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Original Article

The impact of progesterone receptor negativity on oncological outcomes in oestrogen-receptor-positive breast cancer

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Abstract

Background: Oestrogen receptor (ER) status provides invaluable prognostic and therapeutic information in breast cancer (BC). When clinical decision making is driven by ER status, the value of progesterone receptor (PgR) status is less certain. The aim of this study was to describe clinicopathological features of ER-positive (ER+)/PgR-negative (PgR-) BC and to determine the effect of PgR negativity in ER+ disease.

Methods: Consecutive female patients with ER+ BC from a single institution were included. Factors associated with PgR- disease were assessed using binary logistic regression. Oncological outcome was assessed using Kaplan–Meier and Cox regression analysis.

Results: In total, 2660 patients were included with a mean(s.d.) age of 59.6(13.3) years (range 21–99 years). Median follow-up was 97.2 months (range 3.0–181.2). Some 2208 cases were PgR+ (83.0 per cent) and 452 were PgR- (17.0 per cent). Being postmenopausal (odds ratio (OR) 1.66, 95 per cent c.i. 1.25 to 2.20, $P < 0.001$), presenting with symptoms (OR 1.71, 95 per cent c.i. 1.30 to 2.25, $P < 0.001$), ductal subtype (OR 1.51, 95 per cent c.i. 1.17 to 1.97, $P = 0.002$) and grade 3 tumours (OR 2.20, 95 per cent c.i. 1.68 to 2.87, $P < 0.001$) were all associated with PgR negativity. In those receiving neoadjuvant chemotherapy (308 patients), pathological complete response rates were 10.1 per cent (25 of 247 patients) in patients with PgR+ disease versus 18.0 per cent in PgR- disease (11 of 61) ($P = 0.050$). PgR negativity independently predicted worse disease-free (hazard ratio (HR) 1.632, 95 per cent c.i. 1.209 to 2.204, $P = 0.001$) and overall survival (HR 1.774, 95 per cent c.i. 1.324 to 2.375, $P < 0.001$), as well as worse overall survival in ER+/HER2- disease ($P = 0.004$).

Conclusions: In ER+ disease, PgR- tumours have more aggressive clinicopathological features and worse oncological outcomes. Neoadjuvant and adjuvant therapeutic strategies should be tailored according to PgR status.

Introduction

Contemporary multimodal breast cancer (BC) management is driven by tumour biology. Assessment of the steroid hormone receptors (oestrogen receptor (ER) and progesterone receptor (PgR)) and the human epidermal growth factor receptor-2 (HER2) are critical components of prognostication and targeted treatment planning[1,2]. ER and PgR are expressed in 80 per cent and 60 per cent of BC respectively. These hormone receptors are commonly used as prognostic markers for BC, as hormone-receptor-positive (HR+) disease is typically associated with favourable patient outcomes, due to its less aggressive biology[1,3] and because tumour expression of ER+ allows for targeted treatment with anti-oestrogen endocrine hormonal therapy (EHT)[4,5]. Current EHT primarily targets the ER, which predicts response to anti-oestrogen therapeutic strategies[6]. The clinical importance of standard PgR assessment is less clear but it is likely that it provides valuable prognostic information at diagnosis, which may aid therapeutic decision making[7].

PgR is a ligand-activated nuclear transcription factor that mediates progesterone activity[8]. ER+ cancers are typically PgR+, and PgR is an oestrogen-regulated gene with interplay between ER and PgR believed to be pivotal in biological responses to EHT[9]. Additionally, PgR+ cancers depend upon oestrogen expression for tumour proliferation as well as acting as a function of the ER-alpha signalling pathway[10]. The dependence of PgR expression on ER activity means that ER and PgR expression are typically concordant[11]. However, 20 per cent of invasive BC demonstrates mixed hormone receptor status, with ER+/PgR- being the most common hormone receptor subgroup[12,13]. Thus, when determining the prognostic significance of single HR positivity, the ER+/PgR- subgroup of breast cancers is the most clinically relevant group to investigate.

The importance of PgR status in clinical decision making remains a matter of debate when compared with ER status. While some authors argue that PgR provides invaluable prognostic information[14], others have questioned its value and have

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suggested removing standard PgR assessment in newly diagnosed BC[15]. Despite the fact that PgR- tumours are likely to be more aggressive than PgR+ disease[16], ER+/PgR+ and ER+/PgR- cancers are typically treated in the same manner, and there have been limited developments in efforts to produce a potential therapeutic means of targeting the PgR[17,18]. Decisions regarding cytotoxic neoadjuvant (NAC) and adjuvant chemotherapy (AC) are guided more often by pathological factors such as tumour size, nodal status and genomic testing, rather than PgR status[19–21]. However, PgR expression is considered, as part of genomic panels such as OncotypeDX™ (ODX, Genomic Health, Redwood City, CA, U.S.A.) in combination with other characteristics of tumour biology, in guiding personalized adjuvant therapies[22,23].

The primary aim of this study was to assess the impact of PgR negativity on oncological outcomes in ER+ BC patients. The secondary aim was to compare the presentation and clinicopathological features of ER+/PgR+ and ER+/PgR- BCs and determine associations and predictors of PgR- disease.

Methods

Study design and patient selection

This study was granted institutional review board approval from the Galway University Hospitals (GUH) Clinical Research Ethics Committee. A single-centre, retrospective observational cohort study was undertaken. This study included all BC patients diagnosed and treated in GUH, a tertiary referral BC centre for the west of Ireland, over an 11-year period between January 2005 and December 2015. Included patients had a diagnosis of ER+ BC and were identified from a prospectively maintained institutional database. Detailed information regarding patient demographics, clinicopathological data, neoadjuvant treatment regimens, surgical management, ODX testing, adjuvant treatment regimens, disease recurrence and survival was collected using this database, and all data were cross-referenced with patient electronic and medical records.

Patient process

Patients presented either symptomatically or through *BreastCheck*, Ireland's national mammography-based breast screening programme of women aged 50–70 years. Each patient underwent triple assessment. Clinical examination was conducted by a consultant breast surgeon. Standard radiological assessment consisted of mammography and ultrasonography; MRI was considered and used in select cases (i.e., dense breast tissue, invasive lobular carcinoma histological subtype, BRCA mutation carrier and diagnostic uncertainty after using other modalities). Imaging assessments were then reviewed by a dedicated breast radiologist. Diagnosis was confirmed by radiologically guided or clinical core biopsy reported on by a dedicated consultant breast pathologist. All breast tissue specimens were analysed in the accredited pathology laboratory. Staging was performed in accordance with the American Joint Committee on Cancer (AJCC), version 8 Guidelines[24].

Histopathological assessment and immunohistochemistry

ER and PgR status was routinely analysed using the Allred scoring system[25]. HER2 status was assessed using immunohistochemistry (IHC), and those scoring 2+ were submitted for fluorescence *in situ* hybridization for confirmation of HER2 receptor status. Tumour specimens were graded using the Nottingham Histologic Score system (also termed 'the Elston-Ellis modification of Scarff-Bloom-Richardson grading system'), as per the WHO Classification of Tumours Guidelines[26]. Tumour lymphatic invasion was evaluated using IHC staining with D2-40 and vascular invasion using CD34[27]. Tumour perineural invasion was evaluated using IHC staining with S-100 and a broad-spectrum keratin stain (AE1/AE3)[28]. Ki67 was evaluated using MIB1 antibody testing[29].

Multidisciplinary approach to care

Each case was discussed at the breast multidisciplinary meeting held weekly at the tertiary referral centre. Multidisciplinary decisions regarding patient-specific treatment considered clinical, radiological and pathological factors as well as patient performance status, family history and genetic testing results. Adjuvant prescription of chemoendocrine therapies for a number of patients diagnosed with ER+/HER2-, lymph node negative (LN-) BC after 2007 were informed by recurrence score genomic panel-based testing (RS). Patients returned to the tertiary referral centre for examination by a specialized breast surgeon postoperatively and returned yearly for routine clinical and mammographic follow-up for 10 years following diagnosis.

Follow-up

Patient follow-up was recorded through a prospectively maintained database. The median and mean lengths of follow-up were calculated using the reverse Kaplan–Meier method[30]. BC recurrence and overall survival data were calculated from a prospectively maintained institutional database. All data were cross-referenced with patient electronic and medical records. Survival status as well as cause of death were confirmed from data obtained from national registries. The authors defined disease-free survival (DFS) as 'freedom from invasive disease recurrence'.

Statistical analysis

Clinicopathological and IHC correlates of PgR- were determined using independent Student's t, χ^2, one-way ANOVA and Kruskal–Wallis tests as appropriate. Univariable logistic regression analysis was used to assess the association between variables and negative PgR status expressed in crude odds ratios (OR) with 95 per cent confidence intervals. Variables with $P < 0.050$ in univariable analysis were included in the multivariable logistic regression analysis. Binary logistic regression analysis was used to identify variables that contributed independently to negative PgR expression. Only patients undergoing surgical resection of their primary breast tumour were included for survival analyses. Kaplan–Meier curves, the log rank (Mantel–Cox) test, and Cox regression were used to associate survival with clinical, pathological and IHC characteristics expressed as hazard ratios (HR) with 95 per cent confidence intervals. All tests of significance were two-tailed, with $P < 0.050$ indicating statistical significance. Data were analysed using SPSS™ (IBM SPSS Statistics for Mac, Version 26.0. Armonk, NY) version 26.

Results

Patient demographics

There were 2660 consecutive patients diagnosed with and treated for ER+ BC between January 2005 and December 2015 included in this study. There were 2208 patients with PgR+ tumours (83.0 per cent) and 452 (17.0 per cent) were PgR- (*Appendix* S1). The mean(s.d.) age at diagnosis was 59.6(13.3) years (range 21–99 years). At the time of BC diagnosis, 1900 patients (71.4 per cent)

were postmenopausal, and 2059 patients presented through the symptomatic breast pathway (77.4 per cent). The vast majority of cancers were invasive (2425, 91.2 per cent). The median follow-up was 97.2 (range 3.0–181.2) months[30].

Clinicopathological characteristics associated with PgR status

Clinicopathological and molecular characteristics are shown in *Table 1*. Using binary logistic regression it was demonstrated that being postmenopausal at the time of diagnosis (OR 1.66), presenting with symptoms (OR 1.71), having IDC subtype (OR 1.51) and grade 3 tumours (OR 2.20) were all predictive of PgR- status (*Table 2*). Other patient and tumour features not associated with PgR status are outlined in *Tables 1* and *2*.

Treatment characteristics and PgR status

Treatment characteristics for PgR+ and PgR- groups are outlined in *Table 3*. Some 291 patients with PgR+ disease did not undergo surgical resection of their BC (13.2 per cent), 122 of which had stage 4 disease at presentation (41.9 per cent). Of those with PgR- disease, 62 patients did not undergo primary surgery (13.7 per cent), 25 of which were unresectable at presentation

Table 1 Correlation of clinicopathological, immunohistochemical and molecular factors with progesterone receptor expression ($n = 2660$)

Clinicopathological characteristics	PgR+ ($n = 2208$)	PgR- ($n = 452$)	P
Age at diagnosis (years)*	59.8 (21–99) 59.4 (13.5)	60 (30–92) 61.0 (12.4)	0.029¶
Menopausal status at diagnosis			
Premenopausal	590 (26.7)	87 (19.2)	<0.001§
Perimenopausal	67 (23.0)	16 (3.5)	
Post-menopausal	1551 (70.3)	349 (77.2)	
Presentation			
Symptomatic	1700 (77.0)	359 (79.4)	<0.001†
Screening	508 (23.0)	93 (20.6)	
Invasive tumour component			
Invasive	2005 (90.8)	420 (92.9)	0.919†
Non-invasive	203 (9.2)	32 (7.1)	
Histological tumour type			
Invasive ductal carcinoma	1637 (74.1)	321 (71.0)	0.070§
Invasive lobular carcinoma	370 (16.8)	78 (17.3)	
Mucinous carcinoma	53 (2.4)	10 (2.2)	
Other	145 (6.6)	46 (10.1)	
Tumour size (mm)*	19 (0–150) 22.50 (2.52)	17 (0–200) 23.17 (2.89)	0.724¶
Tumour grade			
Grade 1	464 (21.0)	91 (20.1)	<0.001§
Grade 2	1297 (58.8)	227 (50.2)	
Grade 3	447 (20.2)	134 (29.7)	
Lymphovascular invasion			
Present	558 (25.3)	108 (23.9)	0.027†
Absent	1650 (74.7)	344 (76.1)	
Perineural invasion			
Present	167 (7.6)	16 (3.5)	0.724†
Absent	2041 (92.4)	436 (96.5)	
ER score*	8 (3–8) 7.69 (0.07)	8 (3–8) 7.07 (0.16)	<0.001#
HER2 status			
Negative	2013 (91.2	358 (79.2)	<0.001‡
Positive	195 (8.8)	94 (20.8)	
Ki67			
Low (<6%)	65 (2.9)	7 (1.5)	0.013#
Intermediate (6–14%)	145 (6.6)	19 (4.2)	
High (>14%)	193 (8.7)	38 (8.4)	
Clinical tumour stage			
0–1	969 (43.9)	223 (49.3)	0.061§
2	901 (40.8)	172 (38.1)	
3	218 (9.8)	31 (6.9)	
4	120 (5.4)	26 (5.8)	
Clinical nodal stage			
0	1307 (59.2	265 (58.6)	0.846§
1	630 (28.5)	126 (27.9)	
2	189 (8.6)	36 (8.0)	
3	82 (3.7)	25 (5.5)	
Clinical metastatic stage			
0	2086 (94.5)	425 (94.0)	0.186†
1	122 (5.5)	27 (6.0)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range), mean(s.d.). PgR+, progesterone receptor positivity; PgR-, progesterone receptor negativity; ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2. †Student independent *t*-test, ‡Fisher's exact test, §χ^2 test, ¶one-way ANOVA test, #Kruskal-Wallis test.

Table 2 Significant clinical and pathological correlates of negative PgR expression following univariable and multivariable binary logistic regression analysis

Parameter	Odds ratio Univariable	P	Odds ratio Multivariable	P
Age >65 years	0.92 (0.73–1.17)	0.501		
Being postmenopausal at diagnosis	1.76 (1.31–2.35)	<0.001	1.66 (1.25–2.20)	<0.001
Presentation (symptomatic)	1.70 (1.34–2.14)	<0.001	1.71 (1.30–2.25)	<0.001
Side affected	1.00 (0.98–1.01)	0.404		
Invasive component	1.00 (1.00–1.00)	0.928		
IDC subtype	1.27 (1.06–1.52)	0.009	1.51 (1.17–1.97)	0.002
Size >50 mm	0.95 (0.66–1.37)	0.774		
Grade 3	1.76 (1.39–2.22)	<0.001	2.12 (1.68–2.87)	<0.001
Lymphovascular invasion	1.00 (1.00–1.00)	0.053		
Perineural invasion	1.00 (1.00–1.00)	0.583		
HER2+	1.00 (1.00–1.00)	0.002		
Clinical T-stage	0.93 (0.68–1.27)	0.656		
Clinical N-stage	0.93 (0.75–1.16)	0.532		
Clinical M-stage	1.09 (0.68–1.73)	0.730		

Values in parentheses are 95% confidence intervals. PgR+, progesterone receptor positivity; PgR-, progesterone receptor negativity; ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma.

Table 3 Treatment characteristics and their association with progesterone receptor expression ($n = 2660$)

Treatment characteristics	PgR+ ($n = 2208$)	PgR- ($n = 452$)	P
Neoadjuvant chemotherapy			
Underwent treatment	247 (11.2)	61 (13.5)	0.361†
Did not undergo treatment	1961 (88.8)	391 (86.5)	
Primary surgery ($n = 2307$)			
Breast conserving surgery	1367 (61.9)	270 (59.7)	0.439‡
Mastectomy	550 (24.9)	120 (26.6)	
None	291 (13.2)	62 (13.7)	
Axillary surgery ($n = 2307$)			
SLNB	1100 (57.4)	222 (56.9)	0.450†
ALND	817 (42.6)	168 (43.1)	
ODX score ($n = 341$)	17.5 (7.2), 16 (3–47)*	24.2 (10.1), 24 (6–59)*	<0.001§
Low risk (score 0–10)	23 (7.9)	1 (2.0)	
Intermediate risk (score 11–25)	233 (80.3)	32 (62.7)	
High risk (score >25)	34 (11.7)	18 (35.3)	
Adjuvant chemotherapy			
Underwent treatment	847 (38.4)	167 (37.0)	0.263†
Did not undergo treatment	1361 (61.6)	285 (73.0)	
Adjuvant radiotherapy			
Underwent treatment	1523 (69.0)	321 (71.0)	0.425†
Did not undergo treatment	685 (31.0)	131 (29.0)	
EHT in invasive cases ($n = 2425$)			
Underwent treatment	1968 (98.4)	410 (96.7)	0.008†
Did not undergo treatment	33 (1.6)	14 (3.3)	

Values in parentheses are percentages unless indicated otherwise; * mean(s.d.), median (range). ODX, OncotypeDX™ testing; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; EHT, adjuvant endocrine hormone therapy. † Student independent *t*-test, ‡Fisher's exact test, §one-way ANOVA test.

(40.3 per cent). Neoadjuvant chemotherapy (NAC) was prescribed in 11.2 per cent of PgR+ cases, and in 13.5 per cent of PgR- cases. Pathological complete response (pCR) rates were 10.1 per cent (25 of 247 patients) in those with PgR+ disease *versus* 18.0 per cent in those with PgR- disease (11 of 61) ($P = 0.050$). Of the HR+, HER2+ cohort, 67.5 per cent were PgR+ and 32.5 per cent PgR- respectively. Of those achieving pCR with PgR+ disease, 44.0 per cent had HER2+ disease (11 of 25 patients), and 36.4 per cent of those with PgR-/HER2+ disease achieved successful pCR (4 of 11). The vast majority of patients received EHT (98.2 per cent). Of the 47 patients who did not receive EHT, 19 (40.4 per cent) refused therapy, seven were considered a venous thromboembolic risk (14.9 per cent) and 21 were lost to follow-up (44.7 per cent). Patients with PgR+ disease were more likely to receive EHT than those with PgR- disease (98.4 *versus* 96.7 per cent). Twenty-seven of the 289 HER2+ patients (9.3 per cent) did not receive anti-HER2 therapy (i.e., Trastuzumab), as a result of poor tolerance, co-morbid state or patient preference. The impact of radiotherapy (XRT) and PgR status on survival is outlined in *Appendix* S2.

Oncological outcome based on PgR status

The median overall survival (OS) was 84 (range 3.0–280.6) months and 5-year OS was 88.8 per cent (2362 of 2660 patients). The median DFS was 81 (range 3.0–272.2) months and 5-year DFS was 90.3 per cent (2401 of 2660 patients). For patients with PgR+ disease, local recurrence rates were 2.0 per cent (45 of 2208) *versus* 2.4 per cent in those with PgR- disease (11 of 452) ($P = 0.599$). Distant recurrence rate was 11.7 per cent in those with PgR+ cancer (258 of 2208) *versus* 15.0 per cent in PgR- disease at median follow-up (68 of 452) ($P = 0.049$).

Kaplan–Meier analyses demonstrated significantly worse 5-year DFS (91.0 *versus* 85.8 per cent, $P = 0.003$) and OS (90.0 *versus* 83.9 per cent, $P < 0.001$) for patients with PgR- BC (*Fig. 1*). This survival difference remained in multivariable analysis, where PgR- independently predicted worse DFS (HR 1.632) and OS (HR 1.774) (*Tables 4* and *5*).

On Kaplan–Meier analysis, treatment with systemic AC was not associated with DFS irrespective of PgR status, but it was associated with improved OS for both cohorts (*Fig. 2*). However, this did not reach statistical significance in multivariable analysis (*Table 5*). Subgroup analysis based on HER2 status demonstrated that patients with PgR-/HER2- disease had a worse DFS (5-year DFS 85.7 *versus* 89.6 per cent, $P = 0.059$) and OS (5-year OS 82.0 *versus* 91.0 per cent, $P = 0.004$) compared with their PgR+/HER2- counterparts (*Fig. 3*). In patients with HER2+ disease, PgR status failed to impact survival outcomes significantly (*Fig. 3*). However, HER2 status was not an independent predictor of survival in multivariable analysis (*Table 5*).

Other factors associated with DFS and OS in multivariable analysis

Other independent predictors of worse DFS in multivariable analysis included age greater than 65 years at diagnosis (HR 1.499), being symptomatic at presentation (HR 2.810), grade 3 tumours (HR 1.546), clinical nodal stage (HR 1.907) and requiring mastectomy (HR 1.935) (*Table 4*). Similarly, age at diagnosis greater than 65 years (HR 2.249), being postmenopausal at diagnosis (HR 1.482), being symptomatic at presentation (HR 2.121),

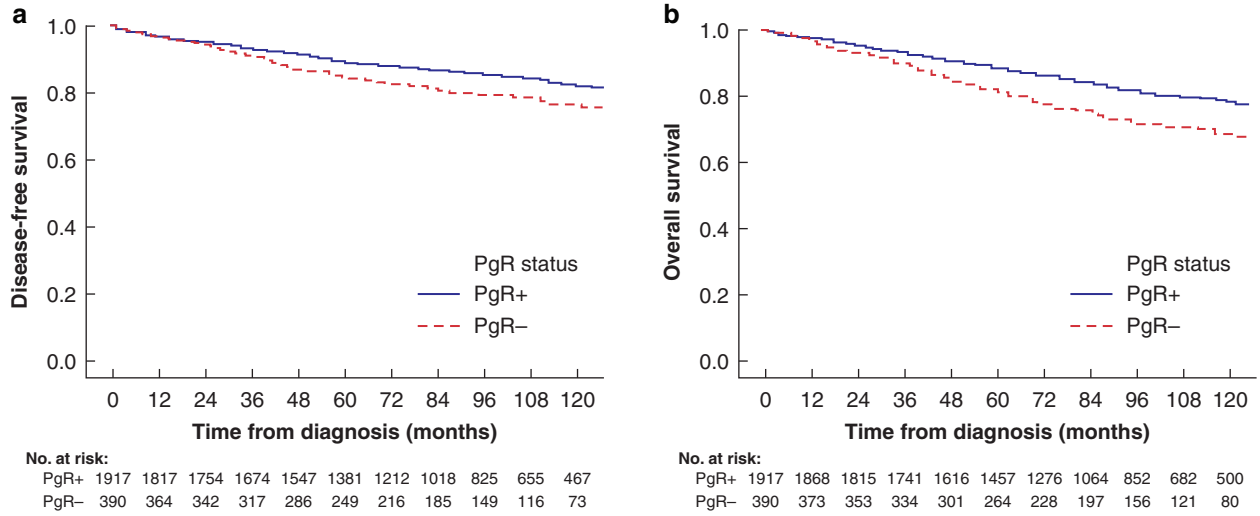

Fig. 1 Kaplan–Meier analyses illustrating survival based on progesterone receptor (PgR) status in patients diagnosed with oestrogen-receptor-positive breast cancer

a Disease-free survival ($P = 0.003$, log rank test). **b** Overall survival ($P < 0.001$, log rank test).

Table 4 Univariable and multivariable Cox hazard regression analyses for clinicopathological patient and treatment factors associated with worse disease-free survival within oestrogen-receptor-positive breast cancer patients

Parameter	Hazard ratio Univariable	*P*	Hazard ratio Multivariable	*P*
Age >65 years	1.855 (1.462–2.353)	<0.001	1.499 (1.152–1.950)	0.003
Being postmenopausal at diagnosis	0.976 (0.758–1.256)	0.849		
Presentation (symptomatic)	4.799 (3.047–7.559)	<0.001	2.810 (1.713–4.608)	<0.001
Left breast affected	1.000 (0.999–1.002)	0.789		
Invasive component	0.996 (0.980 – 1.013)	0.646		
IDC subtype	1.102 (0.862–1.408)	0.440		
Size >50 mm	3.018 (2.294–3.971)	<0.001		
High grade	2.040 (1.616–2.576)	<0.001	1.546 (1.196–2.000)	0.001
Lymphovascular invasion	1.000 (0.999–1.000)	0.007		
Perineural invasion	1.000 (1.000–1.000)	0.178		
PgR-	1.354 (1.020–1.796)	0.036	1.632 (1.209–2.204)	0.001
HER2+	0.999 (0.999–1.000)	0.004		
Clinical T-stage	3.176 (2.442–4.132)	<0.001		
Clinical N-stage	3.273 (2.578–4.157)	<0.001	1.907 (1.437–2.530)	<0.001
Neoadjuvant chemotherapy	1.000 (0.999–1.001)	0.995		
Mastectomy	2.072 (1.735–2.476)	<0.001	1.935 (1.468– 2.551)	<0.001
High ODX	1.934 (0.768–4.873)	0.162		
Adjuvant chemotherapy	1.000 (1.000–1.000)	0.757		
Adjuvant radiotherapy	0.661 (0.505–0.865)	0.003		
SERM/AI	1.507 (0.623–3.648)	0.363		

Values in parentheses are 95% confidence intervals. PgR+, progesterone receptor positivity; PgR-, progesterone receptor negativity; ER, oestrogen receptor; HER, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma; ODX, OncotypeDX™ genomic testing; SERM, selective oestrogen receptor modulator; AI, aromatase inhibitor.

Table 5 Univariable and multivariable Cox hazard regression analyses for clinicopathological patient and treatment factors associated with worse overall survival within oestrogen-receptor-positive breast cancer

Parameter	Hazard ratio Univariable	P	Hazard ratio Multivariable	P
Age >65 years	3.291 (2.655–4.080)	<0.001	2.249 (1.652–3.060)	<0.001
Being postmenopausal at diagnosis	1.746 (1.336–2.284)	<0.001	1.482 (1.035–2.121)	0.032
Presentation (symptomatic)	3.921 (2.626–5.856)	<0.001	2.121 (1.254–3.590)	0.005
Left breast affected	1.000 (0.999–1.002)	0.838		
Invasive component	0.996 (0.983–1.010)	0.613		
IDC subtype	1.163 (0.917–1.475)	0.213		
Size >50 mm	3.007 (2.309–3.918)	<0.001		
High grade	1.820 (1.449–2.285)	<0.001	1.448 (1.112–1.885)	0.006
Lymphovascular invasion	1.000 (0.999–1.001)	0.025		
Perineural invasion	1.000 (1.000–1.000)	0.475		
PgR-	1.465 (1.123–1.911)	0.005	1.774 (1.324–2.375)	<0.001
HER2+	0.999 (0.998–1.000)	<0.001		
Clinical T-stage	3.567 (2.786–4.568)	<0.001	1.784 (1.004–3.170)	0.049
Clinical N-stage	2.973 (2.360–3.745)	<0.001	2.016 (1.511–2.690)	<0.001
Neoadjuvant chemotherapy	1.000 (0.999–1.001)	0.452		
Mastectomy	2.003 (1.616–2.482)	<0.001	1.341 (1.011– 1.780)	0.042
High ODX	1.877 (0.602 – 5.852)	0.278		
Adjuvant chemotherapy	1.000 (1.000–1.000)	0.287		
Adjuvant radiotherapy	0.564 (0.440–0.723)	<0.001	0.593 (0.440 – 0.799)	0.001
SERM/AI	1.142 (0.540– 2.414)	0.729		

Values in parentheses are 95% confidence intervals. PgR+, progesterone receptor positivity; PgR-, progesterone receptor negativity; ER, oestrogen receptor; HER, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma subtype; ODX, OncotypeDX™ genomic testing; SERM, selective oestrogen receptor modulator; AI, aromatase inhibitor.

grade 3 tumours (HR 1.448), clinical tumour stage (HR 1.784), clinical nodal stage (HR 2.016) and requiring mastectomy (HR 1.341) also predicted worse OS, while receiving XRT (HR 0.593) predicted improved OS (*Table 5*).

Discussion

This large retrospective cohort study analysed the clinical features and prognostic significance of PgR expression in patients diagnosed with ER+ BC in a tertiary referral centre. Patients with PgR- disease were more likely to be postmenopausal at the time of diagnosis, symptomatic at presentation and to have a high histological grade. Oncological outcomes were worse in patients diagnosed with PgR- BC *versus* their PgR+ counterparts, and this effect was independent of other clinicopathological and treatment factors. These results are consistent with other studies and a recent meta-analysis, where PgR negativity independently predicted worse oncological outcome in patients with ER+ BC[14,16]. These data suggest that PgR assessment should remain part of routine work-up for all patients diagnosed with ER+ BC to inform patient prognosis better and aid the clinical decision-making process.

A number of studies have described PgR- BC independently predicting high RS[31,32], and the present series highlights the increased incidence of high RS in PgR- BC (11.7 per cent in PgR+ *versus* 35.3 per cent in PgR-). This is unsurprising as ODX score is derived from an equation which is largely dependent upon ER, PgR, *ERBB2* (HER2) scores[23], and it has been proposed that statistical models based on clinicopathological information such as PgR status could act as a surrogate in situations where ODX testing is not affordable or routinely available[33]. While the Trial Assigning Individualized Options for Treatment (or TAILORx trial) demonstrated the limited impact of chemotherapy in women with ER+, HER2-, LN- BC with an RS in the mid-range (11 to 25) there is evidence that low-grade, PgR- tumours should not be considered low risk regardless of RS[31]. Moreover, the typical patient enrolled in TAILORx was 55 years old, had a 1.5-cm, intermediate-grade, PgR+ tumour with an RS of 17, making it difficult to extrapolate this data for younger women, with high-grade tumours or with PgR- disease. Consequently, PgR status may also help inform clinical decision making when used in combination with ODX, particularly in intermediate-risk groups[34].

One in eight patients in this study received NAC, and PgR expression significantly affected pathological response rates in those in receipt of this therapy. The use of NAC in HR+ BC is usually reserved for patients with locally advanced (IIb, IIIa, IIIb, or IIIc) disease, in those with HER2+ disease, in patients hoping to achieve breast conservation surgery (BCS) with increased tumour to breast ratio and in patients who require preoperative downstaging[35]. Although ER+ cancers do respond to NAC, pCR rates are typically low, reaching only 10–15 per cent in most trials[35], and results from this study mirror these reports (11.7 per cent). However, there is evidence that patients in the ER+/PgR-, HER- group are more likely to undergo BCS compared with the ER+, PgR+, HER- group (62 *versus* 29 per cent) after NAC[36]. pCR results in this study are consistent with a pooled analysis of 10 prospective RCTs containing data from 5613 patients illustrating that ER+/PgR- cohorts have higher rates of pCR than those with ER+/PgR+ disease (PgR- 18.0 per cent *versus* PgR+ 10.1 per cent)[36,37]. PgR negativity is also an independent predictor of axillary nodal pCR in this group, which is associated with long-term clinical benefit in BC[35]. While preliminary data suggest that genomic panel-based recurrence score tests, such as ODX[37], may be expanded to the neoadjuvant setting to help predict response to NAC for ER+ disease, these results require further validation. In the interim, PgR status should remain an important determinant in guiding NAC prescription and predicting response for this cohort of patients[38].

The prognostic and predictive role of HER2 expression in BC is well described[39]. In this study, HER2 positivity (HER2+) was found in 20.8 per cent of the ER+/PgR- group *versus* 8.83 per cent of the ER+/PgR+ group, consistent with other reports[16,40]. PgR- mediated crosstalk with epidermal growth factor receptor has been provided as the rationale for the increased incidence of HER2

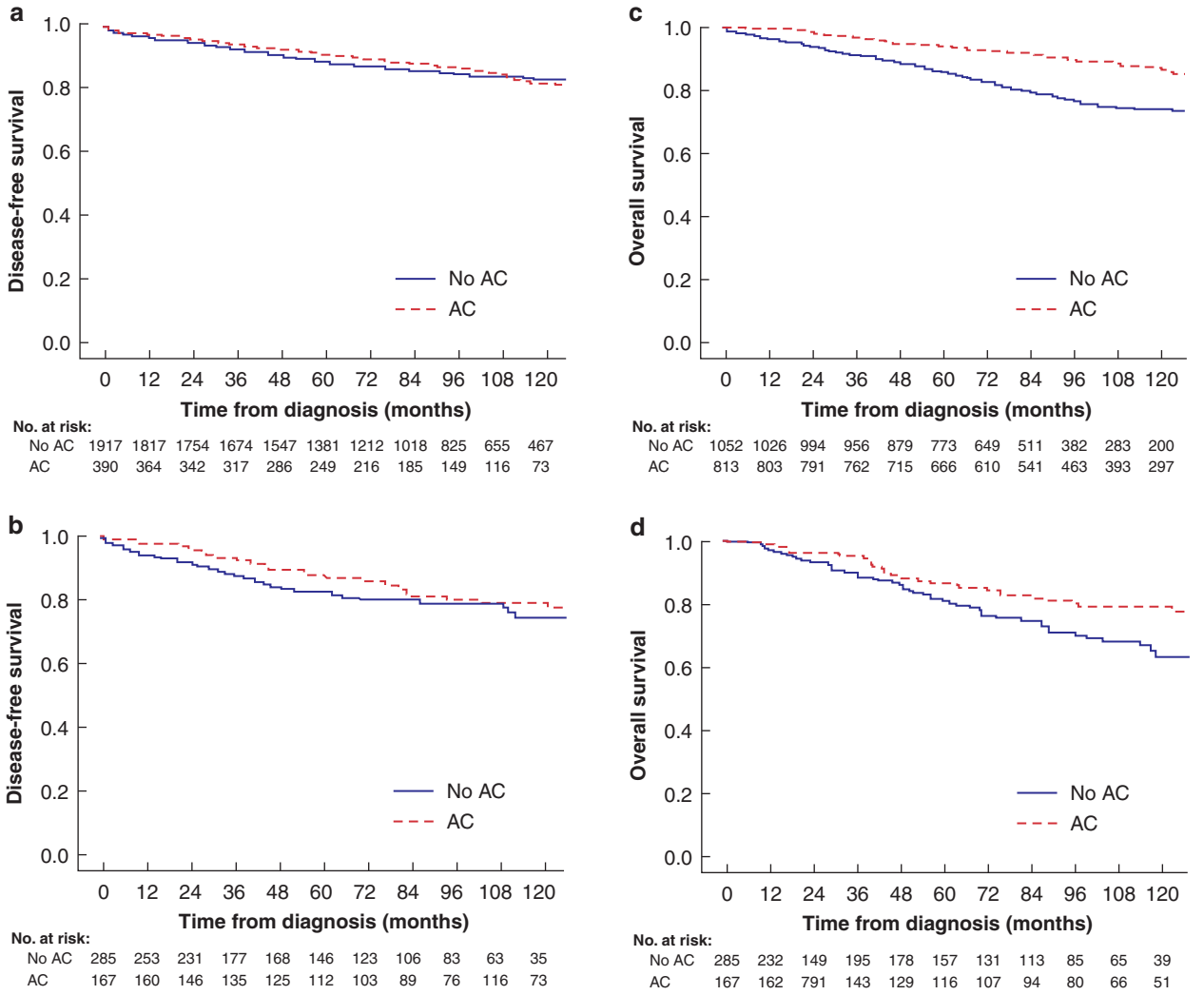

Fig. 2 Kaplan–Meier analyses illustrating survival in those receiving adjuvant chemotherapy (AC) based on progesterone receptor (PgR) status in patients diagnosed with oestrogen-receptor-positive breast cancer

a Disease-free survival with adjuvant chemotherapy prescribed in PgR+ breast cancer ($P = 0.645$, log rank test). **b** Disease-free survival with adjuvant chemotherapy prescribed in PgR- breast cancer ($P = 0.241$, log rank test). **c** Overall survival with adjuvant chemotherapy prescribed in PgR+ breast cancer ($P < 0.001$, log rank test). **d** Overall survival with adjuvant chemotherapy prescribed in PgR- breast cancer ($P = 0.017$, log rank test).

expression in the ER+/PgR- group[41]. Bae and colleagues previously demonstrated that there is little difference in survival outcomes based on PgR status in HER2+ patients, as they respond better to contemporary multimodal treatment, including systemic chemotherapy and targeted anti-HER2 therapy. In contrast, patients with ER+/PgR-/HER2- disease had worse oncological outcomes than their PgR+ counterparts[41]. These results are confirmed in the present study, with PgR-/HER2- patients exhibiting significantly worse OS than PgR+/HER2- disease, while those with HER2+ disease displayed similar survival outcome irrespective of PgR status. These results reiterate that more aggressive treatment of patients with ER+/PgR-/HER2- disease is warranted in clinical practice, particularly given that survival outcomes for this cohort are equivalent to those with triple negative BC (TNBC) after 10 years[41].

Molecular cross-talk between ER and growth-factor-receptor signalling pathways leads to modulation of both ER and PgR function[17,18,42]. It has been proposed that PgR negativity may indicate impaired growth factor signalling via the PI3K-Akt-MTOR pathway with resultant resistance to tamoxifen[43,44]. At present PgR status is not considered to confer selective advantage between EHT types[45] and ER status remains the only factor predictive of tamoxifen benefit[46]. However, the absence of this synergistic response to EHT and relative endocrine resistance is a possible explanation for the worse outcomes associated with PgR- disease[14–16,21,43,44,47]. Given these data, perhaps conscious consideration should be given to novel therapeutic strategies when treating patients with the PgR- subtype, particularly in cases of HER2- disease where the option of targeted anti-HER2 therapy or systemic chemotherapy may not be clinically indicated[19,20]. The potential value of studying this subgroup as a separate arm in RCTs investigating novel therapeutic agents for treatment of TNBC should be considered given their worse outcomes with contemporary multimodal therapy[48]. Alternatively, the development of therapeutics capable of converting PgR- to PgR+ BC may offer a potential approach to ameliorate the worse prognosis of PgR- disease[49].

Despite their worse prognosis, the authors advocate no change to surgical practice for patients with PgR- disease. Even in the analyses of the most aggressive of TNBCs, the introduction of more radical surgery has failed to improve prognosis[50] and can cause increased morbidity[51]. Relatedly, the association of mastectomy with worse survival is reflective of the underlying

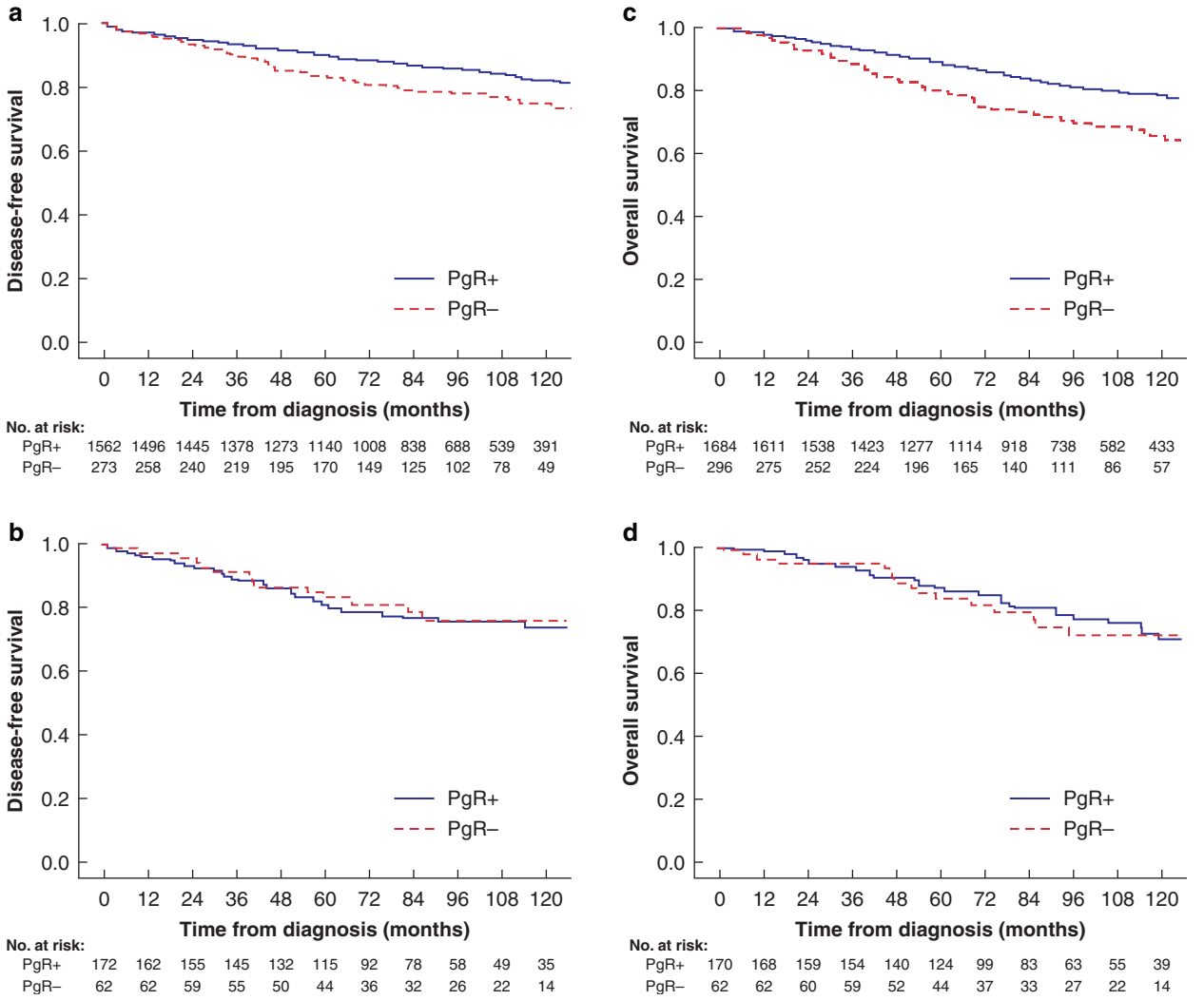

Fig. 3 Kaplan–Meier analyses illustrating the impact of progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) status on survival in patients diagnosed with oestrogen-receptor-positive breast cancer

a Impact of PR status on disease-free survival in patients with HER2- disease ($P = 0.001$, log rank test). **b** Impact of PR status on disease-free survival in patients with HER2+ disease ($P = 0.707$, log rank test). **c** Impact of PR status on overall survival in patients with HER2- disease ($P < 0.001$, log rank test). **d** Impact of PR status on overall survival in patients with HER2+ disease ($P = 0.768$, log rank test).

indication for the procedure[52]. Mastectomy is typically indicated for tumours at advanced stages, where BCS is not feasible[53]. In this study patients undergoing mastectomy were more likely to have higher grade (30.6 *versus* 20.3 per cent grade 3 tumours), more advanced nodal disease (25.0 *versus* 6.4 per cent) and distant metastasis (9.3 *versus* 2.6 per cent), and were more likely to require NAC (21.6 *versus* 7.4 per cent) than those undergoing BCS. It is somewhat surprising that receipt of XRT was associated with improved OS but not DFS in multivariable analysis, given it is an integral component of locoregional therapy. However, randomized data and meta-analyses demonstrate that the addition of XRT to surgery, regardless of surgical approach (BCS or mastectomy), appears to reduce the risk of distant recurrences and death[54,55]. This may suggest an 'abscopal' or immunogenic effect beyond the immediate zone of locoregional irradiation that alters the natural history of distant micrometastases[56]. However, the selection bias to spare older, more comorbid patients the additional burden of XRT is an important confounder.

This study is subject to the inherent limitations of a single-centre, retrospective cohort study, including selection, ascertainment and confounding bias. The study time period also coincided with changes towards a refined approach to AC prescription within the ER+/HER2-/LN- cohort, following publication of the results of the TAILORx study from Sparano and co-workers in 2018[57]. Despite outlining the lack of consideration for the role PgR status in therapeutic decision making, the authors acknowledge that RS relies upon genomic information with regard to PgR receptor expression, which subsequently contributes to chemoendocrine prescription[22].

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Supplementary material

Supplementary material is available at *BJS Open* online.

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