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Original article

The IL-1β signaling axis as a prognostic determinant in early-stage breast cancer: integrated analysis of tumor and circulating biomarkers

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Summary

Background. Chronic inflammation contributes to breast cancer progression, yet the prognostic relevance of inflammatory signaling pathways in early-stage disease remains incompletely defined. Interleukin-1β (IL-1β) is a key pro-inflammatory cytokine regulated by inflammasome activation and receptor-mediated signaling. This study evaluated the clinical and prognostic significance of major IL-1β pathway components in early-stage invasive breast cancer.

Methods. A retrospective cohort of 562 patients with early-stage invasive breast cancer treated between 2018 and 2025 was analyzed. Tissue microarrays were constructed, and immunohistochemistry was used to assess intratumoral expression of caspase-1, IL-1 receptor type I (IL-1R I), IL-1 receptor type II (IL-1R II), IL-1 receptor accessory protein (IL-1RacP), and IL-1 receptor antagonist (IL-1RA). Protein expression was quantified using H-scores and dichotomized by survival-based cut-offs. Circulating IL-1β levels were measured by ELISA in a subset of patients (n = 66). Associations with clinicopathological features, disease-free survival (DFS), and breast cancer-specific survival (BCSS) were evaluated.

Results. High intratumoral caspase-1 expression was associated with favorable tumor characteristics, reduced recurrence and metastasis, and improved DFS and BCSS. In contrast, elevated IL-1R II expression correlated with disease recurrence and shorter DFS. IL-1β expression alone showed no independent prognostic significance. Combined analyses demonstrated improved outcomes in tumors with preserved caspase-1 and IL-1β expression. Circulating IL-1β levels were higher in basal-type tumors but showed limited prognostic value.

Conclusions. Prognostic effects of IL-1β signaling in early-stage breast cancer depend on inflammasome integrity and receptor regulation rather than cytokine abundance alone. Integrated pathway profiling may improve biologically meaningful prognostic stratification.

Keywords: IL-1β, Caspase-1, Inflammasome, Tumor microenvironment, Inflammation, Prognostic biomarkers, Triple-negative breast cancer

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Introduction

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women worldwide, with over 2.3 million new cases reported annually [1]. Despite major advances in early detection, molecular subtyping, and systemic therapy, disease recurrence and metastatic progression continue to occur in a substantial proportion of patients with early-stage disease [2,3]. Traditional prognostic factors such as tumor size, grade, lymph node status, and hormone receptor expression do not fully capture the biological heterogeneity un-

derlying clinical outcomes, underscoring the need for additional biologically informative biomarkers [4].

Chronic inflammation has emerged as a critical driver of tumor initiation, progression, and immune evasion across multiple cancer types, including breast cancer [5,6]. Among inflammatory pathways, interleukin-1 beta (IL-1β) occupies a central role as a potent pro-tumorigenic cytokine capable of modulating angiogenesis, epithelial mesenchymal transition, immune cell recruitment, and metastatic niche formation [7-9]. Elevated IL-1β signaling has been linked to aggressive tumor phenotypes, treatment resistance, and poor survival, particularly in basal-like and triple-negative breast cancer (TNBC) [10-12].

IL-1β bioactivity is tightly regulated at multiple levels. It is synthesized as an inactive precursor and requires proteolytic cleavage by caspase-1 within inflammasome complexes to become biologically active [13]. Once released, IL-1β signals through the type I IL-1 receptor (IL-1R I) in conjunction with the IL-1 receptor accessory protein (IL-1RacP), initiating downstream NF-κB and MAPK signaling cascades [14]. In contrast, IL-1 receptor type II (IL-1R II) acts primarily as a decoy receptor, sequestering IL-1β and attenuating inflammatory signaling, while the IL-1 receptor antagonist (IL-1RA) competitively inhibits receptor activation [15]. Dysregulation of this finely balanced signaling network can shift the tumor microenvironment toward either tumor-promoting inflammation or immune restraint.

Recent experimental and translational studies have highlighted the dual and context-dependent role of IL-1β signaling in breast cancer biology [16,17]. While IL-1β can promote tumor growth and metastasis, components of the inflammasome pathway, particularly caspase-1, have also been associated with tumor-suppressive immune responses and improved clinical outcomes in selected contexts [18,19]. These apparently paradoxical effects suggest that the prognostic relevance of IL-1β signaling cannot be inferred from single markers alone but rather requires integrated, pathway-level evaluation of its regulatory components.

Although circulating IL-1β has been explored as a biomarker in advanced and metastatic breast cancer [20], data linking serum IL-1β levels with intratumoral expression of IL-1β signaling components and long-term outcomes in early-stage disease remain limited. Furthermore, intratumoral IL-1β expression may not reflect tumor-cell intrinsic signaling but instead represent the composite activity of stromal and immune compartments within the tumor microenvironment. Comprehensive analyses simultaneously assessing caspase-1, IL-1 receptors, and IL-1β—together with detailed clinicopathological correlations—are therefore scarce, particularly in large, well-characterized cohorts with extended follow-up.

In this study, we investigated the expression patterns and prognostic significance of key IL-1β pathway components caspase-1, IL-1R I, IL-1R II, IL-1RacP, and IL-1RA in a large cohort of patients with early-stage invasive breast cancer. Using tissue microarray-based immunohistochemistry and objective survival-based cut-off determination, we evaluated their associations with clinicopathological features, disease recurrence, and survival outcomes. In addition, we examined circulating IL-1β levels in a subset of patients to explore systemic inflammatory correlates. By integrating tumor-based and serum-based analyses, this study aims to clarify the complex role of IL-1β signaling in breast cancer progression and to identify biologically meaningful inflammatory biomarkers with potential prognostic and therapeutic relevance.

Methods

Study Cohort and Clinical Data

This retrospective study included 562 patients with early-stage invasive breast cancer who underwent primary surgical treatment between 2018 and 2025. Clinicopathological data collected included patient age, tumor size, histological grade, pathological stage, lymphovascular invasion (LVI), lymph node (LN) status, estrogen receptor (ER), progesterone receptor (PgR), HER-2 status, molecular subtype, disease recurrence, and distant metastasis.

ER and PgR positivity were defined as nuclear staining in > 1% of tumor cells. HER-2 positivity was defined as IHC score 3+, with equivocal (2+) cases confirmed by fluorescence in situ hybridization. Triple-negative breast cancer was defined by the absence of ER, PgR, and HER-2 expression. Long-term follow-up data were available for disease-free survival (DFS) and breast cancer-specific survival (BCSS) analyses.

Ethical approval was obtained from the Institutional Review Board (IRB) of Komar University of Science and Technology (KUST), Sulaymaniyah, Iraq (Approval No. KUST-FA25-07-04-DEN). The study was conducted in accordance with institutional ethical guidelines and the principles of the Declaration of Helsinki.

Tissue Microarray Construction and Immunohistochemistry

Formalin-fixed paraffin-embedded (FFPE) tumor specimens were assembled into tissue microarrays (TMAs) to enable high-throughput and standardized biomarker evaluation. Immunohistochemical

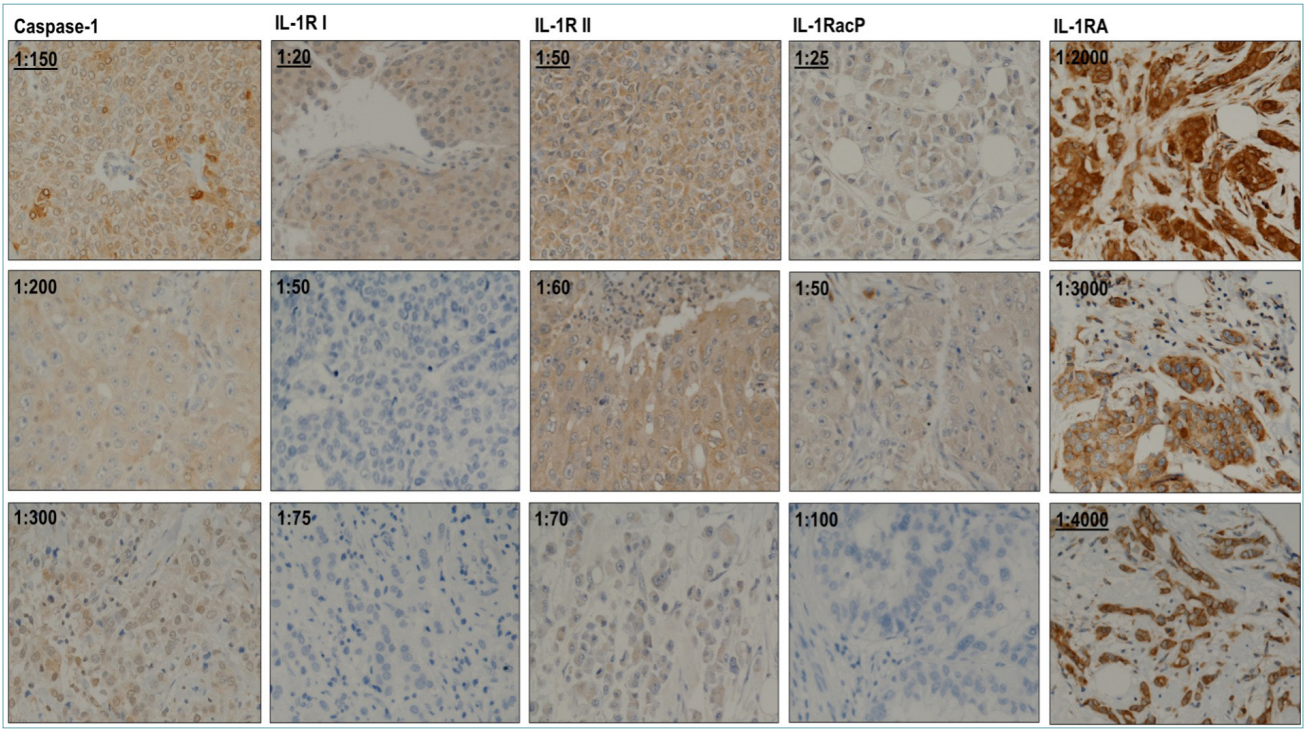


Figure 1. Optimisation of anti-caspase-1, anti-IL-1R I, anti-IL-1R II, anti-IL-1RacP, and anti-IL-1RA antibodies. Different concentrations of each antibody were applied on breast tumour composite sections, and optimal concentration was chosen depending on heterogeneous staining pattern with no background staining (200X magnification).

staining was performed to assess the expression of caspase-1, IL-1 receptor type I (IL-1R I), IL-1 receptor type II (IL-1R II), IL-1 receptor accessory protein (IL-1RacP), and IL-1 receptor antagonist (IL-1RA) using commercially validated primary antibodies and optimized staining protocols.

Antibody selection was based on manufacturer validation data, prior peer-reviewed publications, and reproducible staining patterns in FFPE breast cancer tissues. Each staining run included appropriate positive and negative tissue controls to ensure specificity and technical reliability. Detailed antibody information is provided in Supplementary File S1. Representative immunohistochemical staining patterns are illustrated in Figure 1.

Evaluation of Protein Expression

Protein expression was assessed using a semi-quantitative H-score system, which integrates staining intensity and the percentage of positively stained tumor cells, yielding scores ranging from 0 to 300. Scoring was independently performed by two observers blinded to clinicopathological data and patient outcomes. Inter-observer agreement was evaluated using intraclass correlation coefficients, demonstrating good to excellent concordance.

Objective cut-off points for dichotomizing tumors into low- and high-expression groups were determined using X-tile bioinformatics software, based on breast cancer-specific survival.

Serum IL-1β Measurement

Serum samples collected within ±31 days of surgery and prior to loco-regional radiotherapy were available for a subset of patients (n = 66). Circulating IL-1β concentrations were measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Associations between serum IL-1β levels and clinicopathological variables were subsequently evaluated.

Statistical Analysis

Associations between biomarker expression and clinicopathological parameters were assessed using the Chi-square test or Fisher's exact test, as appropriate. Survival curves were generated using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test. Multivariate survival analyses were performed using Cox proportional hazards regression models, adjusting for established prognostic factors.

Statistical analyses were conducted using SPSS soft-

ware (version 22.0). A p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 562 patients with early-stage invasive breast cancer were included in this study. Most patients were older than 40 years (503 cases, 89.5%), while 59 patients (10.5%) were 40 years of age or younger. Tumors larger than 2 cm were observed in 343 cases (61.0%), whereas 212 tumors (37.7%) measured 2 cm or less. The majority of tumors were classified as pathological stage I (360 cases, 64.0%), followed by stage II (134 cases, 23.8%) and stage III disease (62 cases, 11.0%). High-grade tumors (grade III) accounted for nearly half of the cohort (278 cases, 49.5%) (Tab. I).

Hormone receptor positivity was common, with estrogen receptor (ER)-positive tumors identified in 401 patients (71.3%) and progesterone receptor (PgR)-positive tumors in 348 patients (61.9%). HER-2 overexpression was detected in 99 cases (17.6%), while triple-negative breast cancer accounted for 84 cases (15.0%). During follow-up, disease recurrence occurred in 239 patients (42.6%), and distant metastasis was documented in 174 patients (31.0%) (Tab. I).

Table I. Clinicopathological characteristics of the study cohort (n = 562).

Variable	Category	n (%)
Age (years)	≤40	59 (10.5)
Age (years)	> 40	503 (89.5)
Tumor size (cm)	≤2	212 (37.7)
Tumor size (cm)	> 2	343 (61.0)
Tumor stage	I	360 (64.0)
Tumor stage	II	134 (23.8)
Tumor stage	III	62 (11.0)
Tumor grade	I	102 (18.1)
Tumor grade	II	178 (31.6)
Tumor grade	III	278 (49.5)
ER status	Positive	401 (71.3)
ER status	Negative	161 (28.7)
PgR status	Positive	348 (61.9)
PgR status	Negative	214 (38.1)
HER-2 status	Positive	99 (17.6)
HER-2 status	Negative	463 (82.4)
Molecular subtype	Non-triple-negative	478 (85.0)
Molecular subtype	Triple-negative	84 (15.0)
Recurrence	No	323 (57.4)
Recurrence	Yes	239 (42.6)
Distant metastasis	No	388 (69.0)
Distant metastasis	Yes	174 (31.0)

Expression Patterns of IL-1β Pathway Components

Immunohistochemical analysis demonstrated detectable expression of caspase-1, IL-1 receptor type I (IL-1R I), IL-1 receptor type II (IL-1R II), IL-1 receptor accessory protein (IL-1RacP), and IL-1 receptor antagonist (IL-1RA) within tumor cells. Representative staining patterns and antibody optimization data are shown in Figure 1 and Figure 2.

Across the cohort, staining was predominantly cytoplasmic, although membranous localization of IL-1 receptors was observed in a subset of tumors. Occasional nuclear staining was noted for IL-1R II and IL-1RA. Expression levels varied considerably between tumors, ranging from absent or weak staining to strong immunoreactivity, reflecting marked inter-tumoral heterogeneity (Fig. 1).

Association with Clinicopathological Features

High caspase-1 expression was significantly associated with favorable clinicopathological features. Elevated caspase-1 levels were more frequently observed in ER-positive tumors ($p = 0.005$) and PgR-positive tumors ($p < 0.001$), and were significantly less common in triple-negative ($p = 0.001$) and basal-like tumors ($p = 0.001$). Importantly, high caspase-1 expression was associated with reduced rates of disease recurrence ($p = 0.003$) and distant metastasis ($p < 0.001$), suggesting a protective biological role (Tab. IV).

In contrast, increased IL-1R I expression was significantly associated with lower histological grade ($p = 0.0001$) and more favorable Nottingham Prognostic Index categories. High IL-1R II expression was significantly associated with disease recurrence ($p = 0.006$), consistent with its role as a decoy receptor regulating IL-1β signaling. Elevated IL-1RacP expression correlated with ER positivity and non-basal molecular subtype, whereas IL-1RA expression showed no consistent association with clinicopathological variables (Tab. II).

Survival Analysis

Kaplan-Meier survival analysis demonstrated that patients with high caspase-1 expression experienced significantly longer disease-free survival compared with those with low expression ($p = 0.002$). A similar association was observed for breast cancer-specific survival, with improved outcomes in patients exhibiting high caspase-1 expression ($p = 0.004$) (Fig. 2).

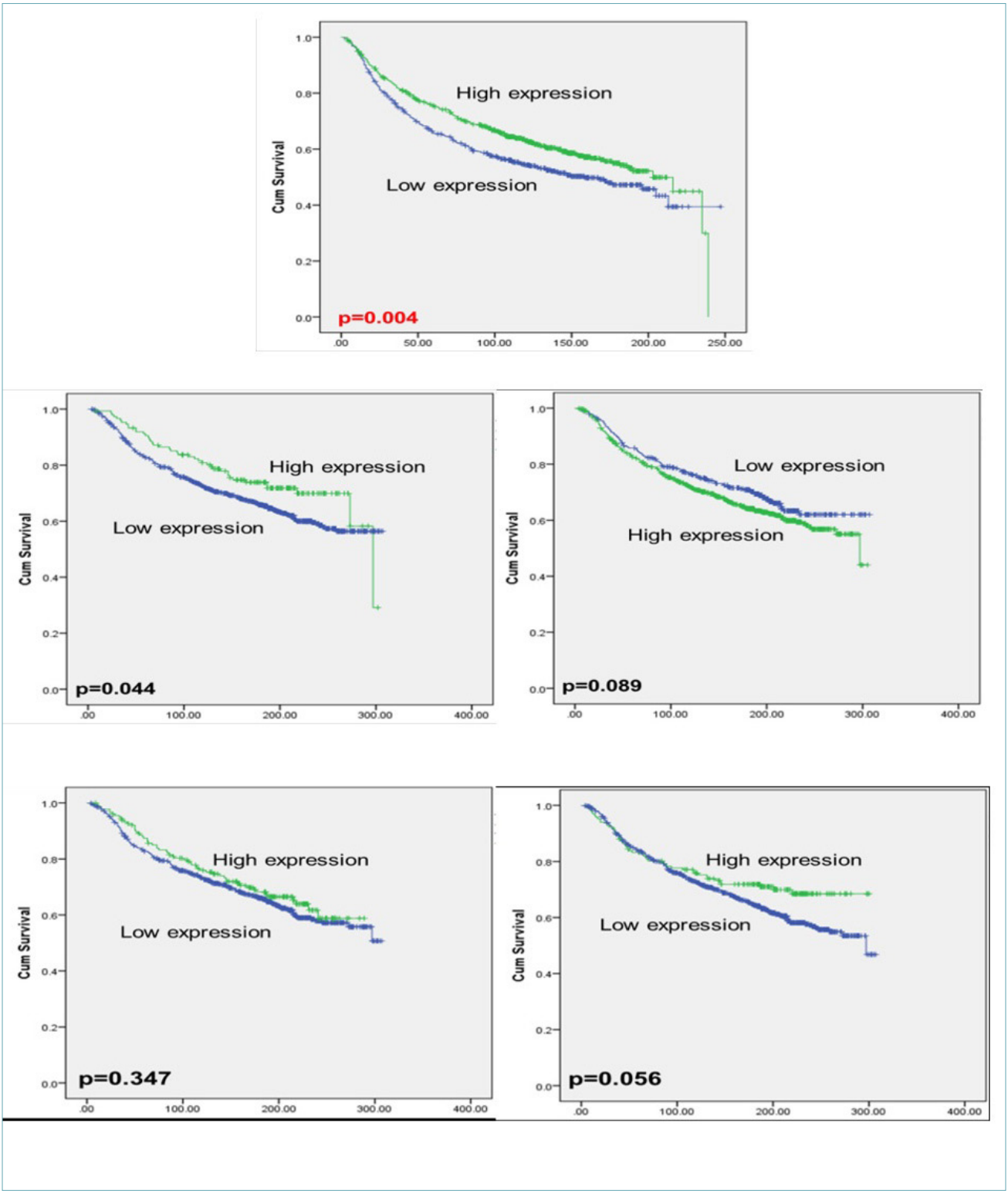


Figure 2. Kaplan-Meier analysis of the association between caspase-1, IL-1 receptors, IL-1 receptor accessory protein (IL-1RacP), and IL-1 receptor antagonist (IL-1RA) expression and breast cancer-specific survival. Survival differences were assessed using the log-rank test. High caspase-1 expression was significantly associated with improved breast cancer-specific survival (A, p = 0.004). IL-1 receptor type I showed a statistically significant but modest association (B, p = 0.044), while no significant associations were observed for IL-1 receptor type II (C, p = 0.089), IL-1RacP (D, p = 0.347), or IL-1RA (E, p = 0.056).

Table II. Association between IL-1β pathway components and clinicopathological variables.

Variable	Caspase-1 (High)	IL-1R I (High)	IL-1R II (High)	IL-1RacP (High)	IL-1RA (High)
ER positivity	Yes (p = 0.005)	NS	NS	Yes (p = 0.004)	NS
PgR positivity	Yes (p < 0.001)	NS	NS	NS	NS
Lower tumor grade	NS	Yes (p = 0.0001)	NS	NS	NS
Triple-negative subtype	Less frequent (p = 0.001)	Less frequent (p = 0.029)	NS	Less frequent (p = 0.003)	NS
Basal subtype	Less frequent (p = 0.001)	NS	NS	Less frequent (p = 0.003)	NS
Recurrence	Lower (p = 0.003)	NS	Higher (p = 0.006)	NS	NS
Distant metastasis	Lower (p < 0.001)	NS	NS	NS	NS

Table III. Multivariate Cox regression analysis for disease-free survival.

Variable	HR	95% CI	p-value
Caspase-1 (High vs Low)	0.75	0.58-0.96	0.024
IL-1R II (High vs Low)	1.21	0.92-1.58	0.173
Tumor stage	2.56	1.71-3.84	< 0.001
Tumor grade	1.28	0.93-1.78	0.136
LVI	1.60	1.23-2.09	< 0.001
LN status	0.56	0.34-0.91	0.020

Conversely, high IL-1R II expression was associated with shorter disease-free survival (p = 0.005) (Fig. 3). No significant associations were observed between IL-1R I, IL-1RacP, or IL-1RA expression and survival outcomes. Multivariate Cox proportional hazards analysis for disease-free survival (DFS) demonstrated that high caspase-1 expression remained independently associated with improved DFS after adjustment for established clinicopathological factors, whereas IL-1R II did not retain independent significance (Tab. III)

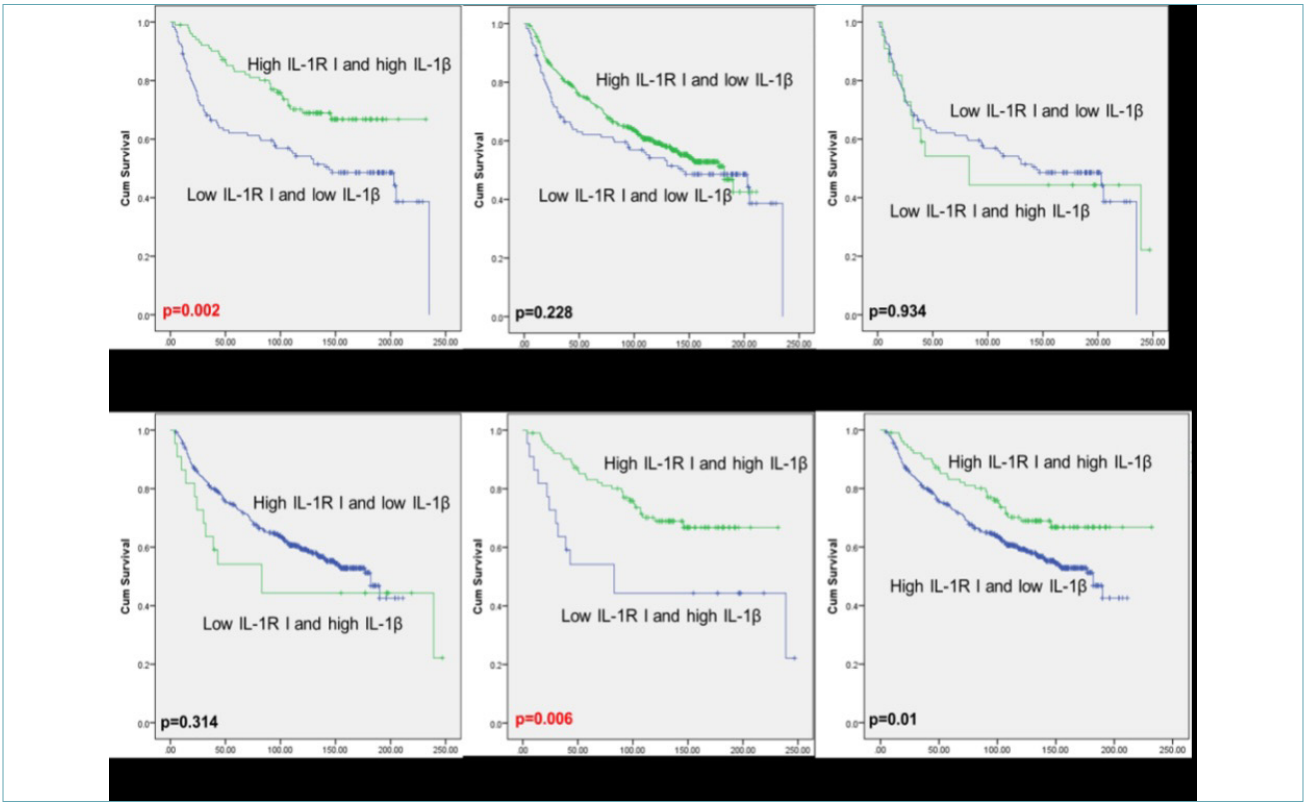


Figure 3. Kaplan-Meier analysis of IL-1R I and tumour IL-1β expression subgroupings and disease-free survival. Significance was determined using the log-rank test. Patients with high IL-1R I and IL-1β expression had longer disease-free intervals compared with other patients whose tumour either had low IL-1R I and low IL-1β expressions (p = 0.002), or low IL-1R I and high IL-1β expressions (p = 0.006).

Combined Expression of IL-1β and Signaling Components

Combined expression analyses demonstrated that patients whose tumors exhibited high caspase-1 and high IL-1β expression experienced improved disease-free survival compared with those showing low expression of both markers ($p < 0.001$) (Fig. 4) Similarly, favorable survival patterns were observed in patients with high IL-1R I and high IL-1β expression. However, these associations did not remain significant after multivariate adjustment, indicating that combined IL-1β signaling effects are influenced by other dominant prognostic factors.

Serum IL-1β Levels and Clinicopathological Associations

Associations between serum IL-1β levels and clinicopathological variables are summarized in Table IV. Analysis of circulating IL-1β levels revealed a significant association with molecular subtype. Patients with basal-type tumors exhibited significantly higher serum IL-1β concentrations compared with those with non-basal tumors ($p = 0.002$). No significant associations were observed between serum IL-1β levels and tumor size, grade, hormone receptor status, recurrence, or distant metastasis. Furthermore, serum IL-1β concentrations did not show a strong correlation with intratumoral expression of IL-1β pathway components.

Table IV. Association between serum IL-1β levels and clinicopathological features

Variable	Association	p-value
Basal molecular subtype	Higher IL-1β	0.002
ER status	No association	NS
Tumor grade	No association	NS
Recurrence	No association	NS
Distant metastasis	No association	NS

Discussion

This study provides a comprehensive evaluation of the IL-1β signaling axis in early-stage invasive breast

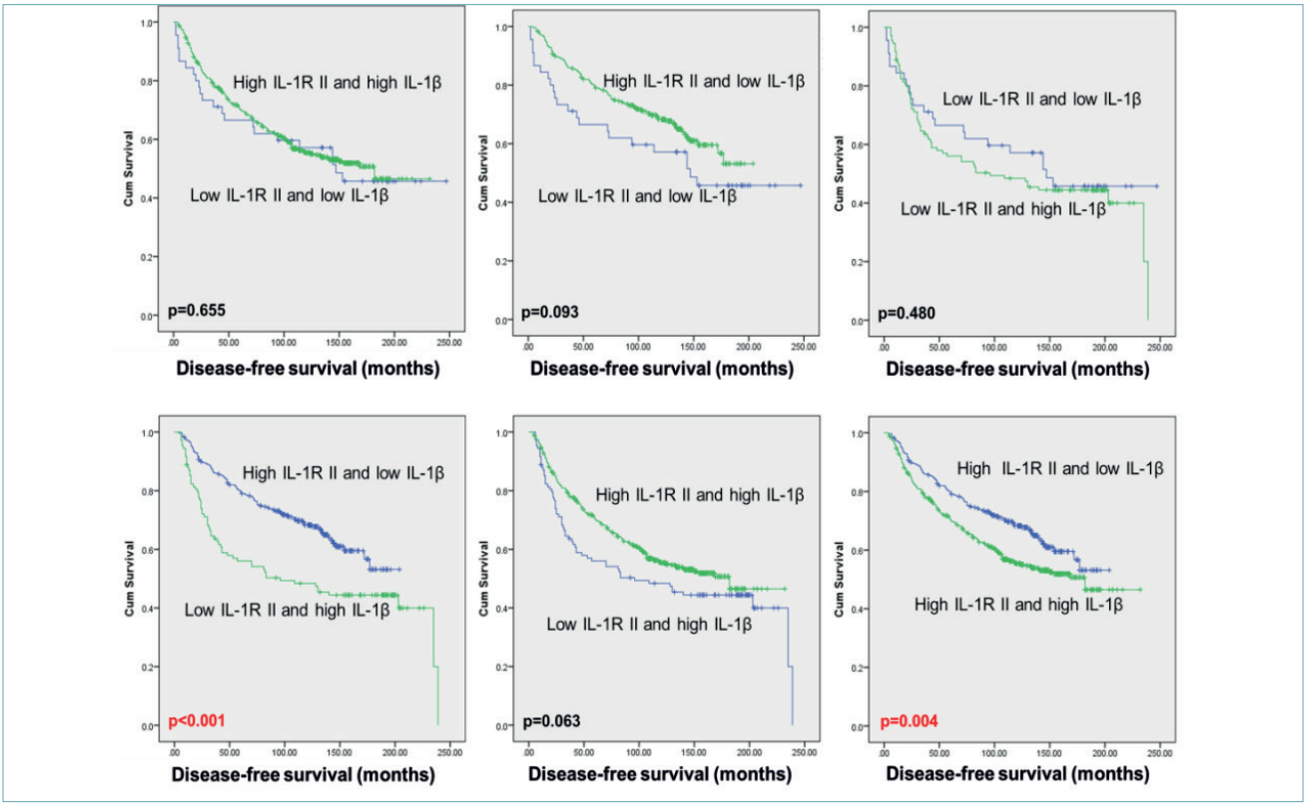


Figure 4. Kaplan-Meier analysis of IL-1R II and tumour IL-1β expression subgroupings and disease-free survival. Significance was determined using the log-rank test. Patients with high IL-R II and low IL-1β expression had longer disease-free intervals compared to patients whose tumour either expressed low IL-1R II and high IL-1β ($p < 0.001$) or expressed high IL-1R II and high IL-1β ($p = 0.004$).

cancer by integrating intratumoral expression of inflammasome components and IL-1 receptors with circulating IL-1β levels and long-term clinical outcomes. Our findings support the concept that IL-1β signaling exerts context-dependent effects in breast cancer, governed by the interplay between cytokine availability, receptor configuration, and inflammasome integrity rather than IL-1β abundance alone [17,21,22]. Importantly, such context-dependent behavior is not unique to the IL-1β pathway but represents a broader feature of cancer-related signaling networks. Pathways such as NF-κB activation and heme metabolism similarly exhibit dual pro- or anti-tumor roles depending on cellular context, tumor microenvironment, and immune interactions [5,23-25].

A key observation of this study is the association between high intratumoral caspase-1 expression and favorable clinical outcomes, including reduced recurrence and improved disease-free and breast cancer-specific survival. Recent studies demonstrate that caspase-1 is not merely a cytokine-processing enzyme but also a critical regulator of inflammasome-dependent immune activation and immunogenic cell death [13,19,21]. In breast cancer, preserved inflammasome activity has increasingly been linked to enhanced immune surveillance and restrained tumor progression, particularly in early disease where immune-epithelial interactions remain relatively intact [26]. Collectively, these findings suggest that caspase-1 expression may reflect a biologically competent inflammatory pathway associated with improved tumor control.

In contrast, elevated expression of IL-1 receptor type II (IL-1R II), a non-signaling decoy receptor, was associated with disease recurrence. Emerging evidence indicates that IL-1R II upregulation suppresses productive IL-1 signaling and promotes immune escape by skewing the tumor microenvironment toward a tumor-supportive inflammatory state [17,23,27]. Our findings indicate that functional inhibition of IL-1 signaling via receptor imbalance may be as biologically relevant as cytokine overexpression, a concept increasingly emphasized in contemporary cancer-inflammation literature [23,28]. Notably, IL-1R II is an inducible receptor, and its expression can be upregulated by inflammatory stimuli, including IL-1β itself, suggesting the presence of a dynamic feedback regulatory loop within the IL-1 signaling axis. This reciprocal regulation further underscores the complexity of IL-1β pathway activity and highlights the importance of considering both ligand and receptor dynamics when interpreting its biological and prognostic effects.

The prognostic inconsistency of IL-1β expression alone further underscores the dual and context-dependent nature of this cytokine. Although IL-1β has been shown to promote angiogenesis, invasiveness, and metastatic niche formation particularly in aggressive and triple-negative breast cancer subtypes [29-31]. Recent translational studies highlight that its biological impact is critically shaped by downstream signaling competence and immune context [26,32]. This provides a plausible explanation for the lack of independent prognostic value of IL-1β expression observed in our multivariate analyses.

Analysis of circulating IL-1β levels revealed higher concentrations in patients with basal-type tumors, consistent with modern data linking systemic inflammation to aggressive breast cancer phenotypes [30,31,33]. However, serum IL-1β showed no significant association with survival or recurrence and correlated poorly with intratumoral expression of IL-1β pathway components. These findings align with recent studies demonstrating that systemic cytokine levels often reflect host inflammatory status rather than tumor-specific signaling dynamics, thereby limiting their prognostic utility when used in isolation [28,34].

From a therapeutic perspective, IL-1β has emerged as a promising target for tumor microenvironment modulation. Preclinical and translational studies suggest that IL-1β inhibition can remodel immune suppression and enhance responses to immunotherapy [13,17,27]. However, accumulating evidence cautions that non-selective inhibition of IL-1β or inflammasome activity may inadvertently suppress beneficial immune mechanisms, particularly caspase-1-dependent antitumor responses [13,19,21]. Our findings therefore support a biomarker-guided strategy for inflammatory pathway targeting rather than indiscriminate cytokine blockade.

Notably, high caspase-1 expression remained independently associated with improved disease-free survival after multivariate adjustment, whereas the remaining IL-1β pathway components did not retain independent prognostic significance. This observation is consistent with recent large-scale prognostic analyses demonstrating that inflammatory biomarkers refine biological understanding but rarely override classical determinants such as tumor stage, lymphovascular invasion, and nodal status in early breast cancer [32,34,35]. Nevertheless, pathway-level inflammatory profiling may improve biological insight and aid in patient stratification. **Several limitations of this study should be acknowledged.** First, the retrospective design precludes definitive causal inference, although the large, well-characterized cohort with long-term follow-up strengthens the robustness of the observed associations. Second, biomarker expression was assessed at a single time point, and dynamic changes in IL-1β signaling during disease progression or

treatment were not evaluated. Third, circulating IL-1β analysis was performed in a subset of patients, which may limit statistical power for serum-based correlations. Fourth, caspase-1, although a key effector of inflammasome activation, is not entirely specific to a single inflammasome complex, and additional canonical components such as NLRP3 and ASC were not assessed; therefore, the findings should be interpreted as reflecting inflammasome-related activity rather than direct characterization of specific inflammasome complexes. Fifth, Ki-67 proliferation index data were not available for all cases, precluding evaluation of proliferation as a potential confounding factor. Sixth, immunohistochemical assessment was not stratified by tumor versus stromal compartments, which may have distinct biological and prognostic implications. Finally, the study did not include evaluation of inflammatory infiltrates, limiting interpretation of the IL-1β signaling axis within the broader immune context of the tumor microenvironment. Future prospective studies incorporating longitudinal sampling, a broader panel of inflammasome markers, proliferation indices, compartment-specific analyses, and immune profiling will be important to further clarify the biological and therapeutic relevance of IL-1β pathway regulation in breast cancer.

Conclusion

This study shows that IL-1β signaling in early-stage breast cancer is governed by the integrity and regulation of the inflammatory pathway rather than by IL-1β expression alone. High intratumoral caspase-1 expression is associated with favorable tumor characteristics and improved survival, suggesting a protective role for intact inflammasome activity. In contrast, increased IL-1 receptor type II expression is linked to disease recurrence, highlighting the importance of receptor-mediated modulation of inflammatory signaling within the tumor microenvironment. The limited prognostic value of circulating IL-1β further underscores the distinction between systemic inflammation and tumor-specific signaling. Collectively, these findings support integrated assessment of IL-1β pathway components as a biologically meaningful approach for prognostic stratification and for guiding precision anti-inflammatory strategies in breast cancer.

Ethics Approval and Consent to Participate

This study received ethical approval from the Institutional Review Board (IRB) of Komar University of Science and Technology (KUST), Sulaymaniyah, Iraq (Approval Number: **KUST-FA25-07-04-DEN**). All procedures involving human participants and biological samples were conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki.

The study included two types of human samples. Archived formalin-fixed paraffin-embedded (FFPE) tissue specimens were obtained retrospectively from pathology archives and were used without direct patient involvement; therefore, the requirement for informed consent for FFPE samples was waived by the IRB.

For peripheral blood samples, all participants were provided with detailed written information regarding the study objectives and procedures, and written informed consent was obtained from each participant prior to blood collection.

Participation was entirely voluntary, and participants were informed of their right to withdraw at any stage without any consequences. All clinical and laboratory data were anonymized and de-identified prior to analysis, and confidentiality was strictly maintained.

Consent for Publication

Not applicable. This study does not include any individual person's data in any form (including images, videos, or case details).

Conflicts of Interest Statement

The author declares no conflict of interest related to this study.

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Author Contributions

The author (Hersh Abdul Ham-Karim) solely conceived, designed, conducted, analyzed, and wrote the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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