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Review

Brugada Syndrome within Asian Populations: State-of-the-Art Review

Muzamil Khawaja [1], Yusuf Kamran Qadeer [2], Rehma Siddiqui [3], Mihail G. Chelu [4], Noppawit Aiumtrakul [5], June K. Pickett [2,5], Ramon Brugada [6,7], Josep Brugada [8,9,10], Pedro Brugada [11,12,13] and Chayakrit Krittanawong [14,*]

1 Cardiology Division, Emory University School of Medicine, Atlanta, GA 45267, USA
2 Michael E. DeBakey VA Medical Center, Section of Cardiology, Baylor College of Medicine, Houston, TX 77030, USA
3 Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA
4 Cardiology, Texas Heart Institute, Houston, TX 77030, USA
5 Department of Medicine, University of Hawai'i at Mānoa, Honolulu, HI 96822, USA
6 Cardiology, Cardiac Genetics Clinical Unit, Hospital Universitari Josep Trueta, Hospital Santa Caterina, 17007 Girona, Spain
7 Cardiovascular Genetics Center and Clinical Diagnostic Laboratory, Institut d'Investigació Biomèdica Girona-IdIBGi, 17190 Salt, Spain
8 Cardiovascular Institute, Hospital Clínic, 08036 Barcelona, Spain
9 Pediatric Arrhythmia Unit, Hospital Sant Joan de Déu, 08950 Barcelona, Spain
10 Department of Medicine, University of Barcelona, 08036 Barcelona, Spain
11 Cardiovascular Division, Free University of Brussels (UZ Brussel) VUB, B-1050 Brussels, Belgium
12 Medical Centre Prof. Brugada, B-9300 Aalst, Belgium
13 Arrhythmia Unit, Helicopteros Sanitarios Hospital (HSH), Puerto Banús, 29603 Marbella, Spain
14 Cardiology Division, NYU Langone Health and NYU School of Medicine, New York, NY 10016, USA
* Correspondence: chayakrit.krittanawong@nyulangone.org

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Abstract: Brugada syndrome (BrS) is an inherited cardiac channelopathy with variable expressivity that can lead to sudden cardiac arrest (SCA). Studies worldwide suggest that BrS and Brugada pattern (BrP) have low prevalences in general. However, studies also note that BrS is most prevalent among certain Asian populations. Among the different global regions, the highest prevalence is believed to be in Southeast Asia, followed by the Middle East, South Asia, East Asia, Europe, and North America. It is not only important to recognize such varying degrees of BrS prevalence within Asia but also to understand that there may be significant differences in terms of presenting symptoms, occult risk factors, and the impact on clinical outcomes. The importance of identifying such differences lies in the necessity to develop improved risk assessment strategies to guide secondary prevention and treatment for these patients. Specifically, the decision to pursue placement of an implantable cardiac defibrillator (ICD) can be lifesaving for high-risk BrS patients. However, there remains a significant lack of consensus on how to best risk stratify BrS patients. While the current guidelines recommend ICD implantation in patients with spontaneous Type 1 ECG pattern BrS who present with syncope, there may still exist additional clinical factors that may serve as better predictors or facilitate more refined risk stratification before malignant arrhythmias occur. This carries huge relevance given that BrS patients often do not have any preceding symptoms prior to SCA. This review seeks to delineate the differences in BrS presentation and prevalence within the Asian continent in the hope of identifying potential risk factors to guide better prognostication and management of BrS patients in the future.

Keywords: Brugada syndrome; Brugada pattern; Asia; sudden cardiac death; risk stratification

1. Introduction

Brugada Syndrome (BrS) is an autosomal dominant cardiac disorder that can lead to sudden cardiac death. It was first described by Pedro and Josep Brugada in 1992 as an electrocardiographic pattern of a right bundle branch block and ST elevations in the right precordial leads [1]. However, the definition of BrS has changed significantly over the last three decades due to frequent criticism over inconsistencies with an accurate diagnosis. This is especially clinically relevant since individuals with BrS often display no symptoms and have no family history of sudden cardiac death but may still be at high risk for malignant arrhythmias. In fact, asymptomatic people comprise about 63% of newly diagnosed Brugada patients [2]. If present, however, the typical clinical presentation is syncope or resuscitated sudden death in the third or fourth decade of life due to polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) [2]. Pre-syncopal symptoms usually occur at night or at rest, especially after a large meal and may even be precipitated by a fever in younger populations. However, there is no current consensus on how to best risk stratify asymptomatic or mildly symptomatic patients. In addition, it is unknown what role the age of the patient may play on the overall risk for malignant arrhythmia.

The etiology of the ECG changes and arrhythmogenicity of BrS is complex. Although BrS is known to be associated with many genes, the voltage-gated sodium channel α Type V gene (*SCN5A*) is currently the only gene for which a definitive clinical validity has been established [3]. However, only 30–35% of diagnosed BrS cases are attributable to pathogenic variants in known genes, and there is significant variability in phenotypic expression [4]. Moreover, BrS is largely believed to be an autosomal dominant channelopathy, although recent data suggest that it follows a more complex polygenic inheritance model. As such, genetic analysis currently has little to contribute to the diagnosis, prognosis, and therapeutic management.

BrS overall is quite rare, with a worldwide prevalence estimated to be 0.05% while Brugada pattern is estimated to be 0.4% [5,6]. However, BrS has been found to have a higher prevalence in individuals of Southeast Asian descent [5]. For instance, a large-scale study on BrS prevalence (N = 369,068) noted the pooled prevalence of BrS is thought to be as high as 6.8 per 1000 in Thailand, which is 14 times higher than the worldwide prevalence of roughly 0.05% [7]. Among the different global regions, the highest prevalence of BrS was found in Southeast Asia (3.7 per 1000), followed by the Middle East, South Asia, East Asia, Europe, and North America [7]. Several studies have examined the variability in BrS presentation and clinical outcomes across the Asian continent, which may provide valuable insight into certain unidentified or unvalidated risk factors for the disease. This article seeks to elucidate the prevalence and variable clinical manifestations of Brugada Syndrome within Asia to guide better prognostication and management for BrS patients in the future.

2. Diagnostic and Risk Stratification Criteria

Before understanding the diagnosis and definitions of BrS, it is important to first recognize the difference between BrP and BrS. BrS refers to the presence of the typical Brugada ECG pattern associated with BrS, along with clinical manifestations of the disease. Meanwhile, BrP refers to specific ECG patterns associated with Brugada syndrome that manifests in asymptomatic patients. These ECG findings can be persistently present or unmasked by several different stimuli, such as infection, fever, toxins, or medications. There are three types of BrP. Type 1 BrP is characterized by coved-type ST-segment elevations $\geq$ 2 mm (0.2 mV) in $\geq$1 right precordial lead(s) (V1–V3) positioned in the second, third or fourth intercostal space [8]. Type 2 BrP on ECG is characterized by saddleback ST-segment elevation $\geq$ 0.5 mm (generally $\geq$ 2 mm in V2) in $\geq$1 right precordial lead (V1–V3), followed by a convex ST and a positive T wave in V2 and variable morphology in V1 [8]. Type 3 BrP is characterized by either a saddleback or a coved pattern with an ST-segment elevation < 1 mm [8]. As for BrS, several diagnostic criteria for BrS were proposed in 1992 [1], 2001 [9], 2002 [10], 2005 [11], 2013 [12], 2015 [13], and most recently, 2022 [14]. The latest 2022 European Society of Cardiology (ESC) guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death have further modified the criteria for BrS diagnosis [14]. In patients without other cardiac diseases, the presence of either spontaneous Type 1 BrP on ECG or evidence of fever or sodium channel blocker-induced Type 1 BrP in patients who survive ventricular fibrillation or polymorphic ventricular tachycardia cardiac arrest indicates a Class I recommendation for a diagnosis of BrS. Meanwhile, the ESC guidelines give a Class IIa recommendation for a BrS diagnosis in patients with no other cardiac disease and induced Type 1 Brugada pattern with either a family history of BrS, sudden death (<45 years of age), arrhythmic syncope, or nocturnal agonal respiration. The presence of inducible Type 1 BrP on ECG without such additional factors is given a Class IIb recommendation for diagnosis. There is no mention of Type 2 or 3 BrP in these ESC guidelines for diagnosis.

Despite multiple revisions and improvements to diagnostic criteria, risk stratification remains a significant challenge for BrS patients. Several stratification models have been evaluated over the years with assessments of various risk factors, including specific ECG parameters, family history, gender, syncope and even genetic *SCN5A* variant status. However, they have only repeatedly noted syncope and spontaneous Type 1 ECG patterns to be significant predictors of arrhythmias [15–18]. To tackle this issue, a conference report in 2016 proposed the Shanghai scoring system to aid with both diagnosis and prognostication [8]. The system's probable or definite diagnosis of BrS required a score ≥ 3.5 and relied on identifying one of the three types of BrP on ECG along with factoring in elements from the patient's clinical history, family history and genetic testing. Type 1 BrP was considered diagnostic of BrS by yielding a score of 3.5. However, if a Type 1 BrP was unmasked by fever or with provocative drug challenge, patients required further relevant positives from clinical history, family history, or genetic test results to achieve a score ≥ 3.5. Type 2 or 3 BrP on ECG that converts with provocative drug challenge would receive two points and require additional elements from the history to qualify as probable/definite BrS. While this scoring system initially showed significant promise for risk stratification, its current value is unclear as several validation studies have demonstrated mixed results [18,19]. However, there may be other unidentified risk factors that could play a role in stratification. Hence, the following sections describe the prevalence of BrS throughout the Asian continent, along with any potential predictive risk factors within these subgroups.

3. Prevalence of Brugada Syndrome in Asia

According to the proposed Shanghai scoring system [8], the estimated prevalence of asymptomatic BrS (ECG Type 1) and Type 2/3 BrP in Asia ranges from 0.00% to 1.77% and 0.014% to 15.96%, respectively. However, it is worth noting that most of these studies were conducted in adult males, and the Shanghai score may underestimate the true prevalence of Brugada syndrome [20–30]. The following sections discuss the relative trends of the prevalence of BrS and BrP within general adult populations (ages 18+) across different regions of Asia. Table 1 depicts the prevalence of BrS and Type 2/3 BrP across different regions of Asia, as evidenced in the subsequently mentioned studies.

Table 1. Prevalence of BrS and Type 2/3 BrP in Asia.

Country	Author, Year	Study Design	Study Group	Sample	Mean Age ± SD (Years)	% Male	BrS n (%)	% Male	Type 2/3 BrP n (%)	% Male
							Based on J-Wave Syndrome Expert Consensus Conference Report in 2016 (Proposed Shanghai Score System for Dx of BrS)			
Taiwan, China	Juang, 2015 [31]	Cohort	Adults aged $\geq$ 55 years from Healthy Aging Longitudinal Study in Taiwan, China	5214	69.3 ± 8	48.5	4 (0.08%)	75	169 (3.24%)	75
	Juang, 2011 [32]	Cross-Sectional	Hospital-based population seeking medical care for non-cardiovascular reasons in a tertiary medical center, Taiwan	20,562	49 ± 21	38.8	1 (0.005%)	0	25 (0.12%)	0
Japan	Tsuneoka, 2016 [33]	Cohort	Health checkup in the Circulatory Risk in Community Study (CRICS), Osaka/ Akita/ Ibaraki, Japan	7178	51.8 ± 7.1	40.2	8 (0.11%)	87.5	84 (1.17%)	88.1
	Tsuji, 2008 [34]	Cross-Sectional	Annual health examination Osaka, Japan	13,904	58 ± 10	26.51	37 (0.27%)	84	61 (0.44%)	83.8
	Ito, 2006 [23]	Cross-Sectional	Middle-aged or elderly Japanese-American men participated in theinitial examination of the Honolulu Heart Program, Oahu, Hawaii	8006	54.1 ± 5.5	100	12 (0.15%)	100	11(0.14%)	100
	Oe, 2005 [35]	Cohort	Health examination first-year elementary school children (aged six to seven years) in Izumi City, Osaka, Japan	21,944	6–7	51.41	1(0.005%)	0	3(0.015%)	66.67
	Yamakawa, 2004 [36]	Cross-Sectional	Health examinationKanagawa, Japan	20,387	9.7 ± 3.2	51.18%	1 (0.005%)	100	3(0.015%)	66.67
	Yoshinaga, 2004 [29]	Cohort	Seventh-grade healthy male adolescent, Kagoshima, Japan	7022	12	100	0 (0%)	N/A	1 (0.014%)	100
			Tenth grade healthy male adolescent, Kagoshima, Japan		15		1 (0.014%)	100	2 (0.028%)	100
	Sakabe, 2003 [37]	Cohort	General healthcheckup	3339	N/A	79.25	16 (0.48%)	N/A	53 (1.5%)	N/A

Table 1. *Cont.*

Country	Author, Year	Study Design	Study Group	Sample	Mean Age ± SD (Years)	% Male	BrS n (%)	% Male	Type 2/3 BrP n (%)	% Male
							Based on J-Wave Syndrome Expert Consensus Conference Report in 2016 (Proposed Shanghai Score System for Dx of BrS)			
	Atarashi, 2001 [20]	Cross-Sectional	Working adults Tokyo, Japan	10,000	42 ± 9	89.1	54 (0.54%)	N/A	51 (0.51%)	N/A
	Miyasaka, 2001 [38]	Cross-Sectional	Health examination Osaka, Japan	13,929	58 ± 10	26.5	18 (0.13%)	N/A	81 (0.58%)	N/A
	Furuhashi, 2001 [39]	Cross-Sectional	Health examination Asahikawa, Japan	8612	49.2 (range 22 to 84)	69.52	7 (0.08%)	100	10 (0.15%)	100
Korea	Uhm, 2011 [28]	Cross-Sectional	Healthy young Korean men	10,867	20.9 ± 4.5	100	0 (0%)	N/A	98 (0.9%)	100
	Shin, 2005 [27]	Cross-Sectional	Healthy Korean men	225	44 ± 13	100	0 (0%)	N/A	3 (1.34%)	N/A
Thailand	Rattanawong, 2017 [25]	Cohort	Thai workers in the central part of Thailand	2446	40.8 ± 7	74.3	10 (0.4%)	100	21 (0.85%)	100
	Rattanawong, 2015 [40]	Cross-Sectional	Non-febrilepatients in an emergency department setting, Buriram, in the northeastern part of Thailand	249	51.2 ± 18	N/A	2 (0.80%)	N/A	7 (2.80%)	100
	Makarawate, 2015 [24]	Cross-Sectional	Healthy Thai men, Khon Kaen, in the northeastern part of Thailand	282	27.82 ± 8.66	100	5 (1.77%)	100	45 (15.96%)	100
Singapore	Shen, 2020 [26]	Cross-Sectional	Health examinationbefore compulsory military service, Singapore	54,599	18.7 ± 1.6	100	3 (0.005%)	100	284 (0.52%)	100
	Sidik, 2009 [41]	Cohort	Patients presented with pre-syncope, syncope, and/or palpitations without a known cause at an arrhythmia clinic, Singapore	392	49.6 ± 19.1	55.9	19 (4.85%)	94.7	9 (2.30%)	100

Table 1. *Cont.*

Country	Author, Year	Study Design	Study Group	Sample	Mean Age ± SD (Years)	% Male	BrS n (%)	% Male	Type 2/3 BrP n (%)	% Male
							Based on J-Wave Syndrome Expert Consensus Conference Report in 2016 (Proposed Shanghai Score System for Dx of BrS)			
Philippines	Gervacio-Domingo, 2008 [22]	Cross-Sectional	General population from the 2003 Philippine National Nutrition and Health Survey	3907	50 ± N/A	100	7 (0.18%)	85.7	87 (2.22%)	85.7
Pakistan	Wajed, 2008 [42]	Cross-Sectional	Healthy young students in Hayatabad, Peshawar	1100	20.7 ± 5.92	64.73	2 (0.18%)	50	7 (0.64%)	50
Turkey	Bozkurt, 2006 [43]	Cross-Sectional	Healthy university students in Southern Turkey	1238	38.9 ± 17.6	54.2	1 (0.08%)	100	5 (0.40%)	100
Iran	Bigi, 2007 [44]	Cross-Sectional	Patients presentingwith palpitation in southern Iran	3895	38.2 ± 11.9	46	14 (0.36%)	78.6	86 (2.21%)	78.6
Israel	Adler, 2013 [45]	Cross-Sectional	Non-febrile patients in the emergency department.	909	61 ± 19	9	1 (0.11%)	N/A	4 (0.44%)	100

3.1. East Asia

There have been several studies evaluating the prevalence of BrS and BrP in East Asia. In the Republic of China, Taiwan, two adult patient studies in 2011 and 2015 by Juang et al. reported prevalences of asymptomatic Brugada-type ECG pattern and Type 2/3 BrP that ranged between 0.005–0.08% and 0.12–3.24%, respectively. The study in 2015 consisted of asymptomatic healthy elderly patients (mean age 69 years) and had higher prevalences for BrS or Type 2/3 BrP than the study in 2011. Surprisingly, the highest BrS or Type 2/3 BrP prevalences were observed in females in the 2011 study. The 2015 study also notably found no significant difference in all-cause mortality and cardiac mortality rates between subjects with and without Brugada ECG patterns during the four-year follow-up. Overall, the prevalence of the Brugada ECG pattern in adults aged 55 years and older in Taiwan was higher than the average worldwide prevalence but was not associated with increased mortality. For the Japanese population, there were 10 studies involving over 110,000 subjects in healthy patients, one of which was conducted in Hawaii [27]. The estimated prevalence of BrS and Type 2/3 BrP among the Japanese ranged from 0.00% to 0.54% and 0.014% to 1.5%, respectively [20,23,29,33–39]. Meanwhile, few Korean studies have been conducted, but both studies found no BrS but did note that Type 2/3 BrP was found in 0.9–1.34% of patients [27,28].

As for clinical outcomes, only a few of these studies in Japan evaluated patients with long-term follow-up. Ito et al., for example, examined asymptomatic Brugada-type ECG patterns amongst Japanese men but found no associated risk of either sudden death or total mortality after a 30-year follow-up [23]. Tsuneoka et al. [33] noted similar results with asymptomatic BrP not increasing the risk for sudden cardiac death after about 18.7 mean years of follow-up. There were similar findings from other studies as well, wherein asymptomatic BrP was not associated with increased fatal arrhythmias, syncope, and cardiovascular or even all-cause mortality [34,35,38]. Conversely, Atarashi et al. found that symptomatic (syncope) Japanese adults with either coved or saddleback ST elevation on ECG at baseline had a much higher incidence of cardiac events at three-year follow-up when compared to their asymptomatic counterparts [20]. Another interesting finding was from the study by Sakabe et al. This group investigated the prognosis of healthy subjects with right precordial ST-segment elevation without a family history of sudden death. The study found patients with a coved or saddleback type of ST elevation to have a significantly low risk for fatal arrhythmia [37].

These studies collectively demonstrated a higher prevalence of BrS in Japan but more Type 2/3 BrP in Taiwan within East Asia. Although clinical outcome data is lacking from Taiwan, the studies from Japan demonstrate that asymptomatic BrP, regardless of type, may not have significant cardiovascular risk as compared to symptomatic BrP. In addition, there may be a role for family history as a risk factor for cardiovascular mortality.

3.2. Southeast Asia

Although Japan and Taiwan had the highest prevalences for BrS and Type 2/3 BrP in East Asia, respectively, Thailand may have even higher rates of both BrP and BrS. In fact, the highest prevalence of both asymptomatic Type 1 BrP (1.77%) and Type 2/3 BrP (15.96%) was found in Thailand by Makarawate et al. in a study population of healthy young to middle-aged men in the Khon Kaen province of northeastern Thailand [24]. Similar rates of BrS and Type 2/3 BrP were found by Chantapoh et al. [30] and Rattanawong et al. within a northeastern region of Thailand [46]. As for symptomatic subjects, Sidik et al. reported a significant prevalence of BrS as high as 4.85% in middle-aged or elderly patients presenting with pre-syncope, syncope, and/or palpitations without a known cause at an arrhythmia clinic in Singapore [41]. This same group of study patients also had a 2.30% prevalence of Type 2/3 BrP. Meanwhile, in the Philippines, Gervacio-Domingo et al. reported that the prevalences of BrS and Type 2/3 BrP were lower than in Thailand. These rates were 0.18% and 2.22%, respectively, in healthy Filipino males [22]. Overall, these results demonstrate a significantly higher prevalence of all three Brugada phenotypes (symptomatic and asymptomatic) in Thailand within South Asia, and even more so than in any other Asian country.

Unfortunately, there is a significant paucity of data on the clinical outcomes of BrS in Southeast Asia. It is unclear why this lack of data exists, but it may be related to difficulties with BrS diagnosis, the complex and ever-changing definition of BrS, as well as a lack of proper resources to execute large-scale studies. Nevertheless, there are currently ongoing observational studies seeking to assess clinical outcomes in Southeast Asian patients.

3.3. South Asia and the Middle East

There is limited data available on South Asian populations regarding Brugada syndrome prevalence and clinical outcomes. One study was conducted on healthy students in Peshawar, Pakistan. They found prevalences of 0.18% of BrS and 0.64% in Type 2/3 BrP [42]. The Middle East, however, has more data. It is important to recognize that the predominant ethnicity in the Middle East is Caucasian. The highest prevalence rates in the Middle East for BrS and BrP were found in Iran, with 0.36% for BrS and 2.21% for Type 2/3 BrP. This study was conducted on symptomatic patients presenting with palpitations [44]. While the prevalence in Turkey and Israel were similar, around 0.08–0.11% for BrS and 0.40–0.44% for Type 2/3 BrP, all of the Type 2/3 BrP cases in the two countries were men [43,45]. Bigi et al. also reported on the prevalence of BrS and BrP among Iranian patients presenting with only palpitations. They found prevalences of 0.36% for BrS and 2.21% for Type 2/3 BrP [41,44]. None of the studies on this region in Asia had examined clinical outcomes. The reason behind the lack of data in this area is unclear and may be like why Southeast Asia also lacks studies on clinical outcomes for BrS and Brp patients.

4. Pediatric and Young Populations

Apart from a patient's geographic origin, symptomatology, or family history, age may offer insight into a patient's risk profile for poor clinical outcomes with Brugada syndrome. Three studies from Japan were conducted on pediatric subjects less than 18 years of age. Studies by Oe et al. [35] and Yamakawa et al. [36] investigated over 20,000 children with ages ranging between 6 and 13 years old, with equal proportions of males and females. Both studies found the same result: there was only one case of BrS (0.005%) and three cases of Type 2/3 BrP (0.015%).

When prevalences of BrP and BrS were investigated in a smaller group of older children by Yoshinaga et al. [29], they found no BrS cases and only one case of Type 2/3 BrP (0.014%) among 7022 twelve-year-old students. The investigators re-evaluated the same group of students three years later and notably found the prevalence increased up to one case of BrS (0.014%) and two cases of Type 2/3 BrP (0.028%), according to the criteria from the Shanghai scoring system.

However, the diagnostic criteria in this study were originally based on the conventional criteria from 2001, which required ST-segment elevation $\geq$ 1 mm (0.1 mV). There were actually 2 (0.028%) and 7 (0.10%) subjects fulfilling the conventional criteria for BrS and Type 2/3 BrP. Interestingly, one subject showed a conventional Brugada ECG pattern again three years later. This shows again that the Shangai score underestimates the true prevalence of BrS.

In young adults, the other three studies from Korea [28], Singapore [26], and Pakistan [42] were conducted on healthy individuals who were around 20 years old. The prevalence of BrS and Type 2/3 BrP ranged around 0.00% to 0.18% and 0.52% to 0.9%, respectively, with the lowest prevalence of BrS (0.00%) and the highest prevalence of Type 2/3 BrP (0.9%,) in the Korean population. As can be seen, the prevalences of both BrS and Type 2/3 BrP in young populations slightly increased along with increasing age.

BrS was not found among any seventh-grade male children in Japan by Yoshinaga et al., nor in Korea by Uhm et al. and Shin et al. In addition, the lowest prevalence of Type 2/3 BrP (0.014%) was found in the same seventh-grade Japanese children group [23,24,27].

Studies in other southeastern Asian countries, such as Singapore and the Philippines, have found lower rates of BrS/Brp. Shen et al. reported that the prevalence of BrS was 0.005% and that Type 2/3 BrP was 0.52% from 54,599 adolescent males who were recruited for military service in Singapore [26]. Moreover, the prevalence of both BrS and Type 2/3 BrP was profoundly increased among symptomatic patients in arrhythmia clinic settings from a study by Sidik et al., as mentioned earlier. Most of the BrS cases (94.7%) and all of the Type 2/3 BrP cases were men in this study [41]. Data on clinical outcomes for these populations is still lacking.

5. Elderly Population

A study of 5214 healthy elderly Taiwanese individuals with a mean age of approximately 69.3 ± 8 years and equal proportions of males and females reported that the prevalences of BrS and Type 2/3 BrP were 0.08% and 3.24%, respectively [31]. The prevalence of Type 2/3 BrP in this age group seemed higher than in younger Asian populations in all previous studies, except in the endemic area of Northeastern Thailand [24].

On the other hand, a study of 909 non-febrile adults (up to the elderly population) in Israel demonstrated that the prevalences of BrS and Type 2/3 BrP were 0.11% and 0.44%, respectively [45]. Compared with the healthy middle-aged group in the same ethnicity from Turkey, the percentages of BrS and Type 2/3 BrP were quite similar [43].

6. Fever-Induced Brugada Electrocardiogram Pattern

Fever can induce BrP and trigger ventricular arrhythmias [47–49]. Four studies demonstrated the prevalence of fever induced BrP in Asia. Among all cases of fever-induced Type 1 BrP in Asia, the most common cause of fever in patients with BrP was an infection, especially in the respiratory tract. One study found nine of twenty-five BrP cases to be induced by fever, with two patients out with pharyngitis, one with bronchitis, and six with pneumonia. At the time of Type 1 BrP diagnosis, the average body temperature was approximately 39 °C, and the mean age was around 40 years old (37.7, 46, and 48.2 years in India, Israel, and Thailand, respectively) [21,45,46,50].

In Northeastern Thailand, Rattanawong et al. studied the prevalence of Type 1 BrP in 152 febrile patients compared to 249 non-febrile patients (4.0% vs. 0.8%, respectively, $p = 0.037$) from an endemic area [46]. The mean age between the febrile and non-febrile groups did not differ (54.8 ± 19.6 and 51.2 ± 18.0 years, respectively, $p > 0.05$). Type 1 BrP was found in six febrile patients (five males and one female) and two males in the non-febrile group. Therefore, Type 1 BrP was five times more common in febrile than in non-febrile adults, and the prevalence of Type 1 BrP was up to 5.3% among febrile male adults. In the febrile group, the mean temperature was 38.8 ± 0.8 °C, three patients had cardiac symptoms, two patients had a family history of sudden death in a first-degree relative, and five of six patients had a fever from an infectious cause. After the fever subsided, all the Type 1 BrP disappeared, one patient had ECG converted to Type 2 BrP, and another one had ECG converted to right bundle branch block [41]. This pattern of conversion was previously reported [40]. In six of eight patients, Type 1 BrP was detected using high precordial leads (V1 and V2 at the second intercostal space). The investigators reported that the prevalence of Type 2 BrP between febrile versus non-febrile groups did not differ (2.0% vs. 2.8%, respectively, $p > 0.05$) [46]. Furthermore, Type 3 BrP was not found. No ventricular arrhythmia was detected during the study. All BrS and Type 2 BrP patients were followed up by a telephone call one year after the diagnosis [46].

A study by Adler et al. in Israel reported the prevalence of fever-induced Type 1 BrP in 402 febrile patients compared with 909 non-febrile patients [45]. The percentage of males was higher in the febrile group (60% vs. 49%, $p = 0.001$). There were eight febrile patients and only one non-febrile patient who had Type 1 BrP (2% vs. 0.1%, respectively, $p = 0.0001$). This study found that Type 1 BrP was 20 times more common in febrile than in non-febrile patients. In the febrile group with Type 1 BrP, seven of them (87%) were male, the mean age was 46 years (range 31–57 years), the mean temperature was 39 °C (range 38.4–40 °C), none of them had a history of cardiac symptoms or a family history of sudden death or Brugada syndrome, and seven of eight patients had a fever from an infectious cause. There was one patient who had persistent Type 1 BrP in the absence of fever, which is one of the exclusion criteria in a study by Rattanawong et al. At 30 ± 13 months of diagnosis, none of the subjects had arrhythmic events. The prevalence of Type 2/3 BrP was also significantly higher in febrile than in non-febrile patients: seven (1.7%) versus four (0.4%), respectively, $p = 0.0175$. In the febrile group with Type 2/3 BrP, five (71%) were male, the mean age was 41 years (range 27–78 years), and the mean temperature was 39 °C (range 38.3 –39.5 °C). For male patients, the prevalence of Type 1 BrP in febrile and non-febrile patients were 3% and 0.2%, respectively ($p = 0.0015$). Meanwhile, the prevalence rates of Type 2/3 BrP in the febrile and non-febrile groups were 2.1% and 0.7%, respectively ($p = 0.039$) [45].

A study by Viswanathan et al. in India investigated the prevalence of BrP only in febrile patients. This study defined fever as a temperature above 37.2 °C. The prevalence of Type 1 BrP and Type 2 BrP were 11 (2.10%) and 12 (2.29%), respectively. Type 3 BrP was not found. BrP was significantly associated with male gender, higher body temperature, and lower systolic blood pressure. In those with Type 1 BrP, ECG abnormalities were found. There were four cases of atrial enlargement (two each of right and left) and three cases of left ventricular hypertrophy confirmed by echocardiogram. After the fever subsided, one patient had persistent BrP even one week after discharge. He was lost to follow-up thereafter. The investigators did not report which type of BrP was recorded in this case [50].

Lastly, the Turkish study by Erdogan et al. in 103 febrile males showed 10 cases of Type 2/3 BrP, consisting of two cases of Type 2 and eight cases of Type 3 BrP. In order to detect BrP, the second intercostal space (ICS) lead was highly sensitive compared with the 4th ICS lead ($p = 0.016$). There was only one subject (1%) who had Type 2 BrP that completely reverted to a normal ECG when the fever subsided. However, if we exclude the persistent fever-induced BrP case in this study, according to a study by Rattanawong et al., the prevalence of fever-induced Type 2/3 BrP would be 0.97% [33].

The pathophysiology of fever induced BrP is still unknown. Some previous studies found that temperature dependence of both wild-type and mutated *SCN5A* cardiac sodium channels might play an important role in depolarization and repolarization defects [51,52].

Conversely, other studies did not find any defect of the same channels at high temperatures. A study by Keller et al. reported that variants of the channels found in patients who were fever-induced Type 1 BrP showed severe to absolute loss of sodium current at physiological temperatures. Hence, further loss of function during the febrile state could not be explained [53].

However, three of four studies in febrile subjects were conducted before the Shanghai score system for diagnosis of BrS was proposed in 2016. When Type 1 BrP is unmasked by fever, patients require further components from the clinical history, family history, or genetic test results to achieve a score ≥ 3.5 for a definite diagnosis of BrS [8]. Lacking this information might overestimate the prevalence of BrS among febrile patients. However, using the Shangai scoring system may underestimate the true prevalence.

Therefore, a larger multicenter study of BrS and BrP should be conducted based on recent criteria, including specific clinical history, family history, and genetic testing in both healthy and febrile populations. The prevalence of transient or persistent fever induced BrP should be counted separately. In addition, there may be utility in using high precordial lead placement to improve diagnostic sensitivity. Table 2 summarizes the prevalence of fever induced Brugada pattern across Asia.

Table 2. Prevalence of Fever-Induced Brugada Electrocardiogram Pattern in Asia.

Country	Author, Year	Study Design	Study Group	Sample	Mean Age ± SD (Years)	% Male	Type 1 BrP n (%)	% Male	Type2/3 BrP n (%)	% Male
Thailand	Rattanawong, 2015 [40]	Cross-Sectional	Febrile patients, emergency department setting, Buriram, the northeastern part of Thailand	152	54.8 ± 19.6	N/A	6 (4.0%)	83.33%	3 (2.0%)	N/A
India	Viswanathan, 2017 [50]	Cross-Sectional	Patients aged ≥ 13 years admitted with acute febrile illness (fever < three weeks)	525	$35.94 \pm$ N/A	72%	11 (2.10%)	100%	12 (2.29%)	91.67%
Turkey	Erdogan, 2012 [21]	Cross-Sectional	Febrile male patients in an emergency department	103	37.7 ± 10.8	100%	0 (0.00%)	N/A	10 (9.70%)	100%
Israel	Adler, 2013 [45]	Cross-Sectional	Febrile patients in an emergency department	402	62 ± 22	60%	8 (2%)	87%	7 (1.7%)	71%

7. Conclusions

The prevalence rates of asymptomatic BrS and Type 2/3 BrP in Asia range from 0.00% to 1.77% and 0.014% to 15.96%, respectively. Even within the Asian continent, there are significant differences in prevalence, with studies showing pooled Type 2/3 BrP prevalence as highest in Southeast Asia, followed by East Asia and then South Asia. Compared to the rest of the world, Asia has significantly higher rates of BrS and BrP. The most accepted theory behind such higher prevalence in Asia centers around ethnic-specific polymorphisms that may modulate the activity of the primary disease-causing variant. While there are higher rates of prevalence within Asia, studies assessing clinical outcomes note similar risk factors for non-Asian patients when evaluating the risk for SCD or malignant arrhythmias. Syncope, family history of SCD and Type 1 BrP appear to be the most common risk factors for such outcomes. However, this review does point out that the country of origin may play a role in a patient's baseline risk for having underlying BrS or BrP. However, there are significant limitations to many of these studies, including a lack of uniform clinical outcome assessment across the continent and different definitions of BrS utilized in the studies. In the future, it will be important to focus more on additional risk factors that could play a role in SCD in these patients that were not included in these studies.

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