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

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Today's paper

ORIGINAL ARTICLE

WILEY

Applying mixture cure survival modeling to medication persistence analysis

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Abstract

Purpose: Standard survival models are often used in a medication persistence analysis. These methods implicitly assume that all patients will experience the event (medication discontinuation), which may bias the estimation of persistence if long-term medication persistent patients rate is expected in the population. We aimed to introduce a mixture cure model in the medication persistence analysis to describe the persistence pattern, identify factors associated with persistent patients, and demonstrate its application using a real-world data analysis.

Methods: A cohort of new users of statins was used to demonstrate the difference between the standard survival model and the mixture cure model in the medication persistence analysis. The mixture cure model estimated effects of variables, reported as odds ratios (ORs) associated with likelihood of being long-term persistent and effects of variables, reported as hazard ratios (HR) associated with time to medication discontinuation among non-long-term persistent patients.

Results: Long-term persistent rate was estimated as 17% for statin users aged between 45 and 55 versus 33% for age less than 45 versus 4% for age greater than 55 via the mixture cure model. The HR of covariates estimated by the standard survival model (HR = 1.41, 95% CI = [1.35, 1.48]) were higher than those estimated by the mixture cure model (HR = 1.18, 95% CI = [1.15, 1.19]) when comparing patients with age greater than 55 to those between 45 and 55.

Conclusions: Compared with standard survival modeling, a mixture cure model can improve the estimation of medication persistence when long-term persistent patients are expected in the population.

KEYWORDS

cure survival fraction, medication persistence, mixture cure model, pharmacoepidemiology, survival analysis

Key Points

- Current medication persistence analysis evaluating the risk (or determinants) of discontinuing medication is still limited to traditional survival analysis, which implicitly assumes the population has no long-term medication persistent ("cured") fraction.
- An advanced survival method, mixture cure model, is proposed to overcome the limitation of the standard survival analysis in medication persistence evaluation when long-term medication persistent patients exist in a population.

- 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)

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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*

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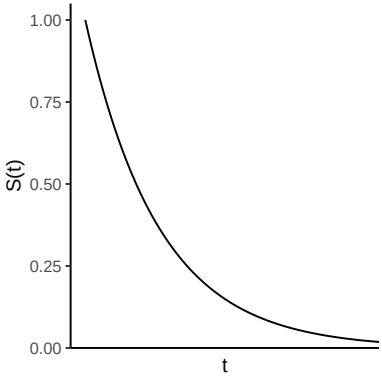
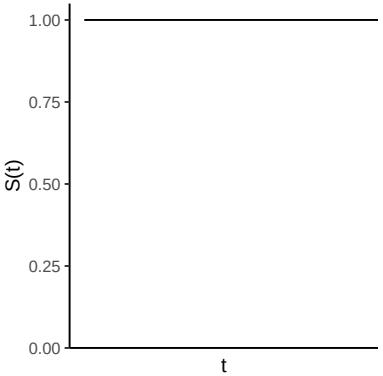
Mixture cure models 1



A bit of this...



and a little bit of that

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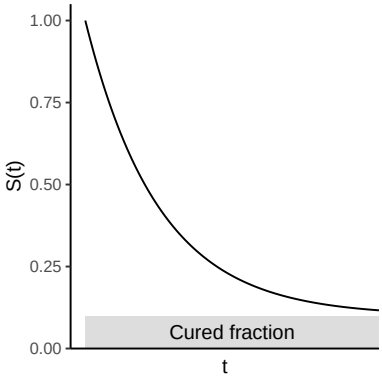
Mixture cure models 2



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

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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

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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

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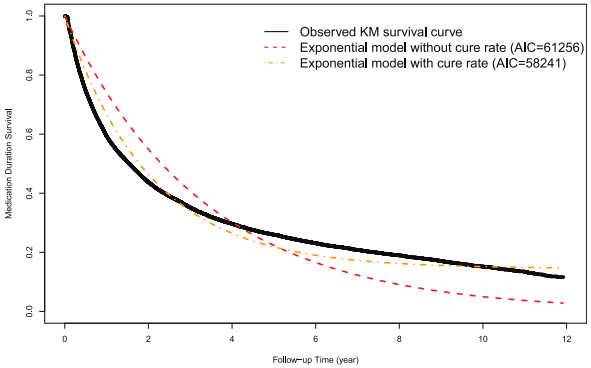
Cai et al example 2



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)

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*

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Worked (trivial) example in R

```
> head(disp)
    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=disp, dist="exp", mixture=T)
Call:
flexsurvcure(formula = Surv(d, 1 - cens) ~ 1, data = disp, 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
```

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The wild west of survival models...

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

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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. permissable gap
- Watch this space, there is plenty of room for new ideas

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Thanks

- Andrea

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References

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