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Original Article

Modeling the Prognostic Impact of Circulating Tumor Cells Enumeration in Metastatic Breast Cancer for Clinical Trial Design Simulation

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Abstract

Despite the strong prognostic stratification of circulating tumor cells (CTCs) enumeration in metastatic breast cancer (MBC), current clinical trials usually do not include a baseline CTCs in their design. This study aimed to generate a classifier for CTCs prognostic simulation in existing datasets for hypothesis generation in patients with MBC. A K-nearest neighbor machine learning algorithm was trained on a pooled dataset comprising 2436 individual MBC patients from the European Pooled Analysis Consortium and the MD Anderson Cancer Center to identify patients likely to have CTCs ≥ 5/7 mL blood (StageIV^{aggressive} vs StageIV^{indolent}). The model had a 65.1% accuracy and its prognostic impact resulted in a hazard ratio (HR) of 1.89 (Simulated^{aggressive} vs Simulated^{indolent} $P < .001$), similar to patients with actual CTCs enumeration (HR 2.76; $P < .001$). The classifier's performance was then tested on an independent retrospective database comprising 446 consecutive hormone receptor (HR)-positive HER2-negative MBC patients. The model further stratified clinical subgroups usually considered prognostically homogeneous such as patients with bone-only or liver metastases. Bone-only disease classified as Simulated^{aggressive} had a significantly worse overall survival (OS; $P < .0001$), while patients with liver metastases classified as Simulated^{indolent} had a significantly better prognosis ($P < .0001$). Consistent results were observed for patients who had undergone CTCs enumeration in the pooled population. The differential prognostic impact of endocrine- (ET) and chemotherapy (CT) was explored across the simulated subgroups. No significant differences were observed between ET and CT in the overall population, both in terms of progression-free survival (PFS) and OS. In contrast, a statistically significant difference, favoring CT over ET was observed among Simulated^{aggressive} patients (HR: 0.62; $P = .030$ and HR: 0.60; $P = .037$, respectively, for PFS and OS).

Key words: clinical trial model; machine learning; liquid biopsy; biomarker; K-nearest neighbor.

Implications for Practice

Circulating tumor cells (CTC)-based risk stratification may have a role for future treatment strategies, as it enables the selection of subgroups with differential response potential. Machine learning can simulate CTCs-based staging in scenarios of particular interest to identify subpopulations for hypothesis generation which may benefit from higher intensity treatments due to a more aggressive outcome and inform future clinical trials designs.

Background

Metastatic disease occurs in approximately 20%-50% of patients with early breast cancer (BC) and in 6%-10% of newly diagnosed BC cases. Different disease subtypes account, at least partially, for the variability in overall survival (OS) which can range from months to several years.[1,2] As increasing knowledge is generated regarding new therapeutic agents, it is important to identify new predictive factors that help treatment selection. To date, the most established predictive markers in metastatic breast cancer (MBC) are the expression of HR and HER2. Patients with HR-positive/HER2-negative MBC often respond to endocrine therapy (ET) alone or in combination with targeted agents with generally fewer side effects and toxicities than chemotherapy (CT). ET-based therapies in combination with CDK4/6 inhibitors are therefore the preferred treatment approach in most cases of HR-positive MBC, reserving CT for patients with extensive symptomatic visceral disease and/or defined endocrine resistance. To date, there are no predictive biomarkers driving treatment choice regarding targeted therapies such as inhibitors of cyclin-dependent kinase (CDK) 4/6.

While circulating tumor cells (CTCs) are recognized as an independent prognostic marker for OS, their role in supporting clinical management of MBC is still not well defined.[3-5] A previous effort to prospectively evaluate the clinical utility of CTCs enumeration in MBC was performed in the SWOG 0500 trial. In this study, clinicians were guided to maintain or switch chemotherapy regimen based on an early CTCs evaluation after 21 days of therapy.[6] Although the study showed no OS differences in patients with persistently elevated CTCs that changed CT regimen, the prognostic potential of CTCs was further confirmed. The study's sampling timeframe, however, was not strictly biology driven, since CTCs dynamics is not just treatment-induced but also likely the result of tumor biology evolution.[7] Moreover, the CT selection was driven by the clinician's choice and not by biology-defined targets.

Table 1. Patients' characteristics across the CTCs enumeration subgroups.

Variable	Stage IV^{indolent}	Stage IV^{aggressive}	*P*-value
ER			.001
Negative	372 (3.22%)	244 (23.99%)	
Positive	859 (69.78%)	773 (76.01%)	
PR			.076
Negative	553 (44.92%)	419 (41.20%)	
Positive	678 (55.08%)	598 (58.80%)	
HER2			<.001
Negative	896 (72.79%)	808 (79.45%)	
Positive	335 (27.21%)	209 (20.55%)	
Bone involvement			<.001
No	557 (45.25%)	222 (21.83%)	
Yes	674 (54.75%)	795 (78.17%)	
Liver involvement			<.001
No	818 (66.45%)	502 (49.36%)	
Yes	413 (33.55%)	515 (50.64%)	

The Stage IV^{indolent} and Stage IV^{aggressive} subgroups are characterized by significantly different characteristics both in terms of tumor biology and clinical behavior.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

The strong prognostic stratification achieved by CTCs enumeration can have potential applications in identifying patients that will likely benefit from intensive treatments, while reserving less toxic treatments for those with an inherently indolent disease.[8]

Current clinical trials usually do not include a baseline CTCs enumeration in their design, primarily due its perceived costs and technical complexity, notwithstanding software solutions that minimize inter-operator variability. Therefore,

there is an unmet need to evaluate biomarker-assisted decisional algorithms.[9]

The aim of this study was to generate a classifier to simulate the prognostic stratification of CTCs in existing datasets for hypothesis generation in precise MBC scenarios. This classifier has the potential to inform and potentially drive future clinical trials design.

Methods

Study Population and Ethical approval

The model was trained on a pooled dataset based on data from 2436 individual MBC patients from 17 European Centers participating in the European Pooled Analysis Consortium (EPAC) and the MD Anderson Cancer Center (MDACC).[5] The database characteristics were previously published.[4]

The anonymized data were transferred to the Robert H. Lurie Comprehensive Cancer Center-Bioinformatics Core Facility. A retrospective Institutional Review Board-approved protocol was used to access and analyze the data. CTCs enumeration was performed through the CellSearch platform (Menarini Silicon Biosystems, PA) and the patients were classified accordingly based on a 5 CTCs per 7.5 mL cut off in Stage IV^{aggressive} (5 ≥ CTCs) and Stage IV^{indolent} (5 < CTCs).[3,4]

Features Selection and Training of the Machine Learning Classifier

K-nearest neighbor (KNN) is a supervised machine learning algorithm that can be used to solve both classification and regression problems. After a training phase during which labeled data are analyzed, the model abstracts a function that can be used to infer an appropriate output when new unlabeled data are evaluated. The KNN algorithm classifies objects based on their proximity in the feature space through a majority vote of its neighbors. The object is therefore assigned to the class that is most common among its KNN, where K is a positive integer that is typically small. If $K = 1$, then the object is assigned to the class of its nearest neighbor.

Baseline features linked to tumor biology were tested through Chi square test for association with respect to Stage IV^{aggressive} and consistently selected based on both clinical and statistical significance (Table 1).

The model was then trained based on estrogen receptor (ER) status (positive vs negative, 1% threshold), progesterone receptor (PR) status (positive vs negative, 1% threshold), HER2 status (positive vs negative), treatment line (continuous variable), bone and liver involvement (yes vs no).

Patients with all the necessary features (2248) were then 3:1 randomly assigned to a training set (1687) and a validation set (561) (Supplementary Fig. 1).

The model was built using R (The R foundation for Statistical Computing. version 3.3.1) and the "caret" package.[10]

CTCs Simulation on an Independent Database

The classifiers' performance was tested on an independent retrospective database of 446 consecutive HR-positive HER2-negative MBC patients treated with first-line ET or CT at the University Hospitals of Naples and Udine, Italy, between 2004 and 2014. Patients' characteristics were previously published.[11] This study was previously approved by the Review Committees of each center. CTCs risk stratification was simulated through the "caret" package.[10]

Statistical Analysis

Categorical variables were reported as frequency distribution, whereas continuous variables were described through median and interquartile range (IQR).

Overall survival (OS) was defined as the time from baseline CTCs enumeration to death from any cause or date of

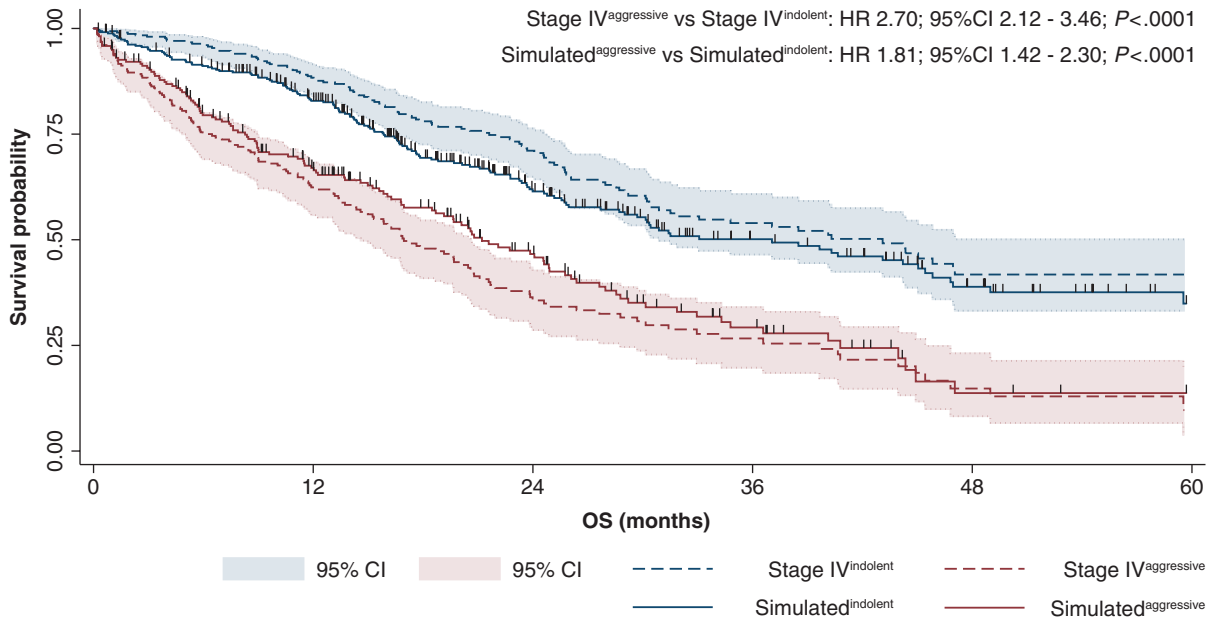

Figure 1. Comparison between the CTC-based risk stratification (Stage IV^{indolent} vs Stage IV^{aggressive}) and the KNN simulation (Simulated^{indolent} vs Simulated^{aggressive}). The model was capable to simulate a comparable risk stratification with respect to CTCs enumeration both for StageIV^{indolent} (CTCs vs Simulation HR 1.18, 95%CI 0.93-1.51, $P = .177$) and StageIV^{aggressive} (CTCs vs Simulation HR 0.88, 95%CI 0.70-1.09, $P = .242$).

last follow-up. Progression-free survival (PFS) was defined as the time from baseline CTCs enumeration to disease progression (according to RECIST criteria) or death from any cause or date of last follow-up. Censoring was applied to patients without an endpoint event at the last follow-up visit. Survival was represented by Kaplan-Meier estimator plot and analyzed by log-rank test and by uni- and multivariable Cox regression models.

Changes in the predictive power of the Cox regression models using the simulated CTCs enumeration were investigated through Harrell's c concordance statistics.

Differences in distribution of CTCs enumeration, according to the simulated CTCs status across MBC subtypes, were tested through the Mann-Whitney *U* test.

Statistical analysis was conducted using StataCorp 2016 Stata Statistical Software: Release 15.1 (College Station, TX, USA), and R (The R foundation for Statistical Computing. version 3.3.1).

Data Availability

The datasets supporting the conclusions of this article are available from the corresponding author on reasonable request.

Results

From the initial cohort of 2436 patients, 2248 (92.4%) had no missing data and were therefore eligible for the model training (Table 1).[4] Consistent with previously reported data, CTCs enumeration was associated with specific baseline characteristics. In particular, Stage IV^{aggressive} patients were more likely to be ER positive (P = .001), HER2 negative (*P* < .001), and have bone or liver metastasis (*P* < .001).

CTCs Enumeration Can Be Simulated Through Machine Learning

Based on these premises, a KNN model was trained with a resulting 65.1% accuracy (95% CI [CI]: 61.0%-69.0%), 72.6% sensitivity (95%CI: 68.95-76.33%) and a 55.9% specificity (95%CI: 51.8-60.0%) (Supplementary Table S1).

The proportion of correctly classified observations was higher in patients without detectable CTCs (78.3% classified as Simulated IV^{indolent}) than in patients with CTCs enumeration higher than the 75th percentile (21 CTCs; 62.6% classified as Simulated^{aggressive}).

In the validation cohort, the prognostic impact of the CTCs enumeration was hazard ratio (HR) 2.76 (95%CI 2.18-3.49; *P* < .001) for Stage IV^{aggressive} vs Stage IV^{indolent}.

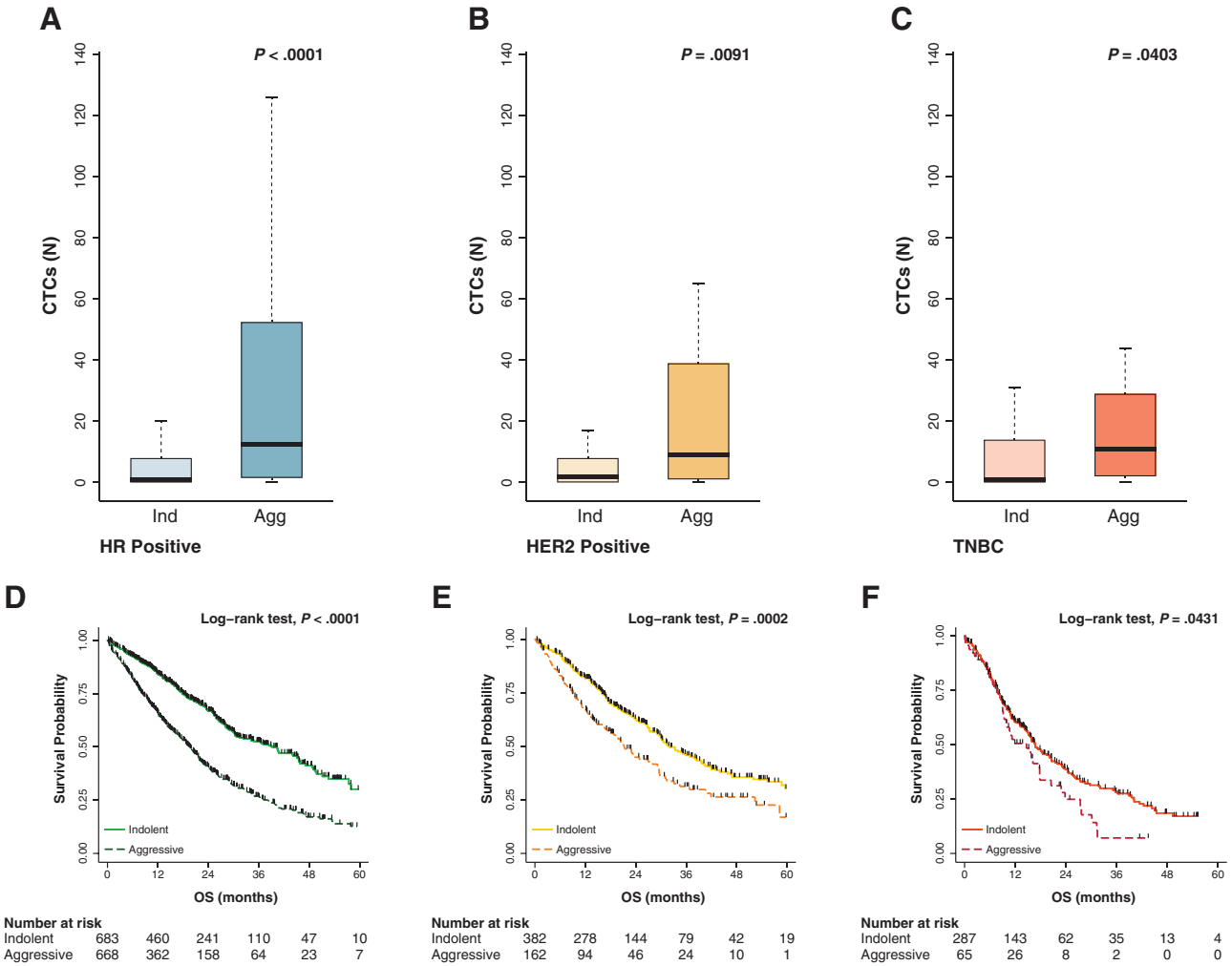

Figure 2. CTCs enumeration simulation across MBC subtypes. Patients classified as Simulated^{aggressive} (Agg) had a significantly higher CTCs enumeration with respect to Simulated IV^{indolent} (Ind) in HR-positive MBC (A), HER2-positive MBC (B) and TNBC (C). Patients classified as Simulated^{aggressive} experienced a significantly worse prognosis (D).

Consistently, the classifier resulted in a HR of 1.89 (95%CI 1.50-2.38; $P < .001$) for Simulated^{aggressive} vs Simulated IV^{indolent} (Fig. 1).

Patients classified as Simulated^{aggressive} had a significantly higher number of CTCs with respect to Simulated IV^{indolent} (median CTCs 11.5, IQR: 1-44 vs 2, IQR 0-9; $P = .0001$, respectively, for Simulated^{aggressive} and Simulated IV^{indolent}).

CTCs Classifier and Breast Cancer Subtypes

The classifier's performance was then tested in the overall population across different MBC subtypes.

Patients classified as Simulated^{aggressive} had a significantly higher CTCs enumeration with respect to Simulated IV^{indolent} in HR-positive MBC (median CTCs 10, IQR: 1-60.5 and 1, IQR 0-11; $P < .0001$, respectively) (Fig. 2A), HER2-positive MBC (median CTCs 8, IQR: 1-32 and 1, IQR 0 – 6; P = .0091, respectively) (Fig. 2B) and TNBC (median CTCs 11, IQR: 2-52 and 2, IQR 0 – 16; P = .0403, respectively) (Fig. 2C). Patients classified as Simulated^{aggressive} experienced a significantly worse prognosis (Fig. 2D, E), especially in the HR-positive subgroup (Fig. 2D).

CTC-Based Risk Stratification Can Be Simulated on an Independent Real-World Dataset

To test the consistency and applicability of the classifier in a real-world MBC cohort, a proof-of-concept analysis was performed on an independent database comprising 446 HR-positive, HER2-negative MBC patients. Patients' characteristics were previously published. Three patients were excluded from the analysis due to missing PR status.[11]

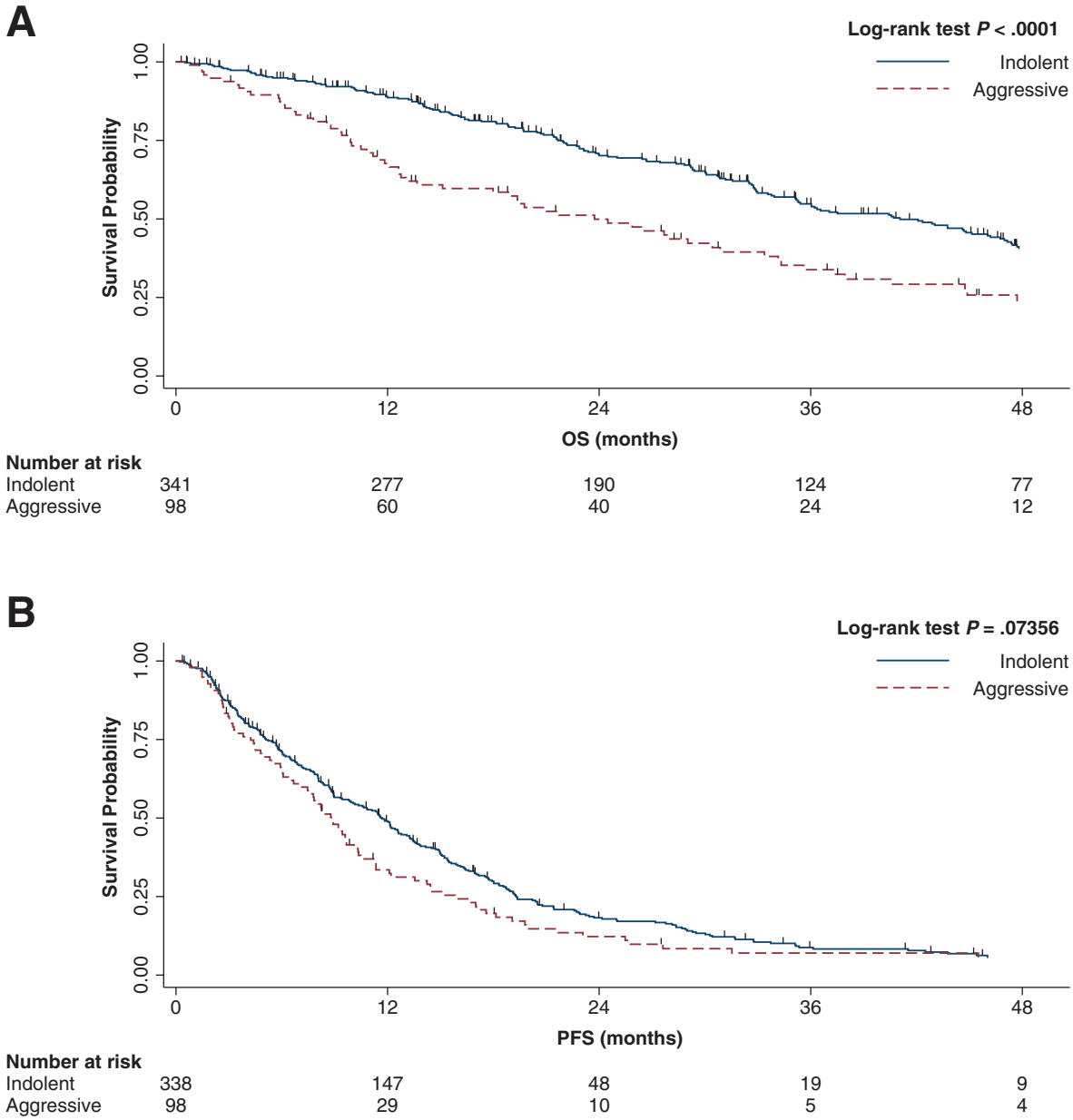

Figure 3. CTCs enumeration simulation of on an independent cohort comprising HR-positive, HER2-negative first-line MBC patients. The classifier was capable to stratify patients both in terms of OS (A) and PFS (B).

Of the 443 eligible patients, 345 (77.9%) were classified as Simulated IV^{indolent} and, among them, 126 (36.5%) received first-line CT, whereas 219 (63.5%) received ET without targeted companions (eg, PI3K inhibitors, CDK 4/6 inhibitors (CDK4/6i)). On the other hand, 98 patients (22.2%) were classified as Simulated^{aggressive} and among them 46 (46.9%) received first-line CT, while 48 (53.1%) received ET. Patients classified as Simulated^{aggressive} had a significantly worse outcome compared with the Simulated IV^{indolent} subgroup, in terms of OS (HR: 1.82; 95%CI 1.38-2.39; *P* < .001; median: 23.74 vs 41.06 months) (Fig. 3A) and a non-significant numerical difference with respect to PFS (HR: 1.24; 95%CI 0.98-1.59; *P* = .074, median: 8.91 vs 11.70 months) (Fig. 3B).

The prognostic impact for OS was also investigated through multivariable analysis to test the independent role of the classifier on outcome. Simulated^{aggressive} retained its prognostic significance in terms of OS (HR: 1.58; 95%CI 1.17-2.15; *P* = .003; Table 2) and its addition increased the model's overall concordance index (Harrell's C = 0.6381 and 0.6581, respectively, before and after the addition of the classifier to the multivariable model).

The model was also able to further stratify clinical subgroups usually considered prognostically homogeneous. Similarly to what was observed with CTCs enumeration in the pooled population (Fig. 4A), patients with bone only metastases classified as Simulated IV^{aggressive} had a significantly worse prognosis with respect to the Simulated IV^{indolent} counterpart (P < .0001) (Fig. 4C). Consistently, patients with liver metastases classified as Simulated IV^{indolent} had a significantly better prognosis than the Simulated IV^{aggressive} counterpart (*P* < .0001; Fig. 4D).

CTCs Classifier and Impact of Treatment Type

As a proof of principle, the differential prognostic impact of first-line ET and CT was explored across the Simulated^{aggressive} and Simulated^{indolent} subgroups. Consistently with previously published results, no significant differences were observed between ET and CT in the overall population, both in terms of PFS (HR: 1; 95%CI 0.81-1.23; *P* = .998) and OS (HR: HR: 0.92; 95%CI 0.72-1.18; *P* = .511) (Fig. 5A, D). Similar results were obtained in the Simulated^{indolent} subgroup (HR: 1.13; 95%CI 0.89-1.44; *P* = .301 and HR: 0.95; 95%CI 0.72-1.28; P = .759 respectively for PFS and OS) (Fig. 5B, E). On the other hand, a statistically significant difference, favoring CT over ET was observed among Simulated^{aggressive} patients (HR: 0.62; 95%CI 0.40 – 0.96; P = .030 and HR: 0.60; 95%CI 0.37 – 0.97; *P* = .037, respectively, for PFS and OS; Fig. 5C, F).

Discussion

The present study explored the concept of simulating the CTC-based prognostication to investigate the impact of different therapeutic approaches in existing databases that are lacking for this characterization. A KNN supervised machine

Table 2. Main prognostic factors in terms of OS both on uni and multivariable analysis

Variable	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
BC subtype						
Luminal A	1			1		
Luminal B	1.57	1.16-2.12	0.003	1.46	1.06-2.00	.020
BMI						
≤25	1					
>25	1.15	0.87-1.53	0.327			
CTCs simulation						
Simulated^{indolent}	1			1		
Simulated^{aggressive}	1.82	1.38-2.39	< 0.001	1.58	1.17-2.14	.003
Age at treatment start						
<70 years	1					
≥70 years	1.84	1.43-2.36	< 0.001	2.08	1.57-2.76	<.001
ET naïve						
No	1			1		
Yes	0.71	0.55-0.90	0.005	0.51	0.29-0.89	.017
CT naïve						
No	1					
Yes	0.81	0.63 -1.02	0.077			
Stage IV onset						
Relapsed	1			1		
De novo	0.73	0.57 - 0.94	0.016	1.03	0.58-1.82	.931
ECOG PS						
0-1	1			1		
≥2	1.62	1.17-2.25	0.004	1.58	1.11-2.25	.011

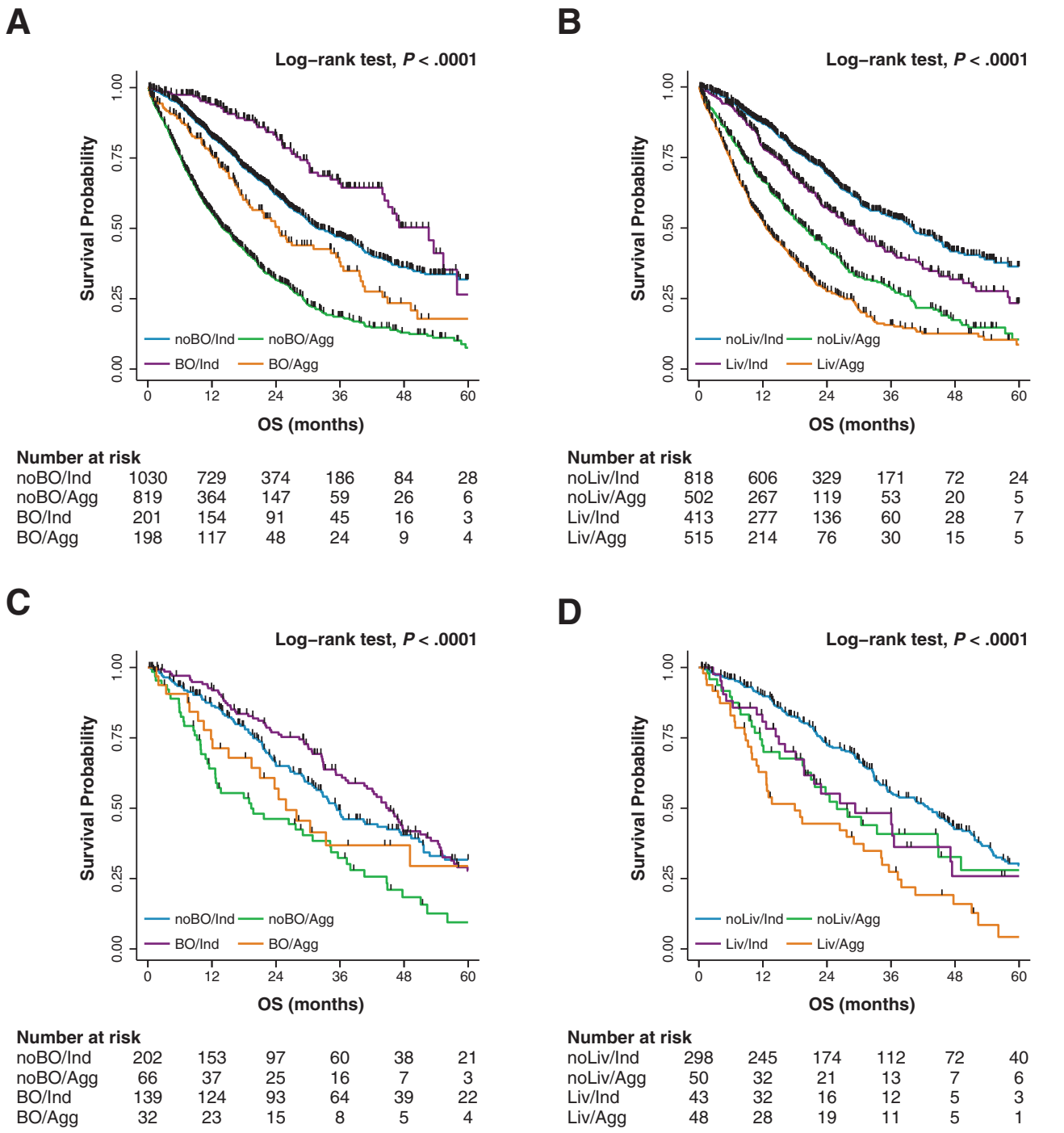

Figure 4. CTCs stratification and simulation among patients with bone-only (BO) disease (A, C) and liver (Liv) involvement (B, D). In the pooled population, patients with bone only metastases classified as StageIV^{aggressive} had a significantly worse prognosis with respect to StageIV^{indolent} ($P < .0001$) (A). Similar results were observed in the Simulated counterpart ($P < .0001$) (C). Consistently, patients with liver metastases classified as StageIV^{indolent} had a significantly better prognosis than the StageIV^{aggressive} counterpart ($P < .0001$) (B) Similar results were observed in Simulated^{indolent} patients with liver metastases ($P < .0001$) (D).

learning model was trained on a pooled dataset of 2436 MBC patient from EPAC and MDACC with a resulting 57.1% sensitivity (95%CI: 50.8-63.3%), a 61.6% specificity (95%CI: 55.9-67.0%) and a notably comparable risk stratification with respect to the real CTCs enumeration (StageIV^{indolent} vs Simulated^{indolent} HR 1.18, 95%CI 0.93-1.51 $P = .177$; StageIV^{aggressive} vs Simulated^{aggressive} HR 0.88, 95%CI 0.70-1.09, $P = .242$).

As a proof of concept, the classifier was applied to a real-world cohort of 446 patients affected by HR-positive HER2-negative MBC to investigate the differential prognostic impact of first-line ET and CT across the Simulated^{aggressive} and the Simulated^{indolent} subgroups in a clinically homogeneous population. The dataset was previously analyzed through a propensity score matching approach to explore the prognostic impact of CT vs ET as first-line treatment showing

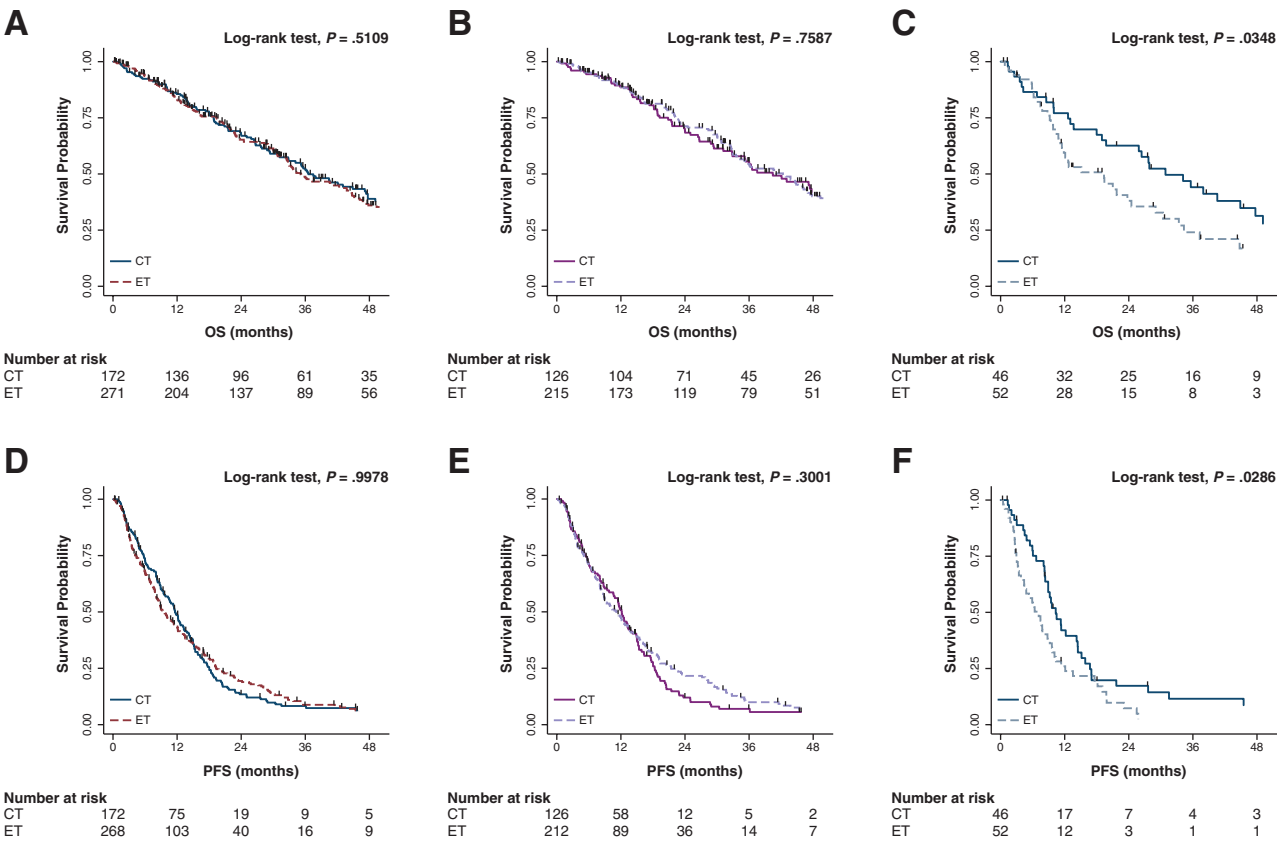

Figure 5. Impact of first-line ET and CT in terms of OS and PFS according to the classifier's stratification. No significant impact was observed in the total population (A, D) nor in the Simulated^{indolent} subgroup (B, E) in terms of OS and PFS, while a significantly different outcome was observed in the Simulated^{aggressive} subgroup (C, F).

no significant differences.[11] As expected, Simulated^{aggressive} patients experienced a worse outcome both in terms of PFS and OS (Fig. 3), the latter confirmed also in multivariable analysis. Intriguingly, a differential prognostic impact of ET and CT was observed within the 2 simulated cohorts. In the Simulated^{indolent} subgroup, no difference in outcome was observed when patients were treated with ET or CT. In contrast, the Simulated^{aggressive} subgroup had a significantly better outcome in patients receiving CT over ET, both in terms of PFS and OS (Fig. 5).

The use of ET-based treatments with respect to CT, is supported by a therapeutic benefit burdened by lower toxicities and better quality of life. Moreover, novel combinations of ET plus targeted treatments, including CDK4/6i, have shown remarkable efficacy in patients with HR-positive HER2-negative MBC.[12,13] Therefore, current guidelines recommend ET-based treatments with CDK4/6i as first-line therapy for HR-positive HER2-negative MBC, whereas CT should be considered as the preferred treatment strategy in patients with visceral disease that acutely threaten organ function.[11]

Bone-only disease is often regarded as a distinct clinical subgroup characterized by a favorable prognosis and a prolonged OS, and therefore these patients are potentially eligible to receive a lower-intensity treatment and disease monitoring.[14] However, we observed a subset of patients with CTC-defined bone-only disease that experienced a significantly worse prognosis (Fig. 4) which accounted for 49.6% of patients with bone-only disease in the pooled cohort (198 out of the total 399). The present study, therefore, suggests that additional biomarkers, such as CTCs enumeration, could be useful to further stratify this subpopulation and identify patients that may benefit from a different therapeutic approach. Many studies have been conducted so far to evaluate clinical features such as disease-free interval, number, and type of metastatic sites as clinical markers potentially useful to guide treatment decision. However, none of these have been shown to be a useful predictive marker.[15] In this scenario, CTCs enumeration could provide a potentially useful tool.

A similar concept was explored by the phase III STIC CTCs trial.[8] The study randomized 761 MBC patients between a clinically-driven choice or a CTC-driven choice defined on the established ≥5 CTC/7.5ml cutoff.[4] Patients classified as "high risk" based on the assigned approach received CT, while those classified as "low-risk" received ET. PFS was showed to be not inferior in the CTC-driven with respect to the clinically-driven one (HR 0.98, 90%CI 0.84-1.13).[8] Intriguingly, StageIV^{aggressive} patients that were clinically defined as "low-risk" had a significantly longer PFS when treated with CT (in the CTCs arm) with respect to those treated with ET (in the clinically driven arm), highlighting the impact of treatment type on patient outcome (PFS HR 0.67, 95%CI 0.49-0.92 P = .01). Importantly, these results are consistent with those generated by the classifier in our study, further supporting its reliability and potential utility.

One limitation of this study is the lack of inclusion of patients treated with CDK4/6i. On the other hand, this is the first proposed "in silico" approach capable to stratify patients according to the simulation of CTCs-based staging.

Of note, since the classifier was trained using the widely established ≥5 CTC/7.5 ml cutoff and a large un-selected MBC cohort, it offers a generalizable platform for hypothesis generation that can be transferred to a broad variety of real-world or clinical trial databases.[3-6,8,9]

Previous attempts have been made to explore new subgroups with differential treatment benefits through machine learning algorithms. Patient-level data from 4580 breast cancer patients enrolled in 8 randomized clinical trials treated with CDK4/6i were analyzed through random survival forest models based on clinical baseline characteristics with a resulting 69.2% accuracy.[16]

The present study designed a classifier with a 65.1% accuracy based on a strong, setting-independent biological biomarker, enabling its application on a broader set of clinical questions.

Although the present study provided evidence of an in silico simulation of the CTC-based stratification, its main objective was not to replace the real CTCs enumeration, which has specific biological implications and is certainly more solid in PFS and OS prognostication. It rather identifies patients with comparable prognostic characteristics for hypothesis generation and the subsequent design of prospective, biomarker-driven, clinical trials with the ultimate goal of catalyzing sample size optimization and clinical trials optimization by exploring different levels of treatment intensity and the impact of methodological aspects in subpopulations with different risk profiles.[17]

Conclusion

The present study showed the feasibility of a KNN machine learning classifier to simulate a baseline CTCs-based staging. This model could be used for hypothesis generation in specific case scenarios of interest to identify subpopulations which may benefit from higher intensity treatments due to a more aggressive outcome, representing a valuable tool for future clinical trials design and prospective, biomarker-driven, validation studies.

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Compliance with Ethical Standards

Ethical approval: The anonymized EPAC/MDACC data were transferred to the Robert H. Lurie Comprehensive Cancer Center-Bioinformatics and a retrospective Institutional Review Board-approved protocol was used to access and analyze the data. The combined Udine/Neaples cohort was previously approved by the Review Committees of each participant center.

Conflict of Interest

Lorenzo Gerratana: Eli Lilly and Novartis (H), Menarini Silicon Biosystems (RF); **Jean-Yves Pierga**: Seagen, Daiichi Sankyo, Pfizer, AstraZeneca, MSD, Gilead, Roche, Novartis, Exact Sciences (C/A), Menarini, Servier (RF), Viatris, Lilly, Pierre Fabre Oncology (H); **Andrew A. Davis**: Menarini Silicon Biosystems (RF); **Justin Stebbing**: Vaccitech, Heat Biologics, Eli Lilly, Alveo Technologies, Pear Bio, Agenus, Equilibre Biopharmaceuticals, Graviton Bioscience Corporation, Celltrion, Volvox, Certis Oncology Solutions, Greenmantle, Zedsen, Bryologyx and Benevolent AI (SAB), Lansdowne partners and Vitruvian (C/A); Xerion and BB Biotech Healthcare Trust PLC (Other—Leadership, Board of Directors); **Carlos Caldas**: AstraZeneca (SAB), AstraZeneca, Genentech, Roche, Servier, Cycle Therapeutics (RF—inst); **Michail Ignatiadis**: Novartis, Seattle Genetics (C/A), Roche, Pfizer, Natera Inc (RF—inst); Carmine De Angelis: Roche, AstraZeneca, Lilly, GSK, Novartis, Pfizer (C/A), Novartis, Pfizer, Lilly (H), Novartis (RF—inst); **Sarah Jane Dawson**: AstraZeneca, Inivata (SAB), **Wolgang Janni:** Menarini (RF); **Erich-Franz Solomayer:** Amgen, AstraZeneca, Celgene, Clovis Oncology, Eisai, Erbe, Gedeon Richter, Genomic Health, Jenapharm, Johnson Johnson, Matramed, Medac, Mentor, Novartis Pfizer, Pharma Mar, MSD, Roche, Samsung, Storz, Tewa, Vifor (H); **Mario Giuliano:** Lilly, Novartis, Pfizer, Roche, MSD, Seagen, AstraZeneca (C/A, H); **Fabio Puglisi**: Amgen, Astrazeneca, Daichii-Sankyo, Eisai, Eli Lilly, MSD, Novartis, Pierre-Fabre, Roche, Seagen (C/A), AstraZeneca, Eisai, Roche Other, Celgene, GlaxoSmithKline, Roche (RF); **Massimo Cristofanilli**: Pfizer, Merus, Novartis, CytoDyn (H), Menarini, Olaris, Lilly, Celcuity, AZ (C/A), Lilly, Pfizer, Menarini, Guardant, AZ (RF). The other authors indicated no financial relationships.

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Author Contributions

Conception/design: L. G., A.A.D., F.P., M.C. Provision of study material/patients: L.G., J.Y.P., J.R., A.A.D., F.H.W., L.D., T.F., F.N., R.G.-C., D.M., S.G., J.A.G-S., J.S., C.C., P.G., L.M., R.Z., M.B., A.F.d.L., L.D.M.A., M.I., M.-T.S., D.G., C.D.A., S.-J.D., W.J., V.C., S.R., E.-F.S., F.P., M.G., K.P., F. -C.B., M.C. Collection and/or assembly of data: L.G., J.-Y.P., J.R., A.A.D., F.H.W., L.D., T.F., F.N., R.G.-C., D.M., S.G., J.A.G.-S., J.S., C.C., P.G., L.M., R.Z., M.B., A.F.d.L., L.D.M.-A., M.I., M.-T.S., D.G., C.D.A., S.-J.D., W.J., V.C., S.R., E.-F.S., F.P., M.G., K.P., F.-C.B., M.C. Data analysis and interpretation: L.G., A.A.D., F.H.W., M.B., C.D.A., F.P., M.G., F.-C.B., M.C. Manuscript writing: L.G., J.-Y.P., J.R., A.A.D., F.H.W., L.D., T.F., F.N., R.G.-C., D.M., S.G., J.A.G.-S., J.S., C.C., P.G., L.M., R.Z., M.B., A.F.d.L., L.D.M.-A., M.I., M.-T.S., D. G., C.D.A., S.-J.D., W.J., V.C., S.R., E.-F.S., F.P., M.G., K.P., F.-C.B., M.C. Final approval of manuscript: All authors.

Supplementary Material

Supplementary material is available at The *Oncologist* online.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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