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Estimating Survival of Spinal Muscular Atrophy Patients Using an Individual-Patient Data Enhanced Methodology

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INTRODUCTION

In rare diseases like spinal muscular atrophy (SMA), small sample sizes often cause discrepancies in survival estimates and economic evaluations due to inaccurate extrapolation of Kaplan-Meier (KM) curves. Accessing individual patient data (IPD) can improve accuracy, but it's limited by privacy concerns and unwillingness to share data. Developing a method to estimate IPD from published KM curves, and aggregating it across regions, could enhance the reliability of epidemiological and economic analyses. We modified Guyot's method to reconstruct IPD from KM curves and applied it to aggregate IPD from different KM curves to better estimate the overall survival of SMA patients.

METHODS

The methodology comprised five phase as illustrated in figure 1.

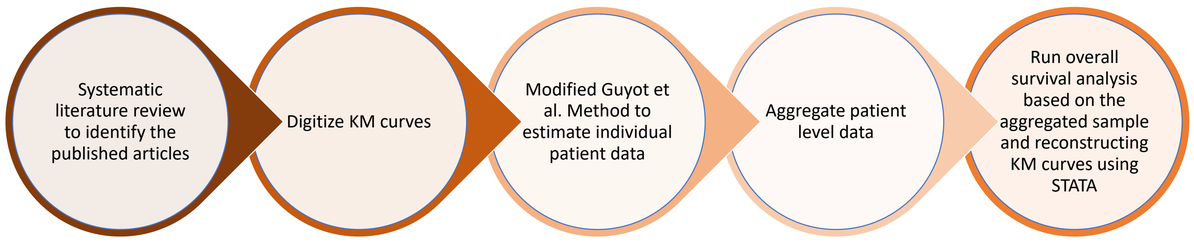

Figure 1: Steps of the study

MODIFICATIONS TO GUYOT'S METHODS

We modified Guyot's method to enhance the estimation of IPD as follows:

1. To estimate the number of censored patients for large intervals, the difference in survival until the next period is multiplied by the number at risk ($N_{at\ risk}$) at the start, then subtracting the $N_{at\ risk}$ reported for the next period gives the censored estimate. If no intervals are available, the entire dataset is treated as one interval. The estimated censoring rate is calculated by dividing the number of censored patients by the period they were censored in, and GOAL SEEK is used to calibrate the model to match reported patient numbers.

2. We assumed *varying censoring rates (Non-linear censoring rate) as function of the number at risk at the beginning of any small interval and large interval* while in Guyot's method, censoring occurs at a constant rate within each time interval (linear rate).

3. We *accumulate the number of censored patients* till the number sum up to an integer as illustrated in table 1. In Guyot's method, the number of censored patients was rounded to the nearest integer. This method improves the accuracy of censoring rate estimation especially in studies of rare diseases (as in the case of SMA) where the sample size is usually small.

Table 1 Cumulative censoring rate calculation

Time	Censoring rate	N risk	Number of censored patients	Cumulative # censored patients	Censored patients
0		1707			
4	a	x	1.5	1.5	1
10	a	y	0.7	2.2	1
20	a	z	0.2	2.4	0
24	a	≈943	2.3	4.7	2
	b			4.7	0

VALIDATION VERSUS REAL DATA

To validate our method, we used the reverse engineering approach. We used a publicly available survival dataset for which the IPD is available. We generated a KM from the IPD, then we estimated the cumulative censored number of patients over time as described before and compared the actual to the estimated.

To compare the accuracy of our method, we calculated the squared residual of the censoring rate –R^2- (the error in estimating the censoring rate, which is the lower, the better) as shown in figure 2.

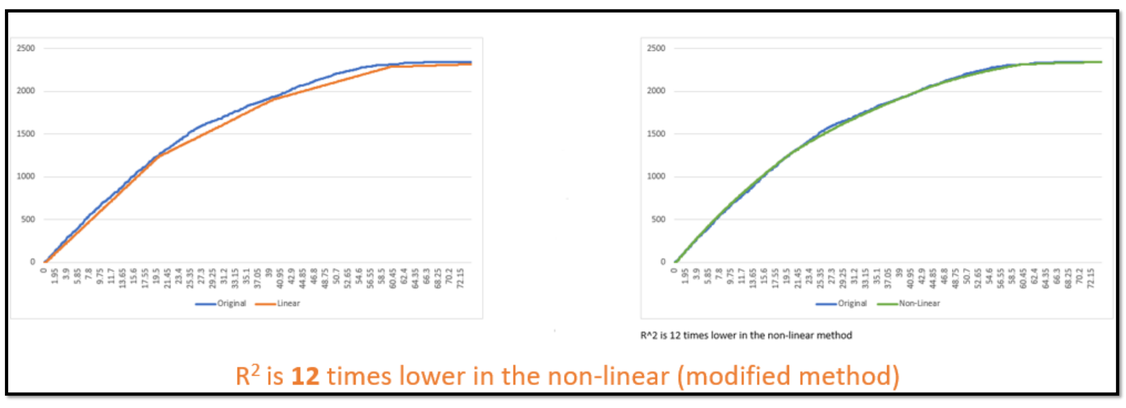

Figure 2: Reduced error rate for censoring rate estimation in the non-linear method

RESULTS

The systematic literature review yielded seven included studies, most of them about SMA type I. IPD from these studies was successfully estimated, and survival analysis was performed separately for SMA subtypes. The median survival was 40.6 , 568.2 months for type I and II, respectively. For type III, no disease-specific mortality was observed across the studies.

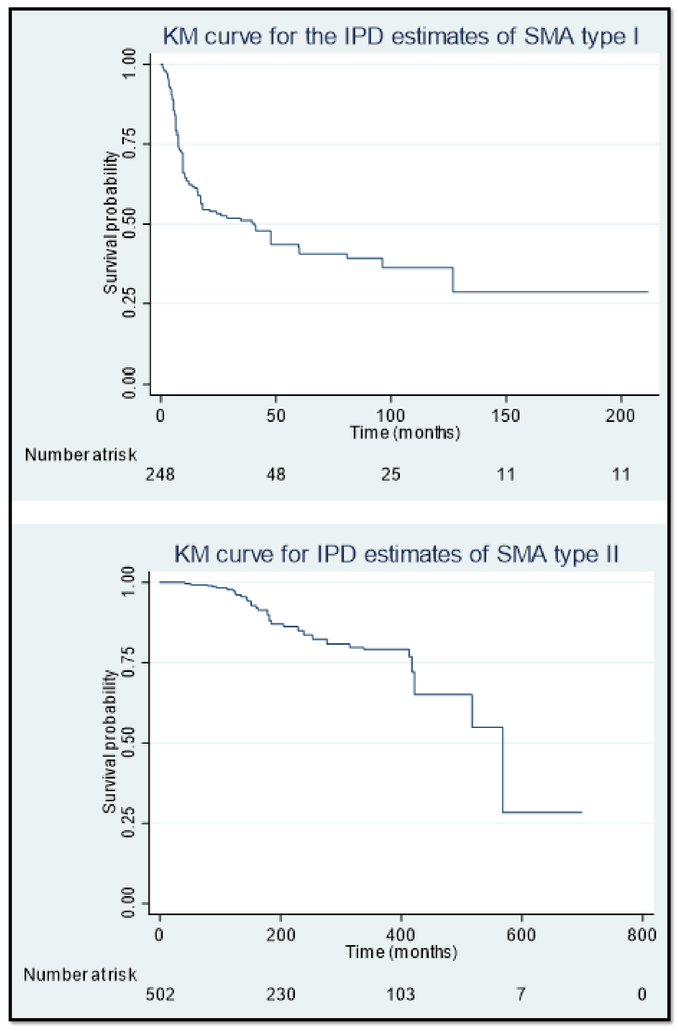

Figure 3: Reconstructed Kaplan-Meier curve from estimated individual patient data

CONCLUSION

The study represents an improvement to existing method for estimating IPD from published KM curves. This improvement can help researchers better estimate IPD for meta-analysis and obtain more precise estimates of transition probabilities in health economic models. For SMA, our results provide the most comprehensive survival data to date where data about patients' survival is scarce.

REFERENCES

1. Guyot, P., Ades, A., Ouwens, M.J. et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 12, 9 (2012). https://doi.org/10.1186/1471-2288-12-9