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The effective duration of systemic therapy and the neutrophil-to-lymphocyte ratio predict the surgical advantage of primary tumor resection in patients with de novo stage IV breast cancer: a retrospective study

Rie Sugihara[1], Hidetaka Watanabe[1], Shuntaro Matsushima[3], Yuriko Katagiri[1], Shuko Saku[1], Mina Okabe[3], Yuko Takao[1], Nobutaka Iwakuma[3], Etsuyo Ogo[2], Fumihiko Fujita[1] and Uhi Toh[1*]

Abstract

Background The primary tumor resection (PTR) of de novo stage IV breast cancer (DnIV BC) is controversial, and previous studies have suggested that the neutrophil-to-lymphocyte ratio (NLR) could be a poor-prognosis factor for BC. We investigated PTR's surgical advantage related to clinical outcomes, the surgery timing in responders to systemic therapy, and whether the NLR can predict the benefit of surgery for DnIV BC.

Patients and methods We retrospectively analyzed the cases of the DnIV BC patients who received systemic therapies and/or underwent PTR at our institution between January 2004 and December 2022. Blood tests and NLR measurement were performed before and after each systematic therapy and/or surgery.

Results Sixty patients had undergone PTR local surgery (Surgery group); 81 patients had not undergone surgical treatment (Non-surgery group). In both groups, systemic treatment was performed as chemotherapy (95%) and/or endocrine therapy (92.5%) ($p < 0.0001$). The groups' respective median progression-free survival (PFS) durations were 88 and 30.3 months ($p = 0.004$); their overall survival (OS) durations were 100.1 and 31.8 months ($p = 0.0002$). The Surgery-group responders to systemic therapy lasting > 8.1-months showed significantly longer OS ($p = 0.044$). The PFS and OS were significantly associated with the use of postoperative systemic therapy ($p = 0.0012$) and the NLR ($p = 0.018$). A low NLR (≤ 3) was associated with significantly better prognoses (PFS and OS; $p < 0.0001$).

Conclusions A longer effective duration of systemic therapy (> 8.1 months) and a low pre-surgery NLR (≤ 3.0) could predict PTR's surgical advantage for DnIV BC. These variables may help guide decisions regarding the timing of surgery for DnIV BC.

Keywords Breast cancer, Metastatic cancer, Primary tumor resection, Neutrophil-to-lymphocyte ratio

*Correspondence:
Uhi Toh
utoh@med.kurume-u.ac.jp
[1]Department of Surgery, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan
[2]Department of Radiology, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan
[3]Department of Breast Surgery, National Hospital Organization Kyushu Medical Center, 1-8-1 Jigyohama Chuo-ku, Fukuoka, Japan

Introduction

Despite recent advances in the systemic treatment of de novo stage IV or recurrent metastatic breast cancer (BC), the median survival for patients with stage IV BC typically ranges from 18 to 36 months, and the prognosis may vary widely by the condition of patient's tumor status, age, and biologic subtype, and the efficacy of systemic therapies [1–3]. The use of surgical resection for the primary tumor in patients with de novo stage IV breast cancer (DnIV BC) is controversial, as several prospective randomized trials demonstrated no significant benefit of surgical resection regarding the patients' overall survival (OS) or quality of life compared to the use of systemic therapy without surgery for the primary tumor [4–6].

However, it was also reported that among patients in whom disease control and a response to systemic therapy were achieved, local resection for the primary tumor significantly improved the 5-year OS rate [7]. Recent retrospective studies revealed that resection of the primary tumor improved the local failure rate and could prolong the OS in selected patients, and the results of multivariable analyses also consistently suggest surgical advantages regarding the survival outcome for optimal local resection of the primary tumor [8–18]. Many unresolved clinical questions remain, including which cohort of patients can truly benefit from local surgery and systemic treatment for the primary tumor, plus the optimal timing of treatment for these selected patients [15–18].

Many research groups have evaluated the neutrophil-to-lymphocyte ratio (NLR, i.e., the ratio between the absolute neutrophil count and the absolute lymphocyte count) in patients with BC to determine whether the NLR could be used to predict these patients' prognoses and their response to systemic chemotherapy, and a meta-analysis indicated that an elevated baseline NLR value before a first treatment is a poor-prognosis factors in patients with BC [19–23]. However, our literature search identified no study evaluating the impact of the kinetics of the NLR in patients with de novo stage IV (DnIV) BC who have undergone local surgery for their primary tumor and similar patients who did not undergo surgery.

We thus conducted the present study to (*i*) investigate the surgical advantage of primary tumor resection (PTR) on clinical outcomes, (*ii*) identify the optimal surgery timing in patients with DnIV BC who responded to their initial systemic therapies, in a comparison with patients who did not undergo PTR, and (*iii*) determine whether the NLR could be applied as a novel biomarker for the prediction of the benefit of surgical operation for patients with DnIV BC.

Patients and methods

Patients

We retrospectively analyzed the cases of 141 patients with de novo stage IV BC that were included in the dataset of Kurume University Hospital and National Kyushu Medical Center between January 2004 and December 2022. The median follow-up duration was 24.2 months (range 0.6–203.6 mos.). All 141 patients received systemic therapies according to the guidelines and/or underwent the local resection of the primary tumor for the control of local failure symptoms of the BC tumor and/or metastatic reginal lymph nodes (including pain, ulceration, bleeding, non-healing wound, and local edema). The timing of the local resection for DnIV BC was discussed with the patients and determined at the discretion of the attending physicians based on the patients' tumor status and local symptoms, and *this decision was further highly dependent on the stability of the systemic disease based on the therapeutic effects of chemo-endocrine therapies before surgery of PTR.* (Table 1*)*.

We divided the 141 patients into the Surgery group of patients who had undergone PTR local surgery and the Non-surgery group of patients who had not undergone any surgical treatment, as illustrated in Fig. 1.

Assessment of the tumor status

The clinical and pathological tumor stage and T and N factors were stratified based on the Seventh Edition of the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumors [24]. Breast cancer was confirmed histologically by a core needle biopsy and staged by systemic imaging studies using computed tomography, ultrasonography, and bone scintigraphy.

The patients' breast cancers had been classified into subtypes according to the immunohistochemical expressions of estrogen receptor (ER), progesterone receptor (PgR), and epidermal growth factor receptor 2 (HER2) and categorized as follows: the luminal type (ER-positive and/or PgR-positive, HER2-negative), the luminal HER2 type (ER-positive and/or PgR-positive, HER2-positive), the HER2-enriched type (ER-negative, PgR-negative, and HER2-positive), and triple negative (TN)BC (negative for ER, PgR, and HER2) [25].

In this study, we defined oligo metastasis as low-volume metastatic disease, with a limited number and size of metastatic lesions (up to five lesions, though not necessarily in the same organ) based on the international consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). The term 'visceral metastases' in this study refers to DnIV BC that has spread to the liver or lungs with more than five metastatic lesions in multiple internal organs [26].

To evaluate the efficacy of the systemic treatment regimens, we calculated the overall response rate (ORR),

Table 1 Patient demographic and clinical characteristics (surgery group vs. non-surgery group)

	Surgery group (*n* = 61)	**Non-surgery group (*n* = 80)**	***p*-value**
Age, yrs; mean	59.9	63.1	0.6
Subtype:			0.047
Luminal	30 (50%)	46 (57.5%)	
Luminal HER2	4 (6.7%)	9 (11.3%)	
Her2	19 (31.7%)	10 (12.5%)	
Triple negative	7 (11.7%)	14 (17.5%)	
Metastasis statuses: *			
1) By metastatic number in each organ			0.002
Oligo	25 (41%)	36 (59%)	
Bone	7	9	
Lung	11	2	
Liver	2	0	
Brain	1	0	
Lymph node	4	2	
Visceral	14 (17.5%)	66 (82.5%)	
Lung	15	10	
Liver	8	25	
Pleural dissemination	6	14	
Peritoneal dissemination	0	6	
Brain	5	2	
Meningeal dissemination	6	1	
Other	2	5	
2) By number of metastatic organs in visceral cases			0.22
Within single organ	8(22.2%)	21(31.8%)	
Spread to multiple organs (≥ 2)	28(77.8%)	45(68.2%)	
Systemic therapy:			< 0.0001
No. of treatment regimens:			
1	13 (21.3%)	29 (36.2%)	
2	21 (34.4%)	17 (21.2%)	
≥ 3	16 (26.2%)	27 (33.7%)	
Regimen:			
Chemotherapy	14 (23.3%)	29 (36.7%)	
Anthracycline	1	1	
Taxane	11	21	
Anthracycline + taxane	26	15	
Anti-Her2 therapy	27	16	
Immune checkpoint inhibitor	0	2	
Other	9	16	
Endocrine	5 (8.3%)	27 (34.2%)	
Aromatase inhibitor	16	31	
Tamoxifen	3	12	
Fulvestrant	1	17	
C + E	38 (63.3%)	17 (21.5%)	
None	3 (5%)	6 (7.56%)	
Best therapeutic response:			< 0.0001
CR	7 (17.5%)	1 (1.32%)	
PR	15 (37.5%)	8 (10.5%)	
SD	17 (42.5%)	4 (5.3%)	
PD	1 (2.5%)	42 (55.3%)	
Surgery:		None	
Partial mastectomy	8 (13.1%)		
Mastectomy	51 (83.6%)		
Other	2 (3.27%)		

Table 1 (continued)

	Surgery group ($n=61$)	Non-surgery group ($n=80$)	*p*-value
Axillary dissection:			
Yes	55 (90.1%)		
No	4 (6.55%)		
Surgical margin:		None	
Positive	5		
Negative	27		
Pre ALC, /μL; mean	1,626	1,674	0.21
NLR, mean:			
Pre	2.94	3.62	0.19
6 mos.	3.18	2.86	0.94
1 yr	2.95	2.42	0.54
2 yrs	2.5	2.58	0.56

The data are number and percentage unless otherwise indicated. ALC: absolute lymphocyte count, C+E: chemotherapy plus endocrine therapy, CR: complete response, mos.: months, NLR: neutrophil-to-lymphocyte ratio, PD: progressive disease, PR: partial response, SD: stable disease. *: The oligo metastasis is defined as low-volume metastatic disease, with a limited number and size of metastatic lesions (up to five lesions). Visceral metastases have spread to the liver or lungs with more than five metastatic lesions in multiple internal organs based on the international consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7)

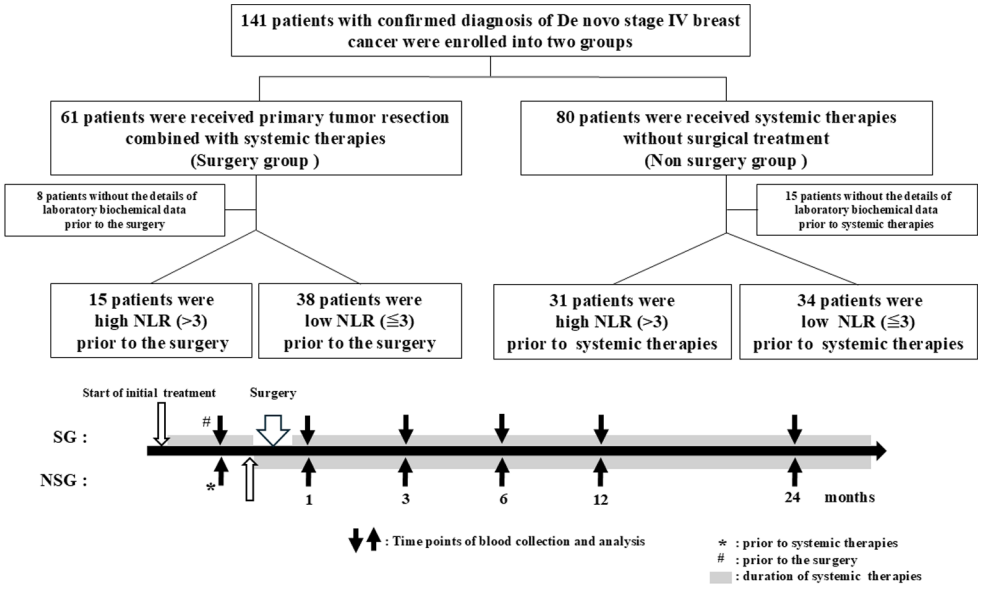


Fig. 1 The flowchart of patient selection and the time points of blood selection and evaluation. *Upper panel*: The cases of 141 patients with de novo stage IV breast cancer (BC) were investigated. We divided the patients into the Surgery Group (Surgery group) who had undergone local surgery (primary tumor resection) and the Non-surgery group (Non-surgery group) of patients without surgical treatment. *Lower panel*: The neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) were analyzed within 1 month before the patients' surgeries and at 1, 3, 6, 12 and 24 months after the surgery for the Surgery group, and within 1 month before the systemic treatment and at 1, 3, 6, 12, and 24 months after the start of the initial systemic therapy for the Non-surgery group

overall survival time (OS), and progression-free survival (PFS). The OS was assessed monthly and was calculated as the length of time from the start of treatment to the patient's death. The PFS was assessed monthly and was calculated as the time from the start of treatment to either the confirmation of progressive disease (PD) or death, whichever occurred first. All clinical evaluations in this study were performed by image assessment. We evaluated therapeutic antitumor effects by using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [27].

Blood sample analysis

Routine laboratory blood examinations were performed before and after each course of systematic therapy and/or surgery in a central laboratory of Kurume University Hospital using XN-10 blood analysis system. (SYSMEX corp., Kobe, Japan). The kinetics of peripheral blood neutrophils, the absolute lymphocyte count (ALC), and the

NLR were analyzed simultaneously. The data of the NLR and ALC were collected and evaluated within 1 month before the surgery and at 1, 3, 6, 12, and 24 months after the surgery for the Surgery group patients and within 1 month before the systemic treatment and at 1, 3, 6, 12, and 24 months after the start of the initial systemic therapy for the Non-surgery group patients (Fig. 1).

We used the NLR value of 3.0 as the cutoff value based on the median value from this dataset; a high NLR was defined as >3.0, and a low NLR was defined as ≤3.0. The patient selection flowchart and the time points of blood selection and evaluations for this study are depicted in Fig. 1.

Statistical analysis

The associations between the NLR and clinicopathological variables and the significance of different prognostic markers were analyzed using the χ^2 test (or Fisher's exact test when necessary). The Kaplan-Meier method was used to estimate the OS and PFS. We used the log-rank test to compare the OS and PFS values. Univariate and multivariate analyses of the study parameters were applied, using a backward stepwise method for the variable selection in the multivariate analyses. Probability (p)-values<0.05 were considered significant. The statistical analyses were performed using JMP 16 software (SAS, Cary, NC, USA).

Results

Patient characteristics

The characteristics of the 141 patients with DnIV BC are summarized in Fig. 1; Table 1. The median follow-up time from study enrollment was 47.3 months in the Surgery group ($n=61$) and 11.35 months in the Non-surgery group ($n=80$). The mean age was 59.9 years in the Surgery group and 63.1 years in the Non-surgery group ($p=0.6$). All of the 61 patients in the Surgery group underwent loco-regional PTR surgery, and systemic treatment was performed in 50 of these 61 patients before their surgery. In the Non-surgery group, 74 of the 80 patients had received systemic treatment, and 42 patients were still receiving treatment at the data cutoff point.

Radiotherapy was performed for 10 patients with positive surgical margins and/or multiple metastatic lymph nodes after primary tumor resection and for 10 patients during systemic treatment in each group. The biological subtypes in the Surgery and Non-surgery groups were identified as Luminal in 30 patients (50%) and 46 patients (57.5%) respectively, Luminal Her2 in four (6.7%) and nine patients (11.3%), as pure Her2 in 19 (31.7%) and 10 patients (12.5%), and as TNBC in seven (11.7%) and 14 patients (17.5%) ($p=0.047$). The Surgery group had more patients with the Her2 type compared to the Non-surgery group.

There were 25 patients with oligo metastases in the Surgery group (42%), and 66 patients with visceral metastases in the Non-surgery group (82.5%) ($p=0.002$). In detail, the sites of oligo metastases in the Surgery and Non-surgery groups were diagnosed in seven and nine patients with bone metastases, 11 and two patients with lung metastases, and four and two patients with lymph node metastases, respectively. Two patients with liver metastases and a single patient with brain metastasis were also observed in the Surgery group.

In contrast, the sites of visceral metastases were identified in the Surgery and Non-surgery groups: eight and 25 patients with liver metastases, 15 and 10 patients with lung metastases, five and two patients with brain metastases, six and one patient with meningeal dissemination, two and five patients with multiple metastases in different organs, respectively, and six patients with pleural dissemination in each group (Table 1).

The treatment (systemic therapies and surgical PTR) and clinical responses in the Surgery and Non-surgery groups.

In the Surgery group, systemic treatment was performed in 14 patients (23.3% by chemotherapy; five patients (8.3%) by endocrine therapy, and in the remaining 38 patients (63.3%) by the combination of chemotherapy followed by endocrine therapy (C+E); three patients (5%) did not receive systemic therapy before or after their surgery. The preoperative treatment regimens using chemotherapies included anthracycline (A) for one patient, taxane (T) for 11 patients, A+T for 26 patients, and other cytotoxic regimens for nine patients with the use of anti-Her2 therapies including trastuzumab with/without pertuzumab combined with a conventional chemotherapy for 17 patients, and using endocrine therapies including an aromatase inhibitor (AI) for 16 patients, tamoxifen for three patients, and fulvestrant for one patient.

In the Non-surgery group, the systemic therapies included chemotherapy for 29 patients (36.7%), endocrine therapy for 27 patients (34.2%), and C+E therapy for 17 patients (31.5%); six patients (7.5%) did not receive any treatment ($p<0.0001$). The systemic treatment regimens using chemotherapies included A for one patient, T for 21 patients, A+T for 15 patients, and other cytotoxic regimens such as eribulin, capecitabine, fluorouracil and others for 16 patients. The anti-Her2 therapies included trastuzumab with/without pertuzumab combined with conventional chemotherapy for 16 patients, and the endocrine therapies included an AI for 31 patients, tamoxifen for 12 patients, fulvestrant for 17 patients, and immune checkpoint inhibitors for two patients (atezolizumab for one patient and pemblolizumab for the other).

The clinical responses of the local primary tumor to the systemic therapies in the Surgery group before the surgery were seven (17.5%) complete responses (CRs), 32 (80%) partial responses (PRs) or stable disease (SD) and one patient (2.5%) with progressive disease (PD). The corresponding values in the Non-surgery group were one (1.3%) CR, 12 (15.8%) cases with a PR or SD, and 42 (55.3%) cases with PD ($p<0.0001$) (Table 1).

The locoregional PTR surgery with/without axillary lymph node resection after systemic therapies included a total mastectomy for 51 patients and partial mastectomy or tumor resection for eight patients; 55 patients had undergone the axillary lymph node resection simultaneously. The details of the surgical procedure were not recorded for two patients. The pathological diagnoses indicated that five patients with and 27 patients without positive surgical margins. An unclear surgical margin was observed on the surgical specimens of the remaining 29 patients.

The PFS and OS rates in the surgery and non-surgery groups

The median PFS and OS values were 88 months and 100.1 months in Surgery group and 30.3 months and 31.8 months in the Non-surgery group. Significantly better prognoses were thus achieved by the patients in the Surgery group compared to the Non-surgery group in both PFS ($p=0.004$) and OS ($p=0.0002$) (Fig. 2A, B). Further, the PFSs of Surgery group after surgery were 92.8 and 59.7 months in patients with Luminal type ($n=30$) and Her2+type ($n=23$) DnIV BC, respectively. And the PFS in 7 patients with TNBC was not reached. In contrast, the PFSs of Non-surgery group after first systemic treatment were 44.1, 28.6 and 10 months in patients with Luminal type ($n=36$), Her2+type($n=17$) and triple negative($n=7$) DnIV BC, respectively. In addition, the patients in the Surgery group who had responded to their systemic therapy prior to undergoing a PTR and whose systemic disease was well controlled over an 8.1-month period showed significantly longer OS compared to the patients who had responded to the systemic therapy within <8.1 months ($p=0.044$) (Fig. 2C).

In contrast, the effective duration of the systemic therapy was not significantly associated with PFS among the patients in the Surgery group ($p=0.297$, Suppl. Fig. S1). Similarly, there was no significant association between the effectiveness duration of systemic therapy and the PFS or OS for the patients in the Non-surgery group (data not shown). Compared to the patients with positive surgical margins, those with negative surgical margins had significantly better clinical outcomes: PFS ($p=0.01$) and OS ($p=0.008$) (Fig. 2D, E).

The associations between clinical factors, the NLR, and the ALC with the Surgery group's PFS and OS.

The univariate analysis results identified the following as significant factors in the Surgery group: the use of

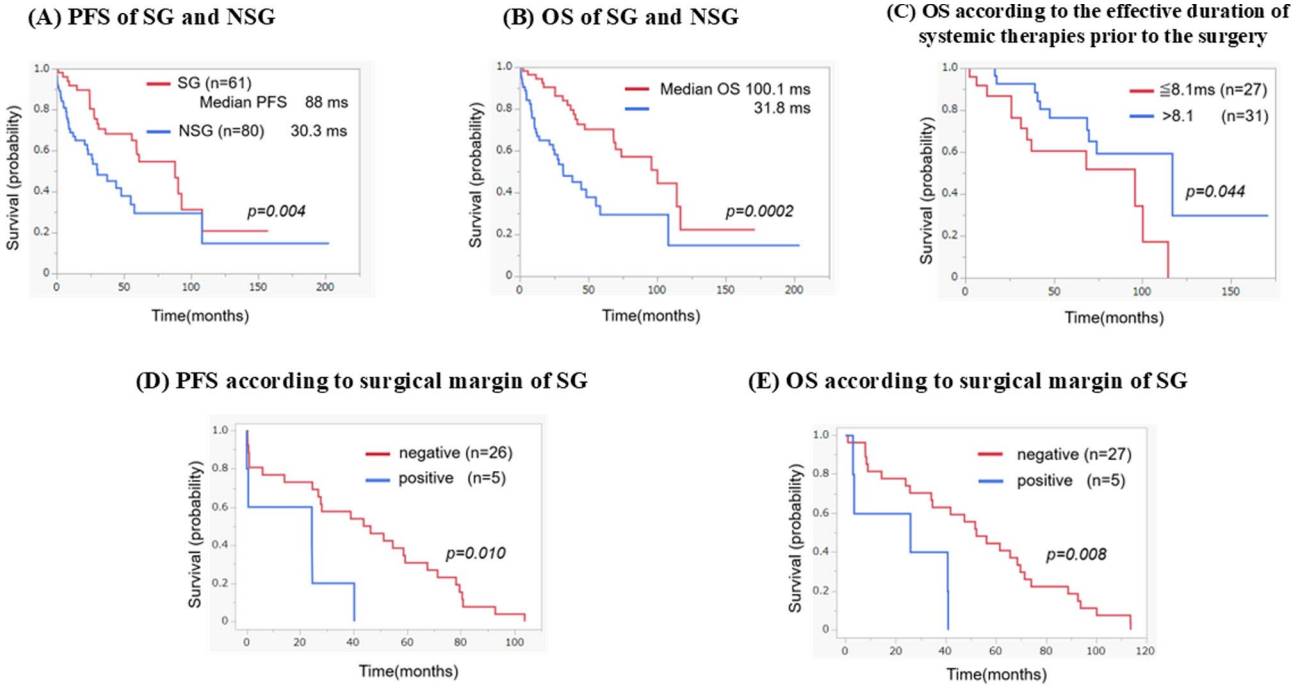


Fig. 2 The survival times in the Surgery group and Non-surgery group. Kaplan-Meier curves of progression-free survival (PFS) in each group. **A**: Kaplan-Meier curves of PFS in each group. **B:** Kaplan-Meier curves of OS in each group. **C**: Kaplan-Meier of OS in the Surgery group according to the effective duration of systemic therapies prior to the surgery **D:** Kaplan-Meier curves of PFS according to the surgical margin of primary tumor resection in the Surgery group. **E:**Kaplan-Meier curves of OS according to the surgical margin of primary tumor resection in the Surgery group

postoperative systemic therapy ($p=0.008$), the NLR value prior to the surgery ($p<0.0001$), and the post-operative NLR value at 1 year post-surgery ($p=0.034$). The results of the multivariate analysis revealed a significant association with the PFS and OS for the use of postoperative systemic therapy ($p=0.0012$) and the preoperative NLR value ($p=0.018$) (Table 2).

The Kaplan-Meier (log-rank test) analysis demonstrated that the patients with a low NLR (≤3) prior to surgery or at 1 year after surgery had significantly better prognoses based on both PFS (Fig. 3A, B) and OS (Fig. 3D, E) compared to the patients with a high NLR (>3) ($p<0.0001$ and $p=0.034$); in addition, a low NLR was associated with a significantly better PFS until 2 years after PTR surgery ($p=0.024$) (Fig. 3C). This OS trend was observed until 2 years post-surgery ($p=0.074$) (Fig. 3F). In contrast, the patients' ALC values prior to surgery and at 1 or 2 years after surgery had no significant association with PFS or OS (Suppl. Fig. S2).

The associations between clinical factors, the NLR, and the ALC with the Non-surgery group's PFS and OS.

The univariate analysis revealed that in the Non-surgery group, the use of systemic therapy ($p<0.0001$) and the clinical responses to systemic therapy ($p=0.0012$) were significantly associated with prognosis of DnIV BC, whereas other clinical factors including the biological subtype, the histology of primary or metastatic BC, and the metastasis status did not show this association. In contrast, the Non-surgery patients' ALC value at 6 months ($p=0.026$) and the ALC and NLR at 1 year after the start of systemic therapy ($p=0.007$ and 0.001) were significantly associated with PFS (Table 3). The results of the multivariate analysis demonstrated significant associations of clinical factors including metastatic lymph node status ($p<0.0001$), and the use of systemic therapies and the clinical responses to these therapies ($p=0.0006$ and $p=0.0018$) were significantly associated with PFS simultaneously. The NLR values at 6 months and 1 year after the start of systemic therapy were also significant ($p=0.025$ and 0.0005) (Table2). Moreover, there were also no significant associations between NLR and nuclear grade ($p=0.157$) in both groups.

The Kaplan-Meier (log-rank test) analysis showed that there was no significant difference associated with PFS or OS between the patients with a high ALC value (>1500/μL) and those with a low ALC (<1500/μL) before and at 6 months or 1 year after the initiation of systemic therapy. In contrast, the limited number of patients with a high ALC at 2 years after the start of systemic therapy ($n=3$) had significantly better PFS and OS outcomes ($p<0.0001$) (Suppl. Fig. S3). Similarly, the limited number of patients with a low NLR (≤3) at 1 year ($n=5$) and at 2 years ($n=1$) after the start of systemic therapy had significantly better clinical outcomes for both PFS and OS ($p=0.012$ and

Table 2 Univariate and multivariate analyses of the clinical characteristics related to the prognosis of de novo stage IV (dnIV) breast cancer for the surgery group

Clinical factor		Univariate *p*-value	Multivariate *p*-value
Subtype:		0.28	
Luminal	30 (50%)		
Luminal Her2	4 (6.7%)		
Her2	19 (31.7%)		
Triple negative	7 (11.7%)		
Histology:		0.14	
IDC	41 (67.2%)		
ILC	4 (6.56%)		
Mucinous	6 (9.84%)		
Special	3 (5.92%)		
Metastasis status:		0.43	
Oligo	25 (41%)		
Visceral	14 (17.5%)		
Systemic therapy:			
Pre		0.97	
Chemotherapy	14 (23.3%)		
Endocrine	5 (8.3%)		
C + E	38 (63.3%)		
None	3 (5%)		
Post		0.008	0.0012
Chemotherapy	13 (21.3%)		
Endocrine	18 (29.5%)		
C + E	23 (37.7%)		
None	7 (11.5%)		
Duration prior to the surgery (0.24–102.3 mos.):		0.044	
>8.1 mos.	31		
≤8.1 mos.	27		
No. of lymph node metastases:		0.308	
>3	15		
≤3	45		
Pre ALC, /μL:		0.51	
>1500	28		
≤1500	2		
1-year ALC:		0.41	
>1500	13		
≤1500	25		
2-year ALC:		0.91	
>1500	18		
≤1500	17		
Pre NLR:		<0.0001	0.0018
>3	15		
≤3	28		
1-year NLR:		0.034	
>3	10		
≤3	28		
2-year NLR:		0.074	

Table 2 (continued)

Clinical factor		Univariate *p*-value	Multivariate *p*-value
> 3	8		
≤ 3	27		

The data are number and percentage. ALC: absolute lymphocyte count, C+E: chemotherapy plus endocrine therapy, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, mos.: months, NLR: neutrophil-to-lymphocyte ratio

<0.0001) compared to the patients with a high NLR (>3) (1 year: $n=5$, 2 years: $n=3$) (Suppl. Fig. S4).

The kinetics of the NLR and ALC in Surgery group and Non-surgery group

As illustrated in Fig. 4, the Surgery group's ALC (number/μL) and NLR values before and at 1, 3, 6, 12, and 24 months after the surgery were 1,534 and 2.37, 1,353 and 2.5, 1,207 and 2.33, 1,315 and 2.11, 1,354 and 2.05, and 1,500 and 2.03, respectively. In the Non-surgery group, the ALC and NLR values before and after systemic treatment were 1,501 and 2.76,1,341 and 2.57,1,341 and 1.99, 1,338 and 2.03, 1,535 and 1.75, and 1,509 and 1.71, respectively (Fig. 4). Our kinetics analyses revealed that both the ALC and the NLR decreased significantly after surgery in the Surgery group and after the start of the systemic therapies in the Non-surgery group at 6 months, and then the ALC re-elevated and recovered at 1 year and 2 years in both groups to the level at the initial treatment, whereas the decreased NLR continued at 1 and 2 years in both groups.

Discussion

The current clinical management for patients with DnIV breast cancer is complicated due to the heterogeneity of the disease presentation. The management generally addresses the widespread nature of the disease, which often involves multiple organs. Systemic therapy remains the standard of care, as recommended by clinical practice guidelines [28, 29], although the locoregional failure of DnIV BC could be controlled by surgical intervention, i.e., primary tumor resection. No significant improvement in OS was identified in several prospective clinical trials [4–6], but the role of locoregional treatment, including surgical PTR, is promising and evolving.

Recent evidence suggests that although loco-surgical resection is traditionally reserved for palliation, its use may provide a survival advantage in certain subsets of patients, particularly those with a limited number of metastases or 'oligometastatic' disease, which is characterized by solitary or few metastatic lesions that are limited to a single organ [16–18, 28]. Moreover, the results of multivariable analyses have consistently suggested a survival benefit of the optimal local treatment of the primary tumor (although a publication bias of reporting only positive studies cannot be excluded)[30]. This approach is supported by the U.S. National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), which acknowledge the potential benefits of intensive locoregional management including surgery, radiation, and regional chemotherapy in patients with localized metastatic disease [28, 29].

Tumor reduction surgery as known as 'debulking surgery' has been noted for its clinical effectiveness in other common solid tumors such as ovarian, colorectal, gastric, and renal cancers and malignant melanoma, where it can significantly improve survival rates when combined with chemotherapy [31, 32]. Nevertheless, the decision to proceed with surgical resection for DnIV BC must be made carefully, as multiple clinical factors including the patient's overall clinical status, the extent of metastatic spread, and the potential impact on the patient's quality of life should be taken into consideration.

The debate regarding the locoregional resection of primary tumors in DnIV BC is multifaceted, with both potential benefits and drawbacks having been identified. A PTR may offer advantages such as the removal of the source of further metastatic spread, potentially increasing the efficacy of systemic therapies by reducing the number of cancer cells, including those resistant to treatment. A PTR could also lead to the restoration of tumor immunocompetence by eradicating the primary tumor bulk, which is thought to modulate the immune system through the release of immunosuppressive factors [10]. However, the removal of the primary tumor might also eliminate a source of antiangiogenic factors and growth factor inhibitors, possibly leading to an accelerated relapse due to the tumor's removal, the release of growth factors related to surgical wounding [30, 35, 36], and immunosuppression caused by surgery and anesthesia [38]. These contrasting perspectives highlight the complexity of treatment decisions for individuals with DnIV BC, where the balance between potential therapeutic benefits and the risk of adverse outcomes must be carefully considered. Ongoing research and clinical trials aim to provide clearer guidance on the role of locoregional surgery in the management of DnIV BC.

Our present findings demonstrated a survival benefit for optimal surgical resection of the primary tumor in patients with DnIV BC (here, the Surgery group) compared to patients who did not undergo surgery, regardless of the metastatic status such as the presence of oligo metastasis or visceral metastasis. Notably, the duration of the effectiveness of systemic therapies prior to the surgery appears to play a critical role. The present patients who responded to systemic therapies for >8.1 months before undergoing a PTR achieved significant improvement in PFS ($p=0.004$) and OS ($p=0.0002$) compared to those who did not respond to systemic therapies over

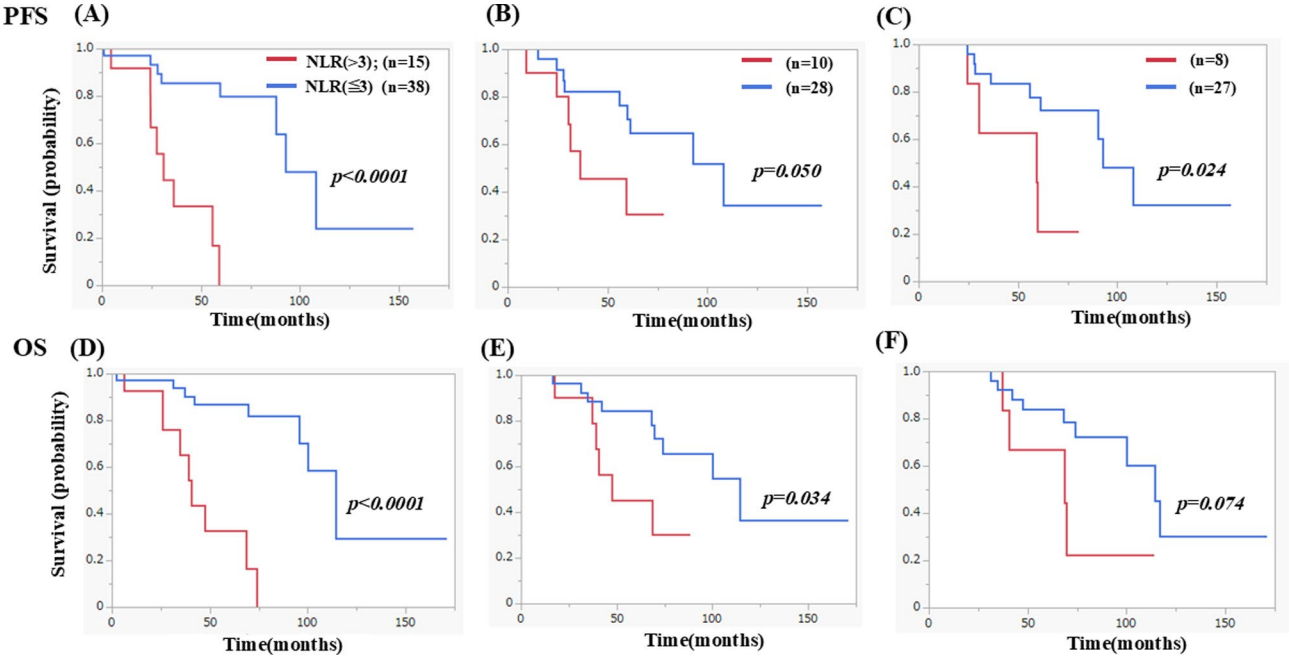


Fig. 3 The PFS and OS rates in the Surgery group according to the patients' NLR values prior to surgery **(A**, **D)**, at 1 year **(B**, **E)**, and 2 years **(C**, **F)** after the surgery. *Upper panel*: Kaplan-Meier curves of PFS according to the patients' NLR values prior to the surgery **(A)** and at 1 year **(B)** and 2 years **(C)**.*Lower panel*: Kaplan-Meier curves of OS according to the patients' NLR values prior to the surgery **(D)** and at 1 year **(E)** and 2 years **(F)**

the same period (Fig. 2). This suggests that the length of time a patient responds to systemic therapies before undergoing surgery could serve as a predictive marker for survival outcomes in patients with DnIV BC, potentially guiding clinical decisions regarding the timing of surgical intervention such as a PTR.

Our statistical analysis also indicated that compared to the patients in the Non-surgery group, the patients in the Surgery group showed significantly less oligo-metastasis ($p=0.002$) and had better clinical response rates (CR and PR) ($p<0.0001$) to the systemic therapies, and were more frequently administered the combination of chemotherapy and endocrine therapy ($p<0.0001$), despite the absence of significant differences in the subtype, histology, and metastasis status between the two groups.

However, patients who had undergone a complete surgical resection for a locoregional tumor with a negative surgical margin after receiving persistently effective systemic treatment may have better clinical outcomes. These results are consistent with those of several previous studies [15, 38, 39] and suggest that DnIV BC patients with only a few metastases and who consistently responded to the systemic chemo-endocrine treatment may be appropriate candidates for PTR.

The NLR and the ALC have been considered simple and minimally invasive markers that reflect the balance of the responses of neutrophils (pro-inflammatory) and lymphocytes (anti-inflammatory). ALC as an immune response indicator reflects the immune capacity in patients with cancer while NLR provides the condition of the balance between immune response and inflammation. Together, they could help in understanding the patient's overall onco-immunologic status and potential response to treatments. A low baseline ALC can be associated with a weakened immune system and poorer prognosis in triple negative breast cancer [40, 41].

These two parameters have been studied extensively in cancer research, particularly in BC. The NLR has been shown to be an independent prognostic factor for survival in most adjuvant treatments, and a high NLR which can result from a low ALC has been consistently associated with worse survival outcomes for patients with early-stage BC [19, 40–42]. However, conflicting results exist for early-stage BC patients receiving neoadjuvant chemotherapy (NAC) and for advanced-stage BC patients, and most studies failed to indicate a significant association between the NLR and the pathologic complete response (pCR) rate [40–43]. The correlation of the NLR with survival is less clear in NAC and advanced BC cases including DnIV BC cases [23, 41, 43]. Moreover, some data suggest that inflammatory blood markers such as the NLR, the ALC, and the platelet-to-lymphocyte ratio (PLR) could also be predictive of chemotherapy-related toxicity [44–49].

The results of our present analyses demonstrated that (*i*) a preoperative high NLR (>3) was significantly associated with poor prognosis, and (*ii*) this trend of NLR>3 could persist to 2 years postsurgery in DnIV BC patients

Table 3 Univariate and multivariate analyses of the clinical characteristics related to the prognosis of de novo stage IV (dnIV) breast cancer for the Non-surgery group

Clinical factor		Univariate *p*-value	Multivariate *p*-value
Subtype:		0.64	
Luminal	46 (57.5%)		
Luminal Her2	9 (11.3%)		
Her2	10 (12.5%)		
Triple negative	14 (17.5%)		
Histology:		0.45	
IDC	73 (91.3%)		
ILC	5 (6.25%)		
Metastasis status:		0.99	
Oligo	36 (59%)		
Visceral	66 (82.5%)		
Systemic therapy:		< 0.0001	0.0006
Chemotherapy	29 (36/7%)		
Endocrine therapy	27 (34.2%)		
C + E	17 (21.5%)		
None	6 (7.59%)		
Best therapeutic response:		0.0012	0.0018
CR	1 (1.32%)		
PR	8 (10.5%)		
SD	4 (5.3%)		
PD	42 (55.3%)		
cN:		0.25	< 0.0001
0	5		
1	34		
2	15		
3	21		
Pre ALC, /μL:		0.19	0.410
>1500	32		
≤1500	33		
6-month ALC:		0.026	0.201
>1500	16		
≤1500	21		
1-year ALC:		0.007	0.662
>1500	15		
≤1500	11		
Pre NLR:		0.52	
>3	15		
≤3	11		
6-month NLR:		0.05	0.025
>3	12		
≤3	25		
1-year NLR:		0.001	0.0005
>3	5		
≤3	21		

The data are number and percentage. ALC: absolute lymphocyte count, C + E: chemotherapy plus endocrine therapy, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, mos.: months, NLR: neutrophil-to-lymphocyte ratio

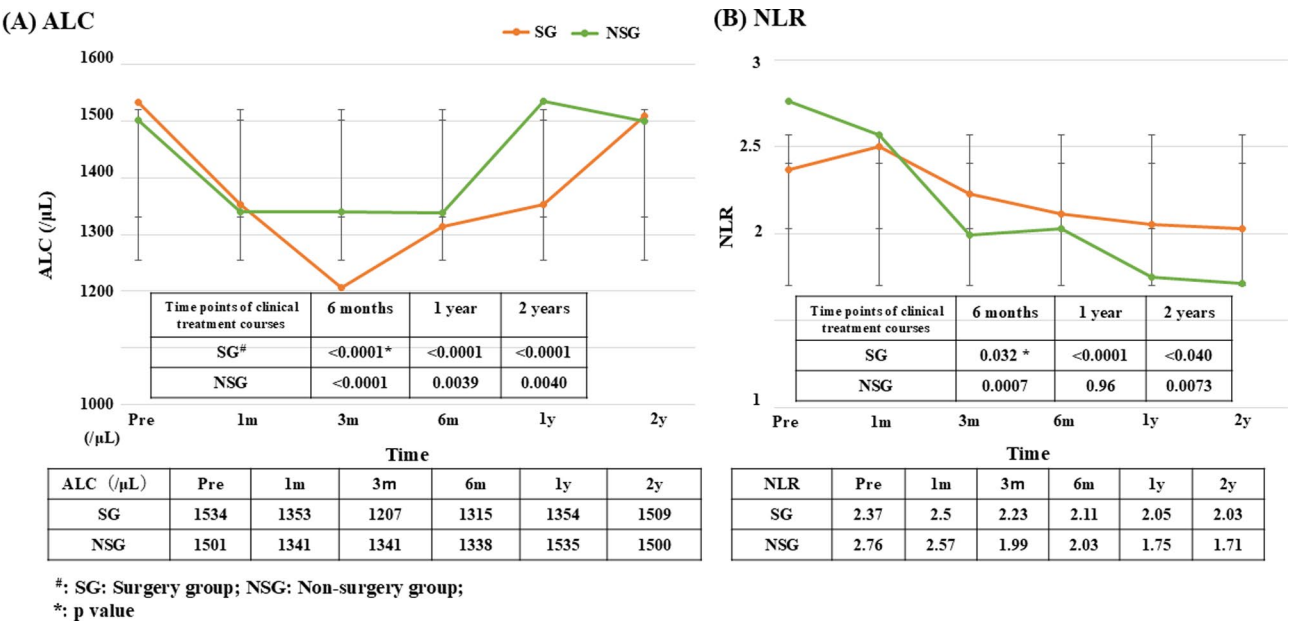
who underwent a resection of their primary tumor (Surgery group) (Fig. 3A–F). This correlation was also observed in the limited number of patients who did not undergo a PTR at 1 to 2 years after starting an initial systemic treatment (Non-surgery group) (Supp. Fig. S4). This suggests that the NLR may not only be a novel marker to select appropriate DnIV patients for a PTR who responded to systemic therapy prior to surgery; the NLR may also be a predictive marker of clinical outcomes in patients who received systemic treatment but did not undergo a surgical intervention.

In addition, the kinetics of the NLR data demonstrated that the NLR decreased significantly until 2 years post-surgery and/or systemic treatment in both of our patient groups (Fig. 4). This result suggests (consistently with other studies) that (*i*) the NLR also could become a biomarker for predicting the effectiveness of systemic treatments for DnIV patients, and (*ii*) the consistent decrease in the NLR might be associated with better clinical outcomes in these patients [19, 40–45],[19], [41–45].

We also observed that in both the Surgery and Non-surgery patients, the ALC decreased significantly at 3 months and recovered from 6 months to the level seen at the start of the initial systemic treatment. This indicates that the surgery and/or systemic therapy could induce temporary immunosuppression for DnIV BC patients, and in particular the decrease in the ALC could be continued to 3 months after surgery and/or the start of the systemic treatment, but after that time point it conversely recovered from 6 months until 2 years after the initiation of the systemic therapies (Fig. 4). Moreover, although the ALC had no significant relationship with the clinical outcomes of PFS and OS in the Surgery and Non-surgery groups in this study, several research groups have reported that a low ALC (lymphopenia) after systemic treatment was correlated with chemotherapy-related toxicity, particularly with febrile neutropenia [46–48] Unfortunately, we could not collect the toxicity profiles of the systemic therapies used in our present patient series for a specific analysis of its predictive value.

To our best knowledge, this study is the first to report that (*i*) the duration of systemic therapies with effectiveness continued over 8.1 months could be appropriate timing to select appropriate DnIV BC patients for PTR, and (*ii*) these patients could benefit most from the surgery; (*iii*) the kinetics of the NLR could be a predictive marker of clinical outcomes including PFS and OS for DnIV BC patients after surgery and/or systemic treatment in both patients who do and do not undergo surgical intervention.

However, some limitations of this study should be considered. The study design was retrospective, and there was an insufficient number of patients for long-term follow-up, which is a potential weakness of the presented



ALC (/μL)	Pre	1m	3m	6m	1y	2y
SG	1534	1353	1207	1315	1354	1509
NSG	1501	1341	1341	1338	1535	1500

NLR	Pre	1m	3m	6m	1y	2y
SG	2.37	2.5	2.23	2.11	2.05	2.03
NSG	2.76	2.57	1.99	2.03	1.75	1.71

#: SG: Surgery group; NSG: Non-surgery group;
*: p value

Fig. 4 Kinetics of the absolute lymphocyte count (ALC) and neutrophil-to-lymphocyte ratio (NLR) according to the clinical treatment courses: **A**: The ALC (number/μL) before and at 1, 3, 6, 12, and 24 months after the surgery in the Surgery group *(orange curve)* or the initial systemic therapy in the Non-surgery group (*green curve*). **B**: The NLR before and at 1, 3, 6, 12, and 24 months after the surgery in the Surgery group (*orange curve*) or the initial systemic therapy in the Non-surgery group (*green curve*)

data. The differences in the initial conditions for starting systemic therapies due to varying statuses of metastases and biological subtypes. These differences could have impacted the response to systemic therapies before the surgery. More cases of oligo metastasis were present in the Surgery group, and more cases of visceral metastasis were included in the Non-surgery group. More patients received the combination of chemotherapy and endocrine therapy and there were more effective clinical benefits from the systemic therapies in the Surgery group (90.5%), and fewer effective cases in the Non-surgery group (39.5%). These differences or bias may have resulted in an overestimation of the clinical outcome benefits in the Surgery group, but this may be unlikely because the statistical analysis revealed that adding the tumor size or biologic subtypes did not result in a significant association with the Surgery group's PFS or OS. Additional study limitations are that the median follow-up duration in the Non-surgery group was short at 11.4 months, and the lack of analysis data for toxicity and quality of life.

Conclusion

Our results indicate that a longer duration of effectiveness from the systemic therapies and a lower neutrophil-to-lymphocyte ratio (NLR) (≤3.0) prior to the surgery could be used to predict the surgical advantage of primary tumor resection in patients with DnIV breast cancer. This suggests that a > 8.1-month duration after systemic therapy could be an appropriate timing to perform local surgical control for these patients with preferable outcomes. Moreover, the kinetics of the NLR could be a predictive marker of clinical outcomes for DnIV BC patients after surgery and/or systemic treatment.

It is important to note that further investigations are mandatory to confirm whether surgery may be truly beneficial for selected stage IV BC patients with substantial survival benefit compared to patients with the same clinical background who do not undergo surgery. These issues should be addressed as a next step of further prospective clinical studies with attention paid to the role of the NLR and the duration of systemic therapy for the prediction of a surgical advantage for patients with DnIV breast cancer.

Abbreviations

ALC	Absolute Lymphocyte Count
BC	Breast Cancer
C + E	Chemotherapy Plus Endocrine Therapy
CR	Complete Response
DnIV	De novo Stage IV
ER	Estrogen Receptor
Her2	Epidermal Growth Factor Receptor 2
NLR	Neutrophil-to-Lymphocyte Ratio
OS	Overall Survival
pCR	pathologic Complete Response
PD	Progressive Disease
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PLR	Platelet-to-Lymphocyte Ratio
PR	Partial Response
PTR	Primary Tumor Resection
SD	Stable Disease

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Study concept and design, analysis and interpretation of data, drafting and revising of the article: R.S, U.T. Medical care and data collection: R.S, U.T, S.M, Y.K, S.S, M.O, Y.T, N.I, E.O, F.F. All the authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Kurume University (no. 22278). All work described in this study has been carried out in accordance with the Declaration of Helsinki.

Consent for publication
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Competing interests
The authors declare no competing interests.

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