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ORIGINAL RESEARCH

Clinical Prognosis and Nomograms for Hormone Receptor-Positive and Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Patients Treated with Palbociclib and Endocrine Therapy

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Background: This study aimed to analyze factors affecting the prognosis of patients with hormone receptor-positive (HR+) and human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (MBC) treated with palbociclib and endocrine therapy (ET).

Methods: Patients with HR+/HER2- MBC who were treated with palbociclib plus ET between January 2019 and December 2020 at Shandong Cancer Hospital were recruited. Clinicopathological data, treatment outcomes, and survival were from electronic medical system and telephone follow-up.

Results: A total of 90 eligible patients were recruited in this study; 55 (61.11%) patients preferred chemotherapy as first treatment, and 35 (38.89%) preferred ET as first treatment. The percentages for 1st, 2nd line, and ≥3 lines applying palbociclib were 17.78%, 16.66%, and 65.56%, respectively. In the univariate analysis, multiple factors influenced the primary overall survival (pOS, from initial diagnosis of BC to death), progression-free survival (PFS), and mOS (from diagnosis of metastasis to death). Meanwhile in the multivariate analysis, pPR (progesterone receptor of primary tumor) and prior ET response were independent risk factors for pOS, PFS, and mOS. Lower pPR and prior ET resistance predicted poorer pOS, PFS, and mOS in HR+/HER2- MBC patients. Number of lines of palbociclib application was an independent risk factor for pOS and mOS and presented higher points both in the pOS and mOS nomograms, meaning that palbociclib had a more significant impact on pOS and mOS compared to other factors. The nomograms showed excellent discrimination and prediction accuracy with area under curves (AUC) of 0.974 for pOS, 0.627 for PFS, and 0.881 for mOS, respectively.

Conclusion: This real-world single-center study of patients with HR+/HER2- MBC showed that early application of palbociclib combined with ET may bring better PFS, but not pOS and mOS. pPR and prior ET response were independent risk factors affecting prognosis.

Keywords: breast cancer, prognosis, palbociclib, endocrine therapy, CDK4/6i

Introduction

Breast cancer (BC) accounts for the highest number of new diagnoses (310,720) and the second highest number of cancer deaths (42,250) in women in the USA in 2024.[1] In China and the whole world, the numbers are 416,371 and 2,261,419 of new diagnoses, and 117,174 and 466,003 of deaths, respectively.[2] The paramount biological subtype of BC is hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-), and 70–80% of breast cancer cells express estrogen receptor-α (ER+).[3] Endocrine therapy (ET) is a pivotal treatment for this type of BC, whether early or advanced.

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Palbociclib is the first oral cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) applied in HR+/HER2- metastasis BC (MBC), combined with aromatase inhibitor (AI) or fulvestrant. In PALOMA-1 and PALOMA-2 clinical trials, palbociclib combined with letrozole significantly improved the median progression-free survival (mPFS) of MBC patients without prior ET or chemotherapy compared with letrozole alone or with placebo.[4,5] In PALOMA-3 clinical trial, palbociclib combined with fulvestrant prolonged the mPFS to 9.2 months compared with fulvestrant plus placebo in MBC patients who relapsed or progressed during prior ET.[6] It is precisely based on these excellent clinical effects that palbociclib has been approved for first-line treatment of HR+/HER2- MBC. Grade 3–4 neutropenia is the most common adverse reaction and the most likely cause of discontinuation of palbociclib.[7] However, just as cancer cells may become resistant to chemotherapy, they may also develop primary or acquired resistance to ET plus palbociclib. Due to palbociclib's recent entry into the Chinese market, its high price, and its non-inclusion in medical insurance, not all patients were able to apply palbociclib as early as possible after the diagnosis of metastasis in the past few years, and many started taking it only after the progression of chemotherapy. As we all know, many clinical trials are accompanied with strict conditions for enrollment. Patients with underlying diseases and other comorbidities are not suitable for enrollment. Moreover, in the real-world setting, many patients are more inclined to choose chemotherapy to improve symptoms as soon as possible due to visceral crisis, tumor rupture, and bleeding, rather than ET as the first choice. It may be too idealistic to directly apply clinical trial results to clinical practice, so we retrospectively analyzed the real-world application of palbociclib in the hope of providing guidance for clinical practice.

Nomograms, generated by regression analysis of clinicopathological characteristics, have been proven to be a reliable predictive tool that can accurately predict the prognosis of many cancers.[8] If a patient has multiple clinicopathological characteristics with high scores in a nomogram, it may indicate poor prognosis. In MBC patients, the frequency of follow-up examinations can be appropriately increased with shortened interval time, thus tumor progression can be detected in a timely manner, and treatment plans can be adjusted immediately. In this retrospective study, we collected clinical and pathological data of patients who received palbociclib treatment during the period January 2019 to December 2020 in a single center in China, and followed up on the treatment outcomes of the patients. We attempted to analyze the treatment outcomes of patients with different application lines and constructed nomograms based on patient data to predict patient prognosis, which may assist clinicians in adjusting treatment strategies in a timely manner.

Materials and Methods

Patients

Women with HR+/HER2- MBC who used palbociclib with ET between January 2019 and December 2020 at Shandong Cancer Hospital and Institute, Shandong First Medical University, and Shandong Academy of Medical Sciences were enrolled in this study. Only palbociclib, the unique one of CDK4/6is, was available in Chinese hospitals in this period. Patients with distant organ metastasis or non-regional lymph node metastasis confirmed by clinical examination, imaging examination, or puncture cases were considered MBC. HR+ was defined as ER+ or progesterone receptor (PR)-positive by immunohistochemistry. HER2- was defined as 0, 1+ by immunohistochemistry, or 2+ and gene not amplified by fluorescence in situ hybridization. Patients met the following criteria: aged ≥18, not suffering from other tumors, never received prior CDK4/6i treatment, tolerable adverse reactions to palbociclib, and received continuous palbociclib until the disease progressed. Patients who did not receive continuous palbociclib or had intolerable adverse reactions were excluded. All patients signed informed consent forms, agreeing that their clinicopathological data could be used for clinical research. This study was approved by the Medical Ethics Committee of Shandong Cancer Hospital and Institute, Shandong First Medical University, and the Shandong Academy of Medical Sciences. The guidelines outlined in the Declaration of Helsinki were followed. Early BC (EBC) was followed up once every 3 months in the first 2 years, every 6 months in the following 3–5 years, and once a year since then. MBC patients were followed up every 2–3 months from the diagnosis of metastasis. Kim et al[9] reported that higher on-treatment derived neutrophil-to-lymphocyte ratio (dNLR) was associated with worse PFS. In this study, we also explored the impact of these hematological indicators on patient PFS of palbociclib and overall survival (OS). The blood test results came from the last test before the start of palbociclib treatment, and were at least 2 weeks away from the end of the previous cycle of chemotherapy. The calculation formula are as follows:

FMR = Fibrinogen / Mean platelet volume
NLR = Neutrophil / Lymphocyte
MLR = Monocyte / Lymphocyte
PLR = Platelet / Lymphocyte
PDF = Platelet × D dimer × Fibrinogen
FD = Fibrinogen × D dimer
dNLR = Neutrophil / (Leukocyte-Neutrophil).

Outcomes

pOS was defined from the primary diagnosis of BC to death or the last time of follow-up. pER, pPR, and pKi67 were defined as ER, PR, and Ki67 of the primary tumor. mOS was defined from the diagnosis of metastasis to death or the last time of follow-up. mER, mPR, and mKi67 were defined as ER, PR, and Ki67 of the metastatic tumor. PFS was defined from oral administration of palbociclib to disease progression during follow-up examinations. Head, chest, and abdominal computed tomography scans or magnetic resonance imaging were performed every 8–12 weeks to evaluate therapeutic efficacy. The last follow-up time was June 2023. In our study, the number of treatment lines was defined as the sequence of rounds of systemic anti-tumor therapy that patients received from the diagnosis of metastasis. Every change in protocol was usually considered as a new line treatment. When a patient chose chemotherapy and the tumor did not progress, but was subsequently maintained with ET, it was considered as second-line treatment.

Statistical Analysis

The modest cutoff points for FMR, NLR, MLR, PLR, PDF, FD, and dNLR were obtained by receiver operating characteristics (ROC) curve analysis. Survival curves were plotted by Kaplan–Meier method and compared with log rank test. Variables with $p < 0.05$ in the univariate analysis were recruited into multivariate Cox proportional hazard regression models with backward likelihood ratio (LR) method to screen for independent risk factors. Nomograms for pOS, PFS, and mOS were constructed with independent risk factors. ROC curves were used to assess the accuracy of the prediction model, with a reasonable range of 0.5 (random) to 1.0 (perfect). The y-axis of the calibration curve represents the actual observed survival rate, and the x-axis represents the survival rate predicted by the established nomograms.

$P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS statistics 19.0 (SPSS company, Chicago, Illinois, USA) and R4.0.3 (The R project for Statistical Computing, www.r-project.org).

Results

Patient Characteristics and Treatment Patterns

Initially, a total of 123 patients with MBC received palbociclib treatment. In 2019 and 2020, palbociclib was not brought into medical insurance in China. Because of palbociclib's expensive price (high cost for continuous application) and intolerable adverse reactions, 90 patients were eventually included in this study. Table 1 shows the baseline characteristics of patients at the initiation of palbociclib. The mean ages for diagnosis of BC and MBC were 46 (range: 27–73) and 51 (range: 27–76), respectively. A total of 14 (15.56%) patients were initially diagnosed with metastasis. All premenopausal patients were treated with gonadotropin-releasing hormone analogue or underwent ovarian resection concurrent with ET. All patients had the HR and HER2 status of at least the primary tumor or metastatic lesion puncture tissues, and 36 (40%) patients were treated according to the HR and HER2 of primary tumor due to inability or refusal to undergo puncture. A total of 62 (68.89%) patients were diagnosed with visceral metastasis, 47 (52.22%) with liver metastasis, 34 (37.78) with lung metastasis, 15 (16.67%) with pleural metastasis, 56 (62.22%) with bone metastasis, 13 (14.44%) with brain metastasis, and 38 (42.22%) with distant lymph node metastasis. A total of 55 (61.11%) patients preferred chemotherapy as first-line treatment, although there may be no visceral crisis. Twenty-four (26.67%) patients were resistant to prior ET, and 15 (16.67%) patients underwent dose reduction because of adverse reactions. The most common partner with ET were SERD (Fulvestrant, 80%) and AI (Letrozole, Anatrazole, and Eximetam, 18.89%). Only 16 (17.78%) patients preferred palbociclib with ET as the first-line therapy.

Table 1 Patient Characteristics

Characteristics		All Patients (n=90)	Characteristics		All Patients (n=90)
Diagnosis age	≤46	44 (48.89%)	mPR	≥10%	27 (30%)
	>46	46 (51.11%)		<10%	27 (30%)
Relapse age	≤51	41 (45.56%)		Loss	36 (40%)
	>51	49 (54.44%)	mKi67	≥25%	36 (40%)
T stage at diagnosis	T1-2	66 (73.33%)		<25%	18 (20%)
	T3-4	14 (15.56%)		Loss	36 (40%)
	Loss	10 (11.11%)	Number of metastatic site	1	22 (24.44%)
N stage at diagnosis	N0	23 (25.55%)		2–3	51 (56.67%)
	N1-3	60 (66.67%)		≥4	17 (18.89%)
	Loss	7 (7.78%)	Visceral metastasis	Yes	62 (68.89%)
M stage at diagnosis	0	76 (84.44%)		No	28 (31.11%)
	1	14 (15.56%)	First-line treatment options	Chemotherapy	55 (61.11%)
pER	≥50%	53 (58.89%)		ET	35 (38.89%)
	<50%	19 (21.11%)	Dosage of palbociclib (mg)	75	4 (4.45%)
	Loss	18 (20%)		100	11 (12.22%)
pPR	≥10%	65 (72.22%)		125	75 (83.33%)
	<10%	20 (22.22%)	Palbociclib primary resistance	Yes	20 (22.22%)
	Loss	5 (5.56%)		No	70 (77.78%)
pKi67	≥20%	36 (40%)	Prior ET response	Sensitive	66 (73.33%)
	<20%	32 (35.56%)		Resistant	24 (26.67%)
	Loss	22 (24.44%)	Concomitant ET	AI	17 (18.89%)
mER	≥50%	40 (44.44%)		SERD	72 (80%)
	<50%	14 (15.56%)		Others	1 (1.11%)
	Loss	36 (40%)	Lines of palbociclib	1	16 (17.78%)
				2	15 (16.66%)
				≥3	59 (65.56%)

Note. Loss indicates missing data.

Abbreviations: pER, estrogen receptor of primary tumor; pPR, progesterone receptor of primary tumor; pKi67, Ki67 of primary tumor; mER, estrogen receptor of metastatic tumor; mPR, progesterone receptor of metastatic tumor; mKi67, Ki67 of metastatic tumor; ET, endocrine therapy; AI, aromatase inhibitor; SERD, selective estrogen receptor down regulator.

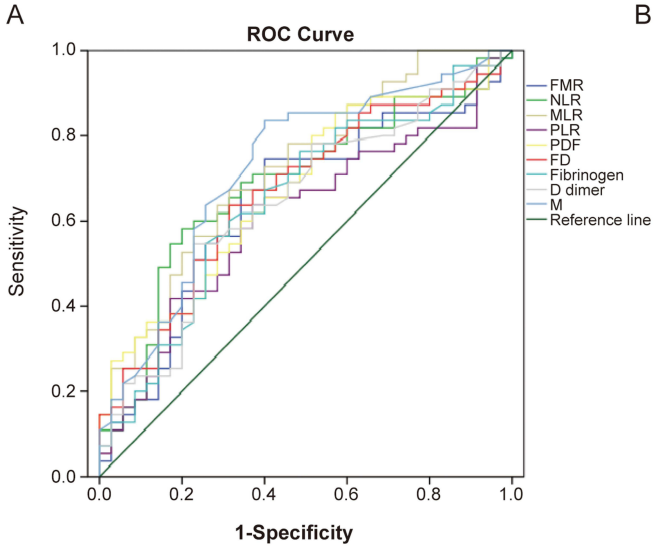
Survival Analysis

By June 2023, 55 patients had died of BC. The modest cutoff points and area under the curve (AUC) are shown in Figure 1. dNLR with AUC 0.570 and *p* value 0.266 are not shown in this figure.

As shown in Table 2, in the univariate analysis, we found that the following characteristics were all significantly associated with pOS, PFS, and mOS: N stage at diagnosis, mPR, mKi67, number of metastatic sites, palbociclib primary resistance, prior ET response, concomitant ET, FD, NLR, MLR, FMR, and M. In addition, pKi67, mER, and fibrinogen were significantly associated with pOS. Visceral metastasis, lines of palbociclib, D dimer, and PDF were significantly associated with PFS. pKi67, mER, lines of palbociclib, and D dimer were significantly associated with mOS. Part of the survival curves are shown in Figure 2.

In the multivariate COX regression analysis, the independent risk factors for pOS were TNM stage ($p = 0.005$, HR [95% CI] = 3.168 [1.418–7.076]), pER ($p = 0.003$, HR [95% CI] = 0.093 [0.019–0.493]), pPR ($p = 0.010$, HR [95% CI] = 0.124 [0.025–0.604]), mPR ($p < 0.001$, HR [95% CI] = 0.079 [0.022–0.284]), prior ET response ($p < 0.001$, HR [95% CI] = 20.585 [4.331–97.830]), lines of palbociclib ($p = 0.002$, HR [95% CI] = 0.036 [0.005–0.285]), and FD ($p = 0.001$, HR [95% CI] = 60.902 [5.160–718.739]) (Table 3). The independent risk factors for PFS were N stage at diagnosis ($p = 0.038$, HR [95% CI] = 1.605 [1.027–2.509]), M stage at diagnosis ($p = 0.026$, HR [95% CI] = 0.128 [0.021–0.780]), pPR ($p = 0.017$, HR [95% CI] = 0.122 [0.021–0.691]), pKi67 ($p = 0.038$, HR [95% CI] = 3.325 [1.067–10.364]), prior ET response ($p = 0.001$, HR [95% CI] = 31.895 [3.976–255.827]), and NLR ($p = 0.002$, HR [95% CI] = 5.956 [1.973–19.978]) (Table 4). The number of lines of palbociclib treatment was not recruited in the regression model and not an independent risk factor. The independent risk factors for mOS

A



B

Variables	AUC	Cutoff point	p-value
FMR	0.643	0.315	0.023
NLR	0.685	1.536	0.003
MLR	0.719	0.267	<0.001
PLR	0.609	/	0.083
PDF	0.675	278.388	0.005
FD	0.669	2.039	0.007
Fibrinogen	0.650	3.480	0.017
D dimer	0.645	0.700	0.021
M	0.724	0.315	<0.001

Figure 1 ROC curves and optimal cut-off points for hematologic variables. (**A**) ROC curves for FMR, NLR, MLR, PLR, PDF, FD, and M; (**B**) AUC and optimal cut-off points for FMR, NLR, MLR, PLR, PDF, FD, and M.

Abbreviations: FMR, fibrinogen-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PDF, platelet × D dimer × fibrinogen; FD, fibrinogen × D dimer; M, monocyte; AUC, area under the curve.

were T stage at diagnosis ($p = 0.038$, HR [95% CI] = 1.925 [1.036–3.575]), pPR ($p = 0.002$, HR [95% CI] = 0.066 [0.012–0.378]), mPR ($p = 0.042$, HR [95% CI] = 0.184 [0.036–0.940]), mKi67 ($p = 0.002$, HR [95% CI] = 24.826 [3.153–195.472]), prior ET response ($p = 0.010$, HR [95% CI] = 25.976 [2.163–312.014]), concomitant ET ($p = 0.032$, HR [95% CI] = 0.179

Table 2 Univariate Analysis of Characteristics for pOS, PFS, and mOS

Characteristics	p value (pOS)	p value (PFS)	p value (mOS)
Diagnosis age	0.134	0.083	0.205
Relapse age	0.091	0.674	0.379
T stage at diagnosis	0.090	0.507	0.355
N stage at diagnosis	**0.001**	**0.010***	**0.046***
M stage at diagnosis	0.116	0.657	0.969
pER	0.722	0.315	0.636
pPR	0.670	0.869	0.706
pKi67	**0.002****	0.055	**0.002****
mER	**0.003****	0.474	**0.037***
mPR	**0.001****	**0.001****	**0.002****
mKi67	**<0.001****	**0.002****	**<0.001****
Number of metastatic sites	**0.038***	**0.003****	**0.023***
Visceral metastasis	0.256	**0.008***	0.180
First-line treatment options	0.242	0.257	0.198
Dosage reduction	0.227	0.748	0.300
Primary palbociclib resistance	**<0.001****	**0.043***	**0.038***
Prior ET response	**<0.001****	**0.006***	**0.001****
Concomitant ET	0.833	0.774	0.900
Lines of palbociclib	0.653	**0.014***	0.363
FD	**0.032***	**0.002****	**0.005***
NLR	**0.001****	**<0.001****	**0.001****
MLR	**0.003****	**<0.001****	**0.002****
FMR	**0.010***	**0.002****	**0.020***

(*Continued*)

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Table 2 (Continued).

Characteristics	p value (pOS)	p value (PFS)	p value (mOS)
M	**0.007***	**<0.001****	**0.005***
Fibrinogen	**0.023***	**0.004****	0.170
D dimer	0.054	**0.025***	**0.021***
PDF	0.089	**0.013***	0.060

Note: Analyzed with Kaplan–Meier method and compared with log rank tests. Bold text indicates all values with $p < 0.05$.

Abbreviations: pOS, from initial diagnosis of breast cancer to death; PFS, progression-free survival; mOS, from diagnosis of metastasis to death; pER, estrogen receptor of primary tumor; pPR, progesterone receptor of primary tumor; pKi67, Ki67 of primary tumor; mER, estrogen receptor of metastatic tumor; mPR, progesterone receptor of metastatic tumor; mKi67, Ki67 of metastatic tumor; ET, endocrine therapy; FD, fibrinogen × D dimers; NLR, neutrophils-to-lymphocytes ratio; MLR, monocytes-to-lymphocytes ratio; FMR, fibrinogen-to-mean platelet volume ratio; M, monocyte; PDF, platelets × D dimers × fibrinogen. *$p < 0.05$, **$p < 0.005$.

[0.037–0.861]), lines of palbociclib ($p < 0.001$, HR [95% CI] = 0.061 [0.014–0.273]), MLR ($p = 0.020$, HR [95% CI] = 0.236 [0.069–0.799]), and M ($p < 0.001$, HR [95% CI] = 31.037 [5.897–163.356]) (Table 5). Prior ET response and pPR were independent risk factors for pOS, PFS, and mOS.

Predictive Models for pOS, PFS, and mOS Nomograms

We tried to construct predictive nomograms to evaluate the prognosis and guide treatments based on these independent risk factors in the survival analysis. The dependent variables were mortality for pOS and mOS, and disease progression rate for PFS. The nomogram scores were based on the weights of the variables in the model, and the lengths were positively associated with their influence on the efficacy prediction. We take integer years, 10 years for pOS, 1 year for PFS, and 5 years for mOS that are close to the average for evaluation. The scores of all variables were added to get the total score perpendicular to the risk axis of 10-year pOS, 1-year PFS, and 5-year mOS rate. Number of lines of palbociclib treatment was determined as the best predictor for mOS, and showed excellent prediction in pOS. TNM stage at diagnosis was the best predictor for pOS and PFS (Figure 3A–C). The higher segments of lines of palbociclib corresponded with higher points both in the pOS and mOS models. All of these models demonstrated ideal sensitivity and specificity. The AUC for the pOS model was 0.974, for the PFS model 0.627, and for the mOS model 0.881 (Figure 4A–C). In Figure 4D–F, we validated the nomograms for pOS, PFS, and mOS, and nomogram for pOS and mOS demonstrated better prediction compared to nomogram for PFS (the red line was closer to the diagonal).

Discussion

Clinical trials are generally based on strict screening conditions and treatment supervision, free of charge, and give no financial burdens to patients. Patients are usually in good physical condition with no concurrent diseases, younger, sensitive to prior ET and clinical trial medication, and with better tolerance. In the real world, patients have a wider age distribution, with various complications and physical conditions. They may have received multiple treatments in the past, and their tolerance for adverse reactions may be lower. So, it may be inappropriate to translate clinical trial results to the clinics in a straightforward manner. These encouraging data from the palbociclib randomized trials need to be confirmed in the real world, especially in patients with fewer choices, who are weaker, or with more pretreated conditions.

Although palbociclib has been in the Chinese hospitals for several years, due to the high price and strict clinical trial standards, not all HR+/HER2- MBC patients were lucky to use palbociclib in the early days.[10,11] In clinical works, we often encounter the following factors that limit the first-line use of CDK4/6i in HR+/HER2- MBC. CDK4/6i is not popular in many primary hospitals. Patients with rapidly progressing or symptomatic tumors often require immediate treatment, limiting the opportunity to initiate CDK4/6 inhibitors as first-line therapy. There may be patients newly diagnosed with stage IV MBC, with metastases limited to bone or lymph nodes, and these patients may be more likely to

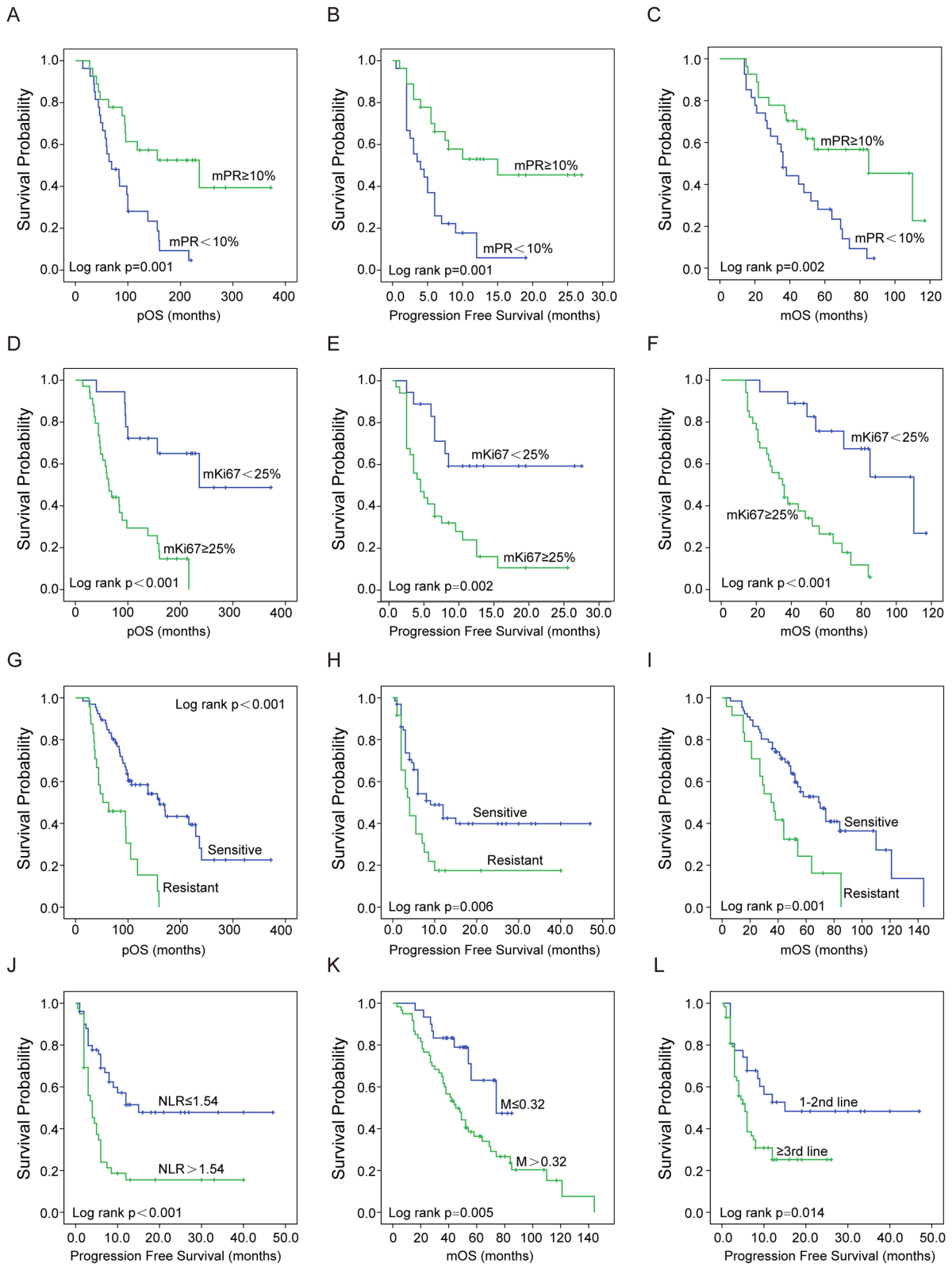

Figure 2 Kaplan–Meier curves for pOS, PFS, and mOS based on different variables. (**A**–**C**) Kaplan–Meier curves for pOS, PFS, and mOS based on mPR; (**D**–**F**) Kaplan–Meier curves for pOS, PFS, and mOS based on mKi67; (**G**–**I**) Kaplan–Meier curves for pOS, PFS, and mOS based on prior ET response; (**J**) Kaplan–Meier curves for PFS based on NLR; (**K**) Kaplan–Meier curves for mOS based on monocyte; (**L**) Kaplan–Meier curves for PFS based on lines of palbociclib.

Abbreviations: pOS, from initial diagnosis of breast cancer to death; PFS, progression-free survival; mOS, from diagnosis of metastasis to death; mPR, progesterone receptor of metastatic tumor; mKi67, Ki67 of metastatic tumor; NLR, neutrophils-to-lymphocytes; M, monocyte.

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Table 3 Multivariate Analysis of Characteristics for pOS

Characteristics	HR (95% CI)	p value
TNM stage	3.168 (1.418–7.076)	0.005
pER	0.093 (0.019–0.439)	0.003
pPR	0.124 (0.025–0.604)	0.010
mER	5.099 (0.861–30.192)	0.073
mPR	0.079 (0.022–0.284)	<0.001
Prior ET response	20.585 (4.331–97.830)	<0.001
Concomitant ET	4.883 (0.825–28.921)	0.081
Lines of palbociclib	0.036 (0.005–0.285)	0.002
FD	60.902 (5.160–718.739)	0.001
D dimer	0.125 (0.013–1.169)	0.068

Note: Analyzed with Cox proportional hazard regression models.
Abbreviations: pOS, from initial diagnosis of breast cancer to death; pER, estrogen receptor of primary tumor; pPR, progesterone receptor of primary tumor; mER, estrogen receptor of metastatic tumor; mPR, progesterone receptor of metastatic tumor; ET, endocrine therapy; FD, fibrinogen × D dimers.

Table 4 Multivariate Analysis of Characteristics for PFS

Characteristics	HR (95% CI)	p value
N stage at diagnosis	1.605 (1.027–2.509)	0.038
M stage at diagnosis	0.128 (0.021–0.780)	0.026
pPR	0.122 (0.021–0.691)	0.017
pKi67	3.325 (1.067–10.364)	0.038
mER	4.252 (0.873–20.717)	0.073
Visceral metastasis	0.259 (0.059–1.131)	0.072
Palbociclib primary resistance	7.942 (0.816–77.339)	0.074
Prior ET response	31.895 (3.976–255.827)	0.001
NLR	5.956 (1.973–17.978)	0.002

Note: Analyzed with Cox proportional hazard regression models.
Abbreviations: PFS, progression-free survival; pPR, progesterone receptor of primary tumor; pKi67, Ki67 of primary tumor; mER, estrogen receptor of metastatic tumor; ET, endocrine therapy; NLR, neutrophils-to-lymphocytes tatio.

have a better quality of life after surgery, and prefer chemotherapy to shrink the tumor before surgery. Therefore, our research on the use of CDK4/6i in the real world was particularly necessary.

Chen et al[12] reported on a Chinese retrospective study in 696 HR+/HER2- MBC patients, in which 77.01% of patients received chemotherapy as first-line treatment, and 20.69% of patients received ET as first-line treatment. Those with ET maintenance showed a longer PFS than did those with chemotherapy maintenance, but the difference was not significant. While in our study, 38.89% of patients received ET as the first-line therapy, and the first-line treatment options resulted in no significant difference in PFS and OS. We came to unanimous results with a higher proportion of first-line ET. Lee et al[13] reported that patients who were not exposed to cytotoxic chemotherapy before palbociclib showed better PFS compared to patients pretreated with chemotherapy. We found that number of lines of palbociclib was an independent risk factor for pOS and mOS, although not for PFS. The mean PFS for 1–2nd line and ≥3 line treatment were 15.4 and 6.6 months, respectively. In Monarch 1 clinical trial, following a median of 1 (1–3) line of chemotherapy and 2 (1–6) lines of ET, another CDK4/6i, abemaciclib, generated a median PFS of 6.0 months and OS of 17.7 months, which was similar to our results.[14] We had fewer first-line patients mainly due to the fact that reimbursed fulvestrant was preferred by more patients, and the high proportion of prior ET resistance led to worse mean PFS. In our study, patients with 1–2nd line treatment of palbociclib application presented better PFS than did those with ≥3 lines, but their OS showed no

Table 5 Multivariate Analysis of Characteristics for mOS

Characteristics	HR (95% CI)	p value
T stage at diagnosis	1.925 (1.036–3.575)	0.038
pPR	0.066 (0.012–0.378)	0.002
mPR	0.184 (0.036–0.940)	0.042
mKi67	24.826 (3.153–195.472)	0.002
Palbociclib primary resistance	8.835 (0.886–88.069)	0.063
Prior ET response	25.976 (2.163–312.014)	0.010
Concomitant ET	0.179 (0.037–0.861)	0.032
Lines of palbociclib	0.061 (0.014–0.273)	<0.001
MLR	0.236 (0.069–0.799)	0.020
M	31.037 (5.897–163.356)	<0.001

Note: Analyzed with Cox proportional hazard regression models.
Abbreviations: mOS, from diagnosis of metastasis to death; pPR, progesterone receptor of primary tumor; mPR, progesterone receptor of metastatic tumor; mKi67, Ki67 of metastatic tumor; ET, endocrine therapy; MLR, monocytes-to-lymphocytes ratio; M, monocytes.

significant differences. This was slightly different from the results of the PALOMA clinical trials, which compared the application of palbociclib and placebo combined with ET, while all of our patients were treated with palbociclib. In the SONIA study, patients in strategy A group received first-line treatment with a AIs combined with CDK4/6i, followed by fulvestrant, and strategy B received first-line treatment with AIs followed by fulvestrant combined with CDK4/6i.[15] Patients in strategy A had statistically significant and clinically meaningful superior PFS2 (from randomization to second objective progression), but not significant OS. Our research findings were more similar to those of the SONIA study. This may suggest that if patients use palbociclib, earlier application may produce better PFS than later application, which was also consistent with a previously published study.[16] There is still controversy over whether the benefits of PFS will translate into benefits for OS. Our conclusion may be due to the small sample size.

Several researches have confirmed that ER, PR, and Ki67 in primary tumor and metastatic lesion were related to prognosis and clinical outcomes.[17,18] In our study, according to the results of our multivariate analysis, the ER, PR, and Ki67 status of both primary tumors and metastatic lesions were closely related to pOS, mOS, or PFS of palbociclib in patients with HR+/HER2- MBC. We attempted to compare whether changes of ER, PR, and Ki67 in primary tumors and metastases were associated with the prognosis of MBC patients. Unfortunately, we found no positive dependence between the rise or decline of ER, PR, and Ki67 with the prognosis of MBC patients, regardless of the magnitude of the changes. This may be related to the small sample, as some patients failed or refused to puncture, without a comparison between the primary tumor and metastatic lesions. There were some inconsistencies with conventional cognition in the nomograms, such as in the pOS nomogram, higher pER and pPR scored higher than lower. Perhaps it was precisely because of the small number of patients and the fact that chemotherapy was the main treatment at that time, patients used less palbociclib and the number of lines was used relatively later. Patients with a higher HR-positive percentage may be less sensitive to chemotherapy. We think that metastatic tumors may have a more complex tumor microenvironment than the primary lesion, and more characteristics related to primary tumors in multivariate analysis led to lower AUC for PFS. Perhaps we need to include some samples or blood test indicators from patients after metastasis to better predict prognosis, such as PIK3CA, ctDNA.

A large number of articles have reported that hematologic blood markers may be closely related to the prognosis of BC patients. Moon et al[19] reported that a higher NLR at 5 years after initial diagnosis was associated with late recurrence in years 5–10 during follow-up. Inoue et al[20] reported that oligometastatic BC patients with lower NLR presented better OS. Zhang et al[21] reported that neoadjuvant chemotherapy BC patients with lower LMR (lymphocyte-to-monocyte ratio) presented shorter DFS and poor survival. Wang et al[22] found that lower fibrinogen levels predicted higher pathological complete response rate as well as a longer recurrence-free survival. In our research, we also found that FD, NLR, and MLR were significantly associated with pOS, PFS, and mOS, respectively. There were no scientifically accurate explanations why

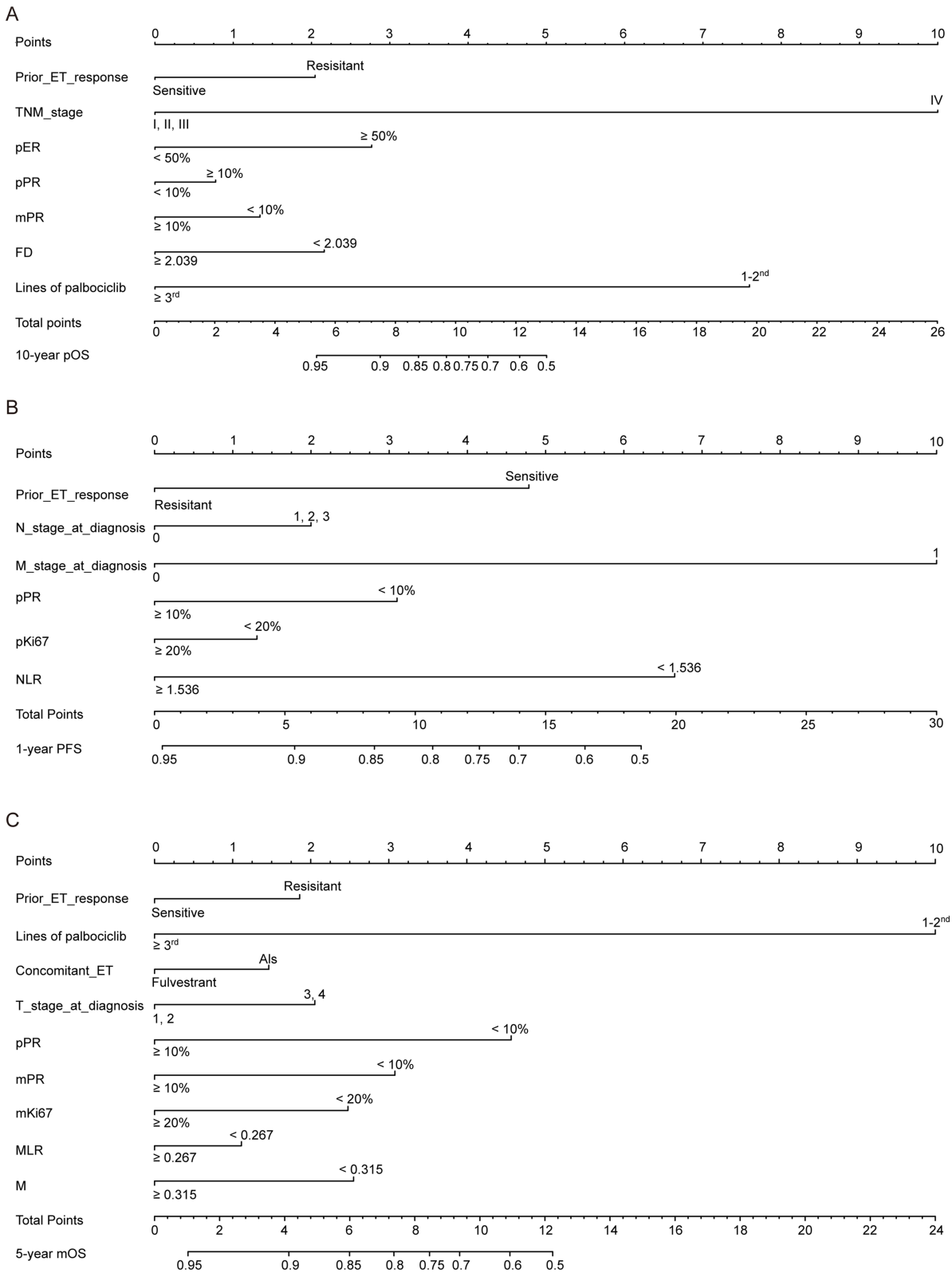

Figure 3 Nomogram models predict the probabilities of pOS, PFS, and mOS. (**A**) nomogram model for pOS; (**B**) nomogram model for PFS; (**C**) nomogram model for mOS. **Abbreviations**: pOS, from initial diagnosis of breast cancer to death; PFS, progression-free survival; mOS, from diagnosis of metastasis to death; ET, endocrine therapy; pER, estrogen receptor of primary tumor; pPR, progesterone receptor of primary tumor; mPR, progesterone receptor of metastatic tumor; FD, fibrinogen × D dimer; pKi67, Ki67 of primary tumor; NLR, neutrophil-to-lymphocyte ratio; mKi67, Ki67 of metastatic tumor; MLR, monocytes-to-lymphocytes ratio; M, monocyte.

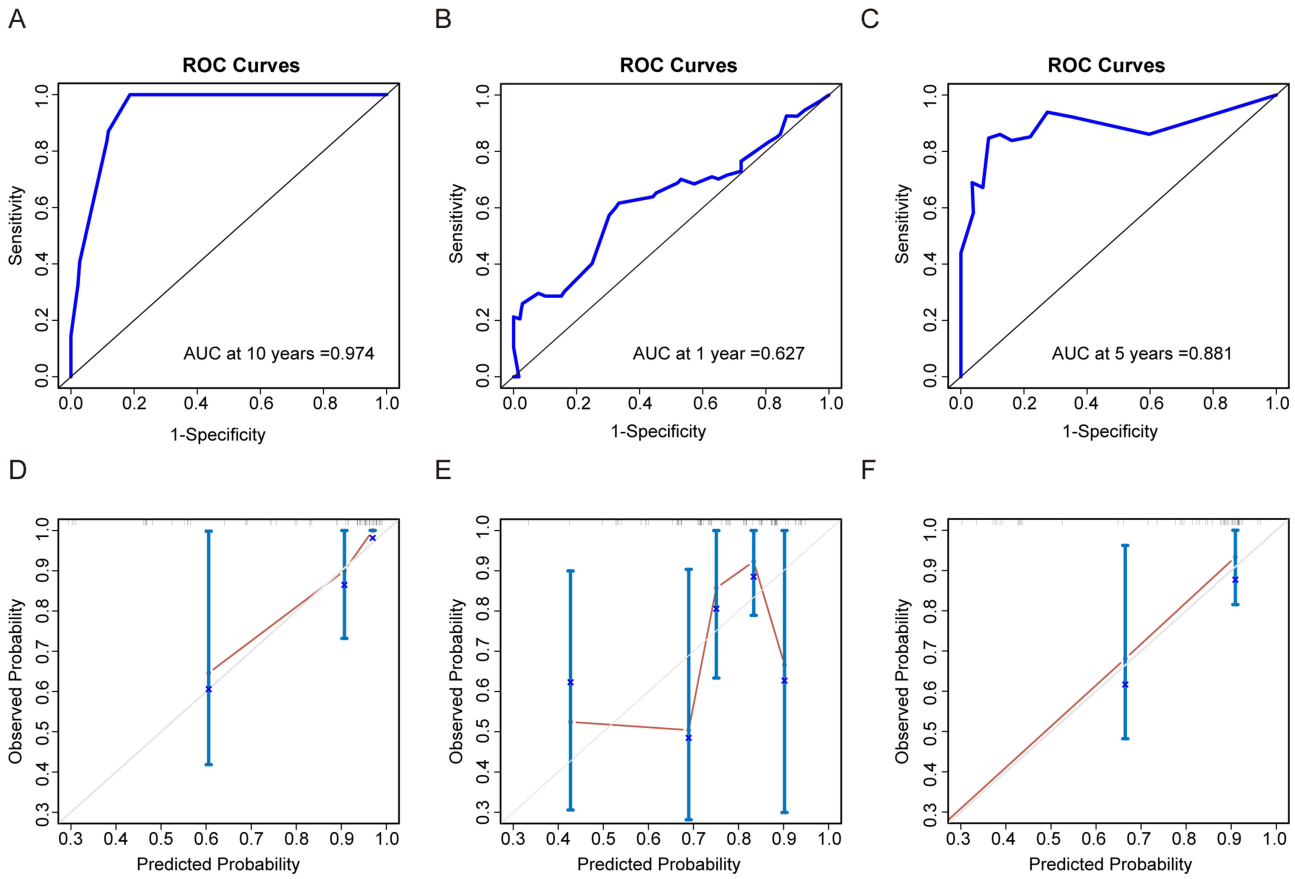

Figure 4 ROC curves of the abilities of the nomograms, (**A**) for pOS at 10 years, (**B**) for PFS at 1 year, and (**C**) for mOS at 5 years, and the calibration curves for predicting patient survival (**D**) for pOS at 10 years, (**E**) for PFS at 1 year, and (**F**) for mOS at 5 years. The diagonal line represents ideal agreement between predicted and observed probabilities.

survival was strongly correlated with these indicators, but cellular studies may give us some insight. Cancer-associated adipocytes may produce excess granulocyte colony-stimulating factor (G-CSF) and secrete it into the tumor microenvironment, which in turn promotes EMT in BC cells by activating the stat3 signaling pathway and elevating the peripheral neutrophils by itself.[23] Granulocyte macrophage CSF (GM-CSF) produced by BC cells could promote tumor progression through the modulation of host immune cells, while disruption of GM-CSF enhanced the efficacy of immune therapy.[24] The elevated plasma fibrinogen induced the expression of intercellular adhesion molecule 1 (ICAM1), which promoted tumor cell migration, cell adhesion, angiogenesis, and increased vascular endothelial permeability.[25] The exact reason why these indicators reflect the PFS of palbociclib was unknown. We speculate that changes in the expression of some intrinsic genes may promote the proliferation of tumor cells and release the inhibitory effect of palbociclib on the cell cycle, which may also be related to the changes in the immune microenvironment as well as immune evasion.

There are several limitations in this study. Firstly, this was a single-center study with a small number of patients, which may lead to selection bias. Secondly, the choice of patients' treatment regimens was influenced by affordability, and patients who could afford palbociclib may have more options for subsequent treatment, which may contribute to prolonging OS. Finally, patients may not be willing to try various treatment options after developing resistance to palbociclib and multiple chemotherapy regimens. Other important information was worthy of being recorded and analyzed, such as the patient's willingness to receive treatment, complications, and management.

Conclusions

Patients who received palbociclib earlier achieved longer PFS compared to those who received it later, but there was no difference in OS, meaning that the benefits of PFS may not translate into benefits of OS. pPR and prior ET response were

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independent risk factors for pOS, PFS with palbociclib, and mOS in patients with HR+/HER2- MBC. Our nomograms will be helpful in predicting the efficacy of palbociclib, identifying and screening of patients who may be resistant to palbociclib, and guiding treatment choices. But they need to be validated with larger samples of clinical data.

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