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Clinical Outcomes Among Major Breast Cancer Subtypes After Neoadjuvant Chemotherapy: Impact on Breast Cancer Recurrence and Survival

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Abstract. *Background/Aim: Prior studies have underlined the prognostic relevance of pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) in breast cancer. However, an accurate demonstration of treatment efficacy is dependent on its potential to predict long-term outcomes of recurrence and death, and this issue remains somewhat controversial. Patients and Methods: One hundred and sixty-nine patients with breast cancer (BC) treated with NAC followed by surgery were enrolled in this retrospective study. After carrying out multivariable analyses, involving baseline characteristics (tumor stage, nodal status, histological grade, biological profile) and response status, we analysed the association between pCR and disease-free (DFS) and overall survival (OS) in various subtypes. Moreover, we investigated several residual disease-scoring combinations to check whether they could discriminate prognostic subsets according to their variable tumor range after NAC. Results: Overall, factors associated with pCR were non-luminal subtype (p<0.001), high grade (p=0.001) and HER2-overexpression (p=0.001). Residual tumor and nodal stage after NAC significantly correlated with DFS (p=0.007) and OS (p<0.001). Similarly, pCR after NAC showed significantly better DFS (p=0.01), particularly for HER2-positive (p=0.003), triple-negative (p=0.019) and HER2-positive Luminal B profiles (p=0.019). However, there was no statistical difference in the OS among patients who had PCR, compared to absence of pCR (p=0.40). Conclusion: Extent of residual disease and evidence of regression provide helpful prognostic details in BC patients treated with NAC. Achieving pCR after NAC is related with significantly better DFS, with the potential of maximized breast and axillary conservation based on clinical response. The distribution of expertise in a cross-disciplinary setting could provide safe and favourable prognosis, while improving cosmetic outcomes and quality of life.*

Neoadjuvant chemotherapy (NAC) represents an increasingly frontline treatment opportunity for patients with high-risk localized breast cancer (BC). Such treatment aims to render locally advanced disease resectable, improve eligibility for conserving surgery, and increase survival (1). The frequency of pathological complete response (pCR), no residual invasive disease on evaluation of resected breast specimens and lymph nodes after preoperative therapy, has been utilized as the primary criterion to evaluate predictive biomarkers and the efficacy of treatment, including new agents (2). Based on large randomized trials, women who undergo primary systemic approach typically have clinical response rates between 50% and 90% and pCR rates from 4% to 30%, thus enabling the prospective to allow less extensive surgery, lower morbidity, and upgrade cosmetic

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outcome and quality of life (3). Furthermore, favorable locoregional control may be obtained with oncoplastic procedures that facilitate removal of a larger specimen with a significantly lower incidence of involved margins and better functional outcomes in comparison to traditional breast conservation (4-5).

In this context, new investigational drugs should be included into standard management for early-stage BC to provide the optimal clinical benefit for most patients. However, this ambition must be balanced against the limited data available and uncertainty about whether increment in pCR will predict improvements in long-term DFS and OS.

For regulatory purposes, neoadjuvant trials should enroll patients who have the greatest probability of recurrence on the basis of traditional histologic factors or appropriately validated genomic features. The highest incidence of pCR has been usually recorded among triple-negative (TN) phenotypic subsets and those with HER2-positive tumors (HER2+), among whom the chance of survival may be similar to that of more prognostically favorable profiles (6). Patients with ER/PR-positive disease (Luminal A/B HER2–) are less likely to have a pCR to NAC and more feasible to live longer with available therapy. Achieving pCR is, thus, uncertain in predicting durable clinical profit in these subsets (7). Therefore, some unresolved topics remain, including the definition of several response pathways that ideally predict long-term clinical outcomes, the intrinsic pathological BC subtypes most likely to show such complete regression, and the significance of improvements in disease-free (DFS) and overall survival (OS). For example, a trend towards a significant benefit of pCR for hormone receptor-positive (HR+) disease is observed, likely driven by higher grade and/or Luminal B subtypes, where the recurrence risk tends to be in a shorter time frame, while late recurrences are more often seen with Luminal A tumors (8). Thus, including all subtypes, not stratifying patients according to clinicopathological criteria and tailored therapies might consequently mitigate the prognostic value of pCR, with potentially further limitations to extrapolate relevant data of treatment efficacy.

In this study, we aimed to detect clinical and pathological features associated with pCR, while investigating the capacity of primary tumor response as a surrogate parameter for long-term outcomes. We had two key objectives: to define the association between pCR and disease-free and overall survival, and identify the BC subtypes in which pCR is best related with long-term benefit. Moreover, we investigated several residual disease-scoring classifications to assess whether they could differentiate prognostic subsets of patients according to their variable tumor burden after NAC, whose relevance has been subjected to long-standing controversy (9).

Patients and Methods

Study design and conduct. After obtaining approval from the Institutional Review Board, we retrospectively analyzed data from 169 female patients with stage 1-3 invasive BC diagnosed between 2004 and 2020, who had undergone NAC and definitive breast surgery (either mastectomy with or without reconstruction or lumpectomy followed by an appropriate staging procedure). All patients with a minimal follow-up of six months were included.

Critical eligibility criteria were as follows: pathologically confirmed invasive ductal carcinoma (DC) or lobular carcinoma (LC) by core needle biopsy before any treatment; measurable disease either by palpation, ultrasound, mammography and MRI; determined hormone receptor (HR), Ki-67 and HER2 status; at least two cycles of chemotherapy and availability of complete information on clinical and pathological responses. Patients with primary metastatic disorder, other prior malignancies, or previous treatment for invasive BC were excluded. All systemic regimens were anthracycline and taxane-based, with the exception of patients with HER2-positive tumors that received trastuzumab concomitantly with chemotherapy, as well as postoperatively to complete one full year of treatment. All patients with HR positive tumors were subject to receive at least five years of endocrine therapy. Adjuvant radiotherapy was recommended for patients who underwent conserving surgery, as well as for mastectomy cases with initial stage cT3, cT4, cN2 or cN3 disease according to national guidelines.

The following information was described from each selected case: dates of patient enrollment, baseline characteristics, histopathological results at surgery, tumor stage, additional postsurgical treatments, number of patients achieving pCR, duration of follow-up, and number of outcome events by pCR status. Furthermore, the extent of primary breast surgery (conservative or radical) performed after NAC according to standards and individualized concepts was calculated and compared with overall pathological complete response. When available, prognostic details based on the major breast cancer subtypes were extracted.

DFS survival and OS were evaluated from date of registration to the earliest occurrence of progression resulting in locoregional relapse, distant metastases or death, and differentiated by the presence or absence of pCR. Patients alive with or without an event were censored at the last study follow-up date.

Classification of groups and staging. We systematically identified clinical and pathological factors associated with achieving pCR, evaluating various predictors of response according to patient characteristics and tumor profiles on the basis of traditional markers. The intrinsic BC subtypes were identified according to the pathological criteria suggested by the St. Gallen International Expert Consensus Report 2013 (10). Patients were classified based on the receptor status of their primary tumor as follows: luminal A (ER+ or PR+, and HER2–); luminal B HER2– (ER+, HER2– and at least one of Ki-67 "high" or PR "negative or low"); luminal B HER2+ (ER+, HER2-overexpressed or amplified, any Ki-67, any PR); HER2 (ER– or PR–, and HER2+), and triple-negative (ER– or PR–, and HER2–). Tumors were considered HER2-positive only if they were either scored 3+ by IHC (strong, complete membrane-staining in >30% of cancer cells) or showed HER2 amplification (ratio >2) using fluorescence *in situ* hybridization (FISH). In the absence of positive FISH data, tumors scored 2+ using IHC were deemed negative for HER2. Tumors were also categorized as Luminal and Non-Luminal according to HR expression.

Furthermore, a useful surrogate definition was developed to distinguish the pathological characterization of steroid hormone receptor status and the threshold value for "high Ki-67" based on a combination of estrogen receptor (ER= ≥1%), progesterone receptor (PgR=≥1%) and Ki-67 status (≥20%), in order to determine whether some variables could be considered as independently associated with pCR, irrespective of treatment assignment (11-12).

The number, maximum size and nuclear grade of the involved invasive breast cancers and of the axillary lymph node (ALN) metastases were also evaluated after surgical treatment. The primary disease was classified as multifocal at the time of initial diagnostic work-up if the radiologist or histological assessment available after surgery described two or more tumors separated by ≥1cm of normal-parenchyma.

Endpoints. The primary purpose of this analysis was the validation of pCR as surrogate endpoint of the effect on survival of neoadjuvant therapy in BC, evaluating the relationship between treatment efficacy and the best long-term prognostic discrimination. Results were examined in the overall study population and in sub-analyses based on tumor subtype and treatment characteristics, including event data and survival estimates. Accepted definitions of pCR were ypT0 ypN0 (no invasive or noninvasive residual in breast or nodes) and ypT0/is ypN0 (no invasive residual in breast or nodes; noninvasive breast residuals allowed), as suggested by FDA guidelines (13).

We further examined three residual disease-scoring classifications to determine whether they could discriminate prognostic subsets of patients with residual invasive BC: ypT/N staging system according to TNM (14); and histologic breast regression score (RS) as proposed by Sinn, with RS 4 suggesting no viable tumor cell residuals in the breast, RS 3 only non-invasive residuals, RS 2 only focal (<5 mm) invasive residuals, RS 1 minimal signs of tumor regression, and RS 0 no signs of regression, respectively (15). Moreover, the prognostic value of pCR was assessed according to type of treatment, y p-stage within each intrinsic BC subtype, and adjusted for pretreatment clinical and pathologic features. The data were rated in a secure database, de-identified and exported for analyses.

Statistical analysis. Baseline factors were correlated with pCR using two-sided χ^2 or Fisher's exact test. Means, standard deviations (SDs), and 95% confidence intervals were calculated for all the quantitative variables. Disease-free (DFS) and overall survival (OS) were calculated and plotted as Kaplan-Meier curves. Hazard ratios (HRs), 95% CIs, and corresponding p-values of disease progression or death between the pCR and no-pCR arm were calculated using Cox regression analysis. The proportion of patients with a pCR was extracted from each phenotypic subset as the surrogate end-point for the investigation. Prognostic data of the residual disease scores was evaluated in a Cox regression model. This test was also used with pCR as categorized covariate to define the prognostic impact of pCR in various BC molecular subtypes. All statistical and stratified analyses were performed using IBM SPSS 23 software (IBM, SPSS Statistics, Chicago, IL, USA). All p-values were two-sided. A *p*-value of <0.05 was considered significant.

Results

Patient baseline characteristics. The current study included available data from 169 patients with either invasive ductal (n=153) or lobular type (n=16) treated with neoadjuvant chemotherapy and surgery. Median age at time of study entry was 51.2 years (range=27-81 years); 45.6% (n=77) of the patients were peri- or postmenopausal. The primary disease was classified as multifocal in 63 (37.3 %) and multicentric in 27 (16 %) at the time of initial diagnostic work-up. Median tumor size was 3.1 cm (range=1.1-9.3 cm); 125 patients had operable and 44 had locally advanced BC.

Defining pretreatment characteristics, 5.2% (n=8) were scored as Grade 1 (G1), 41.3 % (n=64) as Grade 2 (G2), and 53.5% (n=77) as Grade 3 (G3). The incidence of luminal and non-luminal tumors was 69.2% (n=117) and 30.8% (n=52), respectively. The majority of patients had luminal B HER2-tumors (33.7%, n=57), followed by HER2-positive luminal B (18.9%, n=32), non-luminal HER2-positive (16%, n=27), luminal A (16.6%, n=28), and triple-negative (14.8%, n=25). Tumors were stained positive for ER in 116 (68.6%) and for PR in 96 (56.8%). Overexpression of c-erbB-2 was found in 59 cases (34.9%). One hundred and thirty-one patients (77.5%) had a high Ki-67 expression (≥20%).

Regarding tumor stage after neoadjuvant chemotherapy (ypT), ypT0 was diagnosed in 30 (17.7%) ypTis in 15 (8.9%), ypT1 in 70 (41.4%), ypT2 in 39 (23.1%), ypT3 in 12 (7.1%) and ypT4 in 3 (1.8%). Among all patients, 82 (48.5%) were staged as ypN0 and 87 (51.5%) suffered from ipsilateral axillary lymph node metastases. Nodal stage (yN) was categorized as ypN1 in 40 (23.7%), ypN2 in 34 (20.1%), and ypN3 in 13 (7.7%). The axillary downstaging rate after NAC in patients with cytologically proven lymph node metastases was 30% (17 of 57).

Relative to the extent of surgical treatment, only 51 cases (30.2%) had conservative breast surgery, while an immediate reconstruction with tissue expander or definitive prosthesis was performed in 79% of mastectomy candidates (94 of 118). However, 17.9% (21 of 118) of patients who underwent a radical approach had a pCR in the specimen. Sentinel node biopsy (SNB) was performed in only 17.2% (29 of 169), while among patients who had node-negative disease the axillary dissection rate was 37.8% (53 of 140).

Outcome analysis. The median follow-up period was 50.8 months (range=6-196 months). At the end of the follow-up, 34 (20.1%) patients showed disease progression (10 patients developed locoregional recurrent disease, and 29 had distant metastases).

Locoregional recurrence (LR) was observed in 7.8% (4 of 51) of conservative and 5.1% (6 of 118) of radical surgery respectively, with an overall rate of 5.9%. Fifty percent (5 of 10) of these patients developed distant relapse and subsequent BC related death in 40% of cases (2 of 5).

No different LR rate was recorded in patients with multifocality and multicentricity compared to patients with a single detected lesion (6.3% *vs*. 5.6%; 7.4% *vs*. 5.4%) respectively.

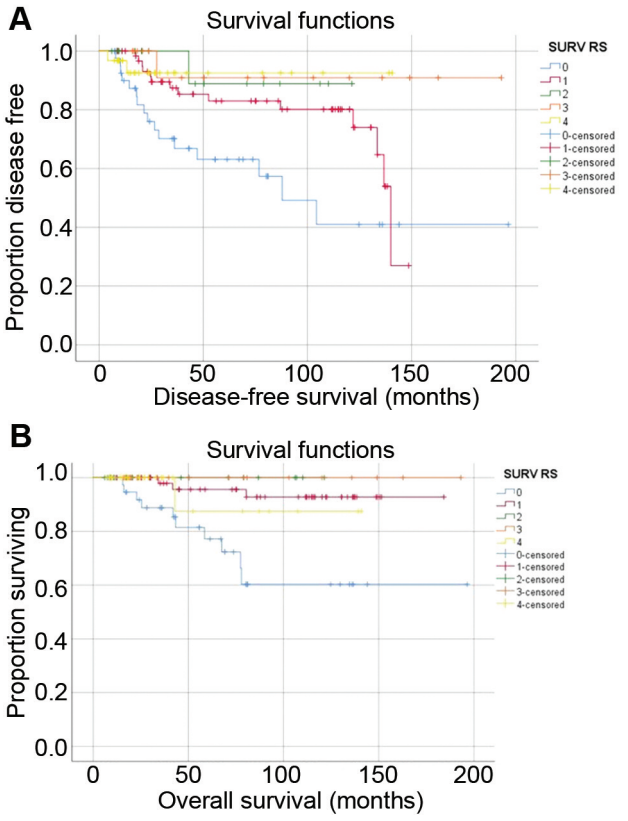

Figure 1. *Disease-free survival (A) and overall survival (B) in 169 patients according to histologic breast regression score (RS).*

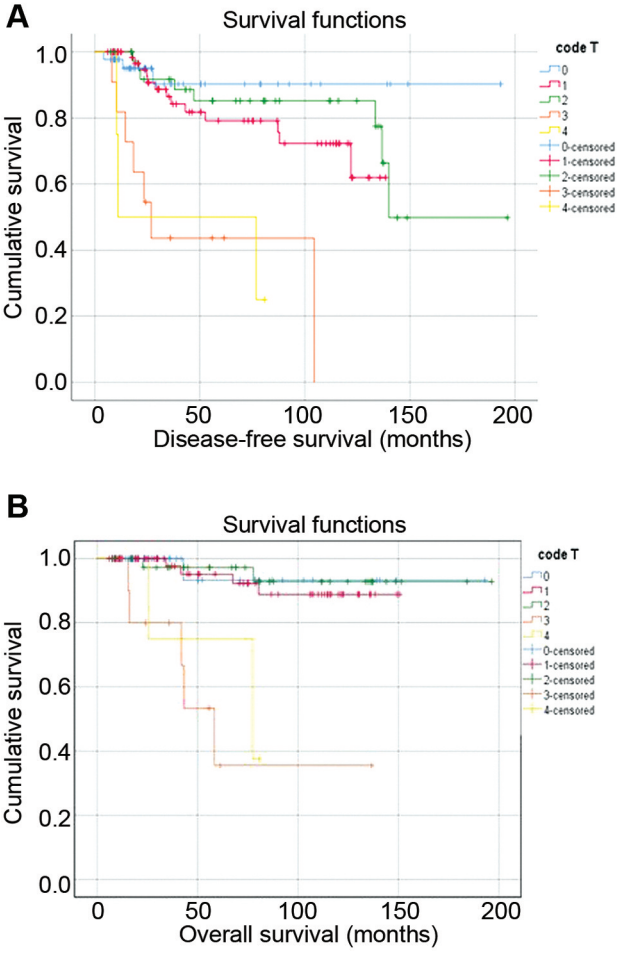

Figure 2. *Disease-free survival (A) and overall survival (B) in 169 patients according to postoperative tumor size (ypT stage). DFS, Disease-free survival; OS, overall survival.*

Between the five intrinsic BC subtypes, non-luminal HER2-positive subtype had the highest total distant recurrence incidence (25.9%, 7 of 27), followed by luminal B (22.8%, 13 of 57), HER2-positive luminal B (15.6%, 5 of 32), luminal A (10.7%, 3 of 28) and triple negative tumors (4%, 1 of 25).

No distant recurrences occurred in the non-luminal, compared to the luminal group (15.4%, 8 of 52 *vs.* 17.9%, 21 of 117; p=019). However, given the greater prevalence of luminal subtype among the study population, the majority of cases who experienced distant relapse had positive expression of HR-related genes (72.4%, 21 of 29), information that is relevant in evaluation of the effects on outcome and cost-effectiveness of current operating strategies.

Specifically, after long-term follow-up, our case dataset included 12 patients with a single site (41.4%) of metastasis and 17 patients (58.6%) with multiple sites. Following to the distant relapse rate among cases (n=29), metastases were more frequent in bone (51.7%, 15 of 29) and liver (51.7%, 15 of 29) than in lung (31%, 9 of 29), brain (27.6, 8 of 29) and distant nodes (24.1%, 7 of 29), respectively. There were 14 (8.3%) deaths reported during the follow-up period for all patients group, five of them (35.8%) in non-luminal HER2-positive, four (28.6%) in luminal B patients, three (21.4%) in HER2-positive luminal B subgroup, one in TN (7.1%) and one (7.1%) among luminal A patients.

Correlation between PCR rate and clinicopathological factors. The overall pCR rate was 23.7% (40 of 169) and significantly different between molecular subtypes (p=0.001), with the highest frequency seen in non-luminal HER2-positive tumors (44.4%, 12 of 27), followed by triple-negative (44%, 11 of 25) and HER2-positive luminal B profiles (40.6%, 13 of 32). Only 7% of luminal B patients (4 of 57) had a pathological complete response in breast and axillary samples, whereas none of luminal A patients had a pCR.

On the basis of subtypes, more complete tumor response occurred in the non-luminal than in the luminal population

Table I. *Prognostic impact of residual disease scoring systems on disease-free survival (DFS) and overall survival (OS) (RS, ypT, ypN).*

Score	All patients		No. of patients with event	DFS			No. of patients who died	OS		
	No.	%		HR	95%CI	*p*-Value		HR	95%CI	*p*-Value
ypT staging system	169									
ypT0-Tis	45	26.6	3	0.06	0.01 to 0.33	0.001	1	0.07	0.007 to 0.80	0.033
ypT1	70	41.4	13	0.17	0.04 to 0.60	0.006	4	0.12	0.2 to 0.67	0.016
ypT2	39	23.1	8	0.11	0.02 to 0.44	0.002	2	0.08	0.01 to 0.58	0.012
ypT3	12	7.1	7	0.88	0.22 to 3.47	0.864	5	1.51	0.28 to 7.96	0.623
ypT4	4	1.8	3	1		0.000	2	1		0.000
ypN staging system	169									
ypN0	82	48.5	4	0.05	0.01 to 0.20	0.000	2	0.07	0.01 to 0.42	0.003
ypN1	40	23.7	7	0.15	0.05 to 0.46	0.001	2	0.11	0.02 to 0.62	0.012
ypN2	34	20.1	16	0.55	0.22 to 1.36	0.198	6	0.38	0.10 to 1.36	0.145
ypN3	13	7.7	7	1		0.000	4	1		0.009
Histologic breast RS	169									
RS 4 (no viable tumor residuals)	31	18.3	2	1		0.019	1	1		0.053
RS 3 (only noninvasive residuals)	16	9.5	1	0.05	0.04 to 5.55	0.572	0	0.00	0.000	0.980
RS 2 (only focal invasive residuals)	16	9.5	1	0.83	0.07 to9.21	0.880	0	0.00	0.000	0.982
RS 1 (minimal signs of regression)	64	37.9	14	1.93	0.43 to 8.53	0.386	3	0.65	0.06 to 6.31	0.712
RS 0 (no signs of regression)	42	24.8	16	4.48	1.02 to 19.52	0.046	0	4.42	0.56 to 34.72	0.157

ypT, Postoperative tumor size; ypN, postoperative nodal stage; RS, regression score; HR, hazard ratio; CI, confidence interval.

(44.2%, 23 of 52 *vs*. 14.5%, 17 of 117; $p<0.001$). Thus, the relationship of disease regression to hormone receptor status showed that there was a higher frequency of pCR in HR– than in HR+ patients. As expected, frequency of PCR in low (G1-2) grade categories was low (12.5%, 9 of 72) and more than doubled in the high (G3) grade (34.9%, 29 of 83; $p=0.001$). The probability of pCR appeared to be not significantly stronger in patients with a Ki-67 index >20% than in those categorized as ≤20 (25.9% *vs*. 15.8% $p=0.278$).

However, considering the mean quantitative expression of ki-67, it was significantly higher in patients who experienced pCR as compared to those without pCR (46.3±23.4 *vs*. 33.3±20.6; $p=0.001$). With regard to c-erb-2 status the association with pCR was more marked in HER2 positive patients than in the negative subgroup (42.4% *vs*. 13.6% $p=0.001$).

Moreover, both a primary breast tumor and axillary complete downstaging were more frequent in HER2-enriched (HER2-positive luminal B, non-luminal HER2-positive) and TN compared to Luminal A/B phenotypes respectively (87% *vs*. 13%; 82% *vs*. 18%; $p<0.001$). According to clinical and pathologic threshold values applied in this study, there was no significant difference in the pCR rate between the multifocal or not (18.8% *vs*. 25.5%; $p>0.05$), or multicentric or not disease group (22.2 *vs*. 23.9; $p>0.05$). Although a higher number of pCR rate was observed in younger (<50 years) than peri- or postmenopausal patients (26.1% *vs*. 20.7%), we did not detect a directly proportional interaction between a higher response and age in this study ($p>0.05$).

Correlation between residual score and outcome. Overall, histologic breast RS was significantly related with DFS ($p=0.007$) and OS ($p<0.001$). Hazard ratios for DFS were lowest when specified as non-invasive or *in situ* residuals (HR=0.5), and increased uniformly when only focal invasive residuals (HR=0.8) or minimal (HR=1.9) or no signs of regression (HR=4.5; 95%CI=1.02-19.5; $p<0.007$) were included in the analysis. Furthermore, patients with no signs of regression experienced a significantly worst overall survival compared with no viable tumor residuals, with a four times higher risk of death (HR=4.427; 95% CI=0.56-34.72; $p<0.001$), as outlined in Figure 1.

Tumor stage after NAC (ypT) was significantly associated with prognosis ($p<0.001$), especially for patients with ypT0/is who had a significantly better DFS and OS as compared to residual invasive cancer stages (ypT3, ypT4), (DFS: HR=0.06; 95% CI=0.01-0.33; $p<0.001$; OS: HR=0.07; 95% CI=0.07-0.8; $p<0.001$). Comparable results were observed for nodal stage ypN0/ypN1 relative to patients with ypN2-3 (DFS: HR=0.05; 95% CI=0.01-0.2; $p<0.001$; OS: HR=0.07; 95% CI=0.01-0.42; $p<0.001$) (Table I; Figures 2 and 3).

Prognostic information of PCR in various subpopulations. Overall, patients who had no pCR, compared to presence of pCR, had significantly bad DFS (HR=7.96; 95% CI=1.08-58.46; $p=0.01$), as outlined in Figure 4. However, there was no significant difference in the OS between patients who had

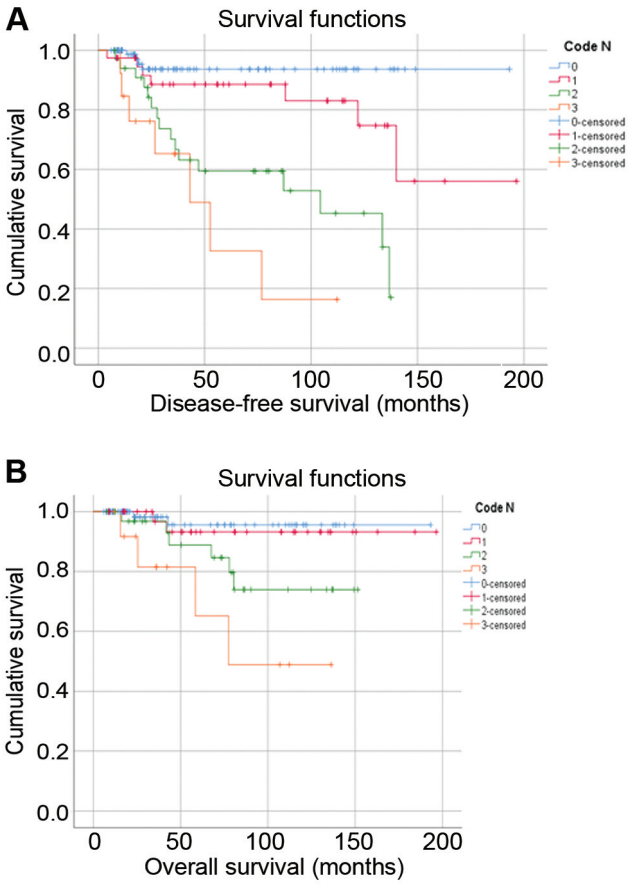

Figure 3. *Disease-free survival (A) and overall survival (B) in 169 patients according to postoperative nodal (ypN) stage. DFS, Disease-free survival; OS, overall survival.*

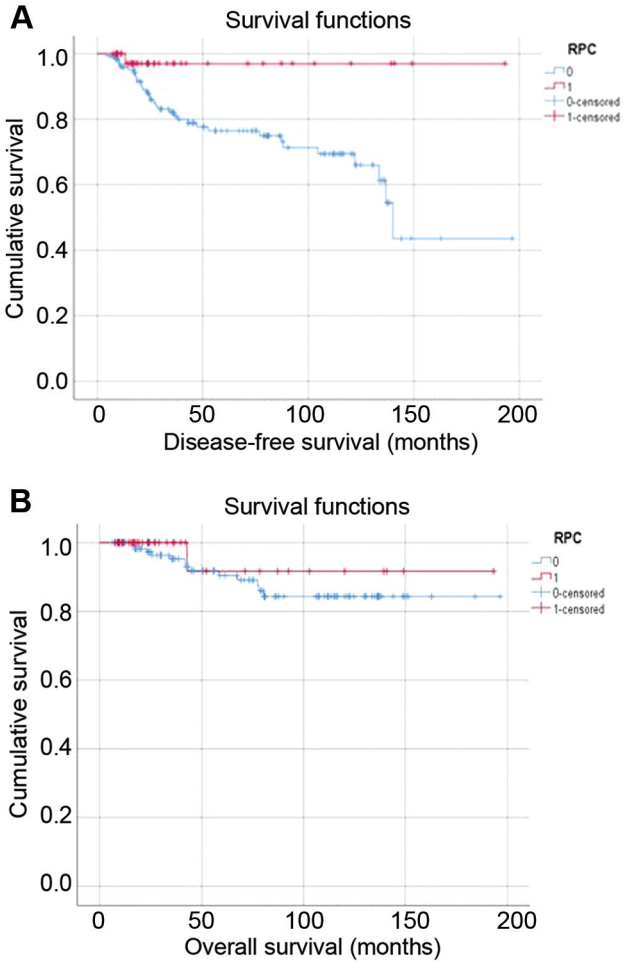

Figure 4. *Association of pathological complete response (PCR) with disease-free survival (A) and overall survival (B).*

pCR, as compared to absence of pCR (p=0.40). In addition, we designed model-based survival curves to evaluate the temporal relationship between pCR and DFS, overall and by BC subtypes. As demonstrated in Figure 4, patients who had a pCR achieved a 5-year DFS of 97%, while those without pCR had a 5-year DFS of 76% (p=0.015). Non- comparable results were observed for OS, since patients who experienced pCR achieved a 5-year overall survival of 91.7%, while those without a pCR achieved a 5-year OS of 90.5% (p=0.40).

We evaluated the association between pCR and clinical outcomes by five major clinical subtypes of BC. The association of residual disease with lower DFS was statistically significant in all patients with non-luminal HER2-positive BC (HR=10.77; 95% CI=1.42-81.42; p=0.003), TN (HR=7.53; 95% CI=1.02-55.35; p=0.019), Luminal B (HR=7.18; 95% CI=0.96-53.63; p=0.025), and HER2-positive Luminal B (HR=7.73; 95% CI=1.04-57.35; p=0.019). Since none of luminal A patients had a pCR, this analysis was not performed.

Among patients with non-luminal HER2-positive BC, patients with pCR had a 5-year DFS of 100%, while those without pCR had a 5-year DFS of 32.1% (p=0.003). For TN subgroup, patients with pCR had a 5-year DFS of 100%, while those without pCR had a 5-year DFS of 84.6% (p=0.019). Among Luminal B and HER2-positive Luminal B, those with pCR had a 5-year DFS of 100% and 92.3%, while those without a pCR had a 5-year DFS of 74.8% and 65.1% respectively (p=0.025 and p=0.019), as outlined in Figure 5.

No significant relationship between pCR and improved survival was noted in patients with non-luminal HER2-positive BC (p=0.115), triple-negative (p=0.394), luminal B (p=0.321) and HER2-positive luminal B (p=0.318). Since none of luminal A patients had a PCR, this analysis was not performed.

Among non-luminal HER2-positive patients with PCR the 5-year OS was 100%, while those without PCR had a 5-year OS of 63.5% (p=0.115). For TN patients, those who

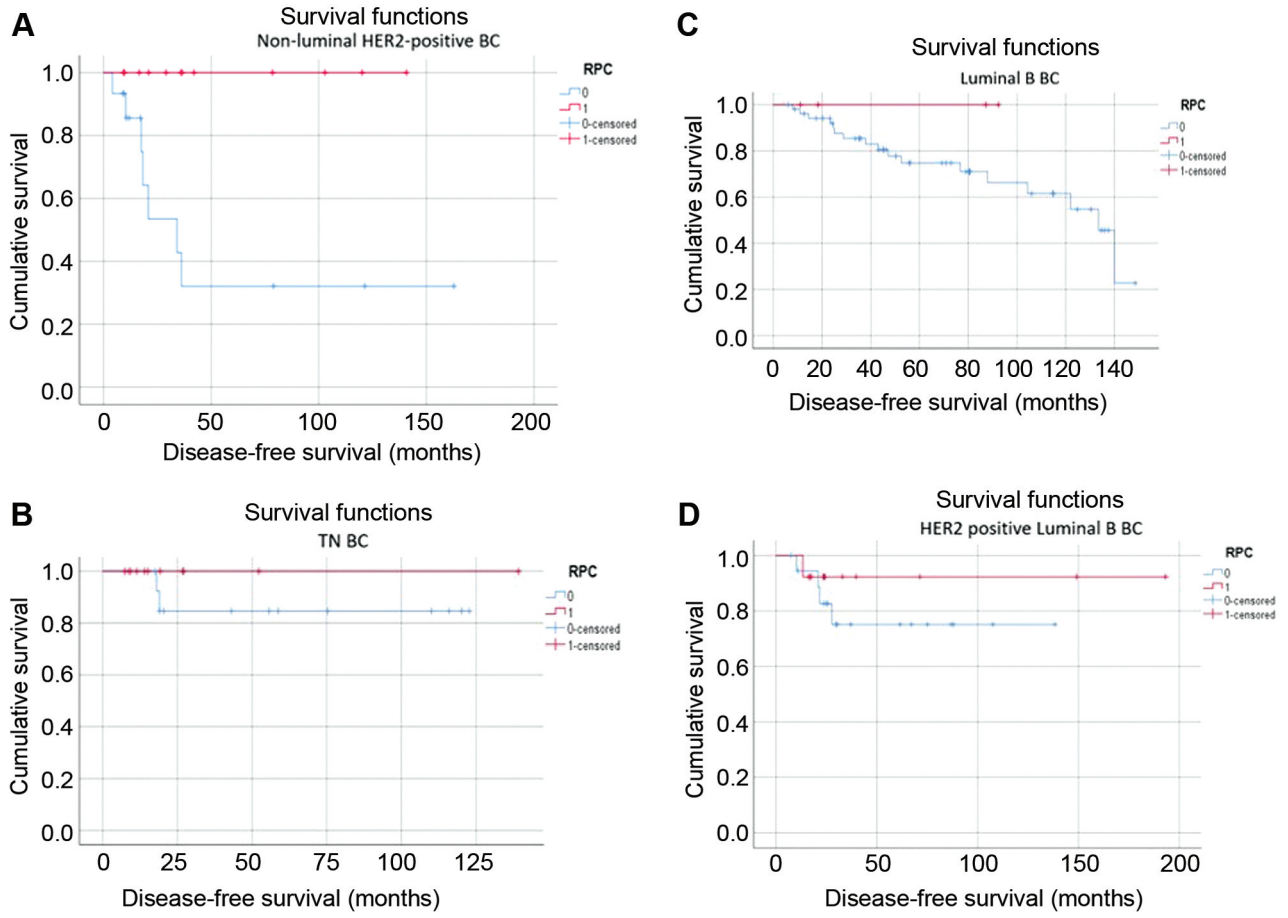

Figure 5. *Relationship between pathological complete response (PCR) and disease-free survival (DFS) among the major breast cancer (BC) subtypes. (A) Non-luminal HER2-positive BC, (B) TN BC, (C) Luminal B BC, (D) HER2-positive luminal B BC.*

experienced PCR achieved a 5-year OS of 100%, while those without PCR achieved a 5-year OS of 90% (p=0.394). Among luminal B and HER2-positive luminal B patients, those with PCR had a 5-year OS of 100% and 85.6%, while those without a PCR had a 5-year DFS of 95.2% and 75% respectively (p=0.321 and p=0.318) (Figure 6).

Discussion

This study strengthens existing data that ER-PR positive and slowly proliferating tumors are significantly related with unfavorable effect to neoadjuvant chemotherapy (16). Modelled estimates indicated that BC subtype was connected with pCR rate (p<0.001), being significantly superior for the HER2 positive/HR– and triple negative disease in direct comparison with the HR+/HER2– profile. These results have great clinical, biologic and research impact, especially in electing appropriate candidates for this approach *versus* traditional adjuvant chemotherapy.

From a biological perspective, the relatively low pCR rates in the HR+/HER2– group firmly supports the existing indication that the majority of these tumors are generally resistant to chemotherapy, and that our efforts should concern on alternative treatment modalities (17). In addition, recent studies have attested that outcomes are generally good for this subset of patients, whether they obtain pCR or not, meaning that attainment of pCR may not be prognostic for survival for this particular BC profile (18).

Our results indicating reasonably high pCR rates for HER2-positive disease, further suggest that the position that NAC is an attractive option for patients with this subtype, with evidence of a determinant effect through inclusion of target therapies (trastuzumab) to anthracycline-taxane-based NAC (19-20). In addition, a high pCR rate after NAC is also a significant property of TN BC, and pCR has been decisively confirmed to be a typical marker anticipatory of clinical response and survival in this category (7, 21). Furthermore, several studies have demonstrated that the

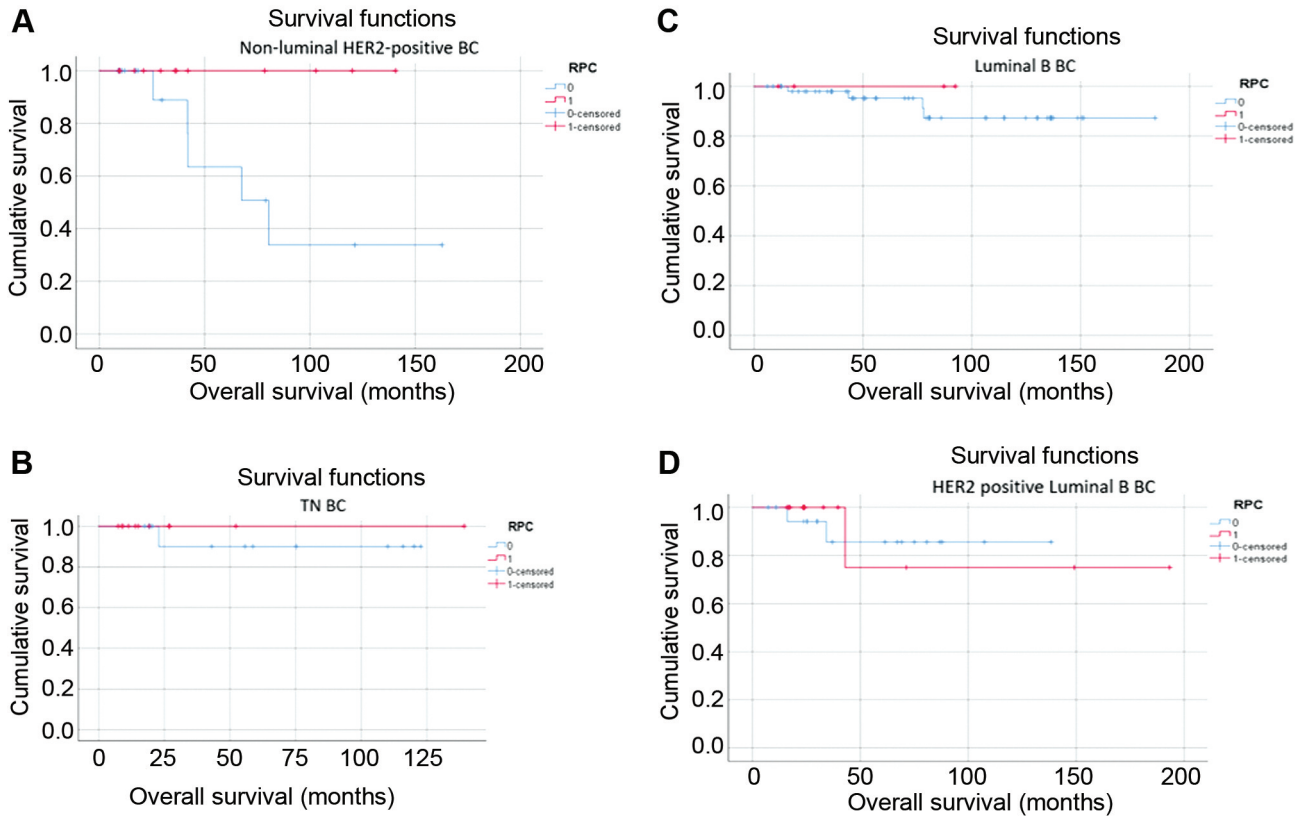

Figure 6. *Relationship between pathological complete response (PCR) and overall survival (OS) among the major breast cancer (BC) subtypes. (A) Non-luminal HER2-positive BC, (B) TN BC, (C) Luminal B BC, (D) HER2-positive luminal B BC.*

addition of platinum agents to anthracycline and/or taxane regimens in the NAC setting – more than six cycles, four kinds of drugs, 16 weeks of treatment duration and sequential chemotherapy – has promise for successful outcomes in this special disease phenotype, increasing the pCR rate (22-25).

In this context, high tumor grade remained significantly linked with increased response to NAC, in line with the finding that the majority of ER/PR-negative cases were assigned to the high-risk subgroup (G3=88.5%, 46 of 52), whereas among ER/PR-positive a substantial proportion had low scores (G1/2=68.4%, 80 of 117). Moreover, when gene expression data of histological grade was prospectively collected before primary systemic treatment, a high index score was associated with pCR or minimal residual disease, adding predictive details over and above other clinical parameters involved in the proliferation pathway (26). However, the observation that the genomic grade covariate continues to be a predictor for poor prognosis among ER-positive cases, highlights the difficulty of understanding survival curves when a molecular marker interacts with several biological and clinical disease features (27). In this regard, determination of the Ki-67 index is equally strongly recommended at the time of planning targeted therapies, given that its positivity is connected with an increased probability of relapse and worse overall survival, as well to chemotherapy sensitivity especially in the higher index group (>40%) (28). The following study interestingly shows that in some cases using a continuum of Ki-67 measures may be more effective than categorizing these values as ≤20% and >20%, in order to better predict the efficacy of treatment regimens and pCR achievement and not to verify a stronger concordance with molecular studies in distinguishing luminal A from B subtype (10).

Furthermore, our results indicated that neoadjuvant setting for operable BC may definitely facilitate breast conserving surgery (BCS), even if this benefit has not been fully realized. According to a systematic review of the literature, only 31 percent of patients who became suitable for BCS (assessed on clinical response) underwent less extensive surgical treatment (29). The main factors that affected the decision not to shift to BCS, even though it was feasible, were clinical assessment before NAC, multicentricity and tumor size at presentation, resulting in potentially

unnecessary radical surgery, especially mastectomy. In this context, we firmly think that optimization of the surgical benefits of NAC needs to be better understood and explored, considering the effectiveness of safety and aesthetic outcomes of therapeutic mammoplasty, characterized by adequate control and equivalent overall survival, relative to the traditional mastectomy (30). Thus, once the appropriate volume displacement or replacement procedure has been selected as the technique for BCS, wide margins of excision can certainly be achieved at no extra cost to the aesthetic outcome, tailoring this surgery to the degree of response to chemotherapy and lessening late radiotherapy effects in large breasted women especially due to dose inhomogeneity (31).

Similarly, even though multifocal and multicentric tumors have commonly been considered a contraindication to BCS because of documented high local recurrence proportion, more recent evidence in line with our results does not support this view, as long as the same pCR rate had been achieved with no further differences in the occurrence of regional relapses (32-33). However, LR after NAC was a strong predictor of overall survival according to several studies that suggested a poorer prognosis for these patients, as well as having a clearly distinct ability to metastasize to distant organs according to various molecular subtypes (34-36).

From these data sets it is clear that the surgeon should have an active role in decision-making, resulting in less extensive surgical operations even in the absence of axillary lymphadenopathy or in cases of clinical conversion from cytologically-proven positive status. In fact, the use of NAC to downstage the nodal disease and subsequently permit targeted axillary dissection is currently being evaluated through several studies resulting in a variable range of axillary pCR according to BC molecular subgroups (37-38). Regarding the feasibility of SNB after primary systemic treatment, further refinement with the use of dual mapping with isotope and dye, removal of at least three nodes, as well as marking of the metastatic node with a clip before NAC, with subsequent resection of the clipped node, resulted in a successful identification rate of 94% and a false-negative as low as 7%, allowing comparable locoregional control, but with less morbidity and superior functional results (39-40). In this context, the ongoing evolution of metabolic imaging clearly represents a promising development, given that improved predictive models based on axillary and locoregional PET/TC findings might be useful to ensure local disease control with the appropriate therapeutic strategy, as well as to characterize the different pathological stages of BC (41). Therefore, a proved conversion to node-negative disease could not only be independently related with improved DFS and OS as an early surrogate for these outcomes, but it could also represent the theoretical basis to switch from planned axillary clearance to axillary conservation, potentially improving quality of life (42).

Consequently, the amount of residual and the indication of potential regression could provide helpful additional prognostic details in BC patients treated with NAC. Several other authors have described improved long-term outcomes in patients with pCR compared to those with residual tumor at the time of surgery (43-44). Our analysis confirmed this finding in various tumor subtypes and subgroups according to other baseline features (Table I).

In preoperative patients, correlation between primary response and subsequent outcome is clinically relevant mainly because it might enable one to discriminate patients who, after surgery, had an excellent from those whose prognosis was poor and who, therefore, might be candidates for additional therapy. In patients treated with NAC, the resulting pathologic lymph node status was also, not surprisingly, related to tumor response, as well as to prognostic outcome since it is frequently associated with subsequent development of distant relapse and death (45). Consequently, even if we could not analyse other pCR scores (*e.g.*, residual cancer burden, grading by Miller -Payne), we recommend that a further thorough testing of all these multivariate models is necessary to determine whether more extensive pathologic assessments are needed in order to improve the long-term prognosis prediction (46-47).

Our study continues to demonstrate a statistically significant relation between pathological tumor response to preoperative chemotherapy and the outcome measures, thus suggesting that the underlying biologic features required for this clinical benefit may also provide true chemosensitivity to locoregional and distant micrometastatic disease.

The results of this comprehensive meta-analysis overall suggest that pCR is a strong surrogate endpoint of disease-free survival, particularly for non-luminal BC, as already stressed by others (6-48). In this regard, the NAC setting has, therefore, become recognized as an efficient model of drug development, since it utilizes an adaptive strategy for matching target therapies with the patients most likely to benefit from them (49).

Our results support this approach, and continued exploration of novel neoadjuvant clinical trial design is needed to advance this field. For HER2+ breast cancer, neoadjuvant settings are now exploring regimens featuring HER2-directed agents only based on pCR as primary endpoint and where the ultimate intent of treatment is to prevent disease recurrence (50). The evidence also showed that dual-agent HER2 blockade increases the number of patients achieving a pCR compared to single-agent HER2-directed treatment, without notably affecting safety (20).

In triple-negative BC, the addition of a platinum agent to anthracyline/taxane-based treatment has been shown to increase pCR rates, but at the expense of greater toxicity (51). Thus, even demonstrating an absolute increase in pCR rates, the impact of this dose-dense and sequential administration of

cytotoxic drugs on long-term survival remains to be seen, due to the greater frequency of skipped doses and early treatment modifications (52). Important objectives in this non-uniform entity with several dysfunctional pathways of sensitivity consist of defining clinically relevant patient subgroups and determining whether other agents should be added to existing regimens with proof that this translates into long term benefits.

In this context, with the small sample size, we could not confirm that the subsets with pCR had a substantially superior prognosis, comparable to that with tumor residuals in breast and nodes. As has been reported through five years of follow-up, there continues to be no statistically significant difference in the rates of overall survival, although there was a trend towards a higher proportion of superior outcome with complete pathological response, especially in HER2 and TN BC subtypes. Other studies were surprisingly unsuccessful to show a relation between different pCR definitions and outcome, probably because of limited sample sizes (53, 54). With small numbers of patients and few events in each group, this study was not able to detect anything over and above a large difference in overall survival between the residual invasive carcinoma and pCR group, and is it not possible therefore to make definitive conclusions. Thus, further analysis of large prospective randomised trials and other databases are required to confirm these findings.

Moreover, our study has several and supplementary potential limitations. First, in addition to the heterogeneity of the patient population and the response to therapy that has already been discussed, the imprecise categorization of BC subtypes due to the lack of gene profiles should also be considered as potential confounder. Second, there was a difference in the types of neoadjuvant therapies employed and the study results are broadly based on primary systemic approach in general rather than a specific therapeutic regimen. Third, important elements regarding family background, genetic testing results, adjuvant treatment and mammographic findings were not available from this database; however, additional investigations of the feasibility of these profiling data will be helpful in rating the benefit of these classifications. Finally, the median follow-up time overall for the study was only four years, which is short for the natural history of certain subtypes of BC (HR+), where pCR is less common and is not so strongly related with prognosis. Despite these potential limitations, we were able to acquire relevant details from this retrospective analysis, and the power of the data appears to be high. Further studies will be required to confirm the findings based on this analysis.

Conclusion

The findings reported herein confirm that the association between the magnitude of treatment-induced pCR change is clearly different with regard to primary tumor characteristics and molecular subtypes. On the other hand, further validation of these clinically distinct biological profiles may be helpful in defining a risk-adapted breast conserving surgery with the capacity to promote less extensive locoregional procedures, reducing morbidity, and enhancing cosmetic outcome and quality of life. In this context, the neoadjuvant therapy model strongly provides a potential efficient trial perspective to explore the efficacy of novel therapies utilizing pCR as a surrogate indication for disease-free and overall survival, but also evaluation of residual disease could provide relevant meaningful information and long prognostic data. As more is interpreted regarding tumor behavior, it is hoped that the recognition of subtype-specific divergences in short- and long-term prognosis will inevitably guide to characterization of their prognostic effect over time, improving outcomes for high-risk patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

P.O. and A.G. performed the study. M.S, G.S., L.C., T.T. and B.C. contributed to the collection of samples, analysis, and data management. E.I. and F.P. contributed to the interpretation of data with generation of graphics and review of the article. P.O, A.G. and E.I. wrote and revised the manuscript. V.A provided supervised the retrospective evaluation of data. All Authors read and approved the manuscript.

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