Applying Mixture Cure Survival Modeling to Medication Persistence Analysis

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BACKGROUND

- Treatment of chronic diseases often involves the long-term use of pharmacotherapy. In pharmacoepidemiology, both adherence and persistence can be used as effective measurements of medication-taking behavior.
- Administrative claims data are frequently used by researchers to evaluate medication persistence. For these evaluations, medication persistence is typically defined as the duration of time from initiation to permanent discontinuation of therapy or until gaps between refills exceeds a defined permissible time.
- Currently, medication persistence analysis for estimating the effects of factors on persistence is **limited to traditional survival methods**, such as the Kaplan-Meier (KM) method or Cox proportional hazards (PH) regression model.
- However, the traditional methods assume all subjects will experience the event of interest, meaning there are no 'cured' (non-susceptible) patients among the censored patients.
- In medication persistence analysis, this assumption might overestimate the cumulative incidence or effects of variables on risk of medication discontinuation if long-term persistency exits in the population.
- Ignoring the presence of long-term medication persistent users may lead to inaccurate conclusions on the effects of factors associated with medication persistence.

OBJECTIVE

To introduce mixture cure model in medication persistence analysis to describe the characteristics of long-term and short-term persistent patients and demonstrate its application using a real-world data analysis.

METHODS

Overview of Mixture Cure Model (Boag 1949): $S_{pop}\,(t|X,\,Z) = \pi(Z)Su(t|X) + 1 - \pi(Z)$

- T denote time to discontinue medication. S_{pop} indicates survival related to the entire population.
- $1 - \pi(Z)$ is probability of being long-term persistence ('cured' or unsusceptible, depending on sets of covariates Z),
- $Su(t|X)$ denotes drug survival probability among those short-term persistent patients (known as 'uncured' or susceptible patients, depending on sets of covariates X). X and Z might be identical or partially or completely different.

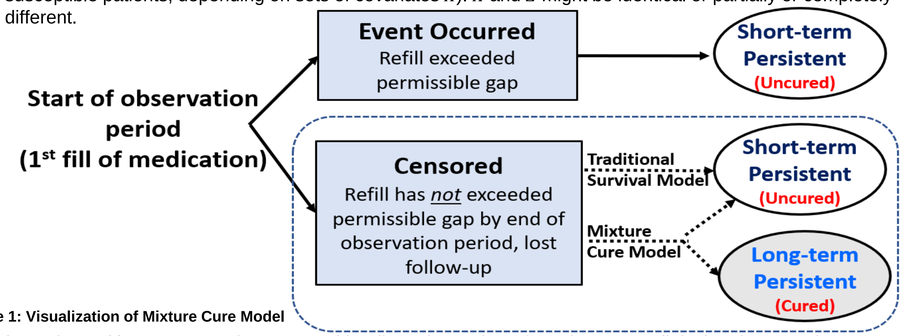


Figure 1: Visualization of Mixture Cure Model

- The estimated long-term persistent rate with adjusted covariates is an important clinical and economic measure in the medication utilization management and can be modeled via *a logistic regression* model.
- The effects of covariates on the risk of medication discontinuation among those short-term persistent patients can be modeled by regular survival models such as a *Cox PH model*

Table 1: Three possible states of individual's persistency and two subpopulations under cure model framework

Censored	Persistency	Possible state of individual's persistency
No	Short-term	Individual has stopped medication. Persistent time is non-censored.
Yes	Short-term	Persistent time is censored. Individual eventually stop medication.
Yes	Long-term	Persistent time is censored. Individual never stop medication.

RESULTS

- The study used new users of statins identified using longitudinal South Carolina State Health Plan (private insurance) and Medicaid Databases to demonstrate the application. The cohort was defined from 01/01/2008-12/31/2010. The index date was the first initiation of a statin. The patients' prescription claims data were followed until 12/31/2019.
- Through '**smcure**' R package, odds ratios (ORs) along with 95% confidence intervals (CIs) for variables associated with the likelihood of being long-term persistent were estimated using the logistic regression; hazard ratios (HRs) along with 95% CIs for variables associated with time to discontinue medication among the short-term persistent (susceptible/"uncured") patients were also estimated.

Table 2: Results of standard Cox PH and mixture cure model analyses

		COX PH Model		Mixture Cure Model			
		HR	95% CI	OR	95% CI	HR	95% CI
Univariate	Age [45,55)	Refence					
	< 45	1.48*	(1.42, 1.54)	1.83*	(1.58, 2.11)	1.37*	(1.31, 1.44)
180 days	55+	1.54*	(1.48, 1.61)	4.32*	(3.36, 5.55)	1.25*	(1.18, 1.32)
Permissible	Female	1.17*	(1.13, 1.21)	1.65*	(1.42, 1.92)	1.06*	(1.01, 1.11)
Gap	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)
Multivariate	Age [45,55)	Refence					
	< 45	1.30*	(1.25, 1.35)	1.31*	(1.11, 1.55)	1.29*	(1.09, 1.52)
180 days	55+	1.46*	(1.40, 1.53)	2.48*	(2.01, 3.05)	1.30*	(1.24, 1.37)
Permissible	Female	1.06*	(1.03, 1.10)	1.27*	(1.11, 1.44)	1.02	(0.98, 1.06)
Gap	Comorbidity	1.01	(0.97, 1.04)	1.02	(0.86, 1.21)	1.00	(0.96, 1.05)
	Private insurance	0.46*	(0.44, 0.48)	0.07*	(0.05, 0.09)	0.71*	(0.68, 0.75)
Multivariate	Age < 45	1.28*	(1.22, 1.33)	1.37*	(1.14, 1.64)	1.25*	(1.18, 1.31)
	55+	1.43*	(1.37, 1.49)	2.30*	(1.82, 2.92)	1.31*	(1.25, 1.38)
120 days	Female	1.07*	(1.03, 1.11)	1.24*	(1.07, 1.44)	1.04	(0.99, 1.09)
Permissible	Comorbidity	1.00	(0.96, 1.04)	1.02	(0.87, 1.19)	0.99	(0.95, 1.03)
Gap	Private insurance	0.48*	(0.46, 0.50)	0.04*	(0.03, 0.06)	0.72*	(0.68, 0.75)
Multivariate	Age < 45	1.25*	(1.20, 1.30)	1.28*	(1.02, 1.60)	1.23*	(1.17, 1.30)
	55+	1.41*	(1.35, 1.48)	2.73*	(1.95, 3.82)	1.32*	(1.25, 1.39)
90 days	Female	1.06*	(1.02, 1.10)	1.19	(0.94, 1.51)	1.04	(0.84, 1.30)
Permissible	Comorbidity	1.00	(0.96, 1.04)	1.01	(0.81, 1.27)	1.00	(0.95, 1.04)
Gap	Private insurance	0.48*	(0.46, 0.50)	0.02*	(0.01, 0.04)	0.72*	(0.68, 0.76)

Table 3: Estimated long-term persistent (cure) fractions using a mixture cure model

Model	Variable	Estimated long-term fraction
Univariate Mixture Cure Model	Age < 45	10%
	Age [45, 55)	17%
180 days	Age 55+	4%
Permissible Gap	Male	15%
	Female	9%
	Private insurance	26%

RESULTS (Cont'd)

Figure 2: Fitted Persistence Curves with Different Survival Models

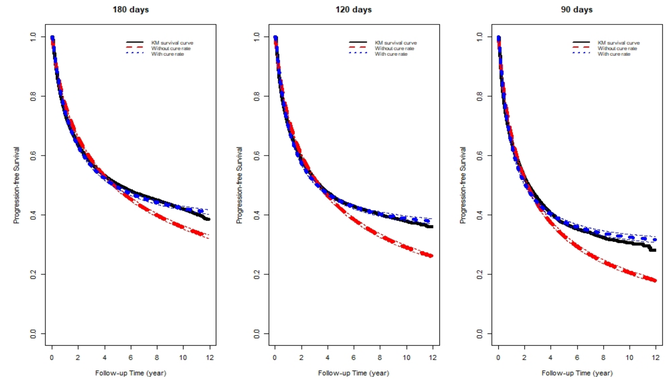
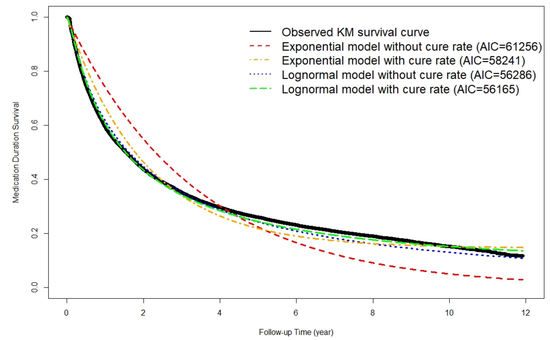


Figure 3: Fitted Persistence Curves with Different Survival Models (Permissible Gap = 180 days)



CONCLUSIONS

- 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.
- In addition to estimating risk of medication discontinuation, the mixture cure model can identify the long-term persistent fraction, which is a useful clinical and economic measure.
- Mixture cure model provides a more comprehensive picture of medication persistence by including long-term persistent patients.

REFERENCES

Cai C*, Love BL, Yunusa I, Reeder CE. Applying mixture cure survival modeling to medication persistence analysis. Pharmacoepidemiology Drug Safety. 2022;31(7):788-795. doi:10.1002/pds.5441

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