Prognostic Value of Pretreatment Monocyte-to-Lymphocyte Ratio in Prostate Cancer: A Focused Systematic Review and Corrected Meta-analysis

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Abstract

Background: The monocyte-to-lymphocyte ratio (MLR) is an inexpensive systemic inflammatory marker, but its prognostic value in prostate cancer remains uncertain. This focused review evaluated whether pretreatment MLR is associated with overall survival (OS).
Methods: A broader systematic search of Semantic Scholar, Scopus, PubMed/MEDLINE, Crossref, the Cochrane Library, and Web of Science identified studies of blood-cell ratios in prostate cancer. For this focused analysis, reports were rechecked for direct MLR measurement or a mathematically convertible reciprocal lymphocyte-to-monocyte ratio (LMR), an extractable hazard ratio (HR) with 95% confidence interval (CI), and OS. Log HRs were harmonized to compare high versus low MLR and pooled with a random-effects inverse-variance model. Study quality was assessed using the Newcastle-Ottawa Scale.
Results: Three studies involving a total of 427 patients were included in the overall survival analysis. Two studies evaluated metastatic prostate cancer, while one study included non-metastatic patients. Elevated MLR was significantly associated with poorer overall survival, with a pooled hazard ratio (HR) of 2.59 (95% CI 1.84–3.63; $p < 0.00001$). No significant heterogeneity was observed among the included studies ($I^2 = 0\%$; $\chi^2 = 0.26$, $p = 0.88$; $Tau^2 = 0.00$), indicating a highly consistent prognostic effect across studies.
Conclusions: Elevated MLR was associated with poorer overall survival in patients with prostate cancer, with a consistent direction of effect across the included studies. However, MLR-specific prognostic evidence remains sparse and is currently insufficient to support routine clinical use. Further studies using contemporary MLR-specific searches, standardized ratio definitions, prespecified cutoffs, and adequately adjusted prospective cohorts are required to validate its prognostic utility.

Keywords: prostate cancer; monocyte-to-lymphocyte ratio; overall survival; prognosis; meta-analysis

1. Introduction

Prostate cancer is one of the most frequently diagnosed malignancies among men and remains a major cause of cancer-related morbidity and mortality worldwide. Its incidence varies substantially across geographical regions, reflecting differences in population ageing, genetic susceptibility, environmental exposures, access to prostate-specific antigen (PSA) testing, and diagnostic practices (Rawla, 2019; Culp et al., 2020; Wang et al., 2022). The clinical course of prostate cancer is highly heterogeneous, ranging from indolent, organ-confined tumours that may never become clinically significant to rapidly progressive metastatic disease and lethal metastatic castration-resistant prostate cancer (mCRPC) (Raychaudhuri, Lin and Montgomery, 2025; Chakrabarti et al., 2025). This heterogeneity presents an important challenge in prognostic assessment and treatment selection.

Current prognostic evaluation incorporates anatomical disease stage, serum PSA concentration, histological grade or International Society of Urological Pathology grade group, tumour burden, metastatic sites, performance status, molecular characteristics, and treatment context. These parameters guide decisions ranging from active surveillance and local therapy to androgen-deprivation therapy, chemotherapy, androgen-receptor pathway inhibitors, radioligand therapy, and other systemic treatments (Raychaudhuri, Lin and Montgomery, 2025; Chakrabarti et al., 2025). Nevertheless, patients with apparently similar clinicopathological characteristics may experience markedly different treatment responses and survival outcomes. Conventional factors may therefore not fully capture the biological interaction between the tumour, its microenvironment, and the systemic host response. This limitation has encouraged investigation of accessible biomarkers that could complement established prognostic models without substantially increasing cost or procedural burden.

Inflammation is increasingly recognised as a fundamental component of cancer development and progression. Chronic inflammatory signalling may promote genomic instability, tumour-cell proliferation, angiogenesis, epithelial–mesenchymal transition, invasion, immune escape, and metastatic dissemination (Grivennikov, Greten and Karin, 2010; Quail and Joyce, 2013). In prostate cancer, inflammatory mediators within the primary tumour and its surrounding microenvironment may contribute to disease progression, the establishment of metastatic niches, and resistance to systemic treatment (Archer, Dogra and Kyprianou, 2020). Systemic inflammatory responses may consequently provide indirect information regarding tumour aggressiveness, host immune competence, and the biological effects of advanced disease. Blood-count-derived inflammatory indices are particularly attractive because they are inexpensive, minimally invasive, widely available, and routinely assessed before most oncological treatments.

Among these indices, the monocyte-to-lymphocyte ratio (MLR) has emerged as a biologically plausible prognostic biomarker. MLR is calculated by dividing the absolute peripheral-blood monocyte count by the absolute lymphocyte count. An elevated MLR may result from monocytosis, lymphopenia, or a combination of both abnormalities. Monocytes are recruited into tumour tissue, where they may differentiate into tumour-associated macrophages. These macrophages can promote tumour growth and dissemination through the secretion of cytokines, chemokines, proteolytic enzymes, and proangiogenic factors, while also contributing to extracellular-matrix remodelling and immunosuppression (Quail and Joyce, 2013; Mantovani et al., 2017). Their activity may be particularly relevant in advanced prostate cancer, in which interactions among tumour cells, immune cells, and the bone microenvironment contribute to metastatic progression and treatment resistance (Archer, Dogra and Kyprianou, 2020).

Conversely, circulating lymphocytes represent an important component of adaptive antitumour immunity. Cytotoxic T lymphocytes can recognise tumour-associated antigens and directly eliminate malignant cells, while other lymphocyte subsets coordinate immune surveillance and regulate antitumour responses. A reduced lymphocyte count may reflect impaired cell-mediated immunity, systemic immunosuppression, nutritional deterioration, or the physiological effects of advanced malignancy. MLR therefore integrates two opposing components of the host response: monocyte-associated protumour inflammation and lymphocyte-mediated antitumour immune competence. A high MLR could consequently indicate a biological environment characterised by increased inflammatory activity and weakened immune surveillance, providing a potential explanation for its association with adverse outcomes across several solid malignancies (Nishijima et al., 2015; Mantovani et al., 2017; Xiang et al., 2024).

Population-based evidence has also demonstrated associations between MLR and the presence or clinical characteristics of prostate cancer, supporting further evaluation of this index as an accessible biomarker (Wang et al., 2024). However, diagnostic association should not be interpreted as evidence of prognostic utility. A clinically useful prognostic biomarker must provide reproducible information regarding outcomes such as overall survival independently of established clinicopathological factors. The prognostic value of

blood-derived inflammatory indices may additionally differ between localised and metastatic disease. In non-metastatic prostate cancer, an elevated inflammatory ratio may reflect occult aggressive biology or an increased risk of treatment failure. In metastatic disease, it may more directly reflect systemic tumour burden, immune dysregulation, and resistance to therapy. Treatment-related factors—including corticosteroids, chemotherapy, androgen-receptor-targeted treatment, infection, and bone-marrow involvement—may also alter peripheral monocyte and lymphocyte counts and confound their association with survival.

Previous systematic reviews have primarily evaluated the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio or have examined the reciprocal lymphocyte-to-monocyte ratio (LMR) across prostate cancer and other solid tumours (Nishijima et al., 2015; Salciccia et al., 2024; Xiang et al., 2024). In comparison, MLR-specific prognostic evidence in prostate cancer remains limited. Available studies have included heterogeneous populations encompassing non-metastatic disease, castration-resistant prostate cancer treated with docetaxel, and mCRPC treated with ^177Lu-PSMA-617 (Shigeta et al., 2016; Huszno et al., 2022; Sahin et al., 2023). Differences in disease stage, treatment setting, biomarker timing, cut-off selection, follow-up duration, and statistical adjustment may limit direct comparison among these studies.

Despite its biological plausibility and practical advantages, MLR has not been incorporated into routine prostate cancer risk stratification. The limited number of studies, inconsistent biomarker definitions, variable cut-off values, and differences in adjustment for established prognostic factors prevent firm conclusions regarding its independent clinical utility. A focused synthesis is therefore required to quantify the available association, assess its consistency across study populations, and identify limitations that should inform future research. Accordingly, this systematic review and meta-analysis aimed to evaluate the association between pretreatment monocyte-related inflammatory measures and overall survival in patients with prostate cancer, while explicitly examining the methodological implications of combining MLR, reciprocal LMR, and absolute monocyte-count evidence.

2. Methods

This systematic review and meta-analysis was derived from a broader review of peripheral blood inflammatory ratios in prostate cancer and was structured in accordance with PRISMA 2020. The broader review searched Semantic Scholar, Scopus, PubMed/MEDLINE, Crossref, the Cochrane Library, and Web of Science, supplemented by reference-list screening. Search concepts combined prostate cancer terms (prostate cancer, prostate carcinoma, or prostatic neoplasm), inflammatory-ratio terms (including monocyte-to-lymphocyte ratio, MLR, lymphocyte-to-monocyte ratio, and LMR), and prognostic terms (prognosis, survival, mortality, or hazard ratio). The source document applied an approximately 15-year publication window.

Eligible studies enrolled adults with histologically or clinically diagnosed prostate cancer; evaluated a pretreatment monocyte-related inflammatory marker, including MLR, reciprocal LMR, or the absolute monocyte-count marker retained in the original synthesis; assessed OS; and reported an HR with a 95% CI. Observational cohorts and randomized-trial secondary analyses were eligible. Reviews, editorials, case reports, conference abstracts without sufficient data, duplicate populations, and inaccessible full texts were excluded.

The broader review identified 938 database records and 15 records from other sources, ultimately retaining 24 studies across all inflammatory ratios. For the present analysis, the three reports used in the original MLR pooling were extracted for exposure definition, sample size, disease state, treatment, outcome, adjusted HR, and 95% CI. The Newcastle-Ottawa Scale (NOS) was used to assess selection, comparability, and outcome ascertainment; scores of 7-9 were interpreted as generally high methodological quality.

The original reported HRs were retained without reciprocal inversion to reproduce the same direction and interpretation. Log HRs and standard errors were calculated from the reported 95% CIs and combined using

inverse-variance random-effects meta-analysis. Between-study heterogeneity was summarized with Cochran's Q, tau^2, and I^2. Because fewer than 10 studies were available, funnel-plot asymmetry.

3. Results

Three retrospective reports, totalling 427 patients, were included in the original quantitative synthesis: Huszno et al. (2022), Shigeta et al. (2016), and Sahin et al. (2023). Shigeta et al. (2016) evaluated absolute monocyte count rather than a ratio; it was nevertheless retained to reproduce the source three-study pooling. The derivation of the analytic set is shown in Figure 1.

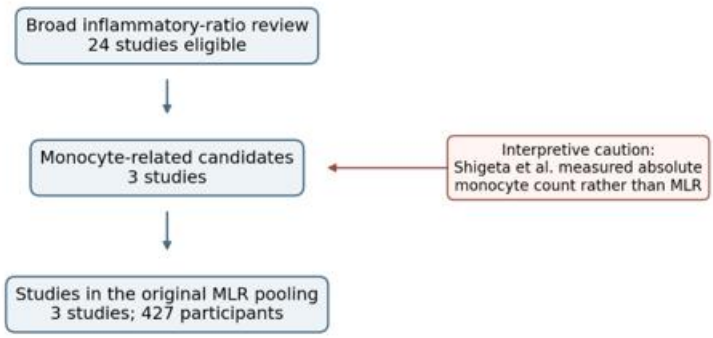


Fig. 1. Derivation of the original three-study analytic set from the broader inflammatory-ratio review.

Huszno et al. (2022) included 214 patients with non-metastatic prostate cancer and reported LMR rather than MLR. Shigeta et al. (2016) included 152 patients with metastatic castration-resistant prostate cancer treated with docetaxel and evaluated absolute monocyte count. Sahin et al. (2023) included 61 patients with metastatic castration-resistant prostate cancer treated with 177Lu-PSMA-617 and directly reported MLR. All three were retrospective cohorts, and their populations, treatments, and exposure definitions differed.

Table 1. Characteristics of studies included in the original three-study synthesis.

Study	Country	Design	Population/treatment	n	NOS
Huszno et al. (2022)	Poland	Retrospective cohort	Localized prostate cancer treated with radiotherapy	214	9
Shigeta et al. (2016)	Japan	Retrospective cohort	Metastatic castration-resistant prostate cancer treated with docetaxel	152	8
Sahin et al. (2023)	Turkiye	Retrospective cohort	mCRPC treated with 177Lu-PSMA-617	61	8

Huszno et al. (2022) reported an HR of 3.14 (95% CI 1.38-7.17), Shigeta et al. (2016) reported an HR of 2.46 (95% CI 1.56-3.89), and Sahin et al. (2023) reported an HR of 2.53 (95% CI 1.35-4.76). All three original estimates were positioned on the same adverse side of the null in the source pooling.

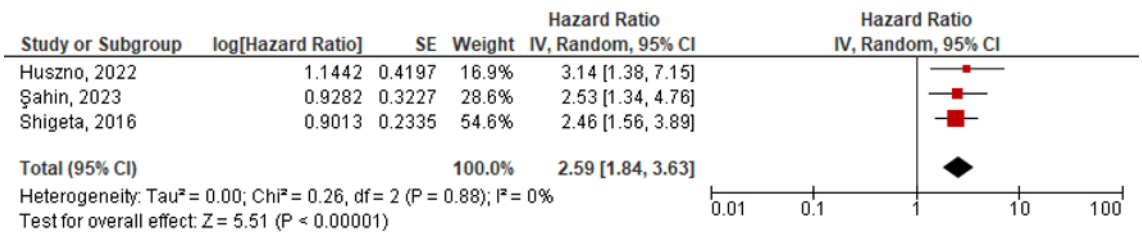
The random-effects pooled estimate showed a significant association between a higher monocyte-related inflammatory marker and poorer OS (HR 2.58, 95% CI 1.84-3.62; z=5.51; p<0.001). No statistical heterogeneity was detected (Q=0.26, df=2; I2=0%; tau2=0.00). The apparent consistency should be interpreted cautiously because statistical homogeneity does not correct the different exposure definitions.

Table 2. Original study estimates and meta-analytic result for overall survival.

Study	Reported HR (95% CI)	Pooling treatment	Pooled-input HR (95% CI)	Weight*
Huszno et al. (2022)	3.14 (1.38-7.17)	Retained as reported	3.14 (1.38-7.17)	16.8%
Shigeta et al. (2016)	2.46 (1.56-3.89)	Retained as reported	2.46 (1.56-3.89)	54.5%
Sahin et al. (2023)	2.53 (1.35-4.76)	Retained as reported	2.53 (1.35-4.76)	28.7%
Pooled	-	Random effects	2.58 (1.84-3.62)	100%

*Random-effects inverse-variance weight. CI, confidence interval; HR, hazard ratio; *MLR, monocyte-to-lymphocyte ratio. Shigeta et al. measured absolute monocyte count.*

Figure 2. Forest plot of the original three-study pooling for overall survival.



4. Discussion

In the original three-study synthesis, a higher monocyte-related inflammatory marker was associated with approximately 2.6-fold higher mortality in prostate cancer (HR 2.58, 95% CI 1.84-3.62). The direction of association was consistent across the three reported estimates, and no statistical heterogeneity was detected. These results support the potential prognostic relevance of systemic monocyte-lymphocyte balance.

Biological plausibility supports this observation. A high MLR may indicate relative monocytosis, lymphopenia, or both. Monocytes can supply tumor-associated macrophages that promote angiogenesis, invasion, and immune suppression, whereas low lymphocyte availability may reflect impaired antitumor immunity (Nishijima et al., 2015; Xiang et al., 2024; Wang et al., 2024). Direct evidence has also linked MLR to prostate cancer diagnosis and adverse clinical features (Xu et al., 2021; Wang et al., 2024).

The included cohorts represented different clinical settings. Huszno et al. (2022) studied non-metastatic disease, whereas Shigeta et al. (2016) and Sahin et al. (2023) evaluated metastatic castration-resistant disease receiving docetaxel or radionuclide therapy. Despite these clinical differences, the reported HRs were similar. However, the small number of studies means that the apparent I2 of 0% should not be interpreted as proof of biological equivalence.

The principal methodological limitation is exposure inconsistency. Huszno et al. (2022) reported the reciprocal LMR, and Shigeta et al. (2016) evaluated absolute monocyte count rather than MLR. Retaining these estimates without inversion reproduces the original analysis but does not create a strictly MLR-specific effect. Because MLR and LMR point in opposite mathematical directions, future syntheses should prespecify the target ratio and harmonise reference groups before pooling.

A subsequent meta-analysis of LMR in prostate cancer included six studies and reported prognostic relevance for LMR (Xiang et al., 2024). This reinforces the need for an updated search and careful separation of MLR, LMR, and absolute monocyte count in any final journal submission.

This analysis applies an inverse-variance random-effects model and appropriately avoids formal publication-bias testing with only three studies. Its limitations are substantial: the search was originally designed for several biomarkers rather than MLR alone; the exact search date and complete strategies were unavailable; all cohorts were retrospective; disease states and treatments differed; cutoffs were not standardized; one study measured absolute monocyte count; another reported reciprocal LMR; and aggregate data prevented consistent adjustment for stage, grade, prostate-specific antigen, performance status, treatment line, infection, corticosteroid use, and other inflammatory conditions.

The pooled association is promising but does not yet justify use of MLR as a stand-alone prognostic biomarker. Future studies should define MLR consistently as absolute monocytes divided by absolute lymphocytes, prespecify clinically justified cutoffs, record the timing of blood collection relative to treatment, exclude or adjust for acute inflammation and immunomodulating medication, and report multivariable HRs for standardised outcomes. Prospective multicentre cohorts and individual-patient-data meta-analysis would allow assessment across localized, metastatic hormone-sensitive, and metastatic castration-resistant disease.

5. Conclusion

The original three-study meta-analysis found that a higher monocyte-related inflammatory marker was associated with poorer OS in prostate cancer (pooled HR 2.58, 95% CI 1.84-3.62), without detected statistical heterogeneity. However, the limited number of retrospective cohorts and inconsistent definitions of MLR, LMR, and absolute monocyte count weaken certainty and prevent immediate clinical application. Updated MLR-specific evidence with standardized definitions and adequately adjusted prospective cohorts is required.

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