# PS4-07-02: DETERMINANTS OF EARLY AND LATE RELAPSE IN PATIENTS WITH EARLY TRIPLE-NEGATIVE BREAST CANCER FROM THE PROSPECTIVE CANTO COHORT

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## BACKGROUND

- Triple-negative breast cancer (**TNBC**) carries a high risk of **early relapse: ≅ 10-20%** of patients recur within 12 months after completion of curative therapy[1].
- Early relapse is associated with **poor prognosis**, significantly worse than late relapse (**mOS 10.1** vs 17.1 months, respectively; aHR: 1.92 [95% CI 1.73–2.13], $p < 0.001$)[2].
- Early-relapsing TNBCs display an **aggressive, chemoresistant and poorly immunosensitive phenotype** (lower immune signatures, basal-like immune-suppressed subtype and enrichment for *TP53* mutations)[3,4].
- Early relapsed TNBC patients are often excluded from most ongoing clinical trials exploring innovative strategies (i.e. ADCs, immunotherapies, targeted agents etc)
- **Clinical and biological determinants** of relapse timing enabling early identification of patients at high risk remain poorly defined.
- Identifying key factors associated with early and late relapse may help inform and tailor therapeutic interventions of early-stage TNBC.

**This study aims to develop a predictive model exploring associations between clinical factors and the timing of relapse in patients with TNBC enrolled in the prospective French CANTO cohort (NCT01993498), which provides detailed clinical, therapeutic and sociodemographic data.**

## METHODS

### DESIGN & POPULATION

- Prospective analysis of early-stage TNBC from the CANTO cohort (2012–2023)
- Clinical, pathological and treatment variables summarized descriptively summary

### PROPORTIONAL HAZARDS ASSESSMENT & MODELING

- PH assumptions were assessed using Schoenfeld residuals and cumulative-hazard plots.
- Several covariates had stronger effects within the first 24 months
  - → **time-varying fixed-effect multivariable Cox model** with 24-month split and covariate–time interactions to estimate associations in the **early (≤24 m)** and **late (>24 m)** periods

### MODEL BUILDING

- **Bidirectional stepAIC** from a priori model: age and grade (with time period interaction), breast surgery type and TNM stage
- Add clinically relevant candidate variables (demographic/pathology/treatment) one at time
- Compare by **AIC** (parsimony favored); report **HR (95% CI)**

## RESULTS

**COHORT FLOW & TIMING (Figure 1).** Among 999 patients with early-stage TNBC, 24% experienced a relapse (N=239) and 76% did not (N=760). Of all relapses, 49% occurred within 24 months (early relapse, N=118) and 51% thereafter (late relapse N=121), indicating a pronounced early-hazard phase. Median follow-up was 74.3 months (IQR 46.8–97.9).

**BASELINE CHARACTERISTICS (Table 1).** The median age at diagnosis was 52.9 years (IQR 45.1–61.9). Stage distribution was predominantly stage II (56 %). Chemotherapy was delivered in 93.5% (adjuvant 51 %, neoadjuvant 42 %). Breast-conserving surgery was performed in 72% and mastectomy in 28 %; around half of the patients (48%) underwent axillary dissection.

**TIME-VARYING MULTIVARIABLE MODELING (Table 2).** The final model retained the **pre-specified predictors** (age, grade, breast surgery type, and TNM stage) and additionally **BMI, smoking status, axillary surgery type, and chemotherapy exposure**, modeled with a time-period split.

**TNM stage** exhibited a strong prognostic role in both early and late periods, with stage III disease consistently associated with higher relapse risk compared to stage I (HR: 2.44; 95% CI: 1.44–4.14; $p < 0.001$).

- **Early relapse:** underweight status (BMI < 18.5 Kg/m2) strongest predictor (HR: 3.35; 95% CI: 1.58–7.11; $p = 0.002$).; axillary dissection (HR: 1.60; 95% CI: 1.00–2.55; $p = 0.05$) and receipt of (neo)adjuvant chemotherapy (HR: 1.51; 95% CI: 0.95–2.40; $p = 0.078$) trend toward a significant increased risk.
- **Late relapse:** older age (per year) associated with increased risk (HR: 1.03; 95% CI: 1.01–1.04; $p = 0.003$); smokers with borderline association (HR: 1.61; 95% CI: 0.98–2.63; $p = 0.06$).

| Variables | Relapse | | Total ( N= 999) |
|---|---|---|---|
| | No (N = 760) | Yes (N = 239) | |
| **Age at diagnosis** | | | |
| **Med [IQR]** | 52.8 [45.0;61.3] | 53.1 [45.3;62.7] | 52.9 [45.1;61.9] |
| **BMI (Kg/m²)– no (%)** | | | |
| **Normal (18.5-24.9)** | 386 (75.4%) | 126 (24.6%) | 512 (51.7%) |
| **Low (< 18.5)** | 14 (50%) | 14 (50%) | 28 (2.8%) |
| **High (≥ 25)** | 355 (78.7%) | 96 (21.3%) | 451 (45.5%) |
| **Smoking status – no (%)** | | | |
| **Smoker** | 146 (71.2%) | 59 (28.8%) | 205 (20.9%) |
| **Ex – smoker** | 151 (74%) | 53 (26%) | 204 (20.8%) |
| **Non – smoker** | 454 (79.4%) | 118 (20.6%) | 572 (58.3%) |
| **Alcohol consumption – no (%)** | | | |
| **Yes** | 88 (70.97%) | 36 (29.03%) | 124 (12.88%) |
| **No** | 647 (77.12%) | 192 (22.88%) | 839 (87.12%) |
| **Grade – no(%)** | | | |
| **G1** | 12 (85.7%) | 2 (14.3%) | 14 (1.4%) |
| **G2** | 133 (74.7%) | 45 (25.3%) | 178 (18.2%) |
| **G3** | 599 (76%) | 189 (24%) | 788 (80.4%) |
| **TNM stage – no (%)** | | | |
| **I** | 284 (85.5%) | 48 (14.5%) | 332 (34.4%) |
| **II** | 403 (74.2%) | 140 (25.8%) | 543 (56.3%) |
| **III** | 44 (48.9%) | 46 (51.1%) | 90 (9.3%) |
| **Breast surgery – no (%)** | | | |
| **Conservative surgery** | 569 (80.4%) | 139 (19.6%) | 708 (71.7%) |
| **Mastectomy** | 184 (65.7%) | 96 (34.3%) | 280 (28.3%) |
| **Axillary surgery – no (%)** | | | |
| **Dissection** | 322 (67.9%) | 152 (32.1%) | 474 (47.7%) |
| **Sentine node biopsy (SLNB)** | 435 (83.6%) | 85 (16.3%) | 520 (52.3%) |
| **Chemotherapy – no (%)** | | | |
| **Yes** | 704 (75.5%) | 228 (24.5%) | 932 (93.5%) |
| **Adjuvant** | 413 (80.8%) | 98 (19.2%) | 511 (51.2%) |
| **Neoadjuvant** | 291 (69.1%) | 130 (30.9%) | 421 (42.2%) |
| **No** | 54 (83.1%) | 11 (16.9%) | 65 (6.5%) |
| **Chemotherapy type – no (%)** | | | |
| **Anthracycline** | 18 (72%) | 7 (28%) | 25 (2.5%) |
| **Anthracycline + Taxanes** | 647 (75.7%) | 208 (24.3%) | 855 (85.8%) |
| **Taxanes** | 39 (76.5%) | 12 (23.5%) | 51 (5.1%) |
| **Radiotherapy – no (%)** | | | |
| **Yes** | 709 (76.5%) | 218 (23.5%) | 927 (93.4%) |
| **No** | 45 (69.2%) | 20 (30.8%) | 65 (6.5%) |

**Table 1. Baseline patient, tumor, and treatment characteristics.**

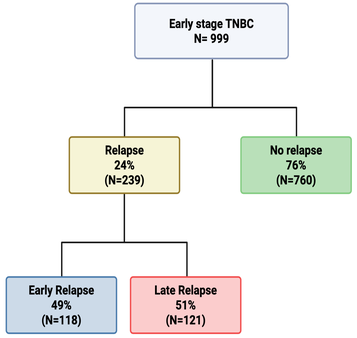



**Figure 1. Cohort study flow chart.**

| Variables | EARLY RELAPSE (≤24 months) N = 118 | | LATE RELAPSE (>24 months) N = 121 | |
|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| **Age (per year)** | 1.00 (0.98–1.01) | 0.7 | 1.03 (1.01–1.04) | 0.003 |
| **Smoking** | | | | |
| *Smoker* | 1.30 (0.81–2.08) | 0.3 | 1.61 (0.98–2.63) | 0.060 |
| *Ex-smoker* | 0.88 (0.51-1.52) | 0.6 | 1.73 (1.12–2.69) | 0.014 |
| ***BMI**** | | | | |
| *Low* | 3.35 (1.58–7.11) | 0.002 | 1.78 (0.63–5.01) | 0.3 |
| *High* | 0.69 (0.44-1.06) | 0.090 | 0.94 (0.64–1.38) | 0.8 |
| **Stage** | | | | |
| *II* | 1.38 (0.93–2.04); $p = 0.11^{\dagger}$ | | | |
| *III* | 2.44 (1.44–4.14); $p < 0.001^{\dagger}$ | | | |
| **Grade** | | | | |
| *G2* | 0.27 (0.03–2.19) | 0.2 | 1.19 (0.16–8.93) | 0.9 |
| *G3* | 0.60 (0.08–4.41) | 0.6 | 0.81 (0.11–5.97) | 0.8 |
| **Breast Surgery** | | | | |
| *Mastectomy* | 1.28 (0.94–1.72); $p = 0.11^{\dagger}$ | | | |
| **Axilla Surgery** | | | | |
| *Dissection* | 1.60 (1.00–2.55) | 0.050 | 1.25 (0.81–1.92) | 0.3 |
| **Chemotherapy** | | | | |
| *(Neo)adjuvant cht* | 1.51 (0.95–2.40) | 0.078 | 1.10 (0.71–1.70) | 0.7 |

Reference categories: Smoking = non-smoker; BMI = normal (18.5-25 Kg/m²); Stage = stage I; Grade = G1; Breast Surgery = conservative surgery; Axilla Surgery = SNLB; Chemotherapy = no chemoterapy

BMI categories: Low <18.5 kg/m²; Normal 18.5–24.9 kg/m²; High ≥25 kg/m².

**Table 2. Relapse risk predictive model by time period** (time-varying Cox, 24-month split). HR (95% CI) for Early ≤24 m and Late >24 m. A-priori set: age and grade (time-stratified), surgery (mastectomy vs BCS) and TNM stage; other covariates tested singly with covariate×time and retained by AIC. Stage and breast surgery are time-independent (same effect in Early and Late phases ) and are shown as a single estimate ($^{\dagger}$).
*Colors*: red significant ; purple borderline/trend

## CONCLUSIONS

- Early and late relapses in early-stage TNBC are driven **by distinct clinical factors**.
- Our findings integrate clinicopathological variables to support the development of models reflecting individual relapse risk and timing.
- **Early relapses (≅ 50% of the events)** were strongly associated with underweight status, and **high disease burden at diagnosis**, as indicated by stage III disease and high treatment intensity, including axillary dissection and chemotherapy.
- **Late relapses** were associated with older age and stage III disease.

**These data suggest distinct profiles for early and late relapse, informing individualized, risk-adapted strategies and highlighting the need for biological investigations into early relapse in TNBC.**

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