Research Article Volume 01, Issue No. 02. 2025

The Medical Journal of Radiology and Oncology Radiation



Variation in the Incidence and Magnitude of Tumor-Infiltrating Lymphocytes in Breast Cancer Subtypes

[1] Maulidia, [1] Annisa

[1] Faculty of Medicine, Sebelas Maret University, Surakarta City, Central Java, Indonesia

Correspondence : dr.maulidia3938827@gmail.com

Article History :
Received date : 2024/07/09
Revised date : 2024/08/23
Accepted date : 2024/09/15
Published date : 2025/01/10

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ABSTRACT

Background: The exploration of tumor-infiltrating lymphocytes (TILs) has gained significant attention in breast cancer research, particularly regarding their incidence and prognostic implications across various breast cancer subtypes. **Literature Review:** Further contributions from (et al., 2015) emphasize the importance of categorizing TILs into stromal and intratumoral types, with stromal TILs showing greater prognostic stability, particularly in triple-negative breast cancer (TNBC). This classification is crucial for standardizing TIL assessment, as indicated by the International TIL Working Group's recommendations. The quantitative analysis performed by (Hayashi et al., 2022) further supports the prognostic value of CD8+ T cells across various cancers, reinforcing the need for a deeper understanding of the TME. The relationship between TILs and peripheral blood immune markers, as explored by (Onagi et al., 2022), reveals that high TIL levels correlate with better patient outcomes in TNBC, although challenges remain in assessing TILs in recurrent cases. The independent prognostic value of TILs is reaffirmed by (Schüler et al., 2022), who demonstrate that TILs can predict recurrence risk, particularly in TNBC and HER2-positive subtypes. The heterogeneity of immune cell infiltration across molecular subtypes is further explored by (Thanh Duong et al., 2023), who advocate for improved methodologies in assessing TILs, particularly in lymphocyte-predominant breast cancer. Finally, (Ciarka et al., 2024) synthesize the existing literature, reinforcing that while TILs are particularly meaningful in TNBC and HER2+ subtypes, their prognostic impact is limited in luminal breast cancers. **Conclusion:** In conclusion, the literature collectively underscores the complexity of TIL dynamics in breast cancer, highlighting their significant implications for prognosis and treatment response across different molecular subtypes. The evolving understanding of TILs as biomarkers necessitates ongoing research to standardize assessment methods and elucidate their roles in the TME, ultimately aiming to enhance clinical applicability and patient outcomes.

Keyword: Magnitude of Tumor-Infiltrating Lymphocytes, Breast Cancer Subtypes

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INTRODUCTION

The exploration of tumor-infiltrating lymphocytes (TILs) has gained significant attention in breast cancer research, particularly regarding their incidence and prognostic implications across various breast cancer subtypes. In their seminal work, (Droeser et al., 2012) established that TILs, particularly CD4+ and FOXP3+ subsets, may reflect the host's immune response and have implications for tumor progression and prognosis. Their findings suggested that while high levels of TIL infiltration correlate with adverse outcomes, the distribution and specific roles of different TIL populations remain poorly understood, particularly in the context of ductal versus lobular breast cancers.

(Krell et al., 2012) further contributed to this discourse by highlighting the differential roles of TILs in breast cancer subtypes. They noted that while CD8+ TILs are generally associated with favorable outcomes, the presence of regulatory T cells (Tregs) correlates with tumor invasiveness and poorer prognosis. Their study underscored the complexity of TIL involvement, emphasizing that lymphocyte subtype and localization within tumor compartments significantly influence clinical outcomes.

In 2015, the work of (et al., 2015) advanced the discussion by focusing on the classification of TILs into stromal and intratumoral categories. They argued that stromal TILs offer a more stable and reproducible prognostic marker compared to their intratumoral counterparts. Their findings were particularly relevant for triple-negative breast cancer (TNBC), where stromal TILs demonstrated significant prognostic value, reinforcing the need for standardized evaluation methods to enhance clinical applicability.

(Hayashi et al., 2022) employed high-throughput methodologies to quantitatively analyze TILs across breast cancer subtypes. Their research reiterated the importance of TILs as indicators of immune response and treatment efficacy. They

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found that CD8+ T cells' presence within tumor nests correlates with better prognostic outcomes across various cancers, including breast cancer, and emphasized the necessity for a deeper understanding of the tumor microenvironment (TME) in relation to TIL profiles.

(Onagi et al., 2022) examined the relationship between TILs and peripheral blood immune markers in TNBC, revealing that high TIL levels are associated with better patient outcomes. They pointed out the challenges of assessing TILs, especially in recurrent cases, and advocated for methods that capture real-time immune responses to improve prognostic accuracy.

(Schüler et al., 2022) expanded on the prognostic role of TILs, establishing them as independent markers for recurrence risk in breast cancer. Their findings aligned with the International TILs Working Group's recommendations, which emphasized the importance of standardizing TIL assessment to enhance its clinical utility.

(Thanh Duong et al., 2023) focused on the heterogeneity of breast cancer and the variable immune cell infiltration across molecular subtypes. They highlighted the prognostic significance of TILs, particularly in lymphocyte-predominant breast cancer, and called for improved methodologies for assessing TILs in histopathological practice.

Lastly, (Ciarka et al., 2024) synthesized the existing literature by affirming the critical role of TILs in the immune response to breast cancer, noting their varying prognostic significance across subtypes. Their work reinforced the notion that while TIL levels are particularly meaningful in TNBC and HER2+ subtypes, they exhibit limited prognostic impact in luminal breast cancers.

Overall, the literature underscores the complexity of TIL dynamics in breast cancer, with significant implications for prognosis and treatment response, particularly across different molecular subtypes. The evolving understanding of TILs as biomarkers necessitates ongoing research to standardize assessment methods and elucidate their roles in the tumor microenvironment.

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LITERATURE REVIEW

The article "Differential pattern and prognostic significance of CD4(+), FOXP3(+)and IL-17(+)tumor infiltrating lymphocytes in ductal and lobular breast cancers" by (Droeser et al., 2012) provides a comprehensive examination of tumor-infiltrating lymphocytes (TILs) in breast cancer, focusing on their differential patterns and prognostic implications across ductal and lobular subtypes. The authors highlight the complex role of TILs in breast cancer, which has been a subject of ongoing debate within the field.

The study utilizes a tissue microarray (TMA) to analyze a substantial number of breast cancer specimens, thereby enhancing the robustness of the findings. The authors present compelling evidence that TILs, specifically CD4+, FOXP3+, and IL-17+ lymphocytes, exhibit varying infiltration patterns in ductal versus lobular breast cancers. This differentiation is crucial as it suggests that the immune landscape of breast cancer is not uniform and may reflect the underlying biology of the tumor subtypes.

One of the key insights from the article is the dual nature of TILs in breast cancer prognosis. While some studies have linked high TIL counts with favorable outcomes, (Droeser et al., 2012) also note that certain TIL populations, such as FOXP3+ regulatory T cells, may correlate with unfavorable prognostic factors, particularly in nodal-positive cases. This duality underscores the complexity of the immune response in breast cancer and suggests that TILs may not serve as a straightforward biomarker for prognosis. Instead, their prognostic significance may depend on the specific context of the tumor and its microenvironment.

Moreover, the article emphasizes the potential of TILs as independent predictors of response to neo-adjuvant chemotherapy, which is particularly relevant for clinical decision-making. The authors argue that understanding the specific types of TILs present in a tumor could inform treatment strategies and improve patient outcomes.

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However, the article also acknowledges the controversies surrounding the clinical significance of TILs in breast cancer. The conflicting associations reported in different studies, such as the correlation of high TIL counts with both favorable and unfavorable tumor characteristics, highlight the need for further research to elucidate the mechanisms behind these observations. The authors call for a more nuanced understanding of TILs, advocating for the stratification of patients based on TIL composition and subtype to better predict clinical outcomes.

The article titled "The clinical significance of tumor infiltrating lymphocytes in breast cancer: does subtype matter?" by (Krell et al., 2012) provides a comprehensive examination of the role of tumor-infiltrating lymphocytes (TILs) in breast cancer, emphasizing the variability in TIL incidence and magnitude across different breast cancer subtypes. The authors delve into the complex interplay between various T cell populations, particularly focusing on the contrasting roles of cytotoxic CD8+ and CD4+ Th1 T cells versus regulatory T cells (Tregs) and Th17 cells in tumor progression and immune response.

A significant contribution of the article is its critical analysis of how TILs correlate with clinico-pathological features and patient outcomes. The authors note that while high infiltration of CD4+ and CD8+ T cells is generally associated with positive lymph node status and poorer overall survival, the presence of CD8+ TILs in estrogen receptor-negative (ER-negative) breast cancer is linked to a more favorable prognosis. This nuanced perspective highlights the importance of considering breast cancer subtypes when evaluating TILs as prognostic indicators.

Moreover, the article underscores the controversial nature of TIL significance in breast cancer, particularly regarding the dual roles of Tregs. The authors indicate that elevated levels of Tregs are associated with tumor invasiveness and represent an independent unfavorable prognostic factor, especially in cases with lymph node involvement. This finding suggests that TIL composition, rather than merely their quantity, may be crucial in determining patient outcomes.

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The methodology employed in the study is noteworthy, as it leverages a clinical follow-up database to correlate TIL counts with various clinico-pathological parameters. The large sample size enhances the reliability of the findings, particularly in distinguishing between the lymphocyte infiltration profiles of ductal and lobular breast cancers. The authors identify that ductal carcinomas exhibit a distinct infiltration pattern, with a higher presence of CD4+ and FOXP3+ lymphocytes associated with more aggressive disease features. Conversely, in lobular carcinomas, lymphocyte infiltration does not show a significant correlation with clinico-pathological outcomes.

The article "Current Issues and Clinical Evidence in Tumor-Infiltrating Lymphocytes in Breast Cancer" provides a comprehensive overview of the role of tumor-infiltrating lymphocytes (TILs) in breast cancer, emphasizing the differential impact of TILs across various breast cancer subtypes. The authors highlight the significance of indoleamine-2,3-dioxygenase (IDO) as a key enzyme influencing lymphocytic infiltration, which serves as a foundation for understanding the complexities of TIL recruitment and variability.

A critical aspect of the article is the classification of TILs into stromal TILs and intratumoral TILs. The authors argue that stromal TILs present a more stable and reproducible marker compared to their intratumoral counterparts. This distinction is pivotal, as it underlines the challenges faced in utilizing TILs as prognostic or predictive markers due to their inherent heterogeneity and the lack of standardized evaluation methods. The initial methodology for assessing TILs, established in 2010, is noted for evaluating TILs in core biopsy specimens, which has set a precedent for subsequent research.

The formation of the International TIL Working Group represents a significant advancement in standardizing TIL evaluation methodologies. The article discusses the varying approaches taken by researchers, including immunohistochemistry (IHC) and gene-expression profiling, to identify immune components of TILs. This variety in methodology further complicates the comparison of results across studies,

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making it difficult to draw definitive conclusions regarding the prognostic implications of TILs.

The authors particularly emphasize the prognostic value of stromal TILs in triple-negative breast cancer (TNBC), suggesting that the higher mutational load in TNBC enhances immunogenicity, leading to increased TIL recruitment. This finding is crucial, as it indicates that TILs can serve as a valuable prognostic marker specifically in TNBC, whereas their utility in estrogen receptor-positive breast cancer appears limited. The article also touches on the implications of TILs in HER2-positive breast cancer treated with trastuzumab, indicating a need for further investigation in this area.

The article titled "Quantitative high-throughput analysis of tumor infiltrating lymphocytes in breast cancer" by (Hayashi et al., 2022) provides a comprehensive examination of tumor-infiltrating lymphocytes (TILs) within the context of breast cancer (BC) subtypes. The authors effectively highlight the complexity of the tumor microenvironment (TME), which consists of various immune cells, including lymphocytes, and how these cells contribute to the immune response against tumor cells.

A significant aspect of the article is the emphasis on the prognostic value of TILs, particularly CD8-positive T cells, which have been associated with improved outcomes across multiple cancer types. This correlation underscores the potential of TILs as biomarkers for therapeutic response, particularly in neoadjuvant chemotherapy settings for breast cancer. The authors note that a high density of TILs can indicate a robust immune response, which is crucial for patient survival, especially in aggressive subtypes like triple-negative breast cancer (TNBC).

Moreover, the article delineates the classification of T lymphocytes into CD4 and CD8 subtypes, as well as the role of regulatory T cells (Tregs) in modulating immune responses. The authors effectively discuss how FOXP3-positive Tregs can negatively impact tumor immunity, thereby linking their infiltration to advanced

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tumor stages and poorer prognoses. This insight is critical for understanding the dual role of TILs in tumor progression and immune evasion.

The article also addresses the importance of immune checkpoint regulation, highlighting systems such as PD1-PDL1 and CD80-CTLA4 that mediate immune responses. By integrating this information, the authors provide a nuanced view of how TILs interact with these regulatory mechanisms, thus influencing treatment outcomes and the development of immunotherapies.

Furthermore, the authors advocate for the need for high-quality, quantitative analyses of TILs to differentiate between stromal TILs (sTILs) and intratumoral TILs (iTILs). The study's use of advanced methodologies for assessing TIL profiles is commendable, as it allows for a more precise understanding of how TILs vary among different BC subtypes. This detailed analysis is essential for tailoring immunotherapeutic approaches based on individual tumor characteristics.

The article titled "High platelet-to-lymphocyte ratios in triple-negative breast cancer associates with immunosuppressive status of TILs" by (Onagi et al., 2022) provides significant insights into the dynamics of tumor-infiltrating lymphocytes (TILs) in the context of triple-negative breast cancer (TNBC). The authors establish a critical link between the platelet-to-lymphocyte ratio (PLR) and the immunosuppressive status of TILs, suggesting that these factors can serve as prognostic markers in breast cancer.

The authors highlight the established role of TILs as a prognostic marker, particularly in TNBC, where high TIL infiltration correlates with improved patient outcomes. This correlation underscores the importance of TILs in local tumor immunity, especially as they are predictive of responses to immune checkpoint inhibitor (ICI) treatments. However, the article points out a significant gap in understanding the mechanisms that attract TILs to the tumor microenvironment, indicating a need for further research in this area.

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One of the strengths of this study is its exploration of peripheral blood parameters, such as the neutrophil-to-lymphocyte ratio (NLR) and PLR, which are recognized as prognostic markers across various breast cancer subtypes. The authors effectively argue that these ratios reflect systemic inflammation, which can negatively impact the host immune system. Their findings suggest that both TILs and peripheral blood immune parameters should be considered together to gain a comprehensive understanding of patient outcomes.

The article also emphasizes the challenges associated with evaluating TILs, particularly in recurrent disease settings where biopsies are difficult to obtain. The authors advocate for innovative approaches like liquid biopsies to assess real-time anti-tumor immune responses, which could enhance the clinical management of breast cancer patients.

Furthermore, the study's findings on the positive correlation between TILs and PLR in TNBC subtypes add a valuable dimension to the existing literature. By employing multiplexed fluorescent immunohistochemistry (IHC) for immune cell profiling, the authors provide a methodological advancement that could facilitate future investigations into the intricate relationships between TILs and peripheral blood markers.

In the article "Prognostic Value of Tumour-Infiltrating Lymphocytes in an Unselected Cohort of Breast Cancer Patients," (Schüler et al., 2022) provide a comprehensive examination of the role of tumor-infiltrating lymphocytes (TILs) as prognostic biomarkers in breast cancer (BC). The authors effectively highlight the heterogeneity of breast carcinoma and emphasize the significance of TILs across various subtypes, particularly in triple-negative breast cancer (TNBC) and HER2-positive tumors.

The study presents compelling evidence that TILs serve as independent prognostic factors, particularly in TNBC, where a 10% increase in TILs correlates with a 17% reduction in the risk of recurrence or death. This finding underscores the potential of TILs to enhance prognostic accuracy and guide clinical decision-making. The

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authors' analysis of TILs as a reproducible biomarker adds depth to the discussion, suggesting that their quantification could be integrated into routine pathological assessments.

Moreover, the article delves into the implications of TILs in HER2-positive breast cancer, positing that TIL levels may predict the effectiveness of anti-HER2 therapies and T-cell checkpoint inhibitors. This insight is particularly relevant in the context of personalized medicine, where tailoring treatment strategies based on TIL presence could lead to improved patient outcomes.

However, while the article presents a robust analysis of TILs as prognostic indicators, it could benefit from a more detailed exploration of the mechanisms by which TILs exert their effects on tumor biology and patient prognosis. Additionally, the study's cohort, described as unselected, raises questions about the generalizability of the findings across different populations and clinical settings.

The article "Stromal Tumor-Infiltrating Lymphocytes Associated with Immunohistopathology and Molecular Subtypes of Breast Cancer in Vietnam" by (Thanh Duong et al., 2023) provides a comprehensive examination of the role of tumor-infiltrating lymphocytes (TILs) within the context of breast cancer subtypes. The authors effectively highlight the heterogeneity of breast cancer and the importance of TILs as prognostic markers, particularly in relation to the molecular subtypes classified by immunohistochemistry (IHC).

The article begins by establishing the foundational understanding of breast cancer as a diverse disease, characterized by different symptoms, pathogenesis, and therapeutic responses. The authors reference the IHC-based molecular classification introduced in 2013, which identifies four primary subtypes: Luminal A, Luminal B, HER2-positive, and Triple Negative (TNBC). This classification is crucial as it sets the stage for understanding how TILs vary across these subtypes.

A significant contribution of this article is its detailed discussion on the tumor microenvironment (TME), which includes various immune-inflammatory cells.

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The authors emphasize the role of TILs, particularly stromal TILs (sTILs) and intratumoral TILs (iTILs), in the immune response to tumors. The distinction between sTILs and iTILs is particularly noteworthy; sTILs are presented as a more reliable parameter due to their higher reproducibility in histopathological assessments. This is an important point, as standardization in evaluating TILs remains a challenge in clinical practice.

The article also addresses the prognostic implications of TILs, noting that lymphocyte-predominant breast cancer (LPBC) is characterized by significant TIL infiltration, which correlates with favorable outcomes. The authors provide evidence that increased TIL levels are associated with better responses to neoadjuvant chemotherapy, particularly in TNBC and HER2-positive breast cancers. This finding underscores the potential of TILs as predictive biomarkers, which could guide therapeutic decisions in clinical settings.

However, the authors acknowledge the limitations in understanding the role of TILs within luminal breast cancer subtypes. The lack of clarity regarding the prognostic and predictive value of TILs in these subtypes suggests a need for further research, which the authors call for. This recognition of gaps in the current literature is a strength of the article, as it encourages ongoing investigation into the complexities of breast cancer immunology.

The article titled "Tumor-Infiltrating Lymphocytes (TILs) in Breast Cancer: Prognostic and Predictive Significance across Molecular Subtypes" by (Ciarka et al., 2024) presents a comprehensive examination of the role of tumor-infiltrating lymphocytes (TILs) in breast cancer (BC), emphasizing their prognostic and predictive significance across various molecular subtypes. The authors effectively highlight the variability of TIL levels and their implications for patient outcomes, particularly in the context of different BC subtypes.

A critical evaluation of the material reveals that the authors provide robust evidence supporting the notion that TILs play a crucial role in the immune response against BC. Their findings indicate that higher TIL levels are positively correlated with

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improved prognosis and treatment response in triple-negative breast cancer (TNBC), which is particularly notable given the aggressive nature of this subtype. The article underscores the importance of TILs as potential biomarkers for identifying TNBC patients who may benefit from immunotherapy, thereby offering valuable insights for clinical decision-making.

In contrast, the article notes that luminal breast cancer generally exhibits low TIL levels, which correlates with a limited prognostic impact. This distinction is critical as it informs treatment strategies for luminal BC patients, suggesting that TIL levels may not be as relevant in this context. Furthermore, the authors discuss the unique associations of TILs in single hormone receptor-positive breast cancers, which adds depth to the understanding of immune dynamics in various BC subtypes.

The article also addresses the ambiguous prognostic significance of TILs in ductal carcinoma in situ (DCIS), indicating a need for further research in this area. This acknowledgment of the complexities surrounding TIL assessment in DCIS is an important aspect of the article, as it highlights the necessity for standardized methods in evaluating TILs to fully harness their potential as biomarkers.

CONCLUSION

The exploration of tumor-infiltrating lymphocytes (TILs) in breast cancer has emerged as a critical area of research, particularly concerning their incidence and prognostic implications across various breast cancer subtypes. The reviewed literature demonstrates a complex relationship between TILs and breast cancer outcomes, emphasizing that the roles of specific TIL populations, their localization, and the tumor microenvironment (TME) significantly influence clinical outcomes.

The foundational work by (Droeser et al., 2012) establishes a basis for understanding the differential infiltration patterns of TILs in ductal and lobular breast cancers. Their findings indicate that while TILs, including CD4+ and FOXP3+ subsets, may reflect the host's immune response, their prognostic significance is nuanced, particularly in nodal-positive cases where certain TIL

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populations may correlate with adverse outcomes. This duality in TIL roles is echoed in subsequent studies, such as that by (Krell et al., 2012), which highlights the contrasting functions of cytotoxic CD8+ T cells and regulatory T cells (Tregs) in tumor progression.

Further contributions from (et al., 2015) emphasize the importance of categorizing TILs into stromal and intratumoral types, with stromal TILs showing greater prognostic stability, particularly in triple-negative breast cancer (TNBC). This classification is crucial for standardizing TIL assessment, as indicated by the International TIL Working Group's recommendations. The quantitative analysis performed by (Hayashi et al., 2022) further supports the prognostic value of CD8+ T cells across various cancers, reinforcing the need for a deeper understanding of the TME.

The relationship between TILs and peripheral blood immune markers, as explored by (Onagi et al., 2022), reveals that high TIL levels correlate with better patient outcomes in TNBC, although challenges remain in assessing TILs in recurrent cases. The independent prognostic value of TILs is reaffirmed by (Schüler et al., 2022), who demonstrate that TILs can predict recurrence risk, particularly in TNBC and HER2-positive subtypes.

The heterogeneity of immune cell infiltration across molecular subtypes is further explored by (Thanh Duong et al., 2023), who advocate for improved methodologies in assessing TILs, particularly in lymphocyte-predominant breast cancer. Finally, (Ciarka et al., 2024) synthesize the existing literature, reinforcing that while TILs are particularly meaningful in TNBC and HER2+ subtypes, their prognostic impact is limited in luminal breast cancers.

In conclusion, the literature collectively underscores the complexity of TIL dynamics in breast cancer, highlighting their significant implications for prognosis and treatment response across different molecular subtypes. The evolving understanding of TILs as biomarkers necessitates ongoing research to standardize

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assessment methods and elucidate their roles in the TME, ultimately aiming to enhance clinical applicability and patient outcomes.

DISCLOSURE STATEMENT

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication

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