing with the third reviewer, if needed, and reaching consensus. The screening was done in two stages. (1); Title/ Abstract screening and (2); Full-text screening. Search results were exported from each database (e.g., Excel/CSV) and deduplicated prior to screening. Study records and extracted variables were recorded in Microsoft Excel. The study selection process was documented using a PRISMA 2020 flow diagram. Data extraction was done by one person and checked by at least one person.

Quality assessment / Risk of bias analysis The risk of bias assessment was done independently by two reviewers blinded to each other's decisions. Evaluation of the quality of the studies was based on guidelines from Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK). We used a modified version of the REMARK checklist. The scale consists of 9 nine items and the full score attainable was 9 points. The cut-off was set at 4,5 (50%) to remove articles due to poor quality. Articles that scored 4,5 or under, were excluded.

Strategy of data synthesis The reporting of our findings will be guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement. We will conduct statistical analysis to combine data across studies. Depending on the available data, stratified analysis will be conducted. A meta-analysis will be performed for individual biomarkers, if at least five independent studies report comparable effect estimates for the same biomarker and outcome, and at least three biomarkers meeting these criteria can be found from the final list of articles. Pooled effect sizes will be calculated using hazard ratios with 95% confidence intervals (inverse variance). When multiple effect estimates are reported for the same biomarker, the most fully adjusted multivariate hazard ratio will be preferentially extracted. A random effects model will be used, given the anticipated clinical and methodological heterogeneity across studies. Statistical heterogeneity will be assessed using the I^2 statistic and the τ^2 estimates. Sensitivity analysis will be performed by excluding studies at high risk of bias.

Subgroup analysis No formal subgroup analyses are planned beyond outcome-specific meta-analyses.

Sensitivity analysis In case we perform a meta-analysis, we may perform sensitivity analysis.

Language restriction The review will only include studies published in English.

Country(ies) involved Finland.

Keywords Penile cancer; Penile squamous cell carcinoma; Biomarkers; Prognosis; Survival; Patient outcomes; Human tissue; Cancer-specific survival (CSS); Overall survival (OS).

Dissemination plans The results of this systematic review will be disseminated through publication in a peer-reviewed scientific journal and presentation at relevant national conference.

Contributions of each author

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