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Clinicopathological and molecular characterization of inflammatory breast cancer, the prospective INFLAME registry study

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Inflammatory breast cancer (IBC) is rare, with challenging diagnostics and unfavorable outcomes. Therefore, more molecular insight into IBC is needed. The comprehensive Dutch prospective INFLAME registry related IBC follow-up and treatment to histopathology and molecular analysis. Of consecutive patients, nationwide identified with newly diagnosed IBC, clinicopathological, treatment and outcome data were collected. Histopathology and RNA-sequencing were related to outcome. 125 IBC patients were enrolled. Forty-one (34%) patients had HER2 + , and 31 (25%) had triple-negative IBC. The estimated 3-year OS was 78% in M0 IBC and 29% in M1. PFS was worst in triple-negative IBC (median 7.9 vs 16.3 and 15.8 months in M1 HER2+ and HR + /HER2- IBC). DFS and OS in M0 IBC were better with guideline-concordant trimodal therapy than without (HR 0.15 and 0.15; $p = 0.000005$ and 0.00038). The unique prospective INFLAME confirms unfavorable IBC characteristics and outcomes. International efforts may support guideline adherence and identify IBC-specific targets.

Inflammatory breast cancer (IBC) is a very rare disease, representing around 1-4% of all breast cancer diagnoses[1,2]. Rapid onset of signs and symptoms, challenging diagnosis, and delayed treatment contribute to its poor outcome[2,3]. Although IBC as a clinical diagnosis is difficult to establish, this was recently improved by a common diagnostic criteria score[4]. IBC itself is an independent factor for adverse outcomes with significantly lower survival times compared to non-inflammatory breast cancer (non-IBC)[2,5]. To counter the rapid growth, combined aggressive systemic and local treatment (trimodal strategy, including the fast start of chemotherapy, followed by ablative non-sparing surgery and radiotherapy) is recommended[3,6–8]. Even in the metastatic IBC setting, surgery for the primary tumor appears to be associated with better overall survival and can be considered following chemotherapy[6,9,10]. Although trimodal treatment has improved the disease outcome in patients with IBC, prospects remain inferior compared to patients with non-IBC[5,11,12]. The cause of this unfavorable disease behavior is not clear. Pathological assessments may show tumor emboli in the dermal lymphovascular spaces, increased vascular endothelial growth factor-D (VEGF-D), and E-cadherin expression[2,13]. Molecular analyses indicate that TP53, MYC, PIK3CA expression and activation occur more often in IBC than in non-IBC and TGF-β signaling is attenuated in IBC[14,15]. But so far, this has not led to IBC-specific targeting. Amplification of the human epidermal growth factor receptor 2 (HER2) is observed relatively often in IBC[3,5,16]. Treatment with trastuzumab and other HER2-targeted agents improves outcome in HER2 + IBC[5,12]. HER2-targeting antibody-drug conjugates may also be effective in HER2-low IBC[17]. Despite these developments, there is room for improvement regarding outcomes in IBC. Therefore, more insights into the specific molecular aspects of IBC are needed. Given the rarity of IBC and the wide variation in practice patterns, a prospective registry study was set up to collect systematic data on patient, disease, treatment and outcome characteristics. INFLAME is the first

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comprehensive cohort with prospective nationwide inclusion of all consecutive patients identified with IBC, linking follow-up and treatment information to histopathology and molecular tissue analysis.

Results

From February 2015 to December 2018, 125 IBC patients were enrolled in the INFLAME registry in 43 Dutch hospitals. Patients from non-participating hospitals were referred to participating hospitals. Three out of the 125 patients did eventually not meet inclusion criteria. Therefore, baseline clinical data was available for 122 patients (Table 1, Fig. 1). The median age at the time of diagnosis was 57 years, with 13 patients (11%) diagnosed with IBC before the age of 40. Median BMI was 28.7 kg/m^2. The median interval between symptoms and diagnosis was 32 days (IQ1 15–IQ3 76 days), and 85 (70%) patients were diagnosed within three months. Pathology results were available for 121 patients. Subtype distribution showed hormone receptor (HR) positive/HER2-negative, HER2-positive, or triple-negative subtype in 48, 41, and 31 of cases (38, 34, and 26% respectively; Table 3). Median age for each subtype was 62 years in HR-positive/HER2-negative, 53 years in HR-negative/HER2-positive, and 56 years in triple-negative subtype. M status, i.e. presence or absence of metastases (M1 or M0), was established in $n = 117$ patients. Of these 117 patients, 42 (36%) had M1 disease with visceral metastases in 22/42 (53%) of cases. From the 75 patients with M0 disease, 60 (80%) had at least one clinically positive lymph node, and analyzing the N-stage, 11 (15%) patients had N0, 31 (41%) had N1, 14 (19%) had N2 and 15 (20%) had N3 disease (Table 1). In four patients, M status was unknown because no curative treatment was considered feasible and additional imaging procedures were omitted. In one patient, M status was unknown due to the presence of inconclusive lung nodules at baseline.

Treatment practice patterns

Detailed information regarding systemic treatment, surgery, and radiotherapy was obtained from all participating hospitals (Table 2). Out of all 122 patients, sixty-seven (55%) received guideline-concordant trimodal therapy[8], including chemotherapy, surgery, and radiotherapy. Trimodal therapy was mostly given in patients with M0 IBC (80% of patients with M0 compared to 19% of patients with M1 IBC) and patients with good performance (59% of patients with WHO 0-1 compared to only one patient out of the 8 patients with WHO 2–3).

The majority of patients ($n = 102$, 83%) received chemotherapy. Fast initiation of systemic treatment within 2 weeks after diagnosis, as recommended, was observed in 32 (31%) patients, and the median interval between diagnosis and start was 19 days. In the majority of patients, surgery was performed ($n = 79$, 65%), with 65 (82%) surgeries performed in the M0 setting and 13 (16%) in the M1 setting, which accounts for 31% of patients with M1 disease. Ten out of 75 patients with M0 disease and 27 out of the 42 patients with M1 disease did not receive surgery. Reasons for refraining from surgery are shown in Supplementary Table S4. Six patients (2 with N0, 3 with N1, and 1 with N3 disease) received non-guideline concordant[3,6,7,18] sparing surgery of either primary tumor or axilla. The majority of patients received radiotherapy ($n = 87$, 71%), in 70 patients following surgery. Endocrine therapy was started in 62 (94%) of all 66 patients with HR-positive IBC. Three out of the 4 patients with HR-positive IBC who did not receive endocrine therapy, had an estrogen receptor (ER) negative and progesterone receptor (PR) positive tumor. HER2-targeted therapy was started in 39 (95%) of all 41 patients with HER2-positive IBC. One patient with HER2-positive IBC did not receive HER2-targeted therapy because of older age and frailty and in one other HER2-positive patient, it was unknown whether HER2-targeted therapy was given.

Outcomes

M0 IBC: After neo-adjuvant systemic treatment, a pathological complete response (pCR) was documented in 33 (51%) patients. The pCR rate was the highest in patients with the HER2-positive subtype (22 out of 26 patients; 85%), followed by the triple-negative subtype (8 out of 15 patients; 53%) and the HR-positive/HER2-negative subtype (3 out of 24, 13%). The estimated 3-year disease free survival (DFS) rate was 67% (56–81) and the median DFS was not reached (Fig. 2). The estimated 3-year overall survival (OS) rate was 78% (69 – 89) and the median OS was not reached. Per subtype, the estimated 3-year OS rate was 84% (70–99.7) in patients with HR-positive/HER2-negative IBC, 85% (68–100) in patients with HER2-positive IBC and 61% (42–88) in patients with triple-negative IBC. DFS and OS were better in patients receiving trimodal treatment (chemotherapy, surgery and radiotherapy) compared to patients who did not receive trimodal treatment: DFS not reached versus median 15.1 months (5.3–NE; HR 0.15 (0.06–0.36); $p = 0.000005$); OS not reached versus median 31.2 months (9.6–NE; HR 0.15 (0.06–0.42; $p = 0.00038$).

M1 IBC: For patients with M1 disease, the median progression free survival (PFS) was 14.0 months (95%CI 11.2–22.6) (Fig. 3). Median PFS by subtype was 15.8 months (13.6–31.6) for HR-positive/HER2-negative, 16.3 (8.8–NE) for HER2-positive, and 7.9 (3.5–NE) for triple-negative IBC. Median OS was 18.9 months (15.9 –35.6) with a 3-year survival rate of 29% (17–48). Per subtype, the estimated 3-year OS rate was 32% (16–64) in patients with HR-positive/HER2-negative disease, 33% (12–92) in patients with HER2-positive disease, and 9% (1 – 59) in patients with triple-negative disease. Out of the 33 patients with M1 disease whose PFS data were available, 8 patients received trimodal treatment including surgery of the primary tumor. Median PFS in these patients was 29.4 months (16.6–NE) compared to 13.4 months (9.8–16.8; $p = 0.058$) in patients who did not receive trimodal treatment. A similar trend was seen for OS, with a median OS of 33.7 months (23.8–NE) in the trimodal group versus 16.9 months (13.9–28.7) in patients who did not receive trimodal treatment (HR 0.41 (0.13 – 1.05) $p = 0.065$.

Transcriptomic analyses

In addition to the histopathology results, tissue was available from 122 patients for molecular analysis. Out of these 122 patients, 81 had a baseline diagnostic biopsy, 35 had resection material and 30 had both available. In 58 samples from 50 patients, sufficient quality RNA and RNA sequencing data was available for PAM50 molecular intrinsic subtypes analysis. Sixteen (32%) patients had luminal A subtype, 9 (18%) patients luminal B, 12 (24%) patients HER2-enriched, 12 (24%) patients basal, and 1 (2%) patient had normal breast-like subtype (Table 3). Three-year survival rate was highest for patients with luminal A and lowest for patients with basal subtype (Supplementary Figure S1). Regarding tumor-infiltrating lymphocytes (TIL), the median of the normalized expression level of the TIL mRNA score in the INFLAME cohort was 4.90 (IQ1 4.46 – IQ3 5.40). A trend was observed for a longer OS in thirteen patients with a mRNA TIL score above IQ3 compared to 37 patients with a mRNA TIL score below IQ3, however, this was not statistically significant ($p = 0.068$; Supplementary Figure S2b). Out of the 10 patients with M0 disease and available data on both TIL score and DFS, four patients with a high mRNA TIL score (above IQ3) had a significantly longer DFS compared to the six patients who did not ($p = 0.0038$; Supplementary Figure S2a). Out of the 15 patients with M1 disease and available data on TIL score and PFS, only one patient had an mRNA TIL score below IQ3. In eight patients, two samples were available. In four patients, discordant results regarding subtype were found between the two samples (Supplementary Table S1). In these four patients, two discrepancies were found between biopsies from contralateral breasts, one between a biopsy and the resection material, and one between different localizations within the same breast (Supplementary Table S2). In two of these four patients, results were completely discordant and in the other two patients, probability scores were close to each other (Supplementary Table S3).

Data from the current INFLAME cohort were compared to publicly available data from 136 non-IBC samples[19]. When comparing luminal versus non-luminal (i.e. HER2-enriched and basal subtypes), there was a significantly higher number of non-luminal breast cancers in the INFLAME cohort ($p = 0.031$). However, the difference in the distribution of all PAM50 subtypes was not statistically significant between the

Table 1 | Patient and disease characteristics by M-status

Total number of patients	M0 patients *n* = 75	M1 patients *n* = 42	*Total (including Mx[a])* *n* = 122
Age (years)			
≤40	8 (11)	4 (9)	13 (11)
41–50	14 (19)	10 (24)	24 (20)
51–65	29 (39)	16 (38)	45 (37)
66–75	18 (24)	5 (12)	24 (20)
>75	6 (8)	7 (17)	16 (13)
Median (min; max)	57 (34–86)	57 (30–91)	57 (30–93)
Sex, *n* (%)			
Female	75 (100)	42 (100)	122 (100)
BMI, *n* (%)			
Underweight (<19)	1 (1)	0 (0)	2 (1)
Healthy weight (19–25)	21 (28)	13 (31)	34 (28)
Overweight (25-29)	27 (36)	11 (26)	39 (32)
Obese (>30)	26 (35)	17 (41)	46 (38)
Unknown	0 (0)	1 (2)	1 (1)
Median (min; max)	28.4 (16.4–44.9)	27.8 (20.2–48.2)	28.7 (16.4–48.1)
WHO performance status, *n* (%)			
0	56 (75)	25 (60)	83 (68)
1	11 (15)	12 (29)	25 (20)
2	2 (3)	4 (9)	6 (5)
3	1 (1)	0 (0)	2 (2)
4	0 (0)	0 (0)	0 (0)
Unknown	5 (6)	1 (2)	6 (5)
Time between onset symptoms and pathological diagnosis (days) Median (min; max)	31 (0–357)	46 (0–360)	32 (0–360)
Time between pathological diagnosis and systemic therapy (days) Median	18	20	19
Antibiotics prescribed, *n* (%)			
No	50 (67)	28 (67)	81 (66)
Yes	25 (33)	12 (28)	39 (32)
Unknown	0 (0)	2 (5)	2 (2)
ER status, *n* (%)			
Negative	39 (52)	17 (41)	58 (47)
Positive	36 (48)	24 (57)	63 (52)
Unknown	0 (0)	1 (2)	1 (1)
PR status, *n* (%)			
Negative	50 (67)	26 (62)	74 (61)
Positive	25 (33)	15 (36)	47 (39)
Unknown	0 (0)	1 (2)	1 (1)
HR status, *n* (%)			
Negative	37 (49)	16 (38)	55 (45)
Positive	38 (51)	25 (60)	66 (54)
Unknown	0 (0)	1 (2)	1 (1)
HER2 status, *n* (%)			
IHC 0+	19 (25)	7 (17)	28 (23)
IHC 1+	17 (23)	15 (36)	32 (26)
IHC 2 + ISH negative	6 (8)	6 (14)	12 (10)
IHC 2 + ISH positive	2 (3)	0 (0)	2 (2)
IHC 3+	23 (31)	10 (22)	33 (27)
Unknown IHC, ISH negative	3 (4)	2 (4)	7 (5)
Unknown IHC, ISH positive	5 (7)	1 (2)	6 (5)
Unknown	0 (0)	1 (2)	2 (2)

Table 1 (continued) | Patient and disease characteristics by M-status

Total number of patients	M0 patients *n* = 75	M1 patients *n* = 42	*Total (including Mx[a])* *n* = 122
Subtypes			
HR-positive/HER2-negative	26 (35)	19 (45)	48 (39)
HER2-positive	30 (40)	11 (26)	41 (34)
Triple-negative	19 (25)	11 (26)	31 (25)
Unknown	0 (0)	1 (2)	2 (2)
Histological subtype, *n* (%)			
Invasive carcinoma of no-special type	61 (81)	28 (67)	98 (80)
Invasive lobular carcinoma	10 (13)	6 (14)	18 (15)
Other	3 (4)	6 (14)	3 (2)
Unknown	1 (1)	2 (5)	3 (2)
Histological grade, *n* (%)			
I	2 (3)	4 (10)	7 (6)
II	26 (35)	11 (26)	37 (30)
III	24 (32)	10 (24)	36 (30)
Unknown	23 (30)	17 (40)	42 (34)
Ki-67, *n*(%)			
Low (<20%)	8 (11)	5 (12)	13 (11)
High (≥20%)	22 (29)	9 (21)	31 (25)
Not tested	45 (60)	28 (67)	78 (64)
E-cadherin, *n* (%)			
Negative	7 (9)	5 (12)	14 (11)
Positive	36 (48)	16 (38)	52 (43)
Not tested	32 (43)	21 (50)	56 (46)
BRCA1 or BRCA2 mutation, *n* (%)			
Negative	12 (16)	4 (10)	16 (13)
Positive	1 (1)	3 (7)	5 (4)
Not tested	62 (83)	35 (83)	101 (83)
cN status, *n* (%)			
cN0	11 (15)	3 (7)	15 (12)
cN1	31 (41)	8 (19)	40 (33)
cN2	14 (19)	14 (33)	28 (23)
cN3	15 (20)	11 (26)	27 (22)
cNx	4 (5)	6 (14)	12 (10)
pN status, *n* (%)			
pN0	2 (3)	1 (2)	3 (3)
pN1	11 (15)	6 (14)	17 (14)
pN2	6 (8)	4 (10)	10 (8)
pN3	6 (8)	6 (14)	12 (10)
pNx	50 (67)	25 (60)	80 (65)
Site of metastases, *n* (%)			
Bone-only		6 (14)	
Non-visceral disease		11 (26)	
Visceral disease		22 (53)	
Unknown		3 (7)	

BMI body mass index, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormonal receptor, *IHC* immunohistochemistry, *ISH* in situ hybridization, *WHO* World Health Organization.

[a]In 5 patients, M status remained unknown. In 4/5 patients because curative treatment was not considered feasible and additional staging procedures were omitted, and in 1/5 patient due to the presence of inconclusive lung nodules at baseline.

INFLAME and a non-IBC cohort (Table 3, p = 0.21). There was no difference in mRNA TIL score between the INFLAME cohort and the non-IBC cohort, regardless of PAM50 intrinsic subtype ($p > 0.05$; Supplementary Figure S3).

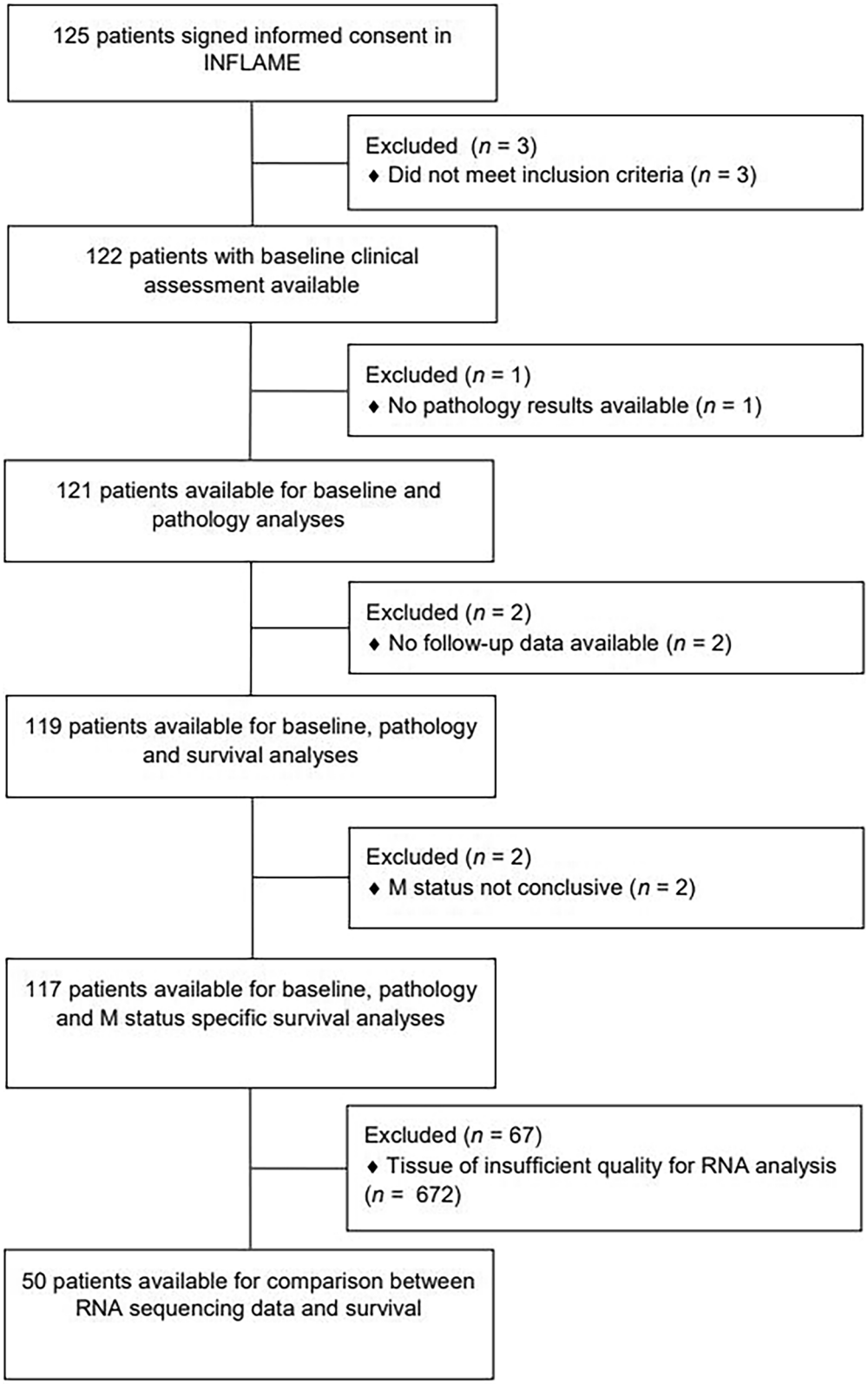

Fig. 1 | Flow diagram. Showing patients included in the INFLAME study and eligible for this analysis.

Discussion

The INFLAME study is a Dutch prospective registry, set up to improve (molecular) IBC insights, increase awareness, improve diagnostic and treatment protocols in national guidelines, and ultimately to improve outcomes in IBC. With nationwide coverage of participating hospitals and accessible consultations supporting inclusion of most IBC patients, we observed a frequency of <0.25% of the yearly Dutch breast cancer incidence, in line with previous reports[3,5]. This study confirms the unfavorable aspects of this disease, with rapid onset at a relatively young age, high stage, and poor outcome, despite guideline-concordant treatment for most patients.

Table 2 | Treatment by M status

Total number of patients	M0 patients *n* = 75	M1 patients *n* = 42	Total (including Mx[a]) *n* = 122
Chemotherapy, *n* (%)			
No	7 (9)	7 (17)	18 (15)
Yes	68 (91)	33(79)	102 (83)
Unknown	0 (0)	2(4)	2 (2)
Type of chemotherapy, *n* out of patients that received chemotherapy (%)	*n* out of 68 (%)	*n* out of 33 (%)	*n* out of 102 (%)
Anthracycline and taxane	45 (66)	9 (27)	55 (54)
Anthracycline, taxane and platin	4 (6)	1 (3)	5 (5)
Taxane without anthracycline	10 (15)	9 (27)	18 (18)
Antracycline without taxane	1 (1)	5 (15)	7 (7)
Capecitabine	0 (0)	4 (12)	4 (4)
Platin and taxane	8 (12)	2 (7)	10 (10)
Platin alone	0 (0)	1 (3)	1 (1)
Other	0 (0)	2 (6)	2 (2)
Chemotherapy started within 2 weeks, *n* out of patients that received chemotherapy (%)	*n* out of 68 (%)	*n* out of 33 (%)	*n* out of 102 (%)
No	42 (62)	22 (67)	65 (64)
Yes	25 (37)	7 (21)	32 (31)
Unknown	1 (1)	4 (12)	5 (5)
Surgery performed, *n* (%)			
No	10 (13)	27 (64)	41 (34)
Yes	65 (87)	13 (31)	79 (65)
Unknown	0 (0)	2 (5)	2 (1)
Type of breast surgery, *n* out of patients that underwent surgery	*n* out of 65 (%)	*n* out of 13 (%)	*n* out of 79 (%)
(Modified) radical mastectomy	57 (88)	12 (92)	68 (86)
Breast-conserving surgery	4 (6)	0 (0)	6 (8)
Other	1 (2)	0 (0)	1 (1)
Unknown	3 (4)	1 (8)	4 (5)
Type of lymph node surgery, *n* (%)			
No lymph node dissection	11 (15)	29 (69)	46 (38)
ALND	57 (76)	10 (24)	69 (57)
SLN biopsy	5 (7)	0 (0)	5 (4)
Unknown	2 (3)	3 (7)	2 (1)
Radiotherapy, *n* (%)			
No	9 (12)	19 (45)	33 (27)
Yes	66 (88)	21 (50)	87 (71)
Unknown	0 (0)	2 (5)	2 (1)
Trimodality treatment (chemotherapy, surgery and radiotherapy), *n* (%)			
No	16 (21)	36 (86)	53 (43)
Yes	59 (79)	8 (19)	67 (55)
Unknown	0 (0)	2 (2)	2 (2)
Endocrine therapy, *n* out of patients with HR-positive disease (%)	*n* out of 38 (%)	*n* out of 24 (%)	*n* out of 66 (%)
No	2 (5)	0 (0)	3 (5)
Yes	36 (95)	24 (100)	62 (94)
Unknown	0 (0)	0 (0)	1 (1)
Type of endocrine therapy, *n* out of patients that received endocrine therapy (%)	*n* out of 36 (%)	*n* out of 24 (%)	*n* out of 62 (%)
Tamoxifen	23 (64)	5 (21)	30 (48)
Aromatase inhibitor	13 (36)	13 (54)	27 (44)
Other	0 (0)	4 (17)	4 (6)
Unknown	0 (0)	2 (8)	1 (2)
HER2 targeted therapy, *n* out of patients with HER2-positive disease (%)	*n* out of 29 (%)	*n* out of 11 (%)	*n* out of 41 (%)
No	1 (3)	0 (0)	1 (2)
Yes	29 (97)	10 (91)	39 (95)
Unknown	0 (0)	1 (9)	1 (2)
Type of HER2 targeted therapy, *n* out of patients that received HER2 targeted therapy (%)	*n* out of 29 (%)	*n* out of 10 (%)	*n* out of 38 (%)
Trastuzumab	11 (38)	5 (50)	16 (42)
Trastuzumab and pertuzumab	18 (62)	5 (50)	22 (58)

ALND axillary lymph node dissection, *HER2* human epidermal growth factor receptor 2, *HR* hormonal receptor, *SLN* Sentinel lymph node.

[a]In 5 patients, M status remained unknown. In 4/5 patients because curative treatment was not considered feasible and additional staging procedures were omitted, and in 1/5 patient due to the presence of inconclusive lung nodules at baseline.

Worldwide, INFLAME is a unique comprehensive cohort with prospective nationwide inclusion of all consecutive patients identified with IBC, linking follow-up and treatment information to histopathology and molecular tissue analysis. This allows relating clinical outcome data to pathology and molecular analysis, in a rare cancer type as IBC. The INFLAME study shows that performing a prospective registry in a very rare disease such as IBC, is feasible.

In line with previous studies, the patients in the INFLAME cohort were with a median age of 57 years relatively younger than the average breast cancer population[5,6]. Additionally, the INFLAME cohort consisted of a relatively high number of patients with obesity (38%), which is a known risk factor for IBC[2]. Patients presented with higher stages (45% N2 or N3; 36% M1) than expected in the general breast cancer population and worse outcomes[20]. This is in line with previous observations in IBC and recent data from the M1 setting, which also show similar 3-year survival rates[2,5,6,21]. The outcome was best in the HER2-positive and HR-positive/HER2-negative IBC group, underlining the impact of optimal systemic therapy. However, it is still worse compared to HER2-positive non-IBC (estimated 3-year OS rate in M1 HER2-positive IBC of 33% versus >70% in non-IBC[22], and in M0 HER2-positive IBC of 85% versus >90% in non-IBC[23,24]). The same trend is seen in the other subtypes (for example, the estimated 3-year OS of only 32% in HR-positive M1 IBC versus >65% in HR-positive non-IBC[25]) and for M0 and M1 disease[26,27]. Although this is not a direct comparison and is limited by small numbers, these findings are in line with IBC as an independent factor for adverse outcomes, as previously described[2,5]. Among M0 patients, overall pCR rates were relatively high compared to previous studies in IBC. This is mainly driven by the high pCR rate in the HER2-positive group, in line with improving results in this subgroup (also without anthracyclines) and in breast cancer in general[20,28,29].

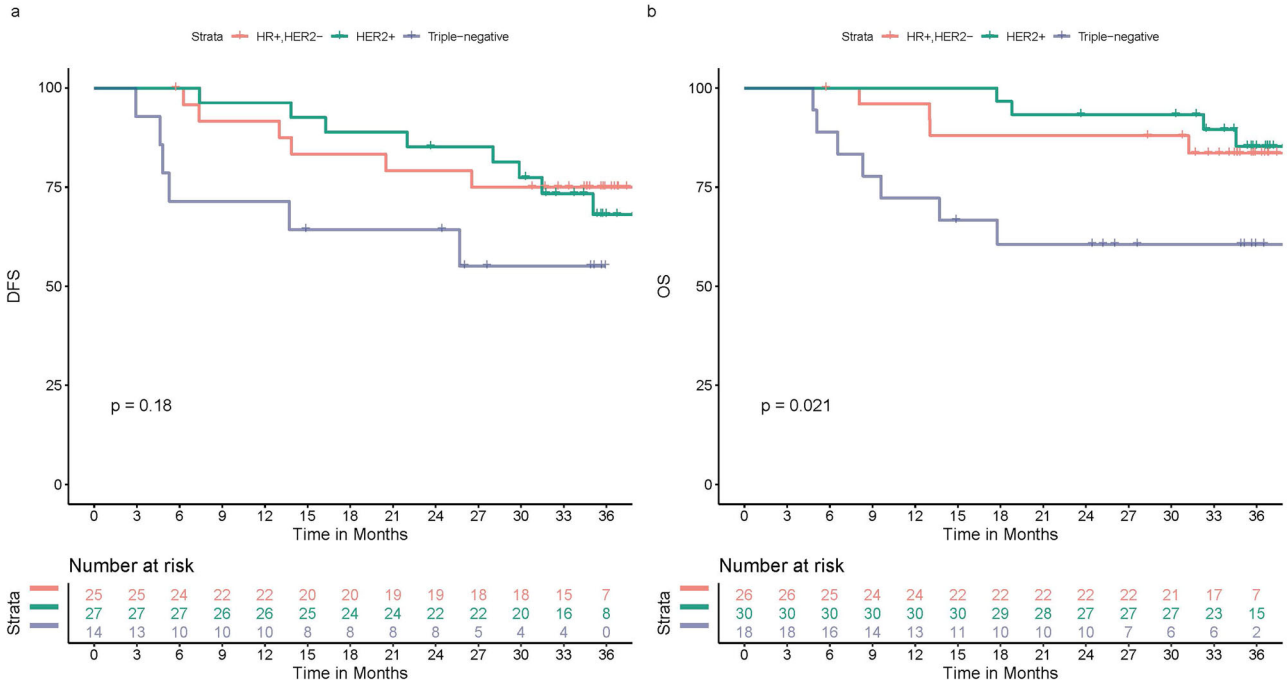

Fig. 2 | Survival by subtype in M0. Disease-free survival (DFS) (**a**) and overall survival (OS) (**b**) by subtype in M0 inflammatory breast cancer. HER 2, human-epidermal growth factor receptor 2; HR, hormonal receptor.

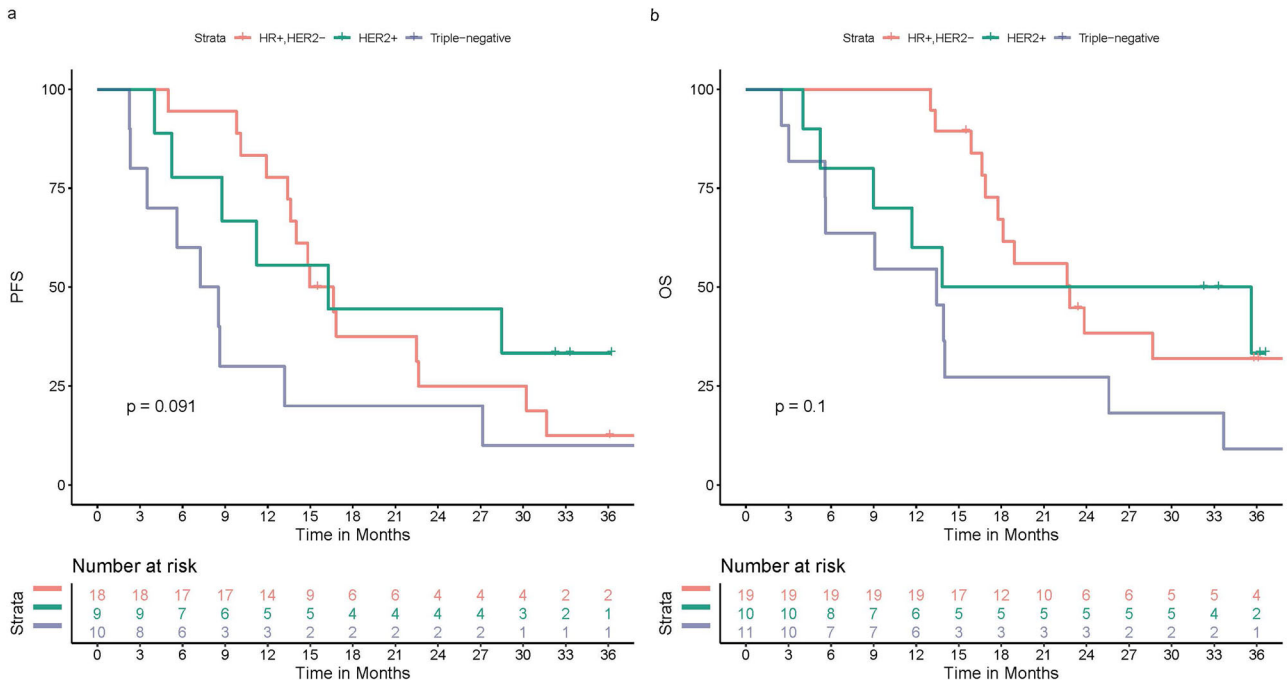

Fig. 3 | Survival by subtype in M1. Progression free survival (PFS) (**a**) and overall survival (OS) (**b**) by subtype in M1 inflammatory breast cancer. HER 2, human-epidermal growth factor receptor 2; HR, hormonal receptor.

Regarding treatment practice patterns, the majority of patients in INFLAME received guideline-concordant treatment. The frequent study team consultations may have contributed to this. Currently, a declining guideline adherence rate is observed, even down to 24–31%[30–32]. This could be related to continuously improving systemic therapy responses (particularly in HER2 disease), and ongoing de-escalation of (axillary) surgery in non-IBC[33–35]. Nonetheless, in INFLAME we found that the guideline-concordant trimodal therapy, including surgery, was related to a better disease outcome in M0 IBC, with the same trend in M1 disease. In the M0 setting, some patients received non-guideline concordant sparing surgery of either primary tumor or axilla. So far, non-sparing surgery is recommended[3] based on reduced overall and IBC-specific survival in retrospective analyses, underestimation of axillary involvement with imaging and sentinel node procedures, and high local recurrence rates >90% with skin-sparing mastectomies with immediate reconstruction[7,8,18,36,37]. Although the number of patients is small, also our prospective data seem to

Table 3 | PAM50 intrinsic subtypes comparison between IBC and non-IBC cohort

Source	INFLAME (*n* = 58)	Sinicropi et al. (*n* = 136)
PAM 50 intrinsic subtype, n (%)		
Luminal A	20 (35)	63 (46)
Luminal B	10 (17)	19 (21)
HER2-enriched	13 (22)	18 (14)
Basal	14 (24)	20 (15)
Normal	1 (2)	5 (4)

support ablative surgery. Therefore, the decrease of guideline-concordant treatment[30–32] in clinical practice is a concern that should preferably be addressed in future studies. In the M1 setting, the positive effect of trimodal therapy in the current study is in line with previous IBC data showing better outcomes in M1 disease with local treatment[6,9,10]. Nonetheless, this observed effect could be influenced by selection bias, as therapy was prescribed at the physicians' discretion and patients with poor performance were less likely to receive trimodal therapy (Supplementary Table S4). However, surgery should still be considered in M1 disease as a palliative measure as local progression can be debilitating, regardless of potential survival benefit.

RNA sequencing data from the current IBC cohort shows a representation of all PAM50 intrinsic subtypes, with more non-luminal subtypes compared to non-IBC[19]. These findings are in line with a previous study, which analyzed RNA expression in IBC using microarrays[15]. The current study is the first to describe TIL mRNA score in an IBC cohort, compared to a non-IBC cohort[19]. This cohort was specifically chosen to allow a valid methodological comparison, as comparable FFPE tissues were analyzed using an equivalent RNA sequencing method. Others have found that TILs are higher in IBC[38]. No differences were observed between these cohorts, regardless of subtyping, which could be due to our small sample size. Regarding the comparison between the cohorts, it is unknown whether the non-IBC comparator cohort may have included IBC patients, although the chance is very low. Comparing the cohorts' transcriptomics, an observed batch effect was corrected, which may also have affected the biological differences between the two cohorts. A longer DFS in patients with a high TIL mRNA signature was observed, however, due to the low number of patients, this should be considered as hypothesis generating. This should preferably be confirmed in other data sets. Numbers were too low to draw any conclusions on comparing TIL scores in the different subtypes. In this setting, conducting more translational research in IBC (versus non-IBC) in similar cohorts would be of importance. For example, a recent study found a higher frequency of TP53 mutations and a potential enrichment in NOTCH pathway activation, but a lack of major genomic differences, suggesting additional analyzes beyond somatic DNA-level changes are warranted[39]. More translational research in similar cohorts could enhance generalizability of findings.

This study has limitations. The small sample size is inherently related to the rarity of the disease. This will have affected statistical power to detect differences or correlations, especially in groups based on mRNA results. To maximize accrual, patients could enter throughout the Netherlands, but sample collection in local hospitals may have affected storage and availability of samples for RNA sequencing. Furthermore, PAM50 analysis could only be performed on a subset of IBC tissues, which may have affected the representation of subtypes. In this registry, no non-IBC control group could be included. Systemic treatment has evolved in HER2-positive disease, for instance, patients with M0 HER2-positive disease without a pCR did not have access to adjuvant T-DM1 yet during the study. However, as this was only a very small number of patients ($n = 5$), the possible impact on outcome data is likely limited. Furthermore, patients with both M0 and M1 disease were enrolled, of all intrinsic subgroups, in an already small patient group. Although this limits possible comparisons, it is very much in line with clinical practice. Furthermore, in view of >35% of patients presenting with M1 disease, excluding them would have had an unacceptable impact on patient numbers as well. Another limitation is the relatively short follow-up period of three years. For non-IBC, particularly HR-positive disease, this would certainly be insufficient. However, the event rate of 50% in HR-positive IBC is such that this follow-up is unfortunately appropriate, although a longer follow-up remains of interest. The strengths of the INFLAME study are its prospective multicenter set-up with the collection of patient-matched tissue and treatment and outcome data. This reduces bias due to patient selection and limited clinical context, such as can be observed in rare diseases. Furthermore, this study only included patients that had an expert verified diagnosis according to international consensus[3]. This is of importance, as distinction between IBC and non-inflammatory locally advanced breast cancer (LABC) is challenging in clinical practice[40]. The short median time between onset of symptoms and pathological diagnosis, and the high representation of TNBC and HER2-positive subtypes in this cohort align with IBC (and not with LABC). Although the incidence of IBC within the Netherlands was very low and patients may have been missed, the joint effort of the majority of hospitals, the BOOG network, the focus on awareness, and the accessibility of consultations enabled this registry despite diagnostic and logistical challenges. Improving awareness of this rare disease was supported with information material also for general practitioners[41], patient advocate involvement, (inter)national presentations, and the first Dutch IBC guideline.

Concluding, INFLAME shows that performing a prospective registry in a very rare cancer type such as IBC is feasible. This study confirms unfavorable IBC characteristics, with rapid onset, relatively young age, high stage, high local recurrence rate (despite guideline-concordant treatment in most patients), and unfavorable outcome. Further international efforts may support guideline adherence and the identification of treatment targets for IBC. IBC-specific funding opportunities and trials would be better supported if IBC is recognized as a rare cancer not only in the US (Genetic and Rare Diseases (GARD) center of the National institutes of Health (NIH)[42], but also elsewhere (the European Information Network on Rare Cancers, in which IBC is not included at present)[43]. Only with substantial international collaborative (translational) efforts and data sharing, the outcome in this rare disease can improve.

Methods

Eligible patients were patients with IBC according to international guidelines[3], of all stages (i.e. III or IV in IBC), before the start of systemic therapy. The study was approved as a registry by the Medical Ethical Committee of the University Medical Center Groningen (UMCG) (MREC#2014/345) and registered in the trial register in the Netherlands (OMON register, NL-OMON28954; 2015-03-06). The study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment. Through the Dutch Breast Cancer Research Group (BOOG), all Dutch hospitals could include patients. In case of doubt (due to challenging clinical diagnosis) the INFLAME study team could be consulted. Patients were enrolled only after careful assessment of symptoms and history consistent with IBC. Information on patient and disease characteristics was obtained from the local hospitals. Biopsy tissue was collected if available. Tissue was also sampled at surgery after preoperative systemic therapy, if applicable. Formalin-Fixed, Paraffin-Embedded (FFPE) breast tumor tissue obtained during a diagnostic biopsy and surgical resection of all patients was collected if available. Clinical and follow-up data regarding patient and disease characteristics, treatment, and outcomes (disease recurrence or progression, new primary cancer, and overall survival, OS) were obtained from local hospitals at baseline and 1, 2, and 3 years after registration in the trial. Ablative (or non-sparing) surgery is defined as mastectomy or ablation, and sparing surgery as breast-conserving surgery. Disease-free survival (DFS) was defined as the time between pathological diagnosis of the primary tumor and either local or distant recurrence. Progression-free survival (PFS) was defined as time between diagnosis of metastatic disease and progression.

Pathology

Standard histopathological evaluation including staging, grading, immunohistochemical (IHC) staining for estrogen receptor (ER), progesterone receptor (PR), and HER2, and Ki-67 scoring was performed locally and evaluated centrally, prior to any neoadjuvant treatment. ER, and PR were considered positive if ≥10% of the tumor cells stained positive, according to Dutch guidelines[44]. Hormone receptor (HR) was considered positive when either ER or PR was positive. HER2 status was determined according to the American Society of Clinical Oncology (ASCO)/College of American Pathologists guidelines (CAP) guidelines[45]. Only tissues with a tumor percentage of at least 30% were selected for RNA sequencing. Breast cancer subtypes were categorized according to ESMO guidelines, into HER2-positive, HR-positive/HER2-negative, and triple-negative disease[46,47]. FFPE tissues were collected for RNA sequencing analysis and centrally reviewed for sufficient tumor material by a breast pathologist at the EMC (CvD).

RNA sequencing and analysis

RNA was isolated using the AllPrep DNA/RNA Micro Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. RNA concentrations were measured with a Nanodrop 2000 system. The input for the RNA sequencing was 500 ng and was analyzed by Novogene (Cambridge, UK) for Illumina RNA sequencing using a ribosomal RNA depletion method. Raw sequencing data were aligned to the GRCh38 reference genome using STAR version 2.6.1 d[48]. To sort the aligned data, mark duplicate reads, and perform a flagstat analysis, sambamba version 0.8.1 was used[49]. RNA sequencing data from the current study were compared to a publicly available dataset composed of data from non-IBC breast cancer, in which comparable FFPE tissues were analyzed using an equivalent RNA sequencing method[19]. Since only raw read counts were available from this dataset, read counts of our INFLAME cohort were merged, resulting in a total of 11,459 genes that overlapped between the two datasets. Gene length corrected trimmed mean of M-values (GeTMM) normalization was performed on all samples[50]. Subsequently, t-distributed Stochastic Neighbor Embedding (tSNE) analysis was performed and showed large differences between the batches, which was corrected by using ComBat[51]. After these normalization and correction steps, the available samples were categorized according to molecular intrinsic subtypes using the PAM50-methodology and R package 'genefu'[52]. The average expression of the genes in tumor-infiltrating lymphocytes (TILs) mRNA signature was determined as described previously[53]. This signature has been validated previously and was applicable for the transcriptomic data available in our cohort[54].

Statistics

Descriptive statistics were used for baseline characteristics. Survival time was compared between groups according to the Kaplan-Meier method using the log-rank test. DFS and PFS definitions did not include death as an event. The influence of clinicopathological factors on survival was analyzed with univariate and multivariate analyses using Firth-corrected Cox regression. The difference in TIL mRNA score was assessed using the Wilcoxon rank-sum test and the difference in PAM50 was evaluated using χ^2 test or Fisher's exact test. All statistical analyses were performed using IBM SPSS statistics for Windows, version 26 (IBM Corp., Armonk, NY) and R version 4.0.3 for Windows. All p-values are two-tailed with a threshold for statistical significance of $P \leq 0.05$.

Data availability

The data that support the findings of this study are available from Dutch Breast Cancer Research Group (BOOG), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of BOOG.

Code availability

The underlying script used to generate results reported in this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author. All analyses were performed using IBM SPSS statistics for Windows, version 26 (IBM Corp., Armonk, NY) and R version 4.0.3 for Windows.

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References

1. Goldner, B., Behrendt, C. E., Schoellhammer, H. F., Lee, B. & Chen, S. L. Incidence of inflammatory breast cancer in women, 1992-2009, United States. *Ann. Surg. Oncol.* **21**, 1267–1270, https://doi.org/10.1245/s10434-013-3439-y (2014).
2. Robertson, F. M. et al. Inflammatory breast cancer: the disease, the biology, the treatment. *CA Cancer J. Clin.* **60**, 351–375, https://doi.org/10.3322/caac.20082 (2010).
3. Dawood, S. et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann. Oncol.* **22**, 515–523, https://doi.org/10.1093/annonc/mdq345 (2011).
4. Jagsi, R. et al. Inflammatory breast cancer defined: proposed common diagnostic criteria to guide treatment and research. *Breast Cancer Res. Treat.* **192**, 235–243, https://doi.org/10.1007/s10549-021-06434-x (2022).
5. Dano, D. et al. Metastatic inflammatory breast cancer: survival outcomes and prognostic factors in the national, multicentric, and real-life French cohort (ESME). *ESMO Open* **6**, 100220, https://doi.org/10.1016/j.esmoop.2021.100220 (2021).
6. Dawood, S. et al. Identifying factors that impact survival among women with inflammatory breast cancer. *Ann. Oncol.* **23**, 870–875, https://doi.org/10.1093/annonc/mdr319 (2012).
7. Gradishar, W. J. et al. Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J. Natl. Compr. Cancer Netw.* **20**, 691–722, https://doi.org/10.6004/jnccn.2022.0030 (2022).
8. Ueno, N. T. et al. International consensus on the clinical management of inflammatory breast cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. *J. Cancer* **9**, 1437–1447, https://doi.org/10.7150/jca.23969 (2018).
9. Partain, N. et al. The role of Mastectomy in de novo stage IV inflammatory breast cancer. *Ann. Surg. Oncol.* **28**, 4265–4274, https://doi.org/10.1245/s10434-020-09392-8 (2021).
10. Lehrberg, A. et al. Trends, survival outcomes, and predictors of nonadherence to mastectomy guidelines for nonmetastatic inflammatory breast cancer. *Breast J.* **27**, 753–760, https://doi.org/10.1111/tbj.14283 (2021).
11. Dawood, S. et al. Differences in survival among women with stage III inflammatory and noninflammatory locally advanced breast cancer appear early: a large population-based study. *Cancer* **117**, 1819–1826, https://doi.org/10.1002/cncr.25682 (2011).
12. Jiao, D. et al. Comparison of survival in non-metastatic inflammatory and other T4 breast cancers: a SEER population-based analysis. *BMC Cancer* **21**, 138, https://doi.org/10.1186/s12885-021-07855-z (2021).
13. Yamauchi, H. et al. Inflammatory breast cancer: what we know and what we need to learn. *Oncologist* **17**, 891–899, https://doi.org/10.1634/theoncologist.2012-0039 (2012).
14. Ross, J. S. et al. Comprehensive genomic profiling of inflammatory breast cancer cases reveals a high frequency of clinically relevant genomic alterations. *Breast Cancer Res. Treat.* **154**, 155–162, https://doi.org/10.1007/s10549-015-3592-z (2015).
15. Van Laere, S. J. et al. Uncovering the molecular secrets of inflammatory breast cancer biology: an integrated analysis of three distinct Affymetrix gene expression datasets. *Clin. Cancer Res.* **19**,

4685–4696, https://doi.org/10.1158/1078-0432.Ccr-12-2549 (2013).
16. Kupstas, A. R. et al. Biological subtype, treatment response and outcomes in inflammatory breast cancer using data from the National Cancer Database. *Br. J. Surg.* **107**, 1033–1041, https://doi.org/10.1002/bjs.11469 (2020).
17. Tarantino, P. et al. HER2-low inflammatory breast cancer: Clinicopathologic features and prognostic implications. *Eur. J. Cancer* **174**, 277–286, https://doi.org/10.1016/j.ejca.2022.07.001 (2022).
18. Nakhlis, F. Inflammatory breast cancer: Is there a role for deescalation of surgery?. *Ann. Surg. Oncol.* **29**, 6106–6113, https://doi.org/10.1245/s10434-022-12138-3 (2022).
19. Sinicropi, D. et al. Whole transcriptome RNA-Seq analysis of breast cancer recurrence risk using formalin-fixed paraffin-embedded tumor tissue. *PLoS ONE* **7**, e40092, https://doi.org/10.1371/journal.pone.0040092 (2012).
20. Nederlandse Kankerregistratie (NKR), *IKNL,* nkr-cijfers.iknl.nl (17-06-2024).
21. van Uden, D. J. P. et al. Metastatic behavior and overall survival according to breast cancer subtypes in stage IV inflammatory breast cancer. *Breast Cancer Res.* **21**, 113, https://doi.org/10.1186/s13058-019-1201-5 (2019).
22. Swain, S. M. et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* **21**, 519–530, https://doi.org/10.1016/s1470-2045(19)30863-0 (2020).
23. Tolaney, S. M. et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N. Engl. J. Med.* **372**, 134–141, https://doi.org/10.1056/NEJMoa1406281 (2015).
24. Piccart-Gebhart, M. J. et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N. Engl. J. Med.* **353**, 1659–1672, https://doi.org/10.1056/NEJMoa052306 (2005).
25. Im, S.-A. et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N. Engl. J. Med.* **381**, 307–316, https://doi.org/10.1056/nejmoa1903765 (2019).
26. Slamon, D. et al. Ribociclib plus endocrine therapy in early breast cancer. *N. Engl. J. Med.* **390**, 1080–1091, https://doi.org/10.1056/NEJMoa2305488 (2024).
27. Schmid, P. et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N. Engl. J. Med.* **386**, 556–567, https://doi.org/10.1056/NEJMoa2112651 (2022).
28. van Ramshorst, M. S. et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* **19**, 1630–1640, https://doi.org/10.1016/s1470-2045(18)30570-9 (2018).
29. van der Voort, A. et al. MRI-guided optimisation of neoadjuvant chemotherapy duration in stage II-III HER2-positive breast cancer (TRAIN-3): a multicentre, single-arm, phase 2 study. *Lancet Oncol.* **25**, 603–613, https://doi.org/10.1016/s1470-2045(24)00104-9 (2024).
30. Tadros, A. et al. Trends in guideline-concordant care for inflammatory breast cancer. *JAMA Netw. Open* **8**, e2454506, https://doi.org/10.1001/jamanetworkopen.2024.54506 (2025).
31. Leone, J. P. et al. Survival outcomes and treatment patterns by tumor subtype (TS) in stage III inflammatory and non-inflammatory breast cancer (BC). *J. Clin. Oncol.* **42**, 607–607, https://doi.org/10.1200/JCO.2024.42.16_suppl.607 (2024).
32. Iwai, Y. et al. Guideline-concordant surgical care for lobular versus ductal inflammatory breast cancer. *Ann. Surg. Oncol.* **31**, 5929–5936, https://doi.org/10.1245/s10434-024-15540-1 (2024).
33. Gentilini, O. D. et al. Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes: the SOUND randomized clinical trial. *JAMA Oncol.* **9**, 1557–1564, https://doi.org/10.1001/jamaoncol.2023.3759 (2023).
34. Man, V., Duan, J., Luk, W. P., Fung, L. H. & Kwong, A. Different strategies in de-escalation of axillary surgery in node-positive breast cancer following neoadjuvant treatment: a systematic review and meta-analysis of long-term outcomes. Breast Cancer. https://doi.org/10.1007/s12282-025-01692-9 (2025).
35. Jatoi, I., Benson, J. R. & Toi, M. De-escalation of axillary surgery in early breast cancer. *Lancet Oncol.* **17**, e430–e441, https://doi.org/10.1016/S1470-2045(16)30311-4 (2016).
36. Rueth, N. M. et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. *J. Clin. Oncol.* **32**, 2018–2024, https://doi.org/10.1200/jco.2014.55.1978 (2014).
37. Nakhlis, F. et al. Patterns of breast reconstruction in patients diagnosed with inflammatory breast cancer: the Dana-Farber Cancer Institute's Inflammatory Breast Cancer Program experience. *Breast J.* **26**, 384–390, https://doi.org/10.1111/tbj.13509 (2020).
38. Belkacem, O. et al. Prognostic value of tumor-infiltrating lymphocytes (TILS) and their association with clinicopathological features in breast cancer: a retrospective study involving 53 cases. J. Senol. Breast Dis.https://doi.org/10.1016/j.senol.2021.07.003 (2022).
39. Priedigkeit, N. et al. Clinicogenomic characterization of inflammatory breast cancer. bioRxiv.https://doi.org/10.1101/2024.05.07.592972 (2024).
40. Anderson, W. F., Chu, K. C. & Chang, S. Inflammatory breast carcinoma and noninflammatory locally advanced breast carcinoma: distinct clinicopathologic entities?. *J. Clin. Oncol.* **21**, 2254–2259, https://doi.org/10.1200/jco.2003.07.082 (2003).
41. Schroder, C. P. et al. Herkennen van inflammatoir mammacarcinoom. *Huisarts en Wet.* **60**, 404–406 (2017).
42. Genetic and Rare Diseases (GARD). *Inflammatory Breast Cancer.*https://rarediseases.info.nih.gov/diseases/6784/inflammatory-breast-cancer.
43. Executive Agency for Health and Consumers (EAHC) of the European Commision. *Cancer List*.https://www.rarecarenet.eu/rarecarenet/cancerlist.
44. Federatie Medisch Specialisten. Richtlijnendatabase, Richtlijn Borstkanker, 310–312. https://richtlijnendatabase.nl/richtlijn/borstkanker/inflammatoire_borstkanker.html (2023).
45. Wolff, A. C. et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J. Clin. Oncol.* **36**, 2105–2122, https://doi.org/10.1200/jco.2018.77.8738 (2018).
46. Gennari, A. et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann. Oncol.* **32**, 1475–1495, https://doi.org/10.1016/j.annonc.2021.09.019 (2021).
47. Loibl, S. et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* **35**, 159–182, https://doi.org/10.1016/j.annonc.2023.11.016 (2024).
48. Dobin, A. et al. STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* **29**, 15–21, https://doi.org/10.1093/bioinformatics/bts635 (2013).
49. Tarasov, A., Vilella, A. J., Cuppen, E., Nijman, I. J. & Prins, P. Sambamba: fast processing of NGS alignment formats. *Bioinformatics* **31**, 2032–2034, https://doi.org/10.1093/bioinformatics/btv098 (2015).
50. Smid, M. et al. Gene length corrected trimmed mean of M-values (GeTMM) processing of RNA-seq data performs similarly in intersample analyses while improving intrasample comparisons. *BMC Bioinform.* **19**, 236, https://doi.org/10.1186/s12859-018-2246-7 (2018).
51. Johnson, W. E., Li, C. & Rabinovic, A. Adjusting batch effects in microarray expression data using empirical Bayes methods. *Biostatistics* **8**, 118–127, https://doi.org/10.1093/biostatistics/kxj037 (2007).

52. Parker, J. S. et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J. Clin. Oncol.* **27**, 1160–1167, https://doi.org/10.1200/jco.2008.18.1370 (2009).
53. Massink, M. P. G. et al. Proper genomic profiling of (BRCA1-mutated) basal-like breast carcinomas requires prior removal of tumor infiltrating lymphocytes. *Mol. Oncol.* **9**, 877–888, https://doi.org/10.1016/j.molonc.2014.12.012 (2015).
54. Hammerl, D. et al. Clonality, antigen recognition, and suppression of CD8(+) T cells differentially affect prognosis of breast cancer subtypes. *Clin. Cancer Res.* **26**, 505–517, https://doi.org/10.1158/1078-0432.Ccr-19-0285 (2020).

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Author contributions

J.vG. - Data cleaning and analysis, wrote main manuscript. E.J. - Data cleaning and analysis, wrote main manuscript. Jasmine M. - Data analysis and wrote main manuscript. G.vdS. - Data collection. E.vl-S - Study execution and data collection. M.S. - Data analysis. C.vD. - Pathology assessment, data collection and analysis. S.W. - Sample collection and data analysis. J.W. - Pathology assessment and study design. G.S.- Study design and study execution. John M. - Study design, study execution, data and sample collection, data analysis. C.S. - Study design, study execution, project oversight, data analysis and interpretation, wrote main manuscript. Furthermore, all authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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