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Early detection of triple-negative breast cancer: evidence of a favourable prognostic impact in a comparative analysis of screen-detected versus symptomatic cases

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Abstract

Purpose Mammographic screening is effective in reducing breast cancer mortality, but the impact of screening on triple-negative breast cancers (TNBCs) outcomes remains debated. This study aims to determine if screen detection is an independent prognostic factor for TNBCs and to analyse the radiological and pathological differences between screen-detected and symptomatic TNBCs.

Methods This retrospective cohort study analysed 353 histologically confirmed TNBC cases diagnosed between 2013 and 2020 at a single institution in Turin, Italy. Cases were categorized into screen-detected and symptomatic groups based on initial presentation. Clinical, radiological and pathological characteristics as well as disease-free survival (DFS) and overall survival (OS) were compared between groups. Statistical analyses included Kaplan-Meier survival curves and Cox proportional hazard models, adjusting for several clinical and biological variables.

Results 50.1% of cases were screen-detected and 49.9% were symptomatic. Screen-detected cases were more commonly smaller (T1 or T2) (96.6%) than symptomatic cases (75%) ($p < 0.001$). Also, compared to symptomatic tumours, screen-detected ones were more often node negative (62.4% vs. 48%, $p = 0.007$) and diagnosed at a lower stage (85.4% vs. 63.8%, $p < 0.001$), with better DFS and OS. Detection method was not an independent prognostic factor, while stage at diagnosis, vascular invasion, histologic type and tumour-infiltrating lymphocytes (TILS) were more significant predictors of prognosis. Radiological and biological features were similar between the two groups.

Conclusions TNBCs correlate with favourable pathological features and improved survival outcomes in univariate analyses, but these benefits diminish when accounting for traditional prognostic factors. Hence, the better prognosis observed among screen-detected cases is more likely due to stage shift rather than tumour biology.

Keywords Triple-negative breast cancer, Screening, Prognosis, Early detection

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Introduction

Breast cancer (BC) is the most prevalent cancer globally, accounting for 11.7% of all cancer cases, with approximately 2.3 million new cases and 685,000 deaths reported worldwide in 2020 [1]. In Italy BC is the most frequently diagnosed cancer among women, with an estimated 55,900 new cases in 2023 [2].

BC is a heterogeneous disease characterized by variations in hormonal receptors expression, HER2 status and Ki67 levels. These variations delineate distinct immunophenotypic subgroups with significant clinical and therapeutic implications, such as luminal A/B, HER2 positive and triple-negative BCs (TNBCs) subtypes [3]. TNBCs, in particular, are defined by the absence of estrogen receptor (ER), progesterone receptor (PR) and HER2, and they constitute approximately 15–20% of total BC cases. TNBCs are generally associated with aggressive behaviour, poor prognosis and insensitivity to hormonal and anti-HER2 therapies [4, 5].

It is well established that mammographic screening can detect early stage BC, frequently with no lymph nodes involvement, leading to a 20–35% reduction in BC mortality [6]. This benefit may be partly attributed to the earlier detection of BCs in their natural course, resulting in an apparent survival improvement (lead-time bias) and the higher likelihood of detecting slow-growing less aggressive tumours (length bias) [7].

Screen-detected BCs are typically luminal tumours, whereas HER2 + and TNBC cases are less frequently identified within screening programs [8, 9]. Nonetheless, literature indicated that screen detection remains an independent prognostic factor, even after adjusting for clinical and biological variables, suggesting that molecular subtypes alone do not fully account for the favourable prognosis of screen-detected lesions [10–13]. However, it remains unclear whether screen detection has an independent impact on prognosis in more aggressive subtypes, such as TNBCs. A recent study addressed this issue, demonstrating a better prognosis for screen-detected TNBCs compared to those diagnosed as interval cancer or outside screening programs, although the results did not always achieve statistical significance [14].

It is important to underline that TNBCs are generally characterized by the presence of a mass rather than isolated microcalcifications, which facilitates their clinical detection as symptomatic lesions [15, 16]. However, TNBCs are known to comprise a heterogeneous group of diseases with distinct histological and biological patterns [17] and there is a lack of comprehensive understanding regarding the differences between various TN subtypes and their radiological features [18], which may influence the efficacy of mammographic screening.

Therefore, the aims of this study are as follows:

- to assess whether screen detection is an independent prognostic factor for TNBCs;
- to investigate the different radiological and pathological patterns in screen-detected and symptomatic TNBCs.

Methods

Study design and population

This single-centre retrospective study was conducted on a cohort of histologically confirmed TNBCs diagnosed at the Pathology Unit of the AOU "Città della Salute e della Scienza" of Turin, Italy, between 2013 and 2020.

The date of diagnosis was defined as the date of histological diagnosis from either the surgical sample or the biopsy. Age at diagnosis was computed by subtracting the date of birth from the date of diagnosis.

Triple-negative definition

Cases were classified as triple-negative based on the absence of ER and PR expression, as well as the lack of HER2 overexpression/gene amplification. The cut-off for ER and PR positivity was set at < 1%, in accordance with the St. Gallen Consensus of 2011 [3]. HER2 status was assessed following the guidelines recommended by the American Society of Clinical Oncology/College of American Pathologists [19].

Method of detection

Cases were categorized as screen-detected if they were initially identified by mammography performed within the organized screening program according to the standard protocol or through opportunistic screening, in absence of symptoms.

Cases were classified as symptomatic if they were diagnosed based on specific symptoms, such as palpable masses, changes in breast skin, nipple retraction, breast pain, or swelling. Interval cancers, which are cancers diagnosed after a negative mammography but before the next scheduled screening invitation, were included in the symptomatic category.

Case series description

Clinical, pathological and radiological data were retrieved from hospital records and screening databases.

Pathological tumour size, lymph node involvement and presence of metastasis were classified according to the TNM system. Tumour size (pT) was dichotomized into two categories ("1–2" and "3–4"), as well as lymph node involvement ("no" for N0 and "yes" for N1/2/3). For cases that underwent neoadjuvant chemotherapy, pre-treatment clinical T and N stages were used as a proxy for pT and pN. A dichotomous variable for stage at diagnosis was then created: "stage I-II" and "stage III-IV".

Treatment data collected included neoadjuvant chemotherapy and pathological response, adjuvant chemotherapy, radiotherapy and type of surgery. A three-category variable was created to summarize neoadjuvant therapy and pathological response: "No neoadjuvant chemotherapy", "Yes, with a complete response", "Yes, with a partial or absent response".

Surgical treatment was classified into two categories: "Conservative surgery" (including excisional biopsy, tumorectomy, extensive resection or quadrantectomy), and "Radical surgery" (including radical mastectomy).

Pathological data on histologic type, histologic grade, vascular invasion, Ki67, androgen receptor (AR) and tumour-infiltrating lymphocytes (TILS) were retrieved. Histologic type was classified into four categories: "Non-special type (NST)", "Metaplastic", "Lobular" and "Others". Histologic grade was dichotomized into "Low grade" (G1-G2) and "High grade" (G3). A 1% threshold was used for AR [20]. Tumours were classified as highly proliferative if their Ki67 value was 20% or higher [21]. For TILS, no universally accepted cut-off has been established yet. In this study a 30% threshold was chosen, as it is the most commonly applied in the relevant published research [22].

Radiological features were retrieved from diagnostic mammograms. In particular, for screen-detected cases, data were collected from the mammogram that first identified the tumour. For symptomatic cases, the mammogram performed after the presentation of symptoms was used. A variable defining the mammographic pattern was constructed, with the following categories: "Mass with calcifications", "Mass without calcifications", "Calcifications only", "Architectural distortion", "Focal asymmetry" and "Negative".

Follow-up

Data regarding disease progression and mortality were retrieved from clinical charts, with all patients retrospectively followed up until the end of August 2023. Recurrence was defined as loco-regional disease recurrence on the ipsilateral or contralateral breast, chest wall, or lymph nodes, or as the appearance of distant metastasis. Specific cause of death was not available. Disease-free survival (DFS) and overall survival (OS) were the primary outcomes for survival analyses.

DFS was defined as the interval from the date of diagnosis to the identification of loco-regional or distant recurrence. Patients lost to follow-up or who died in the follow-up period were censored at the date of their last hospital visit.

OS was defined as the time from the date of diagnosis to the date of death from any cause. Patients still alive at the end of the follow-up period were censored at the date of their last hospital visit.

Statistical analysis

Categorical variables were described using absolute numbers and percentages. Differences in proportions between screen-detected and symptomatic cases were estimated through the Chi-squared test or the Fisher exact test, when appropriate.

Continuous variables were described as median and interquartile range (IQR). Normality distribution was assessed through the Shapiro-Wilk test and the Wilcoxon rank-sum test was used for group comparison.

Survival curves for both DFS and OS, according to the method of detection, were generated using the Kaplan-Meier method and compared with the log-rank test.

Cox proportional hazard models were fitted to estimate hazard ratios (HR) for recurrence and death adjusting for several clinical, pathological and biological variables. Covariates included in the models were selected based on their clinical and biological relevance. The final models included the following covariates: method of detection, age at diagnosis, stage, neoadjuvant therapy and pathological response, type of surgery, vascular invasion, histologic type, histologic grade, Ki67 and TILS. Missing information was addressed including missing values as a separate category. A sensitivity analysis was performed to assess if results were consistent when models were restricted to women eligible for organized screening (ages 45–75). Proportional hazard assumptions were tested using the Schoenfeld residual test.

In addition, a mediation analysis was conducted in order to test the hypothesis that screen detection is associated with survival outcomes through the presence of mediators, such as the stage at diagnosis and vascular invasion (see Appendix A).

All statistical tests were two-sided, with a p-value < 0.05 considered statistically significant.

All analyses were performed using Stata 15.1 statistical software (StataCorp LLC) and R version 4.3.0.

Results

Case series description

The initial cohort comprised 365 cases, of which 12 were relapses of previously diagnosed cancers and were therefore excluded. Thus, the final dataset included 353 cases.

Table 1 reports the baseline descriptive statistics of tumour features, therapeutic variables and clinical outcomes stratified by detection method for a total of 353 TNBCs, of which 177 (50.1%) were screen-detected and 176 (49.9%) were symptomatic. The median age for symptomatic cases was 57 years (IQR 45–73) while for screen-detected cases it was 62 years (IQR 52–71), with the difference being statistically significant ($p = 0.028$).

Screen-detected cases were more frequently classified as T1 or T2 (96.6% vs. 75%, $p < 0.001$) and were more often node negative (62.4% vs. 48%, $p = 0.007$), with a

Table 1 Descriptive statistics of triple-negative breast cancers (TNBCs) features, therapeutic variables and clinical outcomes stratified by detection method

		Method of detection				
		Screen-detected		Symptomatic		
		N	%	*N*	%	*p*-value
Total		177	50.1%	176	49.9%	
Age at diagnosis (years)	Median (IQR*)	62 (52–71)		57 (45–73)		0.028
Tumour size	T1-2	170	96.6%	132	75%	< 0.001
	T3-4	6	3.4%	44	25%	
Nodal status	Negative	108	62.4%	84	48%	0.007
	Positive	65	37.6%	91	52%	
Stage	I-II	141	85.4%	111	63.8%	< 0.001
	III-IV	24	14.6%	63	36.2%	
Neoadjuvant chemotherapy	No	137	79.2%	96	55.2%	< 0.001
	Yes	36	20.8%	78	44.8%	
Pathological response	Complete	7	22.6%	15	22.4%	0.997
	Partial	20	64.5%	43	64.2%	
	Absent	4	12.9%	9	13.4%	
Adjuvant chemotherapy	No	51	31.3%	60	34.5%	0.533
	Yes	112	68.7%	114	65.5%	
Radiotherapy	No	49	30.4%	53	30.5%	0.996
	Yes	112	69.6%	121	69.5%	
Type of surgery	Conservative	117	74.0%	94	56%	0.001
	Radical	41	26.0%	74	44%	
Disease progression	No	120	80.0%	109	67.7%	0.014
	Yes	30	20.0%	52	32.3%	
Death from any cause	No	129	82.7%	117	75.6%	0.117
	Yes	27	17.3%	41	24.4%	
Follow-up (years)	Median (IQR*)	3.7 (2.3–6.1)		2.9 (1.5–5.1)		0.001

*Interquartile range

lower stage at diagnosis (85.4% vs. 63.8%, $p < 0.001$). Symptomatic cases more commonly received neoadjuvant chemotherapy (44.8% vs. 20.8%, $p < 0.001$) and underwent more radical surgical procedures (44% vs. 26%, $p = 0.001$). Among the 144 patients who received neoadjuvant chemotherapy, pathological response data were available for 98 cases (86.7%). Of these, 22 tumours (22.4%) achieved a pathological complete response, 63 (64.3%) had a partial response and 13 (13.3%) showed no response, with no significant differences between screen-detected and symptomatic cases.

Radiological and pathological patterns

Information on mammographic features was available for 278 patients. As shown in Table 2, there were no significant differences in mammographic features between screen-detected and symptomatic TNBCs. In both groups TNBCs most frequently presented as a mass without calcifications (60% in the screen-detected group and 47.3% in the symptomatic one) and only in a minority of cases presented as architectural distortion or isolated microcalcifications.

Screen-detected and symptomatic cancers also showed similar characteristics concerning histologic type and grade, vascular invasion, TILS and AR (Table 2). The only difference was observed for Ki67, with symptomatic cases showing a median value of 55% compared to 50% of screen-detected cases ($p = 0.01$). However, this difference was not confirmed when Ki67 was modelled as a categorical variable with a 20% cut-off (Table 2).

Mammographic features were further explored according to histologic type. Lobular cancers seemed to have different mammographic features compared to the other histologic types, with a higher proportion of lesions presenting as isolated calcifications and focal asymmetries. However, these differences did not reach statistical significance (Table 3).

Prognostic impact of screen detection

The median follow-up period was 3.7 years (IQR 2.3–6.1) for cases detected through screening and 2.9 years (IQR 1.5–5.1) for symptomatic cases ($p = 0.001$). Loco-regional or distant progression occurred more frequently in the symptomatic group (32.3% vs. 20%, $p = 0.014$). No significant difference was observed in all-causes mortality (Table 1).

Figures 1 and 2 report the survival curves for disease-free survival (DFS) and overall survival (OS) respectively,

Table 2 Descriptive statistics of triple-negative breast cancers (TNBCs) radiological and pathological characteristics stratified by detection method

		Method of detection				
		Screen detected		Symptomatic		
		N	%	*N*	%	*p*-value
Mammographic features	Mass with calcifications	21	16.1%	24	16.2%	0.200
	Mass without calcifications	78	60.0%	70	47.3%	
	Calcifications only	4	3.1%	3	2.0%	
	Architectural distortion	7	5.4%	14	9.5%	
	Focal asymmetry	14	10.8%	28	18.9%	
	Negative	6	4.6%	9	6.1%	
Histologic type	Non-special type (NST)	127	71.8%	126	71.6%	0.579
	Metaplastic	12	6.8%	11	6.2%	
	Lobular	5	2.8%	10	5.7%	
	Others	33	18.6%	29	16.5%	
Histologic grade	1–2	40	23.7%	32	20.1%	0.439
	3	129	76.3%	127	79.9%	
Vascular invasion	No	91	56.9%	73	49%	0.165
	Yes	69	43.1%	76	51%	
AR*	< 1%	48	53.3%	57	62.6%	0.205
	≥ 1%	42	46.7%	34	37.4%	
Ki-67	< 20%	26	14.7%	18	10.2%	0.204
	≥ 20%	151	85.3%	158	89.8%	
TILS**	< 30%	104	78.8%	113	81.3%	0.606
	≥ 30%	28	21.2%	26	18.7%	
		Median	**IQR**	**Median**	**IQR**	
Ki-67 (continuous)		50%	30–65	55%	35-72.5	0.01
TILS (continuous)**		5%	1–20	5%	1–20	0.559

*Androgen Receptor

**Tumour Infiltrating Lymphocytes

Table 3 Triple-negative breast cancers (TNBCs) mammographic features based on histologic types

	Histologic Type								
	NST*		Metaplastic		Lobular		Others		*p*-value
Mammographic features	*N*	%	*N*	%	*N*	%	*N*	%	
Mass with calcifications	30	15.2%	4	22.2%	1	7.7	10	20.0%	0.082
Mass without calcifications	110	55.9%	8	44.4%	4	30.8	26	52.0%	
Calcifications only	3	1.5%	0	0.0%	2	15.4	2	4.0%	
Architectural distortion	12	6.1%	1	5.6%	1	7.7	7	14.0%	
Focal asymmetry	31	15.7%	3	16.7%	4	30.8	4	8.0%	
Negative	11	5.6%	2	11.1%	1	7.6	1	2.0%	
Total	197	100%	18	100%	13	100%	50	1	

*Non-Special Type

based on the detection method. Screen-detected cases showed better survival outcomes both for DFS and OS (log-rank = 0.0019 and log-rank = 0.019, respectively).

In the multivariable analysis, the detection method was not an independent predictor of disease progression or mortality. However, a shorter DFS was significantly associated with advanced stage (HR 2.41, 95% CI 1.43–4.05), partial or absent pathological response after neoadjuvant chemotherapy (HR 2.24, 95% CI 1.23–4.09), vascular invasion (HR 2.95, 95% CI 1.67–5.20) and metaplastic or others special-type histology (HR 3.44, 95% CI 1.46–8.10 and HR 2.53, 95% CI 1.41–4.53, respectively) (Table 4).

Similarly, OS was associated with advanced stage (HR 1.78, 95% CI 1.00-3.18), vascular invasion (HR 2.51, 95% CI 1.36–4.62), metaplastic or others special-type histology (HR 2.73, 95% CI 1.00-7.40 and HR 2.62, 95% CI 1.40–4.87, respectively) and TILS ≥ 30% (HR 0.30, 95% CI 0.12–0.76) (Table 4).

Intriguingly, we identified 20 tumours characterized by the simultaneous presence of the four most significant positive prognostic factors that emerged in our analysis

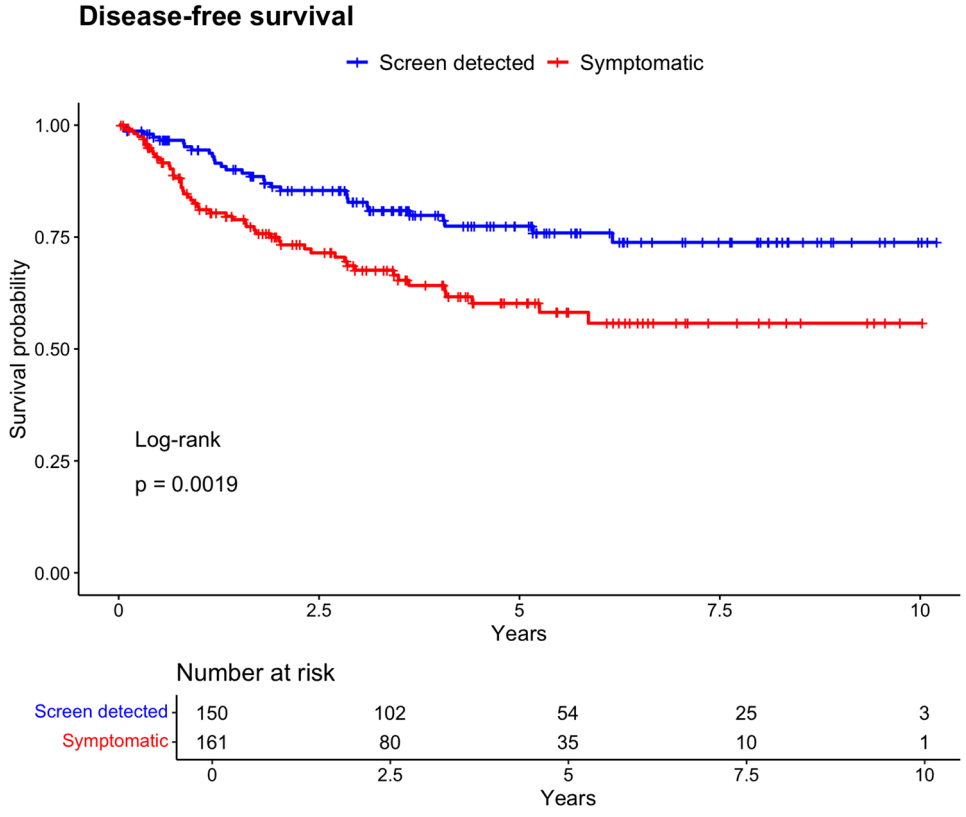

Fig. 1 Kaplan-Meier curves and log-rank test comparing disease-free survival (DFS) between screen-detected and symptomatic triple-negative breast cancers

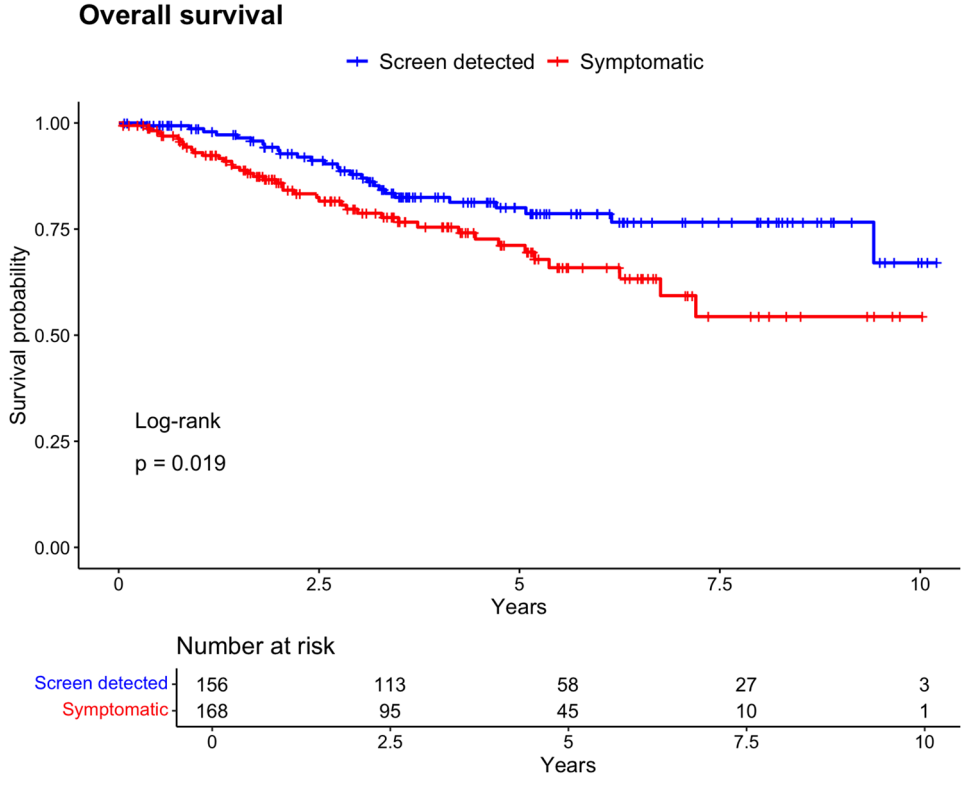

Fig. 2 Kaplan-Meier curves and log-rank test comparing overall survival (OS) between screen-detected and symptomatic triple-negative breast cancers

Table 4 Cox multivariable models for disease-free survival (DFS) and overall survival (OS)

		DFS		OS	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Age at diagnosis (years)		1.00 (0.98–1.02)	0.691	1.01 (0.99–1.04)	0.232
Method of detection	Screen-detected	1.00		1.00	
	Symptomatic	1.49 (0.91–2.47)	0.115	1.30 (0.76–2.20)	0.334
Stage at diagnosis	I-II	1.00		1.00	
	III-IV	2.41 (1.43–4.05)	0.001	1.78 (1.00-3.18)	0.05
Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	1.00		1.00	
	Yes, with a complete response	1.88 (0.44–7.92)	0.391	0.20 (0.04–1.05)	0.06
	Yes, with a partial or absent response	2.24 (1.23–4.09)	0.009	1.36 (0.64–2.86)	0.413
Adjuvant chemotherapy	No	1.00		1.00	
	Yes	1.47 (0.82–2.64)	0.200	0.86 (0.46–1.60)	0.630
Type of surgery	Conservative	1.00		1.00	
	Radical	0.80 (0.48–1.34)	0.405	0.99 (0.56–1.73)	0.967
Vascular invasion	No	1.00		1.00	
	Yes	2.95 (1.67–5.20)	< 0.001	2.51 (1.36–4.62)	0.003
Histologic type	Non-special type (NST)	1.00		1.00	
	Metaplastic	3.44 (1.46–8.10)	0.005	2.73 (1.00-7.40)	0.049
	Lobular	1.66 (0.60–4.58)	0.330	1.84 (0.60–5.63)	0.287
	Others	2.53 (1.41–4.53)	0.002	2.62 (1.40–4.87)	0.002
Histologic grade	1–2	1.00		1.00	
	3	0.69 (0.35–1.39)	0.303	0.84 (0.41–1.75)	0.647
Ki-67	< 20%	1.00		1.00	
	≥ 20%	1.54 (0.63–3.81)	0.344	1.29 (0.47–3.55)	0.619
TILS*	< 30%	1.00		1.00	
	≥ 30%	1.00 (0.62–1.94)	0.739	0.30 (0.12–0.76)	0.011

*Tumour-Infiltrating Lymphocytes

(stage I-II at diagnosis, absence of vascular invasion, NST or lobular histologic type and TILS ≥ 30%).

Within this subgroup, only 2 events of progression and 1 event of death were observed. Despite the low number of events, lesions with all the four positive prognostic factors (Group 1), seemed to show better survival outcomes for both DFS and OS compared to all other lesions (Group 2), (Supplementary Figs. 1 and 2).

In the sensitivity analysis restricted to the age group 45–75 years, considering only women eligible for invitation in the organized screening, the method of detection continued to show no association with both DFS and OS in the multivariable analysis (Supplementary Table 1).

According to the results of the mediation analysis, stage at diagnosis and vascular invasion likely acted as mediators in the association between screen detection and survival outcomes (see Appendix A).

Discussion

This study assessed whether screen detection is an independent prognostic factor for triple-negative breast cancers (TNBCs) and investigated the differences in radiological and pathological patterns between screen-detected and symptomatic TNBCs. The findings revealed that screen-detected TNBCs, compared to symptomatic cases, were generally diagnosed at an earlier stage, being more often smaller and node negative, leading to better survival outcomes in univariate analyses. However, multivariable analyses indicated that the method of detection was not an independent predictor of disease-free survival (DFS) or overall survival (OS). Prognosis was more strongly influenced by traditional factors such as stage at diagnosis, response to neoadjuvant chemotherapy, vascular invasion and histological subtype.

It is well established that screen-detected BCs are typically characterized by an earlier stage at diagnosis, with lower lymph node involvement and grade [23–25]. However, few studies have specifically evaluated TNBCs according to the detection method.

Kim et al. compared 142 screen-detected cases with 429 symptomatic cases, finding a higher proportion of small and node negative tumours in the screen-detected group [26]. Alanko et al. found similar results, observing a higher proportion of TN tumours less than 20 mm in the screen-detected group, but they did not find any difference regarding nodal status, probably due to the small sample size [14]. Our results are coherent with the findings of these studies, as we found that screen-detected cases were more likely to be small, node negative and diagnosed at an earlier stage. This could explain the tendency towards a more conservative surgical approach

and less frequent use of neoadjuvant chemotherapy in screen-detected cases.

Considering the mammographic features, the majority of TNBCs appeared as masses with or without calcifications and secondarily as focal asymmetries, with only a few cases that appeared as isolated microcalcifications. These results are coherent with other studies, giving a potential explanation for the lower proportion of TNs among screen-detected BC [15, 16, 27, 28].

However, in our sample no differences emerged regarding mammographic features between screen-detected and symptomatic cases. This result may be consistent with the lack of biological differences between the two categories of tumours. Actually, in line with previous research, no differences were observed between screen-detected and symptomatic TNBCs considering histologic grade, histologic type, vascular invasion, AR and TILS [14, 26, 29]. Only a slight difference was observed between the two populations of lesions concerning the distribution of Ki67 modelled as a continuous variable, suggesting a lower proliferative activity in the screen-detected cases. It should be considered that this difference, despite being statistically significant, might be clinically irrelevant. In addition, it was not confirmed when Ki67 was categorized with a 20% cut-off, which is the most commonly applied threshold in the context of breast cancer [21]. Globally, these results suggest that screen-detected and symptomatic TNBCs are mainly distinguished by the stage at diagnosis and not by biological features.

These findings were also coherent with the survival analysis. In agreement with the study by Alanko et al. [14], we found that screen-detected tumours showed a better prognosis in the univariable survival analysis, considering both DFS and OS. However, screen detection lost its independent prognostic value after adjusting for stage at diagnosis and several biological variables (vascular invasion, histologic grade, histologic type, Ki67 and TILS), in line with other studies [26, 29]. Hence, it becomes evident that the improved prognosis of screen-detected cases was primarily due to earlier stage at diagnosis rather than to the screen detection itself. However, our sample also included women not eligible for the organized screening, who could only have attended opportunist screening. To evaluate the impact of screen detection in women eligible for invitation in the organized screening, we conducted a sensitivity analysis restricted to the subcategory of women aged 45–75 years, and the results were unchanged. These results highlight the importance of screening, leading to early detection and better prognosis also among TNBCs.

It should be acknowledged that screen detection might be associated with early stage at diagnosis and other relevant factors, such as vascular invasion, which are likely to act as mediators in the association between detection method and survival outcomes. For this reason, we tested this hypothesis with a mediation analysis (see Appendix A), according to which stage at diagnosis and vascular invasion seemed to act as mediators. However, the results were at the limits of significance and the performance and interpretation of this analysis were made difficult by the small sample size and the few numbers of cases.

In agreement with the results of another Italian study conducted on a large cohort of TNBCs [30], higher stage at diagnosis seemed to be one of the major prognostic factors influencing both DFS and OS. However, considering that TNBCs are a heterogeneous group of diseases, we analysed the impact of additional specific histopathological factors. Although no differences were observed in screen-detected and clinical TNBCs, we found that generally metaplastic histologic type rather than NST had a higher probability of disease progression. This result strengthens the ones from Montagna et al., which found a worse DFS and OS among a small sample of metaplastic TNBCs, although not confirmed in the multivariable analysis [31]. Moreover, analysing histological types, isolated calcifications and focal asymmetries seemed to be more frequent among lobular tumours rather than among other subtypes, even if these differences did not reach statistical significance.

Finally, in our study and in line with previous data, we found that both presence of TILS and vascular invasion were significantly associated with prognosis independent by method of detection [22, 32].

Considering all these results, our study highlights and supports the importance of morphological prognostic factors (stage, vascular invasion, histologic type and TILS) able to identify subgroups of TNBCs with different clinical behaviour, in both screen-detected and symptomatic tumours.

Main strengths

The study possesses several notable strengths that contribute significantly to understanding triple-negative breast cancers (TNBCs). Firstly, it benefited from a robust dataset comprising 353 histologically confirmed TNBC cases, ensuring comprehensive data for analysis. This dataset included detailed clinical and pathological variables such as tumour size, lymph node involvement, treatment modalities (including neoadjuvant chemotherapy and surgical approaches) and histological subtypes like metaplastic and lobular carcinomas.

Moreover, the study rigorously evaluated mammographic features, categorizing tumours based on specific patterns such as masses with or without calcifications, architectural distortion and focal asymmetry. This detailed radiological analysis enhanced the understanding of TNBC presentations.

Clinically, the study's findings underscored the critical role of stage at diagnosis, vascular invasion and histologic subtype as prognostic factors in TNBCs. Both large sample size and inclusion of both screen-detected and symptomatic cases enhanced the generalizability of results, contributing to global knowledge on TNBC management.

In summary, these strengths highlight the study's substantial contribution to advancing knowledge on TNBCs, particularly regarding the impact of detection methods and the complex interplay of biological and pathological factors in disease prognosis.

Main limitations

The retrospective nature of the study may have introduced selection bias and limited the ability to establish causality. Additionally, data regarding the specific cause of death was not available, preventing the assessment of breast cancer-specific mortality. Although the follow-up period was sufficient for initial survival analysis, longer follow-up would provide more comprehensive insights into long-term outcomes.

Furthermore, TNBCs encompass a variety of histological and molecular subtypes, which might not have been fully accounted for in the analysis, potentially affecting the generalizability of the findings.

Finally, we could not estimate the potential presence and magnitude of lead-time bias, and this should be considered when interpreting the results of the survival analysis. However, TNBCs are an aggressive subtype of breast cancer with a generally short lead time; hence, we hypothesize that the impact of lead-time bias among screen-detected cases was small.

Future research with larger sample sizes, longer follow-up periods, and more precise biological characterization of triple-negative tumours is needed to further strengthen and expand these findings. In addition, future studies should aim to better clarify the role of mediators in the association between detection method and prognosis, as well as the potential impact of lead-time bias.

Conclusions

To the best of our knowledge, this study encompassed the largest cohort of TNBC patients categorized by the method of detection. It elucidated the nuanced impact of screen detection on the prognosis of TNBCs, demonstrating that early detection is associated with better clinical outcomes, primarily due to its correlation with favourable prognostic features. Screen-detected TNBCs were more likely to be smaller, node-negative and diagnosed at a less advanced stage. Consequently, they exhibited better prognostic outcomes in the univariable analysis. However, the prognostic role of the detection method was not confirmed in the multivariable analysis. Given that screen-detected and symptomatic tumours did not differ significantly in several biological and radiological variables, the stage shift appeared more crucial than tumour biology in explaining the overall better survival outcomes among screen-detected cases.

Stage at diagnosis, vascular invasion, histologic type and TILS were reaffirmed as important prognostic factors in TNBCs and could be used to identify a subgroup of TNBCs with a better prognosis. While screen detection itself may not be an independent prognostic factor, its association with early-stage diagnosis and absence of vascular invasion underscored the importance of early detection strategies. The preliminary results of the mediation analysis (see Appendix A) strengthened these results, suggesting the potential role of stage at diagnosis and vascular invasion as mediators in the association between screen detection and survival outcomes.

Moreover, identifying a favourable prognostic subgroup within TNBCs offers a promising avenue for further research and potential stratification of treatment approaches. These findings advocate for continued efforts in optimizing screening protocols and advancing our understanding of TNBC heterogeneity to improve patient outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14067-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions

Conceptualization: IC, GF, LG, SR.Data Curation: SR, DC, GC, FB, MDR.Formal analysis: SR, GF, AC.Methodology: SR, GF, AC.Supervision: IC, PC, LG, GF.Writing–original draft: SR. Writing– review & editing: SR, IC, GF, AC, LG, PC.All authors have reviewed and approved the final manuscript.

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Data availability

The datasets generated during and/or analysed during the current study are not publicly available due to privacy issues but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study obtained ethical approval from the Committee for Human Biospecimen Utilization (Department of Medical Sciences– ChBU), which belongs to the University of Turin (Turin, Italy). All the data were recorded anonymously. The study did not impact patients' treatment, and due to its retrospective nature, informed consent was not required.

Competing interests

The authors declare no competing interests.

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