出國報告（出國類別：進修）

急性腎損傷之臨床研究

服務機關：台中榮民總醫院重症醫學部

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一、摘要

急性腎損傷的發生率隨著人口的老化、平均壽命延長，以及醫療的進步，其發生率呈現逐年增加的趨勢，而加護病房的病人發生急性腎損傷的比例更高達 50%。由於急性腎損傷發生後會增加日後心血管疾病和慢性腎臟病的風險，如何早期預測並加以預防，是臨床上面臨的研究難題。而引發急性腎損傷背後的原因十分複雜，且重症病人的共病症和異質性又高，臨床研究上如何精確篩選出特定的病人進行臨床試驗，也是一大挑戰。

本人於民國 108 年 8 月 1 日至 109 年 7 月 31 日前往美國加州大學舊金山分校，跟隨 Professor Kathleen Liu 做臨床研究，透過文獻回顧了解過去該領域在臨床研究設計上所面臨的困境，在教授指導下學習撰寫該主題的綜論和觀點投稿於 Nature Review Nephrology，並進一步於 UCSF 進修 clinical epidemiology 和 Biostatics 兩門研究所課程，學習基礎流病的觀念和統計軟體的操作，再藉由參加人工智慧機器學習的工作坊，嘗試利用不同的方式來做資料分析，以期用新的方式來解決過去研究的困境。此外，於臨床研究期間也同時參加 UCSF 腎臟科以及重症部的定期研究會議和教學活動，了解頂尖醫學中心的運作方式做為日後的參考。雖然後來因COVID-19疫情的關係，中斷了後續的臨床研究病人收案和資料分析計畫，但是在 UCSF 擔任訪問學者期間，認識了許多急性腎損傷和重症透析領域的學術領導者，獲得不少寶貴的經驗和交流，可作為未來臨床和研究發展的參考依據。

關鍵字：急性腎損傷、機器學習

二、 目的

隨著急重症領域照顧的進步和全人醫療觀念的引進，於過去 10 幾年間，國際上開始了 Critical Care Nephrology 的研究領域。腎臟科在重症的照顧角色發展，開始由過去的會診醫師角色逐漸轉變為專責重症醫師，針對加護病房的重症病人提供個人化的醫療照顧。為發展本院急重症在 Critical Care Nephrology 的臨床研究及病人照護，於是選定急性腎損傷的研究主題，前往 UCSF medical center，跟隨同時具備腎臟科和重症醫師背景的 Professor Kathleen Liu，學習如何在該領域建立臨床研究的基礎，並改善臨床照護的流程。

三、 過程

在急性腎損傷(Acute kidney injury, AKI)領域，由於背後造成 AKI 的原因種類和機轉的不同，在過去的研究上，類似的議題常得到不同的研究結果，即便累積了很多研究文章，仍然無法藉由高標準的研究設計，產出具代表性的研究結論。在指導教授的安排下，於到美的前三個月先參加 UCSF 臨床研究所 Clinical research MAS 的兩個課程，包含 Clinical Epidemiology、Biostatics 兩門課，主要在建立基本的流行病學基礎知識以及熟悉生物統計軟體 STATA 的操作。Clinical Epidemiology 的課程主要是由 Professor Michael Khon 和 Professor Tom Newman 共同授課，兩位教授分別是 UCSF 的急診醫師和小兒科醫師，課程內容主要將基礎的流行病學理論結合臨床研究，將生硬的流行病學理論，藉由實際的分析論文實例，讓選課的臨床醫師對於每天遇到的臨床問題、研讀的論文有更好的研究設計判斷和解析其統計方式上的能力。為期十二週的課程中，與來自 UCSF 各個不同次專科的 research fellow 一起修課，在大堂課結束後，回家完成作業，並於隔週的小組討論時間輪流上台發表意見，解釋自

已答案的邏輯，並針對同學的答案回饋意見。小組討論由前一年完成該門學科的醫師擔任助教，主持討論會的進行，指導教授則在旁聆聽討論過程，並在需要時澄清問題重點和觀念。期中考試則是自行挑選一篇已發表的研究論文，運用課堂上學到的理論，設計一個期末考題，如出的題目夠好，則放入期末考考題中。

UCSF 的 research fellow 畢業的學校有來自 Harvard medical school、Stanford medical school 等名校， 在課堂上與這些同學及教授的互動中，無論在流病知識、邏輯的建立、以及醫療制度的差異性上，都獲得很多的收穫。Biostatics 的課程，則是透過 STATA 軟體，學習資料前處理，檢視初步資料分布型態，以及將 clinical epidemiology 中學到的流病觀念，實際動手做分析。在上完大堂課後，教授會給予範例資料和問題，於 lab 時間做練習，助教則會在教室內協助軟體操作上的問題。

在順利修完兩門課，並通過期末考後，指導教授評估我的學習狀況，提供了我一個撰寫綜論的練習機會。由於指導教授在 AKI 的學術地位受到尊崇，Nature Review Nephrology 期刊邀請 Professor Liu 針對 2019 年一整年 AKI 領域的研究，挑選具代表意義的五篇文章做介紹，並提供個人對 AKI 領域未來發展的看法。很榮幸指導教授給我這個期刊邀稿的機會學習。Professor Liu 首先要求我將過去一年 AKI 相關的所有研究發表論文做清單的整理，按照研究的主題區分臨床和基礎兩部分，再接著由 high impact factor 的期刊逐一做地毯式瀏覽，過濾出具創新主題的研究文章，再接著細看其研究方法，確認研究方法嚴謹度符合一定的標準後，挑出 10 多篇文章放入候選名單。 接著則是先根據自己的想法，跟教授討論這十多篇文章的研究目的、方法、以及結果，還有對 AKI 研究帶來的貢獻，逐一決定各篇文章的重要

性排名。

在這撰寫綜論的過程中，讓我跳脫既有的研究小主題，有機會用更宏觀的角度來看整個 AKI 領域的研究和發展，並且思考怎樣的研究水平才能突破既有框架，為該領域作出有意義的貢獻。最後，我和指導教授共同決定了五篇文章，包含探討 AKI 目前的主流定義是否需要再做修改、外科手術前 dickkopf-3(DKK3)這個反應腎小管壓力的 biomarker 用來評估術後 AKI 風險的價值、潛在類別分析（Latent Class Analysis）在篩選 AKI 族群的角色、人工智慧的深度學習在預測住院中 48 小時內發生 AKI 的應用，以及動物實驗中 AKI 對於心臟的影響。在文章撰寫的過程中，指導教授給予我相當多的意見和建議，也協助我做英文書寫的修飾，最後有幸通過雜誌社的審閱核可並接受，於 2020 年 03 月將文章刊登於 Nature review nephrology（附錄）。

有鑒於大數據時代的來臨，免費開放的資料庫越來越多，也有許多認同資訊免費共享的人將資料庫處理的程式編碼放在開放的網站，提供有相同研究興趣的全球同好使用。機器學習在 AKI 以及重症的應用更是在過去幾年來開始蓬勃發展。因此，我特別商請指導教授提供相關的學習管道和資源，希望有機會能夠實際接觸該領域的人才，學習機器學習的基本入門應用。Professor Liu 透過 UCSD 的 Professor Mehta, 引介我參加 UAB-UCSD O'Brien Center 於 2020 年 1 月 15-17 日為期 3 天的 Healthcare Data Analytics Workshop(課程內容如附錄)。在三天的工作坊中，我們先於一週前線上完成 MIMIC-III 的 IRB 課程，取得認證的 IRB 證書後寄給審核 MIMIC III 的資料庫管理單位，待審核通過後再自行下載資料庫到電腦，並攜帶至工作坊開始學習。課程的安排分為幾個部分，首先是介紹在網路上有哪些免費的資料庫可以

下載分析，例如：https://www.data.gov/open-gov，為美國聯邦政府的公開資訊網站，供民眾免費下載瀏覽，http://healthdata.gov 則是有許多醫院和 Medicare 保險的資料可以下載分析。接著則是教我們下載 SQL(Structured Query Language)的程式，練習如何用 SQL 抓取 MIMIC-III 資料庫內的目標檔案。最後再介紹學員利用 MIMIC-III 已經建立好的程式碼套組，跑 machine learning 對 Sepsis 的預測。雖然在沒有資工背景的前提下參加工作坊無法完全消化講師的內容，coding 的速度也跟不上，但是最大的收穫，則是認識了免費重症資料庫的架構和實作的經驗，知道未來如何和跨領域的人才合作。

在參加完工作坊後，因今年的 AKI-CRRT 25 週年年會也剛好在 San Diego 舉辦，所以，在指導教授的安排下，也於 2020 年 2 月 23-27 日前往 San Diego 開會。今年的會議印象最深刻的，是得到大會頒發特殊貢獻研究獎，來自辛辛那提兒童醫院小兒腎臟科的 Dr. Goldstein 分享他的 NINJA (Nephrotoxic Injury Negated by Just-in-time Action)-AKI prevention quality improvement 的研究內容。作者藉由醫院的即時電子病歷系統，挑選小兒科病房的病人電子藥單同時有三種以上腎毒性藥物，或是單一種腎毒性藥物使用超過三天以上，但是臨床上近期內未檢測腎功能(血清肌酸酐)的病患做即時的提醒，建議主責的醫師是否加開腎功能檢驗，以作藥物的調整和監測。簡單的主動提醒系統，配合不過度干涉臨床醫師的治療介入，讓這個品質改善計畫得到高達 99%的正面回饋，大部分的臨床團隊都會主動加開檢驗單，而 AKI 的發生率和同時合併三種腎毒性藥物的比例也有顯著下降，其論文獲刊登在 Impact factor 8 分的 Kidney International (doi:10.1016/j.kint.2016.03.031.) 該團隊利用臨床上觀察到的問題，思考流程上的改進，配合該醫院的文化，設計出一個簡單又有效的流程改善，配合嚴謹的研究

設計和資料分析，成功說服同僚，非常值得借鏡。

在美進修的最後三分之一期程，原先規劃好要著手收集 UCSF 敗血症的病人，做 AKI biomarker 的分析，並且安排 UCSF ICU 一個月的臨床跟診查房，無奈 2020 年 3 月 16 日開始，舊金山市府率先全美第一個宣布 shelter in place，要求所有非 essential workers 待在家，學校也全部改為線上學習。在此政策下，UCSF 宣布所有的 visiting scholar 不得進入醫院，除非是動物實驗室的基本維護人力、或是第一線醫護人員還是有特殊理由不得中斷的臨床試驗計畫研究人員，才得以允許回醫院工作。因此，從 3 月中一直到 7 月底回台，就跟家人待在家裡，只能透過視訊會議討論研究計畫，以及參與醫院的全院 grand round。在沒有收取病人的資料和檢體下，研究計畫被迫中止。不過在疫情期間指導教授仍然給予我學習當期刊 reviewer 的工作，分配給我幾個 high impact factor 的投稿文章，協助做評論審查，也讓我從中學到不少東西。

四、 心得

本次於 UCSF 當訪問學者的一年間，透過與當地醫師和基礎研究人員的互動，學習該研究團隊的文化和運作模式，再加上指導教授提供的學習資源，讓我收穫很多。雖然不幸遇到 COVID-19 疫情，導致原先的研究計畫被迫中斷，但是也從中瞭解美國在疫情期間因為文化上的差異以及政治的因素，導致疫情一發不可收拾的原因。從這次的疫情，也讓我意識到未來的學習和研究會更朝無國界的方向發展，疫情期間的免費線上資源和視訊會議討論，以及

PubMed 上 COVID-19 的學術文章免費下載，都讓實際上的距離不再成為隔閡，而許多學校和機關團體，也都因應疫情而發展出更彈性的學習和研究資源，這也可讓疫情相對穩定的台灣提供參考，如何建立臨床研究資料庫的基礎建設，提供日後免費的開放性數據，在兼顧病患隱私和資料安全下，創造更大的研究資源和空間。

五、 建議

1. 建立本院重症資料庫去辨識資料的整合開放平台：

過去在重症的研究，多以單一醫院甚至單一個加護病房的病人做資料分析。但在目前的大數據時代，建立重症電子病歷的資料串連和統整，將數據結構化並去辨識，則是未來研究的趨勢。本次前往機器學習工作坊中所使用的美國 MIMIC-III 重症資料庫，即是一個很好的典範。該資料庫為麻省理工學院和 Beth Israel Deaconess Medical Center 合作，將該醫院所有加護病房入院病人的臨床生理參數、檢驗檢查報告、病歷紀錄等在完成去辨識處理後，累積 2000 年到 2012 年共 4 萬多筆病人的資料做成 26 個 table 供全球有興趣的人員下載做研究分析。在全球都朝人工智慧的領域發展時，資料庫的基礎建設十分關鍵，建議醫院能整合本院的資料庫做串連，再邀集法規專家，針對資料庫去辨識後的申請和使用做規範，以利後續研究發展。

2．延攬常駐的數據分析師，與臨床醫師做跨領域的合作

在參與 MIMIC-III 工作坊中，臨床醫師使用 SQL 和 data mining 的經驗和技術都跟資工背景出生的工程師有一段落差，如果醫院能夠有 data analysist 的人才，無論是在基因體的數據

分析，或是臨床資料的數據分析，都能跟臨床醫師發揮跨領域合作的效果，加速研究的速度和產能。

3．研究團隊文化的建立

在 UCSF 進修期間，發現好的團隊文化和制度是吸引人才、讓組織不斷進步的關鍵。在 Professor Liu 的團隊裡，指導教授常常說很多東西她也不知道，需要靠團隊的智慧來讓研究前進，所以她對任何問題都保持開放的態度，不會先入為主的否定成員的意見，針對成員間遇到的問題，她則會積極向外尋求可以協助的人才，撮合雙方的合作，讓團隊的資源和人脈越來越廣。Professor Liu 在我剛到美國的前一個月，會買書、買草莓送我小孩、關心我家人的適應狀況，告訴我車子要停醫院附近的哪裡才不用被收費等生活上的細節，在她的團隊裡，工作氣氛非常融洽，向心力很強，她告訴我，在 UCSF，你不只要認真，也要對人友善，因為這是這個地方的核心價值。這也讓我體認到，在這個年代，獨善其身是無法完成大事的，建立好的團隊和工作氛圍，讓成員一起成長才是最重要的。

六、附錄

附錄

ACUTE KIDNEY INJURY IN 2019

Exciting developments in the field of acute kidney injury

Chun-Te Huang and Kathleen D. Liu

Acute kidney injury (AKI) is an important clinical problem that is associated with adverse short- and long-term outcomes. Studies published in 2019 provide new insights into the staging, risk stratification and subphenotyping of AKI as well as the adverse effects of AKI on the heart.

Over the past 10 years, the pace of acute kidney injury (AKI) research has accelerated — perhaps in part owing to the recognition of AKI as a disease with long-term sequelae, including an increased risk of chronic kidney disease (CKD) and death. Here, we highlight some of the key developments in the past year.

The development of consensus definitions of AKI, which enable more uniform analyses and a more standardized approach in clinical practice, has led to substantial progress in the field. At present, the Kidney Disease: Improving Global Outcomes (KDIGO) classification system defines stage 1 AKI as an increase in serum creatinine (SCr) levels of either 0.3 mg/dl (26.5 µmol/l) within 48 h or >50% from baseline within 7 days (FIG. 1). However, these two definitions are probably not equivalent. In 2019, this issue was highlighted by the findings of an analysis by Sparrow et al.[1], which included data from a cohort of 81,651 hospitalized patients. They demonstrated that among patients with baseline SCr ≥0.7 mg/dl (61.9 µmol/l) those who experienced a 0.3 mg/dl increase in SCr within 48 h had clinically meaningful differences in outcomes, including length of hospital stay and mortality, compared with those who experienced a 50% increase in SCr from baseline within 7 days. By contrast, they did not find differences in clinical outcomes between patients with KDIGO stage 3 AKI defined according to absolute versus relative increases in SCr. These findings suggest that the KDIGO AKI definition should be revised because the staging may equate states that are not the same. In addition, the AKI definition should also potentially incorporate aetiology, pathophysiology and novel biomarkers.

Although SCr remains the most widely used biomarker to evaluate renal function, it is known to be a delayed functional marker with important limitations, including its close relationship with muscle mass and decreased production during acute illnesses including sepsis. Kidney damage biomarkers, such as neutrophil gelatinase-associated lipocalin and kidney injury molecule 1, may help to identify subclinical AKI when the SCr is unchanged despite tubular injury. However, the sampling time frame is crucial for these biomarkers, and their levels rise only when AKI has already occurred. The best approach to the management of AKI is prevention. Can we use a biomarker to predict whether or not AKI will occur and its outcome? Schunk et al.[2] examined the clinical utility of urinary Dickkopf-related protein 3 (DKK3) as a predictive biomarker for AKI following elective cardiac surgery. Urinary DKK3 is a stress-induced glycoprotein that is secreted by renal tubular epithelial cells and modulates Wnt–β-catenin signalling, which is thought to trigger tubulointerstitial fibrosis. The researchers hypothesized that higher preoperative levels of urinary DKK3 would be

> “The best approach to the management of AKI is prevention”

associated with greater rates of postoperative AKI and CKD. They initially tested the predictive value of urinary DKK3 in a cohort of 733 patients and identified a cut point for clinical decision-making. In this derivation cohort, urinary DKK3 levels had adequate discrimination (area under the curve 0.783) and good calibration for prediction of post-operative AKI. In a validation cohort of patients from the RenalRIP randomized clinical trial of remote ischaemic preconditioning (RIPC) for prevention of AKI in the setting of cardiac surgery[3], Schunk et al. found that higher urinary DKK3 levels were associated with a higher risk of AKI in patients who received the sham procedure but not in those who received RIPC. As the RenalRIP trial reported a significant reduction in the risk of AKI in patients who received RIPC compared with those who underwent the sham procedure (other studies of RIPC have reported negative findings), Schunk et al. suggest that DKK3 may enable the identification of high-risk patients who are likely to benefit from preventive interventions. Notably, albuminuria and proteinuria were not included in this analysis; therefore, the utility of DKK3 above and beyond these biomarkers is unknown. This point is important because albuminuria and proteinuria are important risk factors for AKI and CKD progression, and their measurement is widely available and fairly inexpensive. Nonetheless, this paper highlights a novel use

Key advances

- The Kidney Disease: Improving Global Outcomes (KDIGO) definitions of stage 1 acute kidney injury (AKI) based on absolute versus relative changes in serum creatinine levels were associated with different outcomes in a retrospective cohort study[1], highlighting the potential need for revisions to current AKI definitions.
- Urinary Dickkopf-related protein 3 is a potential pre-operative biomarker for risk of AKI following elective cardiac surgery[2].
- An unbiased discovery method can identify distinct pathophysiological subphenotypes of septic AKI; these subphenotypes had differential treatment responses in a post hoc analysis of clinical trial data[5].
- A deep learning approach using electronic health record data can identify patients at high risk of AKI[8].
- In a mouse model, AKI results in direct cardiac injury and dysfunction[9].

of biomarkers to risk-stratify patients in the pre-operative setting.

One of the major challenges in AKI clinical trials is the heterogeneous nature of the disease. Traditionally, AKI is subdivided into prerenal, intrinsic and postrenal aetiologies, although the term 'prerenal' has been criticized because it refers to numerous conditions with varying pathophysiologies and treatments. Moreover, even with chart review by expert nephrologists, the distinction between disease states such as prerenal AKI and acute tubular necrosis can be challenging[4]. Could unbiased methods better identify subphenotypes of disease? Latent class analysis is an unbiased technique that has been used successfully to identify subphenotypes in other diseases including asthma and the acute respiratory distress syndrome[5]. In a recent study, Bhatraju et al.[6] applied latent class analysis to identify two subphenotypes of AKI and validated these subphenotypes in independent cohorts. Perhaps most intriguingly, in a cohort of patients with septic shock from the VASST trial[7], clinical outcomes and vasopressin response differed between the two subphenotypes. This study demonstrates that latent class analysis is a novel method to identify distinct pathophysiological subphenotypes of AKI, which may facilitate improvements in the identification of patients for enrolment in clinical trials.

> One of the major challenges in AKI clinical trials is the heterogeneous nature of the disease

Electronic health records present an opportunity to apply artificial intelligence to solve a number of clinical problems. Deep learning uses recurrent neural networks akin to the human brain to process data and build an internal memory that tracks relevant information. In 2019, Tomasev et al.[8] developed a deep learning approach to predict AKI (with a lead time of 48 h) using data from the United States Department of Veterans Affairs. Their final model predicted 55.8% of all inpatient episodes of AKI and 90.2% of dialysis-requiring AKI, with a ratio of two false alerts for every true alert in the test subgroup. This collaboration between computer science and medicine demonstrates the immense possibilities for risk prediction using comprehensive electronic health record data. That said, more studies are needed to demonstrate how deep learning and other artificial intelligence techniques can be best applied and fine-tuned for maximal clinical impact. In particular, recent pragmatic trials of AKI interventions have suggested that increased awareness of AKI may lead to increased diagnosis; whether increased diagnosis will lead to better treatment or to unnecessary therapies is unknown[9]. To move forwards, a deeper understanding is needed of how pragmatic AKI interventions such as routine identification of at-risk patients or patients with early AKI impact processes of care and therefore may impact clinical outcomes such as length of hospital stay and mortality.

Finally, an experimental study by Fox et al.[10] highlighted the impact of AKI on the functions of distant organs, including the heart. In mice following ischaemic AKI, analysis of the cardiac metabolomics profile revealed evidence of energy depletion and oxidative stress, whereas echocardiographic findings provided evidence of diastolic dysfunction. In humans, little is known about the impact of AKI on distant organ function, and this area is likely an important avenue for future research.

In sum, the past year has seen a number of exciting developments in the field of AKI. We anticipate and look forward to further developments in the next year and indeed the next decade.

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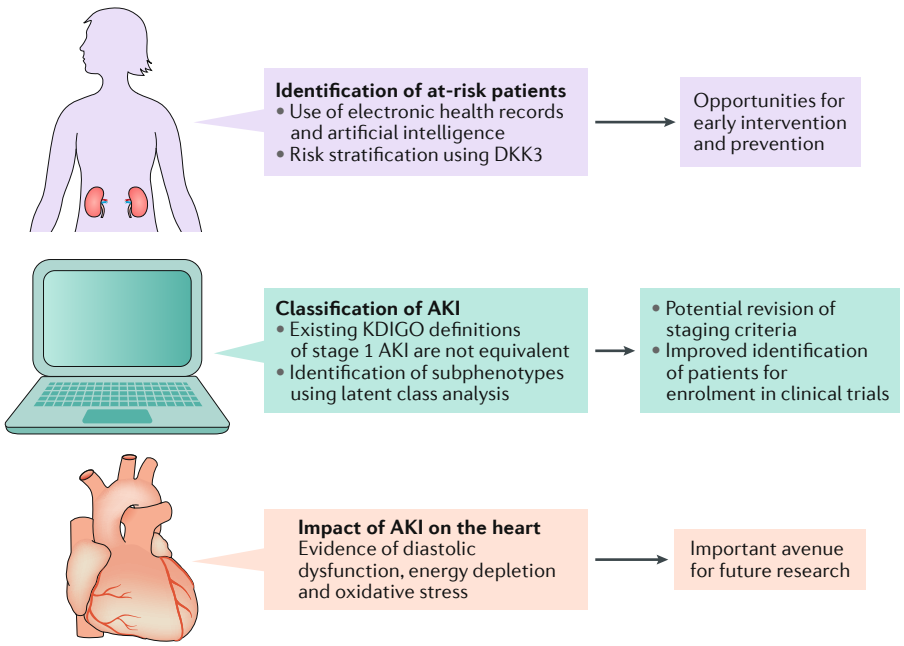

Fig. 1 | **Advances in acute kidney injury in 2019.** Key studies published in 2019 reported novel approaches to the identification of at-risk patients, provided new insights into patient classification and highlighted the impact of acute kidney injury (AKI) on the heart. These advances could potentially lead to opportunities for early intervention and prevention, improvements in patient classification that could facilitate patient identification for clinical trials and new avenues for future research into the effects of AKI on remote organs. DKK3, Dickkopf-related protein 3; KDIGO, Kidney Disease: Improving Global Outcomes.

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Competing interests
The authors declare no competing interests.