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# International Journal of Advanced Research

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## REVIEWER'S REPORT

**Manuscript No.: IJAR-57686**

**Title: Predictive Factors of Pathological Complete Response after Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer: Real-World Experience from the Department of Medical Oncology, Hassan II University Hospital, Fez, Morocco**

**Recommendation:**

Accept as it is .....

Accept after minor revision.....

**Accept after major revision .....YES**

Do not accept (*Reasons below*) .....

| Rating | Excel. | Good | Fair | Poor |
|---|---|---|---|---|
| Originality | | √ | | |
| Techn. Quality | | | √ | |
| Clarity | | √ | | |
| Significance | | √ | | |

**Reviewer's ID: JPR-094**

## Detailed Reviewer's Report

**# Reviewer's Report**

**# Overall Evaluation**

**This manuscript presents a retrospective monocentric observational study evaluating predictive factors of pathological complete response (pCR) in triple-negative breast cancer (TNBC) patients treated with neoadjuvant chemotherapy (NACT) in a Moroccan tertiary center. The topic is clinically relevant, especially for low- and middle-income countries where access to advanced targeted therapies and molecular testing remains limited. The manuscript demonstrates practical real-world experience and identifies several factors associated with pCR, including platinum-based chemotherapy, high Ki-67, elevated TILs, BRCA mutations, histological grade, and timing of surgery.**

**The study contributes regional data from North Africa, where published evidence is relatively scarce. However, several methodological and reporting limitations reduce the scientific robustness of the conclusions. The absence of multivariate analysis, limited BRCA testing, small sample size, and inconsistencies in statistical reporting require substantial revision before publication.**

**# Strengths of the Manuscript**

**### 1. Clinically Relevant Topic**

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**The manuscript addresses TNBC, an aggressive breast cancer subtype with major therapeutic challenges. Identifying predictors of pCR is clinically important because pCR correlates with improved survival outcomes.**

**### 2. Real-World Data from a Resource-Limited Setting**

**The study provides valuable real-world evidence from Morocco, an underrepresented region in oncologic literature. Such contextualized data are important for global oncology practice.**

**### 3. Focus on Biomarker-Driven Management**

**The analysis of Ki-67, TILs, BRCA mutations, histological grade, and platinum use aligns with current trends toward personalized medicine.**

**### 4. Appropriate Definition of pCR**

**The definition of pCR (ypT0/Tis ypN0) follows accepted international standards.**

**### 5. Inclusion of Practical Organizational Factor**

**The assessment of the interval between NACT and surgery is a meaningful and relatively original aspect with potential clinical implications.**

**### 6. Literature Integration**

**The discussion appropriately references landmark trials such as GeparSixto, BrighTNess, and CALGB 40603.**

**# Weaknesses of the Manuscript**

**### 1. Small Sample Size**

**The cohort includes only 76 patients, limiting statistical power and generalizability.**

**### 2. Absence of Multivariate Analysis**

**The lack of multivariate logistic regression is a major limitation. Univariable analysis alone cannot determine independent predictors due to confounding among variables such as Ki-67, grade, TILs, and platinum use.**

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**### 3. Extremely Limited BRCA Testing**

**Only two patients underwent BRCA testing. Drawing conclusions regarding BRCA-associated pCR from such a tiny subgroup is statistically unreliable and potentially misleading.**

**### 4. Retrospective Single-Center Design**

**The retrospective nature introduces selection bias, information bias, and missing-data risks.**

**### 5. Heterogeneity of Chemotherapy Regimens**

**The manuscript states that chemotherapy regimens were not homogeneous, but details regarding regimen composition, dosing, and cycle numbers are insufficiently described.**

**### 6. No Survival Outcomes**

**Disease-free survival (DFS) and overall survival (OS) were not analyzed, reducing the long-term clinical significance of the findings.**

**### 7. Potential Overinterpretation**

**The discussion occasionally overstates conclusions, particularly regarding systematic integration of carboplatin and biomarker-guided therapy, despite limited evidence from this dataset.**

**### 8. Statistical Inconsistencies**

**There are discrepancies between percentages in the Results section and Table 2:**

*** Platinum group pCR rate reported as 65.5% in text but table calculation corresponds to 64.4%.**
*** Non-platinum group reported as 18.2% in text but table shows 19.4%.**
**Such inconsistencies require correction.**

**### 9. Missing Details on TIL Assessment**

**The methodology for TIL scoring lacks sufficient detail:**

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*** Was assessment based on International TILs Working Group recommendations?**
*** Was interobserver agreement evaluated?**
*** Were stromal or intratumoral TILs assessed?**

**### 10. Language and Formatting Issues**

**Several grammatical and formatting problems are present:**

*** Missing spaces ("Metastaticdisease", "ClinicalOncology")**
*** Inconsistent italics for BRCA genes**
*** Repetition of references**
*** Typographical inconsistencies in tables**

**# Key Scientific Points**

**## Major Positive Findings**

*** Platinum-based chemotherapy significantly improved pCR rates.**
*** High Ki-67 expression correlated with better chemotherapy sensitivity.**
*** Elevated TILs showed a strong association with pCR.**
*** Shorter surgery delay after NACT may influence outcomes.**
*** High-grade tumors were more chemosensitive.**

**## Major Concerns**

*** Observed associations may be confounded due to lack of adjusted analysis.**
*** BRCA findings are underpowered and should be interpreted cautiously.**
*** Biomarker standardization is insufficiently described.**
*** External validity is limited.**

**# Significance of the Study**

**The manuscript has moderate clinical and regional significance. Its greatest contribution lies in providing real-world TNBC data from Morocco and emphasizing biomarker-based treatment approaches in low-resource settings. The findings generally align with international evidence and reinforce known predictive factors of pCR.**

**However, the study offers limited novelty at the international level because most identified predictors are already well established in previous literature. The**

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**originality mainly derives from the geographic and healthcare context rather than from new biological or therapeutic discoveries.**

**# Specific Recommendations for Improvement**

**## Major Revisions Required**

**### Methodology**

**1. Clarify chemotherapy regimens in detail:**

*** Platinum type**
*** Number of cycles**
*** Dose intensity**
*** Completion rates**

**2. Expand TIL assessment methodology:**

*** Scoring criteria**
*** Pathologist review process**
*** Standardization method**

**3. Provide more details on BRCA testing:**

*** Testing platform**
*** Selection criteria**
*** Germline vs somatic testing**

**4. Include missing clinicopathological variables if available:**

*** Clinical stage**
*** Tumor size**
*** Nodal status**
*** BMI/comorbidities**

**### Statistical Analysis**

**5. Consider performing multivariate logistic regression, even if limited to 2–3 key variables.**

**6. Address potential confounding and collinearity among predictors.**

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**7. Correct numerical inconsistencies between text and tables.**

**8. Provide exact p-values where possible instead of only "p < 0.001".**

**### Discussion**

**9. Reduce overstatement regarding clinical implementation.**

**10. Discuss why immunotherapy was not included despite current TNBC standards.**

**11. Compare findings with additional African or Middle Eastern cohorts if available.**

**### Presentation**

**12. Improve English language editing and formatting consistency.**

**13. Revise tables for clarity and accuracy.**

**14. Ensure uniform reference formatting.**

**# Recommendation to the Editor**

**## Recommendation: Major Revision**

**### Justification**

**Although the manuscript addresses an important clinical topic and contributes valuable regional real-world data, several substantial methodological limitations weaken the strength of the conclusions. The absence of multivariate analysis, inadequate BRCA subgroup size, limited methodological detail, statistical inconsistencies, and language issues must be addressed before the manuscript can be considered for publication.**

**With careful revision and improved methodological transparency, the manuscript could become a useful contribution to the literature on TNBC management in resource-limited settings.**

**Major Revision Justification with Issues and Reasons (Line-by-Line Review)**

| Line No. | Issue Identified | Reason for Major Revision |
|---|---|---|

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| Line No. | Issue Identified | Reason for Major Revision |
|---|---|---|
| 7–11 | Background section is overly general and lacks novelty statement | The abstract does not clearly explain what new scientific contribution this Moroccan cohort adds beyond existing international TNBC literature. |
| 12–16 | Retrospective monocentric design with only univariate analysis | The study design inherently limits causal inference and introduces selection bias. Lack of multivariate analysis weakens identification of independent predictors. |
| 17 | Small sample size (n=76) | The cohort is underpowered for strong statistical conclusions, particularly for subgroup analyses. |
| 18–22 | Predictive factors reported without adjustment for confounding | Associations may be misleading because variables such as Ki-67, grade, TILs, and platinum use are biologically interrelated. |
| 18–19 | Inconsistent percentages for platinum response | The abstract reports 65.5% vs 18.2%, whereas Table 2 shows 64.4% vs 19.4%. Numerical inconsistency raises concerns regarding data accuracy. |
| 20–21 | BRCA conclusion based on only two patients | Statistical conclusions from two BRCA-positive patients are unreliable and clinically underpowered. |
| 24–27 | Overstated conclusion regarding biomarker-driven personalized strategies | The study lacks sufficient methodological rigor and validation to support broad clinical implementation claims. |
| 33–38 | Introduction lacks regional epidemiological data | The manuscript does not provide Moroccan or North African TNBC epidemiology to justify the local importance of the study. |
| 39–49 | Literature review is incomplete | Important modern TNBC treatment paradigms, including immunotherapy integration, are insufficiently discussed. |
| 50–55 | Aim of study is insufficiently specific | The manuscript does not clearly define primary and secondary endpoints. |
| 57–61 | Single-center retrospective study | This design limits external validity and increases institutional treatment bias. |
| 62–68 | Inclusion criteria insufficiently detailed | No information regarding staging criteria, ECOG status, or baseline disease burden is provided. |
| 70–73 | Exclusion criteria incomplete | Potential confounding factors such as inflammatory breast cancer or prior |

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| | | malignancy are not addressed. |
| 75–87 | Data collection methodology lacks standardization details | No explanation is provided regarding pathology review consistency or missing data management. |
| 79 | Ki-67 assessment methodology incomplete | The manuscript does not specify antibody clone, scoring method, cutoff rationale, or interobserver reproducibility. |
| 80–81 | TIL assessment poorly standardized | The authors do not state whether International TILs Working Group guidelines were followed. |
| 82–83 | BRCA testing performed selectively | This introduces major selection bias because only high-risk patients underwent testing. |
| 84–85 | Chemotherapy regimen insufficiently described | Details regarding carboplatin dosing, cycle numbers, and regimen heterogeneity are missing. |
| 86–87 | Surgery interval categorization not justified | The rationale for selecting the ≤6 weeks threshold is not adequately explained. |
| 92–100 | Statistical analysis inadequate | Univariable analysis alone cannot determine independent predictive factors. |
| 98–99 | No multivariate logistic regression performed | Even limited multivariate modeling could have been attempted with selected variables. |
| 101–104 | Ethical approval statement incomplete | IRB approval number and approval date are not reported. |
| 107–114 | Baseline characteristics insufficient | Important variables such as TNM stage, nodal status, tumor size, BMI, and comorbidities are absent. |
| 109–110 | Inclusion of one male patient not discussed | Male TNBC may differ biologically and clinically; inclusion rationale is not explained. |
| 111 | Ki-67 cutoff (>52%) appears arbitrary | The basis for this threshold is not referenced or justified scientifically. |
| 113–114 | Only two BRCA-positive patients identified | The subgroup is too small for meaningful inferential statistics. |
| Table 1 | Formatting issues and duplication | "Characteristic" is repeated; formatting reduces readability and professionalism. |
| 118–120 | pCR rate interpretation limited | No comparison with institutional historical data or regional cohorts is provided. |
| 121–136 | Univariable analysis only | Potential confounding remains unresolved throughout all reported associations. |

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| 123–124 | Platinum chemotherapy association may reflect selection bias | Patients receiving platinum may have had biologically different disease characteristics. |
| 125–126 | Ki-67 findings may overlap with grade effect | Without adjustment, the independent contribution of Ki-67 cannot be determined. |
| 127–128 | TIL findings lack pathology standardization | Interobserver variability may significantly affect TIL scoring reliability. |
| 129–130 | Histological grade association may not remain significant after adjustment | Authors themselves acknowledge possible overlap with Ki-67. |
| 131–132 | Surgical timing conclusion may be confounded | Delays may reflect patient fitness, healthcare access, or disease complexity rather than direct biological effect. |
| 133–134 | BRCA odds ratio extremely unstable | OR 24.4 with CI 1.1–530 demonstrates severe statistical imprecision due to tiny sample size. |
| Table 2 | Statistical presentation inconsistencies | Some percentages in text and table do not match. |
| 138 | Typographical error in statistical footnote | "*Fisher's exact test" formatting is incorrect and inconsistent. |
| 141–150 | Discussion overstates comparability with Western centers | A small retrospective cohort cannot support equivalence claims with large international studies. |
| 151–165 | Platinum recommendation too strong | The manuscript advocates systematic carboplatin use without randomized evidence from this cohort. |
| 157–162 | HRD biology discussed without direct assessment | The study did not evaluate HRD status, making mechanistic claims speculative. |
| 166–172 | Clinical application of Ki-67 overemphasized | Ki-67 lacks universal standardization and reproducibility across laboratories. |
| 173–182 | TIL conclusions may overstate applicability | TIL assessment variability and lack of central review reduce reproducibility. |
| 183–188 | Authors acknowledge confounding but fail to address it statistically | This weakens confidence in grade-related conclusions. |
| 189–196 | Surgical timing findings require cautious interpretation | Observational associations cannot establish causality. |
| 197–206 | BRCA discussion disproportionately extensive | Extensive interpretation from only two BRCA-positive patients is scientifically weak. |

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|---|---|---|
| 207–209 | Age analysis underdeveloped | No subgroup analysis by menopausal status or age categories was performed. |
| 210–220 | Limitations acknowledged but insufficiently addressed | The manuscript recognizes major weaknesses but does not adequately mitigate them analytically. |
| 211–212 | Incorrect statement regarding inability to perform multivariate analysis | With 29 events, limited multivariate analysis may still have been feasible. |
| 213 | No central pathology review | Introduces interobserver variability and potential measurement bias. |
| 214–215 | Treatment heterogeneity | Different platinum regimens and dosing schedules reduce internal consistency. |
| 217–218 | No survival endpoints included | Lack of DFS or OS data significantly limits clinical impact. |
| 219–220 | "Proof of concept" claim exaggerated | The study remains exploratory and hypothesis-generating rather than practice-changing. |
| 223–269 | Multiple formatting inconsistencies in references | Journal names, spacing, and typography are inconsistent throughout the reference section. |
| References overall | Some references are duplicated conceptually | Denkert et al. appears twice with overlapping citation themes, requiring clarification. |

**Overall Justification for Major Revision**

***Why Major Revision Instead of Minor Revision?***

The manuscript requires **major revision** because the concerns affect:

**Scientific validity**

**Statistical reliability**

**Interpretation of conclusions**

**Methodological transparency**

**Clinical applicability**

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The primary issues include:

Lack of multivariate analysis

Small and underpowered cohort

Extremely limited BRCA subgroup

Potential confounding bias

Incomplete methodological standardization

Statistical inconsistencies

Overinterpretation of findings

Absence of survival outcomes

Treatment heterogeneity

Language and formatting deficiencies

These limitations substantially weaken the robustness of the conclusions and require comprehensive revision before the manuscript can be considered for publication.