

RESEARCH ARTICLE

Comparing Role of Two Chemotherapy Regimens, CMF and Anthracycline-Based, on Breast Cancer Survival in the Eastern Mediterranean Region and Asia by Multivariate Mixed Effects Models: a Meta-Analysis

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Abstract

Purpose: To assess the role of two adjuvant chemotherapy regimens, anthracycline-based and CMF on disease free survival and overall survival breast cancer patients by meta-analysis approach in Eastern Mediterranean and Asian countries to determine which is more effective and evaluate the appropriateness and efficiency of two different proposed statistical models. **Materials and Methods:** Survival curves were digitized and the survival proportions and times were extracted and modeled to appropriate covariates by two multivariate mixed effects models. Studies which reported disease free survival and overall survival curves for anthracycline-based or CMF as adjuvant chemotherapy that were published in English in the Eastern Mediterranean region and Asia were included in this systematic review. The two transformations of survival probabilities ($\text{Ln}(-\text{Ln}(S))$ and $\text{Ln}(S/(1-S))$) as dependent variables were modeled by a multivariate mixed model to same covariates in order to have precise estimations with high power and appropriate interpretation of covariate effects. The analysis was carried out with SAS Proc MIXED and STATA software. **Results:** A total of 32 studies from the published literature were analysed, covering 4,092 patients who received anthracycline-based and 2,501 treated with CMF for the disease free survival and in order to analyze the overall survival, 13 studies reported the overall survival curves in which 2,050 cases were treated with anthracycline-based and 1,282 with CMF regimens. **Conclusions:** The findings illustrated that the model with dependent variable $\text{Ln}(-\text{Ln}(S))$ had more precise estimations of the covariate effects and showed significant difference between the effects of two adjuvant chemotherapy regimens. Anthracycline-based treatment gave better disease free survival and overall survival. As an IPD meta-analysis in the Italy the results of Angelo et al in 2011 also confirmed that anthracycline-based regimens were more effective for survival of breast cancer patients. The findings of Zare et al 2012 on disease free survival curves in Asia also provided similar evidence.

Keywords: Meta-analysis - disease free and overall survival - multivariate mixed models - CMF - anthracycline

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Introduction

In different types of cancer, breast cancer is the most relevant one among females in the world and is the second principal reason of cancer death in women. More than one million new cases are reported annually of which 60% are in developing countries. Generally the increasing rate in developing countries is higher than developed countries (Katalinic et al., 2009; Zare et al., 2012).

Obesity, alcohol consumption, diet in high saturated fat, early onset of menarche and late menopause are the most important risk factors of breast cancer. Breast cancer is seen mostly in adults over 50 years of age in Western countries whereas in EMRO and Asian countries, breast

cancer is rising in younger women and diagnosed at higher stages. The young women in these regions are more likely to be at risk due to their tendency to follow western people lifestyle. Since of poor educations, cultural and social obstacles, traditional attitudes and lack of screening programs, it comes up at later grades in developing countries (Mousavi et al., 2007; Katalinic et al., 2009; Zare et al., 2013).

Researchers believe one of the most considerable measure of medical care for cancer patients is survival rate and is used more to compare the efficiency of different treatments. Also it would be helpful to take further preventive actions for breast cancer patients and improve prognosis of them (Arkoob et al., 2010; Sharif et al., 2010).

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Usual practice in the reporting the results of RCT's was to produce the sufficient statistics for each treatment, means and standard deviations for continuous outcomes, number and percentage for binary outcomes. It was recommended by guidelines that for primary and secondary studies results should be provided as a summary of the outcome in each group, with the contrast between two groups (Guyot et al., 2012).

Production of sufficient statistics expedite the inclusion of primary study in subsequent meta-analysis. However publishing results from trails with survival time are not amenable of these principles. Due to censorship, the mean of survival time is a biased estimate of expected survival when censored observation exist (Klein, 2005). It was advised that the effect measure for survival time should be declared as a hazard ratio or difference median survival time between each treatment. But they are severely limited. For the evidence synthesis i.e. meta-analysis using median survival times at a particular point in time are not reasonable measures of survival outcomes, due to potential bias could arise if time points are subjectively chosen by the reviewer or selectively reported by the trialist at times of maximal or minimal difference between groups. It also, requires that all trials reported data at same time point and it causes results have a serious under- or overestimation of the treatment effect and major loss of statistical power. Hazard ratio is also limiting and unsatisfactory, as it require proportional hazard, an assumption which is rarely checked (Arends et al., 2008; Guyot et al., 2012).

In the earlier works the authors have attempted to extracted data from the reported Kaplan-Meier (KM) curves in order to perform meta-analysis. In this paper we extracted the survival probabilities and corresponding times from the graphs and developed two models in order to compare the efficiency of the different treatments.

We used graphdigitizer software in the coordinates of the KM curves from the published graph. Survival rate of breast cancer is affected by detection at early stages and proper treatments, adjuvant chemotherapy after breast conservative surgery or mastectomy or modified radical mastectomy reduce the chance of cancer coming back and also the chance of death (Society, 2007). In order to specify the best chemotherapy regimens for breast cancer patients many study had been done, in some researches Anthracycline_based are recommended as the first choice of adjuvant therapy, although there were studies which illustrate CMF (Cyclophosphamide, Methotrexate, Fluorouracil) regimens could reduce the chance of recurrence and death rate to 24% (Ismaili et al., 2010). This study was an effort to detect the more effective chemotherapy regimens between CMF and Anthracycline_based on the survival of breast cancer patients by a systematic review.

Materials and Methods

Search strategy

An extensive literature review was performed using different databases such as Medline, science direct, Chinese information literature database, japan information on science and technology and web of science. Firstly, all

medical subjects' headings related to breast cancer, two chemotherapy regimens Anthracycline_based and CMF and survival analysis according to the Asian and East Mediterranean countries which had been published in English considered. Secondly in order to find more related studies the appropriate keywords and thesaurus terms have been searched. Finally the ones which reported survival curves had been selected to assess and more consideration. This review was carried out up to July 30th 2014.

Quality assessment and data extraction

Performing the search we obtained 50 results. These included the studies which were reported disease free survival curves or overall survival curves for one or two adjuvant chemotherapy regimens, CMF and Anthracycline_based separately for breast cancer patients of Asian and East Mediterranean region countries. The patients who had positive estrogens or progesterone receptor should had been drew hormone therapy in all reports. All patients who were needed, received radiotherapy. This review include the studies that researchers provided survival curves in some subgroups for one of the two mentioned chemotherapies that we considered each subgroup as an independent study. Definition of overall survival time is the length of time after treatment for a specific disease that patients survives. The time without any sign of disease or death is nominated as disease free survival. We have summarized and tabulated Location, date, the type of chemotherapy regimens, number of patients and some other consideration in each paper for comparison. Since this review is carried out on studies in EMRO and Asia the most patients were younger with high stages of disease.

A total of 32 studies had the inclusions criteria for the present analysis that all of them reported disease free survival curves and only 13 of them reported overall survival curves. We analyzed data for 6925 patients who received Anthracycline_based and 3056 patients who received CMF treatment on disease free survival, 2050 receiver of Anthracycline_based and 1282 receivers of CMF for overall survival curves. In order to specify the survival proportions and its time, graphdigitizer software was used and all curves were digitized (time was determined in month). Firstly we changed the format of the images of the survival curves to JPG and imported them in graphdigitizer software. Then, according to the survival curves the time and survival proportions axes were scaled. Finally we determined the failure times and their corresponding survival probabilities (See the survival curves of each study in Appendix).

Meta-analysis

Multivariate meta-analysis is increasingly used in medical statistics (Arends et al., 2008). The multivariate random mixed effect model was applied in this study and in order to had sensible estimations and interpretations of the roles of covariates on survival probabilities, two different models were suggested and the response variables modeled to both fixed and random effects of covariates such as treatment group and Ln(time).

The first model which was proposed by Lidia Arend

Table 1. Characteristics of 32 Studies Retained for Meta-analysis

Study(year) (Reference)	Location	Follow-up (time)	No. of patients	Chemotherapy Regimens (No.)	Considerations
Kuru et al. (2005) (Camlibel et al., 2005)	Turkey	100-months	688	Anthracycline_based, CMF (248),(340)	Patients have among 1-3 positive nodes&339 Patients have more than 3positive nodes
Zhang et al. (2008) (Zhang et al., 2008)	China	42-months	665	Anthracycline_based, CMF (181),(255)	Patients in HER2 over-expressed &235 Patients in HER2 over-expressed with node-positive
Ismaili et al. (2009) (Ismaili et al., 2009)	Morocco	100-months	244	Anthracycline_based, CMF (110),(134)	
Fang et al. (2009) (Li et al., 2009)	China	60-months	43	Anthracycline_based	
Faradmal et al. (2010) (Faradmal et al., 2010)	Iran	8-years	43	Anthracycline_based , CMF	18 patients are in high risk of breast cancer&25 patients are in low risk of breast cancer
Ismaili et al. (2010) (Ismaili et al., 2010)	Morocco	100-months	349	Anthracycline_based, CMF (202),(147)	Patients treated with>= 2 cycles of concurrent CT with RT &61 Patients treated with breast conservative surgery
Abbas et al. (2011) (Abbas et al., 2011)	Egypt	30-months	267	Anthracycline_based	67 patients treated with RT before CT& 150 patients were treated in a sandwich scheme of RT& CT &50 patients received RT after CT
Gupta et al. (2011) (Gupta et al., 2011)	India	100-month	91	Anthracycline_based	just 54 patients received chemotherapy
Yao et al. (2011) (Yao et al., 2011)	China	100-month	489	Anthracycline_based	99 HER-2+/non pCR, 17 HER-2+/pCR, 277 HER-2-/non pCR & 96 HER-2-/pCR
Wang et al. (2012) (Wang et al., 2012)	China	60-months	687	CMF (117)	
Huizha et al. (2012) (Wu et al., 2012)	China	115-month	762	Anthracycline_based	66.9% CT+TT& 33.1%CC
Cong et al. (2012) (Xue et al., 2012)	china	120-month	3566	Anthracycline_based (2896),(670)	
Minghua et al. (2012) (Ji et al., 2012)	China	50-month	153	Anthracycline_based	45 with no adverse genotype & 108 with 1 or 2 genotype
Tokiniwa et al. Japan (2012) (Tokiniwa et al., 2012)	Japan	100-month	71	Anthracycline_based	33Topo+ & 38Topo-
HM Earl et al. (2012) (Earl et al., 2012)	Jordan	120-month	2391	Anthracycline_based, CMF(1156),(1202)	
S.chen et al. (2013) (Chen et al., 2013)	China	60-month	245	Anthracycline_based	26 HER-2+/Topo- ,67 HER-2-/Topo-, 55 HER-2+/Topo+ & 97 HER-2-/Topo-
Sharma et al. (2013)	India	60-month	43	Anthracycline_based	just 26 patients received Anthracycline_based
Dian Chen et al. (2014) (Chen et al., 2014)	China	222-month	186	CMF	88 modified radical mastectomy &98breast conservative surgery

*RT- Radiotherapy CT- Chemotherapy

et.al 2008, the Ln-minus-Ln of survival proportion was nominated dependent variable and Ln(time) and treatment were included as covariates(Arends et al., 2008), at the second model just dependent variable was changed to the

logit of survival probabilities. The two models included both fixed and random effects of covariates. (See details in Appendix (Dear, 1994; Arends et al., 2008)).

$$\begin{aligned}
 \ln(-\ln(S_i)) &= X_i\beta + z_i b_i + \varepsilon_i \\
 b_i &\approx N(o, D) \\
 \varepsilon_i &\approx N(o, V_i) \\
 \ln(S_i / (1 - S_i)) &= X_i\beta^* + z_i b_i^* + \varepsilon_i^* \\
 b_i^* &\approx N(o, D^*) \\
 \varepsilon_i^* &\approx N(o, V_i^*)
 \end{aligned}
 \tag{1}$$

In order to compare these two models, if the logit transformation of the survival proportion and the covariate Ln (time) have been related by a linear pattern we should assume log logistic distribution for the time, but if the relation between Ln-minus-Ln survival proportion and Ln (time) be linear then Weibull distribution could be used to more needed analysis.

The β parameters were estimated with GLS in an iterative manner and continued to reach convergence (Dear 1994). Applying these transformations on the survival probabilities made us sure that the fitted survival probabilities changed between 0 and 1 (Arends et al., 2008).

SAS, Proc MIXED and STATA software were used

and the following models were fitted on the data which extracted from the Kaplan-Meier curves:

$$\ln(-\ln(S_i)) = \beta_0 + \beta_1 \text{treatment}_i + \beta_2 \ln(\text{time}_i) + b_{0i} + b_{1i} \text{treatment}_i + b_{2i} \ln(\text{time}_i) + \varepsilon_i \tag{3}$$

$$\ln(S_i / (1 - S_i)) = \beta_0^* + \beta_1^* \text{treatment}_i + \beta_2^* \ln(\text{time}_i) + b_{0i}^* + b_{1i}^* \text{treatment}_i + b_{2i}^* \ln(\text{time}_i) + \varepsilon_i^* \tag{4}$$

Results

Treatment was a dichotomous variable which used to show the chemotherapy regimens, ‘0=CMF, 1=Anthracycline_based’. Random effects were applied for intercept, treatment effect and slope of Ln (time). The results were given in Table 2 and Table 3 for disease free survival and overall survival respectively

The estimate coefficients of treatment variable in the two models showed significant difference between Anthracycline_based and CMF chemotherapy regimens. According to the models (3) and (4) it would be appear that the patients who received Anthracycline_based regimens had a greater chance to survive without any sign

Table 2. Results of Fitting Models (3) and (4) for Disease Free Survival

Models	Ln (-Ln(\hat{S}_i))		Ln($\hat{S}_i / (1 - \hat{S}_i)$)	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Regression coefficients				
Intercept	-5.83 (0.67)	<0.001	6.24 (0.74)	<0.001
Treatment	-0.38 (0.10)	0.03	0.73 (0.26)	<0.001
Ln (time)	1.50 (0.09)	<0.001	0.3(0.78)	<0.001
covariance parameter	Estimate		Estimate	
Variance				
Intercept	5.69		6.8	
Treatment	0.1		0.13	
Ln(time)	0.09		0.13	
Covariance's				
Intercept*Treatment	-0.69		-0.81	
Intercept*Ln(time)	-0.59		-0.7	
Treatment*Ln(time)	0.04		0.03	
Variance(residual)	0.06		0.18	

Table 3. Results of Fitting Models (3) and (4) for Overall Survival

Models	Ln (-Ln(\hat{S}_i))		Ln($\hat{S}_i / (1 - \hat{S}_i)$)	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Regression coefficients				
Intercept	-4.86 (0.40)	<0.001	4.81 (0.49)	<0.001
Treatment	-0.43 (0.18)	0.029	0.61 (0.35)	0.038
Ln(time)	1.16 (0.09)	<0.001	1.29(0.19)	<0.001
covariance parameter	Estimate		Estimate	
Variance				
Intercept	2.62		3	
Treatment	0.54		0.81	
Ln(time)	0.27		0.37	
Covariance's				
Intercept*Treatment	-0.05		-0.13	
Intercept*Ln(time)	-0.49		-0.44	
Treatment*Ln(time)	-0.25		-0.41	
Variance(residual)	0.11		0.24	

SE- Standard Error

CMF and Anthracycline-based Breast Cancer Treatment and Survival in the Eastern Mediterranean and Asia: a Meta-analysis of disease or death. The parameters of covariance matrices for two models were illustrated that some are significantly different from zero, it was considered adding term to improve the models but no extension was statistically significant or it cause no convergence. The regression coefficients on overall survival probabilities also declared that in order to have greater survival chance the breast cancer patients should receive Anthracycline_based regimens rather than CMF.

Assessing the quality of two proposed models by comparing the results of Table 2 and Table 3, according to the coefficients and its standard error of the independent variables, model with dependent variable $Ln(-Ln(S_i))$ represented the parameter estimations more precise than the model included $Ln(-Ln(S_i))$ as dependent variable. The standard errors for the treatment effect parameters in the model (3) were 0.18 and 0.103 for disease free survival and overall survival respectively however for the second they were 0.353 and 0.269, generally the standard errors of parameter estimations in model (3) were less than the standard errors of the same parameter estimations in the model (4), so we can conclude that the parameters of model (3) are more precise and this model was more valid.

According to equation (3) and (4), for disease free survival, the survival proportions can be estimated by (5):

$$\hat{S}_i = \exp(-(\exp(-4.869 - 0.438 \text{treatment}_i + 1.16 \ln(\text{time}_i) + b_{0i} + b_{1i} \text{treatment}_i + b_{2i} \ln(\text{time}_i)))) \quad (5)$$

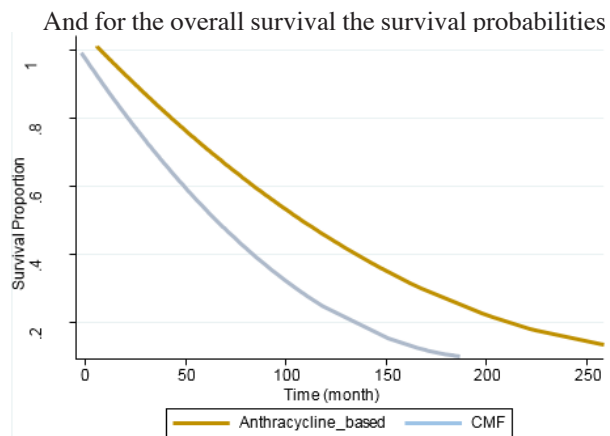


Figure 1. Mean Disease Free Survival Curves of the Two Chemotherapy Regimens

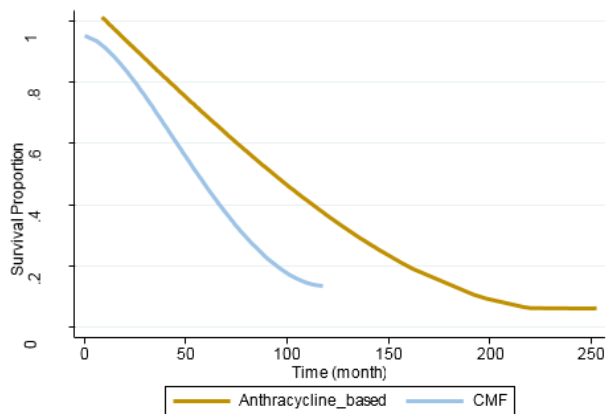


Figure 2. Mean Overall Survival Curves of the Two Chemotherapy Regimens

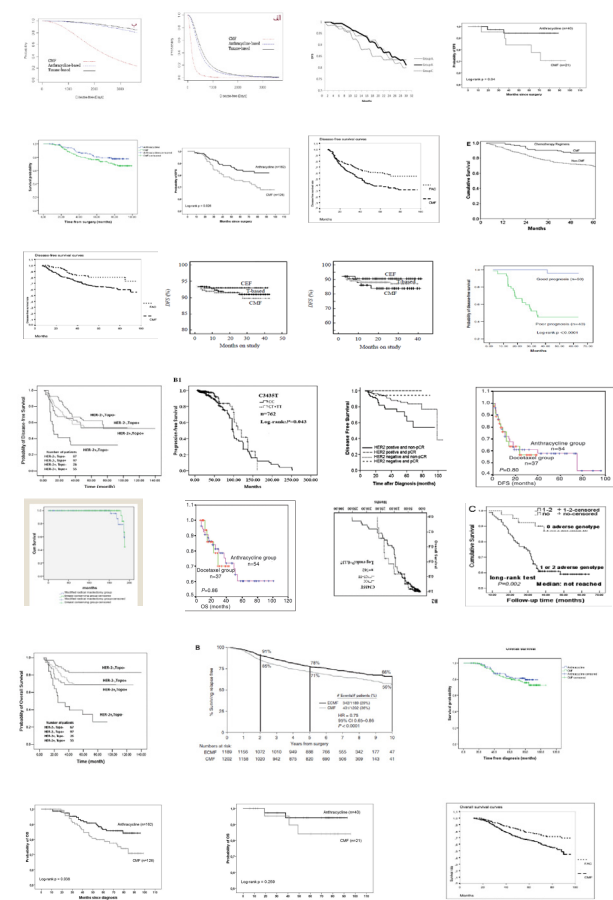
were estimated by (6),

$$\hat{S}_i = \exp(-(\exp(-5.838 - 0.66 \text{treatment}_i + 1.508 \ln(\text{time}_i) + b_{0i} + b_{1i} \text{treatment}_i + b_{2i} \ln(\text{time}_i)))) \quad (6)$$

Changing the treatment from CMF to Anthracycline_based at a specified time caused the $Ln(-Ln(S_i))$ varied -0.438 units that it means Anthracycline_based regimen was more effective on survival of breast cancer patients. Adding another terms such as interaction between $Ln(\text{time})$ and treatment to improve the model was perused, but no expansions were significant or lead to loss information about covariance matrix.

The mean estimated survival curves of each treatment for disease free survival and overall survival are shown in Figure 1 and 2. From the two figures objectively we concluded that the patients who received Anthracycline_based regimens had more chance to survive during the time than the other group.

The studies to be combined in the meta-analysis are indexed by l , in each study one or two treatments are considered that be showed by j . The index k counts the time points. The S_{ljk} shows the survival proportion in l th study for j th treatment at k th time point in each treatment of each study. S_i is a column vector of S_{ljk} and ϵ_i is a column vector of residual. The β is the parameter vector containing the fixed effects. Z_i is design matrix for random effects. The vector of random coefficient b_i are assumed to be independently and normally distributed with expectation zero and between-studies covariance matrix D and are independent from the ϵ_i 's.



The Disease Free Survival and Overall Survival Curves in Different Studies (in appendix)

The ϵ_i 's just in the same treatment within the same study are expected to be related.

According to Dear et al. they made use fact that the covariance of proportions between time points t_{ijk} and $t_{ijk'}$ are given by

$$cov(S_{ijk}, S_{ijk'}) = SE_{ijk} \sqrt{\frac{S_{ijk}(1-S_{ijk'})}{(1-S_{ijk})S_{ijk'}}} SE_{ijk'}$$

$$\begin{aligned} \ln(-\ln(s_i)) &= X_i\beta + Z_i b_i + \epsilon_i & \ln(S_i/(1-S_i)) &= X_i\beta^* + Z_i b_i^* + \epsilon_i^* \\ b_i &\sim N(o, D) & b_i^* &\sim N(o, D^*) \\ \epsilon_i &\sim N(o, V_i) & \epsilon_i^* &\sim N(o, V_i^*) \end{aligned}$$

$$\begin{aligned} V_i &= \begin{pmatrix} V_{i1} & o \\ o & V_{i2} \end{pmatrix} & V_i^* &= \begin{pmatrix} V_{i1}^* & o \\ o & V_{i2}^* \end{pmatrix} \\ V_{ij} &= \frac{SE_{ijk}}{\hat{S}_{jk}} \frac{SE_{ijk'}}{\sqrt{(1-S_{jk})S_{jk'}}} \frac{SE_{ijk'}}{\hat{S}_{jk} \ln(\hat{S}_{jk})} & V_{ij}^* &= \frac{SE_{ijk}}{\hat{S}_{jk}} \frac{SE_{ijk'}}{\sqrt{(1-S_{jk})S_{jk'}}} \frac{SE_{ijk'}}{\hat{S}_{jk} (1-\hat{S}_{jk})} \end{aligned}$$

Discussion

The gold standard approach for meta-analysis of survival data or survival curves is to obtain individual patients data from the studies. IPD meta-analysis has big advantages such as the investigator can test the assumptions that has not done in previous studies and the researcher can handle the outlier better. However it is not possible or practical to gather individual patient data. Obtaining the information of studies and articles is not easy as the most important part of systematic reviews.

Statistical techniques development for meta- analysis of survival studies have focused mainly in the combination of studies comparing two arms with the purpose to estimate a pooled measure of the intervention effects (Guyot et al., 2012). However, hazard ratio as a measure of the intervention effects which is commonly pooled in meta-analysis may not discover all the things and pooled survival proportions in each arm is more useful to complete the information of the interventions effects. Furthermore many studies in epidemiology intend to appraise the effects time-dependent variables, Hence methods to provide a summary survival curve in a single arm or population in clinical researches is a real need. In order to obtain a summary survival curves a few methods have been proposed which is the simplest approach is that the survival probabilities treated as proportions then combined them at the same time points using either fixed effect univariate approach or the Dersimonian and Larid method (random effect) (DerSimonian et al., 2007; Guyot et al., 2012). Since in each analysis only a part of data is used it can lead to loss power. In order to enhance the quality of secondary analysis of time-to-event data since the survival proportions which are reported from survival curves in each study for each treatment are correlated over time, the data have a multivariate essence, therefore multivariate models are more useful. One reason for this is that it gives a more informative analysis of time-dependent variables. Secondly the effects of several covariates on survival probabilities can estimated simultaneously. Finally the flexibility of modeling enable us to analyze all available data have been published, especially when the curves reported in a single arm.

The proposed methods in this paper were based on a multivariate mixed-effect model. First model with $\ln(-\ln(S_i))$ dependent variable was proposed by Lidia R. Arends 2008 (Klein, 2005; Arends et al., 2008), and to evaluate the efficacy of this model, second model with $\ln(S_i/(1-S_i))$ response was suggested. In the first model difference in $\ln(-\ln(S_i))$ between two groups could be interpreted as $\ln(HR)$ over time and if the relationship between \ln -minus- \ln of the survival proportion and $\ln(time)$ have a linear pattern then Weibull distribution could be used to more needed analysis while in the second model the ratio of $\ln(\hat{S}_i/(1-\hat{S}_i))$ for two groups shows the survival odds at a specified time and if $\ln(\hat{S}_i/(1-\hat{S}_i))$ and $\ln(time)$ be relevant in a linear form we can use log logistic distribution for further analysis (Klein, 2005). The random effects in the model showed that the parameters fluctuate around a value with some variance. In order to have precise estimates with high power of covariate's effects simulation study could determine the appropriate transformation. As a comparable study an IPD meta-analysis has been done by Angelo et al. (2011) to compare the impacts of these two chemotherapy regimens on disease free survival of breast cancer patients that it had been also showed a significant difference in support of Anthracycline_based treatment over CMF (Leo et al., 2011). Another meta-analysis approach study had been done by Najaf et al. (2012) on disease free survival curves that showed Anthracycline_based as more effective regimens. This paper followed the study of Najaf Zare et al up to July 30th and extends the results (Zare et al., 2013). We showed and confirmed that the Anthracycline_based regimens had more positive effect on disease free survival and overall survival curves than CMF regimen and reduced the chance of recurrence and death in breast cancer patients. Lastly as a limitation it should declared that the studies with different type of Anthracycline_based regimens had been considered.

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