Nomogram for predicting cancer specific survival in inflammatory breast carcinoma: a SEER population-based study

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The clinicopathological features of inflammatory breast carcinoma (IBC), the effect of therapeutic options on survival outcome and the identification of prognostic factors were investigated in this study. Information on IBC patients were extracted from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015. Cox proportional hazard regression was used to determine potential significant prognostic factors of IBC. A nomogram was then constructed to evaluate patient survival based on certain variables. Univariate and multivariate analyses revealed that race ($p < 0.001$), M stage ($p < 0.001$), surgery ($p = 0.010$), chemotherapy (CT) ($p < 0.001$), tumor size ($p = 0.010$), estrogen receptor ($p < 0.001$), progesterone receptor ($p = 0.04$), and human epidermal growth factor receptor 2 ($p < 0.001$) were all independent risk factors. The concordance index (C-index) of the nomogram was 0.735, which showed good predictive efficiency. Survival analysis indicated that IBC patients without CT had poorer survival than those with CT ($p < 0.001$). Stratified analyses showed that modified radical mastectomy (MRM) had significant survival advantages over non-MRM in patients with stage IV IBC ($p = 0.031$). Patients treated with or without CT stratified by stage III and stage IV showed better survival than those without stage III and IV ($p < 0.001$). Trimodality therapy resulted in better survival than surgery combined with CT or CT alone ($p < 0.001$). Competing risk analysis also showed the same results. The nomogram was effectively applied to predict the 1, 3 and 5-year survival of IBC. Our nomogram showed relatively good accuracy with a C-index of 0.735 and is a visualized individually predictive tool for prognosis. Treatment strategy greatly affected the survival of patients. Trimodality therapy was the preferable therapeutic strategy for IBC. Further prospective studies are needed to validate these findings.

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16   **Abstract**

17   The clinicopathological features of inflammatory breast carcinoma (IBC), the effect of therapeutic

18   options on survival outcome and the identification of prognostic factors were investigated in this

19   study. Information on IBC patients were extracted from the Surveillance, Epidemiology, and End

20   Results (SEER) database between 2010 and 2015. Cox proportional hazard regression was used to

21   determine potential significant prognostic factors of IBC. A nomogram was then constructed to

22   evaluate patient survival based on certain variables. Univariate and multivariate analyses revealed

23   that race ($p < 0.001$), M stage ($p < 0.001$), surgery ($p = 0.010$), chemotherapy (CT) ($p < 0.001$),

24   tumor size ($p = 0.010$), estrogen receptor ($p < 0.001$), progesterone receptor ($p = 0.04$), and human

25   epidermal growth factor receptor 2 ($p < 0.001$) were all independent risk factors. The concordance

26   index (C-index) of the nomogram was 0.735, which showed good predictive efficiency. Survival

27   analysis indicated that IBC patients without CT had poorer survival than those with CT ($p < 0.001$).

28   Stratified analyses showed that modified radical mastectomy (MRM) had significant survival

29   advantages over non-MRM in patients with stage IV IBC ($p = 0.031$). Patients treated with or

30   without CT stratified by stage III and stage IV showed better survival than those without stage III

31   and IV ($p < 0.001$). Trimodality therapy resulted in better survival than surgery combined with CT

32   or CT alone ($p < 0.001$). Competing risk analysis also showed the same results. The nomogram

33   was effectively applied to predict the 1, 3 and 5-year survival of IBC. Our nomogram showed

34   relatively good accuracy with a C-index of 0.735 and is a visualized individually predictive tool

35   for prognosis. Treatment strategy greatly affected the survival of patients. Trimodality therapy was

36   the preferable therapeutic strategy for IBC. Further prospective studies are needed to validate these

37   findings.

38 **Introduction**

39 Inflammatory breast carcinoma (IBC) is an uncommon subtype of locally advanced breast cancer

40 with a poor prognosis and is characterized by aggressive behavior and rapid progression

41 (Robertson et al., 2010). Management involves the coordination of multidisciplinary treatment and

42 usually includes neoadjuvant chemotherapy, ablative surgery if a tumor-free resection margin is

43 expected and locoregional radiotherapy. This multimodal therapeutic approach has significantly

44 improved patient survival. However, the median overall survival (OS) among women with IBC is

45 still poor. Clinically, IBC is characterized by the rapid onset of breast warmth, erythema, and

46 edema often without a well-defined mass. Along with extensive breast involvement, women with

47 IBC often have early involvement of the axillary lymph nodes. The median survival time of IBC

48 treated by surgery alone or combined with radiotherapy (RT) is less than 15 months and the local

49 recurrence rate is approximately 50% (Zucali et al., 1976). Despite the significant progress made

50 in the treatment of this aggressive form of breast cancer, most women with IBC will relapse and

51 succumb to this disease. Limited research with small cohorts have focused on the prognostic value

52 of RT and CT (Semiglazov et al., 2007; Jardel et al., 2018). A few studies have analyzed the

53 clinicopathological features related to OS, such as lymph node status and human epidermal growth

54 factor receptor 2 (Her-2) status (Dawood et al., 2008; Wecsler et al., 2015). It is important to

55 evaluate the effect of trimodality therapy in IBC patients. In addition, high risk patients who need

56 more aggressive locoregional treatment are not well-defined in the literature. The current

57 investigation aimed to determine the clinicopathological features of IBC and identify reliable and

58   comprehensive prognostic factors based on a large cohort, which will help to predict the survival

59   outcome of patients with IBC and choose the appropriate treatment strategy.

60   Previous studies of IBC patients from the SEER database have reported that breast cancer

61   subtype is clinically useful for predicting survival outcome in IBC (Wu et al., 2019). The

62   identifying factor of survival was related to race/ethnic group (Il'Yasova et al., 2011) and the

63   overall survival IBC patients from the SEER database has been reported to be associated with

64   socioeconomic position (Liu et al., 1998; Schlichting et al., 2012). In contrast, we determined the

65   independent prognostic factors of IBC, and then constructed a nomogram.

66   A nomogram, a statistic-based tool to calculate the risk of clinicopathological features of a

67   cancer, has been widely developed to evaluate survival in cancer patients (Zhou et al., 2015; Sun

68   et al., 2017). It has been proved to be accurate with the advantage of visualization and

69   quantification with a friendly interface for doctors and patients. In this study, a nomogram was

70   constructed to predict 1-, 3-, and 5-year cancer-specific survival (CSS) according to multivariate

71   analyses based on this large cohort, and to identify the exact therapeutic effect of various surgical

72   procedures,   RT   and   CT.

Materials and Methods

Data source and inclusion criteria

We retrieved patient data from the SEER database (SEER*Stat 8.3.5, http://seer.cancer.gov/). The SEER database is free to the public and is updated annually, with routinely collected general messages from patients, primary tumor characteristics, treatments, survival and follow-up, etc. In this study, the data were updated in November 2016, and released on April 16, 2018. The target population downloaded from the database was from 1973 to 2015. We extracted IBC patients between 2010 and 2015 as data on Her-2 status was released from 2010. Patients were included in this study if they met the following criteria: patients who had IBC with the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3): 8530 as the histopathology code, positive histology, complete survival month flag and active follow-up. Patients confirmed by autopsy only or death certificate only and those with invalid follow-up data were excluded. In total, 883 patients were selected for further analysis in this study. Data downloaded from SEER did not require patients' informed consent and may be reproduced or copied without permission. This study was approved to be exempted by the Institutional Review Committee of Zhongshan Hospital (Fudan University, Shanghai, China).

Endpoints and statistical analysis

OS was calculated from the date of first diagnosis to the date of death or last contact. CSS was measured from the date of first diagnosis to the date of death due to breast carcinoma. However,

92   patients who died of other causes were considered censoring events. All statistical analyses were

93   performed using SPSS 24.0 (IBM Corp, Armonk, NY, USA) or R package 3.4.4 software

94   (http://www.r-project.org/; R Foundation for Statistical Computing, Vienna, Austria). Cox

95   proportional hazard regression was applied to identify significant prognostic factors with hazard

96   ratios (HRs) and 95% confidence intervals (95% CIs). Variables in the univariate analysis with *p*-

97   values < 0.05 were selected for multivariate analysis using backward stepwise regression

98   (likelihood ratio). The nomogram was constructed based on multivariate analysis results, and was

99   evaluated by the concordance index (C-index), the calibration curves and receiver operating

100 characteristics (ROC) curves. The value of the C-index ranges from 0.5 to 1.0 and a larger value

101 indicates better accuracy of predicting efficiency (Koepsell TD, 2014; Ma et al., 2018). The

102 calibration curves were based on 1,000 times bootstrap resampling. The Kaplan-Meier method and

103 log-rank test were performed to obtain survival curves and the differences between groups were

104 compared using R project 3.4.4 with the survival package. We also performed competing risk

105 analysis. All differences with *p* values < 0.05 were considered to be statistically significant.

106 **Results**

107 **Patient characteristics**

108 A total of 883 patients diagnosed with IBC were extracted from the SEER database between 2010

109 and 2015 according to the abovementioned inclusion criteria. The results of univariate/multivariate

110 analyses based on CSS and OS as well as 5-year OS are summarized in Tables 1-3, respectively.

111 The median age of the IBC patients was 57 (range, 22–97) years. The majority (693, 78.5%) were

112 White. The 5-year OS of White vs. Black patients was 49.4% vs. 29.7% and the HR for CSS was

113 1.90 (95% CI 1.43-2.53, $p < 0.001$). The 3- and 5-year OS of patients with IBC was 54.4% and

114 47.4%, respectively. The median OS was 43.0 (95% CI, 32.4–53.6) months. Tumor staging

115 followed the criteria of the 7th edition of American Joint Committee on Cancer (AJCC) for breast

116 cancer. Most patients (572, 64.8%) were stage III, while 311 (35.2%) were stage IV. Patients who

117 were treated with surgery accounted for 58.2%, of which, 352 (39.9%) patients underwent MRM

118 and 162 (18.3%) patients were treated by non-MRM including 30 (3.0%) with breast-conserving

119 surgery, 118 (13.4%) with total (simple) mastectomy, 9 (1.0%) with radical mastectomy and 5

120 (0.9%) with extended radical mastectomy. The HR and 95% CI of the non-MRM group vs. the

121 MRM group was 0.41 (0.30–0.57) vs. 0.33 (0.26–0.43) for CSS. RT (396/883, 44.8%) and CT

122 (721/883, 81.7%) were also main treatments for patients with IBC.

123 Univariate analysis of CSS for IBC using Cox regression analysis demonstrated that age (p

124 $= 0.016$), race ($p < 0.001$), N stage ($p < 0.001$), M stage ($p < 0.001$), surgical modality ($p <$

125 0.001), radiation status ($p < 0.001$), CT status ($p < 0.001$), tumor size ($p = 0.015$), estrogen

126   receptor (ER) ($p < 0.001$), progesterone receptor (PR) ($p < 0.001$), Her-2 ($p < 0.001$) and marital

127   status ($p = 0.002$) were all significant prognostic factors, and corresponded to those for OS. All

128   the significantly different variables were included in the multivariate analyses of CSS and OS

129   (Table 1 and Table 2). Finally, race (Black, HR = 1.77), M stage (M1, HR = 2.93), surgery (non-

130   MRM, HR = 0.74; MRM, HR = 0.60), CT status (Yes, HR = 0.46), tumor size (2-5 cm, HR =

131   0.91; >5 cm, HR= 1.48; Diffuse, HR = 1.39), ER (Positive, HR = 0.52), PR (Positive, HR =

132   0.64) and Her-2 (Positive, HR = 0.12) were confirmed as independent prognostic factors of IBC.

133   A nomogram was constructed to evaluate patient survival based on multivariate analysis

134   (Figure 1A). The points from each independent prognostic factor listed in the nomogram were

135   added together. The 1, 3 and 5-year CSS rates for patients with IBC were estimated by applying

136   three point scales at the bottom of the nomogram, respectively. The C-index of this model was

137   0.735 which showed an excellent predictive efficiency. We performed a calibration plot to

138   resample the validation of the nomogram based on 1000 bootstraps to confirm the agreement

139   between the actual and predicted 1, 3 and 5-year CSS rates (Figure 1B-D). A series of receiver

140   operating characteristics (ROC) curves were performed to verify the accuracy of the nomogram

141   (Figure S1A-C).

142   **Survival analyses in subgroups of patients with inflammatory breast carcinoma**

143   Survival curves were used to compare the CSS of patients with IBC according to the following

144   parameters: TNM stage, CT, surgical modality, and treatment pattern by subgroup analyses. All

145   883 patients classified by different surgical modalities achieved statistically significant survival (p

146 < 0.001) (Figure 2A). There was no significant difference in CSS between the MRM and non-

147 MRM group ($p = 0.23$) (Figure 2B). When the patients were stratified by TNM stage III and IV,

148 the p values were 0.5 (Figure 2C) and 0.031 (Figure 2D), respectively. Patients treated with CT

149 had better survival ($p < 0.001$) (Figure 3A). Competing risk analysis showed the same results

150 (Figure S2). Furthermore, subgroup analyses stratified by TNM stages (Figure 3B, 3C) indicated

151 that patients in the TNM stages benefitted from CT in terms of CSS ($p < 0.001$). When patients

152 were classified by different treatment patterns (Figure 4), such as surgery alone, RT alone, CT

153 alone, surgery combined with RT, surgery combined with CT, RT combined with CT, or surgery

154 combined with RT and CT, there were significant differences between them. The results indicated

155 that surgery combined with RT and CT was the optimal treatment pattern. A further subgroup

156 analysis of the treatment modalities was performed and the treatments which resulted in greatest

157 survival (Figure 4) were surgery combined with RT and CT, followed by CT and RT, and CT

158 alone with significant differences between the three groups ($p < 0.001$). Competing analysis

159 revealed the same results (Figure S3).

160 **Discussion**

161 IBC is uncommon and the most lethal form of breast carcinoma, and leads to a worse prognosis

162 compared with other forms of breast carcinoma, with significantly lower OS, (3-year OS, 42% vs.

163 85%) (Chang et al., 1998). Treatment with multimodal therapies has significantly improved the

164 survival of patients with IBC in recent years, especially when targeted therapy is available (Gianni

165 et al., 2010). However, survival is still poor with a 5-year OS of 30-40% (Hance et al., 2005; Ueno

166 et al., 1997). The 3- and 5-year OS of patients with IBC was 54.4% and 47.4% in this study, which

167 is consistent with the above previously published reports. To date, there are still many uncertainties

168 regarding the optimal treatment of IBC. As a result of small sample sizes, various treatment

169 patterns, and variable response criteria, evidence-based management has been determined largely

170 by institutional experience or based on other types of breast carcinoma (Panades et al., 2005). This

171 study analyzed the survival of a large cohort of patients with IBC based on the SEER database and

172 confirmed eight independent prognostic factors including race, M stage, surgical modality, CT

173 status, tumor size, ER, PR and Her-2 status, based on the nomogram which will provide the first

174 comprehensive evaluation profile to help physicians make a reasonable treatment decision and

175 estimate prognosis in IBC patients.

176   ER, PR and Her-2 status are important prognostic factors in IBC. Endocrine therapy is an

177 important treatment strategy for patients with breast carcinoma who are either ER or PR positive.

178 However, information on endocrine therapy in IBC patients is not available in the SEER database.

179 Her-2, is an oncogene and is overexpressed and/or amplified in approximately 30% of patients

180 with breast carcinoma (Slamon et al., 1987), and is related to increased aggressiveness, a higher

181 recurrence rate and mortality (Romond EH, 2005). Furthermore, it was reported that Her-2 was

182 overexpressed and amplified by 36-60% in patients with IBC than in those with non-IBC (Parton

183 et al., 2004; Guerin et al., 1990). Patients with positive expression of Her-2 showed shorter

184 recurrence-free survival and OS compared with patients without Her-2 amplification in a study of

185 breast carcinoma by Slamon et al (Slamon et al., 1987). However, the role of Her-2 as a poor

186 prognostic factor in breast carcinoma was altered by the introduction of trastuzumab, a monoclonal

187 antibody which targets the Her-2 receptor (Wecsler et al., 2015). Data from the SEER database

188 showed that IBC patients with HoR+/Her2- subtype had poorer breast cancer-specific survival and

189 OS than those with HoR+/Her-2 subtype (Wu et al., 2019). Her2-positive status in this study had

190 a protective effect in patients with IBC, which was in accordance with previous reports based on

191 the SEER database (Li et al., 2017).

192   Surgery and RT are important locoregional therapies in IBC. However, either surgery alone

193 (Fields et al., 1989) or RT alone (Jaiyesimi et al., 1992) produced disappointing results in the

194 treatment of IBC. Even though combining surgery with RT significantly improves locoregional

195 control, with disease-free survival as high as 24 months (Perez & Fields, 1987), the median

196 survival of the two treatments combined ranges from 7 to 29 months and was not significantly

197 different from either treatment alone. Data on IBC patients from the SEER database showed that

198 surgery combined with RT significantly improved 5-year OS by 15% (Muzaffar et al., 2018).

199 However, RT was not an independent prognostic factor of CSS in IBC patients. Researchers have

200 now realized that breast cancer is a systemic disease. Locoregional therapy is not enough to prevent

201 distant metastasis. Therefore, systemic CT has been combined with surgery, RT, hormonal therapy

202 and molecular targeted therapy. In this study, IBC patients treated with CT vs. without CT achieved

203 a 5-year OS of 52.1% vs. 25.1% and a median OS of 63.0 vs. 15.0 months, respectively. These

204 results are consistent with previous reports which showed that CT improved the 5-year OS of

205 patients with IBC to 30-40% (Fields et al., 1989). Interestingly, our stratified analysis of surgical

206   modalities based on TNM stage revealed that stage IV patients achieved a significant difference

207   in survival when treated with MRM compared with non-MRM. Nevertheless, no difference was

208   observed in stage III IBC patients. In this study, 118 (72.8%) patients in the non-MRM group

209   underwent total (simple) mastectomy. Only 9 (1.0%) patients underwent radical mastectomy and

210   5 (0.9%) patients underwent extended radical mastectomy. MRM is the most commonly used

211   surgical approach of choice, as it allows both removal of the main tumor mass and adjacent

212   glandular tissue with suspected infiltration and multifocality, and a sentinel axillary lymph node.

213   This procedure significantly reduces primary tumor burden and peripheral subclinical lesions.

214   Theoretically, it should bring marked benefits to both stage III and IV patients. A comprehensive

215   explanation to rationalize these observations is still required. Lymph node status is also an

216   important prognostic factor in IBC (Liang et al., 2015) and positive node status was reported to be

217   a negative prognostic factor (Wecsler et al., 2015). However, N stage in our study was not

218   statistically significant in multivariate analysis. A total of 355 patients in our study received no

219   surgery; the N stage in these patients was categorized only by clinical features without pathology

220   confirmation. We assume that inaccurate N stage or less important than M stage in multivariate

221   Cox regression analysis could be the reasons why lymph node status was not included as a

222   prognostic factor of IBC.

223   Trimodality treatment is recommended following the sequence of CT (including trastuzumab

224   and hormonal therapy when necessary), then surgery and RT (Robertson et al., 2010). Two

225   prospective randomized trials involving 68 patients with IBC treated with three cycles of CAF

226 (cyclophosphamide, doxorubicin, and 5-fluorouracil) or CEF (cyclophosphamide, epirubicin, and

227 5-fluorouracil) followed by surgery, adjuvant therapy, and RT, reported a 5-year OS of 44% and

228 a 10-year OS of 32% (Baldini et al., 2004). Our subgroup analysis based on treatment group

229 including CT alone, CT combined with surgery, and CT combined with surgery and RT showed

230 the advantage of trimodality treatment on survival. It was reported that patients with ER-negative

231 IBC benefitted from paclitaxel together with anthracycline-based regimens and obtained improved

232 progression-free survival and OS (Cristofanilli et al., 2007; Cristofanilli et al., 2004). The optimal

233 chemotherapeutic regimens and optimal combination of targeted treatments deserve further

234 investigation.

235   To our knowledge, no nomogram model has been established to predict the survival of

236 patients with IBC. As 34.4% of deaths are not attributed to primary breast cancer, CSS was used

237 here to exclude the potential impact of other factors. It is worth mentioning that our study included

238 a large sample size of 883 patients which is difficult to achieve in a single institute clinical trial.

239 In addition to race, Her-2 and hormone receptor status have been reported as prognostic factors for

240 OS in IBC. All prognostic factors in the present study have not been reported in association with

241 CSS. This nomogram included surgical modalities (MRM vs. non-MRM), and MRM was

242 confirmed to be a protective factor for CSS compared to non-MRM. The nomogram with

243 predictive accuracy was constructed based on comprehensive clinical pathological features in this

244 study. However, there are some limitations that should be noted. The SEER database did not

245 provide sufficient information on systemic therapy, such as CT regimens in patients with IBC,

246   Her2-positive patients treated with or without trastuzumab, and hormone receptor-positive patients

247   treated with or without hormonal therapy. Furthermore, limited information on local therapy, such

248   as the sequence of RT and surgery, radiation dose and radiation fields, constrained our

249   identification of more prognostic factors associated with detailed treatment information.

250   Additionally, a prospective study should be conducted to validate the reliability of these results.

251   **Conclusions**

252   A nomogram can be effectively applied to predict the 1-, 3- and 5-year survival of IBC patients.

253   Our nomogram showed relatively good accuracy with a C-index of 0.735 and is a visualized

254   individually predictive tool for prognosis. Treatment strategy greatly affected the survival of

255   patients. Trimodality therapy was the preferable therapeutic strategy for IBC. Further prospective

256   studies are needed to validate these findings.

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262   **Conflicts of interest**

263   The authors declare no competing interests.

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Figure 1

Nomogram and calibration curves of patients with inflammatory breast carcinoma

(A) A nomogram for the prediction of 1-, 3- and 5-year cancer-specific survival in IBC patients. Calibration curves of the nomogram prediction of (B) 1-year, (C) 3-year, and (D) 5-year survival of patients with IBC.

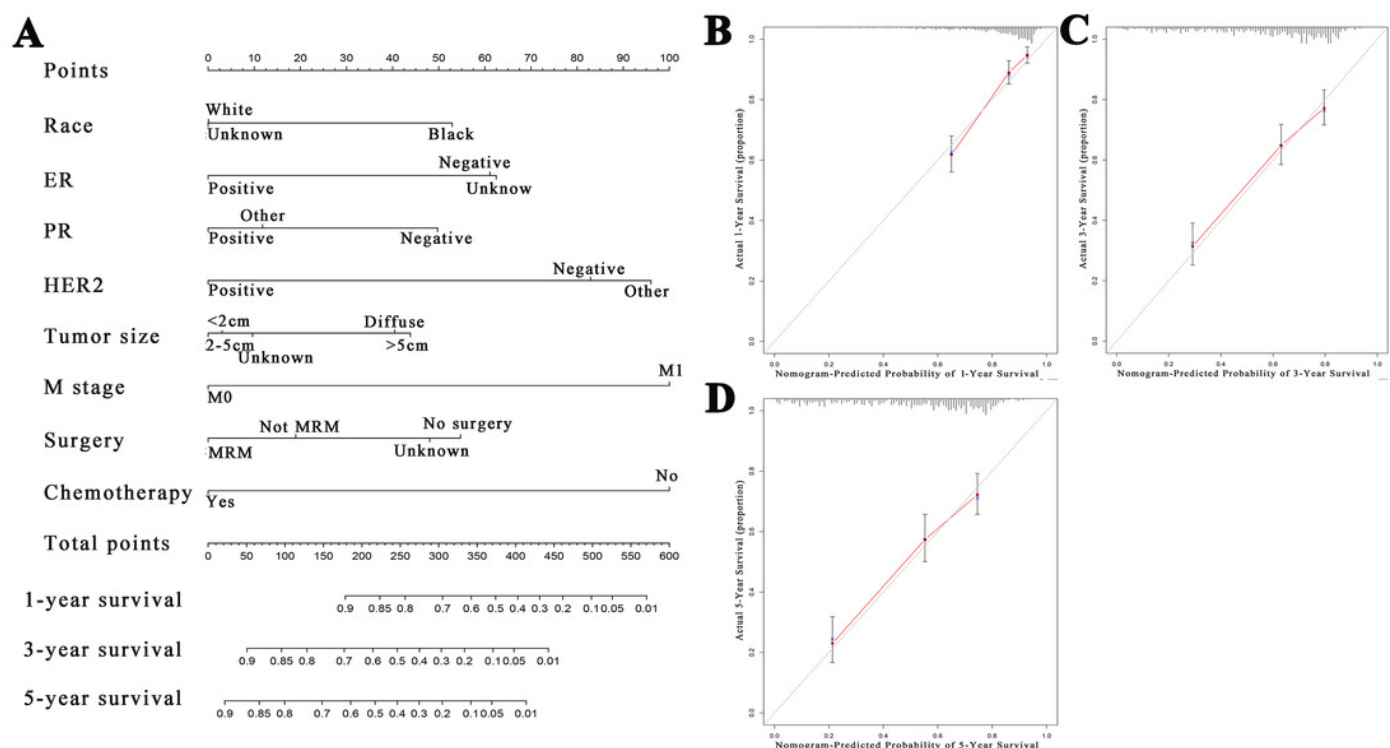



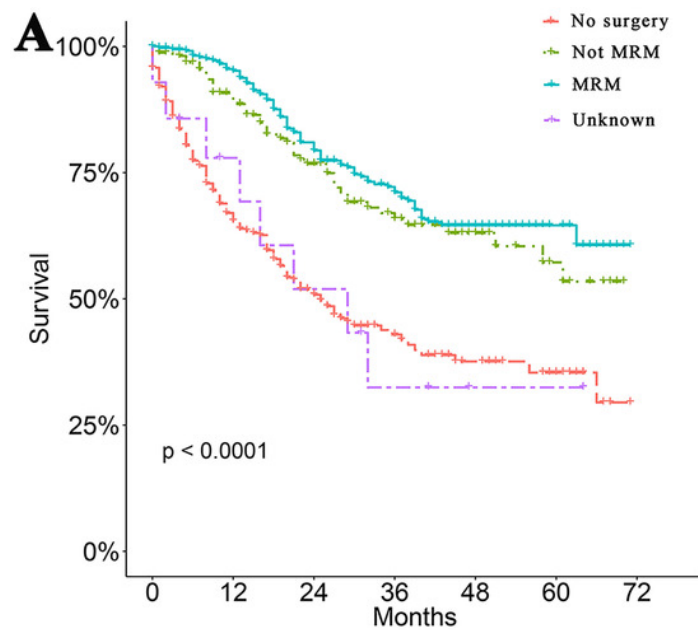
Figure 2

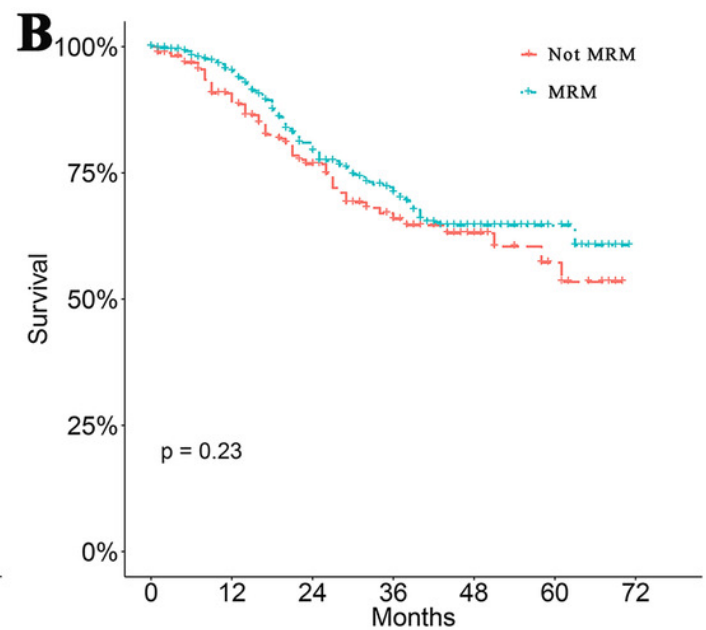
Survival analyses based on surgery and stratified analyses TNM stage

(A) Survival analyses of patients based on surgical modalities. (B) Survival analyses of patients with modified radical mastectomy (MRM) or non-MRM. Survival analyses of patients with MRM or non-MRM stratified by TNM stage. Five-year survival (C) stage III (MRM vs. non-MRM, 68% vs. 64.3%). (D) stage IV (MRM vs. non-MRM, 43.2% vs.18.9%).

A

Legend:
- No surgery
- Not MRM
- MRM
- Unknown

p < 0.0001

Patients at risk

	0	12	24	36	48	60	72
No surgery	355	174	97	48	27	13	0
Not MRM	162	126	86	59	28	15	0
MRM	352	277	202	134	79	40	0
Unknown	14	9	6	3	1	1	0

B

Legend:
- Not MRM
- MRM

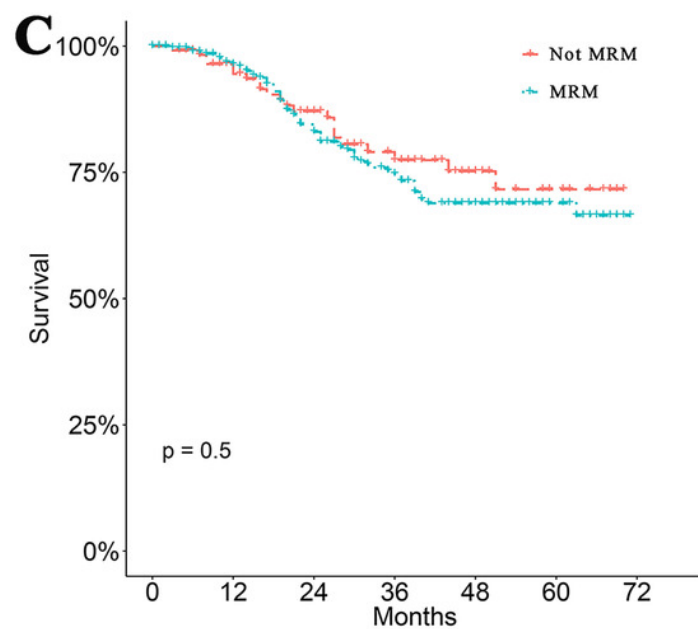
p = 0.23

Patients at risk

	0	12	24	36	48	60	72
Not MRM	162	126	86	59	28	15	0
MRM	352	277	202	134	79	40	0

C

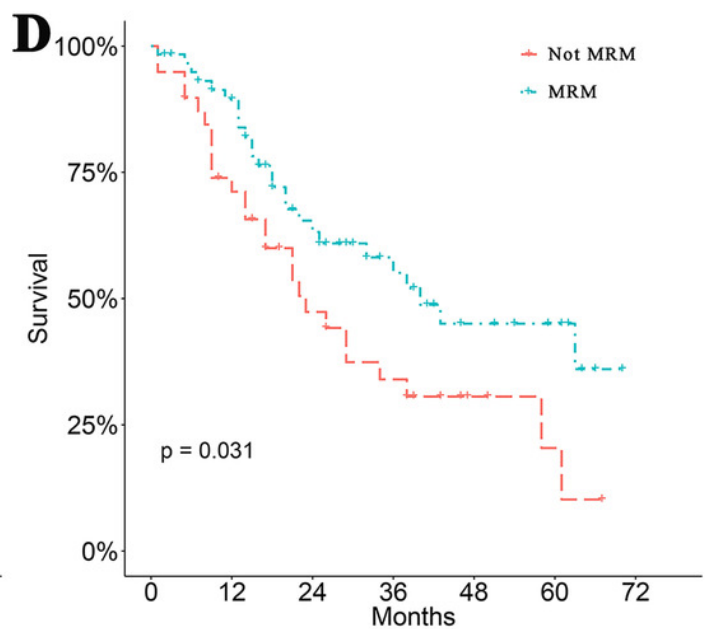
Legend:
- Not MRM
- MRM

p = 0.5

Patients at risk

	0	12	24	36	48	60	72
Not MRM	123	99	71	49	24	13	0
MRM	291	228	173	115	68	33	0

D

Legend:
- Not MRM
- MRM

p = 0.031

Patients at risk

	0	12	24	36	48	60	72
Not MRM	39	27	15	10	4	2	0
MRM	61	49	29	19	11	7	0

Figure 3

Survival analyses based on chemotherapy and stratified analyses based on TNM stage

(A) Survival analyses of patients with IBC treated with or without chemotherapy (CT). Survival analyses of patients with or without CT stratified by TNM stage. (B) stage III (Yes vs. No, 70.7% vs. 37.4%) (C) stage IV (Yes vs. No, 39.7% vs. 8.3%).

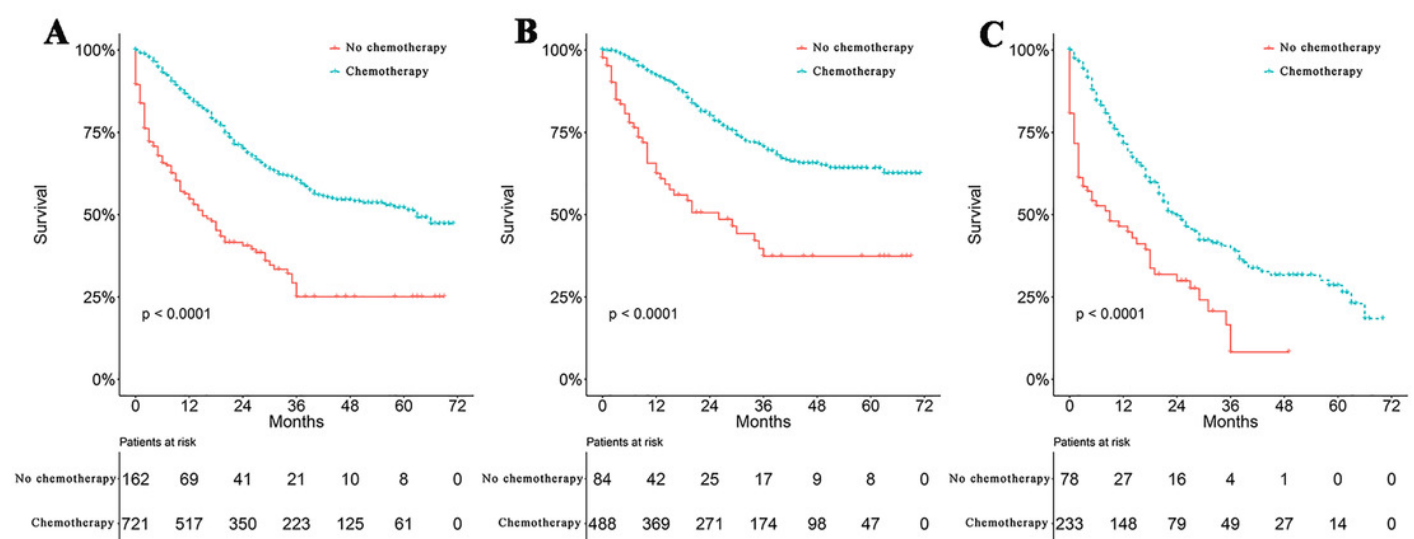
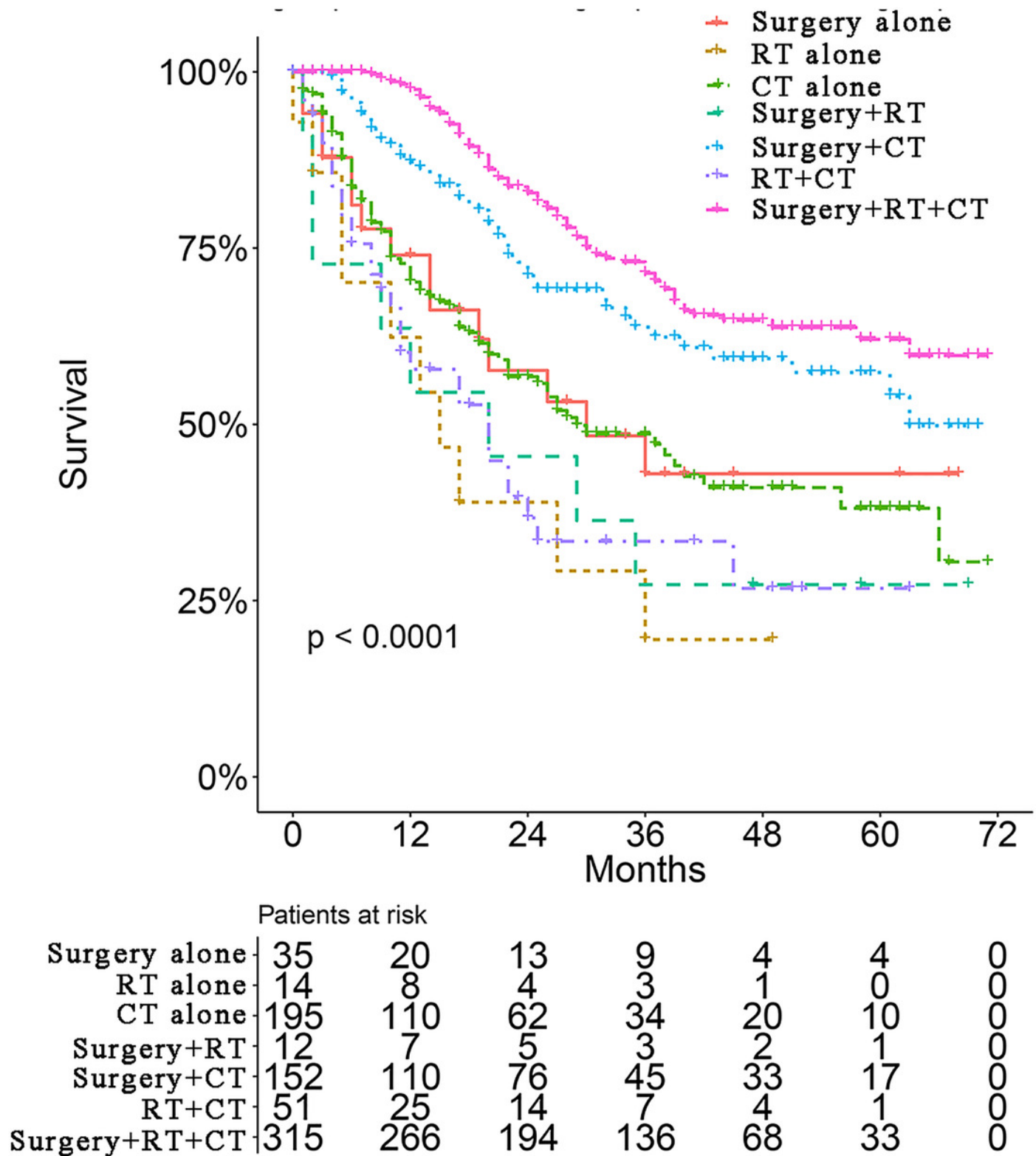



Figure 4

Survival analyses of patients with IBC treated with different strategies

Patient characteristics and analyses based on cancer specific survival status

1   Table 1. Patient characteristics and analyses based on cancer specific survival status

Patient characteristics	Number	Univariate analysis		Multivariate analysis	
	(%)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age			0.016		
<50	234(26.5)	1[Reference]			
50-59	262(29.7)	1.03(0.76-1.40)	0.857		
60-69	199(22.5)	1.10(0.79-1.52)	0.583		
≥70	188(21.3)	1.59(1.15-2.18)	0.005		
Race			<0.001		<0.001
White	693(78.5)	1[Reference]		1[Reference]	
Black	123(13.9)	1.90(1.43-2.53)	<0.001	1.77(1.31-2.38)	<0.001
Unknown	67(7.6)	1.10(0.71-1.68)	0.680	1.09(0.70-1.68)	0.705
N stage			<0.001		
N0	144(16.3)	1[Reference]			
N1	372(42.1)	1.49(1.02-2.18)	0.038		
N2	138(15.6)	1.38(0.89-2.16)	0.152		
N3	177(20.0)	1.85(1.22-2.78)	0.003		
N_X	52(5.9)	3.08(1.87-5.07)	<0.001		
M stage			<0.001		<0.001
M0	572(64.8)	1[Reference]		1[Reference]	
M1	311(35.2)	3.23(2.57-4.06)	<0.001	2.93(2.27-3.79)	<0.001
Surgery			<0.001		0.010

No surgery	355(40.2)	1[Reference]		1[Reference]	
Not MRM	162(18.3)	0.41(0.30-0.57)	<0.001	0.74(0.52-1.04)	0.086
MRM	352(39.9)	0.33(0.26-0.43)	<0.001	0.60(0.45-0.82)	<0.001
Unknown	14(1.6)	0.96(0.47-1.96)	0.911	1.11(0.54-2.30)	0.778
Radiation			<0.001		
No	487(55.2)	1[Reference]			
Yes	396(44.8)	0.57(0.45-0.72)	<0.001		
Chemotherapy			<0.001		<0.001
No	162(18.3)	1[Reference]		1[Reference]	
Yes	721(81.7)	0.41(0.32-0.54)	<0.001	0.46(0.34-0.63)	<0.001
Tumor size			0.015		0.010
<2cm	68(7.7)	1[Reference]		1[Reference]	
2-5cm	186(21.1)	0.90(0.55-1.47)	0.664	0.91(0.55-1.50)	0.715
>5cm	257(29.1)	1.40(0.89-2.20)	0.151	1.48(0.94-2.35)	0.093
Diffuse	179(20.3)	1.61(1.00-2.57)	0.048	1.39(0.86-2.25)	0.178
Unknown	193(21.9)	1.21(0.75-1.96)	0.429	0.95(0.57-1.57)	0.834
ER			<0.001		<0.001
Negative	386(43.7)	1[Reference]		1[Reference]	
Positive	455(51.5)	0.54(0.42-0.68)	<0.001	0.52(0.37-0.71)	<0.001
Unknown	42(4.8)	1.30(0.82-2.07)	0.267	1.22(0.37-4.06)	0.746
PR			<0.001		0.04
Negative	499(56.5)	1[Reference]		1[Reference]	
Positive	331(37.5)	0.60(0.46-0.77)	<0.001	0.64(0.45-0.91)	0.013

Other*	53(6.0)	1.28(0.84-1.95)	0.261	0.61(0.22-1.69)	0.337
Her-2			<0.001		<0.001
Negative	496(56.2)	1[Reference]		1[Reference]	
Positive	311(35.2)	0.49(0.38-0.65)	<0.001	0.12(0.04-0.39)	<0.001
Other*	76(8.6)	1.26(0.87-1.83)	0.221	1.16(0.66-2.03)	0.617
Marital status			0.002		
Married	400(45.3)	1[Reference]			
Divorce or widow	238(27)	1.29(0.97-1.71)	0.078		
Single	201(22.8)	1.47(1.10-1.95)	0.008		
Unknown	44(5.0)	2.10(1.35-3.29)	<0.001		

2 Abbreviations:

3 ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; MRM =

4 Modified radical mastectomy; *Other = borderline + unknown; Reference = This group is set as a reference group.

Patient characteristics and analyses based on overall survival status

1   Table 2. Patient characteristics and analyses based on overall survival status

Patient characteristics	Number	Univariate analysis		Multivariate analysis	
	(%)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age			<0.001		
<50	234(26.5)	1[Reference]			
50-59	262(29.7)	1.06(0.78-1.43)	0.727		
60-69	199(22.5)	1.21(0.88-1.65)	0.237		
≥70	188(21.3)	1.91(1.42-2.58)	<0.001		
Race			<0.001		0.003
White	693(78.5)	1[Reference]		1[Reference]	
Black	123(13.9)	1.70(1.29-2.24)	<0.001	1.64(1.23-2.18)	0.001
Unknown	67(7.6)	0.98(0.65-1.49)	0.093	0.99(0.65-1.52)	0.993
N stage			<0.001		
N0	144(16.3)	1[Reference]			
N1	372(42.1)	1.35(0.95-1.91)	0.096		
N2	138(15.6)	1.34(0.90-2.02)	0.153		
N3	177(20.0)	1.64(1.12-2.40)	0.011		
N_X	52(5.9)	3.21(2.04-5.05)	<0.001		
M stage			<0.001		<0.001
M0	572(64.8)	1[Reference]		1[Reference]	
M1	311(35.2)	2.98(2.40-3.69)	<0.001	2.58(2.03-3.29)	<0.001
Surgery			<0.001		0.004

No surgery	355(40.2)	1[Reference]		1[Reference]	
Not MRM	162(18.3)	0.39(0.29-0.54)	<0.001	0.71(0.51-0.99)	0.043
MRM	352(39.9)	0.33(0.26-0.42)	<0.001	0.59(0.45-0.79)	<0.001
Unknown	14(1.6)	0.84(0.41-1.71)	0.633	0.94(0.45-1.94)	0.864
Radiation			<0.001		
No	487(55.2)	1[Reference]			
Yes	396(44.8)	0.57(0.46-0.71)	<0.001		
Chemotherapy			<0.001		<0.001
No	162(18.3)	1[Reference]		1[Reference]	
Yes	721(81.7)	0.35(0.28-0.44)	<0.001	0.39(0.29-0.51)	<0.001
Tumor size			0.025		0.033
<2cm	68(7.7)	1[Reference]		1[Reference]	
2-5cm	186(21.1)	0.97(0.61-1.55)	0.904	0.97(0.61-1.56)	0.907
>5cm	257(29.1)	1.39(0.90-2.15)	0.140	1.47(0.95-2.29)	0.870
Diffuse	179(20.3)	1.63(1.04-2.55)	0.035	1.43(0.90-2.56)	0.131
Unknown	193(21.9)	1.33(0.85-2.09)	0.218	1.07(0.66-1.72)	0.786
ER			<0.001		
Negative	386(43.7)	1[Reference]		1[Reference]	
Positive	455(51.5)	0.59(0.47-0.73)	<0.001	0.56(0.41-0.76)	<0.001
Unknown	42(4.8)	1.33(0.85-2.07)	0.211	1.02(0.34-3.05)	0.972
PR			<0.001		0.021
Negative	499(56.5)	1[Reference]		1[Reference]	
Positive	331(37.5)	0.64(0.51-0.82)	<0.001	0.63(0.45-0.87)	0.006

Other*	53(6.0)	1.31(0.88-1.95)	0.19	0.70(0.28-1.75)	0.445
Her-2			<0.001		<0.001
Negative	496(56.2)	1[Reference]		1[Reference]	
Positive	311(35.2)	0.51(0.39-0.65)	<0.001	0.46(0.35-0.60)	<0.001
Other*	76(8.6)	1.27(0.89-1.81)	0.18	1.12(0.66-1.88)	0.677
Marital status			0.002		
Married	400(45.3)	1[Reference]			
Divorce or widow	238(27)	1.47(1.14-1.90)	0.003		
Single	201(22.8)	1.40(1.06-1.84)	0.017		
Unknown	44(5.0)	1.91(1.22-2.97)	0.004		

2   Other*= borderline + unknown.

Five-year overall survival of patients with IBC

1   Table 3. List of 5-year overall survival for patients with inflammatory breast carcinoma

Patient characteristics	Number	Kaplan-Meier	
	(%)	5-OS (%)	Median OS (months)
Age			
<50	234(26.5)	52.7	*
50-59	262(29.7)	52.8	63
60-69	199(22.5)	45.4	40
≥70	188(21.3)	35.2	26
Race			
White	693(78.5)	49.4	58
Black	123(13.9)	29.7	25
Unknown	67(7.6)	54.9	61
N stage			
N0	144(16.3)	61.6	*
N1	372(42.1)	48.7	56
N2	138(15.6)	48.5	49
N3	177(20.0)	43.3	36
N_X	52(5.9)	19.7	18
M stage			
M0	572(64.8)	60.4	*
M1	311(35.2)	24.0	21
TNM stage			
III	572(64.8)	60.4	*

IV	311(35.2)	24.0	21
Surgery			
No surgery	355(40.2)	29.3	21
Not MRM	162(18.3)	54.2	*
MRM	352(39.9)	60.5	*
Unknown	14(1.6)	32.5	29
Radiation			
No	487(55.2)	41.2	34
Yes	396(44.8)	54.2	*
Chemotherapy			
No	162(18.3)	25.1	15
Yes	721(81.7)	52.1	63
Tumor size			
<2cm	68(7.7)	53.3	*
2-5cm	186(21.1)	54.0	*
>5cm	257(29.1)	43.2	37
Diffuse	179(20.3)	40.3	29
Unknown	193(21.9)	50.1	66
Breast Subtype			
Her2-/HR+	293(33.2)	47.0	56
Triple Negative	200(22.7)	28.7	20
Her2+/HR-	151(17.1)	52.0	63
Her2+/HR+	159(18.0)	71.3	*

Unknown	80(9.1)	39.6	22
ER			
Negative	386(43.7)	39.5	29
Positive	455(51.5)	54.7	*
Unknown	42(4.8)	35.8	21
PR			
Negative	499(56.5)	43.5	35
Positive	331(37.5)	54.2	66
Other*	53(6.0)	38.8	22
Her-2			
Negative	496(56.2)	39.3	35
Positive	311(35.2)	62.7	*
Other*	76(8.6)	40.2	26
Number of LN			
Negative	104(11.8)	73.0	*
Positive	422(47.8)	52.8	63
Other	357(40.4)	34.2	25
Marital status			
Married	400(45.3)	53.6	66
Divorce or widow	238(27)	41.2	36
Single	201(22.8)	45.3	39
Unknown	44(5.0)	31.9	25

2 *There are no results