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Original article

Prognostic model for advanced breast carcinoma with luminal subtype and impact of hormonal maintenance: Implications for post-progression and conditional survival

Luisa Carbognin [a, b], Isabella Sperduti [c], Mariangela Ciccarese [d], Alessandra Fabi [e], Luciana Petrucelli [d], Sabrina Vari [e], Rosa Chiara Forcignanò [d], Rolando Nortilli [a, b], Cecilia Vicentini [a], Sara Pilotto [a], Sara Merler [a], Ilaria Zampiva [a], Matteo Brunelli [b, f], Erminia Manfrin [b, f], Diana Giannarelli [c], Giampaolo Tortora [a, b, 1], Emilio Bria [a, b, *, 1]

[a] Medical Oncology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[b] Breast Unit, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[c] Biostatistics, 'Regina Elena' National Cancer Institute, Roma, Italy
[d] Medical Oncology, 'Vito Fazzi' Hospital, Lecce, Italy
[e] Medical Oncology 'A', 'Regina Elena' National Cancer Institute, Roma, Italy
[f] Department of Pathology and Diagnostics, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy

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ABSTRACT

Background: The aim of this analysis was to develop and validate a prognostic model for advanced breast cancer (ABC) with luminal subtype based on the combination of clinical, pathological and therapeutic predictors to provide a practical tool to evaluate patients' prognosis.

Methods: Clinical and pathological data were retrospectively correlated to progression-free and overall survival (PFS/OS) using a Cox model. Significant treatment variables were adjusted with the propensity score analysis. A continuous score to identify risk classes was derived according to model ratios. The performance of the risk-class model was tested for post-progression survival (PPS) and conditional survival (CS) as well.

Results: Data from 335 patients (3 institutions) were gathered (median follow-up 58 months). At multivariate analysis Ki67, Performance Status (PS) and number of metastatic sites were significant predictors for PFS, whereas Ki67, PS, brain metastases, PFS after 1st-line therapy, number of chemotherapy lines, hormonal therapy and maintenance were significant predictors for OS. The hormonal maintenance resulted to be prognostic after adjustment with propensity score analysis. A two-class model significantly differentiated low-risk and high-risk patients for 2-year PFS (31.5% and 11.0%, $p < 0.0001$), and 3-years OS (57.1% and 4.8%, $p < 0.0001$). A three-class model separated low risk, intermediate-risk, and high-risk patients for 2-year PFS (40.8%, 24.4%, and 11.0%, $p < 0.0001$) and 3-year OS (68.1%, 24.8%, and 4.8%, $p < 0.0001$). Both models equally discriminate the luminal ABC prognosis in terms of PPS and CS.

Conclusions: A risk stratification model including '*easy-to-obtain*' clinical, pathological and therapeutic parameters accurately separates luminal ABC patients into different risk classes.

Introduction

The advanced breast cancer (ABC) with luminal subtype (which accounts for the majority of ABC) is generally characterized by a favorable outcome, although the overall prognosis appears currently unpredictable, reflecting the biological heterogeneity of such disease [1–5].

Therefore, the identification of prognostic factors for luminal ABC represents a relevant aspect for clinical practice in order to

* Corresponding author. Medical Oncology, University of Verona, Azienda Ospedaliera Universitaria Integrata, P.le L.A. Scuro 10, 37124, Verona, Italy. Tel.: +39 0458128124; fax: +39 0458027410.
E-mail address: emilio.bria@univr.it (E. Bria).
[1] G.T. and E.B. share last co-authorship.

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select appropriate treatment strategies. With regard to candidate clinicopathological factors, age, patient comorbidities, metastatic free interval, site and number of distant metastasis represent the most reliable variables [6–8]. Nevertheless, several findings on prognostic factors vary considerably and do not constantly emerge in all studies. Moreover, the majority of data derives from trials including all biological subtypes of BC, thereby limiting its clinical utility in the specific context of luminal ABC.

In this regard, a prognostic index allowing ABC patients to be stratified into different risk-classes was performed and validated in a study comprising 233 patients where more than half of the patients had no available data for hormonal receptor status [9]. Another prognostic nomogram to predict overall survival (OS) by using clinical and laboratory characteristics was developed in women starting 1st-line chemotherapy for ABC with undetermined HER2 status [10].

Hormonal therapy represents the treatment milestone for luminal ABC, while the hormonal maintenance is considered one of the opportunities most commonly adopted in the context of clinical practice, although the absence of reliable evidences not clearly establishing the magnitude of such approach in terms of patients' benefit [11–13].

The preliminary stratification of patients according to prognosis allows the identification of those patients emerging as '*outliers*', or rather biologically different from the majority of the population affected by the same biologically-defined disease. These patients may harbor a series of molecular aberrations potentially driving their featured clinical behavior. In this regard, the assignment of a reliable clinical significance to a particular genomic alteration, that can impact on patient prognosis and determine susceptibility to selective targeted therapies, represents a major challenge for translational research. This approach to selectively identify potential predictors of prognosis and (eventually) resistance to a given treatment in the context of '*best*' and '*worst*' prognostic performers, represents nowadays one of the strategy that may successfully integrate the clinical findings with the newest genetic acquisitions [14].

The purpose of the current analysis was to create and validate a prognostic nomogram for luminal ABC according to the combination of clinical, pathological and therapeutic predictors in the context of a multicenter '*real world*' population, to identify prognostic '*outliers*' to be further analyzed with molecular and genomic technologies.

Materials and methods

A step-by-step protocol was followed according to the methodological approach for building a nomogram for cancer prognosis proposed by Iasonos et al. [15] with respect to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria for the conduction of a retrospective study in the context of an unselected population [16,17].

Patients' population

Clinical charts of consecutive patients affected by luminal ABC diagnosed at 3 Italian institutions (University Hospital of Verona, Hospital 'Vito Fazzi' of Lecce, and 'Regina Elena' National Cancer Institute, Rome) between January 1995 to December 2014 were considered eligible. Inclusion criteria were either '*de novo*' or distant relapsed luminal ABC diagnosis (stage IV) and availability of clinical, pathological and therapeutic parameters. Luminal subtype was defined as estrogen receptor (ER) and/or progesterone receptor (PgR) positivity ($\geq$1%) and HER2-negativity. The pathological variables (histotype, ER, PgR, HER2, Ki67, grading) were tested in the primary tumors.

End-points

The aim of this analysis was to create a prognostic nomogram on the basis of clinical, pathological and therapeutic factors in the context of a multicenter population of luminal ABC, in order to identify prognostic '*outliers*'. The model was developed on the basis of a multivariate analysis exploring the independent impact of these factors on progression-free survival (PFS), defined by the time between treatment initiation and tumor progression or death for any cause and OS, defined by the time between diagnosis of ABC and death for any cause or last follow-up.

Statistical analysis

Descriptive statistics was used to summarize pertinent study information. Follow-up was analyzed and reported according to Shuster et al. [18]. The hazard ratio (HR) and the 95% confidence intervals (95% CI) were estimated for each variable using the Cox univariate model [19]. The included variables in the univariate analysis for PFS and OS were age at diagnosis of metastasis, performance status (PS), surgery of the primary, grading, stage at diagnosis, multifocality, ER and PgR expression, Ki67, histology, luminal subtype, adjuvant systemic therapy (chemotherapy and hormonal therapy), metastasis-free interval, site of distant metastases (bone, visceral, brain), number of metastatic sites, systemic therapy for metastatic disease (chemotherapy, hormonal therapy and maintenance). A multivariate Cox proportional hazard model with clinical, pathological and therapeutic factors was developed using the stepwise regression (forward selection, enter limit and remove limit, $p = 0.10$ and $p = 0.15$, respectively), to identify independent predictors of outcomes. In case of therapeutic variables of interest at multivariate analysis for OS (i.e. hormonal maintenance), survival curves were adjusted for propensity score in order to reduce bias [20,21]. In order to screen the potential pre-treatment value of non-therapeutic variables, a further analysis by considering only pre-treatment factors was performed as well. Further details about the statistical analysis are reported in Supplementary Material.

Internal validation analysis

To address the multivariate model overfit and to validate the results, a cross-validation technique, which evaluates the replication stability of the final Cox multivariate model in predicting all outcomes, was also investigated, using a resampling procedure [15,22–24]. Further information is listed in Supplementary Material.

Prognostic score assessment

Two different methods were adopted to derive risk classes [25]: (i) for model A, the score was dichotomized according to prognosis with the maximally selected log-rank statistics analysis (the best '*splitter*' cut-off is determined) [26]; (ii) for model B, patients' outcomes (PFS and OS) were displayed by dividing patients into three risk classes, by considering cutoffs chosen at approximately equal distance along the range of values [27].

Post-progression and conditional survival

The risk class model for OS was than applied to post-progression survival (PPS, defined by the time between tumor progression after