A Survival Analysis Study of

Methadone Treatment Clinics for Heroin Addicts

Abstract

Methadone is a kind of opioids and is widely used in the treatment of heroin addicts. In a 1991 Australian study by Caplehorn et al, two methadone treatment clinics for heroin addicts (238 participants) were completed to assess patient time remaining under methadone treatment. Using Cox proportional hazards model and discrete-time model, we find that hazard of dropping out of methadone treatment for clinic 2 participants is 63.6% lower that clinic 1 participants ($p<.001$). For every 1mg/day increase in maximum methadone dose, the hazard of dropping out of methadone treatment decreases by 3.5% ($p<.001$). Thus, we should be aware of the type and dose of methadone treatment for heroin addicts.

Background

Opioids are a class of drugs that chemically related and interact with opioid receptors to produce morphine-like effects, including opiate, morphine, heroin, etc. (National Institute on Drug Abuse, 2017). Opioids are powerful pain relievers and widely used medically for treating severe pain, suppression of diarrhea, depression disorder, etc. (National Institute on Drug Abuse, 2017) However, use of opioids can generate dependence and misuse can lead to overdose incidents and deaths. Opioid abuse and addiction is a serious public health problem worldwide. Centers for Disease Control and Prevention data shows that in United States, rates of opioid overdose deaths jumped from 7.9 per 100,000 in 2013 to 9.0 per 100,000 in 2014, which is a significantly increase. (Centers for Disease Control and Prevention, 2016) In 2017, President Donald Trump also declared that the opioid crisis is a public health emergency in the United States. (Merica, D, 2017)

Methadone is a kind of opioids and is widely used in relieving pain and opioid addict treatment.

Retention of patients in methadone treatment (Methadone Hydrochloride, 2017). And previous study implied that dosage and type of methadone treatment are significant factors that influence the time of retention of treatment. In a 1998 Italy study, researchers find that patients taking ≥60 mg/day of methadone were 70% more likely to remain in treatment than those receiving a <30 mg daily dose (D' Ippoliti et al, 1998).

In this study, by using survival analysis, we hypothesis that there is correlation between maximum dose of methadone (mg/day) and time of dropping out of methadone treatment. The study also investigates other factors that may have an influence on time of dropping out of methadone treatment, such as if have prison record, the type of methadone treatment clinic.

Method Description

There were 238 heroin addicts entered maintenance program between February 1986 and August 1987 in a 1991 Australian study by Caplehorn et al. All subjects then had been assessed at a centralized unit and referred to one of two other units for maintenance. (Caplehorn, J et al, 1991)

Two methadone treatment clinics for heroin addicts were completed to assess patient time remaining under methadone treatment. A patient's survival time was determined as the time (in days) until the person dropped out of the clinic or was censored. The two clinics differed according to its live-in policies for patients.

The dependent variable of this study is time of dropping out of methadone treatment. The independent variable of this study is maximum dose of methadone (mg/day), if have prison record, the type of methadone treatment clinic.

The Cox proportional hazards model is suitable for this study because the dependent variable is a binary variable (dropping out of treatment or not dropping out of treatment). Also, the survival time and censoring data is available. The study window is defined as the largest days of retention of the treatment, which is 1076 days. Censoring is defined as loss of connection or retention in treatment at end of the study window. The Cox proportional hazards model has no requirement for the assumption about the underlying distribution of survival times and the hazard for any individual is a fixed proportion of the hazard for any other individual. Efron method consider all possible underlying orderings that might exist, but use a numeric approximation to simplify the computations. We also tested if there is interaction effect of the Cox proportional hazards model. Model-predicted survivor curves is also generated to give a more direct way to observe the influence of independent variables.

Kaplan-Meier survival curves and lifetable was generated to give a description of the survival analysis. Binary logistic regression is used to generate the discrete-time model. p-value is two-tailed and the significance level is 0.05.

The analysis was conducted using Stata 14.0.

Results

Descriptive statistics

There are 238 participants involved in this study.

163(68.5%) of participants attended methadone treatment clinic 1, and 75(31.5%) of participants attended methadone treatment clinic 2. 127(53.36%) of participants had a prison record, and 111(46.64) of participants don't have a prison record.

The mean maximum dose of methadone (mg/day) of all participants is 60.40±14.45 mg/day (range: 20-110 mg/day). For participants entered methadone treatment clinic 1, the mean maximum dose of methadone is 58.96±12.40 mg/day (range: 20-80 mg/day). For participants entered methadone treatment clinic 2, the mean maximum dose of methadone is 60.40±14.45 mg/day (range: 40-110 mg/day).

Kaplan-Meier survivor curves

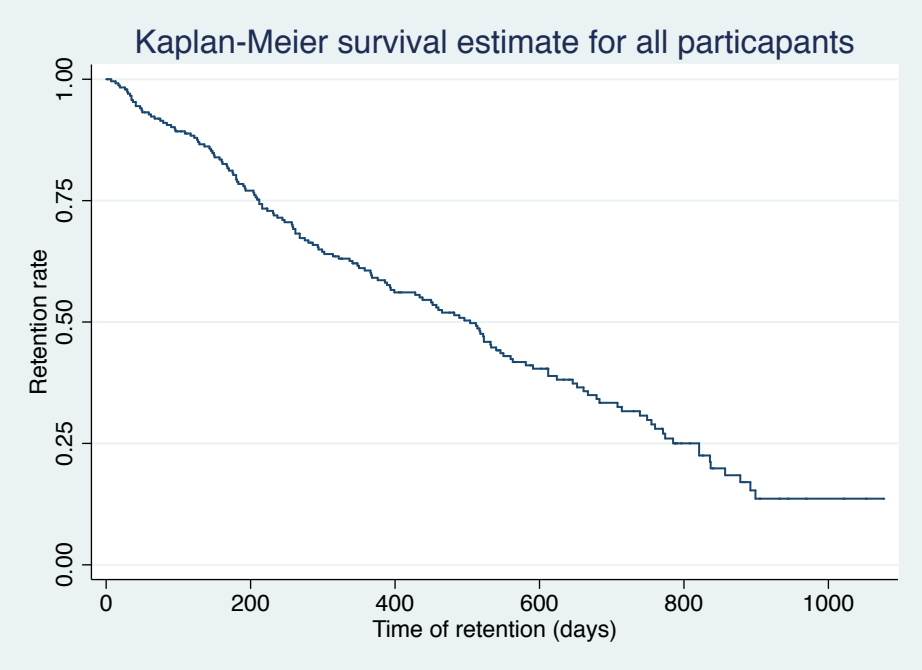

Figure 1. Kaplan-Meier survival curve for all participants

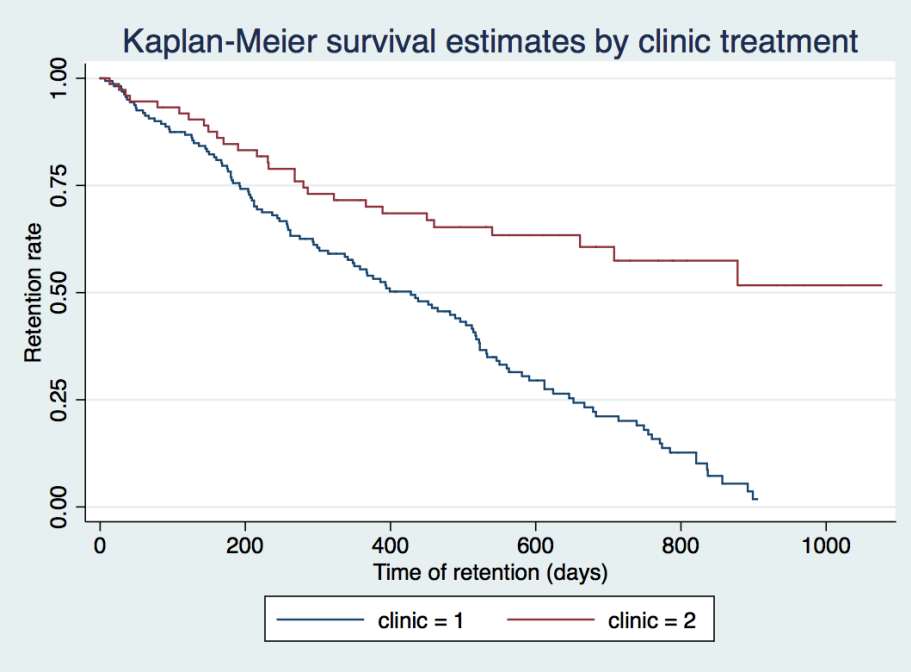

Figure 2. Kaplan-Meier survival curves by clinic treatment

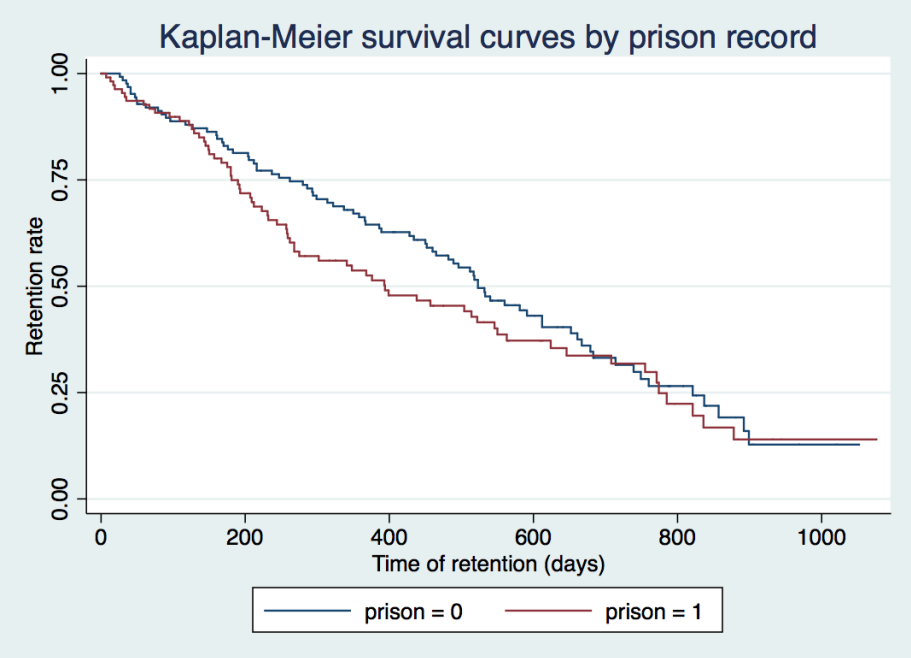

Figure 3. Kaplan-Meier survival curves by prison record

For all participants, the mean time of retention is 402.57 days, the median time of retention is 367.50 days, the time range of retention is 2- 1076 days. The cumulative retention rate dropped to 0.75 at around 210 days, 0.50 (median of survivor functions) at around 500 days, 0.25 at around 800 days.

From Figure 2. Kaplan-Meier survival curves, we can see that during time period 0-50 days clinic 2 participants have a similar cumulative retention rate with clinic 1 participants. During time period 50-1076 days, clinic 2 participants have a higher cumulative retention rate than clinic 1 participants.

From Figure 3. Kaplan-Meier survival curves, we can see that during time period 1-120 days and 700-1076 days, participants with prison record and participants without prison record have similar cumulative retention rate. During time period 120-700 days, participants with prison record have a lower cumulative retention rate that participants without prison record.

Test of group differences in survival times

From Log-rank test of group differences in survival times, we find there is significant difference between treatment clinic 1 and treatment clinic 2 in survival times, (chi-square(1)=27.98, $p<.001$).The difference between participants with prison record and participants without prison record is insignificant, (chi-square(1)=1.26, $p>.05$).

Cox proportional hazards model

The Cox proportional hazards model (Table 1.) is significant in predicting dropping out of methadone treatment (chi-square(3)=64.56, $p<.0001$). Clinic treatment type (1 or 2) and maximum methadone dose (mg/day) are significant predictors in predicting dropping out of methadone treatment ($p<.001$), while if have prison record is insignificant in predicting dropping out of methadone treatment ($p>.05$).

For Cox proportional hazards model, holding other variables constant, the hazard of dropping out of methadone treatment for clinic 2 participants is 63.6% lower that clinic 1 participants (p<.001), Holding other variables constant, for every 1mg/day increase in maximum methadone dose, the hazard of dropping out of methadone treatment decreases by 3.5% (p<.001).

Comparison between Cox proportional hazards model and discrete-time model

Model	**Discrete-time model**	**Cox model**
Variable	**Odds ratio**	**Hazard ratio**
Type of clinic treatment (1)		
2	0.339***	0.364***
History of prison record (no)		
Yes	1.367	1.386
Maximum methadone dose (mg/day)	0.963***	0.965***
Quarter(3-month) indicator		
_d1	0.095***	
_d2	0.132**	
_d3	0.176**	
_d4	0.118**	
_d5	0.151**	
_d6	0.270*	
_d7	0.170**	
_d8	0.280	
_d9	0.543	
Constant	-30.85***	
Model Chi-Square (df)	77.91 (12)***	64.56 (3)***
Number of study subjects	238	238
Number of subject 3-months	1161	
*: p<0.05		
**: p<0.01		
***: p<0.001		

Table 1. Comparison between Cox proportional hazards model and discrete-time model

Both Cox proportional hazards model and discrete-time model are significant at predicting dropping out of methadone treatment (p<.0001). And in these two models, clinic treatment type (1 or 2) and maximum methadone dose (mg/day) are both significant predictors in predicting dropping out of methadone treatment (p<.001). If have prison record is insignificant in predicting

dropping out of methadone treatment (p>.05) in both models. For discrete-time model, quarter indicator _d1, _d2, _d3, _d4, _d5, _d6, _d7 are significant at predicting dropping out of methadone treatment (p<.05). For type of clinic treatment (1), History of prison record (no), maximum methadone dose (mg/day) variables, their odds ratios in discrete-time model is slightly smaller than their hazard ratios in Cox regression model, but they hold the same significance level.

Test interaction effects in Cox regression

Variable	Hazard ratio
Type of clinic treatment (1)	
2	0.519*
History of prison record (no)	
Yes	3.203*
Maximum methadone dose (mg/day)	0.963***
clinic*prison	0.497

Variable	Hazard ratio
Type of clinic treatment (1)	
2	0.723
History of prison record (no)	
Yes	1.365
Maximum methadone dose (mg/day)	0.980
clinic*dose	0.988

Variable	Hazard ratio
Type of clinic treatment (1)	
2	0.369***
History of prison record (no)	
Yes	0.813
Maximum methadone dose (mg/day)	0.961***
prison*dose	1.009

*: p<0.05 **: p<0.01 ***: p<0.001

Table 2. Test interaction effects in Cox regression

Interaction terms are created (clinic*prison, clinic*dose, prison*dose) to test interaction effects in Cox regression. And it aims to test whether the effect of one variable depend on another variable. Then three interaction terms were each put in original Cox regression model (Table 1.). The results show that all three interaction terms are insignificant (p>.05). So the interaction effect is insignificant in the original Cox regression model (Table 1.).

Model-predicted survivor curves

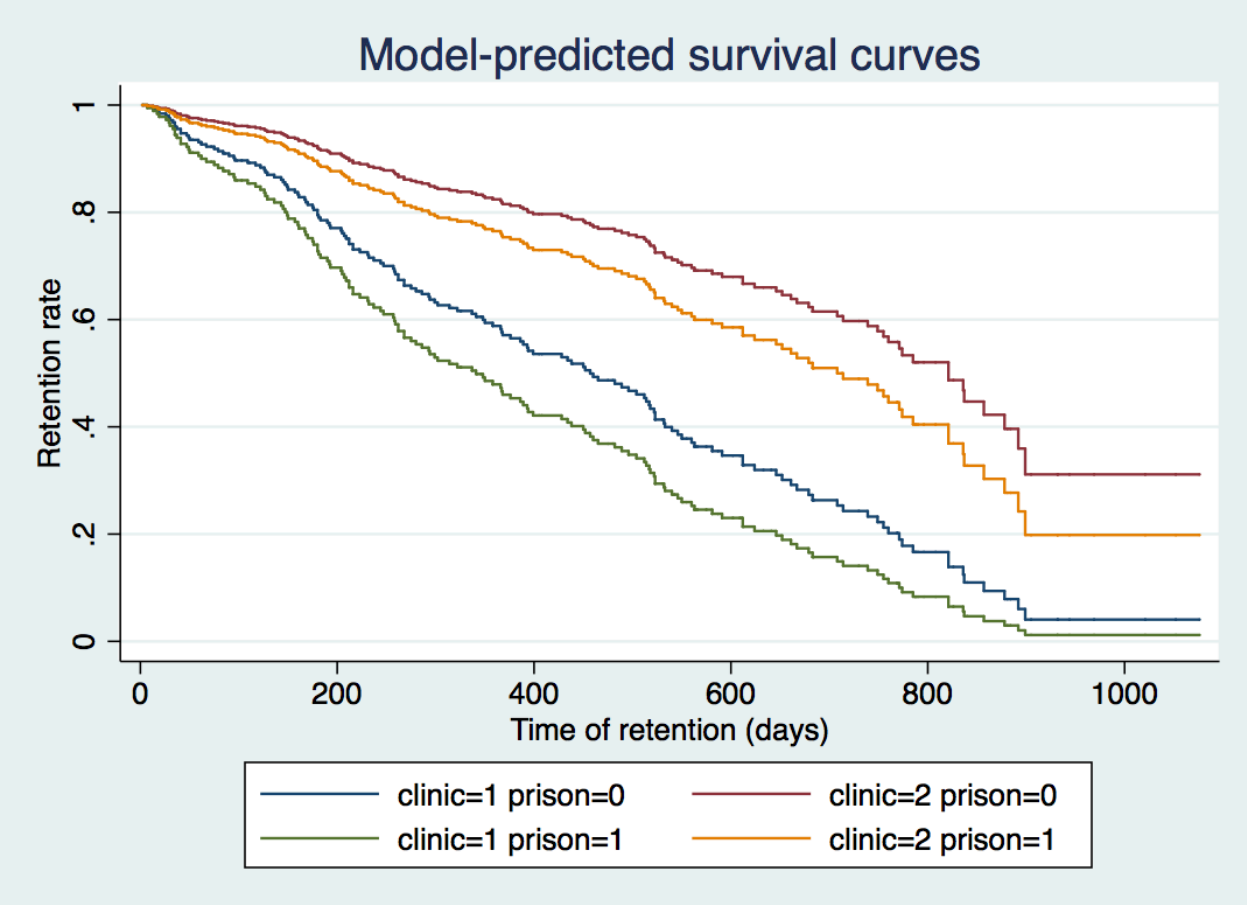

Figure 4. Model-predicted survivor curves

Those participants with clinic 2 treatment and without prison record have the lowest dropping speed, while participants with clinic 1 treatment and with prison record have the highest dropping speed. The predicted model also shows that participants in clinic 2 treatment have higher dropping

speed than participants clinic 1 treatment, participants with prison record have higher dropping speed than participants without prison record. All 4 curves have no significant intersect indicates that there is no interaction effect between prison record and type of clinic treatment.

Summary

Overall by using Cox proportional hazards model, we find that holding other variables constant, the hazard of dropping out of methadone treatment for clinic 2 participants is 63.6% lower that clinic 1 participants ($p<.001$), for every 1mg/day increase in maximum methadone dose, the hazard of dropping out of methadone treatment decreases by 3.5% ($p<.001$). If has prison record is insignificant in predicting dropping out of methadone treatment ($p>.05$). The interaction effect is insignificant so the model is reliable. However, after adding clinic*prison interaction term into the Cox model, the if has prison record variable, which is insignificant in original Cox model (Table 1.), become a significant predictor in the new model ($p<.05$). So we further study the effect of if has prison record variable.

The strength of this study is using Cox proportional hazards model and a competing discrete-time model. Both of model are good fit to the original data ($p<.0001$). The result of discrete-time model is similar to Cox proportional hazards model, which check the robust of Cox proportional hazards model.

The limitation of this study is only 238 participants involved in this study, which is a relatively small sample. And all participants are from an Australian study, which is also region limited and may not be generalizable.

Overall, this study implies that dosage and type of methadone treatment have impacts on the retention time of treatment. Thus, we should be aware of these two factors in future methadone treatment.

Reference

Caplehorn, J. R., & Bell, J. (1991). Methadone dosage and retention of patients in maintenance treatment. The Medical Journal of Australia, 154(3), 195-199.

Opioids. (n.d.). National Institute on Drug Abuse (NIDA). Retrieved November 27, 2017, from https://www.drugabuse.gov/drugs-abuse/opioids

Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. (2016, January 01). Centers for Disease Control and Prevention. Retrieved November 27, 2017, from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm?s_cid=mm6450a3_w

Merica, D. (2017, October 26). Trump declares opioid epidemic a public health emergency. Retrieved November 27, 2017, from http://www.cnn.com/2017/10/26/politics/donald-trump-opioid-epidemic/index.html

Methadone Hydrochloride Monograph for Professionals. (n.d.). Retrieved December 14, 2017, from https://www.drugs.com/monograph/methadone-hydrochloride.html

D'Ippoliti, D., Davoli, M., Perucci, C. A., Pasqualini, F., & Bargagli, A. M. (1998). Retention in treatment of heroin users in Italy: the role of treatment type and of methadone maintenance dosage. Drug and alcohol Dependence, 52(2), 167-171.

. **ta clinic**

Coded 1 or 2	Freq.	Percent	Cum.
1	**163**	**68.49**	**68.49**
2	**75**	**31.51**	**100.00**
Total	**238**	**100.00**	

. **ta prison**

0=none, 1=prison record	Freq.	Percent	Cum.
0	**127**	**53.36**	**53.36**
1	**111**	**46.64**	**100.00**
Total	**238**	**100.00**	

. **sum dose**

Variable	Obs	Mean	Std. Dev.	Min	Max
dose	**238**	**60.39916**	**14.45013**	**20**	**110**

. **sum dose if clinic==1**

Variable	Obs	Mean	Std. Dev.	Min	Max
dose	**163**	**58.95706**	**12.40338**	**20**	**80**

. **sum dose if clinic==2**

Variable	Obs	Mean	Std. Dev.	Min	Max
dose	**75**	**63.53333**	**17.81613**	**40**	**110**

```
. stset survt, failure(status==1)

     failure event:  status == 1
obs. time interval:  (0, survt]
 exit on or before:  failure

--------------------------------------------------------------------------
        238  total observations
          0  exclusions
--------------------------------------------------------------------------
        238  observations remaining, representing
        150  failures in single-record/single-failure data
      95812  total analysis time at risk and under observation
                                                at risk from t =         0
                                     earliest observed entry t =         0
                                          last observed exit t =      1076

. stdescribe

         failure _d:  status == 1
   analysis time _t:  survt
```

		per subject			
Category	total	mean	min	median	max
no. of subjects	238				
no. of records	238	1	1	1	1
(first) entry time		0	0	0	0
(final) exit time		402.5714	2	367.5	1076
subjects with gap	0				
time on gap if gap	0				
time at risk	95812	402.5714	2	367.5	1076
failures	150	.6302521	0	1	1

```
. sts list

        failure _d:  status == 1
  analysis time _t:  survt
```

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
2	238	0	2	1.0000	.	.	.
7	236	1	0	0.9958	0.0042	0.9703	0.9994
13	235	1	0	0.9915	0.0060	0.9665	0.9979
17	234	1	0	0.9873	0.0073	0.9611	0.9959
19	233	1	0	0.9831	0.0084	0.9555	0.9936
26	232	1	0	0.9788	0.0094	0.9499	0.9911
28	231	0	2	0.9788	0.0094	0.9499	0.9911
29	229	1	0	0.9745	0.0103	0.9442	0.9885
30	228	1	0	0.9703	0.0111	0.9386	0.9857
33	227	1	0	0.9660	0.0118	0.9331	0.9828
35	226	2	0	0.9574	0.0132	0.9223	0.9769
37	224	1	0	0.9532	0.0138	0.9170	0.9738
41	223	2	0	0.9446	0.0149	0.9065	0.9675
47	221	1	0	0.9403	0.0155	0.9013	0.9642
49	220	1	0	0.9361	0.0160	0.8962	0.9610
50	219	1	0	0.9318	0.0165	0.8911	0.9577
53	218	0	2	0.9318	0.0165	0.8911	0.9577
59	216	1	0	0.9275	0.0169	0.8859	0.9543
62	215	1	1	0.9232	0.0174	0.8808	0.9509

Log-rank test for equality of survivor functions

clinic	Events observed	Events expected
1	**122**	**90.91**
2	**28**	**59.09**
Total	**150**	**150.00**

chi2(1) = **27.89**
Pr>chi2 = **0.0000**

```
. sts test prison

         failure _d:  status == 1
   analysis time _t:  survt
```

Log-rank test for equality of survivor functions

prison	Events observed	Events expected
0	**81**	**87.75**
1	**69**	**62.25**
Total	**150**	**150.00**

chi2(1) = **1.26**
Pr>chi2 = **0.2617**

```
. stcox clinic prison dose, efron

        failure _d:  status == 1
  analysis time _t:  survt

Iteration 0:   log likelihood = -705.53931
Iteration 1:   log likelihood = -674.40512
Iteration 2:   log likelihood = -673.26371
Iteration 3:   log likelihood = -673.25914
Iteration 4:   log likelihood = -673.25914
Refining estimates:
Iteration 0:   log likelihood = -673.25914

Cox regression -- Efron method for ties

No. of subjects =          238                 Number of obs    =         238
No. of failures =          150
Time at risk    =        95812
                                               LR chi2(3)       =       64.56
Log likelihood  =   -673.25914                 Prob > chi2      =      0.0000
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
clinic	.3642569	.0782749	-4.70	0.000	.2390527	.555037
prison	1.386184	.2318044	1.95	0.051	.9988011	1.923814
dose	.9652489	.0061573	-5.54	0.000	.9532561	.9773927

```
. logistic _Y clinic prison dose _d1-_d12
note: _d11 != 0 predicts failure perfectly
      _d11 dropped and 7 obs not used

note: _d12 != 0 predicts failure perfectly
      _d12 dropped and 3 obs not used

note: _d10 omitted because of collinearity

Logistic regression                             Number of obs     =      1,159
                                                LR chi2(12)       =      77.91
                                                Prob > chi2       =     0.0000
Log likelihood = -407.59253                     Pseudo R2         =     0.0872
```

_Y	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
clinic	.3392712	.0780125	-4.70	0.000	.2161825	.5324434
prison	1.367087	.2523629	1.69	0.090	.9520622	1.963031
dose	.9633387	.0068119	-5.28	0.000	.9500798	.9767826
_d1	.0951631	.0563665	-3.97	0.000	.029805	.3038421
_d2	.1320178	.0776662	-3.44	0.001	.0416744	.4182107
_d3	.1755626	.1031561	-2.96	0.003	.0554993	.5553624
_d4	.1181005	.072492	-3.48	0.001	.0354626	.3933083
_d5	.151227	.0929251	-3.07	0.002	.0453511	.5042792
_d6	.2697055	.1625372	-2.17	0.030	.0827781	.8787473
_d7	.1695038	.1120819	-2.68	0.007	.0463805	.6194755
_d8	.2795829	.1872447	-1.90	0.057	.0752379	1.038926
_d9	.5436526	.3643305	-0.91	0.363	.1461793	2.021887
_d10	1	(omitted)				
_d11	1	(omitted)				
_d12	1	(omitted)				
_cons	30.85191	24.55793	4.31	0.000	6.482328	146.8362

```
. stcox clinic prison dose clinicprison, efron

        failure _d:  status == 1
  analysis time _t:  survt

Iteration 0:   log likelihood = -705.53931
Iteration 1:   log likelihood = -672.92177
Iteration 2:   log likelihood = -671.93354
Iteration 3:   log likelihood = -671.93136
Refining estimates:
Iteration 0:   log likelihood = -671.93136

Cox regression -- Efron method for ties

No. of subjects =          238                 Number of obs    =         238
No. of failures =          150
Time at risk    =        95812
                                               LR chi2(4)       =       67.22
Log likelihood  =   -671.93136                 Prob > chi2      =      0.0000
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
clinic	.5193427	.1501064	-2.27	0.023	.2947338	.9151201
prison	3.202806	1.730686	2.15	0.031	1.110633	9.236142
dose	.9636986	.0062758	-5.68	0.000	.9514764	.9760779
clinicprison	.4969269	.213344	-1.63	0.103	.2142145	1.152752

```
. stcox clinic prison dose clinicdose, efron

        failure _d:  status == 1
  analysis time _t:  survt

Iteration 0:   log likelihood = -705.53931
Iteration 1:   log likelihood = -676.02458
Iteration 2:   log likelihood = -672.97355
Iteration 3:   log likelihood =   -672.915
Iteration 4:   log likelihood = -672.91491
Refining estimates:
Iteration 0:   log likelihood = -672.91491

Cox regression -- Efron method for ties

No. of subjects =          238                 Number of obs    =         238
No. of failures =          150
Time at risk    =        95812
                                               LR chi2(4)       =       65.25
Log likelihood  =   -672.91491                 Prob > chi2      =      0.0000
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
clinic	.7230558	.6140756	-0.38	0.703	.1368563	3.820136
prison	1.365285	.2297157	1.85	0.064	.9817584	1.898637
dose	.979819	.0188156	-1.06	0.288	.9436265	1.0174
clinicdose	.9883799	.0140075	-0.82	0.410	.9613035	1.016219

```
. stcox clinic prison dose prisondose, efron

        failure _d:  status == 1
  analysis time _t:  survt

Iteration 0:   log likelihood = -705.53931
Iteration 1:   log likelihood = -674.27365
Iteration 2:   log likelihood = -673.01038
Iteration 3:   log likelihood = -673.00507
Iteration 4:   log likelihood = -673.00507
Refining estimates:
Iteration 0:   log likelihood = -673.00507

Cox regression -- Efron method for ties

No. of subjects =          238                 Number of obs    =         238
No. of failures =          150
Time at risk    =        95812
                                               LR chi2(4)       =       65.07
Log likelihood  =   -673.00507                 Prob > chi2      =      0.0000
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
clinic	.3694133	.0797134	-4.61	0.000	.2420121	.5638817
prison	.8132888	.6236874	-0.27	0.788	.1809186	3.656001
dose	.9618425	.0077777	-4.81	0.000	.9467187	.9772078
prisondose	1.009126	.0128434	0.71	0.475	.9842645	1.034615