Bayesian IPD Meta-Analysis of Time-to-Event Data in Metastatic Breast Cancer

MSR49

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CONCLUSIONS

- With IPD, the Bayesian approach is more reliable due to its ability to incorporate prior information. The Bayesian parametric survival model yielded robust and consistent treatment effect estimates, aligning with frequentist methods
- This approach confirmed traditional Cox model (frequentistic) findings and demonstrated the potential of Bayesian methods to enhance the precision and reliability of survival analyses in clinical research

PLAIN LANGUAGE SUMMARY

- Meta-analyses combine and analyze data from multiple studies to improve reliability and precision of effect estimates
- Bayesian analysis integrates prior knowledge (such as findings from previous studies or expert opinions) with existing data, offering a more adaptable and comprehensive method for evaluating treatment outcomes. This method enhances the ability to draw conclusions by considering uncertainty and variability more effectively than traditional approaches
- The study found that patients treated with the intervention experienced a 26% lower risk of death compared to those receiving other standard treatments, based on the calculated hazard ratio of 0.74 with Bayesian IPD model compared to 0.70 with the traditional Cox model

INTRODUCTION

- Meta-analyses enhance precision in treatment effect estimates by aggregating data from multiple studies. Although well-established for continuous and binary outcomes, research on time-to-event outcomes often relies on Cox proportional hazard models[1]
- By integrating prior information and updating findings iteratively, Bayesian analysis provides a robust framework for meta-analyzing time-to-event outcomes using individual patient data (IPD)[2]
- Unlike the Frequentist approach, the Bayesian method offers flexibility in interpreting treatment effects by incorporating prior and posterior distributional assumptions without sample size constraints[3]

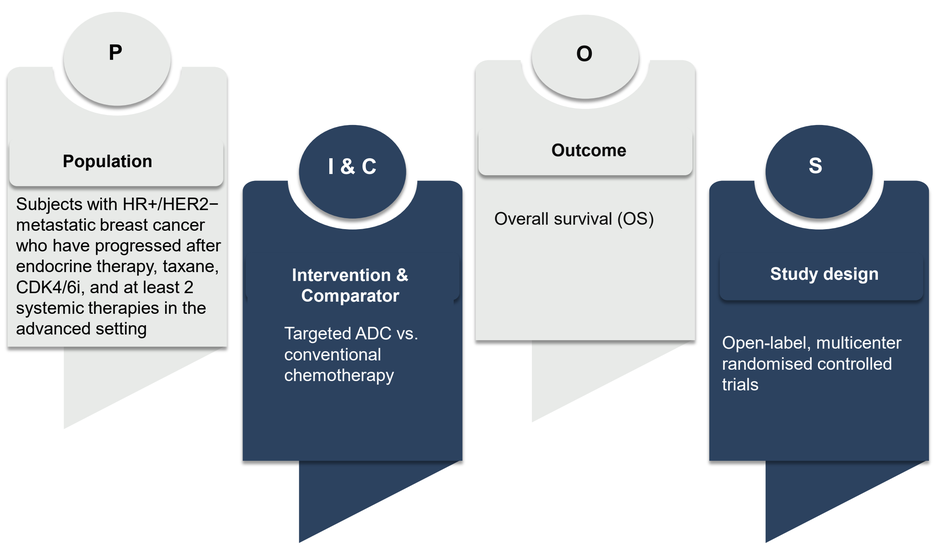
OBJECTIVE

- This study aimed to meta-analyze data from two clinical trials in metastatic breast cancer patients using a Bayesian parametric survival model

METHODS

- Two randomized controlled phase III trials assessing the intervention vs. comparator in patients with hormone receptor-positive and human epidermal growth factor receptor 2 negative (HR+/HER2−) metastatic breast cancer (MBC) who had previously received endocrine therapy, taxane, and at least two systemic therapies in the advanced setting were included in this analysis **(Figure 1)**

Figure 1 : PICOS criteria for inclusion in the meta-analysis



ADC: Antibody-drug conjugate; CDK4/6i: CDK4/6 inhibitor; HER2-: Human epidermal growth factor receptor 2 negative; HR+: Hormone receptor-positive

- Bayesian regression survival analysis was performed to model time-to-event data, utilizing Weibull and exponential distributions[4]
- The Bayesian framework allowed incorporation of prior knowledge into the estimation process, thereby offering greater flexibility
- The overall survival (OS) data was meta-analyzed using Bayesian parametric survival models in STATASE17
- The "bayes: streg" command was used to fit statistical models, incorporating clinical and statistical covariates from both the trials **(Table 1)**
- Prior CDK4/6 inhibitor use and duration, visceral disease, treated or stable brain metastasis, and early relapse were considered the important clinical covariates in the analysis[5]

Table 1: List of statistically significant covariates in both the trials

Trial 1	ECOG performance status, target, and nontarget liver lesions, mean disease duration, TPC distribution, and prior endocrine therapy in the metastatic setting
Trial 2	Age, liver metastasis at baseline, mean time from metastatic disease diagnosis to randomization, and prior anthracycline use

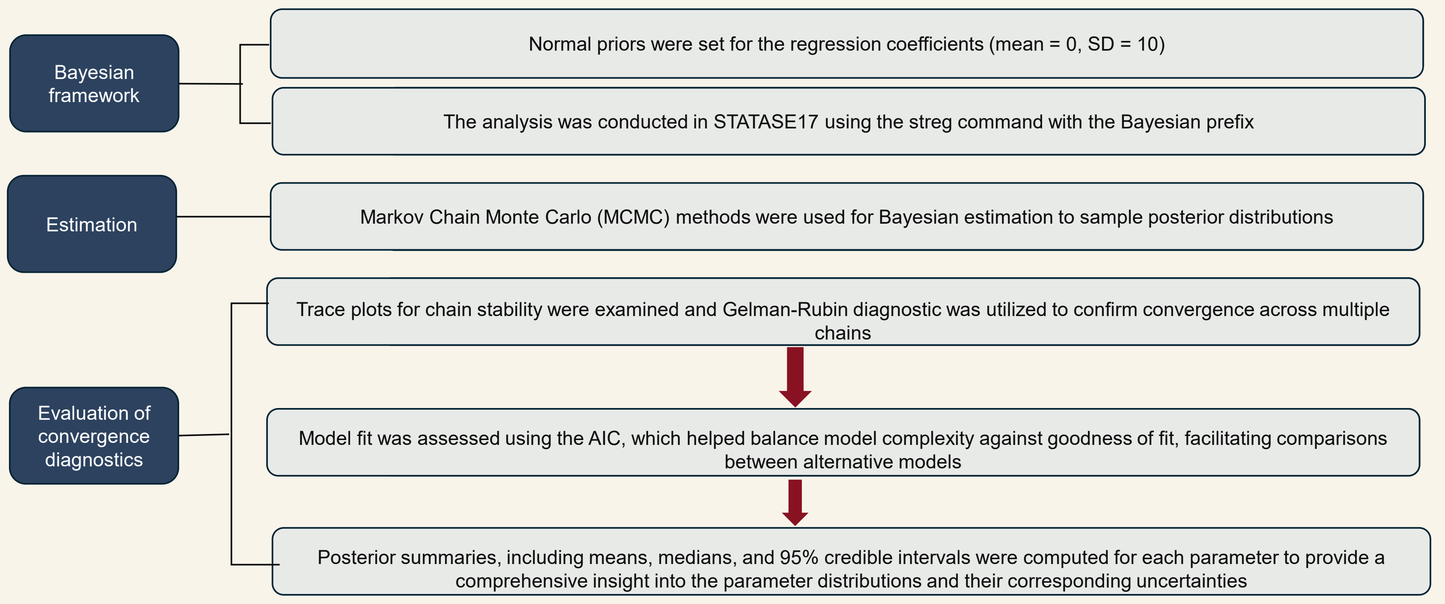
ECOG: Eastern Cooperative Oncology Group; TPC: Treatment of physician's choice

- The random-walk Metropolis-Hastings algorithm was used for efficient sampling using default normal priors
- The pooled hazard ratio (HR) was estimated via a two-stage meta-analysis using Bayesian exponential and Weibull distributions
- Normal priors were specified for the regression coefficients for both distributions, with a mean of 0 and a standard deviation of 10. This choice represented a relatively non-informative prior, allowing the observed data to drive the posterior estimates

METHODS (CONTD.)

- **Figure 2** illustrates the process for evaluating convergence in Bayesian analysis. Trace plots and Gelman-Rubin diagnostics are used to ensure chain stability across multiple iterations. Model fit is assessed via the Akaike Information Criterion (lower the AIC, the better the model fit) to balance complexity and goodness of fit. Posterior summaries, including means, medians, and 95% credible intervals, are then computed to provide insights into the uncertainty and distribution of parameters[6]
- This Bayesian approach allowed derivation of probabilistic interpretations of the parameter estimates, providing nuanced insights into the effects of the covariates on survival outcome
- By integrating prior clinical data with trial outcomes, this Bayesian analysis delivered a thorough and accurate assessment of the OS data, providing valuable insights into the critical factors affecting patient outcomes

Figure 2 : Steps in evaluating Bayesian model convergence and posterior summaries

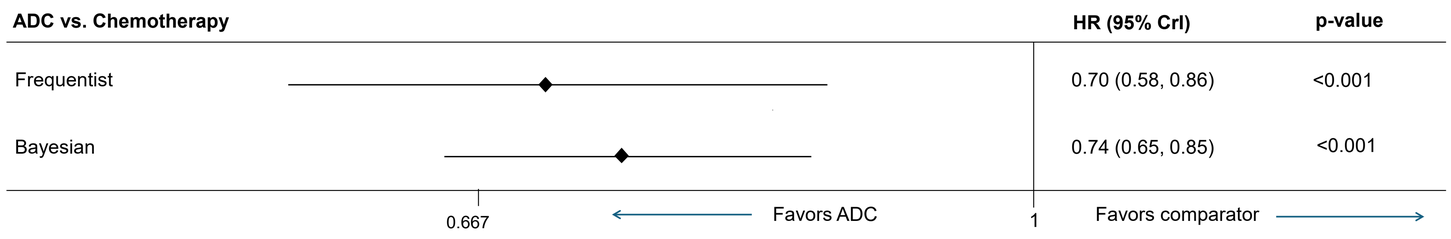


AIC: Akaike Information Criterion; SD: Standard deviation

RESULTS

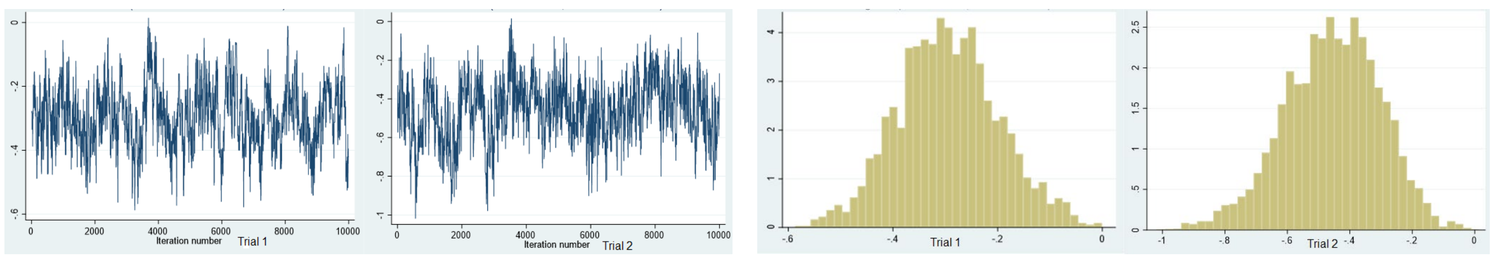
- Results from both statistical distributions were consistent. The Weibull model was preferred due to its superior goodness of fit statistic (i.e., Akaike Information Criterion; 2,124 vs 2,207 for Weibull and Exponential, respectively) and visual inspection of the fitted curve
- The intervention showed a statistically significant improvement in OS compared to the comparator (HR 0.74, p<0.001) in patients with MBC after adjusting for covariates. These results were consistent with frequentist meta-analyses using Cox models (HR: 0.70, p<0.001) **(Figure 3)**
- The good convergence of chains indicated in trace plots and well-defined posterior distribution presented in histograms suggested stable and reliable treatment effect estimates in the Bayesian IPD meta-analysis (**Figure 4**)

Figure 3: Meta-analysis results using Bayesian parametric survival model



CI: Confidence interval; HR: Hazard ratio; N: Sample size

Figure 4: Trace plots (left) and histograms (right) for Trail 1 and Trial 2 in Bayesian analysis



LIMITATIONS

- Pooling data from both the trials adds valuable diversity in patient characteristics and treatment protocols, enhancing result applicability. However, differences in methodologies between studies present challenges that require careful consideration to fully understand their impact on the findings
- The analysis relies on published studies with significant results. Future research and additional data will further refine and validate the treatment effect estimates, potentially leading to more precise conclusions
- The Bayesian approach allows for the use of flexible prior distributions. While this study utilized default normal priors, exploring alternative priors through sensitivity analyses could provide more nuanced insights and reinforce the robustness of the results
- Geographic and regional differences between the trials provide important context for treatment variations. These trial-level factors need to be considered when interpreting pooled estimates to account for potential regional biases

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Disclosures

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