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Survival status and Predictors of mortality among breast cancer patients in Ethiopia: A Systematic Review and Meta-analysis

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Abstract

Objectives: This study aimed to evaluate survival outcomes and identify key mortality predictors among breast cancer patients in Ethiopia.

Study design: A systematic review and meta-analysis.

Study participants: the study used eleven primary studies, involving a total of 4,131 participants.

Primary and secondary outcome measurement: The study's primary outcome is survival status, measured by survival and mortality rates. The survival rate was calculated based on the percentage of patients alive at one, three, or five years, while the mortality rate was based on the percentage of deaths. The secondary outcome identified mortality predictors among breast cancer patients in Ethiopia.

Methods: We searched PubMed, Embase, Web of Science, Scopus, and Google Scholar until July 1, 2024, following PRISMA guidelines. Study quality was assessed using the Newcastle-Ottawa Scale. A random effects model estimated pooled survival and mortality rates, while adjusted hazard ratios (AHR) were calculated using either a random effect or fixed effect model. Egger's test and funnel plots were used to examine publication bias. I2 statistics and the Cochran Q test were used to evaluate heterogeneity.

Results: Eleven studies were analyzed. The pooled mortality rate was 36%. Survival rates at one, three, and five years were 85%, 66%, and 22%, respectively. Key mortality predictors included advanced clinical stage, rural residence, positive lymph node status, no hormonal therapy, histologic grade III, hormone receptor negativity, and comorbidities.

Conclusion: Breast cancer in Ethiopia poses a high mortality rate primarily due to late-stage diagnosis, rural residency, histologic grade III, positive lymph node status, and comorbidities. To improve survival outcomes, it is crucial to expand access to early screening, particularly in rural areas, implement comprehensive treatment protocols, and strengthen healthcare infrastructure to address these critical factors

Keywords: Breast cancer, Mortality rate, Predictors

Strengths and limitations

- This systematic review and meta-analysis represent a national estimation conducted in Ethiopia.
- However, it may lack full national representativeness, as no data were available from the Benishangul Gumuz, Afar, Gambella, Somalia, Dire Dawa, and Harar regions.
- Additionally, we were unable to compare the impact of different treatment modalities on breast cancer mortality due to the lack of available data

Introduction

Breast cancer is a leading cause of cancer-related morbidity and mortality in the world, with 2.3 million new cases and 685,000 deaths reported in 2020 (1). Despite challenges in diagnostic systems in Africa, breast cancer accounts for one in four diagnosed cancers and one in five cancer deaths among women (2). With an expected 15,244 new cases and 8,159 deaths from the disease in 2018, breast cancer is the most common cancer in Ethiopia and the primary cause of cancer-related deaths among women (3). Common risk factors for breast cancer in Ethiopia include a family history of the disease, early menarche, post-menopausal status, and never having breastfed (4). Without early detection and treatment, breast cancer can lead to local and distant metastases, ultimately resulting in death (5).

The five-year survival rate for breast cancer varies significantly from country to country due to differences in healthcare systems, early detection programs, lifestyles, and socioeconomic status. For instance, the five-year survival rate for breast cancer patients is 84% in the US, 89.5% in Australia, 81% in Europe (6), 69.55% in Iran (7), 74% in Vietnam (8), 51.07% in Indonesia (9), 49.45% in Malaysia (9), and 66.1% in India (10). In Sub-Saharan Africa, the five-year survival rate is 53.4% in South Africa (11).

The survival of breast cancer patients is influenced by various factors, including socio-demographic variables (age, education, financial status, and family history), tumor characteristics (size, nodal status, metastasis, stage, location, and histology grade), comorbidities, and treatment type (12, 13).

In Ethiopia, although some primary studies have reported the overall five-year survival rate, mortality rate, and predictors of breast cancer (14-16), there is a lack of comprehensive data on the

national survival status and predictors of mortality of breast cancer patients. Therefore, the aforementioned deficits were intended to be filled by this systematic review and meta-analysis.

Methods

Study protocol registration and reporting

The results of this review were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (17). The protocol was registered under the CRD42024575074 registration number in the Prospero database.

Search strategies and sources of information

From June 15 to July 1, 2024, searches were conducted in PubMed, Embase, Scopus, Web of Science, and Google Scholar databases to identify relevant articles. The search terms used included "breast cancer," "breast neoplasm," "breast tumor," "mammary cancer," "outcomes of breast cancer," "breast malignancy," "survival status," "survival rate," "mortality," "death," "mortality rate," "predictors," "determinant," "risk factors," and "Ethiopia." These terms were combined using the search operators "OR" and "AND." Cross-references from the bibliographies of selected studies were also reviewed to enhance search coverage. Additionally, articles with incomplete data were accessed by contacting the corresponding authors. All search records were imported into EndNote X9, where duplicates were eliminated.

Inclusion and exclusion criteria

All observational studies that had reported the survival status and/or at least one predictor of mortality of women breast cancer patients and published in English were considered. The study time was not restricted in any way. Citations without abstract and/ or full-text, anonymous reports, editorials, case reports, and qualitative studies were excluded from the analysis.

Data extraction

Three independent reviewers (HA, HKN, DGA) used a structured data extraction form to extract the data. The extraction process was repeated when variations in the extracted data were observed. If discrepancies between the reviewers persisted, another two reviewers (NDB and LM) were involved to resolve them. The data extraction form included the following details: author, year of

publication, region, study design, sample size, Median survival time, study quality, survival rate at one, three, and five years, overall mortality rate, and selected predictors of mortality from breast cancer.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (18). This tool comprises three sections: **selection** (4 questions), **comparability** (1 question), and **outcome** (3 questions). Studies were scored based on their overall ratings and categorized into three quality groups: **Good quality**: three or four stars in the selection domain, one or two stars in the comparability domain, and two or three stars in the outcome domain. One or two stars in the comparison domain, two or three stars in the outcome domain, and two stars in the selection domain indicate a **fair quality. Poor quality** is declared when zero or one star in the selection domain, zero star in the comparability domain, or zero or one star in the outcome domain is found (Supplementary Table 2). Finally, we included only good or fair-quality studies in the analysis.

Outcome measurement

The first of the two outcomes of this study is survival status, which refers to whether study participants are alive or deceased. This outcome is expressed as the survival rate or mortality rate. The survival rate was computed by multiplying by 100 and dividing the total number of observed patients by the number of living patients at one, three, or five years of follow-up. Similarly, the mortality rate was calculated by dividing the number of deaths during the follow-up period by the total number of observed patients and multiplying by 100. The secondary outcome of this analysis focused on identifying predictors of mortality among breast cancer patients in Ethiopia.

Data processing and analysis

The necessary data were extracted into an Excel spreadsheet and then exported to STATA version 17 software for further statistical analysis. The general characteristics of primary studies are described in tables. To compute the pooled survival and mortality rates, the survival rate at different observation years, the mortality rate, and their respective standard errors in each primary study were considered. The log hazard ratio for each factor was determined to find the predictors

of mortality rate in breast cancer patients. This effect measure was then utilized to construct the pooled AHR.

Heterogeneity test and publication bias

The Cochran Q-test and Higgins's I^2 test statistics were calculated to evaluate heterogeneity across all studies. In this context, I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively (19). Due to the significant heterogeneity among the studies, a random-effects model was employed to determine the survival status, and a either fixed effect or random effect model was used to determine the AHR (20). To assess publication bias, a funnel plot was generated, and Egger's test was performed with a significance level of less than 0.05 (21, 22).

Results

Characteristics of included studies

A total of 674 articles were initially retrieved from PubMed, Embase, Web of Science, Scopus, and Google Scholar databases. After removing 243 duplicates, 431 articles remained. Screening titles and abstracts led to the exclusion of 395 articles. The full texts of the remaining 36 articles were assessed, resulting in the exclusion of 25 due to poor quality, different outcomes, or failure to report the outcome of interest. Finally, 11 studies met the inclusion criteria and were included in this systematic review and meta-analysis. Fig. 1 depicts the retrieval procedure in detail.

Description of studies

Based on our assessment, using NOS, all of the studies had good quality. These studies were conducted between 2018 and 2024 and involved a total of 4,131 patients diagnosed with breast cancer and started follow-up. Four of the studies were conducted in the Amhara region (14, 23-25), three in Addis Ababa (26-28), two in the Southern Nations, Nationalities, and Peoples' Region (SNNPR) (29, 30) one in Oromia region (31), and one in Tigray region (32). In terms of study design, only one study employed a retrospective cross-sectional approach (28), which was considered only for the determination of the mortality rate. In contrast, the others utilized a cohort study design. Based on publication years, only three studies were published before 2020 (26, 28,

31). According to the findings of primary studies, the mortality rate among breast cancer patients ranged from 11.8% (33) to 69.6% (30), and all of them were institution-based studies (Table 1).

Table 1: Table 1: Basic information of included studies

No	Author	P. Year	Study area	Study design	Sample size	Number of death	Mortality rate	Median Survival time	Survival rate		
									One year	Three years	Five years
1.	Feleke et al.	2022	Amhara	Cohort	322	95	29.5	45	NR	NR	NR
2.	Misganaw et al.	2023	Amhara	Cohort	410	139	33.9	38.3	83	53	11.4
3.	Shita. et al.	2023	SNNPR	Cohort	302	67	22.2	50.8	83	63.1	NR
4.	Gashu et al.	2024	Amhara	Cohort	382	148	38.7	42	NR	NR	NR
5.	Tiruneh et al.	2021	Amhara	Cohort	482	165	34.2	17	NR	NR	25.8
6.	Bacha et al.	2021	SNNPR	Cohort	642	447	69.6	10	NR	NR	NR
7.	Tesfay et al.	2021	Tigray	Cohort	186	22	11.8	34.5	NR	NR	NR
8.	Areri et al.	2019	AA	Cohort	627	169	26.9	36.5	97.2	80.8	46.2
9.	Dagne et al.	2019	AA	CS	303	141	46.5	NA	NA	58	NA
10.	Belete et al.	2022	AA	Cohort	368	99	26.9	58.7	NR	NR	NR
11.	Eber-Schulz et al.	2018	Oromia	Cohort	107	57	53.3	28	78	NR	NR

Note: NA= Not applicable, NR = No report

Pooled survival status among breast cancer patients in Ethiopia

A total of eleven studies were analyzed to estimate the pooled mortality rate among breast cancer patients. The heterogeneity among these studies was very high, with an I^2 value of 98.2% ($p = 0.00$). Using a random-effects model, the pooled mortality rate was calculated to be 36% (95% CI: 25% - 46%) (Figure 2).

Four studies reported a one-year survival rate, based on a combined sample size of 1,446 patients. The random-effects model analysis showed significant heterogeneity (I^2 = 96.99%, p = 0.00) and estimated a one-year survival rate of 85% (95% CI: 75% – 96%).

Three studies provided data on the three-year survival rate, with a total sample size of 1,339 patients. The analysis indicated substantial heterogeneity (I^2 = 98.02%, p = 0.00) and estimated a three-year survival rate of 66% (95% CI: 48% – 84%).

Three studies also reported the five-year survival rate, with a combined sample size of 1,519 patients. The random-effects model analysis showed very high heterogeneity (I^2 = 99.25%, p = 0.00) and estimated the five-year survival rate to be 22% (95% CI: 1% – 43%).

Subgroup analysis of Mortality rate

To address the observed heterogeneity in the study (I^2 = 98.2%), a subgroup analysis of mortality rates was conducted based on region, sample size, and year of publication. The analysis by region revealed that the mortality rate among breast cancer patients was highest in studies conducted in the SNNPR (52%, 95% CI: 49% - 55%), compared to those in the Amhara region (34%, 95% CI: 31%-38%) and Addis Ababa (33%, 95% CI: 22% - 44%) (Figure 3). Additionally, when analyzing based on sample size, studies with more than 384 participants reported a higher mortality rate (41%, 95% CI: 21% - 62%) than those with 384 or fewer participants (32%, 95% CI: 23%-42%) (Figure 4). Furthermore, studies published before 2020 showed a higher breast cancer mortality rate (42%, 95% CI: 25% -59%) compared to those published in 2020 or later (33%, 95% CI: 20% - 49%) (Figure 5).

Publication bias

To evaluate publication bias, we utilized a funnel plot and Egger's regression test. An uneven distribution in the funnel plot (Figure 6) is a subjective indicator of publication bias. Although the objective p-value from Egger's regression test was 0.792, indicating no significant publication bias, we concluded that publication bias was present.

Trim and fill analysis

In our systematic review, we employed a funnel plot and Egger’s regression test to assess the presence of publication bias. The funnel plot revealed an asymmetrical distribution, which is a

visual indicator of potential bias. To mitigate the impact of this bias on our pooled mortality rate, we conducted a trim-and-fill analysis. This method adjusts for publication bias by identifying and 'trimming' outlier studies that cause asymmetry in the funnel plot. It then fills the plot with imputed studies, symmetrically opposite to the trimmed studies, to reflect a more accurate distribution of the data. As a result of this process, two additional studies were included in our analysis. This adjustment aims to provide a more balanced and unbiased estimate of the pooled effect, enhancing the validity of our review's conclusions (**Figure 7**).

Predictors of breast cancer mortality

Data on ten variables—cancer clinical stage, lymph node status, residence, hormonal therapy, menopausal status, histologic grade at diagnosis, hormone receptor status, comorbidities, tumor size, and use of chemotherapy—were extracted into an Excel spreadsheet as two-by-two tables and analyzed separately. The analysis identified advanced cancer stage (stage III and IV), rural residence, positive lymph node status, no hormonal therapy, histologic grade III, hormone receptor negativity, and comorbidities as predictors of breast cancer mortality. Specifically, patients diagnosed at advanced cancer stage had a 4.14-fold higher risk of death compared to those diagnosed at stage I (AHR: 4.14; CI: 2.53–6.78). Rural residents were at a higher risk of death compared to urban dwellers (AHR: 1.65; 95% CI: 1.27-2.14). Patients with positive lymph node status were 2.85 times more likely to die than those with negative lymph node status (AHR: 2.85; 95% CI: 1.50-5.44). Similarly, patients who did not receive hormonal therapy were 2.02 times more likely to die compared to those who received it (AHR: 2.02; 95% CI: 1.59-2.56). Patients with negative hormone receptor status had a 1.54 times higher risk of death compared to those with positive hormone receptor status (AHR: 1.54; 95% CI: 1.05–2.25). The hazard of death was 76% higher for patients with histologic grade III tumors compared to those with grade I tumors (AHR: 1.76; 95% CI: 1.29–2.41). Additionally, the risk of death was 124% higher in patients with comorbidities compared to those without (AHR: 2.24; 95% CI: 1.41–3.56) (Table 4). However, pooling the effect sizes for some variables was not feasible due to inconsistencies in categorization across primary studies. For example, while four studies assessed the effect of age on breast cancer mortality, the effect sizes were not pooled due to inconsistent age categorization.

Table 2 Predictors of breast cancer mortality in Ethiopia

Variables	Exposed	Comparator	Included studies	Total participant	AHR (95%)	I^2
Cancer stage	Stage III and VI	Stage I	7	2,893	4.14(2.81,6.78)	76.2
Lymph node status	Positive	Negative	6	2,572	2.85(1.50,5.44)	95.2
Residence	Rural	Urban	4	1,497	1.65(1.27,2.14)	44.5
Hormonal therapy	No	Yes	3	1,405	2.02(1.59, 2.56)	83.8
Histologic grade at diagnosis	Grad III	Grade I	4	1,887	1.76(1.29,2.41)	8.4
Hormone receptor status	Negative	Positive	2	475	1.54(1.05,2.25)	0
Comorbidity	Yes	No	5	2,109	2.24(1.41,3.56)	77.8

Discussion

In Ethiopia, breast cancer continues to be the most common cancer, and the main cause of cancer-related death (34). Moreover, limited resources, insufficient screening programs, and challenges in early diagnosis and treatment may contribute to rising mortality rates (35). The survival outcomes and predictors of mortality among breast cancer patients in primary studies in Ethiopia are not well consistent. Therefore, this study aimed to determine the pooled survival outcomes and identify predictors of mortality among breast cancer patients in Ethiopia.

In this review, the 1-, 3-, and 5-year survival rates for breast cancer were 85% (95% CI: 75–96), 66% (95% CI: 48–84), and 22% (95% CI: 1–43), respectively. The 1 and 3-year survival rates observed in our study align with findings from similar reviews conducted in various regions around the world (36-40). However, we observed a great variation in a 5-year survival rate between our study and studies done both in developed and developing countries in the world. Thus a 5-year

survival rate in our study is much lower than a study done in the USA, which was reported by Siegel et al as 91% (41). The 5-year survival rate for women with breast cancer in developing countries, reported to be 0.46 in Uganda and 0.58 in Zimbabwe, was also higher than the rate observed in our study (42). The differences in survival rates among these studies can indeed be attributed to host factors, tumor factors, and medical factors, with a significant emphasis on the availability and effectiveness of screening programs, early detection, and access to modern medical care (37). However, the higher survival rates observed in American and European countries compared to our study are likely due to the impact of screening programs, early detection, and advancements in modern medical care (43, 44).

This systematic review and meta-analysis revealed a pooled mortality rate of 36% (95% CI: 75%, 96%) for breast cancer patients, indicating that one in three breast cancer patients succumbs to the disease. This mortality rate exceeds the national average death rate for cervical cancer, which stands at 16.39% (45), and lung cancer, at 10% (46), but is lower than the mortality rate for colorectal cancer, which is 40.5% (47).

In this systematic review, we have identified several critical factors that significantly contribute to breast cancer mortality. These include advanced cancer stage at diagnosis, rural residence, positive lymph node status, no hormonal therapy, histologic grade III, hormone receptor negativity, and the presence of comorbidities. In the discussion that follows, we will delve into the implications of these predictors, exploring how each factor individually and collectively influences mortality outcomes in breast cancer patients.

The pooled prevalence of advanced cancer-stage diagnosis among breast cancer patients in Ethiopia is 65.85% (48). According to our review, this prevalent factor increases the hazard of death by fourfold (AHR: 4.14) among breast cancer patients. This association was also observed in previous studies conducted in Hawaii, USA, Nigeria, and Uganda (49-53), more importantly, Bray et al. point out that the prognosis of breast cancer is much better when the disease is detected early, with a 5-year survival rate of about 97% for localized cases. However, this rate drops drastically to around 25% for cases where the disease has metastasized (54). This information emphasizes the importance of early detection and timely intervention in improving survival rates for breast cancer patients.

Our findings also revealed that breast cancer patients in rural areas have a higher mortality rate (AHR: 1.65) compared to those in urban areas. This outcome is consistent with studies conducted across different regions (55). The higher mortality hazard can be attributed to lower levels of health awareness in rural communities. Moreover, even those who were aware of their condition often faced challenges accessing healthcare services due to limited resources in local hospitals. Supporting this, a study found that women living in rural areas had significantly lower odds of receiving different treatment modalities like surgery, radiation, and surgery with radiation (56).

Patients with positive lymph node status faced an increased hazard of death (AHR: 2.85) compared to those without. This result was consistently observed in multiple studies conducted across various countries (57, 58). This could be the result of a higher recurrence rate that is linked to a worse survival rate (59).

This review also highlights a significant finding: women diagnosed with histologic grade III breast cancer faced a mortality rate (AHR: 1.76) that was 76% higher than those diagnosed with grade I. This finding aligns with previous studies conducted in various Asian countries (60-62), which have similarly reported poorer outcomes for patients with higher-grade tumors. The reason behind this could be attributed to the aggressive nature of high-grade cancer cells, which are typically more invasive and linked to a worse prognosis (63).

Moreover, the review underscores the strong association between co-morbidities and the increased hazard of mortality (AHR: 2.24) in breast cancer patients. This finding is consistent with earlier research from different countries (64-66). The increased vulnerability to treatment toxicity, possibly due to the physiological disturbance of patients with existing co-morbid conditions, may explain this correlation (67). Additionally, the presence of co-morbidities may influence the cancer's morphology, histology, differentiation, and proliferation status (68), further complicating the disease and its treatment outcomes.

The review identified no hormone therapy as another significant predictor of mortality, revealing that individuals who underwent hormone therapy had a 100% lower risk of death compared to those who did not receive such treatment. These findings align with previous research conducted across various continents (8, 61, 69, 70). About this, our review also revealed that the hazard of mortality (AHR: 1.54) was significantly higher in patients with hormone receptor-negative tumors compared to those with hormone receptor-positive tumors. This finding aligns with the results of

previous studies (71, 72). One possible explanation for this disparity is that women with hormone receptor-positive tumors tend to present with more favorable clinical characteristics. Specifically, they are more likely to have early-stage tumors, exhibit moderate differentiation, have negative lymph node status, and achieve clear deep surgical margins (73, 74). These factors contribute to a better overall prognosis and lower mortality risk in hormone receptor-positive patients compared to their hormone receptor-negative counterparts.

This systematic review and meta-analysis provide a national estimation of breast cancer mortality in Ethiopia. However, the study may not be fully representative of the entire country, as data were unavailable from several regions, including Benishangul Gumuz, Afar, Gambella, Somalia, Dire Dawa, and Harar. Additionally, the analysis could not compare the impact of different treatment modalities on breast cancer mortality due to a lack of available data.

Implication of the review

The results of this systematic review and meta-analysis have important implications. First, they add to the current knowledge base by offering critical insights into mortality rates and predictors among breast cancer patients in Ethiopia. This information will be valuable for healthcare professionals, researchers, and policymakers, as it deepens their understanding of factors influencing patient outcomes, informs clinical decision-making, and aids in the allocation of resources. Additionally, the findings underscore the need for further research and support the creation of evidence-based strategies aimed at improving patient care and reducing mortality rates among Ethiopian breast cancer patients.

Conclusion

Breast cancer remains a significant health challenge in Ethiopia, characterized by high mortality rates largely due to late-stage diagnoses. The study highlights a stark contrast in 5-year survival rates between Ethiopia and other countries in the world, underscoring the critical need for improved screening programs and early intervention. Factors such as advanced clinical stage, rural residency, histologic grade III, positive lymph node status, and comorbidities were identified as key predictors of mortality, emphasizing the importance of comprehensive healthcare strategies to improve survival outcomes for breast cancer patients in Ethiopia.

Authors Contributors

The authors have made substantial contributions to this study. HA formulated the research question, drafted the initial manuscript, designed the search strategy, revised and approved the final version of the article. HKN and DGA refined the database search strategy, developed the data extraction form, and approved the final version of the article. LM and NDB reviewed the data extraction form and also approved the final version of the article.

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Competing interests

None declared.

Patient consent for publication

Patients and the public did not participate in the design, execution, reporting, or dissemination plans of this research

Data availability statement

All data relevant to the study are included in the article or uploaded as online supplemental information.

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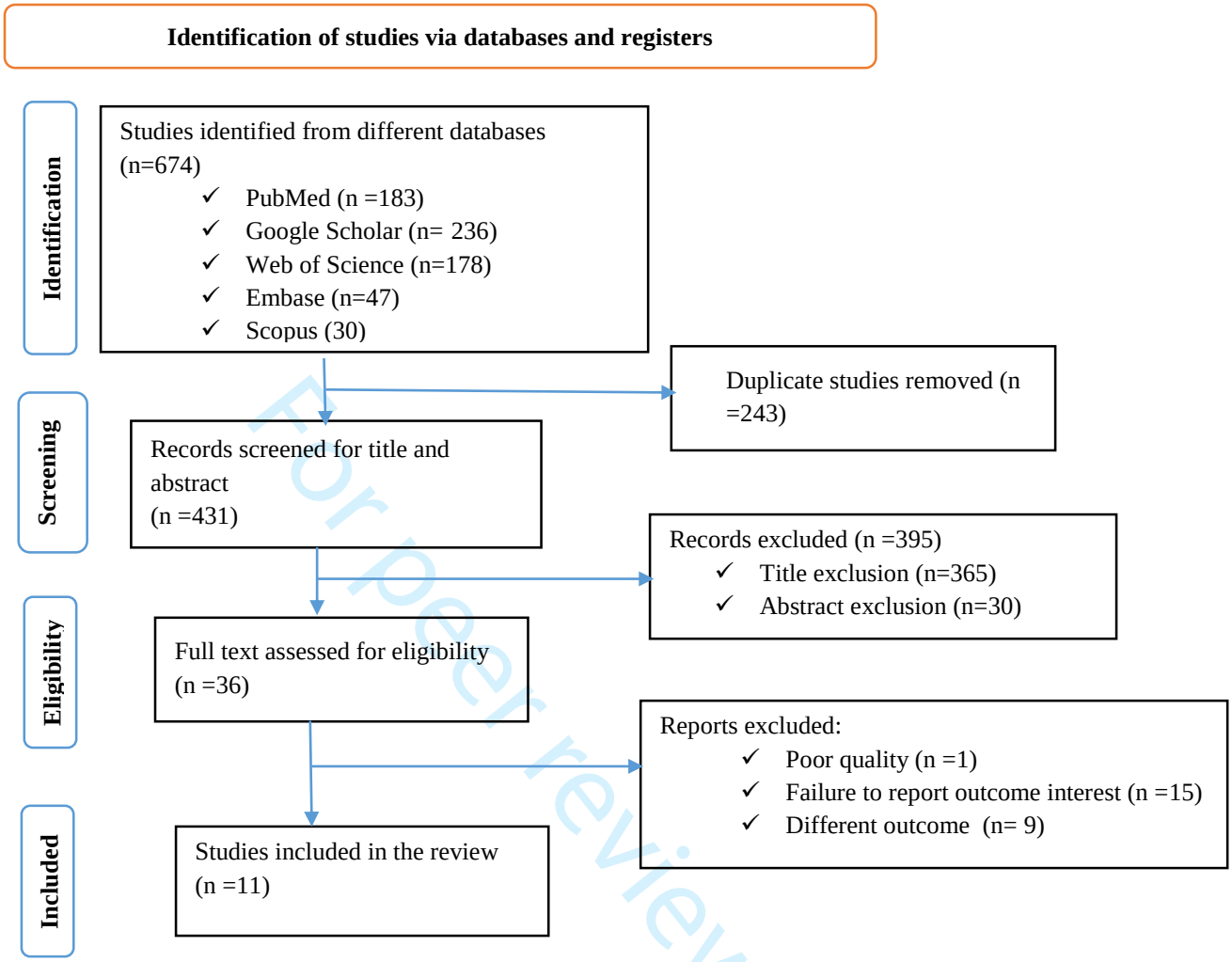

Figure 1: PRISMA flow chart for the flow of information through the phase of systematic review

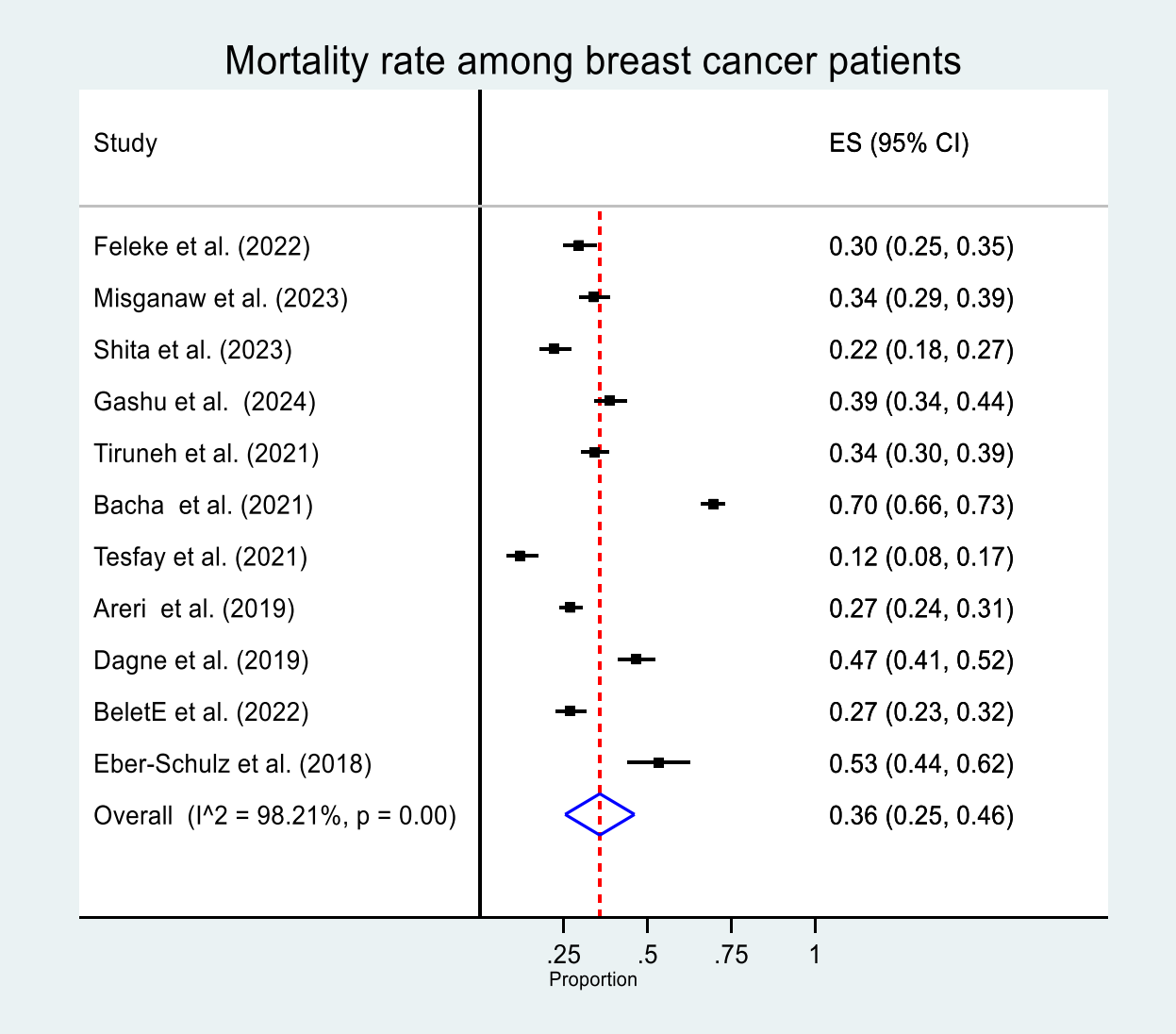

Fig. 2 Forest plot showing the pooled mortality rate among breast cancer patients in Ethiopia.

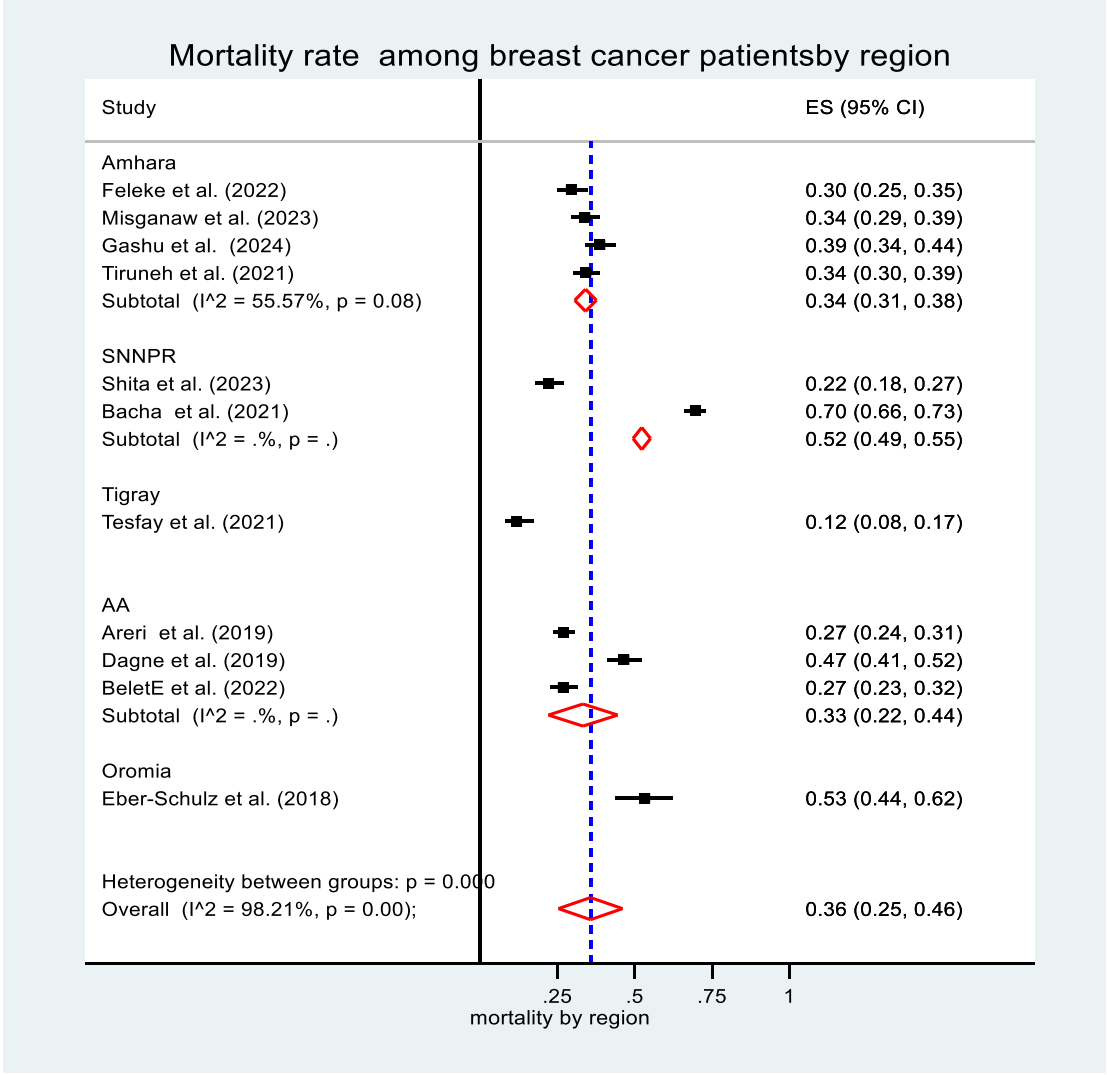

Fig. 3 Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

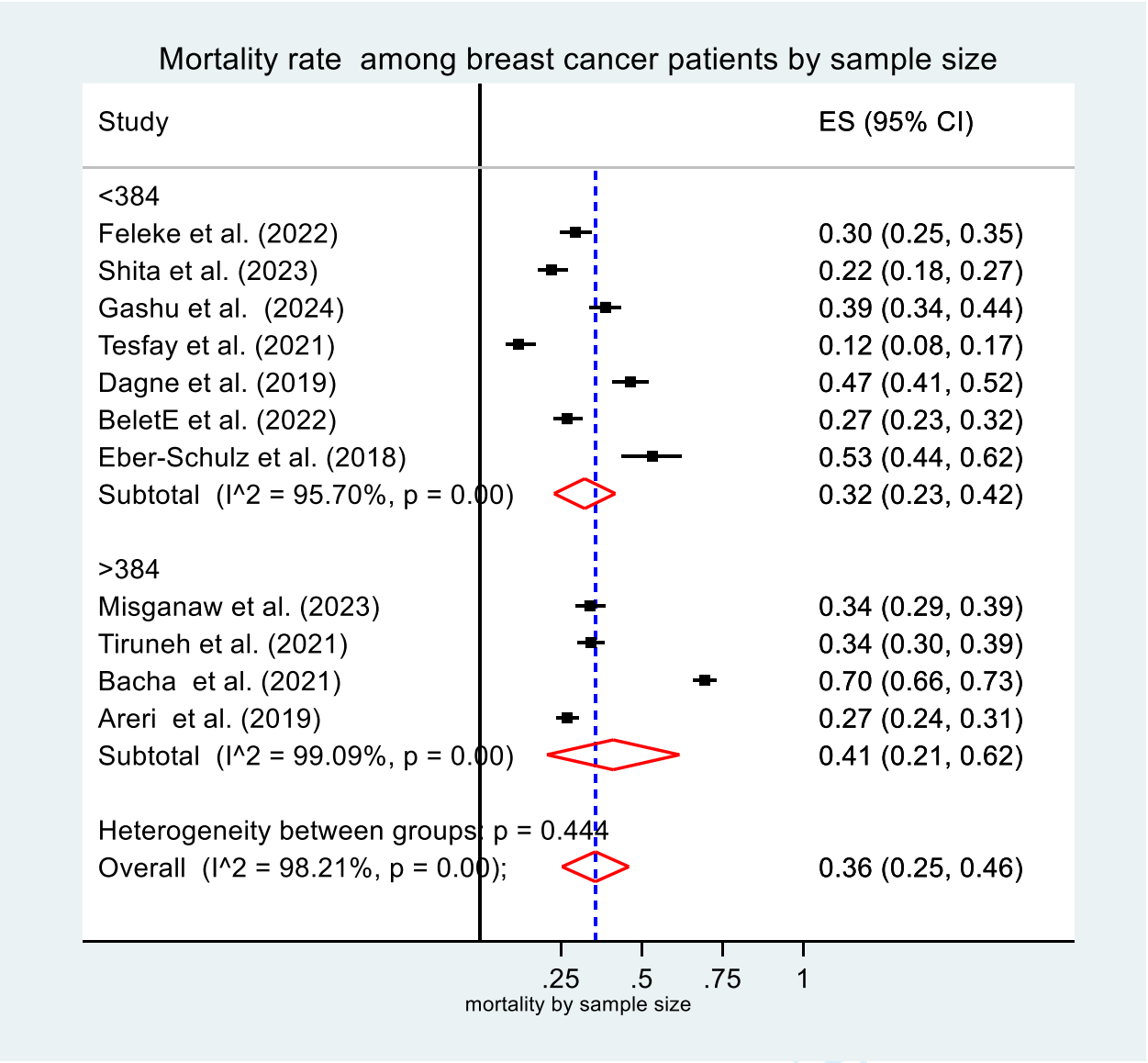

Fig.4 Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

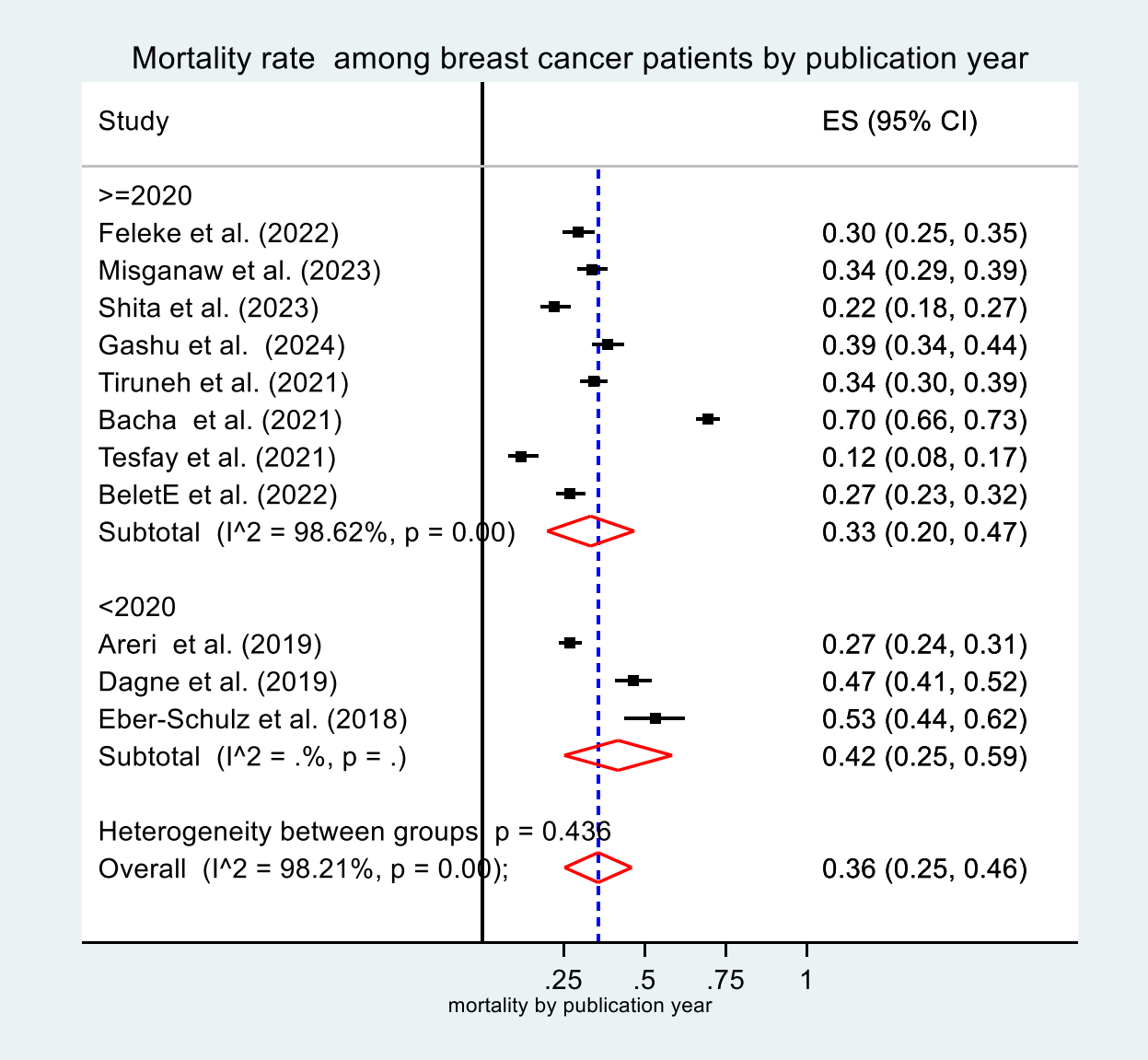

Fig. 5 Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

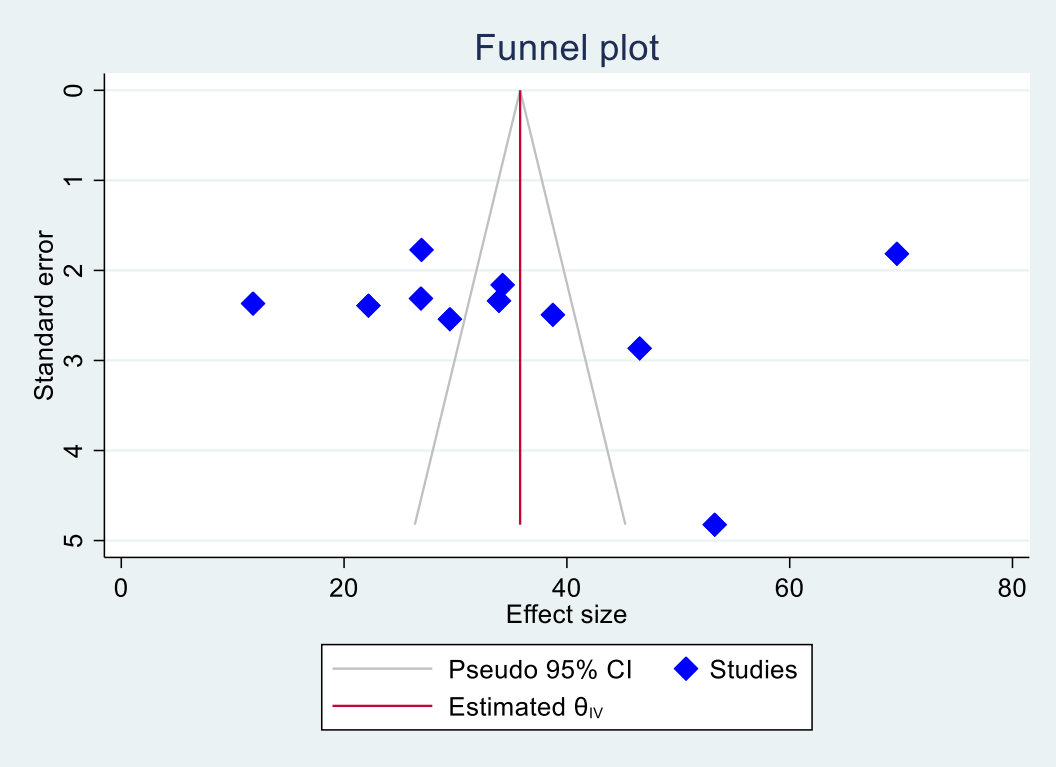

Fig. 6 Funnel plot showing the results of the publication bias among studies.

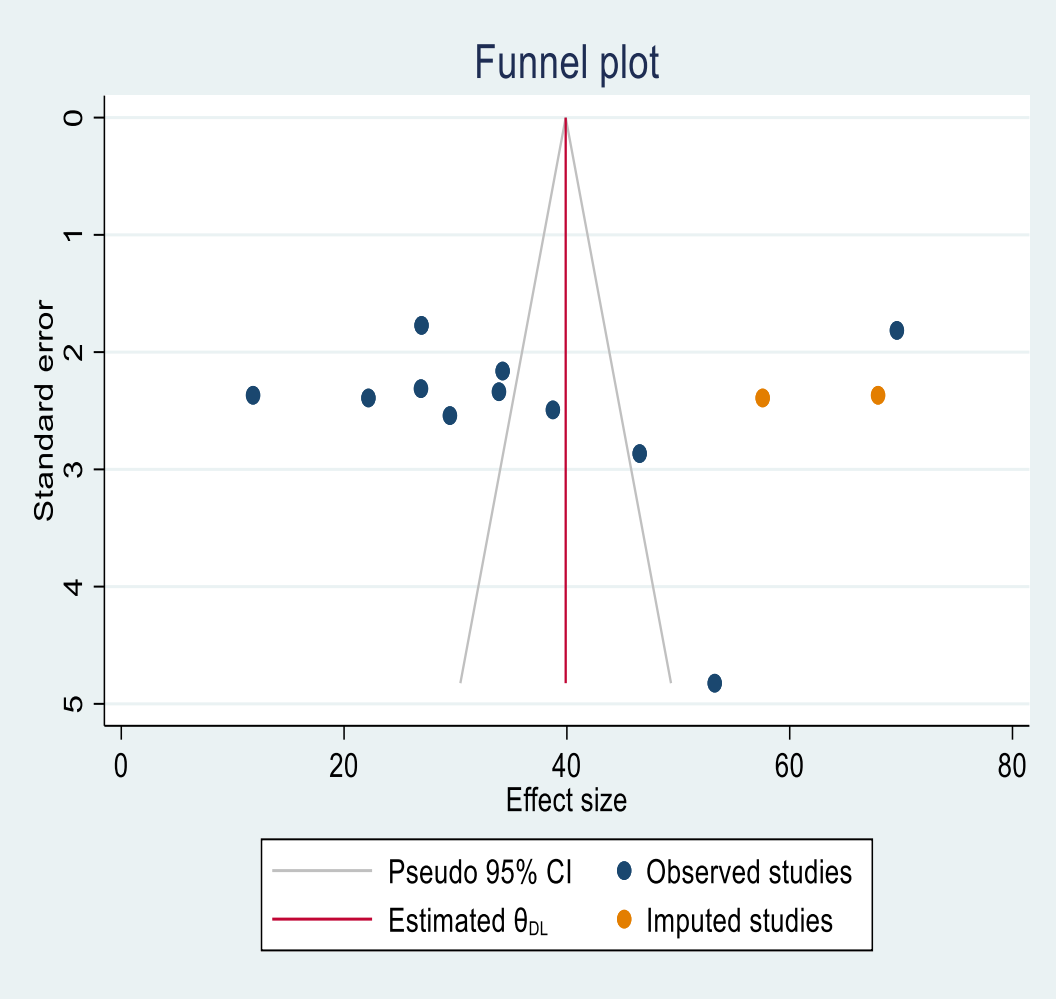

Fig. 7 Funnel plot after trim and fill analysis for the pooled mortality rate among breast cancer patients in Ethiopia

The Full Search Strategy (Or Strategies) For All Databases

Title: **Survival status and Predictors of mortality among breast cancer patients in Ethiopia: A Systematic Review and Meta-analysis**

Search

1. **PubMed**
    - MeSH Heading:
        - Breast cancer: "breast cancer," "breast neoplasm," "breast tumor," "mammary cancer," "outcomes of breast cancer," "breast malignancy,"
        - Mortality rate: "survival status," "survival rate," "mortality," "death," "mortality rate,"
        - Predictor: "predictors," "determinant," "risk factors,"

    Combination**:** ((((((((((((((breast cancer[Title/Abstract]) OR (breast neoplasm[Title/Abstract])) OR (breast tumor[Title/Abstract])) OR (mammary cancer[Title/Abstract])) OR (outcome breast cancer[Title/Abstract]))) OR (breast malignancy[Title/Abstract])) AND (mortality rate[Title/Abstract])) OR (survival status[Title/Abstract])) OR (mortality[Title/Abstract])) OR (death[Title/Abstract])) OR (mortality rate[Title/Abstract])) OR (survival rate[Title/Abstract]))) AND (predictor[Title/Abstract])) OR (determinant[Title/Abstract])) OR (risk factor[Title/Abstract])) AND (Ethiopia[Title/Abstract])

    - Date: 15/06/2024
    - Number of Articles: 183
2. **Google Scholar**

- Advanced search:
  With all of the words - Survival status and Predictors of mortality among breast cancer patients
  With the exact phrase – breast cancer, Ethiopia
  With at least one of the words- “breast neoplasm," "breast tumor," "mammary cancer," "outcomes of breast cancer," "breast malignancy,"
  Date: 21/06/2024
- Number of articles: 236

3. **Web Of Science**
    - Combination: "Breast cancer" OR "Breast carcinoma" OR "Breast neoplasm" OR "Breast Tumor" OR "Breast malignancy" OR "mammary cancer" OR "human mammary carcinoma" OR "malignant neoplasm of the breast" OR "human mammary neoplasm" (Topic) and "survival status" OR "survival rate" OR death OR "mortality rate" OR mortality and predictors OR determinant OR” risk factors” (Topic) and Ethiopia (Topic) and English (Languages)

- Date:28/07/2024
- Number of articles: 178

4. **Embase**
    - Combination: exp breast cancer/ OR Breast neoplasm. mp. OR exp breast carcinoma/ OR exp breast tumor/ OR Breast malignancy. mp. OR mammary cancer.mp OR human mammary carcinoma. mp. OR malignant neoplasm of Breast.mp. OR human mammary neoplasm. mp. AND mortality rate. mp. OR mortality. mp. OR death. mp. OR survival status. mp. OR survival rate. mp.AND exp Ethiopia/ or (Ethiopia).
    - Date: 09/07/2024
    - Number of articles: 47
5. **Scopus**

- Combination: survival status AND predictors AND of AND mortality AND among AND breast AND cancer AND patients AND Ethiopia AND (LIMIT-TO (EXACT KEYWORD, "Human")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (TITLE-ABS-KEY, “Ethiopia”)
- Date: 15/07/2024
- Number of articles: 30

BMJ Open

Survival status and Predictors of mortality among breast cancer patients in Ethiopia: A Systematic Review and Meta-analysis

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Manuscript ID	bmjopen-2024-092725.R1
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health services research
Keywords:	Ethiopia, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health Surveys

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Survival status and Predictors of mortality among breast cancer patients in Ethiopia: A Systematic Review and Meta-analysis

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Abstract

Objectives: This study aimed to evaluate survival outcomes and identify key mortality predictors among breast cancer patients in Ethiopia.

Study design: A systematic review and meta-analysis.

Study participants: The study used eleven primary studies, involving a total of 4,131 participants.

Data sources: We searched PubMed, Embase, Web of Science, Scopus, and Google Scholar until March 7, 2025, following PRISMA guidelines.

Eligibility criteria for selecting studies: All observational studies that had reported the survival status and/or at least one predictor of mortality of women breast cancer patients were considered.

Data extraction and synthesis: Three independent reviewers (HA, HKN, DGA) used a structured data extraction form to extract the data. To compute the pooled survival and mortality rates, the survival rates at different observation periods and the mortality rates reported in the included studies were extracted.

Results: Eleven studies were analyzed. All studies were of good quality based on NOS. However, heterogeneity was high (I^2 = 98.2%, p = 0.00). Funnel plots showed significant publication bias. GRADE assessment indicated moderate certainty for mortality rates and predictors, limited by heterogeneity and regional data gaps. The pooled mortality rate was 36% (95% CI: 25% - 46%). Survival rates at one, three, and five years were 85% (95% CI: 75%–96%), 66% (95% CI: 48%–84%), and 22% (95% CI: 1%–43%), respectively. Key mortality predictors included advanced clinical stage (AHR: 4.14; CI: 2.53–6.78), rural residence (AHR: 1.65; 95% CI: 1.27-2.14), positive lymph node status (AHR: 2.85; 95% CI: 1.50-5.44), no hormonal therapy (AHR: 2.02; 95% CI: 1.59-2.56), histologic grade III (AHR: 1.76; 95% CI: 1.29–2.41), hormone receptor negativity (AHR: 1.54; 95% CI: 1.05–2.25), and comorbidities (AHR: 2.24; 95% CI: 1.41–3.56).

Conclusion: Breast cancer in Ethiopia poses a high mortality rate primarily due to late-stage diagnosis, rural residency, histologic grade III, positive lymph node status, and comorbidities. To improve survival outcomes, it is crucial to expand access to early screening, particularly in rural areas, implement comprehensive treatment protocols, and strengthen healthcare infrastructure to address these critical factors.

PROSPERO registration number: CRD42024575074

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information. Extracted data are available on request to the corresponding author.

Strengths and limitations

- This systematic review and meta-analysis represent a national estimation conducted in Ethiopia.
- However, it may lack full national representativeness, as no data were available from the Benishangul Gumuz, Afar, Gambella, Somalia, Dire Dawa, and Harar regions.
- Additionally, we were unable to compare the impact of different treatment modalities on breast cancer mortality due to the lack of available data.

Introduction

Breast cancer is a leading cause of cancer-related morbidity and mortality in the world, with 2.3 million new cases and 685,000 deaths reported in 2020 [1]. Despite challenges in diagnostic systems in Africa, breast cancer accounts for one in four diagnosed cancers and one in five cancer deaths among women [2]. With an expected 15,244 new cases and 8,159 deaths from the disease in 2018, breast cancer is the most common cancer in Ethiopia and the primary cause of cancer-related deaths among women [3]. Common risk factors for breast cancer in Ethiopia include a family history of the disease, early menarche, post-menopausal status, and never having breastfed [4]. Without early detection and treatment, breast cancer can lead to local and distant metastases, ultimately resulting in death [5].

The five-year survival rate for breast cancer varies significantly from country to country due to differences in healthcare systems, early detection programs, lifestyles, and socioeconomic status. For instance, the five-year survival rate for breast cancer patients is 84% in the US, 89.5% in Australia, 81% in Europe [6], 69.55% in Iran [7], 74% in Vietnam [8], 51.07% in Indonesia [9], 49.45% in Malaysia [9], and 66.1% in India [10]. In Sub-Saharan Africa, the five-year survival rate is 53.4% in South Africa [11].

The survival of breast cancer patients is influenced by various factors, including socio-demographic variables (age, education, financial status, and family history), tumor characteristics

(size, nodal status, metastasis, stage, location, and histology grade), comorbidities, and treatment type [12, 13].

In Ethiopia, although some primary studies have reported the overall five-year survival rate, mortality rate, and predictors of breast cancer [14-16], there is a lack of comprehensive data on the national survival status and predictors of mortality among breast cancer patients. Understanding survival outcomes and associated factors is crucial for improving cancer care and guiding evidence-based interventions. Therefore, this systematic review aims to comprehensively evaluate the survival outcomes and identify key predictors of mortality among breast cancer patients in Ethiopia. By addressing the existing knowledge gaps, this review will provide valuable insights into the current situation and highlight critical factors influencing survival. Furthermore, the findings will be compared with evidence from other settings globally, offering a broader perspective for tailoring healthcare interventions and policy recommendations in the Ethiopian context.

Methods

Study protocol registration and reporting

The protocol for this systematic review and meta-analysis was registered in the PROSPERO database (Registration ID: CRD42024575074) according to PRISMA guidelines [17]. At the time of registration, no secondary outcome measures were planned. However, during the review process, the idea of secondary outcome analysis emerged to provide a more comprehensive understanding of the research question. This additional analysis was included to enrich the findings without altering the study's primary objectives.

Search strategies and sources of information

Searches were conducted in PubMed, Embase, Scopus, Web of Science, and Google Scholar databases to identify relevant articles. The search terms used included "breast cancer," "breast neoplasm," "breast tumor," "mammary cancer," "outcomes of breast cancer," "breast malignancy," "survival status," "survival rate," "mortality," "death," "mortality rate," "predictors," "determinant," "risk factors," and "Ethiopia." These terms were combined using the search operators "OR" and "AND" (Supplementary file 1). Cross-references from the bibliographies of

selected studies were also reviewed to enhance search coverage. All search records were imported into EndNote X9, where duplicates were eliminated.

Inclusion and exclusion criteria

All observational studies that had reported the survival status and/or at least one predictor of mortality of women breast cancer patients were considered. The review included only studies available online until March 7, 2025. Citations without abstracts and/or full text, anonymous reports, editorials, case reports, and qualitative studies were excluded from the analysis (Table S1).

Data extraction

Three independent reviewers (HA, HKN, DGA) used a structured data extraction form to extract the data. The extraction process was repeated when variations in the extracted data were observed. If discrepancies between the reviewers persisted, another two reviewers (NDB and LM) were involved in resolving them. The data extraction form included the following details: author, year of publication, region, study design, sample size, median survival time, study quality, survival rate at one, three, and five years, overall mortality rate, and selected predictors of breast cancer mortality.

Quality assessment

The quality of the cohort studies was assessed using the Newcastle-Ottawa Scale (NOS) by two independent reviewers. This tool assesses three key components: the selection of study groups, the comparability of study groups, and the ascertainment of exposure or outcome [18]. The primary component, focusing on the methodological quality of each study, was rated on a four-star scale. The second component, addressing the comparability of the studies, was graded with up to two stars. The final component, which evaluated the results and statistical analysis of each study, was graded with up to three stars. Overall, the NOS uses three categorical criteria to assign a maximum score of 9 points. Studies with scores of ≥7 points were categorized as "good" quality, those scoring 4 to 6 points as "fair" quality, and those with ≤3 points as "poor" quality (Table S2).

The quality of the cross-sectional study included in this systematic review and meta-analysis was assessed using the modified Newcastle-Ottawa Quality Assessment Scale for cross-sectional studies [19]. This evaluation encompassed various domains, including methodological quality,

sample selection, sample size, comparability of groups, outcome assessment, and statistical analysis (Table S3).

Outcome measurement

The first of the two outcomes of this study is survival status, which refers to whether study participants are alive or dead. This outcome is expressed as the survival rate or mortality rate. The survival rate was computed by multiplying by 100 and dividing the total number of observed patients by the number of living patients at one, three, or five years of follow-up. Similarly, the mortality rate was calculated by dividing the number of deaths during the follow-up period by the total number of observed patients and multiplying by 100. The secondary outcome of this analysis focused on identifying predictors of mortality among breast cancer patients in Ethiopia.

Data processing and analysis

The required data were extracted into an Excel spreadsheet and then transferred to STATA version 17 software for advanced statistical analysis. The general characteristics of the primary studies were summarized in tables. To compute the pooled survival and mortality rates, the survival rates at different observation periods and the mortality rates reported in the included studies were extracted. Each survival rate's natural logarithm (LN) was calculated, and the standard errors for both the survival rates and the log-transformed survival rates were computed using Excel. Similarly, for the hazard ratio (HR) calculation, the hazard ratios and their lower and upper boundary confidence intervals (CIs) were extracted. The LN of each hazard ratio was calculated, and the standard errors of the log-transformed hazard ratios were determined. These calculations, conducted in Excel, provided input data for the meta-analysis to ensure accuracy and consistency. The Cox proportional hazards (PH) model was used for multivariate analysis. This semi-parametric model allows for the adjustment of multiple covariates simultaneously, providing hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards (PH) assumption was checked using Log-Log Plots - Visual inspection of log-log survival curves was conducted to confirm parallelism.

Heterogeneity test, publication bias, and certainty evidence

The Cochran Q-test and Higgins's I^2 test statistics were calculated to evaluate heterogeneity across all studies. In this context, I^2 values of 25%, 50%, and 75% indicate low, moderate, and high

heterogeneity, respectively [20]. Given the anticipated heterogeneity in breast cancer outcomes across different regions and healthcare settings in Ethiopia, a random-effects model was selected a priori to account for variability between studies [21]. This approach provides a more conservative estimate of the overall effect size and is better suited for synthesizing data from studies with high heterogeneity. To ensure the robustness of the model, subgroup Analysis was done where studies were stratified by region, sample size, and publication year to identify potential sources of heterogeneity. To assess publication bias, a funnel plot was generated, and Egger's test was performed with a significance level of less than 0.05 [22, 23]. To assess and adjust for potential publication bias, we conducted a trim-and-fill analysis using the random-effects model. This method estimates the number of missing studies due to publication bias and recalculates the pooled effect size after inputting these studies.

The certainty of evidence for the pooled estimates of survival rates, mortality rates, and predictors of mortality was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. The GRADE approach evaluates the certainty of evidence based on five domains: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. The certainty of evidence is categorized into four levels: high, moderate, low, or very low.

Sensitivity Analysis

To assess the robustness of the pooled estimates, a leave-one-out sensitivity analysis was conducted. This involved systematically excluding each study one at a time and recalculating the pooled mortality rate to determine whether any single study had a disproportionate influence on the overall results. The analysis was performed using STATA version 17, and the results were compared to the original pooled estimates to evaluate consistency.

Patient and public involvement

None

Results

Characteristics of Included Studies

A total of 674 articles were initially retrieved from PubMed, Embase, Web of Science, Scopus, and Google Scholar databases. After removing 243 duplicates, 431 articles remained. Screening titles and abstracts led to the exclusion of 395 articles. The full texts of the remaining 36 articles were assessed, resulting in the exclusion of 25 due to different outcomes or failure to report the outcome of interest. Finally, 11 studies met the inclusion criteria and were included in this systematic review and meta-analysis. Fig. 1 depicts the retrieval procedure in detail.

Based on our assessment, using NOS, all the studies were of good quality. These studies were conducted between 2018 and 2024 and involved a total of 4,131 patients diagnosed with breast cancer and started follow-up. Four of the studies were conducted in the Amhara region [14, 24-26], three in Addis Ababa [27-29], two in the Southern Nations, Nationalities, and Peoples' (SNNP) Region [30, 31], one in Oromia region [32], and one in Tigray region [33]. In terms of study design, only one study employed a retrospective cross-sectional approach [29], which was considered only for the determination of the mortality rate. In contrast, the others utilized a cohort study design. Based on publication years, only three studies were published before 2020 [27, 29, 32]. According to the findings of primary studies, the mortality rate among breast cancer patients ranged from 11.8% [34] to 69.6% [31], and all of them were institution-based studies (Table S4).

The median age of participants ranged from 39 to 47 years across the studies, with most patients being diagnosed in their early 40s. However, age categorization varied significantly between studies, limiting the ability to pool age-specific outcomes. A significant proportion of patients were diagnosed at advanced stages (Stage III and IV), with reported rates ranging from 56.2% to 83.4% across studies. Rural residency significantly varied across studies ranging from 29.1% to 64%.

Pooled survival status among breast cancer patients in Ethiopia

A total of eleven studies were analyzed to estimate the pooled mortality rate among breast cancer patients. The heterogeneity among these studies was very high, with an I^2 value of 98.2% ($p = 0.00$). Using a random-effects model, the pooled mortality rate was calculated to be 36% (95% CI: 25% - 46%) (Fig 2). The leave-one-out sensitivity analysis demonstrated that the pooled mortality rate and survival rates were robust to the exclusion of any single study. The pooled mortality rate remained within the range of 34% to 38% (95% CI: 23%–47%) when each study was excluded, indicating that no single study had an undue influence on the overall estimate.

Four studies reported a one-year survival rate, based on a combined sample size of 1,446 patients. The random-effects model analysis showed significant heterogeneity (I^2 = 96.99%, p = 0.00) and estimated a one-year survival rate of 85% (95% CI: 75%–96%). Three studies provided data on the three-year survival rate, with a total sample size of 1,339 patients. The analysis indicated substantial heterogeneity (I^2 = 98.02%, p = 0.00) and estimated a three-year survival rate of 66% (95% CI: 48%–84%). Three studies also reported the five-year survival rate, with a combined sample size of 1,519 patients. The random-effects model analysis showed very high heterogeneity (I^2 = 99.25%, p = 0.00) and estimated the five-year survival rate to be 22% (95% CI: 1%–43%).

Subgroup analysis of mortality rate

To address the observed heterogeneity in the study (I^2 = 98.2%), a subgroup analysis of mortality rates was conducted based on region, sample size, and year of publication. The analysis by region revealed that the mortality rate among breast cancer patients was highest in studies conducted in the SNNPR (52%, 95% CI: 49% - 55%), compared to those in the Amhara region (34%, 95% CI: 31%-38%) and Addis Ababa (33%, 95% CI: 22% - 44%) (Fig 3). Additionally, when analyzing based on sample size, studies with more than 384 participants reported a higher mortality rate (41%, 95% CI: 21% - 62%) than those with 384 or fewer participants (32%, 95% CI: 23%-42%) (Fig 4). Furthermore, studies published before 2020 showed a higher breast cancer mortality rate (42%, 95% CI: 25% - 59%) compared to those published in 2020 or later (33%, 95% CI: 20% - 49%) (Fig 5).

Publication bias

To evaluate publication bias, we utilized a funnel plot and Egger's regression test. An uneven distribution in the funnel plot is a subjective indicator of publication bias. Although the objective p-value from Egger's regression test was 0.792, indicating no significant publication bias, we concluded that publication bias was present (Fig. 6).

Trim and fill analysis

In our systematic review, we employed a funnel plot and Egger's regression test to assess the presence of publication bias. The funnel plot revealed an asymmetrical distribution, which is a visual indicator of potential bias. To mitigate the impact of this bias on our pooled mortality rate, we conducted a trim-and-fill analysis. This method adjusts for publication bias by identifying and

'trimming' outlier studies that cause asymmetry in the funnel plot. It then fills the plot with imputed studies, symmetrically opposite to trimmed studies, to reflect a more accurate distribution of the data. As a result of this process, two additional studies were included in our analysis. This adjustment aims to provide a more balanced and unbiased estimate of the pooled effect, enhancing the validity of our review's conclusions (Fig 7).

Predictors of breast cancer mortality

Data on ten variables—cancer clinical stage, lymph node status, residence, hormonal therapy, menopausal status, histologic grade at diagnosis, hormone receptor status, comorbidities, tumor size, and use of chemotherapy—were extracted into an Excel spreadsheet as two-by-two tables and analyzed separately. The analysis identified advanced cancer stage (stage III and IV), rural residence, positive lymph node status, no hormonal therapy, histologic grade III, hormone receptor negativity, and comorbidities as significant predictors of breast cancer mortality. Specifically, patients diagnosed at advanced cancer stages (III and IV) had a 4.14 times higher hazard of death compared to those diagnosed at stage I (AHR: 4.14; CI: 2.53–6.78). Rural residents experienced a 65% higher hazard of death compared to urban residents (AHR: 1.65; 95% CI: 1.27–2.14). Patients with positive lymph node status faced nearly three times the hazard of death compared to those with negative lymph node status (AHR: 2.85; 95% CI: 1.50–5.44). Similarly, patients who did not receive hormonal therapy had a twofold higher hazard of death compared to those who received it (AHR: 2.02; 95% CI: 1.59–2.56). Patients with negative hormone receptor status had a 54% higher hazard of death compared to those with positive hormone receptor status (AHR: 1.54; 95% CI: 1.05–2.25). The hazard of death was 76% higher for patients with histologic grade III tumors compared to those with grade I tumors (AHR: 1.76; 95% CI: 1.29–2.41). Additionally, patients with comorbidities experienced a 124% higher hazard of death compared to those without comorbidities (AHR: 2.24; 95% CI: 1.41–3.56) (Table S5). Pooling the effect sizes for some variables was not feasible due to inconsistencies in categorization across primary studies. For instance, while four studies examined the effect of age on breast cancer mortality, the effect sizes could not be pooled because of inconsistent age categorizations.

Discussion

In Ethiopia, breast cancer continues to be the most common cancer and the main cause of cancer-related death [35]. Moreover, limited resources, insufficient screening programs, and challenges in early diagnosis and treatment may contribute to rising mortality rates [36]. The survival outcomes and predictors of mortality among breast cancer patients reported in primary studies in Ethiopia show considerable inconsistency. Therefore, this study aimed to determine the pooled survival outcomes and identify predictors of mortality among breast cancer patients in Ethiopia.

The 1- and 3-year survival rates observed in our study align with findings from similar reviews conducted in various regions around the world [37-41]. However, we observed a great variation in a 5-year survival rate between our study and studies done both in developed and developing countries in the world. Thus a 5-year survival rate in our study is much lower than a study done in the USA, which was reported by Siegel et al. [42]. The 5-year survival rate for women with breast cancer in developing countries, reported in Uganda and in Zimbabwe, was also higher than the rate observed in our study [43]. The differences in survival rates among these studies can indeed be attributed to host factors, tumor factors, and medical factors, with a significant emphasis on the availability and effectiveness of screening programs, early detection, and access to modern medical care [38]. However, the higher survival rates observed in American and European countries compared to our study are likely due to the impact of screening programs, early detection, and advancements in modern medical care [44, 45].

This systematic review and meta-analysis revealed that one in three breast cancer patients succumb to the disease. This mortality rate exceeds the national average death rate for cervical cancer [46], and lung cancer [47], but is lower than the mortality rate for colorectal cancer [48].

In this systematic review, we have identified several critical factors that significantly contribute to breast cancer mortality. These include advanced cancer stage at diagnosis, rural residence, positive lymph node status, no hormonal therapy, histologic grade III, hormone receptor negativity, and the presence of comorbidities. In the discussion that follows, we will delve into the implications of these predictors, exploring how each factor individually and collectively influences mortality outcomes in breast cancer patients.

The prevalence of advanced-stage breast cancer diagnosis among patients in Ethiopia is significantly high [49]. According to our review, this prevalent factor increases the hazard of death by fourfold among breast cancer patients. This association was also observed in previous studies

conducted in Hawaii, USA, Nigeria, and Uganda [50-54]; more importantly, Bray et al. point out that the prognosis of breast cancer is much better when the disease is detected early, increasing a 5-year survival rate by about two times for localized cases. However, this rate drops drastically to around twenty-five percent for cases where the disease has metastasized [55]. This information emphasizes the importance of early detection and timely intervention in improving survival rates for breast cancer patients.

Our findings also revealed that breast cancer patients in rural areas have a higher mortality rate compared to those in urban areas. This outcome is consistent with studies conducted across different regions [56]. The higher mortality hazard can be attributed to lower levels of health awareness in rural communities. Moreover, even those who were aware of their condition often faced challenges accessing healthcare services due to limited resources in local hospitals. Supporting this, a study found that women living in rural areas had significantly lower odds of receiving different treatment modalities like surgery, radiation, and surgery with radiation [57].

Patients with positive lymph node status faced an increased hazard of death compared to those without. This result was consistently observed in multiple studies conducted across various countries [58, 59]. This could be the result of a higher recurrence rate that is linked to a worse survival rate [60].

This review also highlights a significant finding: women diagnosed with histologic grade III breast cancer faced a mortality rate that was 76% higher than those diagnosed with grade I. This finding aligns with previous studies conducted in various Asian countries [61-63], which have similarly reported poorer outcomes for patients with higher-grade tumors. The reason behind this could be attributed to the aggressive nature of high-grade cancer cells, which are typically more invasive and linked to a worse prognosis [64].

Moreover, the review underscores the strong association between co-morbidities and the increased hazard of mortality in breast cancer patients. This finding is consistent with earlier research from different countries [65-67]. The increased vulnerability to treatment toxicity, possibly due to the physiological disturbance of patients with existing co-morbid conditions, may explain this correlation [68]. Additionally, the presence of co-morbidities may influence the cancer's morphology, histology, differentiation, and proliferation status [69], further complicating the disease and its treatment outcomes.

The review identified no hormone therapy as another significant predictor of mortality, revealing that individuals who underwent hormone therapy had a 100% lower risk of death compared to those who did not receive such treatment. These findings align with previous research conducted across various continents [8, 62, 70, 71]. About this, our review also revealed that the hazard of mortality was significantly higher in patients with hormone receptor-negative tumors compared to those with hormone receptor-positive tumors. This finding aligns with the results of previous studies [72, 73]. One possible explanation for this disparity is that women with hormone receptor-positive tumors tend to present with more favorable clinical characteristics. Specifically, they are more likely to have early-stage tumors, exhibit moderate differentiation, have negative lymph node status, and achieve clear deep surgical margins [74, 75]. These factors contribute to better overall prognosis and lower mortality risk in hormone receptor-positive patients compared to their hormone receptor-negative counterparts.

This review has several limitations. The high heterogeneity among studies, likely due to variations in sample size, geographic location, and healthcare quality, may affect the pooled estimates and generalizability of results. While a random-effects model was used, the wide confidence intervals suggest cautious interpretation. Although Egger's test showed no significant publication bias, funnel plot asymmetry indicates potential unpublished studies, possibly overestimating mortality rates. Data gaps from regions like Benishangul Gumuz, Afar, and Gambella limit national representativeness, as outcomes may vary due to differences in healthcare access and socioeconomic factors. Variability in study quality, inconsistent categorization of variables (e.g., age, tumor size), and lack of data on treatment modalities further constrain the analysis. Despite these limitations, the findings underscore the need for improved early detection, standardized data collection, and future research to explore treatment impacts and include underrepresented regions

Conclusion

Breast cancer remains a significant health challenge in Ethiopia, characterized by high mortality rates largely due to late-stage diagnoses. The findings of this review underscore the urgent need for targeted interventions to improve early detection and treatment of breast cancer, particularly in rural areas of Ethiopia. Given the higher mortality rates observed among rural residents, it is crucial to implement community-based screening programs that leverage mobile health units and community health workers to reach underserved populations. These programs should focus on

raising awareness about breast cancer symptoms, the importance of early diagnosis, and the availability of treatment options. Additionally, training local healthcare providers in rural areas to perform clinical breast examinations and refer suspected cases to specialized centers could significantly reduce delays in diagnosis. Strengthening referral systems between rural health facilities and urban cancer treatment centers, coupled with financial support for transportation and treatment costs, could further improve access to timely and effective care. Public health campaigns should also address cultural barriers and stigma associated with breast cancer, encouraging women to seek medical attention at the earliest signs of the disease.

Contributors

The authors have made substantial contributions to this study. H.A. formulated the research question, drafted the initial manuscript, designed the search strategy, revised, and approved the final version of the article. H.K.N. and D.G.A. refined the database search strategy, developed the data extraction form, and approved the final version of the article. L.M. and N.D.B. evaluated the data extraction form and approved the finalized version of the article. Hailu Aragie is the guarantor of this study.

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Competing interests

None declared.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. Extracted data are available on request to the corresponding author.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

This study does not involve human participants. Ethical approval was not required for this systematic review, since all data came from published articles.

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Figure Legends

Figure 1: PRISMA Flow Chart

Figure 1. PRISMA flow chart for the flow of information through the phases of the systematic review.

The chart outlines the process of study identification, screening, eligibility assessment, and inclusion. A total of 674 studies were identified from databases (PubMed, Google Scholar, Web of Science, Embase, and Scopus). After removing duplicates (n = 243), 431 records were screened by title and abstract. Of these, 395 were excluded, and 36 full-text articles were assessed for eligibility. Finally, 11 studies were included in the review.

Figure 2: Forest Plot (Pooled Mortality Rate)

Figure 2. Forest plot showing the pooled mortality rate among breast cancer patients in Ethiopia.

The plot displays the combined mortality rate estimates from included studies. Each study is represented by a square, with horizontal lines indicating the 95% confidence intervals. The diamond at the bottom represents the overall pooled estimate.

Figure 3: Forest Plot (Subgroup Analysis 1)

Figure 3. Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

This plot presents the results of a subgroup analysis, stratifying studies by region. Each subgroup is summarized with its pooled estimate and confidence intervals.

Figure 4: Forest Plot (Subgroup Analysis 2)

Figure 4. Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

This plot provides additional subgroup analysis, comparing mortality rates by sample size. The pooled estimates and confidence intervals are displayed for each subgroup.

Figure 5: Forest Plot (Subgroup Analysis 3)

Figure 5. Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

This plot illustrates further subgroup analysis by publication year. The results are presented with pooled estimates and 95% confidence intervals.

Figure 6: Funnel Plot (Publication Bias)

Figure 6. Funnel plot showing the results of the publication bias assessment among studies.

The funnel plot evaluates potential publication bias in the included studies. Each dot represents a study, plotted by its effect size against its standard error. Symmetry around the vertical line suggests a publication bias.

Figure 7: Funnel Plot (Trim and Fill Analysis)

Figure 7. Funnel plot after trim and fill analysis for the pooled mortality rate among breast cancer patients in Ethiopia.

This plot displays the results of the trim and fill analysis, which adjusts for potential publication bias. The filled studies are shown as additional dots, and the adjusted pooled estimate is indicated.

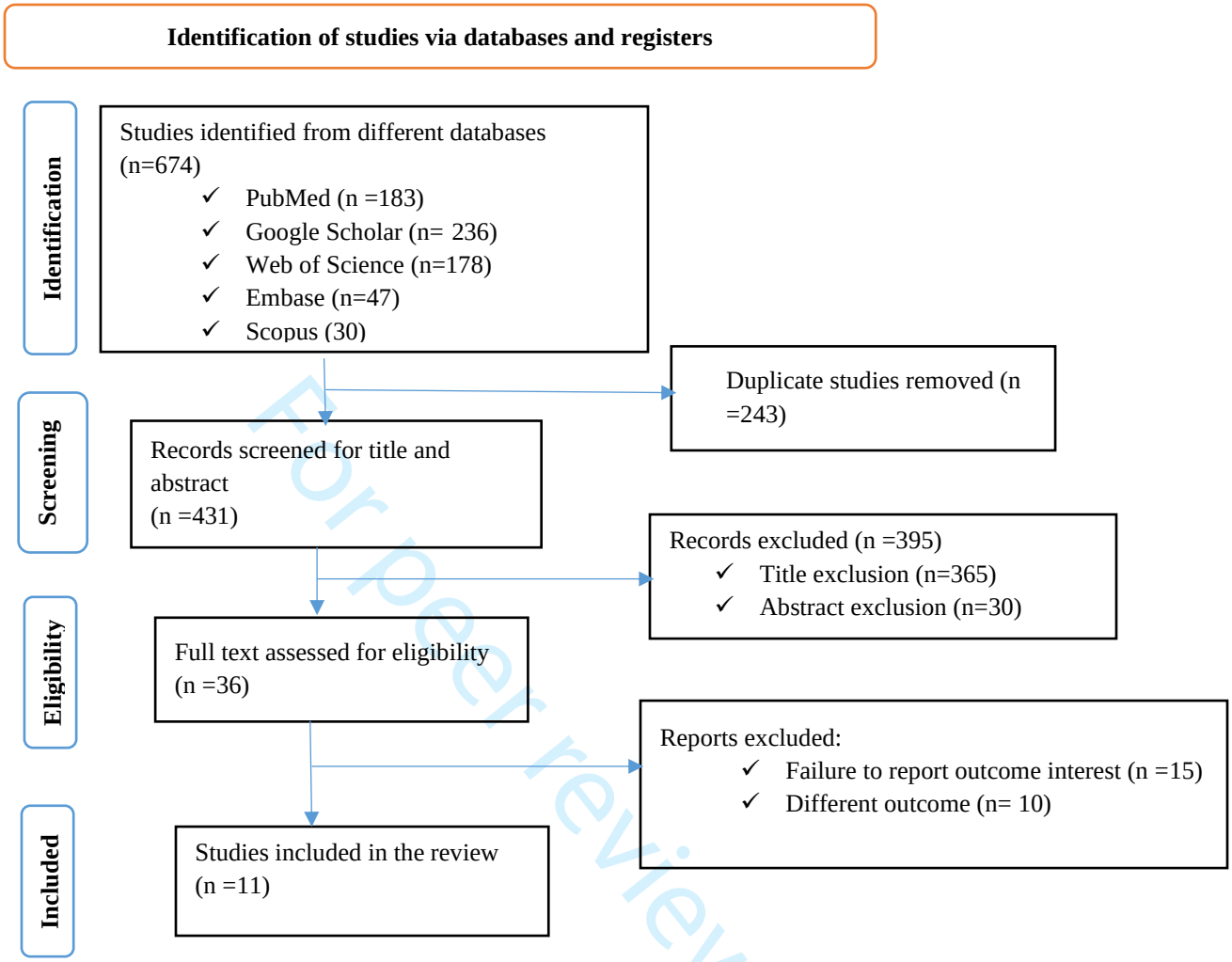

Figure 1: PRISMA flow chart for the flow of information through the phase of systematic review

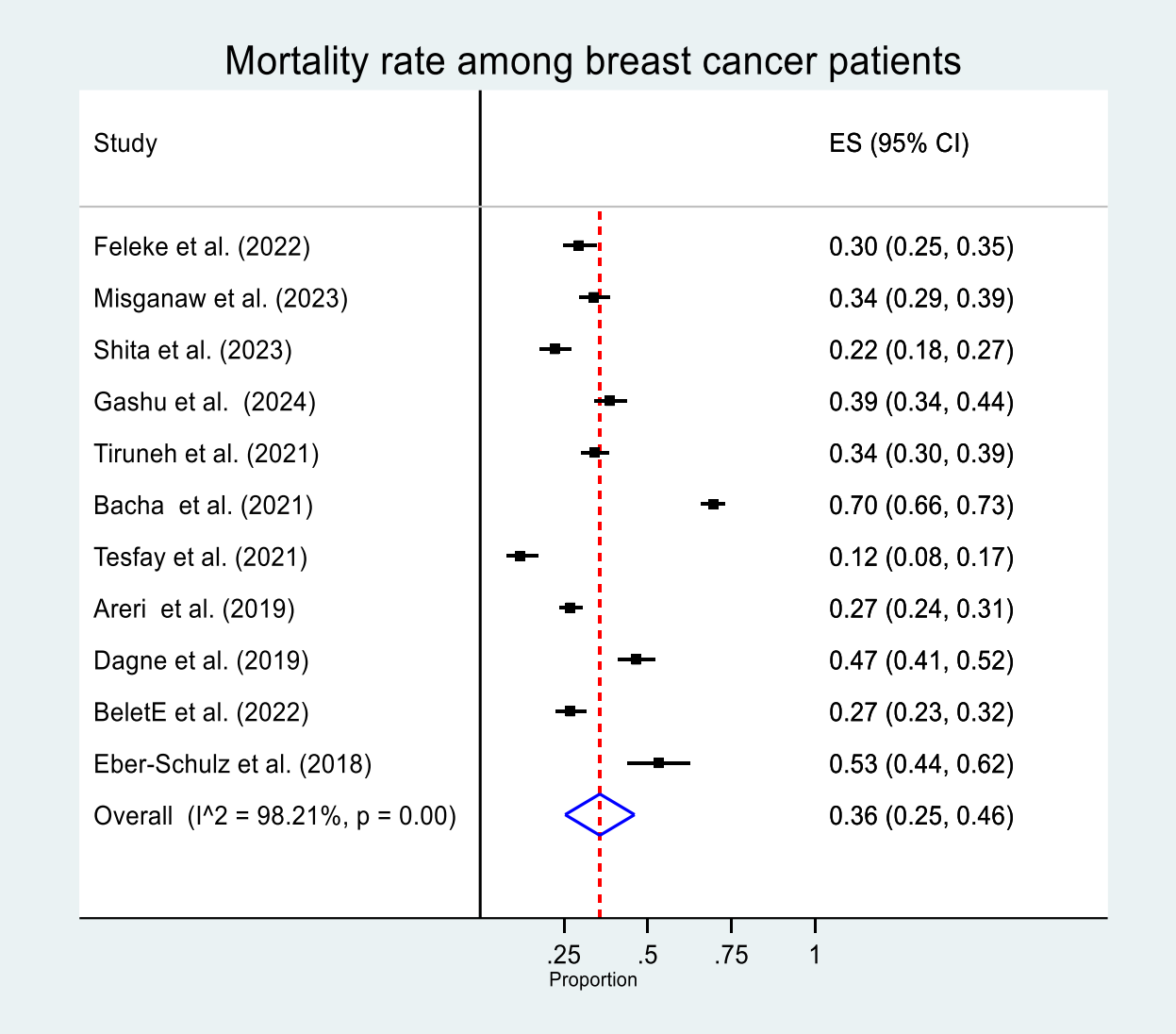

Fig. 2 Forest plot showing the pooled mortality rate among breast cancer patients in Ethiopia.

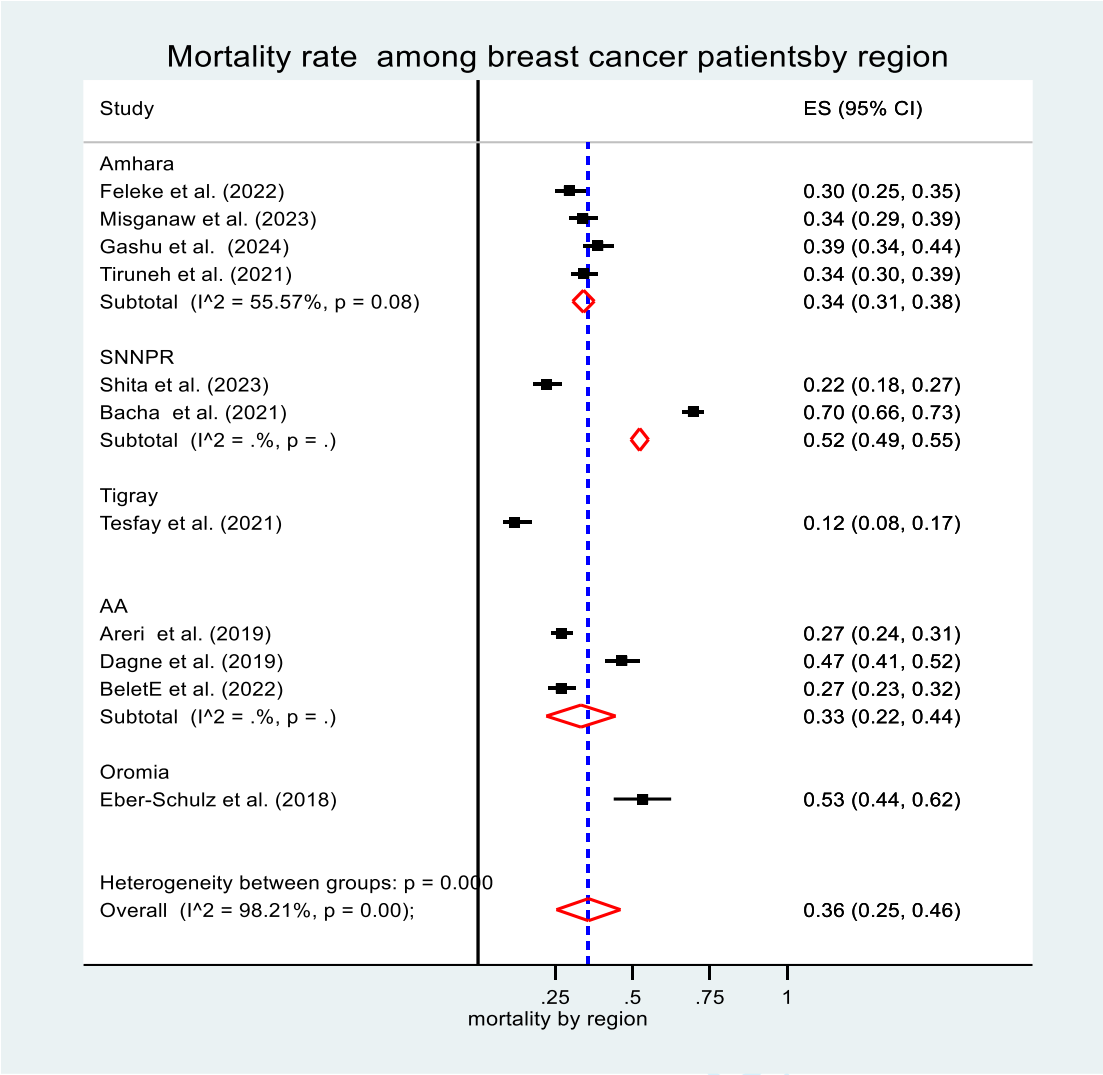

Fig. 3 Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

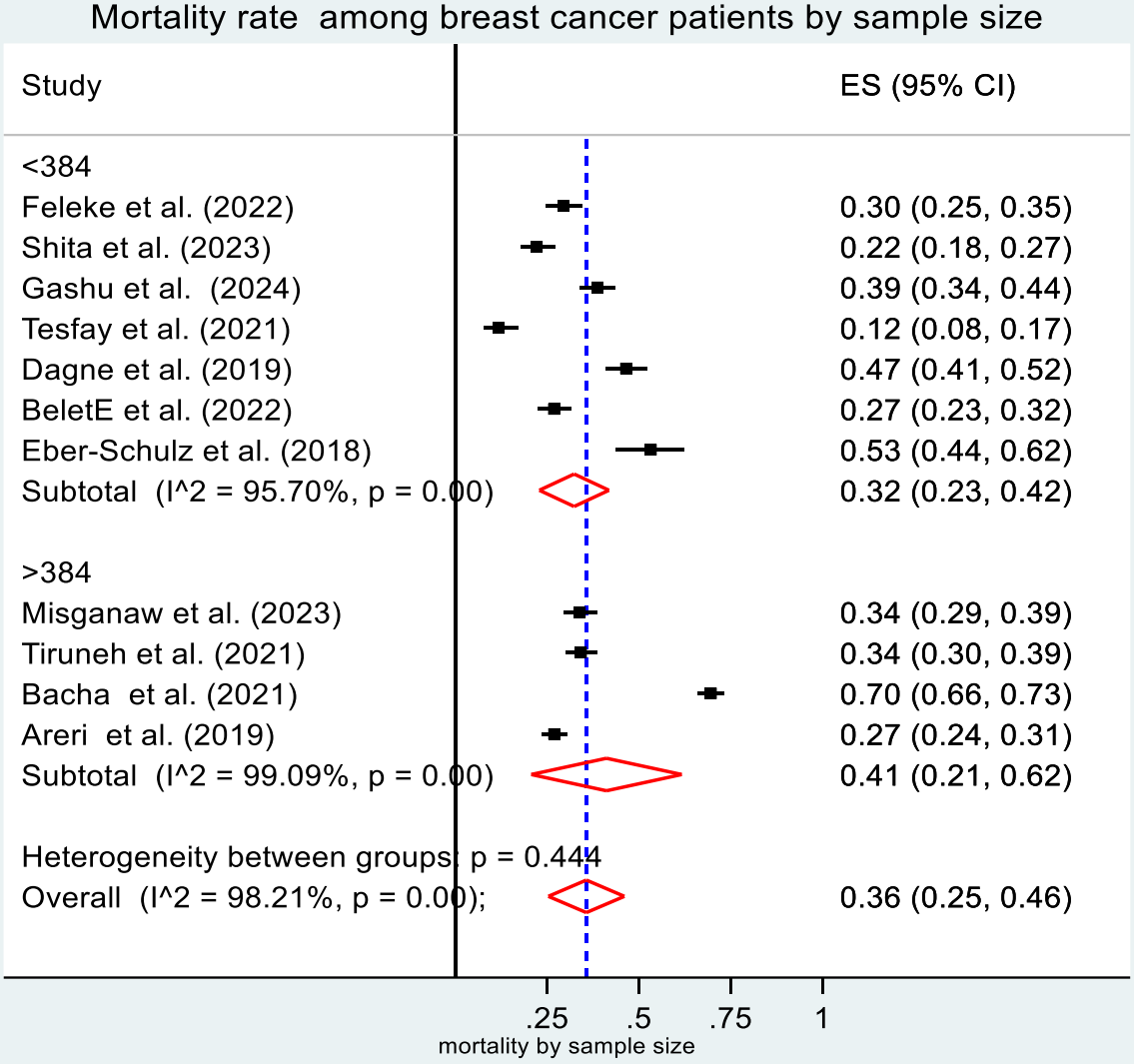

Fig.4 Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

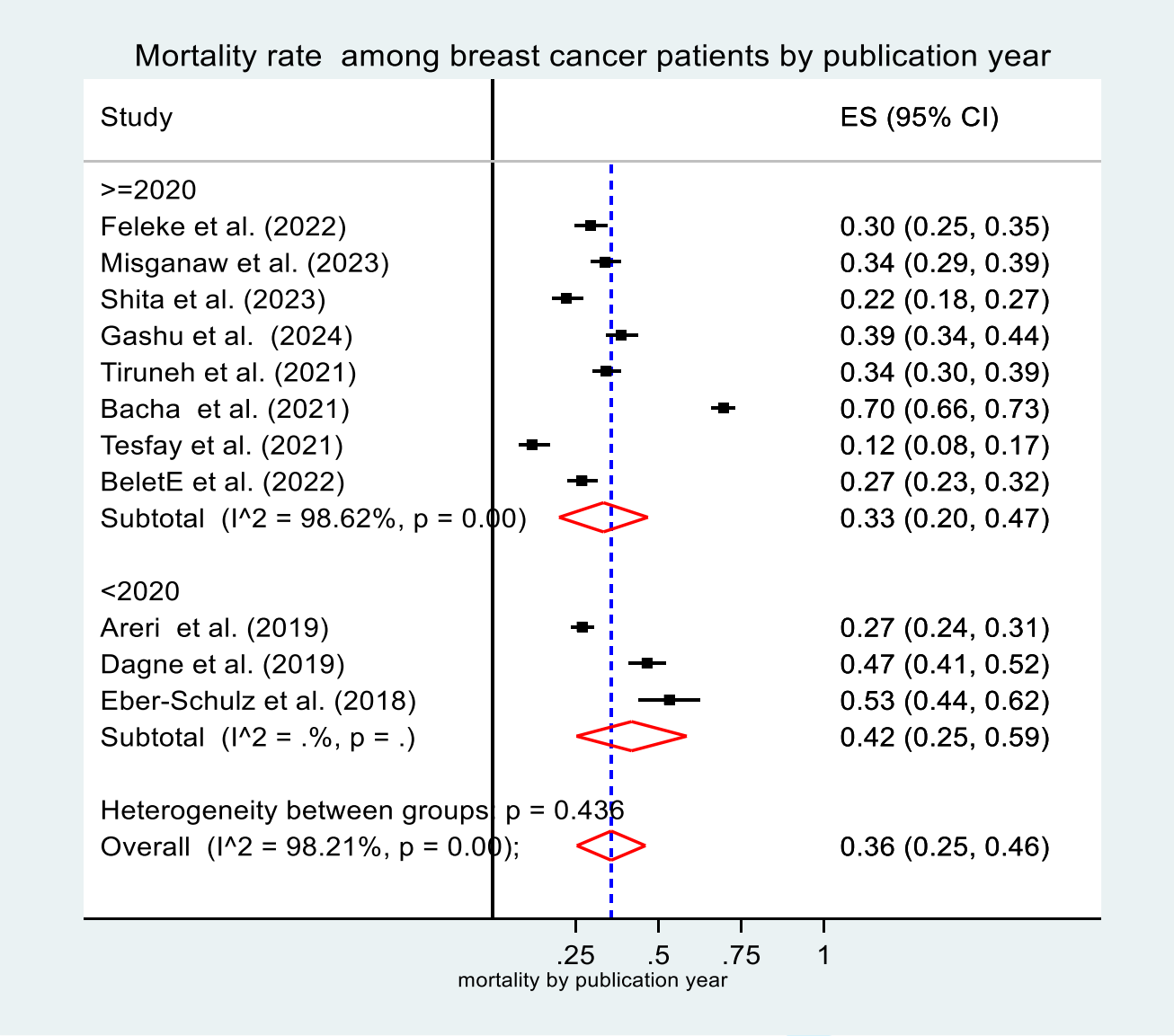

Fig. 5 Forest plot showing the subgroup analysis of mortality rate among breast cancer patients in Ethiopia.

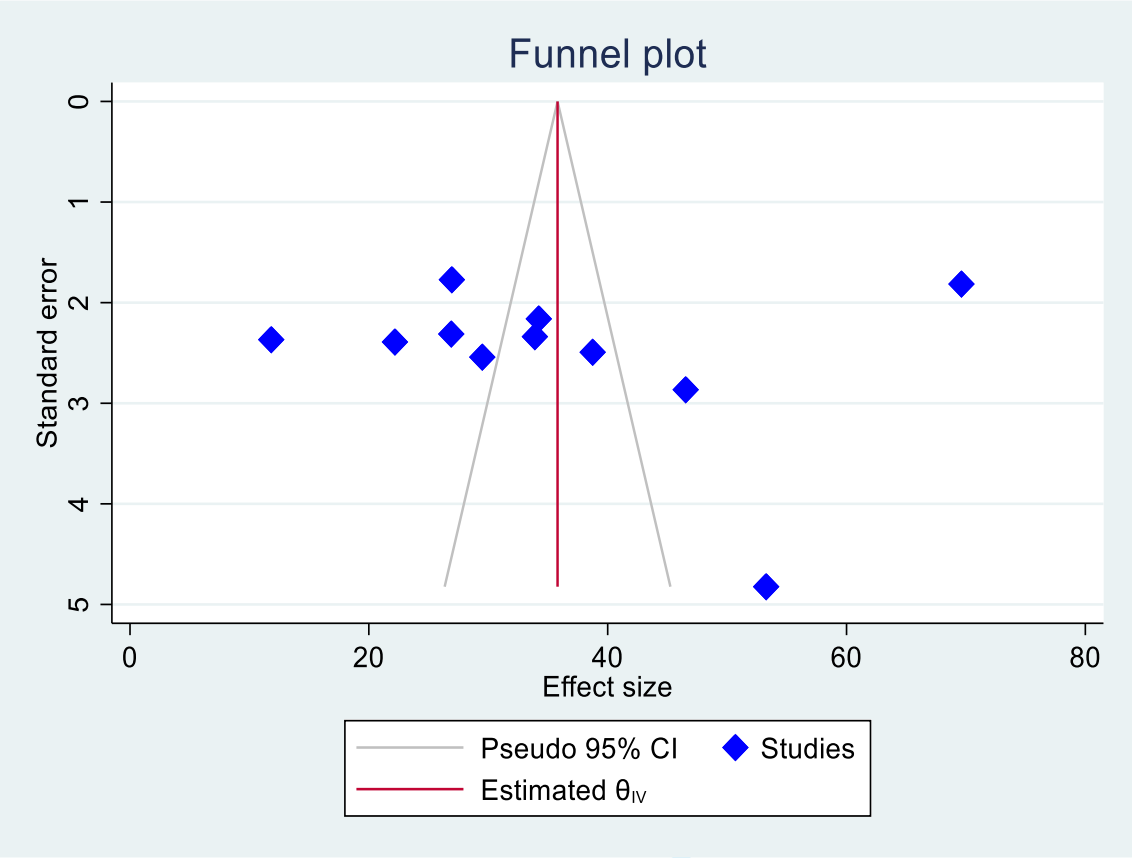

Fig. 6 Funnel plot showing the results of the publication bias among studies.

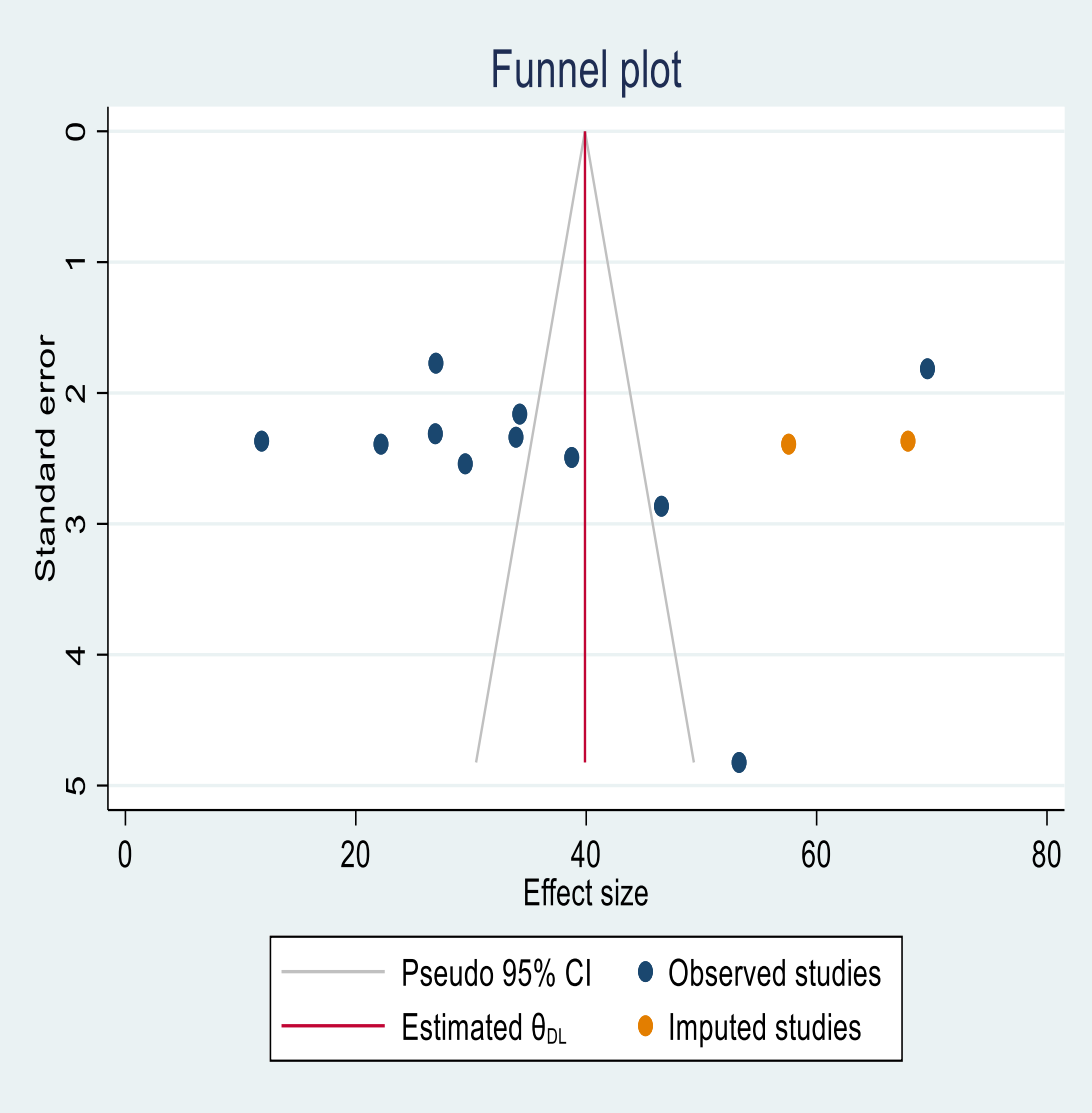

Fig. 7 Funnel plot after trim and fill analysis for the pooled mortality rate among breast cancer patients in Ethiopia

The Full Search Strategy (Or Strategies) For All Databases

Title: **Survival status and Predictors of mortality among breast cancer patients in Ethiopia: A Systematic Review and Meta-analysis**

Search

1. **PubMed**
    - MeSH Heading:
        - Breast cancer: "breast cancer," "breast neoplasm," "breast tumor," "mammary cancer," "outcomes of breast cancer," "breast malignancy,"
        - Mortality rate: "survival status," "survival rate," "mortality," "death," "mortality rate,"
        - Predictor: "predictors," "determinant," "risk factors,"

    Combination**:** ((((((((((((((breast cancer[Title/Abstract]) OR (breast neoplasm[Title/Abstract])) OR (breast tumor[Title/Abstract])) OR (mammary cancer[Title/Abstract])) OR (outcome breast cancer[Title/Abstract]))) OR (breast malignancy[Title/Abstract])) AND (mortality rate[Title/Abstract])) OR (survival status[Title/Abstract])) OR (mortality[Title/Abstract])) OR (death[Title/Abstract])) OR (mortality rate[Title/Abstract])) OR (survival rate[Title/Abstract]))) AND (predictor[Title/Abstract])) OR (determinant[Title/Abstract])) OR (risk factor[Title/Abstract])) AND (Ethiopia[Title/Abstract])

    - Date: 15/06/2024
    - Number of Articles: 183
2. **Google Scholar**

- Advanced search:
  With all of the words - Survival status and Predictors of mortality among breast cancer patients
  With the exact phrase – breast cancer, Ethiopia
  With at least one of the words- “breast neoplasm," "breast tumor," "mammary cancer," "outcomes of breast cancer," "breast malignancy,"
  Date: 21/06/2024
- Number of articles: 236

3. **Web Of Science**
    - Combination: "Breast cancer" OR "Breast carcinoma" OR "Breast neoplasm" OR "Breast Tumor" OR "Breast malignancy" OR "mammary cancer" OR "human mammary carcinoma" OR "malignant neoplasm of the breast" OR "human mammary neoplasm" (Topic) and "survival status" OR "survival rate" OR death OR "mortality rate" OR mortality and predictors OR determinant OR” risk factors” (Topic) and Ethiopia (Topic) and English (Languages)

- Date:28/07/2024
- Number of articles: 178

4. **Embase**
    - Combination: exp breast cancer/ OR Breast neoplasm. mp. OR exp breast carcinoma/ OR exp breast tumor/ OR Breast malignancy. mp. OR mammary cancer.mp OR human mammary carcinoma. mp. OR malignant neoplasm of Breast.mp. OR human mammary neoplasm. mp. AND mortality rate. mp. OR mortality. mp. OR death. mp. OR survival status. mp. OR survival rate. mp.AND exp Ethiopia/ or (Ethiopia).
    - Date: 09/07/2024
    - Number of articles: 47
5. **Scopus**

- Combination: survival status AND predictors AND of AND mortality AND among AND breast AND cancer AND patients AND Ethiopia AND (LIMIT-TO (EXACT KEYWORD, "Human")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (TITLE-ABS-KEY, “Ethiopia”)
- Date: 15/07/2024
- Number of articles: 30

Table 1: Studies Identified in the Literature Search

Study Id	Authors	Year	Title	Included/excluded	Reason of exclusion (if applicable)
1	Belete et al	2022	The Effect of Estrogen Receptor Status on Survival in Breast Cancer Patients in Ethiopia. Retrospective Cohort Study	Included	
2	Abate SM et al	2016	Trends of Breast Cancer in Ethiopia	Excluded	Fail to report outcome of interest
3	Tesfaye, et al	2021	Survival analysis of Time to Death of Breast Cancer Patients: in case of Ayder Comprehensive Specialized Hospital Tigray, Ethiopia.	Included	
4	Kantelhardt, et al	2013	Breast cancer survival in Ethiopia: A cohort study of 1,070 women	Excluded	Fail to report outcome of interest
5	Tiruneh M, et al	2021	Survival and Predictors of Mortality among Breast Cancer Patients in Northwest Ethiopia: A Retrospective Cohort Study	Included	
6	Misganaw M, et al	2023	Mortality rate and predictors among patients with breast cancer at a referral hospital in northwest Ethiopia: A retrospective follow-up study	Included	
7	Eber-Schulz, et al	2018	Survival of breast cancer patients in rural Ethiopia	Included	
8	Shita, et al	2023	Survival and predictors of breast cancer	Included	

Table 1: Studies Identified in the Literature Search

			mortality in South Ethiopia: A retrospective cohort study		
9	Areri et al	2019	Survival status and predictors of mortality among Breast Cancer patients in adult Oncology Unit at Black Lion Specialized Hospital, Addis Ababa, Ethiopia,2018.	Included	
10	Ayele et al	2022	Breast cancer morbidity and mortality in rural Ethiopia: data from 788 verbal autopsies	Excluded	Different outcome
11	Shiferaw et al	2020	Incidence and Predictors of Recurrence among Breast Cancer Patients in Black Lion Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia: Retrospective Follow-up Study with Survival Analysis	Excluded	Different outcome
12	Feleke et al	2022	Survival analysis of women breast cancer patients in Northwest Amhara, Ethiopia	Included	
13	Balcha et al	2021	Risk Factors Affecting Survival Time of Breast Cancer Patients: The Case of Southwest Ethiopia	Included	
14	Shita et al	2020	Survival and Predictors of Mortality among	Excluded	Fail to report outcome of interest

Table 1: Studies Identified in the Literature Search

			Breast Cancer Patients Diagnosed at Hawassa Comprehensive Specialized and Teaching Hospital and Private Oncology Clinic in Southern Ethiopia: A Retrospective Cohort Study		
15	Gashu, et al	2024	Assessing the survival time of women with breast cancer in Northwestern Ethiopia: using the Bayesian approach	Excluded	Fail to report outcome of interest
16	Gebremedhin, et al	2023	Association of Delay in Breast Cancer Diagnosis with Survival in Addis Ababa, Ethiopia: A Prospective Cohort Study	Excluded	Different outcome
17	Marin , et al	2023	Application of parametric survival analysis to women patients with breast cancer at Jimma University Medical Center	Excluded	Different outcome
18	Biru, et al	2022	Survival Analysis of Recurrent Events on Women Breast Cancer: The case of Tikur Anbessa Specialized Hospital, Ethiopia	Excluded	Different outcome
19	Deressa, et al	2019	Breast cancer care in northern Ethiopia – cross-sectional analysis	Excluded	Different outcome
20	Hagos, et al	2023	Time-to-death predictors on breast cancer	Excluded	Fail to report the outcome of interest

Table 1: Studies Identified in the Literature Search

			patients in northern Ethiopia: a retrospective cross-sectional study		
21	Fentaw, et al	2023	Comparative Analysis of Women's Breast Cancer Survival Time at Three Selected Government Referral Hospitals in Ethiopia's Amhara Region Using Parametric Shared Frailty Models	Excluded	Different outcome
22	Ballé, et al	2024	PAM50 breast cancer subtypes and survival of patients in rural Ethiopia without adjuvant treatment: a prospective observational study	Excluded	Different outcome
23	Ersumo, et al	2006	Breast Cancer in an Ethiopian Population, Addis Ababa	Excluded	Different outcome
24	Desalegn, et al	2022	Intrinsic subtypes in Ethiopian breast cancer patient	Excluded	Different outcome
25	Wondimu, et al	2019	Survival Analysis of Breast Cancer Patients: A Case Study at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia	Excluded	Fail to report outcome of interest
26	Gebremariam, et al	2021	Delayed initiation of adjuvant chemotherapy among women with breast cancer in Addis Ababa, Ethiopia	Excluded	Different outcome

Table 1: Studies Identified in the Literature Search

27	Fufa, et al	2020	Survival Analysis of Cancer Patients at Teaching Hospitals in Ethiopia	Excluded	Fail to report outcome of interest
28	Dutamo, et al	2019	Survival Analysis of Determinants of Breast Cancer Patients at Hossana Queen Elleni Mohammad Memorial Referral Hospital, South Ethiopia: Bayesian Application of Hypertabastic Proportional Hazards Model	Excluded	Fail to report outcome of interest
29	Tesfaye, et al	2021	Joint modeling of longitudinal change in tumor cell level and time to death of breast cancer patients: In case of Ayder comprehensive specialized Hospital Tigray, Ethiopia	Excluded	Different outcome
30	Timotewos, et al	2018	First data from a population-based cancer registry in Ethiopia	Excluded	Fail to report outcome of interest
31	Yismaw, et al	2022	Analysis of Risk Factors of Death among Breasts Cancer Patients in Ethiopia: Parametric shared frailty model	Excluded	Different outcome
32	Yoseph, et al	2021	Retrospective Analysis of Breast Cancer Cases Operated in Jush within Four Years Time Period, Jimma, Ethiopia	Excluded	Different outcome

Table 1: Studies Identified in the Literature Search

33	Hadgu, et al	2017	The Impact of Cancer in the Tigray Region of Ethiopia: A Secondary Analysis	Excluded	Fail to report outcome of interest
34	Tesfaye et al	2021	Survival analysis of Time to Death of Breast Cancer Patients: in case of Ayder Comprehensive Specialized Hospital Tigray, Ethiopia.	Included	
35	Dagne, et al	2019	Assessment of breast cancer treatment outcome at Tikur Anbessa Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia	Included	
36	Gash, et al	2024	Gashu C, Aguade AEJBwsh. Assessing the survival time of women with breast cancer in Northwestern Ethiopia	Included	

Table 2. Newcastle-Ottawa Quality Assessment Scale for cohort studies

Authors, Publication year	Selection				Comparability	Outcome			Total score	Quality *
	Representativeness of the exposed cohort (*)	Selection of the non-exposed cohort (*)	Ascertainment of exposure (*)	Demonstration that outcome of interest was not present at start of study (*)	Comparability of cohorts based on the design or analysis (**)	Assessment of the outcome (*)	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts (*)		
Feleke et al, 2022	-	*	*	*	*	*	*	*	7	Good
Misganaw et al, 2023	*	*	*	*	*	*	*	*	8	Good
Shita. et al, 2023	*	*	*	*	*	*	*	*	8	Good
Gashu et al, 2024	*	*	*	*	*	*	*	*	8	Good
Tiruneh et al, 2021	*	*	-	*	*	-	*	*	6	Good
Bacha et al, 2021	*	*	*	*	*	*	*	*	8	Good
Tesfay et al,2021	*	*	-	*	*	-	*	*	6	Good
Areri et al, 2019	*	*	*	*	*	-	*	*	8	Good
Belete et al, 2022	*	-	*	*	*	*	*	*	8	Good
Eber-Schulz et al, 2018	-	*	*	*	*	*	*	*	8	Good

Table 3. Newcastle-Ottawa Quality Assessment Scale for cross-sectional studies

	Selection				Comparability	Outcome		Total score	Quality of the study
Authors, Publication year	Representativeness (*)	Sample size (*)	Non respondents (*)	Ascertainment of the exposure (risk factor) (**)	The subjects in different outcome groups are comparable (*)	Assessment of the outcome (**)	Statistical test (*)		
Dagnet et al, 2019	1	1	1	2	1	2	1	9	Good

Table 4. Characteristics of the included studies

No	Author	P. Year	Study area	Study design	Sample size	Number of deaths	Mortality rate	Median Survival time	Survival rate		
									One year	Three years	Five years
1.	Feleke et al.	2022	Amhara	Cohort	322	95	29.5	45	NR	NR	NR
2.	Misganaw et al.	2023	Amhara	Cohort	410	139	33.9	38.3	83	53	11.4
3.	Shita. et al.	2023	SNNPR	Cohort	302	67	22.2	50.8	83	63.1	NR
4.	Gashu et al.	2024	Amhara	Cohort	382	148	38.7	42	NR	NR	NR
5.	Tiruneh et al.	2021	Amhara	Cohort	482	165	34.2	17	NR	NR	25.8
6.	Bacha et al.	2021	SNNPR	Cohort	642	447	69.6	10	NR	NR	NR
7.	Tesfay et al.	2021	Tigray	Cohort	186	22	11.8	34.5	NR	NR	NR
8.	Areri et al.	2019	AA	Cohort	627	169	26.9	36.5	97.2	80.8	46.2
9.	Dagne et al.	2019	AA	CS	303	141	46.5	NA	NA	58	NA
10.	Belete et al.	2022	AA	Cohort	368	99	26.9	58.7	NR	NR	NR
11.	Eber-Schulz et al.	2018	Oromia	Cohort	107	57	53.3	28	78	NR	NR

Note: NA = Not applicable, NR = No report

Table 5. Summary estimate of HR for predictors of mortality among breast cancer patients in Ethiopia.

Variables	Exposed	Comparator	Included Studies	Total Participant	AHR (95%)	I^2
Cancer stage	Stage III and VI	Stage I	7	2,893	4.14 (2.81,6.78)	76.2
Lymph node status	Positive	Negative	6	2,572	2.85 (1.50,5.44)	95.2
Residence	Rural	Urban	4	1,497	1.65 (1.27,2.14)	44.5
Hormonal Therapy	No	Yes	3	1,405	2.02 (1.59, 2.56)	83.8
Histological Grade at Diagnosis	Grad III	Grade I	4	1,887	1.76 (1.29,2.41)	8.4
Hormone Receptor Status	Negative	Positive	2	475	1.54 (1.05,2.25)	0
Comorbidity	Yes	No	5	2,109	2.24 (1.41,3.56)	77.8