存活分析課程 (2)：競爭風險

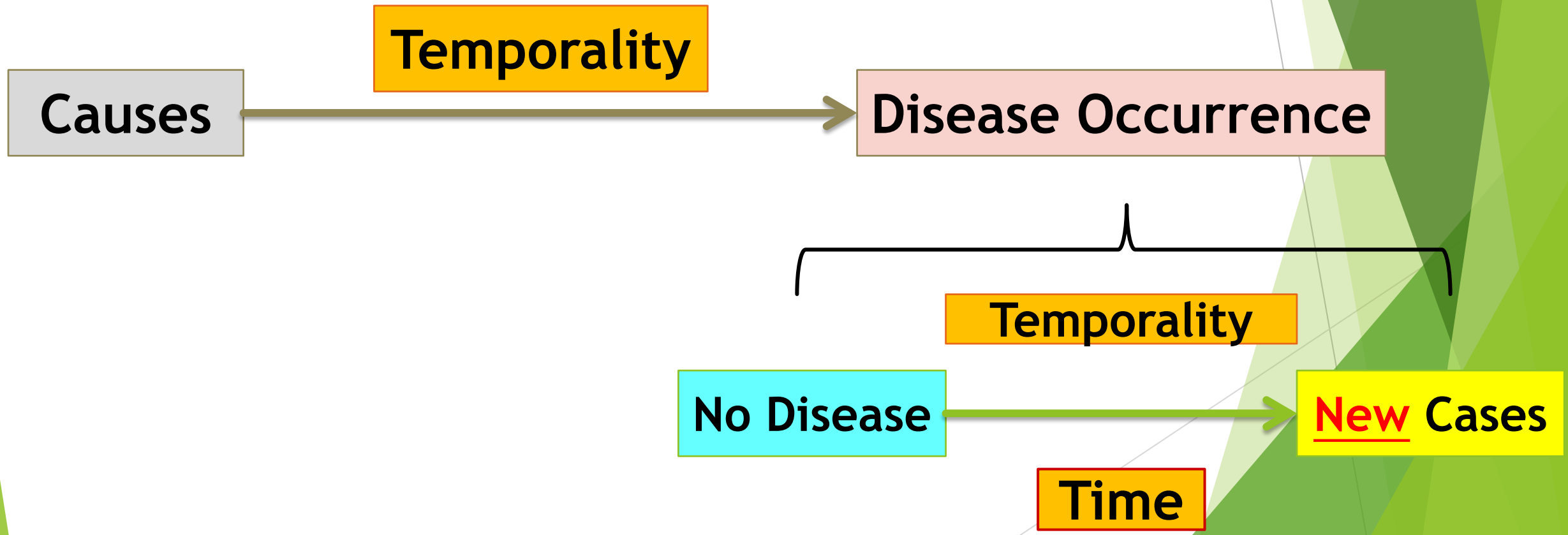
醫學研究部生統小組：陳韻伃 博士

授課日期：111年12月21日

世代研究：

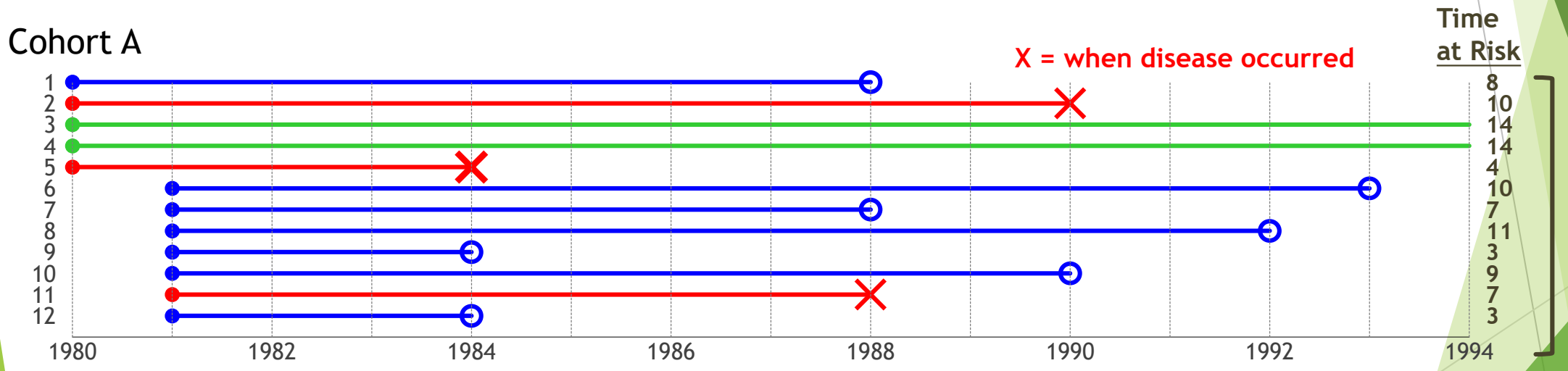
探討疾病的發生率及風險

*判定**因果關係**的必要條件之一



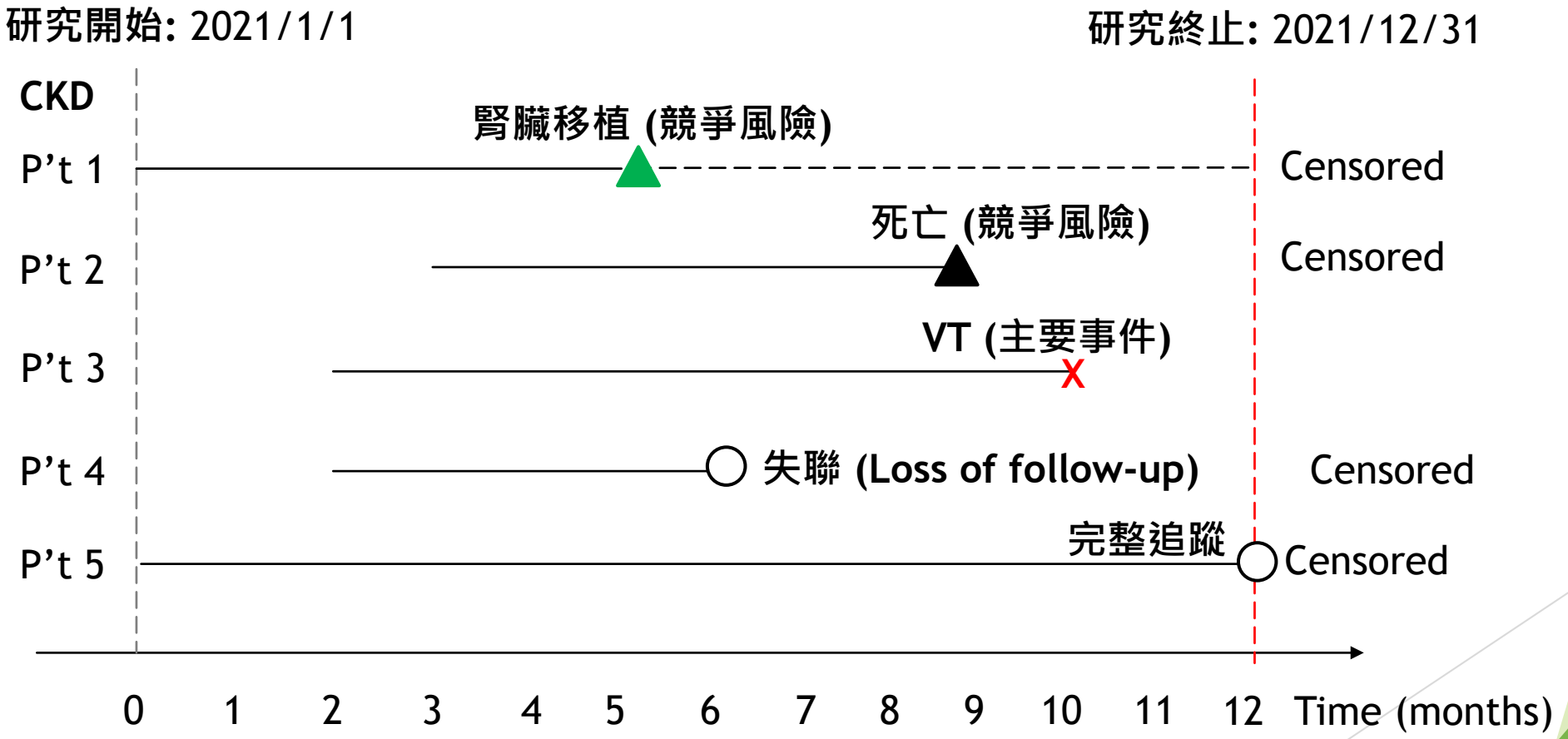
存活分析

- **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



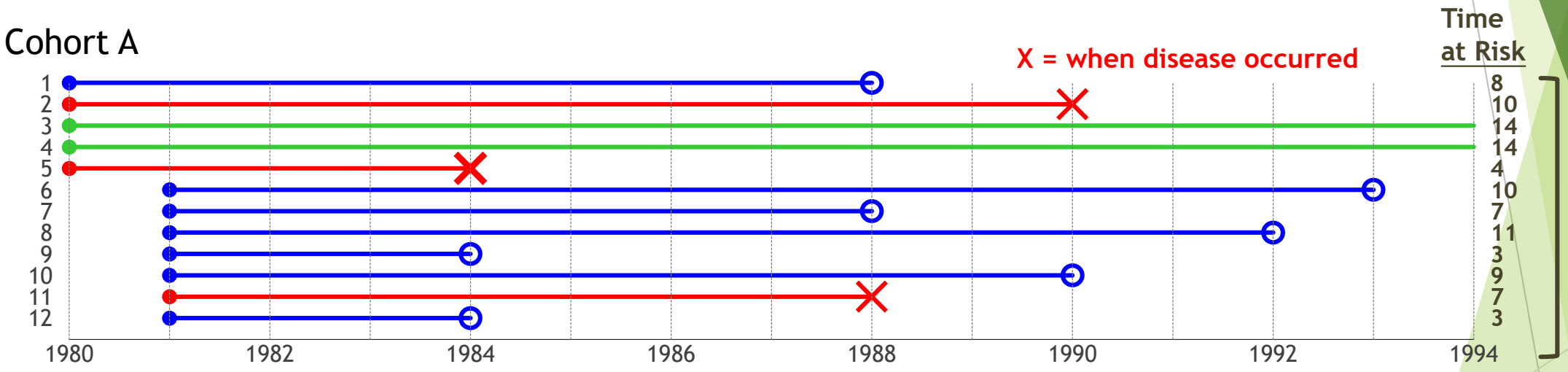
競爭風險 Competing Risk

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



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：

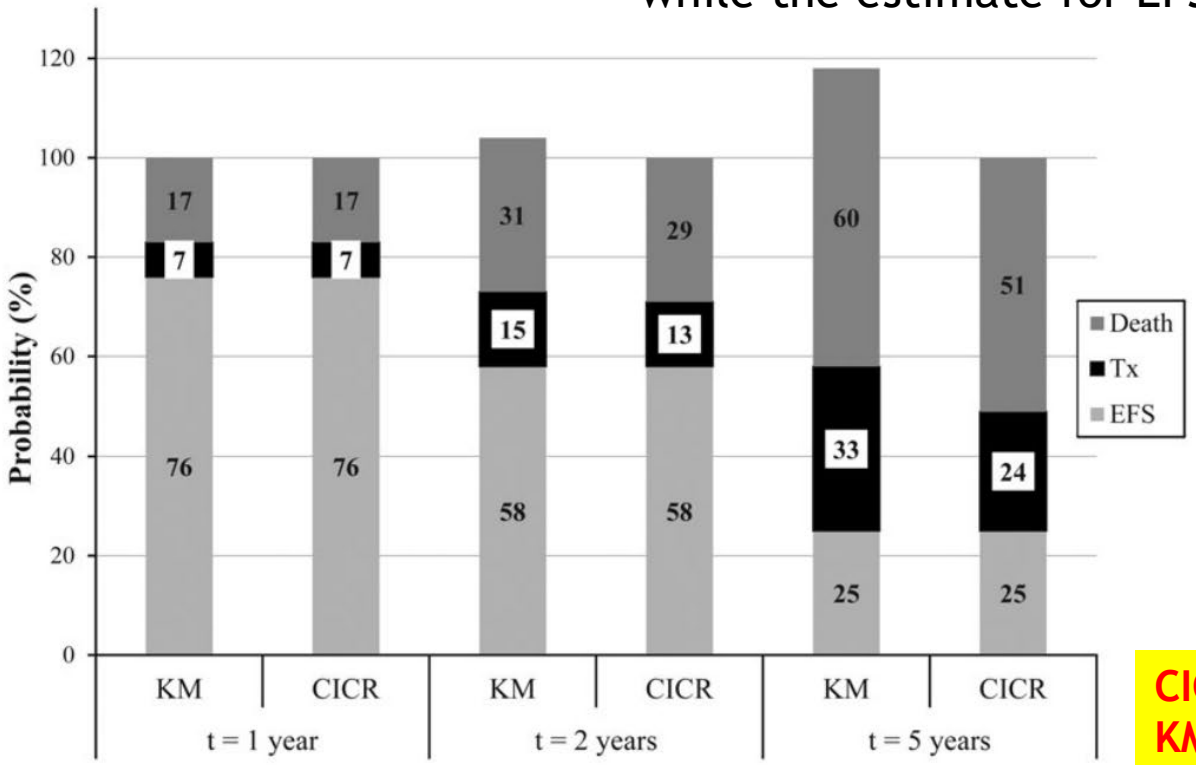
Kaplan-Meier (K-M) survival curve

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



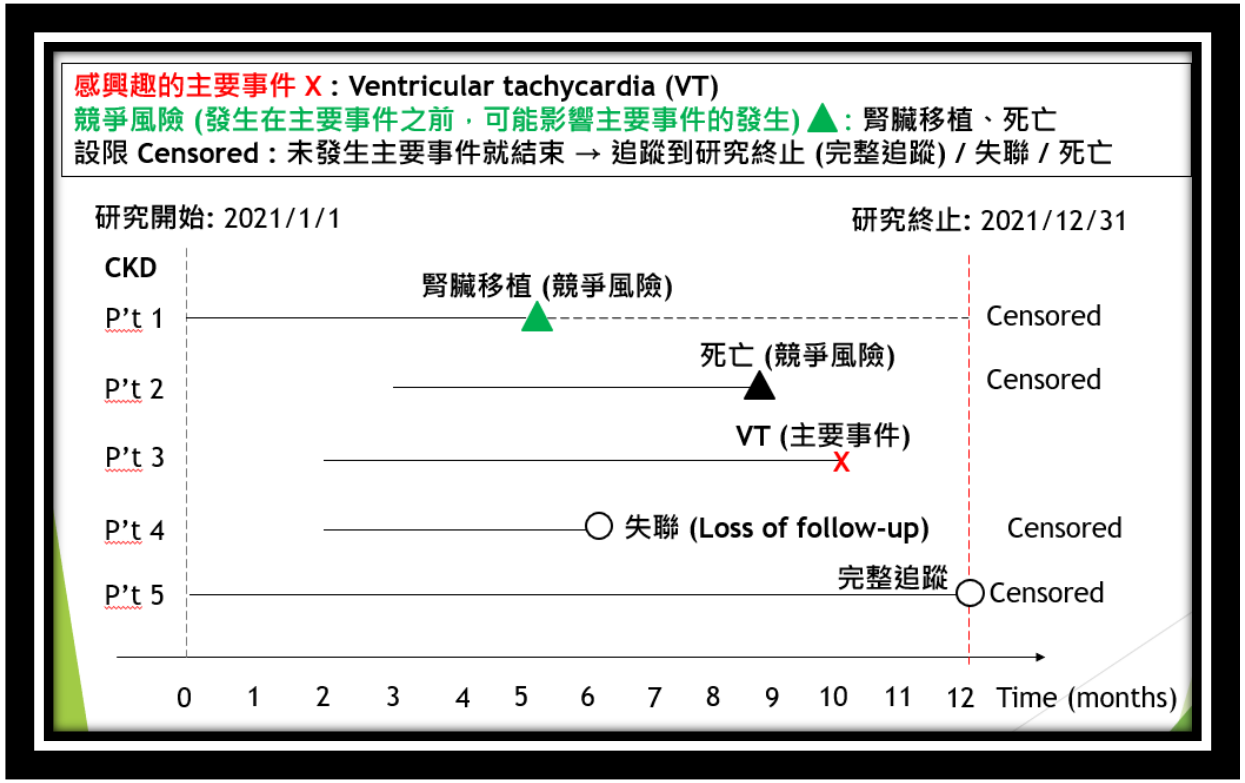
Tx: receiving a transplant
EFS: event-free survival

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.

M. Noordzij et al. Nephrol Dial Transplant (2013) 28: 2670–2677 doi: 10.1093/ndt/gft355

如何處理競爭風險

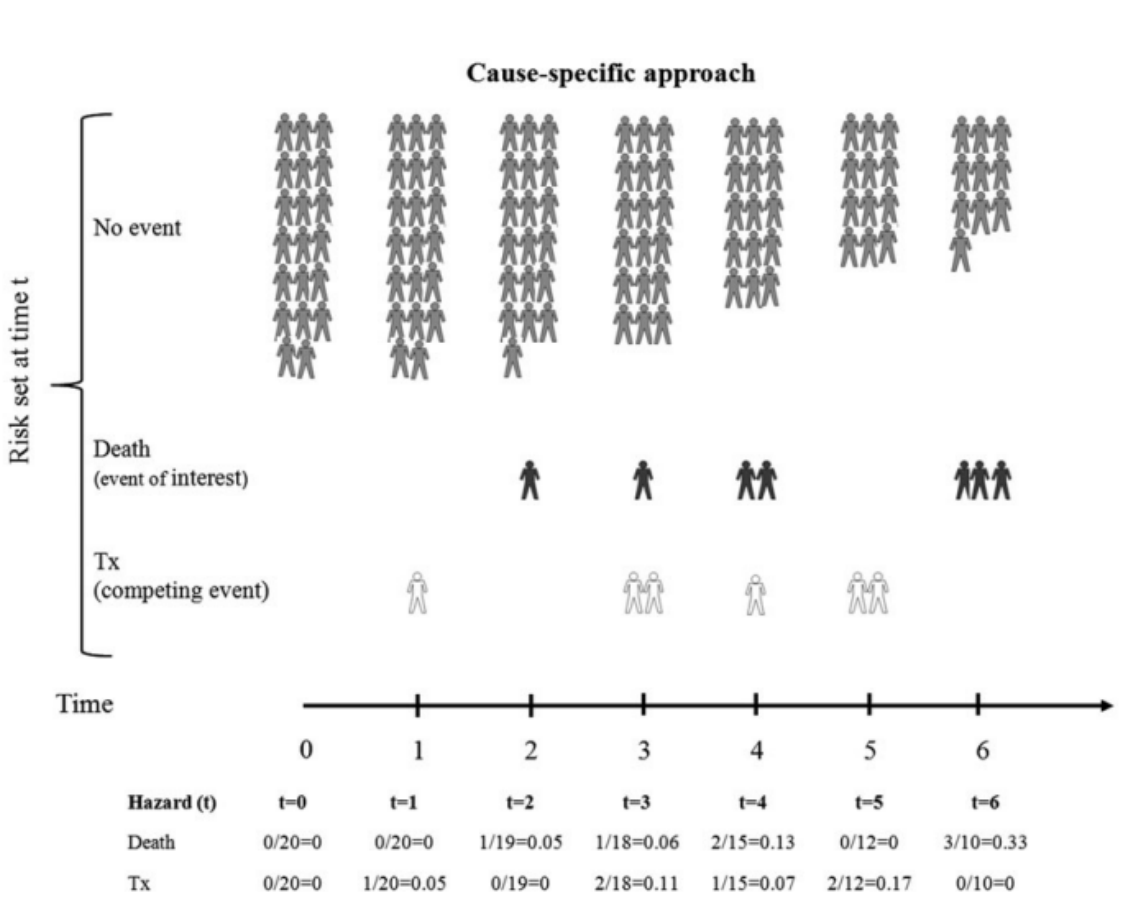


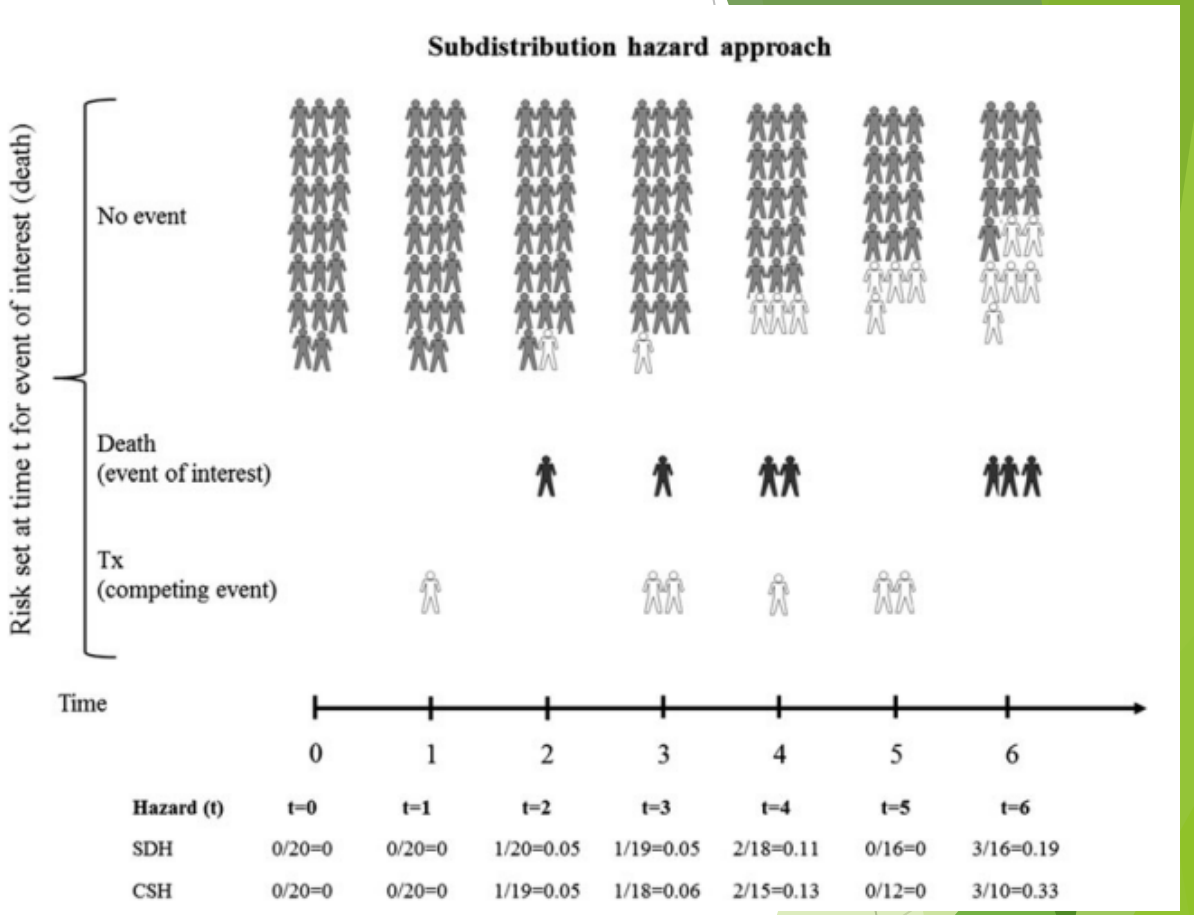
Competing Risk Analysis

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

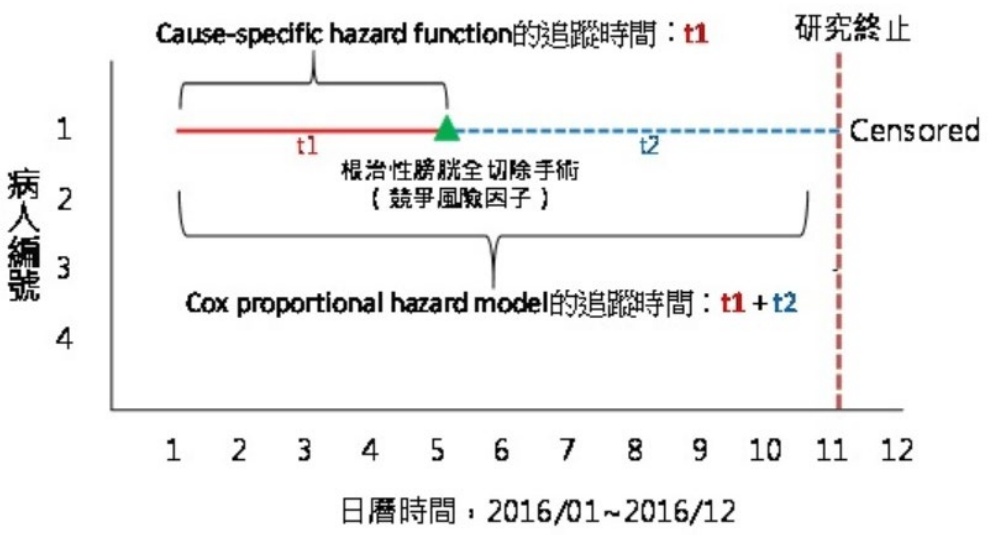


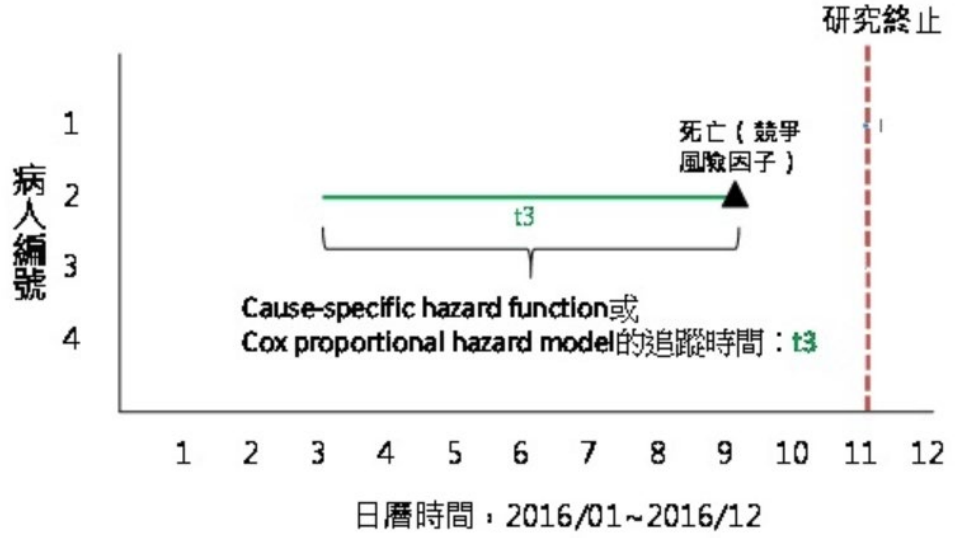


CSH是由Cox model所變化而成，風險集的設定也是採取Kaplan-Meier的估算方法：一旦發生研究興趣事件或是失去追蹤（設限，censor）的個案，在下一個觀察時間，皆從觀察名單中（Population at risk/ patient at risk）被排除。

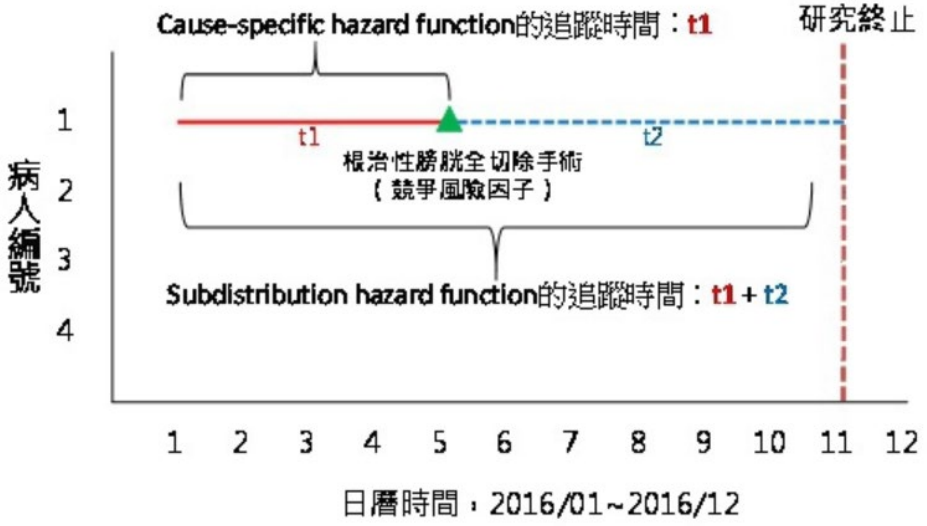
SDH在計算風險集時，並非採用傳統Kaplan-Meier的估算方法，而是採用累積發生函數（Cumulative incidence function, CIF），核心精神為：發生過競爭風險的人，在未來的觀察時間仍會保留在觀察名單（Population at risk）中。

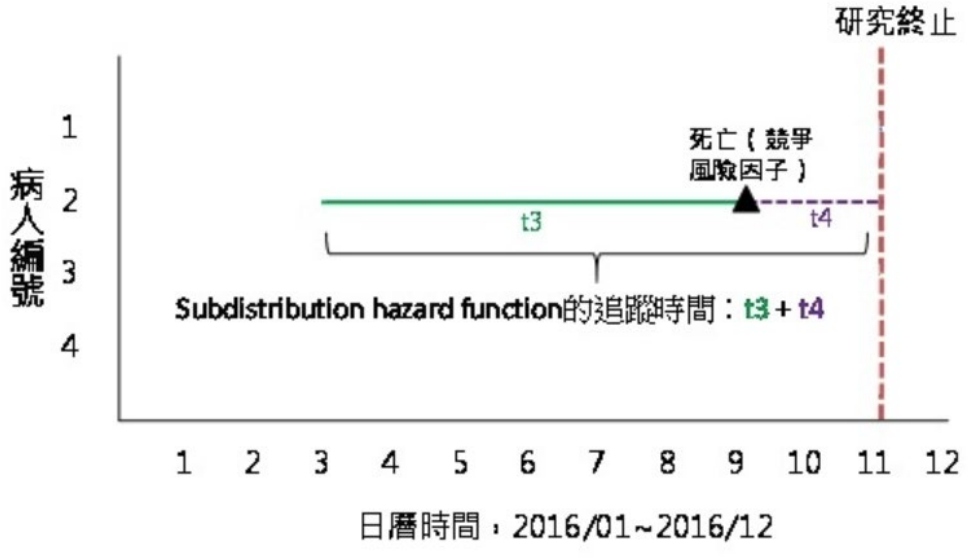
Cause-Specific Hazard Function (CSH)



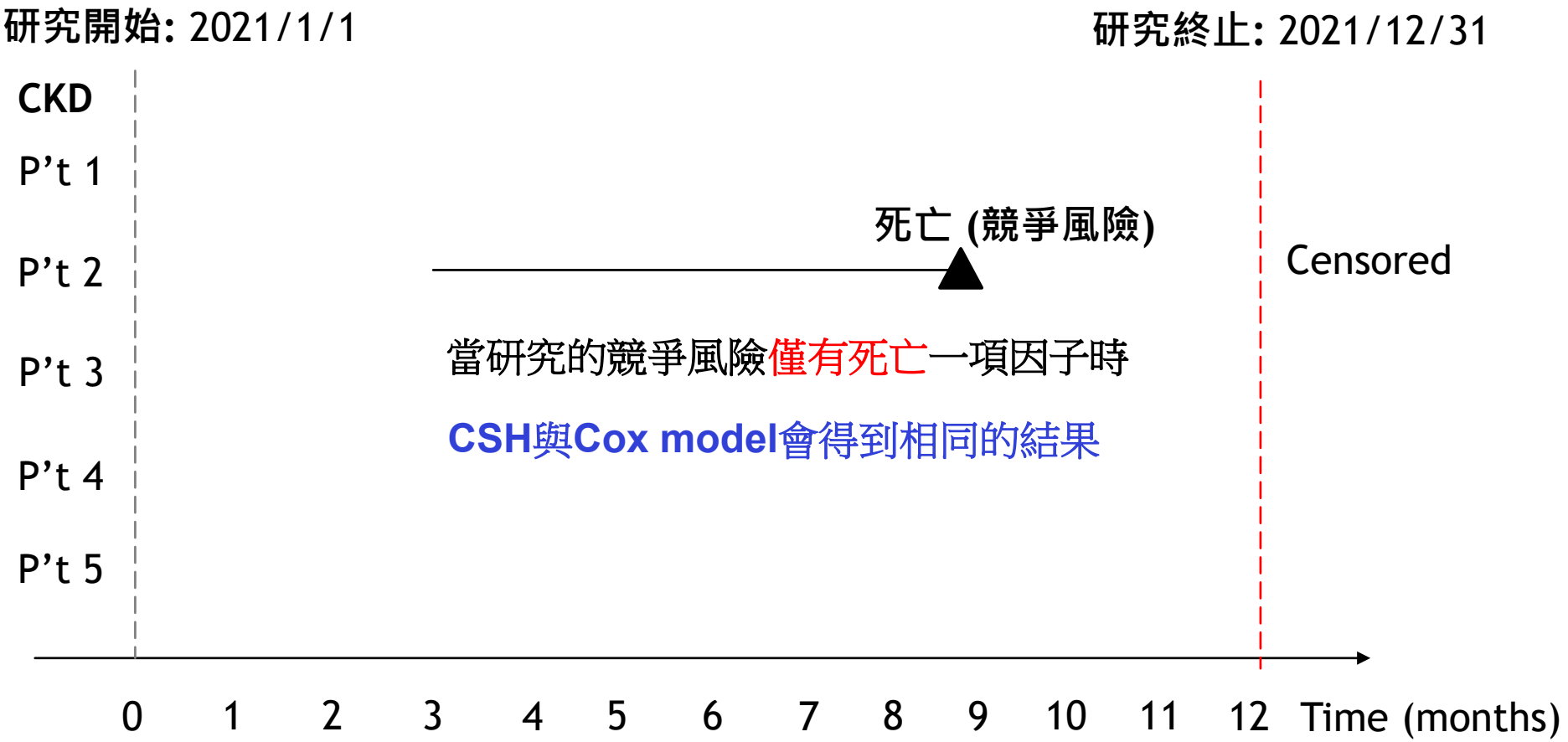


Sub-Distribution Hazard Function (SDH、Fine-Gray)





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	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

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

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

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

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

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

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

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

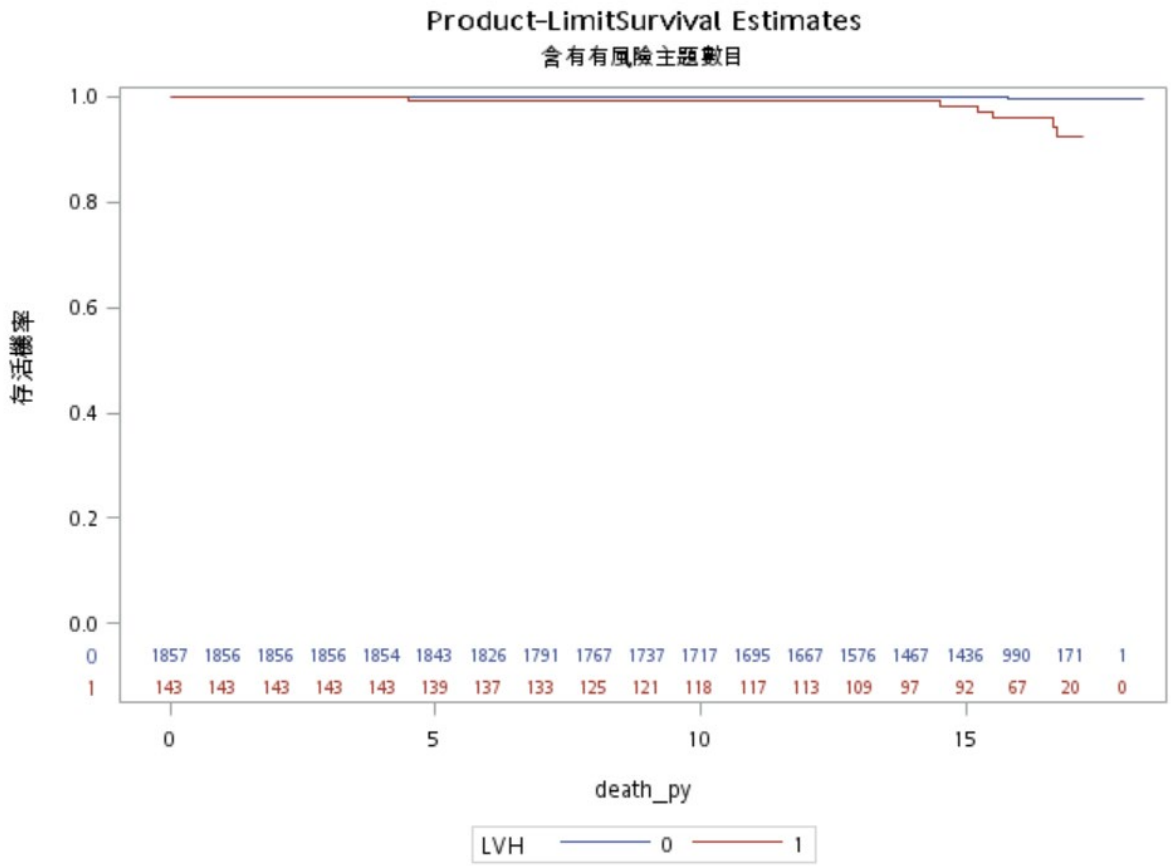
失敗結果摘要

總計	感興趣的事件	競爭事件	設限
2000	13	367	1620

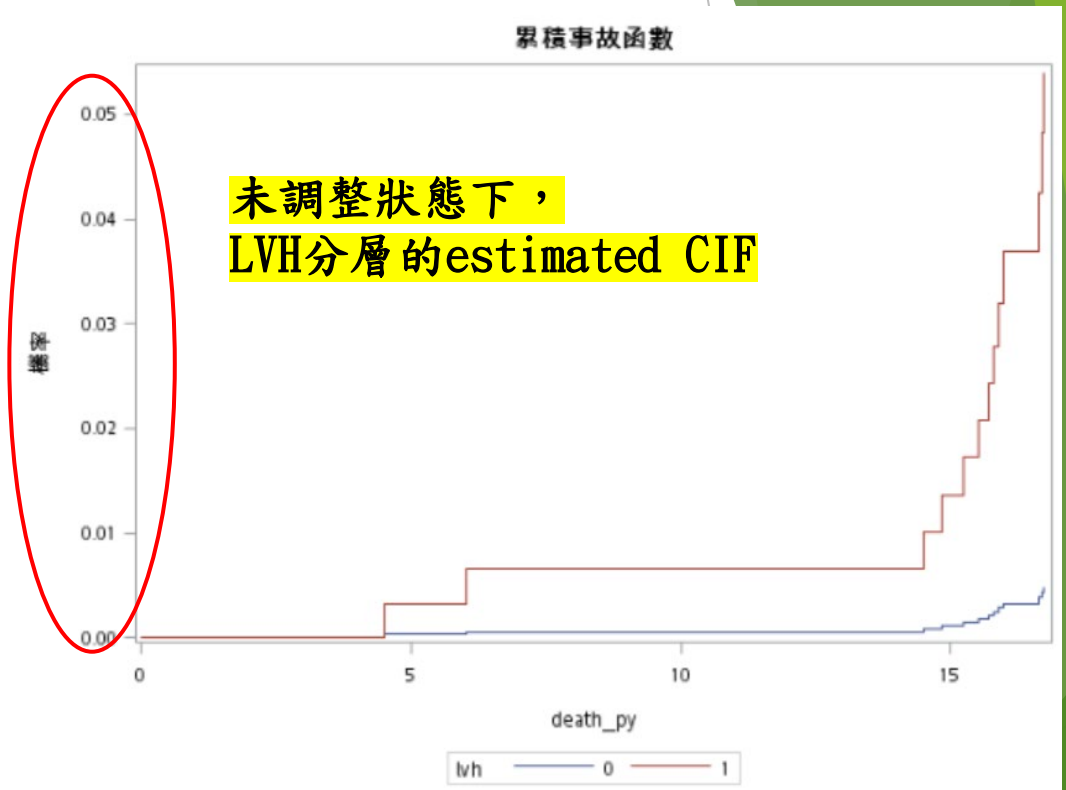
最大概度估計值的分析

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)



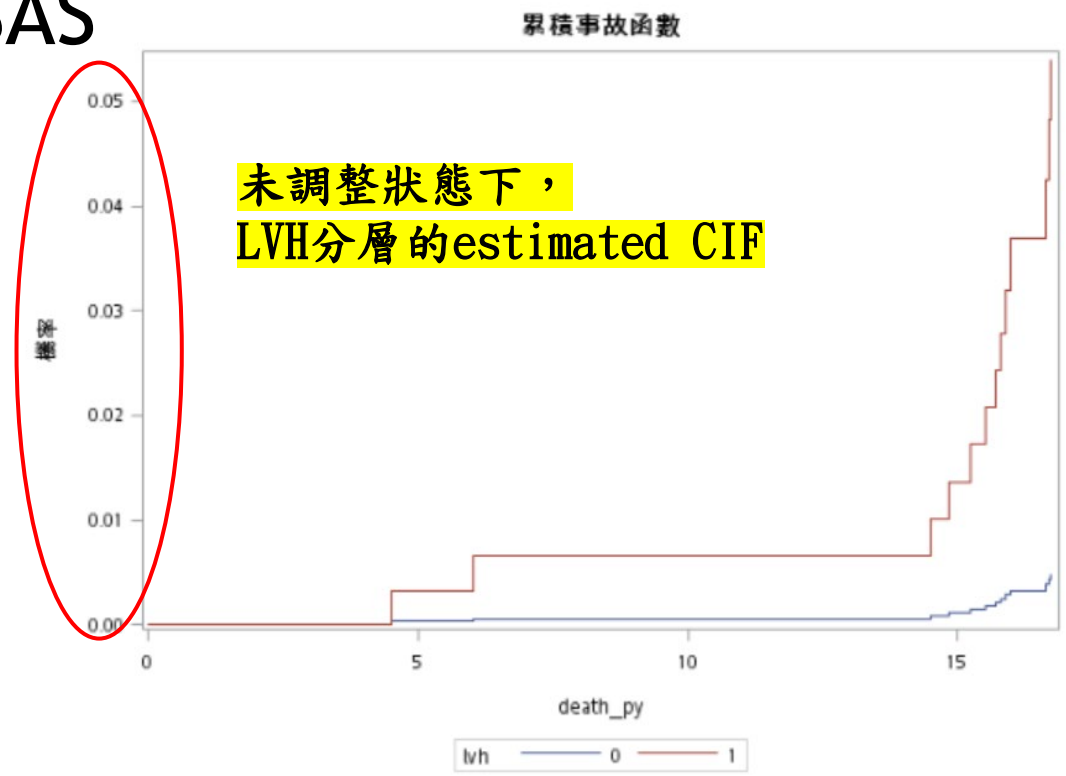
未調整狀態下，
LVH分層的estimated CIF

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	2.43122	0.55581	19.1333	<.0001	11.373	3.826	33.805	LVH 1

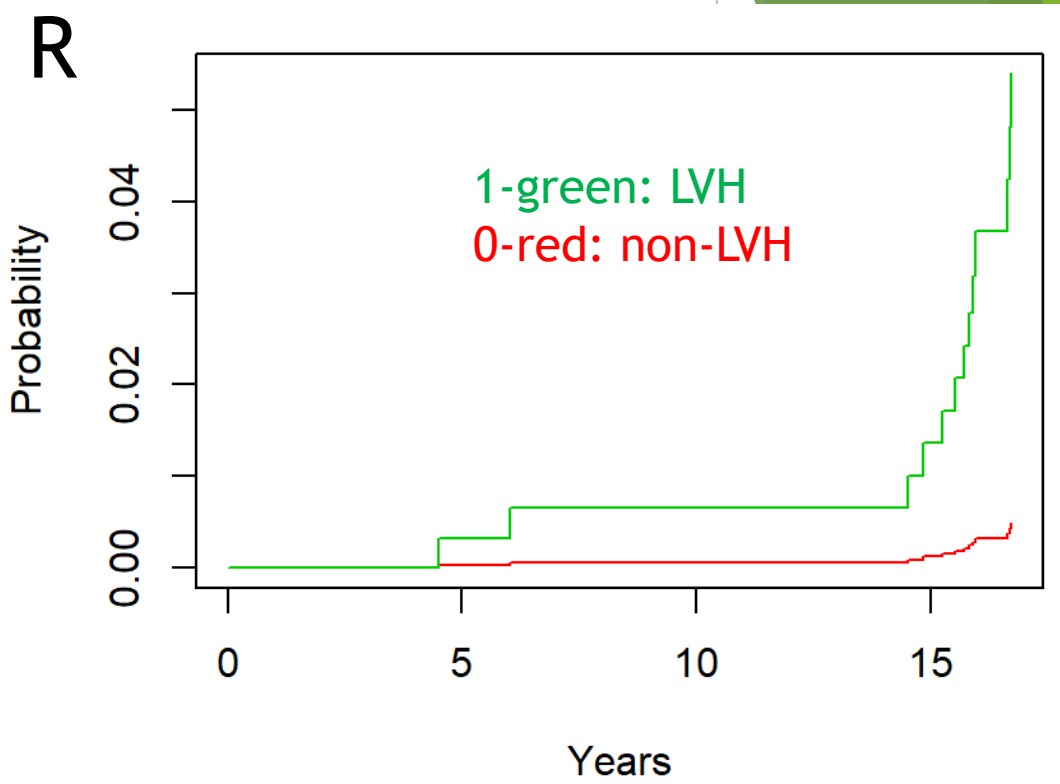
CIF: cumulative incidence functions (using SHD approach)

SAS



未調整狀態下，
LVH分層的estimated CIF

R



SAS

最大概度估計值的分析

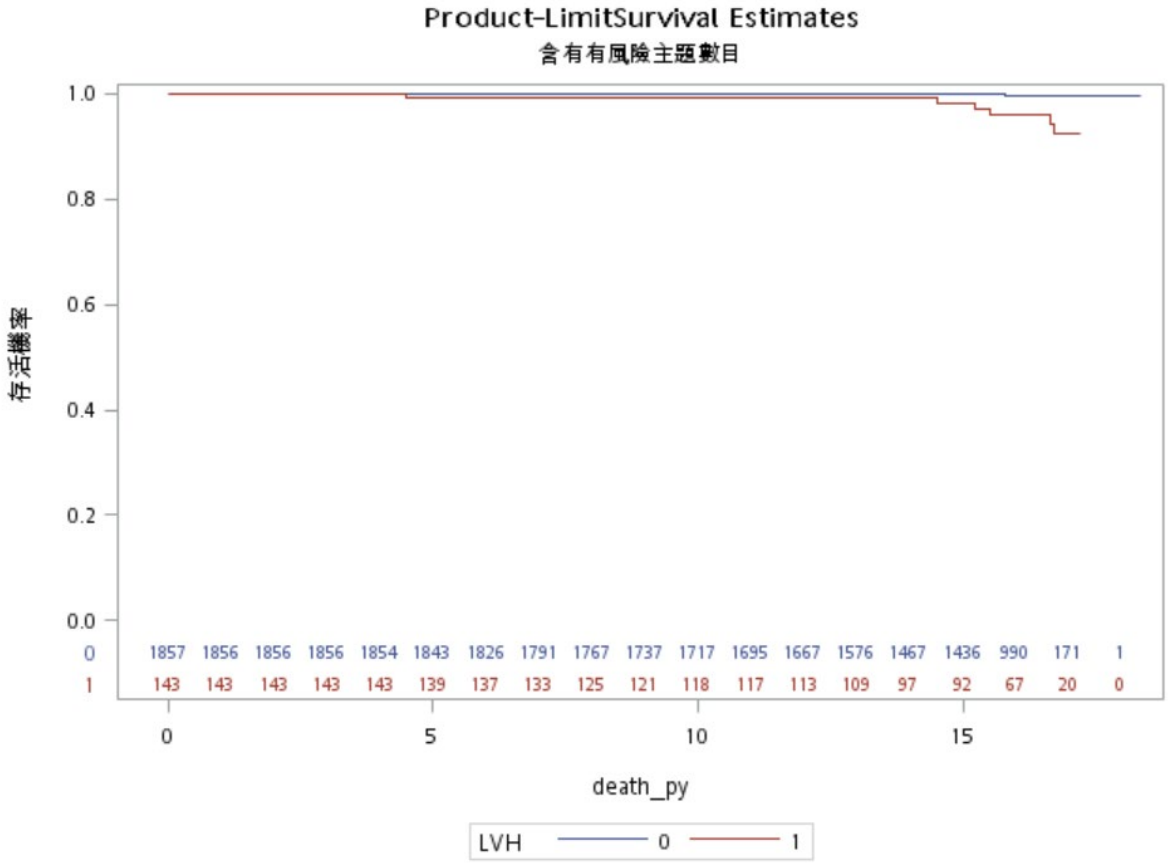
參數		自由度	參數估計值	標準誤差	卡方	Pr > ChiSq	危險比	95% 危險比信賴界限		標籤
LVH	1	1	2.43122	0.55581	19.1333	<.0001	11.373	3.826	33.805	LVH 1

R

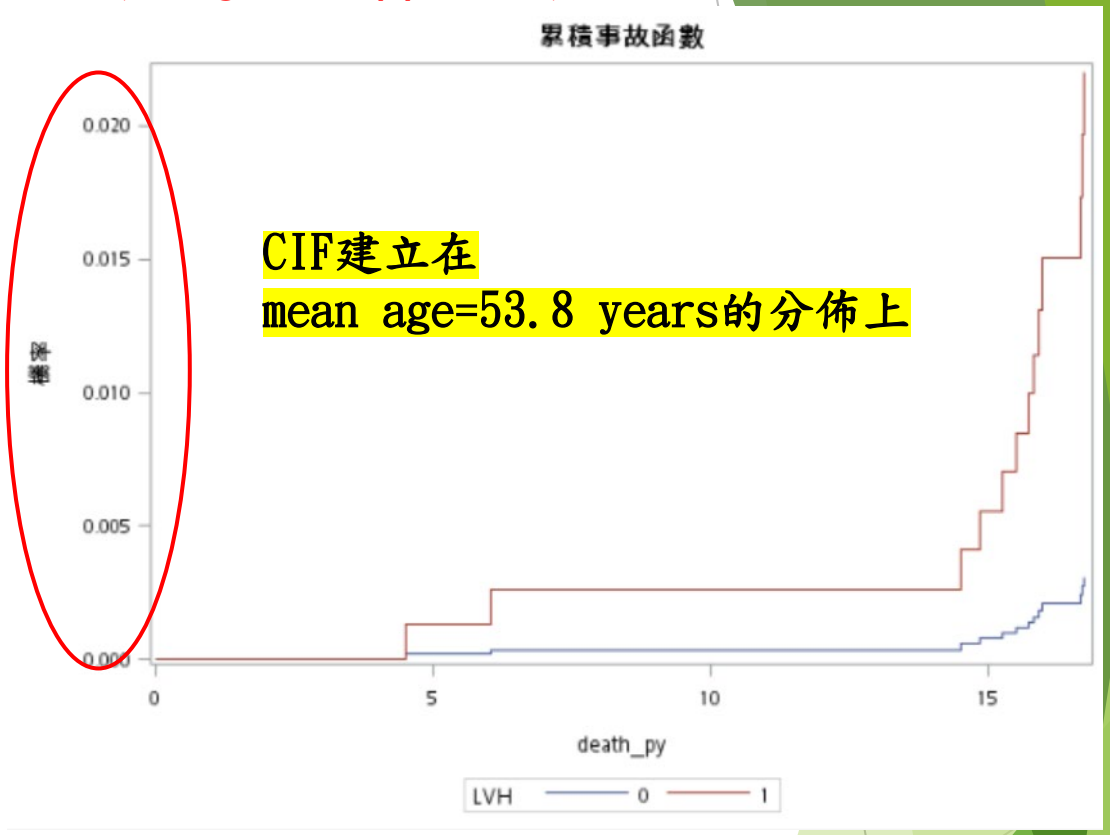
```
Competing Risks Regression

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)



CIF建立在
mean age=53.8 years的分佈上

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	

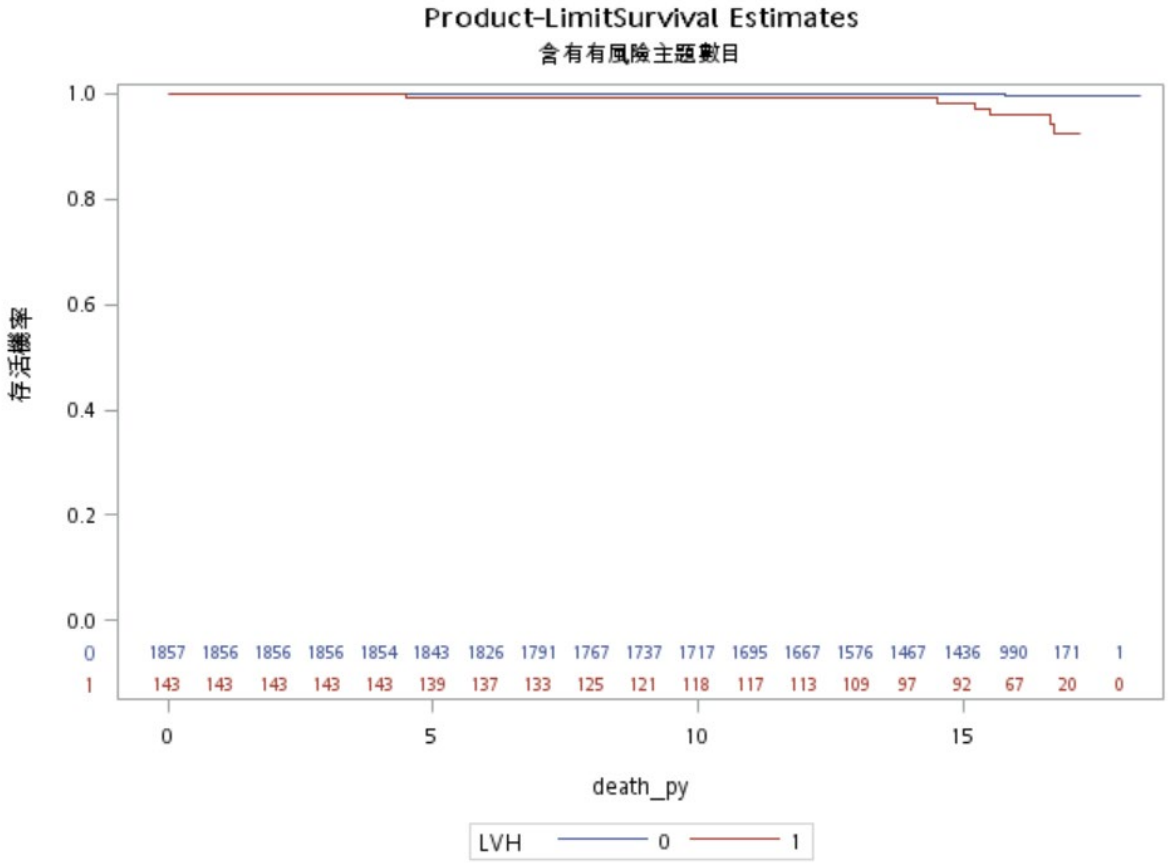
R

```
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
```

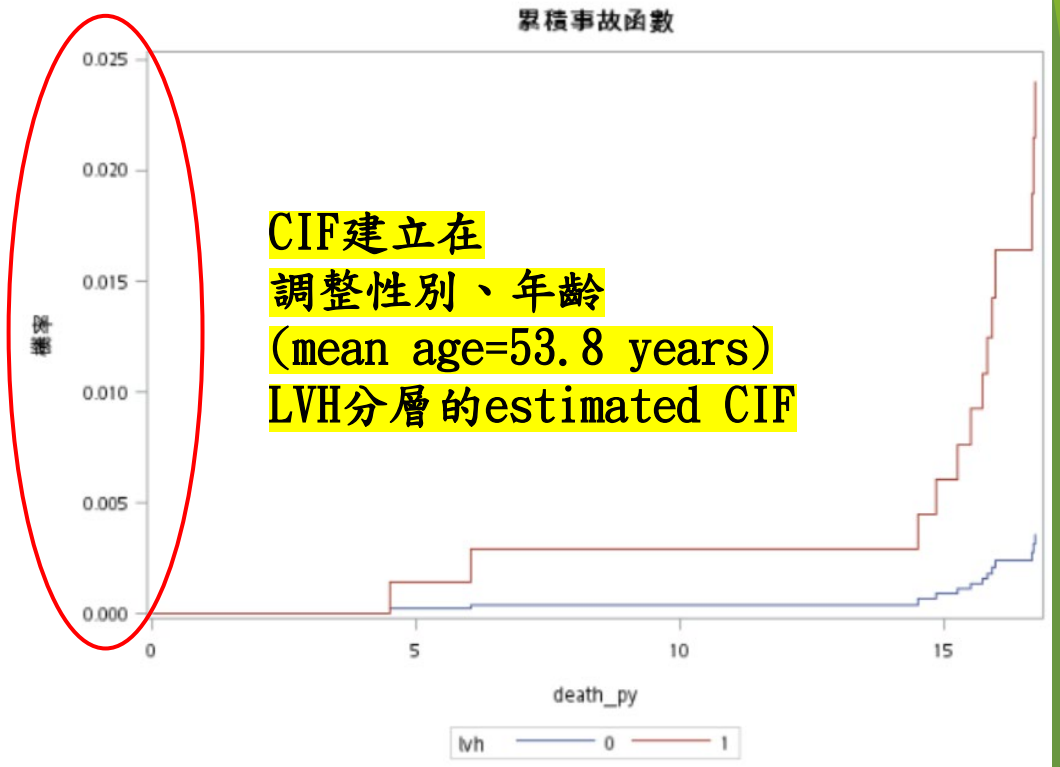
P<0.001

P<0.001

Kaplan-Meier Survival Curve



CIF: cumulative incidence functions (using SHD approach)



CIF建立在
調整性別、年齡
(mean age=53.8 years)
LVH分層的estimated CIF

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
Age   0.0817     1.085   0.0195  4.200 2.7e-05
Sex -0.2592     0.772   0.5939 -0.437 6.6e-01
```

P=0.0013
P<0.001
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.

M. Noordzij et al. Nephrol Dial Transplant (2013) 28: 2670–2677 doi: 10.1093/ndt/gft355

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
(1) *Prognostic research question: calculation of survival probability* (a) Unadjusted: Kaplan–Meier method (b) Adjusted: multivariate Cox regression (2) *Aetiological research question: estimation of effect (hazard ratio)* (a) Unadjusted: univariate Cox regression (b) Adjusted: multivariate Cox regression	(1) *Prognostic research question: calculation of survival probability* (a) Unadjusted: CICR method (b) Adjusted: subdistribution hazards model (Fine and Gray) (2) *Aetiological research question: estimation of effect (hazard ratio)* (a) Unadjusted: univariate cause-specific proportional hazards model[a] (b) Adjusted: multivariate cause-specific proportional hazards model[a]

[a]The 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).

Cumulative incidence competing risk (CICR)

M. Noordzij et al. Nephrol Dial Transplant (2013) 28: 2670–2677 doi: 10.1093/ndt/gft355

Thank you for listening