

“Method of the month”: Mixture cure survival models for medicine persistence

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Today's paper



- C. Cai et al. Applying mixture cure survival modeling to medication persistence analysis *Pharmacoepidemiol Drug Saf*, 2022;1-8. doi:10.1002/pds5441.

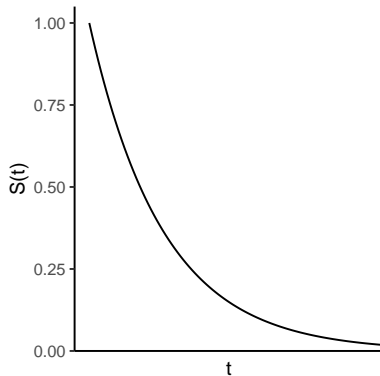
Recap of survival analysis

- Time-to-event analysis is fundamental to cohort studies
- Unbiased estimates require proper handling of censoring
- Kaplan–Meier analysis estimates empirical survival curve
- Cox regression allows semiparametric estimation (PH assumption)

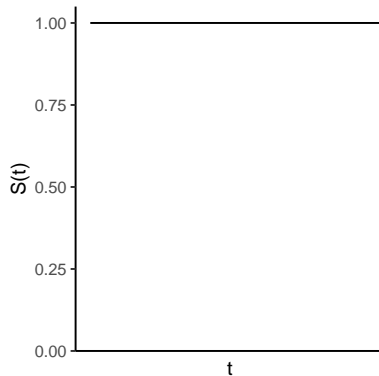
Cure survival models

- Simple survival models consider all cohort members as susceptible
 - Good assumption for short follow-up
- But if there is a long plateau at the tail of the survival curve
 - Evidence for a “cured” fraction
- *By definition, 100% of cured cohort members will be censored*

Mixture cure models 1

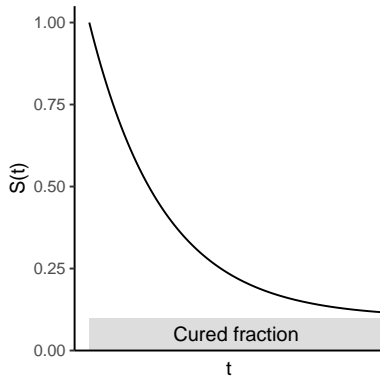


A bit of this...



and a little bit of that

Mixture cure models 2



$$S_{pop}(t|X, Z) = \underbrace{\pi(Z)S_u(t|X)}_{\text{uncured}} + \underbrace{1 - \pi(Z)}_{\text{cured}}$$

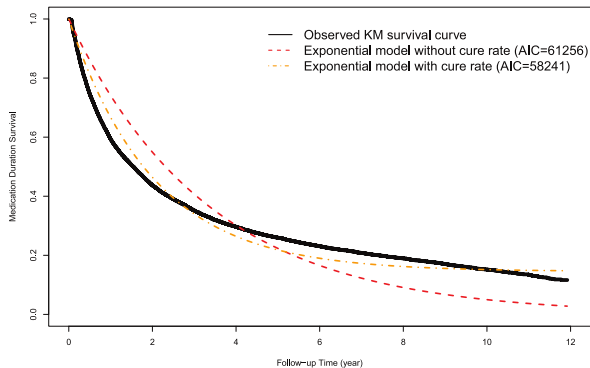
What's this got to do with medicine persistence?

- Time-to-event analysis is the obvious way to measure persistence, with discontinuation as the event
- Empirically, there may be distinct short- and long-term persistence patterns
- In chronic disease, consider the long-term persistent as the “cured” fraction
- If there is cured fraction, PH assumption is violated

Cai et al example 1

- South Carolina health Plan and Medicaid
- Prescription claims 2008 to 2019
- Statin new users (12-month washout)
- Participants who died excluded
- Age group, gender, comorbidity and insurance covariates
- Results shown for 180-day permissible gap

Cai et al example 2



Fitted persistence curves with different survival models

Cai et al. (2022)

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Cai et al example 3

	Standard COX PH Model		Mixture cure model			
	HR	95% CI	OR	95% CI	HR	95% CI
Age [45,55)	Reference					
< 45	1.48*	(1.42, 1.54)	1.83*	(1.58, 2.11)	1.37*	(1.31, 1.44)
55+	1.54*	(1.48, 1.61)	4.32*	(3.36, 5.55)	1.25*	(1.18, 1.32)
Female	1.17*	(1.13, 1.21)	1.65*	(1.42, 1.92)	1.06*	(1.01, 1.11)
Comorbidity	1.20*	(1.16, 1.24)	2.01*	(1.73, 2.33)	1.04*	(1.00, 1.09)
Private insurance	0.44*	(0.43, 0.46)	0.06*	(0.05, 0.08)	0.71*	(0.67, 0.74)

Variable	Estimated long-term fraction (%)
Age < 45	10
Age [45, 55)	17
Age 55+	4
Male	15
Female	9
Private insurance	26

Cai et al. (2022)

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Statistical inference

- Test if the cured fraction > 0
- Test if the follow up is long enough
- *n.b. in the Cai et al (2022) paper this is done using parametric models*

Worked (trivial) example in R

```
> head(displ)
      d cens
1 129    0
2  28    0
3  47    0
4 223    0
5 129    0
6  21    0
> flexsurvcure(Surv(d, 1-cens)~1, data=displ, dist="exp", mixture=T)
Call:
flexsurvcure(formula = Surv(d, 1 - cens) ~ 1, data = displ, dist = "exp",
             mixture = T)

Estimates:
      est      L95%      U95%      se
theta 0.095714 0.073067 0.124438    NA
rate  0.010287 0.009380 0.011282 0.000484

N = 1000, Events: 863, Censored: 137
Total time at risk: 112600
Log-likelihood = -5044.493, df = 2
AIC = 10092.99
```

The wild west of survival models...

- There's more to life than just Cox models:
 - Parametric survival
 - Accelerated failure time
 - Shared/conditional frailty
 - ...

Summary

- If short-term and long-term persistence are distinct, try a cure model
- Estimating cure models can be tricky
- Statistical tests can clarify which model to use
- Still many parameters to twiddle e.g. permissible gap
- Watch this space, there is plenty of room for new ideas

Thanks

■ Andrea

References

- J. Amdahl. *flexsurvcure: Flexible Parametric Cure Models*, 2020. URL <https://CRAN.R-project.org/package=flexsurvcure>. R package version 1.2.0.
- C. Cai, Y. Zou, Y. Peng, and J. Zhang. smcure: An R-package for estimating semiparametric mixture cure models. *Computer Methods and Programs in Biomedicine*, 108(3):1255–1260, Dec. 2012. doi: 10.1016/j.cmpb.2012.08.013.
- C. Cai, B. L. Love, I. Yunusa, and C. E. Reeder. Applying mixture cure survival modeling to medication persistence analysis. *Pharmacoepidemiology and Drug Safety*, 2022. doi: 10.1002/pds.5441.
- M. Othus, B. Barlogie, M. L. LeBlanc, and J. J. Crowley. Cure Models as a Useful Statistical Tool for Analyzing Survival. *Clinical Cancer Research*, 18(14):3731–3736, July 2012. doi: 10.1158/1078-0432.CCR-11-2859.