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Prognostic and Clinical Significance of the Proliferation Marker MCM7 in Breast Cancer

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Keywords
Breast cancer · Minichromosome maintenance complex component 7 · Endocrine therapy · Prognosis · Molecular classes

Abstract

Introduction: Minichromosome maintenance complex component 7 (MCM7) plays an essential role in proliferation and DNA replication of cancer cells. However, the expression and prognostic significance of MCM7 in breast cancer (BC) remain to be defined. In this study, we aimed to evaluate the role of MCM7 in BC. ***Methods:*** We conducted immunohistochemistry staining of MCM7 in 1,156 operable early-stage BC samples and assessed *MCM7* at the transcriptomic levels using publicly available cohorts (n = 13,430). MCM7 expression was evaluated and correlated with clinicopathological parameters including Ki67 labelling index and patient outcome. ***Results:*** At the transcriptomic level, there was a significant association between high *MCM7* mRNA levels and shorter patient survival in the whole cohort and in luminal BC class but not in the basal-like molecular subtype. High MCM7 protein expression was detected in 43% of patients and was significantly associated with parameters characteristic of aggressive tumour behaviour. MCM7 was independently associated with shorter survival, particularly in oestrogen receptor-positive (luminal) BC. MCM7 stratified luminal tumours with aggressive clinicopathological features into distinct prognostic groups. In endocrine therapy-treated BC patients, high MCM7 was associated with poor outcome, but such association disappeared with administration of adjuvant chemotherapy. Patients with high expression of Ki67 and MCM7 showed worst survival, while patients with double low expression BC showed the best outcome compared with single expression groups. ***Conclusion:*** The current findings indicate that MCM7 expression has a prognostic value in BC and can be used to identify luminal BC patients who can benefit from adjuvant chemotherapy.

Introduction

Because of the clinical and molecular heterogeneity of breast cancer (BC), the main limitations of current prognostic and predictive markers remain sensitivity and specificity [1, 2]. There is an urgent need to identify new biomarkers that can refine the prognostic stratification of

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BC, and more precisely, inform individualised responses to therapy [3]. Minichromosome maintenance (MCM) complex plays a key role in cellular proliferation and is considered a critical first step in the formation of a pre-replication complex during DNA replication [4–7]. The MCM complex is composed of six highly conserved MCM proteins, namely, MCM2–7 and highly associated with tumorigenesis [8, 9]. Although MCM2 and MCM3 are significantly upregulated in BC and can potentially be used as substitutes for or to compliment Ki67 labelling index in assessing BC cell proliferation [10, 11], the expression levels, functions, and prognostic values of minichromosome maintenance complex component 7 (MCM7) in BC remain to be defined.

MCM7 overexpression is demonstrated in several tumours, including prostate [12], lung cancer [9], and hepatocellular carcinoma (HCC) [9]. High MCM7 expression was also associated with a negative outcome in patients with non-small cell lung carcinoma [13]. Therefore, inactivation of this gene could be a promising therapeutic target in a variety of cancers. For example, knockdown of MCM7 significantly inhibited cellular proliferation in HCC [14], and its upregulation has been associated with cisplatin resistance in bladder cancer [15]. The present study aimed to evaluate the expression and clinical significance of MCM7 in BC with particular interest on the added value to Ki67 labelling index.

Materials and Methods

Study Cohort

In this study, two cohorts were used: the Nottingham cohort (n = 1,156) was used for the immunohistochemical assessment of MCM7 protein expression. The other cohort included publicly available transcriptomic datasets (the Breast Cancer Gene-Ex-Miner v4.9 [n = 9,476] and the Kaplan-Meier [KM] Plotter [n = 3,951] online dataset) and was used to study the prognostic value of *MCM7* mRNA levels.

MCM7 protein expression: this was evaluated on a large cohort of primary operable BC series from patients who had presented at Nottingham City Hospital, NHS Trust, Nottingham, UK. The clinical and tumour characteristics were available for this cohort (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000540790). In addition, outcome data in the form of BC-specific survival, defined as time (in months) from the date of primary surgery to the time of death by BC, were also available. The mean follow-up time was 135 months, the median was 158 months, and it ranged from 7 to 256 months. Adjuvant treatment was given according to the institutional protocols. Information regarding oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) status was also available. None of the patients received neoadjuvant therapy. Tumours were additionally classified based on ER, PR, and HER2 into three molecular subtypes (luminal, triple-negative (TN), and HER2-enriched) [16]. Information regarding Ki67 expression levels was also available [17–19].

Prior to immunohistochemical staining of the tissue sections, the specificity of the anti-MCM7 antibody (#PA5-79651, Invitrogen, Thermo Fisher Scientific, UK) was validated via Western blotting using cell lysates of MCF7, MDA-MB-231, and SKBR3 human BC cell lines obtained from the American Type Culture Collection, Rockville, MD, USA. The MCM7 primary antibody was used at a dilution of 1:1,000. Proteins were detected using IRDye 800CW fluorescent secondary antibodies (1:5,000 dilution, LI-COR Biosciences), and Odyssey Fc with Image Studio 4.0 (LI-COR Biosciences) was used to visualise the bands. An anti-β-actin primary antibody, A1978 (Sigma-Aldrich) was used as a loading control. Specific bands for MCM7 protein were observed at the predicted molecular weight (80 kDa; online suppl. Fig. 1).

Tumour samples (n = 1,156) were arrayed using the Grand Master® (3DHISTECH®, Budapest, Hungary). Tissue sections were stained using the Novocastra Novolink™ Polymer Detection Systems kit (Code: RE7280-K, Leica, Biosystems, Newcastle, UK) on 4-μm thick dewaxed sections as previously described [20]. MCM7 was diluted at 1:500 in Leica antibody diluent (RE AR9352, Leica, Biosystems, UK) and incubated for 30 min at room temperature. Normal colon tissue was used as a positive control, while negative controls were obtained by omitting the primary antibody.

The percentage of immunohistochemistry-positive tumour cells was calculated. To assess the interobserver concordance, a second observer (MT) scored 20% of the cohort, and intra-class correlation coefficient was (k = 0.81). In this study, the percentage of nuclear and cytoplasmic MCM7 expression was assessed. MCM7 expression levels were categorised into low and high expression based on X-tile software [21, 22]. MCM7 expression was correlated with the clinicopathological parameters and patient outcome.

Statistical Analysis

Statistical Package for the Social Sciences software v.27.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The MCM7 expression percentages of 5 and 70

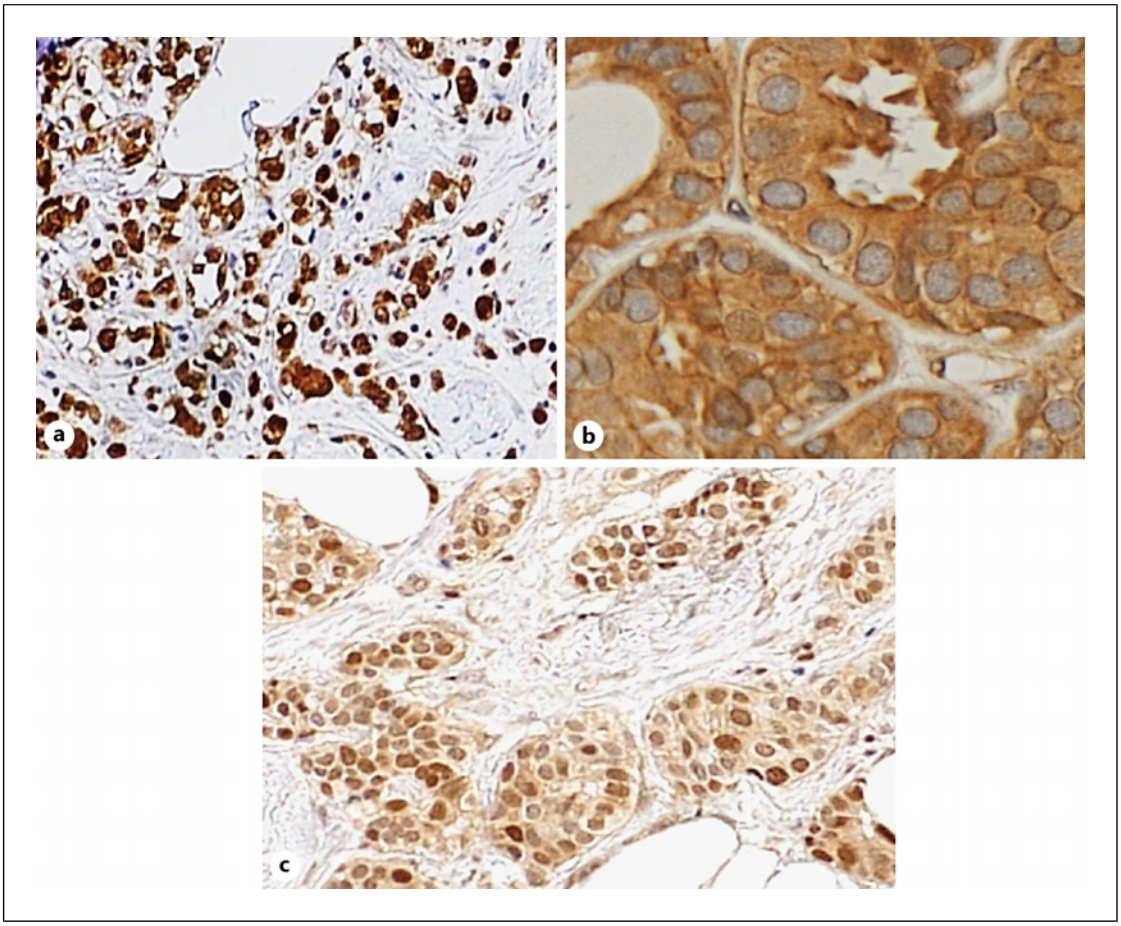

Fig. 1. Breast cancer cases exhibiting nuclear (**a**), cytoplasmic (**b**), and both nuclear and cytoplasmic (**c**) MCM7 expression.

were the optimal cutoffs of nuclear and cytoplasmic expression, respectively. χ^2 tests were used to analyse the categorical data. Outcome analysis was assessed using Kaplan-Meier curves and the log-rank test. Cox regression models were used for multivariate analysis. For all tests, $p < 0.05$ (two-tailed) was considered statistically significant.

Results

MCM7 Protein Expression

The median percentage of MCM7 positivity was 5%, the mean was 25%, and it ranged from 0 to 100%. High MCM7 nuclear expression was detected in 43% (500/1,156) of patients (Fig. 1). High MCM7 expression was significantly associated with younger patient age (<50 years) ($p = 0.02$), premenopausal status ($p = 0.03$), high tumour grade ($p < 0.0001$), no special type tumours ($p = 0.01$), poor NPI groups ($p = 0.002$), and tumours with triple-negative (TNBC) phenotype (Table 1). High cytoplasmic expression was found in 17% (192/1,156) of patients while 8% showed both high nuclear and cytoplasmic MCM7 expression (Fig. 1). However, cytoplasmic expression did not show association with any clinicopathological parameters. Therefore, all the analysis was confined to nuclear expression of MCM7. Based on this, these 8% of cases that showed combined nuclear and cytoplasmic MCM7 expression were included in the final analysis. When we eliminated the later cases from the analysis, the data remain significant in terms of tumour grade ($p = 0.005$), tumour type ($p < 0.0001$), and NPx ($p = 0.018$).

Outcome Analysis

In the whole cohort, high MCM7 expression showed a significant association with shorter survival ($p = 0.004$; online suppl. Fig. 2). In the whole cohort, multivariate

Table 1. Relationship between nuclear MCM7 expression levels and clinico-pathological parameters in BC

Variables	MCM7 expression		χ^2
	low % ≤5	high % >5	*p* value
Age at diagnosis, *n* (%)			
<50 years	188 (52)	174 (48)	4.9
≥50 years	468 (59)	326 (41)	**0.02**
Menopausal state, *n* (%)			
Premenopausal	212 (53)	191 (47)	4.3
Postmenopausal	44 (59)	309 (41)	**0.03**
Tumour size, *n* (%)			
≤2 cm	411 (58)	294 (42)	1.7
>2 cm	245 (54)	206 (46)	0.1
Histologic tumour grade, *n* (%)			
Grade 1	110 (66)	58 (34)	19.1
Grade 2	285 (61)	180 (39)	<**0.0001**
Grade 3	261 (50)	262 (50)	
Histologic tumour types, *n* (%)			
No special type (NST)	428 (56)	333 (44)	
Lobular	46 (45)	57 (55)	10.9
Other special types	28 (56)	22 (44)	**0.01**
NST mixed	154 (64)	88 (36)	
Molecular subtypes, *n* (%)			
Luminal	543 (59)	375 (41)	9.2
HER2-enriched	27 (49)	28 (51)	**0.01**
Triple-negative	82 (48)	90 (52)	
Lymph node invasion, *n* (%)			
Absent	422 (58)	309 (42)	0.7
Present	234 (55)	191 (45)	0.37
Lymphovascular invasion, *n* (%)			
Absent	479 (57)	360 (43)	0.1
Present	177 (56)	140 (44)	0.7
Nottingham prognostic index, *n* (%)			
Good prognostic group	248 (64)	139 (36)	12.78
Moderate prognostic group	311 (53)	277 (47)	**0.002**
Poor prognostic group	97 (54)	84 (46)	

Table 2. Multivariate analysis MCM7 expression in BC

Parameters	BCSS		
	hazard ratio	95% CI	*p* value
MCM7	1.4	1.1–2.0	**0.01**
Tumour size	1.6	1.1–2.2	**0.004**
Lymph node status	2.0	1.6–2.4	<**0.0001**
Lymphovascular invasion	1.6	1.1–2.2	**0.005**

Significant *p* values are shown in bold. BCSS, breast cancer-specific cancer; 95% CI, 95% confidence interval.

analysis showed that high MCM7 was independently associated with shorter survival in presence of other prognostic variables including tumour size, lymph node status, and lymphovascular invasion (Table 2).

When the cohort was classified according to the molecular classes (luminal, TN, and HER2-enriched), there was a significant association between high MCM7 expression and shorter survival in luminal BC ($p < 0.0001$), but no such association was observed in patients with TN or HER2+ molecular subtypes ($p = 0.12$ and $p = 0.61$, respectively; Fig. 2). With classification into four molecular classes, high MCM7 showed a significant association with poor outcome in luminal B BC ($p = 0.04$) but no association

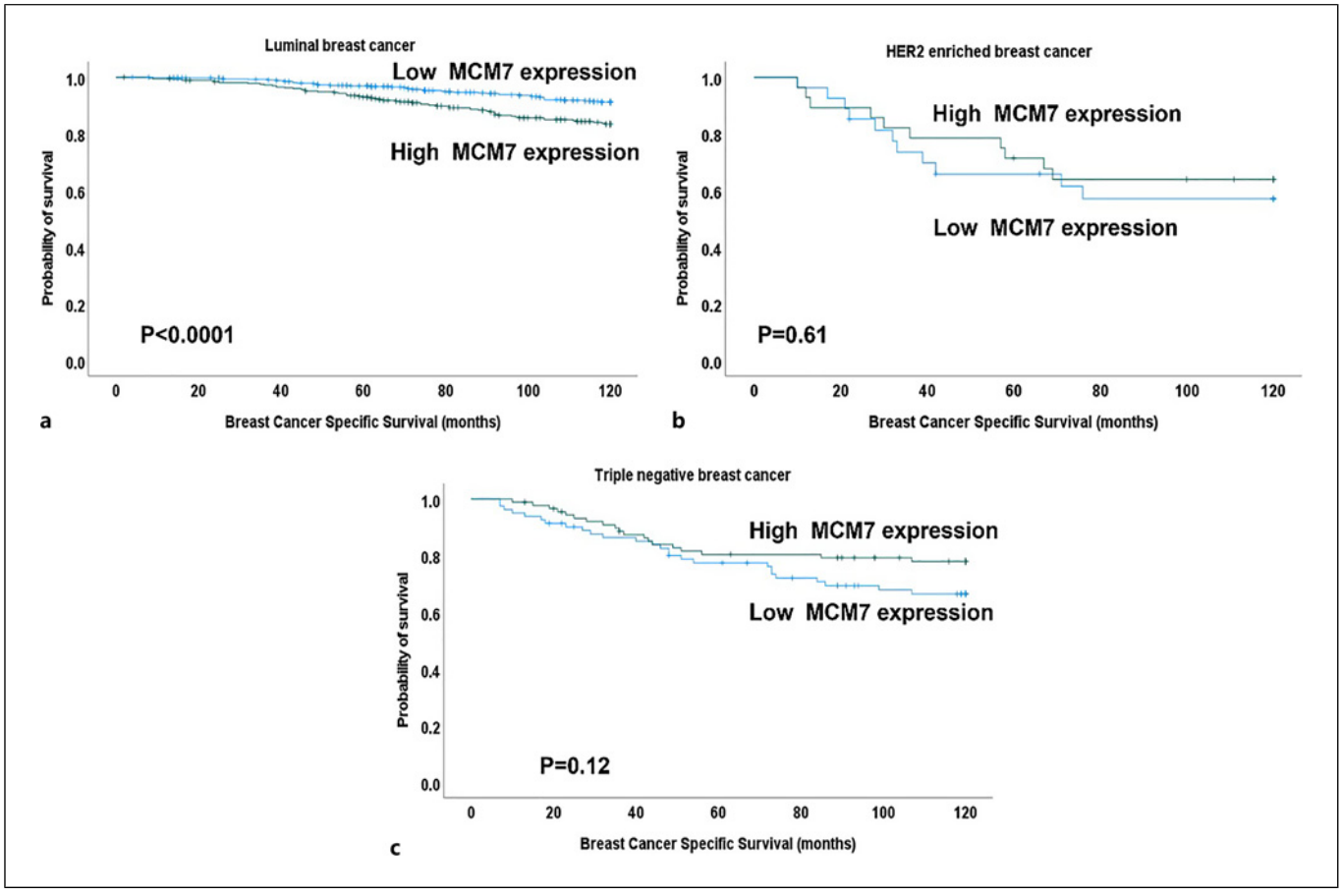

Fig. 2. Kaplan-Meier association of MCM7 with BC-specific survival in different molecular classes. High MCM7 expression shows poor prognosis in luminal BC (**a**), while no association was observed in both HER2-enriched (**b**) and triple-negative (**c**) molecular subtypes.

Table 3. Multivariate analysis MCM7 expression in luminal BC patients who were treated with endocrine therapy

Parameters	BCSS		
	hazard ratio	95% CI	*p* value
MCM7	1.7	1.1–2.5	**0.014**
Tumour grade	2.8	1.8–4.2	<**0.0001**
Lymph node status	2.5	1.6–3.9	<**0.0001**
Tumour size	1.3	0.85–2.0	0.227

Significant *p* values are shown in bold. BCSS, breast cancer-specific cancer; 95% CI, 95% confidence interval.

in other subtypes. With classification of the cohort based on Ki67 status, we found that MCM7 can dichotomise luminal BC patients with high Ki67 into two prognostic groups ($p = 0.018$) but not in the whole cohort.

In our luminal BC cohort, some low-risk patients were diagnosed prior to 1996 and did not receive endocrine therapy. When this luminal cohort was stratified based on endocrine therapy, survival analysis of endocrine therapy-treated patients showed an association between high MCM7 expression and poor outcome ($p = 0.002$). In contrast, no such association was identified in the BC patients who did not receive endocrine therapy ($p = 0.19$; online suppl. Fig. 3). Therefore, further outcome analysis for luminal BC patients was restricted to those who received endocrine therapy.

To further refine the prognostic classification of luminal BC patients, the cohort was stratified based on the clinical risk, then the added prognostic value of MCM7 was evaluated. This analysis demonstrated the ability of MCM7 to prognostically stratify clinically high-risk patients into two distinct subgroups. This included tumours with (i) higher-grade (grade ≥2; $p < 0.0001$), (ii) lymph

Table 4. Co-expression of MCM7 and Ki67 with the clinicopathological parameters in BC

Categories	MCM7-negative Ki67 (negative)	MCM7-positive Ki67 (positive)	Ki67-negative MCM7 (positive)	Ki67-positive MCM7 (negative)	χ^2
					p value
Age, *n* (%)					48.4
<50 years	57 (22)	90 (35)	76 (31)	32 (12)	<**0.0001**
≥50 years	255 (41)	132 (21)	112 (18)	121 (19)	
Menopausal status, *n* (%)					33.1
Premenopausal	79 (27)	92 (32)	84 (29)	36 (12)	<**0.0001**
Postmenopausal	233 (40)	130 (22)	104 (18)	117 (20)	
Tumour size, *n* (%)					37.8
≤2 cm	224 (41)	112 (21)	99 (18)	109 (20)	<**0.0001**
>2 cm	88 (27)	110 (33)	89 (27)	44 (13)	
Tumour grade, *n* (%)					
Grade 1	92 (63)	7 (5)	6 (4)	42 (28)	241.4
Grade 2	164 (44)	84 (23)	42 (11)	80 (22)	<**0.0001**
Grade 3	56 (16)	131 (37)	140 (58)	31 (9)	
Histologic types, *n* (%)					
No special type (NST)	165 (30)	169 (31)	147 (27)	73 (12)	88.5
Lobular	26 (33)	13 (17)	12 (15)	27 (35)	<**0.0001**
Other special types	23 (60)	0 (0)	1 (3)	14 (37)	
NST mixed	98 (48)	40 (19)	28 (14)	39 (19)	
Molecular subtype, *n* (%)					
Luminal	286 (41)	166 (23)	113 (16)	140 (20)	95.1
Triple-negative	20 (16)	41 (32)	59 (46)	8 (6)	<0.0001
HER2+	5 (13)	14 (38)	15 (41)	3 (8)	
Lymph node status, *n* (%)					
Negative	222 (38)	130 (22)	120 (22)	113 (18)	13.66
Positive	90 (32)	92 (32)	68 (23)	40 (23)	**0.003**
Lymphovascular invasion, *n* (%)					
Absent	253 (39)	144 (22)	129 (20)	127 (19)	27.3
Present	59 (26)	78 (35)	49 (27)	26 (12)	<**0.0001**
Nottingham prognostic index, *n* (%)					150.9
Good prognostic group	170 (53)	42 (13)	24 (8)	84 (26)	<**0.0001**
Moderate prognostic group	124 (27)	140 (30)	133 (29)	64 (14)	
Poor prognostic group	18 (19)	40 (43)	31 (33)	5 (5)	

node metastasis ($p = 0.004$), and (iii) high NPI (NPI >3.4; $p = 0.003$). However, there was no association between MCM7 expression and patient outcome in the more indolent tumours including lymph node-negative ($p = 0.075$), grade 1 tumours ($p = 0.29$), and those with a low NPI ($p = 0.39$; online suppl. Fig. 4).

In the subgroup of high-risk luminal BC patients who were given both endocrine therapy and chemotherapy, the association between MCM7 expression and poor outcome lost its significance ($p = 0.07$; online suppl. Fig. 5), suggesting improvement of the outcome of those high-risk MCM7-positive patients by the administration of adjuvant chemotherapy with the endocrine therapy. In the luminal BC patients treated with endocrine therapy, high MCM7 was independently associated with shorter survival in presence of other prognostic variables (Table 3).

MCM7 and Ki67 Protein Expression

MCM7 showed a positive linear correlation with Ki67 labelling index ($p < 0.0001$). When combining MCM7 and Ki67 expression, the cohort was classified into four subgroups. High MCM7 and high Ki67 were observed in 21% of patients, while both low MCM7 and Ki67 expression were present in 36% of the cases. High MCM7

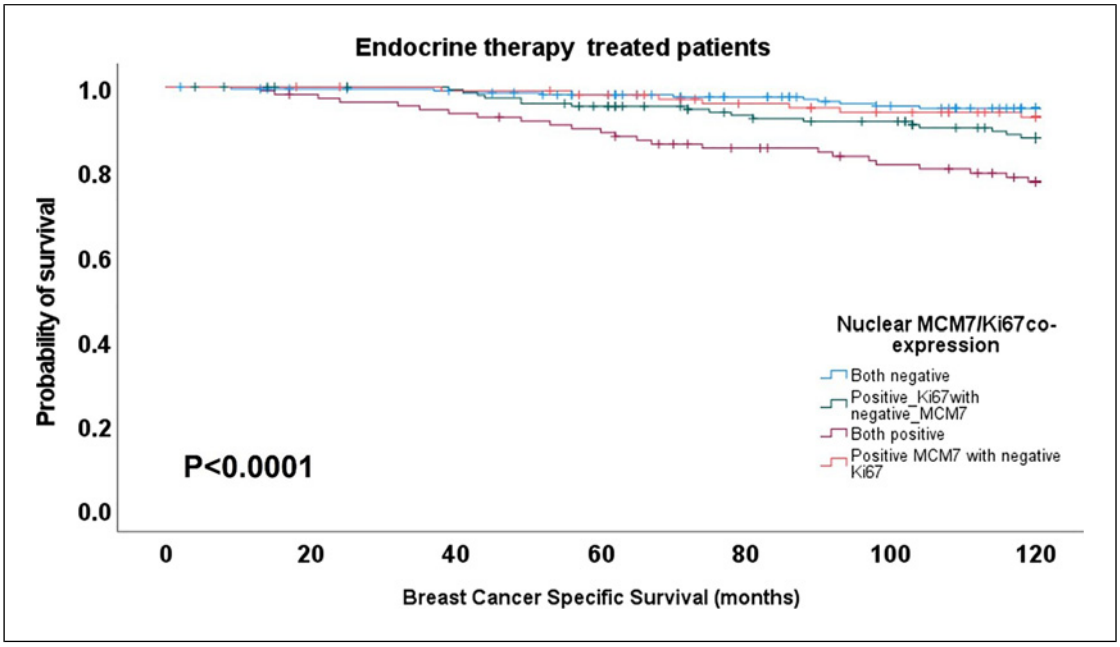

Fig. 3. Kaplan-Meier plots showing a significant association between high MCM7 with high Ki67 and worse survival compared to other groups in endocrine therapy-treated patients.

and low Ki67 were found in 17% of patients, while low MCM7 and high Ki67 were observed in 26% of patients.

When correlated with the clinical parameters in the whole cohort, both high MCM7 and high Ki67 expression showed an association with parameters characteristic of aggressive tumour behaviour as shown in Table 4. Similar findings were observed when the analysis was confined to luminal BC (online suppl. Table 2).

Outcome analysis showed that patients with high MCM7 and Ki67 expression had the worst outcome ($p < 0.0001$). In luminal BC, high MCM7 and Ki67 expression were associated with worst survival while double low expression showed the best survival. Patients with a single high marker (either Ki67 or MCM7) showed similar outcomes, and they had better survival than patients with double high expression, concluding that MCM7 expression can add prognostic and predictive value similar to Ki67 (Fig. 3).

MCM7 *mRNA Expression*

Outcome analysis showed a significant association between high MCM7 mRNA levels and poor survival in the whole Gene-Ex-Miner cohort ($p < 0.0001$), luminal subtype ($p = 0.0045$), and HER2-enriched subtype ($p = 0.025$). However, no association was found between MCM7 and patient outcome in basal-like BC (Fig. 4). Similar results were observed in Kaplan-Meier plotter cohort (online suppl. Fig. 6).

Discussion

DNA replication is an essential step in cell proliferation [7]. MCM family, which participates in DNA replication, is abnormally expressed in cancer cells and more pronounced than normal cells [23]. Elevated expression of the MCMs has been proposed as potential proliferation markers [24]. MCMs are considered important factors in oncogenic signalling pathways and are involved into critical steps in DNA synthesis: (i) DNA replication initiation and (ii) DNA elongation mediated by MCM helicase activities [25]. MCM7, an important subunit of the presumed heteromeric MCM helicase, is involved in tumour formation and progression and plays an essential role in initiating DNA replication. Overexpression of MCM7 has been found in several types of cancers [14, 26]. To investigate the potential oncogenic properties and prognostic value of MCM7 in BC, we assessed MCM7 expression at the transcriptomic and proteomic levels.

In our research, high nuclear MCM7 expression showed significant associations with parameters of aggressive tumour behaviour including high grade tumours. Similarly, high MCM7 expression has been associated with high grade ovarian carcinoma [25] and oral squamous cell carcinoma [27]. The present research in BC and previous research in other cancers, therefore, indicate the strong correlation between MCM7 and tumour grade,

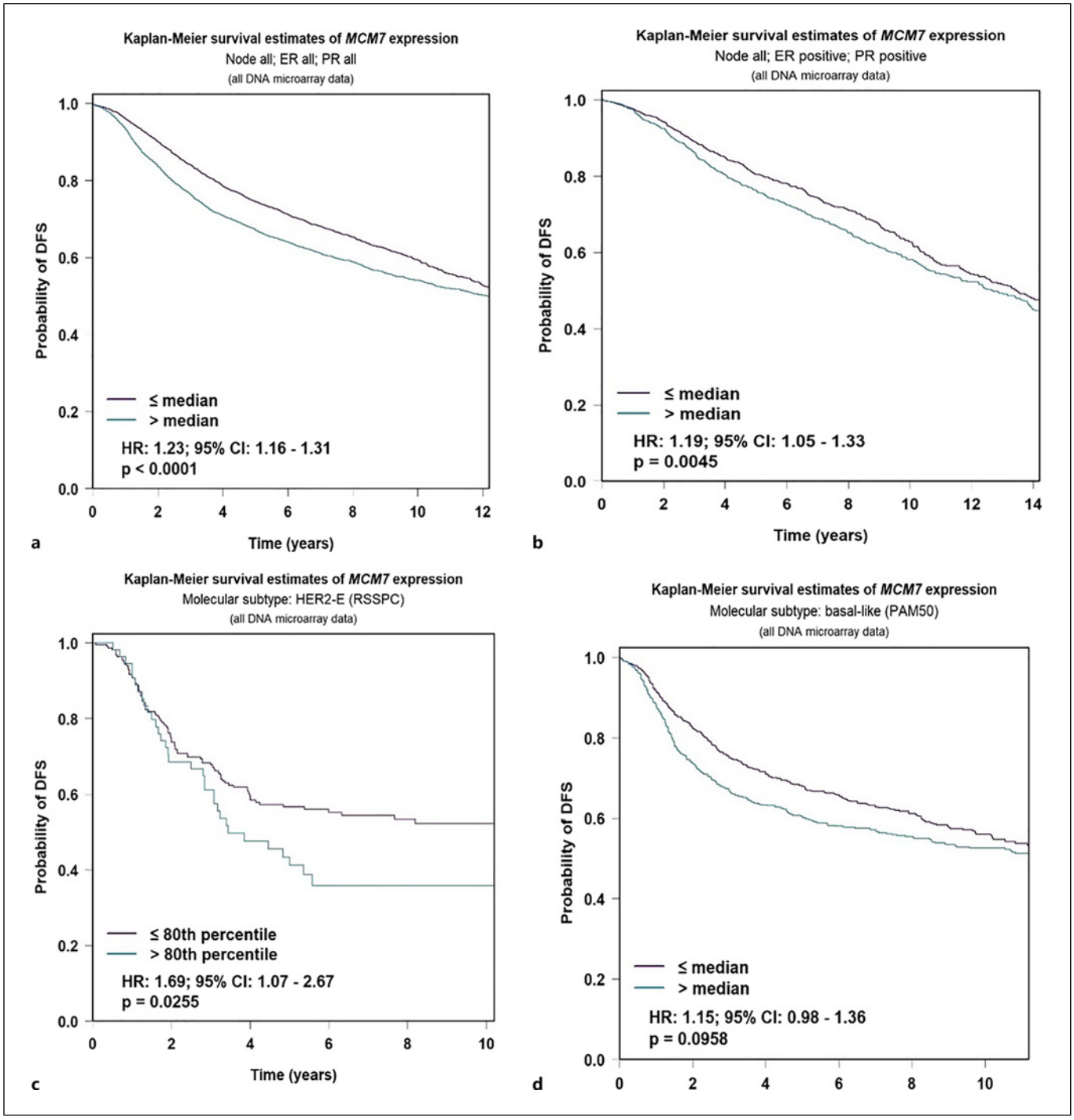

Fig. 4. Kaplan-Meier plots showing a significant association between high *MCM7* mRNA levels and poor outcome in the whole Gen-Ex-Miner cohort (**a**), ER+BC (**b**), and HER2-enriched BC (**c**). **d** No significant association in terms of basal-like BC.

which represents the degree of tumour proliferation. The function of MCM7 is related to cell proliferation, and the proteins are found only in dividing cells [28]. We found that high nuclear MCM7 expression showed a significant association with short survival in BC. Similarly, high MCM7 expression has previously been associated with

worse overall survival in several cancers including HCC [7], lung [29], bladder [30], and prostate [5]. In BC, MCM7 transcripts in BC were upregulated and significantly related to shorter survival [31], and this was consistent with our findings at the mRNA level. The poor prognostic role of MCM7 could be explained by the knockdown of MCM7, leading to inhibition of cellular proliferation in vitro and in vivo via suppression of cyclin D1 expression [26]. MCM7 gene was also included in prognostic gene expression signatures in some tumours including urothelial [32] and HCC [33]. This suggests that MCM7 might be a potential therapeutic target for cancer treatment. Based on this, many MCM7-targeted drugs have been developed [34]. In addition, overexpression of MCM7 in cancer cells may relate to some tumour-specific functions, including growth regulation [35]. We found that high MCM7 expression was associated with endocrine resistance in luminal BC patients. Interestingly, MCM7 and its family are top candidate genes responsible for endocrine-resistant development, and recent evidence suggests that blocking the expression of the genes can inhibit the growth of tamoxifen-resistant cancer cells [36]. Strong positive linear correlation was found in our research between MCM7 and Ki67, the most commonly used marker to assess cellular proliferation in BC [37]. Opposite to MCM7, Ki67 expression is observed in all phases of cell cycle [38]. The present study also showed that MCM7 had similar prognostic and predictive values to Ki67. Similarly, Padmanabhan and colleagues found a similar correlation in prostatic cancer and, with head-to-head comparison, MCM7 was a better discriminatory marker of proliferation between benign epithelium, prostatic intraepithelial neoplasia, and invasive adenocarcinoma than Ki67 [5]. This confirms that MCM7 plays an important role in the proliferation of BC cells [39]. These findings suggest that MCM7 can be used as valid proliferation marker in clinical practice.

Conclusion

The current findings suggest that MCM7 expression may be a useful predictor in patients with early-stage BC. Anti-MCM7 drugs could be valuable therapeutic strategy for MCM7-positive BC patients.

Statement of Ethics

This study was approved by the Yorkshire and the Humber – Leeds East Research Ethics Committee (REC Reference: 19/YH/0293) under the IRAS Project ID: 266925. Written informed consent was obtained from participants. The collected data were fully anonymised.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Funding Sources

No funding was received for this study.

Author Contributions

A.G.L. scored the cases and wrote the manuscript draft, data analysis, and interpretation. M.S.T. helped in double scoring. A.G.L., M.S.T., N.P.M., A.R.G., and C.S.R. agreed with the manuscript results and conclusions and critically reviewed the article. E. Rakha conceived and planned the study, contributed to data interpretation, made critical revisions, and approved the final version.

Data Availability Statement

Data supporting the study can be found in the Supplementary Materials File, and the corresponding author can make any materials available upon request.

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