# Modelling time-to-death utilities as a continuous function, using a rich dataset of patients with non-small cell lung cancer

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## Objectives

- The approach of modelling utility values as time-to-death (TTD) health states was developed in response to perceived shortcomings of the progression-based approach in oncology [1,2]
- Published data supports a link between patient health-related quality of life (HRQL) and proximity to death [3], and that TTD may be a stronger predictor of health care costs than other factors – including age [4,5]
- A simulation study has provided an indication of the situations for which TTD utilities are likely to provide more accurate reflection of HRQL trajectory than progression based approaches [6]
- This analysis develops the approach, by modelling utility values as a continuous function of TTD as opposed to the widely used approach of discrete groupings e.g., 0-4 weeks, 4-26 weeks, 26-52 weeks, >52 weeks
- The analysis is conducted in an unusually rich dataset in advanced non-small cell lung cancer (aNSCLC), with data extending to 5 years

## Methods

- Datasets from the CheckMate-017 and CheckMate-057 trials in aNSCLC were pooled, giving a total of 4850 EQ-5D-3L observations from 788 patients over 5 years [7]
- Of the 788 patients with EQ-5D-3L responses, 718 died within the study period, allowing for a largely complete dataset
- Utility scores were generated using the UK value set [8]. Generalised Estimating Equations (GEE) were used to fit models, with a variety of functional forms to delineate the relationship between utility score and TTD
- The functions tested were TTD in days, Log(TTD), 1/SQRT(TTD), $TTD^2$, $TTD^2$+ TTD, $1/e^{TTD}$, as well as previously published utility groupings [8], and grouping stratified by progression status
- The observed EQ-5D-3L utility versus TTD is shown in Figure 1 split by treatment received, with a clear decrease as patients approach death. As the treatment coefficient was indistinguishable from zero, the data was then pooled for model fitting

**Figure 1. EQ-5D-3L Utility (UK value set) by Time to Death**


- The linear TTD and the two best fitting (continuous) models tested are listed in Table 1, with model fit compared to the use of discrete TTD categories
- Model fit was judged by the Mean Absolute Error (MAE) and Quasi-Information Criterion (QICu), as well as visual inspection

**Table 1. Models fitted to observed data, including MAE and QICu**

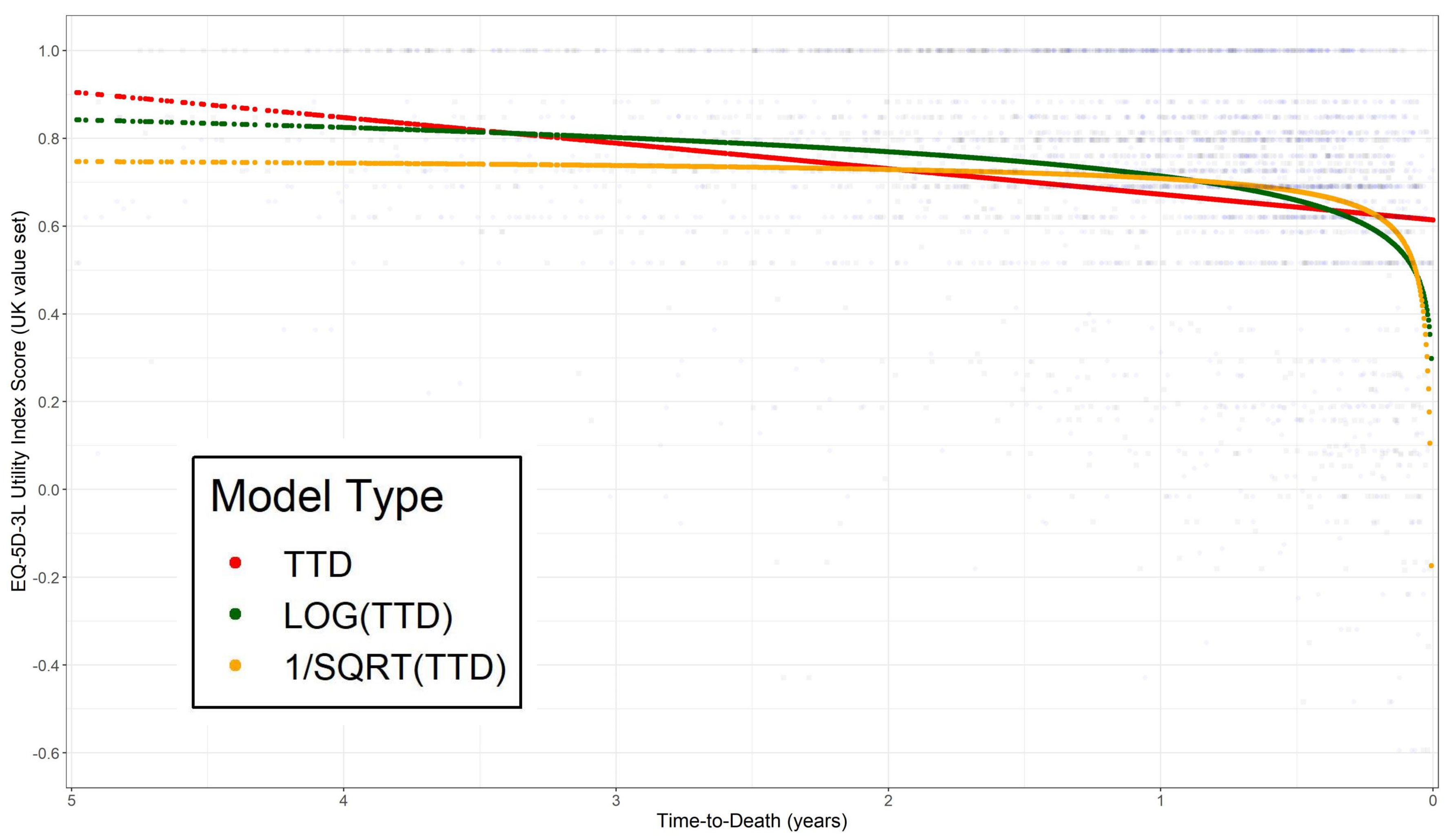
| Statistical model | MAE | QICu |
|---|---|---|
| TTD | 0.183 | 3629 |
| Log(TTD) | 0.178 | 3628 |
| 1/SQRT(TTD) | 0.177 | 3628 |
| *Discrete TTD categories* | *0.178* | *3631* |
| *Progression based utilities* | *0.191* | *3629* |

MAE = Mean Absolute Error, QICu = Quasi Information Criterion. Lower scores represent a better fit for both metrics
TTD = time to death (days). Discrete TTD categories: 0-4 weeks, 4-26 weeks, 26-52 weeks, >52 weeks

## Results

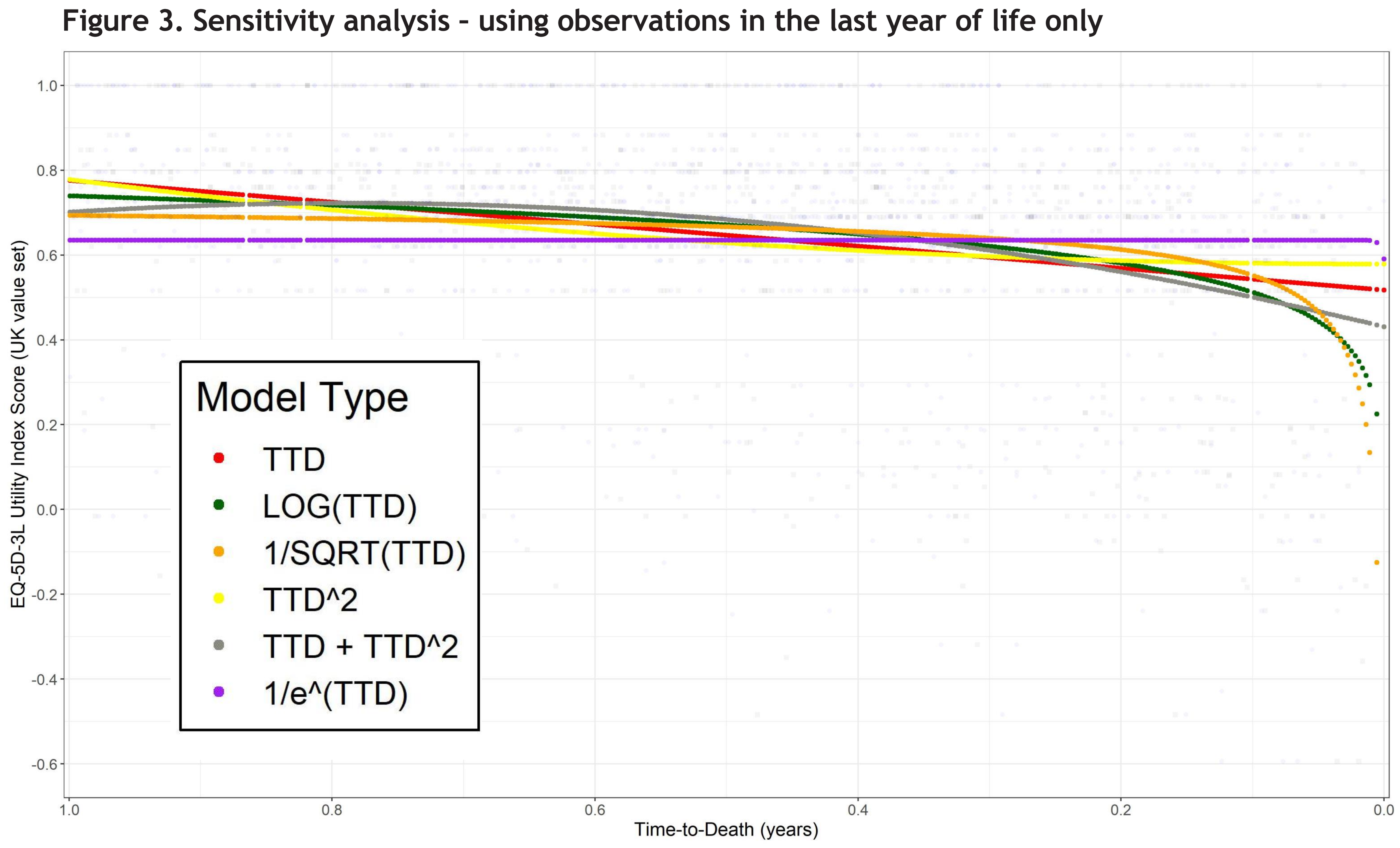
- Utility values showed a clear decline in the 6 months prior to death, with no clear groupings observed visually
- The two preferred models out of six evaluated were in the form 1/SQRT(TTD) and log(TTD). These models yielded a good visual fit (Figure 2) as well as the smallest MAEs (0.177 and 0.178) and QICu (3628 and 3628) values, which show a much better fit than only using linear TTD (Table 1)

**Figure 2. EQ-5D-3L Utility (UK value set) by Time to Death fitted to the pooled datasets**




- The continuous time models compared favourably with the use of previously described discrete TTD categories [9] in having similar MAE (0.178) but lower QICu (3631) whilst not requiring assumptions regarding appropriate groupings
- All TTD models gave lower MAE than analysis of utilities by progression status
- In order to ensure the validity of the results, sensitivity analyses were conducted using splitting analyses by study, using only patients with observed death events, and using only the last year of life (Figure 3), with findings consistent with the base case – though with other models also converging

**Figure 3. Sensitivity analysis - using observations in the last year of life only**




## Conclusions

- The use of a continuous function avoids the need for arbitrary grouping of time to death categories
- The best-fitting models were 1/SQRT(TTD) and Log(TTD), which improve on the statistical fit of progression based utilities
- Further research is required to apply continuous functions to other datasets – both within and outside oncology, ensuring the findings are generalisable
- Consistency across EQ-5D value sets should also be tested

## References

1. Hatswell, A.J. et al. (2014) 'Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death', Health and quality of life outcomes, 12(1), p. 140.
2. Versteegh, M. et al. (2022) 'Estimating Quality of Life Decrements in Oncology Using Time to Death', Value in Health, p. S1098301522020381. Available at: https://doi.org/10.1016/j.jval.2022.06.002.
3. Lorem, G. et al. (2020) 'Self-reported health as a predictor of mortality: A cohort study of its relation to other health measurements and observation time', Scientific Reports, 10(1), p. 4886. Available at: https://doi.org/10.1038/s41598-020-61603-0.
4. Geue, C. et al. (2015) 'Hospital Expenditure at the End-of-Life: What Are the Impacts of Health Status and Health Risks?', PLOS ONE, 10(3), p. e0119035. Available at: https://doi.org/10.1371/journal.pone.0119035.
5. Howdon, D. and Rice, N. (2018) 'Health care expenditures, age, proximity to death and morbidity: Implications for an ageing population', Journal of Health Economics, 57(Supplement C), pp. 60–74. Available at: https://doi.org/10.1016/j.jhealeco.2017.11.001.
6. Hatswell, A.J. et al. (2021) 'What is the Impact of the Analysis Method Used for Health State Utility Values on QALYs in Oncology? A Simulation Study Comparing Progression-Based and Time-to-Death Approaches', Applied Health Economics and Health Policy, 19(3), pp. 389–401. Available at: https://doi.org/10.1007/s40258-020-00620-6.
7. Borghaei, H. et al. (2021) 'Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer', Journal of Clinical Oncology, 39(7), pp. 723–733. Available at: https://doi.org/10.1200/JCO.20.01605.
8. Chaudhary, M. et al. (2020) 'Estimating EQ-5D Utilities for Cost-effectiveness Models Involving Immuno-oncology Treatments'
9. Dolan P (1997) Modeling valuations for EuroQol health states. Med Care 35(11): pp. 1095-108.

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