

## Background

- The incidence of brain metastases (BM) from breast cancer (BC) is increasing and the treatment is still a major challenge.
- In our previous analysis of the Brain Metastases in Breast Cancer (BMBC) registry<sup>1,3</sup> we observed a median overall survival (OS) of 7.4 months after diagnosis of BM.
- Several scores have been developed in order to estimate the prognosis of patients with BM by objective criteria.
- The aim of this retrospective analysis from the BMBC registry was to validate the diagnostic accuracy on the overall survival (OS) of three Graded Prognostic Assessment (GPA) scores in a large cohort of BC patients with BM.<sup>1,2,4</sup>

## Patients and Methods

- All clinical data for this analysis derived from the BMBC registry. For 882 out of 2589 patients included in the registry all GPA scores could be determined.
- The original-GPA score [2] includes age, Karnofsky performance status (KPS), number of BM and extracranial metastases (ECM), the breast-GPA score age, KPS and tumor subtype, and the updated breast-GPA adds subtype to the original GPA score.

### Objectives:

- To assess the prognostic impact of age at first diagnosis of BM, number of BM, biological subtype (according to [2]), ECOG, appearance of ECM)on OS.
- To investigate the association of the OS in the BMBC registry with the survival times estimated by the original GPA, breast-GPA and the updated breast-GPA
- To determine the diagnostic accuracy by time dependent sensitivities, specificities, positive and negative predictive values (PPV, NPV) to identify a long life expectancy (>12 months) as well as the area under the Receiver-Operating-Characteristic (ROC)-curve (AUC).

All reported p-values were two-sided, the significance level was set to 0.05. The data was analyzed using SAS® version 9.4 and R from the R Foundation for Statistical Computing (version 3.6.0).

**Table 1. Baseline characteristics (continuous and categorical parameters)**

Parameter	Category	GPA-subgroup (N=882)	Overall (N=2589)
Age at diagnosis of BM, years	Median (min, max)	57.0 (25.0, 90.0)	57.0 (22.0, 99.0)
Histological tumor type	ductal or ductal-lobular-invasive	691 (78.8)	1876 (73.3)
	lobular-invasive	60 (6.8)	194 ( 7.6)
	other	126 (14.4)	491 (19.2)
	missing	5	28
Tumor grading	G1	16 ( 1.9)	42 ( 1.8)
	G2	324 (38.6)	927 (40.0)
	G3	500 (59.5)	1347 (58.2)
	missing	42	273
Biological subtype (according to [2])	TNBC	197 (22.3)	522 (23.2)
	Luminal A	295 (33.4)	750 (33.3)
	HR+/HER2+	221 (25.1)	556 (24.7)
	(luminal B)		
	HR-/HER2+	169 (19.2)	421 (18.7)
Karnofsky-Index at diagnosis of BM	missing	0	340
	100%	119 (13.5)	154 (13.9)
	80-90%	393 (44.6)	501 (45.1)
	60-70%	267 (30.3)	322 (29.0)
	40-50%	80 (90.1)	103 (9.3)
Number of BM	10-30%	23 (2.6)	31 (2.8)
	missing	0	1478
	1	234 (26.5)	718 (30.9)
	2-3	245 (27.8)	607 (26.1)
ECM at time of BM diagnosis	≥4	403 (45.7)	997 (42.9)
	missing	0	267
	yes	744 (84.4)	2139 (82.7)
	no	138 (15.6)	448 (17.3)
	missing	0	2

**Table 2. Median Survival after the diagnosis of BM with the corresponding 95%-confidence intervals for the three GPA scores**

Parameter	Category	Median Survival	95% CI
Original GPA	0-1	3.71	(3.19-4.67)
	1.5-2.5	10.1	(8.87, 12.3)
	3.0	22.4	(10.8, 28.2)
	3.5-4.0	38.2	(21.2-65.4)
Breast GPA	0-1	2.23	(1.61,2.96)
	1.5-2	5.39	(4.4, 7.10)
	2.5-3.0	8.57	(6.44,10.4)
	3.5-4.0	21.7	(18.4,24.9)
Updated Breast GPA	0-1	2.69	(2.04-3.35)
	1.5-2.0	5.22	(4.40,6.34)
	2.5-3.0	15.2	(12.3-18,5)
	3.5-4.0	32.2	(23.7,43.5)

## Results

**Patient characteristics within the prognostic indices** (for all results see **Table 1**):

- Median age at the diagnosis of BM was 57 years.
- 22.3% of patients (n=197) had a triple-negative (HR-/HER2-), 33.4% (n=295) Luminal A (HR+/HER2-), 25.1% (n=221) Luminal B (HR+/HER2+), 19.2% (n=169) HR-/HER2+ BC (according to Sperduto et al.2012).
- 15.6% of patients (n=138) had no ECM and 45.7% had ≥4 BM.
- More than half of the patients had a good KPS at diagnosis of BM (KPS ≥80%: 58.1%).

**Prognostic factors for worse OS:**

- Age >60 years, evidence of ECM, higher number of BM, triple-negative subtype and low KPS were all associated with worse OS in univariate analysis (p<0.0001 each).

**Median survival within the prognostic indices** (for all results see **Table 2** and **Figures 1-3**):

- For the original GPA score median survival between the subgroups were 3.71 for subgroup 0-1 points, 10.1 for 1.5-2.5, 22.4 months for 3 points and 38.2 months for patients in the group with 3.5-4 points.
- The median survival between the four subgroups of the breast GPA score 0-1, 1.5-2.0, 2.5-3,3.5-4 differed between 2.23, 5.39, 8.57 and 21.7 months.
- Median survival in the updated breast GPA varied between 2.69, 5.22, 15.2 and 32.2 months for the subgroups 0-1, 1.5-2, 2.5-3 and 3.5-4.

**Diagnostic accuracy of the GPA-Scores** (for all results see **Table 3**):

- The original GPA had a high time dependent sensitivity of 92.2%, but a low time dependent specificity of 21.8% to identify patients with a short time life expectancy (>12 months, score value < vs. ≥ 3) with PPV of 62.6 and a NPV of 66.3%.
- The breast-GPA scores showed lower sensitivities, but higher specificities (breast-GPA: 68.7%; updated breast-GPA: 48.1%), higher PPV (breast-GPA: 75.6%; updated breast-GPA: 69.9%) and lower NPV.
- There were no significant differences between the AUC of the scores after 12 months (breast-GPA (73%) vs. updated breast-GPA (74.2%), p=0.09; breast-GPA vs. original GPA (69.5%): p=0.18).

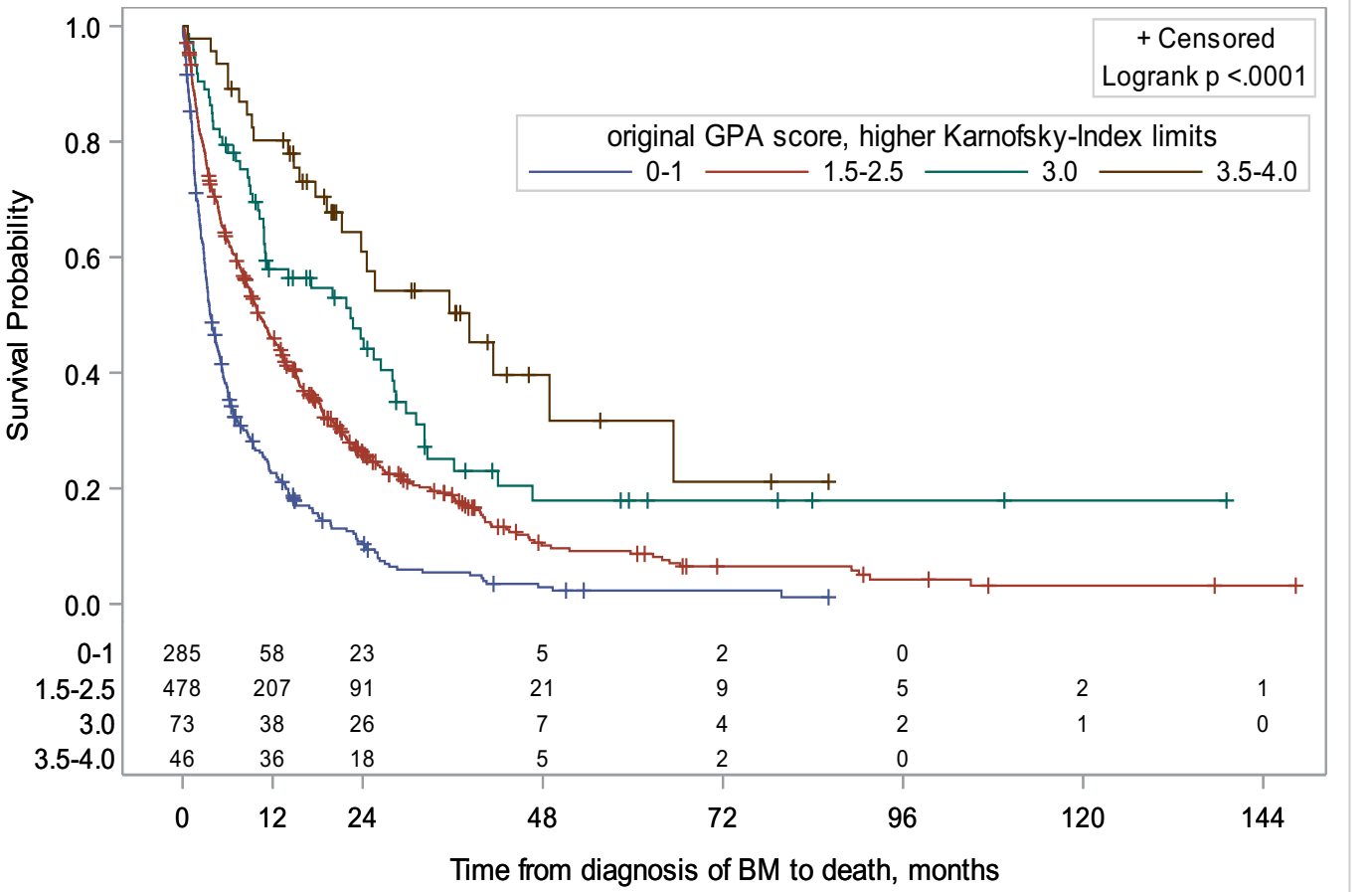
**Table 3. Diagnostic accuracy of the original, breast-GPA and updated breast-GPA score at 3 and 12 months**

GPA score	Time months	sensitivity (%) (95% CI)	specificity(%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Original GPA	3	96.2 (93.7, 98.6)	17.2 (14.2, 20.1)	29.7 (26.4, 33.0)	92.5 (87.7, 97.2)
	12	92.2 (89.9, 94.6)	21.8 (17.4, 26.2)	62.6 (59.1, 66.1)	66.3 (57.7, 75.0)
Breast GPA	3	72.2 (66.5, 77.9)	53.5 (49.6, 57.4)	36.1 (31.8, 40.5)	84.1 (80.5, 87.6)
	12	68.1 (64.0, 72.2)	68.7 (63.8, 73.7)	75.6 (71.6, 79.6)	60.2 (55.4, 65.0)
Updated Breast GPA	3	91.9 (88.4, 95.4)	35.7 (32.0, 39.4)	34.2 (30.5, 37.9)	92.4 (89.0, 95.7)
	12	84.8 (81.7, 88.0)	48.1 (42.8, 53.4)	69.9 (66.2, 73.6)	69.1 (63.2, 74.9)

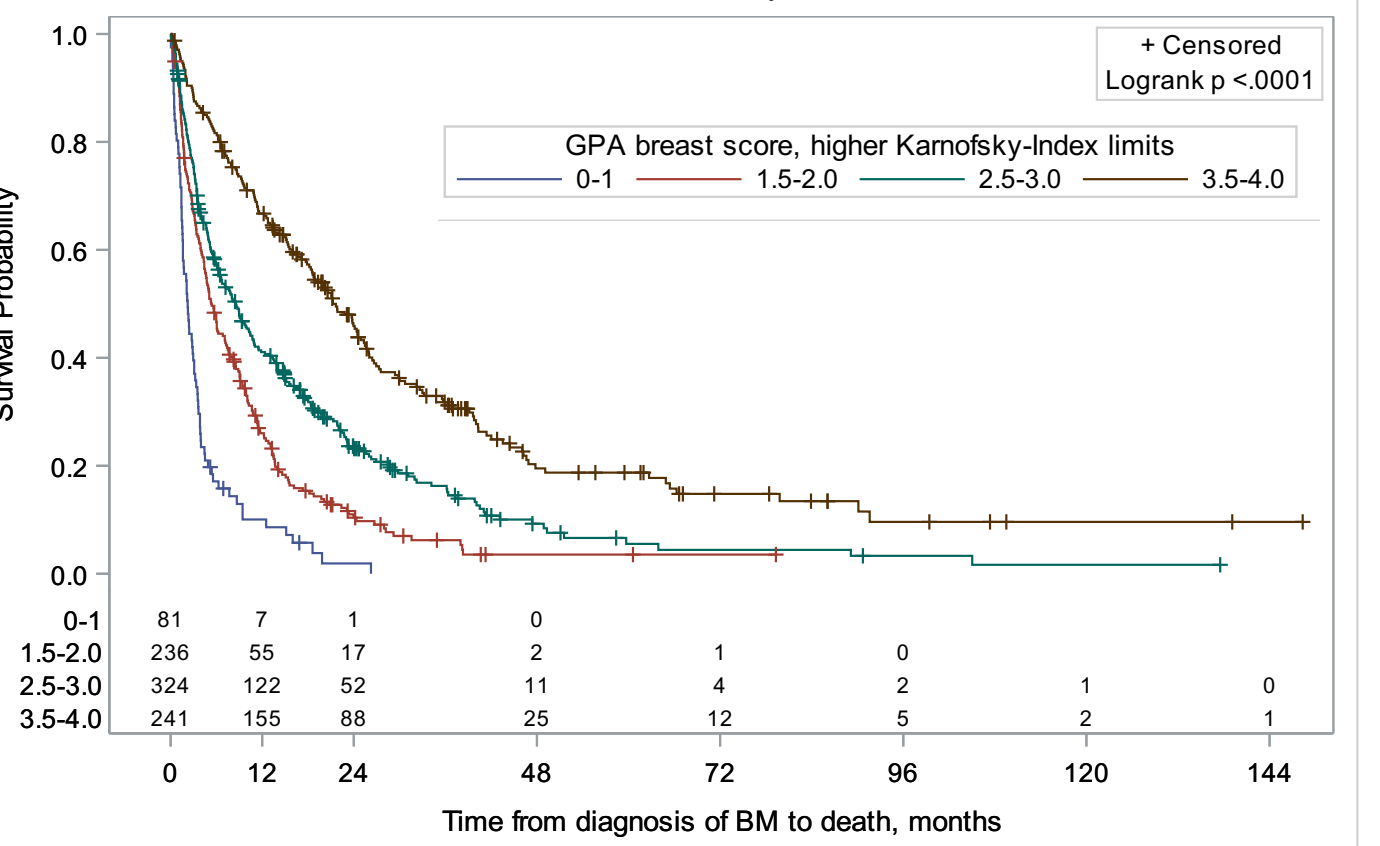
## Conclusions

**In this analysis, several clinical parameters as well as the GPA-scores were significantly associated with OS. However, in our cohort all GPA-scores show only a moderate diagnostic accuracy in predicting the OS. Even the updated breast-GPA with most of the statistically significant parameters included did not result in a better performance.**

**Figure 1. Kaplan-Meier curves for the time from diagnosis of BM to death (original GPA score)**



**Figure 2. Kaplan-Meier curves for the time from diagnosis of BM to death (breast GPA score)**



**Figure 3. Kaplan-Meier curves for the time from diagnosis of BM to death (updated breast GPA score)**

