Variations in mortality across clinical trials: a review of statistical methods for adjusting for the effect of the COVID-19 pandemic

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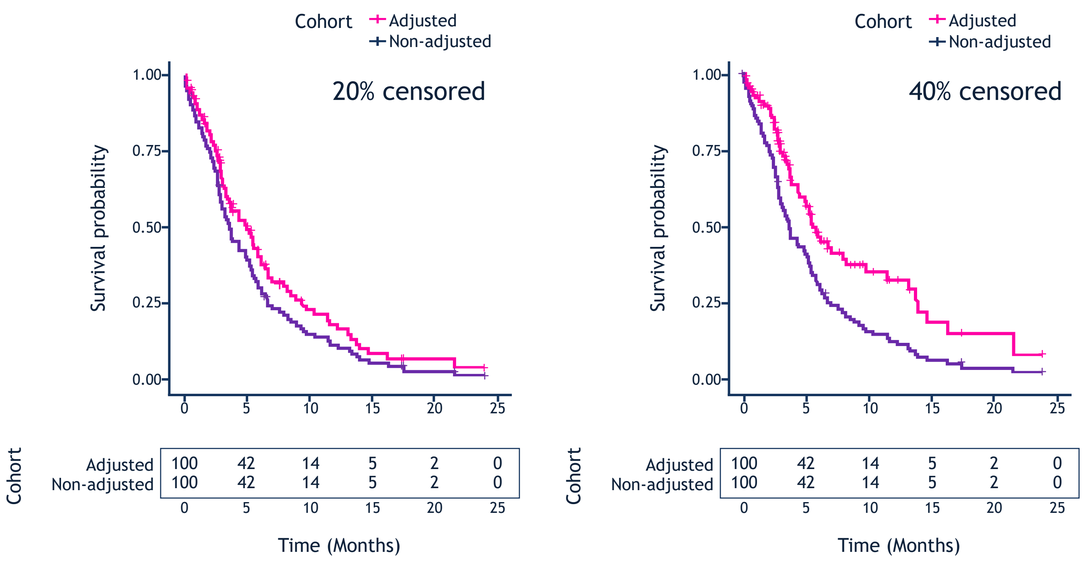
INTRODUCTION

- Real-world evidence shows that immunocompromised and high-risk patients were disproportionately impacted by the COVID-19 pandemic (2020 – 2022).[1]
- This may disproportionately affect the outcome of single-arm trials, where excess mortality would lower the treatment effect associated with an intervention when compared to trials unaffected by the pandemic.
- It is possible to account for excess mortality due to COVID-19 by naïvely censoring deaths related to COVID-19 (Figure 1). However, this may lead to informative censoring, where the reason a patient is censored is linked to their disease prognoses (i.e., COVID-19).[2]
- Treatment switching methods, which exist to estimate the "true" survival associated with the initial treatment for patients who switch treatments, could be applied to estimate the survival efficacy in trials that were affected by COVID-19.
- Here, death due to COVID-19 would be considered as the treatment switching event.

Figure 1: Kaplan-Meier curves of simulated time-to-event data showing the effect of naïve censoring of COVID-19 deaths on survival outcomes under two scenarios: 1) 20% of patients die from COVID-19 and are censored; 2) 40% of patients die from COVID-19 and are censored.



OBJECTIVES

This research aimed to explore whether existing treatment switching methods could be used to estimate treatment effects in the absence of COVID-19, for trials that were affected by the COVID-19 pandemic.

METHODS

- A targeted search was conducted in Google Scholar to identify existing statistical methods for treatment switching. These were validated against methods listed in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 16.[3]
- A list of assumptions and data requirements were catalogued for each method.
- The validity of each assumption and data requirement was assessed in the context of the COVID-19 pandemic, based on the current literature and common trial design.
- Each method was reviewed to determine if it should be used to estimate patient survival in the absence of COVID-19, based on the current understanding of COVID-19 dynamics, potential availability of trial data, and assumptions required.

RESULTS

- Treatment switching methods identified through the targeted search included inverse probability of censoring weights (IPCW), rank-preserving structural failure time models (RPSFTM), expectation-maximization (EM) methods, and "two-stage" estimation methods.
- A summary of the methods used to re-weight patients based on the probability of treatment switching were summarized in the first part of Table 1.
- The list of assumptions required to use the treatment-switching methods for adjusting for COVID-19 are detailed in the second part of Table 1.

RESULTS (cont'd)

Table 1. A Description of Methods Considered for Addressing COVID-19 Pandemic Related Mortality and Assumptions Required for their application

	COVID-19 Pandemic	Treatment-Switching Methods			
Description of Methods		IPCW[4]	Two-stage estimation[5]	EM methods[2]	RPSFT models[6]
Calculates counterfactual survival times (i.e., expected survival time in the absence of the COVID-19 pandemic).		×	✓	✓	✓
Reweights patients who were not artificially censored to reduce bias.		✓	×	×	×
Preserves randomization (i.e., assumes that there is a control arm and intervention arm).		•	✓	•	✓
Required Assumptions					
COVID-19 infection altered the patient's survival time, acting as a switch in survival curves. In the absence of the COVID-19 pandemic, patients with similar characteristics would have similar prognosis.	✓	✓	✓	✓	✓
There is a direct relationship between overall survival and survival to COVID-19-related death (not randomly associated).	✓	×	×	✓	✓
The timing of the COVID-19 infection is directly tied to patients' disease state (usually progression).	×	×	✓	×	×
There are no unmeasured confounding variables that affect the decision to switch treatments (i.e., likelihood of COVID-19 infection), that are prognostic in nature (i.e., affect survival or progression outcomes), and/or are affected by treatment. The disease itself does not influence the risk of COVID-19 infection and mortality.	×	✓	✓	×	×
Patient characteristics are known at time of the COVID-19 infection and periodically assessed for all patients.	✓	✓	✓	×	×
Patient characteristics are known at a secondary baseline when all patients have the option to switch.	×	×	✓	×	×

Abbreviations: EM, expectation-maximization; IPCW, inverse probability of censoring weights; RPSFT, rank preserving structural failure time.

Key for Applicability of Assumptions to COVID-19 Pandemic (Column 2): ✓: Assumption is reasonable, ✓: Assumption may be true, ×: Assumption is not reasonable.

Key for Treatment Method Description & Assumptions section (Rows 1-3) :✓: Statement applies to the given method. • : Method works independently of given condition, ×: Statement does not apply to the method.

Key for Assumptions Required for Each Method (all other rows): ✓: Assumption is required. • : Method works independently of given assumption, ×: Method does not rely on this assumption.

- Note that while EM methods are not included in TSD 16 they are widely used in other fields (computer science and engineering) and have been proposed for use in addressing COVID-19 deaths during the pandemic in single arm cancer trials.[2]
- An additional method, iterative parameter estimation algorithm, listed in TSD 16 was not explored in full as this is an extension of the RPSFT method and would have similar assumptions and data requirements.[3]
- The results showed that the EM method closely aligned with the trends observed in the COVID-19 pandemic (Table 1), as it does not assume that all confounding variables are known, that the infection is tied to patients' disease state, that patients' characteristics are known at the time of infection, and that secondary baseline characteristics are known at the time of the switch.

CONCLUSION

Alternate statistical methods such as treatment switching methods could be used to account for COVID-19 mortality in affected trials.

Assumptions required for EM algorithms closely aligned with conditions observed during the COVID-19 pandemic, with publications[2] supporting the application of this method in this manner. IPCW, two-stage estimation, and RPSFT models required additional assumptions that do not currently apply to the COVID-19 pandemic given our current knowledge of COVID-19 and/or standard trial design.

If information on patient characteristics impacting outcomes after infection with COVID-19 is known and fully captured, IPCW could also be used as an alternate method.

Future research could investigate the feasibility of applying treatment switching methods to adjust for COVID-19 depending on the data collected in trials (e.g., knowledge of prognostic factors, timing of COVID-19 infection, duration of infection, etc.).

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REFERENCES

1. Gao, Y.D., Ding, M., Dong, X., Zhang, J.J., Kursat Azkur, A., Azkur, D., Gan, H., Sun, Y.L., Fu, W., Li, W. and Liang, H.L., 2021. Risk factors for severe and critically ill COVID-19 patients: a review. *Allergy*, *76*(2), pp.428-455.
2. De Felice, F., Mazzoni, L. and Moriconi, F., 2023. An expectation-maximization algorithm for including oncological covid-19 deaths in survival analysis. *Current Oncology*, *30*(2), pp.2105-2126.
3. Latimer, N.R. and Abrams, K.R., 2014. NICE DSU technical support document 16: adjusting survival time estimates in the presence of treatment switching.
4. Howe, C.J., Cole, S.R., Chmiel, J.S., and Muñoz, A. 2011. American Journal of Epidemiology: 173(5), pp.569-577.
5. Latimer, N.R., Abrams, K.R., and Siebert U. 2019. Two –stage estimation to adjust for treatment switching in randomized trials: a simulation study investigating the use of inverse probability weighting instead of re-censoring. *BMC Medical Research Methodology*, 19(1).
6. Bennett, I.A., Paracha, N., Abrams, K., Ray, J. 2018. Accounting for uncertainty in decision analytic models using rank preserving structural failure time modeling: Application to parametric survival models. *Value in Health*, 21, pp. 105-109.

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