

Multistate Survival Modelling of Cardiovascular Admission and Mortality in a Heart Failure Cohort in Singapore

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Introduction

- Heart failure (HF) patients often experience complex clinical trajectories involving hospitalisation and death.
- Conventional survival models that focus on a single endpoint may fail to capture these sequential outcomes adequately.
- This study applies a multistate survival framework to characterise transitions to cardiovascular (CV) admission and death in a hospital-based cohort.

Cardiovascular Disease & Heart Failure

- Cardiovascular disease (CVD) encompasses disorders of the heart and blood vessels, including coronary artery disease, heart failure, stroke, and related conditions, that contribute substantially to morbidity and mortality
- Heart failure (HF) is a syndrome caused by structural or functional cardiac abnormalities that result in impaired ventricular filling or ejection, leading to symptoms, signs, hospitalization, and increased mortality.
- HF is a major subtype of CVD.

Multi-State Model

- Multistate models generalize survival analysis by allowing individuals to move through multiple discrete states over time, rather than a single transition (alive → dead).
- Typical examples:
 - Healthy → Disease → Death*
 - Acute myocardial infarction → Heart Failure → Death*
 - Hospitalized → Discharged → Readmitted → Death*
- Each transition can have its own hazard and its own covariates.

Stata Command: msset

msset declares the multi-state structure of data.

It is conceptually similar to stset, but designed for multiple transitions.

Core role of msset:

- Defines states
- Defines allowed **transitions**
- Defines time variables
- Prepares data for estimation commands such as stcox, streg, etc., by transition

Data

- The HF subjects were recruited by the National University Hospital of Singapore (NUH) from 2011 to 2018.
- Time-to-event data were structured using a multistate setup, and transition-specific parametric survival models were estimated using lognormal distribution.
- The absorbing outcomes were CV admission and all-cause death within two years.
- Baseline covariates included sex, ethnicity, New York Heart Association (NYHA) class, reduced left ventricular ejection fraction (LVEF <40%), age ≥ 65 years, and resting heart rate ≥ 60 bpm.
- Analyzed with Stata MP v19, all statistical tests were conducted at 5% level of significance.

Descriptive Statistics

. tab HF

Heart Failure at Baseline	Freq.	Percent	Cum.
No	988	72.06	72.06
Yes	383	27.94	100.00
Total	1,371	100.00	

. tab NYHA HF

NYHA	Heart Failure at Baseline		Total
	No	Yes	
Class I/II	982	325	1,307
Class III/IV	0	58	58
Total	982	383	1,365

. tabstat Age, stats(median p25 p75 n)

Variable	p50	p25	p75	N
Age	59.05753	51.78082	65.12877	1371

NYHA stands for the New York Heart Association functional classification, a system used to grade the severity of heart failure:

- **Class I** – No limitation of physical activity
- **Class II** – Mild limitation; symptoms with ordinary activity
- **Class III** – Marked limitation; symptoms with less-than-ordinary activity
- **Class IV** – Symptoms at rest

. tab NYHA

NYHA	Freq.	Percent	Cum.
Class I/II	1,307	95.75	95.75
Class III/IV	58	4.25	100.00
Total	1,365	100.00	

Descriptive Statistics

```
. tabstat BMI, stats(median p25 p75 n)
```

Variable	p50	p25	p75	N
BMI	24.9976	22.31169	27.99899	1364

```
. tab Smoke
```

Smoke	Freq.	Percent	Cum.
No	992	72.36	72.36
Ex/Current	379	27.64	100.00
Total	1,371	100.00	

```
. tab Diabetes
```

Diabetes	Freq.	Percent	Cum.
No	1,048	76.44	76.44
Yes	323	23.56	100.00
Total	1,371	100.00	

0: Other, 1: Chinese, 2: Malay, 3: Indian

```
. tab Ethnicity
```

Ethnicity	Freq.	Percent	Cum.
0	7	0.51	0.51
1	895	65.28	65.79
2	333	24.29	90.08
3	136	9.92	100.00
Total	1,371	100.00	

```
. tab Hypertension
```

Hypertension	Freq.	Percent	Cum.
No	798	58.21	58.21
Yes	573	41.79	100.00
Total	1,371	100.00	

Descriptive Statistics

```
. tab3way HF CVAdmission2Year Death2Year
```

Table entries are cell frequencies
Missing categories ignored

Heart Failure at Baseline	Death2Year and CVAdmission2Year			
	0		1	
	No	Yes	No	Yes
No	971	9	8	
Yes	213	121	26	23

No heart failure at baseline

- No CV admission, no death: 971
- CV admission, no death: 9
- No CV admission, death: 8
- CV admission, death: 0

Interpretation

- CV admission is **very rare** in non-HF subjects
- Death is rare
- **No deaths occurred after CV admission**
- Non-HF subjects largely remain stable over 2 years

Heart failure at baseline

- No CV admission, no death: 213
- CV admission, no death: 121
- No CV admission, death: 26
- CV admission, death: 23

Interpretation

- CV admission is **common** among HF patients
- Death occurs **both with and without prior admission**
- A substantial number of deaths occur **after CV admission**

Exploratory Model with Cox Regression

```
. stcox Age i.Ethnicity Gender NYHA Diabetes Hypertension Smoke eGFR60 LVEF if Ethnicity!=0, nolog
```

```
Failure _d: CVAdmission2Year==1
Analysis time _t: Days_CVAdmission2Year
```

Cox regression with Breslow method for ties

```
No. of subjects = 1,307           Number of obs = 1,307
No. of failures = 145
Time at risk    = 773,175

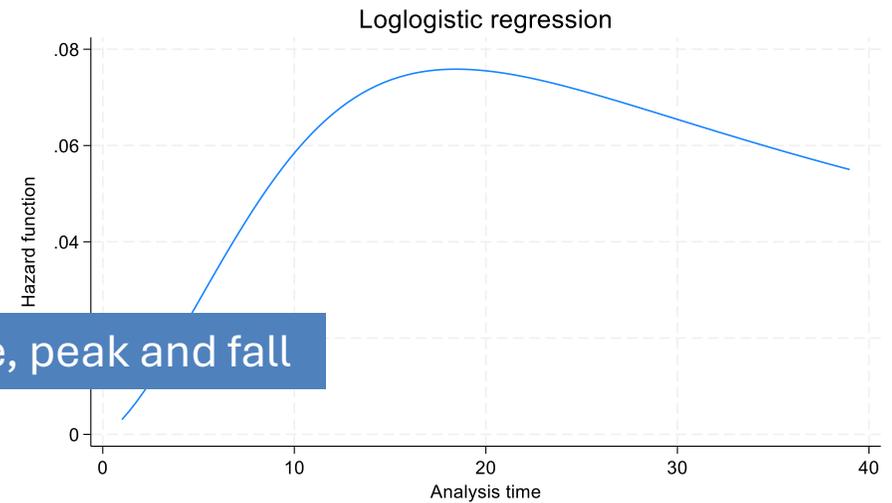
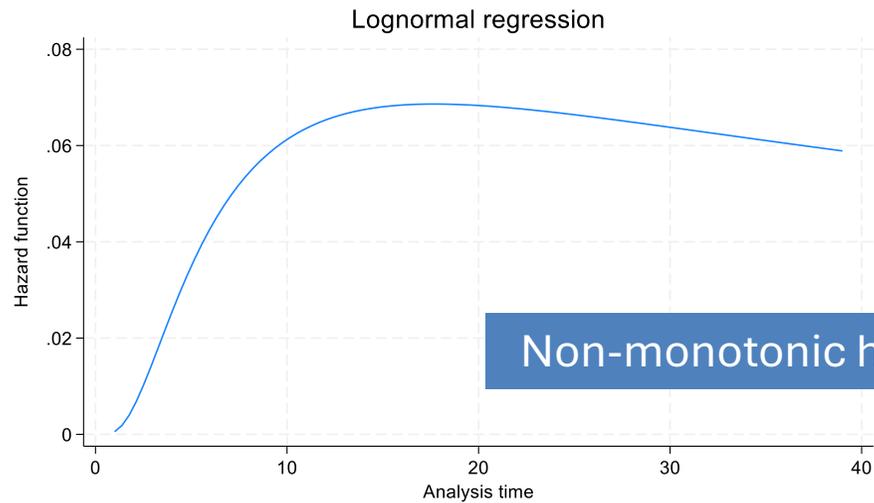
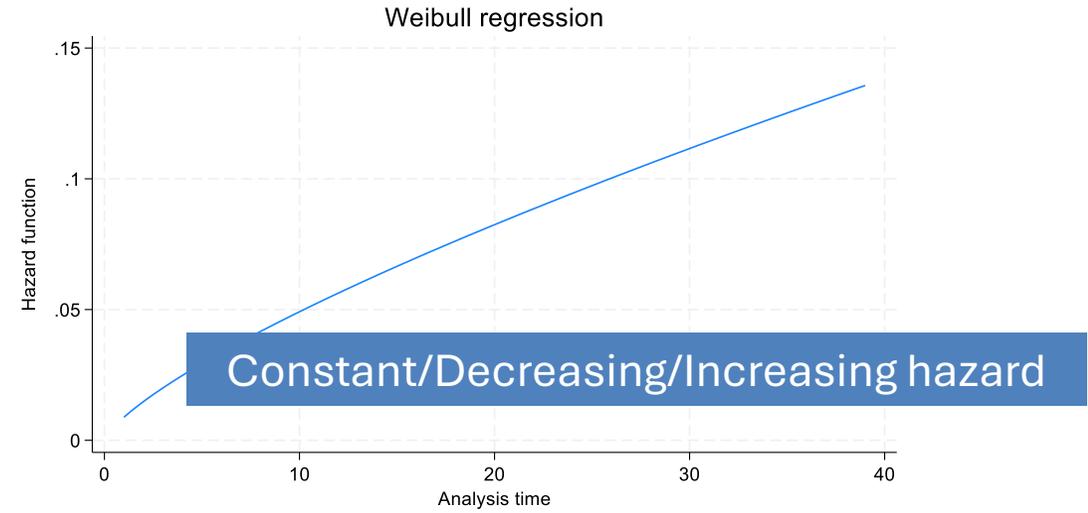
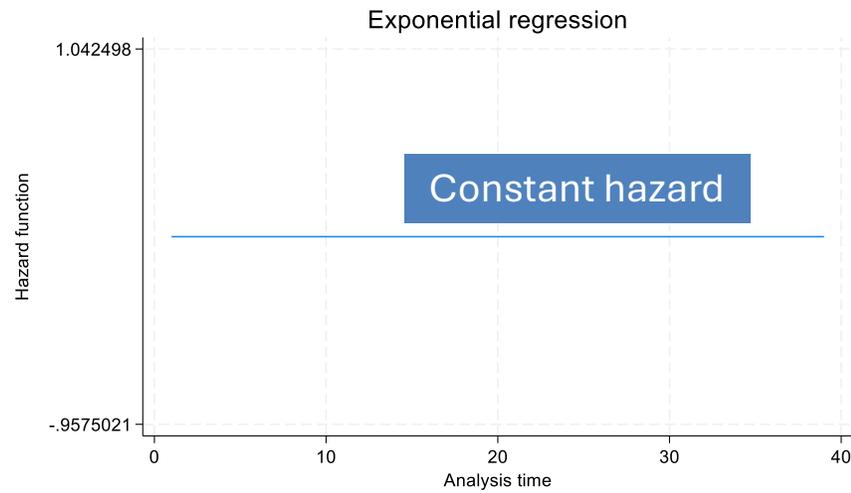
Log likelihood = -844.94778      LR chi2(10) = 342.25
                                Prob > chi2 = 0.0000
```

Omitted “Other” ethnic group

_t	Haz. ratio	Std. err.	z	P> z	[95% conf. interval]	
Age	1.020335	.0099482	2.06	0.039	1.001022	1.040021
Ethnicity						
2	1.437038	.2740591	1.90	0.057	.9888599	2.088343
3	1.15815	.310551	0.55	0.584	.684731	1.958887
Gender	.6155256	.1532111	-1.95	0.051	.3778964	1.002581
NYHA	1.678199	.3829878	2.27	0.023	1.072971	2.624818
Diabetes	2.21322	.4579518	3.84	0.000	1.475356	3.320108
Hypertension	2.107668	.4611189	3.41	0.001	1.372698	3.236155
Smoke	1.517306	.3201347	1.98	0.048	1.003411	2.29439
eGFR60	.4765184	.0873459	-4.04	0.000	.3327011	.6825039
LVEF	.9511497	.0060277	-7.90	0.000	.9394086	.9630376

Note:
Heart failure is captured in
LVEF and NYHA

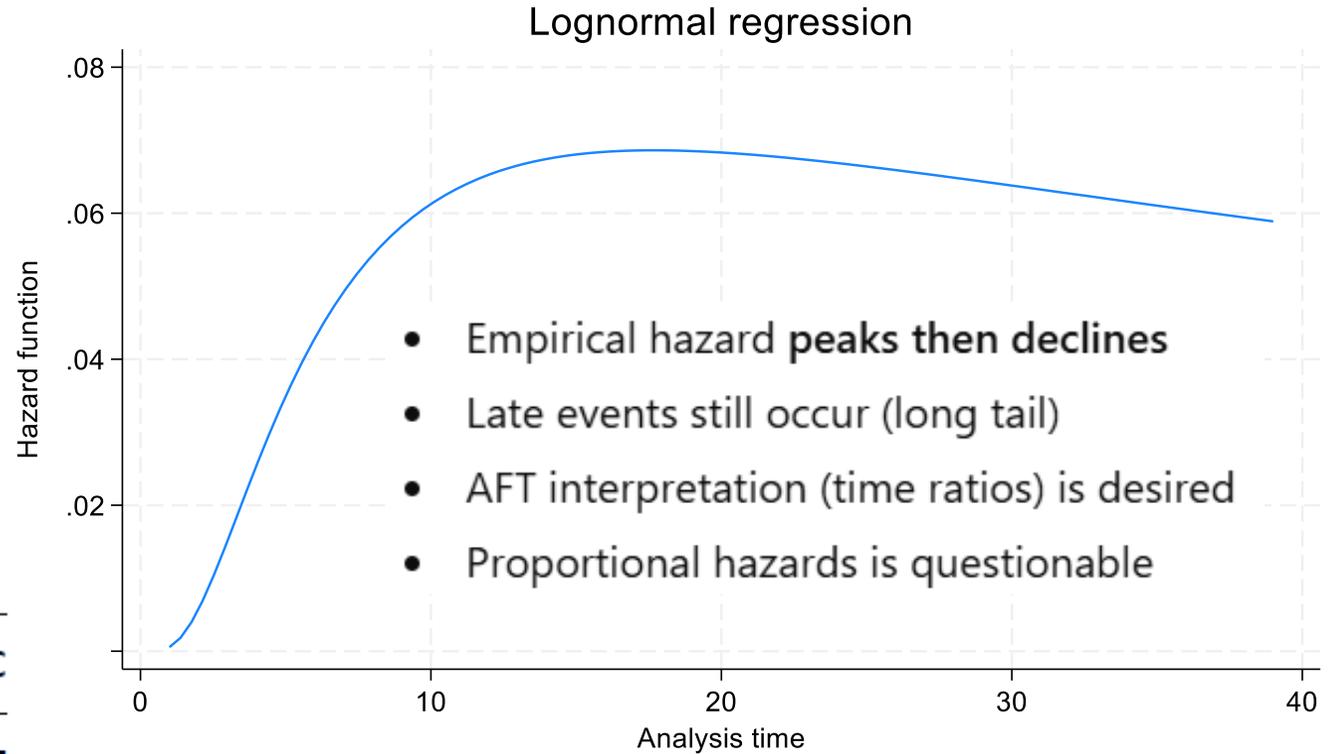
Potential Parametric Model for CV Admission in 2 Years



Results: Selection of Time to CV Admission in 2 Years

Parametric model selection with AIC and BIC

Model	N	df	AIC	BIC
exponential	1,364	1	1368.459	1373.677
gompertz	1,364	2	1353.909	1364.346
loglogistic	1,364	2	1351.78	1362.217
lognormal	1,364	2	1349.175	1359.612
weibull	1,364	2	1352.285	1362.721



Lognormal model is selected

Results: Time to CV Admission

```
. streg Age i.Ethnicity Gender NYHA Diabetes Hypertension Smoke eGFR60 LVEF if Ethnicity!=0, dist(lognormal) tr nolog
```

```
Failure _d: CVAdmission2Year==1
Analysis time _t: Days_CVAdmission2Year
```

Lognormal AFT regression

```
No. of subjects = 1,307           Number of obs = 1,307
No. of failures = 145
Time at risk    = 773,175

Log likelihood = -466.68479       LR chi2(10) = 345.94
                                   Prob > chi2 = 0.0000
```

Accelerated Failure Time (AFT) Model

_t	Time ratio	Std. err.	z	P> z	[95% conf. interval]	
Age	.9732331	.0116519	-2.27	0.023	.9506617	.9963404
Ethnicity						
2	.5627719	.1418171	-2.28	0.023	.3434249	.9222169
3	.7561687	.2770227	-0.76	0.446	.3687913	1.550446
Gender	1.151678	.3361463	0.48	0.629	.6499597	2.040684
NYHA	.3727984	.1295977	-2.84	0.005	.1886109	.7368539
Diabetes	.3662307	.0919133	-4.00	0.000	.223938	.5989377
Hypertension	.4643431	.1172689	-3.04	0.002	.2830543	.7617427
Smoke	.6576165	.175168	-1.57	0.116	.3901574	1.108423
eGFR60	2.136828	.5504071	2.95	0.003	1.289781	3.540163
LVEF	1.062661	.0087751	7.36	0.000	1.045601	1.08
_cons	7932.972	7911.558	9.00	0.000	1123.394	56019.57
/lnsigma	.6828832	.0655121	10.42	0.000	.5544818	.8112846
sigma	1.979577	.1296863			1.741038	2.250798

Cox Regression vs AFT

Covariate	Cox (HR)	AFT (TR)	Interpretation
Age	HR > 1	TR < 1	Older age → earlier CV admission
NYHA	HR > 1	TR < 1	Worse HF severity → faster admission
Diabetes	HR > 1	TR < 1	Diabetes accelerates admission
Hypertension	HR > 1	TR < 1	Hypertension accelerates admission
eGFR60	HR < 1	TR > 1	Reduced renal function → longer time to admission
LVEF	HR < 1	TR > 1	Better cardiac function → delayed admission

Multi-State Model Setup

```
. msset, id(ID) states(CVAdmission2Year Death2Year) times(Days_CVAdmission2Year Days_Death2Year)
```

Time scales

- `Days_CVAdmission2Year` → clock-forward time to CV admission
- `Days_Death2Year` → clock-forward time to death

Each subject contributes **one record per possible transition**, internally expanded by `msset`.

States

State	Meaning	<code>_trans</code>	Transition
State 0	Alive, no CV admission	1	Alive → CV admission
State 1	CV admission	2	Alive → Death
State 2	Death (absorbing)	3	CV admission → Death

Results: Multi-State Model of Death in 2 Years

```
. streg _trans2 _trans3 if Ethnicity!=0, dist(lognormal) tr nolog
```

```
Failure _d: CVAdmission2Year==1  
Analysis time _t: Days_CVAdmission2Year
```

`_trans2` = Alive → Death (without prior CV admission)

`_trans3` = CV admission → Death

Lognormal AFT regression

```
No. of subjects = 2,881  
No. of failures = 459  
Time at risk = 1,649,703
```

```
Number of obs = 2,881
```

```
Log likelihood = -1647.6546
```

```
LR chi2(2) = 396.80  
Prob > chi2 = 0.0000
```

<code>_t</code>	Time ratio	Std. err.	z	P> z	[95% conf. interval]	
<code>_trans2</code>	1	.1434543	-0.00	1.000	.7549035	1.324673
<code>_trans3</code>	.017316	.0042143	-16.67	0.000	.010747	.0279003
<code>_cons</code>	9484.078	1472.342	58.99	0.000	6996.029	12856.97
<code>/lnsigma</code>	.8408804	.0383365	21.93	0.000	.7657424	.9160185
<code>sigma</code>	2.318407	.0888795			2.15059	2.49932

Results: Multi-State Model of Death in 2 Years

```
. stcox _trans3 if Ethnicity!=0, nolog  
  
      Failure _d: CVAdmission2Year==1  
  Analysis time _t: Days_CVAdmission2Year
```

Cox regression with Breslow method for ties

```
No. of subjects =      2,881                Number of obs =  2,881  
No. of failures =       459  
Time at risk    = 1,649,703  
  
Log likelihood = -3308.77                LR chi2(1)      = 515.79  
                                                Prob > chi2    = 0.0000
```

_t	Haz. ratio	Std. err.	z	P> z	[95% conf. interval]	
_trans3	17.56904	1.813833	27.76	0.000	14.35059	21.50931

Discussion & Conclusion

- Cardiovascular admission is associated with an exceptionally large increase in mortality risk, confirming it as a pivotal transition in the multistate progression of heart failure.
- Prevent cardiovascular admission.
- Pay attention to heart failure patients.

THANK YOU