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Predictive Factors for Relapse in Localized Triple-Negative Breast Cancer

—A Retrospective Study at Hassan II University Hospital in Fez-Morocco

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Abstract

Introduction: Triple-negative breast cancer (TNBC) has a poor prognosis with a high relapse rate. This study aims to identify predictors of relapse in a Moroccan cohort. **Methods:** A retrospective study including 130 patients treated between 2016 and 2021. Analysis of clinicopathological characteristics and biological markers (Ki-67, TILs, HER2-low status) was performed. **Results:** The overall relapse rate was 21.5%. Factors significantly associated with an increased risk were: lymph node involvement (39% vs 7% for N0, $p < 0.001$), Ki-67 > 80% (50% relapse rate, $p < 0.001$), and absence of pCR (28% vs 0%, $p < 0.001$). High TILs (≥50%) were protective (12.9% relapse vs 26.8% for low TILs, $p = 0.03$). **Discussion:** Our results confirm data from the literature regarding the prognostic role of nodal status, Ki-67, and pCR. The predictive value of TILs, particularly moderate levels (11% - 49%), warrants further exploration. **Conclusion:** This study identifies high-risk subgroups justifying a personalized therapeutic approach, while highlighting the potential of immunological markers as predictive factors.

Keywords

Triple-Negative Breast Cancer, Relapse, Predictive Factors, TILs, PCR

1. Introduction

Triple-negative breast cancer (TNBC) is a distinct molecular subtype, representing 10% to 15% of all breast cancers [1]. Its particular biological profile, characterized by the absence of hormone receptor expression and HER2 overexpression, confers aggressive clinical behavior and a generally less favorable prognosis than

other subtypes [2]. TNBC is distinguished by a high risk of early relapse, with a peak recurrence within the first 3 years after diagnosis, and a preferential metastatic tropism towards viscera and the central nervous system [3].

Despite recent therapeutic advances, notably the advent of immunotherapy and antibody-drug conjugates, conventional chemotherapy remains the cornerstone of treatment in many clinical contexts, particularly in resource-limited countries [4]. Pathological complete response (pCR) after neoadjuvant chemotherapy has emerged as a major prognostic factor, with crucial implications for relapse-free survival [5]. However, not all TNBCs respond equally to treatment, and identifying predictors of relapse remains an essential clinical challenge.

Several clinical, pathological, and biological parameters have been proposed as potential prognostic markers. Tumor-infiltrating lymphocytes (TILs) have emerged as a promising biomarker, reflecting the interaction between the immune system and the tumor [6]. Similarly, the Ki-67 proliferation index, nodal status, and stage at diagnosis continue to provide valuable prognostic information [7]. More recently, the recognition of the HER2-low subgroup has introduced a new dimension in TNBC classification, with potential therapeutic implications [8].

In this context, we present the results of a retrospective study conducted at the medical oncology department of Hassan II University Hospital in Fez, aiming to identify predictive factors for relapse in a cohort of 130 patients with localized TNBC. Our work is part of ongoing research to optimize risk stratification and personalize therapeutic strategies for this complex clinical entity.

2. Materials and Methods

We conducted a single-center retrospective study including 130 patients with localized triple-negative breast cancer treated at the Department of Medical Oncology, CHU Hassan II in Fez between January 2016 and December 2021. Inclusion criteria were: age ≥ 18 years, histologically confirmed diagnosis of localized TNBC, and eligibility for curative treatment with a minimum follow-up of 3 years.

Data were collected from medical records using a standardized collection form and analyzed using Excel software. The studied parameters included: age, menopausal status, TNM stage, lymph node status, Ki-67 proliferation index, tumor-infiltrating lymphocytes (TILs) level, HER2-low status, and pathological complete response (pCR) after neoadjuvant chemotherapy. Statistical analyses used Chi-square test or Fisher's exact test for qualitative variables, with a significance threshold set at $p < 0.05$.

3. Definitions of Key Variables

HER2-low status: Was defined as a HER2 immunohistochemistry (IHC) score of 1+, or 2+ with a negative in-situ hybridization (FISH/SISH) test, in accordance with the ASCO/CAP guidelines and recent clinical trial criteria [8].

TILs: Stromal TILs were evaluated on standard hematoxylin and eosin (H&E)-stained tumor sections from diagnostic biopsies, the percentage of stromal area

occupied by mononuclear inflammatory cells (lymphocytes and plasma cells) was quantified. For the purpose of statistical analysis, TILs levels were categorized as "low" (<50%) or "high" (≥50%). This cut-off is supported by literature linking high stromal TILs to improved outcomes in TNBC.

Ki-67 proliferation index: Based on the distribution within our cohort and literature thresholds indicating very high proliferative activity, we used a cut-off of >80% to define the "high Ki-67" group.

pCR: Was defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes (ypT0/Tis ypN0) following neoadjuvant chemotherapy.

4. Results

Our study included 130 patients with localized triple-negative breast cancer. The median age was 49 years [range: 29 - 88 years], with 47.5% of patients being postmenopausal. The overall 3-year relapse rate was 23%.

The majority of patients (85%) had a good general status (OMS 1). Stage distribution showed a predominance of advanced stages: stage I (17%), stage II (40%), and stage III (43%). Regarding treatment, 84.6% of patients received neoadjuvant chemotherapy, with a pathological complete response (pCR) rate of 25.45%.

Histopathological analysis showed that 38% of tumors had a Ki67 > 80%, 11.5% had HER2-low status, and 32% had a TILs level ≥ 50%.

Univariate analysis identified several factors significantly associated with relapse: lymph node involvement ($p = 0.000271$), advanced stage ($p = 0.003$), Ki67 > 80% ($p < 0.001$), absence of pCR ($p < 0.001$), and low TILs level ($p = 0.012$). In contrast, HER2-low status ($p = 0.45$), age ($p = 0.32$), and menopausal status ($p = 0.28$) were not associated with relapse risk.

Multivariate analysis confirmed as independent poor prognostic factors the absence of pCR (HR = 4.2; 95% CI 2.8 - 6.3), lymph node involvement (HR = 3.1; 95% CI 1.9 - 5.0), and high Ki67 (HR = 2.8; 95% CI 1.7 - 4.5). The 3-year overall survival was 78%, reaching 100% in patients with pCR versus 68% in its absence ($p < 0.001$), and was significantly better in cases of high TILs (89% vs 72%, $p = 0.015$).

Among the patients who experienced a relapse (n = 28), 75% (n = 21) presented with multisite metastases. The most frequent sites of metastasis were the liver (43% of relapsed patients), the brain (27%), and bones (23%).

5. Discussion

Our single-center retrospective study, including 130 patients with localized triple-negative breast cancer (TNBC) treated between 2016 and 2021, provides valuable insight into prognostic factors in a "real-world" clinical practice setting in Morocco. The overall 3-year relapse rate of 23% in our cohort is at the lower end of the range reported in the literature, typically between 25% and 35% for this particularly aggressive histological subtype [3]. This relative underestimation could

be explained by the specific characteristics of our population and the rigorous follow-up ensured in our center.

5.1. Therapeutic Context and Pathological Response: Historical and Current Perspectives

It is essential to place our results in their historical therapeutic context. Our cohort, recruited before the widespread use of neoadjuvant immunotherapy, received standard chemotherapy according to the practices of the time. This context likely explains the pathological complete response (pCR) rate of 25.45% in our study, a figure lower than the rates now regularly observed with protocols combining chemotherapy and immunotherapy as demonstrated in the pivotal KEYNOTE-522 trial [4]. Nevertheless, our work confirms the robust prognostic value of pCR, with its absence constituting an independent factor for relapse. This result is perfectly consistent with the data from the meta-analysis by Cortazar *et al.*, which established pCR as a reliable surrogate endpoint for long-term survival in aggressive breast cancers [5]. It also aligns with the conclusions of a French CNGOF expert consensus which, as early as 2012, already identified response to chemotherapy as a major prognostic determinant in TNBC [9].

5.2. Tumor Microenvironment and Tumor-Infiltrating Lymphocytes: A Decisive Immune Landscape

The evaluation of tumor-infiltrating lymphocytes (TILs) represents an emerging biomarker of the immune microenvironment whose prognostic importance is increasingly recognized. Our study demonstrates that a TILs level ≥ 50% is associated with a halving of the relapse risk. This observation perfectly agrees with recent data from a large cohort study published in JAMA, confirming that significant lymphocytic infiltration constitutes a favorable prognostic factor in early TNBC [10]. These results also support the work of Salgado *et al.*, who standardized the evaluation of TILs and validated their predictive value [6]. The quantification of TILs, simple and reproducible, could thus contribute to a finer risk stratification in routine practice and help identify patients who could benefit from immunotherapy.

5.3. Established Prognostic Factors: Persistence of their Predictive Value

Our analysis confirms the persistent prognostic value of traditional clinicopathological factors. Lymph node involvement and a Ki-67 proliferation index > 80% emerged as major risk factors, in agreement with the literature [11] [12]. The high proportion of advanced stages (43% stage III) in our series reflects the biological aggressiveness and often late diagnosis of TNBC, underscoring the crucial importance of screening and early diagnosis. These observations corroborate the data from Liedtke *et al.*, who had already established the unfavorable prognosis of advanced-stage TNBC [7].

5.4. HER2-Low Status: Between Biological Reclassification and Therapeutic Implications

Regarding the HER2-low status, identified in 11.5% of our patients, our study did not reveal a significant impact on relapse risk. This lack of association, contrasting with some publications suggesting a potentially more favorable evolutionary profile [13], could be explained by the limited size of this subgroup in our cohort. However, the precise characterization of HER2-low status is of growing therapeutic importance with the advent of new-generation anti-HER2 antibody-drug conjugates, such as trastuzumab deruxtecan, whose efficacy has been demonstrated in metastatic HER2-low breast cancer [8]. The reclassification of TNBC according to HER2-low status therefore represents a major challenge for access to these new therapies.

5.5. Specificities of the Moroccan Population and Regional Implications

Our study has the merit of documenting the characteristics of TNBC in Moroccan population, with a mean age of 49 years and a significant proportion of postmenopausal patients (47.5%). These data differ somewhat from Western series and could reflect specific genetic and environmental particularities. The work of Benider *et al.* had already highlighted certain epidemiological specificities of breast cancer in North Africa [14], justifying the need to conduct regional studies to better adapt management strategies.

6. Limits

The limitations of our study include its retrospective design, its single-center nature, and the modest size of some subgroups. The evaluation of TILs in routine practice, without centralized review, also constitutes a limitation. These elements must be considered when interpreting our results.

7. Conclusion

In conclusion, our study conducted in real-world practice confirms the prognostic value of response to chemotherapy, nodal status, proliferation index, and TILs in localized TNBC. It contributes to the characterization of the HER2-low subgroup and documents for the first time in detail the particularities of TNBC in a Moroccan population. The integration of these parameters into a personalized approach should improve risk stratification and optimize the management of these patients in our regional context.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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