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

1. 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. 參考論文: Predictions of diabetes complications and mortality using hba1c variability: a 10‑year observational cohort study
2. Data preparation:
   1. 資料來源: 三院臨床資料庫
   2. 目標病患: 糖尿病患者
   3. 資料區間 : 2008-2019
   4. 檢樣項目: HbA1c, Creatinine, ALBUMIN, Uric Acid, HDL, LDL
   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 lipoid 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 |

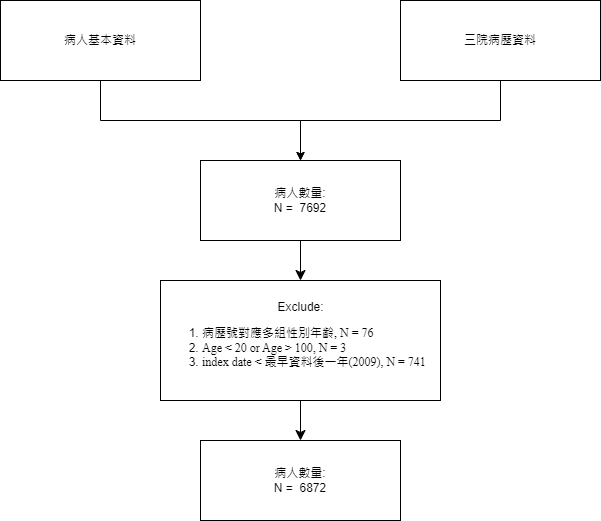
* 1. Index Date定義: 一年內有3次門診紀錄或1 次住院紀錄為新患的糖尿病患者符合條件下的首次看診日
  2. ICD CODE:
     1. 糖尿病:
        1. ICD9: 250, 251.8, 357.2, 362.01, 362.02, 366.41, 583.81
        2. ICD10: E08, E09, E10, E11, E12
     2. 併發症:

|  |  |  |
| --- | --- | --- |
| 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 |
| Cerebrovascular disease  腦血管疾病 | ICD9: 435.9、434.91、432.9、437.1  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 |
| Peripheral vascular disease  周邊動脈疾病 | ICD9: 440.2  ICD10: I70.2, I70.92, I75.01, I75.02 |
| Nephropathy  腎臟病 | ICD9: 583、585、V451  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 |
| Diabetic neuropathy  神經病變 | ICD9: 357.2、337.1、353  ICD10: E08.42, E09.42, E10.40, E10.42, E11.40, E11.42, E13.42, G54, G55, G99.0 |

* + 1. 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 lipoid 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 |

1. 資料處理流程:
   1. 病歷資料歸人
      1. 流程圖:



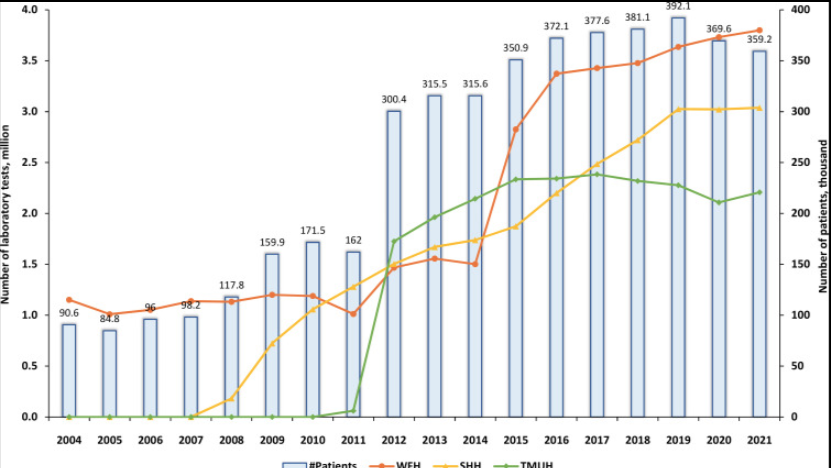
* + 1. 三院病歷資料整理流程:

|  |  |  |
| --- | --- | --- |
| 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

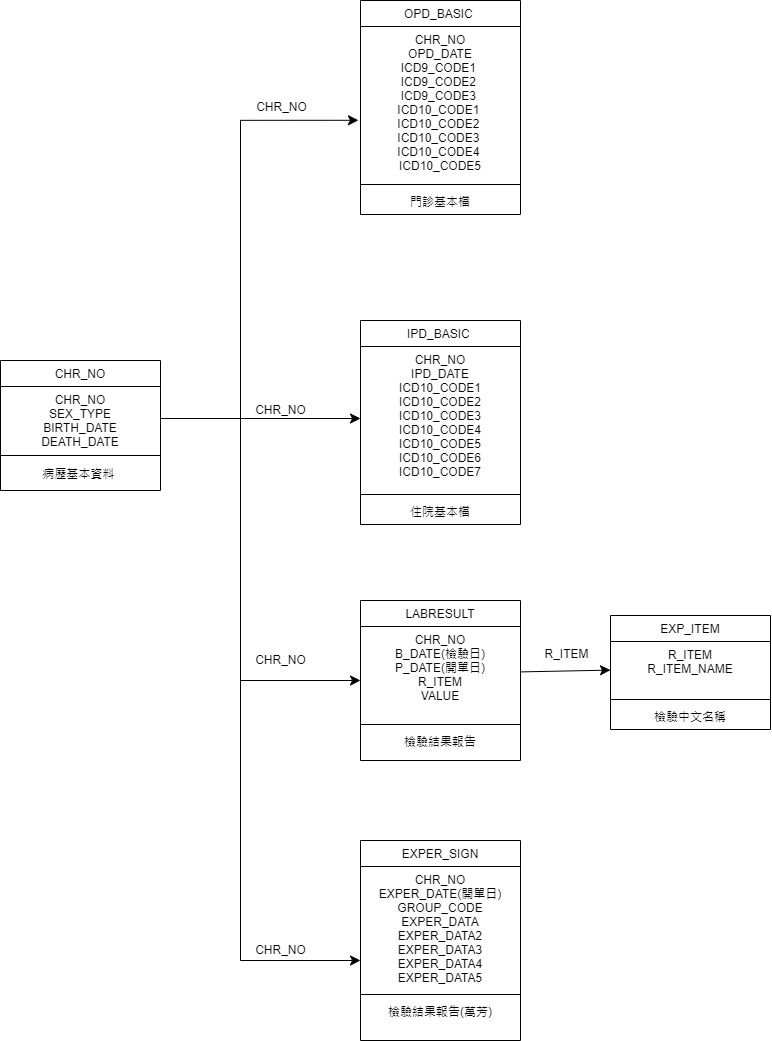
|  |  |  |
| --- | --- | --- |
|  | | overall(N=6872) |
| AGE | | |
|  | Mean(SD) | 68.23(12.23) |
| Median(IQR) | 68.35(17.64) |
| (Min, Max) | (21.63, 99.25) |
| Index\_year | | |
|  | 2009 | 309(4.5%) |
| 2010 | 294(4.28%) |
| 2011 | 653(9.5%) |
| 2012 | 889(12.94%) |
| 2013 | 568(8.27%) |
| 2014 | 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%) |

* + 1. 討論:
       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?
       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 &amp; Care Informatics*, *31*(1). https://doi.org/10.1136/bmjhci-2023-100890

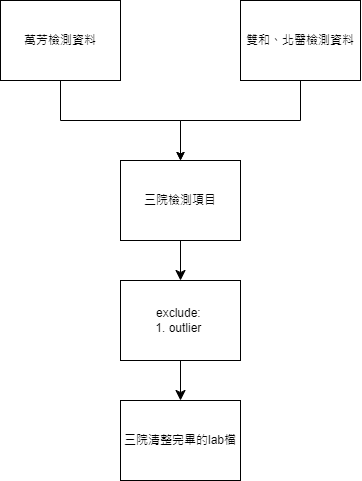
* 1. Lab 資料整理: 檢驗結果報告
     1. 儲存方式: 萬芳與其他兩院分成兩個LAB檔
     2. 三院臨床資料庫架構: 

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

* + 1. 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 |

* + 1. 檢驗結果整理流程圖:



* + 1. 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 |

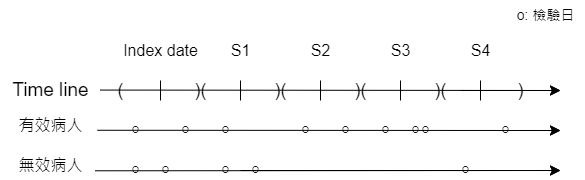
* 1. 篩選要分析的糖尿病患者：
     1. 目的：避免在計算變異程度時受時間影響
     2. 條件: 在定義的Index\_date後的一年內，定期進行指定檢驗項目的患者
     3. 篩選方法：從Index\_date開始，觀察該日期前後45天內是否有檢測紀錄，有的話記為1，沒有則記為0。接著每隔90天進行一次相同的觀察，直到觀察到第360天，確認患者整年是否有進行定期檢測。最終，所有觀察期間內都有檢測紀錄的患者作為分析的對象。
     4. 示意圖:

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 acid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) |

* 1. 併發症整理流程:
     1. Exclude：
        1. index date 前有發生Outcome
        2. index date 後一年內發生Outcome

Table9: 糖尿病患者各併發症情況

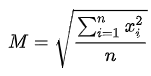
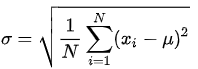
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| test | outcome | # of event | sum of follow up | N | IR% |
| HbA1c | Eye complications | 64 | 5676.915 | 989 | 1.127 |
| Cardiovascular disease | 247 | 3796.921 | 744 | 6.505 |
| Cerebrovascular disease | 136 | 5495.063 | 907 | 2.475 |
| Peripheral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

1. 變數處理:
   1. 控制變數: SEX\_TYPE, Index year, AGE\_GROUP, baseline mean, 共病是否發生
   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 lipoid 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 |

* 1. 其他變數組合: 不同檢驗項目的變異程度指標:
     1. 計算方式:
        1. 對各病患計算每一季的檢測項目平均值（baseline, s1, s2, s3, s4）
        2. 針對這些平均值，計算標準差、變異係數以及均方根
     2. 標準差(SD) 計算方式:



* + 1. 變異係數(CV) 計算方式:
    2. 均方根(RMS) 計算方式:
  1. 反應變數: 病患追蹤日期、是否有發生併發症

1. 分析結果: (以HbA1c為主, 以及其他變異程度有顯著檢驗項目)
   1. 模型: cox model
   2. 模型指標: HR (Hazard ratios), 95% CI, P-value
   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:

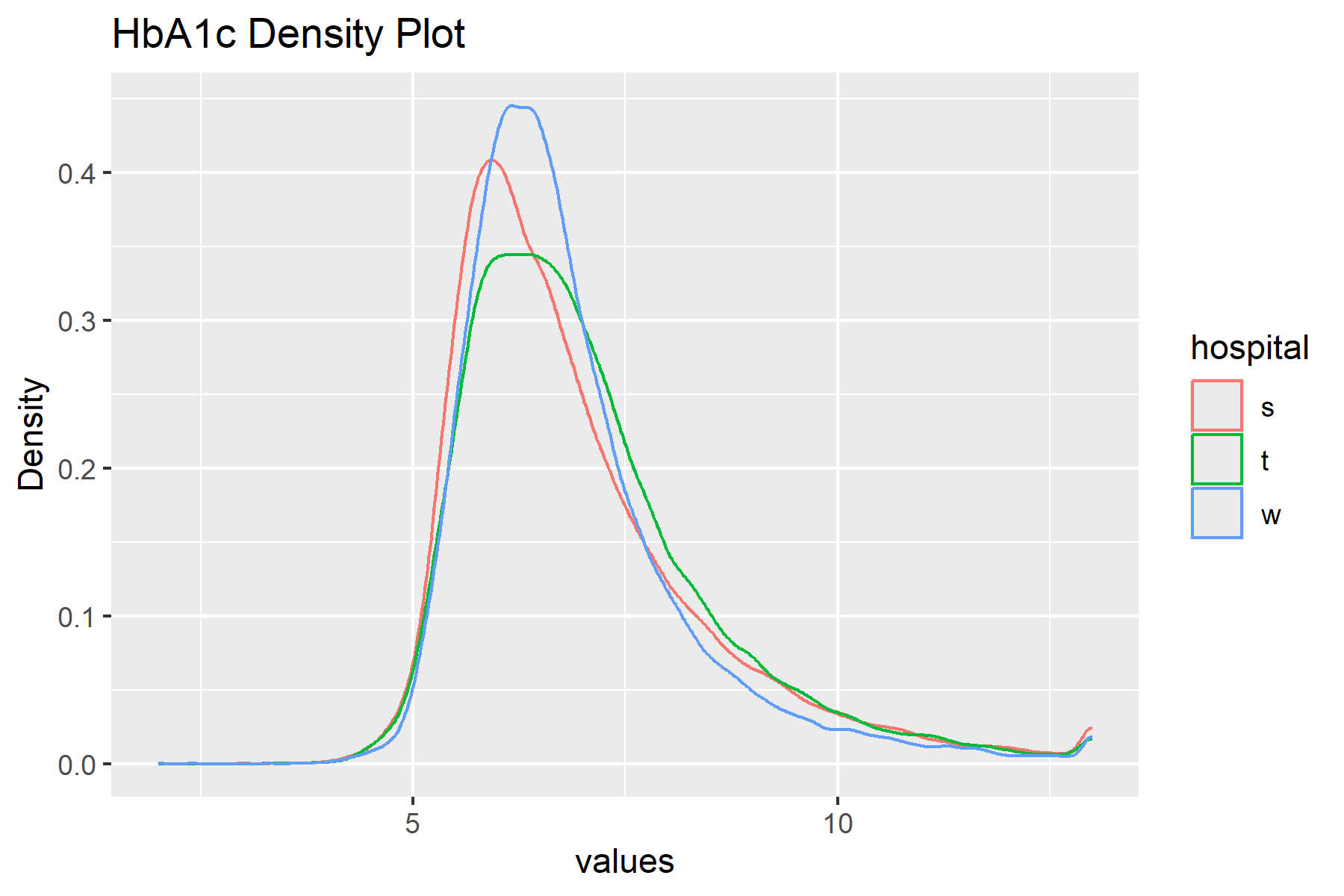
1. 預期結果: 變異程度大, 理論上風險上升HR > 1且顯著, 才可以說考慮這個生理數值是有意義的。
2. 模型結果顯示HbA1c的的變異程度對於Eye complications、 Nephropathy、 Diabetic neuropathy等併發症為重要因子, 符合其他文獻結果, 代表這份資料是具準確性。
3. 模型結果顯示HDL以及Creatinine的的變異程度對於Nephropathy併發症為重要因子, 可以做後續延伸。
4. 模型結果顯示Uric acid的變異程度對Diabetic neuropathy併發症為重要因子, 可以做後續延伸。
5. 資料不顯著的原因: 樣本數過小、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:
   1. 探索加入其他可能的變異性指標，如HVS
   2. Outlier定義
   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
   4. 找出與目標疾病不常做的檢驗項目
   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:

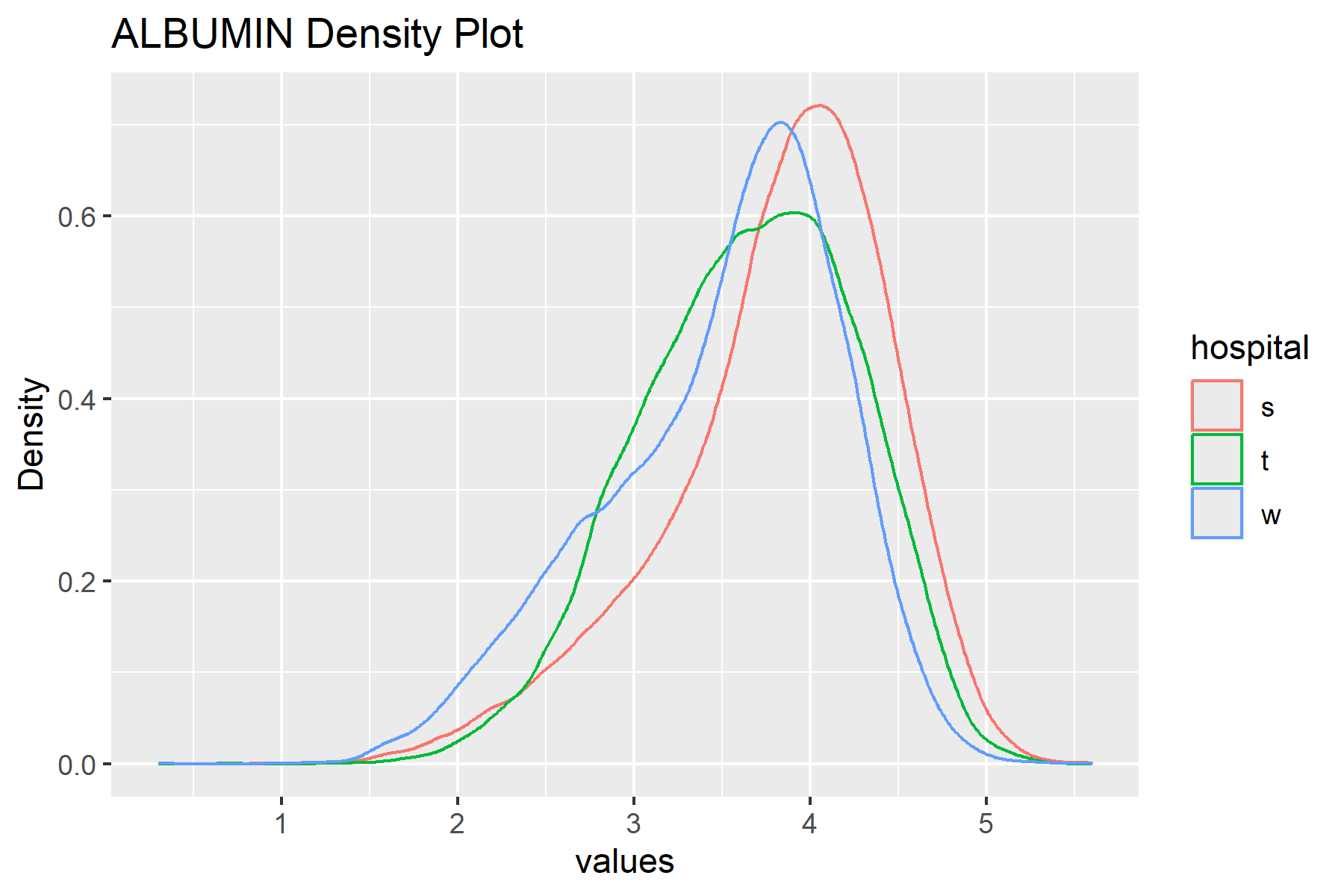
1. 架構是否需要調整
2. Outlier 的定義:
   1. 資料問題:
      1. (北醫、雙和)以及萬芳有些資料單位不一致
      2. 各檢測項目合理的數值之前是如何訂的
   2. 三院檢驗項目數值分佈

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 |

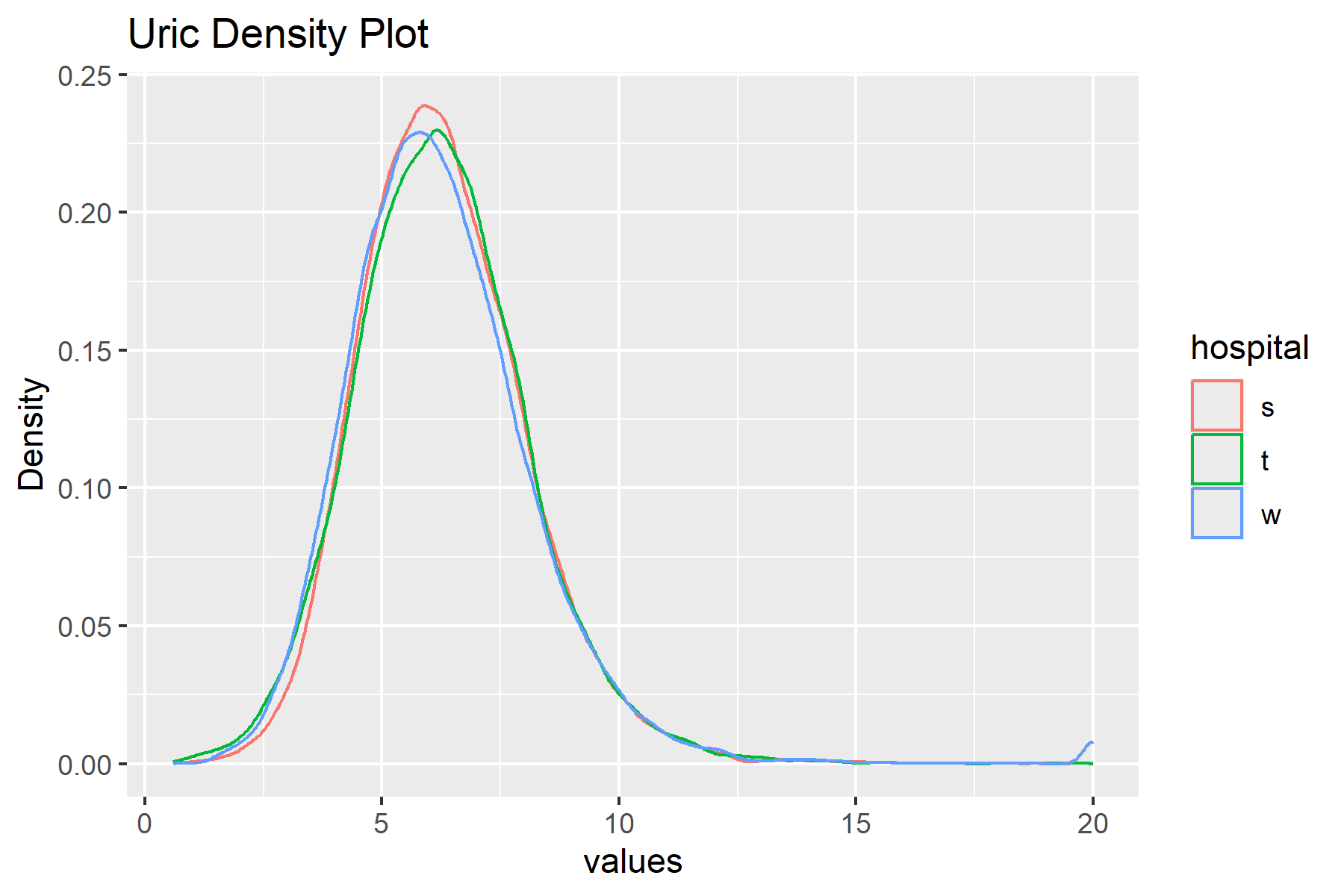
* 1. 檢驗項目的density plot (分三院、有針對outlier 進行壓縮):
     1. HbA1c Test ID: "014701", "F09006B", upper = 13



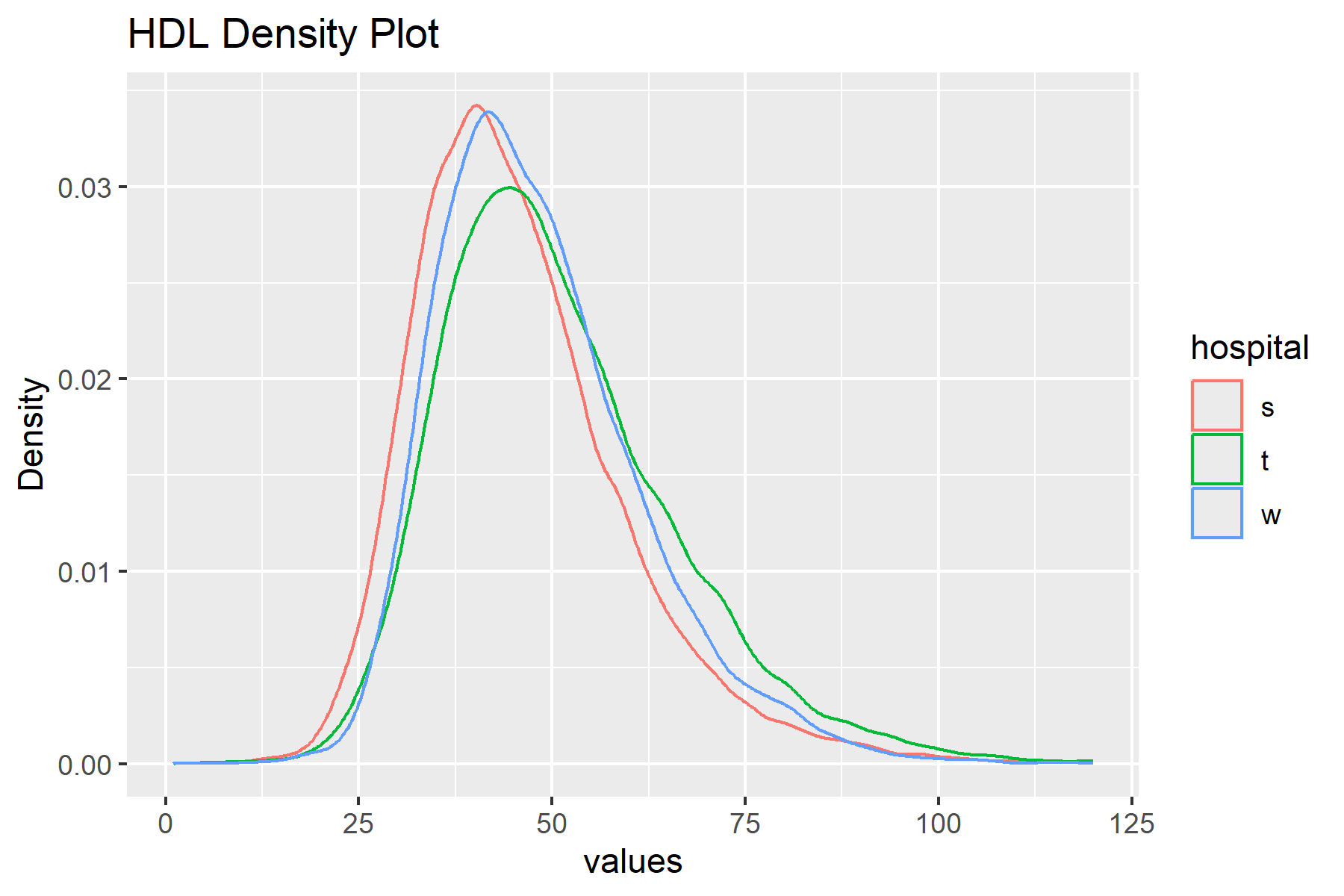
* + 1. ALBUMIN Test ID: "010301", "11D101", "F09038C", upper = 30

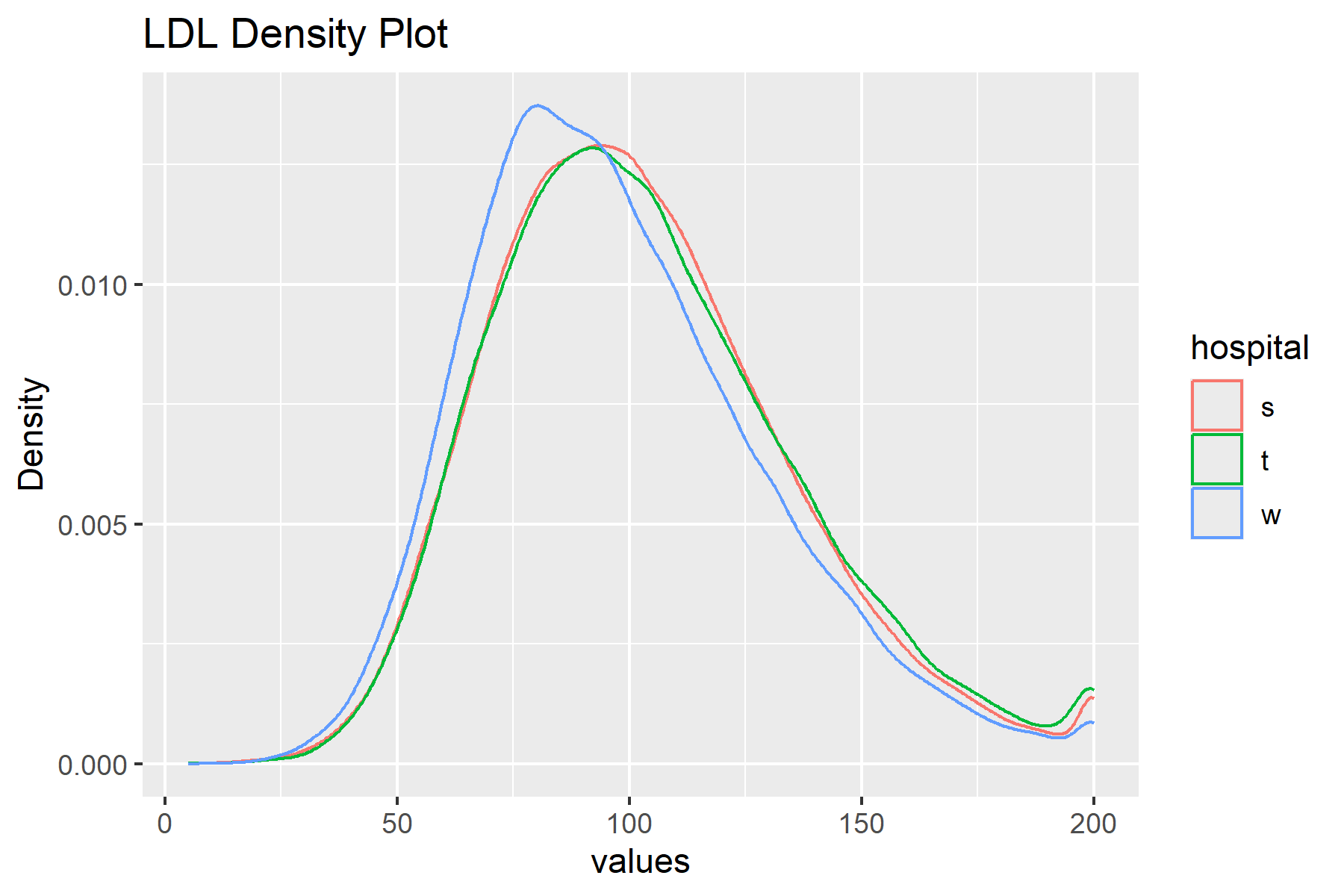


* + 1. Uric Acid Test ID: "011001",” F09013C” upper = 20

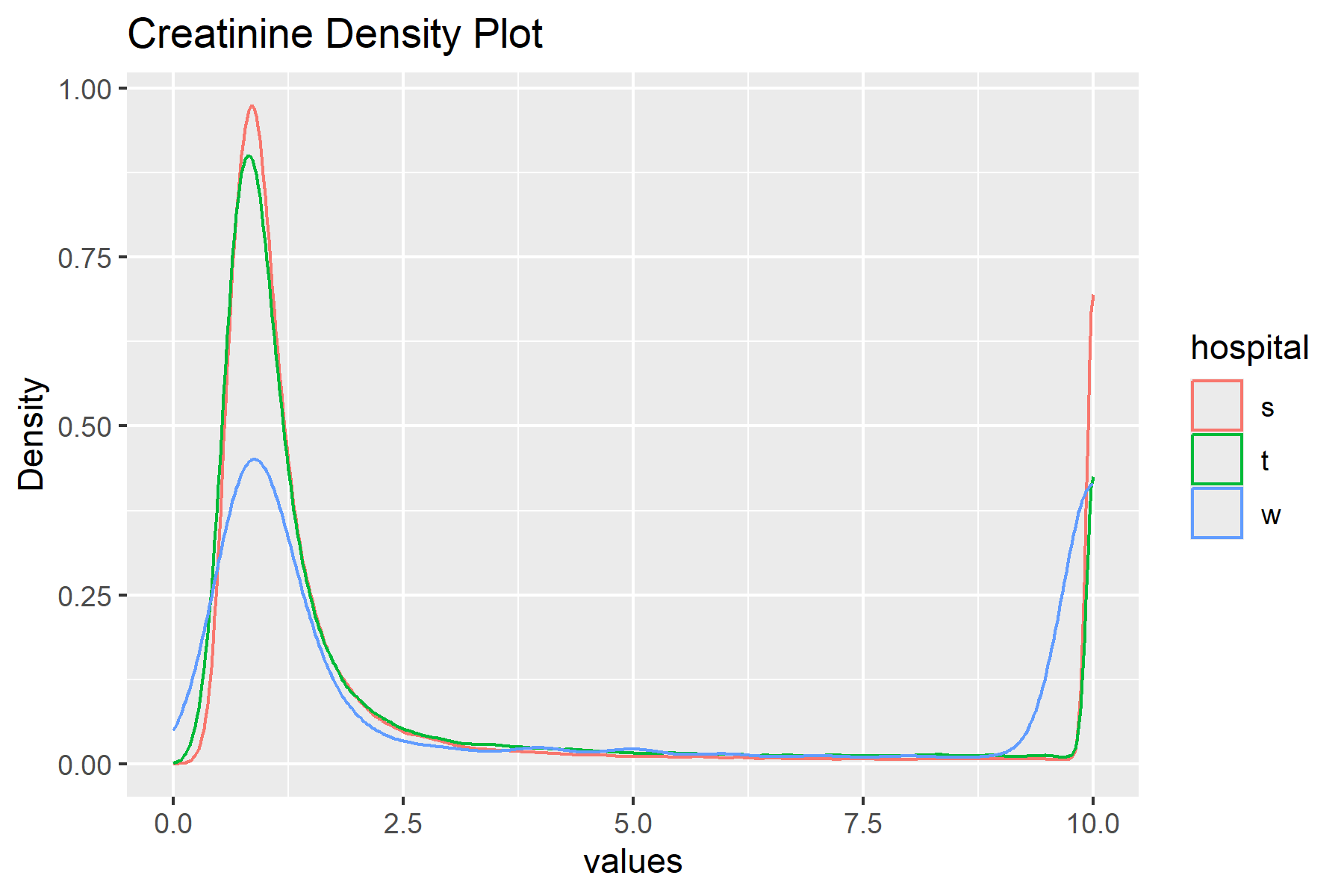


* + 1. HDL Test ID: "F09043A", "011301", upper = 120



* + 1. LDL Test ID: "F09044A", "011401", upper = 200
    2. 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