npj | breast cancer

Article

Published in partnership with the Breast Cancer Research Foundation

https://doi.org/10.1038/s41523-025-00877-x

Clinical outcome and proportion of hereditary cancer genes gPV in TNBC: the HEaRTBeat study

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We aimed to study the proportion of germline pathogenic variants (gPV) in hereditary cancer genes and the clinical–pathological characteristics, local and systemic treatments, pathological complete response (pCR) rate to neoadjuvant therapy, invasive breast cancer-free survival (IBCFS), and overall survival (OS) in triple-negative breast cancer (TNBC) patients, consecutively tested between 2017 and 2024 at Modena and Reggio Emilia University Hospital, Italy. A total of 387 early-stage patients were included in the study. Eighty-seven patients (22%) showed gPV in hereditary predisposing genes, mostly BRCA1/2 (11%), PALB2 (5%), RAD51C/D (2%), MUTYH (2%), ATM (1%), and others (1%). The proliferation index was high in all, whereas the most frequent stage was stage I/II, except in MUTYH gPV carriers. More mastectomies, also contralateral, were performed in gPV than in non-carriers. Finally, 64% gPV achieved pCR compared to 39% non-carriers ($p < 0.001$), although no differences were observed between the two groups in IBCFS or OS.

Triple-negative breast cancer (TNBC) accounts for 10–20% of all breast cancer (BC) cases[1]. Among those, 12–17% are hereditary BC, meaning that they are due to mutations in genes involved in the DNA damage-repair system. These mutations, also defined as germline pathogenic variants (gPVs), regard mostly *BRCA1/2*, but a small and significant percentage of TNBC patients carry gPVs in other genes, mainly in *PALB2, ATM, CHEK2, BARD1*, and *RAD51C/D*[2–4]. All gPVs in DNA-repair genes are responsible for genomic instability and cell proliferation, causing cancer development. On the other hand, drugs that disrupt the DNA cause cancer cell death, due to the impairment of the homologous repair system. This mechanism has been targeted by alkylating agents, as platinum-derived or anthracyclines, and by new drugs, as Poly (ADP-ribose) polymerase inhibitors (PARPi), that prevent the single-strand break repair, taking on an important role in BRCA1/2-related BC therapy.

Hereditary cancer multigene panel testing (MGP) is becoming a common practice because it makes it possible to identify gPVs in non-*BRCA1/2* predisposition genes as well. According to the most recent NCCN guidelines[5], genetic testing for high-penetrance BC susceptibility genes (*BRCA1/2, CDH1, PALB2, PTEN, STK11*, and *TP53*) is recommended for all TNBC patients, regardless of age at onset and family history. The addition of moderate-penetrance susceptibility genes may help to identify a larger number of carriers, although their consequent clinical usefulness in terms of primary and secondary prevention, prognostication, and therapeutic management remains uncertain[6,7].

Although considered the most aggressive form of BC, characterized mainly by poorly differentiated histology and often diagnosed at an advanced stage and in premenopausal women[8], TNBC may exhibit pronounced heterogeneity with regard to histology, patterns of metastatic dissemination, response to therapies, and patient outcomes[9]. Nevertheless, clinicopathologic characteristics and outcome variables of TNBC diagnosed in carriers of gPVs in genes other than *BRCA1/2* are poorly characterized. Knowing how many TNBC carriers carry other gPV and what the outcome is compared to *BRCA1/2* carriers could improve the timing of MGP analysis and the treatment choice for this population.

To achieve this aim, the HEaRTBeat study was designed to calculate the proportion of gPVs and also to evaluate whether hereditary cancer genes could be considered as prognostic factors in TNBC patients from a consecutive series diagnosed at our institution.

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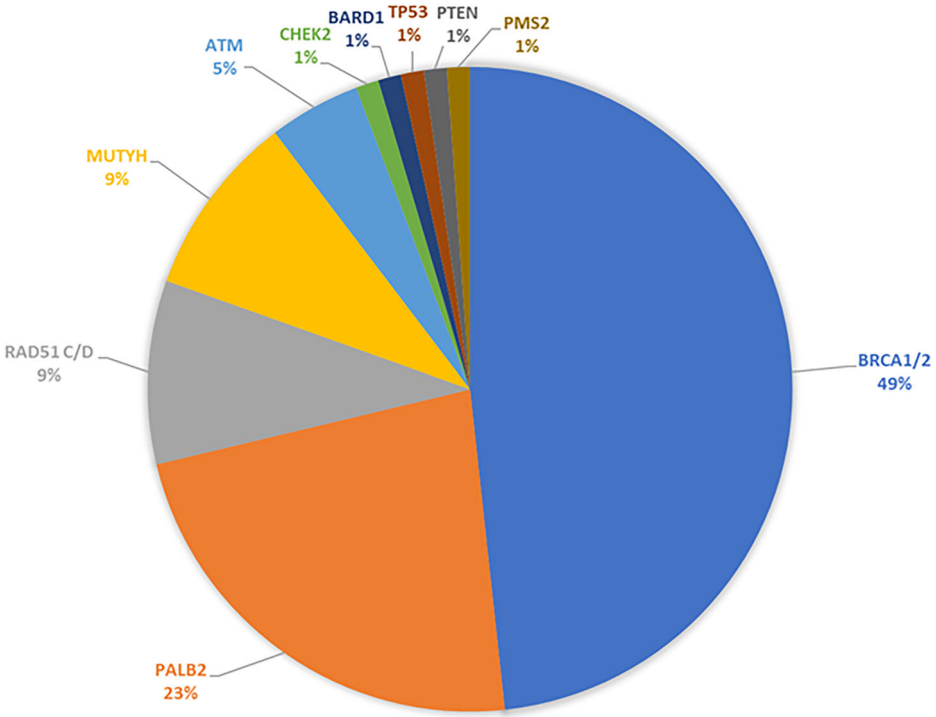

Fig. 1 | Distribution of gPV in hereditary cancer genes (altered gene, %). Of the 387 consecutive TNBC patients enroled in the study, who all performed MGP testing, 87 (22%) were gPV carriers. The percentage distribution of those gPV carriers is shown: blue = BRCA1/2 (BReast Cancer genes 1 and 2; orange = PALB2 (partner and localizer of BRCA2); grey = RAD51 paralog C and D (RAD51C/D); yellow = MUTHY DNA glycosylase; light blue = ataxia-telangiectasia mutated (ATM); green = Checkpoint kinase 2 (CHEK2); dark blue = BRCA1 associated RING domain 1 (BARD1); red = tumour protein p53 (TP53); dark grey = phosphatase and tensin homologue (PTEN); brown = PMS1 homologue 2 (PMS2).

Results

Study cohort

From October 2017 to October 2024, 566 TNBC patients were tested with MGP at the Modena and Reggio Emilia University. Among those, following the exclusion of 179 individuals, a total of 387 TNBC patients were included in the study. Thirteen patients were lost to follow-up (censored), and 37 had incomplete data on all variables. All 387 individuals were evaluated for invasive breast cancer free survival (IBCFS), overall survival (OS), and cumulative incidence function (CIF) analyses, as summarized in the CONSORT diagram (Supplementary Fig. 1). Ninety (22.5%) gPV in hereditary cancer genes were identified. As expected, the most common altered genes were *BRCA1/2* ($n = 42$, 11%), followed by *PALB2* ($n = 20$, 5%), *RAD51C/D* ($n = 8$, 2%), *MUTYH* ($n = 8$, 2%), and *ATM* ($n = 4$, 1%), while five (1%) showed other mutations (Fig. 1). Of note, the c.1187G>A, p.Gly396Asp, was the most represented MUTYH gPV (3/8, 37.5%).

Four patients carried more than one gene with a gPV: a *BRIP1* was associated with a *TP53* gPV, another *BRIP1* was associated with a *BRCA2* gPV, a *MUTYH* was associated with a *BRCA1* gPV and a *RAD51C* was associated with a *BRCA1* gPV.

Clinicopathological characteristics of patients with and without gPV are presented in Table 1. The *p*-values in Table 1 represent both the difference between gPV and non-gPV and the differences among all gPV and the differences in distribution of clinical–pathological characteristics within the specific group (non-gPV, gPV, *BRCA1/2, PALB2, RAD51/d, MUTYH, ATM*, and other gPV). The median age of all patients at diagnosis was 51 years (min 25 years–max 91 years). At data cutoff (October 2024), with a median follow-up of 3.9 years, 55 patients (12%) had died. The majority of all patients had no family history of breast or ovarian cancer ($n = 284$, 73%). In the cohort of TNBC patients with mutations, 27 (31%) had a family history of BC; of these, 15 (36%) were *BRCA1/2*. The most common histotype in both cohorts was infiltrating ductal carcinoma ($n = 371$, 96%) with a poor degree of differentiation ($n = 325$, 84%). Eighty-one percent ($n = 243$) of patients with no mutation had a Ki67 ≥ 20%, and a similar percentage was observed in patients with mutations ($n = 71$, 85%). A prevalence of stage III was also observed in *MUTYH* carriers ($n = 4$, 50%, $p = 0.06$ among gPV carriers).

Treatment modalities are reported in Table 2. A total of 195 patients (50%) received neoadjuvant chemotherapy (NACT): 150 (50%) belonged to the non-gPV cohort, and 45 (52%) were gPV carriers. The most common chemotherapy regimen used was based on anthracyclines and taxanes ($n = 106$, 71% in non-gPV carriers, $n = 23$, 51% in gPV), followed by regimens containing platinum-derived drugs alone or with antiangiogenetic factors, as in the case of the Ca.Pa.Be trial (Carboplatinum, Paclitaxel, and Bevacizumab) or in addition to pembrolizumab ($n = 58$, 30%). A statistically significant difference in favour of anthracyclines and taxanes compared to platinum-derived drugs was seen in the non-gPV patients ($p = 0.001$). In the gPV carriers, platinum-derived drugs, also in combination with pembrolizumab, were more commonly used than in non-gPV carriers, mostly in *BRCA1/2* individuals. Breast-conserving surgery with unilateral quadrantectomy associated with BLS was the most commonly performed surgery in the cohort of TNBC patients without gPV ($n = 164$, 53%) and in the cohort of TNBC patients with gPV ($n = 35$, 39%), ($p = 0.001$), particularly in PALB2 gPV ($p = 0.06$) but a higher proportion of gPV carriers ($n = 29$, 32%) compared to the other group of patients ($n = 51$, 16%) underwent mastectomy plus sentinel lymph node biopsy (SLNB) ($p = 0.04$), mostly in case of *BRCA1/2* gPV, although without statistically significant values in the different mutation subgroups ($p > 0.05$). Two patients did not receive any surgical treatment in the no gPV group, whereas 3 had missing data in the gPV group. Among the 195 patients who underwent NACT, 87 (45%) achieved pCR; of these, 58 (39%) belonged to the non-gPV cohort and 29 (64%) ($p < 0.001$) to the gPV cohort, with a prevalence of *BRCA* ($n = 18$, 69%) followed by *PALB2* ($n = 5$, 71%), *RAD51C/D* ($n = 3$, 75%), *MUTYH* ($n = 2$, 50%) and *ATM* ($n = 1$, 50%) patients. Of note, 53% of patients without gPV achieved pCR with anthracyclines and taxanes ($n = 31$) compared to 42% (24) with platinum-derived drugs ($P < 0.001$), whereas the same regimen was the most used in cases of residual disease ($n = 11$, 79%) ($p = 0.04$) in the gPV group. Contralateral prophylactic mastectomy (evaluated on 137 patients who received mastectomy with or without axillary dissection) was performed in 90% of the gPV ($n = 34$) compared to not gPV ($n = 4$, 10%) ($p < 0.001$). Among 34 gPV carriers who underwent prophylactic contralateral mastectomy, 24 were *BRCA1/2*, 5 *PALB2*, 3 *RAD51C/D*, 1 *ATM*, and 1 other gPV carrier, but no statistically significant difference was seen. Adjuvant therapy was administered to 233 patients (182 without [61%] and 51 [59%] with gPV). The most used regimen was based on anthracyclines and taxanes in both cohorts ($n = 77$, 42%; $n = 21$, 43%,

Table 1 | Clinicopathological characteristics of patients without or with gPV (specifically BRCA1/2, PALB2, RAD51C/D, MUTYH, ATM, and other gPV)

	N	*N* (%)	No gPV	All gPV	*P* values No gPV vs. gPV	*BRCA 1/2*	*PALB2*	*RAD51C/D*	*MUTYH*	*ATM*	OTHER gPV	*P*-value among gPV
		387	300 (78)	87 (22)		42 (11)	20 (5)	8 (2)	8 (2)	4 (1)	5 (1)	
Age at diagnosis (median)	387	51 (25–91)	52(25–91)	50(32–80)	*>0.05*	46(32–69)	58(34–80)	46 (39–62)	52 (39–77)	53 (49–56)	49 (36–63)	*>0.05*
Familiarity	387				*>0.05*							*>0.05*
BC		101 (26)	74 (25)	27 (31)		15 (36)	8 (40)	3 (37)	1 (12)	1 (25)	1 20)	
OC		2 (1)	0	2 (2)		0	0	2 (26)	0	0	0	
None		284 (73)	226 (75)	58 (67)		27 (64)	12 (60)	3 (37)	7 (88)	3 (75)	4 (80)	
Histotype	387				*>0.05*							*>0.05*
IDC		371 (96)	285 (95)	86 (98)		42 (100)	20 (100)	8 (100)	7 (75)	4 (100)	5 (100)	
Other		14 (3)	13 (4)	1 (2)		0	0	0	1 (25)	0	0	
Missing		2 (1)	2 (1)	0								
Grading	387				*>0.05*							*>0.05*
G1		2 (1)	2 (1)	0		0	0	0	0	0	0	
G2		56 (14)	48 (16)	8 (9)		5 (12)	2 (10)	0	0	1 (25)	0	
G3		325 (84)	247 (82)	78 (90)		36 (86)	18 (90)	8 (100)	8 (100)	3 (75)	5 (100)	
Missing		4 (1)	3 (1)	1 (1)		1 (2)	0	0	0	0	0	
Ki67	387				*>0.05*							*>0.05*
<20%		47 (11)	45 (15)	9 (10)		6 (14)	1 (5)	1 (12)	1 (12)	0		
>20%		326 (84)	243 (81)	71 (85)		33 (79)	17 (85)	6 (76)	6 (76)	4 (100)	0	
Missing		14 (5)	12 (4)	7 (5)		3 (7)	2 (10)	1 (12)	1 (12)	0	5 (100)	
Pathological stage	387				*>0.05*						0	*0.06*
Stage I/ II		314 (81)	243 (81)	71 (82)		38 (83)	18 (90)	5 (75)	3 (25)	3 (75)		
Stage III		58 (15)	45 (15)	13 (15)		4 (10)	1 (5)	3 (25)	4 (50)	1 (25)	4 (80)	
Missing		15 (4)	12 (4)	3 (3)		0 (7)	1 (5)	0	1 (25)	0	0	

gPV germline pathogenic variant, *BC* breast cancer, *OC* ovarian cancer, *IDC* infiltrating ductal carcinoma, *G* grading, *Ki-67* Ki-67 antigen.

respectively, $p = 0.01$). More patients without gPV underwent radiotherapy, in line with the high rate of breast-conserving surgery ($n = 217$, 70%) ($p < 0.001$).

Survival outcomes

Median follow-up duration was 3.9 years (range 3.6–4.2) by reverse Kaplan–Meier on OS. At the data cut-off, 66 patients (18%) had a relapse, and the median IBCFS was not reached (Fig. 2A). The 7-year IBCFS was 76%, with no difference seen between gPV and non-gPV carriers (Fig. 2B).

Recurrences were local (including second BC) in 32 (46%) and distant in 34 (52%) patients. The number of events refers only to the first event; no subsequent events in the same patients were recorded, with no statistically significant difference seen between the two groups of patients. Of the 34 distant relapses, only 7 (21%) occurred in the gPV carriers ($P = 0.07$).

Of note, 24 second malignancies other than BC were registered in the whole population during follow-up. Second tumours occurred more frequently in gPV patients (12 cases, 14%) compared to other patients (12 cases, 4%) ($p = 0.005$), with the majority observed in individuals with other gPVs (3 cases, 60%). As expected, gPV patients had an increased proportion of ovarian/gynaecological cancer ($n = 4$, 34%). Patients without gPV developed more gastrointestinal cancers ($n = 3 = 25\%$) and melanoma ($n = 3$, 25%). The distributions of relapses, second tumours, and deaths are presented in Table 3.

The estimated 7-year OS was 80% (Fig. 2C). Overall, 55 patients (14%) died: 27 (49%) were related to BC (54% in gPV vs. 48% in non-gPV, $P = 0.05$), 11 (20%) to other causes, and 17(31%) to a second primary non-BC. In Fig. 2D are shown the OS curves in gPV and non-gPV carriers. No difference in OS was seen between gPV and non-gPV carriers (log rank $p = 0.8$). The distributions of follow-up time by year of diagnosis, as well as the distribution of events, are shown in Supplementary Table 1. From the first to the fourth year of follow-up, more local relapses compared to distant metastasis were seen ($P = 0.05$). In the last 2 years of follow-up, more distant metastases than local relapses were registered. Furthermore, no differences were seen along the follow-up years among causes of death. In the Supplementary Table 2 the percentage of follow-up per year from 2017 to 2023 was shown, with a very high maturity in the earlier cohorts than in the last ones, reporting a median follow-up of 3.9 years.

The CIF for BC-related death and for death from other causes are shown in Supplementary Figs. 2 and 3; at the latest evaluable timepoint, the cumulative incidence of death from other causes exceeded that of BC-related death (12.2% vs. 10.4%).

Among patients treated with NACT, pCR was associated with markedly better outcomes (Fig. 3A and B): the 7-year IBCFS and OS were 93% and 94% in the pCR group versus 52% and 67% in non-pCR patients (log-rank $p = 0.001$ for IBCFS; $p = 0.03$ for OS). Within the pCR cohort, outcomes did not differ by gPV status (Fig. 3C and D); Kaplan–Meier estimates at the last evaluable timepoint (~7 years) were 90% vs. 100% for IBCFS ($p = 0.9$) and 91% vs. 92% for OS ($p = 0.85$) in gPV vs. non-gPV, respectively.

Table 2 | Modalities of treatment of patients without or with gPV (specifically *BRCA1/2, PALB2, RAD51C/D, MUTYH, ATM*, and other gPV)

	N	*N* (%)	No gPV	All gPV	*P* values No gPV vs. gPV	*BRCA 1/2*	*PALB2*	*RAD51C/ D*	*MUTYH*	*ATM*	OTHER gPV	*P* value among gPV
		387	300 (78)	87 (22)		42 (11)	20 (5)	8 (2)	8 (2)	4 (1)	5 (1)	
NACT	387				*>0.05*							*>0.05*
Yes		195 (50)	150 (50)	45 (52)		26 (62)	7 (38)	4 (50)	4 (50)	2 (50)	2 (40)	
No		185 (48)	147 (49)	40 (46)		15 (37)	13 (62)	4 (50)	4 (50)	2 (50)	2 (40)	
Missing		7 (2)	3 (1)	2 (2)		1 (1)	0	0	0	0	1 (20)	
Type of NACT	195				*>0.05*							*>0.05*
EC + TXL/AC + TXL		129 (66)	106 (71)	23 (51)		12 (46)	3 (47)	2 (50)	2 (50)	2 (100)	2 (100)	
CaPaBe/EC + TXL + CBDCA/		58 (30)	39 (26)	19 (42)		13 (50)	3 (47)	2 (50)	1 (25)	0	0	
CBDCA + TXL + PEMBRO/ EC + PEMBRO												
FEC		5 (3)	4 (2)	1 (2)		1 (4)	0	0	0	0	0	
Other		3 (1)	1 (1)	2 (5)		0	1 (6)	0	1 (25)	0	0	
Type of surgery	387				*0.04*							*0.06*
BCS + SLNB		199 (50)	164 (53)	35 (39)		13 (21)	12 (60)	4 (50)	1 (14)	2 (50)	3 (78)	
Mastectomy + SLNB		80 (20)	51 (16)	29 (32)		21 (49)	4 (20)	2 (25)	1 (14)	1 (25)	0	
BCS + AND		46 (11)	37 (12)	9 (10)		4 (10)	1 (5)	0	4 (57)	0	0	
Mastectomy + AND		57 (14)	46 (15)	11 (11)		4 (10)	3 (15)	2 (25)	1 (14)	0	1 (11)	
Missing/No surgery		5 (5)	2[a] (4)	3[b] (8)		0	0	0	1	1 (25)	1 (11)	
pCR after NACT	195				*<0.001*							*>0.05*
Yes		87 (45)	58 (39)	29 (64)		18 (69)	5 (71)	3 (75)	2 (50)	1 (50)	0	
No		103 (53)	89 (59)	14 (31)		8 (31)	2 (29)	1 (25)	2 (50)	1 (50)	0	
Missing		5 (2)	3 (2)	2 (5)		0	0	0	0	0	2 (100)	
Type of NACT of patients in pCR	87				*>0.05*							*>0.05*
EC + TXL/AC + TXL		42 (48)	31 (53)	11 (38)		7 (39)	3 (60)	0	0	1(100)	0	
CaPaBe/EC + TXL + CBDCA/		40 (46)	24 (42)	16 (55)		11 (61)	2 (40)	2 (67)	1(50)	0	0	
CBDCA + TXL + PEMBRO/ EC + PEMBRO												
FEC		2 (2)	2 (3)	0		0	0	0	0	0	0	
Other		3 (4)	1 (2)	2 (7)		0	0	1(33)	1(50)	0	0	
Type of NACT of patients with no pCR	103				*>0.05*							*>0.05*
EC + TXL/AC + TXL		84 (82)	73 (82)	11 (79)		6 (75)	2 (100)	0	2 (100)	1 (100)	0	
CaPaBe/EC + TXL + CBDCA/		16 (15)	14 (16)	2 (14)		1 (12.5)	0	1 (100)	0	0	0	
CBDCA + TXL + PEMBRO/ EC + PEMBRO												
FEC		3 (3)	2 (2)	1 (7)		1 (12.5)	0	0	0	0	0	
Other												
Prophylactic contralateral mastectomy	137				*<0.001*							*>0.05*
Yes		38 (28)	4 (10)	34 (90)		24 (96)	5 (83)	3 (75)	0	1 (100)	1 (100)	

Table 2 (continued) | Modalities of treatment of patients without or with gPV (specifically *BRCA1/2, PALB2, RAD51C/D, MUTYH, ATM*, and other gPV)

	N	*N* (%)	No gPV	All gPV	*P* values No gPV vs. gPV	*BRCA 1/2*	*PALB2*	*RAD51C/ D*	*MUTYH*	*ATM*	OTHER gPV	*P* value among gPV
		387	300 (78)	87 (22)		42 (11)	20 (5)	8 (2)	8 (2)	4 (1)	5 (1)	
No		99 (72)	94 (90)	5 (10)		1 (4)	1 (17)	1 (25)	2 (100)	0	0	
Adjuvant CT	387				*>0.05*							*>0.05*
Yes		233 (60)	182 (61)	51 (59)		24 (57)	12 (60)	7 (87)	5 (62)	2 (50)	1 (20)	
No		145 (37)	111 (37)	34 (39)		17 (40)	8 (40)	1 (13)	3 (38)	1 (25)	4 (80)	
Missing		9 (3)	7 (2)	2 (2)		1 (3)	0	0	0	1(25)	0	
Type of adjuvant CT	233				*>0.05*							*>0.05*
EC + TXL/ FEC + TXL		98 (42)	77 (42)	21 (43)		8 (33)	7 (60)	1 (14)	4 (80)	1 (50)	0 (67)	
FEC		10 (4)	6 (3)	4 (8)		2 (8)	1 (8)	0	0	0	1 (33)	
Cabecitabine		54 (23)	49 (27)	5 (9)		3 (13)	1 (8)	1 (14)	0	0	0	
CMF		16 (7)	11 (6)	5 (9)		2 (8)	1 (8)	1 (14)	0	1 (50)	0	
Immunotherapy		21 (9)	15 (8)	6 (12)		4 (17)	1 (8)	1 (14)	0	0	0	
Ormonotherapy		4 (2)	3 (2)	1 (1)		1 (5)	0	0	0	0	0	
Other		27 (12)	21 (12)	6 (12)		2 (8)	1 (8)	3 (44)	0	0	0	
		3 (1)	0	3 (6)		2 (8)	0	0	1(20)	0	0	
Radiotherapy	387				*>0.05*							*>0.05*
Yes		266 (69)	217 (70)	49 (56)		17 (40)	12 (60)	8 (100)	6 (74)	2 (50)	4 (80)	
No		112 (29)	77 (26)	35 (40)		24 (57)	8 (40)	0	1 (13)	1 (25)	1 (20)	
Missing		9 (2)	6 (4)	3 (4)		1 (3)	0	0	1(13)	1 (25)	0	

gPV germline pathogenic variant, *CT* chemotherapy, *EC* epirubicin, cyclophosphamide, *TXL* Taxol, *AC* adriamycin, *CaPaBe* carboplatin, paclitaxel, bevacizumab, *CDtBCA* carboplatin, *FEC* fluoruracil, epirubicin, cyclophosphamide, *Pembro* pembrolizumab, *BCS* breast conserving surgery, *SLNB* sentinel lymph node biopsy, *AND* axillary nodal dissection, *pCR* pathological complete response, *CMF* cyclophosphamide, methotrexate, fluoruracil.

[a]Two patients belonging to the no gPV group did not receive any surgery.

[b]Three patients in the gPV group had missing data.

The Cox analysis was performed on 350 patients for IBCFS and OS (64 and 55 events, respectively). In the univariate analysis, factors significantly associated with IBCFS rate were pCR (HR = 0.22, $p = 0.009$), stage III (HR = 2.80, $p < 0.001$), and anthracycline- and taxane-based chemotherapy (HR = 2.30, $p = 0.002$). The interaction between mastectomy without gPV (HR = 1.78, $p = 0.05$) and between anthracycline plus taxane without gPV (HR = 3.32, $p < 0.001$) was statistically significant. On multivariate analysis, pCR (HR=0.15, $p = 0.002$), stage III (HR=2.22, $p = 0.006$), anthracycline plus taxane-based chemotherapy (HR=2.38, $p = 0.025$), particularly in patients without gPV (HR=4.10, $p < 0.001$), remained significant independent predictors of IBCFS (Supplementary Table 3). In the univariate analysis, factors significantly associated with OS rate were Ki67 > 20% (HR = 3.35, $p = 0.041$), stage III (HR = 3.11, $p < 0.001$), mastectomy (HR = 1.98, $p = 0.015$), and anthracycline and taxane-based chemotherapy (HR = 2.91, $p < 0.001$). On multivariate analysis, age >60 years (HR = 2.30, $p < 0.01$), stage III (HR = 2.13, $p = 0.015$), and anthracycline plus taxane-based chemotherapy (HR = 2.34, $p = 0.004$) were significant independent predictors of worse OS (Supplementary Table 4). Finally, the IBCFS (Supplementary Fig. 4A and B) and OS (Supplementary Fig. 5A and B) curves in gPV and non-gPV treated with or without platinum-derived drugs were performed. No statistically significant differences were observed.

Discussion

The present study evaluated a prospective cohort of consecutive patients with TNBC analysed with MGP testing for predisposition genes with the aim of finding gPVs other than *BRCA1/2;* this study also describes the patients' clinicopathologic characteristics and outcome variables. The cohort of interest included a total of 387 patients, most of whom were non-gPV carriers (78%); the remaining were *BRCA1/2, PALB2, RAD51C/D, MUTYH*, others, and *ATM* gPV (22%). A previous study on exome sequencing in patients who had undergone NACT revealed a similar proportion of gPV in cancer predisposition genes (21%)[10]. The rate of *MUTYH* gPV was in line with previous series (1.7%)[11]. The c.1187G>A, p.Gly396Asp, was the most represented *MUTYH* gPV (3/7, 47%), as recently reported by Esperon et al., where it was associated with BC in individuals with monoallelic gPV, likely suggesting a role of *MUTYH* in this disease onset[12].

Our patients had mostly IDC, G3, and Ki67 ≥ 20%. Despite these characteristics, all groups of patients were mostly diagnosed at stage I, with the exception of MUTYH gPV, which presented more frequently as stage III at diagnosis. This seems in line with a recent study; although monoallelic *MUTYH* gPV is not thought to confer a meaningfully increased risk of BC development, it may contribute to the pathological aggressiveness of sporadic BC[13].

In terms of local therapy, most of our patients were treated with breast-conserving surgery and SLNB plus radiotherapy, with a prevalence of mastectomy plus SLNB and prophylactic contralateral mastectomy in gPV

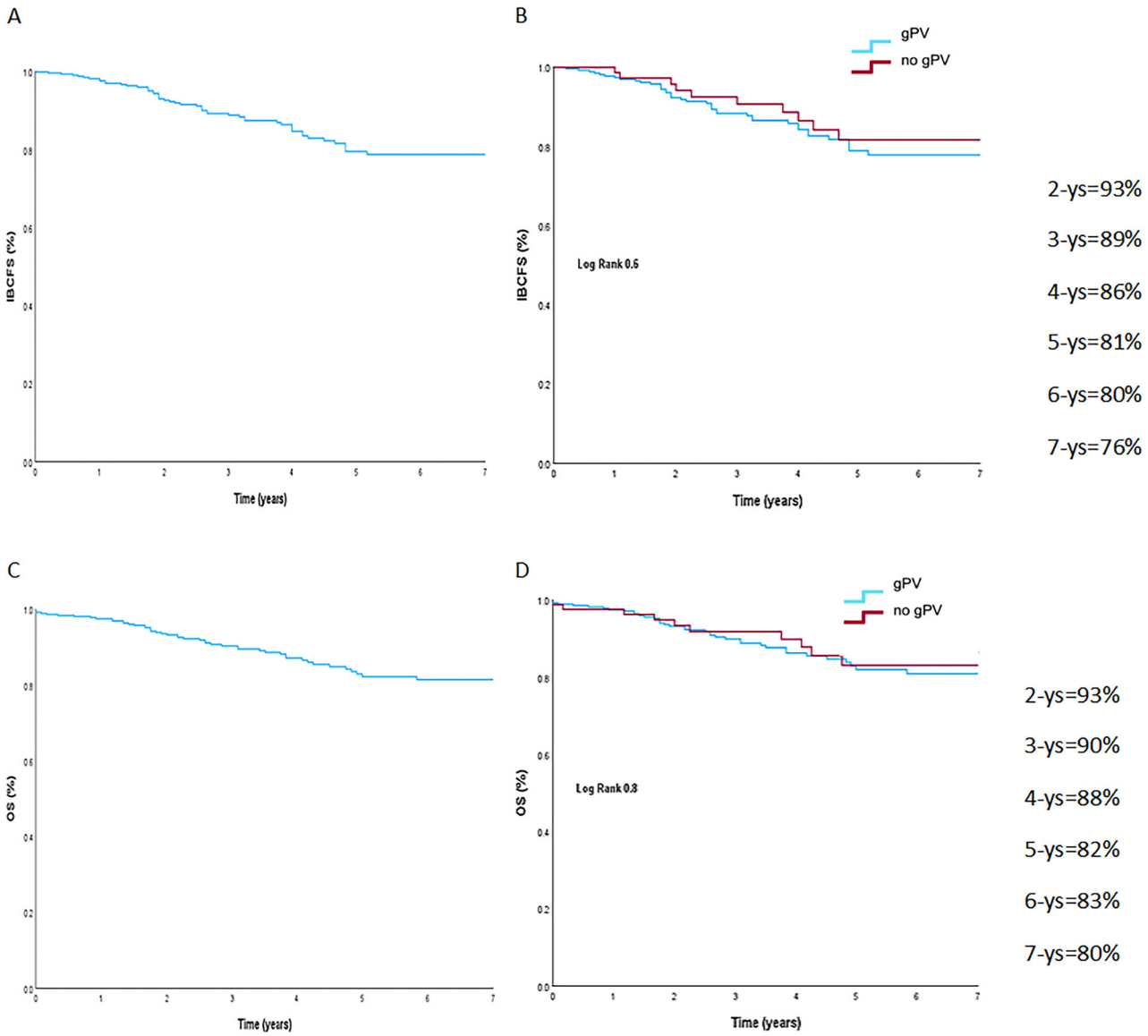

Fig. 2 | Seven-year survival endopints. Invasive breast cancer free survival (IBCFS) (**A**) and OS (**C**); disease-free survival (DFS) and overall survival (OS) between germline pathogenic variants (gPV) and non-gPV carriers (**B**, **D**, respectively). The 7-year IBCFS was 76% (**A**). The 7-year OS was 80% (**C**). No statistically significant differences were observed between gPV and non-gPV carriers in terms of IBCFS (**B**, Log rank = 0.6) or OS (**D**, Log Rank = 0.8). Blue line = gPV carriers; red line = non-gPV carriers. On the right of **B**, **D** are represented the distributions for IBCFS and OS at 2–7 years, respectively.

BRCA1/2 carriers. The tendency toward contralateral prophylactic mastectomy in *BRCA1/2* patients has been shown to reduce the incidence of second BC[14,15], and seems to also impact OS[16]. Recently, it has been proven that *PALB2* gpV carriers also have an increased proportion of contralateral BC, up to 35% at 10 years, justifying the percentage of bilateral mastectomy in our patients[17,18].

Regarding systemic treatments, NACT was utilized in 50% of patients, regardless of the presence of gPV. Due to the high proportion of very early-stage BC at diagnosis [141 patients (36%) were stage IA-B], many patients received adjuvant treatment, as suggested by the ESMO guidelines[19]. Anthracycline/taxane-based regimens were the most used NACT, particularly in the non-gPV carrier group, followed by platinum-based treatments, with or without immunotherapy (46% of all schemes). Twenty-nine patients were treated according to the Keynote-522 trial[20].

Among the 195 patients who received NACT, 87 (45% of the analysed cohort) experienced a pCR, with a 64% proportion in gPV carriers, showing a higher proportion than that observed in the current literature, mostly in cases of *BRCA1/2*. In fact, recent results showed the rate of pCR in TNBC *BRCA1* and *BRCA2* carriers as 46% and 41%, respectively, compared to 69% in our series[21]. Furthermore, data on other genes have not been evaluated yet, although an interesting study by Kneubil et al. reported a statistically significantly lower expression of PALB2 in patients who achieved pCR compared to those who did not[22]. Interestingly, the *RAD51* gene was evaluated in a 4-gene score, showing that a higher score has a nearly fourfold likelihood of achieving pCR with platinum-derived drugs than does a lower score, with a 93% sensitivity[23].

In the adjuvant setting, after the anthracycline/taxane-based regimens, capecitabine therapy was the second most frequently prescribed treatment, mostly in patients without gPV, according to data from the Create-X trial[24]. Regarding other treatments, two patients with *BRCA1/2* gPV received olaparib after NACT, as part of the Olympia trial[25]. The question whether the combination of olaparib and pembrolizumab in patients with residual disease after NACT should be offered remains to be answered, although data from the metastatic setting show a good safety profile[26].

At a median follow-up of 3.9 years, the rate of recurrences differed between the two groups of patients, with less metastatic disease in gPV than

Table 3 | Distribution of relapses, second tumours and deaths between no gPV and gPV carriers (specifically BRCA1/2, PALB2, RAD51C/D, MUTYH, ATM and other gPV)

	N	*N* (%)	No gPV	All gPV	*P* values No gPV vs gPV	*BRCA 1/2*	*PALB2*	*RAD51C/D*	*MUTYH*	*ATM*	OTHER gPV	*P* value among gPV
		387	300 (78)	87 (22)		42 (11)	20 (5)	8 (2)	8 (2)	4 (1)	5 (1)	
Relapsed	387				*>0.05*							*>0.05*
Yes		66 (18)	51 (17)	15 (17)		7 (17)	4 (20)	0	2 (25)	0	2 (40)	
No		313 (80)	243 (81)	70 (80)		34 (81)	16 (80)	8 (100)	6 (75)	3 (75)	3 (60)	
Missing		8 (2)	6 (2)	2 (3)		1 (2)	0	0	0	1 (25)	0	
Type of relapse	66				*0.07*							*>0.05*
Local (also II BC)		32 (46)	22 (45)	10 (59)		6 (86)	2 (50)	0	1 (33)	0	1 (33)	
Metastatic		34 (52)	27 (56)	7 (41)		1 (14)	2 (50)	0	2 (67)	0	2 (67)	
Second tumours other than BC					*0.005*							*>0.05*
No	387	363 (94)	288 (96)	75 (86)		38 (90)	18 (90)	6 (86)	7 (88)	4 (100)	2 (40)	
Yes		24 (6)	12 (4)	12 (14)		4 (10)	2 (10)	2 (14)	1 (12)	0	3 (60)	
Thyroid		5 (21)	2 (17)	3 (25)		0	0	1 (50)	0	0	2 (67)	
Haematological		4 (17)	1 (8)	3 (25)		1 (25)	0	0	1 (100)	0	1 (33)	
OC/Gynecol		5 (21)	1 (8)	4 (34)		3 (75)	0	1 (50)	0	0	0	
GIC		4 (17)	3 (25)	1 (8)		0	1(50)	0	0	0	0	
Melanoma		3 (12)	3 (25)	0		0	0	0	0	0	0	
Lung		2 (8)	2 (17)	0		0	0	0	0	0	0	
Others		1 (4)	0	1 (8)		0	1 (50)	0	0	0	0	
Pts status	387				*>0.05*							*>0.05*
Death		55 (14)	42 (11)	13 (17)		4 (14)	4 (20)	0	2 (25)	0	3 (60)	
Alive		331 (85)	258 (86)	73 (83)		38 (86)	16 (80)	8 (100)	6 (75)	3 (25)	2 (40)	
Missing		1(1)		1 (3)						1 (75)		
Type of death	55				*0.05*							*>0.05*
Related to BC		27 (49)	20 (48)	7 (54)		2 (50)	2 (50)	0	2 (100)	0	1 (50)	
Related to second tumours, not BC		17 (31)	13 (31)	4 (31)		2 (50)	1 (25)	0	0	0	1 (50)	
Related to other causes		11 (20)	9 (21)	2 (15)		0	1 (25)	0	0	1 (100)	0	

gPV germline pathogenic variant, *BC* breast cancer, *OC* ovarian cancer, *GI* gastrointestinal.

in non-gPV, but it was not statistically significant. As expected, both patients with and without gPV with pCR showed better clinical outcomes in terms of DFS and OS. No difference was seen between the two groups of patients, showing that gPV does not represent a prognostic factor. This contrasts with the data from a recent article reporting that gPV *BRCA* carriers maintained an OS advantage, even in a multivariate analysis after treatment based on platinum-derived drugs[27]. In our population, the anthracycline/taxane combination was prognostically unfavourable, mostly in the non-gPV carriers, confirming the need to improve treatment by adding platinum and immunotherapy in the neoadjuvant setting and capecitabine in the adjuvant setting. However, some doubt remains concerning whether anthracyclines are enough in patients with homologues recombination deficiency, although our comparison between gPV and non-gPV patients treated with or without platinum regimens did not find any difference in IBCFS and OS. Finally, age >60 years was an unfavourable prognostic factor in this population; although TNBC occurs at younger ages, the median age at onset in the PALB2 gPV cohort was more advanced (58 years). This result confirms the need to test all TNBC, regardless of the age at onset, as shown in a series of BC arising after age 65, where the lifetime risk of PALB2 gPV was ≥15%[28].

Our study is affected by many limitations. Since gPV in *PALB2, RAD51C/D, MUTYH, ATM*, and other hereditary cancer genes, excluding *BRCA1/2*, totally account for only 12% of all TNBC mutations, our findings do not allow us to draw clear conclusions on the clinical behaviour of these gPV carriers. In fact, subgroup analyses are based on small sample sizes and are therefore underpowered to reliably detect modest effects, increasing the risk of type I error and framing these findings as hypothesis-generating. It could be of interest to verify if some statistically significant trend, mostly related to the surgical treatment, could be improved by increasing the number of gPV carriers with a future multicenter patient collection.

Furthermore, our series does not reflect the current standard of care for TNBC, since only 14% of patients received immunotherapy, reducing the impact of gPV as a predictive factor for cancer treatments.

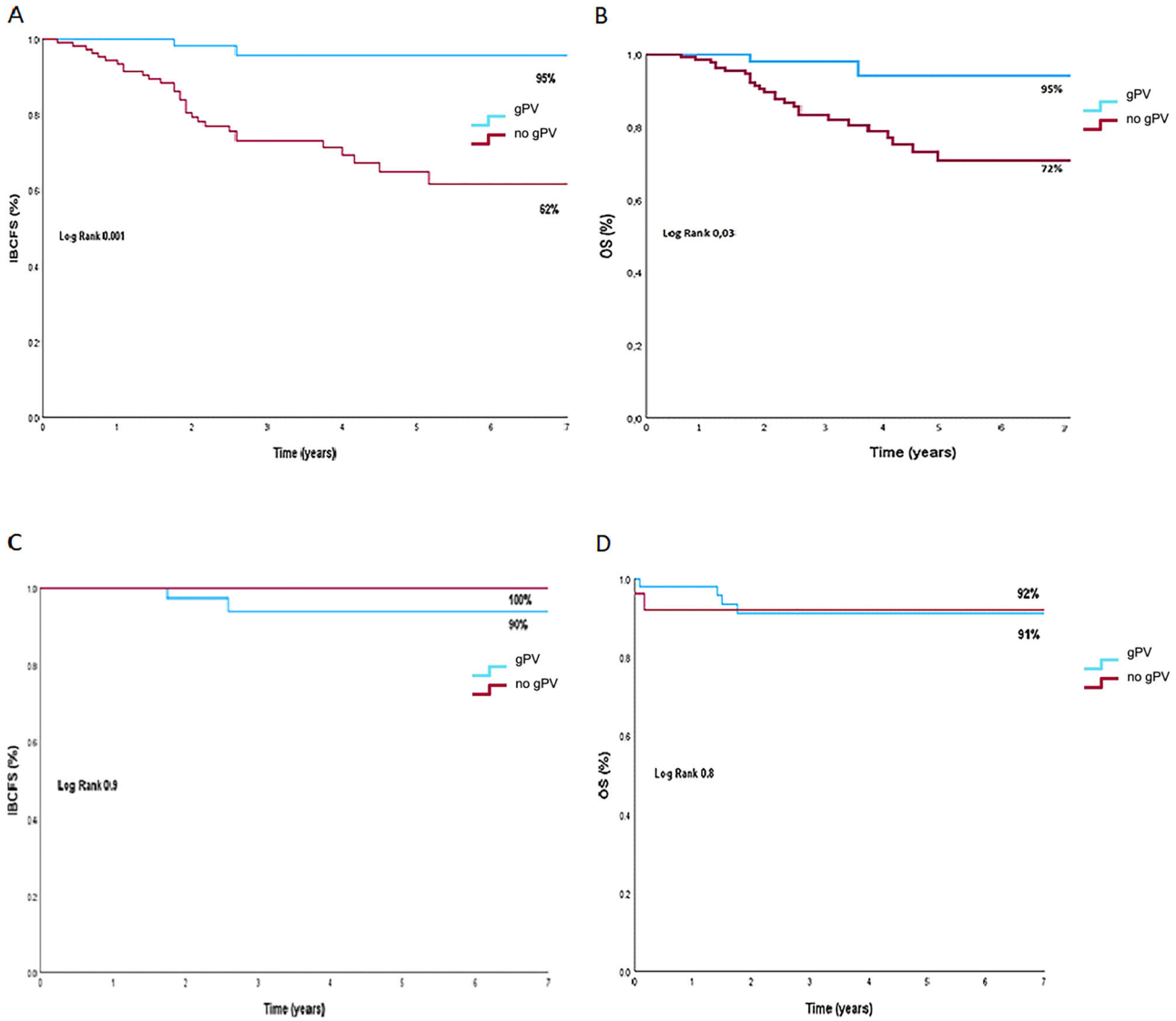

Fig. 3 | Seven-year survival endpoints according to pathological Complete Response (pCR). Invasive breast cancer free survival (IBCSF) (**A**) and overall survival (OS) (**B**) in pathological Complete Response (pCR) and non-pCR patients. Patients with pCR were compared with germline Pathological Variants (gPV) and non-gPV in terms of IBCFS (**C**) and OS (**D**). In patients with pCR (blue line, **A**, **B**), both 7-year IBCFS and OS were 95%, compared to 62% and 72% in patients without pCR (red line, **A**, **B**), respectively. The differences were statistically significant both in terms of IBCFS (log rank < 0.001) and OS (log rank = 0.03). Within the pCR cohort, the 7-year IBCFS was 90% and 100% in gPV (red line, **C**, **D**) and gPV (blue line, **C**, **D**), respectively (log rank = 0.9), and OS was 91% and 92%, respectively (log rank = 0.8).

In conclusion, our work provides some evidence on more bilateral mastectomies, pCR, and second tumours, the proportion in gPV. However, no advantage in OS seems to be observed, probably due to the short follow-up period, which could impact death due to other causes. Finally, the low number of specific gPV subgroups does not allow us to define whether hereditary cancer genes in TNBC could represent a strong predictive factor for treatment response.

Methods

Study population and design

The Modena Family Cancer Clinic (MFCC) of the Haematology and Oncology Department, University Hospital of Modena (Northern Italy), offers genetic testing to individuals with a personal or family history of BC, ovarian, pancreatic, or prostate cancer according to the Italian Association of Medical Oncology (AIOM) recommendations[29,30]. Since it has been recommended that all TNBC be tested for high-moderate penetrance genes, the Clinical Genomics Laboratory of the MFCC began to perform next-generation sequencing (NGS) *multi-gene panel* (MGP) testing in October 2017.

The HEaRTBeat is an observational prospective cohort study including all female consecutive TNBC patients diagnosed at our department from October 2017 to October 2024. MGP testing was offered to all TNBC patients, regardless of age at onset and family history of BC and/or ovarian cancer (OC). Clinicopathologic characteristics and outcome of all TNBC patients, negative or positive *BRCA1/2* or other predisposing genes, were then collected. These included age at first BC diagnosis (in case of metachronous BC), histologic subtype, tumour grading, stage at diagnosis, type of breast and axillary surgery, radiotherapy, chemotherapy, pathological complete response (pCR) to neoadjuvant treatment, rate of local or distant recurrence, rate of second tumours and vital status.

Procedures for MGP testing

Data analysis and variant interpretation performed with Next Generation Sequencing were limited to the following actionable gene set: *APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D,*

STK11, TP53. Variants were reported using the international standard HGVS nomenclature and classified into five classes (Pathogenic, Likely Pathogenic, Variant of Uncertain Significance, Likely Benign, and Benign) according to the American College of Medical Genetics and Genomics criteria[31]. All gene variants or CNVs interpreted as Pathogenic or Likely Pathogenic were confirmed by Sanger sequencing.

Statistical analysis

Patients' clinical and tumour characteristics were evaluated according to hereditary cancer gene status (gPV vs. non-gPV) and period of diagnosis. Patient characteristics are reported as counts and percentages calculated from all data, including those missing.

Comparisons between gPV and non-gPV carriers were performed on full contingency tables using Pearson's χ^2 test or two-sided Fisher's exact test, as appropriate based on expected cell counts. Continuous variables were compared with the Mann–Whitney *U* test. For each variable, a single global *p*-value from the appropriate test is reported. When exploring differences among gPV subgroups (BRCA1/2, PALB2, RAD51C/D, MUTYH, ATM, other), categorical variables were analysed on full row × column tables with χ^2/Fisher as above. In addition, we conducted exploratory within-group analyses on full contingency tables using two-sided Pearson's χ^2 or Fisher's exact test; statistically significant within-group findings ($p < 0.05$) are reported in the Results.

Because of the limited number of patients in the gPV group, no correction for multiple testing among different gPV subgroups was performed, and the reported *p*-value for clinicopathological characteristics, treatment modalities, and distribution of relapse, second tumours, and death were unadjusted for specific covariates.

Invasive breast cancer-free survival (IBCFS) was defined as the time from diagnosis of BC to the date of the first relapse (local recurrence, including diagnosis of second contralateral BC, regional, and/or distant relapse, and excluding second non-breast cancer). Overall survival (OS) was defined as the time from diagnosis of BC to death or last follow-up. Follow-up was censored at the data cut-off date (October 2024), which was used for all analyses, and follow-up information was updated for all patients up to this date. Median follow-up was estimated using the reverse Kaplan–Meier method based on OS time, treating alive patients at data cut-off as events and deaths as censored, rather than by averaging minimum and maximum follow-up times. OS and IBCFS curves (from October 2017 to October 2024, period to which the follow-up was updated) were calculated on 387 patients. As the maximum observable follow-up was <8 years, Kaplan–Meier curves were truncated at 7 years and, consistently, recurrence and death events are reported as grouped 7–8-year estimates (~7.5 years) rather than separate 8-year values, which should be interpreted with caution given the very small numbers at risk. Seven-year survival estimates between gPV and not-gPV carriers were compared with the Log-Rank test that evaluates whether there is a significant difference in the time-to events distribution between the groups. In order to evaluate the competitive risk for death of any cause, the CIF of the deaths for BC, considering the other causes of death as competing events, was calculated on 387 patients according to the Gooley method[32] at 12 years, and the timepoints for years were compared to the Kaplan–Meier estimates.

Because this was an observational study, burdened by missing data in some variables, we decided to perform the Cox proportional hazards (PH) regression on 350 patients, excluding 37 patients lacking all information. The Cox PH models were first used in an univariate analysis to investigate the association between survival outcomes and covariates (age, Ki67 ≤ 20% vs. >20%, stage I/II vs. III, mastectomy vs conservative surgery, bilateral vs. unilateral mastectomy, chemotherapy with Epirubicin, Ciclophosphamide (EC)/Taxol vs. other regimens, gPV vs. not gPV, and pCR vs not) with Hazard ratios (HRs), 95% CIs, and *P*-values used as a summary measure. Subsequently, a multivariate analysis was performed by using Cox PH models, to evaluate which variables were independently associated with outcomes, based on statistically significant covariates found at the univariate and on the effect of the mutation on the treatment (mastectomy and anthracycline-taxane chemotherapies, which were the most used regimens). Specifically, we wanted to assess if neoadjuvant treatment and mastectomy in gPV and non-gPV could be related to IBCFS and OS; these interactions were adjusted for age, pCR, and stage as potential confounders. All the statistical analyses were 2-sided, with $P < 0.05$ considered statistically significant.

Statistical analysis was carried out using the statistical package for social sciences (SPSS 26.0.0; SPSS Inc., Chicago, IL, USA). All analyses were conducted according to the statistical analysis plan of the study, and a statistician was involved in designing and conducting the analyses.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethical Committee of the Area Vasta Emilia Nord (Project and name identification code 125/2021/OSS*/AOUMO: Ruolo clinico delle mutazioni germinali in geni coinvolti nelle sindromi tumorali ereditarie identificate attraverso pannello multigenico/Clinical role of germline mutations in genes involved in hereditary cancer syndromes identified by multigene panel test). Before enroling, all patients provided written informed consent.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to Italian law (GDPR DGL 101/2018) that does not allow us to share clinical and confidential data with a third party. For these reasons, upon reasonable request to the corresponding author, we should ask the hospital for authorization to provide data in patient ID-redacted form.

Code availability

The code used for the data analysis presented in this manuscript utilizes publicly available software packages with no customization (SPSS 26.0.0; SPSS Inc., Chicago, IL, USA; STATA 14; StataCorp LLC, College Station, TX, USA). For gPVs interpretation, the Genome reference was: GRCh37-hg19, and the pathogenic meaning was defined according to the HGVS nomenclature (https://hgvsnomenclature.org).

Received: 9 February 2025; Accepted: 25 November 2025;
Published online: 13 December 2025

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Acknowledgements

We would like to thank and express our gratitude to Jacqueline M. Costa for the English language editing, as well as to our local research association, Associazione Angela Serra per la Ricerca sul Cancro, for kindly providing patients with wigs.

Author contributions

M.R.: Conceptualization, formal analysis, and writing—original draft. C.P.: Conceptualization, formal analysis, and writing—original draft. M.V.: Conceptualization, formal analysis, and writing—original draft. E.T.: Conceptualization and formal analysis, A.T.: formal analysis and writing—original draft. E.B.: formal analysis and writing—original draft. E.G.: Data collection and writing—review and editing, I.M.: Data collection and writing—review and editing, F.D.: Data collection and writing—review and editing; M.C.: Formal analysis. L.M.: Formal and statistical analysis. E.R.: writing—original draft; E.T: Conceptualization and formal analysis; M.D. writing—review and editing L.C.: Conceptualization, formal analysis, and writing—original draft. All authors have read and approved the manuscript.

Competing interests

A.T. received consulting fees and grants from Lilly, Pfizer, Novartis, MSD, AstraZeneca, Gilead, Seagen, Daiichi Sankyo; travel grants from Gilead, Daiichi Sankyo, Menarini, AstraZeneca. L.C. received grants from AstraZeneca, MSD, Pfizer; consulting fees and honoraria from AstraZeneca, Gilead, MSD, Roche, Pfizer, Daiichi Sankyo, Novartis; travel grants from Gilead, Pfizer, Daiichi Sankyo; Advisory Board of AstraZeneca, MSD, Novartis. The remaining authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41523-025-00877-x.

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