ORIGINAL RESEARCH

Low Pulse Pressure After Acute Ischemic Stroke is Associated With Unfavorable Outcomes: The Taiwan Stroke Registry

Sung-Chun Tang, MD, PhD; Jiu-Haw Yin, MD; Chung-Hsiang Liu, MD; Ming-Hui Sun, MD; Jiunn-Tay Lee, MD; Yu Sun, MD, PhD; Chih-Shan Hsu, MD; Mu-Chien Sun, MD; Ching-Huang Lin, MD; Chih-Hung Chen, MD; Li-Ming Lien, MD, PhD; Chih-Hsin Muo, MS; Jiann-Shing Jeng, MD, PhD; Chung Y. Hsu, MD, PhD; Taiwan Stroke Registry Investigators*

***Background*—**Pulse pressure (PP) is related to cardiac function, arterial stiffness, fluid status, and vascular events. This study aimed to explore the prognostic role of PP upon admission in patients with acute ischemic stroke (AIS) based on a nation-wide stroke registry.

***Methods and Results*—**We evaluated the association between PP upon admission and outcomes 3 months after a stroke in patients who had an AIS registered in the Taiwan Stroke Registry, including 56 academic and community hospitals between 2006 and 2013. Three months after the stroke, unfavorable outcomes were defined using a modified Rankin scale of 3 to 6. Of 33 530 patients (female, 40.6%; mean age, 68.8±13.3 years) who had an AIS, PP upon admission had a reverse J-curve association with an unfavorable outcome. After adjusting for clinical variables, including AIS subtypes, initial National Institutes of Health Stroke Scale, and systolic and diastolic blood pressure upon admission, a PP of <50 mm Hg was associated with unfavorable outcomes (P<0.0001). Compared with patients with a PP of 50 to 69 mm Hg, the odds ratios for unfavorable outcomes were 1.24 (95% CI, 1.14–1.36) with a PP of 30 to 49 mm Hg and 1.85 (95% CI, 1.50–2.28) with a PP of <30 mm Hg. Moreover, the prognostic impact of PP upon admission was similar across all AIS subtypes.

***Conclusions*—**Low PP upon admission was associated with unfavorable patient outcomes in AIS. **(*J Am Heart Assoc*. 2017;6: e005113. DOI: 10.1161/JAHA.116.005113.)**

Key Words: blood pressure • ischemic stroke • outcome • pulse pressure • stroke registry

Stroke is a life-threatening disease, leading cause of death, and severe long-term disability worldwide.[1] Among several factors that may increase the risk of stroke, hypertension is the single most important one.[2] Uncontrolled blood pressure (BP) would lead to atherosclerosis and, in turn, harden and weaken the vessels in the brain, heart, and limbs, causing end-organ damage.[3] However, the occurrence of stroke may directly lead to an acute increase in BP.[4,5] Although the role of BP management after a stroke remains controversial, systolic, mean, or diastolic BP levels upon hospital arrival have demonstrated a U- or J-curve association with poststroke mortality and functional dependency.[6–12]

In addition to the steady components of systolic and diastolic values, BP is also characterized by its pulsatile nature and is estimated using pulse pressure (PP).[13,14] PP is the difference between the systolic and diastolic BP; can be conceptualized as being proportional to the stroke volume; and is inversely related to aortic compliance.[15–17] However, it

From the Stroke Center and Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan (S.-C.T., J.-S.J.); Department of Neurology, Cheng Hsin General Hospital, Taipei, Taiwan (J.-H.Y.); Department of Neurology (C.-H. Liu) and Management Office for Health Data (C.-H.M.), China Medical University Hospital, Taichung, Taiwan; Department of Neurology, Kuang Tien General Hospital, Taichung, Taiwan (M.-H.S.); Department of Neurology, Tri-Service General Hospital, Taipei, Taiwan (J.-T.L.); Department of Neurology, En Chu Kong Hospital, New Taipei City, Taiwan (Y.S.); Department of Neurology, China Medical University Beigang Hospital, Taichung, Taiwan (C.-S.H.); Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan (M.-C.S.); Department of Neurology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (C.-H. Lin); Department of Neurology, National Cheng Kung University Hospital, Tainan, Taiwan (C.-H.C.); Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan (L.-M.L.); Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan (C.Y.H.).

An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/6/6/e005113/DC1/embed/inline-supplementary-material-1.pdf

*The Taiwan Stroke Registry Investigators are listed in Appendix S1.

Correspondence to: Jiann-Shing Jeng, MD, PhD, Department of Neurology, National Taiwan University Hospital, No. 7, Chung-Shan South Rd, Taipei 100, Taiwan. E-mail: jsjeng@ntu.edu.tw

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Clinical Perspective

What is New?

- The present study demonstrated a reverse J-curve association of admission pulse pressure with an unfavorable outcome in patients with acute ischemic stroke based on a nation-wide stroke registry.

What are the Clinical Implications?

- Admission pulse pressure is associated with poststroke functional outcomes in patients with acute ischemic stroke.

remained unclear whether a relationship between admission PP and clinical outcomes among patients with acute stroke existed.[18–21] Thus, the present study aimed to explore the prognostic role of admission PP in patients with acute ischemic stroke (AIS) based on a nation-wide stroke registry.

Methods

Taiwan Stroke Registry

Since 2006, the Taiwan Stroke Registry (TSR) has been a nation-wide hospital-based prospective study engaging 56 academic and community hospitals and has 4 steps of quality control to ensure the reliability of the stroke database.[22] The registry enrolls patients who had a stroke and who present to the hospital within 10 days of symptom onset. Study protocols were approved by the institutional review boards of all participating hospitals. Patients who signed the informed consent obtained follow-up 3 months after stroke onset during outpatient clinic visits and/or a telephone interview conducted by trained nurses who served as stroke case managers. Patients were excluded if they were aged <18 years, had a final diagnosis involving a condition other than a stroke, or were lost to follow-up. For patients who had multiple admissions because of a stroke, only the first stroke admission was included for analysis. In the present study, we retrieved the TSR registration data recorded between August 1, 2006 and August 31, 2013 that contained a total of 83 666 patients who had a stroke.

Data Collection and Measurements

Patient characteristics relevant to acute stroke, including stroke type, neurological deficit severity defined by the National Institute of Health Stroke Scale (NIHSS), systolic and diastolic BP upon admission, medical history, pre-existing comorbidities, and demographic data, were collected according to a predefined system. The definition of AIS in the TSR was acute onset of neurological deficit with signs or symptoms persisting longer than 24 hours with or without acute ischemic lesion(s) observed on brain computed tomogram or magnetic resonance imaging scans. Hypertension was considered if subjects were administered antihypertensive medicine before admission, documented to have hypertension in previous clinic visits, or had an average systolic BP of ≥140 mm Hg or diastolic BP of ≥90 mm Hg. Diabetes mellitus was considered if subjects were prescribed oral hypoglycemic agents or insulin for diabetes mellitus; if diabetes mellitus was documented in previous clinic visits or hospital admissions; or if patients had fasting glucose levels of ≥126 mg/dL. Past cerebrovascular events, including a stroke or transient ischemic attack, and a history of cardiovascular diseases, including coronary artery disease, atrial fibrillation, or congestive heart failure, were confirmed based on previous medical records during admission and at clinic visits.

Ischemic stroke was classified into 5 major subtypes according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria into large artery atherosclerosis, small vessel occlusion, cardioembolism, other specific etiologies, and undetermined etiology.[23] As for the 3-month follow-up, patients were assessed upon admission and discharge, during follow-up clinic visits, or through phone calls. The main outcomes were modified Rankin Scale 3 months after stroke onset. Unfavorable outcomes were defined as a modified Rankin Scale of 3 to 6.

Admission BP was obtained by nurses when patients were transferred to wards. Before the study, all designated nurses at the participating hospitals had obtained training on standardized procedures for BP measurement and TSR data entry. After the patients had lain down for 5 minutes, a BP monitor was used to measure systolic and diastolic BP from the arms of each enrolled patient. PP was defined as systolic BP minus diastolic BP.

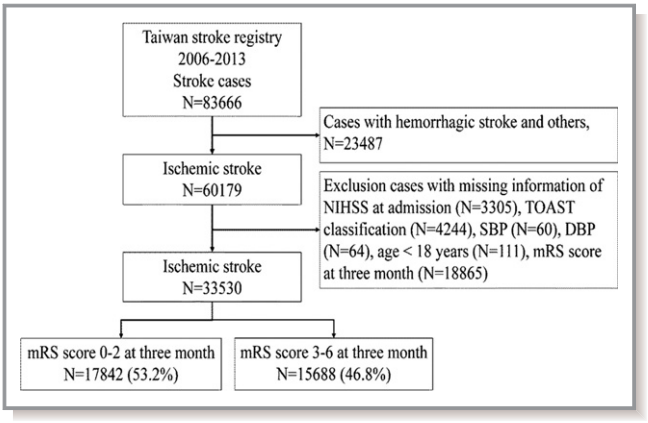

Figure 1. Flow chart of the study subjects. DBP indicates diastolic blood pressure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

Statistical Analysis

All descriptive data are expressed as number of patients, percentage, and mean value with SD. Prognostic factors and poor outcome were determined using univariable and multivariable analyses. In the univariable analysis, unfavorable outcome rates for ischemic stroke in patients with different characteristics are expressed as percentages on a histogram. Distributions in age, sex, NIHSS level, and chronic medical conditions were also assessed using a chi-square or independent *t* test. In the multivariable analysis, a logistic regression method was used to adjust for known prognostic factors with univariable *P* values of <0.10, including age, sex, hypertension, diabetes mellitus, previous stroke, coronary artery disease, atrial fibrillation, dyslipidemia, current smoker, carotid stenosis, receiving thrombolyric therapy, initial NIHSS, and continuous systolic and diastolic BP at admission. Spearman's correlation coefficient was use for the correlation between PP and systolic BP, and PP and diastolic BP. Data were analyzed using SAS software (version 9.2; SAS Institute Inc, Cary, NC). Statistical significance was considered at a *P* value of <0.05.

Results

Study Subject Demographics

Among 83 666 patients who had an acute stroke in the TSR, 23 487 had a hemorrhagic stroke; 18 865 were lost during the 3-month follow-up; and 7784 who had other specified conditions were excluded (Figure 1). The present study included 33 530 patients with AIS (mean age, 68.8±13.3 years; 59.4% males). Detailed demographic and clinical characteristics for this cohort are presented in

Table 1. Three-Month Outcome of Acute Ischemic Stroke Patients

		Modified Rankin Scale		
	Total (N=33 530)	0 to 2 (N=17 842)	3 to 6 (N=15 688)	*P* Value
Mean age, y	68.8±13.3	65.1±12.9	73.0±12.4	<0.0001
Age ≥65 y	21 425 (63.9%)	9423 (52.8%)	12 002 (76.5%)	<0.0001
Female sex	13 622 (40.6%)	6156 (34.5%)	7466 (47.6%)	<0.0001
Stroke risk factors				
Hypertension	24 640 (73.5%)	12 911 (72.4%)	11 729 (74.8%)	<0.0001
Diabetes mellitus	12 293 (36.7%)	6282 (35.2%)	6011 (38.3%)	<0.0001
Previous stroke or TIA	8782 (26.2%)	4090 (22.9%)	4692 (29.9%)	<0.0001
Coronary artery disease	4507 (13.4%)	1998 (11.2%)	2509 (16.0%)	<0.0001
Atrial fibrillation	4363 (13.0%)	1505 (8.44%)	2858 (18.2%)	<0.0001
Dyslipidemia	14 484 (43.2%)	7959 (44.6%)	6525 (41.6%)	<0.0001
Current smoker	8047 (24.0%)	4716 (26.4%)	3331 (21.2%)	<0.0001
Carotid stenosis	2937 (8.8%)	1287 (7.2%)	1650 (10.5%)	<0.0001
TOAST classification				<0.0001
Large artery atherosclerosis	9315 (27.8%)	4376 (24.5%)	4939 (31.5%)	
Small vessel occlusion	12 747 (38.0%)	8759 (49.1%)	3988 (25.4%)	
Cardioembolism	4002 (11.9%)	1571 (8.8%)	2431 (15.5%)	
Specific etiology	574 (1.7%)	257 (1.4%)	317 (2.0%)	
Undetermined etiology	6892 (20.6%)	2879 (16.1%)	4013 (25.6%)	
Characteristics on admission				
NIHSS	6.2±8.1	4.6±6.7	7.9±9.1	<0.0001
Systolic blood pressure, mm Hg	160.2±31.1	160.8±30.1	159.6±32.1	0.0005
Diastolic blood pressure, mm Hg	87.9±19.5	89.0±18.9	86.6±20.1	<0.0001
PP, mm Hg	72.4±23.8	71.8±22.8	73.0±24.8	<0.0001
Thrombolyric therapy	1070 (3.2%)	427 (2.4%)	643 (4.1%)	<0.0001

Values are number (percentage) or mean (SD). NIHSS indicates National Institutes of Health Stroke Scale; PP, pulse pressure; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

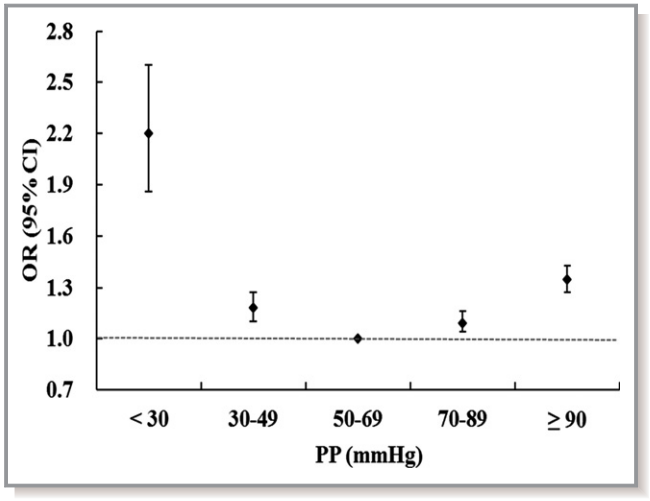

Figure 2. Relationship between admission pulse pressure (PP) and poor outcome at 3 months after acute ischemic stroke reveals a "reversed J-curve" association using logistic regression.

Table 1. Mean values for systolic BP, diastolic BP, and PP upon admission were 160.2±31.1, 87.9±19.5, and 72.4±23.8 mm Hg, respectively. By the way, PP was strongly correlated with systolic BP (r=0.78; P<0.0001), but only very weakly correlated with diastolic BP (r=0.02; P<0.0001). The percentages of mortality and unfavorable outcomes 3 months poststroke were 8.7% and 46.8%, respectively. In addition, all clinical variables in Table 1 were significant between patients who had AIS with favorable and unfavorable outcomes in the univariable analysis. Besides, we compared subjects included in the present study with those who were excluded because of missing information on 3-month outcome (n=18 865). There were similar age and stroke severity (NIHSS at admission) between included (N=33 530) and excluded (N=18 865) populations. But there were different of sex and stroke risk factors containing coronary artery disease, atrial fibrillation, dyslipidemia, and current stenosis.

Association of Admission PP With Outcome

As shown in Figure 2, there is a reverse J-curve association between PP upon admission and unfavorable outcomes. After adjusting for clinical variables, including AIS subtypes, initial NIHSS, and systolic BP and diastolic BP upon admission, PP of <50 mm Hg remained a factor for unfavorable outcomes 3 months poststroke (P<0.0001). Compared with patients with a PP of 50 to 69 mm Hg, the adjusted odds ratio for unfavorable outcomes increased gradually with 1.24 (95% CI, 1.14–1.36) for PP of 30 to 49 mm Hg and 1.85 (95% CI, 1.50–2.28) for PP of <30 mm Hg (Table 2).

Furthermore, regarding ischemic stroke subtypes based on the TOAST classification, the prognostic impact of admission PP on unfavorable outcomes 3 months poststroke are shown in Table 3. There were significantly more unfavorable outcomes if the admission PP was <30 mm Hg across all ischemic stroke subtypes, and if the admission PP of 30 to 49 mm Hg in large artery atherosclerosis and other specific and undetermined etiologies.

Discussion

The present study is a large nation-wide prospective registry of AIS patients who presented with wide-ranging BP levels that were used to derive the pathophysiological significance of PP upon admission. This study had 3 key findings. First, there is a nonlinear reverse J-curve association between the admission PP level and 3-month poststroke functional outcomes. Second, the impact of a low PP on unfavorable outcomes was persistent even after adjusting for some

Table 2. Relation Between Admission PP Levels and Poor Outcome in Acute Ischemic Stroke Patients

	mRS at 3 Months				mRS 3 to 6 vs 0 to 2		
	0 to 2 (N=17 842)		3 to 6 (N=15 688)		Odds Ratio (95% CIs)		
PP, mm Hg	n	%	n	%	Crude	Adjusted*	Adjusted†
<30	232	1.3	393	2.5	2.20 (1.86–2.60)	1.94 (1.62–2.34)	1.85 (1.50–2.28)
30 to 49	2496	14.0	2274	14.5	1.18 (1.10–1.27)	1.27 (1.17–1.37)	1.24 (1.14–1.36)
50 to 69	6106	34.2	4709	30.0	1.00	1.00	1.00
70 to 89	5353	30.0	4513	28.8	1.09 (1.04–1.16)	0.99 (0.93–1.05)	1.01 (0.93–1.09)
≥90	3655	20.5	3799	24.2	1.35 (1.27–1.43)	1.08 (1.01–1.16)	1.14 (0.99–1.31)

PP of 50 to 69 mm Hg as a reference group. mRS indicates modified Rankin Scale; PP, pulse pressure.

*Adjusted for age, sex, hypertension, diabetes mellitus, previous stroke, coronary artery disease, atrial fibrillation, dyslipidemia, current smoker, carotid stenosis, thrombolyric therapy, and National Institutes of Health Stroke Scale at admission.

†Adjusted for age, sex, hypertension, diabetes mellitus, previous stroke, coronary artery disease, atrial fibrillation, dyslipidemia, current smoker, carotid stenosis, thrombolyric therapy, National Institutes of Health Stroke Scale at admission, and systolic and diastolic blood pressure.

Table 3. Relation Between Admission PP Levels and Poor Outcome in Acute Ischemic Stroke Patients by Stroke Subtypes

	Odds Ratio (95% CIs) of mRS 3 to 6 vs 0 to 2							
	Large Artery Atherosclerosis	*P* Value	Small Vessel Occlusion	*P* Value	Cardioembolism	*P* Value	Others	*P* Value
PP, mm Hg								
<30	1.55 (1.04–2.32)	0.03	1.71 (1.12–2.60)	0.01	1.72 (1.03–2.87)	0.04	2.59 (1.71–3.92)	<0.0001
30 to 49	1.35 (1.14–1.60)	0.0006	1.14 (0.97–1.33)	0.11	1.16 (0.90–1.50)	0.25	1.38 (1.14–1.66)	0.0009
50 to 69	1.00		1.00		1.00		1.00	
70 to 89	1.12 (0.97–1.29)	0.14	1.01 (0.88–1.15)	0.90	0.82 (0.65–1.06)	0.11	0.95 (0.80–1.12)	0.52
≥90	1.18 (0.91–1.53)	0.21	1.18 (0.93–1.49)	0.18	0.92 (0.59–1.44)	0.72	1.07 (0.79–1.47)	0.66

The values are adjusted by age, sex, hypertension, diabetes mellitus, previous stroke, coronary artery disease, atrial fibrillation, dyslipidemia, current smoker, carotid stenosis, thrombolyric therapy, National Institute of Health Stroke Scale, and systolic and diastolic blood pressure at admission. mRS indicates modified Rankin Scale; PP, pulse pressure.

well-known outcome parameters, including systolic and diastolic BP. Third, the findings fit all AIS subtypes.

Previously, the relationship between early-stage PP level and stroke outcomes had been investigated only in a few studies. One study containing a total of 2178 patients who had AIS showed that admission PP was not associated with mortality during hospitalization or dependency upon discharge.[18] Another study including 339 patients with first-ever acute stroke (20.6% intracerebral hemorrhage) underwent 24-hour BP monitoring during the first 24 hours of a stroke.[19] The result showed that elevated 24-hour PP levels, but not systolic or diastolic BP, significantly associated with a high risk of long-term recurrence. Aslanyan et al analyzed 1455 cases of AIS with mostly moderate severity.[20] An elevated weighted-average PP during the first 60 hours was associated with a poor stroke outcome at 3 months. Recently, Tien et al reported on 136 ischemic stroke patients with no >50% culprit artery stenosis.[21] This study demonstrated that an elevated PP 24 hours after an emergency department visit for an acute stroke is independently associated with unfavorable 3-month poststroke outcomes. Overall, controversy exists regarding the prognostic role of PP in acute stroke from previous studies.

Theoretically, PP is determined by both cardiac components (stroke volume, heart rate, and left ventricular ejection rate) and arterial circulation properties, such as aortic distensibility and peripheral vascular tone.[24,25] Thus, an increase in PP may occur in patients with major artery stiffness, aortic regurgitation, old age, increased systolic hypertension, or decreased diastolic hypertension. In contrast, a decreased PP may be found with hypovolemia, cardiac failure, cardiac arrhythmia, valvular heart disease, an aortic dissection, or a low BP. Apparently, all the above-mentioned factors affecting PP can precipitate the occurrence of AIS; however, this may increase the risk of stroke in-evolution and poor outcomes in patients with AIS.[26]

Importantly, our study clearly demonstrated a detrimental effect on prognosis in patients with AIS who had a low PP, even after adjusting for systolic and diastolic BP. For every 20 mm Hg decrease in PP to the nadir, the hazard ratio for poor functional outcomes gradually increased to a maximum of around 200%, as compared with 50 to 69 mm Hg. These findings highlight the role of the pulsatile component of BP and the importance of maintaining adequate perfusion and cardiac function on poststroke outcomes. During the acute stage of an ischemic stroke, a low PP may reduce cerebral perfusion by disrupting the autoregulation of cerebral blood flow.[27] Furthermore, concomitant severe cardiac disease may also be an important determinant. Upon review of previous medical literature, a low PP has been shown as an indicator of decreased cardiac function and poor outcomes in patients with myocardiac infarction and a predictor of cardiovascular death in patients with mild to advanced heart failure.[28]

This study had several limitations. First, we did not have BP data that were recorded at multiple time points during the acute phase of a stroke. The present study was based on a single BP measurement upon admission. Fluctuations in BP following admission could also have a significant impact on the short-term mortality rate, but information on this important aspect was not available for the present study. Second, data on cardiac function and echocardiographic findings, including valvular dysfunction, which could have arthropometric effects on PP amplification that could impact stroke mortality, were also not available. Third, those with no consent or lost to follow-up were not included. This may likely bias the association of admission PP with outcome. Nevertheless, the novel finding of a reverse J-curve relationship between admission PP levels and poststroke outcomes drives the need for further studies.

Conclusion

The present study that was based on a large TSR cohort of ischemic stroke demonstrated that admission PP was associated with poststroke functional outcomes in patients with AIS.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Taiwan Stroke Registry Investigators:

China Medical University Hospital: Chung-Hsiang Liu (Principal Investigator), Chon-Haw Tsai, Wei-Shih Huang, Chung-Ta Lu, Tzung-Chang Tsai, Chun-Hung Tseng, Kang-Hsu Lin, Woei-Cherng Shyn, Yu-Wan Yang, Yen-Liang Liu, Der-Yang Cho, Chun-Chung Chen

National Taiwan University Hospital: Jiann-Shing Jeng (Principal Investigator), Sung-Chun Tang, Li-Kai Tsai, Shin-Joe Yeh

E-Da Hospital / I-Shou University: Shih-Pin Hsu (Principal Investigator), Han-Jung Chen, Cheng-Sen Chang, Hung-Chang Kuo, Lian-Hui Lee, Huan-Wen Tsui, Jung-Chi Tsou, Yan-Tang Wang, Yi-Cheng Tai, Kun-Chang Tsai, Yen-Wen Chen, Kan Lu, Po-Chao Liliang, Yu-Tun Tsai, Cheng-Loong Liang, Kuo-Wei Wang, Hao-Kuang Wang, Jui-Sheng Chen, Po-Yuan Chen, Cien-Leong Chye, Wei-Jie Tzeng, Pei-Hua Wu

National Cheng Kung University Hospital: Chih-Hung Chen (Principal Investigator), Pi-Shan Sung, Han-Chieh Hsieh, Hui-Chen Su

Shin Kong WHS Memorial Hospital: Hou-Chang Chiu (Principal Investigator), Li-Ming Lien, Wei-Hung Chen, Chyi-Huey Bai, Tzu-Hsuan Huang, Chi-Ieong Lau, Ya-Ying Wu, Hsu-Ling Yeh, Anna Chang

Kaohsiung Veterans General Hospital: Ching-Huang Lin (Principal Investigator), Cheng-Chang Yen

Kaohsiung Medical University Chung-Ho Memorial Hospital: Ruey-Tay Lin (Principal Investigator), Chun-Hung Chen, Gim-Thean Khor, A-Ching Chao, Hsiu-Fen Lin, Poyin Huang

Chi Mei Medical Center: Huey-Juan Lin (Principal Investigator), Der-Shin Ke, Chia-Yu Chang, Poh-Shiow Yeh, Kao-Chang Lin, Tain-Junn Cheng, Chih-Ho Chou, Chun-Ming Yang, Hsiu-Chu Shen

Chung Shan Medical University Hospital: An-Chih Chen (Principal Investigator), Shih-Jei Tsai, Tsong-Ming Lu, Sheng-Ling Kung, Mei-Ju Lee, Hsi-Hsien Chou

Show Chwan Memorial Hospital: Hsin-Yi Chi (Principal Investigator), Chou-Hsiung Pan, Po-Chi Chan, Min-Hsien Hsu, Wei-Lun Chang, Ya-Ying Wu , Zhi-Zang Huang, Hai-Ming Shoung, Yi-Chen Lo, Fu-Hwa Wang

Cheng Hsin General Hospital: Ta-Chang Lai (Principal Investigator), Jiu-Haw Yin, Chung-Jen Wang, Kai-Chen Wang, Li-Mei Chen, Jong-Chyou Denq

En Chu Kong Hospital: Yu Sun (Principal Investigator), Chien-Jung Lu, Cheng-Huai Lin, Chieh-Cheng Huang, Chang-Hsiu Liu, Hoi-Fong Chan

Far Eastern Memorial Hospital: Siu-Pak Lee (Principal Investigator)

Kuang Tien General Hospital: Ming-Hui Sun (Principal Investigator), Li-Ying Ke

Taichung Veterans General Hospital: Po-Lin Chen (Principal Investigator), Yu-Shan Lee

Ditmanson Medical Foundation Chia-Yi Christian Hospital: Sheng-Feng Sung (Principal Investigator), Cheung-Ter Ong, Chi-Shun Wu, Yung-Chu Hsu, Yu-Hsiang Su, Ling-Chien

Hung

Tri-Service General Hospital: Jiunn-Tay Lee (Principal Investigator), Jiann-Chyun Lin, Yaw-Don Hsu, Jong-Chyou Denq, Giia-Sheun Peng, Chang-Hung Hsu, Chun-Chieh Lin, Che-Hung Yen, Chun-An Cheng, Yueh-Feng Sung, Yuan-Liang Chen, Ming-Tung Lien, Chung-Hsing Chou, Chia-Chen Liu, Fu-Chi Yang, Yi-ChungWu, An-Chen Tso, Yu- Hua Lai, Chun-I Chiang, Chia-Kuang Tsai, Meng-Ta Liu, Ying-Che Lin, Yu-Chuan Hsu

Cathay General Hospital: Tsuey-Ru Chiang (Principal Investigator), Mei-Ching Lee, Pai-Hao Huang, Sian-King Lie, Pin-Wen Liao, Jen-Tse Chen

Changhua Christian Hospital: Mu-Chien Sun (Principal Investigator), Tien-Pao Lai, Wei-Liang Chen, Yen-Chun Chen, Ta-Cheng Chen, Wen-Fu Wang, Kwo-Whei Lee, Chen-Shu Chang, Chien-Hsu Lai, Siao-Ya Shih, Chieh-Sen Chuang, Yen-Yu Chen, Chien-Min Chen

Taipei Tzuchi Hospital, Buddhist Tzuchi Medical Foundation: Shinn-Kuang Lin (Principal Investigator), Yu-Chin Su, Cheng-Lun Hsiao, Fu-Yi Yang, Chih-Yang Liu, Han-Lin Chiang, Ser-Chen Fu

Min Sheng General Hospital: Chun-Yuan Chang (Principal Investigator), I-sheng Lin, Chung-Hsien Chien, Yang-Chuang Chang

Lin Shin Hospital: Ping-Kun Chen (Principal Investigator), Pai-Yi Chiu

National Taiwan University Hospital Yunlin Branch: Yu-Jen Hsiao (Principal Investigator), Chen-Wen Fang

Landseed Hospital: Yu-Wei Chen (Principal Investigator), Kuo-Ying Lee, Yun-Yu Lin, Chen-Hua Li, Hui-Fen Tsai, Chuan-Fa Hsieh, Chih-Dong Yang, Shiumn-Jen Liaw, How-Chin Liao

Cheng Ching General Hospital: Shoou-Jeng Yeh (Principal Investigator), Ling-Li Wu, Liang-Po Hsieh, Yong-Hui Lee, Chung-Wen Chen

China Medical University Beigang Hospital: Chih-Shan Hsu (Principal Investigator), Ye-Jian-Jhih, Hao-Yu Zhuang, Yan-Hong Pan, Shin-An Shih

Taipei Medical University -Wan Fang Hospital: Chin-I Chen (Principal Investigator), Jia-Ying Sung, , Hsing-Yu Weng, Hao-Wen Teng, Jing-Er Lee, Chih-Shan Huang, Shu-Ping Chao

Taipei Medical University Hospital: Rey-Yue Yuan (Principal Investigator), Jau- Jiuan Sheu, Jia-Ming Yu, Chun-Sum Ho, Ting-Chun Lin

Kuang Tien General Hospital Dajia Division: Shih-Chieh Yu (Principal Investigator)

Changhua Christian Hospital Yunlin Branch: Jiunn-Rong Chen (Principal Investigator), Song-Yen Tsai

Chang Bing Show Chwan Memorial Hospital: Cheng-Yu Wei (Principal Investigator), Tzu-Hsuan Huang, Chao-Nan Yang, Chao-Hsien Hung, Ian Shih

Lotung Poh Ai Hospital: Hung-Pin Tseng (Principal Investigator), Chin-Hsiung Liu, Chun-Liang Lin, Hung-Chih Lin, Pi-Tzu Chen

Taipei Medical University-Shuang Ho Hospital: Chaur-Jong Hu (Principal Investigator), Nai-Fang Chi, Lung Chan

Taipei Veterans General Hospital: Chang-Ming Chern (Principal Investigator), Chun-Jen Lin, Shuu-Jiun Wang, Li-Chi Hsu, Wen-Jang Wong, I-Hui Lee, Der-Jen Yen, Ching-Piao Tsai, Shang-Yeong Kwan, Bing-Wen Soong, Shih-Pin Chen, Kwong-Kum Liao, Kung-Ping Lin, Chien Chen, Din-E Shan, Jong-Ling Fuh, Pei-Ning Wang, Yi-Chung Lee, Yu-Hsiang Yu, Hui-Chi Huang, Jui-Yao Tsai

Chi Mei Medical Center, Liouying: Ming-Hsiu Wu (Principal Investigator), Shi-Cheng Chen, Szu-Yi Chiang, Chiung-Yao Wang

Buddhist Dalin Tzu Chi General Hospital: Ming-Chin Hsu (Principal Investigator)

St. MARTIN DE PORRES HOSPITAL: Chien-Chung Chen (Principal Investigator), Po-Yen Yeh, Yu-Tai Tsai, Ko-Yi Wang

Sin-Lau Hospital, Tainan, the Presbyterian Church in Taiwan: Tsang-Shan Chen (Principal Investigator)

Cardinal Tien Hospital: Ping-Keung Yip (Principal Investigator), Vinchi Wang, Kaw-Chen Wang, Chung-Fen Tsai, Chao-Ching Chen, Chih-Hao Chen, Yi-Chien Liu, Shao-Yuan Chen, Zi-Hao Zhao, Zhi-Peng Wei

Yumin Medical Corporation Yumin Hospital: Shey-Lin Wu (Principal Investigator)

Kaohsiung Municipal Hsiao-kang Hospital: Ching-Kuan Liu (Principal Investigator)

Wei Gong Memorial Hospital: Ryh-Huei Lin (Principal Investigator), Ching-Hua Chu

Taipei City Hospital Ren Ai Branch: Sui-Hing Yan (Principal Investigator), Yi-Chun Lin, Pei-Yun Chen, Sheng-Huang Hsiao

National Taiwan University Hospital Hsin-Chu Branch: Bak-Sau Yip (Principal Investigator), Pei-Chun Tsai, Ping-Chen Chou, Tsam-Ming Kuo, Yi-Chen Lee, Yi-Pin Chiu, Kun-Chang Tsai

Taichung Hospital Department of Health: Yi-Sheng Liao (Principal Investigator)

Tainan Municipal An-Nan Hospital-China Medical University: Ming-Jun Tsai (Principal Investigator), Hsin-Yi Kao

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