

[研究議題：Assessing the Relationship Between the Variability of Diagnostic Measures and the Risk of Diabetic Complications]

目的：找出糖尿病潛在的危險生理指標以利提早預測出糖尿病和相關併發症的發生

- 1.1 參考論文: Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study

2 Data preparation:

- 2.1 資料來源: 三院臨床資料庫  
2.2 目標病患: 糖尿病患者  
2.3 資料區間 : 2008-2019  
2.4 檢樣項目: HbA1c, Creatinine, ALBUMIN, Uric Acid, HDL, LDL  
2.5 糖尿病相關併發症和共病列表:

種類	疾病名稱
Complications	Eye complications
	Cardiovascular disease
	Cerebrovascular disease
	Peripheral vascular disease
	Nephropathy
	Diabetic neuropathy
Comorbidity	Essential hypertension
	Peripheral enthesopathies and allied syndromes
	Other ill-defined and unknown causes of morbidity and mortality
	Disorders of lipid metabolism
	Acute upper respiratory infections of multiple or unspecified sites
	Other symptoms involving abdomen and pelvis
	Dermatophytosis
	General symptoms
	Symptoms involving respiratory system and other chest symptoms
	Symptoms involving head and neck

	Contact dermatitis and other eczema
	Viral infection in conditions classified elsewhere and of unspecified site
	Overweight, obesity and other hyperalimentation
	Other and unspecified disorders of joint
	Acute bronchitis and bronchiolitis
	Other disorders of soft tissues
	Nonspecific findings on examination of blood
	Disorders of refraction and accommodation

2.6 Index Date 定義: 一年內有 3 次門診紀錄或 1 次住院紀錄為新患的糖尿病患者符合條件下的首次看診日

2.7 ICD CODE:

2.7.1 糖尿病:

2.7.1.1 ICD9: 250, 251.8, 357.2, 362.01, 362.02, 366.41, 583.81

2.7.1.2 ICD10: E08, E09, E10, E11, E12

2.7.2 併發症:

糖尿病相關併發症	ICD CODE	操作定義
Eye complications 眼部疾病	ICD9: 362.01、362.02、362.55、362.11、365.44、369、361、369.60  ICD10: H33.0, H33.10, H33.11, H33.19, H33.2, H33.3, H33.4, H33.8, E11.31, E11.32, E11.33, E11.34, E11.351, E11.359, H35.03, H35.38, H42, H54.0, H54.1, H54.2, H54.3, H54.8, H54.4, H54.5, H54.6, H54.7	一年內 3 次門診或 1 次住院。
Cardiovascular disease 心血管疾病	ICD9: 414.9、413.9、411.1、412、428、425、402  ICD10: I11, I20.0, I20.8, I20.9, I25.2, I25.9, I42, I43, I50.1, I50.2, I50.3, I50.4, I50.9	

<p>Cerebrovascular disease</p> <p>腦血管疾病</p>	<p>ICD9: 435.9 、 434.91 、 432.9 、 437.1</p> <p>ICD10: I62.9, I63.50, I63.511, I63.512, I63.519, I63.521, I63.522, I63.529, I63.531, I63.532, I63.539, I63.541, I63.542, I63.549, I63.59, I63.8, I63.9, I67.84, I67.81, I67.82, I67.89, G45.9</p>	
<p>Peripheral vascular disease</p> <p>周邊動脈疾病</p>	<p>ICD9: 440.2</p> <p>ICD10: I70.2, I70.92, I75.01, I75.02</p>	
<p>Nephropathy</p> <p>腎臟病</p>	<p>ICD9: 583 、 585 、 V451</p> <p>ICD10: E10.21, E11.21, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N06.0, N06.1, N06.2, N06.3, N06.4, N06.5, N06.6, N06.7, N06.8, N06.9, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N14, N15.0, N15.8, N15.9, N16, N17.1, N17.2, N18.4, N18.5, N18.6, N18.9</p>	
<p>Diabetic neuropathy</p> <p>神經病變</p>	<p>ICD9: 357.2 、 337.1 、 353</p> <p>ICD10: E08.42, E09.42, E10.40, E10.42, E11.40, E11.42, E13.42, G54, G55, G99.0</p>	

### 2.7.3 共病:

糖尿病相關共病	ICD CODE	操作定義
Essential hypertension 本態性高血壓	ICD9: 401 ICD10: I10	一年內 3 次門診或 1 次住院
Peripheral enthesopathies and allied syndromes 外周附著點病變及其相關聯症候群的疾病	ICD9: 726 ICD10: M25.70, M25.71, M25.72, M25.73, M25.74, M25.75, M25.76, M25.77, M66.21, M66.81, M70.1, M70.2, M70.3, M70.4, M70.5, M70.6, M70.7, M75.0, M75.10, M75.11, M75.2, M75.3, M75.4, M75.5, M75.8, M75.9, M76, M77	
Other ill-defined and unknown causes of morbidity and mortality 定義不明和未知原因的發病和死亡	ICD9: 799 ICD10: R09.0, R09.2, R41.89, R44.8, R44.9, R45.0, R45.3, R45.4, R45.87, R45.89, R46, R53.81, R64, R68.13, R68.19, R68.82, R68.89, R69	
Disorders of lipid metabolism 脂質代謝障礙	ICD9: 272 ICD10: E71.30, E75.21, E75.22, E75.24, E75.3, E75.5, E75.6, E77, E78.0, E78.1, E78.2, E78.3, E78.4, E78.5, E78.5, E78.6, E78.70, E78.79, E78.8, E78.9, E88.1, E88.2, E88.89	
Acute upper respiratory infections of multiple or unspecified sites 多部位或未明確部位的急性上呼吸道感染	ICD9: 465 ICD10: J06	
Other symptoms involving abdomen and pelvis 腹部和骨盆的其他症狀	ICD9: 724、789 ICD10: M43.2, M43.8X9 M48.00, M48.04, M48.05, M48.06, M48.07, M48.08, M51.1, M53.2X7, M53.2X8, M53.3, M53.80, M53.84, M53.85, M53.86, M53.87, M53.88, M53.9, M54.03, M54.04, M54.05,	

	M54.06, M54.07, M54.08, M54.09, M54.14, M54.15, M54.16, M54.17, M54.3, M54.4, M54.5, M54.6, M54.89, M54.9, M62.830, M99.22, M99.23, M99.24, M99.25, M99.26, M99.27, M99.28, M99.29, M99.32, M99.33, M99.34, M99.35, M99.36, M99.37, M99.38, M99.39, M99.42, M99.43, M99.44, M99.45, M99.46, M99.47, M99.48, M99.49, M99.52, M99.53, M99.54, M99.55, M99.56, M99.57, M99.58, M99.59, M99.62, M99.63, M99.64, M99.65, M99.66, M99.67, M99.68, M99.69, M99.72, M99.73, M99.74, M99.75, M99.76, M99.77, M99.78, M99.79, R10, R16, R18.8, R19.0, R19.3, R19.8	
Dermatophytosis 真菌引起的皮膚感染	ICD9: 110 ICD9: B35	
General symptoms 非特定的身體症狀	ICD9: 780 ICD10: E03.5, F51.8, G40.909, G47.0, G47.1, G47.20, G47.3, G47.5, G47.61, G47.69, G47.8, G47.9, G93.3, L74.51, L74.52, R40.0, R40.1, R40.20, R40.211, R40.212, R40.221, R40.222, R40.231, R40.232, R40.234, R40.3, R40.4, R41.0, R41.1, R41.2, R41.3, R41.82, R41.89, R41.9, R42, R44.0, R44.2, R44.3, R45.83, R45.84, R50.2, R50.81, R50.9, R52, R53.0, R53.1, R53.8, R55, R56, R61, R68.0, R68.11, R68.12, R68.81, R68.83, R68.89	
Symptoms involving respiratory system and other chest symptoms 呼吸系統和其他胸部症狀	ICD9: 786 ICD10: R04.2, R04.8, R04.9, R05, R06.00, R06.01, R06.02, R06.09, R06.1, R06.2, R06.3, R06.3, R06.4, R06.6, R06.8, R06.9, R07.1, R07.2, R07.8, R07.9, R09.3, R09.89, R22.2, R91.8	

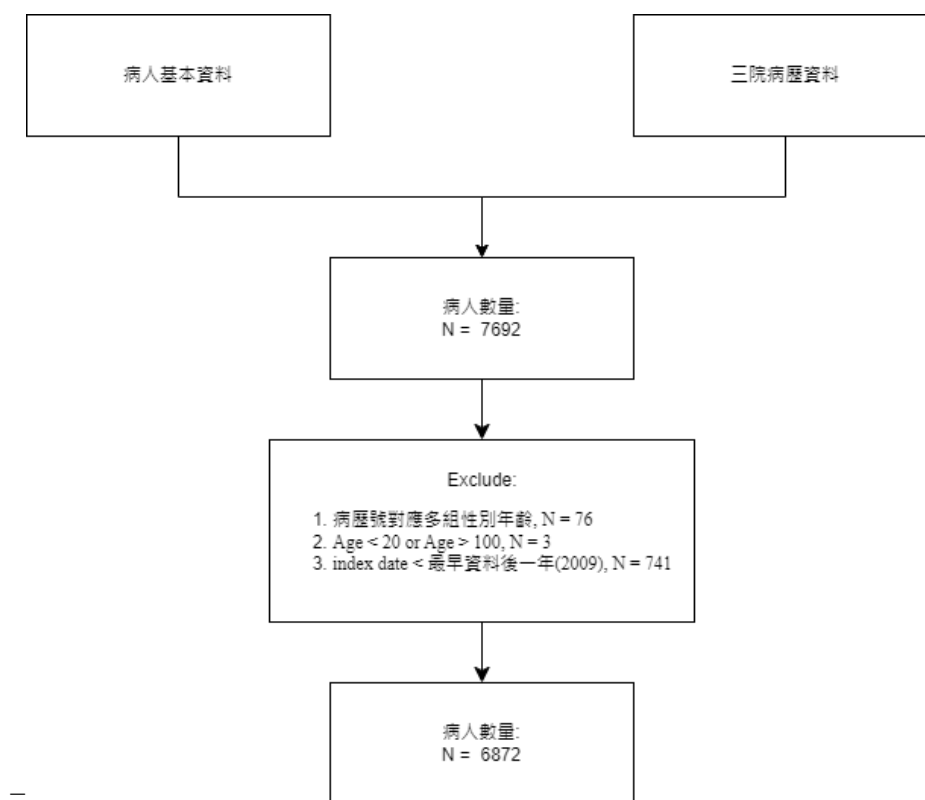
Symptoms involving head and neck 頭部和頸部的症狀	ICD9: 784  ICD10: G44.05, G44.09, G44.1, G44.3, G44.4, G44.52, G44.53, G44.59, G44.81, G44.82, G44.83, G44.84, G44.85, G44.89, R04.0, R04.1, R06.5, R06.7, R07.0, R19.6, R22.0, R22.1, R47.0, R47.1, R47.81, R47.89, R47.9, R48.0, R48.1, R48.2, R48.8, R48.9, R49, R51, R90.0	
Contact dermatitis and other eczema 皮膚疾病	ICD9: 692  ICD10: L23, L24.0, L24.1, L24.2, L24.3, L24.4, L24.5, L24.6, L24.7, L24.8, L24.9, L25, L30.0, L30.2, L30.8, L30.9, L55, L56, L57.1, L57.5, L57.8, L57.9, L58, L59	
Viral infection in conditions classified elsewhere and of unspecified site 病毒引起的感染	ICD9: 79  ICD10: B34.9, E07.81, E79.0, I45.81, N39.0, O28, P09, R03, R09.0, R09.2, R19.5, R29.2, R41.81, R41.89, R44.8, R44.9, R45.0, R45.3, R45.4, R45.87, R45.89, R46, R53.81, R54, R64, R68.13, R68.19, R68.82, R68.89, R69, R70, R71, R73.01, R73.02, R73.09, R73.9, R74, R75, R76, R77, R78, R79.0, R79.1, R79.81, R79.82, R79.89, R79.9, R80.0, R80.1, R80.3, R80.8, R80.9, R81, R82, R83, R84, R85, R86, R87, R88, R89, R90.8, R91.8, R92.0, R92.1, R92.2, R92.8, R93, R94, R97, R99	
Overweight, obesity and other hyperalimentation 超重、肥胖及其他過度營養狀態	ICD9: 278  ICD10: E65, E66.0, E66.1, E66.2, E66.8, E66.9, E67, E68	
Other and unspecified disorders of joint 未明確指定的關節疾病	ICD9: 719  ICD10: M12.2, M12.3, M12.4, M25.0, M25.1, M25.4, M25.50, M25.51, M25.52, M25.53, M25.55, M25.56, M25.57, M25.60, M25.61, M25.62, M25.63, M25.64, M25.65, M25.66,	

	M25.67, M25.8, M25.9, M79.643, M79.646, R26.2, R29.4, R29.898	
Acute bronchitis and bronchiolitis 呼吸道疾病	ICD9: 466 ICD10: J20.8, J20.9, J21	
Other disorders of soft tissues 其他軟組織的疾病	ICD9: 729 ICD10: G47.62, M35.6, M54.10, M54.18, M60.8, M60.9, M70.8, M70.9, M72.9, M79, R25.2, R29.898	
Nonspecific findings on examination of blood 血液檢查時發現的一些非特定 性的異常或發現	ICD9: 790 ICD10: B34.9, E07.81, E79.0, R70, R71, R73.01, R73.02, R73.09, R73.9, R74, R77, R78, R79.0, R79.1, R79.81, R79.82, R79.89, R79.9, R97.2	
Disorders of refraction and accommodation 屈光和調節的疾病	ICD9: 367 ICD10: H52	
Disorders of conjunctiva 眼球表面覆蓋的結膜的各種疾 病	ICD9: 372 ICD10: H10.0, H10.1, H10.2, H10.3, H10.4, H10.5, H10.81, H10.89, H10.9, H11	

### 3 資料處理流程:

#### 3.1 病歷資料歸人

##### 3.1.1 流程圖:



##### 3.1.2 三院病歷資料整理流程:

步驟	說明	患者數量
1	篩選就診紀錄的病例資料、議題相關疾病碼: (糖尿病、相關併發症、控制疾病) 病例	
2	篩選目標病患 (歸人) 操作定義: 一年內 3 次門診或 1 次住院疾病紀錄	N = 7692
3.	合併 1. 病人基本資料、2.目標病患及相關病例資料	
4	Exclude: 3. 是指最早資料 病例資料對應多組性別年齡 (N = 76) 年齡 < 20 或 年齡 > 100 (N = 3) index date < 2009(最早資料後一年) (N = 741)	N = 6872



Table1. 糖尿病患者基線特徵分布

		overall(N=6872)
AGE		
	Mean(SD)	68.23(12.23)
	Median(IQR)	68.35(17.64)
	(Min, Max)	(21.63, 99.25)
Index_year		
	2009	309(4.5%)
	2010	294(4.28%)
	2011	653(9.5%)
	2012	889(12.94%)
	2013	568(8.27%)
	2014	456(6.64%)
	2015	1399(20.36%)
	2016	1026(14.93%)
	2017	620(9.02%)
	2018	467(6.8%)
	2019	191(2.78%)
SEX_TYPE		
	1	3823(55.63%)
	0	3049(44.37%)
AGE_GROUP		
	20-30	17(0.25%)
	30-40	71(1.03%)
	40-50	394(5.73%)
	50-60	1294(18.83%)
	60-70	1974(28.73%)
	70-80	1843(26.82%)
	80-90	1120(16.3%)
	90-100	159(2.31%)

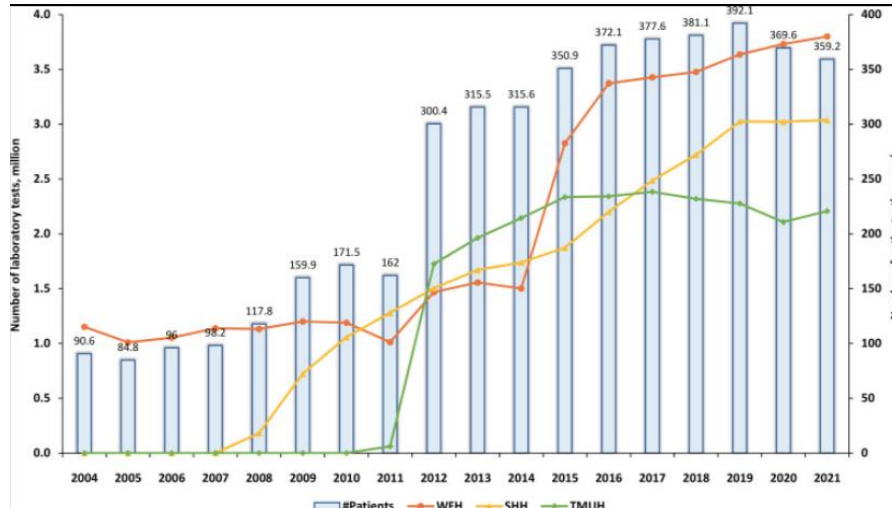
Hypertension_event		
	1	1143(16.63%)
	0	5729(83.37%)
PeripheralEnthe_event		
	1	95(1.38%)
	0	6777(98.62%)
UnknownCauses_event		
	1	7(0.1%)
	0	6865(99.9%)
LipoidMetabDis_event		
	1	992(14.44%)
	0	5880(85.56%)
AcuteURI_event		
	1	33(0.48%)
	0	6839(99.52%)
AbdPelvicSymptoms_event		
	1	135(1.96%)
	0	6737(98.04%)
Dermatophytosis_event		
	1	102(1.48%)
	0	6770(98.52%)
GenSymptoms_event		
	1	654(9.52%)
	0	6218(90.48%)
RespChestSymptoms_event		
	1	196(2.85%)
	0	6676(97.15%)
HeadNeckSymptoms_event		
	1	96(1.4%)
	0	6776(98.6%)

ContactDermEczema_event	1	103(1.5%)
	0	6769(98.5%)
ViralInfection_event	1	200(2.91%)
	0	6672(97.09%)
ObesityHyperal_event	1	13(0.19%)
	0	6859(99.81%)
JointDisorders_event	1	17(0.25%)
	0	6855(99.75%)
AcuteBronchitis_event	1	35(0.51%)
	0	6837(99.49%)
SoftTissueDis_event	1	191(2.78%)
	0	6681(97.22%)
BloodExamFindings_event	1	82(1.19%)
	0	6790(98.81%)
RefractionDis_event	1	9(0.13%)
	0	6863(99.87%)
ConjunctivaDis_event	1	142(2.07%)
	0	6730(97.93%)

### 3.1.3 討論:

3.1.3.1 資料問題: 從 Index year 可以看到三院的臨床資料糖尿病患者大多發生在 2015 和 2016, 是否之前分析也有發現相同的情況?

3.1.3.2 資料數從文獻中有看到資料數有隨年分增加的趨勢



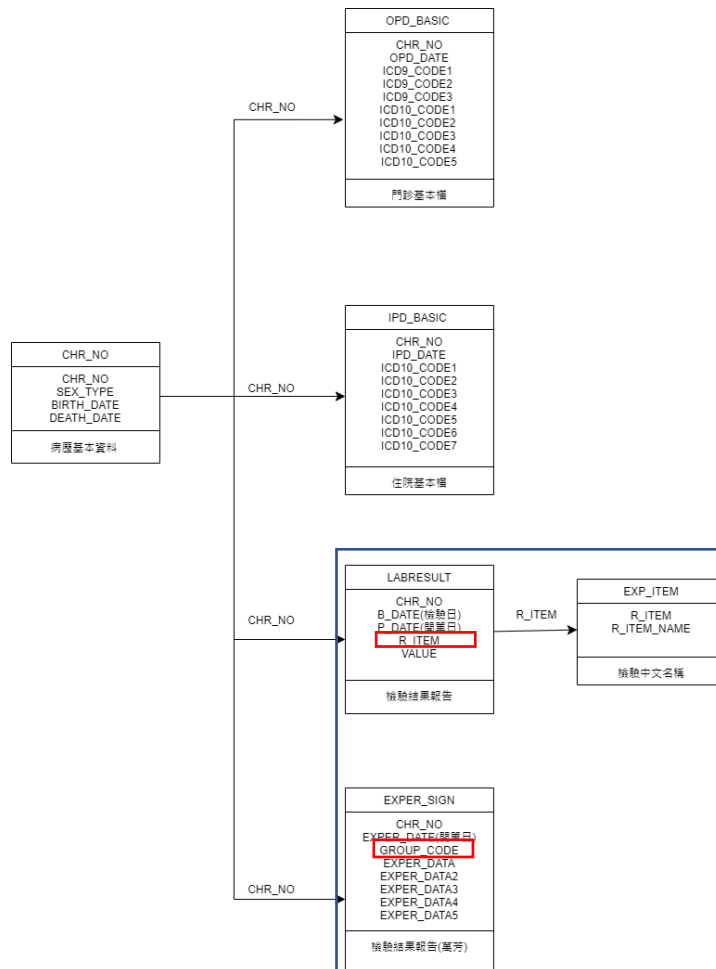
#### Reference:

Nguyen, P.-A., Hsu, M.-H., Chang, T.-H., Yang, H.-C., Huang, C.-W., Liao, C.-T., Lu, C. Y., & Hsu, J. C. (2024). Taipei Medical University Clinical Research Database: A Collaborative Hospital Ehr Database aligned with International Common Data Standards. *BMJ Health & Care Informatics*, 31(1). <https://doi.org/10.1136/bmjhci-2023-100890>

### 3.2 Lab 資料整理: 檢驗結果報告

#### 3.2.1 儲存方式: 萬芳與其他兩院分成兩個 LAB 檔

#### 3.2.2 三院臨床資料庫架構:

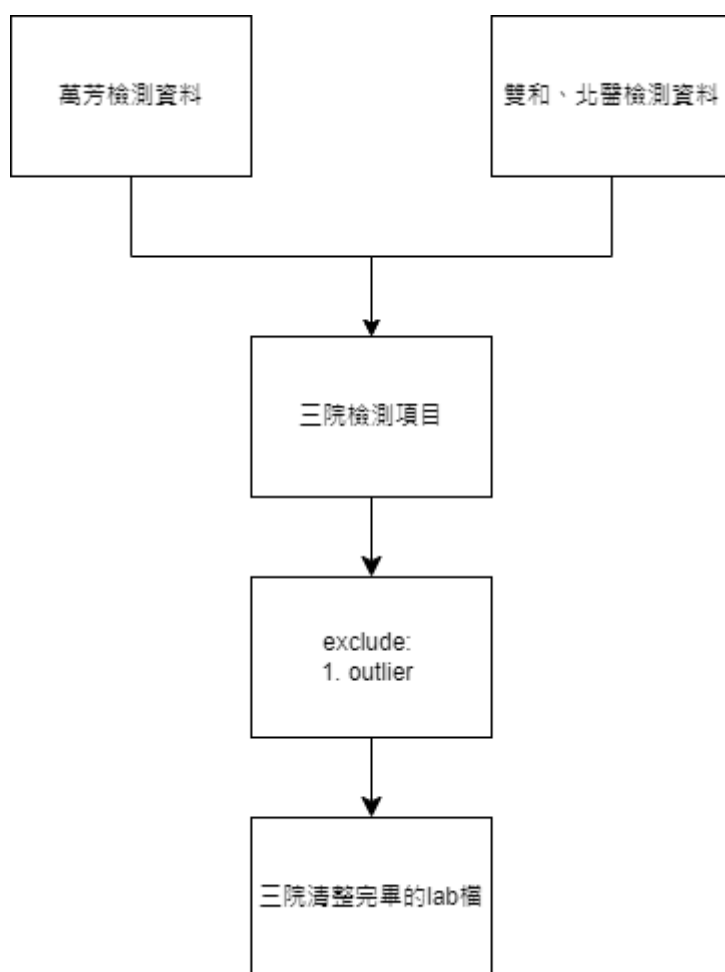


LAB 處理: 檢驗結果皆只有檢驗項目 ID, 需要找對應的檢驗名稱

#### 3.2.3 資料情況:

醫院	檢驗項目 ID	處理方式
萬芳: exper_sign_w	GROUP_CODE (健保碼)	從萬芳的檢驗資訊查詢系統找檢驗項目的健保碼
雙和、北醫: labresult_s(t)	R_ITEM	從 exp_item_s(t) 找出對應 R_ITEM_NAME

### 3.2.4 檢驗結果整理流程圖:



### 3.2.5 檢驗結果資料整理流程:

步驟	說明
1	將兩院與萬芳 lab 資料做合併
2	保留 ID、檢驗日、檢驗項目、檢驗值並重新命名欄位
3.	找尋所需的檢驗項目
4	將單位分開儲存同時排除無法辨識的資料, ex: <, >, NA
6	資料問題: 萬芳部分檢測項目無單位 解決方法: 僅保留 quantile (0.01, 0.99) 的資料

Table2. 三院檢驗項目數值分佈

Test	min	1%	5%	q1	median	q3	95%	99%	max	q1-1.5IQR	q3+1.5IQR
HbA1c*	2	4.9	5.3	5.9	6.6	7.5	9.9	12.2	19.1	3.5	9.9
Creatinine*	0	0.4	0.55	0.81	1.19	4.95	91.7	170.5	6320	-5.4	11.16
ALBUMIN	0.3	2	2.5	3.3	3.8	4.1	4.6	4.9	5.6	2.1	5.3
Uric	0.6	2.6	3.6	5	6.1	7.4	9.4	11.5	4050	1.4	11
HDL	1	23	29	38	46	55	74	91	153	12.5	80.5
LDL	5	42	56	78	98	121	161	196	466	13.5	185.5

### 3.3 篩選要分析的糖尿病患者：

3.3.1 目的：避免在計算變異程度時受時間影響

3.3.2 條件：在定義的 Index\_date 後的一年內，定期進行指定檢驗項目的患者

3.3.3 篩選方法：從 Index\_date 開始，觀察該日期前後 45 天內是否有檢測紀錄，有的話記為 1，沒有則記為 0。接著每隔 90 天進行一次相同的觀察，直到觀察到第 360 天，確認患者整年是否有進行定期檢測。最終，所有觀察期間內都有檢測紀錄的患者作為分析的對象。

3.3.4 示意圖：

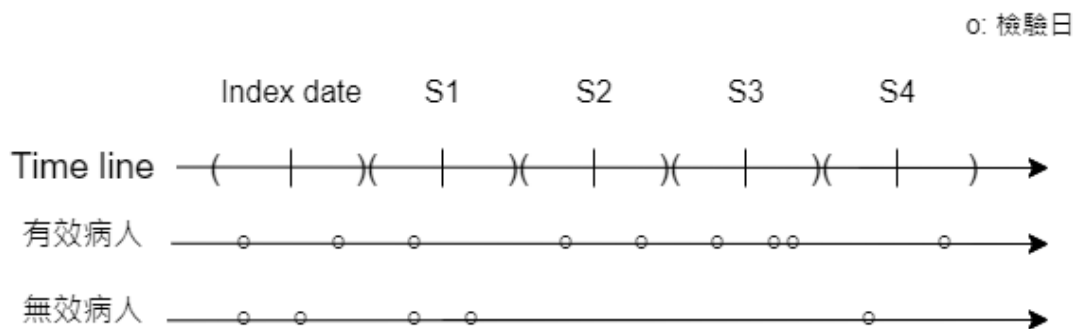


Table3. 糖尿病目標病患各季度 HbA1c 中位數及檢驗頻率

N = 1066		S0	S1	S2	S3	S4
Median	Mean(sd)	7.75(1.52)	7.24(1.21)	7.21(1.22)	7.2(1.19)	7.19(1.19)
	Median(IQR)	7.38(2)	7(1.4)	6.9(1.34)	6.9(1.4)	6.9(1.3)
	(Min, Max)	(5,12.2)	(5,12.2)	(5,12.1)	(5,12.1)	(5.1,12.2)
n	Mean(sd)	1.32(0.54)	1.18(0.41)	1.12(0.35)	1.09(0.3)	1.08(0.28)
	Median(IQR)	1(1)	1(0)	1(0)	1(0)	1(0)
	(Min, Max)	(1,4)	(1,4)	(1,3)	(1,3)	(1,3)

Table4. 糖尿病目標病患各季度 ALBUMIN 中位數及檢驗頻率

N = 174		S0	S1	S2	S3	S4
Median	Mean(sd)	3.75(0.53)	3.85(0.48)	3.88(0.5)	3.84(0.52)	3.85(0.49)
	Median(IQR)	3.85(0.74)	3.9(0.6)	3.9(0.6)	3.9(0.6)	3.9(0.65)
	(Min, Max)	(2.3,4.8)	(2.5,4.8)	(2,4.9)	(2.1,4.9)	(2.25,4.8)
n	Mean(sd)	2.24(1.47)	2.27(1.25)	2.23(1.24)	2.33(1.48)	2.25(1.33)
	Median(IQR)	2(2)	2(2)	2(2)	2(2)	2(2)
	(Min, Max)	(1,11)	(1,9)	(1,11)	(1,12)	(1,8)

Table5. 糖尿病目標病患各季度 Uric 中位數及檢驗頻率

N = 238		S0	S1	S2	S3	S4
Median	Mean(sd)	6.62(1.76)	6.51(1.63)	6.47(1.68)	6.5(1.7)	6.36(1.59)
	Median(IQR)	6.55(2.45)	6.5(2.25)	6.5(2.44)	6.3(2.55)	6.18(2.45)
	(Min, Max)	(2.8,11.4)	(3,11.4)	(3.1,11.05)	(3.4,11)	(3.1,11)
n	Mean(sd)	1.52(0.74)	1.51(0.85)	1.51(0.85)	1.44(0.79)	1.38(0.8)
	Median(IQR)	1(1)	1(1)	1(1)	1(1)	1(0)
	(Min, Max)	(1,4)	(1,5)	(1,5)	(1,5)	(1,6)

Table6. 糖尿病目標病患各季度 HDL 中位數及檢驗頻率

N = 103		S0	S1	S2	S3	S4
Median	Mean(sd)	42.36(12.29)	42.17(10.37)	42.58(11.02)	43.63(12.3)	43.74(12.55)
	Median(IQR)	39.5(13)	39.5(12)	40(13.5)	40(15.5)	40(15)
	(Min, Max)	(26,85)	(24,75)	(24,75)	(26,87)	(25,86)
n	Mean(sd)	1.23(0.51)	1.08(0.27)	1.05(0.22)	1.06(0.24)	1.02(0.14)
	Median(IQR)	1(0)	1(0)	1(0)	1(0)	1(0)
	(Min, Max)	(1,3)	(1,2)	(1,2)	(1,2)	(1,2)



Table7. 糖尿病目標病患各季度 LDL 中位數及檢驗頻率

N = 479		S0	S1	S2	S3	S4
Median	Mean(sd)	104.87(30.47)	99.56(30.93)	98.88(29.98)	97.07(29.67)	96.78(28.27)
	Median(IQR)	104.5(42)	95(44.75)	97(42.5)	93(40.25)	93(38)
	(Min, Max)	(43,196)	(42,195)	(45,190)	(43,196)	(43,178)
n	Mean(sd)	1.33(0.56)	1.17(0.38)	1.11(0.34)	1.11(0.32)	1.08(0.3)
	Median(IQR)	1(1)	1(0)	1(0)	1(0)	1(0)
	(Min, Max)	(1,4)	(1,3)	(1,3)	(1,3)	(1,4)

Table8. 糖尿病目標病患各季度 Creatinine 中位數及檢驗頻率

N = 1072		S0	S1	S2	S3	S4
Median	Mean(sd)	6.47(14.57)	7.85(15.69)	9.68(18.53)	8.74(16.64)	11.23(19.21)
	Median(IQR)	1.26(2.24)	1.33(4.42)	1.41(6.82)	1.4(6.41)	1.6(9.54)
	(Min, Max)	(0.4,150.2)	(0.4,159.4)	(0.4,156.8)	(0.4,156.4)	(0.4,109.7)
n	Mean(sd)	3.28(3.31)	2.67(3.02)	2.64(3.11)	2.81(4.07)	2.7(4.1)
	Median(IQR)	2(3)	2(2)	2(2)	2(2)	2(2)
	(Min, Max)	(1,36)	(1,38)	(1,39)	(1,66)	(1,70)

### 3.4 併發症整理流程:

#### 3.4.1 Exclude :

3.4.1.1 index date 前有發生 Outcome

3.4.1.2 index date 後一年內發生 Outcome

Table9: 糖尿病患者各併發症情況

test	outcome	# of event	sum of follow up	N	IR%
HbA1c	Eye complications	64	5676.915	989	1.127
	Cardiovascular disease	247	3796.921	744	6.505
	Cerebrovascular disease	136	5495.063	907	2.475
	Peripheral vascular disease	10	6482.808	1062	0.154

	Nephropathy	118	5628.518	975	2.096
	Diabetic neuropathy	71	5693.493	971	1.247
ALBUMIN	Eye complications	9	745.011	151	1.208
	Cardiovascular disease	36	404.8822	93	8.891
	Cerebrovascular disease	22	783.2247	150	2.809
	Peripheral vascular disease	4	926.5945	173	0.432
	Nephropathy	16	158.6192	43	10.087
	Diabetic neuropathy	8	857.8575	161	0.933
Uric acid	Eye complications	5	1083.356	215	0.462
	Cardiovascular disease	56	488.7918	122	11.457
	Cerebrovascular disease	25	1077.756	207	2.32
	Peripheral vascular disease	2	1249.326	236	0.16
	Nephropathy	21	567.7041	124	3.699
	Diabetic neuropathy	11	1152.784	221	0.954
HDL	Eye complications	2	482.2356	98	0.415
	Cardiovascular disease	12	225.4932	49	5.322
	Cerebrovascular disease	12	435.3041	90	2.757
	Peripheral vascular disease	0	514.189	102	0
	Nephropathy	6	402.4219	82	1.491
	Diabetic neuropathy	4	461.3562	94	0.867
LDL	Eye complications	18	2326.603	447	0.774
	Cardiovascular disease	105	1527.485	326	6.874
	Cerebrovascular disease	49	2158.455	389	2.27
	Peripheral vascular disease	2	2611.321	478	0.077
	Nephropathy	38	2306.959	434	1.647
	Diabetic neuropathy	23	2374.389	447	0.969
Creatinine	Eye complications	44	5198.627	988	0.846
	Cardiovascular disease	203	3133.041	657	6.479
	Cerebrovascular disease	130	4893.118	887	2.657
	Peripheral vascular disease	9	5867.318	1059	0.153
	Nephropathy	131	3924.871	794	3.338
	Diabetic neuropathy	53	5177.622	967	1.024

資料整理完畢

#### 4 變數處理:

4.1 控制變數: SEX\_TYPE, Index year, AGE\_GROUP, baseline mean, 共病是否發生

4.2 變數解釋:

變數名稱	描述
baseline mean	各季檢測項目的平均值
共病是否發生	Essential hypertension
	Peripheral enthesopathies and allied syndromes
	Other ill-defined and unknown causes of morbidity and mortality
	Disorders of lipid metabolism
	Acute upper respiratory infections of multiple or unspecified sites
	Other symptoms involving abdomen and pelvis
	Dermatophytosis
	General symptoms
	Symptoms involving respiratory system and other chest symptoms
	Symptoms involving head and neck
	Contact dermatitis and other eczema
	Viral infection in conditions classified elsewhere and of unspecified site
	Overweight, obesity and other hyperalimentation
	Other and unspecified disorders of joint
	Acute bronchitis and bronchiolitis
	Other disorders of soft tissues
	Nonspecific findings on examination of blood
	Disorders of refraction and accommodation

#### 4.3 其他變數組合: 不同檢驗項目的變異程度指標:

##### 4.3.1 計算方式:

4.3.1.1 對各病患計算每一季的檢測項目平均值 (baseline, s1, s2, s3, s4)

4.3.1.2 針對這些平均值, 計算標準差、變異係數以及均方根

##### 4.3.2 標準差(SD)計算方式:

$$\sigma = \sqrt{\frac{1}{N} \sum_{i=1}^N (x_i - \mu)^2}$$

##### 4.3.3 變異係數(CV) 計算方式:

$$CV = \frac{\sigma}{\mu} \times 100\%$$

##### 4.3.4 均方根(RMS) 計算方式:

$$RMS = \sqrt{\frac{1}{N} \sum_{i=1}^N x_i^2}$$

#### 4.4 反應變數: 病患追蹤日期、是否有發生併發症

### 5 分析結果: (以 HbA1c 為主, 以及其他變異程度有顯著檢驗項目)

#### 5.1 模型: cox model

#### 5.2 模型指標: HR (Hazard ratios), 95% CI, P-value

#### 5.3 P-value: ∴ p < 0.1, \*: p < 0.05, \*\*: p < 0.01, \*\*\*: p < 0.001

Table5: Cox model 分析結果

Outcome: Eye complications、Test item: HbA1c (N = 989)

Models	Variables	HR	95%CI	P-value
Model1	Baseline	1.188	1.012, 1.396	*
Model2	Baseline	1.085	0.857, 1.375	
	SD	1.448	0.719, 2.916	
Model3	Baseline	1.142	0.922, 1.413	
	CV	4.408	0.026, 738.134	
Model4	Baseline	0.915	0.703, 1.19	
	RMS	1.604	1.138, 2.26	**

Table6: Cox model 分析結果

Outcome: Cardiovascular disease 、 Test item: HbA1c (N = 744)

Models	Variables	HR	95%CI	P-value
Model1	Baseline	0.981	0.9, 1.07	
Model2	Baseline	0.997	0.884, 1.123	
	SD	0.932	0.647, 1.342	
Model3	Baseline	1	0.898, 1.115	
	CV	0.443	0.03, 6.555	
Model4	Baseline	0.943	0.822, 1.081	
	RMS	1.074	0.889, 1.299	

Table7: Cox model 分析結果

Outcome: Cerebrovascular disease 、 Test item: HbA1c (N = 907)

Models	Variables	HR	95%CI	P-value
Model1	Baseline	1.011	0.904, 1.131	
Model2	Baseline	1.078	0.924, 1.256	
	SD	0.742	0.452, 1.216	
Model3	Baseline	1.061	0.925, 1.218	
	CV	0.117	0.003, 4.342	
Model4	Baseline	0.935	0.782, 1.118	
	RMS	1.147	0.903, 1.456	

Table8: Cox model 分析結果

Outcome: Peripheral vascular disease 、Test item: HbA1c (N = 1062)

Models	Variables	HR	95%CI	P-value
Model1	Baseline	0.912	0.589, 1.414	
Model2	Baseline	0.696	0.468, 1.036	.
	SD	3.342	1.211, 9.219	*
Model3	Baseline	0.716	0.481, 1.068	
	CV	9836.151	4.079, 23720382.232	*
Model4	Baseline	0.928	0.6, 1.437	
	RMS	0.966	0.501, 1.86	

Table9: Cox model 分析結果

Outcome: Nephropathy 、Test item: HbA1c (N = 975)

Models	Variables	HR	95%CI	P-value
Model1	Baseline	1.094	0.969, 1.235	
Model2	Baseline	1.084	0.908, 1.294	
	SD	1.039	0.607, 1.778	
Model3	Baseline	1.098	0.936, 1.287	
	CV	0.867	0.017, 44.407	
Model4	Baseline	1.013	0.837, 1.225	
	RMS	1.153	0.885, 1.501	

Table10: Cox model 分析結果

Outcome: Diabetic neuropathy 、Test item: HbA1c (N = 971)

Models	Variables	HR	95%CI	P-value
Model1	Baseline	0.941	0.797, 1.112	
Model2	Baseline	0.997	0.791, 1.258	
	SD	0.769	0.37, 1.6	
Model3	Baseline	1.002	0.812, 1.235	
	CV	0.074	0, 15.706	
Model4	Baseline	0.74	0.569, 0.961	*
	RMS	1.533	1.104, 2.131	*

Table11: Cox model 分析結果

Outcome: Nephropathy 、Test item: HDL (N = 82)

Models	Variables	HR	95%CI	P-value
Model1	Baseline	1.193	1.109,1.283	***
Model2	Baseline	1.309	1.218,1.407	***
	SD	2.555	2.108,3.098	***
Model3	Baseline	1.513	1.402,1.633	***
	CV	Inf	Inf ,Inf	***
Model4	Baseline	Inf	0.652,Inf	.
	RMS	0	0,8.621	.

Table12: Cox model 分析結果

Outcome: Diabetic neuropathy 、Test item: uric acid (N = 221)				
Models	Variables	HR	95%CI	P-value
Model1	Baseline	0.867	0.586,1.284	
Model2	Baseline	0.782	0.541,1.13	
	SD	2.289	0.873,6.005	.
Model3	Baseline	0.828	0.573,1.195	
	CV	150.878	0.255,89293.263	
Model4	Baseline	0.826	0.557,1.225	
	RMS	1.079	0.672,1.732	

Table13: Cox model 分析結果

Outcome: Nephropathy 、Test item: Creatinine (N = 794)				
Models	Variables	HR	95%CI	P-value
Model1	Baseline	1.02	1.011, 1.029	***
Model2	Baseline	1.016	1.005, 1.026	**
	SD	1.013	0.998, 1.029	.
Model3	Baseline	1.02	1.011, 1.029	***
	CV	1.033	0.813, 1.313	
Model4	Baseline	1.003	0.991, 1.015	
	RMS	1.028	1.016, 1.041	***



## 結論:

- 1 預期結果: 變異程度大, 理論上風險上升  $HR > 1$  且顯著, 才可以說考慮這個生理數值是有意義的。
- 2 模型結果顯示 HbA1c 的變異程度對於 Eye complications、Nephropathy、Diabetic neuropathy 等併發症為重要因子, 符合其他文獻結果, 代表這份資料是具準確性。
- 3 模型結果顯示 HDL 以及 Creatinine 的變異程度對於 Nephropathy 併發症為重要因子, 可以做後續延伸。
- 4 模型結果顯示 Uric acid 的變異程度對 Diabetic neuropathy 併發症為重要因子, 可以做後續延伸。
- 5 資料不顯著的原因: 樣本數過小、發病率太低、baseline 每季只算一個 mean 資訊丟失部分資訊
- 6 後續可以做的研究方向:
  - 6.1 探索加入其他可能的變異性指標, 如 HVS
  - 6.2 Outlier 定義
  - 6.3 各季只考慮 mean 會丟失大部分的時間資訊在算平均時可以考慮 weighted average
  - 6.4 找出與目標疾病不常做的檢驗項目
  - 6.5 目前已驗證的數據準確性, 進行與中風相關的分析

討論細項:

1 架構是否需要調整

2 **Outlier** 的定義:

2.1 資料問題:

2.1.1 (北醫、雙和)以及萬芳有些資料單位不一致

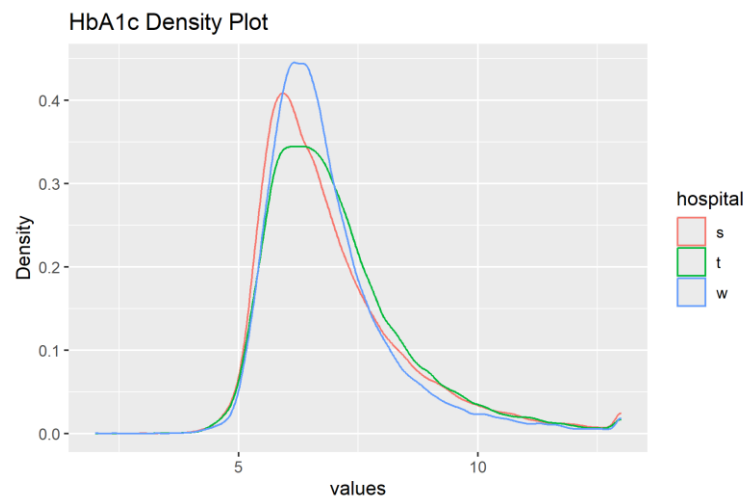
2.1.2 各檢測項目合理的數值之前是如何訂的

2.2 三院檢驗項目數值分佈

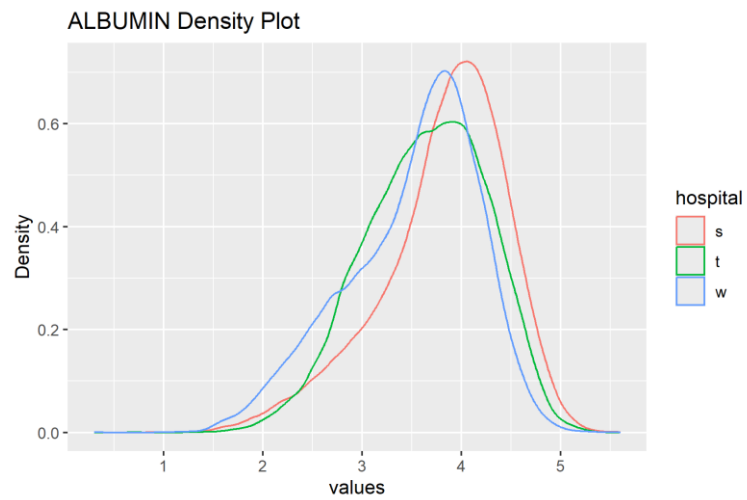
Test	1%	5%	q1	median	q3	95%	99%	q1-1.5IQR	q3-1.5IQR	max	min
HbA1c	4.9	5.3	5.9	6.6	7.5	9.9	12.2	3.5	9.9	19.1	2
ALBUMIN	2	2.5	3.3	3.8	4.1	4.6	4.9	2.1	5.3	5.6	0.3
Uric	2.6	3.6	5	6.1	7.4	9.4	11.5	1.4	11	4050	0.6
HDL	23	29	38	46	55	74	91	12.5	80.5	153	1
LDL	42	56	78	98	121	161	196	13.5	185.5	466	5
Creatinine	0.4	0.55	0.81	1.19	4.95	91.7	170.5	-5.4	11.16	6320	0

2.3 檢驗項目的 density plot (分三院、有針對 outlier 進行壓縮):

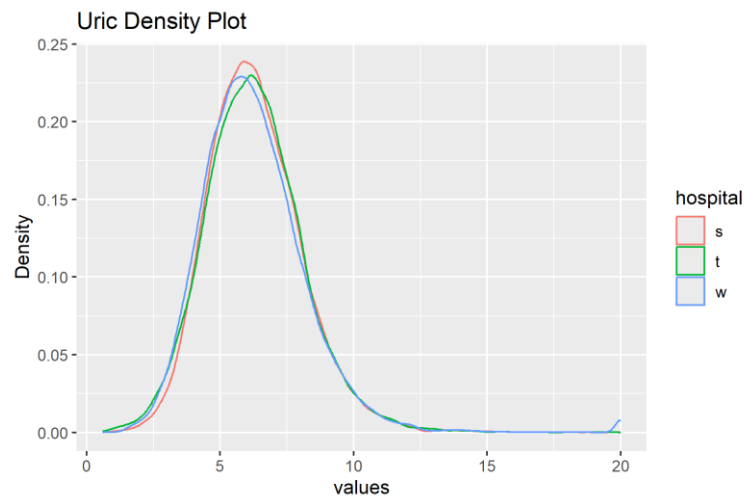
2.3.1 HbA1c Test ID: "014701", "F09006B", upper = 13



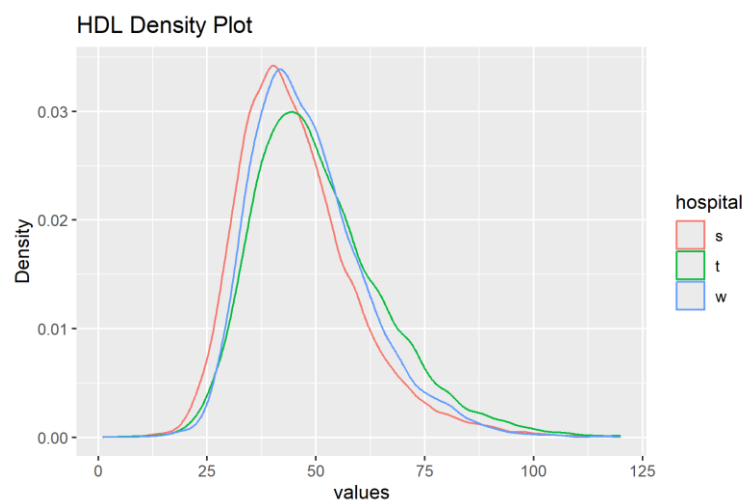
2.3.2 ALBUMIN Test ID: "010301", "11D101", "F09038C", upper = 30



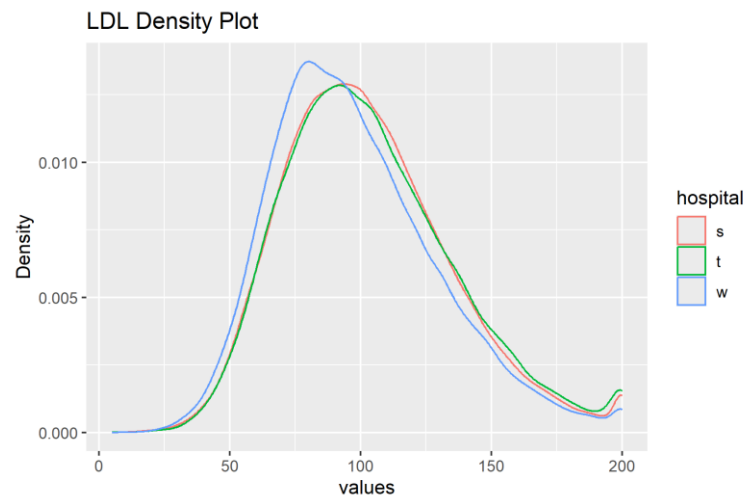
2.3.3 Uric Acid Test ID: "011001", "F09013C" upper = 20



2.3.4 HDL Test ID: "F09043A", "011301", upper = 120

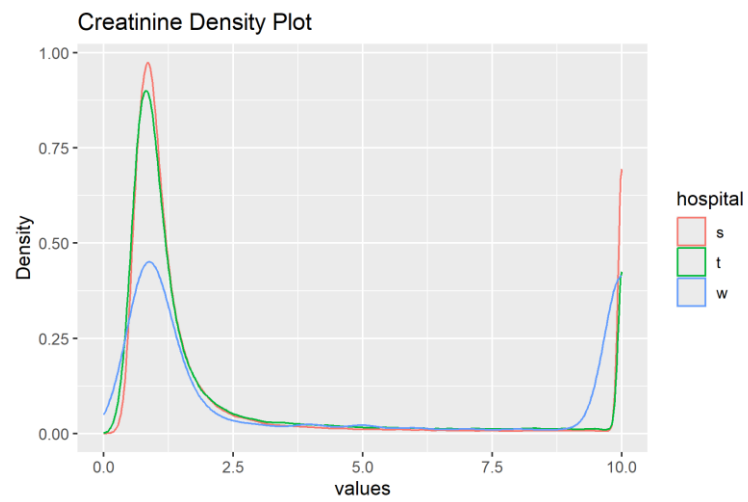


2.3.5 LDL Test ID: "F09044A", "011401", upper = 200



2.3.6 Creatinine Test ID: "F09015C", "11D101", "11A201", "010801", "011C01"

Upper = 10



## 心血管 (cardiovascular disease)相關主題:

自變量：生理數值檢測項目的變異性（皆有人做過）

- 血壓變異性（如日間和夜間的血壓波動）
- 血糖變異性（如血糖的日間波動）
- 血脂變異性（如 LDL 和 HDL 的波動）
- Heart rate

因變量：CVD outcome

- 運動功能障礙: Motor Function Impairment
- 語言障礙: Speech Impairment
- 認知障礙: Cognitive Impairment
- 情緒和心理問題: Emotional and Psychological Problems
- 吞嚥困難: Dysphagia
- 褥瘡: Pressure Ulcers

控制變量：年齡、性別、控制疾病、生活方式因素（如吸煙、飲酒）、中風類型和嚴重程度等。

- 高脂血症（Hyperlipidemia）
- 冠心病（Coronary Artery Disease）
- 慢性腎病（Chronic Kidney Disease）
- 慢性阻塞性肺病（Chronic Obstructive Pulmonary Disease, COPD）
- 心房顫動（Atrial Fibrillation）
- 周邊動脈疾病（Peripheral Artery Disease）
- 肥胖（Obesity）
- 代謝綜合徵（Metabolic Syndrome）
- 睡眠呼吸暫停綜合徵（Sleep Apnea Syndrome）
- 甲狀腺疾病（Thyroid Disorders）
- 腦外傷史（History of Traumatic Brain Injury）
- 抑鬱症（Depression）
- 焦慮症（Anxiety Disorders）
- 酒精使用障礙（Alcohol Use Disorder）
- 藥物濫用（Substance Abuse）
- 缺乏運動（Physical Inactivity）
- 不良飲食習慣（Unhealthy Dietary Habits）

- 家族中風史（Family History of Stroke）
- 高血壓
- 糖尿病