REVIEW ARTICLE
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Effects of clinical heterogeneity on Pregnancy-Associated Breast Cancer survival: a systematic review with meta-analysis

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ABSTRACT

Pregnancy-associated breast cancer is defined as a diagnosis of breast cancer during pregnancy or within 1 year of childbirth. Current evidence shows that Pregnancy-associated breast cancer is associated with poor prognosis; however, no systematic review has summarized and explored how baseline characteristics could impact survival. We aimed to explore the impact of breast cancer characteristics on death and disease relapse. A systematic review with meta-analyses was conducted by searching articles in the main databases (Medline, Embase, and Cochrane) and congress abstracts. Summarized death and disease-free survival hazard ratios were recalculated, and all meta-analyses used a random-effects model. Heterogeneity was reported using the I^2 method. A total of 7143 studies were identified and only 30 studies were included. Pregnancy-associated breast cancer is associated with a 96% (HR 1.96; 95%CI 1.58–2.35) higher risk of death and 82% (HR 1.82; 95%CI 1.45–2.20) risk of death or disease relapse in comparison to a population of non-pregnancy-associated breast cancer or nulliparous breast cancer. Through sensitivity analyses, we identified that clinical outcomes were impacted, possibly due to Ki-67 levels, poorly differentiated tumors, and triple-negative breast cancer frequency in the study. As relevant sources of inconsistencies, such clinical cancer-related characteristics should be better investigated as potential confounders for upcoming Pregnancy-associated breast cancer therapeutic strategies.

KEYWORDS: breast; cancer; pregnancy; breast neoplasm; systematic review.

INTRODUCTION

Pregnancy-associated breast cancer (PABC) is a rare type of cancer diagnosed during pregnancy or 1 year following delivery, impacting women of fertile age (23–47 years)[1].

Diagnosed in advanced stages[2-4], PABC is currently associated with the use of less aggressive treatments to address more safety to both mother and fetus[5]. However, poor prognosis persists even after adjustment for several clinicopathological factors, including age at diagnosis, year of diagnosis, stage, tumor grade, and hormone receptor status[6].

Previous systematic reviews attempted to review and pool the risk of death in PABC. Recently, Shao et al.[7] described that PABC patients had 45% more risk of death and a 39% chance of death or relapse compared to a non-PABC control. As an opportunity, we understood that this review did not explore how heterogeneity could affect their results. That is, we believe that by deepening how inconsistency (represented by I^2 in meta-analyses) affects outcomes, baseline differences in the study population could inform better if there is any subgroup of patients who could have a higher risk of disease relapse or death. In addition to those clinical characteristics, heterogeneity might be related to inclusion criteria, available data, and analyses performed. That said, through this review, we question if all PABC patients have the same survival and disease relapse rates and pool the effects of baseline characteristics on outcomes through meta-analyses.

Therefore, this systematic review with a meta-analytic approach focuses on closing this literature gap and explores

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the impact of heterogeneity on different risks of death and disease relapse, suggesting that clinical characteristics should be explored in further studies in order to improve clinical outcomes of patients with PABC.

METHODS

Protocol registration and rationale of review

Our review adheres to the PRISMA statement, and its protocol was registered at PROSPERO/University of York, and it can be accessed online (https://www.crd.york.ac.uk/prospero/ with protocol number: CRD42021272859).

The strategy for manuscript finding included the use of indexed keywords, such as: "pregnant*" OR "gestation*" OR "childbirth" OR "postpartum" OR "parity" AND "breast" AND "cancer" OR "neoplasia" OR "carcinoma."

In this review, we searched studies that could fulfill the following research question: Which clinical characteristics in PABC are associated with best/worst overall survival (OS) and disease-free survival (DFS) when compared with a population without PABC?

Data sources and searches

We reviewed four formal databases: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Lilacs. Other relevant databases were also studied:

1. The San Antonio Breast Cancer Symposium,
2. American Society of Clinical Oncology (ASCO) abstracts,
3. European Society for Medical Oncology (ESMO) abstracts, and
4. USP Digital Library of Theses and Dissertations.

Searches included published manuscripts from 2000 to August 30, 2021. No language restrictions limited our search strategy. For definition purposes, PABC was considered "the diagnosis of BC in women during pregnancy, or until 1 year of post-partum."

Eligibility criteria included

1. studies with a follow-up period longer than 6 months;
2. participants who were diagnosed with any TNM type of BC;
3. studies that had two groups comparing PABC versus non-PABC or nulliparous BC patients;
4. studies that contained information on OS and/or DFS; and
5. the risk point estimate was reported as a hazard ratio (HR) with 95%CI, or the data were presented such that an HR with 95%CI could be calculated.

Study selection and data extraction

Selection by title and abstract reading, inclusion by full-text reading, and data extraction were performed by two independent reviewers. In case of discrepancies between the two, a third reviewer was invited to make decision.

The following data were extracted:

1. general study information (country that the research was developed, PABC and non-PABC definition, and matching criteria);
2. PABC characteristics (age, stage, histologic grade, TNM, hormonal receptors, and HER2 status);
3. PABC treatment (chemotherapy, hormone therapy, radiotherapy, and type of surgery such as axillary lymph node dissection, breast-conserving surgery, sentinel lymph node dissection, and mastectomy); and
4. outcomes (OS and DFS).

Data synthesis and analysis

We performed a descriptive assessment of the included manuscripts by summarizing them in tables containing their clinical characteristics. Outcomes were meta-analyzed to determine the pooled HR of OS and DFS. To facilitate the interpretation of the results, OS and DFS were modified, so one would interpret them as deaths/mortality and disease relapse or death, respectively. Meta-analyses were conducted considering random-effects models and estimates were reported with their respective 95%CI. Heterogeneity was measured based on the I^2 method, where values >30% were considered heterogeneous. In the case of heterogeneity, sensitivity analyses were conducted by removing the outlier study. For these analyses, we used R-Studio (***meta*** and ***metaphor*** packages)[8] to summarize the occurrence of these events.

RESULTS

A total of 7143 studies were identified, of which 142 titles were screened and compatible with our preestablished inclusion criteria. During the eligibility phase (full-text reading), 30 studies[5,9-37] were included for completed text reading and 23 for meta-analysis (Figure 1). Overall, this systematic review comprised 4406 PABC and 130,860 non-PABC patients.

Pregnancy-associated breast cancer characteristics

Most of the included 30 studies were performed in the USA (20%), France (13.3%), and Korea (10%), among other nationalities: Taiwan, Spain, and Saudi Arabia (6.7%) and Belgium, Brazil, Canada, China, Czech Republic, Greece, Hungary, Israel, Italy, Mexico, and Pakistan (3.3% each). PABC population was commonly matched with non-PABC by age, stage, and year of diagnosis.

PABC patients had an average age of 34.4 years (range: 20–49), with tumors predominantly on stage II (41%) and histological grade 3 (30%) (Table 1). In the TNM classification, T2 (24%) and N0 (13%) were the most reported, and only 3% of the tumors were initially metastatic diseases. Most studies (54%) reported positive hormone receptors; while HER2 status (13%) and subtype of BC, such as TNBC (6%), were not commonly described.

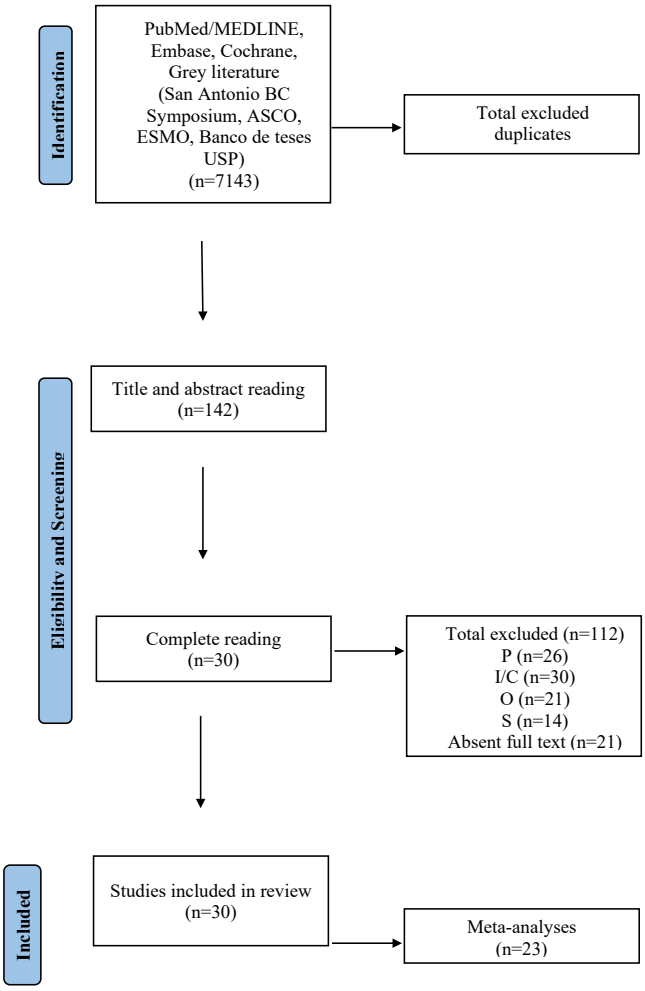

Figure 1. Flowchart of manuscript selection.

When described, 57% (±18%) of patients were hormone positive, 22% (±8%) were HER2+, and 32% (±7%) were TNBC subtype.

Exploring treatment options (Table 2), 72% of the PABC population received chemotherapy, of which only 10% underwent neoadjuvant/adjuvant schemes during pregnancy. Regarding surgical approach, 39% of patients received a mastectomy, 21% had breast-conservative surgery, 18% performed axillary lymph node dissection, and 11% had sentinel lymph node dissection.

Deaths

Overall, 21 studies involving 3383 PABC and 100966 non-PABC patients were included for meta-analysis. PABC patients were associated with a 96% higher risk of death (HR 1.96, 95%CI 1.58–2.35) in comparison to the non-PABC population (Figure 2a). The heterogeneity for this meta-analysis was considered high (I^2=95%).

Through sensitivity analysis (Figure 2b), when studies by *Madaras et al.* and *Mathelin et al.* were removed and a new pooled HR was calculated (HR 1.39, 95%CI 1.21–1.56), heterogeneity dropped down by 22% (I^2 was 95% before sensitivity analysis and 73% after sensitivity analysis). PABC-related death decreased by 56% in comparison to non-PABC. This suggests that studies by Madaras et al. and Mathelin et al. could be considered important sources of heterogeneity that increased the risk of PABC-associated deaths. Finally, through funnel plot analysis, it could be seen that there was publication bias (p=0.03) (Figure 2c).

Disease relapse or death

A total of 986 PABC and 3267 non-PABC patients enrolled in 11 studies were considered for DFS analysis. PABC patients have an 82% (HR 1.82, 95%CI 1.45–2.20) increased risk of death or disease relapse. Heterogeneity for this meta-analysis was also considered high (81%) (Figure 3a).

In sensitivity analysis (Figure 3b), by removing studies by *Siegelmann-danieli et al.* and *Mathelin et al.*, the heterogeneity was reduced by 30%, lowering the risk of disease relapse or death by 29% (pooled HR in sensitivity analysis=1.53, 95%CI 1.29–1.77). There was publication bias for this analysis (p<0.001) (Figure 3c).

DISCUSSION

In these recent meta-analyses about BC and pregnancy, we could identify that PABC, compared to the non-PABC population, has the worst prognosis in observational studies. PABC is associated with a 96% higher risk of death and an additional 82% risk of death or disease relapse in comparison to a population of non-PABC or nulliparous BC.

In addition, the present meta-analysis identified that studies by Madaras et al.[26], Mathelin et al.[27], and Sigelmann-Danielli et al.[35] were essential sources of heterogeneity for mortality and disease relapse outcomes.

Removing studies by Madaras et al. and Mathelin et al. from OS meta-analysis reduced heterogeneity by 22% and PABC-related mortality by 56%. In the meta-analysis of DFS, extracting studies by Sigelmann-Danielli et al. and Mathelin et al. improved heterogeneity by about 30% and minimized PABC-related relapse or death by 29%.

When PABC characteristics from the study by Madaras et al. are explored, it could be seen that all patients had Ki67 levels ≥14%, 84% were considered high histological grade, and almost half were classified as subtype triple negative. All these characteristics are considered predictors of poorer prognosis. Recently, Zhu et al. suggested that in a TNBC population, Ki67 levels were independent predictors of death[38]; however, they identified that the optimal cutoff score for predicting survival was 30% and the population was not specifically for PABC. On the other hand, Madaras et al. provided a lower cutoff point, suggesting that the most recent study by Zhu et al.[38] might provide relevant insights on clinical characteristics that might impact mortality in patients with BC, and possibly also in PABC. However, we found no study about the impact of different Ki67 levels was conducted in the PABC population.

Table 1. Pregnancy-associated breast cancer tumor characteristics

Author, year	Age (range)	Stage n (%)					Grade n (%)			T n (%)					N n (%)				M n (%)	HR n (%)	HER2 n (%)	TNBC n (%)
		0	I	II	III	IV	1	2	3	0	1	2	3	4	0	1	2	3				
Ali et al.[9]	33 (24–42)	NR	5 (12.5)	27 (67.5)	6 (15)	2 (5)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	22 (55)	NR	NR
Amant et al.[10]	33 (31–36)	NR	48 (15.4)	177 (56.9)	86 (27.6)	NR	7 (2.2)	67 (21.5)	237 (76.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	145 (46.6)	99 (31.8)	118 (37.9)
Aziz et al.[11]	32 (20–45)	NR	NR	NR	NR	NR	NR	NR	NR	NR	5 (20.8)	8 (33.3)	11 (45.8)	NR	NR	NR	NR	16 (66.6)	NR	NR	NR	
Bae et al.[12]	20–49	16 (3.9)	92 (22.3)	186 (45.2)	85 (20.7)	23 (5.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	272 (66.1)	91 (22.1)	NR
Baulies et al.[13]	35.3 (30.6–40)	NR	33 (58.9)	15 (26.8)	8 (14.2)	26 (46.4)	9 (16)	NR	22 (39.2)	14 (25)	5 (8.9)	7 (12.5)	NR	NR	NR	NR	NR	46 (82.1)	10 (17.8)	NR		
Beadle et al.[14]	33 (16–35)	NR	9 (8.6)	40 (68.4)	54 (51.9)	NR	2 (1.9)	32 (30.8)	62 (59.6)	NR	20 (19.2)	40 (38.4)	28 (26.9)	15 (14.4)	31 (29.8)	30 (28.8)	31 (29.8)	12 (11.5)	NR	66 (63.4)	NR	NR
Boudy et al.[15]	35 (30.5–39)	NR	NR	NR	NR	NR	1 (2)	20 (40.8)	27 (55.1)	1 (2)	20 (40.8)	13 (26.5)	8 (16.3)	7 (14.2)	NR	29 (59.1)	5 (10.2)	30 (61.2)	6 (12.2)	NR		
Choi et al.[16]	<35–≥35	NR	NR	NR	NR	NR	NR	NR	NR	1 (1.6)	21 (33.3)	25 (39.7)	11 (17.4)	5 (7.9)	29 (46)	16 (25.4)	11 (17.4)	7 (11.1)	2 (3.1)	53 (84.1)	13 (20.6)	NR
Chuang et al.[17a]	20–50	NR	24 (26.7)	51 (56.7)	15 (16.6)	NR	8 (8.9)	37 (41.1)	37 (41.1)	NR	26 (28.9)	44 (48.9)	19 (21.1)	NR	45 (50)	19 (21.1)	12 (13.3)	8 (8.9)	NR	64 (71.1)	12 (13.3)	NR
Chuang et al.[17b]	20–50	NR	86 (24.8)	197 (56.8)	64 (18.4)	NR	20 (5.8)	146 (42)	142 (40.9)	NR	127 (36.6)	145 (41.8)	64 (18.4)	NR	160 (46.1)	83 (23.9)	44 (12.7)	29 (8.3)	NR	245 (70.6)	31 (8.9)	NR
Dimitrakakis et al.[18]	34.3 (29.3–39.3)	NR	1 (2.6)	20 (51.3)	15 (38.5)	3 (7.7)	1 (2.6)	3 (7.7)	34 (87.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	33 (84.6)	NR	NR
Framarino--dei-Malatesta et al.[19]	37.2 (34–40.2)	NR	NR	NR	NR	NR	NR	10 (45.4)	11 (50)	NR	10 (45.4)	7 (31.8)	5 (22.7)	NR	11 (50)	8 (26.4)	3 (14.6)	NR	NR	12 (54.5)	NR	NR
Genin et al.[20]	35 (27–40)	NR	NR	NR	NR	NR	6 (6.9)	27 (31)	32 (36.8)	6 (6.9)	20 (23)	29 (33.3)	27 (31)	NR	31 (35.6)	5 (5.7)	42 (48.2)	17 (19.5)	NR			
Halaska et al.[21]	33.7 (25.9–41.6)	NR	NR	NR	NR	NR	2 (6.2)	15 (46.9)	15 (46.9)	NR	6 (18.7)	26 (81.3)	NR	18 (56.2)	6 (18.7)	22 (68.7)	10 (31.2)	NR				
Ibrahim et al.[22]	34 (28.9–39.1)	NR	2 (2.8)	22 (30.5)	29 (40.3)	19 (26.4)	0 (0)	23 (39.6)	35 (60.4)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iqbal et al.[23]	40 (20–44)	NR	111 (22.1)	237 (47.3)	128 (25.5)	25 (5)	NR	NR	NR	NR	79 (15.8)	127 (25.3)	42 (8.4)	NR	NR	124 (24.7)	NR	255 (50.9)	NR	NR		
Kim et al.[24]	33.7 (29.4–38)	13 (3.8)	62 (18)	154 (44.8)	95 (27.6)	20 (5.8)	10 (2.9)	94 (27.3)	170 (49.4)	13 (3.8)	83 (24.1)	155 (45)	66 (19.1)	25 (7.3)	165 (48)	97 (28.2)	45 (13)	31 (9)	NR	136 (39.5)	69 (20)	NR
Litton et al.[25]	24–45	NR	5 (6.7)	36 (48)	34 (45.3)	NR	0 (0)	12 (16)	63 (84)	NR	NR	NR	NR	NR	NR	NR	NR	NR	25 (33.3)	29 (38.7)	16 (21.3)	24 (32)

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Table 1. Continuation

Author, year	Age (range)	Stage n (%)					Grade n (%)			T n (%)					N n (%)				M n (%)	HR n (%)	HER2 n (%)	TNBC n (%)
		0	I	II	III	IV	1	2	3	0	1	2	3	4	0	1	2	3				
Madaras et al.[26]	34 (28–42)	NR	NR	NR	NR	NR	0 (0)	5 (16.1)	26 (83.9)	2 (6.4)	11 (35.5)	13 (41.9)	5 (16.1)	10 (32.2)	10 (32.2)	6 (19.3)	4 (12.9)	NR	NR	17 (54.8)	6 (19.3)	NR
Mathelin et al.[27a]	33.8 (28.4–39.2)	NR	NR	NR	NR	NR	2 (11)	2 (11)	13 (72)	NR	NR	NR	NR	NR	NR	7 (39)	2 (11)	7 (39)	13 (72)	NR	NR	
Mathelin et al.[27b]	33.3 (29.4–37.2)	NR	NR	NR	NR	NR	5 (23)	7 (32)	9 (41)	NR	NR	NR	NR	NR	NR	5 (23)	4 (18)	15 (68)	19 (86)	NR	NR	
Moreira et al.[28]	35 (31–39)	NR	NR	NR	NR	NR	20 (23)	22 (25.2)	NR	25 (28.8)	61 (70.1)	NR	78 (89.6)	29 (33.3)	39 (44.8)	NR	NR					
Muñoz-Montaño et al.[29a]	35 (21–44)	NR	25 (40.3)	30 (48.4)	7 (11.3)	5 (8)	23 (37)	34 (54.8)	NR	29 (46.8)	33 (53.2)	12 (19.4)	50 (80.6)	NR	31 (50)	14 (22.6)	17 (27.4)					
Muñoz-Montaño et al.[29b]	35 (23–47)	NR	13 (20.6)	31 (49.2)	19 (30.2)	5 (7.9)	19 (30.2)	39 (61.9)	NR	21 (33.3)	42 (66.7)	6 (9.5)	57 (90.6)	NR	20 (31.7)	19 (30.1)	24 (38.1)					
Murphy et al.[30]	NR	NR	NR	NR	NR	NR	2 (2)	11 (11.1)	83 (83.8)	40 (40.4)	48 (48.5)	10 (10.1)	0 (0)	40 (40.4)	29 (29.3)	19 (19.2)	11 (11.1)	NR	65 (65.6)	20 (20.2)	NR	
O'Sullivan et al.[31a]	34.5 (29.5–39.5)	3 (4.6)	10 (15.4)	26 (40)	14 (21.5)	7 (10.8)	1 (1.5)	14 (21.5)	49 (75.4)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	29 (44.6)	13 (20)	NR
O'Sulliva et al.[31b]	34.7 (30.9–38.5)	3 (4)	11 (14.7)	25 (33.3)	16 (21.3)	20 (26.7)	2 (2.7)	11 (14.7)	57 (76)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	42 (56)	19 (25.3)	NR
Ploquin et al.[32]	33 (24–42)	NR	NR	NR	NR	NR	2 (1.8)	29 (26.1)	74 (66.7)	22 (19.8)	46 (41.4)	31 (27.9)	8 (7.2)	59 (53.1)	46 (41.4)	NR	56 (50.4)	24 (21.6)	45 (40.5)			
Reyes et al.[33]	37 (34–39)	NR	7 (16.7)	21 (50)	7 (16.7)	7 (16.7)	1 (2.4)	16 (38.1)	21 (50)	NR	12 (28.6)	16 (38.1)	5 (11.9)	7 (16.7)	21 (50)	14 (33.3)	3 (7.1)	4 (9.5)	7 (16.7)	26 (61.9)	11 (26.2)	9 (21.4)
Rodriguez et al.[34]	20–55	NR	139 (17.4)	415 (52)	130 (16.3)	39 (4.9)	NR	NR	NR	NR	235 (29.5)	332 (41.6)	127 (15.9)	27 (3.4)	NR	NR	NR	NR	NR	455 (57.1)	NR	NR
Siegelmann-Danieli et al.[35]	33 (25–37)	1 (4.3)	15 (65.2)	7 (30.4)	NR	NR	19 (82.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	2 (8.7)	9 (52.9)	NR	NR		
Strasser-Weippl et al.[36]	20–49	11 (10.1)	52 (47.7)	11 (10.1)	2 (1.8)	22 (20.2)	10 (9.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	29 (26.6)	12 (11)	NR	
Suleman et al.[5]	34 (20–45)	NR	42 (38.2)	68 (61.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	15 (13.6)	41 (37.2)	29 (26.3)		
Yang et al.[37a]	34 (25–41)	0 (0)	2 (13.3)	8 (53.3)	3 (20)	2 (13.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	6 (40)	NR	14 (93.3)	6 (40)	NR		
Yang et al.[37b]	34 (25–41)	0 (0)	3 (27.2)	7 (63.6)	1 (0.9)	0 (0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	5 (45.4)	NR	11 (100)	4 (36.3)	NR		

HR: hormonal receptors (estrogen and progesterone); NR: not reported; TNBC: triple-negative breast cancer. [a]Patients diagnosed with PABC during the pregnancy; [b]Patients diagnosed with PABC until 1 year post-delivery.

Table 2. Pregnancy-associated breast cancer treatment characteristics.

Author, year	Chemotherapy n (%)	Chemotherapy during pregnancy n (%)	Hormone therapy n (%)	Radiotherapy n (%)	BCS n (%)	ALND n (%)	SLND n (%)	Mastectomy n (%)
Ali et al. [9]	NR	36 (90)	NR	32 (80)	3 (7.5)	30 (75)	2 (5)	3 (7.5)
Amant et al.[10]	307 (98.7)	200 (64.3)	117 (37.6)	205 (65.9)	140 (45)	NR	NR	147 (47.3)
Azizet et al[11]	21 (87.5)	NR	18 (75)	5 (20.8)	NR	NR	NR	NR
Bae et al.[12]	345 (83.9)	NR	NR	230 (56)	193 (47)	235 (57.2)	145 (35.2)	199 (48.4)
Baulies et al.[13]	42 (75)	7 (16.7)	NR	28 (50)	9 (16.1)	33 (58.9)	NR	34 (60.7)
Beadle et al.[14]	97 (93.3)	NR	29 (27.9)	NR	26 (25)	NR	NR	30 (28.8)
Boudy et al.[15]	49 (100)	49 (100)	29 (59.2)	41 (83.7)	26 (53)	36 (73.5)	13 (26.5)	22 (44.9)
Choi et al.[16]	NR	NR	NR	NR	NR	NR	NR	NR
Chuang et al.[17a]	67 (74.4)	11 (12.2)	45 (50)	42 (46.7)	31 (34.4)	NR	NR	52 (57.8)
Chuang et al.[17b]	283 (81.5)	NR	183 (52.7)	177 (51)	141 (40.6)	NR	NR	181 (52.2)
Dimitrakakis et al.[18]	39 (100)	NR	10 (25.6)	15 (38.5)	NR	NR	NR	NR
Framarino-dei-Malatesta et al.[19]	20 (90.9)	9 (40.9)	NR	NR	12 (54.5)	NR	12 (54.5)	10 (45.4)
Genin et al.[20]	63 (72.4)	NR	36 (41.4)	76 (87.3)	36 (41.4)	4 (4.6)	79 (90.8)	48 (55.2)
Halaska et al.[21]	31 (96.9)	NR	6 (18.7)	15 (46.9)	9 (28.1)	25 (78.1)	4 (12.5)	20 (62.5)
Ibrahim et al.[22]	52 (72.2)	NR	NR	NR	NR	NR	NR	NR
Iqbal et al.[23]	423 (84.4)	NR	NR	366 (73)	NR	NR	NR	NR
Kim et al.[24]	289 (84)	NR	123 (35.7)	178 (51.7)	144 (41.9)	276 (80.2)	41 (11.9)	180 (52.3)
Litton et al.[25]	44 (58.7)	NR	19 (25.3)	49 (65.3)	16 (21.3)	29 (38.7)	42 (56)	54 (72)
Madaras et al.[26]	24 (77.4)	NR	12 (38.7)	22 (71)	10 (32.2)	26 (83.9)	4 (12.9)	19 (61.3)
Mathelin et al.[27a]	NR	16 (89)	8 (44)	15 (83)	9 (50)	17 (94)	NR	9 (50)
Mathelin et al.[27b]	17 (94)	NR	10 (45)	16 (73)	7 (32)	22 (100)	NR	15 (68)
Moreira et al.[28]	NR	NR	NR	NR	NR	NR	NR	NR
Muñoz-Montaño et al.[29a]	NR	58 (93.5)	3 (4.8)	NR	NR	NR	NR	NR
Muñoz-Montaño et al.[29b]	63 (100)	NR	0 (0)	NR	NR	NR	NR	NR
Murphy et al.[30]	96 (97)	36 (36.4)	62 (62.6)	49 (49.5)	25 (25.2)	NR	NR	74 (74.7)
O'Sullivan et al.[31a]	40 (80)	NR	14 (28)	28 (56)	16 (32)	32 (64)	8 (16)	33 (66)
O'Sulliva et al.[31b]	40 (76.9)	NR	21 (40.4)	30 (57.7)	17 (32.7)	32 (61.5)	14 (26.9)	32 (61.5)
Ploquin et al.[32]	108 (97.2)	54 (48.6)	49 (44.1)	106 (95.5)	47 (43.1)	10 (9.5)	104 (99)	62 (56.9)
Reyes et al.[33]	22 (52.4)	NR	NR	NR	NR	NR	NR	NR
Rodriguez et al.[34]	556 (69.8)	NR	NR	310 (38.9)	NR	NR	NR	482 (60.5)
Siegelmann-danieli et al.[35]	23 (100)	NR	NR	NR	11 (47.8)	NR	NR	10 (43.5)
Strasser-Weippl et al.[36]	NR	NR	NR	NR	NR	NR	NR	NR
Suleman et al.[5]	NR	NR	NR	NR	NR	NR	NR	NR
Yang et al.[37a]	NR	5 (33.3)	NR	NR	NR	4 (26.7)	NR	10 (66.7)
Yang et al.[37b]	0 (0)	NR	NR	NR	NR	7 (63.6)	NR	4 (36.4)

ALND: axillary lymph node dissection; BCS: breast-conserving surgery; NR: not reported; SLND: sentinel lymph node dissection. [a]Patients diagnosed with Pregnancy-associated breast cancer during the pregnancy. [b]Patients diagnosed with PABC until 1 year post-delivery.

Importantly, Mathelin et al. reported the highest differences in survival in 5- (p=0.034) and 10-year (p=0.0001) follow-up, when comparing BC versus PABC. Differences in PABC and non-PABC populations might have impacted survival, such as low positive levels of estrogen (p=0.038) and progesterone (p=0.008) receptors between groups. In addition, threefold more patients with distant metastasis were included in the PABC group, compared to the control (p=0.0247). Such unbalanced groups not only depict that such clinical characteristics are important sources of clinical heterogeneity but also evidence that such PABC subgroups have the worst outcomes.

In sensitivity analysis, we also removed the study by Siegelmann-danieli et al. In their publication, the worst outcomes were closely

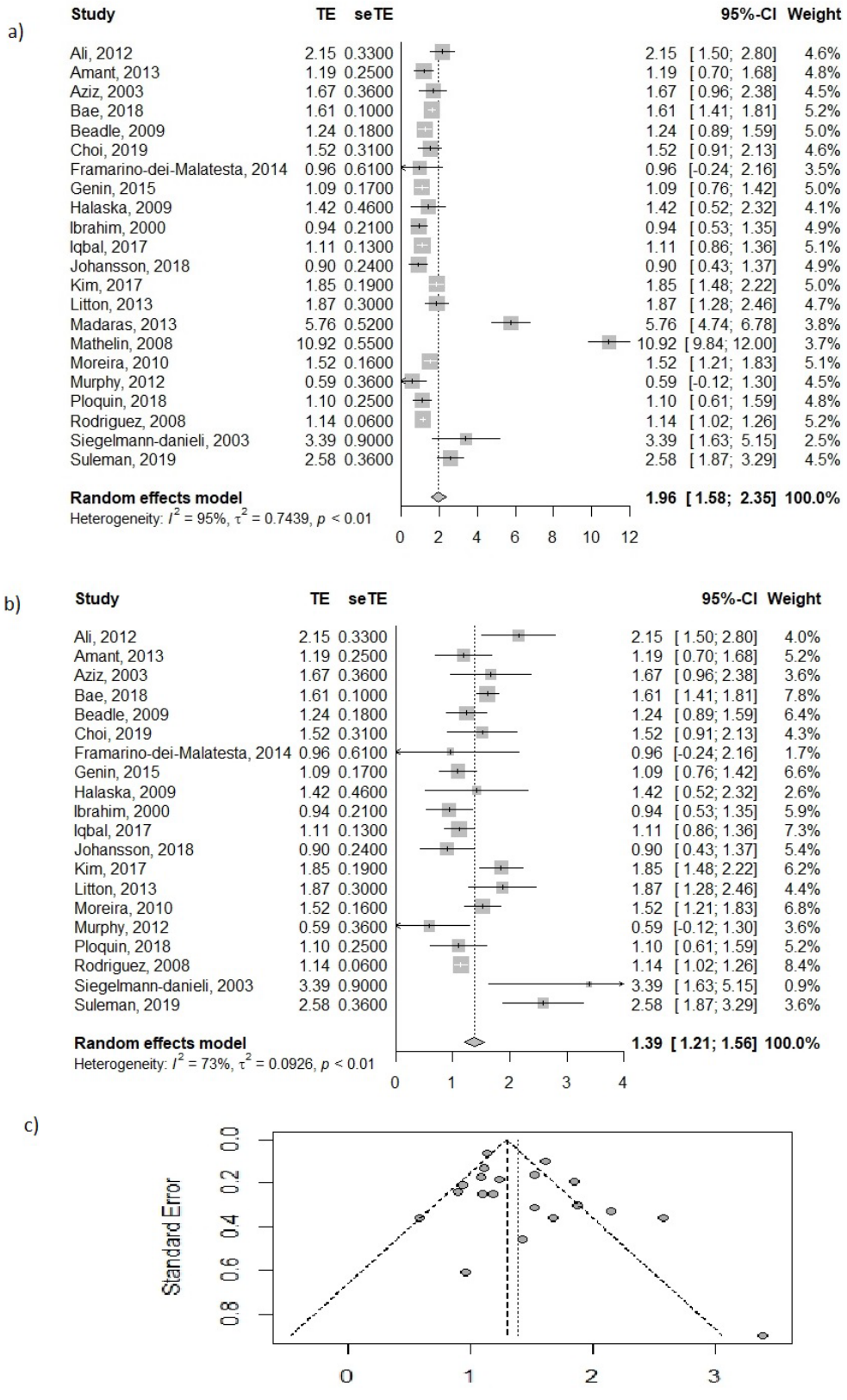

Figure 2. Pregnancy-associated breast cancer deaths compared to non-Pregnancy-associated breast cancer population. **(A)** A meta-analysis of Pregnancy-associated breast cancer vs. non-Pregnancy-associated breast cancer deaths, represented as hazard ratio; **(B)** sensitivity analysis for Pregnancy-associated breast cancer death, removing two outliers; and **(C)** funnel plot of Pregnancy-associated breast cancer death.

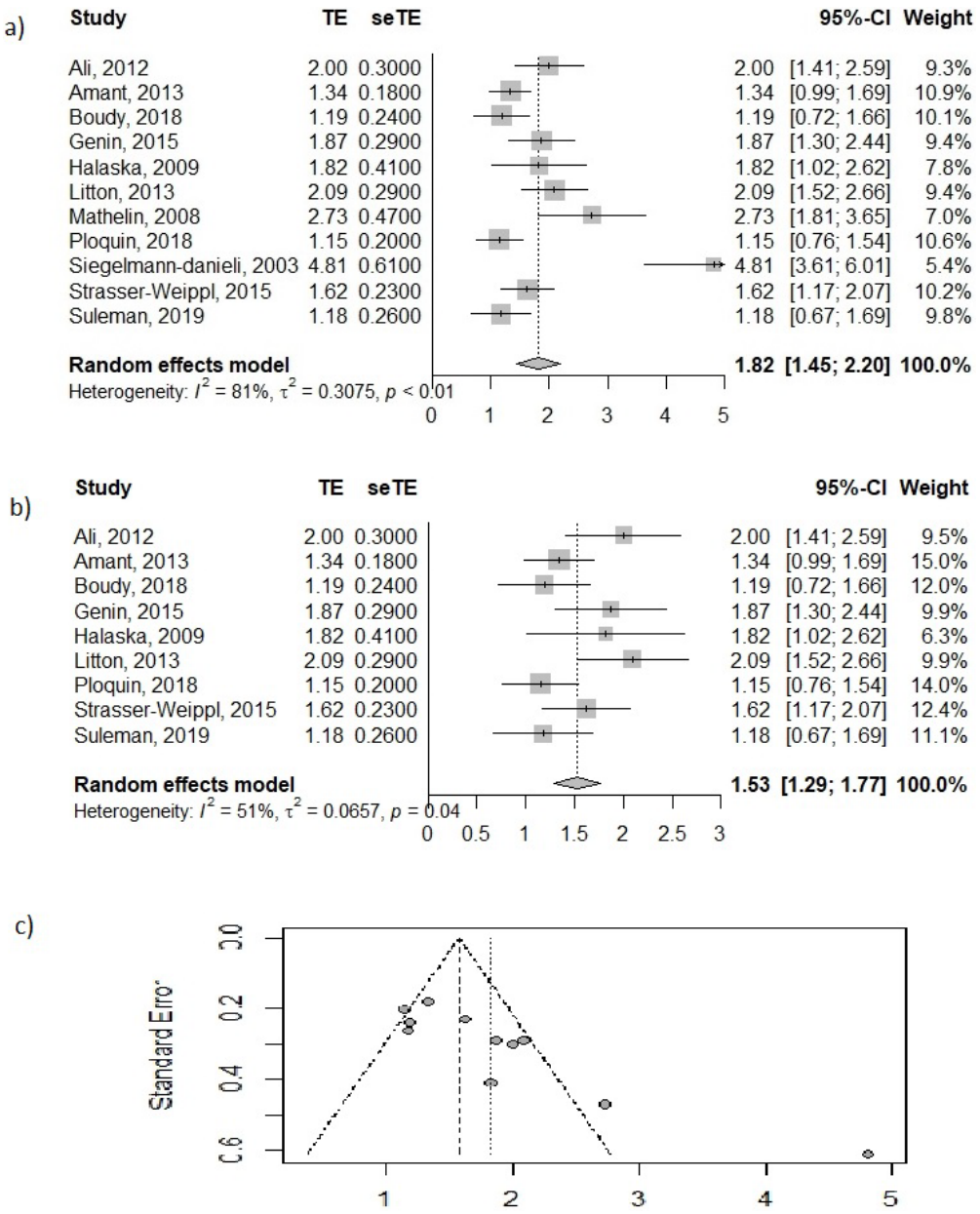

Figure 3. Pregnancy-associated breast cancer deaths or disease relapse compared to non-Pregnancy-associated breast cancer population. **(A)** A meta-analysis of Pregnancy-associated breast cancer vs. non-Pregnancy-associated breast cancer deaths or disease relapse, represented as hazard ratio; **(B)** sensitivity analysis for Pregnancy-associated breast cancer deaths or disease relapse, removing two outliers; and **(C)** funnel plot of Pregnancy-associated breast cancer deaths or disease relapse.

related to tumor staging. It is widely known that advanced disease is associated with higher mortality. Nevertheless, subtypes of BC, such as advanced triple-negative tumors were associated with 2–3 times more risk of mortality (p<0001) when compared to a cohort of non-triple-negative patients, as demonstrated by Saadatmand et al.[39].

Finally, considering the three studies removed for sensitivity analyses[26,27,35], another common feature between them was the high proportion (~70%) of patients with poorly undifferentiated tumors (grade 3 histological classification). As reported before, Rakha et al. showed that such histological subtypes are associated with 20% less chance of survival, in comparison to grade 1 and 2 diseases (chance of survival: 57.6, 61.4, and 81%, respectively, for grade 3, 2, and 1 histological subtypes)[40]. Poorly differentiated tumors are an independent prognostic factor, particularly in triple-negative molecular subtypes[41,42]. As a fact, besides the phenotypic expression of BC, nowadays, the poor prognosis can be attributed to a set of "poor prognostic genes," which include BRCA mutations (BRCAm), for example[43]. Unfortunately, none of the studies included the description of poor prognostic genes

for BC, suggesting that there might be unexplored subgroups of patients who might benefit from different treatment approaches, as nowadays, BRCAm BC might have a better prognosis if treated with recently approved drugs[44] addressed in future research.

Though this review adhered to PRISMA statement standards, it is not absent limitations. For example, as a systematic review with a meta-analytic approach, the study did not analyze patient-level data, which means that the relation between Ki67 and PABC outcomes requires further research specifically addressed for this hypothesis. On the other hand, this review quantitatively addressed this literature gap and might be useful for future studies.

CONCLUSIONS

PABC is correlated with a poorer prognosis, such as a 96% higher chance of dying and an 82% higher risk of disease relapse or death, compared to the non-PABC population. Through sensitivity analyses, we identified that clinical outcomes were impacted, possibly due to Ki67 levels, poorly differentiated tumors, and TNBC. No study addressed genetics profiling, such as BRCAm status, suggesting that besides early diagnosis, these clinical and genetic characteristics might be relevant sources of inconsistency. That is, such clinical sources of heterogeneity should be better investigated regarding the potential to evaluate alternative therapeutic strategies. Finally, further research could benefit from exploring the effect of the homologous recombination deficiency repair pathway on the survival of PABC patients, as it was poorly studied so far.

AUTHORS' CONTRIBUTIONS

MA: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing. TTB: Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. JMR: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RGCL: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. OF: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AM: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LMO: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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