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林新醫學年報 JANUARY


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# 目　　錄

# 林新年報

林新年報為收集院內醫師、醫事人員及行政人員，最近一年的論文，其來源來自於投稿林新年報的論文及已刊登於國內外雜誌論文，期待本院同仁儘量發表，提高本院醫療、護理及醫管專業的水準。論文的電子稿，請 E-mail 至教研部秘書。




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# 序

林新醫院自民國 88 年遷院以來，以「創新、溫馨、效率、品質」的理念，於三年內由地區醫院升格為區域教學醫院，全體同仁的努力有目共睹。醫院的角色也由「全方位的社區醫療服務」另須兼顧「教學的任務」。

「全面醫療品質提昇」及「以病人為中心的服務導向」為本院既定的方針，院方希望全體同仁能提高自己專業的能力，除接受繼續教育訓練外，更鼓勵將寶貴的經驗、想法寫成論文發表。因此除了本院原已制定的論文獎金制度外，更於民國 91 年開始籌劃成立林新醫學年報～LinShin Medicial Annual Report～，鼓勵全院同仁投稿。

很欣慰的林新醫學年報創刊號終於出版了。

一種高水準雜誌的形成是非常不容易的，林新醫學年報創刊號，不論其內容水準如何，畢竟是大家努力的心血。我很誠心的希望「林新醫學年報」能夠長久持續下去，內容更豐富，水準更高。

最後我要感謝全院同仁的支持，在我們共同的努力之下，使夢想成真，踏出了第一步。同時也希望全院同仁共同努力，持續將研究成果投稿於林新醫學年報。

林新醫院 院長 林仁卿

JAN.14, 2020

# 編者的話

林新年報自民國 92 年創刊以來，如今已進入了第 16 年。回顧過去，在院長、歷任副院長、部主任及所有院內同仁的努力下，這本屬於林新醫院的年報，終能按時一期又一期的出版。在院長的帶領及鼓勵下，每一年投稿的件數及論文的品質皆有顯著的進步。希望藉著林新年報，能提高院內同仁論文寫作的動機，將臨床寶貴經驗及想法付諸文字，以達流傳保留目的，提升同仁專業水平，並為醫院留下重要的醫學資料，以利後進學習。希望有朝一日，這份年報能成為同儕審查的醫學期刊，這是我們的目標，也將是林新醫院向醫學中心水平邁進的重要里程碑之一。

106 年起我們已將林新年報電子化，取消紙本印刷，除了響應環保議題外，亦可讓員工在院內任何一台電腦經院內網路讀取年報資料，增加閱讀可近性。

最後我們感謝院內同仁在忙碌的醫療服務之中，還能踴躍的寫作及投稿，才能使這份年報順利出刊。期望未來每一年的年報，都能有更豐富的內容。

林新醫院教研部副院長 張光遠

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# 台灣腎臟移植的過去、現在與未來

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## 摘　要

腎臟移植是末期腎衰竭患者最好的治療模式，不只改善了生活品質，也明顯提高病人之存活率。自從李俊仁教授於 1968 年執行亞洲第一例腎臟移植以來，台灣腎臟移植之歷史至今已屆滿五十年，在移植醫學界的先驅們多年的努力之下，已建立起一套完整的制度，為亞洲地區之楷模。移植病人及移植腎之存活率均不亞於歐美先進國家。然而，腎臟移植並非十全十美，病人仍須面臨許多嚴苛的挑戰如排斥、感染、腫瘤、心血管疾病等。對於慢性排斥，目前仍無有效的治療。台灣末期腎衰竭患者之發生率及盛行率均為世界首位。然而，由於器官之短缺，有幸接受腎臟移植者少之又少，僅佔所有尿毒症患者的 4%。此一強烈的反差是台灣未來需要面對的嚴肅課題。

關鍵詞：腎臟移植 (Renal transplantation)
末期腎臟病 (End-stage renal disease)
器官捐贈 (Organ donation)

## 引　言

根據台灣腎臟醫學會所作之調查，並提供給美國腎臟資料庫系統 (United States Renal Data System , USRDS) 之報告[1]，台灣末期腎臟病的發生率為每百萬人口 476 人，盛行率為每百萬人口 3317 人。兩者皆高居世界第一。從腎臟醫學會統計資料[2] 及衛生福利部國民健康署之台灣腎臟病年報[3] 來看，造成末期慢性腎臟病的主要原因依序為糖尿病，慢性腎小球腎炎、高血壓及慢性腎間質疾病，特別是糖尿病從 2001 年起就超越慢性腎小球腎炎成為尿毒症之罪魁禍首[2]。然而台灣末期腎臟病接受腎臟移植的比率卻只佔所有末期腎臟病人的 4%，即每百萬人口 11.2 人，在 USRDS 的排名中為倒數第三名[1]。由此可見，台灣的腎臟移植仍有極大的發展空間。

## 歷史沿革

1954 年波士頓 Peter Bent Brigham 醫院 (PBBH) ( 目前稱為 Brigham and Women 醫院，為哈佛大學教學醫院之一 ) 的 Murray 醫師所領導的團隊完成了人類史上第一次成功的腎臟移植。因為是同卵雙胞胎間的腎臟移植，因此沒有排斥的干擾。此一劃時代的成就震驚了全世界，也間接促成台大醫院急起直追。1963 年台

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大醫院派遣一般外科李俊仁醫師前往哈佛大學進修兩年，期間李醫師在 PBBH 參與好幾次腎臟移植，其中包括人類第一次非同卵雙胞胎的腎臟移植 (1964 年 )。李教授在其回憶錄：「生命的火焰」[4] 一書中詳細的描述了當年立志從事器官移植的心路歷程。李教授回國後不久，就在 1968 年 5 月 27 日完成了亞洲第一例活體腎臟移植。隨後在 1969 年 5 月 24 日完成了亞洲第一例屍體腎臟移植。因此，台灣堪稱亞洲地區腎臟移植的先驅。李教授在 1971 年發表了最初 11 例腎臟移植的經驗 [5]。這 11 例包括 3 例屍腎移植及 8 例親屬腎臟移植，追蹤時間為 3 至 30 個月不等。李教授在這篇文章中詳細描述了手術方法、免疫抑制劑之使用、術後之併發症及存活狀況，堪稱台灣及亞洲地區移植醫學界的經典之作。有趣的是其中 9 例也同時接受了雙側腎臟切除，主要的目的之一是為了控制血壓。因為後來各種強而有力的降血壓藥物被陸續發明，目前的觀念則認為無需作此一處理。當時所使用之免疫抑制劑為 prednisolone 每日 100-300 毫克及 azathioprine 每天每公斤體重 5-7 毫克。相較於目前的多重選擇，實在不可同日而語，也可以想見當年照顧腎臟移植病人之辛苦。台灣於 1987 年 6 月 19 日公布「人體器官移植條例」[6]，更於 1987 年 9 月 17 日率先亞洲各國，立法公告「腦死判定程序」[7]。鄰國如日本則是在 1997 年，而韓國更遲至 2000 年才立法承認腦死的觀念。2002 年 3 月 7 日台灣成立「器官捐贈移植登錄中心」。此一中心為當年的衛生署捐助設立之財團法人機構。負責建立一套公平、公開、透明化之器官分配原則 [8]。以腎臟移植為例，除了一些基本分配原則外，另設有一份等候者評分標準表。其評分項目涵蓋等候時間、人類白血球抗原 (human leukocyte antigen, HLA) 符合配對、病患年齡、血型、B、C 肝炎病毒感染等項目。為了鼓勵活體腎臟移植，在這套評分系統裏特別加入一項非醫學評分，即曾為活體器官捐贈者，如今變成腎臟移植等待者可以加 4 分。根據這一套評分系統，每當有大愛器官捐贈者出現時，電腦即可根據捐贈者及腎臟移植等待者之資料，為每一位等候者計算分數，由大而小依序分配腎臟。至於「腎臟移植醫院」及「腎臟移植醫師」之資格，也訂有一套嚴格的標準 [9]。由於腎臟移植需要一個團隊及周邊配合單位，因此規定移植醫院必需是評鑑優等之區域醫院等級以上，具有專任外科專科醫師及泌尿專科醫師各二名以上，且至少有腎臟移植醫師一名。至於腎臟移植醫師的資格亦有明確的規定 [9]，其中之一是至少擔任腎臟移植手術第一助手達 20 例及術後照顧 20 例。綜合上述，可見台灣之腎臟移植發展，歷史悠久，制度完善，名列亞洲前茅。表一列舉台灣器官移植醫學發展的重要里程碑。

## 免疫抑制劑之發展

人類早在 20 世紀初期就嘗試動物及人體的腎臟移植 [10]，然而，人們在當時並無「排斥」的概念，也沒有任何免疫抑制劑可以使用。因此，所有的嘗試都失敗了。人類的第一次成功的腎臟移植是在 1954 年由 Murray 醫師所領導的團隊在美國波士頓 Brigham and Women 醫院所完成 [11]。這是一對同卵雙生子間的器官移植，因此沒有排斥的問題。也大約在這個時候，人類發明了第一種免疫抑制劑：可體松 (cortisone)。在六十年代，6-MP (Mercaptopurine, Azathioprine) 陸

**表一：台灣器官移植醫學里程碑**

| 日期 | 重要里程碑 |
|---|---|
| 1968/5/27 | 第一例活體腎臟移植 |
| 1969/5/24 | 第一例屍體腎臟移植 |
| 1984/3/22 | 第一例肝臟移植 |
| 1984/4/1 | 第一例胰臟移植 |
| 1985/8/15 | 台灣移植醫學會誕生 |
| 1987/6/19 | 人體器官移植條例公布實施 |
| 1987/7/17 | 第一例心臟移植 |
| 1987/9/17 | 公告腦死判定程序 |
| 1991/7/10 | 第一例單肺臟移植 |
| 1996/2/24 | 第一例雙肺臟移植 |
| 2002/3/7 | 器官捐贈移植登錄中心成立 |
| 2004/11/22 | 第一例血型不相容活體腎臟移植 |
| 2007/10/27 | 第一例小腸移植 |

續發明，成為控制排斥的藥物。如前所述，台灣早期的腎臟移植即以類固醇 (prednisolone) 和移護寧 (Azathioprine, Imuran) 為主要的抗排斥藥物。七十年代環孢靈 (Cyclosporin A, CsA) 的發明是人類器官移植歷史的重要里程碑 [12]。台灣也於 1985 年由 Sandoz 藥廠 ( 後來併入諾華藥廠，Novartis) 引進環孢靈水劑 (Sandimmun neoral oral solution®)，並於 2001 年引進環孢靈膠囊 (Sandimmun neoral capsule®)。前者人體吸收率較不穩定，使用起來也比較麻煩，需要置於玻璃容器內加果汁或牛奶使用。後者為原型經過改良 ( 微乳化，microemulsified)，吸收率較穩定，使用起來也比較簡單。合併使用類固醇、環孢靈及移護寧使得腎臟移植後第一年的急性排斥率由超過百分之五十大幅下降至百分之三十以下 [13]。九十年代 FK506 (Tacrolimus, prograf®) 則是異軍突起 [14]，挾帶其優異的抗排斥效果橫掃全球。台灣也於 1998 年由藤澤藥廠 (Fujisawa) ( 後來改名為安斯泰來藥廠，Astellas) 引進。該藥廠並於 2009 年引進緩釋型之 FK506 (Advagraf®)。此種劑型因為一天只要使用一次，因此也改善了病人之醫囑遵從性 (adherence)。我們的研究也發現使用 advagraf 其血中 FK506 濃度之變異度 (variability) 明顯下降 [15]，而抗排斥藥物如環孢靈血中濃度之變異度越大則慢性排斥率會上升 [16]。我們在另外一種抗排斥藥物：斥消靈 (sirolimus) 的研究也發現類似的結果 [17]。FK506 和 Cs A 雖然化學結構式不一樣，但是都屬於 calcineurin 抑制劑，而 calcineurin 是 T 淋巴球活化的過程中，極具關鍵性的磷酸酶 (phosphatase)。Calcineurin 可以使活性 T 細胞核因子 (Nuclear factor of activated T-cells, NFAT) 去磷酸化，使其得以從細胞質進入細胞核，並與細胞激素 ( 如 Interleukin 2) 之 DNA 結合。啟動細胞激素之製造。由於多數臨床研究顯示 FK 506 之抗排斥效果優於 CsA，因此 FK 506 逐漸取代 CsA 而成為主流抗排斥藥物。由於 FK 506 極為昂貴，因此健保局要求必需有足夠的證據顯示其療效，這也促成了台灣有史以來在移植醫學界的第一次多中心的人體試驗。此一研究結果也在亞洲移植醫會發表 [18]。其後台灣在 1998 年由羅氏藥廠引進另一類抗排斥藥物：Mycophenolic acid (MPA)，商品名 Mycophenolate Mofetil® (MMF，山喜多 )，2003 年則由諾華藥廠引進另一種 MPA：Mycophenolic sodium (Myfortic®，睦體康 )。MPA 藥理作用類似移護寧，都是屬於「抗代謝」型藥物 (Antimetabolites)，因為可以抑制淋巴球合成 DNA 和 RNA 時所特有之新路徑 (de novo pathway) 而不影響一般細胞合成 DNA 和 RNA 時所使用的另一條路徑 ( 救援路徑，salvage pathway)，因此具有「淋巴球專一性」，是較移護寧更強的免疫抑制劑。MPA 目前已逐漸取代了移護寧，成為免疫抑制的另一類主流藥物。另外一類藥物：mTOR (mammalian target of rapamycin) 抑制劑則由惠氏藥廠 ( 後來併入輝瑞藥廠 ) 於 2002 年引進 Sirolimus (Rapamune®，斥消靈 )。隨後，諾華藥廠也於 2008 年引進 Everolimus (Certican®，卓定康 )。mTOR 是淋巴球經由活化後要進入成熟期過程中重要之蛋白質。mTOR 傳遞之訊號可以使細胞周期從 G1 進入 S 期，並促進 DNA 之合成。此為細胞分裂必要之步驟。因此，mTOR 抑制劑藉由抑制淋巴球之增生達到其抗排斥的效果。mTOR 抑制劑是獨樹一格的免疫抑制劑 [19]。除了具有抗排斥的效果之外，也具有抗纖維化 (Anti-fibrosis)[20] 的效果。由於 mTOR 路徑與腫瘤之發展有密切關係，因此 mTOR 抑制劑也具有抗腫瘤的潛能 [21]。我們根據一項健保資料庫的研究 [22]，發現在台灣腎臟移植病人最常用的免疫抑制劑為類固醇、FK506 及 MMF。使用 mTOR 抑制劑者也達到 23% 之多。

因為腎臟移植術後的第一年是急性排斥的好發期，因此常在手術前後給予強而有力的免疫抑制劑即所謂「誘導治療」(induction therapy)。常用的藥物如第二介白素接受體拮抗劑 (interleukin-2 receptor antagonist) 包括 Basiliximab (Simulect®) 及 Daclizumab (Zenapax®)。前者由諾華藥廠於 1999 年引進台灣，後者為羅氏藥廠所引進但已經下市。其他用於誘導治療的藥物還包括抗胸腺球蛋白 (antithymocyte globulin)、抗淋巴球球蛋白 (Antilymphocyte globulin) 和抗 B 細胞單株抗體 (Rituximb, MabThera®)。表二列舉台灣引進重要免疫抑制劑之年代。

表二：台灣引進重要免疫抑制劑之年代

| 年代 | 免疫抑制劑 | 類別 |
|---|---|---|
| 1985 | Cyclosporine solution | Calcineurin 抑制劑 |
| 1998 | Tacrolimus | Calcineurin 抑制劑 |
| 1998 | Mycophenolate mofetil | 抗代謝物 |
| 1999 | Basiliximab | 第二介白素接受器拮抗劑 |
| 2001 | Cyclosporine capsule (microemulsified) | Calcineurin 抑制劑 |
| 2002 | Sirolimus | m-TOR* 抑制劑 |
| 2003 | Mycophenolate sodium | 抗代謝物 |
| 2008 | Everolimus | m-TOR 抑制劑 |
| 2009 | Tacrolimus, prolonged-release | Calcineurin 抑制劑 |

*mammalian target of rapamycin.

## 腎臟移植存活率

腎臟移植存活率可以分為兩種；其一是病人存活率，另外則是移植腎存活率。根據國家衛生研究院所發表的 2017 年台灣腎病年報 [3]，透析病人的五年存活率為 58.9%，十年存活率為 35.3%。至於腎臟移植病人第一年存活率為 97.7%，五年存活率為 92.3%，十年存活率為 80.7%。很顯然的，儘管腎臟移植病人會面臨諸多挑戰，如感染、排斥、惡性腫瘤……等等，其病人存活率仍遠高於透析病人。至於移植腎之一年存活率為 93.7%，五年存活率為 85.3%，而十年之存活率為 71.6%。亦即超過七成的病人之移植腎可以使用十年以上。根據美國腎臟登錄系統 (USRDS) 最近發佈的 2017 年報 [1]，美國一年移植腎存活率為 96.1%，五年為 84.3%，十年為 66.9%。從以上的數據可以看出台灣腎臟移植之存活率與美國相當。至於腎臟移植之病人存活率，在美國又分為屍腎移植及活體移植，其五年之病人存活率分別為 75.6% 及 87.6%，均低於台灣約 92.3% ( 五年病人存活率，不分腎臟來源 )。我們分析台中榮總 1983 到 2012 年總共 520 例腎臟移植之結果 [23]，其中死亡人數為 83 人。死因第一位是感染 (44.6%)，其次是心血管疾病 (21.7%) 及惡性腫瘤 (12.0%)。我們同時分析不同移植年代與死亡原因之演變，發現最近的 14 年，心血管疾病已經超越感染 (18.2%)，而成為主要的死亡原因 (27.3%)。尿毒症病人死亡原因接近一半是源自於心血管疾病 [24]。我們針對一組平均已追蹤 11 年的腎臟植病人，研究其冠狀動脈鈣化分數 (coronary artery calcium score)，發現鈣化分數在 300 以上者達 27.3%，另外也發現有接近三成 (29.3%) 的病人罹患代謝症候群 (metabolic syndrome)[25]。有代謝症候群的病人其冠狀動脈鈣化分數也顯著升高。可見腎臟移植病人仍屬心血管疾病之高危險族群。

## 腎臟移植之併發症

腎臟移植經過超過半個世紀的發展，如今已是一種成熟的手術。因此，外科併發症並不多見，初期之併發症如輸尿管滲漏，淋巴囊腫 (lymphocele)，血管栓塞等，其發生率都在 5% 以下。後期之併發症較常見的有輸尿管狹窄，腎動脈狹窄，膀胱輸尿管逆流等。內科方面的併發症相對較為常見。主要的併發症包括排斥、感染、惡性腫瘤、代謝性合併症等等。由於免疫抑制劑的高度進展，目前術後第一年的急性排斥率已低於 10%[12]，而第一年的移植腎存活率在 90% 以上。然而隨著時間進展，慢性排斥的機率逐漸增加。目前研究發現，後期之腎功能衰退多半因慢性抗體性排斥 (antibody-mediated rejection) 所引起 [26]。其致病機轉為受腎者因接受移植腎所帶來的異

體抗原 (alloantigen) 之刺激，逐漸產生捐贈者特異性抗體 (donor-specific antibody)，此抗體攻擊腎臟內微小血管，造成腎臟小血管之發炎 (microvascular inflammation)，進而形成移植性腎小球病變 (transplant glomerulopathy)，腎小管旁微血管炎 (peritubular capillaritis)，移植性動脈病變 (transplant arteriopathy) 等。腎臟移植病人之感染大部分仍以呼吸道及泌尿道感染較為常見。BK 病毒腎病變為近年來熱門的話題。其盛行率可達 8%[27]。BK 腎病變與免疫抑制劑的過度使用有關。我們的研究發現盛行率為 5.3%，高達 41.2% 之病人因此種感染而造成移植腎失能 [28]。另外，結核病之發生率亦較正常人高出許多。我們分析台中榮總 20 年之經驗 [29]，在 756 位病人中其發生率為 3.8%，其中肺外結核佔 23%，整體死亡率達 12.9%，是不容輕忽的感染性併發症。惡性腫瘤是另外一個重要的內科併發症。其整體發生率約為正常人的 3-5 倍 [30]，且隨移植時間進展，發生率逐年增加。西方人常發生的腫瘤以皮膚癌最常見，台灣則以泌尿上皮細胞癌 (urothelial carcinoma) 最常見。我們統計台中榮總 730 位腎臟移植病人，發現整體惡性腫瘤之發生率達 8.6%[31]。其中 47.6% 為泌尿上皮細胞癌，佔所有癌症之第一位。其次則為肝癌，佔 29%。最近以台灣健保資料庫所作之分析發現 [32]，腎臟移植病人之惡性腫瘤發生率為一般民眾的 3.75 倍，女性之發生率又多於男性，分別為一般人的 5.04 與 2.88 倍。前三名之惡性腫瘤發生部位為腎臟 (44.29 倍 )，膀胱 (42.89 倍 )，及肝臟 (5.07 倍 )。由此可見，台灣獨特之腫瘤分佈，與西方國家截然不同。其他之代謝性合併症多半與免疫抑制劑之副作用相關，包括肥胖、高血壓、糖尿病、高尿酸、高血脂……等等。

## 台灣腎臟移植面臨之困境

器官短缺是現階段面臨最大的挑戰，台灣目前透析人口已經超過 8 萬人，等待腎臟移植者有 7436 人 [33]，而 2017 年屍腎移植總數為 217 人。可見器官供需存在極大之差距。由於台灣社會屍腎捐贈的風氣仍然不足，因此近年來活體捐贈逐漸風行。2017 年有 112 例活體腎臟移植，約佔所有腎臟移植的三分之一。根據國際器官捐贈與移植登錄組織 (IRODaT) 於 2012 年發表之資料 [34]，顯示台灣每百萬人口活體器官捐贈率為 19.8 人，在世界各國排名第八，高於美國 (15.4 人 ) 及日本 (14.1 人 )，但低於韓國 (40.1 人，世界排名第二 )。根據衛福部於 2016 年發表之論文顯示 [35]：台灣屍體器官捐贈率已由 2005 年之每百萬人口 6.7 人增加到 2015 年之 10.9 人，為亞洲各國 2015 年屍體器官捐贈率之冠。在活體器官捐贈方面也由 2005 年之每百萬人口 6.9 人增加到 2015 年之 25.1 人。相對的，國人赴海外移植的人數則逐年下降。以腎臟移植為例，2005 年赴海外作移植腎臟的人數為 315 人，到 2015 年則僅有 64 人。雖然海外腎臟移植 ( 絕大多數為在大陸接受死刑犯器官 )，其存活率不亞於台灣本土之腎臟移植 [36,37]，然而基於基本人權之普世價值，死刑犯捐贈器官仍然存在許多醫學倫理方面之疑慮。況且研究顯示：海外腎臟移植病人術後十年累計罹患惡性腫瘤的機率 (21.5%) 遠高於台灣本土之移植之病人 (6.8%)[37]，因此不值得鼓勵。活體捐腎風險極低，其死亡率約 0.03%[38]。而術後長期追蹤，發生輕度高血壓及輕微蛋白尿的機會稍有增加，但存活率與一般人無顯著差異。然而最近的研究顯示 [39]，活體捐腎者其長期罹患末期腎臟病之風險高於正常人，約為 0.2-0.5%，但整體而言其發生率仍低。因此在器官短缺的情況之下，世界各國仍然積極推廣活體移植。另一個可以增加器官來源的作法是使用「廣義器官」(expanded criteria donor，ECD)，所謂 ECD 是指捐贈者已知有高血壓，腦中風或高齡等可能影響腎臟功能之情況，相較於標準器官 (standard criteria donor) 其器官品質較差。即使如此，接受 ECD 的腎臟移植仍然比透析治療存活率較佳 [40]。2017 年 12 月 26 日衛生福利部公布「心臟停止死亡後器官捐贈作業參考指引」，准許使用無心跳捐贈者 (Non-Heart beating donor) 的器官。使用此類器官，其腎臟恢復期較長，原發性無功能 (primary nonfunction) 的機會較大，但長期之存活率則無顯著差異 [41]。另外一個可以

增加腎臟來源的方法是在國外已經行之多年的「配對交換捐贈」(Paired-exchange donation)。即兩對原欲作親屬捐贈的家人，檢查結果發現各別捐贈者與受贈者之交叉試驗 (cross match test) 都呈現陽性反應。在此情況之下，如果貿然移植將造成超急性排斥。假設彼此交換捐贈者就可以使交叉試驗呈現陰性反應，則交換兩家人的捐贈者就互不衝突，可以兩全其美。此種捐贈在台灣最近也獲得法律許可，只待部分細節確認即可實施。另外，根據「器官捐贈移植登錄中心」的資料，全國合格的腎臟移植醫院共 36 家，分別位於北區 16 家、中區 10 家、南區 9 家、東區 1 家。然而，其中積極從事腎臟移植工作且成績斐然者不到一半。根據一項台北榮總的研究統計[42]，高移植量的醫院其病人及移植腎之長期存活率都較低移植量的醫院來得高，而各種併發症之發生率也較低。高移植量的醫院其住院天數較短，花費也較少。基於各移植醫院水準不一，器官得來不易，而健保資源有限的多重考量，如何去蕪存菁是必須面對的課題。

## 結　語

台灣之腎臟移植至今已屆滿五十年，是亞洲地區的腎臟移植先驅，成績斐然，不輸歐美先進國家。然而相對於台灣慢性腎臟病之高盛行率，及民眾屍腎捐贈之意願仍然低落，器官供應遠不及於需求。如何開發更多的器官來源，並使其作最佳分配，以獲取最好的存活率，是台灣，也是世界各國努力的方向。另外，長期之腎臟移植病人面臨的最大挑戰是慢性排斥，目前並無有效的治療。這些病人終究會面臨移植腎失能之結局，成為另一批等待腎臟移植者，使得等待名單更長。因此，如何避免慢性排斥之發生是比較務實的作法。過去半個世紀免疫抑制劑之發展雖然突飛猛進，大大的減少急性排斥之發生，並提升術後一年的移植腎存活率，然而長期存活率並沒有同等程度之進步[43]。如何克服這個瓶頸是人類共同的課題。此外，如何讓腎臟移植病人活得更久、更有生活品質也是大家關注的議題。大部分的併發症是免疫抑制劑帶來的副作用。因此，如何讓病人維持一個免疫耐受 (immune tolerance) 的狀態，永遠不需要服用抗排斥藥物，更是人類夢寐以求的夢想。

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# The Past, Present and Future of Renal Transplantation in Taiwan

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Renal transplantation is the best treatment modality for patients with end-stage renal disease, not only because it improves quality of life but also promotes long term survival. It has been 50 years since the first renal transplantation in Asia performed by Professor Chun-Jean Lee in 1968. With the great efforts of transplant pioneers, Taiwan is the leading country in Asia with regards to the legislation of laws in organ transplantation. Statistical analysis of both patient and graft survival revealed an excellent results comparable with western developed countries. However, renal transplant recipients are facing many challenges, such as rejection, infection, malignancy and cardiovascular diseases. Currently, there is no effective treatment for chronic rejection. Taiwan ranks first in the incidence and prevalence of end-stage renal failure around the world. On the contrary, only 4% of the uremic patients undergo renal transplantation due to shortage of organ. The big discrepancy between supply and demand is a serious problem in Taiwan and warrants effective solutions in the future. (J Intern Med Taiwan 2019; 30: 34-41)

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*Review Article*

# Signal Transduction Pathways of Acupuncture for Treating Some Nervous System Diseases

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In this article, we review signal transduction pathways through which acupuncture treats nervous system diseases. We electronically searched the databases, including PubMed, MEDLINE, clinical Key, the Cochrane Library, and the China National Knowledge Infrastructure from their inception to December 2018 using the following MeSH headings and keywords alone or in varied combination: acupuncture, molecular, signal transduction, genetic, cerebral ischemic injury, cerebral hemorrhagic injury, stroke, epilepsy, seizure, depression, Alzheimer's disease, dementia, vascular dementia, and Parkinson's disease. Acupuncture treats nervous system diseases by increasing the brain-derived neurotrophic factor level and involves multiple signal pathways, including p38 MAPKs, Raf/MAPK/ERK 1/2, TLR4/ERK, PI3K/AKT, AC/cAMP/PKA, ASK1-JNK/p38, and downstream CREB, JNK, m-TOR, NF-$\kappa$B, and Bcl-2/Bax balance. Acupuncture affects synaptic plasticity, causes an increase in neurotrophic factors, and results in neuroprotection, cell proliferation, antiapoptosis, antioxidant activity, anti-inflammation, and maintenance of the blood-brain barrier.

## 1. Introduction

Acupuncture is a form of therapy practiced for more than 3000 years in Asia. Medical doctors practice acupuncture under the guidance of meridian theory to achieve "de qi" status [1]. To perform acupuncture, doctors use thin and sterile metal needles to penetrate specific stimulation points termed acupoints. Both manual and electroacupuncture (EA) are used in medical practice. Many studies have reported the benefits of acupuncture for treating diseases such as stroke, musculoskeletal disorders, chronic urticaria, irritable bowel syndrome, overactive bladder, cancer-related fatigue, and pain in humans [2–6]. Furthermore, few adverse effects have been observed when acupuncture is performed correctly, even in children and pregnant women [7, 8]. The widely known mechanism of acupuncture is that it results in the secretion of endorphins that exert an analgesic effect. With advances in understanding, more mechanisms of acupuncture have been determined, including the local segmental effect, somatoautonomic reflex, immune system regulation, neurotransmitter modulation, the neuroendocrine effect, and the functional connectivity neural network [9–11].

Nowadays, signal transduction has been applied for explaining acupuncture mechanisms. The signal transduction pathway of acupuncture has been mentioned with respect to many diseases, including neurological [12], cardiovascular [13], metabolic [14], and gynecological [15] diseases. Among the aforementioned diseases, nervous system diseases are the most common complaints in daily practice. When used to treat nervous system diseases, acupuncture enhances cell proliferation and neuroblast differentiation by increasing the levels of brain-derived neurotrophic factor (BDNF) and phosphorylated cyclic AMP response element-binding (CREB) protein [16]. Acupuncture was reported to exert a neuroprotective effect on dopaminergic neurons through anti-inflammatory and neurotrophic effects [17].

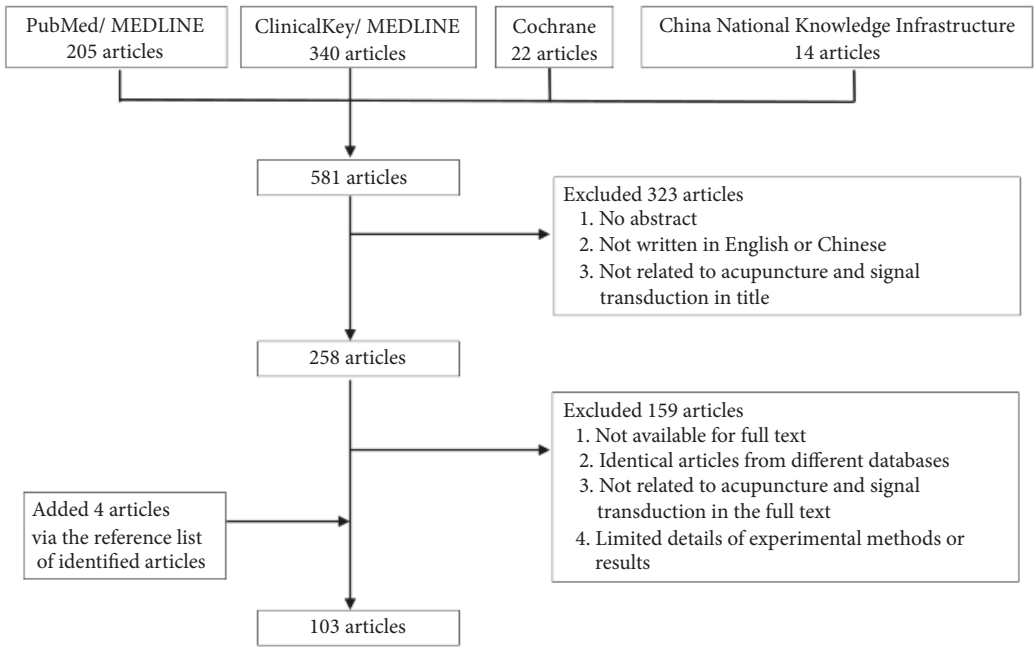


Figure 1: Flow chart of the search processes. The 103 articles were summarized in Tables 1–7.

Other mechanisms, including antioxidation, antiapoptosis, and improved energy metabolism in the brain, have been reported [18–20]. Although many studies on the signal transduction pathway of acupuncture have been conducted, few reviews have been published on this topic. In the present review, we discuss the involvement of the signal transduction pathway as a mechanism underlying the effects of acupuncture when used for treating nervous system diseases.

## 2. Method

We electronically searched the databases, including PubMed, MEDLINE, clinical Key, the Cochrane Library, and the China National Knowledge Infrastructure from their inception to December 2018 using the following MeSH headings and keywords alone or in varied combination: acupuncture, molecular, signal transduction, genetic, cerebral ischemic injury, cerebral hemorrhagic injury, stroke, epilepsy, seizure, depression, Alzheimer's disease (AD), dementia, vascular dementia (VD), and Parkinson's disease (PD). In addition, we used Boolean operators ("not," "and," "or") to narrow or widen search results. All articles written in English or Chinese were manually screened, and relevant studies were identified. We included additional articles after performing a manual review of the reference lists of identified studies or review articles. Excluded articles included those with unavailable full text, those written in other languages, those not mainly related to the mechanism of the signal transduction pathway, or those with limited details of experimental methods or results. Flowchart of the search processes was as shown in Figure 1.

## 3. Cerebral Ischemic Injury

Ischemic injury of the brain, also known as cerebral infarction, is a crucial health issue in the modern world because of its associated disability and socioeconomic burden. Acupuncture has shown beneficial effects on ischemic stroke rehabilitation by exerting the antiapoptosis effect on the ischemic area, promoting neurogenesis and cell proliferation, and regulating cerebral blood flow [21, 22]. A retrospective cohort study reported that acupuncture was effective at reducing the stroke recurrence rate [23]. Ischemic stroke causes neural cell damage related to excitotoxicity, oxygen free radical injury, inflammatory status, and blood-brain barrier (BBB) damage [24]. Experimental pathways that can reverse apoptosis and improve cell proliferation and differentiation have been proposed.

Acupuncture causes an increase in the expression of neurotrophic factors, such as BDNF and glial-derived neurotrophic factor (GDNF), in the central nervous system (CNS), exerts a neuroprotective effect on hypoxic-ischemic insults, and results in neurogenesis after the reconstruction phase [25, 26]. In addition, acupuncture increased the vascular endothelial growth factor (VEGF) level in the hippocampus, promoting the proliferation and differentiation of neuronal stem cells [27]. Thus, acupuncture can be used to treat ischemic injury in the brain. Zhang et al. performed manual acupuncture on GV20 and Ex-HN 1 to increase GDNF and BDNF levels in a rat model [19]. The elevation of the BDNF level was related to the increased expression of BDNF/tyrosine receptor kinase B (TrkB) and the induction of neurogenesis [28].

The mitogen-activated protein kinase (MAPK) family includes ERK1/2, JNK, and p38 MAPK proteins. In animals, the MAPK family is triggered by growth factors, stress, or an inflammatory environment and regulates cell functions, such as proliferation, division, differentiation, survival, and apoptosis. EA can trigger the MAPK family. ERK is believed to mediate reperfusion injury by inhibiting inflammatory reactions and promoting cell proliferation and growth [29]. However, equivocal results have been reported concerning the protective effect of ERK on ischemic brain injury [30, 31]. Some studies have demonstrated that EA protects against ischemic brain injury by reducing infarct volumes and improving neurological outcomes through activation of the ERK1/2 signaling pathway [29, 32–34]. EA is reported to be effective in neuroprotection and neural cell proliferation. The chosen acupoints in EA include GV20, GV14, ST36, and LI11. The activation of the ERK pathway is combined with an increase in BDNF and p-ERK1/2 levels [34]. Some studies have demonstrated that the application of EA on LU5, LI4, ST36, and SP6 was effective in reducing neurogenic deficits and causing antiapoptosis in the brain cortex and hippocampus [35, 36].

Environmental stresses and inflammatory cytokines activate p38 MAPKs and induce apoptosis and inflammation [37]. In the acute phase of ischemic brain injury, the p38 MAPK signaling pathway induces neurotoxicity, whereas in the subacute phase, this pathway serves as a proinflammatory mediator in the neuroprotective antiapoptosis effect [38–40]. Some studies have reported that EA exerts the antiapoptosis effect on the peri-infarct cortex by modulating the ERK/JNK/p38 MAPK signaling pathway [41–44]. The chosen acupoints include GV14, GV20, GV24, GV26, LU5, LILI4, LI11, ST36, and SP6. Liu et al. reported that EA inhibits microglia-mediated neuroinflammation mediated by nuclear factor kappa-light-chain-enhancer of activated B (NF-$\kappa$B) cells, p38 MAPK, and myeloid differentiation primary response 88 (MYD88), as well as simultaneously reducing cytokine tumor necrosis factor-alpha (TNF-$\alpha$), interleukin-1 beta (IL-1$\beta$), and interleukin-6 (IL-6) levels [45].

The p38 MAPK pathway activates the expression of CREB protein and reduces the apoptosis of ischemic neural cells. Acupuncture on GV16, GV20, GV24, ST36, and HT7 also triggered the CREB pathway in the hippocampus and improved cognitive impairment in an animal model [46–51]. The CREB pathway is related to BDNF, p38 MAPK, and $Ca^{2+}$/calmodulin-dependent protein kinase (CaMK) [46, 50, 52]. Lin et al. reported that EA exerted antioxidant and antiapoptosis effects by increasing superoxide dismutase and glutathione peroxidase levels and reducing the malondialdehyde level in the hippocampus and improved the learning and memory ability of rats [48]. A study reported that laser acupuncture on GV20 and HT7 for 14 days excited the cholinergic system and increased CREB, BDNF, and B-cell lymphoma 2 (Bcl-2) levels, thereby improving cognitive impairment in rats [51].

Being a cell cycle initiator, PI3K/AKT pathways are essential for cell survival [53]. However, interactions between transactivation of Raf/MAPK/ERK1/2 and PI3K/AKT systems were noted during ischemia and reperfusion phases. During ischemia, Akt reduces Raf/MAPK/ERK1/2 activity through phosphorylation of Raf-1. During reperfusion, abrupt reactive oxygen species (ROS) increases the phosphatase and tensin homolog and reactivates Raf/MAPK/ERK1/2 signaling [54]. For the modulation of the PI3K pathway, some studies have reported that EA on GV12, GV20, GV24, GV26, KI1, LI11, and ST36 activates the PI3K/AKT pathway and exerts antiapoptosis and neuroprotective effects [12, 55–60]. The effect of EA on the PI3K pathway can activate the downstream mTOR complex 1–UNC-51-like kinase 1 complex–Beclin-1 pathway, reduce caspase-3, caspase-8, and caspase-9 levels, and inhibit the autophagy process [61, 62]. EA also reduces nitric oxide (NO), neuronal NO synthase (nNOS), and inducible NO synthase (iNOS) levels by activating the PI3K pathway [58]. Xie et al. demonstrated that EA improved neurological deficit scores and increased the expression of p-AKT protein and bone marrow CD34+ endothelial progenitor cells in rats [63].

Because of the balance between Raf/MAPK/ERK1/2 and PI3K/AKT systems, some studies have included the pretreatment protocol [64, 65]. EA pretreatment in a rat model reduced the expression of p-Akt protein and prevented the downregulation of tight junction proteins, namely, claudin-5 and occludin, attenuating BBB disruption and brain edema [65].

NF-$\kappa$B is another protein complex related to cell survival. Some studies have demonstrated that EA regulates the NF-$\kappa$B-mediated apoptosis pathway and provides neuroprotection [66, 67].

Acupuncture improved neurogenic defects and cognitive impairment in a cerebral ischemic/reperfusion animal model. In summary, acupuncture not only increases the levels of neurotrophic factors but also modulates signaling pathways, such as Raf/MAPK/ERK1/2 and PI3K/AKT and downstream CREB and NF-$\kappa$B. Therefore, acupuncture results in cell proliferation, antiapoptosis, neuroprotection, and BBB maintenance. The most frequently chosen acupoints include GV20, GV14, and ST36. The mechanisms and main results of identified articles are summarized in Table 1.

## 4. Cerebral Hemorrhagic Injury

Hemorrhagic stroke is less common than ischemic stroke. The causes of hemorrhagic stroke include high blood pressure, brain trauma, aneurysms, arteriovenous malformations, and brain tumors. In cerebral hemorrhagic injury, blood vessel spasms and oxidative stress caused by ischemia and reperfusion cause an injury to neural cells. Acupuncture could improve the hypoperfusion status and hematoma absorption, reduce brain edema, and promote neurogenesis in the brain [68]. Thus, some studies have reported that acupuncture is beneficial for treating cerebral hemorrhage because it results in functional improvements [69, 70]. Acupuncture also regulates inflammatory factors, such as IL-6, IL-1$\beta$, and NF-$\kappa$B, prevents apoptosis by reducing the expression of p53 protein, and promotes neurogenesis by increasing the levels of BDNF and nerve growth factors [71].

Table 1: Signal transduction pathways of acupuncture in treating cerebral ischemic injury.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, MCAO | brain | GV20 | EA, 3mA, 2/20Hz | 30min, QOD for 14 days | increase expression of BDNF/TrkB | elevation of BDNF neuron proliferation | Kim MW, et al. 2012[28] |
| Male, postnatal SD rats, MCAO | hippocampus | GV20, GV14 | EA, 2Hz | 20min, QD for 10 days | increase VEGF and BDNF levels | proliferation and differentiation of neuronal stem cells | Kim YR, et al. 2014[27] |
| Male, postnatal SD rats, CCAO | hippocampus | GV20, Ex-HN 1 | MA, 2Hz for 15 sec | 30min/time, 3 times | increase GDNF and BDNF levels | antiapoptosis | Zhang Y, et al. 2015[19] |
| Either sex, SD rats, CCAO combination with hypoxic treatment | cerebral cortex | MA: GV 20, GV 14, LI 11, KI 1<br>EA: GV 14, LI 11 | MA and EA, 1mA, 1/20 Hz | 10 min, QD | activation of GDNF/RET/Akt pathway | neuroprotection | Xu T, et al. 2016[25] |
| Male, SD rats, MCAO | brain | GV20 | EA, 1 mA, 2/15 Hz | 30min | activation of ERK1/2 pathway | elevation of CB1 neuroprotection | Du J et al. 2010[32] |
| Male, SD rats, MCAO | brain | ST36, LI11 | EA, 1/20 Hz | 30 min, QD | activation of the ERK pathway | elevation of Ras, cyclin D1 and CDK4 neural cell proliferation | Xie G, et al. 2013[33] |
| Male, SD rats, MCAO | brain | GV 20, GV14 | EA,2.7-3.0 mA, 5Hz | 25min, QD for 2 days | activation of MAPK/ERK kinase, ERK1/2 pathway | elevation of BDNF, pRaf-1, pp90RSK, pBad<br>depression of caspase-3 protein<br>neuroprotection | Cheng CY, et al. 2014[34] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA, 1-20 Hz | 30min, QD for 3 days | activation of the ERK1/2 pathway | elevation of p21 or p27<br>depression of cyclin D1, CDK4, cyclin E and CDK2<br>neural cell proliferation | Huang J, et al. 2014[29] |
| Male, SD rats, MCAO | hippocampus | LU5, LI4, ST36, SP6 | EA, 2mA, 2/15 Hz | 20 min, QD for 3 days | activation of the ERK pathway | antiapoptosis | Wu C, et al. 2015[35] |

Table 1: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, MCAO | brain | LU5, LI4, ST36, SP6 | EA,2 mA, 2/15Hz | 20min, QD for 3 days and 7 days | activation of ERK pathway | antiapoptosis | Wu C, et al. 2017[36] |
| Male, SD rats, ligation of common carotid artery and external carotid artery | hippocampus | LU5, LI4, ST36, SP6 | EA, 2/50 Hz | 20 min, QD | regulation of p38 MAPK signal pathway | depression of phosphorylated p38 MAPK antiapoptosis | Lan X, et al. 2017[41] |
| Male, SD rats, MCAO | brain | GV20, GV14, GV26 | MA | 30min/time, 7 times | Inactivation of MAPK/ERK pathway | elevation of Bcl-2 depression of Bax anti-apoptosis | Lin Y, et al. 2017[42] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA, 1mA, 4/20 Hz | 30min, QD for 3 days | modulation of ERK/JNK/p38 signal pathway | elevation of caspase-3, growth factor midkine depression of Bcl-2 anti-apoptosis | Xing Y, et al. 2018[43] |
| Male, SD rats, MCAO | brain | GV20, GV24 | EA, 1mA, 1/20 Hz | 30 min, QD for 10 days | modulation of p38MAPK/ERK1/2/JNK pathway | elevation of ERK1/2, Bcl-2/Bax ratio depression of JNK, p38 MAPK anti-apoptosis | Liu J, et al. 2018[44] |
| Male, SD rats, MCAO | sensorimotor cortex | LI11, ST36 | EA, 0.2mA, 1/20Hz | 30 min, QD for 3 days | inactivation of NF-$\kappa$B, p38 MAPK and MYD88 pathway | depression of TNF-$\alpha$, IL-1$\beta$, IL-6 inhibition of microglia-mediated neuroinflammation | Liu W, et al. 2016[45] |

Table 1: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, MCAO | brain | GV20, GV16 | EA, 5 Hz and 25Hz | 25 min, QD | activation of p38 MAPK/CREB pathway | decrease reactive astrocytosis | Cheng CY, et al. 2015[46] |
| Male, Wistar rats, homologous blood emboli injection of internal carotid artery | hippocampus | ST36 | MA | QD for 14 days | activation of cAMP/PKA/CREB pathway | activation of long-term potentiation | Li QQ, et al. 2015[47] |
| Male, SD rats, MCAO | hippocampus | GV24, GV20 | EA, 1-3mA, 5/20Hz | 30min, QD | increase expression of p-CREB | elevation of superoxide dismutase and glutathione peroxidase, Bcl-2 depression of malondialdehyde, Bcl2-xl anti-oxidase anti-apoptosis | Lin R, et al. 2015[48] |
| Male C57BL/6 mice, bilateral stenosis of the common carotid artery | corpus callosum | GV20, GV14 | EA, 2Hz | 20min, QD for 7 days | p-CREB pathway | oligodendrocyte regeneration | Ahn SM, et al. 2016[49] |
| Female, SD rats, MCAO | hippocampus | GV20, GV24 | EA, 1/20Hz | 30min, QD for 7 days | inactivation of CaM-CaMKIV-CREB pathway | inactivation of CaM-CaMKIV-CREB pathway | Zhang Y, et al. 2016[50] |
| Male, SD rats, MCAO | hippocampus | GV20, HT7 | MA LA, 30 mW, 100Hz | 14 days | enhance cholinergic system | elevation of CREB, BDNF, and Bcl-2 depression of Bax anti-apoptosis | Yun YC, et al. 2017[51] |
| Neonatal SD rats, CCAO | brain | GV20, ST36 | EA, 1mA, 2Hz | 20min | activation of CREB/BDNF pathway | oligodendrogenesis | Pak ME, et al. 2018[52] |

Table 1: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, Wistar rats, MCAO | forebrain | GV20, GV26 | EA, 3mA, 3/20Hz | 60min | activation of Akt | depression of caspase-9 anti-apoptosis | Wang SJ, et al. 2002[55] |
| Male, SD rats, MCAO | brain | GV26, CV 24, | EA,1 mA, 4/16Hz | 30min | activation of PI3K pathway | neuroprotection | Sun N, et al. 2005[56] |
| Male, SD rats, MCAO | brain | GV26, CV24 | EA, 4/16Hz | 30 min | activation of TrkA-PI3K pathway | neuroprotection | Zhao L, et al. 2007[57] |
| Rats, modified intravascular suture technique | hippocampus, cerebral cortex | GV26, CV 24 | acupuncture | -- | activation of TrkA/PI3K pathway | depression of NO, nNOS and iNOS | Chen SX, et al. 2011[58] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA, 1mA, 1/20 Hz | 30 min, QD | activation of PI3K/Akt pathway | elevation of BDNF, GDNF, Bcl-2/Bax ratio anti-apoptosis | Chen A, et al. 2012[59] |
| SD rats, left common carotid artery (LCCA) ligation | cerebral cortex | GV 20, GV 14, LI 11, KI 1 | MA and EA | -- | activation of PI3K/Akt pathway | neuroprotection | Xu T, et al. 2014[60] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA, 4/20 Hz | 30 min, QD for 3 days | activation of PI3K/Akt pathway | elevation of PI3K, p-Akt, p-Bad and Bcl-2 depression of Bax, caspase-3-positive expression anti-apoptosis | Xue X, et al. 2014[12] |
| Male, SD rats, MCAO | brain | GV20, CV6 | EA,1mA, 2Hz | 30min, BID | activation of PI3K/Akt pathway | depression of caspase-3, -8 and -9 anti-apoptosis | Kim YR, et al. 2013[61] |

Table 1: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, MCAO | bone marrow | GV20, LI4, LR3 | EA, 3mA, 2/20Hz | 30min, QD | increase expression of p-Akt protein | elevation of CD 34+ endothelial progenitor cell | Xie CC, et al. 2014[63] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA, 0.2 mA, 1/20 Hz | 30 min, QD for 3 days | activation of mTORC1-ULK1 complex-beclin1 pathway | depression of microtubule-associated protein 1 light chain 3 beta II/I, ULK1, autophagy related gene 13 and Beclin1 anti-autophagy | Liu W, et al. 2016[62] |
| Male, SD rats, MCAO | brain | GV20 | EA, 1mA, 2/15 Hz | 30 min, QD for 3 days | phosphorylation of GSK-3$\beta$ | anti-apoptosis | Wei H, et al. 2014[64] |
| Male, SD rats, MCAO | brain | GV20 | EA, 1mA, 2/15Hz | 30min, QD for 5 days | decrease expression of p-Akt | elevation of claudin-5, occludin decrease blood-brain barrier disruption | Zou R, et al. 2015[65] |
| Male, SD rats, MCAO | brain | GV20, GV24 | EA 1/20Hz | 30min, QD for 10 days | inhibition of NF-$\kappa$B-mediated apoptosis pathway | depression of Bax and Fas anti-apoptosis | Feng X, et al. 2013[66] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA,0.01mA, 1/20Hz | -- | regulation of TLR4/NF-$\kappa$B pathway | depression of TNF-$\alpha$, IL-1$\beta$ and IL-6 neuroprotection | Lan L, et al. 2013[67] |

Abbreviations

--: not mentioned; Bax: Bcl-2 associated X; Bad: Bcl-2-associated death promoter; Bcl-2: B-cell lymphoma 2; BDNF: brain-derived neurotrophic factor; CaMK: Ca2+/calmodulin-dependent protein kinase; cAMP: cyclic adenosine monophosphate; CB1: cannabinoid receptor type 1; CCAO: occlusion of common carotid artery; CDK: cyclin-dependent kinase; CREB: phosphorylated cyclic AMP response element-binding protein; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; GDNF: glial-derived neurotrophic factor; IL: interleukin; JNK: c-Jun N-terminal kinases; MA: manual acupuncture; MAPK: mitogen-activated protein kinases; MCAO: occlusion of MCA; mTOR: mammalian target of rapamycin; MYD88: myeloid differentiation primary response 88; NF-$\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; p38 MAPKs: p38 mitogen-activated protein kinases; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA: protein kinase A; pp90RSK: phospho-90 kDa ribosomal S6 kinase; QD: daily; QOD: every other day; SD rat: Sprague Dawley rat; TLR4: Toll-like receptor 4; TNF-$\alpha$: tumor necrosis factor-alpha; Trk: tyrosine receptor kinase; ULK: UNC-51-like kinase; VEGF: vascular endothelial growth factor.

Acupuncture increased the expression of endogenous GDNF and inhibited the early expression of VEGF, thus regulating nerve remodeling after cerebral hemorrhagic injury [72]. At the level of molecular signal transduction, acupuncture exerts a neuroprotective effect by increasing the angiopoietin level and reducing TNF-$\alpha$ and NF-$\kappa$B levels [73, 74]. Li et al. reported that EA on GV20 and GB7 could reduce BBB permeability and improve brain edema by activating the caveolin-1/matrix metalloproteinase pathway [75]. Antiapoptosis is also an important pathway for neural preservation. Zhu et al. and Li et al. have demonstrated that EA activated the Bcl-2 pathway to increase hematoma absorption and antiapoptosis. This effect is combined with the suppression of caspase-3 and Bcl-2-associated X (Bax) proteins [76, 77]. However, the chosen acupoints were heterogeneous, including ST36, GV14, GV20, GV26, GB7, and PC6.

Taken together, acupuncture could improve neurogenic disability and reduce brain edema by increasing caveolin-1/matrix metalloproteinase levels and inducing antiapoptosis through the activation of the Bcl-2 pathway in a cerebral hemorrhagic model. The mechanisms and main results of identified articles are summarized in Table 2.

## 5. Seizure

Seizure is an abrupt, spontaneous, excessive, or synchronous neuronal activity in the brain that leads to various uncontrolled shaking movements or loss of consciousness. Seizure attack affects 8%–10% of the general population in their lifetimes. The recurrence of seizure results in epileptic syndrome, which affects 2%–3% of the general population [78]. Epileptic seizures can be induced by metabolic imbalance, electrolyte imbalance, encephalitis, traumatic brain injury, brain tumor, stroke, and medication [78]. During the process of an epileptic seizure, changes occur in molecular, anatomical, or circuit development, including cell death, inflammatory cytokine production, and neurotransmitter dysregulation. This process is called epileptogenesis [79]. Involvement of BDNF–TrkB signaling, the mTOR pathway, and the repressor element 1-silencing transcription factor pathway was considered to be the underlying molecular mechanism [79].

In addition to the use of medication, some studies have reported that acupuncture reduced the frequency of seizures and improved the quality of life [80–82]. Some studies reported that acupuncture has effect on change of anatomical, neurotransmitter, inflammatory cytokines and molecular level. The augmentation of $\gamma$-aminobutyric acid neurotransmission, including the upregulation of glutamic acid decarboxylase 67 (GAD67), is a self-protective and anticonvulsive mechanism [83, 84]. Acupuncture reduced seizure attacks by enhancing GAD67 mRNA production in the dentate gyrus of epileptic rats [85]. Acupuncture changed the brain structure and reduced the mossy fiber sprouting in the dentate gyrus and exerted an antiepileptic effect [86]. Inflammation can increase neuronal excitability and result in the frequent onset of epilepsy, which is related to epileptogenesis [87]. Acupuncture also contributes to the antiepileptic effect accompanied by the anti-inflammatory effect of reducing IL-1$\beta$, TNF-$\alpha$, and cyclooxygenase-2 (COX-2) levels in the hippocampus of an epileptic rat model [88, 89]. Wang et al. and Wang et al. have demonstrated that EA attenuated the seizure-induced increase in c-fos protein and preproenkephalin messenger ribonucleic acid (mRNA) levels in the hippocampus of a penicillin-induced seizure rat model [90, 91]. Yang et al. reported that EA on GV16 and GV8 exerted an anticonvulsant effect combined with a reduction in nNOS and iNOS levels [92].

With regard to molecular pathways, acupuncture on the auricular acupoint suppressed transient receptor potential ankyrin 1 (TRPA1) pathways by increasing the phosphorylated protein kinase C (pPKC)-$\alpha$ level and reducing pPKC$\varepsilon$ and pERk1/2 levels in a kainic acid-induced rat model [93]. Liao et al. used a similar rat model and reported that acupuncture exerted an antiepileptic effect by inactivating the Toll-like receptor 4 (TLR4) pathway, which was accompanied by a decrease in pCaMKII$\alpha$, pERK, pp38, pJNK, and pNF$\kappa$B levels [94]. Yang et al. demonstrated that acupuncture on GV20 and GV14 reduced epileptic seizures by exerting a protective effect on the pyramidal cells of hippocampal CA 1 and CA 3. This effect was related to the activation of the PI3 K/Akt pathway [95]. The upregulation of glucose-regulated protein 78 (GRP78) and the downregulation of C/EBP homologous protein (CHOP) prevent neuronal cell death induced by endoreticulum stress. Acupuncture on GV20 and GV14 elevated the GRP78 level, reduced CHOP and caspase-12 levels, and exerted an antiapoptosis effect on the hippocampus, thus reducing epileptic seizure attacks [96, 97].

Taken together, acupuncture exerts the antiepileptic effect by changing anatomical, neurotransmitter, inflammatory cytokines and molecular level. With respect to signal transduction, acupuncture reduces seizure frequency by suppressing TRPA1/pERK and TLR4/ERK pathways and activating the PI3K/Akt pathway. Furthermore, acupuncture augments the antiapoptosis process and provides neuroprotection by increasing the GRP78 level and reducing the CHOP level. The mechanisms and main results of identified articles are summarized in Table 3.

## 6. Depression

Depressive disorders are common psychiatric disorders that affect approximately 17% of people in their lifetimes. A study reported that 12%–20% of depressed patients experience treatment-resistant depression, resulting in a considerable social burden [98]. In addition to medication and psychosocial support, acupuncture serves as an alternative option for patients with depression that exhibits promising effects and fewer side effects [99]. The mechanism of depression includes dysregulation of neuroinflammatory cytokines, neurotransmitters, neuroplasticity, and the neuroendocrine system [100, 101]. At the molecular level, dysregulation of striatal-enriched tyrosine protein phosphatase inactivates the neuronal signaling pathway, including ERK1/2, p38, Src family tyrosine kinases, and glutamate receptors. This process attenuates the neurogenesis effect of BDNF and causes depression [102].

Table 2: Signal transduction pathways of acupuncture in treating cerebral hemorrhagic injury.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, Wistar rats | brain | GV20, GB7 | MA | 30min, QD for 1,2,3,7,10 days | increase GDNF level and modulate VEGF level | elevation of GDNF, VEGF (early)<br>depression of VEGF (late)<br>modulate neuron remodeling | Zhang GW, et al. 2012[72] |
| Male, SD rats, collagenase-induced ICH | right globus pallidus | ST36 | EA,2-20Hz | 30min, QD, 14 days | activation of Ang-1 and Ang-2 | elevation of Ang-1 and Ang-2<br>neuroprotection | Zhou HJ, et al. 2014[73] |
| Male, SD rats, autologous blood-induced ICH | right caudate nucleus | GV20, GB7 | MA, 3-4Hz, 5min | 30min, QD, 7 days | inactivation of TNF pathway | depression of TNF-$\alpha$ and NF-$\kappa$B<br>anti-inflammation | Liu H, et al. 2017[74] |
| Male, SD rats, collagenase-induced ICH | right caudate nucleus | GV20, GB7 | EA,0.2mA, 2Hz | 30min, QD, 1,3,7 days | activation of caveolin-1/matrix metalloproteinase/blood-brain barrier permeability pathway | elevation of caveolin-1, matrix metalloproteinase-2/9<br>reduce blood-brain barrier permeability | Li HQ, et al. 2016[75] |
| Male, SD rats, collagenase and heparin-induced ICH | right caudate putamen | GV20, GV14 | EA,1mA, 3Hz | 10min, QD, 14 days | activation of Bcl-2 pathway | elevation of Bcl-2 protein<br>depression of caspase-3 and Bax proteins<br>increase absorption of hematoma and anti-apoptosis | Zhu Y, et al. 2017[76] |
| Male, Wistar rats, autologous blood-induced ICH | caudate nucleus | PC6, GV26 | EA, 4Hz | 1min | balance of BCL-2 and Bax | elevation of BCL-2 mRNA<br>depression of Bax mRNA<br>anti-apoptosis | Li Z, et al. 2017[77] |

Abbreviations

- -: not mentioned; Ang: Angiopoietin; Bax: Bcl-2 associated X; Bcl-2: B-cell lymphoma 2; EA: electroacupuncture; GDNF: glial-derived neurotrophic factor; ICH: intracranial hemorrhage; MA: manual acupuncture; NF-$\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; QD: daily; SD rat: Sprague Dawley rat; TNF-$\alpha$: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor.

Table 3: Signal transduction pathways of acupuncture in treating seizure.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, lithium-pilocarpine injection | dentate gyrus | ST36 | EA, 1-20mA, 4/20Hz | 30min, QD for 30,45,60 days | activation of GAD 67 | elevation of GAD67 mRNA anti-epileptic | Guo J, et al. 2008[85] |
| Male, SD rats, kainic acid injection | prefrontal cortex, hippocampus, and somatosensory cortex | auricular acupoint | Auricular EA, 2 and 15Hz | 20min, QD, 3 days/wk for 3 wks | inactivation of TLR 4 pathway | depression of pCaMKII$\alpha$, pERK, pp38, pJNK, pNF$\kappa$B anti-epileptic | Liao ET, et al. 2018[94] |
| Male, SD rats, intraperitoneal injection of pentylenetetrazol | hippocampal CA 1 and CA 3 | GV20, GV14 | MA | QD for 5 days | activation of PI3 K/Akt pathway | increase pyramidal cells | Yang, F, et al. 2013[95] |
| Male, SD rats, kainic acid injection | hippocampal CA1 areas | Auricular acupoint | EA, 2Hz | 20min, 3 days/wk for 6wks | Inactivation of TRPA1, pPKC$\alpha$, pPKC$\varepsilon$, and pERk1/2 pathways | elevation of PKC$\alpha$ depression of TRPA1, PKC$\varepsilon$, pERK1/2 anti-epileptic | Lin YW, et al. 2014[93] |
| Male, SD rats, intraperitoneal injection of pentylenetetrazol | hippocampal CA 1 region | GV20, GV14 | MA | 30min | balance of GRP78 and CHOP | elevation of GRP 78 protein depression of CHOP neuroprotection | Yang F, et al. 2014[96] |
| Male, newly-born SD rats, pentylenetetrazol intraperitoneal injection | hippocampus | GV20, GV14 | MA | QD for 7 days | balance of GRP78 and CHOP | elevation of GRP 78 protein depression of CHOP, caspase-12 anti-apoptosis | Zhang, H, et al. 2017[97] |

Abbreviations

Akt: protein kinase B; CaMK: Ca2+/calmodulin-dependent protein kinase; CHOP: C/-EBP homologous protein; COX: cyclooxygenase; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; GAD67: glutamic acid decarboxylase 67; GRP78: glucose-regulated protein 78; IL: interleukin; JNK: c-Jun N-terminal kinases; MA: manual acupuncture; NF-$\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; p38 MAPKs: p38 mitogen-activated protein kinases; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC: protein kinase C; QD: daily; QOD: every other day; SD rat: Sprague Dawley rat; TLR4: Toll-like receptor 4; TNF-$\alpha$: tumor necrosis factor-alpha; TRPA: transient receptor potential ankyrin 1.

Acupuncture treats depression by regulating neurotransmitters, neuroinflammatory cytokines, the hypothalamus–pituitary–adrenal axis, and the hypothalamus–pituitary–sex gland axis [103]. Furthermore, acupuncture plays a role in molecular signaling pathways. Acupuncture elevated BDNF production and excitatory amino acid transporter levels and maintained neural regeneration of the hippocampus in a depressive rat model [104, 105]. The chosen acupoints include GV20, EX-HN3, and PC6 [104, 105]. Fan et al. demonstrated that acupuncture on LI4 and LR3 regulated the expression of soluble N-ethylmaleimide-sensitive factor attachment receptor protein, a fusion mediator, and promoted depression remission [106]. NO is a small molecule that freely diffuses across cell membranes and serves as a neurotransmitter in the CNS. NO initiates the NO-cyclic guanosine monophosphate (NO-cGMP) pathway and activates protein kinases. Acupuncture regulates the NO-cGMP pathway by increasing nNOS and cGMP levels, which contribute to its effect on depression relief [107]. Shao et al. demonstrated that acupuncture on GV20 and PC6 inhibited the proinflammatory pathway of depression by reducing NF-$\kappa$B protein and COX-2 levels [108].

Antidepressants alleviate the symptoms of depression by activating the MAPK/ERK pathway, which increases ERK1/2 and p-ERK1/2 expression. Many studies have reported that acupuncture activates the MAPK/ERK pathway and downstream CREB pathway and elevates BDNF production [109–114]. The most commonly chosen acupoints include GV20 and GV29, followed by EX-HN3, GB34, and PC6. The MAPK/ERK pathway induces neurogenesis and antiapoptosis of hippocampal neurons and eliminates the depression state. EA on GV20 and EX-HN3 also enhances the p-p38MAPK pathway [111]. Some studies have reported that EA on GV20 and GV29 reduced the hippocampal neural apoptotic rate by downregulating the hippocampal p-JNK pathway in depression rat model [115, 116]. Acupuncture also activated the adenyl cyclase (AC)–cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA)–CREB signaling pathway and elevated the BDNF level [117–120]. In the AC–cAMP–PKA–CREB signaling pathway, heterogeneous acupoints were chosen, including GV20, EX-HN1, EX-HN3, ST36, ST40, LI4, and LR3.

Molecular studies have reported that acupuncture plays a role in the neuroendocrine model of depression. Lu et al. demonstrated that acupuncture could relieve the symptoms of depression and increase cortisol, PKA, and PKC levels [117]. Oh et al. reported that acupuncture on HT8 elevated the serum corticosterone level and hippocampal mTOR phosphorylation, Akt, ERK, p70S6K, p4E-BP1, and CREB enhanced the effect of BDNF on neuroprotection and synaptic plasticity. Furthermore, acupuncture elevated the levels of synaptic proteins (e.g., PSD95, Syn1, and GluR1), which are crucial for neuronal synaptic plasticity [121].

The results of the Gene Ontology functional term and Kyoto Encyclopedia of Genes and Genomes database analysis indicated that the regulation of the Toll-like receptor signaling pathway, nucleotide-binding oligomerization domain-like receptor signaling pathway, MAPK/ERK pathway, PI3K/Akt pathway, neurotrophin signaling pathway, TNF pathway, and NF-$\kappa$B pathway is the mechanism through which acupuncture treats depression. The aforementioned pathways cause cell survival, differentiation, antiapoptosis, and synaptic plasticity of neurons, thus alleviating depression symptoms and improving learning/memory dysfunction [122–124].

In summary, acupuncture can treat depression by upregulating MAPK/ERK and AC–cAMP–PKA–CREB pathways and downregulating JNK and NF-$\kappa$B pathways. Because of the aforementioned mechanism, we observed an increase in neuron growth factor levels, neurogenesis, and antiapoptosis accompanied by the alleviation of depression symptoms. The mechanisms and main results of identified articles are summarized in Table 4.

## 7. Alzheimer's Disease

AD is a progressive neurodegenerative disease that is presented with dementia, memory loss, disorientation, personality disorder, mood swings, behavior disturbance, and language problems. Because of patients' cognitive decline, they withdraw from their family and society [125]. Risk factors for AD include genetic factors, a history of head trauma, depression, and hypertension [126]. The progression of AD is associated with the formation of amyloid plaques and neurofibrillary tangles in the brain [126]. Treatment of AD should be started immediately after the diagnosis to prevent cognitive decline. Both patients and their families are involved in administration of medication and psychosocial therapy for AD. Medication for AD includes cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), N-methyl-D-aspartate receptor antagonists (memantine), atypical antipsychotics, antidepressants, and anticonvulsants [126].

In addition to medication, acupuncture has been reported to improve cognitive function and the global clinical status of patients with AD without causing major adverse effects [127, 128]. Mechanisms through which acupuncture improves cognitive impairment in AD include attenuation of A$\beta$ deposits, upregulation of BDNF expression, and regulation of cell proliferation and neural plasticity in the brain [129–131]. Acupuncture also regulates cytokine and growth factor levels associated with survival, proliferation, and differentiation of neural stem cells in the brain to promote the repair of damaged cells [130, 132].

A$\beta$ deposits in the brain disturb BDNF signaling pathways, such as Ras/ERK, PI3K/Akt, and PKA/cAMP, which regulate BDNF expression and cause AD development [133, 134]. Acupuncture on GV20 reduces A$\beta$ deposits in the brain, elevates the BDNF level, and exerts a neuroprotective effect on CNS cells [135, 136]. Lin et al. reported that the signaling pathway of BDNF elevation is mediated by the BDNF–TrkB pathway, which exerts an antiapoptosis effect [136]. The central cholinergic pathway is important for learning acquisition and synaptic plasticity in the mammalian limbic system; thus, increasing the acetylcholine level is a type of treatment strategy for AD. Lee et al. reported that acupuncture enhances the cholinergic system–CREB–BDNF pathway and exerts a neuroprotective effect [135].

Table 4: Signal transduction pathways of acupuncture in treating depression.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| SD rats, CUMS | hippocampus, frontal cortex | GV20, EX-HN3, PC6 | -- | QOD for 28 days | activation of BDNF pathway | elevation of BDNF mRNA and protein neural regeneration | Liang J, et al. 2012[104] |
| Male, SD rats, CUS | hippocampus | LI4, LR3 | EA | QD for 21 days | regulation of soluble N-ethylmaleimide-sensitive factor attachment receptor proteins | depression of SNAP25, VAMP1, VAMP2, VAMP7, and syntaxin1 | Fan L, et al. 2016[106] |
| SD rats, CUMS | hippocampus | GV20, EX-HN3 | EA, 0.6mA, 2Hz | 20min, QD for 21 days | activation of NO-cGMP pathway | elevation of nNOS, cGMP normalize activity of the NO/cGMP pathway | Han YJ, et al. 2009[107] |
| Male, SD rats, CUS | hippocampus | GV20, PC6 | -- | QD for 28 days | Inactivation of NF-$\kappa$B inflammatory pathway | depression of NF-$\kappa$B, COX-2, prostaglandin inhibition of pro-inflammatory pathway | Shao RH, et al. 2015[108] |

Table 4: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, CUMS | hippocampus, prefrontal cortex | GV20, PC6 | MA, rotated 2Hz for 1 min and retained | 10min, QOD for 28 days | activation of ERK-CREB pathway | elevation of ratio of p-ERK1/2 to ERK1/2, ratio of p-CREB to CREB influence BDNF expression | Lu J, et al. 2013[109] |
| Male, SD rats, CUMS | hippocampus | GV20, GB34 | EA, 0.3mA, 2/100Hz | 30min, QD for 14 days | activation of ERK pathway | elevation of p-ERK neural stem cells proliferation | Yang L, et al. 2013[110] |
| Male, SD rats, CUMS | hippocampus | GV20, EX-HN3 | EA, 1-3mA, 2Hz | 15 min, QD for 14 days | modulation of the p-ERK1/2 and p-p38MAPK pathway | elevation of p-ERK1/2, p-p38 | Xu J, et al. 2015[111] |
| Male, SD rats, CUMS | hippocampus | GV20, GV29 | MA, 2Hz for 1min | 10min, QD for 21 days | activation of ERK pathway | elevation of -ERK1/2, CREB, and p-CREB neurotrophy and neurogenesis | Zhang X, et al. 2016[112] |
| Male, SD rats, CUMS | hippocampus | GV20, GV29 | EA, 0.6mA, 2Hz | 20min, QD for 21 days | Activation of MAPK/ERK pathway | elevation of BDNF, ERK, pERK, ribosomal s6 kinase augmentation of BDNF pathway, neurogenesis, anti-apoptosis | Li W, et al. 2017[113] |

Table 4: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, specific pathogen-free SD rats, CRS | hippocampus | GV20, GV29 | EA, 1mA, 2Hz | pre-stress, 20min, QD for 28 days | modulation of MAPK/ERK pathway | elevation of MAPT depression of PKC inhibition of cell differentiation and proliferation | Yang X, et al. 2017[114] |
| Male, SD rats, CUMS | hippocampus | GV20, GV29 | EA | 21 days | inactivation of JNK pathway | depression of p-JNK anti-apoptosis | Dai W, et al. 2010[115] |
| Male, SD rats, CUMS | hippocampus | GV20, GV29 | acupuncture | 20 min, QD | inactivation of JNK pathway | depression of p-JNK protein, MKK 4, MKK 7 protein | Guo Y, et al. 2016[116] |
| Male, SD rats | hippocampus, serum | GV20, EX-HN1, ST36, ST40 | EA | QOD for 21 days | regulation of hypothalamus-pituitary-adrenal axis | elevation of cortisol, PKA, PKC | Lu F, et al. 2008[117] |

Table 4: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, chronic mild stress | hippocampus | LI4, LR3 | EA, 2/20 Hz | 30min, QOD for 42 days | activation of AC-cAMP-PKA pathway | activation of AC-cAMP-PKA pathway | Liu JH, et al. 2012[118] |
| Male, SD rats, CUMS | hippocampus | GV20, EX-HN3 | EA, 0.6mA, 2Hz | 30min, QD for 14, 28 days | activation of CREB and BDNF pathways | elevation of BDNF, TrkB, PKA, pCREB depression of CaMKII anti-apoptosis, neuroprotection | Duan DM, et al. 2016[119] |
| Male, SD rats, CUMS | hippocampus | GV20, EX-HN3 | MA, | pre-stress, 30min for 21 days | Activation of PKA/CREB pathway | elevation of PKA-$\alpha$ and p-CREB | Jiang H, et al. 2017[120] |
| Male, SD rats, Single prolonged stress | Hippocampus, serum | HT8 | MA, rotate 2Hz for 30sec | QD | activation of mTOR pathway | elevation of corticosterone(serum), corticotropin-releasing factor, mTOR phosphorylation, Akt, ERK, p70S6K, p4E-BP-1, CREB, PSD95, Syn1, GluR1 increase synaptic plasticity | Oh JY, et al. 2018[121] |
| Male, Wistar rats, CUMS | hippocampus and serum | GV20, EX-HN3 | EA, 1mA, 2Hz, pre-stress | 60min, QD for 28 days | Regulation of neurotrophin signaling pathway, MAPK/ERK pathway and PI3K/Akt pathway | depression of miR-383-5p and miR-764-5p activation of neurotrophy and inhibition of abnormal apoptosis | Duan DM, et al. 2017[122] |

Table 4: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rats, CRS | hippocampus | GV20, EX-HN3 | not mentioned | 20min, QD for 28 days | down regulation of toll-like receptor signalling pathway and nucleotide-binding oligomerization domain-like receptor pathway | regulating inflammatory response, innate immunity and immune response | Wang Y, et al. 2017 [123] |
| Male, SD rats, CRS | frontal cortex | GV20, GV29 | MA | pre-stress, 20min, QD for 28 days | Toll-like receptor pathway, TNF pathway, NF-$\kappa$B pathway | inhibition of inflammatory process | Wang Y, et al. 2017 [124] |

Abbreviations

AC: adenyl cyclase; Akt: protein kinase B; BDNF: brain-derived neurotrophic factor; CaMK: Ca2+/calmodulin-dependent protein kinase; cAM: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; COX: cyclooxygenase; CREB: phosphorylated cyclic AMP response element-binding protein; CRS: chronic restraint stress; CUMS: chronic unpredictable mild stress; CUS: chronic unpredictable stress; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinases; MA: manual acupuncture; MAPK: mitogen-activated protein kinases; MAPT: microtubule-associated protein Tau; mRNA: messenger ribonucleic acid; mTOR: mammalian target of rapamycin; NF-$\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; nNOS: neuronal nitric oxide synthase; NO: nitric oxide; p38 MAPKs: p38 mitogen-activated protein kinases; PKA: protein kinase A; PKC: protein kinase C; QD: daily; QOD: every other day; SD rat: Sprague Dawley rat; TrkB: tyrosine receptor kinase B; VAMP: vesicle-associated membrane protein.

The p38 MAPKs are activated by environmental stresses and inflammatory cytokines and induce apoptosis and inflammation. In an AD animal model, acupuncture could improve cognitive impairment by reducing p38 MAPK levels, thus reducing neuroinflammation in the CNS [18, 137, 138]. Some studies have reported using Sanjiao acupuncture, which uses CV17, CV12, CV6, ST36, and SP10, as a standard regimen for AD [18, 139, 140]. A DNA microarray analysis demonstrated that Sanjiao acupuncture could reverse gene expression profiles related to aging in the hippocampus of senescence-accelerated mouse prone 10 (SAMP10) mice and reduce oxidative stress–induced damage [18]. Luo et al. reported that Sanjiao acupuncture attenuated cognitive deficits by regulating the G-protein/inositol triphosphate/$Ca^{2+}$ amplitude pathway and signal homeostasis [140]. In an A$\beta$-induced AD model, acupuncture on GV20 and BL23 reduced the level of peroxisome proliferator-activated receptor-$\gamma$ (PPAR-$\gamma$) level and the deposition of Tau protein, thus reducing neuroinflammation [138].

Acupuncture regulated cell cycle and aging in an AD model. N-myc downregulated gene 2 (NDRG2) encodes a cytoplasmic protein that may play a role in neurite outgrowth. Wang et al. demonstrated that EA on GV20 suppressed the astrocyte NDRG2 expression and glial fibrillary acidic protein level, thereby treating memory impairment of amyloid precursor protein/presenilin-1 double transgenic mice [141]. P130, known as retinoblastoma-like protein 2 (RBL2), is a protein encoded by the *RBL2* gene in humans and serves as a tumor suppressor signal. Acupuncture on CV17, CV12, CV6, SP10, and ST36 elevated the p130 level, caused cell proliferation in the brain, and treated dementia and aging-related diseases in SAMP10 mice [139]. Telomerase is a critical enzyme involved in aging and apoptosis. Lin et al. demonstrated that acupuncture on ST35 of telomerase-deficient mice activated the BDNF–TrkB signaling pathway along with elevating BDNF, TrkB, Akt, and ERK1/2 levels, which resulted in an increase in telomerase activity [142]. Acupuncture also modulates the balance of Bcl-2/Bax to regulate the cell cycle of neurons. However, the chosen acupoints were heterogeneous, including LI20, EX-HN3, GV20, BL23, and KI1 [143–145].

Metabolic stress modulates $\beta$-secretase gene transcription and $\beta$-site amyloid precursor protein-cleaving enzyme 1 (BACE1) protein levels in AD through the sirtuin 1 (SIRT1)-PPAR$\gamma$-proliferator-activated receptor $\gamma$ coactivator 1 (PGC-1) pathway [146]. A$\beta$ 25–35 suppresses mitochondrial biogenesis by inactivating the AMP-activated protein kinase (AMPK)–SIRT1–PGC-1$\alpha$ pathway in hippocampal neurons [147]. Therefore, brain energy metabolism impairment is considered an underlying pathogenesis of AD progression. Acupuncture on GV20 elevates glucose transporter (GLUT1 and GLUT3), p-AMPK, p-AKT, and mTOR levels in the hippocampus and cortex. Through regulation of brain energy metabolism, acupuncture has effect on decreasing A$\beta$ deposits, suppressing autophagy process and relieving cognition deficits [148]. Acupuncture improved the spatial learning and memory ability of AD mice by increasing blood perfusion and glucose uptake in the bilateral amygdala, hippocampus, and left temporal lobe [149, 150]. For the molecular signaling pathway, Dong et al. demonstrated in two series studies that acupuncture in GV14 and BL23 exerted AMPK expression, activated SIRT1-PPAR$\gamma$- PGC-1 pathway, and elevated ATP level. Because of the aforementioned mechanism, acupuncture balances brain metabolism and improves cognition impairment of AD mice [20, 151]. Furthermore, the upregulation of SIRT1–PPAR$\gamma$–PGC-1 suppresses BACE1 expression, thus reducing A$\beta$ production in the hippocampus and improving cognitive decline in SAMP8 mice [152].

In summary, acupuncture treats AD by regulating neurotransmitter release, elevating the neurotrophic factor level, and exerting anti-inflammatory effects. Thus, many molecular signaling pathways involved in acupuncture were reported in the AD model, including the BDNF–TrkB pathway, the cholinergic system–CREB–BDNF pathway, G-protein regulation, and the p38 MAPK family. The aforementioned pathways are believed to exert antiapoptosis and anti-inflammatory effects and reduce A$\beta$ deposits in the brain, thereby improving learning ability and memory in AD models. The most commonly chosen acupoints were GV20 and the Sanjiao regimen (CV17, CV12, CV6, ST36, and SP10). Acupuncture regulates cell cycle and aging by modulating NDRG2 and P130 expression, telomerase activity, and Bcl-2/Bax balance. Many studies have reported that acupuncture on GV14 and BL23 modulates brain energy metabolism impairment and treats cognitive impairment. The mechanisms and main results of identified articles are summarized in Table 5.

## 8. Vascular Dementia

VD, which accounts for 15% of dementia cases, is the second most common cause of dementia after AD. Multiple and recurrent ischemia of the brain caused by ischemia or hemorrhage has been found to be the main causes of VD [169]. Although the pathophysiology of VD remains unclear, approximately 15%–30% of patients develop dementia three months after the occurrence of stroke. Furthermore, approximately 20%–25% of patients develop delayed dementia [170]. Because of intricate coordination in the brain and, sometimes, the presence of other brain damage causes, the cognitive changes and declines in VD can be variable, including impairment of attention, information processing, and executive function [169]. Few medications have been approved specifically for the prevention or treatment of VD. Thus, treatment strategies for VD are similar to those for AD and include the use of cholinesterase inhibitors and memantine and providing psychosocial support.

Acupuncture can improve the scores on the Mini-Mental Status Examination, the revised Hasegawa's dementia scale, and activities of daily living examination for VD patients [171, 172]. From the molecular viewpoint, acupuncture on GV20 and KI3 regulates the MAPK/ERK pathway by elevating the pERK level and reducing ionized calcium-binding adaptor molecule 1 (Iba-1), TLR4, and TNF-$\alpha$ levels [153]. Acupuncture reduced relevant proinflammatory factors, thus attenuating neuroinflammation and increasing neuronal synaptic plasticity.

Acupuncture exerted antioxidant and antiapoptosis effects in VD models. Zhu et al. reported that acupuncture on

Table 5: Signal transduction pathways of acupuncture in treating Alzheimer's disease.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rat, scopolamine injection | brain | GV20 | MA | pretreatment for 5 min, QD for 14 days | enhance cholinergic system-CREB-BDNF pathway | elevation of choline acetyltransferase, choline transporter 1, vesicular acetylcholine transporter, BDNF, CREB proteins neuroprotection | Lee B, et al. 2014[135] |
| APP/PS1 mice | brain | GV20 | EA, 1/20 Hz | 30min, QD for 4 weeks | modulation of BDNF-TrkB pathway | elevation of BDNF/proBDNF ratio, p-TrkB depression of $\beta$-amyloid (1-42), p75 anti-apoptosis | Lin R, et al. 2016[136] |
| Male, SAMP10 | hippocampus | CV17, CV12, CV6, ST36, SP10 | MA | QD | regulation of aging gene | elevation of p53, Mad related protein 2, Nucleoside diphosphate kinase B, AT motif-binding factor, Hsp84, Hsp86 depression of p38 MAPK, retinoblastoma-associated protein 1 anti-oxidation | Ding X, et al. 2006[18] |
| SD rat, A$\beta$1-40 injection | hippocampus, frontal cortex | GV20, KI3, ST36 | EA, 1mA, 2Hz | 15min, QD for 12 days | inactivation of p38 MAPK pathway | depression of p-p38 MAPK protein, IL-1beta mRNA decrease neuroinflammation | Fang JQ, et al. 2013[137] |

Table 5: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, SD rat, A$\beta$1-40 injection | hippocampus CA1 | GV20, BL23 | EA, 2mA, 2-4V, 2Hz | 20min, QD, 6 days/ wk for 4 weeks | activation of PPAR-$\gamma$ pathway | elevation of PPAR-$\gamma$ depression of p-p38MAPK, A$\beta$, p-Tau Ser404 protein decrease neuroinflammation | Zhang M, et al. 2017[138] |
| SAMP 10 mice | neocortex and hippocampus | CV17, CV12, CV6, SP10, ST36 | not mentioned | QD for 14 days | p 130 pathway | elevation of p130 cell proliferation | Liu T, et al. 2008[139] |
| Male, SAMP8 mice | cortex and hippocampus | CV17, CV12, CV6, ST36, SP10 | MA, >2Hz | 30sec per acupoint, QD, 21 days | regulation of G protein/ IP3/ Ca2+ amplitude pathway | elevation of physiologically coupled activation rate and maximal coupled activation rate of Gαs and Gαi signal homeostasis | Luo B, et al. 2017[140] |
| Male, APP/PS1 mice | brain | GV20 | EA, 1mA, 2/15Hz | 30min, QD, 5 days/wk for 4 weeks | suppression of astrocytic NDRG2 pathway | depression of Glial fibrillary acidic protein, NDRG2 increase astrocytic reactivity | Wang F, et al. 2014[141] |

Table 5: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| telomerase-deficient mice(TERC-/-) mice | hippocampus and dentate gyrus | ST36 | MA | 30 min, QD for 4 days | activation of BDNF pathway | elevation of BDNF, TrkB, p75NTR, Akt, and ERK1/2<br>increase telomerase activity | Lin D, et al. 2015[142] |
| SD rat, beta-amyloid (Abeta)(1-40) injection | hippocampal | LI20, EX-HN3 | EA, 1-3mA, 80-100Hz | 10min, QD, 5 days/wk for 6 weeks | regulation of Bcl-2/Bax | elevation of Bcl-2<br>depression of Bax<br>anti-apoptosis | Liu ZB, et al. 2011[143] |
| Male, SD rat, A$\beta$1-40 injection | hippocampus CA1 | GV20, BL23 | EA, <2mA, 20Hz | 30 min, QD, 6 days/wk for 4 weeks | downregulation of Notch pathway | elevation of Bcl-2, synapsin-1, synaptophysin<br>depression of Bax, Notch1 mRNA, Hes1 mRNA<br>anti-apoptosis | Guo HD, et al. 2015[144] |

Table 5: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, APP/PS1 mice | hippocampus | GV20, KI1 | EA, 1mA, 2/100Hz | 15min, QD for 3 days | inactivation of caspase-3/ Bax pathway | elevation of Bcl-2/Bax ratio depression of caspase-3-positive cell number and Bax protein anti-apoptosis | Li XY, et al. 2016[145] |
| APP/PS1 mice | hippocampus, cortex | GV20 | EA, 1/20Hz | 30min, QD, 5 days/wk for 4 weeks | regulation of AMPK/mTOR pathway | elevation of GLUT1, GLUT3, p-AMPK, p-Akt, mTOR decrease A$\beta$ (1-42) deposition, decrease autophagy process | Liu W, et al. 2017[148] |
| Male, SAMP8 mice | hippocampus CA1 | GV14, BL23 | EA, 1mA, 2Hz | 20min, QD, 8 days' treatment and 2 days' rest for 3 cycles | activation of AMPK pathway | elevation of p-AMPK balance energy metabolism and improved cognitive impairment | Dong W, et al. 2015[20] |
| Male, SAMP8 mice | hippocampus and frontal cortex | GV14, BL23 | EA, 1mA, 2Hz | 20min, QD, 8 days' treatment and 2 days' rest for 3 cycles | activation of SIRT1-dependent PGC-1$\alpha$ expression pathway | elevation of ATP levels, SIRT1, PGC-1$\alpha$ depression of PGC-1$\alpha$ acetylation improved brain energy metabolism | Dong W, et al. 2015[151] |

Abbreviations

Akt: protein kinase B; AMPK: AMP-activated protein kinase; APP/PS1: amyloid precursor protein (APP)/presenilin-1 (PS1) double transgenic; Bax: Bcl-2 associated X; Bcl-2: B-cell lymphoma 2; BDNF: brain-derived neurotrophic factor; CREB: phosphorylated cyclic AMP response element-binding protein; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; GLUT: glucose transporter; IL: interleukin; IP3: Inositol triphosphate; MA: manual acupuncture; MAPK: mitogen-activated protein kinases; NDRG2: N-myc downregulated gene 2; NMDA: N-methyl-D-aspartate; PGC1: proliferator-activated receptor $\gamma$ coactivator 1; PPAR-$\gamma$: peroxisome proliferator-activated receptors $\gamma$; QD: daily; QOD: every other day; RBL2: Retinoblastoma-like protein 2; SAMP: senescence-accelerated mouse prone; SD rat: Sprague Dawley rat; SIRT1: sirtuin 1; TrkB: tyrosine receptor kinase B.

GV20 and ST36 inactivated the apoptosis signal-regulating kinase 1 (ASK1)–JNK/p38 pathway and elevated thioredoxin-1 and thioredoxin reductase-1 levels [154]. The p38 MAPK pathway activates the expression of CREB and reduces the apoptosis of ischemic neural cells. Some studies have reported that acupuncture activates the cAMP/PKA/CREB pathway and elevates the CREB level [47, 48, 50, 51]. The elevated CREB level upregulates Bcl-2 activity and downregulates Bcl-2xl and Bax activities, consequently preventing the apoptosis of neurons injured by vascular events [48, 51]. The most discussed acupoint was GV20, followed by GV24. Scalp and Sanjiao acupuncture techniques (CV17, CV12, CV6, ST36, and SP10) have been reported to affect the balance between Bcl-2 and Bax expression and antiapoptosis [155, 156]. VD rats had lower expression of mTOR and eukaryotic translation initiation factor 4E (eIF4E) in CA1 accompanied with decreased spatial memory [173]. Zhu et al. demonstrated that EA on GV20, GV14, and BL23 activates the mTOR pathway and increases mTOR and eIF4E levels, thus modulating cell growth, proliferation, and synaptic plasticity [157].

Taken together, acupuncture treats VD by activating MAPK/ERK and ASK1–JNK/p38 pathways; increasing CREB, mTOR, and Bcl-2 levels; and reducing the Bax level. In addition, through the aforementioned mechanism, acupuncture exerts an effect on antioxidant activity, antiapoptosis, and synaptic plasticity. The most commonly chosen acupoints were GV20, GV24, and ST36. The mechanisms and main results of identified articles are summarized in Table 6.

## 9. Parkinson's Disease

PD is a chronic neural degenerative disorder that mainly affects the motor system. Patients with PD experience shaking, rigidity, and walking difficulty. In advanced stages of the disease, behavioral disturbance, depression, poor sleep, and cognitive dysfunction are noted [174]. Treatments such as the administration of L-dopa, dopamine agonists, catechol-O-methyl transferase inhibitors, and monoamine oxidase inhibitor and deep brain stimulation are suggested for treating motor problems of patients with PD. However, dyskinesias and motor fluctuations that develop after a long-term use or high dose use of L-dopa and nonmovement-related symptoms, such as sleep disturbances and psychiatric problems, become problems for patients with PD [174].

Both manual acupuncture and EA help alleviate some motor symptoms in patients with PD and some nonmotor symptoms, such as psychiatric disorders, sleep disorders, and gastrointestinal symptoms. Acupuncture also improved the therapeutic efficacy of levodopa, lowering the necessary dosage [175–177]. Reducing dopaminergic neurons in the substantia nigra (SN) results in PD. Acupuncture has been reported to exert neuroprotective effects that increase the levels of endogenous neurotrophins and modulate the apoptosis and neuroinflammation of dopaminergic neurons in the SN [178, 179]. Neuroimaging findings of the human brain showed that acupuncture on GB34 and the scalp significantly increased glucose metabolism bilaterally in the frontal and occipital lobes and improved motor dysfunction in patients with PD [179, 180].

In light of signal transduction, EA at 2 Hz on GV16 and LR3 inactivate the ERK 1/2 signaling pathway and p38/MAPK signaling pathway, causing an increase in tyrosine hydroxylase–positive neurons and a decrease in COX-2, TNF-$\alpha$, and IL-1$\beta$ levels. The regulation of cytokines reduces the neuroinflammation of the SN and alleviates PD symptoms [158, 159]. Acupuncture also activates the PI3K/Akt pathway, which elevates the Bcl-2 level and reduces dopamine- and cAMP-regulated phosphoprotein of 32 kDa and Fos B. Through the activation of the PI3K/Akt pathway, acupuncture increases the dopamine turnover rate and availability in the synapse of the SN and striatum and regulates the tyrosine hydroxylase–positive cell cycle, thus improving motor function [160–162]. Lu et al. demonstrated that EA on KI3 inactivates pPKA/pPKC/CaMKII$\alpha$ signaling pathways and reduces neuronal excitotoxicity in the hippocampus [163].

Rapamycin, an inhibitor of mTOR, is a potent inducer of autophagy and has an effect on PD [181]. However, rapamycin-based treatments for PD show adverse effects, including dyslipidemia, proliferative dysregulation, and renal dysfunction [182]. Acupuncture on GB34 affected the downstream autophagy–lysosome pathway through the m-TOR-independent pathway; this effect was comparable to that observed in the rapamycin treatment group [164]. Acupuncture induced autophagic clearance of $\alpha$-syn, caused recovery of DA neurons in the SN, and improved motor function of an animal model without any notable adverse effect [164].

Oxidative stress and inflammation both contribute to the neural toxicity and development of PD [183]. Many studies have indicated the use of high-frequency EA for treating PD motor symptoms in animal models [184, 185]. Kim et al. reported that high-frequency EA on GB34 and GB39 increased tyrosine hydroxylase–positive neurons and cytochrome c oxidase subunit Vb and reduced cytosolic malate dehydrogenase, munc18-1, and hydroxyacylglutathione hydrolase levels, thus exerting an antioxidative effect on the SN [165]. Lv et al. demonstrated that EA at 100 Hz on ST36 and SP6 exerted a neuroprotective effect on PD mice and reversed the increase in the levels of Iba-1 and proinflammatory cytokines, including TNF-$\alpha$, IL-6, and IL-1$\beta$, induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), thus suppressing the neuroinflammatory process [166]. The nuclear factor erythroid 2 -related factor 2 (Nrf2)–antioxidant response element (ARE) pathway regulates oxidative stress and inflammatory responses. EA enhances the Nrf2–ARE pathway and regulates the expression of antioxidants, such as the ARE-driven reporter gene, nicotinamide adenine dinucleotide phosphate quinone oxidoreductase, and heme oxygenase-1 (HO-1), thus relieving PD symptoms [166]. Similarly, Deng et al. reported that EA at 100 Hz on ST36 and SP6 elevated HO-1 and glutamate–cysteine ligase modifier subunits and reduced astrogliosis and neuroinflammation through the Nrf2–ARE pathway [167].

PD symptoms were relieved through the modification of TLR/NF-$\kappa$B and Nrf2/HO-1 pathways [186]. EA on GV16 and

Table 6: Signal transduction pathways of acupuncture in treating vascular dementia.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, Wistar rats, homologous blood emboli injection of internal carotid artery | hippocampus | ST36 | MA | QD for 14 days | activation of cAMP/PKA/CREB pathway | activation of long-term potentiation | Li QQ, et al. 2015[47] |
| Male, SD rats, MCAO | hippocampus | GV24, GV20 | EA, 1-3mA, 5/20Hz | 30min, QD | increase expression of p-CREB | elevation of superoxide dismutase and glutathione peroxidase, Bcl-2 depression of malondialdehyde, Bcl2-xl anti-oxidase and anti-apoptosis | Lin R, et al. 2015[48] |
| Female, SD rats, MCAO | hippocampus | GV20, GV24 | EA, 1/20Hz | 30min, QD for 7 days | inactivation of CaM-CaMKIV-CREB pathway | anti-apoptosis | Zhang Y, et al. 2016[50] |
| Male, SD rats, MCAO | hippocampus | GV20, HT7 | MA, LA, 30 mW, 100Hz | 14 days | enhance cholinergic system | elevation of CREB, BDNF and Bcl-2 depression of Bax anti-apoptosis | Yun YC, et al. 2017[51] |
| Mongolian gerbils, CCAO | hippocampal CA1 | KI3, GV20 | EA, 1mA, 2Hz | 20 min, 4 times/ 2 days | regulate MAPK/ERK pathway | elevation of p-ERK depression of ionized calcium-binding adaptor molecule 1, TLR4, TNF-$\alpha$ decrease neuroinflammation, regulate the synaptic plasticity | Yang EJ, et al. 2016[153] |
| Male Wistar rats, two-vessel occlusion model | hippocampus | GV20, ST36 | MA | QD for 14 days | inactivation of ASK1-JNK/p38 pathway | elevation of thioredoxin-1 and thioredoxin reductase-1 anti-oxidase and anti-apoptosis | Zhu W, et al. 2018[154] |

Table 6: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male, Wistar rat, homoblood injection | hippocampal CA1 | CV17, CV12, CV6, ST36, SP10 | MA, 2Hz | 30sec for each acupoint, QD, 6 days/wk for 3 weeks | balance Bcl-2 and Bax expression | elevation of Bcl-2 depression of Bax anti-apoptosis | Wang T, et al. 2009[155] |
| Male, SD rat, using modified Pulsinelli 4-vessel-occlusion method | hippocampal CA1 | Scalp-acupuncture | MA | 30min, QD for 10 days | activation of Bcl-2 pathway | elevation of Bcl-2 anti-apoptosis of astrocytes | Tian WJ, et al. 2015[156] |
| Female, SD rat, CCAO | hippocampus | GV20, GV14, BL23 | EA, 2mA, 4Hz | 30min, QD for 30 days | activation of mTOR pathway | elevation of mTOR and eIF4E modulates cell growth, proliferation and synaptic plasticity | Zhu Y, et al. 2013[157] |

Abbreviations

ASK1: apoptosis signal-regulating kinase 1; Bax: Bcl-2 associated X; Bcl-2: B-cell lymphoma 2; BDNF: brain-derived neurotrophic factor; CaMK: Ca2+/calmodulin-dependent protein kinase; cAMP: cyclic adenosine monophosphate; CCAO: occlusion of common carotid artery; CREB: phosphorylated cyclic AMP response element-binding protein; EA: electroacupuncture; eIF4E: eukaryotic translation initiation factor 4E; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinases; MA: manual acupuncture; MAPK: mitogen-activated protein kinases; MCAO: occlusion of middle cerebral artery; mTOR: mammalian target of rapamycin; PKA: protein kinase A; QD: daily; TLR4: Toll-like receptor 4.

Table 7: Signal transduction pathways of acupuncture in treating Parkinson's disease.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Male SD rats, rotenone injection | substantia nigra | GV16, LR3 | EA, 1mA, 2Hz | 20min, QD for 14 days | inactivation of p38-MAPK pathway | elevation of tyrosine hydroxylase-positive neuron<br>depression of phosphorylated p38-MAPK, COX-2<br>decrease neuroinflammation | Wang SJ, et al. 2013[158] |
| Male SD rats, rotenone injection | substantia nigra | GV16, LR3 | EA, 2mA, 2Hz | 20min, QD for 14 days | inactivation of ERK 1/2 pathway | elevation of tyrosine hydroxylase protein<br>depression of p-ERK 1/2, TNF-$\alpha$, IL-1$\beta$<br>decrease neuroinflammation | Wang SJ, et al. 2014[159] |
| Male C57BL/6 mice, MPTP injection | substantia nigra, striatum | GB34 | MA, 2Hz for 15sec | QD for 7 days | activation of PI3K/Akt pathway | elevation of pAkt prevents MPTP-induced dopaminergic neuron degeneration | Kim SN, et al. 2011[160] |
| Male C57BL/6 mice, MPTP injection | substantia nigra pars compacta, striatum | GB34 | MA, 2Hz for 15sec | QD for 12 days | activation of PI3K/Akt pathway | elevation of dopamine<br>depression of dopamine- and cAMP-regulated phosphoprotein of 32 kDa, Fos<br>increase dopamine turnover rate | Kim SN, et al. 2011[161] |
| Male, C57BL6 mice (MPTP intraperitoneal injection) and SD rats (Sigma-Aldrich injection into substantia nigra) | substantia nigra | GB34, LR3 | EA, 1mA, 50Hz | QD for 5(mice)/7(rats) days | activation of Akt pathway | elevation of BDNF, Bcl-2, tyrosine hydroxylase<br>regulation of cell cycle | Lin JG, et al. 2017[162] |

Table 7: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| Imprinting control region mouse pups, systemic 6-hydroxydopamine injection | hippocampus | KI3 | EA, 1mA, 2Hz | 15min, QD, 5 days/wk for 6wks | inactivation of pPKA/pPKC/CaMKII$\alpha$ signaling pathways | depression of pNR1, pNR2B, pPKA, pPKC, pCaMKII$\alpha$, pERK, pCREB reduce neuronal excitotoxicity | Lu KW, et al. 2017[163] |
| Male C57BL/6 mice, MPTP injection | substantia nigra par compacta | GB34 | MA, 2Hz for 15sec every 5min | 10min, QD for 7 days | m-TOR independent pathway | depression of $\alpha$-synuclein induces autophagic clearance of $\alpha$-syn, dopaminergic neurons protection | Tian T, et al. 2016[164] |
| Male C57BL/6 mice, MPTP injection | substantia nigra, striatum | GB34, GB39 | EA, 1mA, 100Hz | 20min, QD for 12 days | regulation of glyoxalase system | elevation of tyrosine hydroxylase-positive neurons, cytochrome c oxidase subunit Vb depression of cytosolic malate dehydrogenase, munc18-1, hydroxyacylglutathione hydrolase anti-oxidative effect | Kim ST, et al. 2010[165] |
| Male C57BL/6 mice, MPTP injection | midbrain, striatum | ST36, SP6 | EA, 1-1.4mA, 100Hz | 30min, QD for 12 days, except day 7 | activation of Nrf2-ARE pathway | elevation of tyrosine hydroxylase, ARE-driven reporter gene, NQO1, HO-1 depression of ionized calcium-binding adaptor molecule 1, TNF-$\alpha$, IL-6, IL-1$\beta$ anti-oxidative effect | Lv E, et al. 2015[166] |

Table 7: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|---|---|---|---|---|---|---|---|
| GFAP-tTA/tetO-α-syn double transgenic mice | midbrain, striatum | ST36, SP6 | EA, 1-1.2mA, 100Hz | 30min, QD for 28 days | activation of Nrf2-ARE pathway | elevation of Nrf2, HO-1, glutamate-cysteine ligase modifier subunits<br>depression of α-syn<br>decrease astrogliosis and neuroinflammation | Deng J, et al. 2015[167] |
| Male C57BL/6 mice, MPTP injection | striatum, substantia nigra | GB34 | MA, 2Hz, 15sec | QD for 12 days | activation of p53 signaling pathways | elevation of p53<br>dopaminergic neuron protection | Park JY, et al. 2015[168] |

Abbreviations

Akt: protein kinase B; ARE: antioxidant response element; CaMK: Ca2+/calmodulin-dependent protein kinase; cAMP: cyclic adenosine monophosphate; COX: cyclooxygenase; CREB: phosphorylated cyclic AMP response element-binding protein; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; HO-1: heme oxygenase-1; IL: interleukin; MA: manual acupuncture; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR: mammalian target of rapamycin; NQO1: nicotinamide adenine dinucleotide phosphate quinone oxidoreductase; Nrf2: nuclear factor erythroid 2-related factor 2; p38 MAPKs: p38 mitogen-activated protein kinases; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA: protein kinase A; PKC: protein kinase C; pNR: phosphorylated N-methyl-D-aspartate receptor; QD: daily; SD rat: Sprague Dawley rat; TNF-α: tumor necrosis factor-alpha.

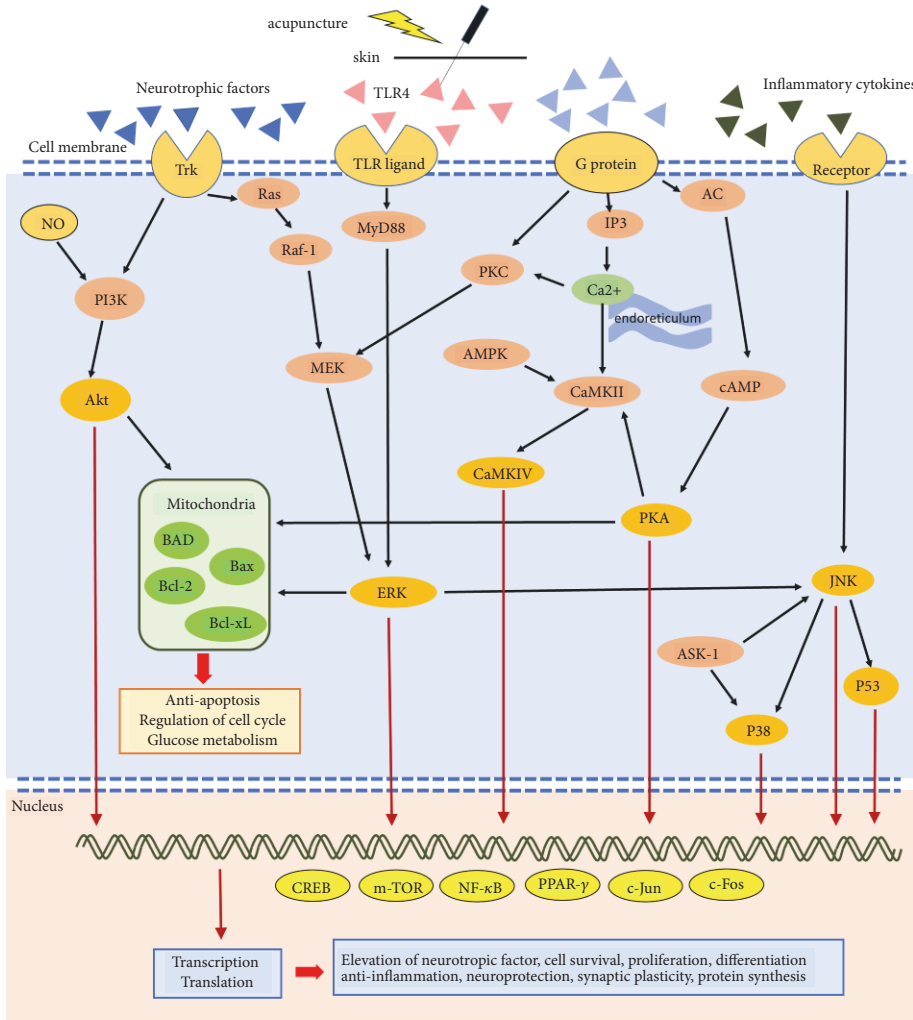


FIGURE 2: Summary of signal transduction pathways through which acupuncture treats nervous system diseases. Acupuncture is applied on acupoints and results in de qi, evoking excitation of cell membrane receptors, such as the Trk and TLR/ligand, and subsequently producing signal transduction. AC: adenyl cyclase; Akt: protein kinase B; AMPK: AMP-activated protein kinase; ASK-1: apoptosis signal-regulating kinase 1; Bad: Bcl-2-associated death promoter; Bax: Bcl-2 associated X; Bcl-2: B-cell lymphoma 2; Bcl2-xl: B-cell lymphoma-extralarge; CaMK: Ca2+/calmodulin-dependent protein kinase; cAMP: cyclic adenosine monophosphate; CREB: phosphorylated cyclic AMP response element-binding protein; ERK: extracellular signal-regulated kinase; IP3: inositol triphosphate; JNK: c-Jun N-terminal kinases; MEK: mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; mTOR: mammalian target of rapamycin; MyD88: myeloid differentiation primary response 88; NF-$\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA: protein kinase A; PKC: protein kinase C; PPAR-$\gamma$: peroxisome proliferator-activated receptor $\gamma$; TLR: Toll-like receptor; Trk: tyrosine receptor kinase.

LR3 upregulated NF$\kappa$B protein expression and downregulated 26S proteasome protein expression in rotenone-induced PD rats [187]. P53 plays a role in DNA repair or cell death depending on the nature and extent of stress and damage [188]. P53 dysfunction was reported in neurodegenerative diseases and cancers [189]. Park et al. demonstrated that acupuncture on GB34 activated the p53 signaling pathway, protected dopaminergic neurons in the SN and striatum, and treated PD symptoms [168].

At the gene level, Choi et al. demonstrated that EA regulated gene expression in the striatum and exerted a neuroprotective effect on MPTP parkinsonism mice [190, 191]. Yeo et al. performed a microarray analysis study of acupuncture on GB34 and LR3 in an MPTP mouse model of parkinsonism and reported that acupuncture reversed the downregulation of five annotated genes and upregulation of three annotated genes through MPTP intoxication [192].

In summary, acupuncture improved motor dysfunction and memory of PD. These effects were accompanied by the regulation of gene expression. Acupuncture modulates neuroinflammation by inactivating ERK 1/2 and p38/MAPK signaling pathway and reduces neuronal excitotoxicity through the pPKA/pPKC/CaMKII$\alpha$ signaling pathway. Acupuncture also regulates apoptosis by balancing the Bcl-2 and m-TOR-independent pathway. The most chosen acupoints include GB34, LR3, and GV16. Moreover, high-frequency EA (100

Hz) on ST36 and SP6 reduces neuroinflammation through the Nrf2–ARE pathway. The mechanisms and main results of identified articles are summarized in Table 7.

## 10. Conclusion

Acupuncture treats nervous system diseases through many signal transduction pathways. Besides increasing the neurotrophic factors level, acupuncture influences pathways including p38 MAPKs, Raf/MAPK/ERK1/2, TLR4/ERK, PI3K/AKT, AC/cAMP/PKA, ASK1–JNK/p38, and downstream CREB, JNK, m-TOR, NF-$\kappa$B, and Bcl-2/Bax balance. We summarized the common signal transduction pathways through which acupuncture treats nervous system diseases (Figure 2). Through the aforementioned pathways, acupuncture affects synaptic plasticity, elevates neurotrophic factors, and results in neuroprotection, cell proliferation, antiapoptosis, antioxidant activity, anti-inflammation, and maintenance of the BBB.

## Data Availability

The data in this study are available to other researchers upon request.

## Conflicts of Interest

We declare that there are no conflicts of interest associated with this manuscript, and no significant financial support was received that would influence our findings.

## Authors' Contributions

Hsiang-Chun Lai collected data and wrote the manuscript, Qwang-Yuen Chang participated in discussions and provided suggestions, and Ching-Liang Hsieh provided an informed opinion and revised the manuscript.

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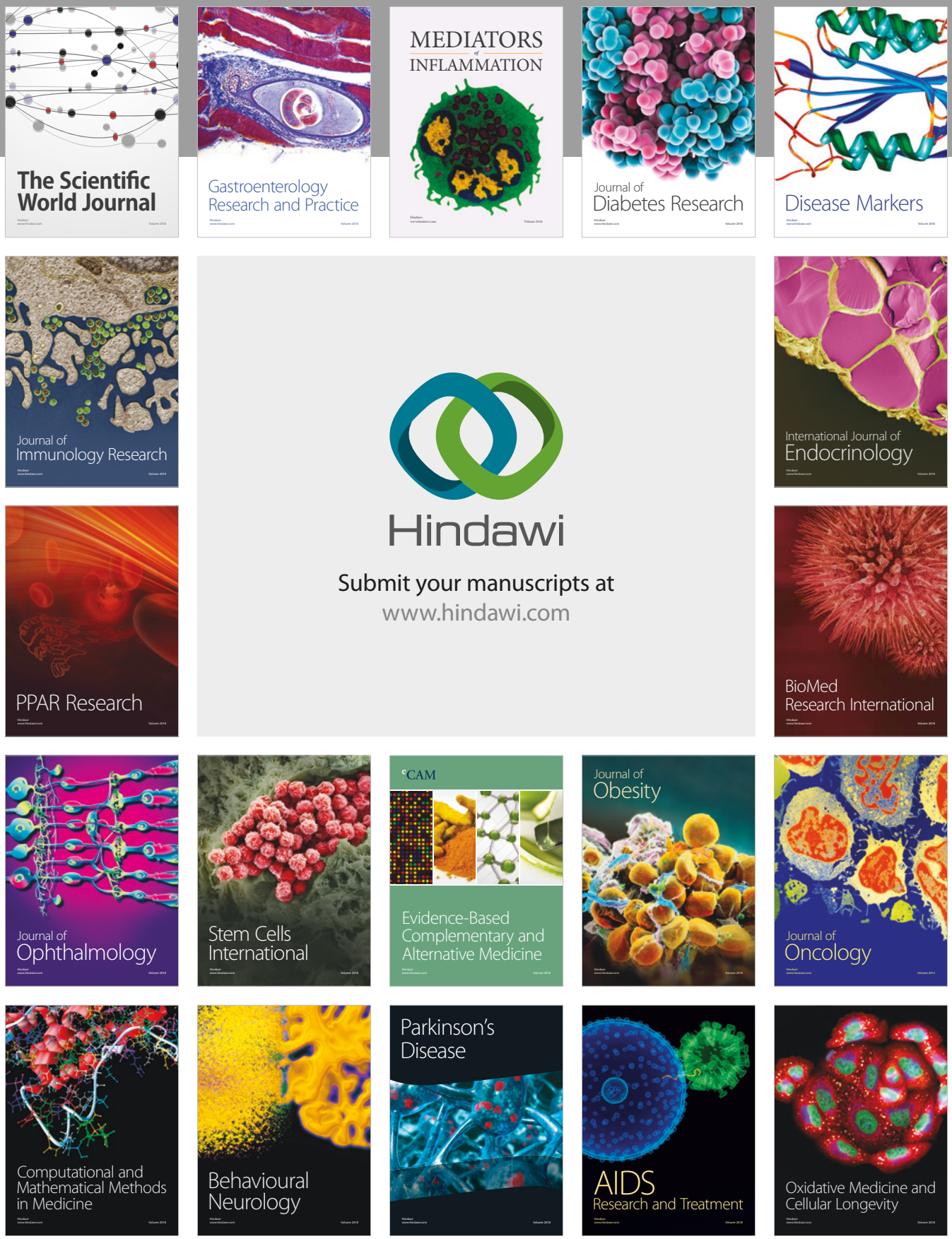
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RESEARCH ARTICLE

# Incidence of stroke in patients with HIV infection: A population-based study in Taiwan

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## Abstract

### Background

Few studies have evaluated whether people infected with human immunodeficiency virus (HIV) are at an increased risk of stroke in an Asian population. We investigated the association between HIV infection and the risk of developing stroke by age, calendar year of HIV diagnosis, and follow-up duration in Taiwan.

### Methods

Using the claims data of a universal health insurance program, we identified 5,961 patients with HIV and 23,844 matched non-HIV subjects without previous stroke from 1998 to 2005 and followed them up until the end of 2011 to measure the incidence of stroke. Cox proportional hazards models adjusted for potential confounders were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), with the non-HIV group as reference.

### Results

During a median follow-up of 8 years, the incidence rates for total, ischemic, and hemorrhagic stroke per 1000 person-years were 2.12, 1.22, and 0.60, respectively, in patients with HIV infection, and 1.98, 1.14, and 0.54, respectively, in the comparison group. HIV infection was associated with an elevated risk of developing total stroke (adjusted HR [95% CI], 1.57 [1.15–2.14]) and ischemic stroke (1.91 [1.25–2.91]) in patients aged less than 45 years, but no association was observed in other age groups (*P* for interaction with age, p = 0.048 and 0.024, respectively). Patients diagnosed with HIV infection in 1998–1999 had a greater HR for total stroke and ischemic stroke than those diagnosed in 2000–2002 and 2003–2005 (*P* for interaction, for total stroke p = 0.034, for ischemic stroke p = 0.056). The HRs did not differ by follow-up duration.

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**Competing interests:** The authors have declared that no competing interests exist.

**Abbreviations:** AIDS, acquired immune deficiency syndrome; c ART, combination antiretroviral therapy; CI, confidence interval; CIC, catastrophic illness certificate; CVD, cardiovascular disease; HAART, highly active antiretroviral therapy; HIV, Human immunodeficiency virus; ICD, International Classification of Diseases; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LHID, Longitudinal Health Insurance Database for one million people insured; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; PLWHA, people living with HIV infection; SIR, standardized incidence ratio.

## Conclusions

HIV infection among a young age group is associated with increased risk of developing overall and ischemic stroke. The findings highlight the importance of screening and correcting risk factors for young stroke prevention immediately and aggressively.

## Introduction

Human immunodeficiency virus (HIV) infection largely affects sexually active young adults. With the development of the combination antiretroviral therapy (cART) regimen, used for people living with HIV/AIDS (PLWHA) since 1996, HIV replication was effectively inhibited, leading to a reduction of the risk of developing an AIDS-defining complication and prolonging the lifespan of patients with HIV [1]. However, the health of effectively treated patients with HIV is not fully restored and has led to a higher prevalence of the disease than in those without HIV infection [2].

Stroke is a significant cause of death and disability worldwide [3]. Acute or chronic infection is well recognized to be a contributing factor in strokes and can influence the outcome of strokes [4]. Several studies have reported the association between HIV infection and the risk of stroke [1, 5–17]. However, most of these studies have been confined to Western populations [1, 5–12, 15–17]. Little is known regarding the association between HIV infection and the risk of stroke in Asian people [6, 13, 14]. Multiple factors, including age, sex, family history, the effect of HIV itself, the effect of antiretroviral therapy, traditional cardiovascular risk factors etc., influence the risk of stroke in HIV-infected individuals. Genetics in different populations also play a role. Epidemiology data have been revealed to be different in Western and Asian countries due to the influence of population-specific phenotypic effects and gene susceptibility on the progression of HIV infection [18, 19]. Black people have shown more prominent cerebrovascular endothelial dysfunction leading to an elevated risk of stroke compared with other race/ethnic groups after adjusting for several traditional vascular risk factors in an ART-treated PLWHA group [20]. A recent multiethnic study revealed that the incidence rate of stroke was greater in non-Hispanic Black people than in other ethnic groups in persons living with HIV infection, but only 2% of the study subjects (n = 116) were Asian/Pacific Islanders [15]. Furthermore, studies of the US population have shown a greater risk of stroke in women and in younger people [8, 12, 15, 16], but limited data is available for other ethnic groups. A recent population-based cohort study in Taiwan reported that patients that are HIV-positive had an increased risk of stroke, as compared with individuals who are HIV-negative [14]. The incidence rate of stroke among individuals that are HIV-infected in that study [14] was lower than that in previous reports in Western countries [5, 7–9, 11, 12]. However, data by types of stroke and whether the HIV-related risk of stroke differs by age and sex was not reported in that study [14]. Furthermore, little is known regarding the risk of stroke in association with HIV infection by calendar years of diagnosis [21] and the duration of follow-up. Using a national database from Taiwan, we explored the risk of overall and different types of stroke in patients with HIV infection by age, sex, calendar year of diagnosis, and follow-up years.

## Methods

### Study design and data source

We conducted a retrospective cohort study using claims data of a universal health insurance program in Taiwan [22]. The National Health Insurance (NHI) program is a mandatory

single-payer national health insurance program providing comprehensive healthcare coverage to more than 99% of the 23 million people in Taiwan [23]. The NHI claims data is provided to scientists for research purposes, and all personal identification information was encrypted for the protection of patient privacy [6]. This study was approved by the Institutional Review Board of China Medical University & Hospital (CRREC-106-074).

## Identification of patients living with HIV infection and the comparison group

Fig 1. shows the flow chart for the subject selection process. We identified a cohort of patients diagnosed with HIV infection for the first time during the period of 1 January 1998 and 31 December 2005, according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 042 and V08 listed in the Registry for Catastrophic Illness Patient Database. Taiwan's NHI defines 31 categories of catastrophic illness, including HIV infection. When patients are diagnosed and confirmed as having such definite catastrophic illnesses, they are qualified to apply for catastrophic illness certificates by their attending physician, and thus become exempt from copayments. To apply for the catastrophic illness certificates for HIV infection, patients' infectious disease physicians must provide pertinent medical records and data for formal review, including clinical histories, the definite positive results of the HIV antibody and antigen combination assays in the laboratory tests, and the results of viral load and CD4 count examinations to validate the diagnoses. An expert committee composed of infectious disease physicians issues catastrophic illness certificates of HIV after a review of the applications. For each of the patients with HIV, the date on which he or she was registered for the catastrophic illness served as the index date. Individuals who had received stroke diagnoses before the index date were excluded from the data analysis.

Using a dataset containing NHI claims of one million subjects randomly selected from the insured population during 1996–2000 (the Longitudinal Health Insurance Database [24]), we randomly selected patients without an HIV diagnosis to form a comparison group. Subjects in the comparison group were frequency matched with those in the HIV infection group at a 4:1 ratio based on age (every 5 years), sex, and the calendar year of the HIV diagnosis and were randomly assigned index dates in the same year of the HIV diagnosis in the HIV infection group. Individuals previously diagnosed with stroke were excluded.

## Follow-up for stroke development

Subjects in the HIV infection group and the comparison group were observed for the occurrence of stroke, defined as a hospital discharge diagnosis with stroke (ICD-9-CM codes 430–438). We classified patients with stroke into three categories: hemorrhagic stroke (ICD-9-CM codes 430–432), ischemic stroke (ICD-9-CM codes 433, 434, and 435.9), and undetermined type of stroke (ICD-9-CM codes 435–438 exclude 435.9). The follow-up period started on the index date and ended at the earliest of the following dates: stroke occurrence, withdrawal from the NHI program, or 31 December 2011.

## Baseline comorbidities

Comorbidities including diabetes mellitus (ICD-9-CM codes 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM codes 272), chronic kidney disease (ICD-9-CM codes 580–587), cancer (ICD-9-CM codes 140–208), coronary heart disease (ICD-9-CM codes 410–414), and atrial fibrillation (ICD-9-CM codes 427.31), which are known risk factors of stroke, were considered as potential confounders (S1 Table). All comorbidities were identified

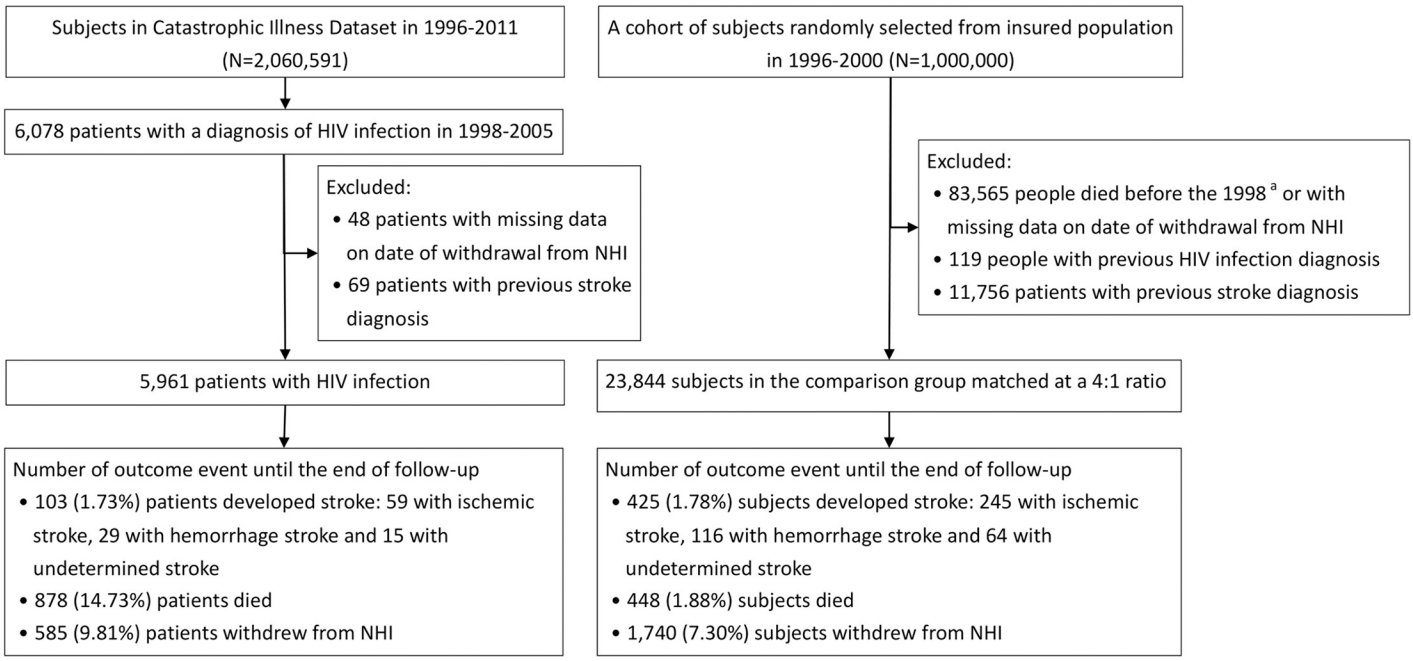


**Fig 1. Flow chart of study subjects' selection.** [a]Death was defined by using hospital discharged records and registry of catastrophic illness dataset. NHI indicates National Health Insurance Program; HIV, human immunodeficiency virus.

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by the presence of diagnosis codes in at least two outpatient claims or one hospital inpatient claim within two years before the index date.

### Statistical analysis

We compared the baseline characteristics of patients with HIV and the comparison group using *t*-tests for continuous variables and chi-squared tests for categorical variables. For each group, the incidence density rates of stroke were calculated by using the number of patients with incident stroke events divided by total follow-up person-years. We used Cox proportional hazards models, which yielded hazard ratios (HR) and 95% confidence intervals (CI), to assess the risk of developing total, ischemic, and hemorrhagic stroke in association with HIV infection. The models were adjusted for age, sex, and the comorbidities to control for potential confounding factors. The Cox models were performed in patient subgroups stratified by age, year of HIV diagnosis, and follow-up period to observe whether the risks differ between the stratifications. Interaction effects of age and year of diagnosis with HIV were examined by using likelihood ratio tests comparing Cox models excluding and including the interaction terms. The proportional hazards assumption, i.e., whether the risk differs by follow-up time, was also tested by including interaction terms between the HIV infection and a function of follow-up time in the models. We used the SAS 9.4 software package (SAS Institute, Cary, NC USA) to perform all data management and analyses.

## Results

### Characteristics of subjects in the HIV-infected group and the comparison group

There were 6,078 patients with HIV infection identified from 1998 to 2005 (Fig 1). We excluded subjects with missing or invalid data on the date of withdrawal from the NHI

program, and those with a previous diagnosis of stroke. The remaining 5,961 patients in the HIV infection group were included in the analysis. A total of 23,844 subjects without HIV infection who met the inclusion criteria were selected in the age-, sex-, and calendar year-matched comparison group.

The ratio of male to female subjects in the HIV-infection cohort was nearly 11.8 (crude number 5495 vs. 466; 92.2% vs. 7.8%) (Table 1). The mean (standard deviation, SD) age at HIV diagnosis was 34.2 (10.9) years for male patients and 36.4 (12.7) years for female patients. Of patients living with HIV infection, 61% had their first diagnosis at age 35 years or younger. The median follow-up time to occurrence of stroke was 8.1 years for the HIV group and 8.4 years for the comparison group (interquartile range, 4.2 years vs. 5.6 years). The mean (SD) age of diagnosis with stroke in the HIV infection cohort was younger than that in the comparison group (50.8 [15.3] years vs. 57.3 [14.3] years, $p<0.0001$). Relative to subjects in the comparison group, patients with HIV infection were more likely to have comorbid diabetes (3.1% vs. 2.2%), chronic kidney disease (1.6% vs. 0.7%), and cancer (1.0% vs. 0.4%).

## HIV infection and the risk of stroke by age and sex

Table 2 shows the incidence rates and HRs for stroke overall and in subgroups stratified by age and sex. During the follow-up period, the incidence rates for total, ischemic, and hemorrhagic stroke per 1000 person-years were 2.12, 1.22, and 0.60, respectively, in the patients with HIV infection. The corresponding rates in the comparison group were 1.98, 1.14, and 0.54. In the multivariable-adjusted models, overall we did not observe a statistically significant association between HIV infection and the risk of developing total stroke (adjusted HR [95% CI], 1.21 [0.98–1.51]), ischemic stroke (1.23 [0.93–1.64]), and hemorrhagic stroke (1.18 [0.78–1.78]). The adjusted HR for total stroke was greater among women than in men (adjusted HR [95% CI], 2.25 [1.15–4.41] and 1.15 [0.91–1.44], respectively), but the sex difference was not statistically significant (for the interaction with sex $p = 0.085$).

The age-stratified analyses showed that HIV infection was associated with an increased risk of total stroke and ischemic stroke in subjects <45 years of age (adjusted HR [95% CI], 1.57 [1.15–2.14] and 1.91 [1.25–2.91], respectively), but not in other age stratifications (for interaction with total stroke $p = 0.048$, for interaction with ischemic stroke $p = 0.024$). Similarly, the HRs differed significantly by age among men. Increased risk was found in men <45 years of age but not in older subjects (for interaction with total stroke $p = 0.056$, for interaction with ischemic stroke $p = 0.034$). Elevated HRs in young patients were also noted among women, but the interaction effect with age was not statistically significant. However, we did not observe associations between HIV infection and the risk of developing hemorrhagic stroke.

## HIV infection and the risk of stroke by year of diagnosis

Table 3 shows the association between HIV infection and the risk of developing stroke in analyses stratified by year of diagnosis of HIV infection. The adjusted HR for total stroke was greater in patients diagnosed with HIV infection in 1998–1999 (HR = 1.51, 95% CI = 1.08–2.10) than those in 2000–2002 (HR = 0.75, 95% CI = 0.48–1.18) and 2003–2005 (HR = 1.44, 95% CI = 0.98–2.11) (p for interaction, $p = 0.034$) (Table 3). Similar results were observed for ischemic stroke but not for hemorrhagic stroke. Patients diagnosed with HIV infection in 1998–1999 had an increased risk of ischemic stroke (HR = 1.73, 95% CI = 1.13–2.65), but no significant association was observed in those diagnosed in 2000–2002 (HR = 0.68, 95% CI = 0.39–1.28) and 2003–2005 (HR = 1.33, 95% CI = 0.80–2.20) (p for interaction, $p = 0.056$) (Table 3).

**Table 1. Characteristics of patients with HIV infection and subjects in the comparison group.**

| Variable | Patients with HIV (n = 5961) | | Comparison group (n = 23844) | | p-value |
|---|---|---|---|---|---|
| Sex[a] (n (%)) | | | | | N.A. |
| Male subjects | 5495 | 92.2 | 21980 | 92.2 | |
| Female subjects | 466 | 7.8 | 1864 | 7.8 | |
| Age at HIV diagnosis, years (n (%))[a] | | | | | N.A. |
| 0–25 | 1101 | 18.5 | 4404 | 18.5 | |
| 25–35 | 2534 | 42.5 | 10136 | 42.5 | |
| 35–45 | 1468 | 24.6 | 5872 | 24.6 | |
| 45–55 | 491 | 8.2 | 1964 | 8.2 | |
| 55–65 | 248 | 4.2 | 992 | 4.2 | |
| ≥65 | 119 | 2.0 | 476 | 2.0 | |
| Median (mean ± SD)[b] | | | | | |
| All | 32.3 (34.3 ± 11.1) | | 32.4 (34.3 ± 11.3) | | |
| Male subjects | 32.2 (34.2 ± 10.9) | | 32.3 (34.2 ± 11.1) | | |
| Female subjects | 33.9 (36.4 ± 12.7) | | 33.9 (36.3 ± 12.9) | | |
| Comorbidities[a] | | | | | |
| Diabetes | 183 | 3.1 | 514 | 2.2 | <0.0001 |
| Hypertension | 245 | 4.1 | 1060 | 4.5 | 0.26 |
| Hyperlipidemia | 137 | 2.3 | 626 | 2.6 | 0.15 |
| Chronic kidney disease | 97 | 1.6 | 170 | 0.7 | <0.0001 |
| Cancer | 60 | 1.0 | 101 | 0.4 | <0.0001 |
| Coronary heart disease | 99 | 1.7 | 339 | 1.4 | 0.17 |
| Atrial fibrillation | 9 | 0.2 | 20 | 0.1 | 0.14 |
| Duration of the follow-up, years (median, (interquartile range))[c] | | | | | |
| Male subjects | 8.1 (4.1) | | 8.4 (5.5) | | <0.0001 |
| Female subjects | 7.6 (4.9) | | 8.4 (5.6) | | <0.0001 |
| All | 8.1 (4.2) | | 8.4 (5.6) | | <0.0001 |
| Age at diagnoses of stroke, years (median (mean ± SD))[b] | | | | | |
| Male subjects | 48.6 (50.3 ± 15.7) | | 56.8 (57.2 ± 14.5) | | <0.0001 |
| Female subjects | 51.1 (54.3 ± 12.4) | | 61.0 (59.2 ± 11.3) | | 0.22 |
| All | 49.1 (50.8 ± 15.3) | | 58.1 (57.3 ± 14.3) | | <0.0001 |

Abbreviations: HIV, human immunodeficiency virus; N.A., not applicable; SD, standard deviation.

[a]Chi-squared test.

[b]T-test.

[c]Wilcoxon Rank sum test.

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## HIV infection and the risk of stroke by follow-up period

Fig 2. shows the analyses of the association between HIV infection and the risk of developing stroke stratified by 1-year intervals of follow-up duration. The adjusted HRs were slightly increased in the first year and in years 5–6 after HIV diagnosis than in other time periods, but the difference in risk was not statistically significant (p = 0.94). The HRs for ischemic stroke and hemorrhagic stroke also did not differ over follow-up time (p = 0.38 and p = 0.90, respectively).

The models were adjusted for age, sex, and comorbidities including diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, coronary heart disease, and atrial fibrillation.

**Table 2. Risk of stroke in relation to HIV infection by age and sex.**

| Age group, years | Total stroke[a] | | | | | Ischemic stroke | | | | | Hemorrhage stroke | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HIV group | | Comparison group | | HR (95% CI)[b] | HIV group | | Comparison group | | HR (95% CI)[c] | HIV group | | Comparison group | | HR (95% CI)[c] |
| | No. event | Rate[b] | No. event | Rate[b] | | No. event | Rate[b] | No. event | Rate[b] | | No. event | Rate[b] | No. event | Rate[b] | |
| **All** | | | | | | | | | | | | | | | |
| **<45** | 55 | 1.29 | 155 | 0.84 | 1.57 (1.15–2.14) | 31 | 0.73 | 73 | 0.40 | 1.91 (1.25–2.91) | 16 | 0.38 | 66 | 0.36 | 1.07 (0.62–1.84) |
| **45–65** | 34 | 6.36 | 196 | 7.23 | 0.82 (0.57–1.19) | 20 | 3.74 | 121 | 4.47 | 0.76 (0.47–1.23) | 10 | 1.87 | 45 | 1.66 | 1.09 (0.54–2.18) |
| **>65** | 14 | 23.57 | 74 | 20.84 | 1.08 (0.60–1.94) | 8 | 13.47 | 51 | 14.36 | 0.91 (0.63–1.96) | 3 | 5.05 | 5 | 1.41 | 3.07 (0.66–14.3) |
| **All** | 103 | 2.12 | 425 | 1.98 | 1.21 (0.98–1.51) | 59 | 1.22 | 245 | 1.14 | 1.23 (0.93–1.64) | 29 | 0.60 | 116 | 0.54 | 1.18 (0.78–1.78) |
| **Male subjects** | | | | | | | | | | | | | | | |
| **<45** | 49 | 1.23 | 146 | 0.85 | 1.47 (1.06–2.04) | 27 | 0.68 | 67 | 0.99 | 1.80 (1.15–2.82) | 15 | 0.38 | 64 | 0.37 | 1.02 (0.58–1.80) |
| **45–65** | 28 | 6.09 | 179 | 7.71 | 0.77 (0.52–1.15) | 16 | 3.48 | 110 | 4.74 | 0.70 (0.41–1.19) | 8 | 1.74 | 41 | 1.77 | 1.00 (0.47–2.13) |
| **>65** | 13 | 24.15 | 69 | 21.28 | 1.09 (0.59–2.00) | 8 | 14.86 | 48 | 14.80 | 0.98 (0.45–2.11) | 3 | 5.57 | 5 | 1.54 | 3.07 (0.66–14.3) |
| **All** | 90 | 2.00 | 394 | 2.00 | 1.15 (0.91–1.44) | 51 | 1.13 | 225 | 1.14 | 1.17 (0.86–1.58) | 26 | 0.58 | 110 | 0.56 | 1.12 (0.73–1.72) |
| **Female subjects** | | | | | | | | | | | | | | | |
| **<45** | 6 | 2.16 | 9 | 0.69 | 3.57 (1.24–10.3) | 4 | 1.44 | 6 | 0.46 | 3.29 (0.93–11.7) | 1 | 0.36 | 2 | 0.15 | 4.19 (0.30–58.2) |
| **45–65** | 6 | 7.98 | 17 | 4.39 | 1.57 (0.56–4.40) | 4 | 5.32 | 11 | 2.84 | 1.82 (0.54–6.10) | 2 | 2.66 | 4 | 1.03 | 1.35 (0.13–13.8) |
| **>65** | 1 | 17.97 | 5 | 16.19 | 1.79 (0.19–17.3) | 0 | 0.00 | 3 | 9.71 | NA | 0 | 0.00 | 0 | 0.00 | - |
| **All** | 13 | 3.63 | 31 | 1.81 | 2.25 (1.15–4.41) | 8 | 2.23 | 20 | 1.17 | 2.16 (0.93–5.01) | 3 | 0.84 | 6 | 0.35 | 2.11 (0.41–10.8) |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

[a]Patients with undetermined stroke were excluded in the analysis by stroke subtypes (n = 79).

[b]Incidence rate per 1000 person-years.

[c]Adjusted for age, sex, and comorbidities including diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, coronary heart disease and atrial fibrillation. P values of test for interaction effect between age and HIV: all subjects, 0.048 for overall stroke, 0.024 for ischemic stroke and 0.386 for hemorrhage stroke; male patients, Interaction p 0.056 for overall stroke, 0.034 for ischemic stroke and 0.354 for hemorrhage stroke; female patients, I0.610 for overall stroke, 0.344 for ischemic stroke and 0.990 for hemorrhage stroke. P values of test for interaction effect between sex and HIV: 0.085 for overall stroke, 0.214 for ischemic stroke and 0.306 for hemorrhage stroke.

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Patients with undetermined stroke were excluded in the analysis by stroke subtypes (n = 79). HR indicates hazard ratio; CI, confidence interval.

## Discussion

The investigation of HIV infection as an independent risk factor of stroke incidence in different countries is worth noting. Our findings provide information for Asian subjects that individuals with HIV infection among a younger age cohort had increased risk of overall and ischemic stroke, and HIV infection-related risk of stroke was higher among subjects diagnosed in the early cART era.

**Table 3. Risk of stroke in patients with HIV infection according to calendar year of diagnosis.**

| Year of diagnosis of HIV infection | Total Stroke[a] | | | | | | | Ischemic stroke | | | | | Hemorrhage stroke | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HIV group | | | Comparison group | | | HR (95% CI)[c] | HIV group | | Comparison group | | HR (95% CI)[c] | HIV group | | Comparison group | | HR (95% CI)[c] |
| | No. | No. Event | Rate[b] | No. | No. Event | Rate[b] | | No. Event | Rate[b] | No. Event | Rate[b] | | No. Event | Rate[b] | No. Event | Rate[b] | |
| **1998–1999** | 1302 | 45 | 3.21 | 5208 | 160 | 2.44 | 1.51 (1.08–2.10) | 28 | 2.00 | 89 | 1.36 | 1.73 (1.13–2.65) | 11 | 0.78 | 47 | 0.72 | 1.18 (0.61–2.27) |
| **2000–2002** | 1786 | 22 | 1.40 | 7144 | 155 | 2.21 | 0.75 (0.48–1.18) | 11 | 0.70 | 87 | 1.24 | 0.68 (0.39–1.28) | 8 | 0.51 | 42 | 0.60 | 0.95 (0.45–2.04) |
| **2003–2005** | 2873 | 36 | 1.91 | 11492 | 110 | 1.39 | 1.44 (0.98–2.11) | 20 | 1.06 | 69 | 0.87 | 1.33 (0.80–2.20) | 10 | 0.53 | 27 | 0.34 | 1.52 (0.72–3.18) |

Abbreviations: No., Number CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

[a]Patients with undetermined stroke were excluded in the analysis by stroke subtypes (n = 79).

[b]Incidence rate per 1000 person-years.

[c]Adjusted for age, sex, and comorbidities including diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, coronary heart disease and atrial fibrillation.

P values of test for interaction effect between HIV infection and year of diagnosis: 0.034 for total stroke, 0.056 for ischemic stroke and 0.643 for hemorrhage stroke.

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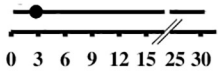
Epidemiological studies in different areas and with different ethnic groups revealed variations in the incidence of stroke among people with HIV infection. In general, studies from Asia yielded lower incidence. Chow et al. reported that the incidence rate of ischemic stroke per 1000 person-years was 5.27 in the HIV cohort and 3.75 in patients without HIV [8], and the incidence of hemorrhage stroke per 1000 person-years was 2.29 in the HIV-infected group compared with 1.23 in non-HIV group [12] in a local US health care system. One recent study in Taiwan showed the incidence rates of total stroke, ischemic stroke, and hemorrhagic stroke were 2.53 vs. 1.4; 1.87 vs. 1.01; 0.66 vs. 0.39 per 1000 person-years in the HIV cohort compared with the non-HIV cohort [14]. Another recent study found 2.2 cardiovascular events per 1000 person-years in the TREAT Asia HIV Observational Database [25]. Our observations revealed that the incidence rate of overall stroke per 1000 person-years was 2.12 among patients with HIV infection and 1.98 among the comparison group, which is lower than the studies reported in Western countries [5, 7–9, 11, 12], but similar to those in Asia [14, 25]. The reasons for the lower incidence rate of stroke in HIV-infected individuals in Asia remain unclear. Explanations may include the differences in study methods such as data sources, survey methods, time periods, the inclusion criteria for subject selection, and different population genetics.

The strength of the associations in our analyses, which showed an adjusted HR of 1.21 (95% CI 0.98–1.51) for total stroke and 1.23 [95% CI 0.93–1.64]) for ischemic stroke, was weaker than that observed in a Danish study [5] and a recent study in Taiwan [14] (HR [95% CI] for total stroke, 1.60 [1.30–1.95] and 1.83 [1.58–2.13], respectively), but similar to findings in a US study (HR [95% CI], 1.21 [1.01–1.46] for ischemic stroke) [8]. The statistical non-significance may reflect insufficient statistical power to detect the moderate association because of the relatively lower incidence of stroke and the smaller number of outcome events in our analysis than in the US study [8]. Furthermore, our study suggests variability of the association across patient subgroups of age and calendar year of diagnosis of HIV infection, which warrants further investigation.

Few studies have reported the association between HIV infection and risk of stroke by age and sex. Our observation was in line with the finding of Chow et al. [8], which showed a

| Years of follow-up | HIV | | | Comparison | | | HR (95% CI)[b] |
|---|---|---|---|---|---|---|---|
| | No. at risk | Event no. | Rate[a] | No. at risk | Event no. | Rate[a] | |
| **All stroke** | | | | | | | |
| 0-1 | 5961 | 18 | 3.17 | 23844 | 38 | 1.60 | 2.02 (1.14-3.56) |
| 1-2 | 5556 | 6 | 1.09 | 23530 | 33 | 1.41 | 0.88 (0.37-2.10) |
| 2-3 | 5436 | 8 | 1.49 | 23278 | 32 | 1.38 | 1.17 (0.53-2.56) |
| 3-4 | 5322 | 7 | 1.33 | 23071 | 45 | 1.96 | 0.74 (0.33-1.65) |
| 4-5 | 5226 | 8 | 1.55 | 22892 | 39 | 1.71 | 1.07 (0.50-2.29) |
| 5-6 | 5125 | 13 | 2.56 | 22707 | 31 | 1.37 | 2.05 (1.07-3.94) |
| 6-7 | 4994 | 8 | 1.82 | 22410 | 45 | 2.45 | 0.84 (0.39-1.80) |
| 7-8 | 3910 | 8 | 2.31 | 17649 | 26 | 1.75 | 1.48 (0.67-3.29) |
| 8-9 | 3062 | 3 | 1.11 | 14038 | 37 | 3.01 | 0.42 (0.13-1.37) |
| 9-10 | 2395 | 7 | 3.37 | 11196 | 29 | 2.96 | 1.23 (0.53-2.82) |
| 10-11 | 1812 | 5 | 3.22 | 8613 | 25 | 3.22 | 1.14 (0.43-3.04) |
| 11-12 | 1319 | 3 | 2.74 | 6405 | 17 | 2.90 | 1.04 (0.30-3.55) |
| 12-13 | 915 | 5 | 6.86 | 4587 | 17 | 3.91 | 1.75 (0.64-4.82) |
| 13-14 | 575 | 4 | 9.27 | 2936 | 11 | 3.95 | 2.20 (0.69-6.98) |
| **Ischemic stroke** | | | | | | | |
| 0-1 | 5961 | 7 | 1.23 | 23844 | 24 | 1.01 | 1.22 (0.52-2.85) |
| 1-2 | 5556 | 4 | 0.73 | 23530 | 18 | 0.77 | 1.11 (0.37-3.28) |
| 2-3 | 5436 | 4 | 0.74 | 23278 | 17 | 0.73 | 1.06 (0.34-3.32) |
| 3-4 | 5322 | 4 | 0.76 | 23071 | 27 | 1.18 | 0.73 (0.25-2.10) |
| 4-5 | 5226 | 4 | 0.77 | 22892 | 20 | 0.88 | 1.10 (0.37-3.26) |
| 5-6 | 5125 | 9 | 1.77 | 22707 | 21 | 0.93 | 2.14 (0.98-4.70) |
| 6-7 | 4994 | 5 | 1.13 | 22410 | 23 | 1.25 | 1.00 (0.37-2.69) |
| 7-8 | 3910 | 5 | 1.44 | 17649 | 14 | 0.94 | 1.70 (0.61-4.74) |
| 8-9 | 3062 | 0 | 0.00 | 14038 | 18 | 1.47 | NA |
| 9-10 | 2395 | 4 | 1.93 | 11196 | 16 | 1.63 | 1.26 (0.41-3.87) |
| 10-11 | 1812 | 4 | 2.58 | 8613 | 19 | 2.44 | 1.19 (0.39-3.61) |
| 11-12 | 1319 | 3 | 2.74 | 6405 | 7 | 1.20 | 2.49 (0.64-9.77) |
| 12-13 | 915 | 3 | 4.11 | 4587 | 13 | 2.99 | 1.22 (0.34-4.42) |
| 13-14 | 575 | 3 | 6.96 | 2936 | 8 | 2.87 | 2.22 (0.57-8.57) |
| **Hemorrhage stroke** | | | | | | | |
| 0-1 | 5961 | 6 | 1.06 | 23844 | 8 | 0.34 | 3.44 (1.18-10.0) |
| 1-2 | 5556 | 1 | 0.18 | 23530 | 10 | 0.43 | 0.45 (0.06-3.52) |
| 2-3 | 5436 | 2 | 0.37 | 23278 | 6 | 0.26 | 1.58 (0.32-7.85) |
| 3-4 | 5322 | 2 | 0.38 | 23071 | 12 | 0.52 | 0.74 (0.16-3.29) |
| 4-5 | 5226 | 3 | 0.58 | 22892 | 16 | 0.70 | 0.92 (0.27-3.18) |
| 5-6 | 5125 | 3 | 0.59 | 22707 | 7 | 0.31 | 1.81 (0.45-7.22) |
| 6-7 | 4994 | 0 | 0.00 | 22410 | 13 | 0.71 | NA |
| 7-8 | 3910 | 3 | 0.86 | 17649 | 6 | 0.40 | 2.54 (0.63-10.3) |
| 8-9 | 3062 | 3 | 1.11 | 14038 | 13 | 1.06 | 1.11 (0.32-3.92) |
| 9-10 | 2395 | 2 | 0.96 | 11196 | 11 | 1.12 | 0.94 (0.21-4.26) |
| 10-11 | 1812 | 1 | 0.64 | 8613 | 3 | 0.39 | 1.61 (0.17-15.5) |
| 11-12 | 1319 | 0 | 0.00 | 6405 | 6 | 1.02 | NA |
| 12-13 | 915 | 2 | 2.74 | 4587 | 3 | 0.69 | 4.25 (0.71-25.6) |
| 13-14 | 575 | 1 | 2.32 | 2936 | 2 | 0.72 | 2.77 (0.25-30.7) |




79 Undetermined stroke is not listed in Fig 2.

[a]Rate, per 1000 person-years.

[b]Adjusted for age, gender, diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, coronary heart disease and atrial fibrillation.

**Fig 2. Risk of stroke in association with HIV infection according to time of follow-up.**

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greater HIV infection-related risk of ischemic stroke in young people and women. However, their study did not report the results of testing for interaction [8] with age and sex. We found that the difference in the risk of total stroke and ischemic stroke associated with HIV infection was statistically significant by age but not by sex. Previous studies have also indicated that the risk of hemorrhagic stroke associated with HIV infection increased particularly in younger patients and with more advanced disease [11, 12, 14, 26]. However, it may not be appropriate to make conclusions about the risk of hemorrhagic stroke in our analysis because the number of events was very small in the age and sex stratifications.

The potential mechanisms of ischemic stroke and hemorrhagic stroke in patients with HIV infection are multifactorial. HIV-related causes of ischemic stroke include aneurismal formation, vasculitis, accelerated atherosclerosis, HIV-associated cerebral blood vessel disease, opportunistic infection or neoplasia, cardioembolism, coagulopathy, and HIV-associated hyperviscosity [1, 27]. Possible HIV-related causes of hemorrhagic stroke include HIV-associated aneurysmal vasculopathy [28], vasculitis [29], immune thrombocytopenia [30], AIDS associated tumors, or infection [31, 32].

Our observations showed that the mean age diagnosed with stroke was 7-years younger in the HIV infection cohort than in the comparison group. This result is consistent with previous studies, which reported that patients with HIV developed stroke younger than those without HIV infection in individuals without traditional risk factors [33], even with good immune function [34], both in ischemic stroke [8, 33] and in hemorrhagic stroke [12, 26]. In Africa, patients with HIV that developed stroke were younger with a median age of 33.4 years in South Africa [33] and 39.8 years in Malawi [35]. Stroke incidence is usually low in young individuals and rises exponentially with age [36], because the vascular risk factors of stroke do not occur frequently in young individuals [37]. The remarkably high risk of stroke association with HIV infection in young people, and the younger age at diagnosis of stroke in the HIV infection group than in the comparison group implies that HIV infection plays an important role in young stroke.

Our finding in the analysis stratified by calendar year of diagnosis is consistent with the study by Alvaro-Meca et al., which revealed a decline in the stroke risk among HIV-infected individuals in more recent years after the introduction of HAART (highly active antiretroviral therapy) [21]. There may be a number of reasons for this decline. First, the adverse side effects of older antiretroviral regimens or more effective treatments in the recent era has led to seeing a higher stroke risk in the early HAART epoch than in more recent periods. Second, limited tools for making a stroke diagnosis in the earlier period might have resulted in an overestimated misdiagnosis [38, 39]. For example, HIV encephalopathy [40] or an HIV-related CNS opportunistic infection can mimic stroke [41].

In a stratified analysis by follow-up duration, we observed greater HRs for stroke in the first year after the diagnosis of HIV infection, but the interaction effect with follow-up time was not statistically significant. However, the number of stroke events in the HIV infection group in the stratifications of follow-up time was small. Further studies with larger sample sizes may help clarify this issue. From a prevention point of view, the importance of earlier risk factor correction and stroke prevention should still be emphasized once the definite diagnoses of HIV infection are established.

Our study has some limitations. First, patient characteristics including smoking history and status, BMI, and laboratory data, are not available in the claims data. Therefore, we were unable to assess the extent to which the confounding effects by these factors, if they exist, could explain the observed association between HIV infection and the incidence of stroke. However, such a confounding effect is unlikely to fully account for all the observed associations, particularly for the subgroups of young patients and those diagnosed in earlier years, in

which the associations were relatively strong. Further studies that collect these variables could help clarify this issue. Second, our necessary reliance on administrative claims data recorded by physicians and hospitals to establish diagnoses of HIV infection and stroke are less accurate than those designed in prospective settings. To minimize bias and strengthen the reliability, only patients with Catastrophic Illness Certificates of HIV infection were included. Issuing the certificates requires approval by an expert committee after review of the medical records. Stroke events were defined as hospitalized patients whose first major diagnoses were stroke. Third, information on the treatments of HIV infection is not available in this study. Thus, we were unable to evaluate the association between the treatments and the stroke risk in patients with HIV infection in this post-cART era. Fourth, our study based on observational claims data analysis cannot establish the mechanism of developing stroke in association with HIV infection. Finally, the non-significant results may be due to insufficient statistical power to detect the moderate association or the small number of events in the analyses of hemorrhagic stroke.

## Conclusions

This nationwide population-based study in Taiwan reveals that young individuals with HIV infection have an elevated risk of subsequent stroke. Ischemic stroke risk was higher in the early stage of antiretroviral therapy and declined in the more recent era. An etiology survey and risk factor control for stroke prevention should be provided to young HIV-infected individuals aggressively and as early as possible.

## Supporting information

**S1 Table. The disease and ICD-9-CM code.**
(DOCX)

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Original Article

# Fertility-preserving treatment of stage IA, well-differentiated endometrial carcinoma in young women with hysteroscopic resection and high-dose progesterone therapy

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ABSTRACT

*Objective:* The standard treatment for endometrial cancer is surgery with hysterectomy. However, this procedure will cause infertility in young women who desire to preserve pregnant ability. Conservative management with hormone therapy has been shown to be satisfactory in both tumor control and fertility preservation. Recently, hysteroscopic tumor resection followed by progestin therapy has been reported to be an alternative strategy. In this study we present our experience with this approach.
*Materials and methods:* Six young patients (30–36 years old) diagnosed with grade 1 stage IA endometrial cancer who wished to preserve fertility were enrolled for this treatment procedure. The patients underwent hysteroscopic tumor resection followed by oral progestin therapy with either megestrol acetate or medroxyprogesterone acetate for at least 6 months. Interval hysteroscopy with biopsy was performed during the treatment course to evaluate disease response.
*Results:* All of the six patients had complete tumor remission after hysteroscopic resection and progestin therapy (five in 6 months, one in 9 months). In a median follow-up of 32 months (range 4–49months), one patient became pregnant spontaneously and delivered a full-term healthy baby via cesarean section. She received a definite surgery 3 months later, and the pathology confirmed no tumor existence. The other five patients were also free of disease at the last follow-up.
*Conclusion:* Hysteroscopic tumor resection followed by progestin therapy for early-stage and well-differentiated endometrial cancer is a safe conservative treatment strategy. It could be an option for young patients who wish to preserve fertility.


## Introduction

Endometrial cancer is the most common gynecological cancer in developed countries. It mainly affects women of postmenopausal age, however, approximately 4–5% of patients are younger than 40 years and most of them have stage I, grade 1 disease. In addition, these patients usually have a better overall 5-year disease-free survival than older women [1].

Although most stage I, grade 1 endometrial cancers are curable with surgical resection and a favorable outcome can be expected, sacrificing the uterus is often unacceptable for young patients who wish to preserve fertility. A conservative and feasible approach to treat this specific group of patients is therefore an important issue.

Because endometrial cancer is well-known as an estrogen-related neoplasm, treatment of this disease with progestins was described as early as decades ago [2–4]. Currently, high-dose progestin therapy has been proved effective in treating early-stage and well-differentiated endometrial cancer [5–9]. This approach meets the requirement of successful disease control while preserving fertility, and it has widely been accepted for the management of young patients whose disease status is suitable for such therapy.

Hysteroscopic tumor resection is another treatment strategy for early-stage endometrial cancer. It was first reported in single case trials [10,11]. This procedure may provide a direct and targeted approach for endometrial lesions. Several subsequent series reported that hysteroscopic tumor resection followed by progestin

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therapy revealed satisfactory oncologic outcomes. A previous literature review included four studies with a total of 36 patients who were treated with hysteroscopic surgery followed by progestin therapy. The complete response rate was 88.9% with tumor recurrence in four patients. Nine patients had a successful pregnancy after achieving complete remission with a pregnancy rate of 25% [12]. Other later studies also reported similar oncologic outcomes and even better fertility rates [13,14].

In this report, we present six young patients with stage I, grade 1 and solitary endometrial carcinoma who were treated with hysteroscopic tumor resection followed by progestin therapy.

## Materials and methods

From 2013 to 2017, six nulliparous women under 40 years of age were diagnosed with stage IA, grade 1 endometrioid endometrial carcinoma. The tumors were positive for estrogen and or progesterone receptors by immnohistochemical studies, and all of the patients wished to preserve fertility. These patients were recruited for the conservative treatment strategy after being counseled about the procedures and the possible risk of tumor recurrence, and all provided informed consent.

The histological type and tumor grading were confirmed by two pathologists from hysteroscopic biopsies. Magnetic resonance imaging (MRI) examination was performed after the pathological diagnosis had been made to evaluate if there is myometrial invasion. The patients then received hysteroscopic tumor resection under general anesthesia with the uterine cavity distended with normal saline under gravity inflow of 70 mm Hg pressure. The outflow fluid was collected and the amount was monitored. A 5-mm cutting loop electrode with 100 W of power was used to resect the tumor lesion and the nearby endometrium until the myometrium underlying the lesion was visualized.

When the tumor histology and grading were further confirmed as endometrioid carcinoma with grade 1 differentiation and there was no lymphovascular space invasion noted in the final pathologic examination, the patients received postoperative progestin therapy of either megestrol acetate (MA) 160 mg daily or medroxyprogesterone acetate (MPA) 500 mg daily for at least 6 months. To monitor disease status, the patients underwent a hysteroscopic biopsy or uterine curettage during follow-up with an interval of 3–4 months depending on the previous pathological findings. A complete response was defined as the absence of any degree of endometrial hyperplasia. The patients were then encouraged to prepare for pregnancy. If the patient did not plan to become pregnant at that time, levonorgestrel IUD was used as maintenance therapy, and the patients were followed up at outpatient department every 3 months. A diagnostic hysteroscopic or uterine curettage biopsy was performed if abnormal uterine bleeding or an endometrial lesion was suspected in an ultrasound examination. The patient was shifted to a complete staging operation if persistent disease was noted after hormone therapy for 6 months or tumor recurrence was confirmed by pathology at follow-up.

## Results

The clinical characteristics of the six patients are summarized in Table 1. The age of the patients ranged from 30 to 36 years, and their body mass index ranged from 28.2 to 36.9. Three patients received MPA and three patients received MA as hormone therapy after hysteroscopic tumor resection. Three patients received two hysteroscopic biopsies, one patient received three hysteroscoic biopsies, and one patient received four hysteroscopic biopsies during follow-up. The other patient (case 6) received uterine curettage alone twice to monitor the tumor response.

**Table 1**
Clinical characteristics of patients (n = 6).

| Patient | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Age (yr) | 34 | 36 | 30 | 31 | 36 | 35 |
| BMI | 28.2 | 29.9 | 35.9 | 23.6 | 24.6 | 36.9 |
| EM thickness (cm)[a] | 2.2 | 1.8 | 2.3 | 1.2 | 2.2 | 2.6 |
| MRI staging | IA | IA | IA | IA | IA | IA |
| ER/PR | +/+ | +/+ | +/+ | +/+ | +/− | +/+ |
| Hormone therapy | MPA | MA | MA | MPA | MPA | MA |
| Disease monitoring | hys | hys | hys | hys | hys | D&C |
| Biopsy number[b] | 4 | 3 | 2 | 2 | 2 | 2 |
| Time to CR (mo) | 9 | 6 | 6 | 6 | 6 | 6 |
| Follow-up (mo) | 39 | 49 | 44 | 25 | 21 | 4 |
| Fertility desire | yes | yes | no | yes | yes | yes |
| Child bearing | 0 | 1 | 0 | 0 | 0 | 0 |

BMI = body mass index; EM = endometrium; MRI = magnetic resonance imaging; ER/PR = estrogen receptor/progesterone receptor; hys = hysteroscopy; CR = complete response.
[a] Measured by ultrasound examination.
[b] Number of biopsy during follow-up.

The median follow-up time from the date of complete remission was 32 months (range 4–49 months). The tumors regressed to atypical endometrial hyperplasia in five patients, and complex atypical endometrial hyperplasia in one patient (case 1) after hormone therapy for 3 months. A complete response was confirmed in five patients after 6 months of hormone therapy, while case 1 needed 9 months to reach a complete response.

No intrauterine adhesion was noted among the five patients who received hysteroscopic examinations during follow-up. However, severe endometrial atrophy with cystic change was noted in one patient (case 1). No other side effect associated with the hormone therapy was noted.

One patient (case 2) became pregnant spontaneously, and she received a cesarean section and delivered a healthy baby at 38 weeks of gestation. A complete staging operation was performed 3 months later, and no evidence of disease was confirmed. Four women are still trying to get pregnant but only two are receiving artificial reproductive technology. The remaining patient has no plan to conceive at present, she is using levonorgestrel IUD as maintenance therapy. All of the six patients were free of disease at the last follow-up.

## Discussion

Conservative treatment for early-stage endometrial cancer in young women has widely been accepted as an alternative to definitive surgical management, as it can both treat the disease and preserve fertility. Currently, the most commonly used strategy is selecting suitable candidates who are diagnosed as stage IA grade 1 endometrioid carcinoma with tumor confined at the endometrium by either MRI or transvaginal ultrasound [15]. High-dose progestin with either MPA at a dose of 400–600 mg/d or MA at a dose of 160–320 mg/d for at least 6 months is recommended [16]. Tumor response rate to conservative therapy has been reported from 50% to 75% [5–9]. A previous systematic review and meta-analysis reported that the pooled live birth rate was 28% in 325 women treated with progestins [5]. However, the reported tumor recurrence rate after conservative management ranges from 30% to 40% [5–9]. Moreover, a Taiwanese series reported that the 5-, 10-, and 15-year cumulative recurrence-free survival rates were 51%, 51%, and 34%, respectively [17]. The high recurrence rate and relatively low long-term survival rate should not be underestimated. Therefore, patients should be encouraged to get pregnant as early as

possible when complete remission of disease is confirmed by pathology examination. A definite surgery is strongly indicated after childbearing to avoid tumor recurrence. In patients with no immediate desire to conceive, maintenance therapy with the insertion of levonorgestrel IUD is recommended [16,18].

Direct tumor resection via hysteroscopy can remove the tumor quickly and effectively. It is reasonable to assume that the tumor control rate with hormone therapy after hysteroscopic resection of the main tumor will be higher because of a reduction in tumor volume. It would also be interesting to investigate whether the duration of postoperative progestin therapy can be shortened after hysteroscopic resection.

Intraperitoneal spread of tumor cells through the fallopian tubes during hysteroscopy has been challenged when making a hysteroscopic diagnosis of endometrial cancer. The increase in intrauterine pressure during perfusion of distention media may increase the risk of dissemination of malignant cells into the peritoneal cavity. Two previous meta-analyses reported that patients who underwent hysteroscopy had a higher rate of malignant peritoneal cytology compared to those who did not undergo hysteroscopy [19,20]. However, another controlled randomized study reported that diagnostic hysteroscopy did not cause an increase in pelvic recurrence rate compared to the non-hysteroscopy group after more than 5 years of follow-up. In addition, no differences in overall survival and disease-free survival were noted between the two groups of patients [21]. At present, hysteroscopy is still regarded to be a safe diagnostic procedure for endometrial cancer [20,21], however, whether the therapeutic use of hysteroscopy would affect the patients' prognosis deserves to observe.

In a review study by Alonso et al., four of 36 cases receiving hysteroscopic resection of endometrial cancer had tumor recurrence, but all the recurrences were either hyperplasia or atypical hyperplasia [12]. A long-term follow-up study included 28 patients with stage IA, grade 1–2 disease who received hysteroscopic resection and postoperative oral megestrol acetate or levonorgestrel IUD insertion. In that study, two patients (7.1%) had persistent disease, one patient (3.6%) had progressive disease and underwent definitive surgery. Another two patients had recurrent disease after a median follow-up of 92 months (range, 6–172 months) [22]. Both of the two patients with recurrence had synchronous ovarian endometrioid carcinoma after staging surgery (stage IIB grade 1 and stage IA, grade 1). Whether the ovarian cancers were related to the previous hysteroscopy could not be clearly confirmed.

A recent meta-analysis compared the effects of three fertility-preserving treatment modalities (oral progestin only, hysteroscopic resection followed by progestin therapy, and levonorgestrel IUD combined with gonadotropin-releasing hormone therapy) on complete remission rate, recurrence rate, and pregnancy rate [23]. The results showed that the hysteroscopy group had the highest complete remission rate (95.3%), and that the oral progestin group had the highest recurrence rate (30.7%). The pregnancy rate was similar among the three groups (52.1%, 47.8%, and 56.0%, respectively). Therefore, hysteroscopic tumor resection followed by progestin therapy seems to be a promising option in treating young patients with early-stage grade 1 endometrial cancer who desire to preserve fertility.

Despite the positive effects of therapeutic hysteroscopic tumor resection, some problems still need to be elucidated. For example, the possibility of the spread of cancer cells into peritoneal cavity still should to be concerned. In addition, whether the injury to the basal layer of endometrium or underlying myometrium by thermal effect or mechanical destruction would bring negative impact on the pregnancy outcome also awaits answer [24]. At present, hysteroscopic tumor resection plus progestin therapy remains a topic of debate, and further data are needed to confirm its safety and feasibility [25].

In conclusion, hysteroscopic tumor resection plus progestational therapy could be considered as a safe treatment strategy with regard to oncological concern. Its pregnancy rate seems not inferior to the hormone therapy. However, careful selection of the candidates and a thorough counseling about tumor treatment and fertility plan are absolutely necessary before starting the treatment.

## Conflict of interest

The authors declare no conflict of interest.

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# Risk of Cancer after Lower Urinary Tract Infection: A Population-Based Cohort Study

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**Abstract:** To investigate the association among lower urinary tract infection (UTI), the type and timing of antibiotic usage, and the subsequent risk of developing cancers, especially genitourinary cancers (GUC), in Taiwan. This retrospective population-based cohort study was conducted using 2009–2013 data from the Longitudinal Health Insurance Database. This study enrolled patients who were diagnosed with a UTI between 2010 and 2012. A 1:2 propensity score-matched control population without UTI served as the control group. Multivariate analysis with a multiple Cox regression model was applied to analyze the data. A total of 38,084 patients with UTI were included in the study group, and 76,168 participants without UTI were included in the control group. The result showed a higher hazard ratio of any cancer in both sexes with UTI (for males, adjusted hazard ratio (aHR) = 1.32; 95% confidence interval (CI) = 1.12–1.54; for females, aHR = 1.21; 95% CI = 1.08–1.35). Patients with UTI had a higher probability of developing new GUC than those without UTI. Moreover, the genital organs, kidney, and urinary bladder of men were significantly more affected than those of women with prior UTI. Furthermore, antibiotic treatment for more than 7 days associated the incidence of bladder cancer in men (7–13 days, aHR = 1.23, 95% CI = 0.50–3.02; >14 days, aHR = 2.73, CI = 1.32–5.64). In conclusion, UTI is significantly related to GUC and may serve as an early sign of GUC, especially in the male genital organs, prostate, kidney, and urinary bladder. During UTI treatment, physicians should cautiously prescribe antibiotics to patients.

**Keywords:** urinary tract infection; genitourinary organs cancer; retrospective cohort study

## 1. Introduction

Urinary tract infection (UTI) is one of the most common infectious diseases and the main cause of community-acquired and nosocomial infections at admission [1]. Patients with UTI usually present with acute clinical UTI or chronic uncomplicated or complicated UTI. Complicated UTI involve individuals with a condition or more resistant pathogen that increases the risk of failing treatment

with functional, metabolic, or structural abnormalities [2]. Moreover, the UTI incidence in women is much higher than that in men, but the majority are simple or uncomplicated UTI that occur in healthy or nonpregnant women [3]. In women, the urethra is close to the vagina and rectum, which can lead to the unintentional introduction of fecal flora into the urinary tract, the most common cause of frequent occurrence of UTI. Furthermore, the risk of bacteria colonization increases in postmenopausal women because of the loss of vaginal pH physiological tuning ability [4].

Lower UTI includes cystitis and prostatitis, and upper UTI include pyelonephritis. The Infectious Diseases Society of America observed a UTI prevalence of 1%–5% in healthy and premenopausal women and 1.9%–9.5% in pregnant women. Symptoms of lower urinary tract are common in men, and the prevalence increases with age. Up to 90% of men aged 50–80 years may suffer from troublesome lower urinary tract symptoms [5].

Inflammation is a main factor in cancer development, but studies on the relationship between UTI and cancer risks are scant [6]. A recent study demonstrated a relationship between UTI and genitourinary cancers (GUC) and confirmed that recurrent UTI are a risk factor for urinary bladder cancer [7]. Moreover, the relationship between UTI and other tumors is important because UTI-caused inflammatory response is a systemic symptom. In addition, UTI can be diagnosed on the basis of a combination of symptoms and a positive urine analysis or culture [8]. Thus, multiple antimicrobial therapies, including treatment with cephalosporin, quinolone, ampicillin, beta-lactam, amoxicillin, nitrofurantoin, sulfamethoxazole, and trimethoprim, can be prescribed [9,10]. Thus, using antibiotics is necessary for UTI treatment. Although evidence for the relationship between UTI and cancer risks is rare, it is reasonable to hypothesize that UTI disorders may still lead to cancers, especially GUC. Therefore, using a nationwide database, this study investigated the association between UTI and antibiotic usage influencing the risk of cancer.

## 2. Materials and Methods

### *2.1. Data Source*

A national large-scale database, the Longitudinal Health Insurance Database (LHID), was used in this study. The 2010 LHID is a subset of the National Health Insurance Database, which is released by the National Health Research Institutes in Taiwan. The 2010 LHIRD, in which 1 million beneficiaries are randomly sampled from National Health Insurance (NHI) system, comprises the claims data of outpatient, admission, and prescription from 2009 to 2013. The NHI system is a single-payer social insurance system, and the coverage was approximately 98% in 2010. To protect the privacy of patients and care providers, the personnel identification numbers are scrambled for de-identification. The study was approved by the Ethical Review Board of Chung Shan Medical University Hospital (CSMU No.: 18096).

### *2.2. Patient Selection (Exposure of UTI Infection)*

This was a retrospective cohort study. We identified patients ($n$ = 140,308) who visited a hospital or were hospitalized for UTI (ICD-9: 599.0, 595.0, 595.9, and 590) and had antibiotic therapy (cephalosporins, quinolone antibacterial, sulfonamides and trimethoprim, ampicillin, amoxicillin, and nitrofurantoin) in the same visit during 2009–2013 as the exposure group. To ensure that only newly identified UTI was included, prevalent cases of UTI in 2009 were excluded. Furthermore, patients newly diagnosed with UTI in 2013 were excluded because they were only followed up for less than 1 year. The index date was the first date of UTI visit or admission; additional exclusion criteria included patients aged less than 20 years old, those having any cancer, those who died, and those who underwent urine examination within 6 months after the index date. A total of 38,084 patients were diagnosed with UTI in this study.

### *2.3. Propensity Score Matching (PSM)*

A potential confounding bias exists in the observational study design. Propensity score matching (PSM) was used to diminish this bias. We used a logistic regression model to estimate the probability (propensity score) of UTI, using such predictors as age, the Charlson Comorbidity Index (CCI), and other comorbidities (hypertension (ICD-9: 401–405), diabetes (ICD-9: 250), dyslipidemia (ICD-9: 272), rheumatic diseases (ICD-9: 714, 710, 720, 696.0, and 696.1), coronary artery disease (ICD-9: 410–414), chronic obstructive pulmonary disease (COPD, ICD-9: 490–492, 493–496), and chronic kidney disease (CKD, ICD-9: 585)). The control (non-UTI exposure during 2009–2013) and study groups were 1:2 propensity-score-matched on the basis of sex because of the specific cancer sites in different genders. The greedy algorithm of PSM was applied using SAS macro [11].

### *2.4. Outcome Measurement of Cancer Event*

Subsequent cancer events were identified according to ICD-9: 140–208 for ≥2 outpatient visits or ≥1 admission. Major cancer sites reported in Taiwan were considered for subevent analysis, including colorectal (ICD-9: 153–154), liver (ICD-9: 155), lung (ICD-9: 162), and breast (ICD-9: 174), bladder (ICD-9: 188), kidney (ICD-9: 189), male genital organs (ICD-9: 185–187), female genital organs (ICD-9: 179–184), and prostate (ICD-9: 185) cancers. All individuals were followed up from the index date until diagnosed with any cancer, death, or end of study (31 December 2013).

### *2.5. Statistical Analysis*

All analyses were performed after stratifying the data by sex because gender-specific cancer sites were analyzed in this study. Chi-squared test was used to analyze the homogeneity of category variables, and univariate and multivariate Cox regression models were conducted to estimate the crude and adjusted hazard ratio (aHR) (95% confidence interval (CI)). All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA). $p$ less than 0.05 indicated statistical significance.

## 3. Results

We identified 38,084 patients diagnosed with UTI from 2010 to 2012 and a total of 76,168 propensity score-matched controls to explore their sequential cancer risk after the index date (Figure 1). The baseline characteristics among the UTI and non-UTI groups stratified by sex are listed in Table 1. After PSM, no significant difference was observed in the distributions of age group, CCI group, and comorbidities (hypertension, diabetes hyperlipidemia, rheumatic diseases, coronary artery disease, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) in both genders. More female UTI cases (the sex ratio, F:M = 31,172:6,912) were observed, especially in women aged 20–44 and 45–65 years. The median of follow-up time was 25 months (Max: 42), because the index date (start point of follow-up) was 6 months after UTI.

The age–sex stratified incidence rate (per 10,000 person-months) and adjusted hazard risks of specific-site cancer (colorectal, liver, lung, genital organs, bladder, kidney, male prostate, female breast cancer, and any cancer) in patients with UTI are presented in Table 2. For men aged 20–64 years, significant aHRs were observed in any cancers (aHR = 1.37, 95% CI = 1.02–1.86), bladder cancer (aHR = 12.10, 95% CI = 2.70–54.19), and kidney cancer (aHR = 5.20, 95% CI = 1.01–26.82). For men aged ≥65 years, the associations were observed in any cancer (aHR = 1.29, 95% CI = 1.08–1.54), colorectal cancer (aHR = 1.59, 95% CI = 1.01–2.52), genital organ cancer (aHR = 2.37, 95% CI = 1.55–3.64), bladder cancer (aHR = 28.60, 95% CI = 6.80–120.28), kidney cancer (aHR = 3.85, 95% CI = 1.42–10.42), and prostate cancer (aHR = 2.44, 95% CI = 1.59–3.74). For women aged 20–64 years, the significant aHRs were estimated in liver cancer (aHR = 2.44, 95% CI = 1.59–3.74), bladder cancer (aHR = 30.02, 95% CI = 3.97–227.28), and kidney cancer (aHR = 2.90, 95% CI = 1.24–6.78). For women aged ≥65 years, the significantly increased aHRs were observed in any cancer (aHR = 1.30, 95% CI = 1.11–1.53), liver

cancer (aHR = 1.54, 95% CI = 1.02–2.33), bladder cancer (aHR = 2.33, 95% CI = 1.01–5.42), and kidney cancer (aHR = 3.40, 95% CI = 1.34–8.64).

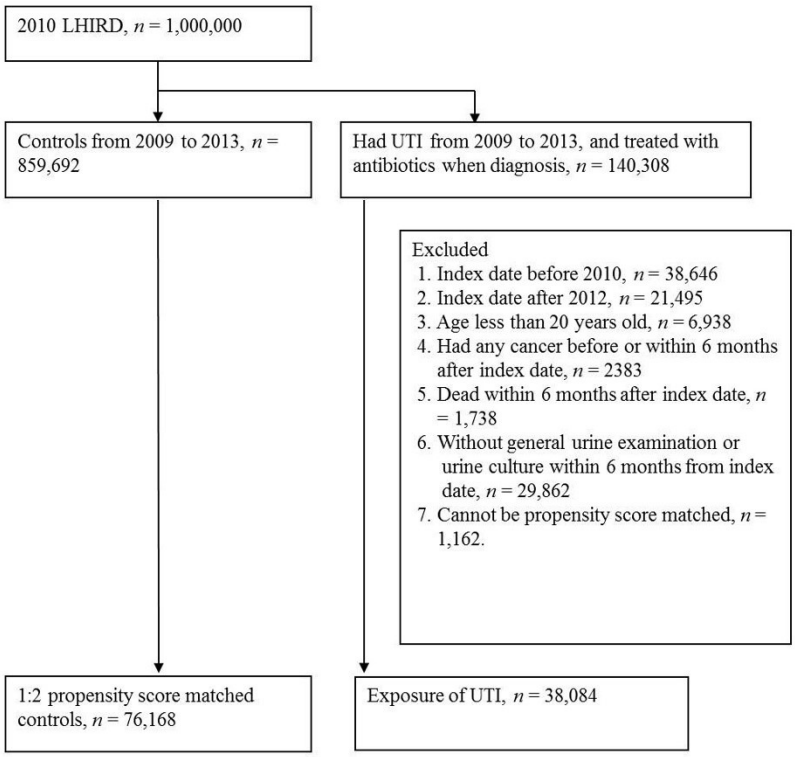


**Figure 1.** Flow chart for patient selection.

**Table 1.** Baseline characteristics of the study population.

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | **Non-UTI N = 13,824** | **UTI N = 6,912** | ***p* Value** | **Non-UTI N = 62,344** | **UTI N = 31,172** | ***p* Value** |
| Age | | | 0.8332 | | | 0.4579 |
| 20–44 | 4355 (31.5%) | 2201 (31.84%) | | 31112 (49.90%) | 15513 (49.77%) | |
| 45–65 | 4411 (31.91%) | 2209 (31.96%) | | 20540 (32.95%) | 10212 (32.76%) | |
| ≥65 | 5058 (36.59%) | 2502 (36.20%) | | 10692 (17.15%) | 5447 (17.47%) | |
| CCIs | | | 0.8214 | | | 0.1808 |
| 0 | 6503 (47.04%) | 3260 (47.16%) | | 37784 (60.61%) | 18906 (60.65%) | |
| 1–2 | 5215 (37.72%) | 2604 (37.67%) | | 20116 (32.27%) | 9961 (31.95%) | |
| 3–4 | 1670 (12.08%) | 846 (12.24%) | | 3765 (6.04%) | 1921 (6.16%) | |
| ≥5 | 436 (3.15%) | 202 (2.92%) | | 679 (1.09%) | 384 (1.23%) | |
| Co-morbidity | | | | | | |
| Hypertension | 5270 (38.12%) | 2661 (38.50%) | 0.5993 | 13847 (22.21%) | 6963 (22.34%) | 0.6605 |
| Diabetes | 2484 (17.97%) | 1248 (18.06%) | 0.8781 | 7391 (11.86%) | 3730 (11.97%) | 0.6221 |
| Hyperlipidemia | 2842 (20.56%) | 1414 (20.46%) | 0.8648 | 10363 (16.62%) | 5189 (16.65%) | 0.9258 |
| Rheumatic diseases | 399 (2.89%) | 207 (2.99%) | 0.6619 | 2650 (4.25%) | 1317 (4.22%) | 0.8544 |
| Coronary artery disease | 1943 (14.06%) | 957 (13.85%) | 0.6814 | 4702 (7.54%) | 2367 (7.59%) | 0.7795 |
| COPD | 2083 (15.07%) | 1047 (15.15%) | 0.8801 | 4970 (7.97%) | 2594 (8.32%) | 0.0645 |
| CKD | 470 (3.40%) | 231 (3.34%) | 0.8279 | 723 (1.16%) | 397 (1.27%) | 0.1312 |
| Pneumonia | 254 (1.84%) | 628 (9.09%) | <0.0001 | 388 (0.62%) | 716 (2.30%) | <0.0001 |

UTI: urinary tract infection; CCI: Charlson Comorbidity Index.

**Table 2.** Age stratified cancer incidence rate (per 10,000 person months) and adjusted hazard ratio (95% C.I.) † in patients with UTI exposure by cancer site.

| | 20–64 y/o Incidence Rate | | aHR | ≥65 y/o Incidence Rate | | aHR |
|---|---|---|---|---|---|---|
| | Non-UTI | UTI | | Non-UTI | UTI | |
| **Male** | | | | | | |
| All cancer | 5.05 | 6.93 | **1.37 (1.02–1.86)** | 27.70 | 35.40 | **1.29 (1.08–1.54)** |
| Colorectal | 0.58 | 0.77 | 1.32 (0.54–3.23) | 3.78 | 5.96 | **1.59 (1.01–2.52)** |
| Liver | 0.72 | 0.77 | 1.05 (0.44–2.47) | 4.04 | 2.61 | 0.65 (0.36–1.19) |
| Lung | 0.67 | 0.77 | 1.46 (0.75–2.86) | 5.98 | 4.10 | 1.13 (0.75–1.70) |
| Genital organs | 0.48 | 0.48 | 1.05 (0.36–3.09) | 3.52 | 8.39 | **2.37 (1.55–3.64)** |
| Bladder | 0.10 | 1.15 | **12.10 (2.70–54.19)** | 0.18 | 5.03 | **28.60 (6.80–120.28)** |
| Kidney | 0.10 | 0.48 | **5.20 (1.01–26.82)** | 0.53 | 2.05 | **3.85 (1.42–10.42)** |
| Prostate | 0.43 | 0.38 | 0.96 (0.29–3.15) | 3.43 | 8.39 | **2.44 (1.59–3.74)** |
| **Female** | | | | | | |
| All cancer | 3.52 | 3.95 | 1.13 (0.97–1.32) | 14.49 | 18.96 | **1.30 (1.11–1.53)** |
| Colorectal | 0.45 | 0.32 | 0.70 (0.42–1.17) | 2.76 | 2.91 | 1.06 (0.71–1.57) |
| Liver | 0.21 | 0.36 | **1.75 (1.00–3.04)** | 1.94 | 3.06 | **1.54 (1.02–2.33)** |
| Lung | 0.25 | 0.47 | 1.22 (0.86–1.71) | 2.56 | 2.52 | 0.75 (0.43–1.32) |
| Genital organs | 0.46 | 0.36 | 0.79 (0.49–1.28) | 0.74 | 1.38 | 1.86 (0.98–3.56) |
| Bladder | 0.01 | 0.24 | **30.02 (3.97–227.28)** | 0.39 | 0.92 | **2.34 (1.01–5.42)** |
| Kidney | 0.07 | 0.21 | **2.90 (1.24–6.78)** | 0.27 | 0.92 | **3.40 (1.34–8.64)** |
| Breast | 1.16 | 1.04 | 0.90 (0.68–1.21) | 1.51 | 1.68 | 1.10 (0.65–1.85) |

† adjusted for age (per 1 year), CCI score, and co-morbidities (including hypertension, diabetes, hyperlipidemia, rheumatic disease, coronary artery disease, COPD, CKD, and pneumonia. Bold font indicates statistical significance ($p < 0.05$).

The significantly increased HRs of any cancer for UTI exposure in men (crude HR = 1.27, 95% CI = 1.09–1.48; aHR = 1.32, 95% CI = 1.12–1.54) and women (crude HR = 1.21, 95% CI = 1.09–1.36; aHR = 1.21, 95% CI = 1.08–1.35) are indicated in Tables 3 and 4. Additionally, we also demonstrated that in individuals aged ≥65 years, a CCI score of ≥5 indicated higher risk of cancer incidence.

**Table 3.** Adjusted hazard ratio of all cancer in males.

| | Crude HR | 95% C.I. | *p* Value | aHR † | 95% C.I. | *p* Value |
|---|---|---|---|---|---|---|
| UTI (Ref: No) | | | | | | |
| Yes | 1.27 | 1.09–1.48 | 0.0023 | 1.32 | 1.12–1.54 | 0.0007 |
| Age (Ref: 20-44) | | | | | | |
| 45-65 | 5.21 | 3.50–7.76 | <0.0001 | 4.69 | 3.14–7.03 | <0.0001 |
| ≥65 | 16.37 | 11.26–23.79 | <0.0001 | 12.32 | 8.29–18.31 | <0.0001 |
| CCIs score (Ref: 0) | | | | | | |
| 1–2 | 2.34 | 1.94–2.82 | <0.0001 | 1.28 | 1.03–1.58 | 0.0230 |
| 3–4 | 3.87 | 3.11–4.81 | <0.0001 | 1.50 | 1.13–1.99 | 0.0046 |
| ≥5 | 5.42 | 3.92–7.49 | <0.0001 | 1.88 | 1.24–2.84 | 0.0027 |
| Co-morbidity | | | | | | |
| Hypertension | 2.69 | 2.31–3.14 | <0.0001 | 1.12 | 0.94–1.34 | 0.1901 |
| Diabetes | 1.76 | 1.49–2.09 | <0.0001 | 0.90 | 0.73–1.10 | 0.2867 |
| Hyperlipidemia | 1.38 | 1.16–1.64 | 0.0002 | 0.93 | 0.77–1.12 | 0.4413 |
| Rheumatic diseases | 1.31 | 0.89–1.94 | 0.1747 | 1.00 | 0.67–1.48 | 0.9981 |
| Coronary artery disease | 2.44 | 2.06–2.89 | <0.0001 | 1.25 | 1.04–1.49 | 0.0165 |
| COPD | 2.02 | 1.70–2.40 | <0.0001 | 1.05 | 0.86–1.27 | 0.6569 |
| CKD | 2.21 | 1.62–3.03 | <0.0001 | 0.98 | 0.70–1.37 | 0.8845 |
| Pneumonia | 2.15 | 1.61–2.88 | <0.0001 | 0.95 | 0.70–1.29 | 0.7612 |

† adjusted for UTI infection, age group, CCI score, and co-morbidities (including hypertension, diabetes, hyperlipidemia, rheumatic disease, coronary artery disease, COPD, CKD, and pneumonia.

**Table 4.** Adjusted hazard ratio of all cancer in Female.

| | Crude HR | 95% C.I. | *p* Value | aHR † | 95% C.I. | *p* Value |
|---|---|---|---|---|---|---|
| UTI (Ref: No) | | | | | | |
| Yes | 1.21 | 1.09–1.36 | 0.0007 | 1.21 | 1.08–1.35 | 0.0009 |
| Age (Ref: 20-44) | | | | | | |
| 45–65 | 4.68 | 3.94–5.57 | <0.0001 | 4.41 | 3.68–5.27 | <0.0001 |
| ≥65 | 10.78 | 9.09–12.78 | <0.0001 | 9.00 | 7.37–11.00 | <0.0001 |
| CCIs score (Ref: 0) | | | | | | |
| 1–2 | 2.16 | 1.92–2.44 | <0.0001 | 1.24 | 1.08–1.43 | 0.0023 |
| 3–4 | 3.86 | 3.27–4.57 | <0.0001 | 1.40 | 1.13–1.74 | 0.0024 |
| ≥5 | 5.47 | 4.02–7.44 | <0.0001 | 1.54 | 1.03–2.29 | 0.0349 |
| Co-morbidity | | | | | | |
| Hypertension | 3.08 | 2.76–3.43 | <0.0001 | 1.11 | 0.97–1.26 | 0.1444 |
| Diabetes | 2.39 | 2.10–2.71 | <0.0001 | 0.95 | 0.81–1.11 | 0.4982 |
| Hyperlipidemia | 1.94 | 1.72–2.19 | <0.0001 | 0.88 | 0.78–1.01 | 0.0774 |
| Rheumatic diseases | 1.28 | 1.00–1.63 | 0.0478 | 0.93 | 0.72–1.18 | 0.5332 |
| Coronary artery disease | 2.51 | 2.18–2.91 | <0.0001 | 1.05 | 0.90–1.23 | 0.5270 |
| COPD | 1.63 | 1.39–1.93 | <0.0001 | 0.91 | 0.76–1.09 | 0.3035 |
| CKD | 3.76 | 2.84–4.97 | <0.0001 | 1.51 | 1.09–2.10 | 0.0141 |
| Pneumonia | 2.18 | 1.52–3.13 | <0.0001 | 0.97 | 0.67–1.41 | 0.8892 |

† adjusted for UTI infection, age group, CCI score, and co-morbidities (including hypertension, diabetes, hyperlipidemia, rheumatic disease, coronary artery disease, COPD, CKD, and pneumonia.

In Table 5, no interaction effect between UTI and pneumonia on cancer incidence was observed. We demonstrated the dose response of antibiotic prescriptions on cancer incidence in men; the significant p for trend was observed in any cancer ($p$ = 0.0130) and bladder cancer ($p$ = 0.0066). However, no significant p trends were observed in women (Table 6).

The Kaplan–Meier curve for specific cancer risk among the study groups are shown in Appendix A Figure A1. Any cancer risk was under proportional hazard assumption; however, bladder and kidney cancer risks were modified after 24 and 18 months, respectively, in the elder (≥65 years old) population.

**Table 5.** Adjusted hazard risk † of cancer in patients with UTI or Pneumonia.

| | Non-UTI and Non-Pneumonia | Only UTI | Only Pneumonia | UTI Combined Pneumonia | *p* for Interaction |
|---|---|---|---|---|---|
| **Male** | | | | | |
| All cancer | Reference | 1.35 (1.15–1.59) | 1.24 (0.75–2.06) | 1.14 (0.80–1.64) | 0.2270 |
| Colorectal | Reference | 1.54 (0.99–2.38) | 1.90 (0.58–6.19) | 1.76 (0.75–4.16) | 0.4963 |
| Liver | Reference | 0.86 (0.52–1.41) | 1.12 (0.27–4.65) | 0.23 (0.03–1.69) | 0.2585 |
| Lung | Reference | 0.79 (0.50–1.24) | 1.32 (0.48–3.68) | 0.78 (0.31–1.93) | 0.6723 |
| Genital organs | Reference | 2.23 (1.49–3.35) | 0.60 (0.08–4.36) | 1.25 (0.49–3.17) | 0.9541 |
| Bladder | Reference | 21.64 (7.71–60.77) | Can not estimate | 7.63 (1.37–42.42) | 0.9879 |
| Kidney | Reference | 4.10 (1.72–9.80) | Can not estimate | 3.84 (0.78–18.87) | 0.9908 |
| Prostate | Reference | 2.29 (1.51–3.45) | 0.61 (0.08–4.45) | 1.28 (0.51–3.26) | 0.9426 |
| **Female** | | | | | |
| All cancer | Reference | 1.20 (1.08–1.35) | 0.85 (0.42–1.72) | 1.24 (0.81–1.90) | 0.6554 |
| Colorectal | Reference | 0.92 (0.68–1.26) | 0.68 (0.10–4.93) | 0.35 (0.05–2.50) | 0.6741 |
| Liver | Reference | 1.57 (1.12–2.21) | 0.72 (0.10–5.19) | 1.76 (0.70–4.41) | 0.6862 |
| Lung | Reference | 1.26 (0.91–1.75) | 2.13 (0.676.79) | 1.95 (0.78–4.85) | 0.6684 |
| Genital organs | Reference | 1.03 (0.70–1.52) | Can not estimate | 1.63 (0.39–6.77) | 0.9735 |
| Bladder | Reference | 4.84 (2.39–9.80) | Can not estimate | 4.60 (0.58–36.22) | 0.9944 |
| Kidney | Reference | 3.43 (1.81–6.51) | 6.44 (0.83–50.19) | Can not estimate | 0.9768 |
| Breast | Reference | 0.96 (0.75–1.24) | 0.79 (0.11–5.66) | 0.43 (0.06–3.08) | 0.6890 |

† adjusted for age group, CCI score, and co-morbidities (including hypertension, diabetes, hyperlipidemia, rheumatic disease, coronary artery disease, COPD, CKD, and pneumonia

**Table 6.** Adjusted hazard risk † of cancer for dosage (days) trend of antibiotics prescriptions in patients with UTI.

| | Days of Antibiotics Prescriptions within 6 Months before Index Date | | | *p* for Trend |
|---|---|---|---|---|
| | 1–6 days | 7–13 days | ≥14 days | |
| **Male** | *n* = 17241 | *n* = 1940 | *n* = 1555 | |
| All cancer | Reference | 1.02 (0.75–1.40) | 1.45 (1.09–1.91) | 0.0130 |
| Colorectal | Reference | 1.16 (0.54–2.46) | 1.05 (0.49–2.23) | 0.8669 |
| Liver | Reference | 0.93 (0.32–2.72) | 1.35 (0.51–3.56) | 0.5874 |
| Lung | Reference | 1.43 (0.60–3.41) | 1.39 (0.58–3.30) | 0.4213 |
| Genital organs | Reference | 0.81 (0.37–1.77) | 1.44 (0.78–2.66) | 0.2860 |
| Bladder | Reference | 1.23 (0.50–3.02) | 2.73 (1.32–5.64) | 0.0066 |
| Kidney | Reference | 0.68 (0.18–2.55) | 1.14 (0.37–3.54) | 0.8995 |
| Prostate | Reference | 0.82 (0.38–1.78) | 1.36 (0.73–2.54) | 0.3822 |
| **Female** | *n* = 80515 | *n* = 9014 | *n* = 3987 | |
| All cancer | Reference | 1.08 (0.88–1.32) | 1.10 (0.87–1.40) | 0.3605 |
| Colorectal | Reference | 1.00 (0.54–1.85) | 1.31 (0.68–2.54) | 0.4775 |
| Liver | Reference | 1.19 (0.67–2.10) | 1.12 (0.58–2.19) | 0.6352 |
| Lung | Reference | 1.53 (0.87–2.69) | 1.49 (0.78–2.85) | 0.1511 |
| Genital organs | Reference | 2.06 (1.10–3.85) | 0.33 (0.08–1.41) | 0.7254 |
| Bladder | Reference | 0.41 (0.12–1.44) | 2.30 (1.01–5.25) | 0.1283 |
| Kidney | Reference | 2.34 (0.97–5.66) | 1.73 (0.58–5.20) | 0.1741 |
| Breast | Reference | 1.13 (0.70–1.83) | 1.42 (0.81–2.49) | 0.2356 |

† adjusted for age group, CCI score, and co-morbidities (including hypertension, diabetes, hyperlipidemia, rheumatic disease, coronary artery disease, COPD, CKD, and pneumonia.

## 4. Discussion

Per the analysis results presented in Figure A1, risk significantly increased not only in GUC but also in any-cancer development. Males older than 65 years exhibited a negative association between UTI and lung cancer risk (Figure A1). In previous reports, cephalosporins and quinolones were associated with antitumor properties [12,13]. The incidence of lung cancer in middle-aged men with UTI may be reduced through antibiotic treatments, and this hypothesis requires more evidence before it can be confirmed.

UTI and pneumonia are clinically common complications, and the results of this work also showed a high correlation between UTI and pneumonia ($p < 0.001$) (Table 3). Some reports have revealed that pneumonia has a high correlation with lung cancer, and Marcus et al. provided evidence of increased lung cancer risk among history of pneumonia rather than immunodeficiency [14]. The association between pneumonia and any cancer is rarely reported. The incidence of association between pneumonia and any cancer was low in both men and women in this study ($p > 0.05$).

UTI is particularly associated with the bladder and kidney cancer in both men and women (Table 2). The significant and large relative risk was found whether in young (20–64 y/o) or elderly (≥65 y/o) population. This evidence reinforces the study hypothesis that UTI directly increase the risk in bladder and kidney cancers, which is consistent with Anderson-Otunu's 2016 report [6]. Vermeulen (2015) revealed that UTI are associated with a high risk of urinary bladder cancer in postmenopausal women, especially in women who smoke or had smoked [7]. In males, the obstructive urinary symptoms induced by benign prostatic hyperplasia include difficulty in urination and urine retention, resulting in UTI caused from urinary stasis [15].

Similarly, Table 6 indicates that the use of antibiotics in the course of UTI treatments increases the risk of bladder and kidney cancers. We analyzed the tumor incidence risk between UTI and pneumonia after antibiotic treatment (Table 5). The correlation coefficient between antibiotic treatment and tumor incidence was considerably low. However, a significant increase was observed in the incidence of bladder cancer in men after antibiotic treatment for more than 7 days (Table 6). These results are contrary to many research conclusions, and most antibiotics

such as cephalosporins, quinolones, and ampicillins are considered as a kind of cancer treatment drug rather than a carcinogen [12,13,16]. However, no report has clarified whether beta-lactams, amoxicillin, sulfamethoxazole, and trimethoprim are carcinogenic or have antitumor properties. Only nitrofurantoin is a possible carcinogen due to its genotoxic and carcinogenic potential structures, despite its antimicrobial property [17–20]. In Kimura's report (2016), nitrofurantoin does not exert sufficient renal carcinogen responses even after 28 days of administration [21]. In a recent study on the structure-related genotoxicity of nitrofurantoin, a new evidence revealed that nitrofurantoin does not increase the mutation frequency in the experimental mice. Nevertheless, nitrofurantoin presents no genotoxicity without oxidative stress [22]. This report provided a safe basis for nitrofuran compound development. The gold standard for UTI diagnosis is isolation and quantification of pathogens in the presence of symptoms and obtaining the antibiotic sensitivity pattern to allow specific treatments. However, in this observational study, we cannot provide the evidence of carcinogen from antibiotics. The length (days) of antibiotics usage also correlated with the severity of infection, that might be the risk factor of cancer. However, the appropriate drug dosage should be based on the severity, characteristics and treatment of the infection situation. Therefore, we should consider antibiotic doses in the treatment of UTI under the premise of controlling infection and avoiding drug resistance. Thus, further research needs to clarify this issue in the future. Women after UTI have higher liver cancer risk as reported in this work, especially approximately 30 months after infection. UTI infection is positively associated with GUC, which is consistent with previous findings. Therefore, this study posits a nonpathogenic causal relationship with UTI symptoms.

Our research has some limitations. First, the database used does not contain information on patients' clinical presentation, for example, the severity of UTI, personal behavioral information such as drinking, smoking habits, and body mass index, and microbiological culture data that might affect UTI occurrence. Second, the NHI system is limited to the population of Taiwan. Our findings reflect the situation in Taiwan, but it may not be applicable to Western populations. These confounding factors might have influenced the results.

## 5. Conclusions

In conclusion, UTI are highly correlated with the incidence of all tumors. Clinicians should therefore refer to tumors screening in UTI patients, especially older patients, and not just patients with GUC. In UTI treatment, especially when multiple pathogenic factors are entailed, antibiotics must be used cautiously, and the time and dose of antibiotics should be minimized. Because UTI may increase the incidence of genital organ, bladder, kidney, male colorectal, prostate, and female liver cancer, knowledge about preventing UTI such as proper drinking water, exercise, and toilet habits should be enhanced in educating the general public.

**Author Contributions:** Conceptualization, C.-H.H., Y.-H.C., S.-F.Y. and C.-B.Y.; Validation, Y.-H.C. and C.-B.Y.; Formal Analysis, H.-W.Y. and J.-Y.H.; Writing—Original Draft Preparation, C.-H.H., S.-F.Y. and C.-B.Y.; Writing—Review and Editing, C.-H.H., S.-F.Y. and C.-B.Y.

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**Conflicts of Interest:** The authors declare no conflict of interest.

## Appendix A

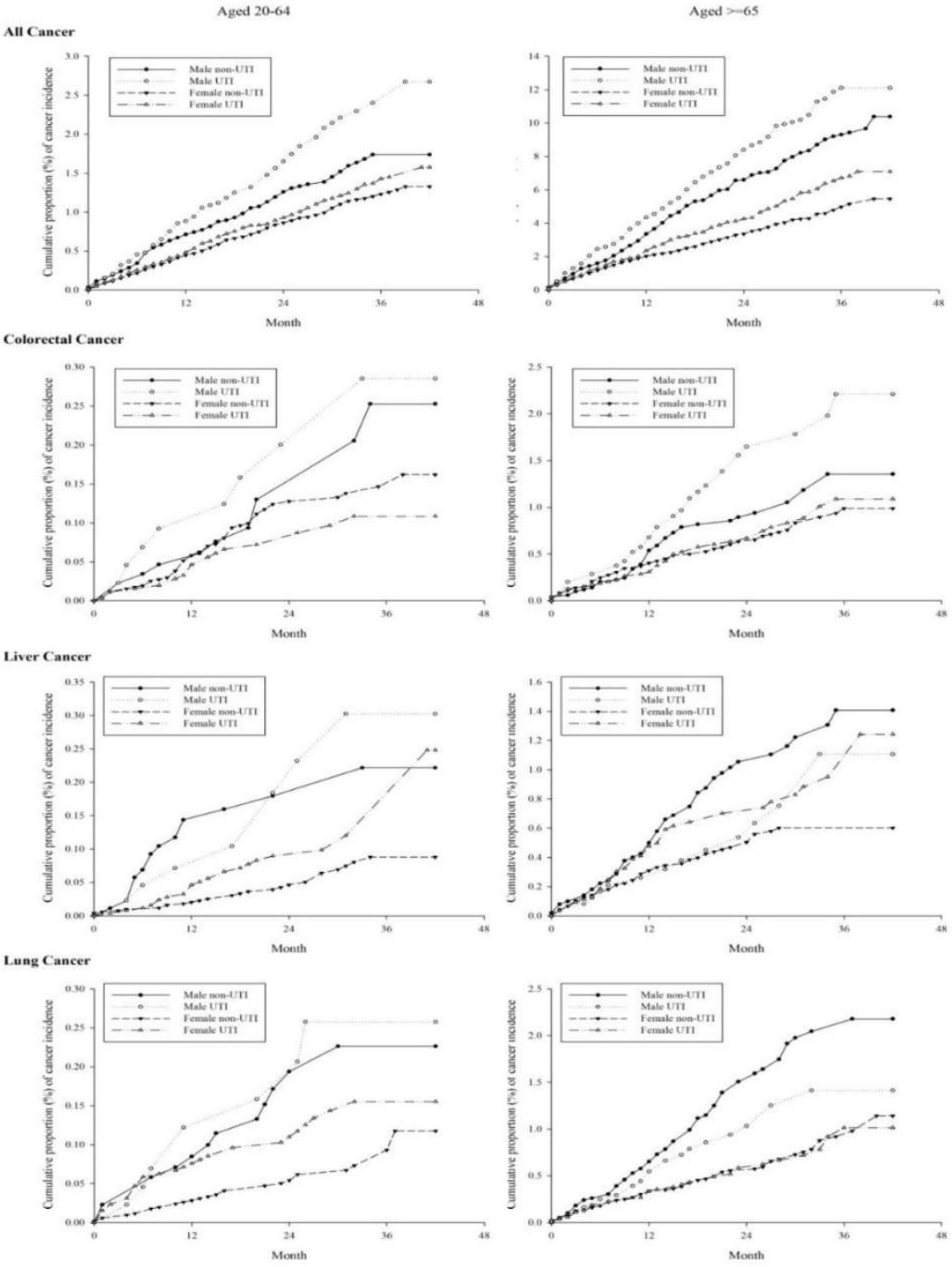


**Figure A1.** *Cont*.

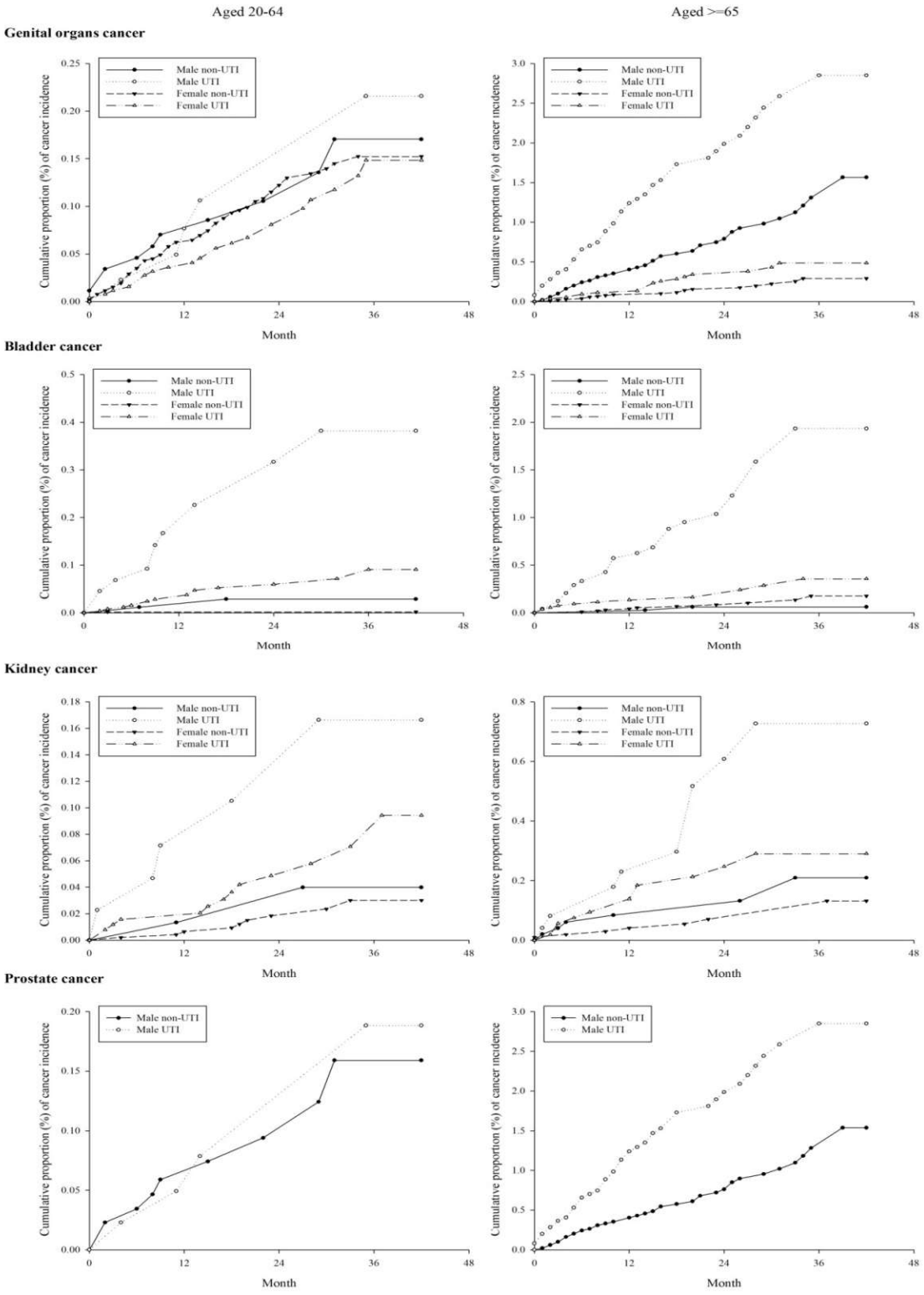


**Figure A1.** *Cont*.

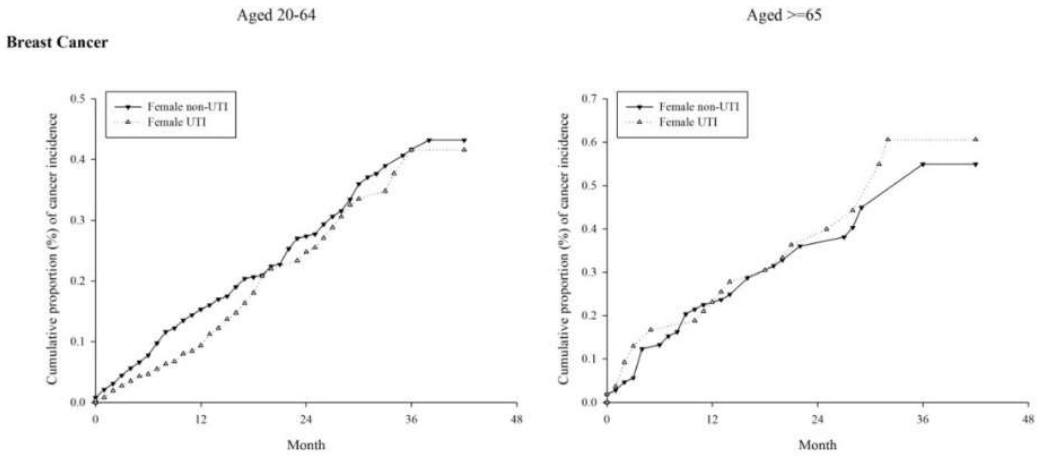


**Figure A1.** Kaplan-Meier curve for specific cancer risk in patients with/without UTI infection stratified by age group.

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# 未成熟血小板(immature platelet fraction ;IPF)之臨床應用

曾美斐、李宜蓁、姚淑婷、林增熙、黃秋媚


## 摘要

未成熟血小板(immature platelet fraction ;IPF)是在血液中循環的網狀血小板（Reticulated platelets;RP），反映骨髓血細胞生成的程度。最近，實驗室建立了一種簡單的測量未成熟血小板的方法使用-自動血球分析儀（Sysmex XN）來計數網狀血小板，藉由原理的改良以及染劑的升級來測量，報告的呈現方式為不成熟血小板片段(immature platelet fraction ;IPF)。目前臨床上 IPF%的應用，對於血小板低下症，可區分血小板的減少是因為血小板生成減少或者是在週邊循環時的破壞增加。對於接受造血幹細胞移植以及癌症化療病患，能提早評估移植後的造血功能恢復情形，IPF 數值上升的時間會比血小板計數提前 3.1 天。此外藉由 IPF%來預測血小板恢復的能力也可以減少不必要的預防性血小板輸注。就臨床而言，測量 IPF%是增加血小板疾病的判讀而非取代，仍須配合實驗室血小板參考數據、血小板功能檢測、及病人臨床症狀。


**. 關鍵字：未成熟血小板 血小板低下症**

## 前言

網狀血小板（Reticulated platelets;RP）是在血液中循環的未成熟血小板(immature platelet fraction ;IPF)，反映骨髓造血細胞生成的程度。傳統流式細胞測量未成熟血小板是過去最常被選用的方法。然而，由於精確度無法確認，價格昂貴，耗時長，操作人員需經長期培訓，缺乏良好的品質監控物質等因素，使得傳統流式細胞儀實驗流程無法標準化。最近，臨床實驗室建立了一種簡單的測量網狀血小板的方法使用-自動血球分析儀（Sysmex XN）來計數未成熟血小板，藉由原理的改良以及染劑的升級來測量，報告的呈現方式為不成熟血小板片段(immature platelet fraction ;IPF)。相關文獻中提到，測量 IPF 對於血小板減少症的鑑別診斷以化療或幹細胞移植後監控骨髓恢復的清況是相當有幫助。血小板減少症與出血風險有關，當病患血小板計數低於 $5x10^3$ / uL~10 $x10^3$ / uL 通常會執行預防性血小板輸注。測定這些需要預防性輸注患者的 IPF，來進一步確認血小板減少是因為血小板生成減少或者是在週邊循環時的破壞增加。在這些患者中，IPF 比率高的族群與周邊血小板破壞增加有關，特別是免疫性血小板減少性紫癜（ITP）和血栓性血小板減少性紫癜（TTP）。相反地，IPF%數值的上升可用於排除生長不良性血小板減少症的診斷，例如再生不良性貧血（AA）。由於 IPF 增加有關骨髓血小板生成增加，測量接受幹細胞移植或是化療後的患者體內的 IPF% ，可以了解是否由骨髓中釋放出血小板。因此，IPF%對於診斷和監測血小板減少症患者治

療過程是相當有幫助的。此外藉由IPF%來預測血小板恢復的能力也可以減少不必要的預防性血小板輸注。以下我們先來認識什麼是血小板低下：

1.血小板低下定義：血小板數量低於正常值：其參考範圍依據年齡而有所不同：參考台大醫院血液檢驗參考範圍(如表一)

表一：

血液生物參考區間

| Age(年齡) / Gender(性別) | 0 days-14 days | 15 days-30days | 31 days-180 days | 0.5 years-6 years | >6 years-18 years | ≧18 years | |
|---|---|---|---|---|---|---|---|
| | | | | | | Male | Female |
| Analyte(檢查項目) | | | | | | | |
| WBC ($10^3$/μL) | 4.94-27.48 | 7.8-15.91 | 6.0-14.99 | 4.86-13.51 | 3.84-11.4 | 3.54-9.06 | 3.54-9.06 |
| RBC ($10^6$/μL) | 4.1-5.74 | 3.16-4.8 | 2.93-4.8 | 3.84-5.07 | 3.9-5.29 | 4-5.52 | 3.78-4.99 |
| HGB (g/dL) | 12.0-20.0 | 10-15.3 | 8.9-12.7 | 10.1-12.7 | 10.6-14.5 | 13.2-17.2 | 10.8-14.9 |
| HCT (%) | 36.0-60.0 | 30.5-45.0 | 26.8-37.5 | 30.8-37.9 | 32.2-43.5 | 40.4-51.1 | 35.6-45.4 |
| MCV (fL) | 91.3-120.0 | 89.4-103.0 | 74.1-96.4 | 69.5-85.0 | 74.4-90.6 | 80.0-100.0 | 80.0-100.0 |
| MCH (pg) | 31.1-35.9 | 29.9-35.3 | 24.4-32.5 | 22.7-28.6 | 24.8-30.2 | 26-34 | 26-34 |
| MCHC (g/dL) | 31-37 | 31-37 | 31-37 | 31-37 | 31-37 | 31-37 | 31-37 |
| PLT ($10^3$/μL) | 144-450 | 248-586 | 229-597 | 189-459 | 175-369 | 148-339 | 150-361 |

台大醫院血液檢驗參考範圍

2.血小板低下常見的症狀：

大部分的病人是無症狀的，一旦出現症狀表示血小板的數量已經過低,通常已經低於五萬(每微升)。若出現症狀,皮膚上的症狀較為常見,比如說：瘀斑 (Petechiae)、紫斑 (Purpura)、瘀血 (Ecchymosis)等；其中瘀斑 (Petechiae)的定義是：皮膚上出現的小出血點，大小 < 3 mm，按壓不會消失。紫斑 (Purpura) 的定義是：大小 1 公分到 3 mm 的出血點。瘀血 (Ecchymosis)的定義是：> 1 公分的出血點

3.血小板低下的成因

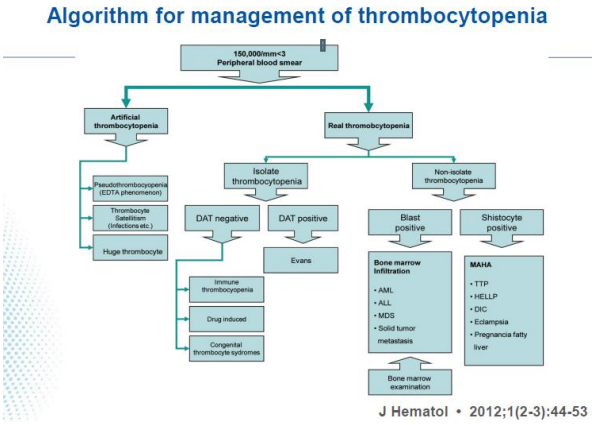
A.破壞的增加，相關的疾病有：原發性血小板缺乏紫斑（Idiopathic Thrombocytopenic Purpura, ITP）、血栓性血小板低下紫斑症（Thrombotic Thrombocytopenic Purpura, TTP）溶血尿毒症候群(Hemolytic uremic syndrome, HUS)。

B.生成減少，相關的疾病有：再生不良性貧血(Aplastic anemia，AA)、骨髓增生不良症候群(Myelodysplastic syndrome , MDS)。

C.治療或是藥物引起。

D.其他可能的原因。

4.臨床上診斷血小板低下的流程〔2〕:(圖一)




5.相關疾病上的檢驗數據(表二)：

(表二)：

| 疾病名稱 | 其他血球 | PLT | IPF |
|---|---|---|---|
| 原發性血小板缺乏紫斑（IdiopathicThrombocytopenic Purpura, ITP） | 其他血球可能都正常 | ↓ | N or↑ |
| 血栓性血小板低下紫斑症（ThromboticThrombocytopenic Purpura, TTP） | 其他血球可能都正常 | ↓ | N or↑ |
| 再生不良性貧血 | 其他血球 | ↓ | ↓ |

Lab Hematol 2006;12(3):125-30.

| | | | |
|---|---|---|---|
| (Aplastic anemia ，AA) | 可能都減少 | | |

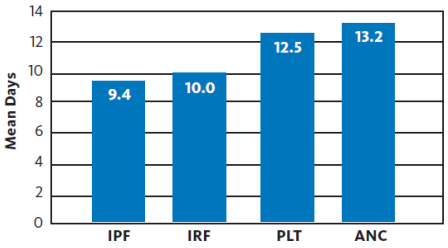



Figure 3: Mean days to recovery for IPF, Immature Reticulocyte Fraction (IRF), platelet count (PLT) and Absolute Neutrophil Count (ANC) following stem cell transplantation[12].

## IPF 的臨床應用與判讀

一、血小板破壞增加以及生成減少中 IPF 表現，可用來區分血小成低下是因骨髓造血功能不良或是因為在週邊血液被破壞過多；在相關研究中指出,在 ITP 以及 TTP 的病患,由於血小板消耗過多，都有 IPF 升高的狀況；而隨著血小板數量的恢復，IPF 會逐漸減少。

二、評估骨髓造血功能恢復：

在先前的幾個研究中指出 IPF 在不同族群病患上的臨床應用，包含了：

1.追蹤造血幹細胞（HPC）移植。

2.血液學惡性腫瘤的骨髓破壞性化療。

3.彌散性血管內凝血（DIC）。

4.治療癌症患者和再生障礙貧血的非骨髓破壞性化療。

5.陣發性夜間血紅素尿症（PNH）。

造血幹細胞移植手術常以嗜中性球恢復的狀況做為手術是否成功的指標，然而 IPF 可能是一個更可靠的參數，因為它不是受移植物抗宿主疾病的影響。在相關文獻中指出〔7〕；50 例接受周邊血幹細胞移植的患者發現 IPF 恢復的時間會比血小板計數恢復提前 3.1 天（如圖二）。

圖二：

基於以上資料,IPF 可用來：

1.提前預測血小板數量的上升：在移植週 邊血液幹細胞的病患中 IPF 的上升會比與血小板的數量提前 3.1 天。

2.可用來評估移植後的造血功能恢復。

3.可用來預測骨髓抑制的病人 PLT 的回復狀況。

三、臨床上如何判讀 IPF

依據本院林增熙醫師在 2018 年發表的相關研究〔13〕如表三,各國生物參考區間都不相同，研究顯示台灣地區 IPF 最新參考區間落在 3.2-3.5%。由於 IPF%檢測對於臨床應用還不算普遍，仍需收集更多的研究個案較為適當。就臨床而言，測量 IPF%是增加血小板疾病的判讀而非取代，仍須配合實驗室血小板參考數據、血小板功能檢測、及病人臨床症狀。

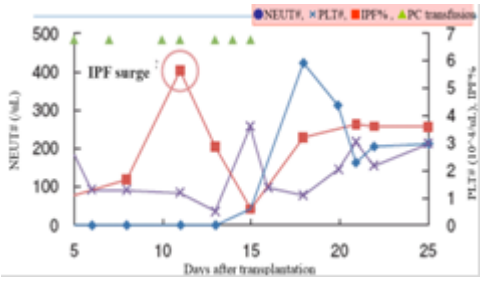
表三：

| Reference | Reference interval | Mean/SD | Median/ min, max | Analyzer/ methods | Health of individual | Ethnic group | n |
|---|---|---|---|---|---|---|---|
| 2 | A-IPF: 3.1 - 16.4 | 8.6/- | -/- | XE-2100/ XE-series [4] | All routine blood normal [β] | UK [λ] | 50 |
| | IPF%: 1.1 - 6.1 | 3.4/- | -/- | | | | |
| 7 | A-IPF: 2 - 12.6 | 5.15/- | -/- | XE/2100/ XE-series [4] | Lab calculation [β] | Italy [λ] | 53 |
| | IPF%: 0.8 - 5.1 | 2.39/- | -/- | | | | |
| 11 | IPF%: 1.3 - 9.0 | 3.7/0.2 | 3.2/0.6, 15.4 | XE-5000/ XE-series [4] | Without clinical disease, HGB, CPR, EGRF, PLT:100-600 [α] | Danish [λ] | 1673 |
| 24 | IPF%: 0.7 - 7.3 | 3.0/1.9 | -/- | XE-2100/ XE-series [4] | Normal PLT [γ] | Japan [β] | 114 |
| 21 | A-IPF:1.8 - 25.2 | 7.5/- | -/- | XE-2100/ XE-series [4] | Health [α] | Japan [β] | 129 |
| | IPF%: 1.0 - 10.3 | 3.3/- | -/- | | | | |
| 22 | IPF%: 2.09 - 2.28 | 2.2/- | -/- | XE-2100/ XE-series [4] | Without clinical disease [α] | India [β] | 945 |
| CS | A-IPF:6.9 - 7.6 | 7.9/3.8 | 7.3/0.6, 10.8 | XN-9000/XN-series [Ψ] | Normal PLT, WBC, RBC, HGB [β] | Taiwan [β] | 478 |
| | IPF%: 3.1 - 3.4 | 3.3/1.7 | 2.9/1.5, 20.9 | | | | |
| 12 | A-IPF: 2.5 - 15.6 | - | 6.2/1.4, 20.6 | XN-2100/XN-series [Ψ] | Normal HGB, WBC, PLT [β] | Korea [β] | 2104 |
| | IPF%:1.0 - 7.3 | -/- | 2.6/0.5, 9.7 | | | | |
| 23 | A-IPF: 1.3 - 7.0 | -/- | 3.05/0.4, 9.0 | XE-2100/ XE-series [4] | Without clinical disease [α] | Korea [β] | 2152 |
| | IPF%: 0.5 - 5.3 | -/- | 1.3/0.2, 4.1 | | | | |
| 25 | IPF%: - | -/- | 1.2/0.3, 5.9 | XE-2100/ XE-series [4] | PLT 150-450 [γ] | Korea [β] | 2039 |

Clin Lab. 2018 May 1;64(5):699-708

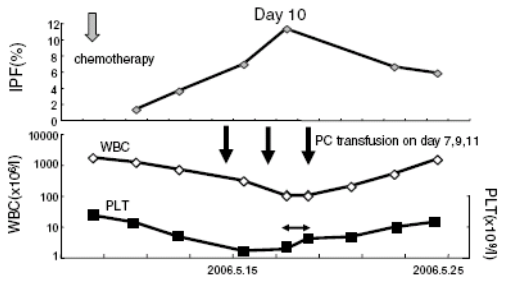
四、減少非必要的血小板輸注

IPF 除了用來鑑別血小板低下的成因,造血幹細胞移植以及癌症化療病患的恢復情況外，也可用來決定血小板輸注的時機如(圖三)在這篇文獻中〔11〕，醫師決定在的 15 天停止血小板輸注,即使血小板數目未見明顯的提升,因為在第 11 天 IPF 出現了顯著的上升,表示新血小板已經開始生成。




BoneMarrow Transplant.; 39:501-507

其他文獻發現〔12〕,接受化療的病患,即使血小板數量沒有顯著的提升,但是因為 IPF 的上升,補充性的血小板輸注即可停止；由此可知,可藉由 IPF 的上升與否,判斷新的血小板是否生成,進一步減少不必要的血小板輸注。




Transfus Apher Sci.2008 Apr ；38(2)：127-32

## 結論

測量未成熟血小板片段（IPF）有助於區分血小板減少症的成因；也可監測骨髓血小板生成情況，進一步減少不必要的預防性血小板輸注。目前市面已有便利準確的檢測平台,本院使用 Sysmex 全自動血液分析儀，進一步提供臨床醫師 IPF 的檢驗結果。期待能提供臨床醫師一個更有臨床價值,更加準確的臨床指標。

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# 最佳化磁敏感加權影像以提高丘腦下核之影像品質

李博元 李覃 楊石崇 李玉玲 劉淵極

## 研究目的

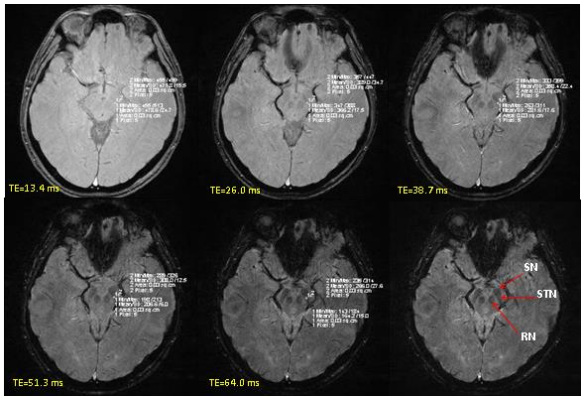
在臨床 MR 影像中要界定丘腦下核與相鄰組織間結構是很模糊的，利用最佳化磁敏感加權影像提高丘腦下核對比度，改善影像品質。

## 研究方法

共收集 7 位接受腦部磁振造影掃描之患者，比較磁敏感加權影像之多重回音序列和常規序列掃描，量測丘腦下核(STN)與相鄰組織間不同 TE 值之 ROI 訊號差異並經由二位放射科醫師進行影像對比度評分，利用 t 檢定統計分析差異。掃描機型為西門子 1.5T 磁振造影掃描儀(Magnetom essenza, Siemens)。

## 研究結果

結果顯示磁敏感加權影像多重回音序列中 TE 64.0ms 具有最佳丘腦下核之影像對比度，與常規序列影像比較 p=0.02，具有顯著差異。




圖一:不同回音時間之磁敏感加權成像訊號圖。

表一:不同回音時間於丘腦下核與相鄰組織之訊號差異分析表。
(TR = 73.0 ms, Echo numbers = 5, Matrix size = 256×256, Thickness = 2 mm)

| 回音時間 (ms) | 丘腦下核 (mean) | 相鄰組織 (mean) | 訊號差異值 | 差異百分比 (%) | p value |
|---|---|---|---|---|---|
| 13.4 | 417.85 | 408.45 | 9.40 | 2.2 | 0.407 |
| 26.0 | 321.65 | 340.10 | 18.45 | 5.7 | 0.266 |
| 38.7 | 239.85 | 303.10 | 63.25 | 26.4 | 0.035 |
| 51.3 | 176.95 | 246.00 | 69.05 | 39.0 | 0.012 |
| 64.0 | 129.00 | 213.15 | 84.15 | 65.2 | 0.005 |

表二:不同回音時間於丘腦下核與相鄰組織間之影像對比度評分表

| 回音時間 (ms) | 放射科醫師 (一) | 放射科醫師 (二) | 評分分數 (mean) | 標準差 (Sd) |
|---|---|---|---|---|
| 13.4 | 1.40 | 1.20 | 1.30 | 0.14 |
| 26.0 | 2.00 | 2.00 | 2.00 | 0.00 |
| 38.7 | 2.60 | 2.40 | 2.50 | 0.14 |
| 51.3 | 3.40 | 3.60 | 3.50 | 0.14 |
| 64.0 | 4.00 | 4.60 | 4.30* | 0.42 |
| 40.0 | 2.80 | 2.53 | 2.67 | 0.19 |

註 1:評分標準依據(優 5:丘腦下核邊緣可見並能明確定義且對比佳；佳 4:邊緣清楚可見，對比佳；可 3:邊緣可見，對比普通；差 2:邊緣模糊，對比差；劣 1:無法辨視)。

註 2: * 與常規序列(回音時間 40 ms)影像比較 p=0.02，具有顯著差異。

## 研究討論

1. 經由不同回音時間於丘腦下核與相鄰組織之訊號差異分析表得知 TE 38.7、51.3 與 64.0 ms 其訊號差異百分比分別為 26.4%、39.0%與 65.2%，遠高於 TE 13.4 及 26.0 ms，並且 p-value 小於 0.05 表示與相鄰組織具有顯著差異。

2. 利用不同回音時間於丘腦下核與相鄰組織間之影像對比度評分表，比較 TE 38.7、51.3、64.0 ms 與常規掃描序列 TE 40 ms 之評分分數，其中以回音時間 TE 64.0 ms 為最高 4.30 分，具有最佳之影像對比度。

## 研究結論

最佳化磁敏感加權影像提高丘腦下核影像品質，可作為增加未來腦部立體定位的另一參考選擇。

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# 利用品管手法以降低藥品盤點人為錯誤率

吳玉品、梁綺芸、林藝璇、蕭玟沁、楊靜怡、楊圳湟、宋睿庭、
羅舒清、林翊嵐、江淑慧

## 目的

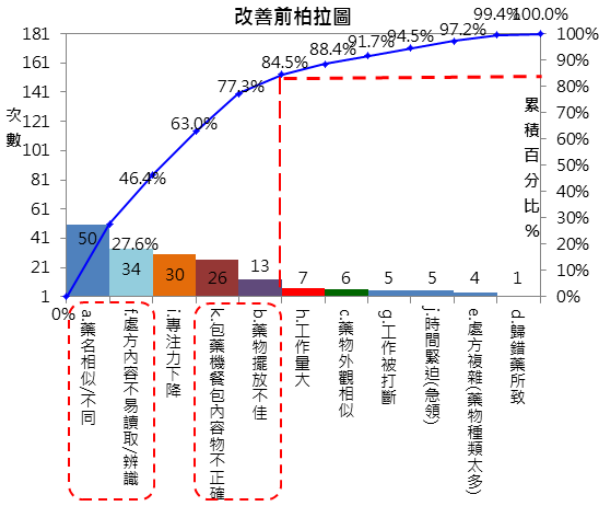
降低住院調劑跡近錯失(Near Miss) 錯誤率在醫院病人用藥安全控管上是相當重要的一環，而藥品調劑是其中最基本的一項工作，如何降低住院調劑跡近錯失(Near Miss) 錯誤率，以確保病患之用藥安全及正確性是本次的目標。.

## 方法

統計 107 年 5 月至 107 年 8 月止，針對中區某區域教學醫院之住院調劑錯誤率結果進行分析。本院住院調劑錯誤率目標值定義為 0.215%，定義為調劑藥師調劑處方後，經審核藥師發現藥品與醫師處方不符者稱之。經審核藥師登記，分析 near miss 之調劑錯誤率。研究期間以品質管理手法，解析造成住院調劑錯誤率之各層面相關原因，再進一步利用 PDCA 品質改善手法，改善住院調劑錯誤率，期望達到目標值。

## 結果

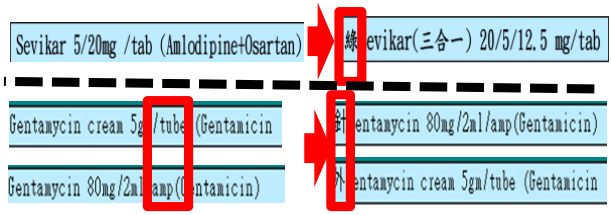
以 107 年 5 月至 6 月蒐集之資料，解析造成住院調劑錯誤率主要因素有：a.藥名相似/不同、b.藥物擺放不佳、c.藥物外觀相似、d.歸錯藥所致、e.處方複雜(藥物種類太多) 、 f.處方內容不易讀取/辨識、g.工作被打斷、h.工作量大、i.專注力下降、j.時間緊迫(急領)、k.包藥機餐包內容物不正確，其中以藥名相似/不同 27.6%、處方內容不易讀取/判讀 18.8%、包藥機餐包內容物不正確名相似/不同 27.6%、處方內容不易讀取名相似/不同 27.6%、處方內容不易讀取/判讀 18.8%、包藥機餐包內容物不正確 14.4%




圖一、利用柏拉圖分析住院錯誤率:將藥名相似/不同、處方內容不易讀取/辨識、包藥機餐包內容物不正確、藥物擺放不佳此四項列為本次改善重點

**對策 1：加註顏色以利區分/加註協助辨識的中文標示**

主要因:藥名相似/不同




**對策 2：張貼提示更換墨水色帶的標準範本**

主要因：處方內容不易讀取/辨識

及藥品擺放不佳 7.2%此四項列為本次改善重點。以 5、6 月之平均調劑錯誤率 0.426%作為改善基準，以藥名相似/不同改善圈能力為 80%、處方內容不易讀取/辨識改善圈能力為 70%，包藥機餐包內容物不正確改善圈能力為 60%、藥物擺放不佳改善圈能力為 80%，遂得目標值為 0.215%。利用 PDCA 手法針對要因改善，於改善期間 107 年 7 月 1 日至 8 月 31 日，以加註顏色及協助辨識的中文標示以利區分、張貼提示更換墨水色帶的標準範本、藥盒貼貼紙定位、拿取藥車針劑之擺放位置定位及調劑台罐裝藥品定位等措施後；8 月調劑錯誤率降低至 0.067%。目標達成率 170%，調劑錯誤率降幅達 84.27%。

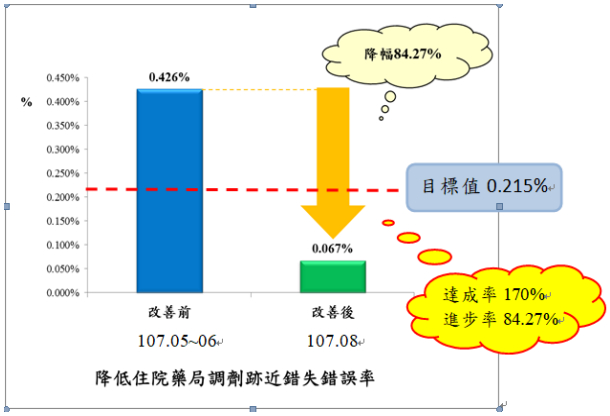
**結論**

根據分析盤點人為錯誤件數來擬定對策，在對策實施並更新盤點流程後，藥品盤點人為錯誤率明顯降低，增加盤點之效率與正確性，如此可減少盤點時間及人力，使藥師能著重在病人藥事服務等方面，以提升病人用藥安全。未來將會持續追蹤統計新出現之錯誤，進行評估與改善。

| 對策 3：藥盒貼貼紙定位 |
| --- |
| 主要因：包藥機餐包內容物不正確 |
| 在藥盒及機台接合處張貼不同顏色、不同方位之圓形貼紙加以區分。藥盒放錯時圓形貼紙明顯不完整，達到第二道辨識效果。 |
|  |

| 對策 4：拿取藥車針劑之擺放位置/調劑台罐裝藥品定位 |
| --- |
| 主要因：藥物擺放不佳 |
| 固定調劑台上針劑盒的位置後，利用照片提醒藥師依照此公版擺放。 |
|  |

圖二、對策擬定




圖三、比較實施前後住院調劑錯誤率之改善幅度高達 84.27%

# Use of Movement Observation and Analysis in Designing Intervention Methods: A Case Report With Acute Ischemic Stroke

Jing-Ling Wang, Pei-Yu Chen

## Background and Purpose

Recently, the Academy of Neurologic Physical Therapy in America has promoted developing movement system diagnosis (MSD). It is because that medical diagnosis is insufficient to guide physical therapy intervention. To establish MSD, standardized examination is needed. Standardized examination includes tests for specific impairments and observational analysis of critical tasks. The aim of this case report is to use observational analysis in designing intervention methods.

## Methods

The case is a 75-year-old male with acute ischemic stroke. The task chosen in observational analysis was based on the motor function of the case. Movement continuum was used in observational analysis, including initial condition, preparation, initiation, execution, and termination. Intervention was designed according to the problem found in observational analysis.

## Results

The case is an acute ischemic stroke with left hemiparesis. He could maintain sitting position 2 weeks after onset, but he still could not sit to stand independently. Therefore, sit to stand was chosen as observational task. At initial condition, he sat on the therapeutic mat with hands on the mat and feet on the floor. During initiation, he inclined his trunk slightly. During execution, he tried to extend his legs without buttocks lift-off. During termination, he fell backward and was failed to standup. According to observational analysis, the case lacked forward and upward weight transfer, and he lacked hip extension during execution. The timing to lift the buttock of the mat could be a problem. Hence, the intervention should include weight transfer and hip extension training.

## Conclusion

Observational movement analysis is convenient to apply in clinical settings, and the results can directly use in task training.

Table 1. Movement continuum of sit-to-stand task

| Initial Condition | Initiation | Execution | Termination |
|---|---|---|---|
| • Hands on mat<br>• Mat lower than tibial tuberosity<br>• Buttocks not at edge, feet on floor, less than hip width, pelvis posteriorly tilted, trunk flexed | • Minimal pelvis or trunk movement<br>• Both hands pushed mat and moved trunk forward | • Extension of knees before hips during first half of execution<br>• Weight transfer slightly forward, then backward to buttocks | • Buttocks back to mat as trunk, hips and knees flexed<br>• Hands on mat |

## Clinical Relevance

Observational analysis is an essential part of MSD and it can apply in movement control and learning.

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# Effect of Approximation on Tension Inhibition of Affected Lower Extremity in Patient With Left Middle Artery Infarction: A Case Report

Chiaoan Yang, Chia-Hsun Hung, Jing-Ling Wang

## Background and Purpose

Approximation is a basic principle for facilitation in proprioceptive neuromuscular facilitation (PNF). It can be used to facilitate motion and stability. The patient with hemiplegia usually has flaccid extremities and cannot ambulate due to the inability to maintain knee extension in stance phase. Therefore, a gaiter is commonly used to maintain the affected knee in extension for bearing weight in stance phase. The purpose of this case report was to investigate the effect of approximation with a gaiter in a patient with left middle artery infarction and right hemiplegia.

## Methods

This case was an 82-year-old female with right hemiplegia and aphasia. She was afraid of weight bearing over the affected side and did not dare to stand without hand support after 15 weeks of stroke onset. A gaiter was used to maintain knee joint in extension. First, the therapist brought the affected leg forward. Then, the therapist gave approximation to the affected leg when the patient moving the sound leg forward. At the same time, the therapist needed to keep the affected leg in a toe-out position to avoid ankle joint inversion during stance phase. Ambulation training was 15 minutes per day. The ambulation function, walking distance during training, and muscle tone of the right ankle joint were recorded.

## Results

Before ambulation training, her Brunnstrom's stage over the right side was II in the upper extremity and III in the lower extremity. Balance was good in static sitting, fair in dynamic sitting, and poor in static standing. The right ankle plantar flexor was hypertonic, and the Modified Ashworth Scale was 1+. This case completed 14 training sessions. At the 12th training session, the ankle joint excessive inversion during stance phase was improved, and the therapist did not need to keep the toe-out position. At the last training session, she could walk 30 meters with quadricane, but she still needed a

gaiter, and the therapist had to assist the affected leg weight-bearing and moving forward. Also, she needed assistance on the sound hand to give the timing to advance. The Modified Ashworth Scale of right ankle plantar flexor was lowered to 1.

## Conclusion

Approximation for facilitation is possible to regulate muscle tone of the ankle plantar flexor which could be applied to ambulation training.

## Clinical Relevance

It is efficient to integrate the basic principle of PNF in a task-oriented training.

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Table 1. Movement continuum of sit-to-stand task

| Initial Condition | Preparation | Initiation | Execution | Termination |
|---|---|---|---|---|
| • Standing: more weight on R > L<br>• Her left hand held a quadricane<br>• Her right leg with gaiter<br>• Level surface indoor | Stimulus Identification<br>• PT brought her right leg forward<br>Response Selection<br>• P't step left leg forward<br>• P't moved left hand forward | • Her body weight shifted to the right leg while weight-bearing over right leg | • P't moved the left leg forward<br>• Then, P't moved a quadricane forward | • PT brought right leg forward (approximation) while her body weight shifted to the left side |

# The Availability of Weight Bearing Training on Spontaneous Intracerebral Hemorrhage Combined Cognitive Impairment: A Case Report

Jing-Ling Wang, Jung-Chuan Tsai

## Background and Purpose

As the progress of cognitive impairment, the ability of activity of daily living will decrease. It is possible to interfere with language and produce emotional problems. A patient with cognitive impairment occurred cerebrovascular accident will significantly interfere with rehabilitation training. Clinically, physical therapy applies weight bearing training to facilitate muscle firing and relaxation. The patient can be positioned passively to achieve the training. The purpose of this case report was to investigate the availability of weight bearing training in post intracerebral hemorrhage (ICH) patient with cognitive impairment.

## Methods

The case was a 73-year-old female with right hemiplegia, dysphagia, and aphasia. She was able to eat and walk independently before this episode. She cannot communicate with others due to aphasia and cognitive impairment. The weight bearing training began at six weeks post onset. The intervention was weight bearing training in different positions, including side-sitting, all four, prone on elbows, and prone on hands (Figure 1). Each position was maintained at least 1 min and up to 5 min. Each training session was 15 min. The position used in training would depend on patient's ability, and it would gradually change as the patient progressed (Table 1).

## Results

The case was ICH in the temporal-occipital region and ICH was removed. The case received nine training sessions. Before intervention, Brunnstrom's stage was IV in the right upper extremity and III in the right lower extremity. Balance was fair in static sitting and poor in dynamic sitting. Transfer needed maximal assistance. The legs of the patient were curled up during transfer. After intervention, Brunnstrom's stage was IV in the right upper extremity and IV in the right lower extremity. Balance was good in static sitting and fair in dynamic sitting. Transfer needed

minimal assistance. The feet of the patient slight touched the floor during transfer.

## Conclusion

It is available to apply weight bearing training in patients with aphasia and patients hard to active participation.

## Clinical Relevance

Clinically, it is hard to instruct patients with aphasia and cognitive impairment in exercise and movement control. Patient positioning can facilitate muscle activation in weight bearing position and muscle relaxation after training.

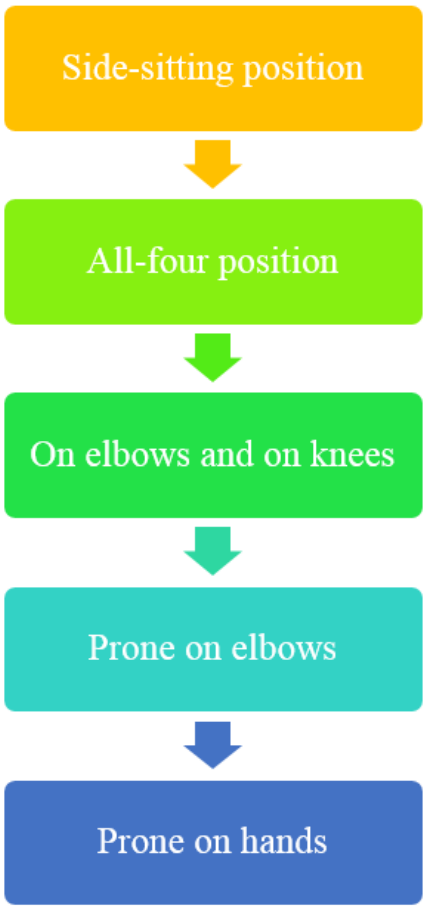


Figure 1. Progression of positioning in weight-bearing training

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Table 1. Content in daily training

| Sessions | Positioning | Content |
|---|---|---|
| 1 | Side-sitting, both legs hanging outside the side of the mat | WB on hand of left upper extremity<br>WB on hand of right upper extremity |
| 2 | Side-sitting, both legs hanging outside the side of the mat | WB on hand of left upper extremity<br>WB on hand of right upper extremity |
| 3 | Side-sitting, both legs bending on the mat | WB on elbow of left upper extremity<br>WB on elbow of right upper extremity |
| 4 | Side-sitting, both legs bending on the mat | WB on elbow of left upper extremity<br>WB on elbow of right upper extremity |
| 5 | On elbows and knees | Transition from side-sitting<br>WB on elbows and knees |
| 6 | All-four | Transition from side-sitting<br>WB on hands and knees |
| 7 | Prone | Transition from WB on elbows and knees<br>WB on elbows in prone |
| 8 | Prone | Transition from all-four<br>WB on hands |
| 9 | Prone | WB on hands<br>Transition back to all-four |

# Consideration of Intervention in Fracture Post-Acute Care: A Case Report with Femoral Neck Fracture

Wei-Jing I, Ai-Hsiang Hsiao, Jing-Ling Wang

## Background and Purpose

Unintentional injury is one of the top 10 causes of death. In 2017, according to the Ministry of Health and Welfare, it was the 9th of the top causes of death in 75-84 years old people. The falls would cause a hip fracture in the elderly, and following reduced walking ability would affect the quality of life and increase fall risk. The purpose of this case report was to investigate the considerations of intervention in patient with femoral neck fracture participated in post-acute care.

## Methods

The case was a 77-year-old female with the right femoral neck fracture. She was independent in activities of daily living before this episode. The first time she came to the rehabilitation center of Lin-Shin Hospital, she could walk with a walker under supervision. She felt pain at operative area when the right hip joint was passively moved near the end range of extension and external rotation. The patient's goal is to walk independently and to climb up and down the stairs by herself. The first step is to reduce the amount of support by assistive device. Following, the next step is to reduce the fall risk. Intervention began six days s/p right hemiarthroplasty. Regular intervention included two modality therapy and one movement therapy, and each item is 15 min. The motor function, Barthel Index and Harris Hip Score (HHS) were measured.

## Results

Two treatment sessions a day. Total 18 treatment sessions were completed. She walked first with a walker, then with a quadricane, and following without assistive devices. Initially, she climbed up and down the stairs with one hand on the handrail and the other hand supported by the therapist. After 5 days of training, she could climb up the stairs without support, but she went down the stairs still needed one hand on the handrail. Rocker Board training was used to enhance even weight-bearing of both legs and weight-transfer during steps after her motor function was achieved. Barthel Index was improved from 50 to 80.

HHS was improved from 63 to 91.

## Conclusion

Post-acute care program can provide a chance for elderly patient with hip fracture to participate in an aggressive rehabilitation program, and the patient can improve motor functions through the program.

## Clinical Relevance

Elderly patients with hip fracture have more opportunity to return to one's regular life through post-acute care program.

## Reference

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2. Lloyd, B. D., Williamson, D. A., Singh, N. A., Hansen, R. D., Diamond, T. H., Finnegan, T. P., . . . Fiatarone Singh, M. A. (2009). Recurrent and injurious falls in the year following hip fracture: a prospective study of incidence and risk factors from the Sarcopenia and Hip Fracture study. J Gerontol A Biol Sci Med Sci, 64(5), 599-609.

Table 1. Daily Progression

| | |
|---|---|
| Pre- PAC | She received walking training with walker for 3 days in VGHTC. |
| PAC: 1st day | Under therapist's instruction, she walked with a quadricane, and climbed up and down the stairs with one hand on the handrail and the other hand supported by the therapist |
| PAC: 1st day to 5th day | She received walking training with a quadricane. |
| PAC: 6th day | She could walk with a cane, and even walk without an assistive device. |
| PAC: 6th day to 7th day | She received walking training with contact guarding. |
| PAC: 8th day to 9th day | She received step exercise and rocker board exercise to improve dynamic balance for fall prevention. |
| PAC: 9th day | She could walk independent, climb up the stairs without support, and go down the stairs with one hand on the handrail. |

# Using proprioceptive neuromuscular facilitation (PNF) techniques improve reaching movement in stroke patient-case report

Shu-Chun Chiang, Chia-Chieh Li

## Background and Purpose

Reaching is an important component of many tasks of daily living. Reaching movement is composed of transportation phase and grasp phase. The transportation phase is bringing the hand to the target, and during this phase, the finger open to a maximum grip aperture. And in the grasp phase, the finger starts to close in anticipation of contact with an object. The two-phase is separately controlled but work coordinate to get smooth reaching movement. However, lots of stroke patients are failed to open their fingers due to agonist muscle weakness and strong flexor synergy. According to studies showed movement deficits in hemiparetic upper extremity may be more a problem of agonist muscle weakness than antagonist muscle spasticity. The purpose of this case report is using proprioceptive neuromuscular facilitation (PNF) pattern and timing for emphasis to enhance finger extensor to improve reaching movement.

## Methods

The case is a 27-year-old male with right hemiplegia, who was diagnosed ICH in 2015. Bruunstrom stage of hand is IV and arm is IV to V, able to shoulder flexion overhead and side horizontal position but unable to pronation and supination with the elbow fully extended. Before intervention, check the stability of the proximal part, including scapula and shoulder, which is not from spasticity. Considering arm reaching needs shoulder flexion and elbow extent, the intervention was blocking stronger shoulder and elbow motion in shoulder flexion-abduction-external rotation with elbow extension pattern to exercise finger extent using repeated stretch reflex (timing for emphasis) (Figure 1).Total procedure is also repeated for 3-4 times.

Figure 1. In shoulder flexion-abduction-external rotational with elbow extent pattern using timing for emphasis to enhance finger extensor.

## Results

Assessing thumb active range of motion (AROM) of abduction and the time of performing a functional activity to evaluate the maximum grip aperture and the coordinate of the transportation phase and grasp phase. Functional activity is the patient in sitting position and taking a peg from pegboard to the box on the right side of the pegboard (the hemi-side)(Figure 2). Before and after intervention thumb AROM of abduction doesn't have too much different (from 30O to 35O). The time of functional activity gets significantly improved (from 50 sec. to 30 sec.). The patient felt extending finger became much easier and got faster on second time(15sec.).

Figure 2. Take a peg from pegboard to a box on patient's hemiside.

## Conclusion

For chronic stroke patients, using PNF techniques enhance finger extensor to improve reaching movement is available.

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# Quality of medical services, patient satisfaction and their usage intention of medical service: A cross-sectional study

**Yen-Hung Chu [1], Shu-Wen Chen [2*]**

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## Introduction

Medical institutes are competed with each other. Patient satisfaction of medical service is a key concept in hospital management.

## Purpose

The purpose of this study was to examine the relationship among medical service quality, patient satisfaction, and their usage intention of the hospital service in the future.

## Methods

A total of 630 randomly selected subjects participated the study Participants were aged from 11 to 70 years old, with 59.5% were female. Questionnaires were used for data collection, from January to March, 2018. Confirmatory factor analysis was used to examine the validity of questionnaires. Higher scores indicated better quality of medical service, better patient satisfaction, and more intention to use medical service in the hospital. Pearson's correlation coefficient was used to evaluate the relationship among the quality of medical service, patient satisfaction, and usage intention of medical service in the future.

## Results

The result showed that the medical service quality was significantly, positive related with patient satisfaction ($r=0.962$, $p<.05$). Patient satisfaction also demonstrated a significant, positive relationship with the usage intention of medical service in the future. ($r=0.182$, $p<.05$). However, usage intention of medical service was positive related with medical services, but not significantly. ($r=0.207$, $p>.05$).

## Discussion

This study has found that usage intention of the hospital service in the future was not significantly related with the quality of medical service. Medical institutes should not limited to treating illness, but also should provide multi-purpose services.

## Conclusion

Increasing medical service quality may enhance patient satisfaction, and patients' satisfaction may strength their intention to use the medical service in the future. Further studies should be conducted in examine the mechanism of patients' usage intention to hospital services.

**Key words :** medical service quality, patients satisfaction, usage intention

# 運用健康信念模式分析一名兒童肥胖的護理經驗

張妙滿/護理部/亞洲大學-健康管理所碩士生

**前言**

根據教育部學生健康檢查資料顯示，我國 103 學年度國小及國中學童過重及肥胖比率各為 29.0%及 28.8%。另在國際比較方面，依據世界肥胖聯盟調查結果，台灣兒童過重及肥胖率與 OECD 33 個國家相比，臺灣男童排行第 6，女童排名第 12(國民健康署,2017)。在肥胖相關的醫療花費方面，國人肥胖與過重引發的心臟疾病、腦血管疾病、糖尿病、高血壓、高膽固醇血症等疾病，經統計過重與肥胖相關醫療支出佔全民健康保險費用的 2.9%，若以 2011 年國民醫療保健支出 9,103 億元計算，肥胖相關醫療保健支出已達 264 億元，造成個人及國家重大經濟及勞動損失。對於成長中的兒童及青少年而言，肥胖產生的影響還包括可能被同儕嘲笑、霸凌，造成低自尊、社會孤立等心理層面的長期影響(國民健康署,2017)。

造成兒童肥胖的原因大多與生活環境及家庭因素密不可分，故應從個案的生活脈絡中抽絲剝繭進行影響因素評估，擬定改善其肥胖問題的健康促進計畫，並落實行動才是治標之本。另因個案為國小學童在生活上尚無獨立能力，生活起居上須仰賴父母親，故計畫訂定與執行時亦需要同步評估父母親可配合的程度，降低執行難度提高個案及個案父母配合的意願才能有效進行改善計畫。

**文獻探討**

**(一)肥胖的定義**

我國教育部重編辭典修訂本將肥胖定義為因體內脂肪異常發育以致形體粗大的現象。韋伯字典(Webster's Dictionary)則將肥胖定義為體內脂肪過低積累儲存。一般肥胖是以 BMI 指數作為判斷標準，但兒童與青少年處於發育階段，身高增長體重也會隨之變動，故我國衛生福利部國民健康署針對兒童制定公告「兒童及青少年生長身體質量指數(BMI)建議值」，該體位標準是以該年齡層身體質量

指數的百分位作為過重或肥胖的切點。

當身體質量指數超過該年齡層的 85 百分位時為過重，超過 95 百分位時為肥胖。

**(二)肥胖的影響**

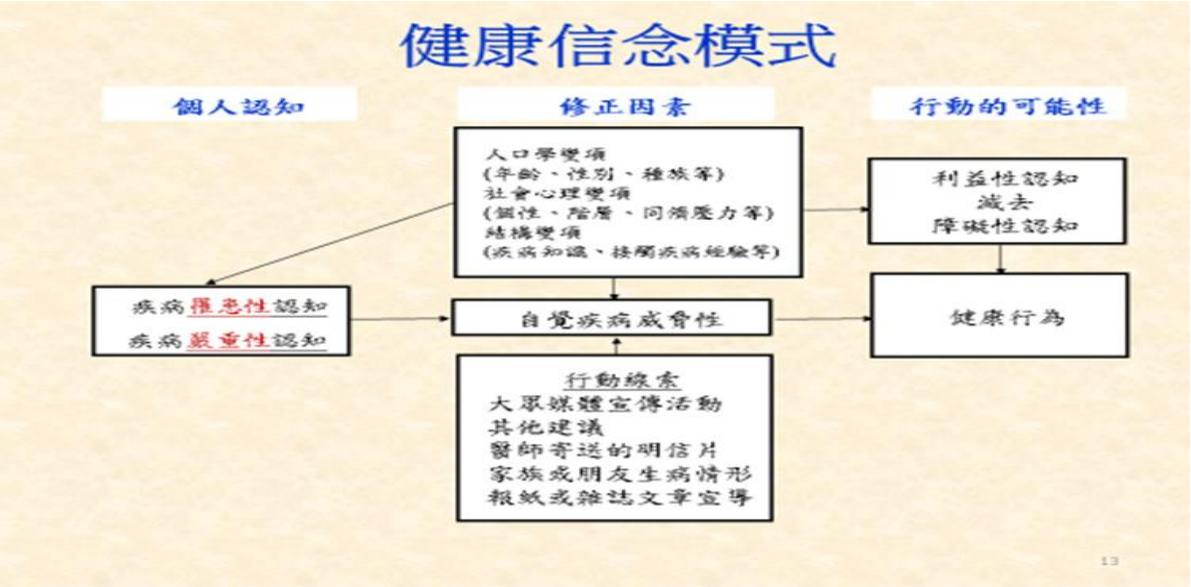
根據世界衛生組織統計 2016 年有超過 3.4 億名兒童與青少年超重或肥胖，肥胖盛行率由 1975 的 4%已上升至 18%(WHO,2017)。國際肥胖任務小組(IOTF)接受 WHO 委託收集世界 28 個主要國家兒童及青少年體重過重及肥胖的盛行率調查，我國盛行率在 IOTF 存有資料的 28 個國家中與美國並列第 7 位，不但遠高過歐洲各主要國家，亦較同源同種的中國大陸高出幾近一倍之多(趙,2008)。肥胖不僅是成人的疾病，對兒童的發育影響更大，兒童期的肥胖會直接影響生長、社會心理發展，更會在成年時造成高脂血症、高血壓、糖尿病 和動脈硬化等，增加成年後相關慢性病的罹病率和死亡率(施、范、熊，2012)。由此可知兒童肥胖在台灣是不容忽視的問題，且一旦罹患肥胖後再減重是困難的過程，因此及早預防不當的體重增加是較好的策略(林、林、楊、周，2014)。

**(三)健康信念模式**

1.理論發展

健康信念模式是 1950 年由 Hochbaum 及羅森斯托克 Rosenstock 等社會心理學家，應用 K. Lewin「場地論」(field theory)的概念，整合彼此的研究結果，所建構的一套適用於解釋民眾預防性健康行為的理論模式(國家教育研究院，2000)。理論發展之初是為了用來解釋及預測人們參與預防及疾病篩檢計畫行為之影響因素，而後 1974 年由 Becker 又修訂用以探討民眾疾病行為、病人角色行為、以及關於慢性病等健康行為(陳、李、李，2003)。

2.理論架構:




健康信念模式中提出個人是否採取健康預防行為涉及兩種期望「對特定疾病或健康狀況可能產生威脅的期望」與「對改善疾病或健康狀況而採取特定行動所需的成本/效益期望」。「對特定疾病或健康狀況可能產生威脅的期望」包含自覺罹患性及自覺嚴重性，「對改善疾病或健康狀況而採取特定行動所需的成本/效益期望」被稱之為自覺行動效益及自覺行動障礙(李，2011)。

健康信念模式幾項要素的**概念型定義**如下:(1)自覺罹患性（ Perceived Susceptibility）：指個人對罹患疾病之可能性的主觀評估； (2)自覺嚴重性（ Perceived Seriousness）：指個人對罹患某病嚴重性的感受(張、葉、陳，2010)，包含身、心、靈、社會等層面；若不覺得自身罹病或無法感受疾病嚴重性及罹病可能性和結果，其遵從性較低(吳，2016)；(3)自覺行動利益（ Perceived Benefits of Taking Action）：指個人對所採取的行動是否能降低罹患性或嚴重性之主觀性評估(張、葉、陳，2010)，亦指病人主觀的評估所採取的行動能有效降低疾病的威脅，學者認為病人感受到治療的好處，則較會遵守治療(吳，2016)； (4)自覺行動障礙（ Perceived Barriers of Taking Action）：指個人在行動過程中對可能存在之障礙的評估；(5)行動線索：指促使個人採取行動的刺激，如人際互動、大眾傳播…等(張、葉、陳，2010)。

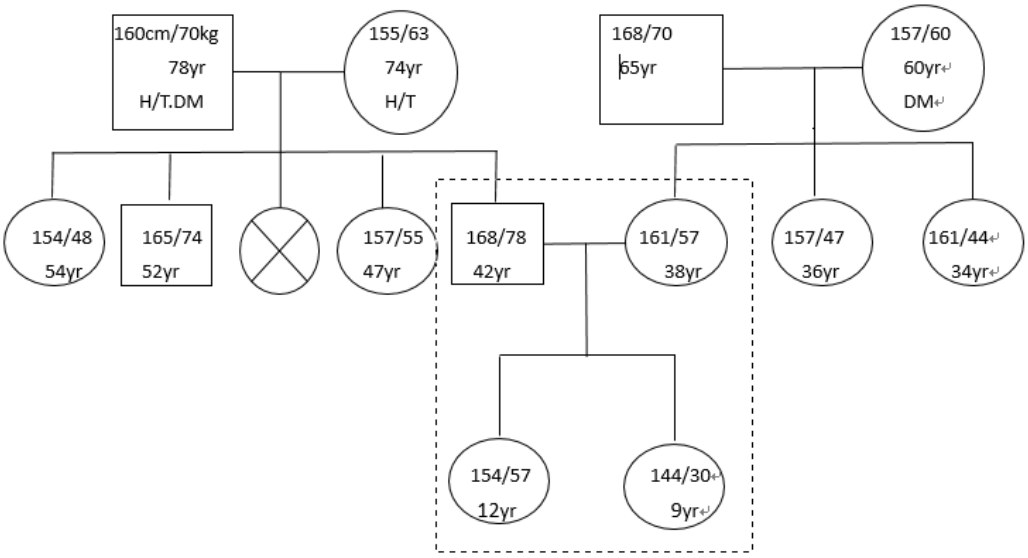
3.臨床運用

健康信念模式在1950年代被提出用以解釋民眾之健康行為以來，一直受到醫療社會學者普遍的重視(李、周、晏，1989)，健康信念模式主要用來解釋或預測跟健康預防行為，如戒菸、減重、疾病檢查等就醫行為。以體重控制運用來說自覺嚴重性衡量的是體重控制不足可能引發的後果，包含身型、人際關係、造成以後慢性疾病及骨骼問題的後果。自覺行動利益是指體重控制的好處(李，2011)。青春期的心理發展特徵包括形成自我認同、尋求獨立自主、建立信仰與價值體系、適應日趨複雜的人際關係等。形成自我認同可說是青春期的心理發展中最主要的課題(高，2008)。個案已開始進入青春期在心理層面方面對身體心像及人際關係的問題關注程度會逐日劇增，但因現在社會競爭壓力大，導致我國學生靜態活動多於動態活動，且因青春期發育身體對能量的需求增加，在活動量減少熱量攝取增加的情況下，就
容易造成體重過重，在學業成就壓力之下，疾病自覺往往就容易被忽略，故如何引導個案及家長面對兒童肥胖的影響，應用健康信念模式提升個案自覺疾病嚴重性、排除行動障礙及增加自覺行動利益，提升自我認同及自我照護能力改善體重過重的現象，在個案體重控制上應會有所改善及助益。

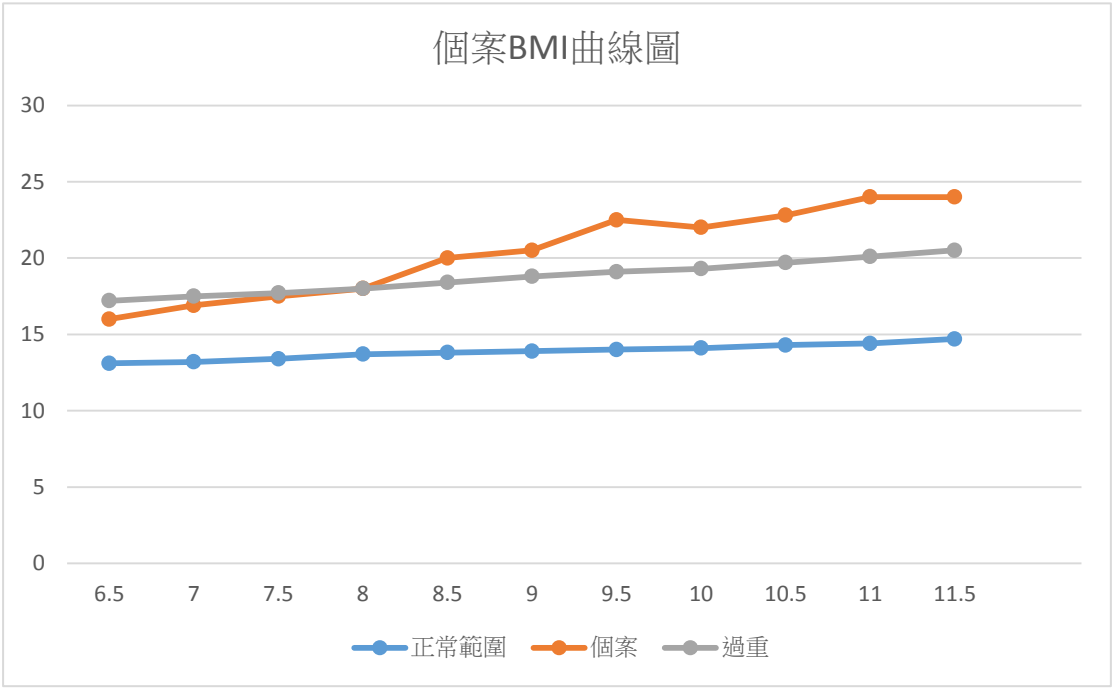
## 一、 護理過程

### (一)個案簡介:

卓0臻，性別女，現在年齡11歲9個月，96/02/04出生，妊娠週數35+3週因破水入院以自然產方式產出，出生體重2240g，沒有住保溫箱於96/02/07正常出院，生長無住院史、無開刀史，0-6歲依兒童發展歷程發展評估皆無落後，個案與雙親及妹妹四人同住，家庭型態為小家庭，沒有特殊宗教信仰，個案父親為科學園區工程師，學歷為碩士，個案母親為公衛護理師，學歷為學士，家中經濟狀況小康，主要照顧者為個案母親，103年9月由新北市移居台中市定居至今(見圖一家族樹圖譜)，個案於8歲起BMI開始超出國民健康署建議標準迄今仍未改善(見圖二個案BMI成長趨勢圖)。




圖一 家族圖譜




圖二、個案 BMI 成長趨勢圖

**心理方面:**依皮亞傑認知發展評估 7-11 歲兒童處於具體運思期，此階段兒童在記憶與語言部份開始增加記憶能力，可學會使用不同的方式幫助記憶、理解及解

釋溝通，能夠表達自己的意思，個案現為11 歲已可針對自我不了解的部分與父母溝通分辨大人的期待(例如:個案會與母親表示我同學也都一樣，我也不是班上最胖的，我的好朋友身材都跟我差不多)。學校與家庭生活方面，此階段兒童學校生活佔其大部分生活時間，個案與學校、安親班同儕相處關係融洽，課業表現正常。自我概念的發展方面，此階段兒童開始減少對父母的依賴與他人接觸增加，並逐漸發展出自己的想法，產生自我期待。個案在自我概念方面對自我身體心像已有出現介意的言詞,亦介意同儕對自己的看法(例如:個案平常不願意購買鮮豔的衣服，只願意購買寬鬆看不出身材的黑色休閒衣褲，也會在購買衣物時表示衣服不好看、不適合自己)。

**情緒方面:**此階段兒童易出現打架、說謊、偷竊、損壞財務及破壞規矩等行為，個案於此方面並無特殊困擾行為。

**靈性方面:**個案家中無特殊宗教信仰,此階段兒童也尚無法評估靈性層面問題發展，故此部分無法評值。

**社會方面:**個案除與父母姊妹同住，母親娘家父母、姨母均住同一社區，生活需求可互相照應，家族親友相處關係融洽，支持系統佳。個案居家鄰近有一大型公園，但因個案大多數時間都在學校或補習班，個案父母則因工作因素故甚少利用此資源。案本身沒有運動習慣，案母沒有三高病史，每週運動三次瑜珈課一小時，個案父親有高血脂病史，未服藥且沒有運動習慣。外祖父無慢性病史每次固定走跑步機1 小時，每週約 2~3 次，外祖母有糖尿病史則每次走跑步機 1 小時及每週一次 1.5 小時瑜珈課。

**(二)健康信念模式護理評估**

**1. 個人認知**

(1)自覺罹患性

**個案方面**:8 歲起體重就開始超出國健署建議標準，但因兒童發展任務中7-12 歲兒童此階段尚無法意識到各項指標對自己的意義。

**父親方面:**態度消極,認為胖瘦都沒有關係，對於肥胖就診僅有第一次陪同個案

到醫院，但不會干涉母親對於就診的花費或抱怨被影響。

**母親方面:**案母對於個案逐年體重增加越來越在意，案 8 歲時僅將個案身高體重曲線資料觀察但並無具體行動。

**外祖父母方面:**_觀念認為發育期要多補充熱量，小時候胖不是胖，長高後自然會變瘦，也認為等個案長大到國高中時，就會因為愛漂亮會自主減重無須在意。家中常有親友餽贈或旅遊帶回的糕點零食，外祖母固定備有一大型零食櫃供個案取用。

綜合上述「**自覺罹患性**」評估個案及家庭成員對於兒童肥胖罹患性知識不足的健康問題。

**(2)自覺嚴重性**

**個案方面:**個案開始注意到自我身體心象的改變，曾主訴外型或穿衣服不美觀，但在肥胖可能造成的合併症尚無認知。

**父親方面:**瞭解肥胖形成的原因及三高造成的影響，但因工作因素有吃消夜習慣，個案習慣與父親分享消夜，父親也認為可以促進親子關係。

**母親方面:**認為肥胖會造成個案現在及未來健康及大影響，故案於 9 歲時由個案母親發現出現第二性徵，求診於小兒遺傳代謝科，並於 106/1-107/7 間每隔四週施打 Leuplin Depot 3.75mg，現已停止施打並定期追蹤。

**外祖父母方面:**對於肥胖對健康的影響聚焦在長大容易有慢性病，僅會擔心個案因為肥胖影響人際關係，但為滿足個案的需求，並未有明確的改善行動。

綜合上述「**自覺嚴重性**」評估中個案及家屬對於兒童肥胖嚴重性認知尚可，但並無法支持讓案家有積極改變的行動。

**2. 行動效益與障礙**

**個案方面:**利益性認知-認為減重讓身材較好，穿衣服較好看，選擇也較多;障礙性認知-個案睡眠時間約 9 小時,除學校體育課程安排外沒有額外的體能活動，才藝課結束回家時間大約晚上 8 點，無法特別運動時間，午餐是學校營養午餐，點心則由安親班準備麵包、紅豆湯、蘇打餅乾等食物，沒有食物選擇自主權。

**父親方面**:利益性認知-對於個案胖瘦並無

知覺故無明顯利益性認知;障礙性認知-案父責任制的職業，延後返家時間，通常在外吃完飯才能回家，或者買消夜回家吃。

**母親方面**:利益性認知-個案體重降低可讓個案身體心像概念及人際關係發展較好及降低慢性病罹病率;障礙性認知-因為雙薪家庭，所以工作時間及其他家務相對會壓縮陪伴個案活動的時間。

**外祖父母方面:**利益性認知-與個案共進高纖晚餐對於自己本身慢性血糖疾病及體重控制也有共通利益;障礙性認知-為個案準備晚餐時，先以高纖及蔬果為主，與之前有魚有肉飲食不同，購買食材較麻煩。

**3. 修正因素**

(1)**整體性評估**:在生理方面個案現在年齡為 11 歲 9 個月，於 107/11/03 量測身高 154cm、體重 57kg、BMI:24，依衛生福利部國民健康署兒童與青少年生長身體質量指數(BMI)建議值評估顯示個案屬於肥胖範圍，沒有其他身體不適主訴，若有感冒或其他疾病症狀習慣藉由西醫途徑就診。

D.I.S.C.兒童人格特質行為心理學（D.I.S.C. Personality Profiles），以心理學家 William Moulton Marston 於 1928 年的一份研究為基礎稱為四型人格把他動物化後，可以分成孔雀、老虎、貓頭鷹、無尾熊。分析後個案分類為 C=Conscientiousness 無尾熊(謹慎型)：此特質做事有步驟，懂得計劃，很謹慎；喜歡保有自己的隱私，比較悲觀，完美主義者，考第 2 名還是覺得不足，喜歡數學，對數字敏感，習慣思考，不怕邏輯辯證題型。特點：性格低調、易相處、無異議、耐心，一但答應下的工作會默默做完。缺點：拒絕改變、目標感不強、迴避壓力、沉默、無主見（需要力量型的人 給於指導，但不要施加壓力）、不善於做決定。

(2)**行動線索**

**個案方面:**就讀健康促進學校，校方進行健康體位計畫活動，學校護理師每學期測量完身高體重後，針對過重的學童加強宣導，使個案簡單解一日蔬果、每日活動量、睡眠時數及飲水量都會影響體重。

**父親方面**:自己健檢報告發現脂肪肝，警覺到肥胖對健康影響,也會開始擔心案也有類似情形。

**母親方面:** 個案因提早出現第二性徵的問題求診於小兒遺傳代謝科,配合醫師、個管師衛教了解,因體重過重與第二性徵提早出現的關係密不可分,開始個案體重控制的相關方式。

**外祖父母方面:** 外祖母有糖尿病史規則就醫服藥,醫院衛教慢性病與肥胖的關連，因為對於自己本身疾病的了解,間接留意個案肥胖的情形。

綜合上述,因個案為學齡期學童，截至目前為止皆是被動姿態,醫療及生活型態決定方式都由共同生活的父母或外祖父母決定，個案不會主動詢問肥胖本身的相關問題和處置顯示個案及其家屬對於體重控制、疾病認知及藥物遵從性上有行動上的配合障礙,且對於預防疾病及偵測疾病的認知不足,家屬對肥胖的認知偏差導致無效性的健康維護能力,故評估結果為有**潛在危險性發育不成比例生長**及**無效性的健康維護能力**的健康問題。

(三)護理計畫與評值

依上述健康信念模式護理理論評估得知個案三個健康問題:

1. **知識缺失/兒童肥胖的認知錯誤**
2. **潛在危險性發育不成比例生長**/營養狀態改變
3. **無效性的健康維護能力**/缺乏健康尋求行為的經驗

1. **知識缺失/兒童肥胖的認知錯誤**

| 主客觀資料 | 護理目標 | 護理措施 | 護理評值 |
|---|---|---|---|
| S1:個案會與母親表示同學也都一樣，我也不是班上最胖的，我朋友身材都跟我差不多。<br>S2:父親認為胖瘦都沒有關係，僅陪同個案就 | 1.個案能說出導致肥胖的原因三項。<br>2.個案確認說出自身該階段的標準值。 | 1-1.由案母與個案一同搜尋肥胖的動畫宣導媒體。<br>1-2.重點提示飲食習慣、食物種類、烹調方式、每日熱量攝 | 1.個案能說出導原因包刮:飲食總量、熱量、烹煮方式等三項。達到與<br>2.個案說出年齡相稱的 BMI 值。 |

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| 診一次。<br>S3:外祖父母對兒童肥胖觀念是發育期要多補充熱量，小時胖不是胖，長高後自然會變瘦，認為個案到國高中就會因為愛漂亮會自主減重，無須在意。<br>O1: 個案**不會主動詢問肥胖**相關的問題和處置，家屬對肥胖的認知偏差。<br>O2: 自我概念的發展方面，此階段兒童開始減少對父母的依賴與他人接觸增加，並逐漸發展出自己的想法，產生自我期待。<br>O3: 對自我**身體心像**已有出現**介意**的言詞，亦介意同儕對自己的看法。 | 3.家庭成員達成共識並依照提供正確知識修正飲食調控計畫行為。 | 入。<br>2-1.協助家人理解其個性特質:**悲觀完美主義，對於肥胖**問題採迴避壓力方式。<br>2-2.同理並試算個案及同學的 BMI 值及自身標準值。<br>3-1.協助家庭成員允許開放性的表達感覺，描述並鼓勵正向行為。<br>3-2.依家庭為中心協助理解個案正值**身體心像**發展需認知，修正確肥胖知識。 | 3.家庭成員外祖父及案父共識個案正飲食調控計畫行為。 |

2.**潛在危險性發育不成比例生長**/營養狀態改變

| 主客觀資料 | 護理目標 | 護理措施 | 護理評值 |
|---|---|---|---|
| S1: 個案平常不願意購買鮮豔的衣服，只願意**購買寬鬆看不出身材的黑色休閒衣褲**，也會在購買衣物時表示衣服不好看、不適合自己。<br>S2:進入青春期後開始**注意到自我身體心象的改變**，曾主訴外型或穿衣服不美觀<br>O1: 107/11/03 量測身高 154cm、體重 57kg、BMI:24 值，顯示個案屬肥胖範圍。<br>O2:個案母親曾與個案溝通健康體重的標準及體重問題，並試圖調整個案飲食改善體重過重現象。<br>O3:個案喜歡醬汁、滷味、義大利麵等食物，平日午餐由學校提供營養午餐，下午點心由安親班準備麵包、紅豆湯、蘇打餅乾等食物，晚餐由外祖父母備晚餐，**假日則均外食**，家中總有親友餽贈的糕點零食，外婆備有大型零 | 1.個案及祖父母能**確認造成**不成比例生長的危險因子。<br>2.個案及祖父母能**陳述對預防及減少**不成比例生長的危險因子。<br>3.個案體重降至該年齡與性別的生長曲線範圍。 | 1-1.由案母收集衛服部公告「兒童及青少年生長身體質量指數(BMI)建議值」，及個案年齡層身體質量指數的目前為過重或肥胖的數據。<br>1-2.選擇適合時機(案母、個案及祖父母同時)時，請個案分享學校健康體位計畫活動，護理師宣導健康一日蔬果、每日活動量、睡眠時數及每日飲水量都會影響到體重的發展。<br>2-1.由案母與其雙親討論個案**預防及減少**生長的危險因子。<br>2-2 鼓勵雙老協助在家執行預防熱量儲存的習慣，促進照護連 | 1.個案能正確說出自己每日過量飲食。<br>2.祖父母能陳述對減少庫存零食，及準備適合祖孫的飲食。<br>3.生長曲線持平中。 |

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| 食櫃供個案取用。<br>O4:學校進行健康體位計畫，在學校護理師的宣導下可以使個案簡單了解一日蔬果、每日活動量、睡眠時數及每日飲水量都會影響到體重的發展。<br>O5:課業壓力大，沒有時間運動，居家鄰近大型公園，但因個案多數時間都在學校或補習班。 | | 續性。<br>3-1.協助案母與個案擬訂專業飲食計劃。<br>3-2.鼓勵案父每周日陪同個案戶**外踏青，替代**分享消夜促進親子關係。<br>3-3.鼓勵親子建立漸進性目標達成的獎勵辦法。 | |

3.**無效性的健康維護能力**/缺乏健康尋求行為的經驗

| 主客觀資料 | 護理目標 | 護理措施 | 護理評值 |
|---|---|---|---|
| O1:醫療及生活型態決定方式都由共同生活的父母或外祖父母決定。<br>O2:個案祖父母有高血壓及糖尿病病史,服藥遵從性差無飲食禁忌,沒有運動習慣。案父親有高血脂病史,未服藥且沒有運動習慣。<br>O3: 外祖父母對於肥胖**對健康的影響**表示清楚知道肥胖可能造成高血壓、高血脂、糖 | 1.個案能描述家人對於其健康照護行為的影響。<br>2.個案能表現出執行健康維護的意願。 | 1-1.依同理心的態度引導說出對祖父母及父親罹病的感受。<br>1-2.依開放性的語言傾聽家人健康維護障礙看法。<br>1-3.引導個案省視自己面對疾病時可能的反應為何？。<br>2-1.提供有關家族 | 1.個案能主動提醒長輩們按時吃藥。<br>2.個案能主動表達自己遵行健康型態的行動方案的意思。 |

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| 尿病，也可能影響人際關係，但為**滿足個案的需求，並未有明確的改善行動。**<br>O4: D.I.S.C 分析:目標感不強 看似懶惰 不願承擔責任 迴避壓力 沉默、馬虎 無主見（**需要力量型的人 給於指導**，但不要施加壓力。<br>O5:依皮亞傑認知發展評估 7-11 歲兒童處能夠表達自己的意思。 | | 慢性病史的罹病及預防知識。<br>2-2.當個案能正確說出高血壓、高血脂、糖尿病等與生活型態相關時，**即時給予肯定與讚賞。**<br>2-3.由專業案母與個案討論其生活型態障礙缺失，提供個案健康型態的可行動方案。 | |

二、討論

成長中兒童的個案，為國小學童在生活上尚無獨立能力，生活起居上須仰賴父母親，加上居住搬遷及重新建立人際互動網對個案生活起居改變致肥胖產生，當個案開始進入青春期，心理層面方面對身體心像及人際關係的問題關注程度會逐日劇增。青春期的心理發展特徵包括形成自我認同、尋求獨立自主、建立信仰與價值體系、適應日趨複雜的人際關係等。形成自我認同可說是青春期的心理發展中最主要的課題(高，2008)。依健康信念模式評估得知個案三個健康問題包括:1.知識不足；2.潛在危險性發育不成比例生長；3.無效性的健康維護能力。故計畫訂定與執行時亦需要同步評估父母親可配合的程度，降低執行難度提高個案及個案父母配合的意願才能有效進行改善計畫。

三、結論

體重過重及肥胖現象日益威脅全世界兒童健康，肥胖的兒童會導致日後肥胖的成年人，並產生高血壓、高血脂、心臟病及糖尿病等慢性合併症年輕化的趨勢(連、高、羅，2012)。個案因進入青春期開始注意自我身體心像，於改善自己的外觀方面具有強烈的動機，配合度也會較好。個案家族中有多人具有三高病史，但對疾病認知及治療配合度差，因造成肥胖因素與家庭生活形態關係密切且影響甚鉅，故若能藉由調整個案的生活型態，藉由健康信念的提升加強個案及家屬的認知並鼓勵家屬積極參與一同改善，才得以達到全人及持續性照護的理想。

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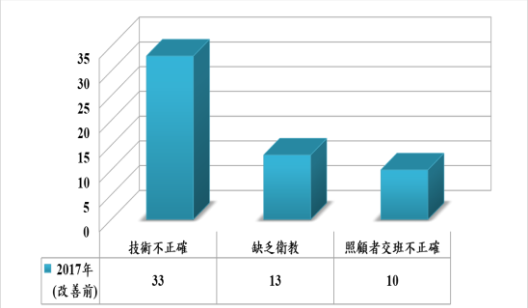
# 運用品管圈手法降低外科住院病人管路滑脫發生率

曹慈翠、吳盈璇

**2013 年醫策會將提升管路安全列入病人安全重要目標。意外事件的預防及監測是醫院護理品質管理中重要之一環，非計劃性拔管亦是品管監測重要指標之一，2017 年 1 月至 12 月因管路發生異常事件共 126 件，並有逐月增加趨勢，故成立專案改善小組，期望透過團隊合作來降低管路異常發生率，落實病人的安全。本研究採回溯性調查法，針對 2017 年外科住院病人管路滑脫發生進行真因驗證。專案經由改善方案的執行確實能降低管路滑脫發生率由 0.05%降低至 0.01%，並持續監控及改善。**

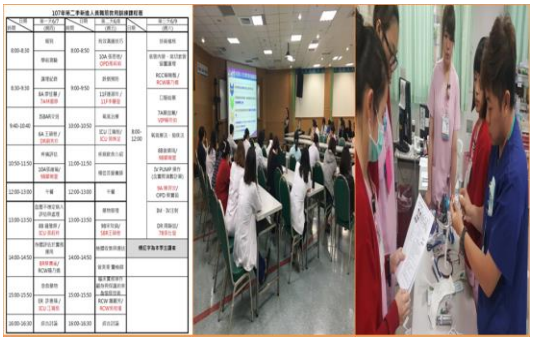
## 目 的

醫策會於2013年將提升管路安全列入病人安全重要目標。95%外科病人手術後會有鼻胃管、導尿管、氣切套管等重要管路留置，留置目的在於維持營養、尿液排泄及呼吸道通暢，留置管路的照護上是屬於高流量、高危險、易發生問題的照護活動。2017年1至12月因管路發生異常事件共126件，並有逐月增加趨勢，其中技術不正確33件、缺乏衛教13件、照顧者交班不正確10件，故成立專案改善小組，期望透過團隊合作來降低管路異常發生率，避免病人因醫療照護過程中的意外而導致不必要的傷害。




## 方 法

本研究採回溯性調查法，並針對2017 年外科住院病人管路滑脫發生進行真因驗證，原因有：1.執行照護時技術不正確；2.缺乏個別性的預防管路滑脫指導內容；3.無輔助照顧者之間交班工具。達成目標措施包括：1.加強護理人員管路教育訓練；2.進行管路技術考核；3.制定個別性衛教指導單張；4.製作「管路留置照護注意事項」衛教海報；5.制定『住院中主要照顧者照護知能暨交班紀錄表』。

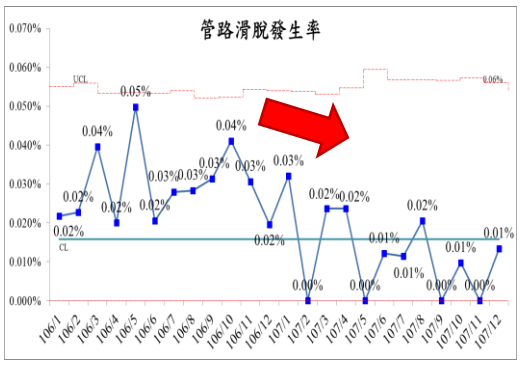


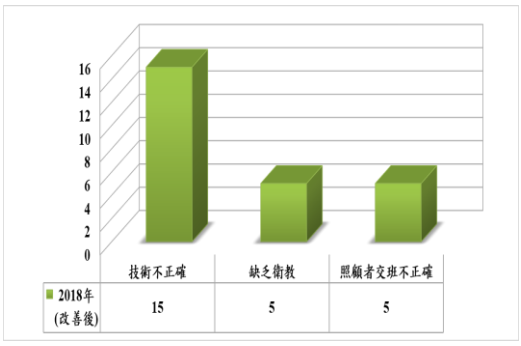
教育訓練課程表　上課實況　單位在職教育



## 結果

本專案有效降低管路滑脫發生率由0.05%降低至0.01%。其中因執行照護技術不正確由改善前33件至改善後15件，缺乏個別性預防管路滑脫衛教由改善前13件至改善後5件、照顧者交班不正確由改善前10件至改善後5件。




## 結論

專案經由改善方案的執行確實能降低管路滑脫發生率，並持續監控及改善。醫療團隊針對管路照護的共識及努力方向：

1.對於管路留置的使用，應以病人為中心做需要性的評估。

2.落實將管路留置必要性評估，列入每日治療計畫或醫療團隊查房及交班事項。

3.建立醫病雙方與醫療團隊間之良好溝通：

(1)主動與病人、家屬、陪伴者或看護者溝通，以利幫助處理病人的不舒適，並增加病人及家屬間了解管路留置的重要性及脫落危險性。

(2)教育陪伴者或照顧者相互交班管路安全照護衛教。

(3)醫護團隊間溝通，儘早移除不必要之管路。

4.加強醫療團隊成員之臨床訓練，包含疼痛照護、物理及藥物約束使用技能，管路留置適當性評估等。

5.確實固定管路並適當使用約束，減少管路意外滑脫。

6.適當使用鎮靜藥物，減輕病人焦慮與不適，以減少自拔比例。

如病人意識混亂，約束替代工具無法抑止管路自拔或滑脫，因此針對意識混亂有管路留置病人研擬相關改善措施，是未來努力的方向。

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# 提升中部某區域教學醫院外科病房腸造口護理完整性

劉雅芬、黃心樹、曹慈翠

## 背景

腸造口術用於緩解腸內壓力並避免對生命的威脅。護理人員若能提供適當和正確的護理知識，則將有助於改善患者的生活品質。

護理人員的腸道護理過程和指導內容不一致，影響護理質量，因此引發改善動機，並成立了專案小組協助了解、改善護理問題，提供適當的護理和相關護理技能，增進患者自我照護能力，提高生活品質。

## 現況分析

本病房為中部某區域教學醫院外科病房，床位 38 床。人力配置為護理人員 11 位(不含護理長)，工作年資分佈如表一。

自 2017 年 12 月至 2018 年 11 月大腸直腸外科手術統計資料顯示接受腸道手術共有 125 位病人，**有接受腸造口手術病患 13** 位，佔 10.4%。

2018 年 7 月，由於護理人員對腸造口術的護理措施不明確，且護理教育內容不一致，於 2018 年 7 月 26 日制定了《腸造口術的標準操作規程》。 並於 2018 年 10 月修訂。(圖 1)

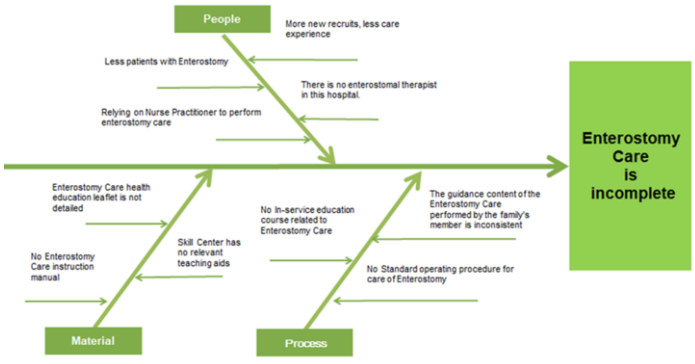



Figure 1 Intestinal stoma care incomplete characteristics factor map

分析的原因表明，本院無專責腸造口治療師及“腸造口護理標準作業流程”，臨床護理師對腸造口護理流程、完整性與腸造口照護認知不足。

**表一單位護理人員基本資料(N = 11)**

| 項目 | 人數 | 百分比(%) |
|---|---|---|
| **性別** | | |
| 女 | 11 | 100 |
| **年齡(歲)** | | |
| 21-30 歲 | 9 | 81.8 |
| 31-40 歲 | 1 | 9.1 |
| >41 歲 | 1 | 9.1 |
| **工作年資(年)** | | |
| 0-1 年 | 2 | 18.3 |
| 1-5 年 | 4 | 36.3 |
| >5 年 | 5 | 45.4 |
| **腸造口照護次數( 次)** | | |
| 1-10 次 | 4 | 36.3 |
| 11-20 次 | 2 | 18.2 |
| >20 次 | 5 | 45.4 |
| **腸造口照護課程時數( 小時)** | | |
| 1-5 小時 | 9 | 81.8 |
| 5-10 小時 | 2 | 18.2 |

## 解決方法

藉由修訂「腸造口護理標準作業程序」、安排護理人員教育課程、修訂「腸造口護理 DOPS 技術稽核表」、腸造口護理技術指導與稽核、增設腸造口照護手冊、拍攝腸造口照護影片、設置腸造口用物包等用於臨床照護。透過此專案實施，增進護理人員腸造口照護能力，提升照護品質（圖 2）。


Figure 2 Improvement measures

結果

結果顯示，腸造口護理的正確完整性從 71.54% 提高到 93.6%，腸造口護理的認知率從 72.7% 提高到 91.4%，有顯著改善(表二)。

**表二腸造口護理完整性改善之前後比較 (N=11)**

| 項目 | 改善前(%) | 改善後(%) |
|---|---|---|
| 目的(9%) | 4.6 | 9 |
| 用物準備(11%) | 5.6 | 9.6 |
| 技術操作(70%) | 50.5 | 65 |
| 注意事項(10%) | 9.1 | 10 |
| 平均完整率(100%) | 71.5 | 93.6 |
| 認知正確率(%) | 72.7 | 91.4 |
| 花費時間(分鐘) | 45 分鐘 | 27.5 分鐘 |

結論

腸造口照護對護理人員來說是較不常遇到的困難技術，且須直接碰觸病患的排泄物，對於大多數的臨床護理師是相當大的壓力。藉由腸造口照護在職訓練及臨床實務操作，提昇臨床護理師認知與執行技術能力、專業知識，進而使病人得到良好完善的照護品質。

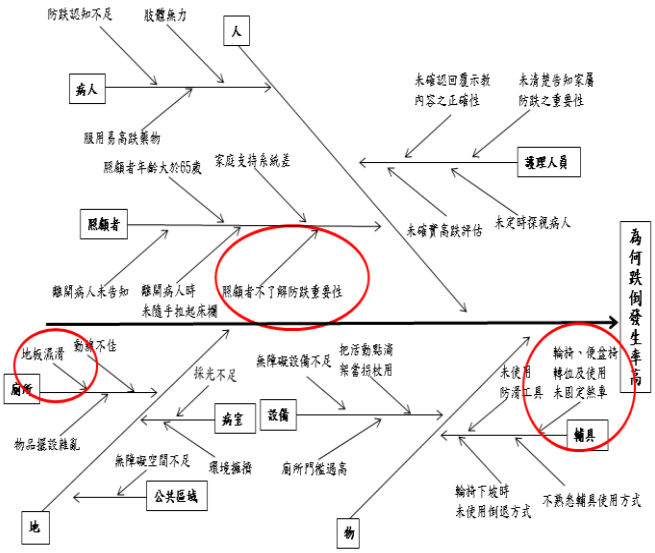
# 運用品管圈手法降低內科住院病人跌倒發生率

鍾雅婷[1]、張仕瑩[1]、張冠儀[1]、張議方[1]、蕭怡珣[1]、林冠華[1]、張雅晴[1]、黃穎溱[1]、張家蓁[1]、曹慈翠[1]、鄭世文[2]、林家瑜[2]

## 目的

根據台灣病人安全通報系統年報顯示，「跌倒事件」一直高居病安通報前三名。本研究顯示內科病房自 105 年至 106 年跌倒件數有增加趨勢，影響人員預防跌倒照護信念及工作滿意度，故成立專案改善小組，以期運用更有效的改善方法來降低病房跌倒發生率，提升照護品質。.

## 現況分析




圖一 ：內科住院病人跌倒之特性要因圖

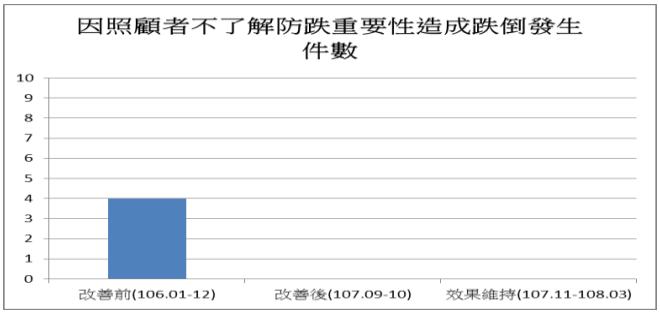
## 對策擬定

| 問題點 | 主要因 | 對策方案 | 評價 可行性 | 經濟性 | 效益性 | 總分 | 採行 | 負責人 | 實施日期 | 對策編號 |
|---|---|---|---|---|---|---|---|---|---|---|
| 跌倒發生率高 | 照顧者不了解防跌重要性 | 1.衛教照顧者離開病室時應告知醫護人員才可離開。 | 41 | 27 | 9 | 77 | | | | |
| | | 2.將防跌照顧事項列表，請照顧者依照衛教單張內容照顧病人。 | 41 | 33 | 23 | 97 | V | 張仕瑩 | 107.08.01-107.08.30 | 1 |
| | 廁所地板濕滑 | 1.請清潔人員加強巡視各病室內廁所，保持乾淨、乾燥。 | 37 | 31 | 37 | 105 | V | 張議方 | 107.08.01-107.08.30 | 2 |
| | | 2.建議醫院重新修繕廁所。 | 17 | 9 | 31 | 57 | | | | |
| | 輪椅、便盆椅轉位及使用未固定煞車 | 1.於輪椅及便盆椅置放處張貼告示牌及使用說明書。 | 41 | 31 | 23 | 95 | V | 林冠華 | 107.08.01-107.08.30 | 3 |

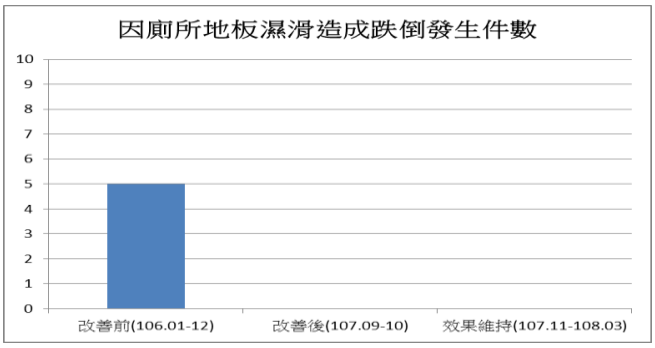
**對策實施**

1.加強護理人員從病人入院起，依病人個別性之照顧重點寫於衛教單張提供照顧者參考，並使用「主要照顧者照護知能紀錄表」教導照顧者之間重點交班。2.製作「病房浴室清潔巡視紀錄單」，請清潔人員每日定時至病房廁所巡視，衛教病人及家屬於洗澡完後須告知護理站，請清潔人員立即前來擦拭保持乾燥。3.輪椅及便盆椅置放處張貼告示牌及製作淺顯易懂說明書。

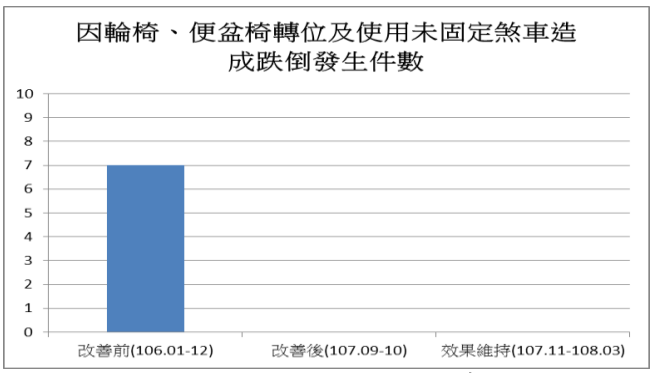
**結果**




**圖二 ：因照顧者不了解防跌重要性造成跌倒件件由 4 件降低至 0 件**




**圖三 ：因廁所地板濕滑造成跌倒件數由 5 件降低至 0 件**




**圖四 ：因輪椅、便盆椅轉位及使用未固定煞車成跌倒件數由 7 件降低至 0 件**

**結論**

將「照顧者知能記錄表」納入「預防病人跌倒與處置作業指導書」及將輔具使用衛教新增於「病人入院護理作業指導書」，使護理人員落實，並新增「病房浴室清潔巡視紀錄單」及設置「注意防跌卡」，將預防病人跌倒的責任落實在醫療團隊每一位成員，以達到提升病人安全目的。

# 癌症末期併呼吸衰竭病人使用非侵襲性呼吸器並介入安寧療護之照護經驗

# The Experience of Implementing Hospice Care in Patient with Terminal Cancer and Respiratory Failure Using Non-Invasive Positive Pressure Ventilator.

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## 目的

臺灣在過去 20 年間安寧緩和條例的推動賦予病人臨終時拒絕心肺復甦術或維生醫療（DNR）的選擇, 2019 年開始施行病人自主權利法對於罹患末期疾病的病人有更多醫療自主與保障其善終權益。當疾病進展導致呼吸衰竭時, 許多人拒絕侵入性治療不插氣管內管, 此時臨床上常用非侵襲性呼吸器(NIPPV)來緩解呼吸困難的症狀。此個案為肝細胞癌(Hepatocellular Carcinoma;HCC)合併呼吸衰竭插管使用呼吸器,拔管後因嚴重腹脹導致肺擴張不全致低血氧及呼吸困難情形使用非侵襲性呼吸器。治療過程中病人因知病程進展至死亡已不可避免, 出現不安與焦慮等問題,在緩和醫療中呼吸治療的介入及應用降低病人生理與心理的不適,改善癌症末期病人生命品質。

## 呼吸治療評估

55 歲男性病人, 有 B 肝、肝硬化及肝癌病史, 因腹脹與呼吸困難入院, 診斷為肝細胞癌合併呼吸衰竭給予插管治療,拔管後出現呼吸窘迫與肺擴張不全情形使用非侵襲性呼吸器。嘗試脫離呼吸器期間給予氧氣面罩 Simple mask 8L/min 與非侵襲性呼吸器交替使用, 每次使用氧氣面罩最長時間為一小時。依據胸腔 X 光影像顯示:雙側下肺葉擴張不全, 腹部鼓脹叩診為濁音(Dullness), 腹部超音波顯示大量腹水, 聽診雙側肺濕囉音。因呼吸困難需倚賴呼吸器及腹脹造成不適, 患者面露愁容, 表示對未來充滿絕望。

## 問題確立

1. 肺部塌陷及擴張不全。
2. 呼吸道清除功能失效。
3. 情緒不安與焦慮。

## 呼吸治療措施

1. 定時翻身改變臥位、抬高床頭 30-40 度以利肺擴張, 呼吸器使用NIPPV PC SIMV+PS mode RR 14bpm/min PC10cmH2O PS 10cmH2O PEEP 10cmH2O FiO2 40% 增加潮氣容積, 改善肺泡換氣, 降低呼吸功並維持血氧濃度(Sp02)大於 90%。放置腹部引流管（Pigtail catheter）需要時進行腹水引流減少腹脹。
2. 教導病人深呼吸及有效咳嗽方法, 八小時給予口服Acetylcysteine 600mg發泡錠並增加胸腔物理治療頻率, 必要時予以抽痰, 呼吸器與氧療設備提供足夠濕氣避免痰液黏稠。
3. 會診安寧療護尊重病人宗教信仰放置念佛機於床旁, 鼓勵家屬幫病人按摩放鬆心情, 引導病人及家屬進行道謝、道歉、道愛、道別的「四道人生」, 必要時給予Morphine靜脈滴注改善呼吸喘的感受。

## 結果評值

病人主訴呼吸器設定NIPPV PC SIMV+PS模式氣流過強, 故調整呼吸器設定參數為NIPPV PSV mode PS12cmH2O PEEP 5cmH2O FiO2 40% 潮氣容積可維持在 550ml以上,病人表示舒適度改善。在進行腹水引流後, 胸腔X光雖呈現雙側下肺葉擴張不全, 但病人感覺呼吸較平順, 呼吸速率約 12~25 次/分, 每次脫離非侵襲性呼吸器時間可延長至兩小時, 增加與家屬說話的時間減少焦慮的情緒。教導有效性咳嗽方式後可自咳痰液, 胸腔X光無新肺炎產生。病人後因肝細胞癌病情進展導致多重器官衰竭且出現休克情形, 在病人與家屬討論後決議僅以非侵襲性呼吸器維持生命, 病人於 6/12 安祥離世,

依照其遺志捐贈大體遺愛人間。

**結論與討論**

對於使用非侵襲性呼吸器的末期病人,除了可減緩呼吸困難症狀外,也可讓病人與家人多一些時間溝通,但須加強痰液清除技術預防痰液蓄積。呼吸治療師在照護上須考量病人的舒適度,以病人為中心提供適當的安寧緩和照護可提升其生命末期生活品質。

**關鍵詞**

非侵襲性呼吸器
(Non-invasive ventilator)
、安寧緩和醫療(Palliative care)

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