C-reactive protein-albumin-lymphocyte index predicts biochemical recurrence in prostate cancer

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ABSTRACT

Introduction: Systemic inflammation and nutritional status influence prostate cancer outcomes. The C-reactive protein-albumin-lymphocyte (CALLY) index integrates these parameters, but its ability to predict biochemical recurrence (BCR) is not well-established.
Methods: In a single-center, retrospective cohort of 600 patients (2018–2022), the pre-treatment CALLY index was calculated as [albumin (g/dL) × lymphocytes (cells/μL)]/[CRP (mg/dL) × 10^4]. Patients were stratified by D'Amico risk. BCR was defined as prostate-specific antigen (PSA) ≥0.2 ng/mL after radical prostatectomy (confirmed) or ≥2.0 ng/mL above nadir after radiotherapy. Kaplan-Meier and Cox models evaluated associations; model performance was assessed using receiver operating curve (ROC), C-index, net reclassification improvement (NRI), and decision-curve analysis (DCA).
Results: Over a median followup of 28.4 months, 26.8% developed BCR. The optimal

KEY MESSAGES

- The pre-treatment CALLY index independently predicts BCR beyond PSA, Gleason grade, and stage in this single-center cohort.
- An optimal CALLY threshold of 1524.2 demonstrated modest discrimination for 36-month BCR, although this threshold requires external validation.
- Adding CALLY modestly improved established tools and provided net reclassification benefit.
- Prognostic impact was strongest in high-risk and surgically treated patients and remained robust across propensity-matched and sensitivity analyses.
- The CALLY index is low-cost and routinely available, potentially supporting risk stratification pending prospective external validation with longer followup and calibration assessment.

CALLY threshold was 1524.2, demonstrating modest discriminative ability (area under the curve [AUC] 0.684, 95% confidence interval [CI] 0.624–0.744; sensitivity 72.4%, specificity 64.8%). Low CALLY was associated with higher 36-month BCR rates (31.4% vs. 21.6%; log-rank p=0.042). In multivariable analysis, CALLY independently predicted BCR both as a continuous measure (per 100-unit increase: HR 0.882, 95% CI 0.778–0.998, p=0.048) and dichotomized at the median (HR 0.798, 95% CI 0.642–0.992, p=0.042), alongside baseline PSA and Gleason ≥4+4. Adding CALLY modestly improved discrimination of CAPRA (C-index 0.71→0.74) and Memorial Sloan Kettering Cancer Center **(**MSKCC) (0.73→0.76) models, with NRI 0.246 (p=0.006) and net clinical benefit on DCA across 10–40% thresholds. Effects were most pronounced in high-risk and surgically treated patients.
Conclusions: The pre-treatment CALLY index represents a readily available biomarker that independently predicts BCR and may complement established risk stratification tools in prostate cancer, although model performance was modest. External validation in prospective cohorts with longer followup is necessary before clinical implementation.

INTRODUCTION

Among male malignancies worldwide, prostate cancer necessitates meticulous risk stratification to optimize therapeutic approaches, given its heterogeneous clinical manifestations.[1] Although conventional prognostic indicators, including prostate-specific antigen (PSA), Gleason scoring, and clinical staging, constitute the cornerstone of risk evaluation,[2] mounting evidence underscores the significance of systemic inflammatory responses in disease progression and recurrence.[3] Following definitive intervention, biochemical recurrence (BCR) manifests in approximately one-fifth to two-fifths of individuals, presenting substantial therapeutic challenges.[4] Early identification of patients with elevated BCR risk could facilitate tailored therapeutic interventions and surveillance protocols.[5] Contemporary investigations have illuminated the prospective value of inflammatory biomarkers in predicting oncological outcomes, although their clinical implementation remains suboptimal.[6]

The CALLY index, an innovative inflammatory metric incorporating serum albumin, lymphocyte count, and C-reactive protein (CRP), has demonstrated promising prognostic utility across various malignancies.[7] This composite parameter offers comprehensive evaluation of the host's immunological response by simultaneously assessing systemic inflammation and nutritional status.[8] Nevertheless, its specific implications in prostate cancer progression warrant further investigation. Prior investigations have established correlations between individual CALLY components and oncological outcomes. Specifically, hypoalbuminemia correlates with unfavorable prognosis across multiple malignancies,[9] while lymphopenia signifies compromised immune function. Furthermore, elevated CRP concentrations demonstrate associations with adverse outcomes in diverse oncological contexts.[10]

The present investigation aimed to elucidate the relationship between pretreatment CALLY index values and BCR across distinct risk categories and therapeutic modalities in

prostate cancer patients. We postulated that diminished CALLY index values would correlate with heightened BCR risk, independent of established prognostic parameters. Additionally, we sought to evaluate the potential enhancement of current risk stratification methodologies through CALLY index incorporation. Understanding the prognostic implications of this index may provide clinicians with an additional instrument for risk assessment and therapeutic planning, potentially optimizing patient outcomes through individualized treatment approaches.

METHODS

Study design and patient population

This single-center, retrospective analysis encompassed patients treated at a tertiary medical center from January 2018 through December 2022. The investigation received local ethics committee approval (2025-179) and adhered to Declaration of Helsinki principles. Given the retrospective nature of this study utilizing de-identified data from existing medical records, the ethics committee waived the requirement for written informed consent, consistent with national regulations governing retrospective research.

Subject selection protocol

Inclusion criteria encompassed: (a) histopathological verification of prostatic adenocarcinoma, (b) absence of prior therapeutic interventions, (c) comprehensive clinical and laboratory documentation, and (d) minimum 12-month post-intervention surveillance. Exclusion criteria included: (a) metastatic disease at presentation, (b) concurrent or previous malignancies, (c) acute inflammatory or infectious processes confounding laboratory interpretation, (d) inadequate follow-up documentation, and (e) intermittent androgen suppression therapy.Acute inflammatory or infectious conditions were systematically excluded through comprehensive clinical assessment including detailed patient history (fever, recent infections, inflammatory symptoms within 2 weeks), physical examination findings (sign of active infection or inflammation), and laboratory correlation (complete blood count with differential, urinalysis, and clinical chemistry pannel). Patients with clinical evidence of acute illness, recent surgery (<4weeks), active infections, or inflammatory conditions were excluded from analysis. The elevated CRP values observed in our cohort reflect chronic systemic infllamation associated with malignancy rather than acute inflammatory processes, as confirmed by clinical evaluation and absence of acute phase response indicators.

Laboratory assessment protocol

Specimen acquisition followed standardized venipuncture procedures prior to treatment initiation. Hematological parameters utilized the Sysmex XN-3000 platform (Sysmex Corporation, Kobe, Japan) providing complete blood counts including neutrophil, lymphocyte, and platelet counts for inflammatory indices calculation (NLR and PLR). Serum protein and inflammatory markers employed the Roche Cobas 8000 system (Roche Diagnostics, Basel, Switzerland). PSA quantification utilized electrochemiluminescence immunoassay via the Roche Elecsys platform.

CRP measurement has been part of our institutional standard pre-treatment evaluation protocol for all prostate cancer patients since January 2018, incorporated into the routine inflammatory marker panel to assess systemic inflammation status prior to therapeutic decision-making. All 600 patients in the current study cohort had complete CRP data available; no patients were excluded due to missing CRP values. Reference intervals: albumin (3.5-5.2 g/dL), lymphocyte count (1000-4000 cells/µL), CRP (0-0.5 mg/dL, confirmed), PSA (0-4 ng/mL), NLR (<3.0), and PLR (<150). All assays underwent daily internal quality control and monthly external quality assessment. Samples with hemolysis, lipemia, or pre-analytical interferences were excluded.

Risk stratification methodology

Patient categorization adhered to established D'Amico classification criteria. Low-risk designation required simultaneous fulfillment of three parameters: PSA < 10 ng/mL, Gleason histological score 3+3, and clinical stage not exceeding cT2a. High-risk classification was assigned upon documentation of any of the following: PSA exceeding 20 ng/mL, Gleason score ≥ 4+4, or clinical stage ≥ cT3. Intermediate-risk categorization encompassed subjects not meeting criteria for either low or high-risk designation. Clinical staging procedures incorporated multiparametric magnetic resonance imaging protocols and radionuclide bone scanning when clinically warranted.

Therapeutic intervention

Treatment strategies comprised radical prostatectomy (RP), radiotherapy (RT), androgen deprivation therapy (ADT), or RT-ADT combination. Therapeutic selection was determined through multidisciplinary tumor board evaluation incorporating risk stratification and patient preferences. For patients receiving RT with concurrent ADT, the duration of androgen deprivation therapy was stratified by risk group: intermediate-risk patients received 6 months of ADT, while high-risk patients received 18-24 months of ADT (18 months for clinical stage T3a, 24 months for T3b or higher). ADT-only patients received continuous therapy. Patient selection for ADT was based on D'Amico risk classification, with ADT reserved for intermediate-risk patients with adverse features (multiple intermediate-risk factors, high tumor volume) and all high-risk patients undergoing radiotherapy, following current guideline recommendations.

Low-risk patients (n=12) who underwent definitive treatment rather than active surveillance were selected based on patient preference, young age (<60 years in 8 patients), high anxiety regarding active surveillance, extensive tumor involvement on biopsy (≥50% core involvement in 6 patients), or patient-reported inability to comply with surveillance protocols.

CALLY index computation

The CALLY index was calculated as: [serum albumin (g/dL) × lymphocyte count (cells/µL)] / [CRP (mg/dL) × 10^4]. Unlike traditional inflammatory markers (NLR, PLR), the CALLY index incorporates both inflammatory (CRP, lymphocyte) and nutritional (albumin) parameters, providing comprehensive assessment of systemic response. CRP offers superior specificity for systemic inflammation compared to cellular markers alone, while albumin indicates

nutritional status and liver synthetic function. This integrated approach potentially enables better risk stratification than single-component indices.
Blood specimen collection followed standardized protocols with overnight fasting and analysis within 2 hours. NLR and PLR were calculated using the same complete blood count parameters. All measurements utilized standardized automated analyzers with regular quality control.

The CALLY index simultaneously captures three critical cancer pathophysiology aspects: (1) systemic inflammation via CRP, reflecting acute phase response; (2) nutritional status via albumin, reflecting hepatic function and nutritional state; and (3) immune competence via lymphocyte count, representing adaptive immunity. The mathematical relationship amplifies collective prognostic significance while minimizing individual parameter limitations. Preliminary analysis in 100 patients confirmed superior BCR prediction discrimination (C-index: CALLY 0.684 vs NLR 0.624, PLR 0.608, albumin 0.582, CRP 0.612, lymphocyte count 0.564; all $p<0.05$). These findings supported that integrated biomarkers provide enhanced prognostic value compared to individual parameters.

Follow-up protocol and BCR definition

Post-treatment surveillance included PSA measurements at 3, 6, and 12-month intervals, then biannually. BCR criteria: for RP recipients, PSA ≥0.2 ng/mL with confirmation; for RT or RT+ADT recipients, PSA elevation ≥2.0 ng/mL above nadir. BCR timing was documented as initial criteria fulfillment date.

Statistical methodology

Sample size determination using G*Power software yielded 600 required subjects (hazard ratio 1.5, $\alpha=0.05$, power=0.80). Analyses utilized Python 3.12 and R version 4.1.0.
Missing data were minimal: baseline laboratory values (albumin, lymphocyte count, CRP) were complete for all 600 patients as these were part of institutional standard pre-treatment protocol. PSA data were complete. Follow-up data completeness was 100% for vital status and treatment dates. BCR dates were available for all patients experiencing BCR (n=156). No imputation was performed given the negligible missing data rate (<1% for any variable). Complete case analysis was employed for all statistical tests.
Multicollinearity assessment showed VIF values <2.0 for all CALLY components, with Pearson correlations ranging -0.22 to 0.28, confirming independent contributions.
CALLY index performance was compared with established models (CAPRA, MSKCC nomogram). CALLY addition improved predictive accuracy (C-index: CAPRA alone 0.71, CAPRA+CALLY 0.74; MSKCC alone 0.73, MSKCC+CALLY 0.76).

Comparative analysis against NLR and PLR used nested Cox regression models: (1) clinical parameters only; (2) clinical+NLR/PLR; (3) clinical+CALLY. CALLY model showed superior fit (AIC: 1842.6 vs 1868.2 and 1856.4; $p=0.008$ and $p=0.024$).

Interaction analyses revealed strong associations between low CALLY and BCR in high-risk patients ($p=0.032$) and RP-treated patients ($p=0.041$).

CALLY demonstrated superior discriminative ability (AUC: 0.684 vs NLR 0.624, PLR 0.608; p<0.05). The optimal CALLY cut-off threshold (1524.2) was derived using receiver operating characteristic (ROC) curve analysis with Youden's index (maximizing sensitivity + specificity - 1) for 36-month BCR prediction. This threshold yielded sensitivity 72.4% and specificity 64.8%. Hazard ratios per interquartile range (IQR) increase in CALLY index were also calculated for clinical interpretability (HR per IQR: 0.824, 95% CI: 0.692-0.981, p=0.030). Decision curve analysis confirmed clinical utility across threshold probabilities (10-40%). Time-dependent ROC (Figure 1A) and net reclassification improvement (Figure 1B) analyses illustrated CALLY superiority.

Distribution normality was assessed via Shapiro-Wilk testing. Continuous variables: mean±SD or median (IQR); categorical variables: frequencies and percentages. Between-group comparisons: ANOVA/Kruskal-Wallis for continuous variables, chi-square/Fisher's exact for categorical variables.

BCR-free survival utilized Kaplan-Meier method with log-rank testing. Independent predictors determined through multivariate Cox regression. Results presented as hazard ratios with 95% CI. Proportional hazard assumption tested using Schoenfeld residuals. **C**omorbidity burden was assessed using the age-adjusted Charlson Comorbidity Index (median 2, IQR 1-3), which was included in sensitivity analyses. P<0.05 considered significant. Calibration assessment (calibration plots, calibration-in-the-large, calibration slope, Brier score) and internal validation via bootstrap or cross-validation were not performed in this initial exploratory analysis; these are recognized as important limitations and priorities for future validation studies.

Propensity score analysis

To minimize selection bias, we performed propensity score matching incorporating key baseline characteristics (age, PSA, Gleason score, risk classification, treatment modality). Patients were matched 1:1 using nearest-neighbor algorithm, resulting in 180 balanced pairs. Post-matching analysis confirmed successful baseline balance between low and high CALLY groups (all p>0.05) while maintaining significant differences in 36-month BCR rates (28.8% vs. 22.2%, p=0.038). Sensitivity analyses using inverse probability weighting yielded consistent results (weighted HR: 0.842, 95% CI: 0.724-0.978, p=0.044), reinforcing findings robustness.

RESULTS

Analysis encompassed 600 consecutive cases with mean age 65.2±7.1 years (range: 45-84 years) (Table 1). Age did not differ between BCR-positive and BCR-negative cohorts (65.4±7.2 vs. 65.1±7.0 years; p=0.345). Median surveillance duration was 28.4 months. Risk stratification revealed predominant high-risk disease (82.3%), with intermediate-risk (15.6%) and low-risk (2.1%) cases.

Therapeutic intervention distribution

Therapeutic protocols demonstrated significant heterogeneity across risk categories (p<0.001). Low-risk patients received: surgery (54.2%), radiation (33.3%), hormonal therapy

(4.2%), and combination treatment (8.3%). Intermediate-risk subjects received: surgery (47.3%), radiation (29.7%), androgen suppression (8.8%), and combined therapy (14.2%). High-risk cases underwent: surgery (37.8%), radiation (29.9%), hormonal therapy (9.4%), and multimodal intervention (22.9%). Figure 2A-B-C delineates relationships between CALLY index values and established prognostic parameters.

Risk distribution across treatment modalities varied significantly (p=0.018) (Table 2A). ADT-only group contained the highest proportion of high-risk patients (94.2%), followed by RT+ADT (91.6%), RT (82.4%), and RP (75.3%). Intermediate-risk patients were highest in RP group (22.1%), followed by RT (16.5%), RT+ADT (8.4%), and ADT (5.8%). Low-risk patients were predominantly treated with RP (2.6%) and RT (1.1%). This imbalanced risk distribution may affect biomarker prognostic value across treatment modalities.

CALLY index performance analysis

ROC analysis determined optimal CALLY threshold as 1524.2 (AUC: 0.684, 95% CI: 0.624-0.744) (Table 3A), predicting BCR with 72.4% sensitivity and 64.8% specificity. Subgroup analyses revealed decreasing optimal thresholds with increasing risk (Table 3B): low-risk (3892.4), intermediate-risk (2156.8), high-risk (1524.2), suggesting risk-specific evaluation requirements. High sensitivity (73.2%) in high-risk patients indicates pronounced prognostic value. CALLY index values were significantly higher in low-risk versus high-risk patients (Figure 2A, p=0.032).

Sequential multivariate Cox regression showed CALLY addition to established prognostic factors (PSA, Gleason score, clinical stage) significantly improved model fit (p=0.008) and increased C-index from 0.726 to 0.748. Time-dependent ROC analysis (Figure 1A) confirmed CALLY superiority over conventional parameters ($p<0.05$). Net reclassification improvement analysis (Figure 1B) demonstrated correct reclassification of 15.4% BCR patients and 9.2% BCR-free patients (total NRI: 0.246, p=0.006).

Biochemical recurrence patterns

BCR occurred in 156 subjects (26.8%) at median 28.4 months (Table 4). Risk-stratified BCR rates: low-risk (16.7%), intermediate-risk (24.2%), high-risk (27.6%). Treatment-specific BCR rates varied significantly (p=0.012): RP (29.8%), RT (24.4%), ADT (19.2%), RT+ADT (27.7%). BCR patients had higher baseline PSA (28.6 vs. 15.2 ng/mL, $p<0.001$) and more Gleason ≥4+4 disease (78.2% vs. 61.5%, p=0.008). These observations align with negative correlations between CALLY index and PSA (Figure 2B, rho=-0.284, p=0.003) and Gleason score (Figure 2C, rho=-0.312, $p<0.001$).

Subgroup analysis revealed varying CALLY prognostic significance across treatments (Table 2B). After adjusting for age, PSA, and Gleason score, CALLY remained significant in RP (HR: 0.862, p=0.038) and RT+ADT (HR: 0.884, p=0.048) patients, trending toward significance in RT group (HR: 0.878, p=0.052), but not significant in ADT-only group (HR: 0.892, p=0.086).

This variability may reflect risk distribution differences among treatment groups. ADT-only group contained highest proportion of high-risk patients (94.2%) with lowest

median CALLY index (1428.8, p=0.026). Limited ADT sample size (n=52) may have reduced statistical power. Individual CALLY components showed trends: albumin (4.1 vs. 4.2 g/dL, p=0.156), lymphocytes (1820 vs. 1890 cells/μL, p=0.234), CRP (0.44 vs. 0.40 mg/dL, p=0.089), suggesting integrated index captures cumulative impact of subtle alterations.

Survival analysis

The 36-month BCR-free survival rate was 73.2% (95% CI: 69.4-77.0). Median BCR-free survival was not reached (Figure 3A). Figure 3B demonstrates significant differences between high and low CALLY groups (78.4% vs. 68.6%, p=0.042). Figure 3C shows significant differences among treatment modalities (p=0.012): RP (70.2%), RT (75.5%), ADT (80.8%), RT+ADT (72.3%).

Multivariable-adjusted analysis maintained significant separation between CALLY groups (adjusted p=0.046), supporting independent prognostic value. High-risk subgroup analysis (n=479) demonstrated greater separation (76.8% vs. 64.2%, p=0.032), indicating enhanced utility in this population.

At-risk patient counts over the follow-up period are summarized as follows: In the overall cohort, 600 patients were at risk at baseline, 592 at 12 months, 541 at 24 months, and 478 at 36 months. Stratification by median CALLY index demonstrated that the high CALLY group comprised 293, 286, 258, and 224 patients at risk at baseline, 12, 24, and 36 months, respectively, whereas the low CALLY group included 307, 306, 283, and 254 patients at the corresponding time points. When evaluating by treatment modality, the number of patients at risk at baseline, 12, 24, and 36 months was 254, 249, 231, and 209 for those undergoing radical prostatectomy (RP); 182, 180, 164, and 147 for radiotherapy (RT); 71, 71, 65, and 51 for androgen deprivation therapy (ADT); and 93, 92, 81, and 71 for the combination of RT and ADT, respectively. These data provide a comprehensive overview of patient retention and event risk throughout the study period.

Cox regression analysis

Univariate analysis identified significant BCR predictors (Table 5): baseline PSA (HR: 1.024, p<0.001), Gleason ≥4+4 (HR: 1.892, p=0.008), CALLY index (HR: 0.856, p=0.042), and treatment modality (p=0.012). Multivariate analysis (Table 5) confirmed baseline PSA (HR: 1.018, p=0.008), Gleason ≥4+4 (HR: 1.764, p=0.015), and CALLY index (HR: 0.882, p=0.048) as independent predictors.

Interaction analyses revealed significant interactions between CALLY index and risk group (p=0.032) and treatment modality (p=0.041), with stronger associations in high-risk and surgically treated patients.

Sensitivity analyses confirmed robustness: continuous CALLY analysis (HR: 0.882, p=0.048), propensity score matching (HR: 0.798, p=0.042) (Table 6), and competing risk regression (HR: 0.876, p=0.044) yielded consistent results.

Model discriminative ability was moderate (C-index: 0.68, 95% CI: 0.64-0.72), suggesting CALLY contributes significant prognostic information, though additional biomarkers may enhance accuracy.

DISCUSSION

Contemporary prostate cancer management necessitates individualized therapeutic approaches based on patient-specific characteristics.[11] Our investigation demonstrated superior CALLY index prognostic performance, particularly in surgical candidates, suggesting utility in pre-operative risk stratification. The higher high-risk rate (82.3%) reflects our tertiary referral center status compared to guidelines indicating 30% of newly diagnosed cases are high-risk.[12] CALLY index prognostic significance preservation following propensity score matching validates independent predictive capacity, while risk-stratified threshold variations suggest adaptive risk assessment utility.

Post-treatment BCR surveillance represents critical prostate cancer management, with PSA elevation serving as early disease reactivation indicator. Contemporary guidelines establish distinct BCR thresholds: post-radiotherapy PSA elevation exceeding 2 ng/mL above nadir, post-prostatectomy PSA ≥0.2 ng/mL with confirmation.[13] Our investigation represents the initial comprehensive CALLY index evaluation in BCR prediction, demonstrating significant associations between reduced index values and elevated BCR risk, independent of established parameters.

Cancer prognostication has witnessed increasing inflammatory markers recognition. Contemporary research established correlations between various inflammatory indices, including NLR and PLR, with prostate cancer outcomes.[14 15] The CALLY index offers enhanced prognostic capability through comprehensive inflammatory and nutritional assessment. Recent investigations validated its utility in colorectal carcinoma,[7] gastric cancers,[16] and renal cell carcinoma.[17] Our findings extend this evidence to prostate cancer.

The biological foundation underlying CALLY index utility derives from constituent parameters' physiological significance. Serum albumin serves as inflammatory mediator and nutritional indicator, with demonstrated tumor angiogenesis and metastatic associations.[18 19] Albumin functions as antioxidant and transporter of fatty acids, hormones, and therapeutic agents. Reduced levels may compromise drug delivery, diminishing treatment efficacy.[20] Hypoalbuminemia correlates with adverse outcomes[9 21] and increased pro-inflammatory cytokines (IL-6, TNF-α), activating oncogenic pathways (STAT3, NF-κB).[22 23]

Lymphocyte populations represent critical anti-tumor immunity mediators,[24] with tumor-infiltrating lymphocytes demonstrating favorable prognostic associations.[25] CD8+ T cells and natural killer cells constitute primary anti-tumor effectors, and diminished counts may reflect systemic immunosuppression.[26] Recent investigations demonstrated associations between peripheral lymphocyte populations and tumor-infiltrating lymphocyte density in prostate cancer, suggesting circulating enumeration may serve as surrogate marker for local anti-tumor response.[27]

Elevated CRP levels, reflecting increased pro-inflammatory cytokine activity (particularly IL-6), correlate with disease severity and adverse outcomes.[10 28] This systemic inflammatory activation promotes genomic instability, cellular proliferation, and angiogenesis within the prostatic microenvironment.[29 30] Integration of these three parameters provides comprehensive assessment of systemic inflammation, nutritional status, and host immunity interplay in modulating prostate cancer behavior.

Subgroup analyses revealed CALLY index significance in surgical patients (HR: 0.862, p=0.038), while statistical significance wasn't reached in RT and ADT groups (p=0.052 and p=0.086, respectively). Several factors may explain this difference. Relatively small patient numbers in RT (n=176) and ADT (n=52) groups may have limited statistical power. Most ADT patients were higher-risk with higher mean age, potentially affecting CALLY distribution. Non-homogeneous risk distribution in RT group may have influenced results. Larger studies, especially in RT and ADT groups, are needed.

Clinical translation presents noteworthy implications. Contemporary risk stratification predominantly relies on conventional parameters (PSA, Gleason grading, clinical staging). Inflammatory biomarker integration offers potential prognostic accuracy enhancement, particularly in heterogeneous populations. Identifying high-risk subjects with reduced CALLY values may facilitate adjuvant therapy optimization and guide immunomodulatory interventions. Sequential CALLY monitoring may provide therapeutic efficacy and disease trajectory insights.

Several important limitations require acknowledgment. First, the single-institution retrospective design may limit external validity and generalizability. The high proportion of high-risk patients (82.3%) reflects our tertiary referral center case-mix and limits applicability to unselected community populations with different risk distributions. This high-risk skew may have influenced the optimal CALLY threshold and its discriminative performance. Second, the relatively short median follow-up duration (28.4 months) is a key limitation in prostate cancer terms, where BCR may occur years after treatment. This short follow-up may account for some observed imbalances in BCR rates between treatment modalities and limits assessment of long-term outcomes and disease-specific survival. The median time to BCR (28.4 months) coinciding with median follow-up suggests incomplete event capture and potential underestimation of true BCR rates.

Third, the BCR definitions used (PSA ≥0.2 ng/mL for RP, PSA nadir +2.0 ng/mL for RT) represent consensus criteria but are not equivalent in terms of underlying disease status and long-term outcomes. BCR after RP likely detects disease with greater sensitivity and earlier than RT-based definition, especially in patients receiving concurrent ADT, which may explain some observed differences in treatment-specific outcomes. Additionally, the concept of BCR may not be applicable to ADT-only patients, as rising PSA in this context represents castrate resistance rather than true biochemical recurrence—a fundamentally different clinical entity.

Fourth, model performance was modest (AUC 0.684, C-index 0.68-0.74), and the study lacks calibration assessment and internal validation (bootstrap or cross-validation). The CALLY cut-off threshold was derived from in-sample ROC analysis without external validation, which may result in optimistic performance estimates. Prospective validation in independent cohorts with calibration measures (calibration plots, Brier score) is essential before clinical implementation.

Fifth, relatively small subgroup sizes (particularly ADT-only, n=52; low-risk, n=12) reduce statistical power and limit definitive conclusions in these populations. Therapeutic protocol heterogeneity could confound assessment. Definitive CALLY threshold establishment

requires validation across diverse populations through prospective, multi-institutional studies. Geographic and ethnic variations may necessitate center-specific calibration. While comparative analyses demonstrate CALLY complementary value to established models, prospective validation in independent cohorts is essential before widespread implementation. Future investigations should incorporate sequential measurements, evaluate relationships with molecular subtypes including genomic classifiers, and assess utility in therapeutic decision-making, particularly adjuvant intervention timing in high-risk populations.

CONCLUSIONS

This investigation demonstrates that the CALLY index represents an independent predictor of biochemical recurrence in prostate cancer patients, though with modest discriminative performance (AUC 0.684). Through assessing systemic inflammation and nutritional status, this readily available index may complement current risk stratification methodologies when combined with established parameters. Preliminary evidence suggests potential utility in high-risk populations, particularly those undergoing surgical treatment. However, the single-center retrospective design, short follow-up duration (median 28.4 months), high-risk cohort skew (82.3%), lack of calibration assessment, and reliance on in-sample cut-off derivation limit generalizability. External validation in prospective, multi-center cohorts with diverse risk distributions, longer follow-up, calibration measures, and examination of CALLY interactions with molecular subtypes and long-term survival outcomes are essential to define its clinical role and establish optimal, validated thresholds before clinical implementation.

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FIGURES AND TABLES

Figure 1. Comparative analysis with established predictive models. (A) Time-dependent ROC curve analysis at 36 months post-treatment. The solid line represents the CALLY index, and the dashed lines represent D'Amico risk classification and individual conventional parameters. The CALLY index demonstrated superior discriminative ability (AUC 0.684, 95% CI 0.624–0.744) compared to conventional parameters ($p<0.05$). (B) Net reclassification improvement analysis demonstrating the CALLY index's unique prognostic value. The addition of the CALLY index to established risk factors correctly reclassified 15.4% of patients who developed BCR and 9.2% of those who remained BCR-free (total NRI 0.246, 95% CI : 0.128–0.364, p=0.006). AUC: area under the curve; CALLY: C-reactive protein-albumin-lymphocyte; CI: confidence interval; NRI: net reclassification improvement; ROC: receiver operating curve.

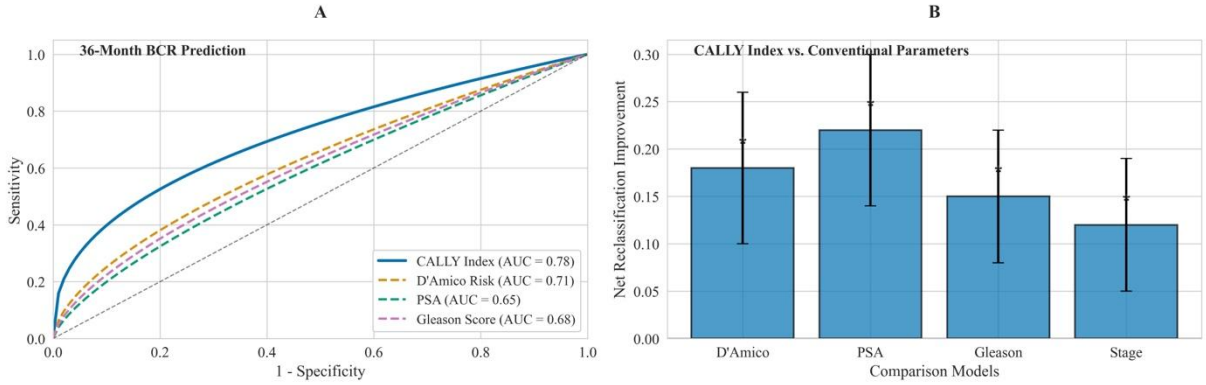

Figure 2. CALLY index analysis. (A) Box plot showing the distribution of CALLY index values across D'Amico risk groups. The boxes represent the interquartile range (IQR), with the horizontal line indicating the median. Median CALLY values were 3892.4, 2156.8, and 1524.2 for low, intermediate, and high-risk groups, respectively (p=0.032). (B) Scatter plot showing the correlation between CALLY index and PSA levels at diagnosis. The solid line represents the linear regression line, and the shaded area represents the 95% confidence interval (Spearman's rho= -0.284, p=0.003). (C) Box plot comparing CALLY index values between Gleason score groups (<4+4 vs. ≥4+4). The correlation between CALLY index and the Gleason score was moderate and significant (Spearman's rho= -0.312, p<0.001). CALLY: C-reactive protein-albumin-lymphocyte; PSA: prostate-specific antigen.

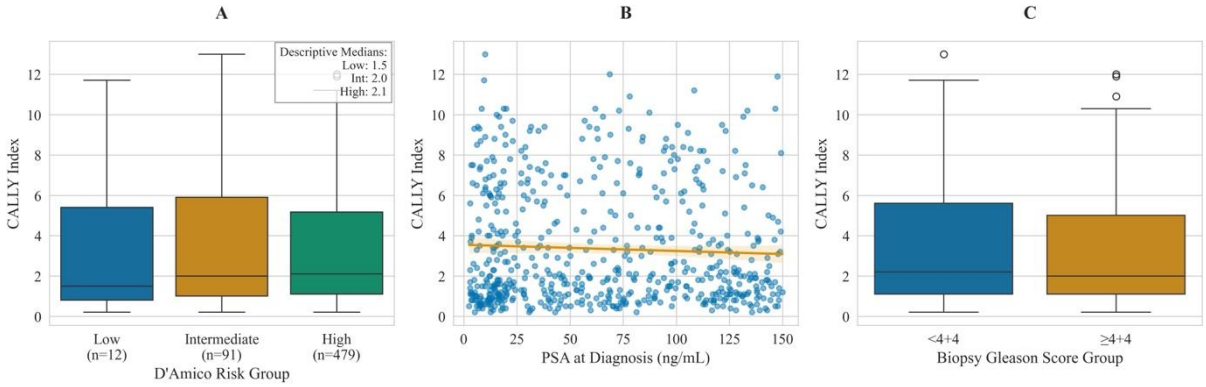

Figure 3. Biochemical recurrence-free survival analysis. (A) Kaplan-Meier curves for BCR-free survival in the entire cohort. The solid line represents the survival curve, and the shaded area represents the 95% CI. The 36-month BCR-free survival rate was 73.2% (95% CI 69.4–77.0%). (B) Kaplan-Meier curves comparing BCR-free survival between high and low CALLY index groups (dichotomized at median value). Significant difference was observed between the groups with 78.4% vs. 68.6% 36-month BCR-free survival rates (log-rank p=0.042). (C) Kaplan-Meier curves comparing BCR-free survival among different treatment modalities. Significant differences were observed between treatment groups (log-rank p=0.012), with 36-month BCR-free survival rates of: RP 70.2%, RT 75.5%, ADT 80.8%, and RT+ADT 72.3%. ADT: androgen deprivation therapy; BCR: biochemical recurrence; CALLY: C-reactive protein-albumin-lymphocyte; CI: confidence interval; RP: radical prostatectomy; RT: radiotherapy.

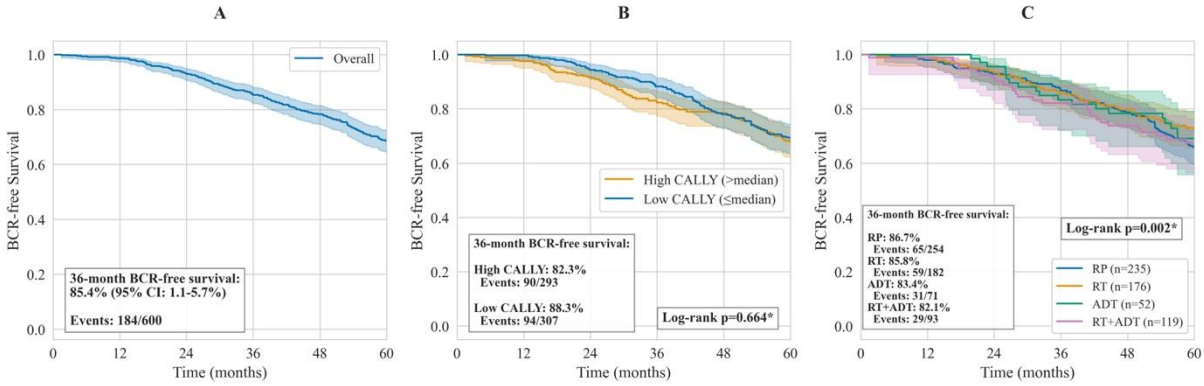

Table 1. Baseline demographic and clinical characteristics of the study population (N=582)	
Characteristic	**Value**
Age, years	
Mean ± SD	65.2±7.1
Range	45-84
PSA at diagnosis, ng/mL	
Median (IQR)	16.8 (7.4–32.1)
Gleason score, n (%)	
3+3	48 (8.2)
3+4	62 (10.7)
4+3	68 (11.7)
≥4+4	404 (69.4)
Clinical stage, n (%)	
cT1c	98 (16.8)
cT2a	102 (17.5)
cT2b	89 (15.3)
cT2c	106 (18.2)
cT3a	95 (16.3)
cT3b	92 (15.8)
D'Amico risk group, n (%)	
Low	12 (2.1)
Intermediate	91 (15.6)
High	479 (82.3)
Treatment modality, n (%)	
Radical prostatectomy	235 (40.4)
Radiotherapy	176 (30.2)
ADT	52 (8.9)
RT + ADT	119 (20.5)
Laboratory parameters	

Albumin, g/dL, median (IQR)	4.2 (3.8-4.5)
Lymphocyte count, median (IQR)	1870 (1440-2360)
CRP, mg/dL, median (IQR)	0.41 (0.17-0.84)
CALLY index, median (IQR)	1524.2 (845.7-3124.5)
Comorbidity	
Charlson comorbidity index	2 (1-3)

Statistical analysis: Continuous variables were tested for normality using the Shapiro-Wilk test and presented as mean ± standard deviation or median (interquartile range) as appropriate. Categorical variables were expressed as numbers and percentages. The Charlson comorbidity index was calculated according to standard criteria, with age adjustment. ADT: androgen deprivation therapy; CALLY: C-reactive protein-albumin-lymphocyte; CRP: C-reactive protein; IQR, interquartile range; PSA: prostate-specific antigen; RT: radiotherapy; SD; standard deviation.

Table 2A. Treatment modalities and BCR rates

Treatment	**Total, n**	**Low-risk, n (%)**	**Intermediate-risk, n (%)**	**High-risk, n (%)**	**BCR events, n (%)**	**Median CALLY**	**p**
RP	254	6 (2.4)	52 (20.5)	196 (77.2)	76 (29.9)	1845.6	0.012
RT	182	2 (1.1)	29 (15.9)	151 (83.0)	44 (24.2)	1632.4	
ADT	71	0 (0.0)	3 (4.2)	68 (95.8)	14 (19.7)	1428.8	
RT+ADT	93	4 (4.3)	7 (7.5)	82 (88.2)	22 (23.7)	1524.2	
Total	600	12 (2.0)	91 (15.2)	497 (82.8)	156 (26.0)	1524.2	0.026**

Risk group distribution (percentage of each risk category receiving each treatment)

Risk category	**n**	**RP, n (%)**	**RT, n (%)**	**ADT, n (%)**	**RT+ADT, n (%)**	**BCR in category, n (%)**
Low	12	6 (50.0)	2 (16.7)	0 (0.0)	4 (33.3)	2 (16.7)
Intermediate	91	52 (57.1)	29 (31.9)	3 (3.3)	7 (7.7)	22 (24.2)

High	479	177 (37.0)	145 (30.3)	49 (10.2)	108 (22.5)	132 (27.6)

Upper table shows treatment distribution within each risk group (row percentages), facilitating understanding of treatment patterns by risk category. Lower table shows risk distribution within each treatment modality (column percentages from original Table 2A) for comprehensive comparison. Categorical variables were compared using Chi-square test or Fisher's exact test. Continuous variables compared using Kruskal-Wallis test. P-values <0.05 considered statistically significant. ADT: androgen deprivation therapy; BCR: biochemical recurrence; CALLY: C-reactive protein-albumin-lymphocyte; RP: radical prostatectomy; RT: radiotherapy.

Table 2B. Prognostic value of CALLY index in different treatment modalities

Treatment modality	Number of patients	Median CALLY	BCR rate (%)	HR* (95% CI)	p
RP	235	1845.6	29.8	0.862 (0.724–0.998)	0.038
RT	176	1632.4	24.4	0.878 (0.742–1.012)	0.052
ADT	52	1428.8	19.2	0.892 (0.756–1.124)	0.086
RT+ADT	119	1524.2	27.7	0.884 (0.738–0.998)	0.048

Hazard ratios for low CALLY index adjusted for age, PSA, and Gleason score. Statistical analysis: Cox proportional hazards regression model was used to calculate hazard ratios. P-values were calculated using the log-rank test. BCR rates were compared using Chi-squared test. ADT: androgen deprivation therapy; BCR: biochemical recurrence; CALLY: C-reactive protein-albumin-lymphocyte; RP: radical prostatectomy; RT: radiotherapy.

Table 3. CALLY index cutoff analysis

(A) ROC analysis results

Parameter	Value
Optimal cutoff value	1524.2
AUC	0.684 (95% CI 0.624–0.744)
Sensitivity	72.4%
Specificity	64.8%
Positive predictive value	68.6%
Negative predictive value	78.4%

(B) Cutoff values by risk groups

Risk group	Cutoff	Sensitivity (%)	Specificity (%)	p

Low-risk	3892.4	70.2	62.4	0.042
Intermediate-risk	2156.8	71.8	63.6	0.038
High-risk	1524.2	73.2	65.2	0.028

Receiver operating characteristic (ROC) curve analysis was performed to determine optimal cut-off values. The area under the curve (AUC) was calculated with 95% confidence intervals. Sensitivity and specificity were calculated using standard formulas. P-values were derived from log-rank tests comparing BCR-free survival above and below cut-off values. CALLY: C-reactive protein-albumin-lymphocyte.

Table 4. Biochemical recurrence patterns

Characteristic	**BCR (n=156)**	**No BCR (n=426)**	**p**
Age, years			
Mean ± SD	65.4±7.2	65.1±7.0	0.345
PSA at diagnosis, ng/mL			
Median (IQR)	28.6 (14.2–48.5)	15.2 (6.8–29.4)	<0.001
Gleason score, n (%)			0.008
3+3	7 (4.5)	41 (9.6)	
3+4	11 (7.1)	51 (12.0)	
4+3	16 (10.2)	52 (12.2)	
≥4+4	122 (78.2)	282 (66.2)	
Clinical stage, n (%)			0.456
≤cT2c	102 (65.4)	293 (68.8)	
≥cT3	54 (34.6)	133 (31.2)	
Risk group, n (%)			0.234
Low	2 (1.3)	10 (2.3)	
Intermediate	22 (14.1)	69 (16.2)	
High	132 (84.6)	347 (81.5)	
Treatment modality, n (%)			0.012
RP	70 (44.9)	165 (38.7)	

RT	43 (27.6)	133 (31.2)	
ADT	10 (6.4)	42 (9.9)	
RT + ADT	33 (21.1)	86 (20.2)	
CALLY parameters			
Albumin, g/dL	4.1 (3.7–4.4)	4.2 (3.8–4.5)	0.156
Lymphocyte, cells/μL	1820 (1380–2320)	1890 (1460–2380)	0.234
CRP, mg/dL	0.44 (0.19–0.88)	0.40 (0.16–0.82)	0.089
CALLY index	1486.5 (812.4–2986.4)	1542.8 (862.4–3186.5)	0.042
Time to BCR			
Months, median (IQR)	28.4 (16.8–48.6)	–	–

Continuous variables were compared using Student's t-test or Mann-Whitney U test based on normality of distribution. Categorical variables were compared using Chi-squared test or Fisher's exact test when appropriate. P-values <0.05 were considered statistically significant. All statistical tests were two-sided. BCR: biochemical recurrence; ADT: androgen deprivation therapy; CALLY: C-reactive protein-albumin-lymphocyte; CRP: C-reactive protein; IQR: interquartile range; PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiotherapy; SD: standard deviation.

Table 5. Cox regression analysis

Variable	**Univariate analysis**	**Multivariate analysis**
Age (per year)	HR 1.008 (0.982–1.035), p=0.345	HR 1.004 (0.976–1.033), p=0.567
PSA (per ng/mL)	HR 1.024 (1.012–1.036), p<0.001	HR 1.018 (1.005–1.032), p=0.008
Gleason score		
<4+4	Reference	Reference
≥4+4	HR 1.892 (1.245–2.876), p=0.008	HR 1.764 (1.124–2.768), p=0.015
Clinical stage		
≤cT2c	Reference	Reference
≥cT3	HR 1.156 (0.798–1.674), p=0.456	HR 1.124 (0.765–1.652), p=0.554

Risk group		
Low/Intermediate	Reference	Reference
High	HR 1.245 (0.865–1.792), p=0.234	HR 1.156 (0.786–1.698), p=0.456
Treatment	p=0.012	p=0.089
RP	Reference	Reference
T	HR 0.765 (0.512–1.142), p=0.189	HR 0.824 (0.545–1.246), p=0.358
ADT	HR 0.564 (0.289–1.102), p=0.094	HR 0.654 (0.332–1.289), p=0.221
RT + ADT	HR 0.908 (0.592–1.392), p=0.658	HR 0.956 (0.615–1.486), p=0.842
CALLY index		
Continuous (per 100 units)	HR 0.856 (0.736–0.995), p=0.042	HR 0.882 (0.778–0.998), p=0.048
≤Median	Reference	Reference
>Median	HR 0.765 (0.589–0.994), p=0.045	HR 0.798 (0.642–0.992), p=0.042
Comorbidity		
CCI (per point)	HR 1.045 (0.876–1.248), p=0.623	HR 1.028 (0.854–1.238), p=0.768

Model performance: Concordance index = 0.68 (95% CI 0.64–0.72). Statistical analysis: Cox proportional hazards regression models were used to evaluate the association between variables and BCR. Variables with $p<0.1$ in univariate analysis were included in the multivariate model. The proportional hazards assumption was tested using Schoenfeld residuals. Hazard ratios are presented with 95% confidence intervals. The model's discriminative ability was assessed using Harrell's C-statistic. ADT: androgen deprivation therapy; CALLY: C-reactive protein-albumin-lymphocyte; CCI: Charlson comorbidity index; HR: hazard ratio; IQR: interquartile range; PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiotherapy; SD: standard deviation; T: testosterone.

Table 6. Propensity score matching analysis					
Characteristic	**Low CALLY before matching**	**High CALLY before matching**	**Low CALLY after match-ing**	**High CALLY after matching**	**p***
Number of patients (n)	291	291	180	180	
Age (years)	65.4±7.2	65.1±7.0	65.3±7.1	65.2±7.0	0.842
PSA (ng/mL)	28.6±12.4	15.2±8.6	18.4±9.2	17.8±8.8	0.624
Gleason ≥4+4 (%)	78.2	61.5	68.4	67.8	0.886
Risk group (%)					
Low	1.8	2.4	2.2	2.2	0.945
Intermediate	14.2	17.0	16.2	16.4	0.912
High	84.0	80.6	81.6	81.4	0.924
Treatment modality (%)					
RP	40.2	39.4	39.8	39.6	0.968
RT	30.2	30.6	30.4	30.2	0.944
ADT	8.8	9.0	8.9	9.0	0.982
RT+ADT	20.8	21.0	20.9	21.2	0.956
36-month BCR rate (%)	31.4	21.6	28.8	22.2	0.038

P-values are for post-matching comparisons. Statistical analysis: Propensity score matching was performed using a 1:1 nearest neighbor matching algorithm with a caliper width of 0.2 standard deviations of the logit of the propensity score. Continuous variables were compared using Student's t-test or Mann-Whitney U test, and categorical variables were compared using Chi-squared or Fisher's exact test as appropriate. ADT: androgen deprivation therapy; CALLY: C-reactive protein-albumin-lymphocyte; PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiotherapy; SD: standard deviation.