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Exploring Prognostic Factors in Breast Cancer Survival: An Analysis of Metastatic Status, Disease Stage Dynamics, and Menopausal Influences on Breast Cancer Survival in a Cohort Study

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Research Article

Keywords:

Posted Date: September 15th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10671404/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Breast cancer is the most common cancer among women worldwide, with an estimated 2.3 million new cases diagnosed and 670,000 deaths in 2022. In 2022, there were 36,710 invasive breast cancer cases among women in the U.S. aged between 40 to 49 years. The overall 5-year survival rate after diagnosis for people with stage 4 breast cancer is 31%. A woman who experiences menopause after age 55 has an increased risk of breast cancer.

Objectives

This study aims to address metastatic patterns, disease stage dynamics, and menopausal influences on Breast Cancer Survival in a large cohort of breast cancer patients.

Methods

This study used a secondary dataset of 1,746 breast cancer cases from a 2018 cohort data of Memorial Sloan Kettering (MSK) Cancer Center, New York. Disease stage, metastatic status and menopause status during diagnosis were the exposure, and overall survival is the outcome where death was the event in this study model. Kaplan-Meier survival analysis and log-rank tests were conducted to estimate and compare the overall survival rate among the groups. A Cox proportional hazards (PH) regression model was used to show the association between prognostic factors and survival outcomes. The model was adjusted for potential confounders such as age and tumor characteristics. Differences in hazard ratios (HR) across variables and subgroups were also investigated.

Results

Majority of the participants were from the 50–59 years of age group (29%). The five-year survival rate is about 80% and the mean and median survival time of this study is about 16 and 17 years respectively. Log-rank test findings showed that Cancer stages (p-value < 0.001) and Menopause (P-value < 0.001) were statistically significant with survival time. Once adjusting for co-variates, the Cox proportional hazard test found a significant association between cancer stages (p-value < 0.001), and metastatic status (p-value < 0.01) with the overall survival. Among the various stages of cancer, metastatic characteristics, and menopausal status, stage IV has the greatest HR (4.22), post-menopause status has 1.49 times higher HR than pre-menopause status and metastatic status has 1.48 times higher HR than non-metastatic status.

Conclusion

Findings suggest that the survival rate among breast cancer patients in this study is significantly influenced by the cancer stage, metastatic patterns, and menopausal status. Hence, it highlights the importance of considering these factors when evaluating prognosis and directing the choice of therapy in breast cancer.

Background

Breast cancer poses a significant health challenge worldwide, exhibiting notable differences in occurrence, fatality, and recovery rates among different populations. As per the World Health Organization (WHO), it stands as the most prevalent cancer among women globally, with approximately 2.3 million new cases reported in 2022 alone (1). More women in the United States (US) are diagnosed with breast cancer than any other type of cancer, besides skin cancer (2). The disease accounts for 1 in 3 new female cancers annually (3). In the United States, there are over 4 million breast cancer survivors, encompassing individuals currently undergoing treatment and those who have finished treatment (2). The most significant risk factor for breast cancer is female sex.

In 2022, there were 36,710 cases of invasive breast cancer diagnosed among women aged 40 to 49 in the United States (4). Approximately about 168,000 women in the US are living with metastatic breast cancer (5) and roughly one-third of women with metastatic breast cancer (MBC) have lived with the disease for 5 or more years (5). Metastatic status indicates the spread of cancer cells from the primary tumor to other areas of the body, a process known as metastasis (6). Though most people with early-stage breast cancer do not go on to acquire MBC, over 85% of patients with MBC have been diagnosed with breast cancer in the early stages (7). About 30% of women who are first diagnosed with early-stage breast cancer will go on to develop metastatic breast cancer (7). In 2020 we found around 31% probability of survival for women diagnosed with distant breast cancer in the US, compared to 99% for those with localized breast cancer at the time of diagnosis (8). Based on data from the National Cancer Center's (NCL) surveillance, the overall 5-year survival rate for individuals diagnosed with stage 4 breast cancer was 31% (9). Although menopause itself may not directly cause cancer, the risk of developing cancer rises with the advancing age in women. Extended estrogen exposure raises the risk of breast cancer in women (10).

The prognosis of breast cancer is influenced by various factors, including metastatic spread, disease stage at diagnosis, and menopausal status. MBC characterized by the dissemination of cancer cells to distant sites such as the bones, lungs, liver, or brain, represents an advanced stage of disease associated with poorer survival outcomes (11). Furthermore, the disease stage serves as a critical prognostic factor, with early detection and diagnosis associated with better treatment response and long-term survival (7). However, despite advances in screening and early detection efforts, a considerable proportion of breast cancers are diagnosed at later stages, posing challenges for effective management and treatment (12). Menopausal status also plays a significant role in breast cancer prognosis and treatment response (10). Postmenopausal women are more likely to develop hormone

receptor-positive breast cancers (13), which may exhibit different biological characteristics and treatment sensitivities compared to premenopausal tumors.

Breast cancer remains a significant public health concern, with diverse clinical outcomes influenced by a myriad of prognostic factors. Despite advances in treatment modalities, the survival rates for breast cancer patients vary considerably, highlighting the need for a comprehensive understanding of the factors impacting disease trajectory and patient outcomes. This study aims to address metastatic patterns, disease stage dynamics, and menopausal influences in a large cohort of breast cancer patients. By exploring the complex interplay between these factors and patient survival outcomes, this research has the following objectives:

Objectives:

1. To examine the association between cancer stage - including metastatic status - and overall survival (OS) among breast cancer patients in a large cohort study.
2. To assess the influence of menopausal status on disease biology, treatment efficacy, and long-term survival in breast cancer patients.

Methodology

Study Design

This study used retrospective data from the cBioPortal for Cancer Genomics, a publicly accessible database containing genomic and clinical data from various cancer studies. We accessed data on March 26, 2024. The dataset includes breast cancer cases from a 2018 cohort at Memorial Sloan Kettering (MSK) Cancer Center, New York. While the initial study began in 2013 (14), the exact cohort enrollment date is not specified in the dataset (15, 16). Data was locked in 2018, and all information was de-identified to ensure patient privacy.

Study population and sample Size

The original dataset has1,918 samples. After cleaning and removing missing data, we had final dataset of 1756 breast cancer cases. After excluding male patients (n = 10), we analyzed data of 1,746 patients.

Data Variables:

Independent Variables: *It includes* metastatic patterns (presence/absence of metastases), disease stage at diagnosis (IA | IB | IIA | IIB | IIIA | IIIB | IIIC | IV), menopausal Status (Peri, Pre and postmenopausal). This study used a TNM cancer staging system. The TNM staging system, developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), is used to describe the extent of cancer in a patient's body (17, 18). Stages are categorized as (a) Early stage: Stage I, and Stage II (localized and regional disease without distant metastasis), (b) Advanced stage (non-metastatic): Stage III (locally advanced disease, no distant metastasis) and (c) Metastatic

stage: Stage IV or any case with documented distant metastasis at diagnosis. For analysis, we further grouped patients into non-metastatic (No) and metastatic (Yes) categories, as metastatic status was the primary variable of interest.

Dependent variables

It includes overall survival (OS) status (censored = 0, event/death = 1), and overall survival in months since initial diagnosis. The overall survival, defined as the time from cancer diagnosis to death from any cause. Patients who were alive at the end of the study period or lost to follow-up were censored at their last known follow-up date. The follow-up period was measured from the date of diagnosis to either the event (death) or the censoring time (last follow-up).

Covariates

It includes demographic variables (age in years, gender (male/female)), tumor characteristics (hormone receptor (HR) status (negative/positive), human epidermal growth factor receptor 2 (HER2) status(negative/positive), overall receptor status (HR^-HER2^- / HR^+HER2^- / HR^-HER2^+ / HR^+HER2^+).

Data Analysis

We used SAS 9.4 software for preanalytical processing and data analysis. Categorical variables were summarized using frequencies and percentages, while continuous variables were summarized using means and standard deviations (SD). Survival distributions and overall survival rate were examined using Kaplan-Meier (KM) survival curves. Survival time was estimated using available follow-up data, with censoring applied where necessary. Median and mean survival times were calculated based on survival analysis methods. We then compared the survival curves using log-rank tests to assess differences in survival based on metastatic patterns, disease stage, and menopausal status. A Cox proportional hazards (PH) regression model was run to examine the association between prognostic factors and survival outcomes. The model was adjusted for potential confounders such as age and overall receptor status. We assessed multicollinearity among covariates using the variance inflation factor (VIF). A cutoff value of 3 was used to indicate potential multicollinearity(20). All variables in the model had VIF values below this threshold, suggesting no serious multicollinearity.

Study model

The final Model of this study is Eq. 1.

$$T|X = (\beta 1 * X1 + \beta 2 * X2 + \beta 3 * X3 + \beta 4 * X4 + \beta 5 * X5) \ldots\ldots (1)$$

Where, X: Overall survival status (Censored = 0, Event/death = 1), T: Overall survival in years since the initial diagnosis, X1: Metastatic Patterns (reference = No), X2: Disease Stage (reference = IA), X3: Menopausal Status (reference = pre), X4: Age, X5: Overall receptor status (reference: HR^-HER2^-).

Ethical Consideration:

This study does not require the Institutional Review Board (IRB) approval because it involves a secondary analysis of publicly available data from the cBioPortal for Cancer Genomics(15). According to the cBioPortal Open Science and Data Access policies, datasets available through the cBioPortal DataHub are publicly accessible and provided for research use in a standardized format to support reproducible research and data reuse. Because the data are de-identified and contain no personally identifiable information, this study does not constitute human subjects research and therefore did not require IRB review or informed consent. Additional information regarding public data access and reuse is available from cBioPortal (https://about.cbioportal.org/) and cBioPortal DataHub (https://docs.cbioportal.org/user-guide/faq/#where-can-i-download-data).

Results

Table 1 describes the general characteristics of the study participants included in this study. The mean age of the participants was 52 years with a standard deviation of (± 12.07 years). The majority of the participants were from 50–59 years of age group (29%) followed by 40–49 years (28%) and 60 years and above (27%). Most of the participants were at the IA stage of breast cancer (28%) followed by at the IV stage (20%). Around 46% of the participants were in their pre-menopause status during the diagnosis of the disease. The tumor status of 72% of the participants was metastatic. Overall, 87% and 13% of the participants were HR and HER2 positive respectively. Among the total cases, the most common subtype was $HR^{+}HER2^{-}$ (78%), followed by $HR^{-}HER2^{-}$ (10%), $HR^{+}HER2^{+}$ (9%), and $HR^{-}HER2^{+}$ (3%).

Table 1
General characteristics of the study participants (n = 1,746)

Characteristic	**n (%) or mean ± SD**
Age (in years)	52.25 ± 12.07
18–29	31 (1.8%)
30–39	240 (13.7%)
40–49	484 (27.7%)
50–59	514 (29.4%)
60 and above	477 (27.3%)
Cancer Stage	
IA	489 (28.2%)
IB	28 (1.6%)
IIA	318 (18.3%)
IIB	189 (10.9%)
IIIA	189 (10.9%)
IIIB	46 (2.7%)
IIIC	120 (6.9%)
IV	354 (20.4%)
Menopause Status	
Peri	100 (5.8%)
Post	834 (48.0%)
Pre	804 (46.3%)
Metastatic	1,254 (71.8%)
HR status	
Negative	226 (12.9%)
Positive	1,520 (87.1%)
HER2 status	
Negative	1,525 (87.3%)
Positive	221 (12.7%)
Overall Receptor *(HR & HER2 status)*	

Characteristic	n (%) or mean ± SD
HR^-HER2^-	168 (9.6%)
HR^-HER2^+	58 (3.3%)
HR^+HER2^-	1,357 (77.7%)
HR^+HER2^+	163 (9.3%)

Figure 1 shows the overall survival probability and survival time of the study participants. Of the total study population, 378 patients (21.7%) experienced the event (death), while 1,368 patients (78.3%) were censored. The mean survival time is approximately 15.7 years. Similarly, the median survival is 16.5 years. These estimates do not imply a 16- or 17-year follow-up from 2018 but rather reflect projected survival probabilities based on retrospective data. The five-year survival rate is 80%. The total number of events (death from breast cancer) was 382 (22%) in this study.

<< Fig. 1: Distribution of survival times>>

We then conducted the log rank test at alpha level 0.05 to compare the two survival curves for Disease stages, metastatic status and menopause status among the participants. From the result presented in Table 2, we can see that the Cancer stages (p-value < 0.001) and Menopause (p-value < 0.001) were statistically significant, indicating that there is significant difference in the survival time between patients in different groups among those variables. Joint log-rank test statistic was 82.56 (p-value < 0.001)

Table 2. Log-Rank Test Results

Variables	Chi-Square	p-value
Cancer Stages	28.09	<0.001*
Metastatic	0.30	0.580
Menopause	15.24	<0.001*

** p-value less than alpha 0.05.*

Figures 2, 3, and 4 show the KM plots of all the independent variables. From the plots, among disease stages, IA and IB had better survival rates than other stages. Similarly, from the metastatic status plot, non-metastatic had better survival rates than metastatic. And from the menopause status plot, we can see that pre- and post-menopauses have similar survival rates.

<< Fig. 2: KM plots for breast cancer stages >>

<< Fig. 3: KM plots for Metastatic patterns in participants >>

<< Fig. 4: KM plots for Menopause status in participants >>

Before conducting the Cox-proportional hazard model, Fig. 5 shows the PH assumptions of metastatic status, disease stage dynamics, and menopausal status within the cohort using a log of negative log (ln-ln) survival plots. From this figure, we can see that all the plots are somehow parallel to each other in each group. This suggests there is no violation of PH assumptions that the hazard ratio (HR) comparing the different groups among all variables remains constant over time.

<< Fig. 5: PH assumptions of metastatic status, disease stage dynamics, and menopausal status using ln-ln survival plots >>

Since there were no-violation assumptions found among all the variables, we ran a simple Cox proportional hazard model (Eq. 1) at alpha level 0.05 with the interaction variables to test whether the survival is different among different groups of all the independent variables after adjusting for age, age groups, number of treatments received, HR status and HER2 status.

Results of the joint Cox PH model, after adjusting for age, and overall receptor status, this study found that cancer stages (p-value < 0.0001), and metastatic status (p-value < 0.004) were significantly associated whereas menopause status (p-value 0.8) was not significant with the survival probability among the different groups. Detailed maximum likelihood estimates of variables and subgroups are presented in Table 3. We removed the interaction terms as they were insignificant.

Among the various stages, IV has the highest HR (4.22) followed by stage IIIB (HR = 2.9). Post-menopause status has 1.49 times higher HR than pre-menopause status. Similarly, the HR of metastatic status is 1.48 times higher than non-metastatic. There is no change in HR with increasing age. The HR+HER2 + group has 0.11 times lower risk compared to the reference category ($HR^{-}HER2^{-}$). The triple-negative breast cancer ($HR^{-}HER2^{-}$) is associated with the poorest survival outcomes.

Table 3
Results of the Cox-proportional Hazard model

Parameter	Categories	HR (95%CI)	p-value
Stage at Diagnosis	*IB*	**1.06(0.38,2.93)**	0.911
(ref: IA)	*IIA*	**0.97(0.67,1.41)**	0.881
	IIB	**1.69(1.14,2.51)**	0.008
	IIIA	**1.58(1.08,2.33)**	0.019
	IIIB	**2.9(1.7,4.96)**	< 0.001
	IIIC	**2.62(1.79,3.84)**	< 0.001
	IV	**4.22(2.97,6)**	< 0.001
Menopausal Status at Diagnosis	*Peri*	**0.96(0.58,1.6)**	0.889
(ref: Pre)	*Post*	**1.49(1.06,2.1)**	0.023
Metastatic *(ref = No)*	*Yes*	**1.48(0.54,4.11)**	0.448
Age (in years)	*Age*	**1(0.98,1.01)**	0.849
Overall receptor status *(ref: HR^-HER2^-)*	*HR^-HER2^+*	**0.24(0.14,0.41)**	< 0.001
	HR^+HER2^-	**0.16(0.12,0.22)**	< 0.001
	HR^+HER2^+	**0.11(0.07,0.17)**	< 0.001

Ref: reference; HR : Hazard ratio; CI: confidence interval

Note

If the HR is greater than 1, it indicates that the risk of experiencing the event is higher in one group compared to the reference group. If the HR is less than 1, it indicates that the risk of experiencing the event is lower in one group compared to the reference group. If HR is exactly 1, it indicates that there is no difference in risk between the two groups.

Discussion

In this study, the mean age of the participants was 52 (± 12.07) years, and 72% of the participants were metastatic. The mean and median survival time of this study is approximately 15.6 and 16.5 years. Total death from breast cancer accounted for 22% in this study. The KM-plot showed that non-metastatic had better survival rates. The lowest survival rates were seen in patients with advanced stage, metastatic status, and post-menopause status. After adjusting for co-variates, this study found that cancer stages (p-value < 0.001) and metastatic status (p-value < 0.01) were both significantly associated with the survival probability among the different groups. Among the various cancer stages, metastatic and

menopause status, stage IV has the highest HR (4.22), post-menopause status has 1.49 times higher HR than pre-menopause status and metastatic status has 1.48 times higher HR than non-metastatic.

According to the American Cancer Society and data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program, the overall 5-year survival rate for individuals diagnosed with stage 4 breast cancer is 31% (22, 23). Our results align with this finding having high hazard risk of disease in high stages. Previous research by Hanish et al. (2021) and Shih et al. (2022) highlighting the significance of cancer stage in determining survival outcomes (24). A retrospective cohort study conducted in 2021 in the east coast region of West Malaysia found the lowest net survival (NS) was 19.6% at 5 years following diagnosis in patients with stage IV breast cancer. Patients with stage IV breast cancer after diagnosis had a 34.78-fold higher mortality risk, found by a nationwide cohort study conducted in Taiwan (25). Consistent with these studies, we found a statistically significant association between cancer stages and survival probability. Specifically, patients diagnosed at later stages, such as stages IV and IIIB, demonstrated higher hazard ratios (HR), indicating poorer survival compared to those at earlier stages. Another study conducted in Mexico and published in 2024 also found notably higher OS rates for stages I-III, which were 90% or higher (26). These findings emphasize the critical need for early detection and intervention strategies to improve outcomes for patients with advanced disease stages.

Furthermore, this study sheds light on the impact of menopausal status on breast cancer survival, corroborating the findings of other literatures (27, 28). In the univariate model in the study by Vu Hang et al. (2019), premenopausal patients seemed to have better survival (HR = 0.61, 95% CI: 0.38–0.95, P = .03) (27). Another study showed that the adjusted hazard ratio of metastatic recurrence for postmenopausal compared to premenopausal women was 1.38 (28). Post-menopausal women exhibited a significantly higher HR compared to pre-menopausal women which aligned with our findings too, suggesting that hormonal changes accompanying menopause may influence disease progression and response to therapy. Whereas another comparative study of pre- and post-menopausal breast cancer (10) did not align with this finding. This study stated that postmenopausal women are at a lower risk of developing breast cancer compared to premenopausal women of the same age which also align with our study findings. There is a limited number of studies specifically focused on menopausal breast cancer in the United States.

Our study emphasizes the pivotal role of metastatic status as a prognostic factor in breast cancer survival, consistent with another literature that showed that patients diagnosed with metastatic positive breast cancer cases in Sweden between 2009 and 2016 had a median OS of 29.8 months from diagnosis. The study also showed that the 5-year survival for this cohort was 30% (30). According to the American Cancer Society, the 5-year relative survival rate for metastatic breast cancer is only 31%. That means that at the end of 5 years, 31% of women diagnosed with metastatic breast cancer (MBC) are still alive (7). Patients with metastatic status exhibited a substantially higher HR compared to those with non-metastatic status. Although MBC remains an incurable disease, the changing treatment landscape has led to slow but consistent improved outcomes for many patients (31).

Our study has several strengths compared to previous research. It includes a large sample of 1,746 participants, enhancing statistical power and generalizability. The analysis explores multiple prognostic factors, such as metastatic status, disease stage dynamics, and menopausal influences, providing a comprehensive understanding of their impact on breast cancer survival. Additionally, we examined key variables like hormone receptor (HR) and HER2 status. The study employs rigorous statistical methods, including log-rank tests and Cox proportional hazards regression, adjusting for confounders to ensure the validity of our findings. However, there are limitations. We assessed the number of treatments received rather than specific treatment types, which may not fully capture their effectiveness. Variability in treatment regimens and patient characteristics could influence survival outcomes, but our dataset lacked detailed treatment information. Additionally, as a retrospective cohort study, our findings may be subject to selection and information bias. Despite adjusting for covariates, unmeasured confounders like race, ethnicity, and income may have influenced the results. The study is based on data from a single hospital, limiting generalizability. Lastly, the lack of comprehensive research on metastatic and menopausal breast cancer in the U.S. makes direct comparisons with existing literature challenging. Future studies should incorporate detailed treatment regimens and broader populations for deeper insights.

Conclusions

This study comprehensively explored the prognostic factors influencing breast cancer survival, focusing on metastatic patterns, disease stage dynamics, and menopausal influences within a large cohort study. Findings suggest that cancer stage, metastatic patterns, and menopausal status have a significant effect on the survival rate among breast cancer patients in this study. Hence, it highlights the importance of considering these factors when assessing prognosis and guiding treatment decisions in breast cancer.

Moving forward, it is recommended that future research efforts should focus on validating these findings in diverse populations and exploring additional factors that may influence survival outcomes. By advancing our understanding of the complex interplay between prognostic factors in breast cancer, we can continue to refine treatment strategies and ultimately improve the well-being of patients affected by this disease.

Declarations

Funding:

This study did not use any funding and was solely conducted in the researcher’s efforts.

Conflict of Interest:

There is no conflict of interest to declare in this paper.

Ethical Approval:

This study does not require the Institutional Review Board (IRB) approval because it involves a secondary analysis of publicly available data from the cBioPortal for Cancer Genomics(15). The data available on cBioPortal is de-identified and freely accessible to the public and therefore does not constitute human subject research.

Consent to participate:

Not applicable as the dataset is de-identified and freely accessible to the public and therefore does not constitute human subject research.

Written Consent for publication:

All authors agreed to submit the current form of manuscript.

Data and Code Availability:

The publicly available Breast Cancer (MSK 2018) dataset was extracted from cBioPortal for the cancer genomics website (15,16). The data used in this study can be found in supplement 1 as “Final dataset used for this study” and analysis code will be made available with proper request.

Author Contributions:

N.J. conceived, designed the study, performed the statistical analyses and wrote the first draft of the manuscript. B.J. contributed to study design, prepare the tables and figures, and critical revision of the manuscript. M.A.O. and S.R. assisted with methodology development, statistical interpretation, and manuscript review. S.K. and G.T. contributed to the literature review, clinical interpretation, interpretation of findings, and manuscript editing. B.A. supervised the study, provided methodological guidance, and critically reviewed the manuscript for important intellectual content.

Acknowledgement:

The authors would like to acknowledge cBioPortal, the cancer genomics website for providing permission to use the data for this study.

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Figures

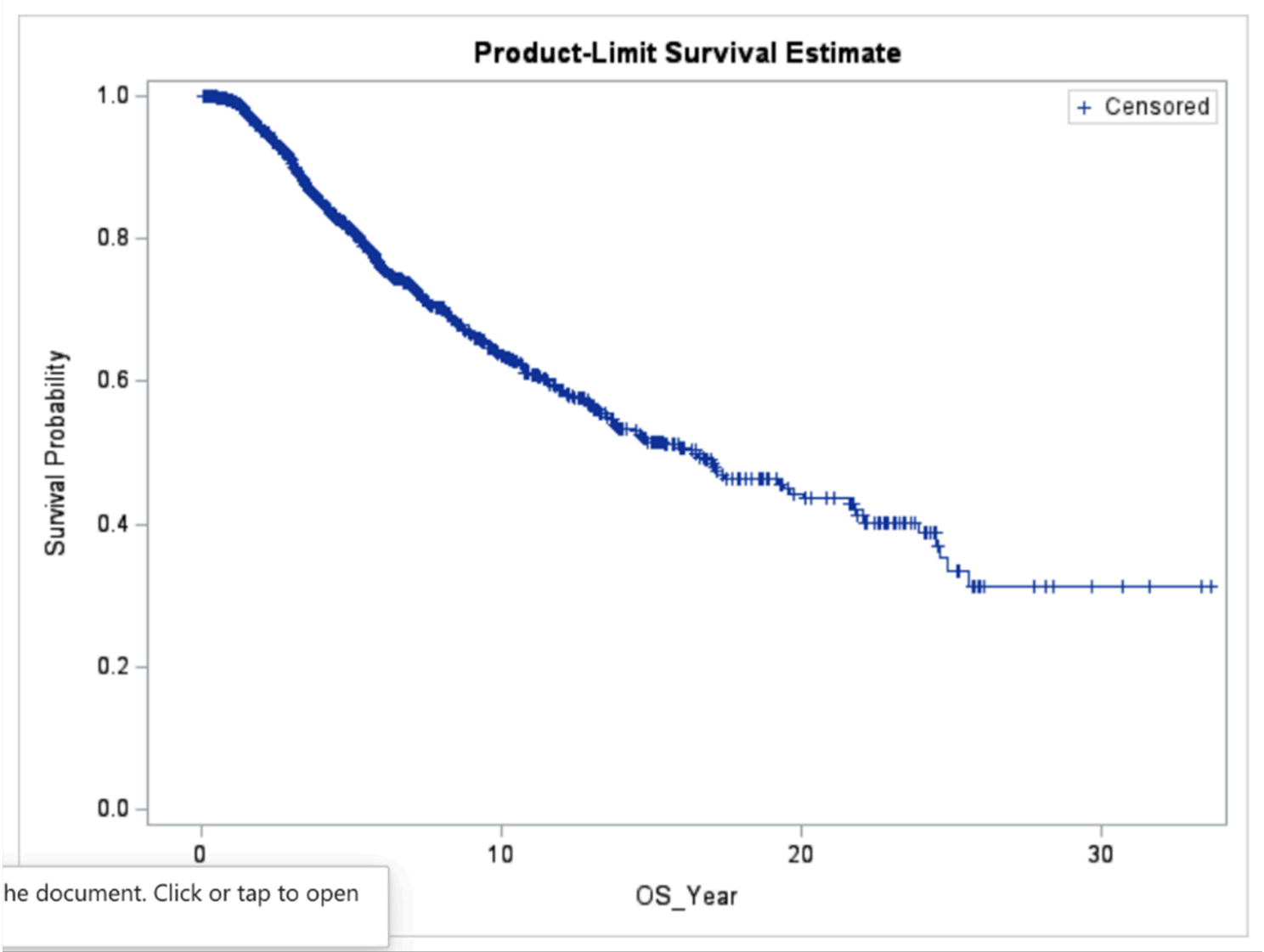


Figure 1

Distribution of survival times

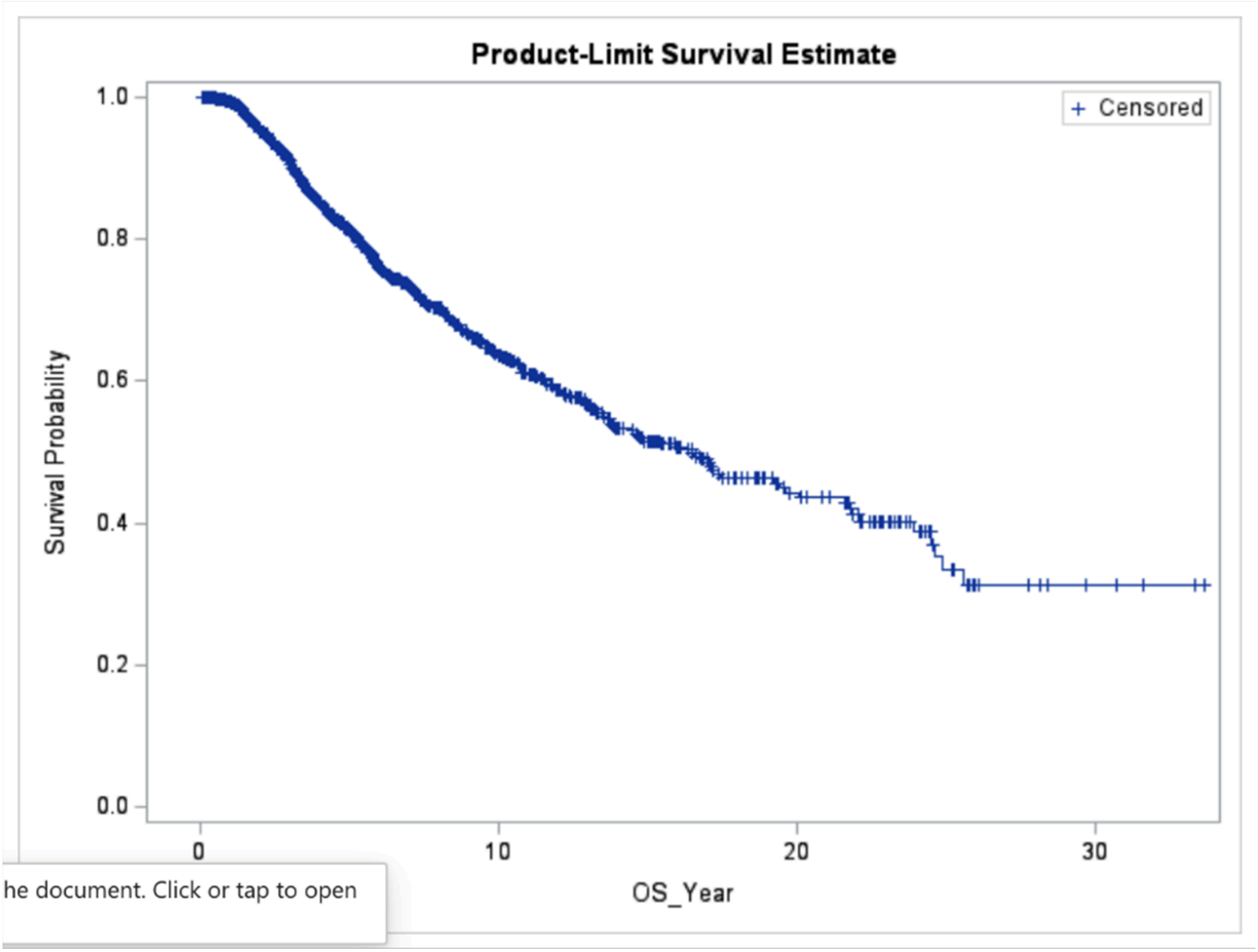


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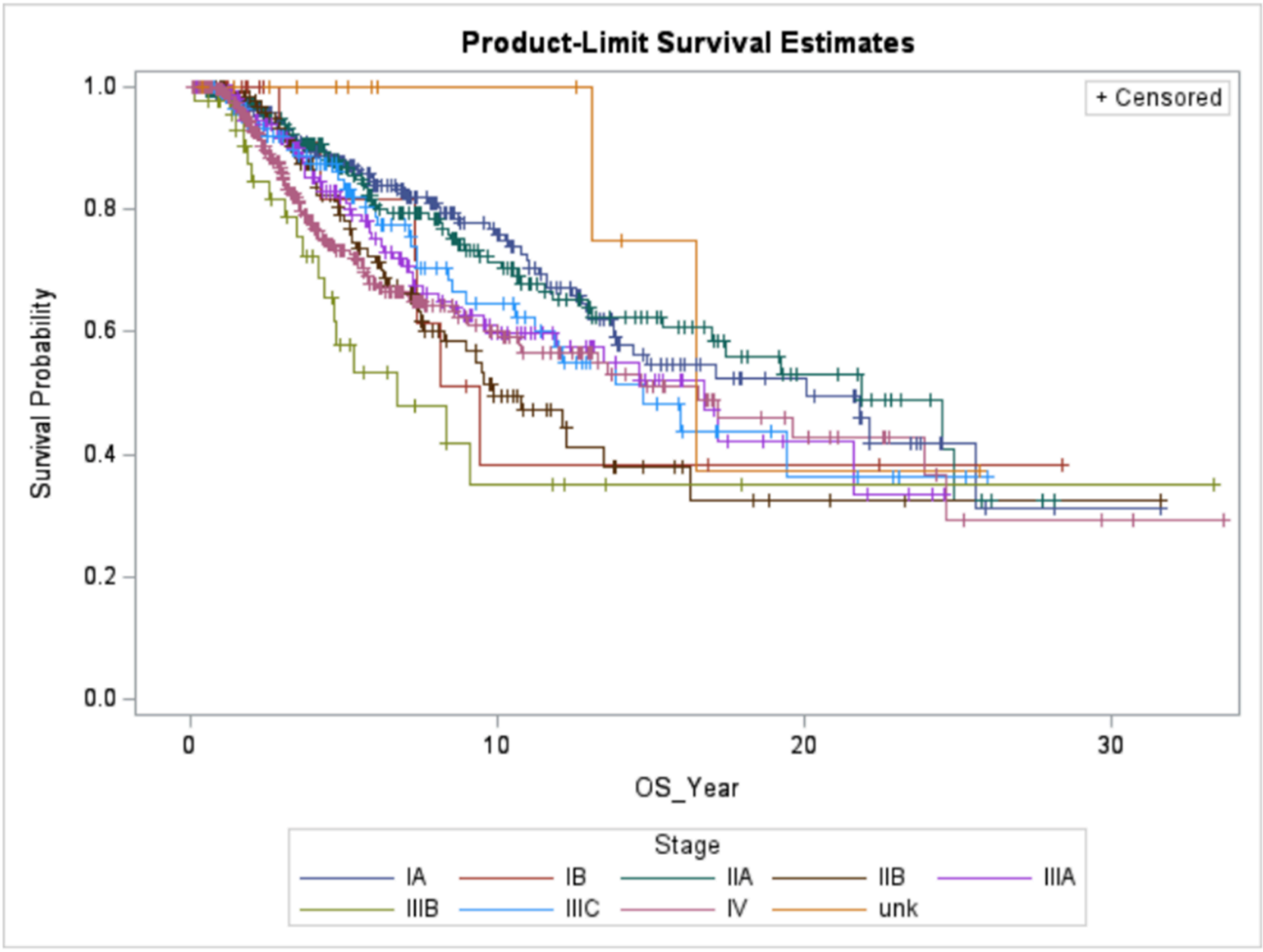


Figure 2

KM plots for breast cancer stages

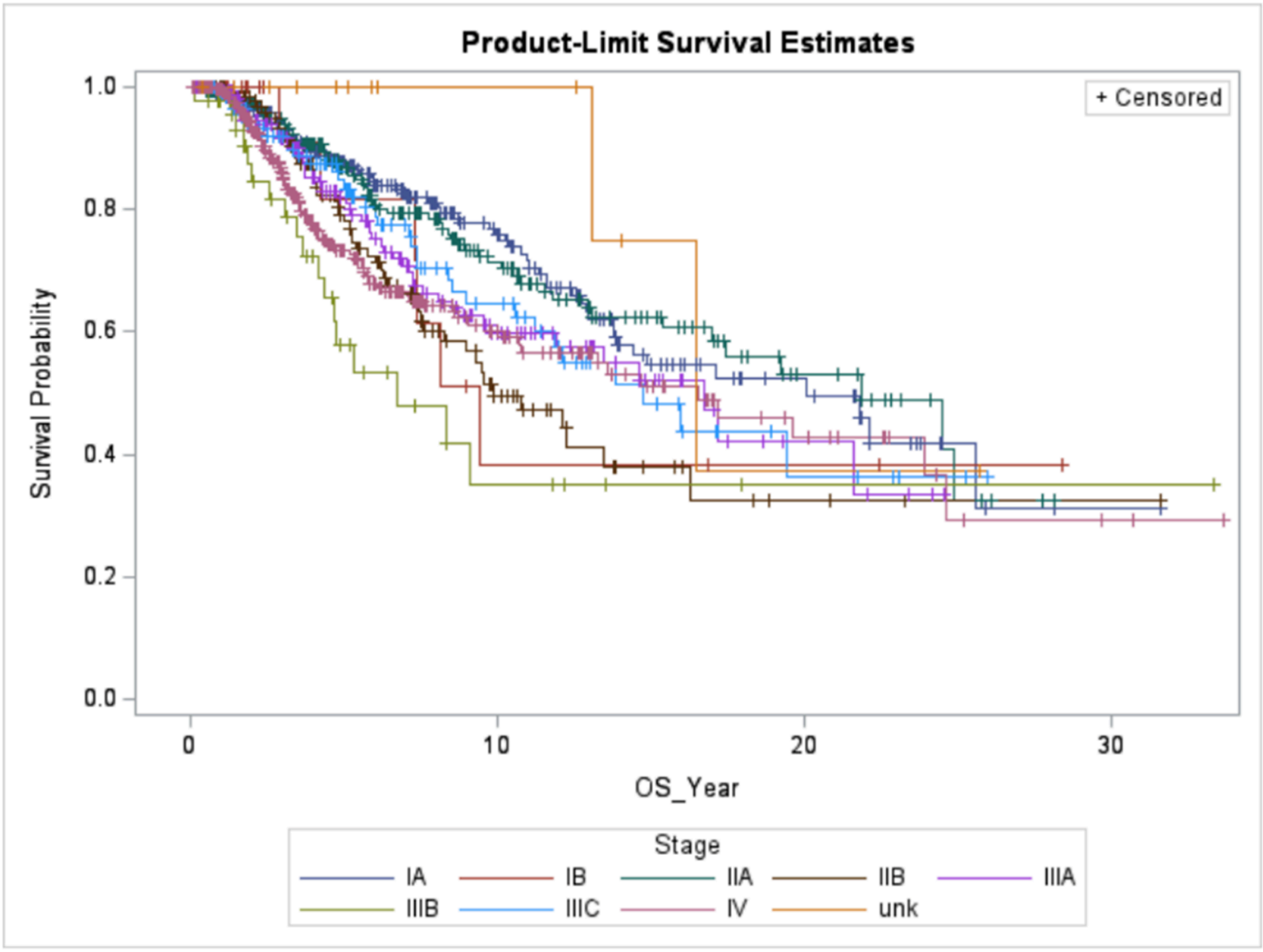


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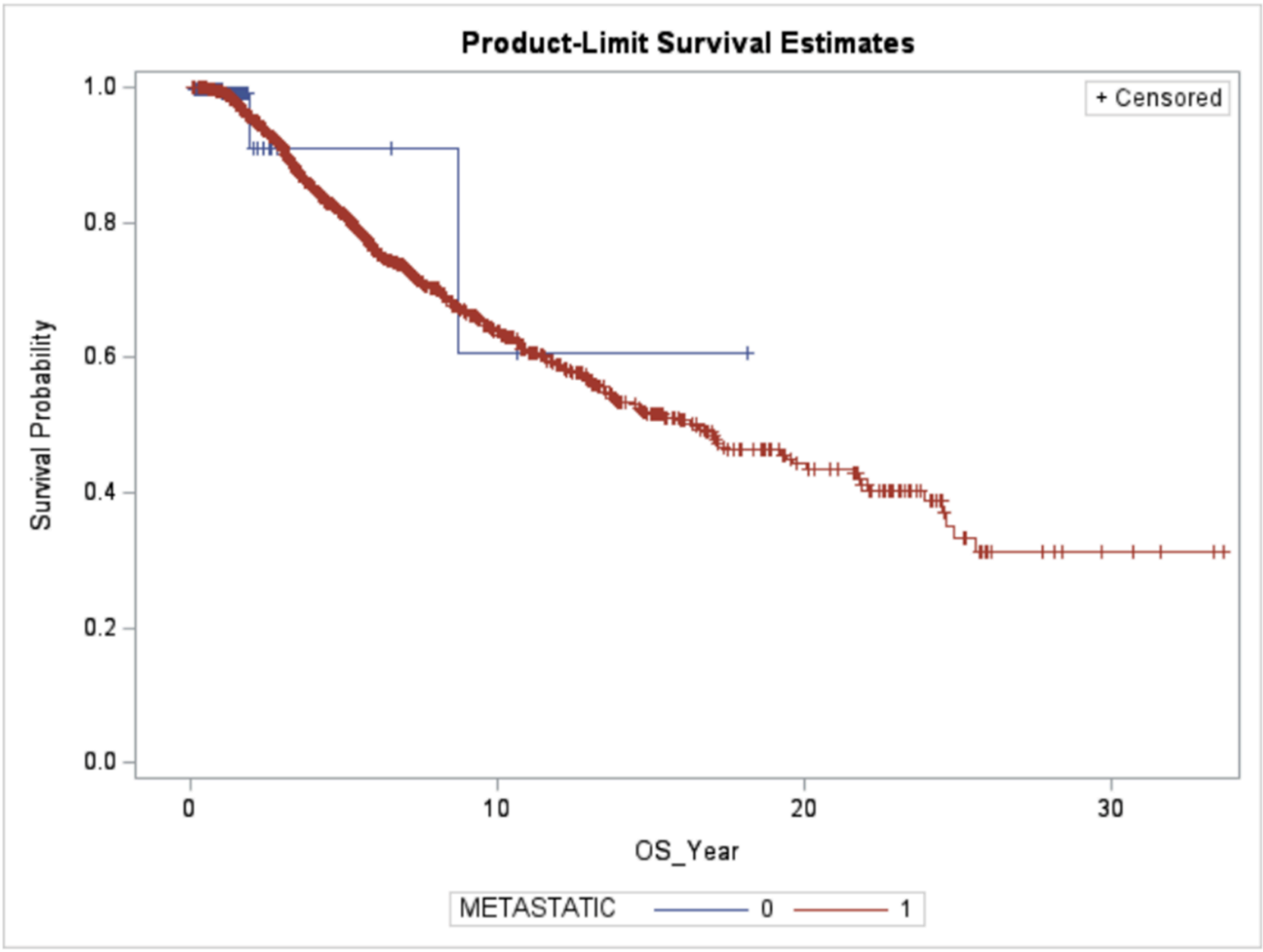


Figure 3

KM plots for Metastatic patterns in participants

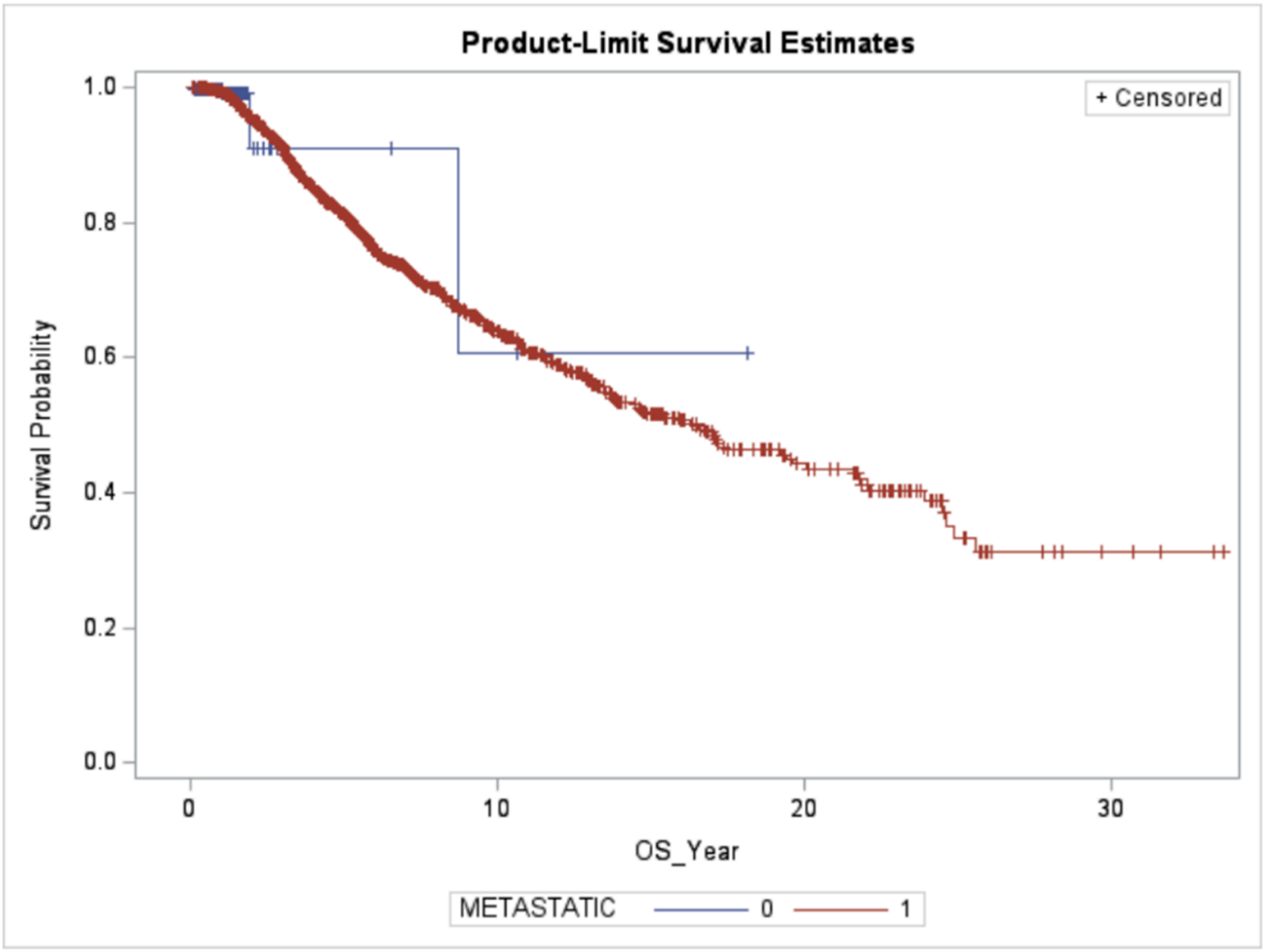


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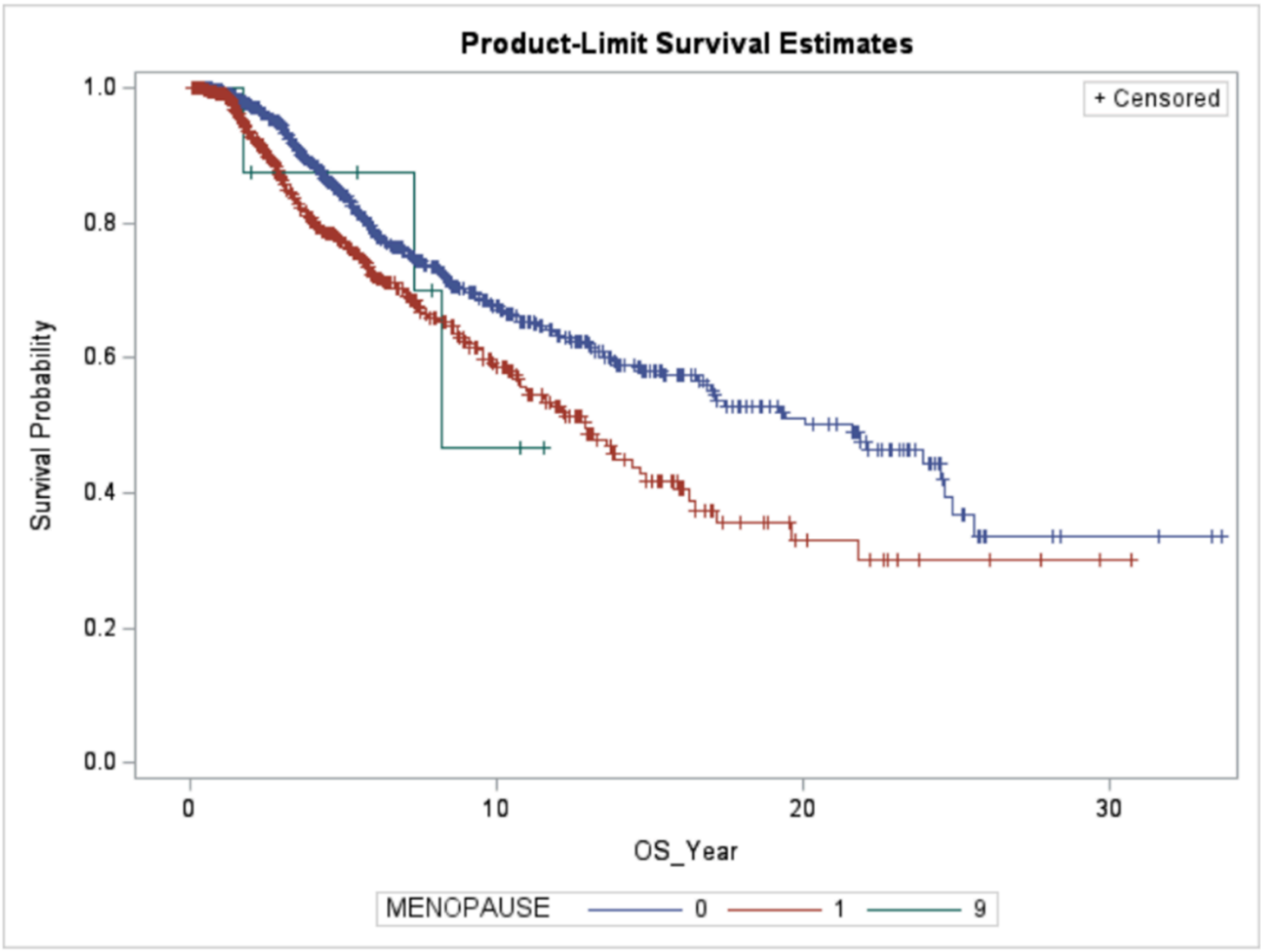


Figure 4

KM plots for Menopause status in participants

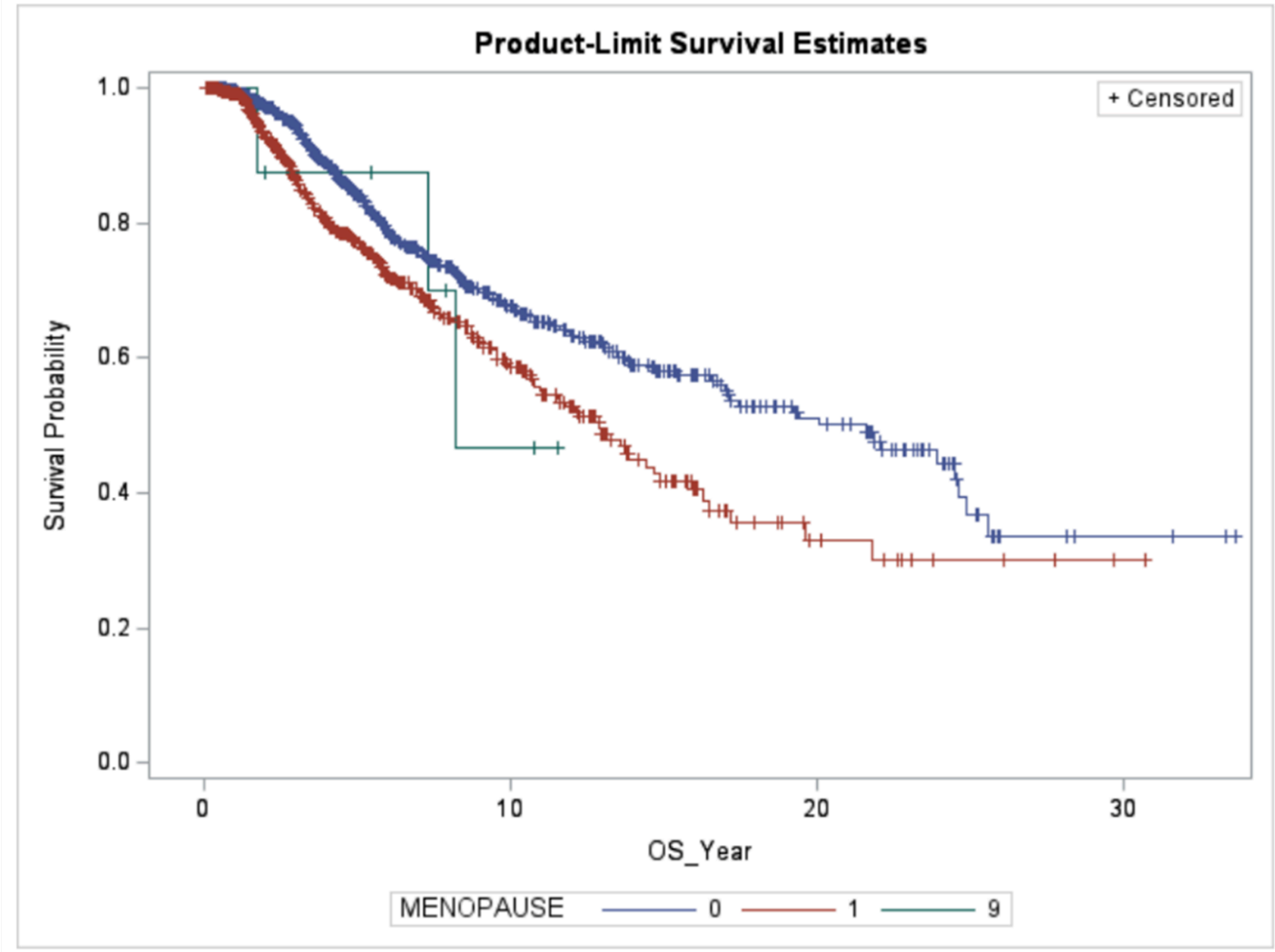


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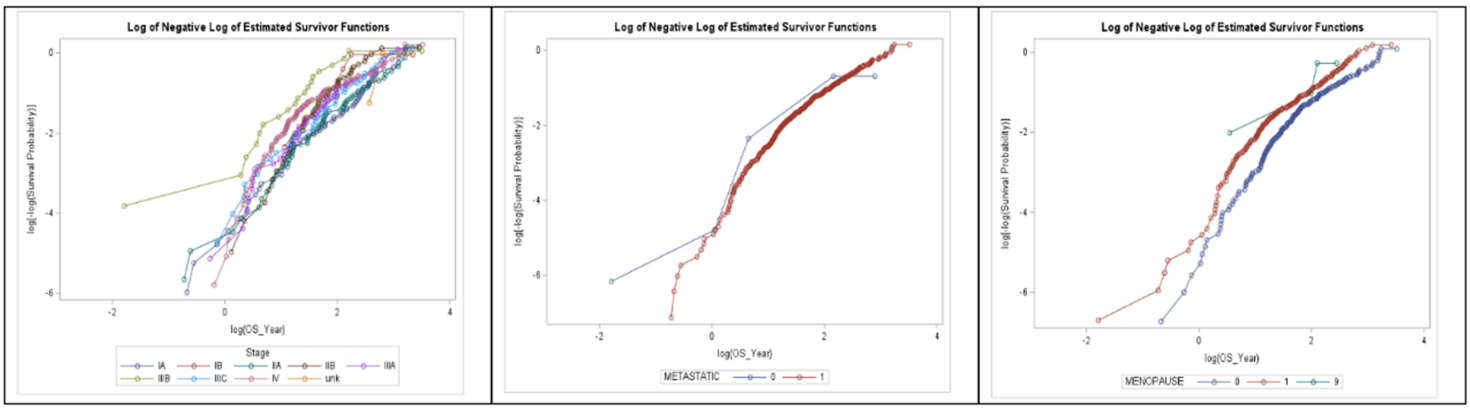


Figure 5

PH assumptions of metastatic status, disease stage dynamics, and menopausal status using ln-ln survival plots

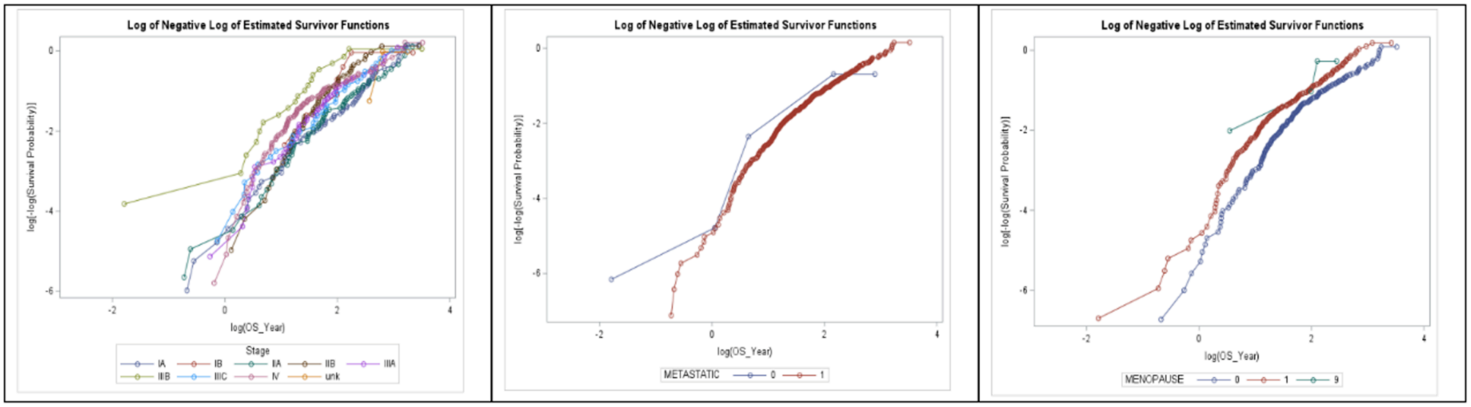


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