會議議程

時間 Time	講題 Topic	講者 Speaker	主持人 Moderator
8:40-9:00	報到 Registration		
9:00-9:05	引言 Introduction	Tai-Horng Young	Ming-Shiang Wu
9:05-9:45	如何撰寫頂尖期刊的研究論文 How to write research articles to be published in top journals	Robert Brierley	Ming-Shiang Wu
9:45-10:30	成果發表 (Oral Presentation)		
	1. Gut *Bifidobacterium longum* is Associated with Better Native Liver Survival in Patients with Biliary Atresia	Chee-Seng Lee	Robert Brierley, Jyh-Ming Liou
	2. Orally fecal gavage enriched distinct gut microbes and metabolites from commensals to mitigate acetaminophen-induced liver injury	Chun-Ju Yang	
	3. Primary antibiotic resistance of *Helicobacter pylori* - Trends in Asia-Pacific regions: An updated systematic review and meta-analysis	Tzu-Chan Hong	
10:30-10:40	中場休息 Coffee breaks		
10:40-11:25	成果發表 (Oral Presentation)		
	4. Early remission of KRAS mutations in cfDNA after chemotherapy can predict better survival in pancreatic cancer patients: a prospective cohort study	Chien-Jui Huang	Robert Brierley, Chun-Ying Wu
	5. Long-Read DNA Sequencing to Reveal Hepatitis B Virus Integrations in Patients with and without Nucleotide Analogue Treatment to Suppress Viral Replication	Yao-Chun Hsu	
	6. Analysis of pre-diagnostic CT images with artificial intelligence facilitates early detection of pancreatic cancer	Po-Ting Chen	

11:25-11:50	成果發表 (E-Poster Presentation)		
	1. Association Between Electronegative Low-Density Lipoprotein and Chronic Hepatitis C Infection	Po-Cheng Liang	Robert Brierley, Jyh-Ming Liou
	2. Predicting the Potential of Eliminating Virus-related Hepatocellular Carcinoma in Taiwan by Deep Machine Learning	Sih-Han Liao	
	3. Cost-effectiveness Analysis of Curative Salvage Treatment for Recurrent Hepatocellular Carcinoma after Primary Liver Resection – a Nationwide Cohort Study	Chun-Ying Wu	
11:50-12:00	Discussion	Robert Brierley,	Yen-Hsuan Ni

來賓簡介-Robert Brierley

Editor-in-Chief of ***The Lancet Gastroenterology & Hepatology.***

Robert Brierley 是 ***The Lancet Gastroenterology & Hepatology*** 的主編。他在牛津大學受過分子和細胞生物化學、臨床藥理學的訓練，也在伯明翰大學學習過臨床腫瘤學。他以技術編輯的身份進入出版界，於 2004 年加入了 ***The Lancet*** 集團（包括 ***The Lancet Infectious Diseases*** 和 ***The Lancet***）。在 2008 年，他提升為高階編階，並於 2012 年晉升為 ***The Lancet Oncology*** 的副主編。Rob Brierley 的研究興趣包括消化道和肝膽管癌症、病毒性肝炎和發炎性腸道疾病。***The Lancet Gastroenterology & Hepatology*** 於 2016 年開始發行，致力於為全球的研究者提供關於肝膽胃腸學門最頂尖的研究和資訊。

Robert Brierley is the Editor-in-Chief of ***The Lancet Gastroenterology & Hepatology.*** He has a background from molecular and cellular biochemistry, clinical pharmacology at University of Oxford and clinical oncology at University of Birmingham. He began his publishing career as a technical editor, and in 2004 he joined ***The Lancet Group*** including ***The Lancet Infectious Diseases*** and ***The Lancet***. He joined ***The Lancet Oncology*** in 2008, becoming Deputy Editor in 2012, before launching ***The Lancet Gastroenterology & Hepatology*** in 2016. Rob's areas of expertise are gastrointestinal and hepatobiliary cancers, viral hepatitis, and inflammatory bowel diseases.

來賓簡介-楊台鴻 (Tai-Horng Young)

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台大醫學院 醫工中心 助理研究員 1993~1994
台大醫學院 醫工中心 副研究員 1994~1998
台灣大學 醫工所 副教授 1998~2000
台灣大學 醫工所 所長 2008~2011
台灣大學 醫工所 教授 2000~迄今
台灣大學 高分子所 合聘教授 2002~迄今

研究專長：

組織工程
幹細胞與神經細胞培養
奈米材料
醫用高分子

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台大醫院院長

台大醫學院內科特聘教授

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台灣醫學會理事長

Education:

M.D. Medicine College of Medicine, National Taiwan University
Ph.D. The Graduate Institute of Clinical Medicine, National Taiwan University.

Awards:

1997 Outstanding Research Award, National Taiwan University Hospital
1998 Outstanding Research Award, Professor Juei-Low Sung’s Research Foundation
1999 Outstanding Article Award, Taiwan Socity of Internal Medicine
2000 Outstanding Research Article, Ming-Tsai Medical Foundation
2003 Outstanding Young Research Award, National Science Council
2006 Outstanding Research Award, National Science Concil
2008 Outstanding Research Award, National Taiwan University Hospial
2008 Emerging Leader Award, Asian Pacific Digestive Week
2008 Medical Research Award, Ching-Hsin Medical Foundation
2011 Outstanding Research Award, National Science Concil
2012 Distinguished Professor, National Taiwan University
2013 Academic Achievement Award, Formosa Medicial Association
2014 Outstanding Research Award, Ministry of Science & Technology
2014 Outstanding Service Team Award, National Taiwan University Hospital
2015 Outstanding Research Award, Hsu Yo-Hsiung Foundation
2015 Outstanding Research Team Award, National Taiwan University Hospital
2015 Outstanding Teacher Award, National Taiwan University
2015 Outstanding Research Award for improvement of population health, Wang Ming-Ning Memorial Foundation
2019 The Ministry of Education's 63rd Annual Academic Awards
2020 Distinguished Research Fellow, Ministry of Science & Technology
2021 Outstanding Research Award for Medicine & Pharmacy Technology, Lee Tien-Te Foundation

Specialty:

Gastrointestinal malignancy, Molecular Biology, Helicobacter pylori, gut microbiota

Publications:

More than 500 papers and 3 Book Chapters

Editorial board:

J Formos Med Assoc, Gut

來賓簡介-倪衍玄 (Yen-Hsuan Ni)

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個人簡介：

台大醫學系畢業，台大臨床醫學研究所博士。目前是台大醫學院小兒科特聘教授，也擔任醫學院院長。研究成果主要如下: 民國七十三年以來，定期進行國內B型肝炎的流行病學調查。目前兒童帶原率 B 型肝炎帶原率已降至 0.6%。這一系列長達30年，是世界上最久的縱向追蹤報告，在 2001 年發表的調查報告已被引用 264 次之多 (***Ann Intern Med*** 2001;135:796-800)。現在新生代肥胖的問題日益嚴重，凸顯脂肪肝的問題，倪院長的研究團隊發現易產生脂肪肝者與 UGT1A1、 PNPLA3、PPAR、GCKR、HO-1、IRGM 基因多型性有關，論文發表於各重要雜誌 (***Pediatrics, J Pediatr, AJCN，Int J Obesity，J Hepatol***)。這些發現相當具創見。近年來腸內菌在健康與疾病之間的關係頗受重視，倪院長有關腸內菌的研究，連續三年獲選為美國消化醫學週口頭報告。先前與肝炎中心合作的相關 B 型肝炎與腸內菌的論文也發表在 PNAS 雜誌。另外腸內菌與過敏相關的論文已被 ***Gastroenterology*** (IF = 18.392)接受。未來將進一步致力於 metagenomics 的研究與服務，倪院長承襲老師指導之肝病研究之外，還努力開創新領域，並且逐步開花結果。

來賓簡介-吳俊穎 (Chun-Ying Wu)

陽明交通大學醫學院副院長

國科會公共衛生與社會醫學學門召集人

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台灣微菌聯盟 創會及現任理事長
台灣醫事法律學會 常務理事
台灣實證醫學學會 理事
台灣肝癌醫學會 理事
Advance in Digestive Medicine 主編
Journal of Gastroenterology & Hepatology 副主編
Gut 編輯委員

學歷
2007 年 國立臺灣大學 醫學博士
2003 年 美國哈佛大學 法學碩士
2000 年 私立東海大學 法學士
1993 年 美國哈佛大學 公衛碩士
1991 年 國立臺灣大學 醫學士

代表性特殊榮譽及得獎紀錄
2021 年 科技部 台灣研究亮點
2018 年 醫師公會全國聯合會 醫療典範獎
2016 年 生技醫療產業策進會 國家新創獎
2015 年 科技部 傑出研究獎
2015 年 亞太消化系醫學會 新興領袖獎

代表性研究成果

吳教授發表了上百篇醫學研究論文，包括 JAMA, Journal of Clinical Oncology, Gastroenterology, JAMA Internal Medicine, Gut, Journal of Hepatology, Hepatology, 等，頂尖醫學期刊。四本法律專書：醫療糾紛的全國性實證研究、醫療過失責任與醫療糾紛鑑定、醫師說明義務法院判決評析、現行醫療鑑定制度介紹及改革建議。胃癌生物標記、胃癌治療、B 型肝炎病毒偵測平台、腸道微菌叢療法、等多國專利。

來賓簡介-劉志銘 (Jyh-Ming Liou)

台大醫學院內科臨床教授

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學歷:

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國立台灣大學 流行病學與預防醫學研究所 博士(2013)

研究主題

劉教授的研究主題著重在消化道癌症分子生物流行病學和幽門螺旋桿菌感染。內容包含了：針對第一線(***Gut*** 2010; 59:572-8. ***Lancet*** 2013;381:205-13. ***Lancet*** 2016;388:2355-65.)、第二線(***Am J Gastroenterol*** 2016;111:381-7. ***Lancet Gastroenterol Hepatol.*** 2023;8:228-241.)幽門螺旋桿菌感染治療的根除方法，且發展出更有效幽門桿菌的檢測工具 (***Gastroenterology.*** 2018;155:1109-1119.)，並探討在社區環境中，真實世界幽門桿菌除菌效益(***Gut*** 2016;65:1784-92)。這些研究成果為幽門螺旋桿菌根除治療提供了共識和指引。(***Clin Gastroenterol Hepatol***. 2022;20:973-983.e1. ***Gut***. 2020;69:2093-2112.)。近年還將研究延伸到幽門螺旋桿菌抗藥性(***Lancet Gastroenterol Hepatol*** 2017;2(10):707-715.)，以及幽門螺旋桿菌除菌過後腸道菌叢菌相的長期變化 (***Lancet Infectious Diseases***. 2019;19:1109-1120)。劉教授曾獲得多個獎項，包括：宋瑞樓教授基金會優秀論文獎 (2011)、台大醫院傑出研究獎-年輕優秀研究獎 (2012)、吳大猷先生紀念獎 (2013)、青杏醫學獎 (2013)、香港國際消化疾病論壇- Young Investigator Award (2015)、永信李天德醫藥科技獎-青年醫藥科技獎(2017)、台大醫院傑出研究獎-醫療技術創新獎 (2018)、台灣科技部傑出研究獎(2018)以及JGH 基金會的新興領袖獎 (2019)。

成果發表–口頭報告 (1)

Gut Bifidobacterium longum is Associated with Better Native Liver Survival in Patients with Biliary Atresia

Chia-Ray Lin, **Chee-Seng Lee**, Huey-Huey Chua, Yen-Hsuan Ni, Huey-Ling Chen
臺大醫院新竹分院

Background: Biliary atresia (BA) is a devastating disease of progressive fibro-obliterative cholangiopathy that causes liver cirrhosis in early infancy. Kasai portoenterostomy (KPE) is the only surgical treatment to restore bile flow. There are multiple pathogenic mechanisms known to contribute to BA, mainly viral infections and immune dysregulation. Emerging evidence revealed the relationship between gut microbial and BA. **Aims:** Most biliary atresia (BA) microbiome studies showed a correlation between gut microbiota with BA outcomes at the bacteria genus level. However, species-specific analysis was limited. Therefore, we aimed to identify the microbiota signature of BA patients before and after the Kasai portoenterostomy (KPE) at a higher level and investigate the microbiota's roles in the BA outcomes. **Methods:** We enrolled BA patients from the time of diagnosis and analyzed the gut icrobiota from fecal samples collected before KPE, after KPE at 2 months old, and 6 months old. Age- matched healthy infants were enrolled as controls (HC). The raw equence data were analyzed by QIIME2, and the effect size between the BA patients and HC was calculated by linear discriminant analysis (LDA) effect size (LEfSe) to determine potential bacterial species that affect BA patient outcomes. Clinical parameters and native liver survival were analyzed in relation to stool microbiota. The median follow-up age was 3.3 years (range 1.3-7.5 years). **Results:** BA had significantly lower microbial diversity than HC 2 months and 6 months after KPE. Principle coordinate analysis (PCoA) demonstrated a distinct BA microbiota compared to HC before and after Kasai operations.). We successfully classified 88.2% and 47.0% ASVs to genus and species levels using the naive Bayes machine learning classifier trained on full-length 16s rRNA sequence of the EZBiocloud database. LEfSe analysis showed Bifidobacterium longum (BL) abundance was lower in the BA compared to the HC early before KPE and persisted through 6 months old. Correlation analysis showed BA patients with BL in microbiota have lower gamma-glutamyl transferase. BA were divided into BL-pos and BL-neg regarding BL detection in fecal samples. BL-pos BA had significantly lower total and direct bilirubin 3 months after KPE. Moreover, BL-pos BA had improved native liver survival (hazard ratio: 7.4, 95% CI: 1.4-37.7, P-value = 0.04). **Conclusion:** Our results indicated that the BA with BL in the gut had improved clinical chemistry parameters and native liver survival.

Gut Bifidobacterium longum is Associated with Better Native Liver Survival in Patients with Biliary Atresia (table and figure)

Table 1 Clinical characteristics of patients with biliary atresia who were followed up longitudinally. BL: *Bifidobacterium longum,* NSD: normal spontaneous delivery.

	BL-***pos***	BL-***neg***	*P*-value
Gender (male:female)	3:7	5:4	0.2729
Age (month)	3.3(1.3-5.7)	3.7(1.7-6.8)	0.2362
NSD (n, %)	8 (80%)	3 (55%)	0.2653
Gestational age (week)	38.5(38-40)	39(36-41)	0.7632
Birth body weight (g)	2922(2750-3406)	2930(2547-4360)	0.8703
Age of Kasai portoenterostomy (days)	33(18-119)	36(11-71)	0.9024
Feeding method			
Exclusive breast milk	2	1	0.0271
Breast milk and infant formula	8	3	
Infant formula	0	5	

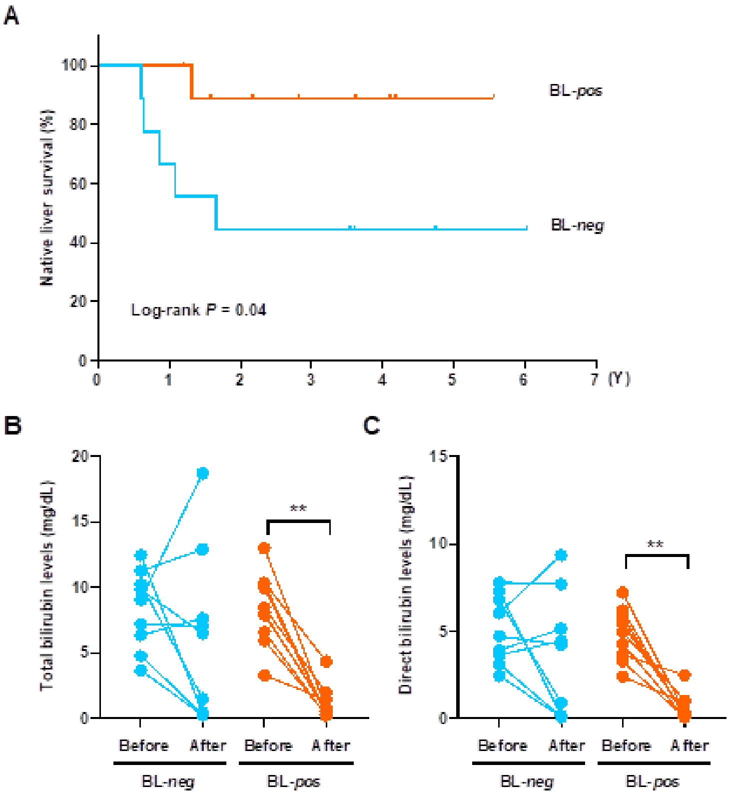

Figure 1. Outcomes BA regards to the BL detection in intestinal microbiota. (A) Native liver survival of BL-*pos* BA and BL-*neg* BA. Dynamic changes of total (B) and direct (C) bilirubin levels before and 3 months after KPE in individual patients with BA that is BL-*pos* or BL-neg. ***P*, < 0.01.

成果發表–口頭報告 (2)

Orally fecal gavage enriched distinct gut microbes and metabolites from commensals to mitigate acetaminophen-induced liver injury

Chun-Ju Yang, Hao-Chun Chang, Pin-Cheng Sung, Wen-Yuan Yang, Sen-Yung Hsieh
林口長庚醫院

Background: Fecal microbiota transplantation (FMT) has sparked great interest in treating certain human diseases with favorable efficacy. Because FMT is relatively inaccessible and unwillingly accepted by patients, oral administration becomes an appealing alternative. Although gut dysbiosis affects the severity of acetaminophen-induced liver injury (AILI), the impacts of commensal gut microbiota on AILI remain controversial. **Purpose:** We aimed to elucidate how gut microbes impact the severity of AILI to identify the microbes or their metabolites that might clinically apply to treat AILI. **Methods:** AILI was created in conventionally housed and germ-free C57BL/6 mice by peritoneal injection of sublethal and lethal doses of acetaminophen. Fecal microbiota and metabolites before and after FMT were assayed using 16S rDNA sequencing and mass spectrometry platforms, respectively. Mechanistic studies were performed in cultured hepatocytes and verified in mice with AILI. **Results:** Whatever commensal gut microbes inconsistently impacted AILI, we found that orally fecal transplantation (OFT) constantly mitigated the severity and lethality of AILI in mice. In addition, oral gavage of pasteurized fecal suspension (OPT) ameliorated AILI, as did OFT. Microbiota profiling and metabolomic assays revealed that Lachnospiraceae (a butyrate producer) and butyrate were enriched in feces after OFT or OPT, respectively. Intraperitoneal administration of butyrate alleviated AILI in mice. Mechanistically, butyrate extenuated APAP-instigated mitochondrial damage, oxidative stress, and ferroptosis by activating the AMPK-ULK1-p62 axis to actuate the Nrf2 anti-stress responses and mitophagy. Compared with N-acetylcysteine (NAC) mono-therapy, cotreatment with butyrate and NAC significantly reduced the lethality of mice with AILI. C**onclusion:** Orally fecal gavage enriched Lachnospiraceae and butyrate in the gut, which induced the Nrf2 anti-stress responses and mitophagy to mitigate AILI. Our findings highlight distinct microbial and biological impacts via orally fecal transplantation from commensal gut microbes and underline the potential of microbial metabolites for new drug development.

Orally fecal gavage enriched distinct gut microbes and metabolites from commensals to mitigate acetaminophen-induced liver injury (table and figure)

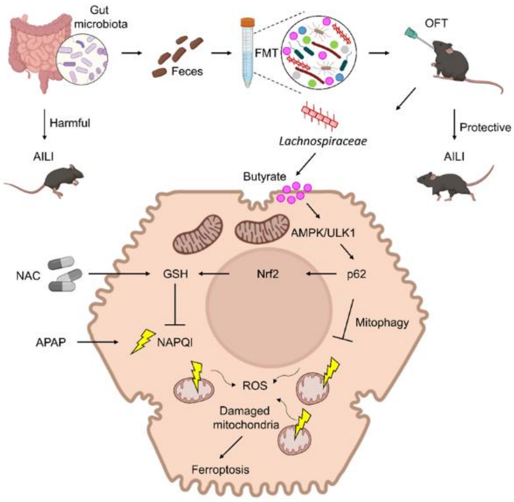

Figure 1. Graphical abstract

Our study shows orally fecal (OFT), or pasteurized fecal transplantation (OPT) mitigates the severity of acetaminophen-induced liver injury (AILI). OFT-enriched Lachnospiraceae and butyrate block AILI-associated ferroptosis by activating the AMPK-p62-Nrf2 anti-stress pathway and mitophagy. Our findings highlight a distinct gut microbiota from conventional colonic fecal transplantation and provide a new direction in treating acetaminophen overdose.

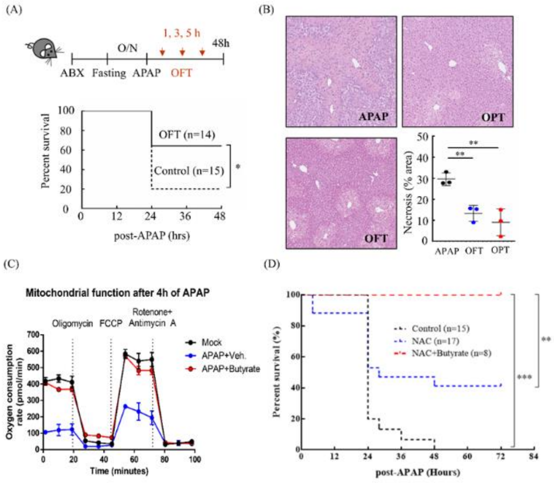

Figure 2. Oral fecal or pasteurized fecal transplantation mitigates AILI's severity and lethality in mice. (A) Orally fecal gavage (OFT) reduced the AILI-induced mortality rate in mice. (B) Oral fecal or pasteurized fecal gavage alleviates AILI-induced liver necrosis in mice. (C) Butyrate restores the APAP-induced mitochondrial dysfunction. (D) Combined NAC + butyrate synergistically protected mice from severe AILI in mice. * $P<0.05$; ** $P<0.01$; *** $P<0.001$

成果發表–口頭報告 (3)

Primary antibiotic resistance of Helicobacter pylori - Trends in Asia-Pacific regions: An updated systematic review and meta-analysis

Tzu-Chan Hong, Ming-Shiang Wu, Jyh-Ming Liou
台大醫院癌醫中心分院

Background: The antibiotic resistance of Helicobacter pylori (H. pylori) is considered an important threat to global health. Knowing the trend and current prevalence of antibiotic resistance are crucial to planning treatment strategy and possible changing of routine daily practice. Previous systemic review and meta-analysis from our group revealed an increasing trend in antibiotic resistance among Asia-Pacific area especially key antibiotics in combination regimens. **Aims:** We aim to update the resistance rate and trend in Asia-Pacific area from periods before 2000 to 2020. **Methods**: This is an updated systemic review and meta-analysis focusing on the primary resistance of H. pylori in Asia-Pacific region. We searched studies from PubMed, Embase and Cochrane trials from September 30,2016 to July 10, 2021 and synthesized with previous review. Studies provided with multiple collection periods will be viewed as individual study periods in the meta-analysis. Meta-analysis was performed with random-effects model. Subgroup analyses was performed by country and periods (before 2000, 2001-2005, 2006-2010, 2011-2015, 2016-2020). The prespecified search protocol is registered in PROSPERO (CRD42022339956). **Results:** A total of 291 studies were eligible for analysis. Overall mean H. pylori resistance were 20% for clarithromycin (95% CI 18-21, 331 study periods and total 63449 strains), 50% for metronidazole (95% CI 46-54, 264 study periods and total 49581 strains), 24% for levofloxacin (95% CI 22-26, 182 study periods and 35615 strains), 3% for tetracycline (95% CI 3-4, 163 study periods and 27678 strains) and 4% for amoxicillin (95% CI 3-4, 231 study periods and 48109 strains). From periods before 2000 to 2016-2020, resistance increased significantly in clarithromycin (7% to 28%), metronidazole (37% to 57%) and levofloxacin (8% to 33%) while trends of tetracycline and amoxicillin remained stable. Multivariate meta-regression model was performed. Resistance to metronidazole, amoxicillin and tetracycline were significantly higher in southern Asia, while Southeastern Asia was found to have the lowest resistant risks in Clarithromycin and Levofloxacin. In the latest period (2016-2020), 5 countries had documented clarithromycin and metronidazole resistant data, ten countries had either clarithromycin resistance above 15% or metronidazole resistance above 40%, namely India, Israel, Korea, Taiwan, Thailand, and 5 countries had resistance to both antibiotics, namely Cambodia, China, Iran, Philippines, Saudi Arabia. **Conclusion:** Rising of resistance in key components in H. pylori eradication regimens are reaching critical threshold. Susceptibility guided therapy may be prioritized in countries with high clarithromycin, metronidazole, or levofloxacin resistance.

Primary antibiotic resistance of Helicobacter pylori – Trends in Asia-Pacific regions: An updated systematic review and meta-analysis (table and figure)

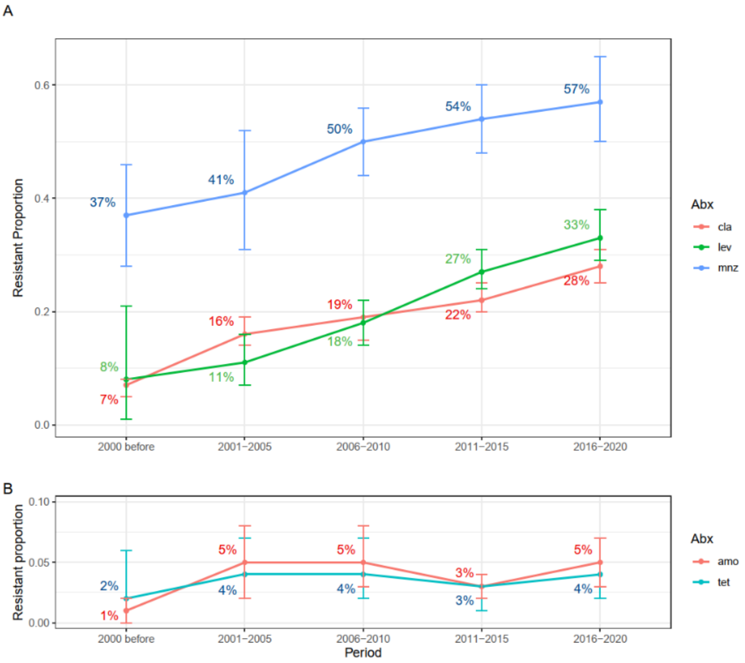

Figure 1. Trends in antibiotic resistance in Asia-Pacific Region

Table 1. Summary table of resistance in the Asia-Pacific region across periods (until 2020)

	Clarithromycin			**Metronidazole**			**Levofloxacin**			**Tetracycline**			**Amoxicillin**		
	Articles (n)	Strains (n)	Prevalence (95% CI)	Articles (n)	Strains (n)	Prevalence (95% CI)	Articles (n)	Strains (n)	Prevalence (95% CI)	Articles (n)	Strains (n)	Prevalence (95% CI)	Articles (n)	Strains (n)	Prevalence (95% CI)
Australia	4	404	0·05 (0·02-0·09)	5	657	0·57 (0·53-0·60)	0	0	--	1	137	0·00 (0·00-0·03)	2	294	0·00 (0·00-0·10)
Bangladesh	2	176	0·23 (0·02-0·56)	2	176	0·87 (0·66-0·99)	1	56	0·66 (0·53-0·78)	2	176	0·05 (0·00-0·28)	2	176	0·06 (0·02-0·10)
Bhutan	3	525	0.00 (0.00-0·02)	3	525	0·81 (0·78-0·85)	3	525	0·06 (0·02-0·10)	3	525	0·00 (0·00-0·01)	3	525	0·00 (0·00-0·00)
Cambodia	2	69	0·26 (0·16-0·37)	2	69	0·91 (0·67-1·00)	2	69	0·63 (0·47-0·77)	2	69	0·00 (0·00-0·02)	2	69	0·05 (0·00-0·16)
China	70	21159	0·29 (0·25-0·32)	60	17643	0·71 (0·66-0·75)	51	17586	0·35 (0·31-0·38)	32	10675	0·02 (0·01-0·03)	55	17863	0·02 (0·01-0·02)
Hong Kong	6	926	0·10 (0·05-0·17)	8	1052	0·53 (0·39-0·66)	1	127	0·17 (0·11-0·24)	1	193	0·00 (0·00-0·01)	3	571	0·00 (0·00-0·01)
India	11	867	0·16 (0·05-0·30)	10	821	0·72 (0·60-0·83)	7	623	0·26 (0·05-0·55)	10	821	0·10 (0·02-0·23)	8	732	0·13 (0·02-0·31)
Indonesia	1	77	0·09 (0·04-0·17)	1	77	0·47 (0·36-0·58)	1	77	0·31 (0·21-0·42)	1	77	0·03 (0·00-0·08)	1	77	0·05 (0·01-0·10)
Iran	22	2024	0·24 (0·19-0·30)	19	1822	0·64 (0·57-0·71)	12	1161	0·17 (0·09-0·27)	15	1533	0·09 (0·03-0·17)	17	1694	0·16 (0·10-0·22)
Israel	3	350	0·34 (0·08-0·67)	3	350	0·40 (0·22-0·60)	2	240	0·03 (0·01-0·06)	3	350	0·01 (0·00-0·06)	3	350	0·03 (0·00-0·10)
Japan	51	15216	0·21 (0·18-0·24)	20	7971	0·11 (0·07-0·15)	4	859	0·37 (0·15-0·62)	4	925	0·01 (0·00-0·05)	22	8970	0·03 (0·01-0·06)
South Korea	48	6093	0·20 (0·17-0·22)	40	4470	0·37 (0·34-0·41)	38	4206	0·23 (0·19-0·28)	37	4071	0·07 (0·04-0·10)	38	4215	0·08 (0·06-0·11)
Laos	1	119	0·12 (0·07-0·19)	0	0	--	1	119	0·13 (0·08-0·20)	0	0	--	0	0	--
Malaysia	9	625	0·04 (0·02-0·08)	10	696	0·43 (0·31-0·55)	6	435	0·04 (0·01-0·09)	5	336	0·00 (0·00-0·00)	6	426	0·00 (0·00-0·00)
Mongolia	3	644	0·33 (0·29-0·38)	3	644	0·74 (0·68-0·80)	1	361	0·41 (0·36-0·46)	1	152	0·25 (0·18-0·32)	3	644	0·14 (0·07-0·22)
Myanmar	1	52	0·00 (0.00-0·04)	1	52	0·37 (0·24-0·50)	1	52	0·06 (0·01-0·14)	1	52	0·00 (0·00-0·03)	1	52	0·00 (0·00-0·04)
Nepal	1	42	0·22 (0·11-0·35)	1	42	0·88 (0·76-0·96)	1	42	0·43 (0·28-0·58)	1	42	0·00 (0·00-0·04)	1	42	0·00 (0·00-0·04)
New Zealand	2	330	0·11 (0·03-0·22)	2	330	0·40 (0·25-0·57)	1	63	0·10 (0·03-0·18)	1	73	0·00 (0·00-0·02)	1	73	0·06 (0·01-0·12)
Pakistan	4	421	0·19 (0·05-0·40)	3	310	0·67 (0·18-0·99)	3	255	0·17 (0·12-0·22)	3	310	0·05 (0·00-0·13)	3	310	0·11 (0·00-0·41)
Philippines	1	42	0·29 (0·16-0·43)	1	42	0·41 (0·26-0·56)	1	42	0·62 (0·47-0·76)	0	0	--	0	0	--
Russia[$]	1	26	0·09 (0·01-0·22)	1	26	0·69 (0·50-0·85)	1	26	0·42 (0·24-0·62)	0	0	--	1	26	0·00 (0·00-0·07)
Saudi Arabia	5	518	0·22 (0·09-0·39)	4	488	0·63 (0·44-0·81)	2	87	0·09 (0·04-0·16)	4	463	0·04 (0·00-0·11)	3	387	0·08 (0·00-0·24)
Singapore	9	1258	0·11 (0·07-0·16)	9	1258	0·40 (0·35-0·45)	6	806	0·10 (0·08-0·13)	7	870	0·04 (0·02-0·08)	8	976	0·03 (0·01-0·05)
Taiwan	38	8629	0·13 (0·12-0·14)	38	8604	0·31 (0·29-0·33)	21	6712	0·18 (0·15-0·21)	19	4858	0·00 (0·00-0·01)	37	8594	0·01 (0·00-0·02)
Thailand	14	1595	0·08 (0·05-0·12)	10	987	0·43 (0·33-0·53)	6	566	0·18 (0·11-0·26)	3	574	0·01 (0·00-0·02)	3	574	0·02 (0·00-0·06)
Turkey	15	954	0·26 (0·19-0·33)	5	236	0·48 (0·37-0·59)	6	287	0·31 (0·26-0·37)	5	236	0·01 (0·00-0·05)	5	236	0·02 (0·00-0·07)
Vietnam	4	308	0·51 (0·27-0·75)	3	233	0·65 (0·49-0·79)	3	233	0·29 (0·17-0·43)	2	160	0·14 (0·01-0·36)	3	233	0·01 (0·00-0·05)
Total	331	63449	0·20 (0·18-0·21)	264	49581	0·50 (0·46-0·54)	182	35615	0·24 (0·22-0·26)	163	27678	0·03 (0·03-0·04)	231	48109	0·04 (0·03-0·04)

[$] Russia: only involved eastern part of Russia

成果發表−口頭報告 (4)

Early remission of KRAS mutations in cfDNA after chemotherapy can predict better survival in pancreatic cancer patients: a prospective cohort study

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Background: Pancreatic ductal adenocarcinoma (PDAC) is notoriously poor prognosis even though patients received treatments. The traditional biomarker, carbohydrate antigen 19-9 (CA19-9), cannot be used for monitoring treatment response in every pancreatic cancer patient. The usage of low-invasive liquid biopsies, e.g. cell-free DNA (cfDNA) from blood, has shown to improve prognostication for several other solid tumors, but has not been precisely proven for PDAC, especially for early prognosis by longitudinal sampling and monitoring. **Aims:** This study was aimed to address the hypothesis that the genetic alterations after systemic chemotherapy, could be served as an early indicator for disease outcomes in pancreatic cancer patients. **Methods:** A total of 65 paired cfDNA samples were collected from the plasma of advanced-staged PDAC patients before and after 1-month chemotherapy. These cfDNA and their corresponding somatic tumor tissue DNA were subjected to next generation sequencing for tumor-associated gene panel analysis. Patients were grouped by three risky levels which were designated in high risk: cfDNA quantity > threshold; medium risk: cfDNA quantity ≤ threshold with specific oncogene mutants after treatment; and low risk: cfDNA quantity ≤ threshold without specific oncogene mutants after treatment. Association of different risk factors with progression-free survival (PFS) and overall survival (OS) were assessed by the Kaplan-Meier log-rank test, univariate and multivariate survival analyses. **Results:** In the prospective cohort, the high risk patients who had > 9.71 ng/mL of cfDNA showed the worst PFS and OS (P < 0.001; log-rank test). The medium risk patients without remission of KRAS mutants in cfDNA after chemotherapy also demonstrated worse PFS and OS than the low risk patients with persistently negative detection or remission of KRAS mutants after chemotherapy (P < 0.01; log-rank test). However, the patients with TP53 mutants in cfDNA after treatments only showed worse OS (P < 0.05; log-rank test) but not PFS (P = 0.442; log-rank test), indicating that remission of KRAS mutants rather than TP53 in cfDNA was a better marker. Similar results were observed by univariate and multivariate Cox regression tests. **Conclusion:** Early molecular remission of KRAS mutants in cfDNA after chemotherapy indicated better survival in pancreatic cancer patients. The serial molecular response of oncogenes in cfDNA after treatment could be served as a powerful biomarker in monitoring clinical outcomes in pancreatic cancer patients.

Early remission of KRAS mutations in cfDNA after chemotherapy can predict better survival in pancreatic cancer patients: a prospective cohort study (table and figure)

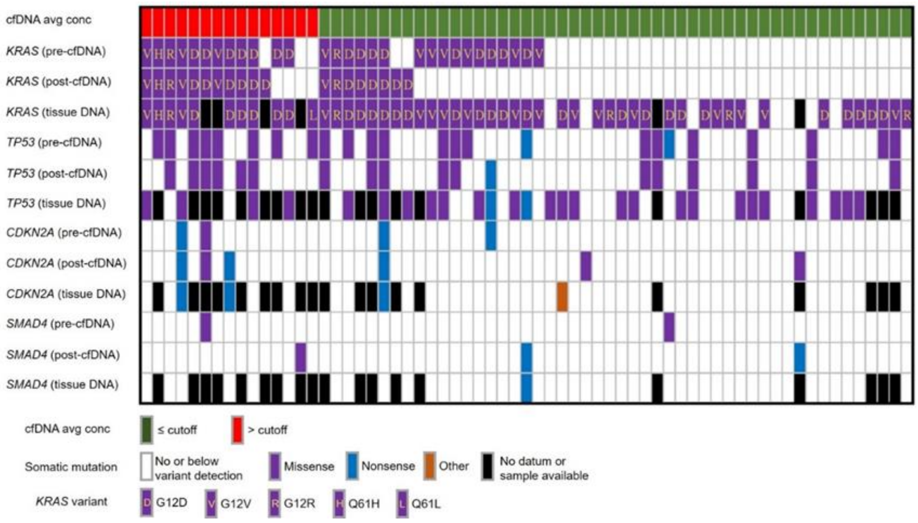


Figure 1. The oncoprint illustration (n = 65) of cfDNA levels and genetic variants in cfDNA or tissue DNA. Abbreviation: cfDNA avg conc, cfDNA average concentration of pre-cfDNA and post-cfDNA; pre-cfDNA, cfDNA from patients before chemotherapy; post-cfDNA, cfDNA from patients after two cycles of chemotherapies.

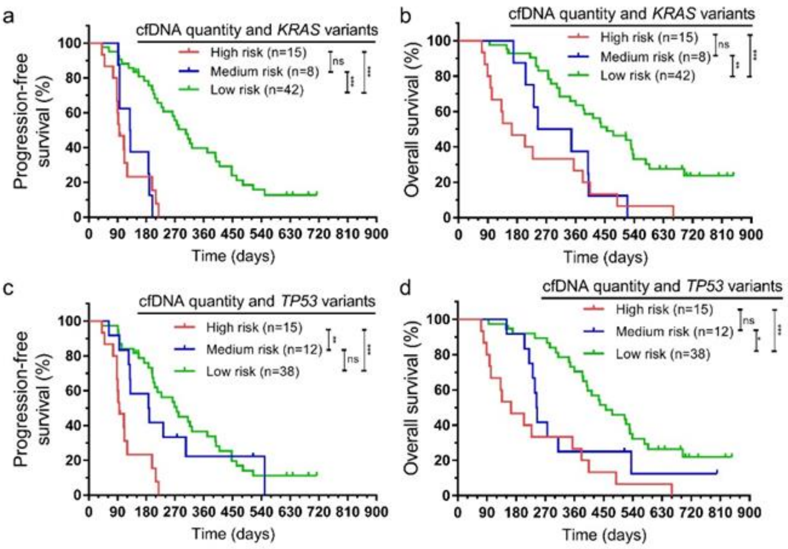


Figure 2. Kaplan–Meier analyses of patients grouped in three different risks**.** Patients were divided into three groups by cfDNA quantity/ KRAS variants (a and b) or cfDNA quantity/ TP53 variants (c and d). Definition and abbreviation: High risk, cfDNA quantity > 9.71 ng/mL; medium risk, cfDNA quantity ≤ 9.71 ng/mL with remained or recurred pathogenic variants on KRAS or TP53 after 1-month treatments; low risk, cfDNA quantity ≤ 9.71 ng/mL without pathogenic variants or with disappeared variants on KRAS or TP53 after 1-month treatments; ns, not significant; ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

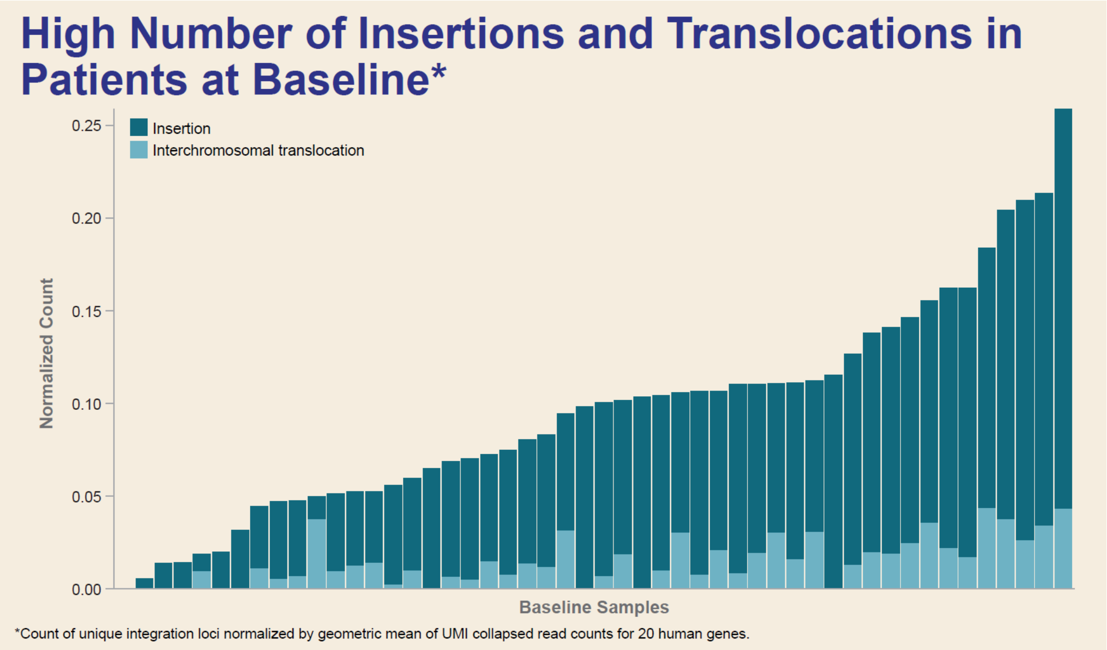
成果發表–口頭報告 (5)

Long-Read DNA Sequencing to Reveal Hepatitis B Virus Integrations in Patients with and without Nucleotide Analogue Treatment to Suppress Viral Replication

Yao-Chun Hsu, David Z. Pan, Cameron M. Soulette, Dong Han, Ricardo Ramirez, Nick van Buuren, Jaw-Town Lin, Cheng-Hao Tseng, Li Li, Simon P. Fletcher, Hongmei Mo, Becket Feierbach, Vithika Suri
義大醫院

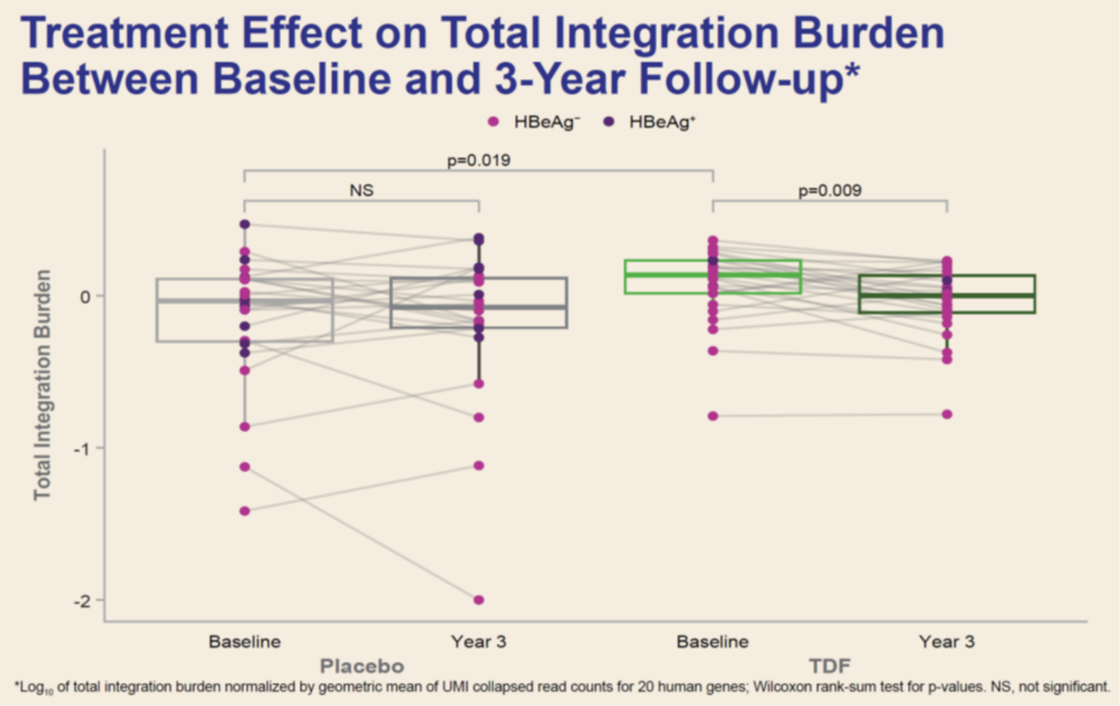
Background: The treatment effects of nucleotide analogue with tenofovir disoproxil fumarate (TDF) on transcriptionally active hepatitis B virus (HBV) integrations has recently been demonstrated in our prior study using short-read RNA-Sequencing, but the complete burden of both expressed and unexpressed integrated HBV DNA has not been clarified. **Aims:** We conducted targeted long-read DNA Sequencing (DNA-Seq) in the current analysis to comprehensively analyze the effect of TDF treatment on HBV DNA integrations. **Methods:** This analysis was based on data and biospecimens collected in a double-blind, randomized placebo-controlled trial (TORCH-B), in which eligible patients with CHB and minimally raised serum ALT (between 1-2 folds the upper limit of normal) were randomized to receive either TDF or placebo for 3 years. Targeted long read DNA-Seq on paired liver biopsies (baseline and year 3 post-treatment) were performed in 28 patients assigned to TDF and 27 patients to placebo. The average on-target read length for the long-read DNA-Seq was 5.5 kilobases (kb). The long-read DNA-Seq data was analyzed using the ViraAL Integrations ANd Translocations (VALIANT) bioinformatics workflow. **Results:** All patients had evidence of integrated HBV DNA at baseline (**Figure 1**). Of these, 98% (n=54/55) had ≥1 integrated HBV sequence(s) flanked by the same human chromosome and 80% (44/55) of patients contained ≥1 integrated HBV sequence(s) flanked by two different human chromosomes, indicating an inter-chromosomal translocation. Although HBV DNA integrations were detected near (≤5kb) 3,264 genes, only 19 of these genes were in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. Integrated HBV DNA near COSMIC genes was found in 15% (n=16/110) biopsies. Consistent with our previous short-read RNA-Seq analysis, there was a significant decrease in integration burden at year 3 post-treatment in TDF-treated (p=0.0076) but not placebo-treated (p>0.05) patients. **Conclusion:** We determined that targeted long-read DNA-Seq analysis revealed pervasive integrated HBV DNA in CHB patients with minimally elevated ALT, with ≥80% individuals having evidence of HBV-induced chromosomal translocation. Inhibition of viral replication using TDF significantly decreased the burden of HBV DNA integrations in these patients. These results suggest that early antiviral treatment for CHB may prevent occurrence of HBV DNA integrations that could be carcinogenic.

Long-Read DNA Sequencing to Reveal Hepatitis B Virus Integrations in Patients with and without Nucleotide Analogue Treatment to Suppress Viral Replication
(table and figure)


High Number of Insertions and Translocations in Patients at Baseline*

*Count of unique integration loci normalized by geometric mean of UMI collapsed read counts for 20 human genes.

Figure 1. HBV DNA integrations was pervasive in patients with CHB and minimally raised serum ALT


Treatment Effect on Total Integration Burden Between Baseline and 3-Year Follow-up*

*Log$_{10}$ of total integration burden normalized by geometric mean of UMI collapsed read counts for 20 human genes; Wilcoxon rank-sum test for p-values. NS, not significant.

Figure 2. Long-read DNA-Seq analysis found the total HBV DNA integration burden was decreased in TDF-treated patients, but not in those receiving placebo

成果發表–口頭報告 (6)

Analysis of pre-diagnostic CT images with artificial intelligence facilitates early detection of pancreatic cancer

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臺大醫院

Background: CT is the major detection tool for pancreatic cancer (PC), but the diagnostic performance of CT is interpreter-dependent, and approximately 40% of PCs less than 2 cm are missed. An end-to-end computer-aided detection (CAD) tool for PC on contrast-enhanced CT images has been developed to supplement radiologist interpretation. **Aims:** This study aims to investigate whether analysis of pre-diagnostic CT images with the CAD tool could facilitate early detection of PC. **Methods:** An end-to-end CAD tool was developed using contrast-enhanced CT images from National Taiwan University Hospital (NTUH) comprising 745 patients with histologically/cytologically-confirmed PC and 2371 controls. The CAD tool was constructed with a deep learning segmentation model and an ensemble classification model based on radiomic analysis and deep learning. The patients with PC between January 2006 and July 2018 were reviewed retrospectively to retrieve pre-diagnostic CT images, and two board-certified experienced abdominal radiologists reviewed the images to determine the tumor location. The diagnosis of PC was verified with cancer registry, and images of patients with indwelling biliary stents, prior pancreatic resection, and prior chemotherapy or immunotherapy for PC were excluded. The pre-diagnostic CT studies were analyzed by the CAD tool and compared with the original formal radiologist reports. **Results:** A total of 71 PC patients with pre-diagnostic CT images were included in this study. The median time between pre-diagnostic CT images and diagnosis was 207 days (interquartile range [IQR] 70 to 892 days). According to the consensus of the two reviewing radiologists, pre-diagnostic CT images of 41 patients had PCs, whereas those of the remaining 30 patients had unremarkable pancreas. Among the 30 cases with unremarkable pancreas, the pre-diagnostic CT studies were performed within one year before cancer diagnosis in three patients and thus were considered as harboring PC. The CAD tool achieved 68.1 % (30/44) overall sensitivity, with 70.7 % (29/41) sensitivity in 41 pre-diagnostic CT images with visible tumors and 33.3 % (1/3) sensitivity in those obtained within one year preceding diagnosis but without visible tumor. Eight of the 41 pre-diagnostic CT images with visible tumors were missed in the original radiologist report, with 6 of them being detected by the CAD tool (Figure 1). The sensitivity of the CAD tool for PC decreased with increasing interval between the pre-diagnostic CT studies and cancer diagnosis (< 3 months before diagnosis, 83.3 %; > 3 to ≤ 6 months, 66.7 %; > 6 to ≤ 12 months, 50%; more than 1 year, 60 %). **Conclusion:** The deep learning and radiomics-based computer-aided detection (CAD) tool could supplement radiologists in detecting PC on pre-diagnostic CT images.

Analysis of pre-diagnostic CT images with artificial intelligence facilitates early detection of pancreatic cancer (table and figure)

Figure 1. A 69-year-old male presented with obstructive jaundice and abdominal CT showed a pancreatic head tumor on 2018/8 (A, arrows). The diagnosis of pancreatic adenocarcinoma was confirmed after the surgical resection. Retrospective review of the pre-diagnostic CT in 2018/4 suspected an equivocal pancreatic head lesion (B, arrows) not identified in the formal radiologist report. The computer-aided detection (CAD) tool detected the pancreatic head cancer in the pre-diagnostic CT (C).

成果發表–電子海報 (1)

Association Between Electronegative Low-Density Lipoprotein and Chronic Hepatitis C Infection

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Background: Patients with chronic hepatitis C virus (HCV) infection display significantly decreased triglyceride, total cholesterol, high-density lipoprotein-cholesterol (LDL-C) and low-density lipoprotein-cholesterol (LDL-C) levels in plasma. However, chronic HCV infections have been shown to have significantly higher mortality such as increased incidence of cancer and cancer-related mortality and extrahepatic diseases such as cardiovascular diseases and cerebral vascular diseases (CVD) than the general population. Plasma LDL has been classified into five charge-defined sub-fractions LDL L1, L2, L3, L4 and L5 by anion-exchange chromatography and L5, the most negatively charged LDL, is more abundant in patients with increased cardiac risks than in the healthy population. **Methods:** Patients with CHC and controls were enrolled. Laboratory data were collected and plasma was tested for the LDL 5 sub-fractions (L1, L2, L3, L4, and L5) using the increasing negative charge on anion-exchange columns. L5% means the percent of L5 in total LDL. L5 concentration ([L5]) estimated by L5%* LDL-C. Patients treated with direct antiviral agents (DAAs) were enrolled for testing the serial change of the L5 at baseline, end-of-treatment (EOT), and end-of-follow-up (EOF) which is the 12 weeks after cessation of therapy with the definition of the sustained virological response (SVR12). **Results:** Total 477 subjects were enrolled. There were 310 (65.0%) with positive anti-HCV and 73 subjects with the baseline, EOT, and EOF samples after DAA treatment for testing the L5% and [L5]. The L5% was an risk factor associated with HCV infection (the risk of L5% >1.8 was approximately ten-fold OR=10.28) and the risk of L5% >5 (OR=8.1) was eight-fold after adjusting the other risk factors. By multivariate analyses, the anti-HCV positivity was the only factor significantly associated with the risk of L5%>1.8. Among patients with HCV infection, L5% was significantly associated with ALT and platelet levels. For patients with DAA therapy, plasma L5 (%) and [L5] significantly decreased by successful anti-viral treatment ($p<0.0001$ for L5% and $p=0.0018$ for [L5]). **Conclusion:** LDL L5, showing an increased level compared to controls, indicates that it can be used as a new biomarker for liver-related disease caused by HCV infection. Although the elevated serum lipid profile has been noted after successful DAA therapy, the decreased levels of L5 after the cure of the HCV RNA implicate a role in the decreased risk of CVD.

Association Between Electronegative Low-Density Lipoprotein and Chronic Hepatitis C Infection (table and figure)

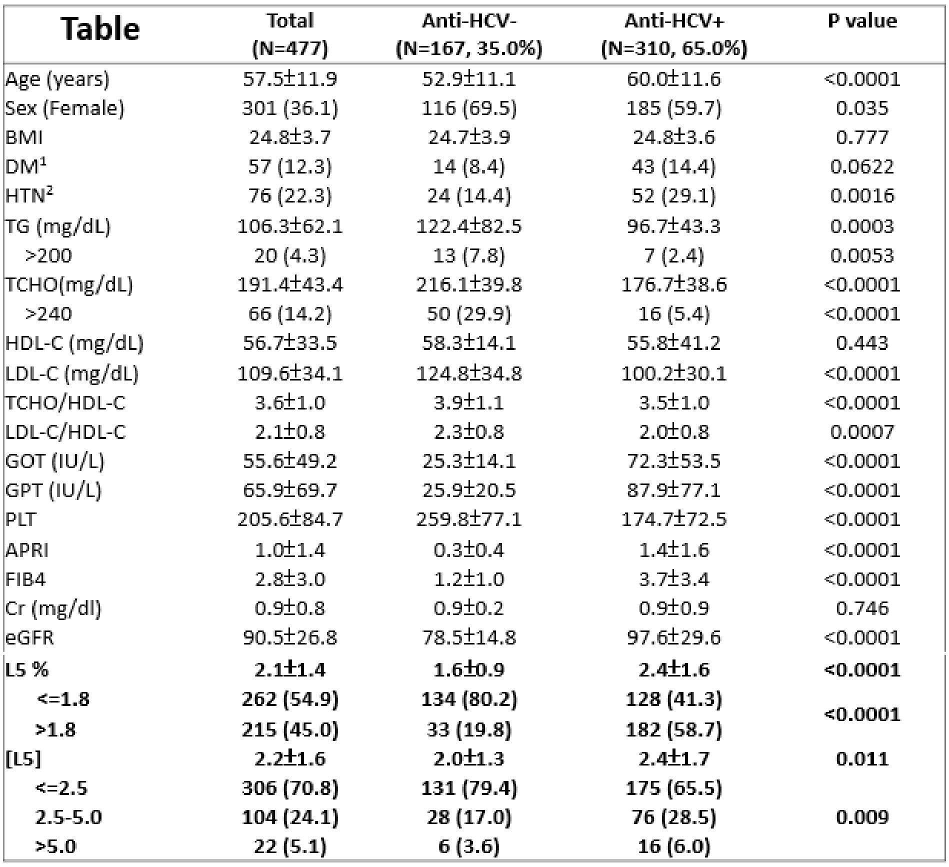

Table	**Total (N=477)**	**Anti-HCV- (N=167, 35.0%)**	**Anti-HCV+ (N=310, 65.0%)**	**P value**
Age (years)	57.5±11.9	52.9±11.1	60.0±11.6	<0.0001
Sex (Female)	301 (36.1)	116 (69.5)	185 (59.7)	0.035
BMI	24.8±3.7	24.7±3.9	24.8±3.6	0.777
DM^1	57 (12.3)	14 (8.4)	43 (14.4)	0.0622
HTN^2	76 (22.3)	24 (14.4)	52 (29.1)	0.0016
TG (mg/dL)	106.3±62.1	122.4±82.5	96.7±43.3	0.0003
>200	20 (4.3)	13 (7.8)	7 (2.4)	0.0053
TCHO(mg/dL)	191.4±43.4	216.1±39.8	176.7±38.6	<0.0001
>240	66 (14.2)	50 (29.9)	16 (5.4)	<0.0001
HDL-C (mg/dL)	56.7±33.5	58.3±14.1	55.8±41.2	0.443
LDL-C (mg/dL)	109.6±34.1	124.8±34.8	100.2±30.1	<0.0001
TCHO/HDL-C	3.6±1.0	3.9±1.1	3.5±1.0	<0.0001
LDL-C/HDL-C	2.1±0.8	2.3±0.8	2.0±0.8	0.0007
GOT (IU/L)	55.6±49.2	25.3±14.1	72.3±53.5	<0.0001
GPT (IU/L)	65.9±69.7	25.9±20.5	87.9±77.1	<0.0001
PLT	205.6±84.7	259.8±77.1	174.7±72.5	<0.0001
APRI	1.0±1.4	0.3±0.4	1.4±1.6	<0.0001
FIB4	2.8±3.0	1.2±1.0	3.7±3.4	<0.0001
Cr (mg/dl)	0.9±0.8	0.9±0.2	0.9±0.9	0.746
eGFR	90.5±26.8	78.5±14.8	97.6±29.6	<0.0001
L5 %	**2.1±1.4**	**1.6±0.9**	**2.4±1.6**	**<0.0001**
<=1.8	**262 (54.9)**	**134 (80.2)**	**128 (41.3)**	**<0.0001**
>1.8	**215 (45.0)**	**33 (19.8)**	**182 (58.7)**	
[L5]	**2.2±1.6**	**2.0±1.3**	**2.4±1.7**	**0.011**
<=2.5	**306 (70.8)**	**131 (79.4)**	**175 (65.5)**	**0.009**
2.5-5.0	**104 (24.1)**	**28 (17.0)**	**76 (28.5)**	
>5.0	**22 (5.1)**	**6 (3.6)**	**16 (6.0)**	

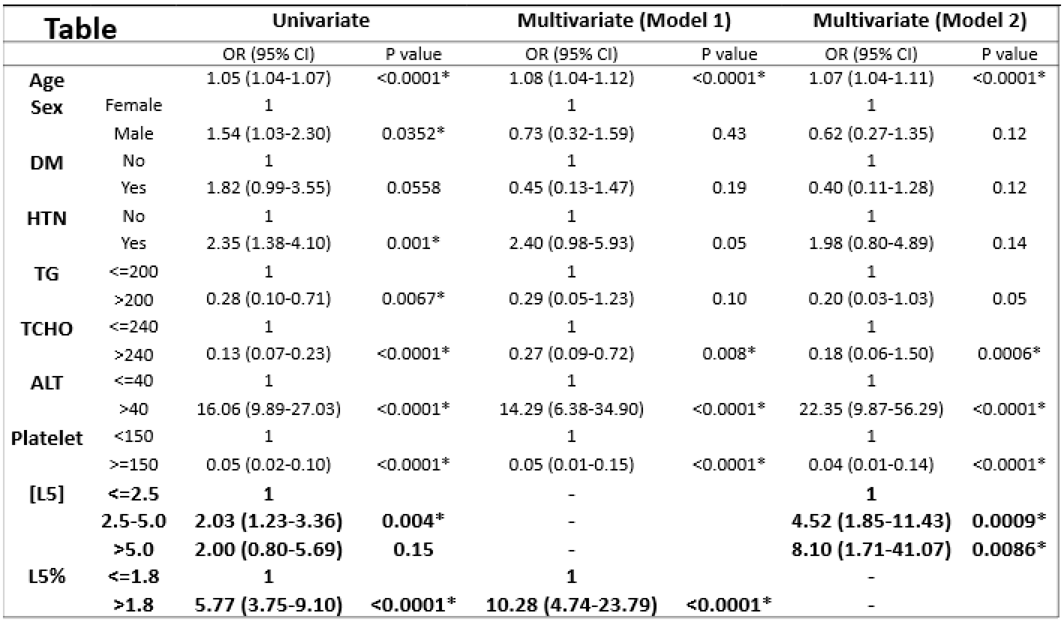

Table		**Univariate**		**Multivariate (Model 1)**		**Multivariate (Model 2)**	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age		1.05 (1.04-1.07)	<0.0001*	1.08 (1.04-1.12)	<0.0001*	1.07 (1.04-1.11)	<0.0001*
Sex	Female	1		1		1	
	Male	1.54 (1.03-2.30)	0.0352*	0.73 (0.32-1.59)	0.43	0.62 (0.27-1.35)	0.12
DM	No	1		1		1	
	Yes	1.82 (0.99-3.55)	0.0558	0.45 (0.13-1.47)	0.19	0.40 (0.11-1.28)	0.12
HTN	No	1		1		1	
	Yes	2.35 (1.38-4.10)	0.001*	2.40 (0.98-5.93)	0.05	1.98 (0.80-4.89)	0.14
TG	<=200	1		1		1	
	>200	0.28 (0.10-0.71)	0.0067*	0.29 (0.05-1.23)	0.10	0.20 (0.03-1.03)	0.05
TCHO	<=240	1		1		1	
	>240	0.13 (0.07-0.23)	<0.0001*	0.27 (0.09-0.72)	0.008*	0.18 (0.06-1.50)	0.0006*
ALT	<=40	1		1		1	
	>40	16.06 (9.89-27.03)	<0.0001*	14.29 (6.38-34.90)	<0.0001*	22.35 (9.87-56.29)	<0.0001*
Platelet	<150	1		1		1	
	>=150	0.05 (0.02-0.10)	<0.0001*	0.05 (0.01-0.15)	<0.0001*	0.04 (0.01-0.14)	<0.0001*
[L5]	**<=2.5**	**1**		-		**1**	
	2.5-5.0	**2.03 (1.23-3.36)**	**0.004***	-		**4.52 (1.85-11.43)**	**0.0009***
	>5.0	**2.00 (0.80-5.69)**	**0.15**	-		**8.10 (1.71-41.07)**	**0.0086***
L5%	**<=1.8**	**1**		**1**		-	
	>1.8	**5.77 (3.75-9.10)**	**<0.0001***	**10.28 (4.74-23.79)**	**<0.0001***	-	

成果發表-電子海報 (2)

Predicting the Potential of Eliminating Virus-related Hepatocellular Carcinoma in Taiwan by Deep Machine Learning

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Background: To reduce the incidence of hepatocellular carcinoma (HCC), three change points of interventions have been implemented in Taiwan, including hepatitis B vaccination from 1984, universal health care from 1995, and antiviral therapy from 2004. When the secular trend of HCC has been improved after cascade of interventions, the next target will be pertaining to when and how the elimination of virus-related HCC could be achieved by adding large-scale antiviral therapy to the current three change-point interventions. **Aims:** The primary aim of this study was to predict when and how the elimination of virus-related HCC could be achieved by adding large-scale antiviral therapy to the causal chains of interventions with deep machine learning method. **Methods:** The digital twin design was envisaged to produce the virtual group after learning parameters that governed the direct and indirect causal chains of three change-point interventions, including the gradual expansion of antiviral therapy when making allowance for the heterogeneity of demographic and geographic variations. Bayesian causal graphic model was adopted to estimate when and how eliminating virus-related HCC with the incidence less than 4 per 100,000 could be achieved with large-scale antiviral therapy. **Results:** Based on the incidence predicted by the virtual group after learning the long-term time trend of HCC incidence pertaining to three-change points of direct and indirect causal chains, the elimination of virus-related HCC in Taiwan would be achieved by the end of 2045 when a further 10,042 virus-related HCC incident cases could be averted after treating 159,992 and 34,624 chronic hepatitis B and C patients with large-scale antiviral therapy, respectively. **Conclusion:** We demonstrate how to use the digital twin design with Bayesian casual graphic model to achieve the elimination of virus-related HCC when adding large-scale antiviral therapy to the existing three change-point interventions for HCC. These findings may provide state-of-the-art evidence-based estimate on the global elimination of virus-related HCC.

Predicting the Potential of Eliminating Virus-related Hepatocellular Carcinoma in Taiwan by Deep Machine Learning (table and figure)

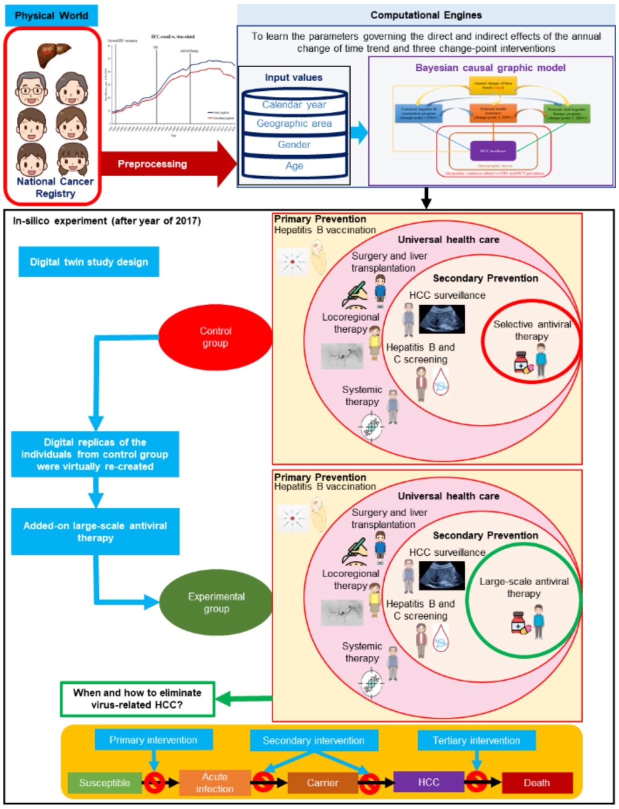

Figure1. The in-silico experiment based on the Bayesian causal graphic model

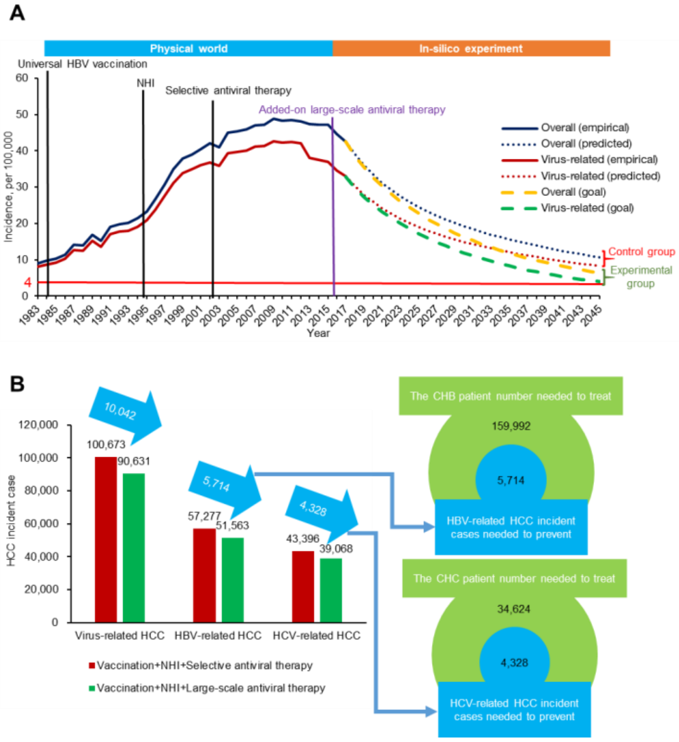

Figure2. The elimination of virus-related HCC predicted by the in-silico experiment

成果發表-電子海報 (3)

Cost-effectiveness Analysis of Curative Salvage Treatment for Recurrent Hepatocellular Carcinoma after Primary Liver Resection – a Nationwide Cohort Study

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Background: Hepatocellular carcinoma (HCC) recurrence after primary liver resection is an essential clinical issue. How to choose the optimal curative salvage treatments is still debated. **Aims:** Cost-effectiveness Analysis was conducted to compare the curative salvage treatments for recurrent hepatocellular carcinoma (HCC) after primary liver resection. **Methods:** A retrospective cohort study was developed using data from the Taiwan National Health Insurance Research Database (NHIRD). The target population was individuals taking one of the curative treatments (resection, radiofrequency ablation [RFA], or liver transplant) for the first recurrent HCC during 1997-2013. Cost-effectiveness analysis, stratified by tumor size and age, with the partitioned survival modeling approach was performed with a 10-year of time horizon from the perspective of health providers. The main measured outcome was the incremental cost-effectiveness ratio (ICER) with the willingness-to-pay set at $65,835 USD (Three times of GDP per capita of Taiwan in the Year 2013) per quality-adjusted life year (QALY) saved. The inverse probability of treatment weighting (IPTW) was applied to mitigate the potential selection bias for estimating medical costs, progression-free and overall survivals. One-way sensitivity analysis and probabilistic sensitivity analysis with 1,000 Monte Carlo simulations were performed to detect the impacts of variation in parameter estimates on the robustness of the conclusion. **Results:** For patients with tumor size >3cm, the ICER of resection compared to RFA was $5,995 USD/QALY for patients below the age of 60 and was $90,202/QALY for those aged 60 and above. For patients with tumor size <3cm, resection was dominant compared to RFA for those aged below 60, while the ICER of resection compared to RFA was $187,626/QALY for those aged 60 and above. The ICER of liver transplant compared to the resection was beyond the threshold of the willingness-to-pay at both age groups. **Conclusion:** For patients with the first recurrent HCC after primary surgical resection, the surgical resection was more cost-effective among the treatments if patients below 60 years old, while RFA was more cost-effective if patients beyond 60 years old. Liver transplant was not a cost-effective option for either age group. This study fills the gap of clinical decision-making for patients with recurrent HCC prior to an HCC resection and provides insight on the designation of healthcare reimbursement.

Cost-effectiveness Analysis of Curative Salvage Treatment for Recurrent Hepatocellular Carcinoma after Primary Liver Resection – a Nationwide Cohort Study (table and figure)

Table 1: Estimates of ICER by Tumor Size and Age

Scenario	Strategy	Cost ($USD)	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness	ICER
Tumor Size ≥3cm						
Age<60	Major RFA	64,686		2.3835		
	Major RR	67,018	2,332	2.7725	0.3890	5,995
Age≥60	Major RFA	46,537		2.3731		
	Major RR	62,043	15,506	2.5450	0.1719	90,202
Tumor Size <3cm						
Age<60	Minor RFA	61,063		3.1177		
	Minor RR	58,577	-2,487	3.3523	0.2346	(10,600) (dominance)
	SLT	385,463	324,400	4.5338	1.4161	229,080 (SLT vs RFA)
Age≥60	Minor RFA	44,667		2.9080		
	Minor RR	50,725	6,058	2.9403	0.0323	187,626 (RR vs RFA)
	SLT	336,537	291,870	3.3505	0.4425	659,593 (SLT vs RFR)

WTP: $65,835

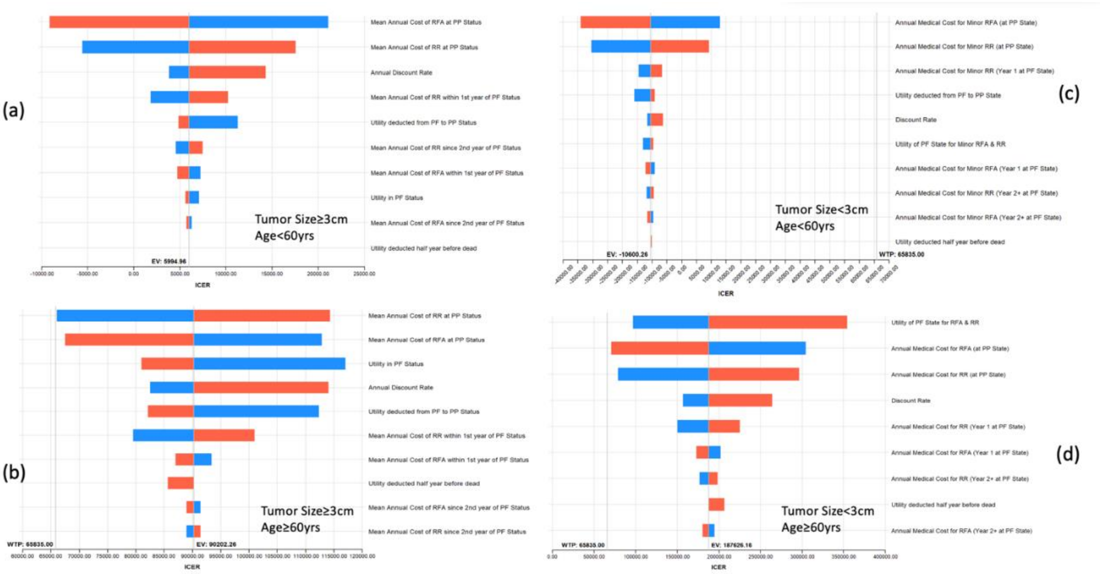

Figure 1: Tornado Diagrams for ICER – RR vs. RFA(ref.)

The red bar indicates the value higher than the base case amount; while the blue bar indicates the value lower than the base case amount.