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Comparison of Clinicopathologic Features and Survival Outcomes of Pleomorphic Lobular, Classical Lobular, and Invasive Ductal Carcinoma

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ABSTRACT

Purpose: The objective of this research is to assess the clinical importance of pleomorphic lobular carcinoma (PLC) by contrasting its survival outcomes and clinicopathological characteristics with those of classical invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC).

Methods: Data from the SEER (Surveillance, Epidemiology, and End Results) database, which covers patients with breast cancer diagnosed between 2010 and 2021, are used in this retrospective analysis. Clinical, pathological, and demographic factors were noted. Kaplan–Meier and Cox regression models were used to conduct survival analyses.

Results: A total of 639,943 patients were included in the study. 182 (0.03%) patients were diagnosed with PLC, 74,565 (11.6%) were with ILC, and 565,196 (88.3%) were with IDC. Compared with ILC and IDC, PLC was associated with higher tumor grade, higher T, N stage, and stage 3–4 AJCC stage, higher hormone negativity, and triple negativity rates. Breast-conserving surgery (BCS) rates were lower in the PLC group, whereas mastectomy, no surgery, and chemotherapy rates were higher. Five-year and 10-year overall survival (OS) and disease-specific survival (DSS) rates were significantly lower in the PLC group than in both ILC and IDC ($p < 0.05$). However, when survival outcomes were evaluated according to stage, no statistically significant differences in overall survival (OS) or disease-specific survival (DSS) were found between PLC and ILC or between PLC and IDC across all disease stages ($p > 0.05$).

Conclusion: PLC, a very rare type of breast cancer, has worse clinicopathological features and worse survival outcomes than both ILC and IDC. These findings highlight the need for more specialized personalized targeted therapeutic strategies for PLC.

1 | Introduction

Pleomorphic lobular carcinoma (PLC) is an extremely rare breast cancer subtype that histologically classified as a subtype of lobular carcinoma [1, 2]. Although its growth pattern is the same as that of classical invasive lobular carcinoma (ILC), it often shows apocrine differentiation [2–5]. PLC, in addition to having the same distinct molecular genetic features as ILC (1q duplication and 16q deletion), exhibit additional genetic such as ERBB2 amplification resembling invasive ductal carcinoma (IDC) and histological changes such as higher grade (often grade 3) than ILC. In this respect, they may have similar and common or different features with both IDC and ILC [6, 7]. In addition, they usually express more P53 and less hormone

receptor [8]. All these features can explain their more aggressive biological behavior. Due to their faster proliferation and difficult clinical-radiological detection, they are usually diagnosed at a more advanced stage. Although the treatment techniques are similar to classical breast cancer, the response rate to treatment is low. Due to all these factors, it may have worse survival rates than both IDC and ILC [9].

Although there are several studies in the literature on the clinicopathological features, molecular behavior, treatment regimen, and prognosis of PLC, the small number of participants due to the rarity of the disease reduces the reliability of these studies. In this regard, the aim of this study was to compare the clinicopathological features, survival, and prognosis of PLC with both ILC and IDC using the latest updated version of the Surveillance, Epidemiology, and End Results (SEER) Program for cancer statistics in the United States in order to maintain the maximum number of patients and increase the reliability of the results.

2 | Materials and Methods

The Surveillance, Epidemiology, and End Results (SEER) 17 Registries Research Plus database was used in this study [10]. Data were obtained using the SEER*Stat program. Data of patients diagnosed with breast cancer between 2010 and 2021 were included. Since HER2 receptor status and molecular classification were added to the SEER database in 2010, the starting year of the study was chosen as 2010 [11].

According to the ICD-O-3 coding system used in histopathologic classification, patients with ICD-O-3 8022/3 pleomorphic lobular carcinoma (PLC), ICD-O-3 8500/3 invasive ductal carcinoma, NOS (IDC), and ICD-O-3 8520/3 invasive lobular carcinoma (ILC) were included. Demographic data, including age, race, and marital status, median household income, and residence type were recorded.

Male patients, those with histopathological subtypes other than PLC, ILC, and IDC as well as patients with T stage T0, Tis, and AJCC Stage 0, were excluded from the study (Figure 1).

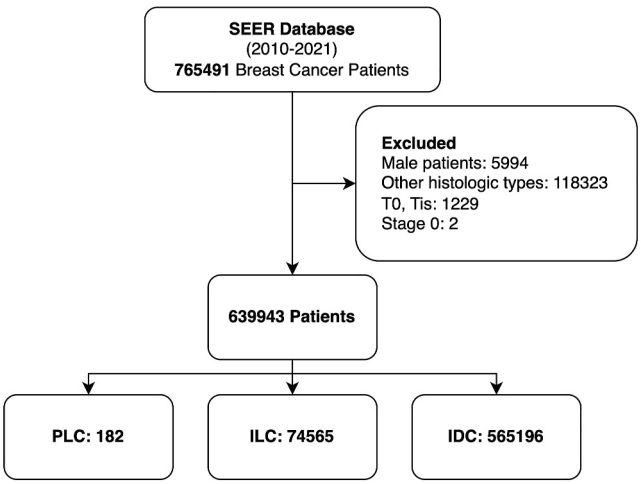

FIGURE 1 | Patient selection flowchart.

Year of diagnosis, localization, side, grade, estrogen receptor status, progesterone receptor status, HER2 receptor status, molecular subtype, tumor size (millimeters), TNM stage, and American Joint Committee on Cancer (AJCC) stage were recorded as clinical and pathological data.

Although the tumor grade was categorized into two groups: low grade (Grades 1 and 2) and high grade (Grades 3 and 4), estrogen–progesterone receptor status and HER2 amplification were classified as positive–negative. In molecular classification, the classification available in the SEER database was used (hormone positive/HER2 negative, hormone positive/HER2 positive, hormone negative/HER2 positive, hormone negative/HER2 positive, and hormone negative/HER2 negative).

In staging, the T stage was categorized as T1–2–3–4; T1A, T1B, T1C, T1mic, and T1NOS were accepted as T1. T4A, T4B, T4C, T4D, and T4NOS were accepted as T4. N stage was classified as N0–1–2–3; N0i-, N0i+, N0m-, and N0m+ were accepted as N0. N1A, N1B, N1C, and N1mi were accepted as N1. N2A and N2B as N2, N3A, N3B, and N3C were accepted as N3. M staging was classified as M0 and M1 and M0 (*i*+) was considered as M0. The staging was classified as stages 1–2–3–4, and stages 1A and 1B were considered as stage 1, stages 2A and 2B were considered as stage 2, and stages 3A, 3B, and 3C were considered as stage 3.

As oncologic data, surgical treatment status, radiotherapy status, chemotherapy status, systemic therapy, the presence of bone-brain-liver-lung metastasis, survival time (months), survival status, and cause of death were recorded.

Surgical status was classified as mastectomy, breast-conserving surgery (BCS), no surgery, and radiotherapy–chemotherapy treatment status as yes–no. Bone-brain-liver-lung metastases were classified as yes–no. Survival status was classified as alive, dead, and cause of death as breast cancer and other. The other group included all causes of death except breast cancer.

2.1 | Statistical Analysis

The statistical analyses were performed using SPSS for Mac (version 29.0.2.0 [20], SPSS Inc., Chicago, IL, USA) and R (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria). The normality of numerical variables was assessed using box plots, the Kolmogorov–Smirnov test, and descriptive statistical methods (mean and standard deviation for normally distributed data and median with interquartile range for abnormally distributed data).

For numerical data, comparisons among the three groups were conducted using a one-way ANOVA for normally distributed variables, whereas the Kruskal–Wallis test was used for nonparametric comparisons. Tukey's post hoc test was applied when equal variances were assumed, whereas Games-Howell post hoc test was used when equal variances were not assumed. Categorical data were analyzed using Pearson's chi-squared test, followed by pairwise post hoc comparisons with Bonferroni correction.

Overall survival (OS) and disease-specific survival (DSS) were estimated using Kaplan–Meier analysis and compared with the log-rank test. To adjust for potential confounding factors, inverse probability of treatment weighting (IPTW) with the propensity score method was applied instead of propensity score matching (PSM).

PSM was not suitable for our dataset due to several reasons. First, there was a significant sample size imbalance among the groups, particularly the relatively small number of patients in the PLC group compared to ILC and IDC. This imbalance made it difficult to match an adequate number of patients without significantly reducing the sample size. Second, applying strict caliper restrictions to improve matching quality resulted in excessive data loss, as many PLC cases could not be effectively matched. Lastly, there was a limited overlap in propensity score distributions between groups, leading to a high proportion of unmatched cases. Given these limitations, IPTW was chosen as it allowed the utilization of the entire dataset while adjusting for covariate imbalances.

The propensity score model included the following covariates: age group, marital status, home location, median household income (MHHI), race, sequence number, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, tumor stage, surgery, radiotherapy, and chemotherapy. Initially, the model also included subtype, tumor (T), and nodal (N) stage, but these were excluded to avoid collinearity with other covariates, particularly since tumor stage (STAGE) already incorporates T and N classifications.

Stabilized IPTW weights were calculated and trimmed at the 95th percentile to reduce the impact of extreme values. Covariate balance before and after weighting was assessed using standardized mean differences (SMDs) and Love plots. After weighting, the Kaplan–Meier survival analysis and Cox proportional hazards regression models were performed using the stabilized weights to estimate adjusted hazard ratios (HRs).

Cox regression analysis was conducted using both univariate and multivariate models to identify independent prognostic factors. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

3 | Results

A total of 639,943 female patients with breast cancer were included in the study, with 182 (0.03%) diagnosed with pleomorphic lobular carcinoma (PLC), 74,565 (11.6%) with invasive lobular carcinoma (ILC), and 565,196 (88.3%) with invasive ductal carcinoma (IDC) (Table 1).

The mean age was highest in the PLC group (65.2 $\pm$ 13.5), followed by ILC (65.0 $\pm$ 12.3) and IDC (61.4 $\pm$ 13.5) ($p < 0.001$). Although patients with PLC and ILC were more likely to be $\geq$ 65 years old, those with IDC were more likely to be under 65. White race was most common in all groups, with the highest proportion in PLC (84.6%). Most patients were married, and the majority lived in urban areas across all groups. The majority of patients in all three groups resided in areas with a median household income above $70,000 (Table 1).

Tumors in the PLC group were more frequently high grade (46.2%), larger in size (median 28.5 mm), and presented with more advanced T and N stages compared to ILC and IDC ($p < 0.001$). Specifically, PLC had the lowest rate of T1 tumors (31.9%) and N0 nodal status (57.1%) and the highest rates of T3–T4 (27.4%) and N2–N3 (17.0%) (Table 1).

The most common tumor subtype in PLC was HR+/HER2− (59.3%), yet triple-negative tumors (HR−/HER2−) were also significantly more frequent in PLC (19.2%) compared to ILC (1.6%) and IDC (11.6%) ($p < 0.001$). ER and PR negativity was significantly higher in PLC than in the other groups ($p < 0.001$) (Table 1).

Bone (7.7%), brain (1.1%), liver (2.7%), and lung (3.3%) metastases were significantly more frequent in the PLC group than in ILC and IDC ($p < 0.001$). Additionally, stage III–IV disease was more common in PLC than in ILC and IDC ($p < 0.001$) (Table 1).

Surgical treatment patterns varied significantly: BCS was less frequently performed in PLC (35.7%) compared to ILC (44.5%) and IDC (53.6%), whereas mastectomy was more common in PLC (47.8%). The rate of no surgery was also higher in PLC (16.5%) ($p < 0.001$). Radiotherapy was administered at similar rates across groups. However, chemotherapy was significantly more common in PLC (53.3%) than in ILC (28.7%) and IDC (41%) ($p < 0.001$). Among patients who underwent mastectomy, the rate of postmastectomy radiotherapy (PMRT) was similar in PLC (32.9%) and ILC (32.8%) but lower in IDC (26.6%) ($p < 0.001$) (Table 1).

In terms of survival outcomes, the 5-year overall survival (OS) rates were 68.2% for PLC, 81.7% for ILC, and 83.0% for IDC ($p < 0.001$). Similarly, the 10-year OS rates were 60.9% for PLC, 65.4% for ILC, and 69.9% for IDC, indicating significantly lower survival in the PLC group ($p < 0.001$). A similar trend was observed in disease-specific survival (DSS), where 5-year DSS rates were 80.7% for PLC, 89.9% for ILC, and 90.4% for IDC, whereas 10-year DSS rates were 75.4%, 82.4%, and 85.6%, respectively ($p < 0.001$). After inverse probability of treatment weighting (IPTW) adjustment, PLC continued to demonstrate lower OS and DSS compared to ILC and IDC, suggesting that the histological subtype remains an independent factor associated with worse prognosis (Figure 2).

When survival outcomes were evaluated according to stage, no statistically significant differences in overall survival (OS) or disease-specific survival (DSS) were found between PLC and ILC or between PLC and IDC across all disease stages ($p > 0.05$). However, a significant difference was observed between ILC and IDC, with survival rates varying between these two histologic subtypes depending on the stage ($p < 0.05$). These findings suggest that while PLC shows a generally worse prognosis overall, the stage-specific survival outcomes are not significantly different from ILC and IDC and the prognostic influence of histologic subtype may be more nuanced in stage-stratified analyses (Figure 3).

TABLE 1 | Clinicopathologic characteristics of pleomorphic lobular carcinoma, invasive lobular carcinoma, and invasive ductal carcinoma.

		PLC (n = 182) n (%)	ILC (n = 74,565) n (%)	IDC (n = 565,196) n (%)	p
Age	Mean ± SD	65.24 ± 13.49	64.96 ± 12.30	61.37 ± 13.52b	< *0.001*
	< 50	20 (11)a	9360 (12.6)a	116,787 (20.7)a	< *0.001*
	≥ 50–64	69 (37.9)a,b	25,727 (34.5)b	209,113 (37)a	
	≥ 65	93 (51.1)a,b	39,478 (52.9)b	239,296 (42.3)a	
Race	White	154 (84.6) a,b	62,501 (83.8)b	436,578 (77.2)a	< *0.001*
	Black	15 (8.2) a,b	6440 (8.6)b	61,891 (11)a	
	Others	12 (6.6) a,b	5018 (6.7)b	61,582 (10.9)a	
	Unknown	1 (0.5)	606 (0.8)	5145 (0.9)	
Marital status	Married	94 (51.6)	40,612 (54.5)	305,837 (54.1)	0.087
	Other	72 (39.6)	29,851 (40)	228,853 (40.5)	
	Unknown	16 (8.8)	4102 (5.5)	30,506 (5.4)	
Localization	Central	9 (4.9)a,b	4187 (5.6)b	27,348 (4.8)a	< *0.001*
	UOQ	54 (29.7)a,b	26,331 (35.3)b	194,805 (34.5)a	
	UIQ	19 (10.4)a,b	7873 (10.6)b	72,845 (12.9)a	
	LOQ	14 (7.7)a,b	5358 (7.2)b	43,287 (7.7)a	
	LIQ	9 (4.9)a,b	2906 (3.9)b	32,044 (5.7)a	
	Overlapping	39 (21.4)a	17,258 (23.1)a	130,701 (23.1)a	
	Not specified	38 (20.9)a	10,652 (14.3)b	64,166 (11.4)c	
Laterality	Right	83 (45.6)a,b	36,295 (48.7)b	278,313 (49.2)b	< *0.001*
	Left	97 (53.3)a	38,024 (51)a	285,955 (50.6)a	
	Bilateral	0 (0)a,b	31 (< 0.1)b	123 (< 0.1)b	
	Paired site	2 (1.1)a	200 (0.3)a	723 (0.1)a	
	Only one side, side unspecified	0 (0)a	15 (< 0,01)a	82 (< 0,01)a	
Median household income	< $50,000	10 (5.5)a,b	3802 (5.1)b	34,919 (6.2)a	< *0.001*
	$50,000–$70,000	49 (26.9)a,b	166,692 (22.4)b	137,608 (24.3)a	
	> $70,000	123 (67.6)a,b	54,071 (72.5)b	392,669 (69.5)a	
Residence type	Urban	166 (91.2)a,b	67,473 (90.5)b	505,738 (89.5)a	< *0.001*
	Rural	14 (7.7)a,b	7031 (9.4)b	58,707 (10.4)a	
	Unknown	2 (1.1)	61 (0.1)	751 (0.1)	
Sequence number	Only one primary	127 (69.8)a,b	48,766 (65.4)b	412,000 (72.9)a	< *0.001*
	2 or more primaries	55 (30.2)a,b	25,799 (34.6)b	153,196 (27.1)a	
Grade	Low	70 (38.5)a	63,106 (84.6)b	343,287 (60.7)c	< *0.001*
	High	84 (46.2)a	5396 (7.2)b	187,075 (33.1)c	
	Unknown	28 (15.4)	6063 (8.1)	34,834 (6.2)	
ER	Positive	124 (68.1)a	71,060 (95.3)b	450,370 (79.7)c	< *0.001*
	Negative	49 (26.9)a	1736 (2.3)b	102,238 (18.1)c	
	Unknown	9 (4.9)	1769 (2.4)	12,588 (2.2)	
PR	Positive	105 (57.7)a	60,100 (80.6)b	391,687 (69.3)c	< *0.001*
	Negative	68 (37.4)a	12,460 (16.7)b	159,510 (28.2)c	
	Unknown	9 (4.9)	2005 (2.7)	13,999 (2.5)	
HER2	Negative	143 (78.6)a	67,404 (90.4)b	445,180 (78.8)a	< *0.001*
	Positive	22 (12.1)a	3634 (4.9)b	89,373 (15.8)a	
	Unknown	17 (9.3)	3527 (4.7)	30,643 (5.4)	

(Continues)

TABLE 1 | (Continued)

		PLC (n = 182) n (%)	ILC (n = 74,565) n (%)	IDC (n = 565,196) n (%)	p
Molecular subtype	HR (+)/HER2 (−)	108 (59.3)a	66,120 (88.7)b	378,921 (67)a	< *0.001*
	HR (+)/HER2 (+)	15 (8.2)a	3267 (4.4)b	61,979 (11)a	
	HR (−)/HER2 (+)	6 (3.3)a	358 (0.5)b	27,132 (4.8)a	
	HR (−)/HER2 (−)	35 (19.2)a	1190 (1.6)b	65,638 (11.6)c	
	Unknown	18 (9.9)	3630 (4.9)	31,526 (5.6)	
Tumor size (mm)	Median (IQR)	28.5 (18–48.5)	20 (12–35)	16 (10–26)	< *0.001*
T Stage	T1	58 (31.9)a	36,183 (48.5)b	333,112 (58.9)c	< *0.001*
	T2	66 (36.3)a,b	23,586 (31.6)b	162,136 (28.7)a	
	T3	35 (19.2)a	9445 (12.7)b	27,753 (4.9)c	
	T4	15 (8.2)a	2230 (3)b	21,748 (3.8)c	
	Unknown	8 (4.4)	3121 (4.2)	20,447 (3.6)	
N stage	N0	104 (57.1)a	49,916 (66.9)b	384,499 (68)c	< *0.001*
	N1	38 (20.9)a,b	715,579 (20.9)b	129,531 (22.9)a	
	N2	17 (9.3)a	3706 (5, 7)b	23,227 (4.1)c	
	N3	14 (7.7)a	3407 (4, 9)a	15,137 (2.7)b	
	Unknown	9 (4.9)	1957 (2.6)	12,802 (2.3)	
AJCC stage	1	46 (25.3)a	40,347 (54.1)b	326,871 (57.8)c	< *0.001*
	2	66 (36.3)a	18,873 (25.3)b	142,934 (25.3)b	
	3	41 (22.5)a	8591 (11.5)b	48,968 (8.7)c	
	4	22 (12.1)a	4416 (5.9)b	28,219 (5)c	
	Unknown	7 (3.8)	2338 (3.1)	18,204 (3.2)	
Bone metastasis	Yes	14 (7.7)a	3424 (4.6)a	18,018 (3.2)b	< *0.001*
	No	164 (90.1)a	70,305 (94.3)a	540,957 (95.7)b	
	Unknown	4 (2.2)	836 (1.1)	6221 (1.1)	
Brain metastasis	Yes	2 (1.1)a	171 (0.2)b	2061 (0.4)	< *0.001*
	No	175 (96.2)a	73,499 (98.6)b	556,581 (98.5)a	
	Unknown	5 (2.7)	895 (1.2)	6554 (1.2)a	
Liver metastasis	Yes	5 (2.7)a	676 (0.9)b	7279 (1.3)a	< *0.001*
	No	173 (95.1)a	73,012 (97.9)b	551,530 (97.6)a	
	Unknown	4 (2.2)	877 (1.2)	6387 (1.1)	
Lung metastasis	Yes	6 (3.3)a	443 (0.6)b	9238 (1.6)a	< *0.001*
	No	171 (94)a	73,223 (98.2)b	549,393 (97.2)a	
	Unknown	5 (2.7)	899 (1.2)	6565 (1.2)	
Surgery	BCS	65 (35.7)a	33,152 (44.5)b	303,203 (53.6)c	< *0.001*
	Mastectomy	87 (47.8)a	33,300 (44.7)a	206,598 (36.6)b	
	No surgery	30 (16.5)a	7895 (10.6)b	53,859 (9.5)c	
	Unknown	0 (0)	218 (0.3)	1536 (0.3)	
Radiotherapy	Yes	84 (46.2)a,b	38,064 (51)b	303,022 (53.6)a	< *0.001*
	No	98 (53.8)a,b	36,501 (49)b	262,174 (46.4)a	
Radiotherapy sequence	After surgery	76 (41.8)a,b	35,188 (47.2)b	276,157 (48.9)a	< *0.001*
	Prior surgery	1 (0.5)a,b	118 (0.2)b	1240 (0.2)a	
	Intraoperative	0 (0)a,b	343 (0.5)b	4659 (0.8)a	
	Unknown radiotherapy sequence	7 (3.8)a,b	2415 (3.2)b	20,966 (3.7)a	
	No radiotherapy	98 (53.8)a,b	36,501 (49)b	262,174 (46.4)a	

(Continues)

TABLE 1 | (Continued)

		PLC (n = 182) n (%)	ILC (n = 74,565) n (%)	IDC (n = 565,196) n (%)	p
PMRT	Yes	28 (32.9)a	10,604 (32.8)a	53,148 (26.6)b	*< 0.001*
	No	57 (67.1)a	21,768 (67.2)a	146,986 (73.4)b	
Chemotherapy	Yes	97 (53.3)a	21,400 (28.7)b	231,549 (41)c	*< 0.001*
	No	85 (46.7)a	53,165 (71.3)b	333,647 (59)c	
Chemotherapy sequence	Adjuvant	79 (43.4)a	17,634 (23.6)b	174,721 (30.9)c	*< 0.001*
	CR to NAC	7 (3.8)a	421 (0.6)b	18,238 (3.2)a	
	PR to NAC	4 (2.2)a,b	1451 (1.9)b	18,359 (3.2)a	
	NR to NAC	1 (0.5)a,b	728 (1)b	4492 (0.8)a	
	Unknown response to NAC	6 (3.3)a,b	1166 (1.6)b	15,739 (2.8)a	
	No chemotherapy	85 (46.7)a	53,165 (71.3)b	333,647 (59)c	
Cause of death	Alive	126 (69.2)a	60,360 (80.9)b	466,516 (82.5)c	*< 0.001*
	Breast cancer	32 (17.6)a	7064 (9.5)b	49,004 (8.7)c	
	Other	24 (13.2)a,b	7141 (9.6)b	49,676 (8.8)a	

Note: a; one way ANOVA test, b; Pearson's chi-squared test, c; Fisher-Freeman-Halton test, d; Mann–Whitney U test, and e; Fisher's exact test. Italicized values in the tables represent p-values. Statistical significance was defined as $p < 0.05$ throughout the analysis.
Abbreviations: BCS, breast-conserving surgery; CR, complete response; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive lobular carcinoma; ILC, invasive lobular carcinoma; IQR, interquartile range; LIQ, lower inner quadrant; LOQ, lower outer quadrant; NAC, neoadjuvant chemotherapy; NR, no response; PLC, pleomorphic lobular carcinoma; PMRT, postmastectomy radiotherapy; PR, partial response; PR, progesterone receptor; SD, standard deviation; UIQ, upper inner quadrant; and UOQ, upper outer quadrant.

Survival outcomes differed markedly using the hormone receptor (HR) status. In the HR-positive group, 5-year OS and DSS rates were 77.8% and 88.2% for PLC, 85.6% and 92.6% for ILC, and 86.8% and 93.3% for IDC, respectively. In the HR-negative group, PLC again showed the worst outcomes, with 5-year OS and DSS rates of 48.8% and 61.5%, compared to 66.4% and 77.3% in ILC and 72.7% and 80.7% in IDC ($p < 0.001$ for all comparisons). These results indicate that PLC has significantly poorer survival than ILC and IDC in both HR-positive and HR-negative subgroups, with the disparity being more pronounced in the HR-negative setting (Figure 4).

In univariate analysis, the risk of death for overall survival (OS) was significantly lower in both ILC (HR: 0.67, 95% CI: 0.52–0.87, and $p = 0.003$) and IDC (HR: 0.60, 95% CI: 0.46–0.78, and $p < 0.001$) compared to PLC. However, in multivariate analysis, no statistically significant difference in OS was observed between PLC and ILC (HR: 0.93, 95% CI: 0.71–1.21, and $p = 0.575$) or IDC (HR: 0.96, 95% CI: 0.74–1.25, and $p = 0.766$).

Similarly, in disease-specific survival (DSS) analysis, univariate results showed a significantly lower risk of breast cancer-related death in both ILC (HR: 0.58, 95% CI: 0.41–0.82, and $p = 0.002$) and IDC (HR: 0.52, 95% CI: 0.37–0.73, and $p < 0.001$) compared to PLC. Yet, after multivariate adjustment, the differences were no longer statistically significant for either ILC (HR: 1.13, 95% CI: 0.80–1.61, and $p = 0.475$) or IDC (HR: 1.07, 95% CI: 0.76–1.51, and $p = 0.708$).

These findings suggest that although PLC is associated with worse survival in unadjusted analyses, histologic subtype alone is not an independent predictor of survival when accounting for patient demographics (age, race, marital status, median household income, and residential area), tumor characteristics (grade, stage, ER, PR, and HER2 status), and treatment modalities (surgery type, radiotherapy, and chemotherapy). Table 2 provides a comprehensive overview of the risk factors affecting OS and DSS for the PLC group.

4 | Discussion

Although PLC is a type of invasive lobular carcinoma that maintains its characteristic development pattern according to the World Health Organization (WHO) and other sources, it has a more aggressive clinical course with a higher degree of cellular atypia and pleomorphism than the classical form [1, 2, 12–14]. PLC has generally been associated in the literature with an aggressive biology due to poor histological grade, higher Ki-67 values, increased HER2 expression, increased lymphovascular invasion, large tumor size, axillary lymph node metastases, and a high risk of recurrence, short time to recurrence, and poor survival compared to ILC [15–23]. It has been observed that studies in the literature generally compare PLC with ILC. Yang et al. SEER database studies compared PLC with IDC only. Our study differs from other studies in that it evaluates PLC with both ILC and IDC and strengthens the literature information by having the largest number of patients.

In their study, using the SEER database, Yang et al. demonstrated that PLC (n:131) had a worse prognosis than IDC (n:460,109) with higher AJCC stage, longer age, greater lymph node involvement, and a worse median survival time [23]. The results of our study confirm this information by showing that patients with PLC have a higher N2 and N3 stage than both ILC and IDC, with higher nodal metastasis rates resulting in a higher AJCC staging. Most studies have shown that PLC, such as ILC, has larger tumor sizes at diagnosis and is associated with

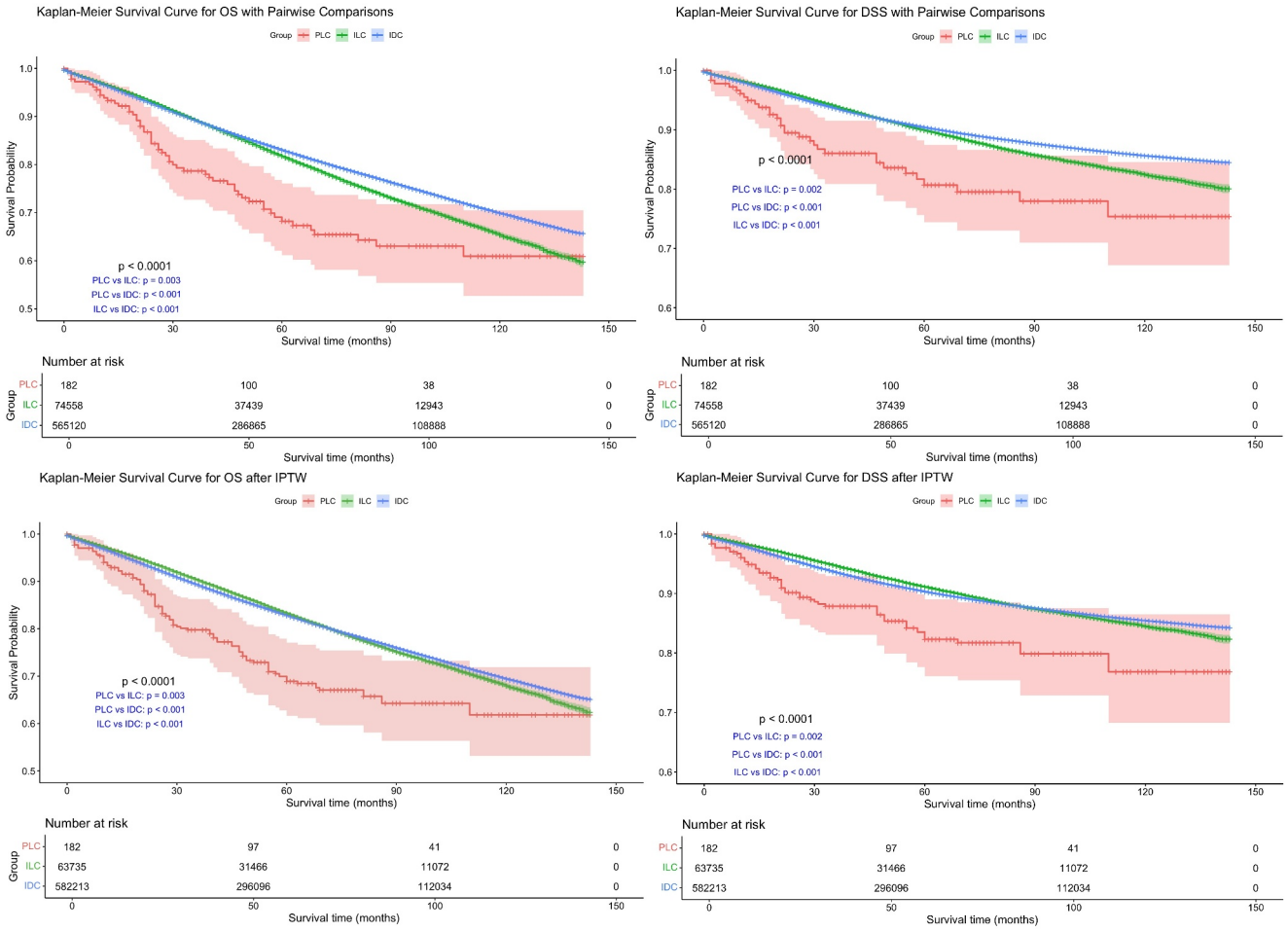

FIGURE 2 | Kaplan–Meier survival curves for OS and DSS. [Colour figure can be viewed at wileyonlinelibrary.com]

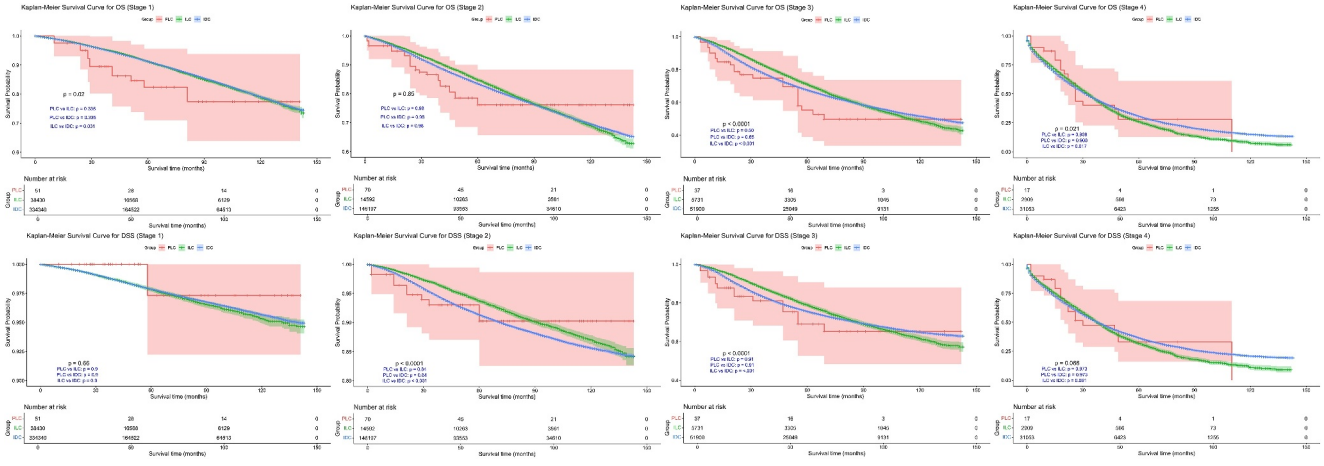

FIGURE 3 | Kaplan–Meier survival curves using AJCC stage. [Colour figure can be viewed at wileyonlinelibrary.com]

higher T stage [18, 24, 25]. In the study by Jung et al., the mean tumor size of PLC (n:35) was 3.2 ± 1.8 cm and that of IDC (n:6184) was 2.2 ± 1.5 cm [9]. In the study by Buchanan et al., the mean tumor size of PLC (n:52) (20 mm) was larger than that of ILC (n:298) (15 mm) [15]. This may be explained by the fact that PLC is difficult to recognize clinically and radiologically because of its spreading pattern in a cell line and tends to grow more rapidly. In our study, PLC was associated with higher T stage and therefore higher tumor size than both ILC and IDC. Beyond high T stage, PLC has been shown to be more likely to be multifocal and multicentric than IDC similar to ILC [9, 18]. Although multifocality and multicentricity could not be assessed in our study, the higher mastectomy and lower BCS rate in PLC compared to IDC may be explained by the higher probability of the tumor being multifocal/multicentric. Additionally, higher no surgery and higher chemotherapy rates also

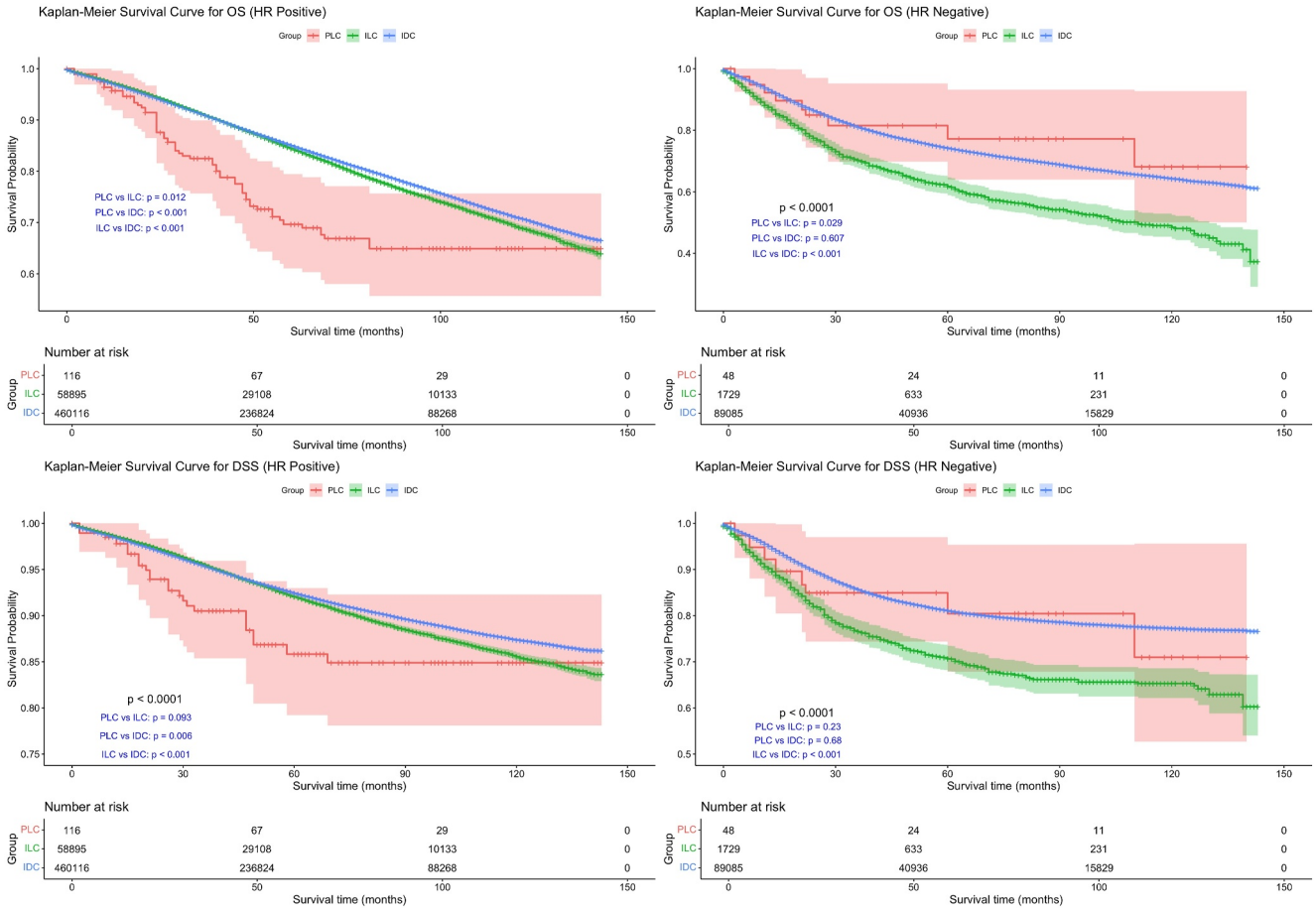

FIGURE 4 | Kaplan–Meier survival curves using HR status. [Colour figure can be viewed at wileyonlinelibrary.com]

explain the higher likelihood of metastatic disease in PLC. Similarly, the lower rate of radiotherapy may be explained by the fact that the disease is more frequently associated with large tumor size or multifocal/multicentric disease and mastectomy is more frequently preferred. On further analysis of the use of postmastectomy RT (PMRT) in the PLC group, considering overall tumor size and other clinicopathological factors, we observed that PMRT rates remained relatively low despite the larger tumor size and more aggressive nature of PLC. This may be attributed to higher mastectomy rates as a result of larger tumor sizes, higher multifocality/multicentricity, or possible differences in clinical decision-making.

It is known that 80%–95% of ILCs are ER-positive and more frequently of the Luminal A subtype compared to IDCs (60%–70%) [21]. Although PLC is often of the hormone-positive molecular subtype, triple negativity or HER2 positivity is more common than ILC [21]. The study by Cha et al. showed that 25% (*n*:12) of PLCs were of the Luminal A subtype, which was significantly lower compared to ILC (*n*:102, 81, 4%) [26]. In contrast, the rates of triple-negative (8.3%; 3.9%, PLC vs. ILC, respectively) and HER2-positive (8.3%; 0%) disease were higher in PLC. Some studies have shown that ER/PR positivity of PLC ranges from 0% to 20% [13, 27, 28]. This is a striking difference compared to ILC. However, later publications show that the hormone receptor status is similar to that seen in ILC (57%–96%) [6, 9, 17]. In our study, although hormone positivity were high in PLC, they were lower than in ILC and IDC, supporting previous studies. In addition, the rate of triple-negative disease in PLC was higher than in ILC and IDC.

Approximately 20%–30% of all breast cancers have HER2 gene amplification [29]. PLC may show variability in HER2 expression across studies. Jacobs et al. observed that none of the PLC patients (*n*:7) had HER2 staining using immunohistochemistry, whereas Middleton et al. reported that 81% of PLCs (*n*:38) had membranous staining for the HER2 receptor [17, 22]. In the Cha et al. study, HER2 positivity in PLC (*n*:12) was 8.3%, whereas in the Jung et al. study (*n*:35), it was 14% [9, 26]. The results of our study are similar to the results of Jung et al. in terms of HER2 positivity (12.1%). Significantly higher than ILC (4.9%) but lower than IDC (%15.8). The reason why HER2 positivity is so variable in PLCs and all other breast cancers may be explained using the different criteria for staining (immunohistochemistry or fluorescence in situ hybridization (FISH)) or using the different genetic characteristics of the patients included in the cohort.

Considering all the factors discussed above, it is expected that the survival rates in PLC are lower than ILC and/or IDC. However, in the survival analysis of Choi et al., it was reported that PLC (*n*:46) did not show any significant difference in overall survival rates compared to ILC (*n*:147) despite having high-risk clinicopathological features [30]. In the SEER study by Yang et al., which compared only PLC (*n*:131) and IDC (*n*:460,109), lower disease-specific survival (DSS) rates were observed in PLC compared to IDC in univariate analysis (hazard

TABLE 2 | Risk factors affecting overall survival and disease specific survival in pleomorphic lobular carcinoma.

	Overall survival				Disease specific survival			
	Univariate		Multivariate		Univariate		Multivariate	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
Age								
< 50	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference
≥ 50–64	0.408	1.874 (0.423–8.307)	< 0.001	1.246 (1.219–1.274)	< 0.001	0.939 (0.917–0.961)	< 0.001	1.095 (1.065–1.125)
≥ 65	0.018	5.566 (1.344–23.043)	< 0.001	2.760 (2.703–2.817)	< 0.001	1.257 (1.229–1.286)	< 0.001	1.515 (1.474–1.558)
Marital status								
Married		Reference		Reference		Reference		Reference
Other	0.016	1.901 (1.125–3.212)	< 0.001	1.527 (1.508–1.547)	< 0.001	1.769 (1.739–1.800)	< 0.001	1.290 (1.265–1.316)
Race								
White	0.198	Reference			< 0.001	Reference	< 0.001	Reference
Black	0.084	1.943 (0.915–4.124)			< 0.001	1.782 (1.743–1.822)	< 0.001	1.182 (1.151–1.215)
Others	0.722	0.773 (0.187–3.195)			< 0.001	0.821 (0.796–0.847)	< 0.001	0.839 (0.809–0.871)
MHI								
< $50,000	0.646	Reference			< 0.001	Reference	< 0.001	Reference
$50,000–$70,000	0.368	1.970 (0.450–8.621)			< 0.001	0.844 (0.817–0.871)	0.004	0.941 (0.903–0.981)
> $70,000	0.354	1.958 (0.472–8.118)			< 0.001	0.686 (0.665–0.707)	< 0.001	0.810 (0.777–0.845)
Residence type								
Urban		Reference				Reference		Reference
Rural	0.155	0.359 (0.087–1.473)			< 0.001	1.173 (1.143–1.204)	0.378	1.016 (0.981–1.053)
Sequence number								
Only one primary		Reference				Reference		Reference
2 or more primaries	0.624	1.154 (0.651–2.044)			< 0.001	1.094 (1.075–1.114)	< 0.001	1.096 (1.073–1.120)
Grade								
Low		Reference				Reference		Reference
High	0.820	1.063 (0.629–1.798)			< 0.001	2.712 (2.664–2.761)	< 0.001	1.725 (1.687–1.765)
ER								
Positive		Reference		Reference		Reference		Reference
Negative	< 0.001	1.623 (1.600–1.646)	< 0.001	1.442 (1.413–1.472)	< 0.001	2.398 (2.354–2.442)	< 0.001	1.334 (1.295–1.373)
PR								
Positive		Reference		Reference		Reference		Reference
Negative	< 0.001	1.628 (1.608–1.648)	< 0.001	1.333 (1.310–1.357)	< 0.001	2.378 (2.338–2.419)	< 0.001	1.541 (1.500–1.583)

(Continues)

TABLE 2 | (Continued)

	Overall survival				Disease specific survival			
	Univariate		Multivariate		Univariate		Multivariate	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
HER2								
Negative		Reference				Reference		Reference
Positive	0.990	1.000 (0.983–1.017)			< 0.001	1.234 (1.207–1.262)	< 0.001	1.521 (1.482–1.561)
AJCC stage								
1	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference
2	< 0.001	1.749 (1.723–1.776)	< 0.001	1.886 (1.855–1.918)	< 0.001	3.806 (3.702–3.914)	< 0.001	3.162 (3.061–3.265)
3	< 0.001	3.570 (3.508–3.634)	< 0.001	4.368 (4.277–4.461)	< 0.001	11.516 (11.194–11.847)	< 0.001	9.476 (9.145–9.818)
4	< 0.001	12.719 (12.499–12.944)	< 0.001	7.245 (7.065–7.428)	< 0.001	47.104 (45.832–48.412)	< 0.001	21.338 (20.510–22.200)
Surgery								
BCS	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference
Mastectomy	< 0.001	1.457 (1.437–1.477)	0.001	1.028 (1.011–1.046)	< 0.001	2.487 (2.433–2.543)	< 0.001	1.359 (1.323–1.397)
No surgery	< 0.001	8.355 (8.231–8.481)	< 0.001	2.692 (2.629–2.757)	< 0.001	16.964 (16.588–17.350)	< 0.001	3.548 (3.422–3.679)
Radiotherapy								
Yes		Reference		Reference		Reference		Reference
No	< 0.001	2.144 (2.118–2.170)	< 0.001	1.450 (1.428–1.473)	< 0.001	2.007 (1.973–2.041)	< 0.001	1.203 (1.176–1.231)
Chemotherapy								
Yes		Reference		Reference		Reference		Reference
No	< 0.001	1.109 (1.096–1.122)	< 0.001	1.526 (1.503–1.550)	< 0.001	1.736 (1.707–1.765)	< 0.001	1.372 (1.340–1.404)

Abbreviations: BCS, breast-conserving surgery; CI, confidence interval; HER2, human epidermal receptor; HR, hazard ratio; and MHI, median household income.

ratio: 0.691, 95% confidence interval 0.534–0.893, and $p < 0.01$), whereas in multivariate analysis, where they also took into account other prognostic factors, no significant difference was shown in terms of DSS [23]. On the contrary, our study showed that PLC has a higher rate of advanced T,N and AJCC stage with a lower both overall and disease-specific survival rates. When evaluating the factors affecting survival outcomes, multivariate analysis revealed that age, marital status, income level, tumor stage and grade, ER, PR, and HER2 status, surgical treatment, chemotherapy, and radiotherapy were all significantly associated with both overall survival (OS) and disease-specific survival (DSS). Older age, being unmarried, lower income, advanced stage, and high-grade tumors, hormone receptor negativity, HER2 positivity, lack of surgery, and absence of systemic therapies were identified as independent poor prognostic factors. Notably, the absence of surgical treatment was associated with a significantly increased risk of mortality, underscoring the critical impact of access to appropriate therapy on survival. These findings suggest that the poor prognosis of PLC may not be solely attributable to its histological subtype but also to more aggressive tumor characteristics and limited treatment application. For all that, when survival outcomes were evaluated according to stage, no statistically significant differences in overall survival (OS) or disease-specific survival (DSS) were found between PLC and ILC or between PLC and IDC across all disease stages.

Today, PLC medical treatment is similar to other breast cancer treatments depending on the stage. Although there are very limited PLC data, it is commonly accepted that adjuvant chemotherapy is less helpful in ILC than in IDC as there is no strong proof to support this claim for PLC [18]. Due in part to poor pathological and biomarker characteristics at presentation and the belief that PLC has worse outcomes, certain oncologists have a predisposition to support adjuvant chemotherapy in PLC. The use of neoadjuvant chemotherapy in locally advanced PLC is also poorly documented. It has been accepted that IDC combined with neoadjuvant chemotherapy yields a higher complete response rate than typical ILC [18]. However, the results of our study show that complete response rates to neoadjuvant chemotherapy were higher in the PLC group than in both groups and also that adjuvant chemotherapy rates were higher in PLC. This issue also requires data proven using extensive research.

5 | Limitations

To our knowledge, this study has the largest number of patients compared to all other studies in the literature on PLC and is different from the others in which it reveals the differences of PLC from both ILC and IDC in terms of both clinicopathology and survival from a broad perspective. However, it is necessary to mention some limitations. The SEER database did not have information on multifocality/multicentricity or gene profile status, such as BRCA1-2. Furthermore, it was not possible to assess significant prognostic factors including the presence of endocrine therapy, adjuvant–neoadjuvant chemotherapy procedure, and Ki-67 levels. Therefore, these factors could not be taken into account in the evaluation.

6 | Conclusion

In this study, it has been shown that PLC had higher grade, lower hormone positivity, higher HER2 positivity, larger tumor size at diagnosis, more axillary lymph node metastases, more advanced TNM stage, and is more associated with aggressive molecular subtypes than both ILC and IDC. In addition, PLC was shown to have lower OS and DSS and thus a worse prognosis compared to both IDC and ILC. Large-scale research is necessary to better understand the clinical and biochemical characteristics of PLC in order to provide individualized therapy choices.

Author Contributions

Ahmet Necati Sanli: conceptualization, investigation, funding acquisition, writing – original draft, methodology, formal analysis, data curation, resources, software, project administration. **Halil Kara:** conceptualization, supervision, writing – review and editing. **Deniz Esin Tekcan Sanli:** conceptualization, investigation, writing – original draft, writing – review and editing, supervision. **A. Enes Arikan:** writing – review and editing, supervision, validation, visualization. **Neslihan Cabioglu:** validation, visualization, writing – review and editing, supervision. **Cihan Uras:** validation, visualization, writing – review & editing, supervision.

Ethics Statement

This study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (30.05.2024; approval number: 2024-09/348).

Consent

Informed consent was not required for this study, as it utilized de-identified, publicly available data from the SEER database, in compliance with applicable ethical guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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