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Summarizing adverse event data in the absence of high-level evidence: the case of hearing implants

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BACKGROUND

Hearing implants (HIs) are used in patients with hearing loss that cannot benefit from hearing aids or reconstructive surgery. Safety plays a critical role in the assessment of these class-III medical devices, but because the concept of RCTs is hardly applicable, adverse event (AE) data is typically generated from prospective or retrospective cohort studies. Summarizing AE data for HIs is therefore often complicated by low data quality.

This study **aims to compare different methods for summarizing incidence rates (IRs) of AEs from real-world evidence**. Both, time-averaged IR (per person-time) and time-specific IR (per 6 months of follow-up) are compared.

METHODS

A systematic literature review was conducted in order to collect input data on the number of minor or major events, the number of patients at risk and duration of follow-up. Data from two different HI systems were pooled. IRs were summarized by either

1. **pooling data** across publications,
2. **meta-analyzing** publication-level IRs, or
3. by means of **survival analysis**.

To ensure comparability among methods, only data meeting the most stringent requirements (survival analysis) were used here. Analyses were conducted in R using custom scripts and functions provided in '*metafor*', '*survival*' and '*survminer*' packages.

RESULTS

The quality assessment revealed that no publications reported IR directly and few reported safety outcomes in a way suitable for IR calculation (Fig. 1). The final dataset included 79 publications and spanned an observation period of up to 60 months (summarized in Tab. 1). The most important findings were:

1. **IR estimates varied considerably among methods** (Fig. 2A-E), with time-averaged IRs showing largest deviations.
2. **Zero values posed a serious challenge to meta-analysis**. Setting custom weights to publication sample size might overcome this issue.
3. **Survival curves could be generated from aggregated data** using mean F/U time as proxy for individual length of follow-up.

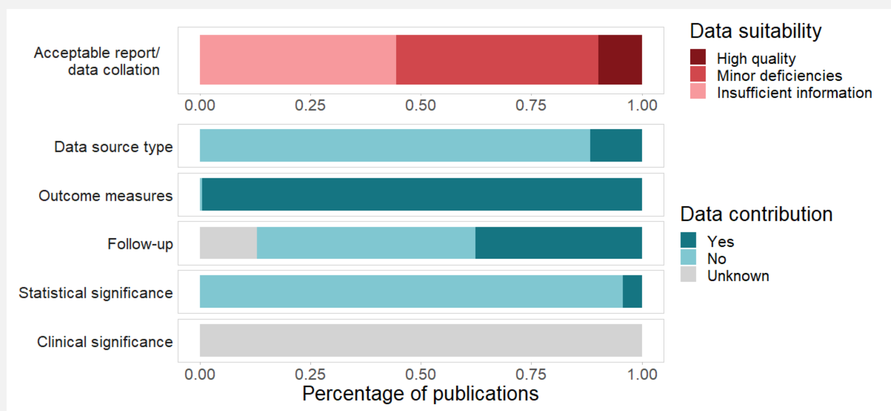

Fig. 1: Summary of the quality assessment at 6 different levels in two categories (colors). Darker colors indicate higher reporting quality.

Tab. 1: Summary of the number of patients at risk as well as number of minor and major events observed over the respective timeframes.

F/U time [months]	6	12	18	24	30	36	42	48	54	60
N at risk	901	589	560	465	376	261	125	84	21	21
N events minor	37	1	0	0	1	2	0	0	0	0
N events major	26	4	3	4	3	4	0	0	0	0

Tab. 2: Final evaluation of methods indicating low effort/high benefit, medium effort/benefit, high effort/low benefit.

	Data pooling		Meta-analysis		Survival analysis
	average	time-specific	average	time-specific	time-specific
Informative value	Low	Medium	Low	Medium	High
Analytical opportunities	Low	Low	Medium	Medium	High
Potential bias	High	Medium	High	Medium	Medium
Available sample size	Large	Medium	Large	Medium	Small
Data extraction effort	Low	High	Low	High	High
Computational effort	Low	Low	Medium	Medium	High

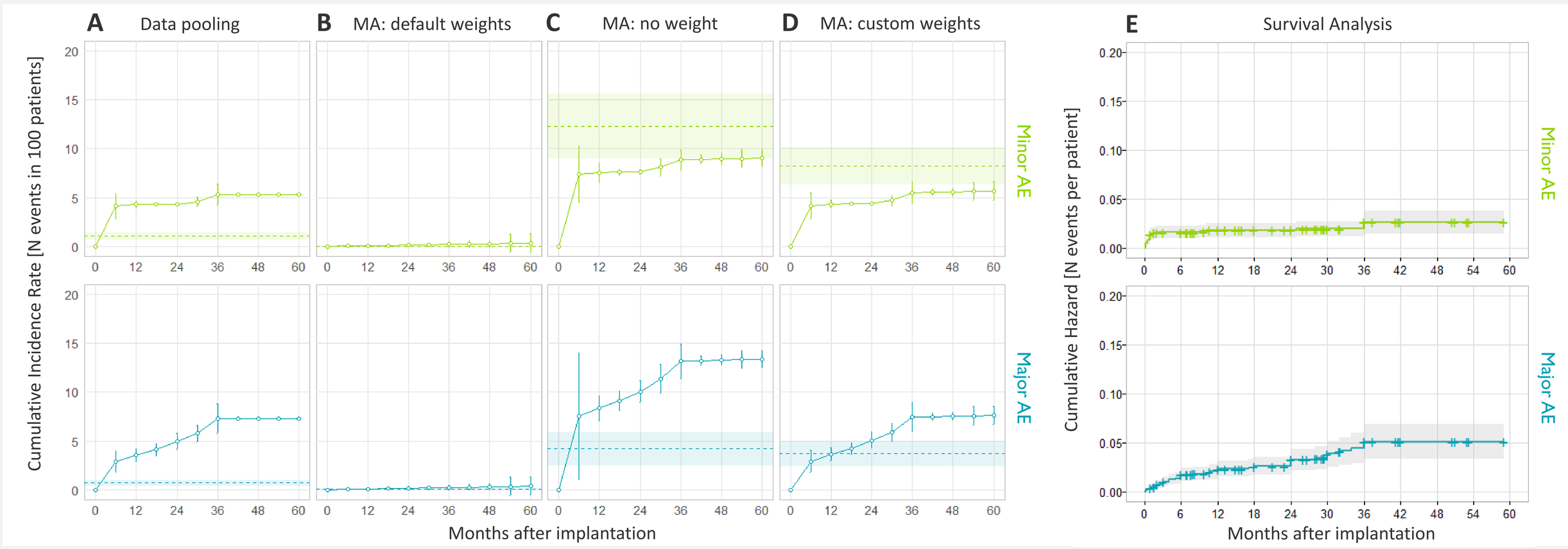

Fig. 2: Comparison of incidence rates calculated via pooling data across publications or via meta-analysis (A-D) and cumulative hazard calculated via the Kaplan-Meier survival estimator (E). Dashed lines and corresponding shaded areas represent the time-averaged IR estimates calculated with each respective method. MA=meta-analysis, AE=adverse event.

Discussion

Neglecting time-specific information when estimating IRs will bias outcomes due to non-linear accumulation of events. While pooling at specific timeframes will give acceptable results, more elaborate methods increase analytical opportunities like testing for differences among subgroups or quantifying the effects of potential confounders. These come at the cost of increased data extraction- and computational effort. In the absence of patient-level data, these methods require at least some assumptions on individual F/U times and the respective number of patients at risk. Depending on their specific needs, different stakeholders should to weight the pros and cons of available methods (Tab. 2) when estimating incidence rates of adverse events in hearing implants.