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Group-Based Trajectory Modelling Considerations: Learnings from a Published Application in Acute Myeloid Leukaemia

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INTRODUCTION

- Adult patients with acute myeloid leukaemia (AML) have a poor prognosis, with an estimated 5-year relative survival rate of 31.9%[1]
- A 2021 study by Sorror et al. showed that while patient preferences for treatment objectives may vary between the outcomes of disease cure, longer life and better quality of life (QoL), almost 50% of patients with high-risk AML ranked QoL as more important than length of life[2]
- Physical well-being (PWB) scores, associated with walking and lower extremity function, are closely associated with health-related QoL in older adults with AML[3]
- PWB can be measured by patient-reported outcome (PRO) instruments. The Functional Assessment of Cancer Therapy General (FACT-G) questionnaire collects self-reported patient data on health condition and overall well-being[3]
- Group-based trajectory modelling (GBTM) is a statistical method that classifies individuals into distinct groups over time within a population of interest[4]
- Often, PRO measurements are analysed as a total score. While GBTM techniques allow for the analysis of PRO measurements over an extended time period[4], their application is limited due to the challenges of high patient attrition in AML, resulting from low survival rates[1]
- A recent publication by Jensen-Battaglia et al. (2024) provided a detailed application of GBTM techniques for the analysis of PRO measurements in adult patients with AML[5]
- Advancing knowledge of group-based patterns in patients with AML will aid clinicians to better identify high-risk patients in ongoing clinical trials, and inform study design for future AML trials

OBJECTIVES

- A critical assessment was conducted to evaluate the methods and findings reported by Jensen-Battaglia et al. to identify the key considerations required when conducting GBTM analyses across different PRO measures collected in AML studies[5]
- The goal of this review was to leverage the authors' findings to inform future implementations of GBTM, and to highlight areas of methodology and reporting that may require additional attention

METHODS

- The publication by Jensen-Battaglia et al. was chosen for an assessment due to its application of GBTM using PRO measurements, detailed reporting and methodological rigor[5]
- The publication was critically assessed by two reviewers to examine the inclusion and exclusion criteria defined for the patient population, covariate selection, model parameters and assessment of model fit
- The assessment summarized five key aspects of study design: inclusion and exclusion criteria, PRO definition and timepoints, GBTM model parameters, assessment of model fit, and missing data
- The demographics and clinical characteristics of each trajectory group were reviewed to understand the potential implications of the different patient groups and how these trajectories may inform clinical decision-making and intervention choices
- The strengths of the authors' study design were highlighted, and additional considerations were noted

RESULTS

Patient population, PRO definition and frequency of reporting in Jensen-Battaglia et al.

- The study by Jensen-Battaglia et al. analysed a total of 343 newly diagnosed adult patients with AML. Patients were pooled from four supportive care studies conducted between 2015 and 2019
- All patients were within the first year of treatment. Patients had a mean age of 69.9 years, with 51.8% of patients having intermediate-risk AML, and 71.1% of patients having received intensive treatment. 58% of patients died during follow-up
- Patients eligible for inclusion in the analysis had between two and five FACT-PWB measurements, and up to 200 days of follow-up. Patients were excluded if they were missing baseline demographic or clinical covariates
- Table 1 highlights learnings from Jensen-Battaglia et al., and our future considerations when defining the patient population for GBTM applications

Table 1. Future considerations when defining the patient population for GBTM

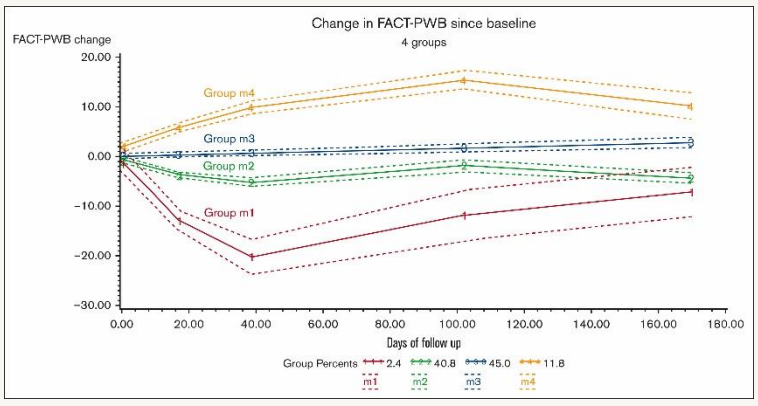
Study design	Strengths	Future considerations
All four supportive care studies that were pooled for analysis had similar patient populations with measurements collected for the FACT-PWB.	Pooling studies increased the analysis power and avoided common limitations of longitudinal analyses, including insufficient power and poor generalizability due to single-site design.[6]	• Rationale to support the choice of included studies identified for analysis should be explicitly stated. • Similarities between patient populations should be highlighted to justify how patient populations were deemed similar enough for a pooled analysis design. • A feasibility assessment is recommended to compare patient characteristics across trials to identify potential sources of heterogeneity.
The distribution of baseline covariates between the patients identified for exclusion and the analysis population were compared using χ^2or Fisher exact test.	The use of a test statistic to compare differences in baseline covariate distributions provided a quantifiable strategy to limit bias at this analysis step.	• Additional information to support the choice of test statistic may improve replicability. • If the patient populations were significantly different, guidance on next steps and/or limitations should be included.
Baseline characteristics of age, gender, race, marital status, education, income, AML risk, treatment regimen, baseline FACT-PWB, depression, and anxiety were determined a priori.	Descriptive statistics for covariates of interest were reported at baseline and by group.	• Clinical evidence is required to support the choice of covariates identified for analysis. • Any treatment-specific or disease-specific relationships between baseline covariates and PRO measures should be explained. • Additional covariates not captured in study design that may influence longitudinal PRO changes should also be noted.

Key: AML, acute myeloid leukaemia; FACT, Functional Assessment of Cancer Therapy; GBTM, group-based trajectory modelling; PRO, patient-reported outcome; PWB, physical well-being.

Model parameters and assessment of model fit in Jensen-Battaglia et al.

- Jensen-Battaglia et al. identified four distinct trajectories using GBTM, presented in Figure 1: m1 (2.4%; steep decline with recovery), m2 (40.8%; slight decline), m3 (45.0%; slight improvement) and m4 (11.8%; early improvement, later decline)
- Trajectories of change in FACT-PWB were used instead of total scores, as change measures help identify patients whose health is likely to decline, irrespective of their baseline values.
- The best model fit considered four factors: (i) Bayes factor improvement (calculated using a bootstrap technique with 500 repetitions to ensure robust estimation); (ii) group size; (iii) average posterior probability of group assignment; and (iv) clinical interpretability
- Baseline FACT-PWB was identified as the only statistically significant predictor of group membership
- Increased uncertainty in the group assignment is reflected in widening confidence interval bands due to increased missing data over follow-up

Figure 1. Trajectories of physical well-being among adults with AML



Key: AML, acute myeloid leukaemia; FACT-PWB, Functional Assessment of Cancer Therapy Physical Well-Being.
Source: Jensen-Battaglia et al.[5]

- A GBTM method extension by Haviland et al. was applied to the model to address loss to follow-up related to non-random mortality.[7] However, Jensen-Battaglia et al. noted that the results may not accurately represent trajectories of patients on less-intensive chemotherapies[5]
- Two sensitivity analyses by Jensen-Battaglia et al. explored the impact of missing data on trajectory results, excluding (a) patients missing data due to death, and (b) patients who died prior to contributing all expected measures of FACT-PWB. Additional exploratory analyses of imputation methods for missing data may provide helpful insights
- Table 2 highlights key take-aways from Jensen-Battaglia et al., and our future considerations when reporting model specifications in applications of GBTM

Table 2. Future reporting requirements for GBTM model specifications

Study design	Strengths	Future considerations
GBTM technique allowed for PRO measurements to be collected at varying timepoints, instead of requiring uniform timepoints across the included trials.	Group size, number of missing observations and average FACT-PWB were reported across timepoints for each group, which highlights patient attrition over time.	• Timepoints for PRO measure collection vary between studies and variability in timepoints may impact prediction accuracy in the model. • A sensitivity analysis exploring the impact of variations in collection time may help improve accuracy in future models.
Patient censoring followed a normal distribution, and cubic polynomials defined the shape of the trajectory curves.	Model specifications, including censoring distribution and polynomial degree, were explicitly defined.	• Additional supporting evidence to describe and justify model selections would support informed model decisions for future GBTM model implementations.
Parameters for the assessment of model fit considered four key factors, including clinical interpretability.	Clinical feedback was used to support model selection, ensuring that the number of groups reflected the clinical experience observed in patients with AML.	• Clinical expertise provides valuable insight into the patient experience and can closely inform observed changes in PRO measurements. • Detailed information on the process to collect clinical feedback will help inform best practice for future PRO studies. • Additionally, in cases where the best fit may vary between the four key factors considered, guidance on selecting the best model fit would be beneficial.
Multinomial logistic regression was used to evaluate the independent association of each baseline factor with group membership.	A results table of odds ratios, 95% confidence intervals and p-values clearly summarized analysis results.	• As group membership is a critical aspect of GBTM models, additional details on the model specification may provide key insights into future applications (e.g. choice of reference group).

Key: AML, acute myeloid leukaemia; FACT, Functional Assessment of Cancer Therapy; GBTM, group-based trajectory modelling; PRO, patient-reported outcome; PWB, physical well-being.

CONCLUSIONS

- This critical assessment highlights the importance of assessing and reporting inclusion and exclusion criteria, PRO definitions, model parameters, model fit, and missing data in GBTM applications. This may provide critical learnings for researchers applying GBTM techniques in future AML trials
- As GBTM techniques become more prevalent for PRO assessment, guidelines of best practices at the clinical trial design phase, including frequency of PRO collection, may increase the validity of the method
- Modelling decisions may influence resulting trajectories. Therefore, clinical expertise is important to ensure group patterns are reflective of the patient experience

REFERENCES

1. National Cancer Institute. Cancer Stat Facts: Leukemia — Acute Myeloid Leukemia (AML). https://seer.cancer.gov/statfacts/html/amyl.html. Accessed: 28 October 2024. 2. Sorror et al. *Blood*. 2021; 138(5):387-400. 3. Loh et al. *Curr Hematol Malig Rep*. 2019; 14(6):523-35. 4. Nagin. *Ann Nutr Metab*. 2014; 65(2-3):205-10. 5. Jensen-Battaglia et al. *Blood Adv*. 2024; 8(11):2612-21. 6. Byant et al. *Oncol Nurs Forum*. 2015; 42(2):E91-E101. 7. Haviland et al. *Sociol Methods Res*. 2011; 40(2):367-90.

An electronic version of the poster can be viewed by scanning the QR code.

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