特 色 論 文

系所	姓名	作者序	論文題目	說明
臨醫所	陳世彬	通訊作者	Blood-Brain Barrier Permeability in Patients With Reversible Cerebral Vasoconstriction Syndrome Assessed With Dynamic Contrast-Enhanced MRI. *Neurology*, *97*(18), e1847-e1859. (IF= 9.901)	過往針對可逆性腦血管收縮症候群(reversible cerebral vasoconstriction syndrome; RCVS)之血腦障壁(blood-brain barrier; BBB)受損，方法是觀察磁振造影上有無巨觀的對比劑滲漏，本研究透過高磁場(3T)動態對比劑顯影磁振造影(dynamic contrast-enhanced magnetic resonance; DCE-MRI)研究更微觀、肉眼不可見的 BBB 的通透性差異。結果發現 RCVS 病患(n = 176)不論有無巨觀可見之對比劑滲漏，全腦平均 BBB 通透性在急性期差異並不顯著，但與恢復期相較，則有明顯較高的 BBB 通透性，且隨疾病有明顯的動態變化。我們研究證實即使磁振造影無巨觀偵測可見對比劑滲漏，RCVS 在急性期仍存在微觀之 BBB 受損的可能性，且此 BBB 通透性改變可能與疾病程度有所相關。本研究更發現 BBB 通透係數(Ktrans)於疾病早期(約頭痛後兩週)與中大腦動脈之 M1 節段在超音波上的 distal-to-proximal ratio of resistance index 係數有高度相關 (rs = 0.801, p < 0.001)，可能作為未來偵測疾病發作的先驅指標。
臨醫所	黃怡翔	通訊作者	Evolutionary Learning-Derived Clinical-Radiomic Models for Predicting Early Recurrence of Hepatocellular Carcinoma	本論文導入人工智慧模式預測肝癌患者手術後復發率，具創新性及臨床實用性，並剛獲得新創獎殊榮。

			after Resection. *Liver Cancer*, *10*(6), 572-582. (IF=11.74)	
醫學系	陳亮恭	通訊作者	Effects of incorporating multidomain interventions into integrated primary care on quality of life: a randomised controlled trial. *The Lancet Healthy Longevity*, *2*(11), e712-e723. (IF=new journal)	前瞻設計的健康照護模式隨機分配試驗，多元介入健促活動結合整合式醫療照獲，驗證在身體、認知功能與價值醫療指標之進步。期刊主編特意邀請專家撰寫評論，代表本文受到極高度的重視，而撰寫評論者對於研究設計的優缺點提出相當重要的看法，高度讚賞本研究使用全人觀點的 well-being 以及 ICHOM value-based health care metrics 指標為主要成效評估要點。
公衛所	蒲正筠	通訊作者	Medication Adherence in Patients With Glaucoma and Disability. *JAMA ophthalmology*, *139*(12), 1292-1298. (IF=7.389)	本研究使用寶貴的身心障礙資料庫，探討不同身障類別對於青光眼用藥持續性的影響。全人口資料解決了過去研究的選樣偏差以及測量誤差的問題。本研究在資料和方法學上均有創新的突破。
醫學系	白雅美	通訊作者	Cancer Risk in Patients With Bipolar Disorder and Unaffected Siblings of Such Patients: A Nationwide	國際首篇以大資料庫發現雙極症患者手足有較高風險罹患癌症, 尤其是 50 歲以下的手足。

			Population-Based Study. *International journal of cancer*. (IF=7.396)	
臨醫所	黃怡翔	通訊作者	Abatacept is second to rituximab at risk of HBsAg reverse seroconversion in patients with rheumatic disease. *Annals of the Rheumatic Diseases.* (IF=19.103)	本研究首次發現生物製劑中 abatacept 僅次於 rituximaby 在 B 型肝炎表面抗原陰性、核心抗體陽性的類風濕關節炎患者，誘發表面抗原陽轉的風險。兩種生物製劑皆會導致 anti-HBs 消失，進而發生 B 型肝炎表面抗原陽轉的 B 型肝炎病毒再活化，因應此風險研究同時提供相對臨床處置之建議。刊登在 Top research journal in Rheumatology。
臨醫所	楊慕華	共同通訊作者	Regorafenib enhances antitumor immunity via inhibition of p38 kinase/Creb1/Klf4 axis in tumor-associated macrophages. *Journal for ImmunoTherapy of Cancer.* (IF=13.751)	Regorafenib may enhance antitumor immunity through modulation of macrophage polarization, independent of its anti-angiogenic effects. Optimization of regorafenib dosage for rational design of combination therapy regimen may improve the therapeutic index in the clinic.
臨醫所	李美璇	通訊作者	Postdiagnosis aspirin use associat-ed with decreased	Nationwide prospective cohort of newly diagnosed BTC between 2007 and 2015 were included and followed until December 31, 2017. Three

			biliary tract can-cer-specific mortality in a large na-tionwide cohort. *Hepatology*. (IF=17.4)	nationwide databases, namely the Cancer Registration, National Health Insurance, and Death Certification System, were used for computerized data linkage. Aspirin use was defined as one or more prescriptions, and the maximum defined daily dose (DDD) was used to evaluate the dose-response relationship. Cox's proportional hazards models were applied for estimating hazard ratios (HRs) and 95% confidence intervals (CIs). Analyses accounted for competing risk of cardiovascular deaths, landmark analyses to avoid immortal time bias were performed. In total, 2,519 of patients with BTC were exposed to aspirin after their diagnosis (15.7%). After a mean follow-up of 1.59 years, the 5-year survival rate was 27.4%. The multivariate-adjusted HR for postdiagnosis aspirin users, as compared with nonusers, was 0.55 (95% CI, 0.51 to 0.58) for BTC-specific death. Adjusted HRs for BTC-specific death were 0.53 (95% CI, 0.48 to 0.59) and 0.42 (95% CI, 0.31 to 0.58) for ≤1 and >1 maximum DDD, respectively, and showed a dose-response trend ($p < 0.001$; nonusers as a reference). Cancer-specific mortality was lower with postdiagnosis aspirin use in patients with all major BTC subtypes. The nationwide study revealed that postdiagnosis aspirin use was associated with improved BTC-specific mortality of various subtypes. The findings suggest that additional

				randomized trials are required to investigate aspirin's efficacy in BTC
公衛所	劉家軒	第一作者	Subsequent primary cancers of the digestive system among childhood and adolescent cancer survivors from 1975 to 2015 in the United States. *American Journal of Gastroenterology*. (IF=10.171)	This large and comprehensive study of childhood and adolescent cancer survivors examined previously unstudied associations for particular types of first primary cancers and subsequent primary digestive system cancers, by providing sex-specific risk estimates and analyzing more recently diagnosed first cancers than that of previous studies.
臨醫所	吳肇卿	通訊作者	Clinical implications on HBV preS/S mutations and the effects of preS2 deletion on mitochondria, liver fibrosis, and cancer development. *Hepatology*. (IF= 14.679)	Highlights of our present findings: lA long-term case-control follow-up study revealed that HCC occurrence was associated with preS mutations (17.6% vs. 8.0%; p=0.008), and preS mutations increased risk of HCC (HR: 3.210, 95% CI: 1.072-9.613; p=0.037). lLongitudinal analysis showed that in patients who had chronic hepatitis B prior to HCC development, antiviral therapy reduced risk of HCC (HR: 3.210, 95% CI: 1.072-9.613; p=0.037). HCC occurrence rate was reduced in patients with preS mutations under antiviral therapy (1-yr: 5% vs. 35%, 3-yr: 7% vs. 41%, 5-yr: 7% vs. 48%; log-rank p<0.001). lExpression of naturally occurring secretion-defective preS2 deletion mutant (preS2ΔMT) in an HBV-

				transfected cell model resulted in HBsAg retention in ER, unfolded protein response, calcium overload in mitochondria with consequent decrease of mitochondrial motility, and reduction of mitochondria membrane potential and ATP production. lIn studies using humanized liver chimeric (hu-FRG) mouse model, serum HBV levels were ~100-fold lower in preS2ΔMT-infected mice than in wild-type HBV-infected mice. Long-term replication of preS2ΔMT HBV led to upregulation of UPR and caspase-3, and enhanced liver fibrosis. Lay Summary: Hepatitis B virus (HBV) preS/S mutation is a major risk factor for hepatocellular carcinoma (HCC) development in chronic hepatitis B (CHB) patients, including those with low HBV DNA or ALT levels, and antiviral therapy is a useful option for those with unmet need. Expression of secretion-defective preS2ΔMT led to mitochondrial dysfunction, and persistent replication of the mutation promoted liver fibrosis and HCC development.
臨醫所	陳世彬	第一及通訊作者	Circulating microRNAs associated with Reversible Cerebral Vasoconstriction Syndrome. *Annals of Neurology*. (IF=9.037)	可逆性腦血管收縮症候群病生理機轉尚未釐清，過去亦無任何可用之生物標記，微核苷核酸(microRNA)近來被認為與血管功能有關，且我們過去研究也發現一些與血管內皮功能相關的微核苷核酸與偏頭痛相關。本研究試圖探討 microRNA 於 RCVS 病生理機轉所扮演角色。我們招募了三組獨立的可逆性腦血管收縮症候群病患及對照組，利用次世代定序及定量 PCR，找到一組 microRNA(miR-130a-

				3p, miR-130b-3p, let-7a-5p, let-7b-5p and let-7f-5p)與 RCVS 病程有高度關聯，並可有效分辨急性期病人與對照組(分辨率達 9 成)，為證實這幾個 microRNA 專一性，我們又另外招募偏頭痛病患(發作期及發作間期)與另一組對照組，發現 let-7a-5p, let-7b-5p 及 let-7f-5p 在偏頭痛病患發作期亦會上升，顯見這些 microRNA 於病生理機轉可能扮演不同角色，有些可能與急性疼痛或三叉神經血管反射有關。生物資訊學分析發現這 5 個 microRNA 的調節基因包括 TGF-β 訊息傳遞途徑裡數個基因及 endothelin-1 強力血管收縮因子，我們亦利用 microRNA 轉殖或病患腦脊髓液在三種不同的內皮細胞株確認生物資訊學找到的幾個基因確實會受這 5 個 microRNA 調控。我們更進一步發現 miR-130a-3p 的增加在病患與血腦障壁破壞有關，而在人類血腦障壁細胞模式中過度表達 miR-130a-3p 亦會增加血腦障壁的通透性。本研究是第一個針對雷擊頭痛病生理機轉深入探討的研究，研究成果預期可應用於臨床輔助診斷，更提供未來探討其病生理機轉研究乃至開發可能治療之重要方向。
急重所	李欣烜	第一作者	Upregulation of ACE2 and TMPRSS2 by particulate matter and idiopathic pulmonary fibrosis: a potential role in severe COVID-19. *Particle and Fibre Toxicology.* (IF=7.546)	Air pollution exposure and idiopathic pulmonary fibrosis (IPF) cause a poor prognosis after SARS-CoV-2 infection, but the underlying mechanisms are not well explored. Angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) are the keys to the entry of SARS-CoV-2. We measured ACE2 and TMPRSS2 levels in lung tissues of control non-IPF and IPF patients, and used murine animal models to study the deterioration of IPF caused by particulate matter (PM) and the

				molecular pathways involved in the expression of ACE2 and TMPRSS2. These data suggested that risk of SARS-CoV-2 infection and COVID-19 disease severity increased by air pollution exposure and underlying IPF. It can be mediated through upregulating ACE2 and TMPRSS2 in pulmonary fibroblasts, and prevented by blocking the IL-8/CXCR1/2 pathway.
公衛所	林雅萍	第一作者	Understanding family dynamics in adult-to-adult living donor liver transplantation decision-making in Taiwan: Motivation, communication, and ambivalence. *American Journal of Transplantation*. (IF=7.338)	1. 本論文為台灣首篇發表於第一級 SCI 國際移植醫學期刊，以質性研究方式深入探討台灣親屬間活體肝臟捐贈移植的溝通與決策過程，闡述捐贈者、受贈者與重要家庭成員之間的互動關係、情感與倫理意義建構。 2. 本文論證台灣社會「以家庭為中心」的醫療決策模式體現於親屬間活肝移植過程，交織社會、經濟、文化、親屬階序、勞務分工與性別規範等多重因素，並歸結出家庭溝通決策的三大類型。 3. 本文提出具有參考價值的臨床案例，說明傳統家庭中潛在的性別角色與權力不對等如何可能影響捐贈者的心理與社會壓力，幫助移植團隊發展更為完善的器捐移植評估指引與照護建議。
藥理所	邱士華	通訊作者	METTL3-dependent N6-methyladenosine RNA modification mediates the atherogenic inflammatory cascades in vascular	本研究係由臺北榮總、國立陽明交通大學、與美國加州大學聖地牙哥分校（UCSD）錢煦院士組成臺美合作研究團隊，此研究發現：「信使核糖核酸(mRNA)甲基化」可能是造成冠狀粥狀動脈硬化的原因之一，研究團隊利用基因療法抑制血管的「甲基化轉移酶」，結果發現此方法能有效控制血管內發炎反應的產生並減少粥狀動脈硬化的發生，提供冠狀動脈疾病預防及治療新契機。於今年(110)年 2 月，榮獲得美國國家科學院院

			endothelium. *Proc Natl Acad Sci USA*. (IF=9.412)	刊(Proceedings of the National Academy of Sciences of the United States of America; PNAS (Vol.118)刊登肯定。
臨醫所	陳世彬	通訊作者	Noninvasive characterization of human glymphatics and meningeal lymphatics in an in vivo model of blood-brain barrier leakage. *Annals of Neurology*. (IF=9.037)	腦部的類淋巴系統(亦稱膠淋巴系統, glymphatic system)及腦膜淋巴系統(meningeal lymphatics)被認為是腦部清除廢物及調節免疫的重要系統，在腦部恆定、睡眠及神經科疾病，包括頭痛與其他神經退化或神經免疫疾病，扮演極為重要的角色，但過去限於技術，研究多僅限於動物實驗，或是病患死後的解剖分析，僅有小規模研究應用侵入性的技術或具有風險的脊髓腔內注射含釓(gadolinium)之顯影劑直接在人體研究。利用可逆性腦血管收縮症候群有血腦障壁破壞的疾病特質，我們開發非侵入性三維高解析度的造影技術(contrasted 3D-isotropic FLAIR imaging)，大規模的在人類成功清楚呈現人類腦部類淋巴系統及腦膜淋巴系統，確認其清除廢物(顯影劑)之途徑，並利用不同時序呈現其動態變化。本研究為全世界第一個利用非侵入性的方法可以在人類清楚看到腦部類淋巴系統的研究，也是截至目前為止最大規模可清楚呈現腦膜淋巴系統的研究，更重要的是，幫助瞭解 glymphatics-menigneal lymphatics 清除腦中廢物的動態時程，造影技術及研究模式將可作為未來研究其他神經疾病之基礎。
傳醫所	許中華	通訊作者	Influence of Traditional Chinese Medicine on Medical Adherence and Outcome in Estrogen Receptor (+) Breast Cancer	敘述乳癌患者使用中醫藥之順從性分析

			Patients in Taiwan: A Real-World Population-Based Cohort Study. *Phytomedicine*. (IF=4.268)	