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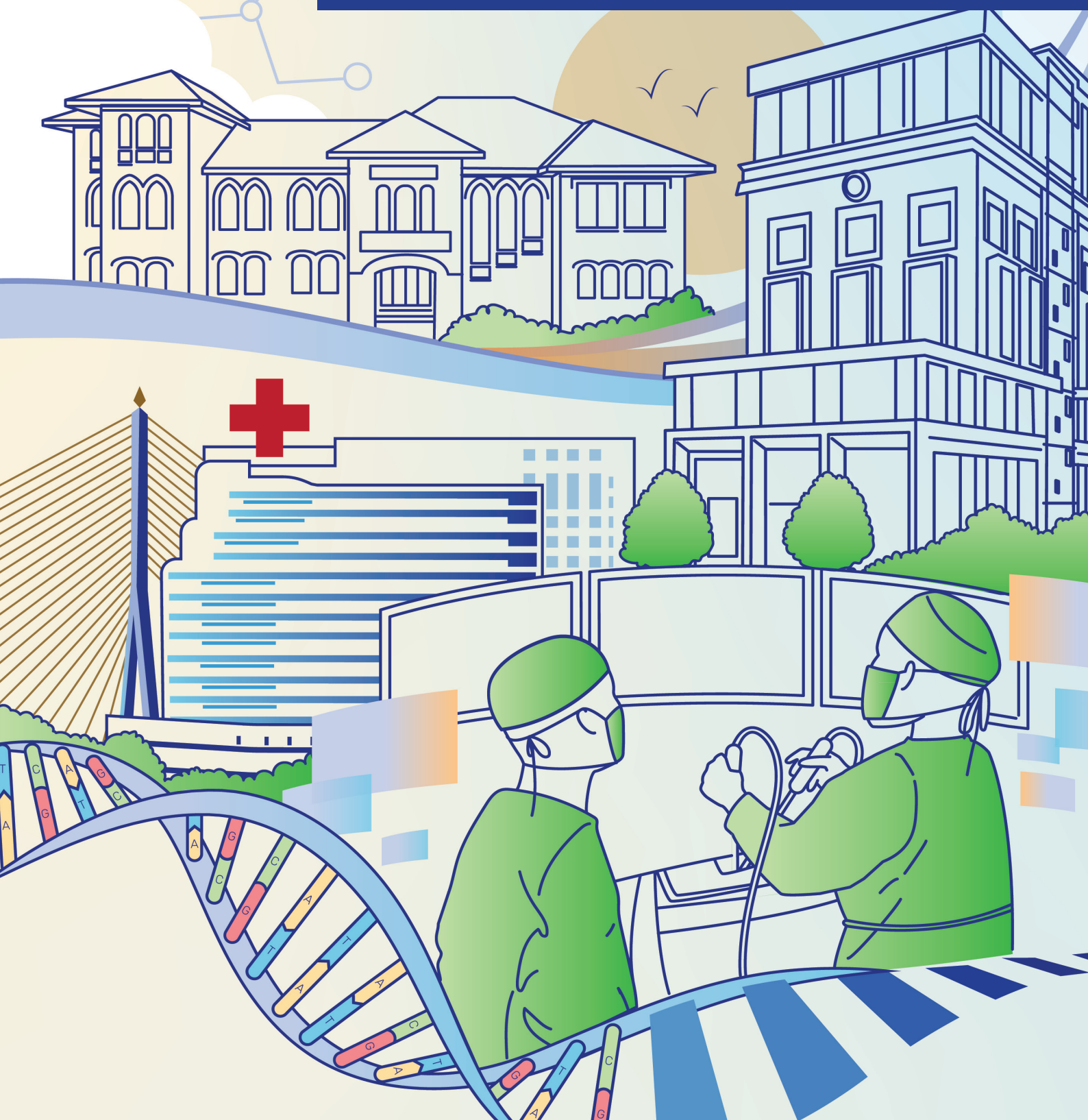

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Prevalence and Factors Associated with Participation in Health Checkups among Thai Adults Aged 19-60 Years: Cross-Sectional Study at Vajira Hospital, Bangkok, Thailand

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ABSTRACT

OBJECTIVE: This study aims to investigate the prevalence of health checkup attendance among Thai adults aged 19-60 years and the factors associated with participation in health checkups.

METHODS: A cross-sectional study was conducted from October to December 2023 among 292 Thai individuals aged 19–60 years who received medical services at Vajira Hospital without prior appointments for chronic disease follow-up. Data were collected using a questionnaire comprising the following four sections: personal information, health-related and health checkups data, possible factors facilitating checkup attendance, and the reasons why non-checkup participants choose not to undergo health checkups. The factors associated with participation in health checkups were identified by multivariable logistic regression analysis with a significance level of 0.05.

RESULTS: A total of 156 volunteers (53.4%) participated in checkups in the past 3 years. The factors associated with participation in checkups included earning more than 20,000 Baht per month (OR 3.06, 95% CI 1.12–8.41), checkups arranged by their workplace (OR 5.64, 95% CI 2.42–13.15), and encouragement by family or friends (OR 2.18, 95% CI 1.06–4.51). Underweight (OR 0.28, 95% CI 0.10–0.81) and overweight individuals (OR 0.23, 95% CI 0.08–0.64) were less likely to participate in health checkups than people with a normal body mass index. Lastly, individuals who could participate in checkups on weekends or holidays were less likely to do so than those unable to participate (OR 0.41, 95% CI 0.18–0.96).

CONCLUSION: A portion of Thai adults aged 19-60 years still fails to attend health checkups. Health checkup utilization must be increased using various strategies, such as encouraging workplace-organized checkups and fostering peer encouragement, especially among low-income and underweight/overweight individuals.

KEYWORDS: health checkups, Thai adults, working-age

INTRODUCTION

In this era of advanced medical innovations, noncommunicable diseases (NCDs) remain a remarkable issue and the leading cause of death worldwide, claiming up to 41 million lives annually and accounting for 74% of all deaths. Approximately 17 million of these deaths occur before the age of 70 years. Cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes are the most prevalent NCDs

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contributing to mortality, accounting for 80% of premature deaths attributed to all NCDs[1].

The impact of NCDs in Thailand aligns with the global data. In 2019, deaths from NCDs ranked the highest with 268,172 individuals, accounting for 54.2% of total deaths[2]. In addition to health consequences, NCDs impose economic burdens, including healthcare costs, loss of economic productivity due to premature deaths, frequent absenteeism, and reduced work capacity. The Ministry of Public Health of Thailand has implemented policies to prevent and control NCDs, including reducing the risk of disease and adopting secondary prevention[3]. Secondary prevention aims to protect infected people from developing complications by early detection through health screenings and appropriate treatment[4].

The National Statistical Office of Thailand[5] reveals that the working-age group constitutes the majority of the country's population, accounting for 46 million people. This group drives the economy of the country and is essential for caring for dependent populations such as children and older adults. However, one in ten of working-age individuals suffer from chronic diseases, with cardiovascular diseases, diabetes, and chronic respiratory diseases being the top three[6]. Therefore, advocating for health promotion, particularly by encouraging regular health checkups, is crucial for the working-age population because it reduces illness, mortality, and hospitalization rates while preparing individuals to become healthy in their elder years[7-9]. In Thailand, health checkups are provided without out-of-pocket fees as part of healthcare insurance schemes, such as social security plans and civil servant benefits[10]. However, the precise number of working-age Thais receiving annual health checkups has never been reported.

This research aims to investigate the prevalence of health checkup attendance and the factors associated with participation in health checkups among Thai adults aged 19-60 years who received outpatient medical services at Vajira Hospital. Various factors, including demographics, socioeconomics, health-related and health checkups data, and possible facilitating or deterring factors for undergoing health checkups, were examined. To formulate strategies that enhance health checkup utilization, healthcare providers must understand relevant factors. These initiatives can advance preventive healthcare practices and foster the overall well-being among Thai adult population, thereby diminishing the illness rates, preventing premature mortality, and facilitating the preparation for healthy aging.

METHODS

The primary objective of the study was to examine the prevalence of health checkup attendance among Thai adults aged 19-60 years. The secondary objective was to investigate the factors associated with participation in health checkups in this population. This research was conducted on a sample of Thai adults who received services at the Family Medicine Clinic, Urban Primary Care Unit, and Non-urgent Outpatient Clinic at the Vajira Hospital from October to December 2023.

This research adopted a cross-sectional design. The sample size was calculated using one sample proportion formula[11]. The appropriate sample size was determined to be at least 285 individuals.

The inclusion criteria for the research participants were as follows: Thai nationality, aged between 19 and 60 years, received services at Vajira Hospital without prior appointments for chronic disease follow-ups, and able to communicate in Thai. The exclusion criteria were as follows: diagnosed with neurological conditions affecting consciousness or communication, legal incapacitation, failing to complete the questionnaire, and withdrawing their consent.

Data were collected using a questionnaire comprising four sections: personal information, health-related and health checkups data, possible factors facilitating health checkup attendance, and the reasons why non-checkup participants choose not to undergo health checkups. The screening for anxiety and depression was

included in the health-related data section using the Thai version of the Hospital Anxiety and Depression Scale developed by Nilchaikovit et al. based on the English version by Zigmond and Snaith[12-13]. The questionnaire was evaluated for Index of Item Objective Congruence (IOC) by three family medicine physicians and received an IOC value of 0.96, indicating high congruence between questions and objectives or content.

Data were analyzed using the statistical software SPSS Version 28.0 (New York, the USA) at a significance level of 0.05. Data were reported using frequencies and percentages. Univariable and multivariable analyses were performed using multiple logistic regression analysis, reporting odds ratios (ORs) and 95% confidence intervals (CI).

For ethical consideration, this research was approved by the Research Ethics Committee, Faculty of Medicine Vajra Hospital, Navamindradhiraj University under the Research Ethics Approval Number COA 158/2566.

RESULTS

Among the 292 participants, 69.5% were female, 60.3% were aged under 35 years old, and 54.8% had a body mass index (BMI) greater than 23 kg/m^2. Most of the participants had completed at least a bachelor's degree (71.3%) and had a monthly income of less than 20,000 Baht (72.6%). The sample population predominantly consisted of students (28.8%), followed by civil servants or government employees (25%). Most of the participants had insufficient income or only sufficient for some months (55.5%) and had health insurance through the universal coverage scheme (47.3%), followed by social security scheme (24%) and civil servant benefits (19.9%). Meanwhile, 12.7% of them had a history of smoking, 27.4% reported alcohol consumption, and 39% had chronic illnesses. Most of these individuals (72.6%) perceived their health status as average, 9.9% had anxiety, and 7.2% reported depressive symptoms (table 1).

Table 1 Personal and health-related information of Thai adults aged 19-60 years who received services at Vajira Hospital (n=292)

Characteristics	n (%)
Personal information	
Sex	
Male	89 (30.5)
Female	203 (69.5)
Age (years)	
19-34	176 (60.3)
35-60	116 (39.7)
Body mass index (kg/m^2)	
Underweight (< 18.5)	35 (12.0)
Normal (18.5-22.9)	97 (33.2)
Overweight (23.0-24.9)	43 (14.7)
Obesity (> 25)	117 (40.1)
Marital status	
Single	170 (58.2)
Married/have a boyfriend/girlfriend	106 (36.3)
Widowed/divorced/ separated	16 (5.5)
Whether or not living with someone	
Living alone	47 (16.1)
Living with someone	245 (83.9)

Table 1 Personal and health-related information of Thai adults aged 19-60 years who received services at Vajira Hospital (n=292) (continued)

Characteristics	n (%)
Education level	
Unschooled	4 (1.4)
Elementary school	17 (5.8)
High school	43 (14.7)
Diploma/vocational certificate	20 (6.8)
Bachelor degree	185 (63.4)
Postgraduate	23 (7.9)
Occupation	
Unemployed	20 (6.8)
Student	84 (28.8)
Freelance	27 (9.2)
Private business/merchant	41 (14)
Private employee	47 (16.1)
Government officer/ state employee	73 (25)
Monthly income	
No income	41 (14)
Less than 5,000 Baht	19 (6.5)
5,000-10,000 Baht	65 (22.3)
10,001-20,000 Baht	87 (29.8)
More than 20,000 Baht	80 (27.4)
Self-rated economic status	
Insufficient	50 (17.1)
Sufficient for some months	112 (38.4)
Living comfortably without saving	76 (26)
Living comfortably with saving	54 (18.5)
Health benefits	
Universal coverage scheme	138 (47.3)
Social security scheme	70 (24)
Government enterprise office	58 (19.9)
State enterprise office/Company's welfare	17 (5.8)
Private medical insurance	9 (3.2)
Health-related information	
Smoking	37 (12.7)
Alcohol drinking	80 (27.4)
Chronic diseases	116 (39.7)
Hypertension	30 (10.3)
Diabetes mellitus	11 (3.8)
Dyslipidemia	20 (6.8)
Dyspepsia/GERD	16 (5.5)
Heart disease/arrhythmia/cardiomegaly/ischemic heart disease	3 (1)
Chronic lung disease/COPD/asthma	4 (1.4)
Osteoarthritis /gout/rheumatoid arthritis	9 (3.1)
Liver disease/fatty liver	6 (2.1)

Table 1 Personal and health-related information of Thai adults aged 19-60 years who received services at Vajira Hospital (n=292) (continued)

Characteristics	n (%)
Depression/anxiety disorder	7 (2.4)
Cerebrovascular disease	3 (1.0)
Others	54 (18.5)
Family history of chronic diseases	155 (53.1)
Self-rated health	
Poor	12 (4.1)
Fair	121 (41.4)
Good	114 (39)
Very good	35 (12)
Excellent	10 (3.4)
Anxiety symptoms	29 (9.9)
Depressive symptoms	21 (7.2)
Health checkup participation in prior 3 years	156 (53.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux; kg/m^2, kilogram per square meters; n, number; SD, standard deviation

A total of 156 participants underwent health checkups in the past 3 years, accounting for 53.4% (table 1). The following are the possible facilitating factors of undergoing health checkups among the sample group: 83.9% were being permitted work leave for health checkups, 78.4% found it convenient to undergo health checkups without additional costs, 40.1% had their workplace arranged for annual health checkups, 71.6% had health checkup facilities near their homes or workplaces, 79.8% could undergo health checkups on weekends or holidays, 50.7% were encouraged by medical personnel to undergo health checkups, 55.5% were encouraged by family members or friends to undergo health checkups, and 67.5% received information about health checkups from various media sources (table 2).

Among the 292 individuals, 136 did not undergo health checkups in the past 3 years. The reasons for not undergoing health checkups included the following: not knowing how to start a health checkup (58.1%), lack of time (51.5%), fear of finding health problems (39%), unnecessary without symptoms of illness (32.4%), concerns about expenses (27.9%), complexity of the health checkup process (16.2%), and difficulty in accessing health checkup locations (15.4%) (table 3).

Table 2 Possible facilitating factors of undergoing health checkups among Thai adults aged 19-60 years who received services at Vajira Hospital (n=292)

Possible facillitating factos	n (%)
Being permitted work leave for health checkups	245 (83.9)
Can undergo health checkups conveniently without additional cost	229 (78.4)
The workplace arranges for health checkups	117 (40.1)
Health checkup facilities are located near home/workplace	209 (71.6)
Possible to undergo health checkups on weekends/holidays	233 (79.8)
Encouraged by medical personnel for health checkups	148 (50.7)
Encouraged by family/friends to get a health checkups	162 (55.5)
Received health checkup information from various media	197 (67.5)

Abbreviation: n, number

Table 3 Reasons for not undergoing health checkups among respondents who did not undergo health checkups in the past 3 years (multiple answers allowed) (n=136)

Reasons for not undergoing health checkups	n (%)
Not necessary without abnormal symptoms	44 (32.4)
Lack of time	70 (51.5)
Concern of expenses	38 (27.9)
Complexity of the health checkup process	22 (16.2)
Not knowing how to start health checkups	79 (58.1)
Fear of finding health problems	53 (39.0)
Place of health checkups is too far/difficult to go	21 (15.4)

Abbreviation: n, number

Several factors were found to be related to health checkup participation among Thai adults aged 19-60 years, and statistical significance (p-value < 0.05) was observed when controlling for confounding factors. First, individuals with a monthly income greater than 20,000 Baht was 3.06 times more likely to undergo health checkups than those with monthly income less than 20,000 Baht a month. Second, individuals whose workplaces arranged health checkups had a 5.64 times higher likelihood of receiving health checkups than those whose workplaces did not arrange health checkups. In addition, individuals who were encouraged by family members or friends to get health checkups were 2.18 times more likely to undergo health checkups than those who did not have such encouragement (table 4).

In terms of BMI, underweight or overweight individuals were less likely to receive health checkups than those with a normal BMI, accounting for percentages of 72% (OR 0.28) and 77% (OR 0.23), respectively. Individuals who could attend health checkups on weekends or holidays were significantly less likely to receive health checkups than those who could not do so, accounting for a percentage of 59% (table 4).

Table 4 Factors associated with participation in health checkups among Thai adults aged 19-60 years who received services at Vajira Hospital (n=292)

	Checkups n (%)	Non checkups n (%)	Univariable analysis		Multivariable analysis	
			Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Personal information						
Female	109 (53.7)	94 (46.3)	1.04 (0.63-1.71)	0.889	1.31 (0.59-2.90)	0.510
Age (years)						
19-34	82 (46.6)	94 (53.4)	Ref		Ref	
35-60	74 (63.8)	42 (36.2)	2.02 (1.25-3.27)	0.004	1.60 (0.64-4.02)	0.314
Body mass index (kg/m^2)						
Underweight (< 18.5)	12 (34.3)	23 (65.7)	0.38 (0.17-0.86)	0.019	0.28 (0.10-0.81)	0.019
Normal (18.5-22.9)	56 (57.7)	41 (42.3)	Ref		Ref	
Overweight (23.0-24.9)	21 (48.8)	22 (51.2)	0.70 (0.34-1.44)	0.330	0.23 (0.08-0.64)	0.007
Obesity (> 25)	67 (57.3)	50 (42.7)	0.98 (0.57-1.69)	0.945	0.80 (0.37-1.70)	0.557
Marital status						
Married/have a boyfriend/girlfriend	46 (43.4)	60 (56.6)	Ref		Ref	
Single	85 (50)	85 (50)	0.77 (0.47-1.25)	0.286	1.28 (0.60-2.71)	0.521
Widowed/divorced/ separated	5 (31.3)	11 (68.8)	1.69 (0.55-5.20)	0.362	4.31 (0.92-20.31)	0.065
Living with someone	112 (45.7)	133 (54.3)	1.24 (0.66-2.31)	0.501	1.04 (0.43-2.53)	0.928
Education level						
Below bachelor degree	34 (40.5)	50 (59.5)	Ref		Ref	
Above bachelor degree	122 (58.7)	86 (41.3)	2.09 (1.25-3.50)	0.005	1.29 (0.52-3.22)	0.585
Occupation						
Unemployed	9 (45.0)	11 (55.0)	1.94 (0.58-6.50)	0.281	3.26 (0.67-15.86)	0.144
Students	34 (40.5)	50 (59.5)	1.62 (0.64-4.11)	0.314	2.69 (0.63-11.60)	0.184
Freelance	8 (29.6)	19 (70.4)	Ref		Ref	
Private business/merchant	14 (34.1)	27 (65.9)	1.23 (0.43-3.51)	0.697	1.04 (0.28-3.89)	0.951

Table 4 Factors associated with participation in health checkups among Thai adults aged 19-60 years who received services at Vajira Hospital (n=292) (continued)

	Checkups n (%)	Non checkups n (%)	Univariable analysis		Multivariable analysis	
			Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Private employee	33 (70.2)	14 (29.8)	5.60 (1.99-15.77)	0.001	2.98 (0.63-14.09)	0.168
Goverment officer/ state employee	58 (79.5)	15 (20.5)	9.18 (3.37-25.02)	< 0.001	3.17 (0.59-17.06)	0.180
Monthly income						
Less than 20,000 Baht	91 (42.9)	121 (57.1)	Ref		Ref	
More than 20,000 Baht	65 (81.3)	15 (18.8)	5.76 (3.09-10.75)	< 0.001	3.06 (1.12-8.41)	0.030
Self-rated economic status						
Insufficient, sufficient for some months	72 (44.4)	90 (55.6)	Ref		Ref	
Living comfortably without saving	45 (59.2)	31 (40.8)	1.82 (1.04-3.15)	0.035	1.52 (0.69-3.31)	0.297
Living comfortably with saving	39 (72.2)	15 (27.8)	3.25 (1.66-6.36)	< 0.001	1.98 (0.76-5.18)	0.162
Health benefits						
Universal coverage scheme	52 (37.7)	86 (62.3)	Ref		Ref	
Social security scheme	43 (61.4)	27 (38.6)	2.63 (1.46-4.76)	0.001	1.17 (0.44-3.15)	0.755
Government enterprise office	41 (70.7)	17 (29.3)	3.99 (2.06-7.73)	< 0.001	0.85 (0.22-3.31)	0.815
State enterprise office/Company's welfare	13 (76.5)	4 (23.5)	5.38 (1.66-17.36)	0.005	1.91 (0.36-10.17)	0.450
Private medical insurance	7 (77.8)	2 (22.2)	5.79 (1.16-28.92)	0.032	3.79 (0.57-25.34)	0.169
Health related information						
Smoking	14 (37.8)	23 (62.2)	0.48 (0.24-0.98)	0.045	1.25 (0.39-3.96)	0.708
Alcohol drinking	36 (45)	44 (55)	0.63 (0.37-1.05)	0.077	0.93 (0.42-2.08)	0.861
Chronic diseases	74 (63.8)	42 (36.2)	2.02 (1.25-3.27)	0.004	1.81 (0.89-3.68)	0.101
Family history of chronic diseases	91 (58.7)	64 (41.3)	1.58 (0.99-2.50)	0.055	1.18 (0.62-2.29)	0.611
Self-rated health						
Poor, fair	67 (50.4)	66 (49.6)	Ref		Ref	
Good, very good, excellent	89 (56)	70 (44)	1.25 (0.79-1.99)	0.340	0.84 (0.43-1.63)	0.598
Anxiety symptoms	6 (20.7)	23 (79.3)	0.20 (0.08-0.50)	< 0.001	0.28 (0.07-1.21)	0.088
Depressive symptoms	7 (33.3)	14 (66.7)	0.41 (0.16-1.05)	0.062	1.67 (0.29-9.58)	0.565
Possible facilitating factors						
Being permitted work leave for health checkups	137 (55.9)	108 (40.4)	1.87 (0.99-3.53)	0.053	1.50 (0.50-3.82)	0.395
Can undergo health checkups conveniently without additional cost	127 (55.5)	102 (44.5)	1.46 (0.83-2.56)	0.185	0.80 (0.35-1.82)	0.596
The workplace arranges for health checkups	95 (81.2)	22 (18.8)	8.07 (4.62-14.10)	< 0.001	5.64 (2.42-13.15)	< 0.01
Health checkup facilities are located near home/workplace	127 (60.8)	82 (39.2)	2.88 (1.70-4.90)	< 0.001	1.54 (0.73-3.25)	0.260
Possible to undergo health checkups on weekends/holidays	123 (52.8)	110 (47.2)	0.88 (0.50-1.57)	0.666	0.41 (0.18-0.96)	0.040
Encouraged by medical personnel for health checkups	90 (60.8)	58 (39.2)	1.83 (1.15-2.92)	0.011	1.13 (0.55-2.31)	0.747
Encouraged by family/friends to get a health checkups	98 (60.5)	64 (39.5)	1.90 (1.19-3.04)	0.007	2.18 (1.06-4.51)	0.035
Received health checkup information from various media	108 (54.8)	89 (45.2)	1.19 (0.73-1.94)	0.491	0.86 (0.43-1.76)	0.687

Abbreviations: CI, confidence interval; kg/m^2, kilogram per square meters; n, number; OR, odd ratio; Ref, reference

DISCUSSION

This study found that 53.4% of participants underwent health checkups in the past 3 years. This figure is relatively higher than that reported by Ohnishi et al and Lal et al[14-15], who studied the working-age population in Japan and found health checkup rates in the past year ranging from 31.8% to 43.9%. The prevalence of health checkups studied in the current research was based on 3-year data according to Thailand's health checkup guidelines[4]; meanwhile, the Japanese study collected 1-year data. Thus, the difference in time frame may have contributed to the high prevalence. In addition, this difference may be attributed to the different characteristics of the populations studied. The population in the current study received services at Vajira Hospital, located in urban areas, where higher rates of health checkups are typically observed compared with those in rural populations[15]. Moreover, the sample group was individuals receiving healthcare services at hospitals, potentially indicating their greater access to medical services compared with the general population.

In terms of positive factors related to receiving health checkups, individuals with a monthly income of more than 20,000 Baht had 3.06 times higher odds of undergoing health checkups compared with those with a lower income. This finding is consistent with previous research findings indicating that individuals with good socioeconomic status

are likely to undergo health checkups[8,16-18]. Meanwhile, individuals facing economic and social challenges are less likely to access healthcare services and have low health literacy[19-20].

Individuals who have their workplace-arranged health checkups were 5.64 times more likely to undergo health checkups than those who do not. This factor is considered the most influential in this study. This finding can be explained by the Health Belief Model theory[20], which describes human health behavior. Having health checkups arranged at the workplace helps reduce perceived barriers, which are significant negative factors affecting health checkups. Therefore, good health checkup behavior is encouraged. The complexity and procedures involved in health checkups, need to take time off work or allocate personal time for health checkups, difficulties traveling to health checkup locations, and relatively high expenses associated with health checkups act as barriers to good health checkup behavior that could be overcome if all workplaces arrange for health checkups.

Another positive factor influencing health checkups is that individuals who were encouraged or recommended by their family members or friends to undergo health checkups were 2.18 times more likely to do so than those not receiving such encouragement. This finding can be explained by encouragement acting as a stimulus, which is required in addition to the perceived benefits of health checkups to induce health-related behaviors according to the Health Belief Model theory[21]. In addition, families promote healthy behaviors among their members[22].

In terms of negative factors affecting health checkups, underweight or overweight individuals were less likely to undergo health checkups than those with normal BMI, accounting for percentages of 72% (OR 0.28) and 77% (OR 0.23), respectively. According to Pengpid[23], individuals with overweight tend to exhibit significantly worse health behaviors than those with normal BMI. This behavior reflects a lack of concern for one's health, leading to less emphasis on health checkups compared with that among individuals with normal BMI. Meanwhile, individuals who undergo health checkups are more likely to receive recommendations for appropriate weight management and thus achieve a normal BMI than those who do not undergo health checkups[24].

Another negative factor found in this study is that individuals who can undergo health checkups on weekends or holidays were 59% less likely to undergo health checkups than those who cannot do so. This factor contradicts the findings of Ohnishi et al[14] in Japan, who found that weekend health checkups promote health checkup behavior. This difference may be attributed to the utilization of healthcare benefits: most Thai individuals can only claim their healthcare benefits during official working hours. If not covered by private health insurance, undergoing health checkups on weekends often requires out-of-pocket expenses. However, unknown confounding factors might exist beyond those considered in this study between the Thai and Japanese populations. Therefore, further research is warranted to investigate the underlying reasons for not undergoing health checkups among individuals influenced by this factor.

The main reasons for not undergoing health checkups are not knowing how to start health checkups (58.1%), followed by lack of time to undergo health checkups (51.5%). According to the Health Belief Model[21], these reasons are perceived barriers to health checkup behavior. Even though this population perceives the benefits of health checkups, the desired behavior will not occur if the perception of barriers outweighs the perception of benefits. Therefore, in addition to providing public awareness of the benefits of health checkups, reducing the perception of barriers to health checkups is one of the measures to solve the problem of nonattendance for health checkups. This measure can be achieved by establishing clear service guidelines in hospitals for those seeking health checkups, setting up clinics specifically for health checkups, widely disseminating information to the public, and providing pre-appointment channels to reduce the time required for health checkups.

The strength of this research lies in its focus on Thai adults aged 19-60 years received services at Vajira Hospital. Multiple logistic regression analysis was conducted to isolate the actual factors associated with health checkups by removing other confounding variables. The findings can serve as a guideline for conducting related studies on health checkup attendance and can be utilized to develop strategies for promoting health checkups.

This research has a limitation. It focuses on Thai adults aged 19-60 years who seek services at Vajira Hospital. This may only represent a part of the adult population. Future studies must include surveying adult population in different areas to obtain a representative sample of the entire population. Further study is also warranted to investigate potential hidden factors among individuals who can undergo health checkups on weekends/public holidays that may contribute to their reluctance to undergo health checkups.

CONCLUSION

The prevalence of health checkup attendance is 53.4% among Thai adults aged 19-60 years received services at Vajira Hospital over the past 3 years. The positive factors significantly associated with health checkups are as follows: monthly income of more than 20,000 Baht, workplace arranging health checkups, and encouragement by family members or acquaintances to undergo health checkups. Meanwhile, the negative factors include low or high BMI and undergoing health checkups on weekends/public holidays. The results indicate that a portion of Thai adults still have not attended health checkups. Healthcare providers should implement strategies to increase health checkup attendance by encouraging workplaces to organize health checkups and campaigning for peer encouragement to undergo health checkups, especially among those with low income and are underweight or overweight.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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DATA AVAILABILITY STATEMENT

All of the data generated and analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Postoperative Visual Outcomes and the Influence of Optic Nerve Status on Visual Acuity in Endoscopic Endonasal Surgery of Non-functioning Pituitary Macroadenoma Patients

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ABSTRACT

OBJECTIVE: To evaluate postoperative visual outcomes including visual acuity (VA) and visual field (VF), and the relationship of optic nerve status and postoperative VA improvement in non-functioning pituitary macroadenoma (NFPA) patients who underwent endoscopic endonasal surgery (EES).

METHODS: Data of NFPA patients with visual impairment who underwent EES with tumor removal were retrospectively reviewed from 2017 to 2021. The postoperative visual outcomes (at least 6 months after surgery), and the relationship between optic nerve status and postoperative VA improvement were analyzed. The extent of resection, postoperative complications, and mortality were evaluated.

RESULTS: Twenty-three patients were included in this study with 86.9% favorable vision after surgery. The VA and VF were separately analyzed. The postoperative VA showed 75.8% improved, 9% stable, and 15.2% worsened in preoperative VA impairment eyes. The optic nerve atrophy group had 65.3% improved, 13% stable, and 21.7% worsened VA. The normal optic nerve group had 52.9% improved, 35.4% stable, and 11.8% worsened VA. The p-value was 0.677 between the 2 groups. The postoperative VF examination showed 68.4% improved and 31.6% stable in VF defective eyes. The gross total resection of tumor provided more improvement of VA (72.2%) but not VF comparison with near-total and subtotal resection of tumor.

CONCLUSION: The EES in NFPAs is considered safe with a satisfactory visual improvement rate. Optic nerve atrophy tends to have a higher rate of postoperative VA deterioration.

KEYWORDS: endoscopic endonasal surgery, non-functioning pituitary adenoma, optic nerve atrophy, pituitary tumor, visual outcomes

INTRODUCTION

Pituitary adenoma is a common brain tumor[1]. Non-functioning pituitary macroadenomas (NFPAs) are defined by a tumor size greater than 10 millimeters; and they do not secrete abnormal pituitary hormones. The common presentations of patients with NFPAs are visual impairment, including decreasing visual acuity (VA) or

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visual field (VF) defects or both, headaches, hypopituitarism, and ophthalmoparesis[2]. The visual impairment the indication for surgery in NFPA. In the current literature regarding pituitary adenoma, the rate of postoperative visual improvement varied between 67.5% and 91%[1,3-7]. The predictive factors associated with visual improvement are duration of symptoms, severity of VF defect and VA, retinal nerve fiber layer thickness, size of tumor, and tumor extension[8]. The optic nerve atrophy or optic disc pallor as a predictive factor is still controversial due to a discrepancy in the results[9-10].

The common route of surgery is transsphenoidal route unless there are contraindications. The transsphenoidal surgery can be either performed by microscope or endoscope. Advancements in endoscopic surgical techniques and technology have enabled endoscopic endonasal surgery (EES) to provide a satisfactory tumor resection rate, postoperative visual improvement, and a low rate of complications, including postoperative meningitis and mortality[2-4,11-12]. The unique complications of EES are postoperative cerebrospinal fluid (CSF) leakage and nasal complications such as anosmia, epistaxis, sinusitis, and nasal crusting[13-15].

In this article, the authors aim to present the postoperative visual outcomes in NFPA patients, and the relationship between preoperative optic nerve status and postoperative VA improvement. We also provide the relationship of extent of resection and postoperative visual examination, complications, and mortality.

METHODS

Pituitary tumor data from the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University were analyzed. The inclusion criteria were NFPA patients who underwent EES with tumor removal by 3 neurosurgeons from 2017 to 2021 due to visual impairments (decreased VA or VF or both) and patient's age more than 18 years old. Patients with pituitary adenoma without visual impairment, recurrent pituitary adenoma, and transcranial surgery were excluded from this study. Primary outcome was postoperative visual status compared with preoperative status. Patients were divided into 2 groups based on postoperative visual examination. The favorable vision group was defined as an improved or stable visual examination (VA or VF) at 6 months after surgery. The unfavorable vision group was defined as a worse visual examination (VA or VF) at 6 months after surgery. The visual assessments were performed by ophthalmologists before and after surgery and included VA, VF, and eye examination. The VA assessment was performed by using standard Snellen chart with pinhole occlude. At least 1 line improvement on Snellen chart was considered as VA improvement. If the VA was severe and unable to read the Snellen chart, the severity of VA was measured as blindness, light perception, hand motion detection, and finger counting. At least 1 step improvement of vision was considered as VA improvement. The VF was assessed by Goldmann perimetry. At least small part improvement of VF within the quarter of defect was considered as VF improvement. The patients with pale optic disc by eyeground examination were considered as the optic nerve atrophy group.

Tumor characteristics were analyzed using magnetic resonance imaging (MRI) of the brain and pituitary gland by radiologist and neurosurgeon. The tumor diameter was measured in width*anteroposterior (AP)*height dimension, and tumor volume was calculated by using BrainLab Iplan software (BrainLab, Feldkirchen, Germany). Preoperatively, the rostro-caudal extensions were documented ventricularly (extended to lateral or third ventricle), subfrontal, sphenoid sinus, clivus and/or posterior fossa extension. The lateral extension was documented using the Knosp classification[12]. Postoperative extent of resection was evaluated using the latest postoperative MRI of the brain and

pituitary gland. Gross total resection (GTR) was defined as none of the tumor seen in the postoperative MRI; near-total resection (NTR) was defined as less than 10% of the residual tumor. More than 10% of postoperative residual tumor was defined as subtotal resection (STR).

Furthermore, patient characteristics, presenting symptoms, intraoperative and postoperative complications (intraoperative major vascular injury, blood loss, postoperative meningitis, diabetes insipidus and postoperative CSF leakage requiring surgical intervention) and mortality were recorded.

This study was approved by the Institutional Review Board of the Faculty of Medicine, Vajira Hospital. The certificate of approval number is 118/2565. Statistics were analyzed using SPSS statistics version 28.0.0.0. Data between the groups were compared using the Fisher's exact test and unpaired t-test as appropriate. P-value < 0.05 was considered as statistically significant.

RESULTS

Thirty-one NFPA patients were surgically treated using the endoscopic endonasal approach. Eight patients were excluded due to intact preoperative visual examination (both VA and VF). A total of 23 patients were included in this study. Patient demographics are shown in Table 1. The mean age was 53.7 years old. Twelve (52.2%) were male and 11 (47.8%) female. The most presenting symptom was visual impairment in 21 patients (91.3%). Three patients presented with symptoms of pituitary apoplexy. Other presentations were ophthalmoparesis due to cavernous sinus invasion, headaches, hypotension, and head injury with incidentally found pituitary tumor.

The tumor characteristics were classified using the Knosp classification, as shown in Table 2. There was no tumor classified Knosp 3b in this study. The rostro-caudal extension of a tumor: 11 tumors were extended into the clivus bone. The sphenoid sinus, third ventricle, subfrontal, corpus callosum, and posterior fossa extension were seen in 8, 8, 3, 1, and 1 tumor, respectively. Five of 23 NFPAs (21.7%) were giant pituitary adenomas with maximal tumor diameter greater than 40 mm.

Table 1 Patient demographics

Characteristics	Value
Number of patients	23
Mean age (years)	53.7 ± 11.3
Sex (n, (%))	
Male/Female	12 (52.2%) / 11 (47.8%)
Clinical presentation (n)	
Visual impairment	21 (91.3%)
Pituitary apoplexy	3 (13%)
Cavernous sinus syndrome	1 (4.3%)
Headache	2 (8.7%)
Hypotension	1 (4.3%)
Incidental finding	1 (4.3%)
Preoperative pituitary hormone deficiency (n)	17 (73.9%)
One axis	3 (13%)
Two axes	8 (34.8%)
Panhypopituitarism	6 (26.1%)

Abbreviation: n, number

Table 2 Tumor characteristics

Characteristics	Value
Tumor volume (mean, mL)	3.95 ± 0.75
Tumor diameter (mean, mm)	26.2 ± 10.3*22.6 ± 9.9*30.1 ± 15.4 (W*AP*H)
Knosp Classification (n, (%))	
Knosp 0	1 (4.3%)
Knosp 1	4 (17.4%)
Knosp 2	5 (21.7%)
Knosp 3a	10 (43.4%)
Knosp 3b	0 (0%)
Knosp 4	3 (13%)
Rostro-caudal extension (n)	
Subfrontal	3 (13%)
Third ventricle	8 (34.8%)
Corpus callosum	1 (4.3%)
Clivus	11 (47.8%)
Posterior fossa	1 (4.3%)
Sphenoid sinus	8 (34.8%)
Extent of resection (n, (%))	
GTR	11 (47.8%)
NTR	8 (34.8%)
STR	4 (17.4%)

Abbreviations: AP, anteroposterior; GTR, gross total resection; H, height; mL, millilitre; mm, millimeter; n, number; NTR, near-total resection; STR, subtotal resection; W, width
The tumor characteristics table provided the mean tumor volume (mL), the mean tumor diameter in W*AP*H dimension, the Knosp classification, the rostro-caudal extension of tumor, and extent of resection. The extent of resection composed of GTR (none of residual tumor), NTR (< 10% of residual tumor), and STR (> 10% of residual tumor).

Twenty patients (86.9%) were in the favorable vision group and 3 patients (13.1%) were in the unfavorable vision group, as shown in Table 3. Moreover, 46 eyes were evaluated VA and VF, separately. Preoperatively, VA examination showed 33 impairments and 9 normal eyes (4 were missed). Twenty-five of the 33 (75.8%) impaired VA eyes were improved, 3 (9%) were stable, and 5 (15.2%) worsened, postoperatively. Of the 9 normal VA eyes, 7 (77.8%) were stable and 2 (22.2%) worsened, postoperatively. The preoperative VF examination showed 38 defective eyes and 8 normal eyes. Among the 38 defective eyes, 26 (68.4%) were improved and 12 (31.6%) were stable, postoperatively. Of the 8 normal VF eyes, 7 (87.5%) were stable and 1 (12.5%) worsened, postoperatively. The relationship between the extent of resection and postoperative visual examination were evaluated. Among the GTR group, the postoperative VA was 72.2% improved, 16.7% stable, and 11.1% worsened. The postoperative VF was 59% improved, 36.5% stable, and 4.5% worsened. Along with NTR and STR groups, the postoperative VA improvements was 50% in both, and the postoperative VF improvement was 50% in NTR group and 62.5% in STR group. The rest of results were shown in Table 3.

The preoperative optic disc examination was performed in 40 eyes: 23 optic discs were pale and 17 optic discs were normal. The pale optic disc group: 15 (65.3%) eyes were improved, 3 (13%) were stable, and 5 (21.7%) worsened in VA after surgery. The normal optic disc group: 9 (52.9%) eyes were improved, 6 (35.3%) were stable, and 2 (11.8%) worsened in VA after surgery, as shown in Table 4. The p-value was 0.677.

Eleven of 23 patients (47.8%) achieved GTR, 8 patients (34.8%) were NTR, and 4 patients

(17.4%) were STR. The factors associated with extent of resection were tumor extension, including cavernous sinus, corpus callosum, posterior fossa, and size of tumor. One of 5 (20%) giant pituitary adenomas achieved GTR. The 3 most common complications were meningitis (13%), CSF leakage (13%), and surgical site hematoma (13%). One patient (4.3%) had persistent CSF leakage and required surgical intervention. Complications and morbidity are shown in Table 5. There were no internal carotid artery injuries or mortalities.

Table 3 Visual outcomes

Visual outcome	Value (n, (%))		
Postoperative visual outcome (n = 23)			
Favorable vision	20 (86.9%)		
Unfavorable vision	3 (13.1%)		
	Postoperative visual examination		
	Improved	Stable	Worsened
Preoperative visual examination			
Visual acuity (total eyes = 46)			
33 Impaired VA	25 (75.8%)	3 (9%)	5 (15.2%)
9 Normal VA	-	7 (77.8%)	2 (22.2%)
4 Missing data			
Visual field (total eyes = 46)			
38 Impaired VF	26 (68.4%)	12 (31.6%)	0 (0%)
8 Normal VF	-	7 (87.5%)	1 (12.5%)
Extent of resection			
11 GTR (total eyes = 22)			
VA (18 eyes, 4 missing data)	13 (72.2%)	3 (16.7%)	2 (11.1%)
VF	13 (59%)	8 (36.5%)	1 (4.5%)
8 NTR (total eyes = 16)			
VA	8 (50%)	5 (31.3%)	3 (18.7%)
VF	8 (50%)	8 (50%)	0 (0%)
4 STR (total eyes = 8)			
VA	4 (50%)	2 (25%)	2 (25%)
VF	5 (62.5%)	3 (37.5%)	0 (0%)

Abbreviations: GTR, gross total resection; n, number; NTR, near-total resection; STR, subtotal resection; VA, visual acuity; VF, visual field
The missing data refers to patients whom preoperative VA data were not available.

Table 4 Preoperative optic nerve status and postoperative visual acuity

	Postoperative VA (n, (%))		
	Improved VA	Stable VA	Worsened VA
Pale optic disc (n = 23)	15 (65.3%)	3 (13%)	5 (21.7%)
Normal optic disc (n = 17)	9 (52.9%)	6 (35.3%)	2 (11.8%)
P-value = 0.677			

Abbreviations: n, number; VA, visual acuity

Table 5 Postoperative complication

Complications	n (%)
Meningitis	3 (13%)
CSF leakage	1 (4.3%)
Surgical site hematoma	3 (13%)
Intracapsular hematoma	1 (4.3%)
Subarachnoid hemorrhage	2 (8.7%)
Ischemic stroke	1 (4.3%)
Internal carotid artery injury	0
Mortality	0
Endocrinological complication	
New pituitary hormone deficiency	4 (17.4%)
One axis	2 (8.7%)
Panhypopituitarism	2 (8.7%)
Diabetes insipidus	3 (13%)
Transient	2 (8.7%)
Permanent	1 (4.3%)

Abbreviations: CSF, cerebrospinal fluid; n, number

DISCUSSION

Visual impairment was the most common presentation in the NFPA patients. The primary goal of surgery was to improve vision (both VA and VF). Multiple factors were associated with postoperative visual improvement as stated in the aforementioned studies[8-10]. Preoperative pale optic disc or optic nerve atrophy are believed to be associated with the reduction of the visual improvement rate.

In this study, the favorable visual outcome was 86.9%, which is comparable with the other studies in the literature[3-5,11-12]. We analyzed separately the postoperative VA and VF. Specifically, the authors aimed to find the relationship between optic nerve status and postoperative VA improvement. We found that the pale optic disc group tended to have postoperative VA deterioration (21.7%) more than the normal optic disc group (11.8%), but statistical analysis showed no significance. The pale optic disc was an indicator of optic nerve atrophy and occurred in long-standing anterior visual pathway compression by pituitary adenoma. This factor risked the optic nerve injury during the surgery. The mobilization of tumor capsule might compress and injury the optic nerve around the optic canal or optic chiasm. Meanwhile, VA improvement in the pale optic disc group was satisfactory compared with the normal optic disc group (65.3% versus 52.9%). The rate of VA improvement in the normal optic disc group was lower than in the pale optic disc group, but the postoperative stable VA rate was 35.3% because there were normal VA patients in the normal optic disc group. In the meta-analysis, the pallor optic disc and preoperative visual status affected the postoperative visual function recovery[8,12]. In contrast, the VF improvement rate was 68.4%, and 31.6% had stable VF, which was the same as preoperative status. None of the VF defective eyes deteriorated after surgery in this study. The multiple factors documented in previous studies may explain the persistent postoperative VF defects[16-17], such as age, duration of symptoms, and the severity of VF defect, all of which were not included in this study.

Moreover, the authors evaluated the relationship between the extent of resection and the postoperative visual improvement. In the GTR group tended to have more improvement in VA while postoperative VA declination occurred the most in the STR group. This might be explained by optic nerves compression by the residual tumor.

Two of GTR group showed worsened postoperative VA, 1 patient was pituitary apoplexy. Attempting the GTR might risk the optic nerve injury during the tumor mobilization. In contrast, the postoperative VF examination was not different among each group. One VF in the GTR group was worsened postoperatively, this might be explained by tumor mobilization during the surgery.

The postoperative Subarachnoid hemorrhage (SAH) in this study occurred in 2 patients (8.7%). One patient required anticoagulant due to postoperative venous thrombosis. Another was attempting removal of tumor within cavernous sinus, the postoperative SAH extended from cavernous sinus bleeding and caused postoperative left cavernous sinus syndrome. None of postoperative SAH patients had worsened VA or VF.

The limitations regarding this study should be noted. This study is retrospective. Furthermore, only a small number of patients were included due to its selective inclusion criteria.

CONCLUSION

The EES of NFPAs is considered safe with a satisfactory visual improvement rate. Surgeons should be aware of the postoperative visual deterioration that can occur in patients with preoperative optic nerve atrophy or pale optic disc. However, surgical intervention remains advantageous treatment among the NFPA patients.

CONFLICT OF INTEREST

The authors have no conflict of interest in this study. They received no financial support.

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None

DATA AVAILABILITY STATEMENT

The data that support the clinical results of this study are not openly available due to the sensitivity of the data. They are, however, available from the corresponding author upon request.

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Original Article

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Exploring the Predictive Capability of Osteoporosis Self-Assessment Tool for Asians Score for Fragility Fractures: A Retrospective Cohort Analysis

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ABSTRACT

OBJECTIVE: The primary objective of the present study was to evaluate the predictive efficacy of the Osteoporosis Self-Assessment Tool for Asians (OSTA) in identifying individuals predisposed to fragility fractures.

METHODS: This retrospective cohort study involved 17,189 adults aged 50 years and older. We examined the relationship between osteoporosis risk and fragility fractures to establish fundamental insights into fragility fracture risk factors. Data were collected from the outpatient orthopedic department. The incidence rates (IRs) per person-year at risk were calculated based on the initial diagnosis of fragility fractures. Poisson regression analysis was used to ascertain the IR ratios (IRR), with adjustments made for factors including age, sex, income, occupation, comorbidities, and estrogen supplementation.

RESULTS: Among the 17,189 patients identified as healthy adults at baseline, 6,996 fragility fractures were recorded. The adjusted IRR for documented fragility fractures demonstrated a significant elevation among individuals categorized as medium or high risk for osteoporosis displayed a 1.24-[95% confidence interval (CI) 1.15-1.33] and 1.66-fold (95% CI = 1.51-1.83), respectively.

CONCLUSION: Our results highlight the increased risk of fragility fractures associated with medium and high-risk osteoporosis, as evaluated by OSTA and provide insights into potential strategies for mitigating the anticipated public health impact of osteoporotic fractures.

KEYWORDS: fragility fracture, incidence, osteoporosis, Osteoporosis Self-assessment Tool for Asians, primary care

INTRODUCTION

Osteoporosis is characterized by the deterioration of bone mass and microarchitecture, leading to reduced bone strength and increased vulnerability to fragility fractures[1]. The prevalence of osteoporosis among Thai males was recorded at 12.6% and 4.6% at the femoral neck and lumbar spine, respectively. Furthermore, the prevalence of osteoporosis among early postmenopausal women seeking care at a tertiary care hospital's menopausal clinic was determined to be 21.3%[2]. Fractures attributable to osteoporosis are often due to low-impact incidents such as falls from a standing height or those which under ordinary circumstances would not cause fractures[3]. The age-adjusted incidence of hip fracture demonstrated an annual increase of 2%, rising from 192.9 (males: 110.8; females: 272.1)

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to 253.3 (males: 135.9; females: 367.9) per 100,000 person-years (PY)[2]. However, the delineation of osteoporotic fractures is not unequivocal and occasionally engenders misconceptions. Despite comprehensive studies demonstrating increased fracture incidence across various anatomical sites in individuals with diminished bone mineral density (BMD) regardless of location[3], reliance solely on low BMD may inadequately discern the propensity for osteoporotic fractures[3], as fractures may occur independently of diminished BMD[4]. Moreover, bone fragility did not appear to play a role in fractures resulting from high-impact trauma. A comparative analysis investigating the BMD of women who experienced fractures from either low- or high-level traumatic events revealed that under high-energy trauma scenarios, individuals with osteoporosis demonstrated increased susceptibility to fractures compared to those without osteoporosis[5].

Understanding the epidemiology of fragility fractures, notably hip fractures, which are linked to increased mortality and disability rates[4], has been a central focus of research, resulting in varied findings across diverse global regions[6]. While female sex and advanced age are firmly established risk factors for osteoporosis, the impact of other demographic parameters remains unclear. Notably, a recent systematic review highlighted the correlation between socioeconomic status and risk of fragility fractures[7]. Therefore, our research, leveraging routinely collected data, sought to elucidate the recording practices regarding osteoporosis and fragility fractures. Concurrently, we aimed to investigate the trends in incidence rates (IRs) across various sociodemographic strata. Insight into the patterns of documented osteoporosis diagnoses is of paramount importance in formulating and implementing public health initiatives and community-based interventions aimed at preventing fragility fractures in the elderly population.

BMD evaluation in the lumbar spine and hip is currently the primary approach for diagnosing osteoporosis. Extensive research has established a strong association between low BMD and major osteoporotic fractures, including those affecting the spine[8], hip[9], humerus[10], and forearm[10]. Given the well-documented correlation between advanced age, reduced body weight, low BMD, and increased fracture risk[6], the World Health Organization developed the Osteoporosis Self-Assessment Tool for Asians (OSTA) score. The OSTA score is computed using body weight and age [(body weight in kilograms–age in years) multiplied by 0.2], and it aims to identify women at risk for osteoporosis[11]. In a proof-of-principle study, OSTA demonstrated superior performance compared to alternative osteoporotic indices, showing a sensitivity of 91%, specificity of 45%, and a receiver operating characteristic curve of 0.79 at a cutoff value of -1[11]. Additionally, minimal disparities in OSTA performance were observed across femoral neck and lumbar spine BMD reference points at the -1 cutoff threshold[12]. By stratifying patients into low- (OSTA > -1), medium- (-1 ≥ OSTA ≥ -4), and high-risk (OSTA < -4) categories for osteoporosis susceptibility[11], it is estimated that individuals with an OSTA score exceeding -4 have a 99.3% probability of not having osteoporosis[13]. With robust validation across populations in Taiwan, China, Korea, Singapore, Malaysia, Thailand, and the Philippines, OSTA has emerged as a dependable and practical screening tool for identifying patients at risk of osteoporosis[14].

The current investigation sought to assess the predictive accuracy of the OSTA in discerning individuals prone to fragility fractures.

METHODS

The Phramongkutklao Hospital Database (PHD) program is a comprehensive system that facilitates access to patient data within Phramongkutklao Hospital, Bangkok, Thailand. For this investigation, a subset of the PHD was utilized, comprising extensive healthcare records pertaining to the ambulatory care services offered by the orthopedic outpatient department. These datasets were randomly sampled from all patients seeking care. Importantly, these datasets can be

linked via encrypted and unique personal identification numbers, thereby enabling the establishment of longitudinal medical histories of individual patients. Diagnostic classification was performed in accordance with the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Approval for this study was obtained from the Institutional Review Board of the Royal Thai Army Medical Department (IRBTA0269/2024).

A retrospective cohort analysis was performed to investigate the association between fragility fractures and osteoporotic risk, which was evaluated using OSTA. The investigation was conducted at Phramongkutklao Hospital, affiliated with Phramongkutklao College of Medicine, in Bangkok, Thailand from January 2009 to December 2023. The inclusion criteria for patients diagnosed with fragility fractures included hip, spine, pelvis, femur (thigh), wrist, and humeral (arm) fractures. These fractures were identified using the ICD-10-CM codes M80.x, M84.3, and M84.4. New-onset osteoporosis diagnoses from 2009 to 2023 were ascertained based on primary discharge diagnoses. The exclusion criteria for the study were individuals aged < 50 years; those with a documented history of prior fractures; individuals with a history of smoking, alcohol addiction, systemic glucocorticoid use, or rheumatoid arthritis at baseline; and those with traumatic fractures resulting from accidents (such as car accidents or falls from heights above chair level), pathological fractures associated with cancer, or fractures affecting the fingers, toes, ankles, face, or skull. Individuals diagnosed with osteoporosis were excluded. Among the 17,189 patients meeting the inclusion criteria, which included 15,525 females, 6,996 were diagnosed with fragility fractures and included in the analysis. Patients without osteoporosis were randomly selected from the PHD to form a comparison cohort. All participants were tracked until December 31, 2023, or until they experienced loss to follow-up, mortality, or voluntary withdrawal from the healthcare system.

The study encompassed various variables, including age (grouped into 50–65 years and > 65 years), sex (male or female), and income. Baseline comorbidities were identified using the ICD-10-CM and Anatomical Therapeutic Chemical (ATC) codes for medications. The specific comorbidities examined included stroke (ICD-10-CM codes: I60-I66), hypertension (ICD-10-CM codes: I10-I15), type 2 diabetes mellitus (ICD-10-CM code: E11), dementia [ICD-10-CM codes: F00, F00.(1,2,9), F01, F01.(0,1,2,3,8,9), F02, F02.(0,1,2,3,4,8), and F03], Alzheimer's disease (ICD-10-CM: G30), depressive disorder [ICD-10-CM codes F32 and F32.(0,1,2,3,8,9), and F33.(0,1,2,3,4,8,9)]. Additionally, this study considered the use of estrogen (ATC codes: T385, Y425, EST103N, PRO108E, and ANG103N), calcium supplementation (ATC codes: CHA103E, CHA106E, CAL107N, and VIT112E), and vitamin D2 supplementation at a dose of 20,000 IU (calciferol; ATC code, VIT112E).

Previous studies have indicated that individual-based low socioeconomic status (SES) is associated with an increased risk of fragility fractures, with a relative risk (RR) of 1.27 (95% confidence interval (CI) 1.12, 1.44)[15]. Furthermore, the overall risk of mortality within one year post-hip fracture in individuals with low SES was found to be 24% higher compared to those with high SES (RR 1.24, 95% CI 1.19 to 1.29) for individual-level SES measures[16]. Therefore, in this study, socioeconomic status, represented by income, is considered an important factor to investigate, as it increases the risk of fragility fractures. In the table, "With Income" means having income, and "No Income" means having no income.

The IR of fragility fractures was determined per PY. This involved compiling the number of patients with an initial recording of the diagnostic read code for fragility fracture and osteoporosis recruitment from 2009 to 2023, followed by dividing this total by the aggregate PY of follow-up across all patient records during this timeframe. IRs were stratified by age, sex, socioeconomic status, and calendar year of diagnosis. Poisson regression analysis was performed to compare

IRs and provide adjusted IR ratios, accounting for age, sex, income, and calendar year. Likelihood ratio tests were performed to investigate potential interactions among the covariates. Statistical analyses were performed using the IBM SPSS statistics software (version 26.0; IBM, Armonk, NY, USA).

RESULTS

Table 1 presents the sociodemographic characteristics and baseline comorbidity status of patients in the fragility and non-fragility fracture cohorts. Within both cohorts, approximately 4.9% of patients were identified as experiencing no income, while 11.2% fell within the underweight range [body mass index (BMI) < 18.5], and 13.8% were classified as high risk for osteoporosis (OSTA < -4). Additionally, all patients exhibited low levels of vitamin D. Patients with fragility fractures demonstrated a higher prevalence of dementia (8.2% vs. 5.3%, p < 0.001), stroke (5.2% vs. 3.9%, p < 0.001), and hypertension (64.7% vs. 62%, p < 0.001) compared to patients without fragility fractures. Moreover, the proportion of patients receiving estrogen and calcium supplementation was significantly lower among those with fragility fractures than among those without.

Table 1 Comparison of baseline characteristics between patients with and without fragility fractures

Characteristics		Fragility fractures			
		No	Yes	Total	P-value
Total		10193	6996	17189	
Age (years)		75.2 ± 9.8	78.6 ± 10	76.6 ± 10	< 0.001*
Sex	Female	8884 (87.2%)	6341 (90.6%)	15225 (88.6%)	< 0.001*
	Male	1309 (12.8%)	655 (9.4%)	1964 (11.4%)	
OSTA	High	1019 (10%)	1343 (19.2%)	2362 (13.8%)	< 0.001*
	Medium	3129 (30.6%)	2505 (35.8)	5634 (32.8)	
	Low	6045 (59.4%)	3148 (45%)	9193 (53.4%)	
Income	With income	9637 (94.5%)	6715 (96%)	16352 (95.1%)	< 0.001*
	No Income	556 (5.5%)	281 (4%)	837 (4.9%)	
BMI (kg/m^2)	< 18.5	576 (9.7%)	553 (13.2%)	1129 (11.2%)	< 0.001*
	18.5-22.9	2444 (41.1%)	1797 (43.1%)	4241 (41.9%)	
	23-24.9	1269 (21.3%)	785 (18.8%)	2054 (20.3%)	
	25-29.9	1344 (22.6%)	813 (19.5%)	2157 (21.3%)	
	≥ 30	315 (5.3%)	226 (5.4%)	541 (5.3%)	
Dementia	No	9649 (94.7%)	6424 (91.8%)	16073 (93.5%)	< 0.001*
	Yes	544 (5.3%)	572 (8.2%)	1116 (6.5%)	
Stroke	No	9794 (96.1%)	6634 (94.8%)	16428 (95.6%)	< 0.001*
	Yes	399 (3.9%)	362 (5.2%)	761 (4.4%)	
Depressive	No	9835 (96.5%)	6746 (96.4%)	16581 (96.5%)	0.864
	Yes	358 (3.5%)	250 (3.6%)	608 (3.5%)	
Type 2 Diabetes mellitus	No	10019 (98.3%)	6856 (98%)	16875 (98.2%)	0.175
	Yes	174 (1.7%)	140 (2%)	314 (1.8%)	
Hypertension	No	3871 (38%)	2470 (35.3%)	6341 (36.9%)	< 0.001*
	Yes	6322 (62%)	4526 (64.7%)	10848 (63.1%)	
Estrogen supplementation	No	10060 (98.7%)	6964 (99.5%)	17024 (99%)	< 0.001*
	Yes	133 (1.3%)	32 (0.5%)	165 (1%)	
Calcium supplementation	No	808 (7.9%)	398 (5.7%)	1206 (7%)	< 0.001*
	Yes	9385 (92.1%)	6598 (94.3%)	15983 (93%)	

Abbreviations: BMI, body mass index; kg/m^2, kilogram per square meter; OSTA, osteoporosis self-assessment tool for Asians
*P-value < 0.001

Table 2 illustrates that patients classified as medium- or high-risk for osteoporosis based on OSTA, with or without comorbidities, were associated with an increased risk of fragility fractures compared with those categorized as low risk for osteoporosis. Specifically, patients identified as medium or high risk for osteoporosis displayed a 1.24-[95% CI = 1.15-1.33] and 1.66-(95% CI = 1.51-1.83) higher risk of developing fragility fractures, respectively, compared to patients categorized as low risk for osteoporosis. Female patients exhibited a 1.38-fold (95% CI = 1.23-1.54) higher risk of fragility fractures compared to male patients. The risk of osteoporotic fractures differs significantly between males and females, with females generally having a higher risk due to factors such as post-menopausal estrogen decline affecting bone density[17]. The OSTA index is primarily designed to assess fracture risk in females[18]. However, when applied to males, it necessitates a different cutoff value to account for differences in bone structure and density between genders. Adjusting the cutoff value for males may result in changes in the assessed fracture risk, potentially leading to more accurate identification of high-risk individuals and better-targeted prevention and treatment strategies. Additionally, patients with a history of stroke or hypertension were associated with a 1.15-(95% CI = 1.02-1.31) and 1.1-fold (95% CI = 1.03–1.18) higher risk of developing fragility fractures, respectively. Analysis of the effects of medication on fragility fracture risk revealed that patients receiving estrogen supplementation exhibited a 0.69-fold lower risk of fragility fractures than those who did not receive any treatment (p = 0.039).

Table 2 Comparison of incident rate ratios between patients with high, medium and low risk of osteoporosis for fragility fracture outcomes

Characteristics		Crude IR (95% CI)	P-value	Adjusted* IRR (95% CI)	P-value
Female		1.33 (1.23-1.44)	< 0.001*	1.38 (1.23-1.54)	< 0.001*
OSTA	High	1.96 (1.81-2.13)	< 0.001*	1.66 (1.51-1.83)	< 0.001*
	Medium	1.39 (1.3-1.49)	< 0.001*	1.24 (1.15-1.33)	< 0.001*
Age > 65 years		1.52 (1.41-1.63)	< 0.001*	1.13 (0.99-1.29)	0.071
No income		1.33 (1.18-1.49)	< 0.001*	0.88 (0.71-1.09)	0.247
BMI < 18.5 kg/m^2		1.28 (1.17-1.4)	< 0.001*	0.94 (0.85-1.04)	0.217
Stroke		1.24 (1.12-1.38)	< 0.001*	1.15 (1.02-1.31)	0.029**
Depressive disorder		1.02 (0.9-1.15)	0.783	1.11 (0.95-1.28)	0.186
Type 2 Diabetes mellitus		1.05 (0.89-1.25)	0.538	1.08 (0.9-1.3)	0.383
Hypertension		1.1 (1.04-1.15)	< 0.001*	1.1 (1.03-1.18)	0.039**
Estrogen supplementation		0.42 (0.3-0.59)	< 0.001*	0.69 (0.48-0.98)	0.039**
Calcium supplementation		1.29 (1.16-1.42)	< 0.001*	1.17 (0.93-1.47)	0.173

Abbreviations: BMI, body mass index; CI, confidence interval; IR: incidence rate; IRR: incidence rate ratio; kg/m^2, kilogram per square meter; OSTA, osteoporosis self-assessment tool for Asians
*P-value < 0.001; **P-value < 0.05

DISCUSSION

Osteoporosis is a pervasive global health issue with a steadily increasing prevalence, posing a mounting burden on society. Regrettably, its insidious nature often renders it asymptomatic until the occurrence of fractures, highlighting the critical need for early detection and assessment of associated risk factors. Such endeavors hold considerable significance in mitigating the profound impact of osteoporosis-related complications on public health. This study conducted in the Thai population sheds light on pertinent demographic associations, offering valuable insights into the epidemiological landscape of osteoporosis.

Our study is the first population-based investigation into the risk of fragility fractures using the classification framework of OSTA, a widely utilized osteoporotic risk assessment instrument, in Thailand. We identified a markedly elevated risk of fragility fractures among patients classified as medium- and high-risk for osteoporosis using OSTA compared with those categorized as low risk. This observed trend persisted across both sexes. Our findings align closely with those of previous research, demonstrating a consistent association between OSTA-scored risk of osteoporosis and heightened susceptibility to bone fractures. Notably, our findings align with those reported by Chang et al.[19], wherein an elevated risk of osteoporosis assessed using OSTA was linked to an increased incidence of bone fractures in female patients with trauma. Elderly females consistently emerge as vulnerable demographic subgroups susceptible to fragility fractures. Irrespective of sex, the sixth decade of life stands out as a prevalent age group for such fractures. This observation is likely attributable to the decline in sex hormones levels experienced by both sexes during this life stage, coupled with sustained outdoor activities amid insufficient physical fitness, which predisposes individuals to fractures from minor trauma amid underlying comorbidities. Conversely, within the relatively younger age bracket of 40-60 years, aberrant BMI, characterized by either low or high values, emerged as a significant contributing factor to fragility fractures, accounting for 38.1% of fractures within this cohort. This underscores the notion that anomalous BMI, irrespective of age or sex, can promote fragility fractures, emphasizing the importance of BMI management in fracture prevention across diverse demographic groups.

According to OSTA, only a minority of patients (13.8%) are at high-risk of osteoporosis (OSTA < -4). However, the Poisson regression analysis in this study underscored a robust association between OSTA score and fragility fractures. Among the prevalent comorbidities, cardiovascular diseases were the most common. Hypertension is related to the occurrence of fragility fractures due to several interconnected mechanisms. Firstly, hypertension can lead to arterial stiffness and reduced blood flow, which can negatively impact bone health by diminishing the supply of essential nutrients and oxygen to the bone tissue. Additionally, high blood pressure is often associated with inflammation and oxidative stress, both of which can contribute to bone resorption and decrease bone mineral density, making bones more susceptible to fractures. Furthermore, antihypertensive medications, particularly diuretics, may affect calcium balance and bone metabolism. Lastly, individuals with hypertension may also have other comorbid conditions, such as diabetes or chronic kidney disease, which further exacerbate the risk of bone fragility and fractures[20]. Serum vitamin D3 levels have also been associated with fragility fractures[21], which highlights the need to comprehensively consider all risk factors, both for individuals with a history of fragility fractures and those who were recently afflicted, to mitigate the risk of recurrent fragility fractures in the same individual. Special attention should be directed towards factors with the potential to predict multiple fragility fractures, such as stroke and hypertension, while acknowledging factors that confer protection against fragility fractures, such as estrogen supplementation. This holistic approach to risk assessment and management is crucial to enhance fracture prevention strategies and promote bone health in affected individuals.

The study has several limitations. Firstly, there is potential for underdiagnosis and undertreatment of osteoporosis among individuals with dementia, as prior research indicates a reduced likelihood of osteoporosis treatment among those with severe dementia[22]. Secondly, the PHD lacks comprehensive information regarding smoking habits, alcohol consumption, socioeconomic status, and family history of systemic diseases, all of which could be pertinent risk factors for osteoporosis[23-24]. Thirdly, the methodological limitations inherent to a retrospective cohort study, including potential biases related to adjustments for confounding variables, may have affected the statistical robustness of the findings. Additionally, although the investigation suggests a lower risk of fragility fractures among patients receiving estrogen supplementation compared to those not undergoing any treatment, it is important to note that some instances of estrogen supplementation may have been administered locally rather than systemically, potentially attenuating the observed effects. The anonymized nature of the data within the PHD precludes access to clinical variables such as imaging and pathology results of the study patients. However, despite these limitations, data pertaining to weight, age, diagnosis of osteoporosis, and fragility fractures remain reliably documented in the database. Furthermore, all participants in the study hailed from the same geographic locale and sought medical attention at outpatient facilities within a single hospital, necessitating a multicenter investigation to afford a more comprehensive and robust analysis. At the study's onset, individuals with a history of fragility fractures in 2009 were excluded from the baseline assessment to identify newly diagnosed cases from 2009 to 2023, thereby enhancing the robustness of the findings. Lastly, the lack of detailed data on smoking, alcohol drinking, socioeconomic status, and family history, as well as the absence of longitudinal data, limits the ability to track the progression of both osteoporosis and dementia over time, underscoring the necessity for further research on these aspects[24].

CONCLUSION

The study provided an early detection method for fragility fractures. The outcomes derived from our comprehensive retrospective population-based investigation revealed an increased risk of fragility fractures among individuals within the Thai population in one institution classified as having medium and high risk of osteoporosis based on OSTA scores. Intriguingly, our analysis also underscores the notable association between estrogen supplementation and a lower risk of fragility fractures among these high-risk patients. This finding highlights the potential utility of estrogen supplementation as a preventive measure against fragility fractures in high-risk individuals, thus warranting further exploration and consideration in clinical practice.

CONFLICT OF INTEREST

Kasidid Lawongsa, Thitiphan Kanchanabul, and Jitrawee Tepakorn declare that they have no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed. For further correspondence, please contact kasidid.lawongsa@gmail.com

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Original Article

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Prevalence and Risk Factors Associated with Frailty Syndrome in Chronic Heart Failure Patients at Heart Failure Clinic at Vajira Hospital

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ABSTRACT

OBJECTIVE: The prevalence of frailty syndrome in patients with chronic heart failure (HF) at Vajira Hospital was investigated, and risk factors associated with frailty syndrome and chronic HF were identified for optimizing management and improving outcomes in this vulnerable population.

METHODS: A prospective cross-sectional study was conducted at chronic HF clinic of Vajira Hospital by history taking, collecting data with questionnaires, and performing specific tests (Fried Frailty Phenotype). Echocardiogram and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were obtained from chronic HF patients from January 2022 to December 2023. A physician collected clinical data and baseline characteristics. All patients were tested for the Fried Frailty Phenotype by a physical therapist. Determinants were evaluated using univariate and multivariate logistic regression models.

RESULTS: A total of 94 patients were enrolled. The prevalence of frailty syndrome in patients with HF was 27.70% (95% CI: 18.90–37.80). Univariate analysis showed that factors associated with increased likelihood of frailty syndrome in patients with chronic HF included chronic kidney disease (CKD stages IV–V, unadjusted OR = 4.00, 95% CI: 1.11–14.43, p-value = 0.03), New York Heart Association (NYHA; III–IV, unadjusted OR = 39.00, 95% CI: 8.30–183.29, p-value < 0.001), left ventricular ejection fraction (≤ 40%, unadjusted OR = 3.84, 95% CI: 1.13–13.02, p-value = 0.031), NT-proBNP (> 1000 pg/mL, unadjusted OR = 5.50, 95% CI: 1.71–17.66, p-value = 0.004) and diuretics (unadjusted OR = 8.33, 95% CI: 1.05–66.22, p-value = 0.045) but multivariate analysis showed only NYHA (III-IV), adjusted OR = 30.51, 95% CI: 6.01–154.94, p-value < 0.001) increase risk of frailty syndrome.

CONCLUSION: The prevalence of frailty syndrome in patients with chronic HF was found, and the main associated factor affecting frailty is NYHA(III-IV). NYHA classification and frailty in HF patients are crucial for comprehensive management. Regular assessment of NYHA class, frailty status, and associated factors (physical, cognitive, nutritional, and psychosocial) is essential for personalized care planning.

KEYWORDS: chronic heart failure, frailty syndrome, Fried Frailty Phenotype

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INTRODUCTION

Heart failure (HF) is a significant health issue in Thailand, as it is in many parts of the world. The prevalence of HF in Thailand has been increasing over the years, primarily due to several factors including an aging population, lifestyle changes, and an increasing burden of cardiovascular risk factors. The study highlighted that the prevalence increased significantly with age, reaching 7.70% among those aged 75 years and older[1-2]. The death rate of HF has increased over the past decade. A five-year European study of death rates from the Framingham Heart Study and the Cardiovascular Health Study reported a death rate of 67% within five years since diagnosis[3]. The death rate or mortality rate is associated with HF in Thailand, like in many other countries, but the key factor associated is aging[4].

HF and frailty often coexist and can have significant implications for patients. Frailty is a condition characterized by decreased physiologic reserve and increased vulnerability to stressors, which can include chronic diseases like HF. The relationship between HF and frailty is related to increasing age, congenital diseases, mechanisms of disease, Inflammatory processes, and increased free radicals. A combination of at least two of these conditions results in poor prognosis[5-6]. The presence of frailty in individuals with HF is associated with worse outcomes. Frailty increases mortality, rehospitalization rate, and medical costs, especially for patients with chronic HF. It also affects the quality of life of both patients and caregivers[7]. Now frailty is not routinely assessed in clinical practice as part of HF management, but its recognition is crucial. Tools such as the Fried Frailty Phenotype or the Clinical Frailty Scale can help in identifying frail patients[8].Therefore, the assessment of frailty status in patients with chronic HF is essential to their prognosis and treatment[9-10].

Methods for measuring frailty in patients with chronic HF have been established, such as the Fried Frailty Phenotype[11], deficit index[12], Edmonton Frailty Scale[13], and Clinical Frailty Scale[14], which mainly consist of questionnaires and physical tests. The Fried Frailty Phenotype is one of the accepted methods and widely used, providing concrete results[15] based on the symptoms of diseases and including three of the following criteria: unintentional weight loss (information is obtained through questionnaire responses); fatigue status measured by the Center for Epidemiological Studies-Depression Scale; muscle weakness measured by handgrip strength; slowness, which is indicated by a decrease in walking time after walking for 15 feet or approximately 4.5 meters relative to normal values based on gender and body mass index (BMI); and low physical activity assessed according to normal values based on gender and height. A questionnaire measurement tool based on the Minnesota Leisure Time Activity questionnaire was used. The level of physical activity was calculated as energy per week (kcal/week). In the evaluation, a total score of 3 indicated frailty; 1–2, onset of frailty; and 0, no frailty. Most studies on frailty in patient groups have used the Fried Frailty Phenotype, including comparative studies that measured the degree of frailty in patients with chronic HF patients with various tools. It was found that the Fried Frailty Phenotype has a higher sensitivity and specificity of 93.00% and 76.00%, respectively[15]. In endurance of patients with respiratory diseases is typically evaluated with a six-minute walking test (6 MWT). It is a simple test, and its results are easy to interpret. it is also applied to groups of patients with cardiovascular diseases, such as chronic HF. A study in a group of patients with chronic HF found that the 6 MWT test results are associated with mortality and disability rates, especially in those with poor left ventricular contraction[16-17].

In previous study showed that the prevalence of frailty in 26 evidence-based studies (systemic review and meta-analysis) related to frailty in patients with chronic HF was 44.50%[18]. A total of 14 ongoing studies is exploring mortality and hospital admission rates of 5186 patients with chronic HF; frailty increased the mortality rate 1.54-fold, the hospital admission rate

increased 1.56-fold, and the change was statistically significant[19]. A recent study in Asian found the prevalence of 69% of HF patients and had a Higher frailty index in older age, Southeast Asian residency, and Malay ethnicity. In frailty, group found more comorbidities than the non-frailty group[20]. In another study of a specific group in HF with reduced ejection fraction group using a 42-item frailty index to identify frailty status found that the frailest patients were female, older, and had more clinical symptoms than non-frailty. High rates of all-cause death or all-cause hospitalization in frailty group[21].

Elderly people with HF are vulnerable. In the past studies were limited generalizability some studies may focus on specific demographics, settings, or conditions, limiting the applicability of findings to other populations or contexts and no study has evaluated frailty in patients with brittle HF in Thailand. Thus, the objective of this study was to determine the prevalence of frailty and to identify the factors involved and tailoring treatment for HF in frail individuals with a multidisciplinary approach involve optimizing medications, focusing on symptom management, encouraging physical activity within the individual's capabilities, and addressing nutritional status.

METHODS

A prospective cross-sectional study was conducted at HF clinic of Vajira Hospital. Patient histories were obtained, and questionnaires and specific tests (Fried Frailty Phenotype) were used. Echocardiogram, and NT-proBNP data from chronic HF patients from January 2022 to December 2023. All patients were tested by a physical therapist using the Fried Frailty Phenotype.

The inclusion criteria included patients aged ≥ 65 years and those with a diagnosis with chronic HF. Chronic HF patients are stage C HF refers to a specific classification of HF according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines[22-23]. The exclusion criteria were acute heart attack defined as acute HF, acute myocardial infarction, pulmonary embolism or cardiogenic shock, hospitalization 3 months, severe heart valve abnormalities defined as severe aortic regurgitation/stenosis or severe mitral regurgitation/stenosis or severe tricuspid regurgitation/stenosis, absence of echocardiogram results, cancer diagnosis, psychiatric disease, myasthenia gravis, major stroke and incapability to communicate or perform tests. This study uses the Fried Frailty Index to evaluate frailty. It consists of five components: unintentional weight loss; has the individual experienced significant weight loss (≥ 10 pounds in the past year) without trying to lose weight, exhaustion, low physical activity, weakness measured using a dynamometer, slow walking speed. Each component is scored 0 or 1, with 1 indicating the presence of that component. A higher score (0-5) indicates greater frailty (0 points = not frail, 1-2 points = pre-frail, 3 or more points = frail). This study was approved by the Institutional Review Board of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University (COA 113/65).

Sample size estimation using sample size calculation formula for proportion estimation:

$$n = \frac{{Z_{\alpha/2}}^2\, p(1-p)}{d^2}$$

when $Z_{\alpha/2}$ defined as 1.96 (standard statistical value under the normal curve that corresponds to the significant level and α = 0.05), d defined as 0.1 (desired margin of error by determining the percentage deviation of 10%), p = 0.474 (population proportion reference from study of the prevalence of frailty in HF[16] when using the formula the sample size calculated is 96 people for each group.

Statistical analyses were performed using SPSS Statistics for Windows, version 26 (IBM Corp., Amok, NY, USA). Baseline characteristics and categorical variables were presented as percentages and numbers. Continuous variables were presented as means and standard deviations. Categorical variables using Chi-Square or Fisher's Exact Tests, and continuous variables were compared using the Independent Samples T-Test,

Mann-Whitney U Test. Two groups (frailty and non-frailty) were compared using one-way ANOVA and Kruskal–Wallis Test for the comparison of more than two groups (non-frailty, pre-frailty, and frailty). Univariable and multivariable analyses of factors associated with frailty syndrome in patients with chronic HF were analyzed using binary logistic regression. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 94 patients with chronic HF were included in this study. The baseline characteristics of patients with chronic HF were as follows: average age, 68.55 ± 7.04 years; male, 77.70%; average BMI, 23.32 ± 4.52 kg/m^2; and comorbidities (diabetes mellitus, 56.40%; hypertension, 90.40%; dyslipidemia, 96.80%); atrial fibrillation, 36.20%; and ischemia heart disease, 57.40%. The patients had New York Heart Association (NYHA) II about 50.00%, the average left ventricular ejection fraction (LVEF) value was 41.09% ± 13.89%, average 6MWT was 298.54 ± 113.03 meters, the median NT-proBNP value was 1459.00 pg/mL (IQR: 420–2863). The patients mostly use angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers/ or angiotensin receptor-neprilysin inhibition, beta blocker and mineralocorticoid receptor antagonist; all data is shown in Table 1.

Table 1 Demographic and baseline characteristics of chronic heart failure patients

Variables	Total (n = 94)	Non-frailty (n = 31)	Pre-frailty (n = 37)	Frailty (n = 26)	P-value
Age (years)	68.55 ± 7.04	68.45 ± 6.62	67.76 ± 7.63	69.81 ± 6.74	0.526
Sex					0.254
Male	73 (77.70)	27 (87.10)	28 (75.70)	18 (69.20)	
BMI (kg/m^2)	23.32 ± 4.52	24.59 ± 4.83	22.72 ± 4.24	22.66 ± 4.37	0.160
Comorbidity					
Diabetes mellitus	53 (56.40)	17 (54.80)	23 (62.20)	13 (50.00)	0.618
Hypertension	85 (90.40)	29 (93.50)	34 (91.90)	22 (84.60)	0.510
Dyslipidemia	91 (96.80)	31 (100.00)	36 (97.30)	24 (92.30)	0.276
Chronic kidney disease					0.311
No	36 (38.30)	12 (38.70)	16 (43.20)	8 (30.80)	
Stage III	43 (45.70)	16 (51.60)	17 (45.90)	10 (38.50)	
Stage IV	13 (13.80)	3 (9.70)	4 (10.80)	6 (23.10)	
Stage V	2 (2.10)	0 (0.00)	0 (0.00)	2 (7.70)	
Atrial fibrillation	34 (36.20)	12 (38.70)	14 (37.80)	8 (30.80)	0.795
Ischemia heart disease	54 (57.40)	16 (51.60)	19 (51.40)	19 (73.10)	0.166
NYHA					< 0.001
I	7 (7.40)	5 (16.10)	2 (5.40)	0 (0.00)	
II	47 (50.00)	19 (61.30)	26 (70.30)	2 (7.70)	
III	37 (39.40)	7 (22.60)	9 (24.30)	21 (80.80)	
IV	3 (3.20)	0 (0.00)	0 (0.00)	3 (11.50)	
LVEF (%)	41.09 ± 13.89	46.54 ± 13.21	40.54 ± 14.29	35.38 ± 11.97	0.009
LVEF group					0.025
≤ 40	45 (47.90)	9 (29.00)	17 (46.00)	19 (73.10)	
40-49	24 (25.50)	11 (35.50)	10 (27.00)	3 (11.50)	
≥ 50	25 (26.60)	11 (35.50)	10 (27.00)	4 (15.40)	
6MWT (m)	298.54 ± 113.03	366.32 ± 64.12	317.22 ± 85.40	191.15 ± 117.83	< 0.001
NT-proBNP (pg/ml)	1459 (420-2863)	767 (354-1796)	1621 (353-2980)	2392 (1453-4447)	0.002
NT-proBNP group ≥ 1000	56 (59.60)	12 (38.70)	22 (59.50)	22 (84.60)	0.002

Table 1 Demographic and baseline characteristics of chronic heart failure patients (continued)

Variables	Total (n = 94)	Non-frailty (n = 31)	Pre-frailty (n = 37)	Frailty (n = 26)	P-value
Medication					
ACEI, ARB, ARNI	77 (81.90)	29 (93.50)	30 (81.10)	18 (69.20)	0.059
Beta Blocker	94 (100.00)	31 (100.00)	37 (100.00)	26 (100.00)	NA
MRA	67 (71.30)	25 (80.60)	25 (67.60)	17 (65.40)	0.364
SGLT2i	36 (38.30)	14 (45.20)	16 (43.20)	6 (23.10)	0.169
Diuretic	76 (80.90)	25 (80.60)	26 (70.30)	25 (96.20)	0.037
CRT	6 (6.40)	1 (3.20)	3 (8.10)	2 (7.70)	0.761
ICD	4 (4.30)	1 (3.20)	2 (5.40)	1 (3.80)	1.000

Abbreviations: 6MWT, six mins walk test; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibition; BMI, body mass index; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; kg/m^2, kilogram per square meter; LVEF, left ventricular ejection fraction; m, minute; MRA, mineralocorticoid receptor antagonist; n, number; NA, data not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association classification; pg/ml, picograms per milliliter; SGLT2i, sodium-glucose transport protein 2 inhibitors
Data are presented as number (%), mean ± standard deviation or median (interquartile range).
P-value corresponds to One-way ANOVA, Kruskal-Wallis Test, Chi-Square Test or Fisher's Exact Test.

Approximately 27.70% (95% CI: 18.90–37.80) of patients with chronic HF were frail, 33.00% (95% CI: 23.60–43.40) were not frail, and 39.30% (95% CI: 29.40–50.0) showed signs of frailty (table 2).

Factors related to frailty in patients with chronic HF patients were assessed with univariate analysis. Simple logistic regression analysis found that the factors related to frailty in these patients were statistically significant (p-value < 0.05), including CKD stages IV–V (unadjusted OR = 4.00, 95% CI: 1.11–14.43, p-value = 0.034), NYHA (III–IV, unadjusted OR = 39, 95% CI: 8.30–183.29, p-value < 0.001), LVEF (≤ 40%, unadjusted OR = 3.84, 95% CI: 1.13–13.02, p-value = 0.031), NT-proBNP ≥ 1000 pg/mL, unadjusted OR = 5.5, 95% CI: 1.71–17.66, p-value = 0.004) and diuretics use (unadjusted OR = 8.33, 95% CI: 1.05–66.22, p-value = 0.045) All results are shown in Table 3. When multiple logistic regression analysis (multivariate analysis) was used, which considers only variables, the factors related to frailty in patients with chronic HF were significantly different (p-value < 0.05) from the factors determined through univariate analysis using simple logistic regression analysis, including CKD, NYHA, LVEF, NT-proBNP, and diuretics use. Factors associated with frailty in patients with chronic HF patients showed statistically significant (p-value < 0.05) when controlling for the influence of co-factors in the analysis, only NYHA factors (III-IV, adjusted OR = 30.51, 95% CI: 6.01–154.94, p-value < 0.001). All results are shown in Table 3.

Table 2 Prevalence of frailty syndrome in chronic HF patients

Variables	Total (n = 94)	Non-frailty (n = 31)	Pre-frailty (n = 37)	Frailty (n = 26)	P-value
All patients	94 (100.00)	31 (33.00)	37 (39.30)	26 (27.70)	
Test 1 (BW)	14 (14.90)	0 (0.00)	7 (18.90)	7 (26.90)	0.003
Test 2 (exhaust)	22 (23.40)	0 (0.00)	2 (5.40)	20 (76.90)	< 0.001
Test 3 (MET/min/wk)	26 (27.70)	0 (0.00)	5 (13.50)	21 (80.80)	< 0.001
Test 4 (WT)	27 (28.70)	0 (0.00)	6 (16.20)	21 (80.80)	< 0.001
Test 5 (HGS)	57 (60.60)	0 (0.00)	31 (83.80)	26 (100.00)	< 0.001
Fried frailty score	1.55 ± 1.50	0.00 ± 0.00	1.38 ± 0.49	3.65 ± 0.63	< 0.001
Min – Max	(0-5)	(0)	(1-2)	(3-5)	

Abbreviations: BW, body weight; HGS, hand grips strength; max, maximum; MET, metabolic equivalents; min, minimum; n, number; wk, week; WT, walking times
Data are presented as number (%), mean ± standard deviation or median (interquartile range).
P-value corresponds to One-way ANOVA, Chi-Square Test or Fisher's Exact Test.

Table 3 Univariate and multivariate analysis of factors associated with frailty syndrome in chronic HF patients

Factors	Univariate analysis		Multivariate analysis	
	OR* (95%CI)	P-value	Adjusted OR** (95%CI)	P-value
Age (years)	1.04 (0.97-1.11)	0.286		
Sex				
Male	1.00	Reference		
Female	1.88 (0.67-5.26)	0.229		
BMI (kg/m^2)	0.96 (0.86-1.06)	0.381		
Comorbidity				
Diabetes mellitus	0.70 (0.28-1.74)	0.441		
Hypertension	0.44 (0.11-1.77)	0.246		
Dyslipidemia	0.18 (0.02-2.07)	0.168		
Chronic kidney disease				
No-CKD	1.00	Reference	1.00	Reference
CKD stage III	1.06 (0.37-3.05)	0.913	0.78 (0.17-3.59)	0.753
CKD stage IV-V	4.00 (1.11-14.43)	0.034	1.09 (0.20-6.12)	0.920
Atrial fibrillation	0.72 (0.27-1.89)	0.501		
Ischemia heart disease	2.56 (0.95-6.88)	0.062		
NYHA				
I-II	1.00	Reference	1.00	Reference
III-IV	39.00 (8.30-183.29)	< 0.001	30.51 (6.01-154.94)	< 0.001
LVEF (%)				
≤ 40	3.84 (1.13-13.02)	0.031	1.23 (0.20-7.52)	0.821
40-49	0.75 (0.15-3.77)	0.727	0.36 (0.04-2.92)	0.339
≥ 50	1.00	Reference	1.00	Reference
NT-proBNP (pg/ml)				
< 1000	1.00	Reference	1.00	Reference
≥ 1000	5.50 (1.71-17.66)	0.004	2.02 (0.40-10.35)	0.398
Medication				
ACEI, ARB, ARNI	0.34 (0.12-1.02)	0.054		
B-Blocker		NA		
MRA	0.68 (0.26-1.80)	0.436		
SGLT2i	0.38 (0.14-1.07)	0.066		
Diuretic	8.33 (1.05-66.22)	0.045	3.40 (0.31-37.69)	0.318
CRT	1.33 (0.23-7.76)	0.749		
ICD	0.87 (0.09-8.73)	0.903		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibition; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; kg/m^2, kilogram per square meter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, data not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association classification; OR, odds ratio; pg/ml, picograms per milliliter; SGLT2i, sodium-glucose transport protein 2 inhibitors

*Unadjusted odds ratio estimated by Logistic regression model.

**Adjusted odds ratio estimated by Logistic regression model adjusting for chronic kidney disease, NYHA, LVEF, NT-proBNP and diuretic drug.

DISCUSSION

Frailty is a strong predictor of adverse outcomes in HF, including increased mortality, hospitalizations, and decreased quality of life. Identifying frailty can help stratify patients into different risk categories and guide appropriate management strategies but now frailty assessment in HF patients remains underutilized despite its potential benefits. In the past, there have been no studies done on urban medicine patients. Thus, in this study, we explored the prevalence and factors associated with fragility in chronic HF patients for the early identification of status and factors of frailty, aiming to for optimizing management and improving outcomes in this vulnerable population.

In this study was showed that the prevalence of frailty in HF patients about 27.70% which is not a small number. Factors of increasing age, LV systolic dysfunction, or high NT-proBNP may be associated factors of frailty syndrome but do not

show statistical significance because confounding factors include unequal medication treatment due to difficult access to services and socioeconomic problems. The key factor associated between HF and frailty is NYHA III–IV, the results show were 39 times more likely to develop frailty compared with the group with NYHA I–II. Thus for frailty patients with NYHA class III-IV HF, there must be early intervention because some patients may be underestimated and incorporate frailty assessment tools (such as the Fried Frailty Phenotype, Clinical Frailty Scale, or others validated in your setting) into routine clinical evaluations consider more specific treatment strategies, comprehensive geriatric assessments, and targeted rehabilitation programs to optimize functional status.

To promote routine frailty assessment in HF care, efforts should focus on raising awareness, providing training, developing standardized assessment tools, and integrating frailty evaluation into existing clinical workflows. Collaborative efforts between cardiologists, geriatricians, nurses, and other healthcare professionals can facilitate the implementation of frailty assessment as part of comprehensive HF management particularly in patients with NYHA class III-IV HF, enhances risk assessment, supports personalized care planning, and improves overall management strategies. This approach not only optimizes patient outcomes but also fosters a more patient-centered and evidence-based approach to healthcare delivery. This study can be adapted to urban medicine patients because the population we studied was the patients we actually encountered and the demographic characteristics were similar, which has not been studied in this way before.

This study has some limitations. The first limitation is only patients with HF at a specific time were included. The second limitation is only includes outpatient HF clinics and is conducted in a single hospital. The third limitation is the number of sample sizes is a small group. Expanding the study to different patient groups and hospitals will facilitate the identification of more factors.

CONCLUSION

The prevalence of frailty syndrome in chronic HF patients was found, and the main associated factor affecting frailty is NYHA(III-IV). NYHA classification and frailty in HF patients are crucial for comprehensive management. Regular assessment of NYHA class, frailty status, and associated factors (physical, cognitive, nutritional, and psychosocial) is essential for personalized care planning. Recognizing frailty in HF patients is essential for optimizing management and improving outcomes in this vulnerable population.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Original Article

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Exploring Cross-Reactivity Among Hen, Duck, and Quail Eggs in Children with Hen's Egg Allergy

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ABSTRACT

OBJECTIVE: To investigate cross-reactivity among hen, duck, and quail eggs in children with suspected egg allergy.

METHODS: A cross-sectional study enrolled 20 children with a history consistent with egg allergy. Specific immunoglobulin E levels to hen's egg white and egg yolk, skin prick test (SPT) to fresh raw hen, duck, and quail eggs, and oral food challenges in selected cases were performed for egg allergy evaluation. Thirty children with a clear history of egg tolerance were recruited as a control group. SPT were performed according to standardized protocols by trained personnel. Mean wheal diameter from SPT measured cross-reactivity and Spearman's correlation examined the cross-reactivity pattern.

RESULTS: The median age of participants with suspected egg allergy was 1.1 years and 3.6 years for the control group. Reported allergic reactions when entering the study were primarily to hen eggs, mainly urticaria/angioedema (70%). Anaphylaxis occurred in 20%. Participants with suspected hen's egg allergy were sensitized to at least one of the avian eggs, while controls showed a negative response. Among these participants, SPT positivity rate for quail eggs was high (60% for whites and 55% for yolks), followed by duck eggs (50% for whites and 30% for yolks). Moderate correlations were found between egg whites and egg yolks within each egg type. A negative correlation was found between hen egg whites and duck egg yolks (r = -0.127), and hen and duck eggs showed a weak correlation (r = 0.169–0.259). Patients with multiple egg sensitizations had a higher prevalence of earlier age of first reaction (p = 0.049) and a maternal history of atopy (p = 0.03).

CONCLUSION: This study suggests lower sensitization rates to duck eggs. Evaluating duck egg reactivity could benefit children with suspected hen's egg allergy.

KEYWORDS: avian eggs, cross-reactivity, duck eggs, egg allergy, food hypersensitivity, quail eggs

INTRODUCTION

Egg allergy is a common childhood food allergy worldwide[1-3], including in Thailand where the prevalence of adverse food reactions is approximately 6% with eggs being the second most common causative food[4]. Egg allergies significantly impact the quality of life of the patient and family[5-6]. Eggs provide fundamental nutrition for children's development and growth as they contain all the essential amino acids, good fat, vitamins, and other microelements. Having to manage an egg-free diet poses constraints on caregivers, making it more difficult to provide comparable nutritional intake,

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for instance, hen's egg avoidance leads to reduced vitamin D intake, which is essential to children's bone health[7].

Current international guidelines recommend avoidance of all avian eggs in patients with an egg allergy due to the limited research on the cross-reactivity between the different bird egg types[8-9]. Thai households can find this challenging as Thai cuisine frequently incorporates eggs in complex dishes, making it difficult to differentiate safe foods for children. Moreover, to completely avoid the offending food may lead to social isolation and increased anxiety.

While some studies have suggested potential variations in cross-reactivity, with individuals with hen's egg allergy potentially showing more tolerance to other egg types[10-13], the extent of these differences remains limited. A pioneer study quantified the cross-reactivity protein occurrences among eggs of various avian species and ranked their allergenic activity in relation to hen egg white (HEw) as follows: turkey, duck, goose, and seagull[10]. This suggested that some individuals with hen's egg allergy may exhibit varying sensitivities to different types of eggs.

Although duck and quail eggs are common ingredients in Thai cuisine and are affordable choices for every household, there remains an absence of studies addressing this knowledge gap. Therefore, this study investigated the cross-reactivity patterns among hen, duck, and quail eggs in Thai children with suspected egg allergy. We explored the possibility of alternative dietary options by examining skin test reactivity and the correlation between the egg whites and yolks of each type.

METHODS

This study enrolled children aged 6 months to 15 years with a history of immediate reaction to one of the avian eggs (hen, duck, and quail). Participants were recruited from the Pediatric Outpatient Clinic between January and December 2023. Children who had a history indicating a likely history of egg allergy underwent further clinical assessment to confirm eligibility for the egg allergy group.

The inclusion criteria for the egg allergy group were based on one of the following criteria within the past 6 months: 1. A convincing clinical reaction to eggs (acute skin eruptions/angioedema, persistent vomiting/diarrhea, bronchospasm within 2 hours), supported by positive skin prick test (SPT) to either egg white or egg yolk and/or a level of specific immunoglobulin E to hen's egg white/egg yolk (HEw-sIgE/HEy-sIgE) > 0.35 kU/L. 2. Previous positive oral food challenge (OFC) test to eggs, or 3. The mean wheal diameter (MWD) of SPT or HEw-sIgE exceeding the previous report of 95% positive predictive value for egg allergy diagnosis (MWD of > 5mm, HEw-sIgE > 2 kU/L in patients younger than 2 years, and MWD of > 7 mm in patients older than 2 years)[14]. For the control group, children with a clear history of regular egg consumption with no reaction were invited to participate. Patients who had a history of taking antihistamines within 7 days, on systemic immunosuppressive medications, denied to undergo SPT, having uncontrolled skin disease in the back area, and had developed severe egg anaphylaxis (grade 4-5 according to the World Allergy Organization Anaphylaxis Guideline 2020)[15] were excluded. A sample size of 23 hen egg-allergic patients was calculated to estimate the population proportion of positive SPTs primarily to quail eggs with 80% power and a 5% significance level. This calculation was based on a previous study reporting a cross-reactivity rate of 69.2% between hen and quail eggs[12].

HEw-sIgE and HEy-sIgE were measured using the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden) with a lower limit of detection of less than 0.35 kU/L. SPTs were performed on the back using fresh raw whites and the yolks of hen, duck, and quail eggs, with a single separate lancet for each allergen. Histamine phosphate (10 mg/ml) and glycerinated saline were used as a positive and negative control, respectively. The wheal diameter was measured 15 minutes after allergen application, and a positive SPT result was defined as a MWD 3 mm larger than the negative control. We also performed SPTs

on participants in the control group to serve as a comparison for the specificity of the skin test. To ensure reliability, SPTs were performed by a trained pediatric resident under the supervision of an allergist. The decision to perform an OFC was a shared decision between an allergist (one of the investigators) and the parents. Blood samples were collected in clotted blood tubes and processed within 7 days. The specimen was stored at 2-8°C until analysis.

The study was approved by the Vajira Institutional Review Board on June 15th, 2022 (COA 144/2565). Written informed consent from parents and assent from children older than 7 years of age were obtained. Demographics and reported allergic reaction were recorded.

Statistical analysis involved descriptive statistics for demographic and clinical characteristics, using percentages and mean ± SD or median (IQR) based on Shapiro-Wilk normality testing. Cross-reactivity was reported as a percentage. Group comparisons employed Chi-square test for categorical and Mann-Whitney U test for continuous variables. Spearman's correlation assessed correlations between wheal sizes. All statistical analyses were conducted using the Statistical Package for Social Sciences, version 24 (SPSS Inc., Chicago, Illinois, USA), and a significance level of $p < 0.05$ was considered statistically significant.

RESULTS

Fifty participants were enrolled, with 20 in the egg allergy group and 30 in the control group. Nineteen of the 20 participants met the diagnostic criteria for hen's egg allergy based on a reported allergic reaction and evidence of sensitization through specific IgE testing (n = 14) or SPT (n = 5). Only one participant underwent an OFC to confirm egg allergy. All participants in the egg allergy group reported a history of allergic reactions specifically to hen's egg. Children in the egg allergy group were significantly younger (median age 1.1 years) compared to controls (median age 3.6 years; p-value < 0.001). Sex distribution was similar between the groups (75% male in egg allergy vs. 70% male in control). Atopic dermatitis was more prevalent in the egg allergy group (65%) compared to the control group (10%) (p-value < 0.001). Children in the egg allergy group were more frequently without siblings (p = 0.02), resided in urban environments (p = 0.02), and were exclusively breastfed (p = 0.034).

The egg introduction behavior of Thai households was also explored. We found that egg introduction was initiated at a median age of 6 months. The median age of initial reaction in the allergy group was also 6 months. Fifty-eight percent of the introductions were with isolated egg yolks, and the predominant cooking method for egg introduction was hard-boiled (94%), with only 6% having consumed fried egg products. There was no significant difference in terms of the timing of egg introduction, the egg component initially introduced, or the egg cooking method used between the 2 groups. Table 1 presents a detailed comparison of all the demographic characteristics. Reported allergic reaction to eggs are demonstrated in Table 2, with urticarial/angioedema being the most common (70%).

Table 1 Demographic data of study participants (n = 50)

Characteristic	Total (n = 50)	Egg allergy (n = 20)	Control (n = 30)	P-value
Age (years), median (IQR)	2.5 (1-5)	1.1 (0.9-1.5)	3.6 (2.8-6.3)	< 0.001
Male sex, n (%)	36 (72)	15 (75)	21 (70)	0.70
No sibling, n (%)	24 (48)	13 (65)	11 (36.7)	0.02
Allergy in mother, n (%)	17 (34)	11 (55)	6 (20)	0.01
Allergy in father, n (%)	16 (32)	9 (45)	7 (23.3)	0.11
Urban living environment, n (%)	43 (86)	20 (100)	23 (76.7)	0.02

Table 1 Demographic data of study participants (n = 50) (continued)

Characteristic	Total (n = 50)	Egg allergy (n = 20)	Control (n = 30)	P-value
Atopic comorbidities				
Atopic dermatitis, n (%)	17 (34)	14 (65)	3 (10)	< 0.001
Recurrent wheezing, n (%)	18 (36)	7 (35)	11 (36.7)	0.90
Multiple food allergy, n (%)	20 (40)	7 (35)	13 (43.3)	0.21
Exclusive breast feeding, n (%)	41 (82)	18 (90)	23 (76.7)	0.034
Egg ingestion during pregnancy (yes), n (%)	47 (94)	20 (100)	27 (90)	0.15
Maternal frequency of egg ingestion during pregnancy (days/week)	3 (3-5.5)	3 (3-7)	3 (3-4)	0.19
Egg introduction				
Age of first introduction (month), median (IQR)	6 (6-6)	6 (6-7)	6 (6-7)	0.69
Age of first reaction (month), median (IQR)	-	6 (6-7.8)	-	N/A
Egg component first introduced				
Egg white, n (%)	0	0	0	N/A
Egg yolk, n (%)	29 (58)	12 (60)	17 (56.7)	0.82
Whole egg, n (%)	21 (42)	8 (40)	13 (43.3)	0.82
Cooking method				
Boil, n (%)	47 (94)	18 (9)	29 (96.7)	0.34
Steam, n (%)	0	0	0	N/A
Fried, n (%)	3 (6)	2 (10)	1 (3.3)	0.34
Baked, n (%)	0	0	0	N/A

Abbreviations: IQR, interquartile range; n, number; N/A, not applicable (used for data not collected, relevant in the control group) Values are expressed as mean ± SD or median (IQR), as appropriate. Comparisons between groups were performed using the Mann Whitney U test for continuous variables and the Chi-square test (or Fisher's Exact test where applicable) for categorical variables. P-value < 0.05 was considered statistically significant.

Table 2 Characteristic of egg allergic reactions

Characteristics	Egg allergy (n = 20)
Anaphylaxis, n (%)	4 (20)
Non-anaphylaxis, n (%)	16 (80)
Skin, n (%)	20 (100)
Acute Atopic dermatitis flare up, n (%)	6 (30)
Urticaria/angioedema, n (%)	14 (70)
Respiratory symptoms, n (%)	1 (5)
Gastrointestinal symptoms, n (%)	3 (15)

Abbreviation: n, number

All participants in the egg allergy group demonstrated sensitization to at least one avian egg. This was confirmed by positive SPT, with hen egg white (HEw) eliciting the largest MWD (7.5 mm, 5-14 mm). MWD for other egg components were: hen egg yolk (HEy): 2 mm (0–4 mm), duck egg white (DEw): 3 mm (1–8 mm), duck egg yolk (DEy): 1.8 mm (0–4 mm), quail egg white (QEw): 4.5 mm (1–7.5 mm), and quail egg yolk (QEy): 3.5 mm (2–7.5 mm). Consistent with the SPT findings, specific IgE levels also showed the highest value for HEw with a median of 1.25 kU/L (0.2-4.1 kU/L). The median HEy-sIgE level was 0.30 kU/L (0.1-0.7 kU/L). In contrast, none of the participants in the control group showed positive skin reactions.

SPT results among participants in the egg allergy group revealed a pattern of sensitization towards other avian eggs. QEw showed the highest SPT positivity rate (60%), followed by QEy at 55%, DEw at 50%, and lastly DEy at 30% (figure 1A). Notably, positive SPTs were more frequent for egg whites compared to yolks across all tested avian eggs. We also investigated the rate of cross-reactivity pairwise between egg components. The study found that the cross-reactivity rates between hen's egg components and quail's egg components are higher than the duck's egg counterparts (figure 1B), with HEw-QEw being the highest (60%). The cross-reactivity between HEw-DEw was lower at 40%. The cross reactivity rates involving HEy components yielded lower rates with the lowest being HEy-DEy (15%).

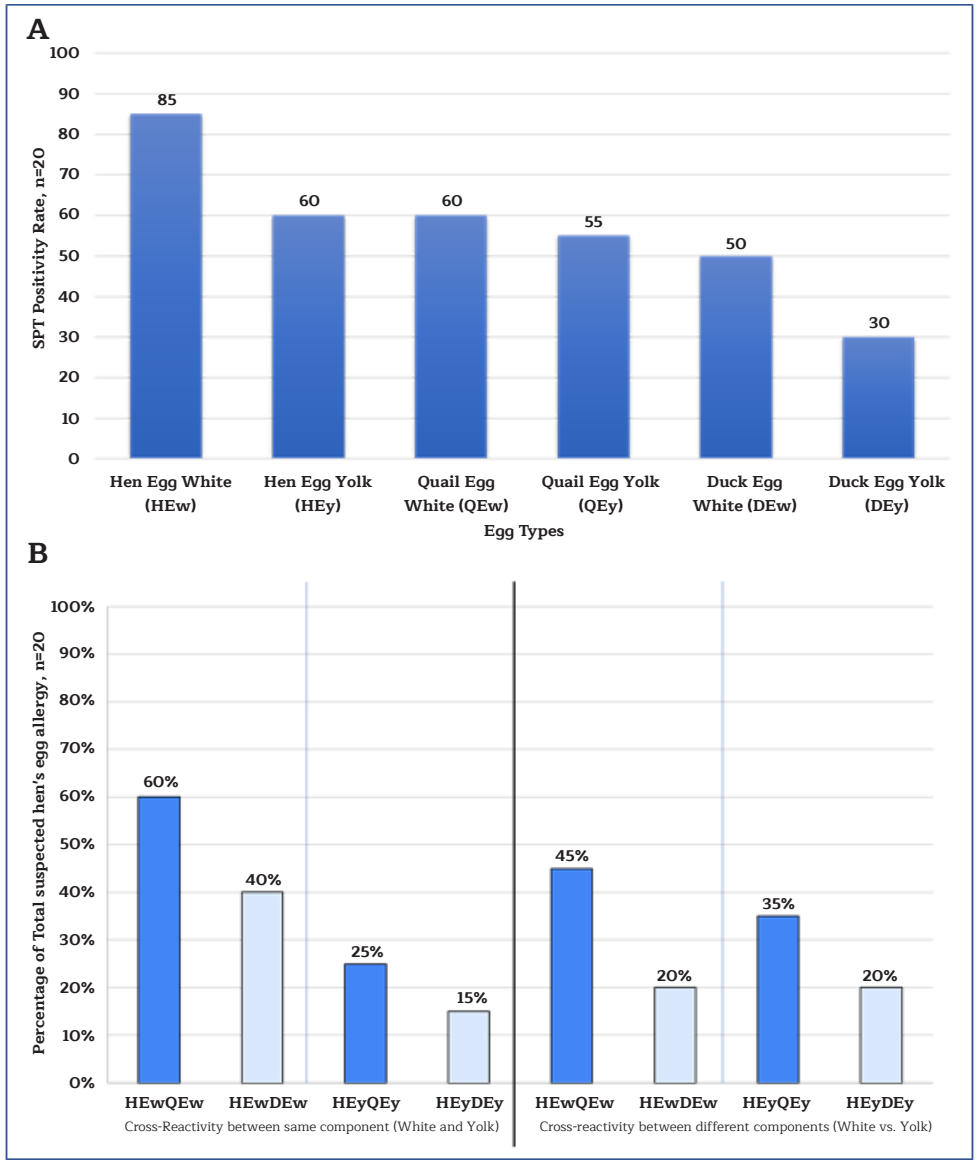

Figure 1 (A) SPT positivity rate (B) Cross-reactivity among egg components of three avians by skin prick test (n = 20)

Abbreviations: DEw, duck egg white; DEy, duck egg yolk; HEw, hen egg white; HEy, egg yolk; QEw, quail egg white; QEy, quail egg yolk

Spearman's correlation analysis revealed significant positive correlations ($p < 0.05$) between the MWD of egg whites and egg yolks within each bird species. Moderate correlations were found between the components of duck-quail eggs (QEw-DEw, r = 0.581, p = 0.009, QEy-DEw, r = 0.544, p = 0.016, and QEw-DEy, r = 0.528, p = 0.02), and quail-HEy (QEw-HEy, r = 0.522, p = 0.022 and QEy-HEy, r = 0.528, p = 0.02). In contrast, weak correlations between duck and hen egg components were found (DEw–HEw, r = 0.185, p = 0.434, DEy–HEy, r = 0.169, p = 0.475 and DEw–HEy, r = 0.259, p = 0.271). A negative correlation was found between HEw and DEy, r = -0.127, p = 0.594, although this was not statistically significant (figure 2).

Participants in the egg allergy group were further subclassified into: 1. The 'pan-egg sensitization' group (n = 9), including children sensitized to all 3 eggs, and 2. The "mono or dual egg sensitization" group (n = 11), including children sensitized to one or two types of eggs. A significantly higher proportion of participants in the pan-egg sensitization group had a history of maternal atopic disease (77.8% versus 36.3%, p = 0.03), and an earlier age of first egg reaction (6 months versus 6.5 months, p = 0.049) compared to the mono or dual sensitization group. Details are provided in Table 3.

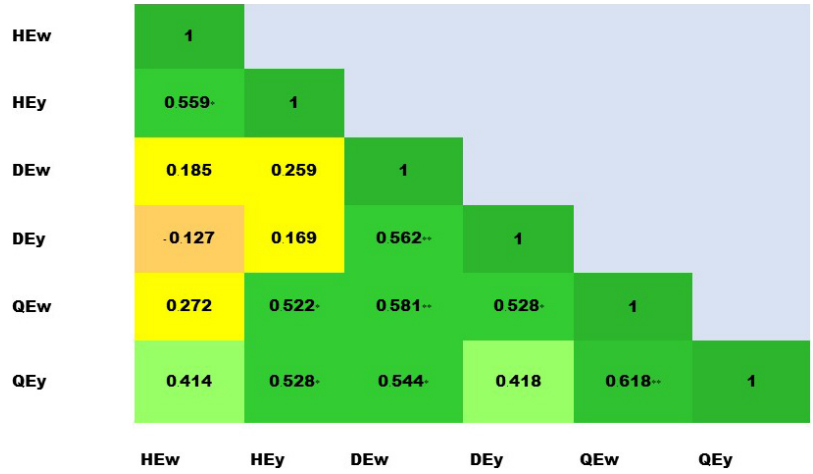

Figure 2 Correlations coefficients of skin prick test wheal sizes of hen, duck, and quail eggs in egg allergy participants (n = 20)

Correlation coefficients were calculated using Spearman's rank correlation test. P-value <0.05 is considered statistical significant

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Abbreviations: DEw, duck egg white; DEy, duck egg yolk; HEw, hen egg white; HEy, egg yolk; QEw, quail egg white; QEy, quail egg yolk

Table 3 Comparison of patients with pan-egg sensitization and with mono- or dual egg sensitization

Characteristics	Pan-egg sensitization (n = 9)	Mono or dual egg sensitization (n = 11)	P-value
Male sex, n (%)	7 (77.8)	8 (72)	0.645
Age (years), median (IQR)	1.1 (0.9-1.9)	1 (0.8-1.5)	0.710
Atopic dermatitis, n (%)	6 (66.7)	8 (72.3)	0.609
Recurrent wheezing, n (%)	3 (37.5)	4 (33.3)	1.000
Maternal atopic disease, n (%)	7 (77.8)	4 (36.3)	0.03
Paternal atopic disease, n (%)	5 (55.6)	4 (36.3)	0.273
Anaphylaxis, n (%)	3 (33.3)	1 (9)	0.14
Age of egg first introduction (months), median (IQR)	6 (6-6.5)	6 (6-8)	0.915
Age of egg first reaction, median (IQR)	6 (6-6)	6.5 (6-8)	0.049
HEw-sIgE (kU/L), mean ± SD	3.2 ± 3.2	1.7 ± 1.9	0.620
HEy-sIgE (kU/L), mean ± SD	0.7 ± 0.9[a]	0.3 ± 0.3	0.409
MWD HEw (mm), mean ± SD	9.7 ± 5.1	8.1 ± 5.9	0.868
MWD HEy (mm), mean ± SD	4.3 ± 4.1	2.2 ± 1.7	0.405

Abbreviations: HEw-sIgE, specific immunoglobulin E to hen egg white; HEy-sIgE, specific immunoglobulin E to hen egg yolk; IQR, interquartile range; kU/L, kilounits per liter; mm, millimeter; MWD, mean wheal diameter; n, number; SD, standard deviation
Values are expressed as mean ± SD or median (IQR), as appropriate. Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the Chi-square test (or Fisher's Exact test where applicable) for categorical variables. P-value < 0.05 was considered statistically significant
a: Missing data for HEy-sIgE in 1 patient

Of those 20 patients with suspected hen's egg allergy, 3 consented to undergo OFC to the egg type with the lowest SPT reactivity, aiming to minimize the risk of severe allergic reactions. All patients displayed an elevated HEw-sIgE level. Patient 1., despite negative SPT result to duck egg, experienced two lesions of urticaria at 2 hours post-challenge, followed by generalized urticaria requiring intravenous antihistamine and systemic corticosteroid. Patient 2. exhibited mild urticaria while approaching the full portion of a hen's egg, and Patient 3. tolerated the quail egg challenge without adverse reaction. Details of the patient characteristics who were underwent OFC are presented in Table 4.

DISCUSSION

This study investigated avian egg cross-reactivity and the characteristics of patients with pan-egg sensitization in Thai children (median age 1 year) with a history of suspected hen's egg allergy. An evaluation of a relatively young age group captured a population where an egg allergy is less likely to have been outgrown compared to studies with older children[11-13]. We prioritized duck and quail eggs due to their culinary importance in Thailand.

Table 4 Clinical and immunological characteristics of patients undergone OFC

No	Age (Year)	Sex	Clinical history of allergy in hen egg	HEw sIgE (kU/L)	HEy sIgE (kU/L)	Comorbidity	Maternal history of atopy	Age of first introduction (months)	Age of first reaction (months)	SPT Mean wheal diameter, mm.								OFC (heated)		
										HEw	HEy	DEw	DEy	QEw	QEy	Histamine	Glycerin	Hen	Duck	Quail
1	1	M	AD flare up	3.46	0.29	AD	No	6	6	7.5	3	2	0	3.5	5	4	0	ND	Urticaria after 2 hours	ND
2	1.2	M	Urticaria	6.14	0.44	AD	No	6	6	6.5	0	13.5	4.5	7.5	3	2	0	Urticaria	ND	ND
3	1.5	M	AD flare up	3.79	0.9	AD	No	6	6	6.5	0	3.5	0	0	0	3	0	ND	ND	Pass

Abbreviations: AD, atopic dermatitis; DEw, duck egg white; DEy, duck egg yolk; HEw, hen egg white; HEy, hen egg yolk; kU/L, kilounits per liter; M, male; ND, not done; OFC, oral food challenge; QEw, quail egg white; QEy, quail egg yolk; SPT, skin prick test

Our study observed a young age of egg allergy onset, often upon first exposure. Skin and gastrointestinal symptoms were predominant with rare respiratory issues. These findings align with previous reports[2,8,16]. Additionally, known risk factors of egg allergy development such as atopic dermatitis[17], a familial history of atopy[18], and the absence of siblings[18] were found more common in our egg allergy group. The high prevalence of atopic dermatitis in our study population suggests a potential link between skin barrier dysfunction and the development of food allergies. This is supported by the concept of the 'dual-allergen exposure' hypothesis, where pre-existing cutaneous sensitization predispose individuals to allergic reactions upon subsequent oral exposure to the same allergen[17]. Despite the limitations of the study design to establish these factors as true risk factors, the observed differences between the egg-allergy group and the control group warrant further investigation in larger prospective studies. The observed egg introduction practices in our study followed the national dietary recommendations and align with the findings of previous studies, including an egg cohort of Thai children commencing with hard-boiled egg yolk at 6 months of age[19-20]. This approach is in contrast with the reports from Australia, where introduction usually commences after 10 months with cooked egg white. This approach was found to be associated with higher allergy risks[21]. This suggests the need for future research that explores the potential benefits of earlier egg yolk introduction in the Thai context.

Compared to an Iranian study[11], our participants showed lower cross-reactivity with duck and quail eggs, and the overall MWD was also smaller. This difference potentially resulted from the younger age of our study group, as the skin reactions were less pronounced in children below 2 years[22], and the regional dietary differences. Notably, QEw displayed the highest cross-reactivity rate, followed by duck egg components. The pattern of SPT results aligns with the observed moderate correlations between quail egg components and duck eggs and HEys, but with a weaker correlation between duck and hen eggs. This suggests that quail egg proteins might share some similarities with both duck and hen eggs, while duck egg proteins might have a more distinct reactivity profile compared to hen eggs. This finding aligns with previous research suggesting DEw might have specific allergenic determinants distinct from HEw[10], identifying duck ovalbumin as the potentially responsible protein with specific antigenic determinants[23-25].

The distinctness of duck egg protein may be explained by avian phylogenetic relationships. Chickens and quails are closely related as they belong to the Galliformes order, while ducks, belonging to the Anseriformes, suggesting a more distant relationship to chickens and quails[26]. While evolutionary relationships may influence allergen structure, further investigation using immunoblotting and component-resolved diagnosis is warranted in order to identify the major allergens responsible for the observed cross-reactivity[27].

To provide an alternative diet option, and share-decision making with the caregivers, we performed OFC to the egg type with the lowest skin reaction from SPT in 3 patients. Despite observing moderate cross-reactivity between hen and quail eggs, we successfully introduced quail eggs into the diet of a 1.5-year-old male participant with hen's egg allergy (table 4, patient 3). Due to constant maternal anxiety, the patient underwent extensive food avoidance, leading to nutritional deficiencies. SPT confirmed hen egg sensitization but was negative for quail eggs, allowing us to perform an OFC to quail eggs, which the patient successfully passed. The safe introduction of quail eggs into the child's diet expanded his dietary options. This case aligns with a study from Japan that reported successful quail egg OFC in 55% of children with a hen's egg allergy[12].

Conversely, Patient 1. developed mild urticaria at 2 hours with a progression to systemic symptoms, despite a negative SPT result on duck eggs. Although a delayed reaction and progression of symptoms is not typical, this characteristic of the reactions after a food challenge has been reported even without further allergen intake[28]. While acute urticaria has various causes, the patient's history indicated no alternative explanations. We therefore recommended continuing duck egg avoidance until later confirmatory testing.

We hypothesized that individuals exhibiting cross-reactivity to all 3 egg types might develop antibodies against the shared proteins existing in those avian eggs, which are responsible for the cross-reaction among those eggs[9]. However, the absence of molecular-level analysis in this study limited our ability to confirm this hypothesis. Nevertheless, we observed the differences in the clinical characteristics between the patients with sensitization to all 3 eggs compared to those with sensitization to fewer egg types. It is important to note that the classification of patients based solely on SPT results may not accurately reflect the true extent of cross-reactivity.

This study has some important limitations. Firstly, the small number of participants affects the generalizability of the findings to a broader population. A larger sample size would enhance the study's reliability. Secondly, while the inclusion of a control group was essential for establishing the specificity SPT in detecting egg allergies, the potential for selection bias cannot be excluded. The requirement for an invasive procedure might have influenced the characteristics of the control group, leading to discrepancies in age between the 2 groups. Additionally, a matched case-control design would have been ideal for establishing robust associations between risk factors and egg allergies. Future studies employing this design are warranted in order to further explore these relationships. Finally, the limited number of participants (n = 3) undergoing OFC significantly restricted out ability to establish definitive IgE-mediated cross-reactivity.

In any future research, an expansion of the sample size and the inclusion of OFC as a confirmatory step would enhance the robustness and reliability of the data. Additionally, incorporating a more detailed analysis of past and current egg consumption patterns in a longitudinal study might offer further understanding of how dietary habits influence the development of cross-reactivity. Moreover, an exploration of the protein composition of avian eggs could unveil the key molecular components influencing allergic responses and clinical cross-reactivity.

CONCLUSION

This study provides preliminary insights into cross-reactivity patterns among hen, duck, and quail eggs in children with a suspected hen's egg allergy. We observed lower sensitization rates and weaker cross-reactivity between duck and hen eggs, suggesting the potential for duck eggs as a dietary alternative for some children with hen's egg allergy. However, the small sample size and limited number of OFCs necessitate a cautious interpretation of these findings. While one participant successfully tolerated quail eggs, further research with a larger cohort is required to confirm this observation and to fully understand the complexity of cross-reactive patterns. Incorporating SPT with the fresh eggs of hens, ducks, and quails, alongside hen egg-specific IgE testing, could be a valuable tool for evaluating children with suspected egg allergy and identifying potential dietary alternatives.

CONFLICT OF INTEREST

The authors report no conflict of interest for this article.

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DATA AVAILABILITY STATEMENT

All of the data generated and analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Review Article

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Epidemiological Relationship of Photoplethysmography Signal Derived from Arterial Stiffness and Blood Pressure to Coronary Artery Disease: A Systematic Review

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ABSTRACT

Current photoplethysmography (PPG) signals and electronic devices had a lot of attention including analysis of coronary heart disease, ageing of blood vessels, metabolic syndrome, endothelial cell damage, predicting the risk of coronary artery disease, and community-acquired pneumonia. This systematic review aims to analyze current technologies used to measure PPG signals. Analysis of PPG signals with patients involved in coronary artery disease and arterial stiffness and other important interests toward the future trends of computational medicine. The hypothesis is that arterial stiffness is epidemiologically related to the risk of coronary heart disease. A systematic search was conducted in different databases to acquire literature examining the use of PPG with coronary artery disease in terms of epidemiological correlations. Search terms included arterial stiffness, epidemiology, PPG, blood pressure, and coronary artery disease. Articles that do not measure PPG signals on real patients/subjects were excluded from the analysis. A total of 17 studies met the inclusion criteria for this systematic review. Nearly half of the studies used PPG with artificial intelligence/machine learning for analytical study patients, while 18% were PPG studies related to endothelial damage and blood pressure profiles, and another 18% were new development of PPG measurement devices. The rest was PPG analyzing coronary artery disease and atherosclerosis. Systematic review findings reveal PPG applications range from the epidemiology of damaged endothelial cell proliferation to advanced digital PPG analysis. Managing cardiovascular risk and exploring new areas including chronic kidney disease and ovarian cancer must be of interest and considered in future studies.

KEYWORDS: biomedical signal, coronary artery disease, photoplethysmography, vascular ageing

INTRODUCTION

Vascular geometry plays an important role in determining endothelial cell function. Changes in the geometry of blood vessels cause dynamic changes in vascular biology that lead to the development of atherosclerotic lesions and subsequently to coronary artery disease[1-7]. These changes can cause infection, causing arterial stiffness, which spreads arterial lesions in the cardiovascular system[1,3]. Numerous epidemiological studies have repeatedly reported that arterial stiffness is associated with the risk of coronary heart disease[8].

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The arterial stiffness index usually estimates the distance traveled by blood flow divided by the time it takes to travel that distance in meters per second. It is a highly standardized, noninvasive technique for the diagnosis and assessment of arterial stiffness[9-10].

Arterial stiffness is a marker of vascular ageing, a predictor of hypertension, and can be characterized by a photoplethysmography (PPG) signal[9-10]. Subsequently, PPG signals are hugely receiving attention and are increasingly being used as noninvasive tools to monitor blood oxygen, heart rate, and blood pressure parameters related to coronary heart disease. It is challenging to exploit the potential of PPG signals as a personal health management device for risk management of coronary artery disease and provide more information than typical coronary artery disease clinical trials. The objective of this systematic review is to analyze and discuss current technologies used to measure PPG signals with patients dealing with arterial stiffness associated with coronary artery disease and other related significant interests. Then, an examination of the epidemiological relationship between PPG signals and coronary heart disease recommended the role of PPG in the development of atherosclerotic lesions. In addition, technical considerations such as software and electronics used for PPG signal processing and machine learning (ML) are also considered. Artificial intelligence (AI) and the possibility of developing computer-aided medical diagnosis systems for noninvasive tools and personalized medicine are included, and future directions are also highlighted.

LITERATURE SEARCH STRATEGY

The structured search was performed on PubMed, ScienceDirect, Scopus, and Google Scholar to identify studies reporting about PPG signals associated with arterial stiffness involving coronary artery disease according to the preferred reporting guideline for systematic reviews and meta-analysis[3,11-12]. The last structured search was completed on 16 April 2024. A variety of key search terms include: [("photoplethysmography" OR "PPG" OR "arterial stiffness") AND ("epidemiology" OR "blood pressure" OR "coronary artery disease")]. We used these key search terms because we intended to cover the analysis of all studies on the epidemiological relationship of PPG signals derived from arterial stiffness linked to coronary artery disease in this review.

ELIGIBILITY CRITERIA FOR ANALYSIS

The analysis criteria are the studies must be peer-reviewed studies that were published in English literature; studies were original research studies that reported findings, characteristics, and features of PPG associated with blood pressure and coronary artery disease epidemiologically; study included at least 10 patients with well-characterized PPG signals, this is because studies with fewer than 10 samples are considered low-level evidence on patients with PPG signals; studies must be published within the last 10 years. Each article was then assessed for title and abstract to determine its relevance to the objectives of the review[2,12-13]. Once the article had passed the title and abstract evaluation, its full text was then extracted for further analysis. These criteria were used with our structured search to classify the search results for inclusion in the analysis in this review. Additionally, studies reported with disaggregated data/single-ended data analysis and a sample size of < 10 patients were excluded from this review due to the low level of evidence. Conferences, commentaries, editorials, opinions, and other types of publications were also excluded.

DATA EXTRACTION AND AGGREGATION

The search results were completed by physically screening the titles and abstracts of all identified literature by an independent evaluator (TC). Data verification was then performed to verify the findings by the data observer (TC and ZS). The following study characteristics of PPG epidemiologically related to blood pressure and coronary heart disease were classified:

first author's name, country, year of publication, sample size, and main study findings. The data aggregation was the main pattern of a summary of the literature on similar directions of investigation[12-13]. Data disaggregation was a separation of collected data into multiple patterns to account for underlying trends and patterns in the focal pattern of the data aggregation[12-13]. As a result, three subgroups of data segmentation were identified from data aggregation: I) arterial AND stiffness AND epidemiology AND PPG, II) arterial AND stiffness AND blood AND pressure AND PPG, and III) arterial AND stiffness AND coronary AND artery AND disease AND PPG.

RESULTS

The literature search identified a maximum of 29,523 titles in ScienceDirect and at least 512 titles in PubMed, while Google Scholar and Scopus listed 20,400 and 2,692 titles, respectively. A total of 53,000 titles were retrieved in the form of [(photoplethysmography_or_PPG_or_arterial-stiffness)+(epidemiology_or_blood-pressure_or_coronary-artery-disease)] format. Therefore, only 214 titles and abstracts were screened. The remainder was separated from the data segmentation keywords because it is irrelevant to the topic. Figure 1 presents a flow diagram gaining the search strategy for selecting these studies. Figure 2 illustrates how blood flow relates to the PPG sensor[14]. Table 1 reveals how algorithms contribute to defining PPG signals[14]. Finally, a total of 17 articles were included in this systematic review. This paper presents a novel epidemiological relationship between PPG signal and arterial stiffness related to coronary artery disease contributed to the fields of urban health and medicine.

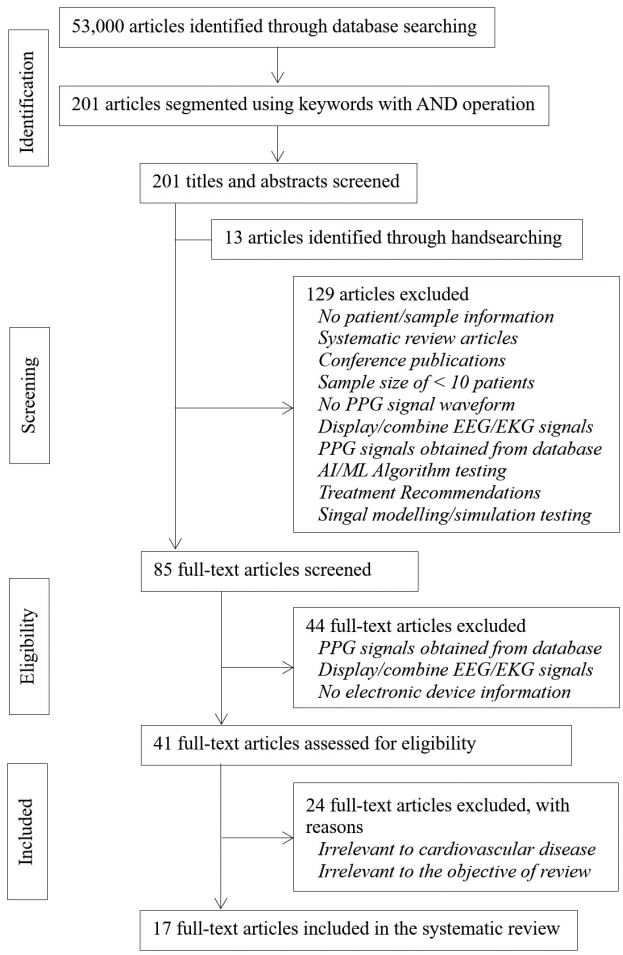

Figure 1 A flowchart shows the search strategy to identify the selected studies

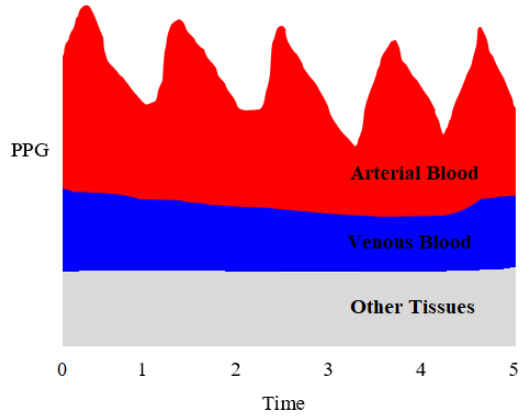

Figure 2 Illustrates how blood flow relates to the photoplethysmography sensor

Table 1 Reveals algorithms that contribute to defining photoplethysmography signals accompanied with Figure 2

PPG algorithm	
Input	Optical radiation
Process	Optical light illuminates through the index finger
	Lights are absorbed and scattered through different tissue layers
	Lights are transmitted through or reflected from the tissue surfaces
	The intensity of the attenuated light passed through Figure 2 (raw PPG signal) is detected by an optical sensor
	An optical sensor records a voltage signal called a photoplethysmography
Output	PPG waveform

Abbreviation: PPG, photoplethysmography

CHARACTERISTICS OF SELECTED LITERATURE

Of the 17 articles, six (35%) used PPG with AI/ML for analytical study patients[15-20], three of which (18%) were PPGs related to endothelial damage and one of them blood pressure profiles[21-23]. One of them (5%) was a technical problem in acquisition of PPG signals[24]. Two of them (12%) were overnight PPG analysis to analyze long-term cardiovascular events and coronary artery disease risk[25-26]. Two of them (12%) were arterial stiffness associated with metabolic syndrome and sports science[27-28]. Finally, three of them (18%) were the development of new PPG measurement devices[29-31]. Table 2 summarizes characteristics of included studies in this systematic review.

Table 2 The characteristics of studies that met the criteria in this review

Country	First author	Year of publication	Sample size	Main study findings
United Kingdom	Sadaf Iqbal[15]	2023	37 patients	Deep learning PPG analysis was confirmed with blood samples of endothelial function, which showed good agreement with coronary artery disease angiography.
Italy	Caterina Franco[21]	2022	23 patients	Hypertensive patients were assessed for endothelial damage and arterial stiffness. This suggests an overall antioxidant capacity related to recovery of arterial stiffness.
Taiwan	Chin-Jung Ku[22]	2022	48 patients	Blood pressure can be measured continuously from a PPG that shows systolic and diastolic blood flow profiles. This result was confirmed with the PPG signal database.

Table 2 The characteristics of studies that met the criteria in this review (continued)

Country	First author	Year of publication	Sample size	Main study findings
China	Chenbin Ma[23]	2024	24 patients	Noninvasive blood pressure using PPG signals to derive blood pressure values confirmed with clinical standards.
Finland	Jukka-Pekka Sirkiä[24]	2024	19 subjects	Identified errors arising from contraction of the sensor pressure while measuring the PPG signal on the index finger. This suggests that PPG device design should account for these errors in changes in diastolic blood pressure levels.
Pakistan	Kehkashan Kanwal[16]	2024	31 subjects	ML-based PPG signal analysis for community-acquired pneumonia (CAP) diagnosis shows potential to improve clinical decision-making and patient outcomes in pediatric pneumonia health care. CAP causes cardiovascular complications (e.g., heart failure, arrhythmias, myocardial infarction and/or stroke).
Turkey	A. Reşit Kavsaoğlu[17]	2015	33 people	Hemoglobin measurement using PPG signals with ML confirms that this noninvasive method may replace clinical laboratory hemoglobin testing with blood samples.
India	Abhishek Chakraborty[18]	2020	52 normal subjects	Myocardial infarction identification using PPG signals with ML shows positive predictive results for the potential development of personalized healthcare systems.
Australia	Sobhan Salari Shahrbabaki[25]	2023	1957 participants	Nocturnal pulse amplitude attenuation derived from overnight PPG signals has been found to be associated with long-term cardiovascular events. The PPG-derived nocturnal pulse wave amplitude attenuation index may be a marker of cardiovascular risk.
Taiwan	Hsin Hsiu[19]	2022	280 subjects	Measurement of arterial pulse waves with ML analysis to discern how vascular aging contributes to the progression of vascular dysfunction. This suggests that the development of wearable devices can be used for noninvasive methods to reduce the threat of vascular dysfunction caused by vascular aging.
Australia	Lisa M. Walter[26]	2018	185 subjects	Overnight PPG analysis of people with sleep breathing problems reveals pulse wave velocity related to arterial stiffness and central systolic blood pressure as predictor of cardiovascular outcome. These results confirm the treatment of breathing disorders and obesity to reduce the risk of cardiovascular disease.
United Kingdom	Elisa Mejía-Mejía[20]	2022	18 healthy subjects	ML analysis of morphological features from PPG along with pulse rate variability features. It shows relatively good and feasible performance in estimating blood pressure. It is a measurement of high blood pressure that causes chronic and acute diseases such as diabetes and heart failure.
Poland	Tadeusz Sondej[29]	2021	108 subjects	A new PPG measurement device has been developed to produce verified pulse wave velocities with SphygmoCor XCEL as a reference device. The new device uses different sensor locations (e.g. on the forehead, left earlobe, right earlobe, fingers, and toes) to provide highly accurate signals. This suggests that PPG devices can be used to generate pulse wave velocity to predict cardiovascular risk, replacing the use of pulse wave velocity devices.

Table 2 The characteristics of studies that met the criteria in this review (continued)

Country	First author	Year of publication	Sample size	Main study findings
Taiwan	Yaw-Wen Chang[27]	2016	65 volunteers	PPG analysis distinguishes different arterial pulse transmission conditions between metabolic syndrome and healthy volunteers. The results confirmed PPG waveforms can provide information about metabolic syndrome-induced changes in arterial pulse transmission and cardiovascular disease.
United States	Nathan Zavanelli[30]	2023	19 variety of ethnicities	A new wireless PPG device has been developed to measure blood pressure for vasoconstriction or atherosclerosis. The device was validated with a commercial device in an overnight PPG analysis with patients with sleep apnea, with a high level of agreement in detecting vasoconstriction.
United Kingdom	Denis J. Wakeham[28]	2023	46 healthy males	The central artery stiffness can adjust the pressor responses during stimuli associated with increases in cardiac output and sympathoexcitation in healthy men. The results suggest differences in systolic pressure between young and healthy middle-aged men. Central arterial stiffness was found to play a greater role than the increase in sympathetic transmission in middle-aged men. Sympathetic transmission involves blood pressure and coronary blood flow.
China	M.A. Xiaotian[31]	2024	133 participants	A multi-sensor pulses diagnostic device that assesses coronary artery lesions using PPG shows practical value in detecting the degree of coronary artery occlusion in patients with coronary artery disease. The results provide valuable insights into the development of new diagnostic devices imbued with time domain analysis principles and their potential in the management of cardiovascular disease.

Abbreviations: CAP, community-acquired pneumonia; ML, machine learning; PPG, photoplethysmography

CURRENT PPG TECHNOLOGY

Pulse oximeter is an instrument used to estimate and display arterial saturation of oxygen. It was originally based on the Beer-Lambert law. Pulse oximetry estimates arterial saturation of oxygen with an accuracy in the range of 90%–100%. Later, Takuo Aoyagi realized that only pulsatile variations in light transmission were required to estimate hemoglobin concentration[32]. Figure 3 shows a simple diagram of a classic pulse oximeter configuration[33]. Nowadays, pulse oximeters have become an important tool in patient monitoring, intensive care units, and operating rooms in hospitals, as well as caring for patients with sleep problems at home.

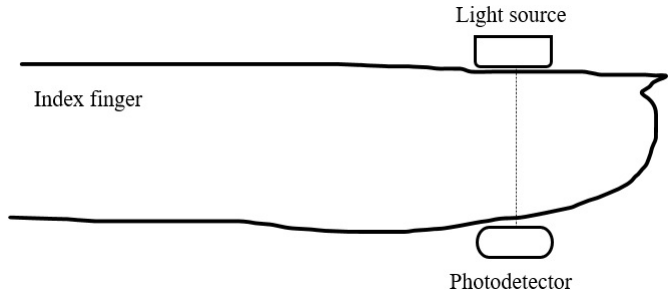

Figure 3 Generalization of optical configuration for PPG transmission mode

Currently, many studies are focused on the research and development of both non-contact and skin contraction pulse oximeters. Zavanelli et al. (2023) developed a soft wireless sternum patch device to be placed on the chest to detect vasoconstriction[30]. His device presents a new concept of modern mobile devices to defeat traditional PPG devices that place sensors on fingers, toes, and ears. His device implants an electronic chip combined with a nanobattery that detects PPG signals at the location of the sternum. The analyzed PPG results of vasoconstriction were verified with a commercial device with an accuracy of 78%. He stated this new paradigm of electronic devices offers continuous monitoring of blood vessel contraction with potentially important medical applications and is broadly applicable to monitoring biological signals from novel anatomical regions such as the sternum.

Xiaotian et al. (2024) researched and developed a new electronic device to detect blockage and narrowing of coronary arteries with an accuracy of 78.79%[31]. Xiaotian's device introduces a new concept of fingertip-PPG signal created by placing sensors on the index finger and wrist. This provides valuable insights into the development of new diagnostic devices embedded in the principles of time domain analysis in the potential management of cardiovascular disease. Owens et al. (2022) developed a 1064 nm pulsed laser source and a short-wave infrared camera with a digital holography system in the off-axis image plane recording geometry[34]. Owen's device produced the pulse diagnostic measurement that can be referenced for pulse rate oximetry. In 2023, Bautista of the UK proposed contactless photoacoustic spectroscopy (cPPG) to measure physiological signals in 654 adults[35]. Bautista's study shows that cPPG is the use of a camera to detect changes in the volume of pulsating blood in the blood vessels in a person's face. Sondej et al. (2021) developed a new device to measure coronary pulse wave velocity from a PPG device to overcome expensive pulse wave velocity measurement devices and complications in the diagnosis of coronary artery disease[29]. Sondej's device was validated with a commercial device, the SphygmoCor XCE (CardieX, New South Wales, Australia). The results of the static analysis signal verification showed that Sondej's device was acceptable for measuring pulse wave velocity. Therefore, the current development trend of PPG technology is based on computer-aided medical diagnosis systems for non-invasive tools and personalized medicine.

PPG FORECASTS CARDIOVASCULAR DISEASE AND EPIDEMIOLOGY

High blood pressure or hypertension is one of the major risks of heart attack, stroke, and kidney failure caused by vascular stiffness or vascular ageing. The PPG signal is a measurement of red blood cells in blood vessels using the transmission of light through tissue[8-10]. It decreases during systole and increases during diastole. The general interpretation of these oscillations is that they are associated with an increase in arterial blood volume during systole. It allows the detection of arterial stiffness from changes in blood flow that occur through the PPG sensor[8-10].

In addition, PPG can also be used to determine pulse wave velocity. Wakeham et al. (2023) examined whether exercise blood pressure is influenced by arterial stiffness[28]. This is an increase in blood pressure in the aortic flow which causes aortic pulse wave velocity. This leads to an assessment of the cardiovascular response to exercise. Previous researchers in 2016, Chang's study characterized the peak-to-peak PPG signal index in patients with metabolic syndrome[27]. Changes in the systolic and diastolic phases in the PPG signal reveal cardiac dysfunction. His investigation demonstrates the clinical application of

finger PPG signal measurement to improve early detection of cardiovascular disease.

Many current studies, Franco et al. (2022), Ku et al. (2022), and Ma et al. (2024) confirm endothelial damage, arterial stiffness, and abnormal blood pressure can be continuously measured using PPG signals that display systolic and diastolic blood flow profiles[21-23]. These non-invasive blood pressure-based PPG signals are obtained a verification by clinical standards to gain accurate blood pressure values. Consistent with these review findings, much previous research suggests that endothelial cell damage in the main bifurcation of the coronary artery may be an epidemiological consequence of endothelial cell damage in the coronary side-branches infected stenosis plaques. Therefore, this systematic review suggests that PPG signals derived from arterial stiffness and blood pressure have a strong epidemiological relationship with coronary heart disease.

PPG WITH AI/ML APPLICATIONS AND FUTURE DIRECTIONS

Analysis of PPG signals characterizing abnormal blood flow and blood pressure profiles is a branch of biomedical computation and mathematical signal processing. AI/ML is the mathematical processing of data to train and predict future data flows, and/or automatic decision-making[12,36-37]. In this review, we have seen that the use of AI/ML with PPG signal processing has increased significantly over the past several decades. Iqbal et al (2023) proposed a deep learning (DL) analysis of bilateral PPG signals on participants with normal and coronary artery disease[15]. Scalogram/spectral images were obtained by measuring PPG with right and left index fingers for image classification using convolutional neural network and k-nearest neighbor (K-NN) for comparison with biochemical markers of endothelial function. Iqbal's algorithm shows a significant agreement found between DL classification of PPG signals and coronary artery disease angiography, with the performance of DL clearly better than the K-NN method. Kanwal et al. (2024) used five different ML classification models with PPG signals: fine decision tree, linear discriminant analysis, weighted KNN, wide neural network, and ensemble of bagged trees[16]. Kanwal's research suggests that using weighted KNN can correctly predict PPG signals for 90 percent of the subjects studied.

Kavsaoğlu et al. (2015) employed ML with PPG signals to create a non-invasive hemoglobin prediction[17]. The most algorithm designs rely on classification and regression trees. Kavsaoğlu's study suggests that promising results can be obtained by using features selected by relief feature selection and support vector regression. With mean square error of 0.0027, his ML platform can predict clinical human hemoglobin levels from PPG signals without collecting and analyzing blood samples. Chakraborty et al. (2020) developed his own algorithm to automatically identify inter-arrhythmic variability in PPG signals for myocardial infarction (MI) analysis[18]. Chakraborty's algorithm is based on classification, mainly characterizing both normal signal properties and MI PPG signals, his algorithm achieved an accuracy of 95.40%, demonstrating that single-lead PPG signals are easy to use, inexpensive, and work independently at home.

Hsiu et al. (2022) used both multilayer perceptron (MLP) and random forest (RF) networks to help differentiate the frequency-domain pulse indices[19]. Hsiu's research reveals that the ML knowledge presented may be useful for the development of non-invasive and easy-to-use measurement techniques to detect changes caused by vascular aging in arterial pulse transmission conditions. Mejía-Mejía et al. (2022) used ML for feature extraction from PPG signals to recognize the time interval between beats to ultimately predict predicted blood pressure values[20]. Mejía-Mejía's study pointed out that the best performance in estimating blood pressure

was obtained from a combined set of features. Therefore, this review proves that almost all ML algorithms with PPG signals based on classification models develop computer-aided medical diagnosis systems with the use of AI/ML for personalized medicine. This is because noninvasive tools are pivotal to the digital economy and future leading technologies in computational research. Future directions are suggested to digitize clinical and hospital data into digital databases. This includes a focus on noninvasive tools for personalized medicine.

The keys contribute to the field of urban health and medicine.

- PPG signals characterize abnormal blood flow and blood pressure profiles to enhance noninvasive cardiovascular monitoring in healthcare.
- AI/ML algorithms with PPG signals based on classification models develop computer-aided medical diagnosis systems for personalized medicine.
- cPPG to measure physiological signals in patients may be considered a new era of the urban healthcare system.

Future directions may include PPG with blood flow in the aorta near the kidneys, causing damage to ovarian endothelial cells and renal arteries. The study of PPG signals and the prediction of chronic kidney disease and ovarian cancer is a new area of investigation that needs much attention.

STUDY LIMITATIONS

The main concerns relate to bias and the strength of the selected articles in terms of their inability to critically evaluate them. Thus, the search strategy for this review followed PRISMA guidelines[3,11-12], which allows researchers to identify and validate findings from a comprehensive literature search by carefully describing keywords that accurately describe the review objectives. In addition, a comprehensive search was conducted across four databases to retrieve full text of original articles to categorize the review objectives. The ScienceDirect site is primarily focused on digital literature. Most researchers do not measure PPG signals from real patients. They use PPG from public databases published on internet. Therefore, their results do not reflect the results of the original study using current technology used to measure PPG signals on patients.

CONCLUSION

The systematic review and meta-analysis provide a detailed analysis of the current literature on current technologies that measure PPG signals in patients with arterial stiffness related to coronary artery disease and other important interests. Despite widespread use of PPG measurement in the past ten years, there is not yet the systematic review studied on the epidemiological relationship between PPG signals and coronary heart disease, as well as the determination of significant AI/ML applications with PPG signals appear to no current direction. Diagnosis of vital signs using PPG such as blood flow and pressure is traditional. Computational analysis of PPG signals relevant to cardiovascular disease prediction still has room for improvement. This systematic review suggests that the development of noninvasive tools for PPG signal analysis is of interest and will benefit knowledge leaders in the digital economy and computational medicine.

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