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REVIEW PAPER

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Hypertension and stroke in Asia: A comprehensive review from HOPE Asia

Yuda Turana MD, PhD[1] | Jeslyn Tengkawan MD[1] | Yook Chin Chia MBBS, FRCP[2,3] | Michael Nathaniel MD[1] | Ji-Guang Wang MD, PhD[4] | Apichard Sukonthasarn MD[5] | Chen-Huan Chen MD[6] | Huynh Van Minh MD, PhD[7] | Peera Buranakitjaroen MD, MSc, DPhil[8] | Jinho Shin MD[9] | Saulat Siddique MBBS, MRCP, FRCP[10] | Jennifer M. Nailes MD, MSPH[11] | Sungha Park MD, PhD[12] | Boon Wee Teo MB, BCh[13,14] | Jorge Sison MD[15] | Arieska Ann Soenarta MD[16] | Satoshi Hoshide MD, PhD[17] | Jam Chin Tay MBBS, FAMS[18] | Guru Prasad Sogunuru MD, DM[19,20] | Yuqing Zhang MD, MSPH[21] | Narsingh Verma MD[22] | Tzung-Dau Wang MD, PhD[23] | Kazuomi Kario MD, PhD[17] | on behalf of the HOPE Asia Network

[1]School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia

[2]Department of Medical Sciences, School of Healthcare and Medical Sciences, Sunway University, Bandar Sunway, Malaysia

[3]Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[4]Department of Hypertension, Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, Shanghai Key Laboratory of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

[5]Cardiology Division, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

[6]Department of Medicine, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan

[7]Department of Cardiology, Hue University Hospital, Hue University, Hue City, Vietnam

[8]Division of Hypertension, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[9]Faculty of Cardiology Service, Hanyang University Medical Center, Seoul, Korea

[10]Punjab Medical Center, Lahore, Pakistan

[11]University of the East Ramon Magsaysay Memorial Medical Center Inc., Quezon City, Philippines

[12]Division of Cardiology, Cardiovascular Hospital, Yonsei Health System, Seoul, Korea

[13]Division of Nephrology, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore City, Singapore

[14]Division of Nephrology, Department of Medicine, National University Health System, Singapore City, Singapore

[15]Section of Cardiology, Department of Medicine, Medical Center Manila, Manila, Philippines

[16]Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia-National Cardiovascular Center, Harapan Kita, Jakarta, Indonesia

[17]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

[18]Department of General Medicine, Tan Tock Seng Hospital, Singapore, Singapore

[19]MIOT International Hospital, Chennai, India

[20]College of Medical Sciences, Kathmandu University, Bharatpur, Nepal

[21]Divisions of Hypertension and Heart Failure, Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[22]Department of Physiology, King George's Medical University, Lucknow, India

[23]Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei City, Taiwan

Correspondence
Yuda Turana, MD, PhD, Department of Neurology, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Pluit Raya 2, Jakarta 14440, Indonesia.
Email: yuda.turana@atmajaya.ac.id

Kazuomi Kario, MD, PhD, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine (JMU), JMU Center of Excellence, Cardiovascular Research and Development (JCARD), Hypertension Cardiovascular Outcome Prevention and Evidence (HOPE) Asia Network/World Hypertension League (WHL), 3311-1 Yakushiji, Shimotsuke, Tochigi 329–0498, Japan.
Email: kkario@jichi.ac.jp

Abstract

Stroke is the primary cause of disability and vascular death worldwide, including Asia. Asian characteristics that differ from the West lead to higher stroke incidence. Stroke epidemiology studies in Asia have shown varying levels of mortality, incidence, prevalence, and burden of disease. Hypertension is the most prevalent risk factor found in Asia. Besides ethnicity that is associated with stroke incidence, both systolic blood pressure, diastolic blood pressure, and blood pressure variability are positively correlated with stroke incidence. Post-stroke cognitive impairment is one of the sequelae that affect one-third of stroke survivors and has become a significant public health concern that is often neglected despite its increasing prevalence. Therefore, it is very important to prevent recurrence by treating stroke optimally and effectively. Increasing awareness and treatment adherence to hypertension, the leading risk factor for stroke, became the main goal in several countries in Asia.

1 | INTRODUCTION

Epidemiology transition has become the leading cause of the substantial increase in the disease burden of non-communicable diseases, such as increased stroke as the primary cause of disability and vascular death worldwide, including Asia.[1] Stroke impacts of decreasing quality of life and its higher average mortality rate compared to Europe, America, and Australia make it a serious problem in Asia.[2,3] More than half of the world population lives in Asia, with the majority in developing countries. 70% stroke incidence and 87% stroke-related deaths happened in low- and lower-middle-income countries.[2,3]

The economic burden of stroke is high and variable in Asia.[4] Average cost per capita for patients with high-risk stroke in 2010 was estimated to reach $ 517.8 per year in China.[5] A review in 2019 that compared stroke cost in Indonesia, Malaysia, and Singapore showed variable cost that was $ 135.55 per day care (3.88% of GDP per capita), $ 227.53 per day care (2.11% of GDP per capita), and $ 366.76 per day care (0.65% of GDP per capita), respectively.[6] The considerable amount of economic burden makes it very necessary for stroke to be given more attention and for more effective health care planning, especially in the primary and secondary prevention, and early detection of the disease. The economic impact of stroke and the association between stroke and blood pressure lead to the importance of knowing more about the relationship between stroke and hypertension in Asia.[7]

Asian characteristics that differ from the West lead to higher stroke incidence, which is even higher than coronary artery disease in some

TABLE 1 Prevalence of stroke, its risk factors, disability-adjusted life year (DALY), and mortality rate of HOPE Asia Network countries

Country	Stroke prevalence	Hypertension prevalence, %	Diabetes mellitus prevalence, %	Smoking, %	Dyslipidemia, %
China	1114.8/100 000 persons (2017)	23.2 (2018)	11.6 (2013)	26.6 (2019)	39.9 (2018)
India	44.29 to 559/100 000 persons (2017)	24 (2015)	8 (2016)	11 (2016)	79 (2014)
Indonesia	10.9% (2018)	34.1 (2018)	10.9 (2018)	29.3 (2018)	35.9 (2013)
Japan	166 per 100 000 person-years (2011)	50.0 (2018)	18.7 (men) 9.3 (women) (2010)	17.8 (2018)	12.2 (men) 21.1 (women) (2018)
Korea	1.71% (2014)	29.1 (2016)	14.4 (2019)	43.1 (men) 5.7 (women) (2019)	40.5 (2019)
Malaysia	11.3% (2017)	30.3 (2015)	17.5 (2015)	22.8 (2015)	47.7 (2016)
Pakistan	4.8% (2006)	46.2 (2017)	26.3 (2017)	14.2 (2017)	39.3 (2017)
Philippines	6.6% (2013)	28 (2013)	5.8 (2016)	20.7 (2018)	46.9 (2013)
Singapore	3.7% (2006)	21.5 (2017)	8.6 (2017)	12 (2017)	33.6 (2017)
Taiwan	6.8% (2016)	25.4 (2016)	15.1 (2016)	14.3 (2016)	36.7 (2016)
Thailand	1.3% (2014)	24.7 (2014)	8.9 (2014)	19.5 (2014)	16.4 (2014)
Vietnam	15.5% (2016)	28.7 (2017)	5.5 (2017)	13.8 (2017)	20.2 (2015)

Asian countries. In this paper, we will discuss the epidemiology of stroke in Asia, specifically countries that are members of the HOPE Asia Network, stroke risk factors, and the role of hypertension in stroke incidence in Asia.

2 | STROKE EPIDEMIOLOGY IN ASIA

Stroke epidemiology studies in Asia have shown varying levels of mortality, incidence, prevalence, and burden of disease. Mortality rate and stroke burden range from the lowest in Japan 43.3 per 100 000 person-years (burden 706.6/100 000 people) and Singapore 47.9 per 100 000 person-years (burden 804.2/100 000 people) to the highest in Indonesia 193.3 per 100 000 person-years (burden 3382.2/100 000 people) and Mongolia 222.6 per 100 000 person-years (burden 4409.8/100 000 people), with hypertension, diabetes mellitus, and smoking as the main risk factors.[8]

The overall incidence of stroke in Asia varied between 116 and 483/100 000 per year.[9] Apart from vast differences between countries, stroke incidence also showed high variation within countries, for instance, the northern area of China showed higher incidence than the southern area, being two times higher in stroke belt area, which is suspected to occur due to high rates of hypertension and obesity in the area.[10]

Moreover, stroke incidence in the younger population has increased globally, with higher consequences physically, psychologically, and socially. Furthermore, other varying risk factors, such as air pollution, obesity, physical inactivity, alcohol consumption, and dyslipidemia, have also increased in the younger population.[11–13] In addition to the younger average age of stroke onset and higher incidence rates, the shift had also changed toward hemorrhagic stroke, which has higher fatality and disability, leading to DALY loss rates up to more than 10-fold higher than the least affected countries.[14] The prevalence of stroke, its risk factors, disability-adjusted life year (DALY), and mortality rate of HOPE Asia Network Countries are shown in Table 1.

3 | STROKE RISK FACTOR IN ASIA

As the second leading cause of death globally, with its significant impacts affecting other areas of life, for example, economically, socially, physically, and psychologically, existing and known risk factors should be thoroughly discussed in the strategy of reducing strokes, especially as 74.2% of the risk is attributable to modifiable risk factors related to lifestyle.[12,78,79]

A previous study that analyzed ethnicity with blood pressure and stroke showed that South Asians had a higher prevalence of dyslipidemia, diabetes mellitus, and central obesity, and twofold higher risk to suffer from stroke than the Europeans.[78] The risk between different ethnicity was also observed in Singapore where Malay people had a lower risk of stroke (OR = 0.4) than the Chinese people.[80]

Hypertension is the most prevalent risk factor found in Asia.[8,9] A study in Sleman District, Indonesia, showed the same pattern where increased age, hypertension, and diabetes mellitus were associated with stroke incidence. It was also observed that stroke risk goes up to almost two times for every additional 10 years lived.[79] A logistic regression analysis comparing stroke risk factors in Sichuan, China, showed low-density lipoprotein cholesterol being the highest risk factor (OR = 2.600), followed by triglycerides (OR = 1.315) and body mass index (OR = 0.217).[81] In Uzbekistan, dominant risk factors after hypertension are smoking and physical inactivity.[2]

Obesity, %	Physical inactivity, %	DALY lost/100 000 people	Stroke mortality/100 000 person-years	Reference
11.9 (2018)	N/A	2,342.3 (2017)	128.2 (2017)	15–21
4 (2016)	33 (2016)	1591.7 (2017)	71.5 (2017)	22–26
21.8 (2018)	33.5 (2018)	3481 (2017)	186.3 (2017)	27–31
32.2 (men) 21.9 (women) (2018)	68.2 (men) 74.5 (women) (2018)	638.9 (2017)	33.6 (2017)	32–35
40.7 (2018)	49.2 (2019)	703 (2013)	34.9 (2017)	36–42
17.7 (2015)	66.5 (2015)	1686.1 (2017)	71.5 (2017)	43–45
43.9 (2017)	58.5 (2016)	2534 (2017)	100.5 (2017)	46–49
31.1 (2013)	40.6 (2018)	2596.8 (2017)	134 0.7 (2017)	50–58
8.7 (2017)	19 (2017)	568.1 (2017)	14.1 (2017)	59–62
52.1 (men) 37.4 (women) (2019)	64.4 (men) 69.3 (women) (2020)	872.3 (2017)	30.8 (2012)	63–67
37.5 (2014)	19.5 (2014)	1128.1 (2017)	62.5 (2017)	69–71
15.6 (2015)	28.1 (2015)	2619.5 (2017)	115.4 (2017)	72–77

Increasing age, no education, and history of smoking were associated with stroke prevalence in Singapore. This logistic regression showed that smoking increased stroke incidence two times higher in 85-year-old group, and no education increased stroke incidence three times.[80]

Other risk factor that also affects the incidence of stroke include air pollution, which, though modifiable, is challenging to avoid.[1,12,82] Main pollutants are particulate matters ($PM_{2.5}$) that could penetrate lung alveoli and brain cells, and gaseous pollutants, for example, ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO).[83] Studies that calculated $PM_{2.5}$ in 79 countries found that an increase in global population-weighted $PM_{2.5}$ of 20.4% was found in South Asia, South-East Asia, and China, with the highest concentration of 194 $\mu g/m^3$ found in Shijiazhuang in China.[84] A meta-analysis, conducted by Pranata et al[85], showed how $PM_{2.5}$ was associated with increased risk of stroke and hypertension. This naturally encourages policymakers and public health practitioners in Asia to be aware of the danger of environmental air pollution and find ways to improve air quality.[86]

4 | HYPERTENSION AS THE MAIN RISK FACTOR FOR STROKE

In the previous part, we have discussed that hypertension is the main risk factor for stroke. Besides ethnicity that is associated with stroke incidence in South Asia, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are positively correlated with stroke incidence unlike west countries where only SBP was correlated.[78]

In the global May Measurement Month (MMM) 2018 report after age and sex standardization, East Asia had the lowest blood pressure average (117.0/75.4 mm Hg). In contrast, South Asia had the highest average (124.6/78.1 mm Hg).[87] MMM 2017 study in Indonesia alone showed 34.5% of respondents with uncontrolled hypertension, while 20.0% were newly diagnosed.[88] This number is almost similar to the national prevalence (34.1%), with a higher proportion in females (32.9% vs. 28.7%) and urban area (31.7% vs. 30.2%).[27] A study conducted in Sleman and Bogor districts, Indonesia, showed a significant association between hypertension and stroke ($P < .001$).[79,89] 73.91% of stroke patients had hypertension. The CSPPT (China Stroke Primary Prevention Trial) proved that the stroke risk was lowest in patients with the average SBP level of 120-130 mm Hg, and the risk increased in those with SBP <120 mm Hg and those with SBP 130-135 mm Hg (J-shaped curve).[90] Atherosclerotic plaques, smooth muscle cell remodeling, cerebral blood flow reduction, and arterial baroreflex dysfunction, which were caused by hypertension, could lead to cerebrovascular diseases, including stroke.[79] It is also found that South Asians had poorer cerebral autoregulation than Europeans, which increased their vulnerability to stroke by putting the brain at risk of ischemia and developing hemorrhagic transformation.[78,91,92]

Overweight and obesity in women and higher waist circumference (a measure of central obesity) in men were significantly associated with uncontrolled hypertension. Other lifestyle factors, such as high salt intake and physical inactivity, were also correlated with higher blood pressure.[93] Excess of sodium intake, associated with fluid retention and increased blood pressure, is also considered as a specific characteristic of hypertension disease in Asia.[94,95] A meta-analysis showed that 5 g per day higher salt intake could increase 23% risk of stroke which became our biggest concern as average daily salt intake in Asia is higher than 12 g.[95,96]

Sub-analysis of the countries that took part in the HBPM Asia BP@Home study showed that Japan and Philippines had the most participants with well-controlled hypertension (64% and 62%), while Indonesia has the least well-controlled participants (23%).[50,97,98] However, HOPE Asia Network has stated in many prior papers on how important it is to detect hypertension and its phenotypes early, including masked uncontrolled hypertension and sustained uncontrolled hypertension, by releasing a guide to home blood pressure monitoring (HBPM) and/or ambulatory blood pressure monitoring (ABPM).[99,100]

5 | BLOOD PRESSURE VARIABILITY AND STROKE

Prior studies showed that hypertension management goal has shifted to prevent end-organ damage by controlling 24-hr blood pressure. Blood pressure variability (BPV), including early morning blood pressure surge (EMBS), could result in the increment of the left ventricular mass index and carotid intima-media thickness, leading to a higher risk of cerebrovascular events.[101] 24-hour blood pressure and BPV were also associated with worse functional outcome after stroke and silent cerebral diseases, including silent cerebral infarction.[102,103] Moreover, high BPV in ischemic stroke was associated with increased 90-day mortality risk.[104]

As ABPM database is widely available nowadays, studies have shown that nocturnal hypertension and nondipper/riser patterns of blood pressure at night are associated with vascular damage, increasing left ventricular preload and afterload, which could trigger stroke.[105,106]

As discussed before, Asians had a higher incidence of stroke and its risk factors, which also include higher morning and nocturnal blood pressure than the Western population. High morning surge could lead to arterial stiffness and a higher risk of cerebrovascular events, including stroke.[101,107] Furthermore, morning hypertension is also known to be the most influential independent risk factor for stroke.[108] It was shown that people who had morning blood pressure surge 55 mm Hg or more had a 2.7 times higher risk of stroke than those who had lower than 55 mm Hg.[101] Therefore, ABPM is also strongly recommended, to measure 24-hour blood pressure, including nocturnal blood pressure, diurnal variations, and morning surge.[109]

6 | POST-STROKE DEMENTIA

Post-stroke cognitive impairment (PSCI) or post-stroke dementia (PSD) is one of the sequelae that affect one-third of stroke survivors

and has become a significant public health concern that is often neglected despite its increasing prevalence.[110,111] Its consequences are often worse than the physical impairment, which tends to improve over time.[111] The prevalence varies between 20% and 80% depending on both the ethnicity and diagnostic criteria.[112] The prevalence of PSD in Asia ranges from 20% in India to 69.8% in South Korea.[112] In China, two studies showed prevalence of 37.1% in Chongqing and 41.8% in Changsha.[112] While Singapore and Hong Kong had a prevalence of 44% (6-month follow-up) and 21.8% (3-months follow-up), respectively, as assessed by MMSE.[112] Important risk factors for PSD related to stroke including index stroke factors (hemorrhagic, recurrent, and location), post-stroke factors (infection, delirium, and early seizures), and neuroimaging factors (presence of atrophy and small-vessel disease).[111] Biomarkers have also been used to predict and detect PSD. These include cerebrospinal fluid and serum biomarkers, genetic markers, peripheral microRNA, inflammatory mediators, and neuroimaging measures.[111] PSCI with no dementia is also known to interfere with the quality of life in stroke patients.[113] This great impact reminds us that it is very important to prevent recurrence and increasing severity by treating stroke optimally and effectively.[111]

7 | STROKE AWARENESS AND SPECIFIC CONCERNS IN ASIA

Although healthy lifestyle campaigns, inclusive of reduction in salt intake and increase in physical activity, and infographics regarding stroke and its risk factors have been increased, awareness of hypertension in Indonesia is still poor.[98] Poor awareness that leads to poor blood pressure control could explain why few adults are effectively treated.[93] Also, despite the knowledge of having hypertension, only 23% had well-controlled blood pressure in Indonesia.[98]

Using the 2017 AHA/ACC classification threshold, home blood pressure monitoring (HBPM) study in Asia found that only 26% of patients were well-controlled, compared with 40% of sustained hypertension, 6% of masked morning hypertension, and 28% of white-coat hypertension.[114] Availability of ABPM and HBPM could improve control and help early detection of uncontrolled hypertension.[109] Previous studies summarized how awareness, treatment, and control rates of traditional risk factors for stroke improved in China, Japan, Mongolia, Korea, and Taiwan compared with decades ago. However, these numbers are still considered low compared with Western countries.[12]

Increasing awareness and treatment adherence to hypertension, the leading risk factor for stroke, became the main goal in several countries in Asia.[50,98,115,116] Generally, Yap *et al* described that treatment adherence in elderly depends on patient factors, medication factors, health care provider factors, and health care system factors.[117] Expensive and unaffordable medicine price, multiple number of doses, and medicines also complicate and reduce treatment adherence in multi-ethnic Asian population.[118] In Pakistan, it was found that, other than lack of literacy and education, there was also a shortage of health care workers.[119] Study in Malaysia showed that more than 60% of participants' overall knowledge of stroke symptoms and actions to be taken was good, higher than India and Oman.[120] Educational program for stroke that is readily available and global campaigns such as MMM, which was very useful in screening hypertension, should continue, to increase not only knowledge but also awareness on how it is vital to keep the blood pressure controlled to prevent stroke incidence.[87,88] A trial to prevent stroke occurrence from the CSPPT in Chinese hypertensive population by consuming folic acid may be considered as an additional primary prevention.[121,122] Furthermore, it is also essential to obtain information from patients or their family about their perceptions on stroke management and find out factors that might be associated with medication compliance.[123,124] However, the role of ethnicity and culture in stroke management is still limited, and we suggest to account these factors for future research.

8 | SUMMARY

Stroke epidemiology studies in Asia have shown varying levels of mortality, incidence, prevalence, and burden of disease. Besides ethnicity that is associated with stroke incidence, both systolic blood pressure, diastolic blood pressure, and blood pressure variability are positively correlated with stroke incidence. Post-stroke cognitive impairment is one of the sequelae that affect one-third of stroke survivors and has become a significant public health concern that is often neglected despite its increasing prevalence. The application in clinical practice includes primary prevention by emphasizing patients' HBPM practice—if applicable—and secondary prevention through recurrence prevention by treating stroke optimally and effectively. Solving stroke and its greatest risk factor, hypertension, increasing awareness, and treatment adherence to hypertension should be on top of public health priority considering its high burden of disease in several countries in Asia.

CONFLICT OF INTEREST

S Park has received research grants and honoraria from Pfizer. S Siddique has received honoraria from Bayer, Pfizer, ICI, and Servier; and travel, accommodation, and conference registration support from Hilton Pharma, Atco Pharmaceutical, Highnoon Laboratories, Horizon Pharma, ICI, and Pfizer. YC Chia has received honoraria and sponsorship to attend conferences and CME seminars from Abbott, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Menarini, Merck Sharp & Dohme, Novartis, Orient Europharma, Pfizer, and Sanofi; and a research grant from Pfizer. Jinho J Shin has received lecture honoraria from Pfizer Inc, Hanmi Pharm. Co. Ltd., Yuhan Co. Ltd., Boryung Pharmaceutical Co. Ltd, and Menarini; consulting fees from Hanmi Pharm. Co. Ltd.; and research grants from Sanofi Pharm. and Hanmi Pharm. Co. Ltd. CH Chen has received honoraria as a member of a speaker's bureau for Pfizer. J Sison has received honoraria from Pfizer, AstraZeneca, Boehringer Ingelheim, and Novartis. GP Sogunuru has received a research grant related to hypertension monitoring and treatment from Pfizer. JC Tay has received advisory board and consultant honoraria from Pfizer. JG Wang has received research grants

from Bayer, Pfizer, and Phillips; and lecture and consulting fees from Bayer, Daiichi Sankyo, Merck Sharp & Dohme, Pfizer, Sanofi, and Servier. Y Zhang has received research grants from Bayer, Novartis, and Shuanghe; and lecture fees from Bayer, Daiichi Sankyo, Novartis, Pfizer, Sanofi, Servier, and Takeda. All other authors report no potential conflicts of interest in relation to this article.

AUTHOR CONTRIBUTIONS

Yuda Turana and Kazuomi Kario conceived and designed the study. Yuda Turana, Jeslyn Tengkawan, Yook Chin Chia, and Kazuomi Kario approved the final version of the manuscript. Yuda Turana, Jeslyn Tengkawan, Yook Chin Chia, Michael Nathaniel, Ji-Guang Wang, Apichard Sukonthasarn, Chen-Huan Chen, Huynh Van Minh, Peera Buranakitjaroen, Jinho Shin, Saulat Siddique, Jennifer M. Nailes, Sungha Park, Boon Wee Teo, Jorge Sison, Jam Chin Tay, Guru Prasad Sogunuru, Yuqing Zhang, Narsingh Verma, Tzung-Dau Wang, and Kazuomi Kario analyzed the data and/or interpreted the data, and drafted the article and/or critically revised the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Yuda Turana https://orcid.org/0000-0003-4527-0285
Jeslyn Tengkawan https://orcid.org/0000-0002-8644-1872
Yook Chin Chia https://orcid.org/0000-0003-1995-0359
Chen-Huan Chen https://orcid.org/0000-0002-9262-0287
Huynh Van Minh https://orcid.org/0000-0003-4273-4187
Jinho Shin https://orcid.org/0000-0001-6706-6504
Saulat Siddique https://orcid.org/0000-0003-1294-0430
Sungha Park https://orcid.org/0000-0001-5362-478X
Boon Wee Teo https://orcid.org/0000-0002-4911-8507
Satoshi Hoshide https://orcid.org/0000-0001-7541-5751
Jam Chin Tay https://orcid.org/0000-0001-7657-4383
Yuqing Zhang https://orcid.org/0000-0001-8142-8305
Narsingh Verma https://orcid.org/0000-0003-0348-7419
Tzung-Dau Wang https://orcid.org/0000-0002-7180-3607
Kazuomi Kario https://orcid.org/0000-0002-8251-4480

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