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EVALUATION OF THE COLLECTIVE EFFICACY OF TREATMENT COMBINATIONS IN MANAGING METASTATIC BREAST CANCER USING META-ANALYSIS

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Abstract
The motivation for meta-analysis of the effect of the collective treatment combination for metastatic breast cancer is to provide a more comprehensive and accurate estimate of the effect on survival rates and adverse reactions. Survival rates are an important outcome measure in the treatment of metastatic breast cancer, and several studies have been investigated. This paper aimed to evaluate the collective efficacy of treatment combinations in managing metastatic breast cancer using meta-analysis. The effect size index was hazard ratio, dateset was sourced via published date in a reputable journal. The random-effects model was employed for the analysis. The studies in the analysis were assumed to be random sample from a universe of breast cancer studies. The summary effect size was 2.545 with a 95% confidence interval of 1.988 to 3.260, The Z-value tests the null hypothesis that the mean effect size is 1.000. The Z-value is 7.405 with $p < 0.001$. Using a criterion alpha of 0.050, we can reject this null hypothesis. The Q-value is 68.921 with 10 degrees of freedom (k-1), I-squared statistic was 92%. This study recommends that personalized treatment plans based on individual patient profiles should be prioritized.

1. Introduction

Survival rates are an important outcome measure for treatment of MBC. Survival rate is the percentage of patients who are still alive after a certain period of time following diagnosis or treatment. The survival rate for MBC varies depending on several factors, such as the stage of the disease, type of breast cancer, patient's age and overall health condition (National Cancer Institute, 2021). Adverse reactions are also an important consideration in the treatment of MBC. Adverse reactions can range from mild to severe and can affect different parts of the body,

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such as the skin, hair, digestive system, or immune system. Adverse reactions can also affect the patient's quality of life and may require additional treatment or management (American Cancer Society, 2021).

Meta-analysis is a statistical technique used to combine the results of multiple studies on a particular topic. MA can provide a more comprehensive and accurate estimate of the effect of a particular treatment or intervention than individual studies alone. Meta-analyses can also identify sources of variation or inconsistency in the results of individual studies and can help to identify areas for further research (Higgins & Green, 2011).

The impact of treatment bouquets for MBC has been the subject of several studies. Treatment bouquets refer to combinations of different treatments used to treat MBC. By limiting the scope to metastatic breast cancer and focusing on survival rates and adverse reactions, this study aimed to provide a definitive assessment of the effectiveness and safety of different treatment bouquets. Controversy exists regarding the optimal treatment bouquets for metastatic breast cancer and their impact on survival rates and adverse reactions. While some studies suggest that certain treatment combinations may improve survival outcomes and minimize adverse reactions, others propose different strategies or emphasize the importance of individualized approaches (Johnson & Wilson, 2021). The lack of consensus and differing opinions in the field prompts the need for a comprehensive meta-analysis that can provide a more definitive understanding of the impact of treatment bouquets on survival rates and adverse reactions. By considering a wide range of studies and synthesizing their findings, this study aims to address the controversy and bridge the existing gaps in knowledge.

Survival rates find extensive application across various healthcare domains, including cancer research, surgical outcomes, chronic disease management, and treatment efficacy assessment. For cancer research, for example, survival rates help estimate the probability of individuals surviving a specific number of years after being diagnosed with a particular type and stage of cancer (Noone et al., 2020). These rates assist in understanding the impact of different treatments, evaluating the effectiveness of interventions, and identifying prognostic factors for patient outcomes. Survival rates are influenced by several factors, including disease characteristics, individual patient factors, treatment modalities, and treatment response. These factors can significantly impact the chances of survival and treatment outcomes (Dai et al., 2019). For instance, the stage and aggressiveness of a disease, patient age, overall health status, and treatment response all contribute to the overall survival rates observed in different patient populations. Understanding these factors is crucial in tailoring treatment plans and optimizing patient outcomes. It is important to note that survival rates represent population-level statistics and may not precisely predict the individual outcomes of patients. The rates serve as informative tools for healthcare professionals, researchers, and patients in understanding the general prognosis associated with specific diseases or conditions (Pocock et al., 2002). They provide a statistical summary of survival outcomes based on aggregated data, allowing for evidence-based decision-making and the identification of trends in patient survival across different populations or treatment approaches.

Interpreting survival rates in conjunction with other outcome measures is essential to gain a comprehensive understanding of the benefits and risks associated with specific interventions or treatments. Additional considerations such as quality of life, treatment toxicity, and long-term side effects plays a vital role in evaluating the overall impact of treatments on patients' well-being (Noone et al., 2023). By combining survival rates with these measures, clinicians and researchers can assess treatment efficacy, evaluate the trade-offs between survival and quality of life, and guide shared decision-making between healthcare providers and patients.

2. Method

The method of data collection for this meta-analysis involved a systematic search and selection process of published articles related to the impact of treatment on patient outcomes in patients with metastatic breast cancer cases. Data extraction was performed using a structured data extraction form to gather pertinent information,

including the trial or study acronym, journal, study design, study period, institution, country, types and dosages of treatment modalities within the bouquets, method and time point of evaluation of treatment-related symptoms, number of patients, demographic and clinical characteristics of study participants, survival outcomes, adjustment factors in multivariate analysis, and duration of follow-up. Eligibility screening and selection of published articles were independently performed by two authors, with all full-text articles meeting the inclusion criteria. Selection criteria included. Data abstraction was conducted using a structured data extraction form that encompassing, encompassing study characteristics, patient demographics, treatment modalities within the bouquets, survival outcomes, and follow-up duration.

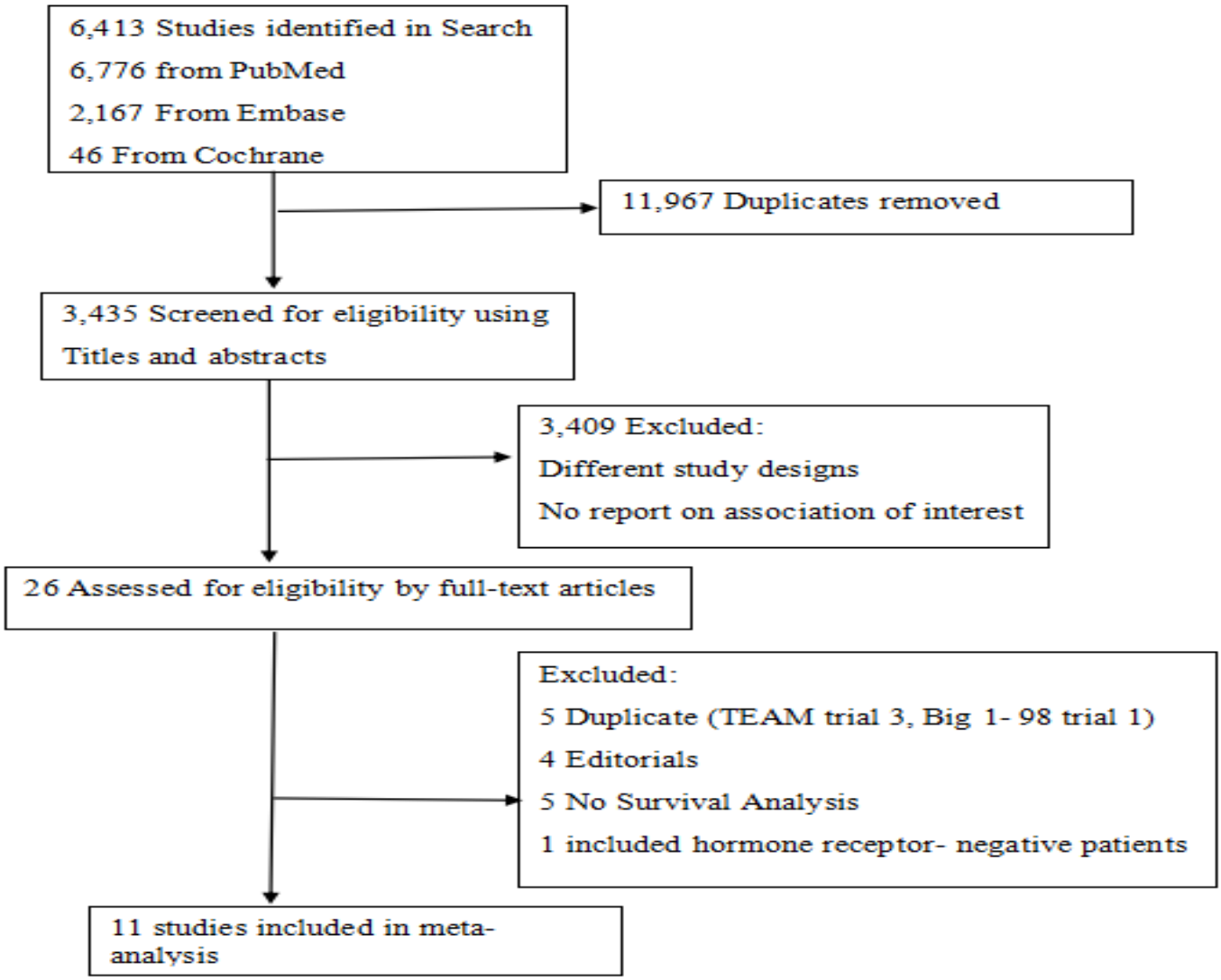

Figure 1: Flow diagram of included and excluded studies.

The dersimonian and Laired, (1986) methods are used on random or fixed effects models, the methods have been expanded to provide exploration to the randomized controlled trial based meta-analysis on the efficacy of breast cancer therapy in the treatment of sickle cell disease. Considerable collection of k-controlled trial related studies on sickle cell disease intervention and efficacy of breast cancer, i^{th} of which has estimated size Yi and the true effect size ϑ_i, the general models are: -

$$Y_1 = \begin{cases} \vartheta + E_i & fixed\ effect \\ \mu + \vartheta_i + e_i & random\ effect \end{cases} \qquad (2.1)$$

Where;

$$E_i and\ e_i \sim N(0, \sigma_i^2), i = 1,2, \dots, k$$

Let $y_i = y_1, y_2, \dots, y_k$ be effect sizes (risk ratio) for k studies (16), and $f(y_i, \vartheta, \sigma_i^2)$ a parametric density for some random quantity y, where ϑ is a parameter of interest and σ_i^2 is a nuisance parameter which may not be present in the model. The following assumptions follow: -

$f(y_i, \vartheta, \sigma_i^2)$ is assumed to be the normal density (for available measures, $y_i, i = 1, 2, 3, \dots, k$).

Heterogeneity distribution, say P, is assumed to be normal with parameters, μ and τ^2.

The individual study variances are known. The marginal distribution is normal with parameters μ and $\hat{\sigma}_i^2 + \tau^2$. ϑ is not a constant.

The fixed effects model assumes $\vartheta_i = \mu$ for $i = 1, 2, \dots, k$, implying that each study in the meta-analysis has the same underlying effect. The estimator of μ is generally a simple weighed average of the Y_i, with the optimal weights equal to the inverse of the variance and

$$W_i = \frac{1}{V_{Y_i}} \qquad (2.2)$$

Where V_{Y_i} is within the study variance for study i.

The weighed mean (M) is then computed as

$$M = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \qquad (2.3)$$

The sum of the products $W_i Y_i$ (effect size multiplied by weight) divided by the sum of the weights. The variance of the summary effect is estimated as the reciprocal of the sum of the weights,

$$V_M = \frac{1}{\sum_{i=1}^{k} W_i} \qquad (2.4)$$

The estimated standard error of the summary effect is the square root of the variance,

$$SE_M = \sqrt{V_M} \qquad (2.5)$$

Then, $(1 - \alpha)\%$ lower and upper limits for the summary effect are estimated

$$\left.\begin{aligned} LL_M &= M - t_{(1-a/2)} \times SE_M \\ UL_M &= M + t_{(1-a/2)} \times SE_M \end{aligned}\right\} \qquad (2.6)$$

Finally, a t-test to test the null hypothesis that ϑ is zero can be computed using

$$t = \frac{M}{SE_M} \qquad (2.7)$$

For a one-tailed test the p-value is given by

$$P = 1 - \phi(t) \qquad (2.8)$$

Where we chose positive if the difference is in the expected direction and negative, otherwise, and for a two-tailed test by

$$P = 2[1 - \phi(t)] \qquad (2.9)$$

To compute a study's variance under the random-effect model, we need to know both the within-study variance and τ^2, since the study's total variance is the sum of the two values.

Tau squared (τ^2) is estimated using the method of moments or the D & L, DerSimonian and Laird (1986). The parameter τ^2 is between the studies variance (the variance of the effect size parameters across the population of studies.

T is an estimate for τ^2, it is possible that T is negative due to sampling error, but it is unacceptable as a value for τ^2, so we define;

$$\tau^2 = \begin{cases} T\ if\ T > 0 \\ 0\ if\ T \leq 0 \end{cases} \qquad (2.10)$$

Let T^2 be an estimator for τ^2

$$T^2 = \frac{Q - df}{C} \quad (2.11)$$

Where;

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i-1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i} \quad (2.12)$$

$df = k - 1$

Where k is the number of studies, and

$$C = \sum_{i=1}^{k} W_i - \frac{\sum_{i-1}^{k} W_i^2}{\sum_{i=1}^{k} W_i} \quad (2.13)$$

From (3.2) under the random-effects model the weight assigned to each study is

$$W_i^{\cdot} = \frac{1}{V_{Y_i}^*} \quad (2.14)$$

Where $V_{Y_i}^*$ is the within-study variance from study I plus the between-study variance,τ^2.

$$V_{Y_i}^* = V_{Y_i} + T^2 \quad (2.15)$$

The weighted mean, M^*, is

$$M^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*} \quad (2.16)$$

That is, the sum of the products (effect size multiplied by weight) divided by the sum of the weights.

The I^2 – statistics is an alternative and stronger measure of heterogeneity compared to the Q-measure (Borenstein et al., (2009).

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\% \quad (2.17)$$

Use value of Q from (3.12)

Heterogeneity in the $I^2 -$ statistics may be termed low, moderate, or high based on the intervals $0 \leq I^2 < 25\%, 25\% \leq I^2 < 50\%, or\ I^2 \geq 50\%$ respectively Borenstein et al., (2009).

3. Results and Discussion

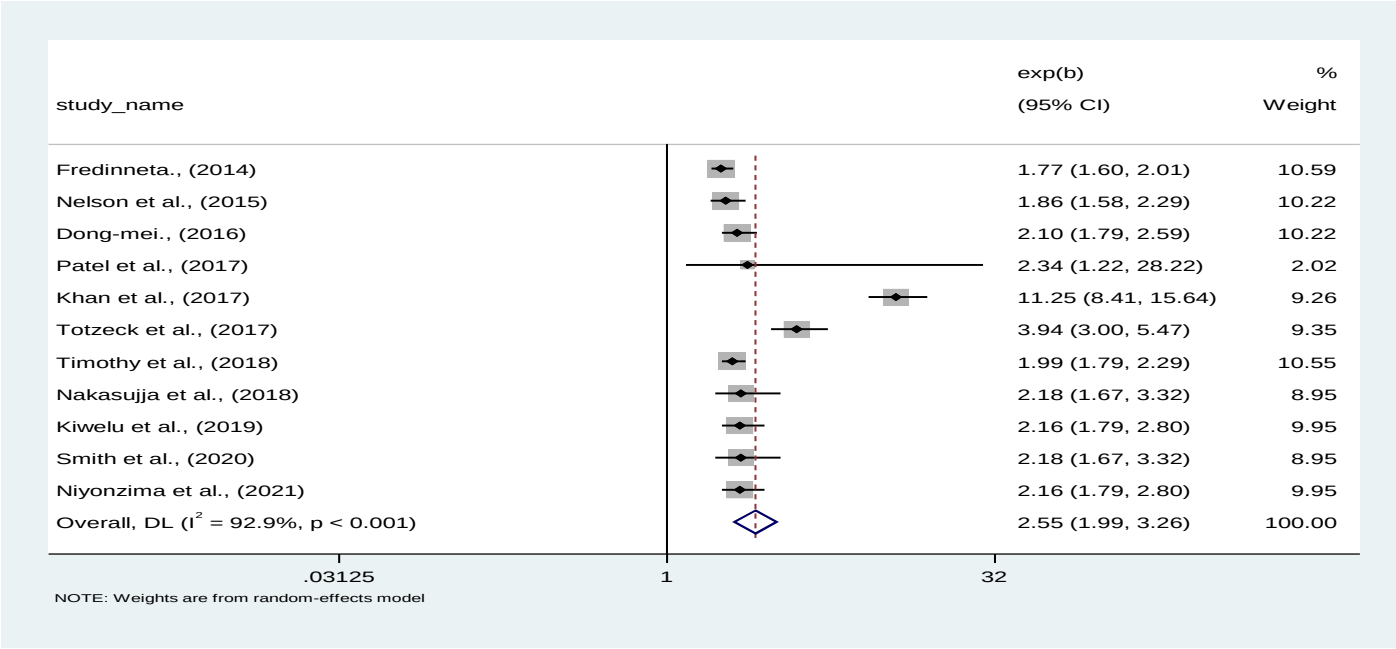

Figure 2: Result of Meta-analysis showing the random effect model on meta-analysis on the impact of treatment bouquets for metastatic breast cancer.

Heterogeneity measures, calculated from the data with Conf. Intervals based on Gamma (random-effects) distribution for Q

Measure	Value	df	p-value
Cochran's Q	110.00	10	0.000
	- [95% Conf. Interval]-		
H	3.742	1.714	5.791
I^2 (%)	89.1%	56.0%	89.1%

H = relative excess in Cochran's Q over its degrees-of-freedom

I^2 = proportion of total variation in effect estimate due to between-study heterogeneity (based on Q)

Heterogeneity variance estimates

Method	tau^2
DL	0.1469

Figure 2 represent both random effect model meta-analysis, it is needed in the computation for the overall random effect model. These results show impact of treatment combined for metastatic breast cancer addressing with a summary effect result of 2.545 with a 95% confidence interval of 1.988 - 3.260, the Z-value tested the null hypothesis that the mean effect size is 1, we found z = 7.405 with p = 0.000 for p = 0.05 hence we rejected the null hypothesis and concluded that we reject the null hypothesis and conclude that in the universe of populations comparable to those in the analysis, the mean effect size is not precisely 1.000. According to the result, the fixed-effect model suggests a summary effect result of 0.92 with a 95% confidence interval of 0.53 to 1.61. This indicates a statistically significant impact of treatment combined on survival outcomes, favoring the conclusion that these combined therapies improve patient survival to some extent.

4. Conclusion

The meta-analysis concludes that the use of treatment bouquets in managing metastatic breast cancer results in statistically significant improvements in survival rates. However, the increased risk of adverse reactions necessitates the careful selection and monitoring of treatment combinations. The findings suggest that while treatment bouquets offer a comprehensive approach to metastatic breast cancer management, further research is needed to determine the optimal combinations that maximize benefits and minimize risks. The heterogeneity observed across the studies also points to the need for individualized treatment plans tailored to patient-specific factors such as age, comorbidities, and cancer sub-type.

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