# Factors Predicting Survival Outcomes in Pregnancy-Associated Breast Cancer; A Systematic Review and Meta-Analysis

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## ABSTRACT

Pregnancy-associated breast cancer (PABC) is breast cancer that is diagnosed during gestation, post-partum, or any time during lactation. The present prognostic meta-analysis was executed to retrieve factors associated with survival outcomes among patients with PABC. The risk of death along with the risk of breast cancer recurrence was evaluated. The literature review was performed through twelve databases on 15th July 2024. All clinical studies included patients with PABC, and evaluated factors associated with survival outcomes were included. These studies have to implement the Cox regression model to calculate the hazard ratio (HR) for the time to relevant outcomes. The present meta-analysis included nine retrospective studies encompassing 9590 patients with PABC. The mortality risk was 14%, while the risk of breast cancer recurrence was 12.1%. Patients with Luminal B breast cancer was at 1.95 times higher risk of mortality. There was a statistically significant association (P<0.001) between clinical stage and overall survival with an HR of 3.74. There was a statistically significant association (P<0.001) between chemotherapy and overall survival (HR; 1.80, 95%CI; 1.50, 2.16). Patients with triple-negative breast cancer was 1.65 times at higher risk of poor survival outcomes. Patients with PABC were at a considerable risk of developing poor overall and disease-free survival outcomes. This risk was more pronounced among patients with luminal B breast cancer, patients with TNBC, patients with advanced tumor stage, and patients treated with chemotherapeutic agents.

***Keywords; Pregnancy, Breast Cancer, Prognosis, Survival***

## INTRODUCTION

Breast cancer is the most common malignancy diagnosed among women during the childbearing period[1]. The most common classification of breast cancer is based on immunohistochemical perspective. Four types of breast cancer are commonly identified including luminal A, luminal B, human epidermal growth factor (HER2) positive, and triple-negative breast cancer[2]. Pregnancy-associated breast cancer (PABC) is breast cancer that is diagnosed during gestation, post-partum, or any time during lactation. PABC is the second most prevalent malignancy affecting pregnant women, with an incidence of nearly 15 to 35 per 100000 deliveries[3,4]. PABC is mainly related to hormonal changes, immune tolerance, breast involution, significant oncogene expression, and inflammatory response associated with pregnancy[5]. Given the trend of childbearing delays and the increase in the worldwide incidence of breast cancer, the proportion of patients with PABC is increasing. The majority of cases are diagnosed during the post-partum period, and fewer are diagnosed during pregnancy. The diagnosis of PABC is often delayed due to the lack of awareness, denial of suspicious clinical manifestations, and the fear of undergoing radiological evaluation during pregnancy. Subsequently, the transient and permanent structural changes of the mammary tissue associated with gestation may mask the manifestations of PABC[6,7].

Pregnancy and the post-partum periods are extremely delicate intervals in a woman's life and have considerable psychological and functional aspects. This highlights the need to provide specific cancer care to pregnant women with an equal emphasis on fetal and maternal health. The aggressiveness of PABC is attributed to the young age at diagnosis, delayed diagnosis, advanced presentation, and pregnancy-associated hormonal changes. PABC has unfavorable clinicopathological features with a high tumor grade, low expression of estrogen and progesterone receptors, larger tumor size, lymphovascular invasion, and lymph node involvement[8-10]. Furthermore, the treatment of PABC is challenging and may be delayed considering the safety of both the mother and her fetus[11,12]. Chemotherapeutic agents are not advisable during the first trimester of pregnancy, whereas hormonal and radiation therapies are not recommended until after delivery[13].

PABC may carry poor clinical and survival outcomes even after controlling variable clinicopathological features[14]. Patients with PABC may have a considerably higher mortality risk and significant risk of disease relapse relative to non-PABC patients[15,16]. Paradoxically, some studies revealed that patients with PABC were not associated with poor prognostic outcomes until they had extremely aggressive tumors[17-19]. While pregnancy may temporarily increase the risk of breast cancer, it may decrease the risk of cancer in the long term[20]. The assessment of survival outcomes among women with PABC is challenging. The majority of previously published studies are based on small cohorts, limited by the retrospective nature and the treatment protocols. Furthermore, the definition of PABC has varied considerably, resulting in heterogeneous results[21].

The literature is doubtful regarding the survival outcomes of PABC. There were no conclusive reports evaluating factors associated with survival outcomes in patients with PABC[22,23]. This highlighted the need for a conclusive report to estimate the demographic-related, tumor-related, and treatment-related factors that may predict survival outcomes in patients with PABC. Such knowledge is essential to assort patients at a higher risk of poor survival outcomes to the necessary management plan and to decrease the potential consequences of PABC

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on both mothers and their fetuses. Therefore, the present prognostic meta-analysis was executed to retrieve factors associated with survival outcomes among patients with PABC. The risk of death along with the risk of breast cancer recurrence was evaluated.

## METHODOLOGY

The steps of the current systematic review and meta-analysis study followed the guidelines and the recommendations offered through the Cochrane Collaboration and Cochrane Handbook of Systematic Reviews and meta-analysis[24] and based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[25]

**The methodology of the study was documented in the** International Prospective Register of Systematic Reviews database (PROSPERO) (Number; [CRD42024571148]).

**Search Methods:** The literature review was performed through twelve databases on 15th July 2024. The following databases were searched using individualized search strings customized for each database: PubMed, ISI, Google Scholar, Scopus, NYAM, SIGLE, VHL, Clinical trials, mRCT, Cochrane Collaboration, EMBASE, and ICTRP. There were no limitations regarding age, gender, publication language, ethnicity, or study region. Citation tracking, cross-referencing, and reviewing the references of the eligible articles were carried out to retrieve all possible relevant articles. The following keywords were used; 'Pregnancy', 'Gestational', 'Breast', 'Cancer', 'Survival', 'Survivability', 'Mortality', 'Prognosis', 'Death' (Supplementary Table 2).

**Study selection:** All clinical studies included patients with PABC, and evaluated factors associated with survival outcomes were included. These studies have to implement the Cox regression model to calculate the hazard ratio (HR) for the time to relevant outcomes. No restrictions were implemented for PABC stage, grade, type, differentiation, or diagnostic criteria. Furthermore, irrelevant articles, review articles, studies with unextractable data, guidelines, cadaveric articles, case reports, erratum, letters, case series, comments, editorials, meeting abstracts, book chapters, and posters were excluded. The title, abstract, and full-text screening processes were performed to disclose the potentially relevant articles that met the eligibility criteria. The articles retrieved from the screening process were exported to an Excel sheet after the initial removal of the duplicated reports using EndNote X9[26]. The screening processes were performed to reveal the finally eligible studies for data extraction. The PRISMA flowchart was designed to document the searching process, screening, and the causes of article exclusion at each step of the literature review.

**Data extraction:** The data were extracted in a well-organized Microsoft Excel sheet. The source-related data were extracted, including the title, study ID, study regions, study period, and study design. The methods-related data were extracted, including the eligibility criteria, the diagnostic criteria for PABC, study endpoints, and follow-up periods. Baseline patients' demographic characteristics were extracted, including sample size, patients' age, age at pregnancy, body mass index (BMI), comorbidities, employment status, family history of breast cancer, marital status, multiparity, nulliparity, the number of trimesters, and weeks of pregnancy. The data relating to PABC were extracted, including the duration of symptoms, delayed diagnosis, laterality, tumor type, disease extent, tumor grade, tumor differentiation, tumor size, lymph node involvement, and hormonal status. The management-related data were extracted, including systematic therapies (chemotherapy, hormonal therapy, immune therapy, and radiotherapy) and surgical management (Breast conserving surgery, mastectomies and breast reconstruction). The survival outcomes were evaluated, including disease-free survival, overall survival, mortality risk, and risk of breast cancer recurrence.

**Quality assessment:** The quality of the included observational studies was assessed using the National Institute of Health (NIH) quality assessment tool[27]. The studies were assorted, based on this quality assessment, into good, fair, and bad when the score was >65%, 30-65%, and < 30%, respectively.

**Data analysis:** The mortality risk and the risk of recurrence were estimated by calculating the event rate and 95% confidence intervals (CIs) for each study following by pooling the effect sizes of all studies to estimate the summary proportion with 95%CI. The pooled summary of HR was computed by pooling the HR from all the relevant articles. The fixed-effect model was used when homogeneity between the effect sizes was revealed; conversely, the random-effects model was used. Statistical heterogeneity was determined using Higgins $I^2$ statistic, at the value of >50%, and the Cochrane Q ($Chi^2$ test), at the value of $p<0.10$[28]. Meta-analysis was performed using Review Manager version 5.4 (Revman 5.4) and Comprehensive Meta-Analysis v3 (CMA V3) software[29, 30]. The significant associations with survival outcomes were revealed when the value of $P<0.05$.

## RESULTS

A systematic search of 12 databases revealed a total of 643 articles. Of them, 227 were excluded, being duplicated, resulting in 416 studies eligible for screening. Furthermore, 380 reports were excluded, and 34 studies were included for full-text screening. Ten articles were eligible for data extraction; two with unextractable data were excluded. One study was identified through citation tracking, resulting in nine articles that were finally included for systematic review and meta-analysis Figure.1.

### DEMOGRAPHIC CHARACTERISTICS OF THE INCLUDED STUDIES

The present meta-analysis included nine retrospective studies encompassing 9590 patients with PABC[12, 31-38]. The average age of the included patients ranged from 30 to 35 years. There were 103 patients with a family history of breast cancer. There were 2397 patients with stage I breast cancer, while 2245 patients had stage III breast cancer. There were 480 patients with stage IV breast cancer. Furthermore, 606 patients had poorly differentiated breast cancer. There were 982 patients with invasive ductal carcinoma, while 23 had invasive lobular carcinoma Table.1.

There were 106 patients with luminal A breast cancer and 244 with luminal B. There were 446 patients with TNBC and 102 patients with HER2-positive breast cancer. There were 2922 patients with ER-positive receptors and 2955 patients with PR-positive receptors. There were 2210 patients with lymph node invasion and 142 with metastatic lesions. Furthermore, 917 patients were subjected to mastectomy, 435 patients subjected to breast conserving surgery, and 7575 patients were treated with chemotherapy. The average follow-up period ranged from 47.5 months to 7.4 years. All the included studies were of good quality, with a score ranging from 80% to 90% Table.2.

### FACTORS ASSOCIATED WITH OVERALL SURVIVAL

#### Age≥35

Six articles evaluated the association between age ≥35 and the overall survival [31-34, 37, 38]. In the random-effects model ($I^2$=78%, p=0.003), there was no statistically significant association between age ≥35 and overall

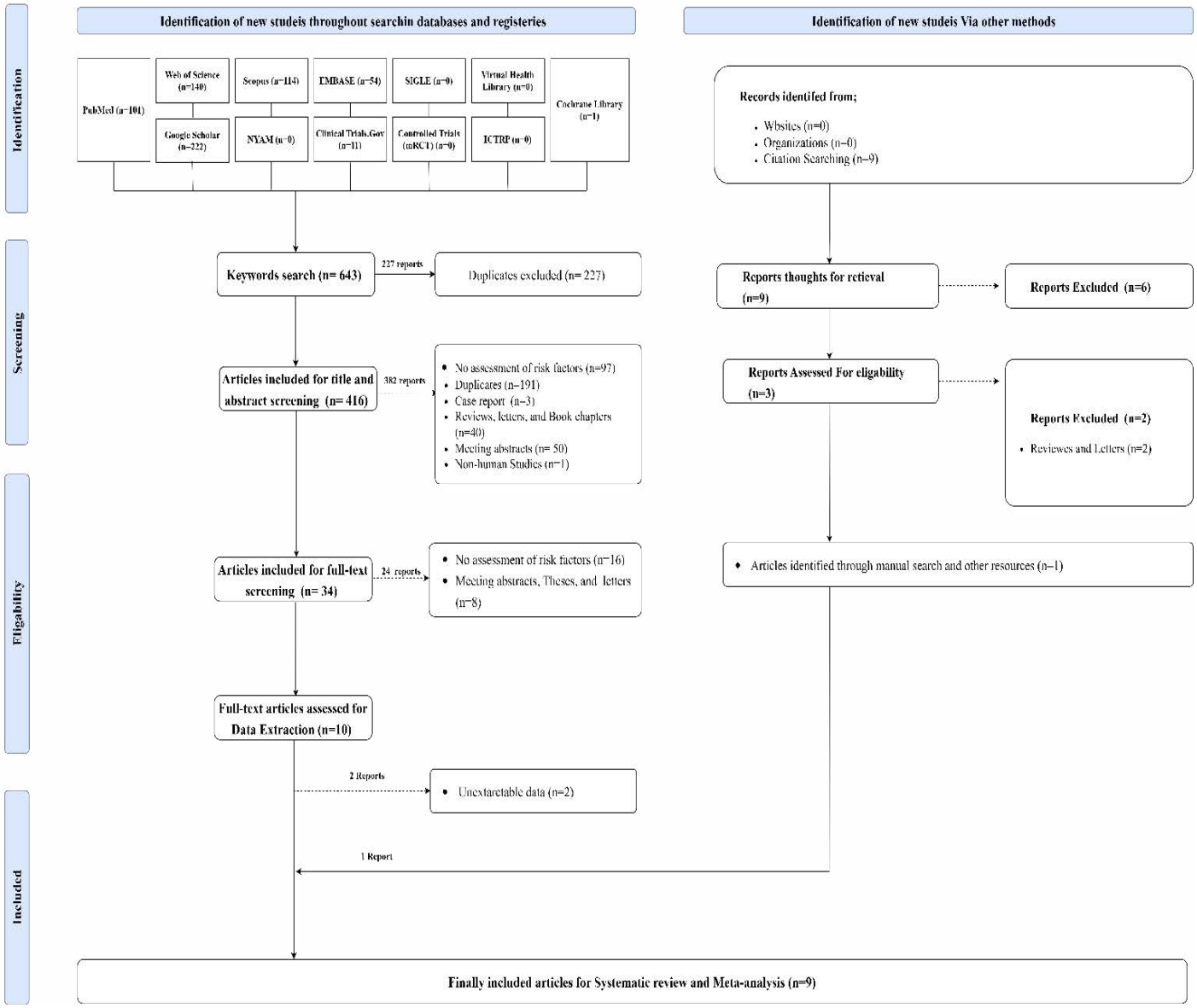


**Figure 1.** PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers, other sources, and screening.

survival (P=0.20) with an HR of 1.17 (95%CI; 0.92, 1.48) Figure.2A.

### Luminal B

The association between Luminal B (HR+ HER+) and the overall survival among patients with PABC was evaluated within three articles[34, 37, 38]. Patients with Luminal B (HR+ HER+) were at 1.95 times higher risk of mortality with a 95%CI of 1.22 to 3.11 (P=0.005) in the random-effects model ($I^2$=0%, P=0.38) Figure.2B.

### Triple-negative breast cancer

Three studies evaluated the association between triple-negative breast cancer and overall survival among patients with PABC[34, 37, 38]. There was a statistically significant association between triple-negative breast cancer and overall survival with an HR of 1.65 (95%CI; 1.17,2.32, P=0.004) in the random-effects model ($I^2$=0%, P=0.89) Figure.2C.

### HER2 subtype

The impact of HER2 subtype breast cancer on the overall survival among patients with PABC was reported in three studies[34, 37, 38]. There was no statistically significant (P=0.08) association between HER2 subtype breast cancer and overall survival with an HR of 4.29 (95%CI 0.83, 22.20) with heterogeneity between the analyzed articles ($I^2$=89%, P=0.0001) Figure.2D.

### ER Negative

Three studies evaluated the association between estrogen receptors negative breast cancer and overall survival among patients with PABC[31-33]. In the random-effects model ($I^2$=39%, P=0.19), there was no statistically significant association between estrogen receptors negative breast cancer and overall survival (P=0.56) with an HR of 0.81 (95%CI; 0.41, 1.62) Figure.2E.

### Clinical stage

Seven studies evaluated the association between clinical stage and overall survival among patients with PABC [12, 31, 34-38]. In the random-effects model ($I^2$=28%, P=0.21), there was a statistically significant association (P<0.001) between clinical stage and overall survival with an HR of 3.74 and 95%CI hovered between 2.50 and 5.50 Figure.2F.

**Table.1** Baseline demographic characteristics of the included studies

| Study ID | Region | Study Design | Study Period | Defining of PABC | Sample Size | Age | Family Historyof breast cancer | Delivery < 30 years | Clinical Stage | | | | | Tumor Grade | | | Tumor Type | | | Mortality | Recurrence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 0 | I | II | III | IV | Well | Moderate | Poor | IDC | ILC | DCIS | | |
| | | | | | Number | Mean±SD | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number |
| 1 | Bae et al., 2018[34] | Korea | Retrospective | January 1, 1996, to December 31, 2015 | During pregnancy or within 1 year after delivery. | 411 | NR | 50 | 175 | NR | 92 | 186 | 85 | 23 | 110 | | 188 | 366 | 4 | 16 | 2 | 7 |
| 2 | Chuang et al., 2018[31] | Taiwan | Retrospective | 2002 to 2014 | During pregnancy | 90 | NR | NR | NR | NR | 24 | 51 | 15 | NR | 8 | 37 | 37 | NR | NR | NR | NR | NR |
| 3 | Gkekos et al., 2024[38] | Norway | Retrospective | 1992 and 2018 | during pregnancy or within 24 months after delivery | 1430 | NR | NR | NR | 24 | | 58 | 73 | 4 | 4 | 25 | 79 | NR | NR | NR | 334 | NR |
| 4 | Gwak et al., 2022[37] | Korea | Retrospective | 1989 and 2014 | during pregnancy or within 1 year after delivery. | 410 | NR | NR | NR | NR | 92 | 93 | 202 | 23 | 32 | 113 | 207 | 387 | 5 | NR | NR | NR |
| 5 | Iqbal et al., 2017[32] | Canada | Retrospective | January 1, 2003, to December 31, 2014 | conception from 11 months before, until 21 months after Diagnosis | 7,553 | NR | NR | NR | NR | 2,082 | 3512 | 1,619 | 340 | NR | NR | NR | NR | NR | NR | 975 | NR |
| 6 | Muñoz-Montaño et al., 2021[35] | Mexico | Retrospective | January 2007 through June 2018 | During pregnancy or within 12 months of delivery | 125 | 35 | NR | NR | NR | 38 | | 61 | 26 | 10 | 42 | 73 | 99 | 12 | NR | NR | 24 |
| 7 | Ramírez-Torres et al., 2023[33] | Mexico | Retrospective | March 1992 and June 2010 | During pregnancy or within 12 months of delivery | 16 | NR | 3 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 7 | 3 |
| 8 | Sule-mann et al.,2022[36] | Nether-lands | Retrospective | January 1st, 1988 and July 1st, 2019 | During pregnancy or≤6 months postdelivery were included | 662 | 34.17±4.198 | NR | NR | NR | 129 | 347 | 130 | 54 | NR | NR | NR | NR | NR | NR | NR | NR |
| 9 | Wang et al., 2019[12] | China | Retrospective | 1 January 2005 to 31 December 2015 | During pregnancy or within 12 months of delivery | 142 | 30 (24–44) | 50 | NR | NR | 8 | 64 | 60 | 10 | NR | 54 | 22 | 130 | 2 | NR | NR | 38 |

**Abbreviations; IDC**=Invasive ductal carcinoma, **ILC**=Invasive lobular carcinoma, DCIS=Ductal carcinoma in situ

**Table.2** Tumor characteristics and quality assessment of the included studies

| | Study ID | Tumor subtypes | | | | | Hormonal Status | | | Lymph node metastasis | Metastasis | Surgical Interventions | | | | Systemic Therapy | | | Follow-up period | Quality assessment | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | ER status | PR status | HER2 status | | | | | | | | | | | | |
| | | Luminal A | Luminal B | TNBC | HER2 | Luminal B (high Ki67) | Positive | Positive | Positive | | | Mastectomy | BCS | ALND | SLN | Chemotherapy | Radiotherapy | Hormonal Therapy | | | |
| | | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | Number | | % | Decision |
| 1 | Bae et al., 2018[34] | 65 | 37 | 124 | 53 | 28 | 143 | 126 | 91 | NR | NR | 199 | 193 | 235 | 145 | 345 | 230 | NR | 53 months | 90% | Good |
| 2 | Chuang et al., 2018[31] | NR | NR | NR | NR | NR | 32 | 32 | 12 | 49 | NR | 52 | 31 | NR | NR | 67 | 42 | 45 | 4.28 (1.13, 10.9) | 80% | Good |
| 3 | Gkekos et al., 2024[38] | 14 | 13 | 117 | NR | NR | 57 | 56 | 67 | 85 | NR | NR | NR | NR | NR | NR | NR | NR | 7.4 years | 90% | Good |
| 4 | Gwak et al., 2022[37] | 17 | 128 | 173 | 49 | NR | NR | NR | NR | NR | NR | 199 | 211 | | NR | 367 | NR | 150 | 87 months | 80% | Good |
| 5 | Iqbal et al., 2017[32] | NR | NR | NR | NR | NR | 2,641 | 2438 | NR | 1,669 | 4 | NR | NR | NR | NR | 6,108 | 5598 | NR | 5.2 years | 90% | Good |
| 6 | Muñoz-Montaño et al., 2021[35] | NR | NR | NR | NR | NR | NR | NR | 33 | 107 | NR | NR | NR | NR | NR | NR | NR | NR | 67.7 months (IQR 24.3, 100.3) | 90% | Good |
| 7 | Ramírez-Torres et al., 2023[33] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 47.5 months (range: 0-81) | 80% | Good |
| 8 | Sulemann et al.,2022[36] | NR | NR | NR | NR | NR | | 227 | 133 | 218 | 52 | 467 | NR | 315 | NR | 562 | NR | NR | 6.5 years (IQR 2.8–13.6 years) | 90% | Good |
| 9 | Wang et al., 2019[12] | 10 | 66 | 32 | NR | NR | 76 | 76 | 42 | 82 | 86 | NR | NR | NR | NR | 126 | 78 | 64 | 63 months | 80% | Good |

**Abbreviations; TNBC=** Triple Negative Breast Cancer, **HER2=** human epidermal growth factor receptor 2, **ER=**Estrogen, **PR=**Progesterone, **BCS=** Breast conserving surgery, **ALND=**Axillary Lymph node dissection, **SLN=**Sentinel Lymphnode

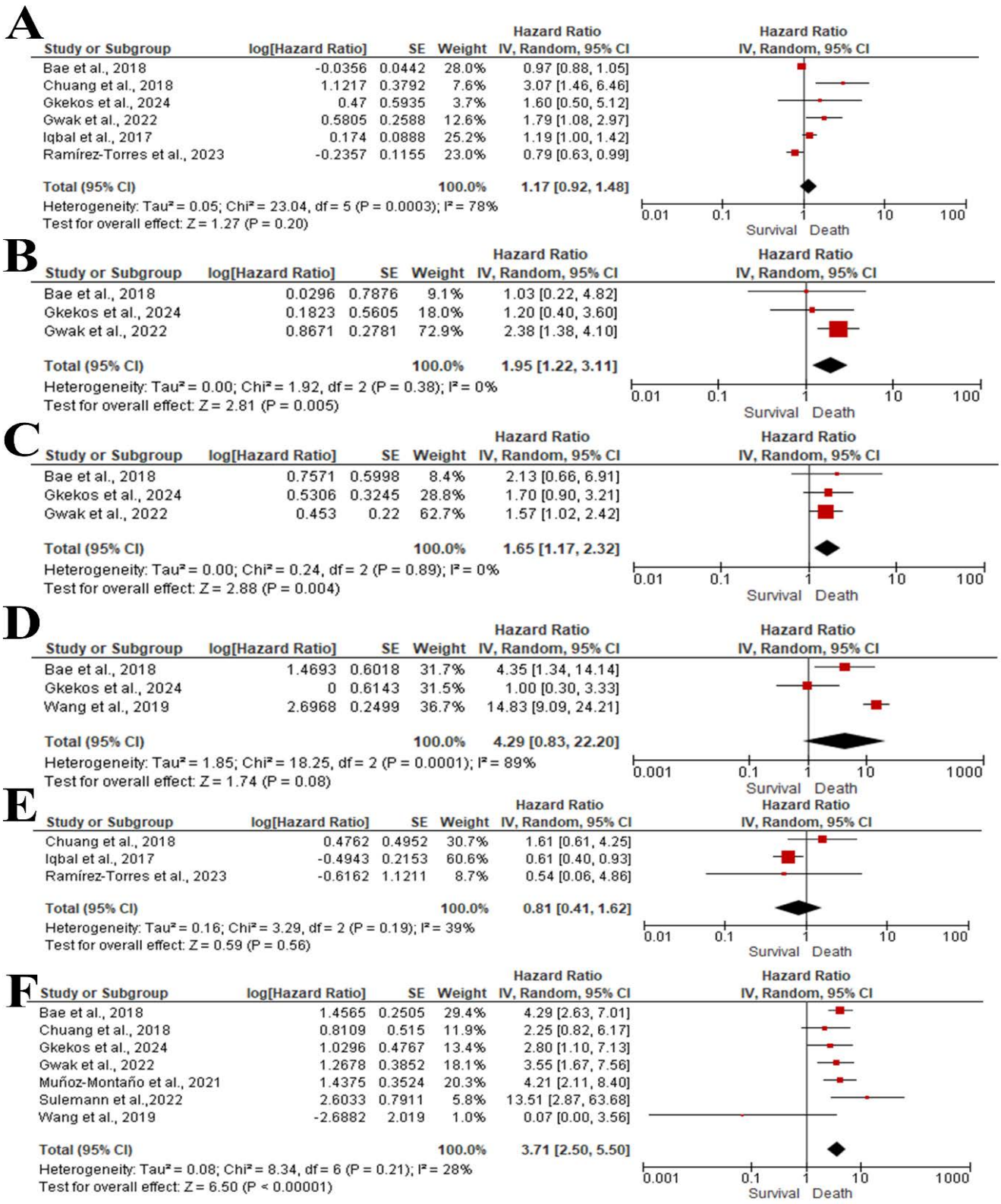


**Figure 2.** Forest plot of summary analysis of the hazard ratio and 95%CI of the association between (A) age ≥35 and the overall survival among patients with pregnancy-associated breast cancer. (B) Luminal B (HR+ HER+) and the overall survival among patients with pregnancy-associated breast cancer. (C) triple-negative breast cancer and overall survival among patients with pregnancy-associated breast cancer. (D) HER2 subtype breast cancer on the overall survival among patients with pregnancy-associated breast cancer. (E) Estrogen receptors negative breast cancer and overall survival among patients with pregnancy-associated breast cancer. (F) Clinical stage and overall survival among patients with pregnancy-associated breast cancer. Size of red squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (IV = inverse variance).

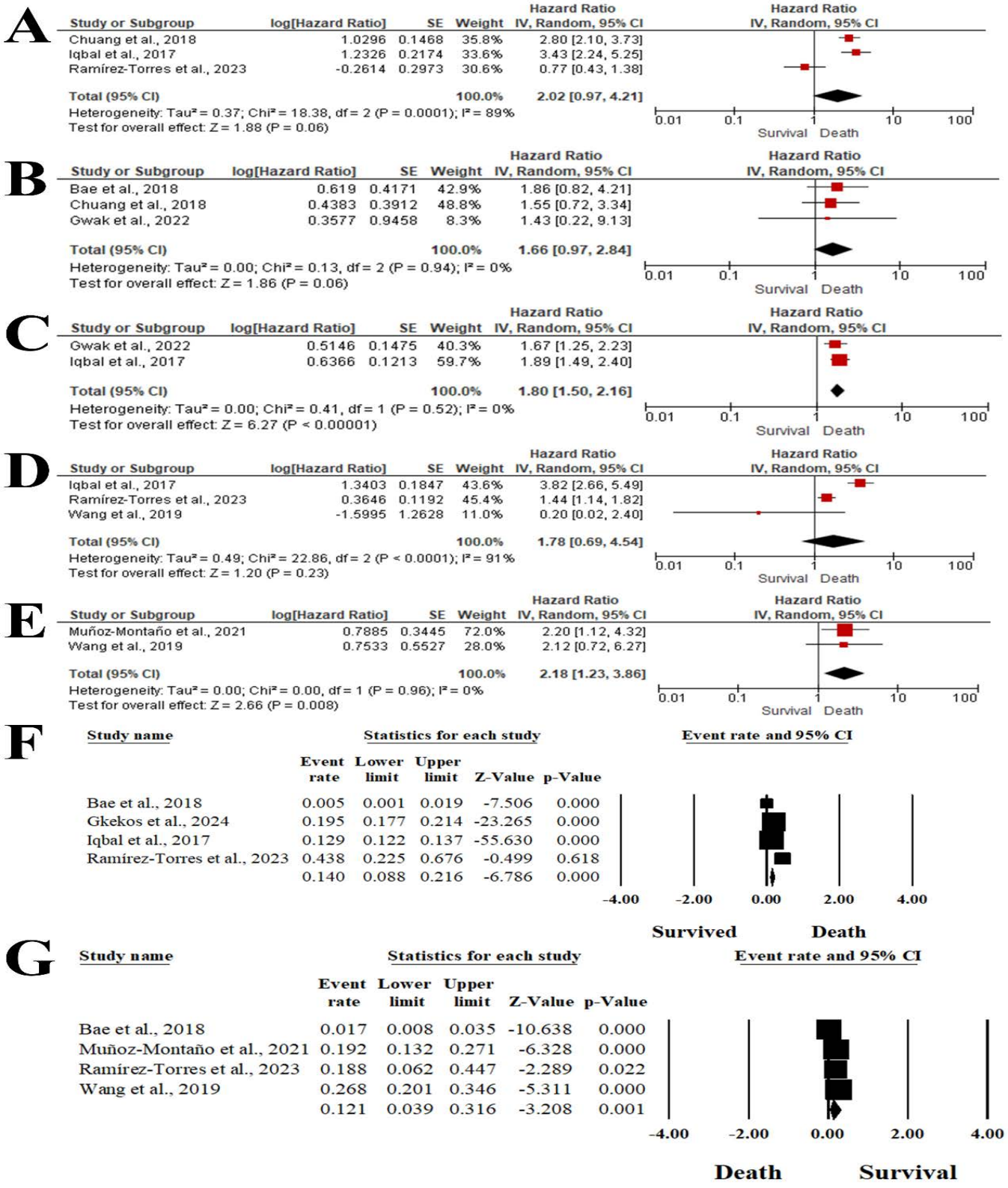


**Figure 3.** Forest plot of summary analysis of the hazard ratio and 95%CI of the association between (A) Tumour size and the overall survival among patients with pregnancy-associated breast cancer. (B) Histological grade and the overall survival among patients with pregnancy-associated breast cancer. (C) Chemotherapeutic agents and overall survival among patients with pregnancy-associated breast cancer. (D) Lymph node invasion cancer on the overall survival among patients with pregnancy-associated breast cancer. (E) Clinical stage and disease free survival among patients with pregnancy-associated breast cancer. (F) The event rate and 95%CI of the mortality risk among patients with pregnancy-associated breast cancer. (G) The event rate and 95%CI of the recurrence risk among patients with pregnancy-associated breast cancer. Size of red or black squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (IV = inverse variance).

### Tumor size

The impact of tumor size on the overall survival among patients with PABC was evaluated within three studies[31-33]. There was no statistically significant (P=0.06) impact of tumor size on the overall survival (HR; 2.02, 95%CI; 0.97, 4.21) in the random-effects model ($I^2$=89%, P<0.001) Figure.3A.

### Histological Grade

Three studies evaluated the association between histological grade and overall survival among patients with pregnancy-associated breast cancer [31, 34, 37]. In the random-effects model ($I^2$=0%, P=0.94), there was no statistically significant (P=0.06) association between histological grade and overall survival (HR; 1.66, 95%CI; 0.97, 2.84) Figure.3B.

### Chemotherapy

Two studies evaluated the association between chemotherapy and overall survival among patients with pregnancy-associated breast cancer[32, 37]. There was a statistically significant association (P<0.001) between chemotherapy and overall survival (HR; 1.80, 95%CI; 1.50, 2.16) in the random-effects model ($I^2$=0%, P=0.52) Figure.3C.

### Lymph node metastasis

Three studies evaluated the association between lymph node metastasis and overall survival among patients with pregnancy-associated breast cancer [12, 32, 33]. There was no statistically significant association between lymph node metastasis and overall survival (HR; 1.78, 95%CI; 0.69, 4.54, P=0.32) in the random-effects model ($I^2$=91%, P<0.001) Figure.3D.

### FACTORS ASSOCIATED WITH DISEASE-FREE SURVIVAL

### Clinical Stage

Two articles evaluated the association between clinical stage and disease-free survival among patients with pregnancy-associated breast cancer [12, 35]. In the random-effects model ($I^2$=91%, P<0.001), there was a statistically significant association between clinical stage (P=0.008) and disease-free survival with an HR of 2.18 (95%CI; 1.32, 3.86) Figure.3E.

### The mortality risk and risk of breast cancer recurrence

Four articles evaluated the mortality risk among patients with pregnancy-associated breast cancer[32-34, 38]. The mortality risk was 14%, with 95%CI ranging from 8.8% to 21.6% (P<0.001). The risk of breast cancer recurrence was reported in four articles[12, 33-35]. The prevalence of tumor recurrence was 12.1% (95%CI; 3.9% to 31.6%, P=0.001) Figure.3F and 3G.

## DISCUSSION

PABC is a complex challenge, necessitating precise diagnosis and timely management. Identifying patients with PABC at a higher risk of poor survival outcomes is essential to ensure the safety of both mother and fetus. The literature showed controversial findings regarding the prognosis of PABC with less emphasis on factors associated with survival outcomes among such patients[22,39]. The present meta-analysis revealed a mortality risk of 14%, along with cancer recurrence risk of 12.1% among patients with PABC. Patients with luminal B breast cancer, patients with TNBC, and patients treated with chemotherapeutic agents were at higher risk of poor survival outcomes. The risk of poor survival outcomes was more than three times higher among patients with advanced tumor stage. There was no statistically significant impact of age ≥35, HER2 subtype breast cancer, estrogen receptors negative breast cancer, tumor size, histological grade, and the risk of poor survival outcomes among patients with PABC.

The present meta-analysis revealed a considerable risk of death and cancer recurrence among patients with PABC. In this respect, Ruiz et al., 2017 reported a significant risk of death among patients with PABC relative to non-pregnant patients. They reported a risk of relapse 1.60 times higher among patients with PABC[40]. Shao et al., 2020 reported poor overall survival, disease-free survival, and cause-specific survival among patients with PABC, which were more pronounced in the post-partum period[15]. The poor survival outcomes associated with PABC are attributed mainly to the delayed diagnosis and the hormonal changes that influence the biology of breast cancer[41]. Mammary gland involution and breast degeneration following pregnancy may explain the poor prognosis of PABC. The delayed diagnosis of PABC allowed more time for tumor growth and proliferation, enhancing the potentiality for locoregional invasion and metastasis. Herein, the majority of patients presented with advanced breast cancer stage an, which is proven in the current meta-analysis to increase the mortality risk by more than three times. Furthermore, pregnancy limited the treatment strategies and allowed only conservative and less invasive procedures to ensure the safety of the mother and fetus[42-44]. In this respect, Raphael et al., 2015 reported that PABC should be managed as aggressively as the guidelines applicable to nonpregnant women[45].

The decision to treat PABC requires a delicate balance between effective breast cancer treatment and maternal-fetal health. Therefore, the decision needed to be individualized considering tumor stage, subtype, hormonal status, and histological differentiation[46]. The present meta-analysis revealed that patients with TNBC were at a higher risk of developing poor survival outcomes. However, there was no significant association between HER2 and ER-negative breast cancer and overall survival. Parallel with this finding, Nolan et al., 2022 revealed that ER receptor status did not considerably affect disease-free survival or hormonal treatment duration among patients who got pregnant after breast cancer[47]. Bakhuis et al., 2021 reported a predominant ER and PR negative profile with over-expression of HER2 receptors among patients with PABC[48]. They highlighted that PABC might be a separate entity with more aggressive behavior when compared to nonpregnant breast cancer patients.

The present study quantified factors associated with overall and disease-free survival among patients with PABC. However, the results of the current prognostic meta-analysis should be cautiously interpreted in the context of some limitations. The main limitation of the included studies is the need to standardize the definition of PABC and diagnostic criteria. This limitation and the difference in study design, clinical stage, grade, tumor size, and differentiation may result in significant heterogeneity between the analyzed predictors. All the included studies were retrospective, conveying a higher risk of information selection and reporting bias. Prospective cohort studies with adequate sample sizes and prolonged follow-up protocols are required to mitigate the limitations of the analyzed observational studies.

## CONCLUSION

**Patients with PABC were at a considerable risk of developing poor overall and disease-free survival outcomes. This risk was more pronounced among patients with luminal B breast cancer, patients with TNBC, patients with advanced tumor stage, and patients treated with chemotherapeutic agents. Such knowledge is essential to assort patients at higher risk of poor survival outcomes**

**to the necessary management plan and to decrease the potential consequences of PABC.**

**Authorship Contribution:** All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

**Potential Conflicts of Interest:** None

**Competing Interest:** None

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