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# Prognostic significance of malignant pleural effusions in patients with advanced luminal B breast cancer

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## Abstract

**Background** Though the survival of breast cancer (BC) patients with malignant pleural effusion (MPE) has been studied, this has not been specifically studied in the luminal B subtype. Therefore, this study investigated the characteristics and survival of luminal B-BC patients presenting with MPE.

**Methods** We retrospectively analyzed 141 patients diagnosed with postoperative advanced Luminal B breast cancer, including 54 cases with MPE and 87 cases without MPE at the Tianjin Cancer Hospital from January 2012 to January 2015. We assessed the clinical characteristics between the groups.

**Results** The mean age of all patients was 47 years, with no significant difference between the two groups. Altogether, 29 (33%), 24 (28%), 28 (32%), 45 (52%), and 10 (11%) patients had lung, liver, bone, lymph node, and chest wall metastases, respectively. In addition, the difference in overall survival between the two groups was not significant ( $P > 0.05$ ). However, cox regression analysis showed that only the tumor clinical stage at initial diagnosis was related to short overall survival. Further, we conducted a subgroup analysis and found that the higher the clinical stage at initial diagnosis in age < 50 years patients, the shorter the overall survival, while age > 50 years patients was not. ( $P < 0.05$ ).

**Conclusions** There was no difference in the overall survival between luminal B-BC patients with MPE and those without. Clinical stages at initial diagnosis were an independent prognostic factor for age < 50 years luminal B BC with MPE overall survival. Our results may help clinicians make positive decisions regarding personalized treatment of luminal B-BC with MPE.

**Keywords** Breast cancer, Malignant pleural effusion, Clinical features, Survival, Luminal B

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## Introduction

Malignant pleural effusion (MPE) is a medical condition often secondary to a variety of diseases, especially cancers and tuberculosis [1]. Cancers that cause MPE in order of frequency are lung cancer, breast cancer, and lymphoma. Breast cancer (BC) is one of the most common cancers and the second leading cause of cancer-associated deaths in women. Some studies have shown that advanced breast carcinoma is the second most common cause of malignant effusions ranging from 7–23% depending on increases in advanced stages, and is often associated with poor prognosis [2, 3]. Although systemic therapy options (surgery, radiotherapy, and chemotherapeutic agents) have been tested, those are largely palliative, including symptomatic control and chemical pleurodesis, which promotes symphysis of the parietal and visceral pleura to prevent exudate accumulation. Furthermore, as previously emphasized, a diverse array of management strategies is now accessible for the management of MPE. Nevertheless, each of these interventions carries its unique implications, encompassing both the patient's burden and the financial strain imposed on the healthcare system [4, 5]. Thus, the recently updated pleural guidelines from the British Thoracic Society (BTS) in 2023 present a comprehensive framework for addressing dyspnea associated with malignant pleural effusions (MPEs). These guidelines meticulously outline various procedural and strategic interventions, emphasizing not only the prognostic implications and potential for lung re-expansion, but also the paramount importance of aligning treatment with patient priorities and preferences. Recognizing the absence of a universally 'correct' definitive management strategy, the BTS guidelines underscore the need for a highly individualized approach that integrates patient-centered considerations, including the choice between inpatient and ambulatory care, to optimize outcomes and ensure patient satisfaction [6].

Luminal B is one of the most frequently occurring in five clinically and biologically relevant molecular subtypes of breast cancer in the population. Compared to patients with the other subtype, those with luminal B tumors have worse prognoses [7]. Moreover, several studies have suggested that the increased approximately 18–45% relapse risk associated with the luminal B phenotype appears to have a predilection for pleural metastases and occur MPE within the first 5 years after surgery [8–10]. Despite the establishment of endocrine therapy and anti-HER2 therapy as cornerstone treatments for luminal B breast cancer, this subtype of malignancy continues to pose a significant therapeutic challenge. Regrettably, despite remarkable advances in patient survival outcomes over recent years, attributed to the employment of diverse therapeutic strategies, luminal B breast cancer remains an incurable condition [11, 12]. Furthermore,

prior investigative endeavors have unveiled that individual diagnosed with luminal B subtype of breast cancer, in whom the presence of MPE, irrespective of its extent, may portend a less favorable prognostic outlook. [13, 14]. Therefore, it is essential to judge the prognosis of luminal B breast cancer patients with MPE to better stratify patients and guide their therapy. However, as far as we know, the survival in luminal B BC patients presenting with MPE has been seldom reported.

This study aimed to investigate previously unreported observations on outcomes in luminal B BC patients presenting with MPE.

## Methods

### Study design

A retrospective review of all consecutive primary BC patients who developed MPE and aged between 18 and 80 years, were eligible for the study. The study site was the Tianjin Cancer Hospital and lasted from January 2012 to January 2015. The inclusion criteria were as follows: (a). diagnosis of luminal B breast cancer verified by biopsy or surgical resection; The exclusion criteria were as follows: (a). patients with double primary malignant tumors; (b). patients without a complete clinical history; (c). patients who developed MPE within one month after surgery. A total of 141 consecutive patients diagnosed with advanced luminal B BC were included in the study. The detailed pathological and histologic type, and Clinical stages at initial diagnosis of the primary tumor were recorded in a questionnaire. The study protocol was approved by the Tianjin Cancer Hospital ethics committee and The Affiliated General Hospital Binhai Hospital of Tianjin Medical University, and informed consent was obtained from all patients. An immunohistochemical (IHC) analysis was performed to classify the patients into molecular subtypes (IHC-based subtypes) [15].

### Clinicopathological evaluation

We retrospectively evaluated clinicopathological factors such as estrogen receptor (ER) and progesterone receptor (PR) status, HER2 status (0–3+score as recommended by the Dako HercepTest kit scoring guidelines with >3+ defined as positive), and Ki67 status (positivity cut-off 14%). Cases with IHC scores of 2+ with gene amplification by fluorescence in situ hybridization (FISH) were considered positive for HER2. A cut-off value of 1% for both receptors was used to classify the expression of ER and PR according to the criteria proposed by the American Society of Clinical Oncology (ASCO) [16]. When immunostaining was observed in more than 1% of the tumor nuclei, the tumor was considered ER- or PR- positive. The definition of luminal B was as follows: either HER2-negative and ER-positive, or HER2-negative and either Ki-67 high or PR low; luminal B-like was

either HER2- and ER-positive, or HER2 overexpressed or amplified, and low or high Ki-67 and PR. The immunostaining results were evaluated independently by two pathologists.

### Diagnosis and therapy for pleural effusions

A posteroanterior chest X-ray (CXR-PA), chest computed tomography (CT) scan or ultrasonography was carried out for the determination of the volume of the effusion and the affected area. MPE was defined by positive pleural fluid cytology, tissue histology or multidisciplinary meeting consensus. The various treatments (chemotherapy, radiotherapy, and hormone therapy) and therapeutic options (thoracenteses and bedside insertion of an indwelling pleural catheter) were extracted from the electronic medical charts.

### Statistical analyses

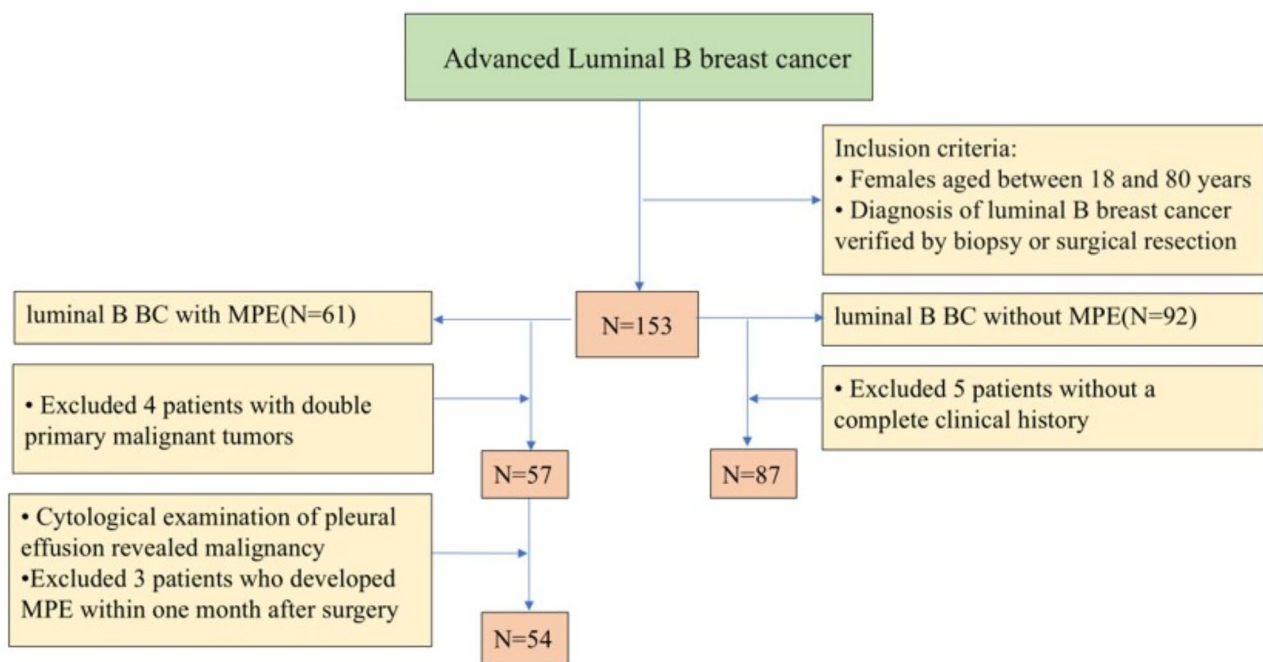
The primary endpoint of this study was overall survival (OS). OS was calculated from the date of primary BC first postoperative diagnosis to the date of death or last follow-up to December 2015. The Student's t-test and the chi-squared test were used to compare the clinical characteristics between groups. Continuous and categorical variables are expressed as percentages.  $P < 0.05$  was considered statistically significant. For categorical variables, missing data were included as a "Unknown" category. The OS rates were calculated using the Kaplan-Meier method, and the groups were compared using the log-rank test. For the multivariate analysis, Cox regression

analysis was used. All analyses were conducted with SPSS version 24.0 statistical software (Chicago, IL, USA).

## Results

### Demographics

The cohort comprised 141 luminal B BC patients among whom 54 (38.3%) had MPE. Amongst the MPE cases, 2 had MPE due to congestive cardiac failure, and they responded to heart disease medical treatment. We analyzed all the 54 cases with MPE [Fig. 1]. All cases were female. The histological distribution included 50 (92.6%) invasive ductal carcinomas, 1 (1.9%) invasive lobular carcinoma, and 3 (5.6%) other types of carcinomas (1 low-grade adenocarcinoma, 1 papillary carcinoma, and 1 neuroendocrine carcinoma). Eight (14.9%) patients were HER2-positive while 46 (85.2%) were negative. The clinical-stage data was available for only 54 patients. The number of patients with tumors in stage I, II, III, and unknown stage was 5 (9.3%), 15 (27.8%), 24 (44.4%), and 10 (18.5%), respectively. The percentage of patients with lung metastatic, liver metastatic, bone metastatic, and others sites metastatic was 22 (40.7%), 12 (22.2%), 27 (50.0%), and 42 (77.8%), respectively. Treatments instituted included chemotherapy (45 patients, 83.3%), radiotherapy (24 patients, 44.4%), endocrine therapy (34 patients, 63.0%), and neoadjuvant chemotherapy (11 patients, 20.3%) [Table 1]. Most of the patients were between 30 and 70 years of age (youngest was 23 years and oldest was 70 years) with mean  $47.0 \pm 10.3$ . In this study, 4 (25.9%), 18 (33.3%), and 22 (40.7%) patients

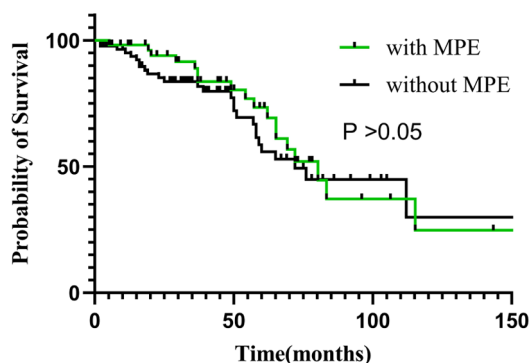


**Fig. 1** Flow diagram of enrolled patients

**Table 1** Characteristic of luminal B breast cancer patients with and without malignant pleural effusions

Variables	With MPE (n=54)	Without MPE (n=87)	P
Age at surgery (years)			0.096
< 50	32 (59.3%)	39(44.8%)	
≥ 50	22(40.7%)	48 (55.2%)	
Primary tumor location			0.186
Left	25 (46.3%)	50 (57.5%)	
Right	26 (48.1%)	36 (41.4%)	
Bilateral	3 (5.6%)	1 (1.1%)	
Clinical stages at initial diagnosis			0.088
Stage I	5 (9.3%)	11 (12.6%)	
Stage II	15 (27.8%)	26 (29.9%)	
Stage III	22 (44.4%)	36 (41.4%)	
Unknown	10 (18.5%)	4 (4.6%)	
Histological type			0.787
Invasive ductal carcinoma	50 (92.6%)	83 (95.4%)	
Invasive lobular carcinoma	1(1.9%)	1(1.1%)	
Others	3 (5.6%)	3 (3.4%)	
HER-2			0.866
Positive	8 (14.9%)	12 (13.8%)	
Negative	46 (85.2%)	75 (86.2%)	
Metastatic site			0.502
Lung	22(40.7%)	29(33.3%)	
Liver	12(22.2%)	24(27.6%)	
Bone	27(50.0%)	28(32.2%)	
Others	42(77.8%)	50(57.5%)	
Neoadjuvant therapy			0.404
Yes	11 (20.3%)	13 (14.9%)	
No	43 (79.6%)	74 (85.0%)	
Adjuvant Therapy			0.316
Chemotherapy	45 (83.3%)	68 (78.2%)	
Endocrine therapy	34 (63.0%)	51 (58.6%)	
Radiotherapy	24 (44.4%)	22 (25.3%)	
Surgical approach			0.260
Radical surgery	49 (83.3%)	84 (96.6%)	
Conservative surgery	5 (9.3%)	3 (3.4%)	

MPE, Malignant pleural effusion



Number at risk	0	50	100	150
With MPE	54	25	4	1
Without MPE	87	30	5	2

**Fig. 2** Survival of patients with malignant pleural effusions or without

**Table 2** Univariable and multivariable analyses for overall survival

Variables	Patients, No	BC with MPE HR	CI (95%)	P
<b>Univariable analyses</b>				
Age at surgery				
<50	22(40.7%)	REF <sup>a</sup>	REF	0.888
≥50	32(59.2%)	1.041	0.597–1.815	
Primary tumor location		0.963	0.551–1.685	0.672
Left	25(46.3%)	2.065	0.271–15.755	
Right	26(48.1%)	2.391	0.315–18.141	
Bilateral	3(5.6%)	REF	REF	
Clinical stages at initial diagnosis				0.036
Stage I	5(9.3%)	2.244	0.488–10.316	
Stage II	15(27.8%)	5.837	1.262–27.002	
Stage III	22(40.7%)	3.626	0.756–17.394	
Unknown	10(18.5%)	REF	REF	
Histological type				0.064
Invasive ductal carcinoma	50(92.6%)	1.400	0.430–4.561	
Invasive lobular carcinoma	1(1.9%)	17.669	1.493–209.4	
Others	3(5.6%)	REF	REF	
Effusion location				0.281
Right side	18(33.3%)	0.506	0.204–1.257	
Left side	14(25.9%)	0.636	0.296–1.370	
Bilateral	22(40.7%)	REF	REF	
Her2 expression	8(14.9%)	1.442	0.593–3.508	0.419
Neoadjuvant	11(20.4%)	1.081	0.466–2.507	0.856
Surgical approach	49(90.7%)	1.230	0.470–3.213	0.673
<b>Multivariable analysis</b>				
Clinical stages at initial diagnosis				0.021
Stage I		0.158	0.028–0.883	
Stage II		0.394	0.130–1.195	
Stage III		1.350	0.504–3.617	
Unknown		REF	REF	

HR, hazard ratio; CI, confidence interval

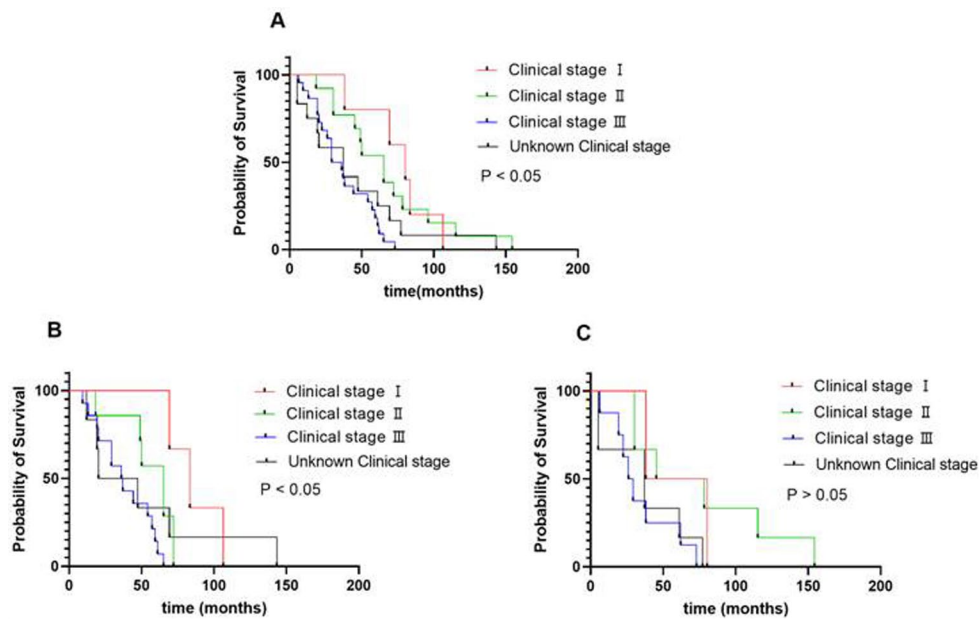
<sup>a</sup> For calculation of HR, a group of patients was defined as a reference

<sup>b</sup> The number of patients was not enough for further calculation

presented with left-sided, right-sided, and bilateral MPE, respectively.

**Survival analysis**

In this study, the median OS for patients with MPE was 44 months. The effect on survival was not significantly different between with MPE and without MPE group ( $P > 0.05$ ) [Fig. 2]. We conducted a univariate analysis and found that clinical stages at initial diagnosis and histological types for OS were significant, and then into the multivariate Cox regression for analysis [Table 2]. Further, we conducted a subgroup analysis and found that the higher the clinical stage at initial diagnosis in age < 50 years



**Fig. 3** A. Overall survival of different clinical stages at initial diagnosis patients with MPE; **BC**. Overall survival of patients with PE of age < 50 and age > 50 years with different clinical stages

**Table 3** Univariable and multivariable analyses luminal B BC with MPE at different age for overall survival

Variables	age < 50 years		P	age > 50 years		P
	HR	CI 95%		HR	CI (95%)	
<b>Univariable analyses</b>						
Clinical stages at initial diagnosis			0.013			0.151
Stage I	0.103	0.018–0.602		0.395	0.064–2.417	
Stage II	0.331	0.102–1.075		0.294	0.066–1.321	
Stage III	1.139	0.391–3.320		1.359	0.395–4.678	
Unknown	REF	REF		REF	REF	
Her2 expression	2.781	0.915–8.449	0.071	0.818	0.269–2.487	0.723
Neoadjuvant	0.954	0.422–2.156	0.909	3.755	0.724–19.483	0.115
Surgical approach	2.459	0.915–6.605	0.074	0.152	0.016–1.466	0.103
Adjuvant Chemotherapy	0.166	0.057–0.486	0.001	3.975	0.514–30.740	0.186
Adjuvant Endocrine therapy	1.019	0.461–2.252	0.963	1.145	0.462–2.838	0.770
Adjuvant Radiotherapy	0.563	0.270–1.174	0.126	0.972	0.384–2.460	0.952
<b>Multivariable analysis</b>						
Clinical stages at initial diagnosis			0.026			
Stage I	0.173	0.027–1.112		-	-	
Stage II	0.574	0.153–2.151		-	-	
Stage III	1.887	0.600–5.935		-	-	
Unknown	REF	REF		-	-	

patients, the shorter the overall survival, while age > 50 years patients was not. ( $P < 0.05$ ) [Fig. 3; Table 3].

**Discussion**

To the best of our knowledge, this is the first research on luminal B BC patients with MPE that has examined survival. Advanced BC patients with MPE were typically considered to have a worse prognosis than those without. However, as shown in the study, we followed up the

141 patients with advanced Luminal B breast cancer, and statistical results revealed that among these BC patients with or without MPE, the survival rate for patients with MPE was not significantly worse than those without MPE. Accordingly, by shedding light on the prognostic value of MPEs in Luminal B BC, our study has not only filled a gap in the existing literature but also provided a fresh perspective that could potentially lead to improved

patient stratification, tailored treatment strategies, and more accurate prognosis predictions.

Luminal B BC as one of the most common of the five related molecular subtypes of breast cancer, which has a higher recurrence risk and a distinctive dissemination pattern. Several studies have suggested luminal BC appear to have a predilection for metastasis to bone and pleura. Besides predilection for the pleura, about 2–11% of patients develop MPEs during the disease course [17, 18]. Moreover, approximately 80% of patients with pleural recurrences develop MPEs within the first 5 years after primary surgery, although pleural recurrences more than 10 years after surgery are rare [19, 20]. Although pleura is a common metastatic site of BC [21], MPE has rarely been reported as the first diagnose in patients with luminal BC. The main reasons the rarely reported of these patients may be underestimated because of the delay in follow-up examinations or the lack of reliable and efficient methods of examination. Conversely, in our research, 38% of luminal B BC patients multisite metastatic breast cancer concomitant with MPE, which was higher than the previous studies. The probable reason for this is that we have a complete follow-up team and have various diagnostic methods of MPE in our organization, thus increasing the corresponding diagnostic rate.

Patients with MPE usually have dyspnea, cough, poor exercise tolerance, an impaired quality of life, and their life expectancy is usually short. In an earlier study of 284 patients with MPE, their median survival time was approximately 13.2 months depending on the stage and histological type of BC [22]. However, our study shows that the median survival time was only 9.8 months in patients diagnosed with luminal B BC after surgery, which was far less in the previous studies. This discrepancy can be attributed to several factors. Firstly, the prognosis of luminal BC patients with multiple metastatic sites was significantly worse than that of patients with single-site metastasis, furthermore, concomitant visceral metastases have a significant negative impact on the patient's prognosis [23, 24]. In our study, 40.7% of patients with advanced Luminal BC had concurrent lung metastases, and 22.2% had liver metastases, potentially contributing to the poorer prognosis. Further analysis revealed that approximately one-third of patients with liver metastases also had simultaneous lymph node, lung, and bone metastases. Previous studies have shown that untreated liver metastases from breast cancer result in a survival time of only 4–8 months [25]. Secondly, the prognosis may be adversely affected by inadequate interdisciplinary therapeutic approaches for treating Luminal B BC with MPE. Specifically, Luminal-HER2-positive tumors are associated with poor outcomes without systemic targeted therapy. The advent of HER2-directed therapies, including monoclonal antibodies, tyrosine kinase inhibitors

(TKIs), and more recently, antibody-drug conjugates (ADCs), has improved the prognosis for patients with advanced Luminal-HER2-positive breast cancer. The DESTINY-Breast03 trial, for example, has established ADC T-DM1 as a preferred second-line treatment in recent years [26]. However, in our study, there was a lack of targeted therapies for this group of advanced luminal-HER2-positive breast cancers for economic reasons or the associated complications. Alternatively, Subclinical multiple organ failure syndrome may also be one of the major causes of poor prognosis in advanced luminal B breast cancer. Unfortunately, because our data lacked specific information on monitoring for subclinical multi-organ failure syndrome, we were unable to examine how multi-organ failure syndrome affected survival rates.

Interestingly, multivariate analysis using the Cox regression model showed that the higher the tumor clinical stage at initial diagnosis, the shorter the OS. Further, we conducted a subgroup analysis and found that the higher the clinical stage in age < 50 years patients, the shorter the overall survival, while age > 50 years patients was not. While, the study boasts a robust evidence base, employing a multi-center dataset and sophisticated statistical analyses to comprehensively evaluate the independent prognostic impact of MPEs. In addition, of the comparison between patients with and without MPEs reinforces the clinical relevance and significance of the findings. Further studies with more patients and prospective design are needed to better interpret the situation.

This study had several limitations. First, because of the retrospective design of the study, different chemotherapy schemas were used depending on the oncologist's decision, and the indication for surgery depended on the surgeon. Second, the sample size of the luminal B BC with MPE group was small, therefore, the prognostic impact of clinical features in luminal B BC with MPE should be investigated in a larger population in subsequent studies. An additional limitation was that the specific cause of death for these patients was not identified. With regard to the missing clinical stages at initial diagnosis in our dataset, we acknowledge that this is an important limitation that merits clarification. This can be attributed to several factors, including the retrospective nature of our data collection, variations in documentation practices across institutions, and the potential for incomplete medical records. And we have conducted sensitivity analyses to assess the impact of excluding patients with unknown clinical stages on our main findings. These analyses help us understand the robustness of our results and the potential bias introduced by the missing data. Despite these limitations, this is the first comprehensive report on the clinical features and survival of patients with luminal B presenting with MPE.

## Conclusions

In conclusion, there was no difference in the overall survival between luminal B-BC patients with MPE and those without. Clinical stages at initial diagnosis were an independent prognostic factor for age < 50 years luminal B BC with MPE overall survival. Our results may help clinicians make positive decisions regarding personalized treatment of luminal B-BC with MPE.

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## Author contributions

Conception and design: Youming Han and Yan Dong; Administrative support: Youming Han; Provision of study materials or patients: Hailong Wang and Han Youming; Collection and assembly of data: Youming Han, Yan Dong, and Hailong Wang; Data analysis and interpretation: Youming Han and Yan Dong; Manuscript writing: Yongming Han; Manuscript revision: Xiang-Min Li, Xiao-Zhang, Xin-Yu Wei, Feng-Wen Qian, and Zhi-Gang Li. Final approval of manuscript: All authors.

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## Data availability

All data supporting the findings of this study are available within the paper.

## Declarations

### Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki and has received ethical approval from the Institutional Review Board (IRB) of the Tianjin Cancer Hospital and The Affiliated General Hospital Binhai Hospital of Tianjin Medical University, approval number 20240101. Patients were consented by an informed consent process that was reviewed by the Ethics Committee of the Affiliated General Hospital Binhai Hospital of Tianjin Medical University.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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