

存活分析課程 (2) : 競爭風險



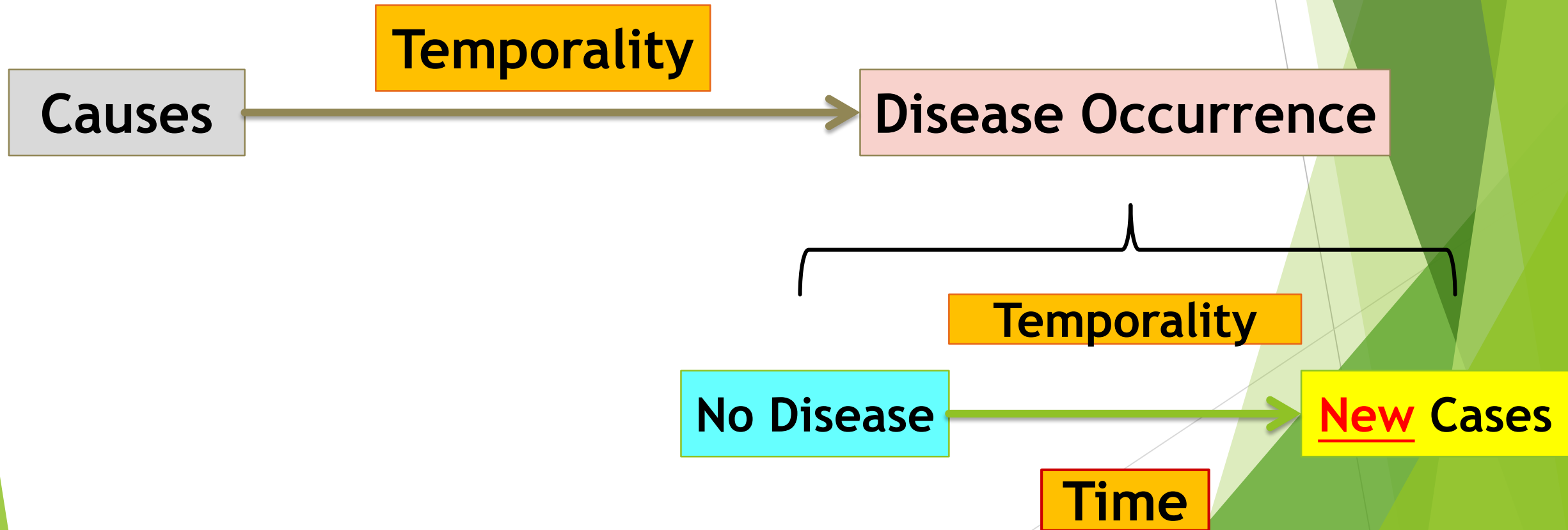
醫學研究部 生統小組 副研究員：陳韻仔 博士

授課日期：112年12月13日

世代研究：

探討疾病的發生率及風險

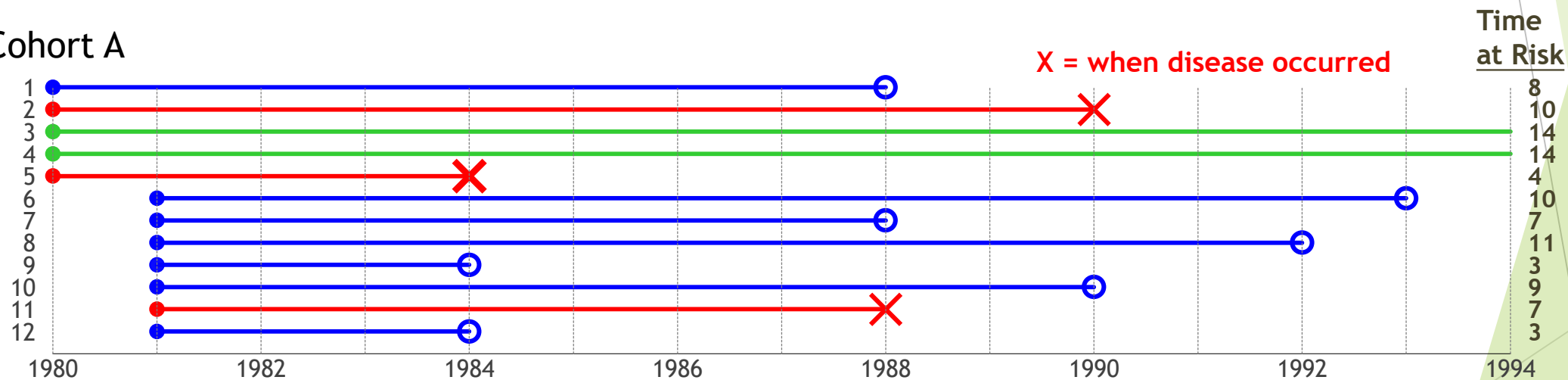
*判定因果關係的必要條件之一



存活分析

- ▶ Follow-up duration: Time at risk (e.g. years)
- ▶ 感興趣的事件 X = **when disease occurred**: Time to event
- ▶ 設限 Censored ○: Time to the end of follow-up / Loss of follow-up / Death

Cohort A



競爭風險 Competing Risk

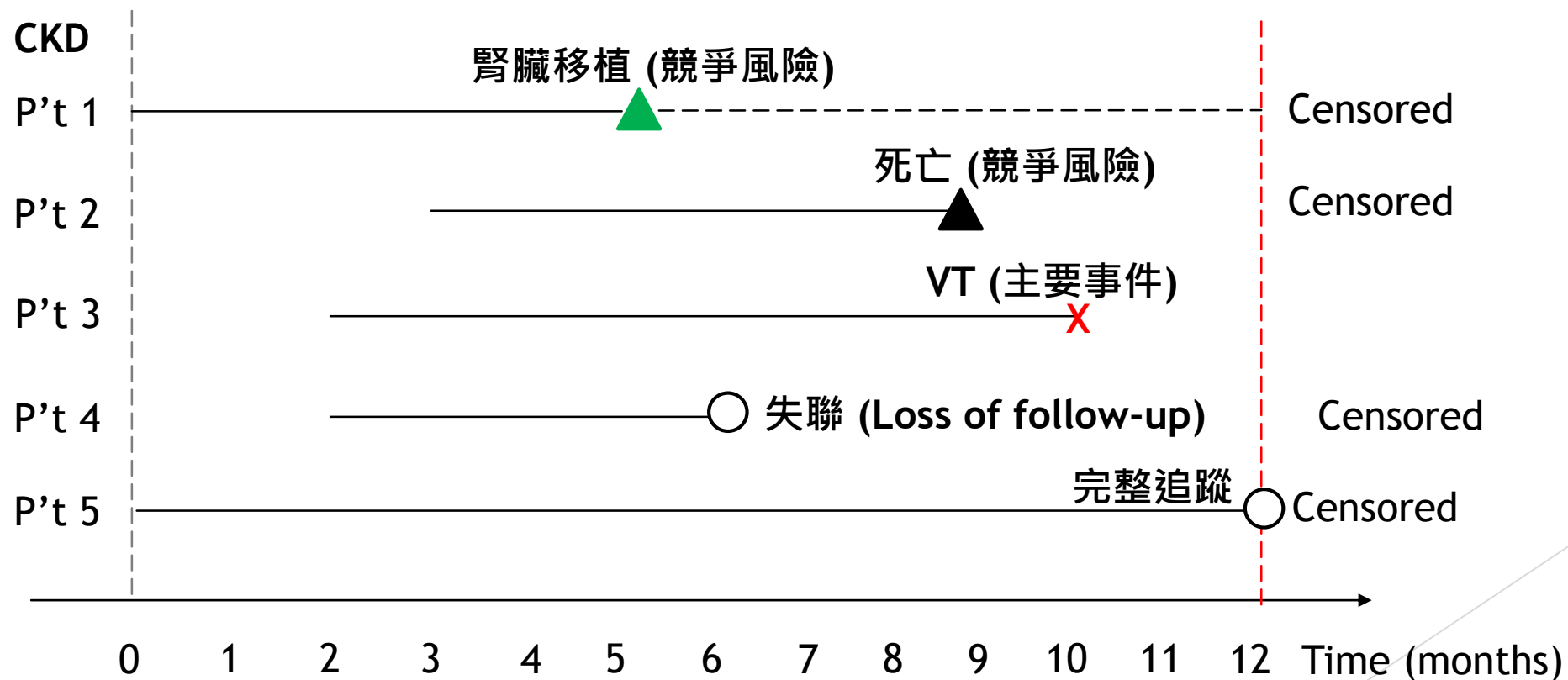
感興趣的主要事件 X : Ventricular tachycardia (VT)

競爭風險 (發生在主要事件之前，可能影響主要事件的發生) ▲: 腎臟移植、死亡

設限 Censored : 未發生主要事件就結束 → 追蹤到研究終止 (完整追蹤) / 失聯 / 死亡

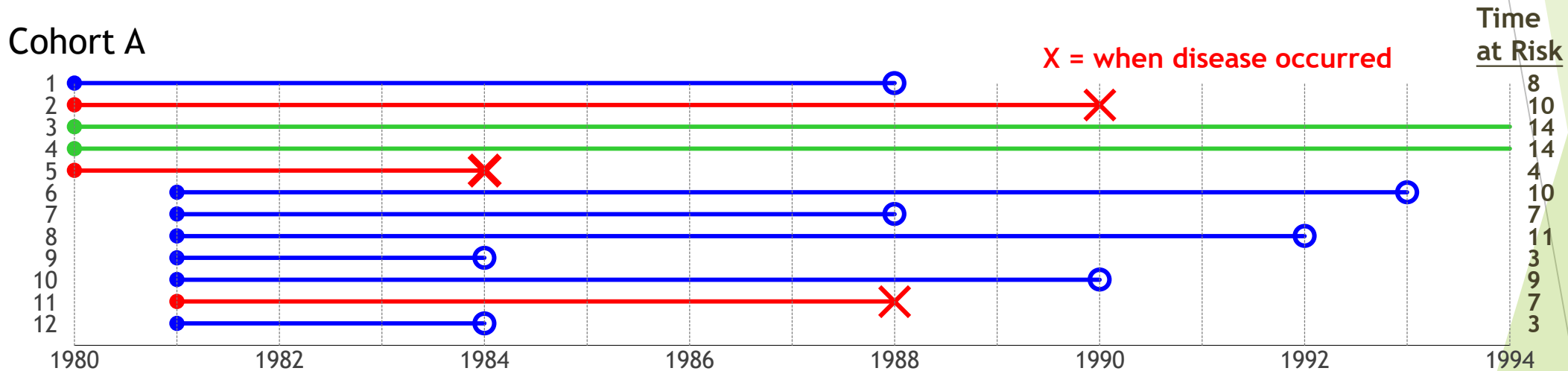
研究開始: 2021/1/1

研究終止: 2021/12/31



存活分析

- ▶ Follow-up duration: Time at risk (e.g. years)
- ▶ 感興趣的事件 X = when disease occurred: Time to event
- ▶ 設限 Censored ○: Time to the end of follow-up / Loss of follow-up / Death



存活分析方法：

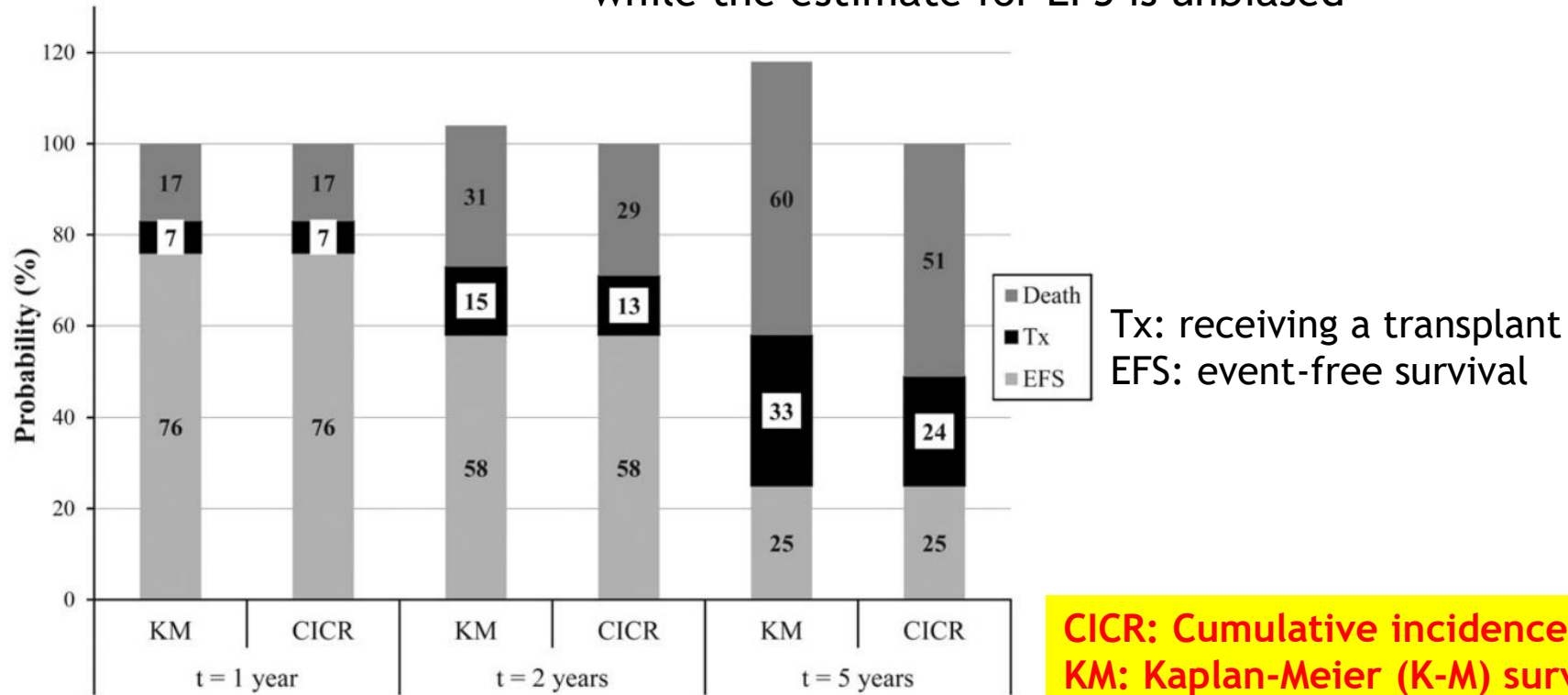
Kaplan-Meier (K-M) survival curve

Cox proportional hazard model

只允許單一事件的發生，所以無法處理競爭風險的問題

為何要處理競爭風險?

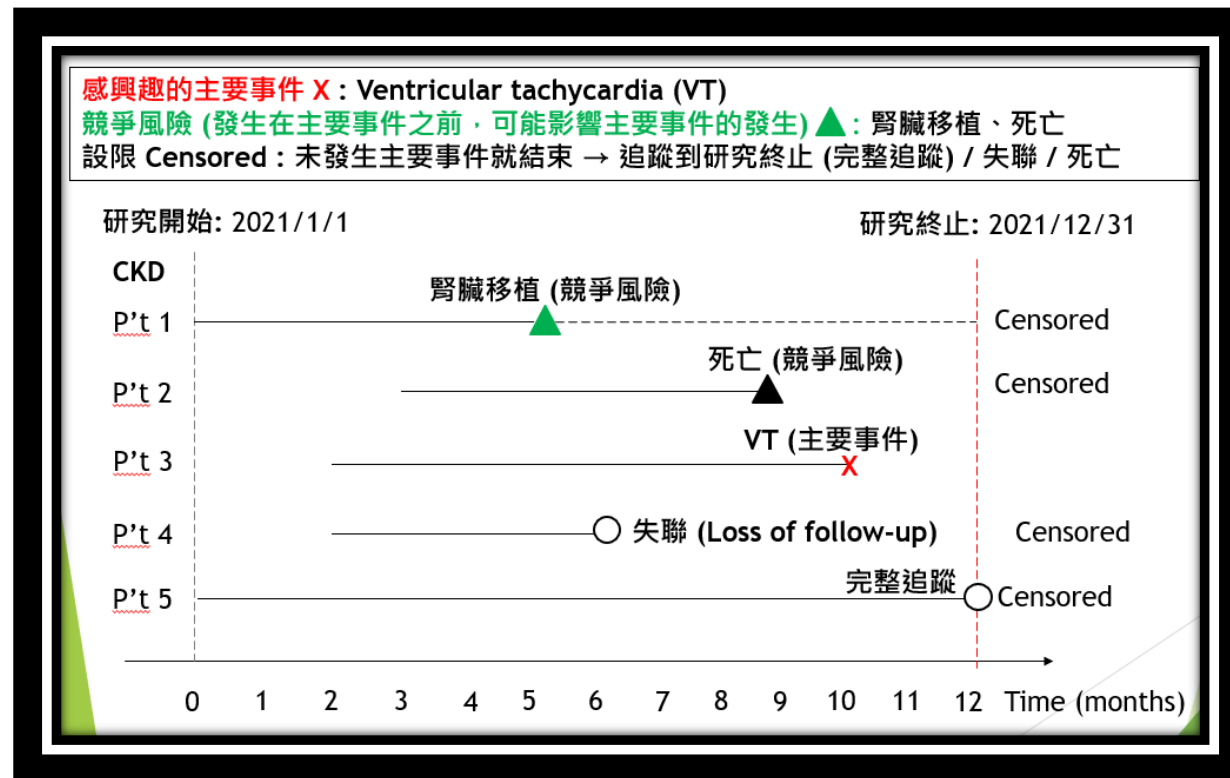
Kaplan-Meier method **overestimates the probabilities of both the event** of interest and the competing event(s), while the estimate for EFS is unbiased



CICR: Cumulative incidence competing risk
KM: Kaplan-Meier (K-M) survival curve

FIGURE 1: Probabilities (in %) of dying (before receiving a transplant) before time t , receiving a transplant (Tx) before time t and being alive and not having received a transplant until time t at $t = 1, 2$ and 5 years from Day 91 after the start of dialysis using the Kaplan–Meier (KM) and CICR method.

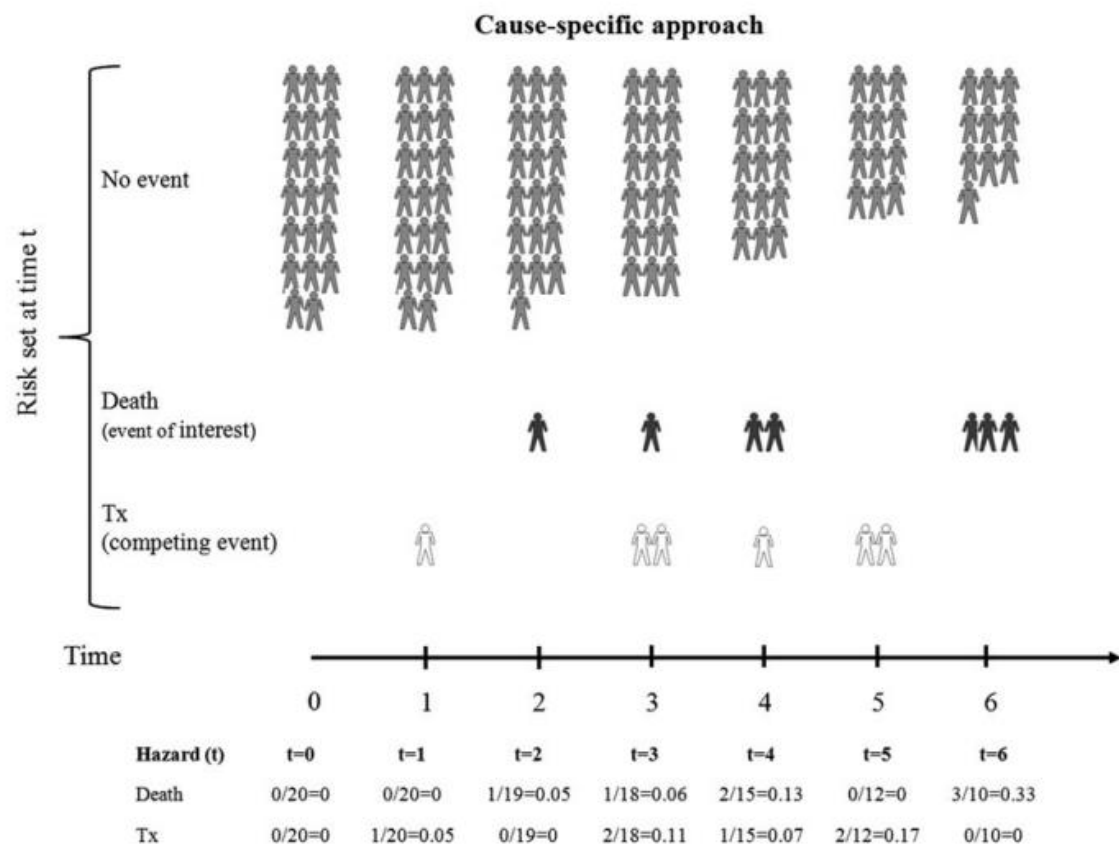
如何處理競爭風險



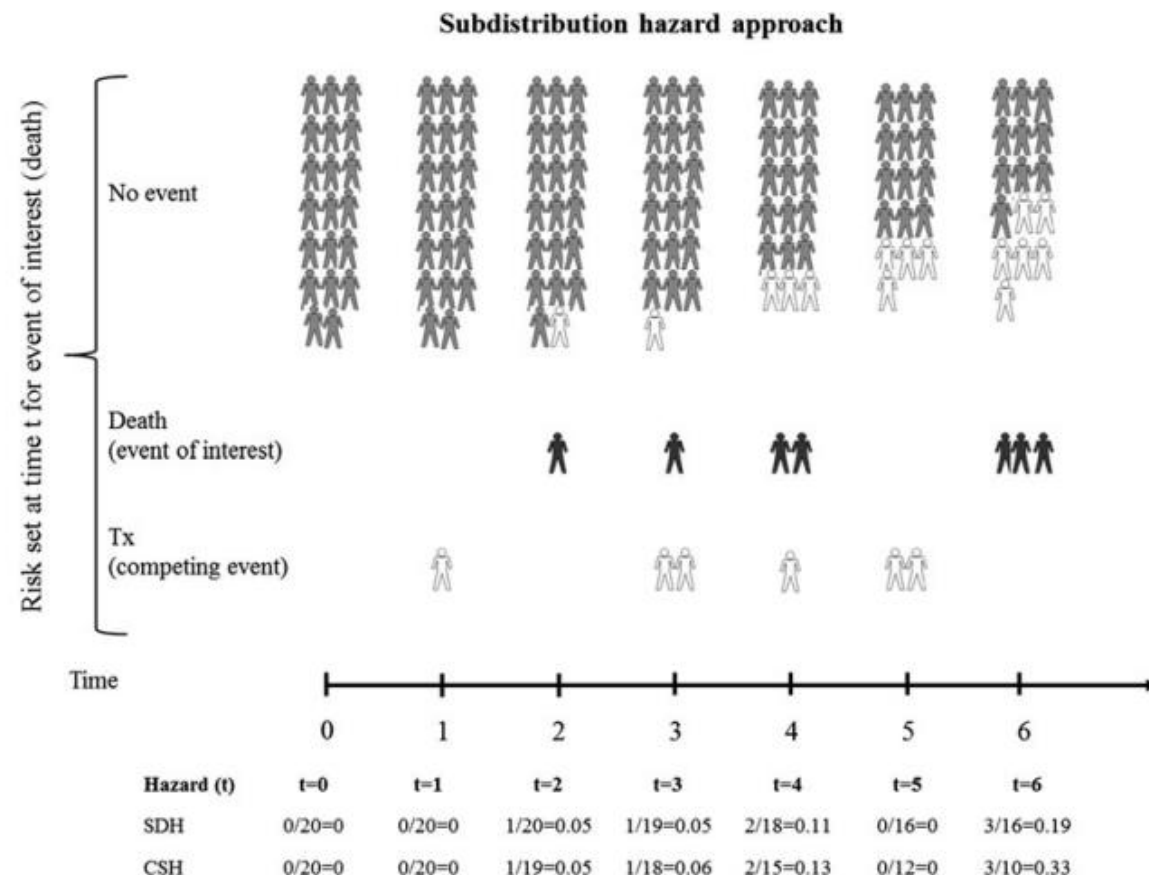
Competing Risk Analysis

- 1、特定因素危險函數
(Cause-Specific Hazard Function, CSH)
- 2、次分佈瞬間危險函數
(Sub-Distribution Hazard Function, SDH, Fine-Gray sub-distribution hazard)

Competing Risk Analysis

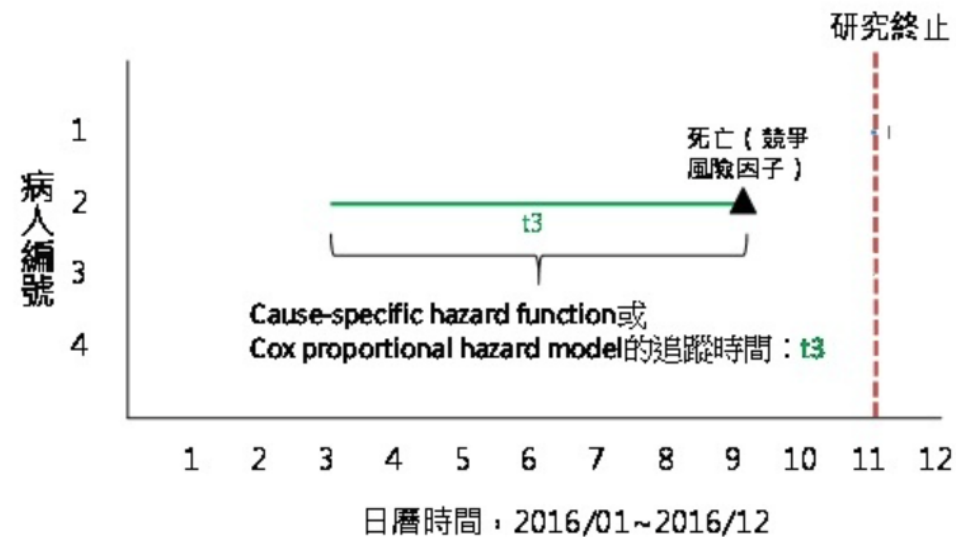
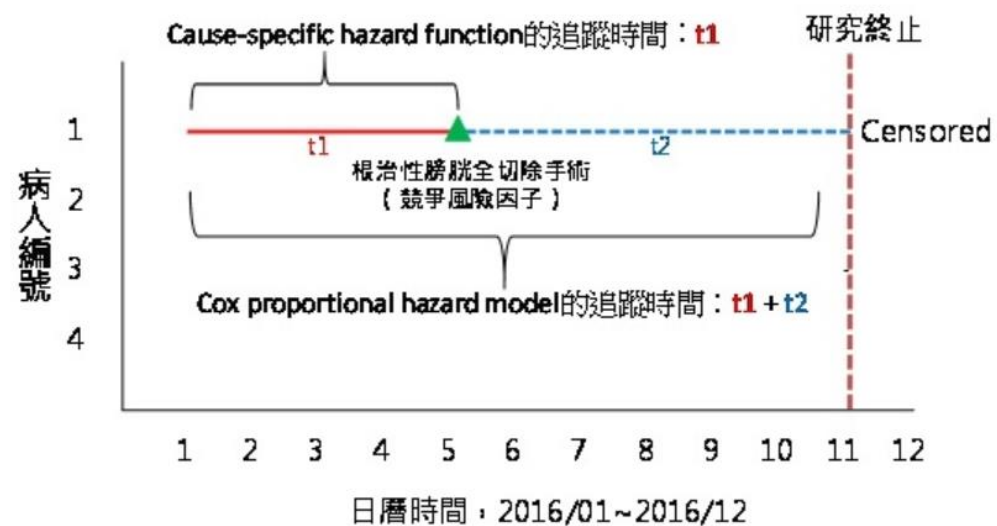


CSH是由Cox model所變化而成，風險集的設定也是採取Kaplan-Meier的估算方法：一旦發生研究興趣事件或是失去追蹤（設限，censor）的個案，在下一個觀察時間，皆從觀察名單中（Population at risk/ patient at risk）被排除。

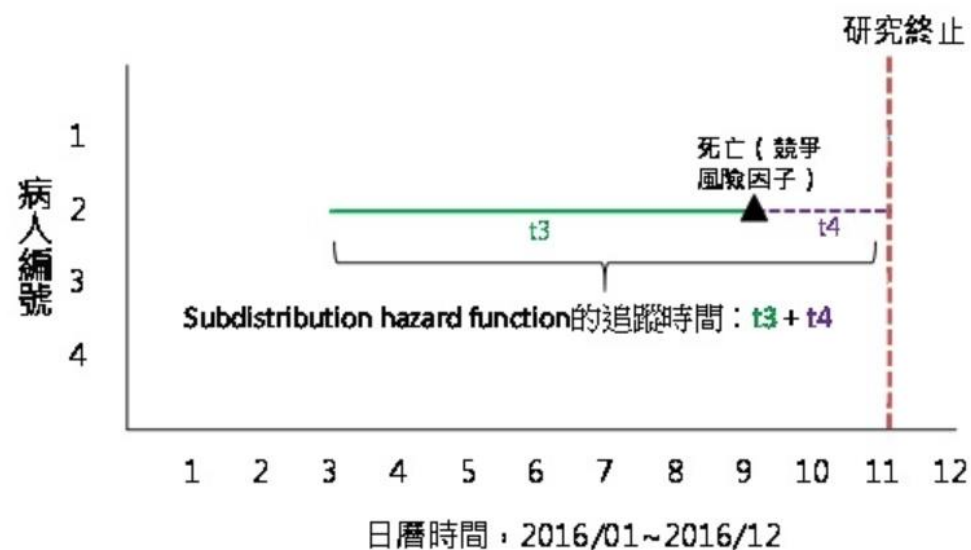
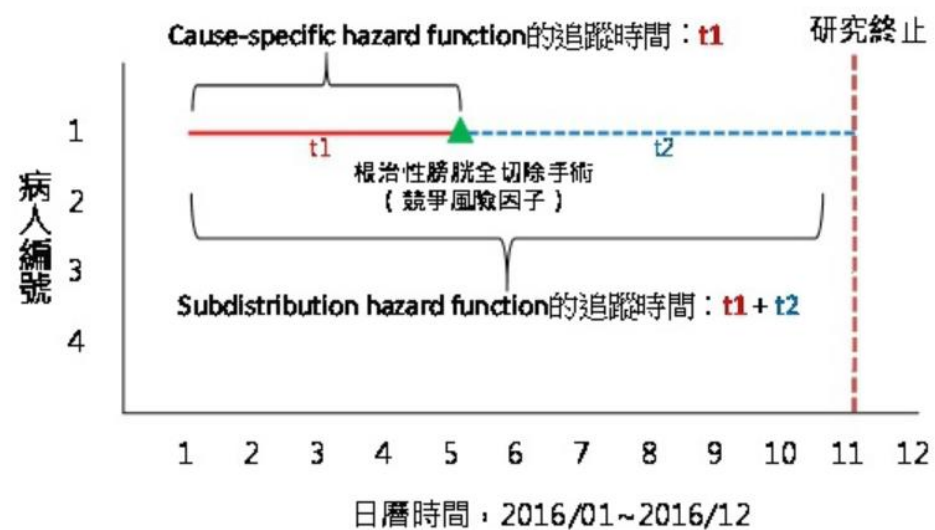


SDH在計算風險集時，並非採用傳統Kaplan-Meier的估算方法，而是採用累積發生函數（Cumulative incidence function, CIF），核心精神為：發生過競爭風險的人，在未來的觀察時間仍會保留在觀察名單（Population at risk）中。

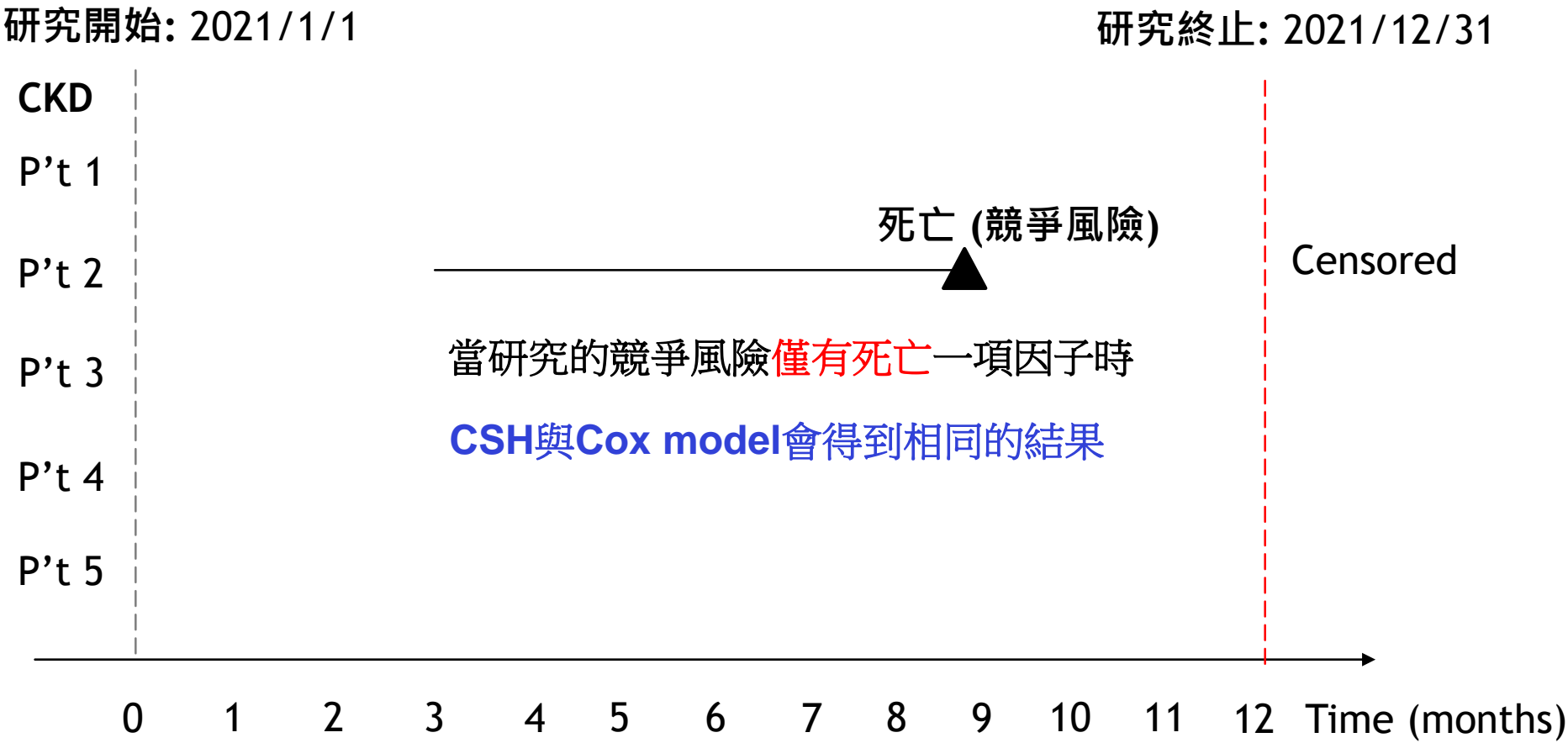
Cause-Specific Hazard Function (CSH)



Sub-Distribution Hazard Function (SDH、Fine-Gray)



Cause-Specific Hazard Function , CSH



發生的競爭風險因子為死亡事件，
無論是CSH發生競爭風險的當下便停止追蹤，
或是Cox model追蹤到研究終止或死亡時，
兩者的追蹤時間皆為死亡事件發生當下的時間

Practice

death	次數	百分比	累計 次數	累計 百分比
0	1620	81.00	1620	81.00
1	380	19.00	2000	100.00

Death:
0=alive
1=death

SCD	次數	百分比	累計 次數	累計 百分比
0	1987	99.35	1987	99.35
1	13	0.65	2000	100.00

SCD (sudden cardiac death):
0=alive or non-SCD
1=SCD

SCD_death	次數	百分比	累計 次數	累計 百分比
0	1620	81.00	1620	81.00
1	13	0.65	1633	81.65
2	367	18.35	2000	100.00

SCD_death:
Alive=0
SCD=1 (competing event of interest)
Non-SCD death=2

case	EF	EF40	death	SCD	SCD_death
68	0.6635329626	0	1	1	1
98	0.6369248479	0	1	1	1
1646	0.7004102791	0	1	1	1
1999	0.3732549467	1	1	1	1
2238	0.5710771554	0	1	1	1
2281	0.5398301887	0	1	1	1
4426	0.7312840892	0	1	1	1
5311	0.5956274173	0	1	1	1
6022	0.6515084689	0	1	1	1
6151	0.7720542773	0	1	1	1
6330	0.8687616577	0	1	1	1
6428	0.6976	0	1	1	1
6702	0.8335304691	0	1	1	1
2	0.6028167371	0	1	0	2
6	0.8957841361	0	1	0	2
19	0.7605274513	0	1	0	2
20	0.79190016	0	1	0	2
22	0.704	0	1	0	2
43	0.619047619	0	1	0	2
45	0.8592623985	0	1	0	2
53	0.6295861926	0	1	0	2
54	0.4967105263	0	1	0	2
60	0.6360154892	0	1	0	2
64	0.705243104	0	1	0	2
69	0.5230073906	0	1	0	2
72	0.7804971184	0	1	0	2
75	0.5626184575	0	1	0	2
90	0.6295861926	0	1	0	2

Traditional:
Cox proportional hazards model

PHREG 程序	
模型資訊	
資料集	DATA.DEMO
應變數	death_py
受限變數	SCD
受限值	0
繫結處理	BRESLOW
讀取的觀測值數目	
使用的觀測值數目	
2000	
2000	

事件數目和設限值的摘要			
總計	事件	設限	設限的百分比
2000	13	1987	99.35

Competing risk-1:
Cause specific hazard-CSH

PHREG 程序	
模型資訊	
資料集	DATA.DEMO
應變數	death_py
受限變數	SCD_death
受限值	0 2
繫結處理	BRESLOW
讀取的觀測值數目	
使用的觀測值數目	
2000	
2000	

事件數目和設限值的摘要			
總計	事件	設限	設限的百分比
2000	13	1987	99.35

競爭事件如果是死亡 (e.g. CVD / SCD) 的話，Cox regression和CSH的估計值會相同

最大概度估計值的分析									
參數		自由度	參數估計值	標準誤差	卡方	Pr > ChiSq	危險比	95% 危險比信賴界限	標籤
age		1	0.10316	0.02429	18.0304	<.0001	1.109	1.057 1.163	
SEX	2	1	-0.56128	0.60900	0.8494	0.3567	0.570	0.173 1.882	SEX 2
HTN	1	1	0.60842	0.64622	0.8864	0.3465	1.838	0.518 6.521	HTN 1
EF40	1	1	3.27205	1.09047	9.0036	0.0027	26.365	3.110 223.481	EF40 1
LVH	1	1	1.81113	0.66068	7.5148	0.0061	6.117	1.676 22.332	LVH 1
cva0	1	1	0.88586	1.07911	0.6739	0.4117	2.425	0.293 20.103	cva0 1

最大概度估計值的分析									
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Competing risk-1:
Cause specific hazard-CSH

PHREG 程序	
模型資訊	
資料集	DATA.DEMO
應變數	death_py
受限變數	SCD_death
受限值	0 2
繫結處理	BRESLOW
讀取的觀測值數目	2000
使用的觀測值數目	2000

事件數目和設限值的摘要			
總計	事件	設限	設限的百分比
2000	13	1987	99.35

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HTN	1	1	0.60842	0.64622	0.8864	0.3465	1.838	0.518	6.521	HTN 1
EF40	1	1	3.27205	1.09047	9.0036	0.0027	26.365	3.110	223.481	EF40 1
LVH	1	1	1.81113	0.66068	7.5148	0.0061	6.117	1.676	22.332	LVH 1
cva0	1	1	0.88586	1.07911	0.6739	0.4117	2.425	0.293	20.103	cva0 1

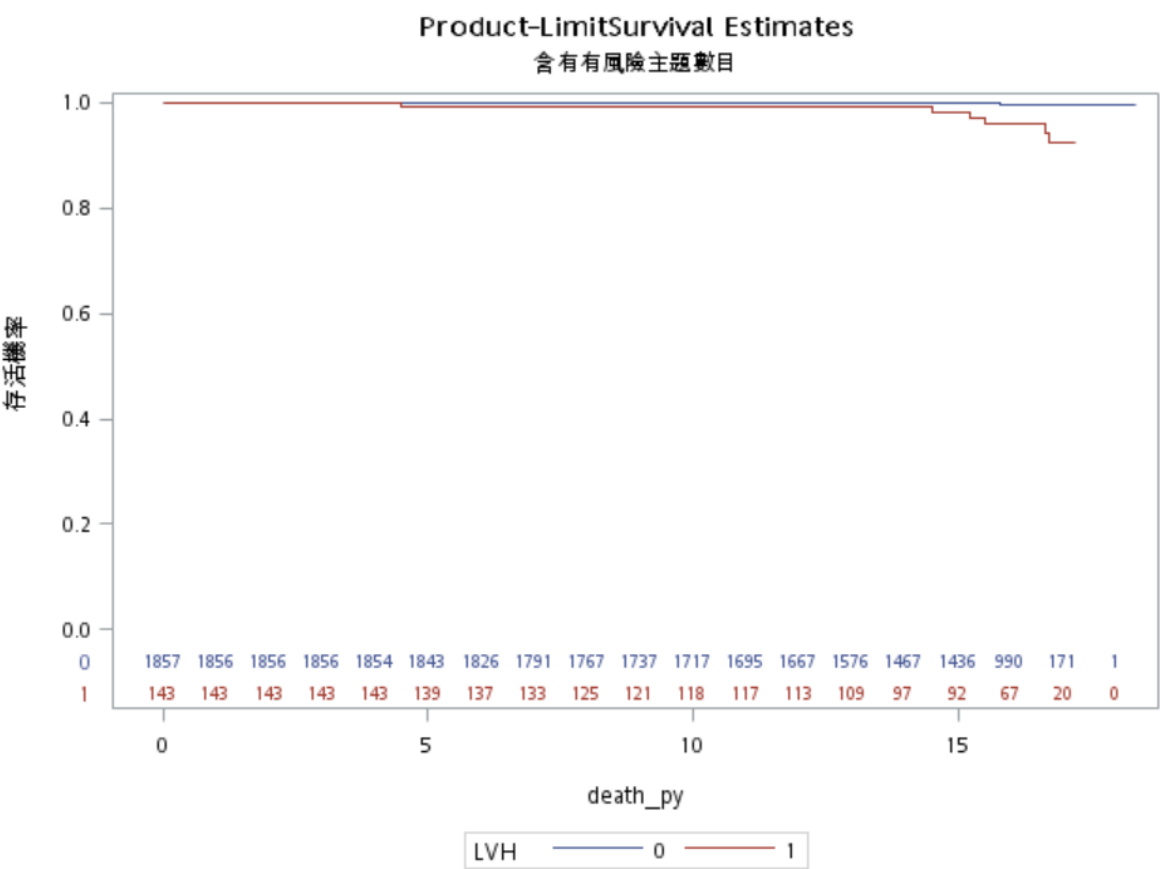
Competing risk-2:
Sub-distribution hazard-SDH

模型資訊	
資料集	DATA.DEMO
應變數	death_py
狀態變數	SCD_death
感興趣的事件	1
競爭事件	2
受限值	0
讀取的觀測值數目	2000
使用的觀測值數目	2000

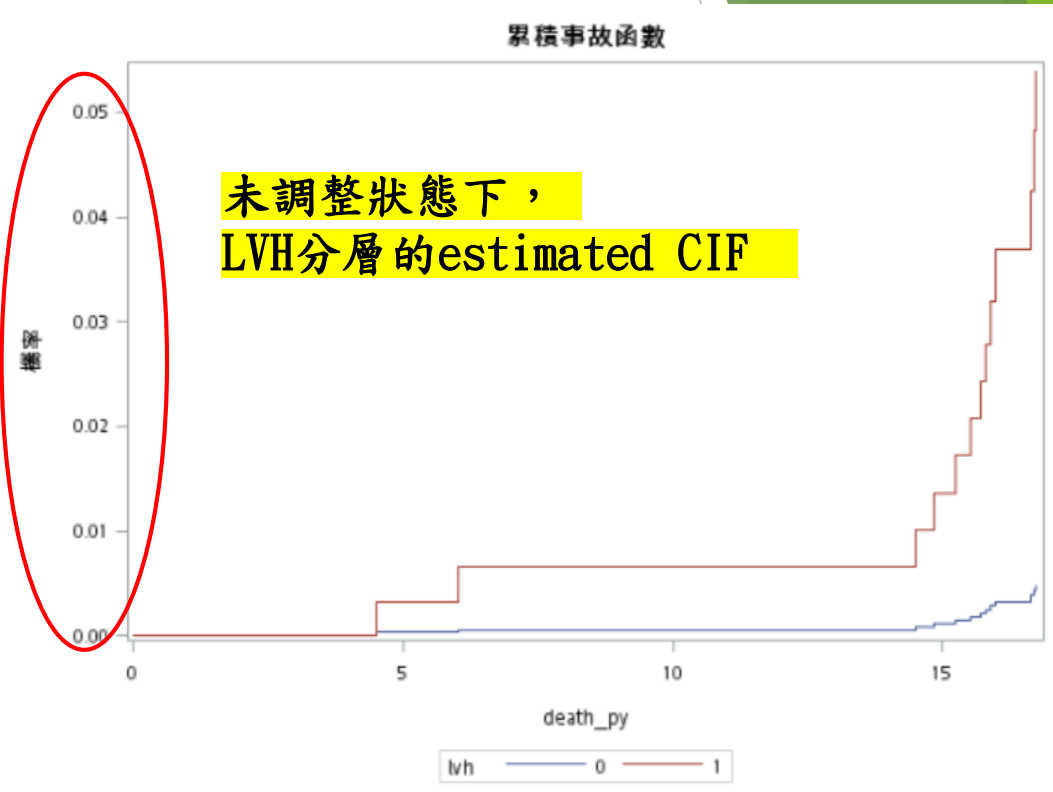
失敗結果摘要			
總計	感興趣的事件	競爭事件	設限
2000	13	367	1620

最大概度估計值的分析										
參數		自由度	參數估計值	標準誤差	卡方	Pr > ChiSq	危險比	95% 危險比信賴界限		標籤
age		1	0.07779	0.02201	12.4918	0.0004	1.081	1.035	1.129	
SEX	2	1	-0.44564	0.60038	0.5510	0.4579	0.640	0.197	2.077	SEX 2
HTN	1	1	0.56340	0.69820	0.6511	0.4197	1.757	0.447	6.902	HTN 1
EF40	1	1	3.07943	1.11870	7.5773	0.0059	21.746	2.427	194.813	EF40 1
LVH	1	1	1.87978	0.69828	7.2469	0.0071	6.552	1.667	25.749	LVH 1
cva0	1	1	-0.22995	1.17476	0.0383	0.8448	0.795	0.079	7.945	cva0 1

Kaplan-Meier Survival Curve



CIF: cumulative incidence functions (using SHD approach)



最大似度估計值的分析									
參數		自由度	參數估計值	標準誤差	卡方	Pr > ChiSq	危險比	95% 危險比信賴界限	標籤
LVH	1	1	2.43122	0.55581	19.1333	<.0001	11.373	3.826 33.805	LVH 1

CIF: cumulative incidence functions (using SHD approach)

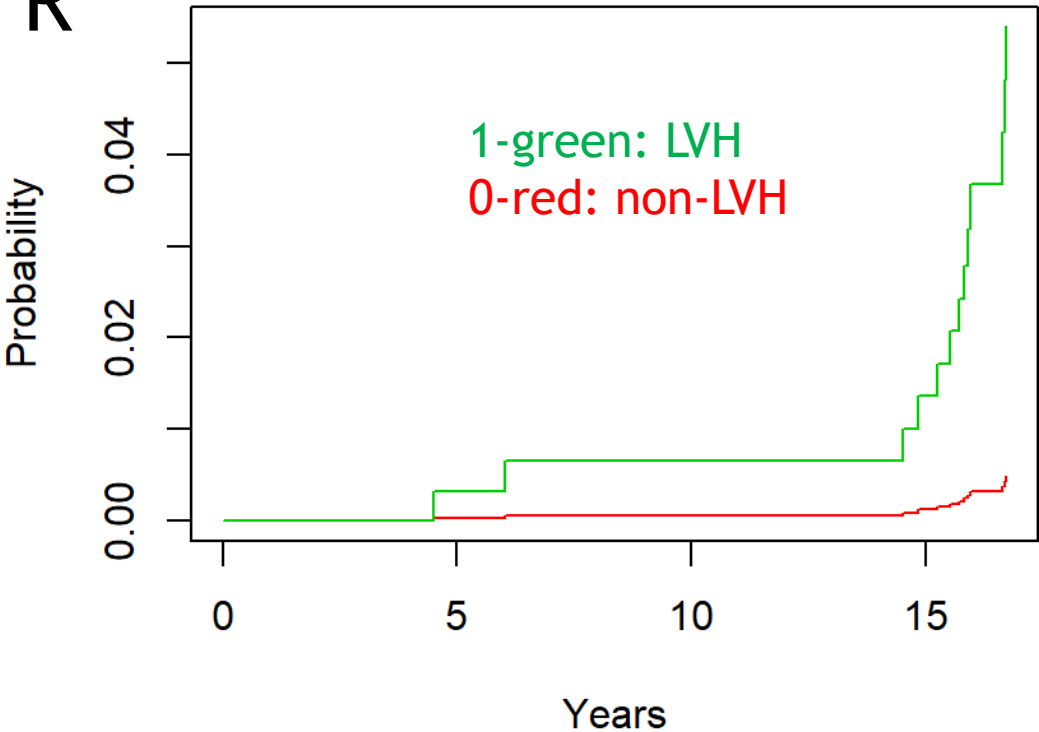
SAS



SAS

最大似度估計值的分析									
參數	自由度	參數估計值	標準誤差	卡方	Pr > ChiSq	危險比	95% 危險比信賴界限	標籤	
LVH	1	1	2.43122	0.55581	19.1333	<.0001	11.373	3.826	33.805
LVH 1									

R

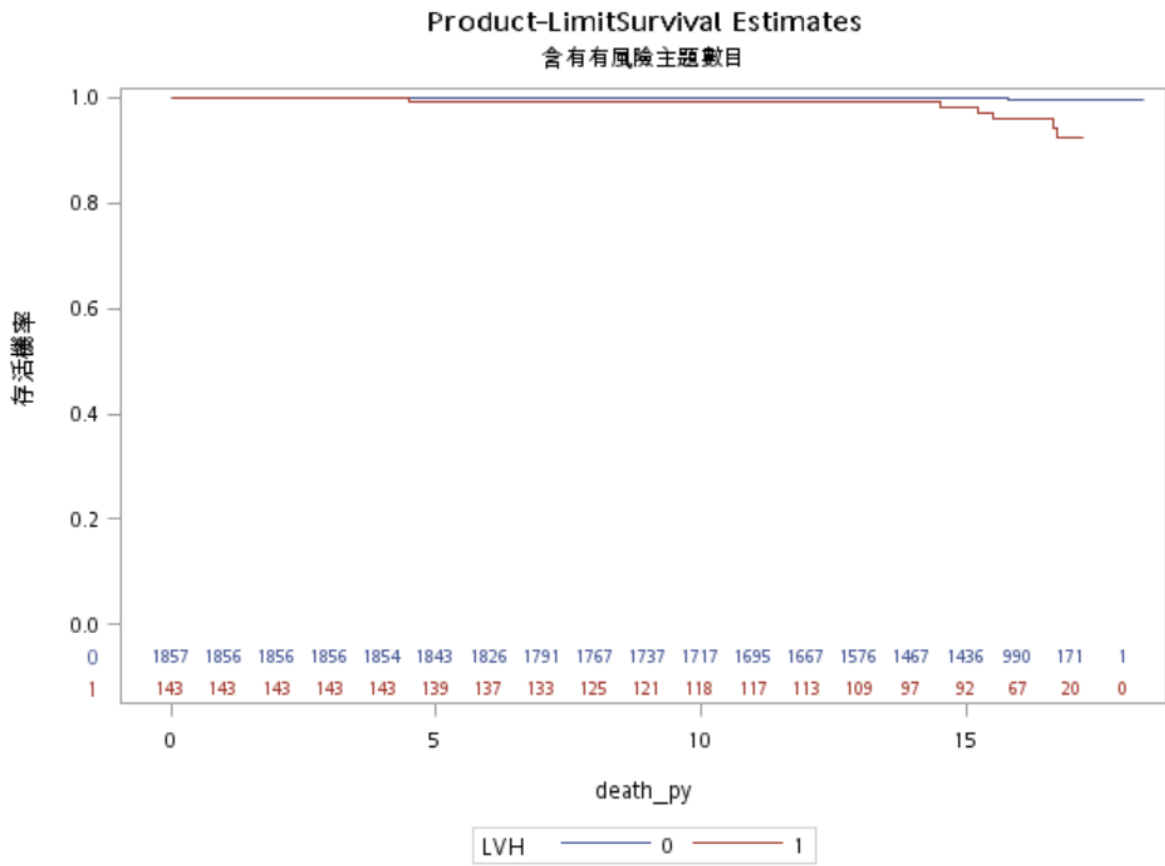


R

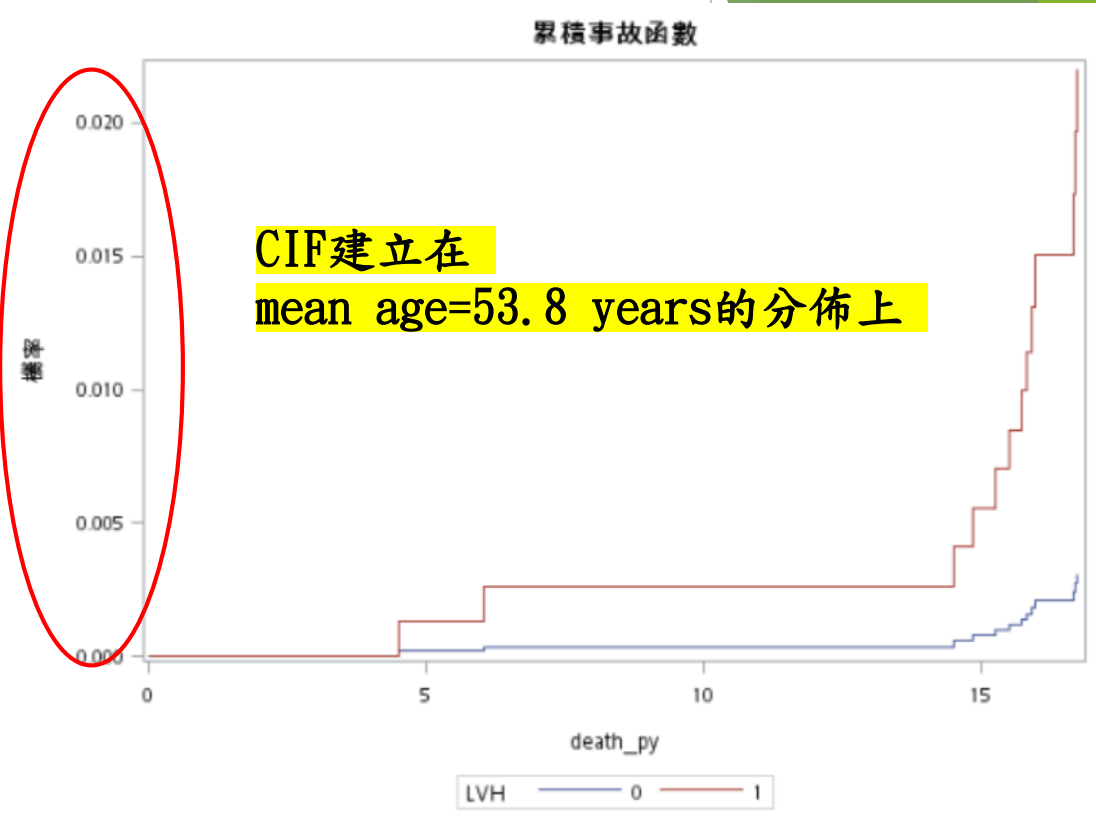
Competing Risks Regression

```
call:  
crr(ftime = ftime, fstatus = fstatus, cov1 = cov1, failcode = 1)  
  
coef exp(coef) se(coef) z p-value  
cov11 2.43 11.4 0.556 4.37 1.2e-05 P<0.001
```

Kaplan-Meier Survival Curve



CIF: cumulative incidence functions (using SHD approach)



SAS

最大概度估計值的分析									
參數		自由度	參數估計值	標準誤差	卡方	Pr > ChiSq	危險比	95% 危險比信賴界限	標籤
LVH	1	1	1.97269	0.57196	11.8956	0.0006	7.190	2.344 22.059	LVH 1
age		1	0.08235	0.01941	18.0058	<.0001	1.086	1.045 1.128	

R

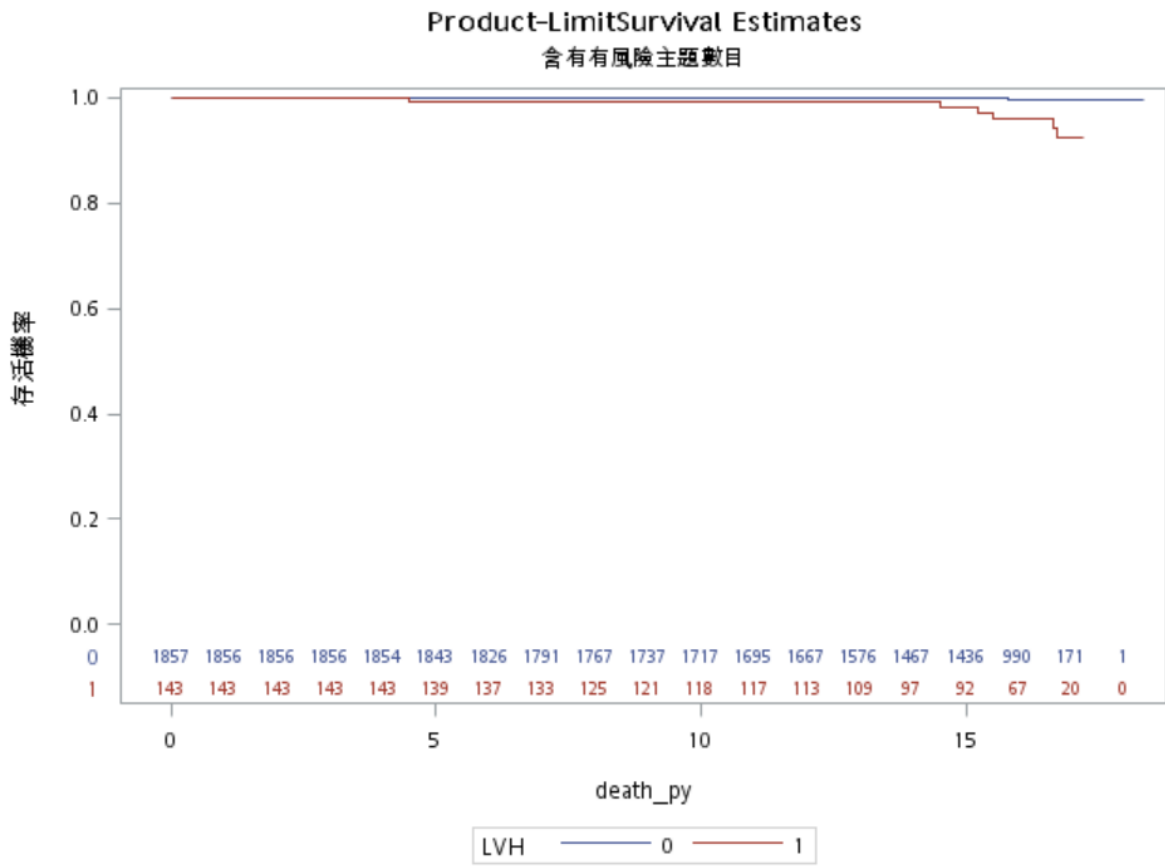
Competing Risks Regression

Call:
crr(ftime = ftime, fstatus = fstatus, cov1 = cov2, failcode = 1)

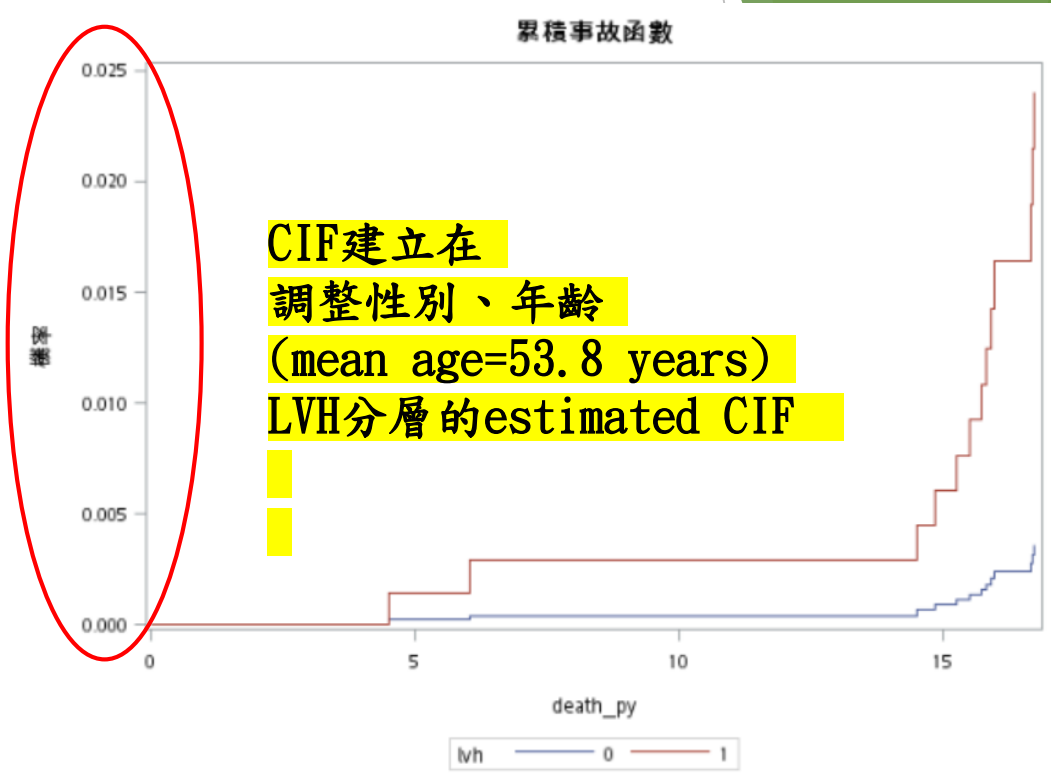
	coef	exp(coef)	se(coef)	z	p-value
LVH	1.9726	7.19	0.5720	3.45	5.6e-04
Age	0.0823	1.09	0.0194	4.24	2.2e-05

P<0.001
P<0.001

Kaplan-Meier Survival Curve



CIF: cumulative incidence functions (using SHD approach)



SAS

最大概度估計值的分析									
參數	自由度	參數估計值	標準誤差	卡方	Pr > ChiSq	危險比	95% 危險比信賴界限		標籤
LVH 1	1	1.91971	0.59487	10.4142	0.0013	6.819	2.125	21.882	LVH 1
age	1	0.08171	0.01945	17.6422	<.0001	1.085	1.045	1.127	
SEX 2	1	-0.25928	0.59386	0.1906	0.6624	0.772	0.241	2.471	SEX 2

R

call:
crr(ftime = ftime, fstatus = fstatus, cov1 = cov3, failcode = 1)

	coef	exp(coef)	se(coef)	z	p-value	
LVH	1.9197	6.819	0.5949	3.227	1.3e-03	P=0.0013
Age	0.0817	1.085	0.0195	4.200	2.7e-05	P<0.001
Sex	-0.2592	0.772	0.5939	-0.437	6.6e-01	P=0.66

是SHR，不是HR

Table 2. HRs and SHRs with 95% confidence interval for all-cause mortality in male versus female (reference group) dialysis patients and in old (≥ 65 years) versus young (< 65 years, reference group) dialysis patients

	Cause-specific approach HR (95% CI)	Subdistribution hazard approach SHR (95% CI)
Death		
Female	1.0	1.0
Male ^a	1.04 (1.02–1.07)	1.03 (0.87–1.23)
Young	1.0	1.0
Old ^b	2.57 (2.52–2.63)	3.47 (3.39–3.55)
Transplantation		
Female	1.0	1.0
Male ^a	1.09 (1.05–1.12)	1.07 (1.04–1.11)
Young	1.0	1.0
Old ^b	0.10 (0.10–0.11)	0.07 (0.07–0.08)
^a Adjusted for age. ^b Adjusted for sex.		

How to Select the Methods for Survival Analysis?

- 1、特定因素危險函數 (Cause-Specific Hazard Function, CSH)
 - (a) For aetiological studies
 - (b) When HRs need to be derived, the cause-specific approach is most appropriate
- 2、次分佈瞬間危險函數 (Sub-Distribution Hazard Function, SDH, Fine-Gray sub-distribution hazard)
 - (a) For prognostic research
 - (b) Most suitable for prediction of a survival probability

No competing risks	Competing risks
<p>(1) <i>Prognostic research question: calculation of survival probability</i></p> <p>(a) Unadjusted: Kaplan–Meier method</p> <p>(b) Adjusted: multivariate Cox regression</p> <p>(2) <i>Aetiological research question: estimation of effect (hazard ratio)</i></p> <p>(a) Unadjusted: univariate Cox regression</p> <p>(b) Adjusted: multivariate Cox regression</p>	<p>(1) <i>Prognostic research question: calculation of survival probability</i></p> <p>(a) Unadjusted: CICR method</p> <p>(b) Adjusted: subdistribution hazards model (Fine and Gray)</p> <p>(2) <i>Aetiological research question: estimation of effect (hazard ratio)</i></p> <p>(a) Unadjusted: univariate cause-specific proportional hazards model^a</p> <p>(b) Adjusted: multivariate cause-specific proportional hazards model^a</p>
<p>^aThe cause-specific approach can be applied by performing ‘standard’ Cox regression analyses, as provided by the conventional statistical software packages, with censoring at the competing event(s).</p>	

生統小組：統計方法教育訓練



Thank you for listening