ORIGINAL ARTICLE

Suicidal ideation and its associated factors among high school adolescents in Haiphong, Vietnam

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ABSTRACT

Suicide is a serious and preventable public health issue. This study aimed to identify the prevalence and associated factors of suicidal ideation (SI) among high school students. This cross-sectional study was conducted among 1,270 high school students. The Global School Student Health Survey (GSHS) questionnaire examined SI and related factors. The participant was identified as having SI by the question, "During the past 12 months, did you ever seriously consider suicide ideation?". Overall, 16.9% of the participants reported having SI during the last year (17.1% males and 16.7% females). Multivariable analysis indicated several factors positively associated with SI: being bullied during the last 30 days (AOR= 2.15, 95%CI: 1.23-3.77), often feeling lonely in the last 12 months (AOR= 1.95, 95%CI: 1.10-3.44), worried and could not sleep at night in the last 12 months (AOR= 4.40, 95%CI: 2.64-7.34), tobacco use in the last 30 days (AOR= 3.76, 95%CI: 1.66-8.54), alcohol use in the last 30 days (AOR= 1.83, 95%CI: 1.26-2.65), no close friends (AOR= 2.03, 95%CI: 1.30-3.17), parents/guardians did not regularly check homework in the last 30 days (AOR= 1.57, 95%CI: 1.09-2.25), parents/guardians did not understand problems and worries of students in the last 30 days (AOR= 3.32, 95%CI: 2.04-5.42) and parents/guardians often displayed disrespect in the last 30 days (AOR= 1.63, 95%CI: 1.13-2.36). SI is widely recognized as a significant predictor of future suicide risk. Therefore, schools, parents, and policymakers need to urgently take measures to prevent deaths from occurring.

Keywords:
suicidal ideation; adolescent; Haiphong; Vietnam

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INTRODUCTION

Adolescence is the transitional stage between childhood and adulthood, encompassing the age range of 10 to 19 years. While adolescence is generally regarded as a period of good health, it is essential to note that mortality, illness, and injury remain significant concerns within this age group.[1] Adolescents account for approximately 35% of the global disease burden.[2]

Suicide is a public health priority, which was the fourth most common cause of death globally among individuals aged 15 to 29 in 2019. According to the World Health Organization (WHO), over 700,000 people die by suicide each year, with 77% of these suicides occurring in low- and middle-income countries.[3] A study conducted across 82 countries in six WHO regions from 2003 to 2015, involving 275,057 adolescents aged 12 to 17 years, revealed a 14.0% prevalence of suicidal ideation (SI) in the last 12 months.

SI refers to the presence of thoughts or preoccupation with suicide, often observed as a symptom of a major depressive episode.[4] It is widely believed that the presence of SI during adolescence significantly elevates the risk of suicide attempts, completed suicides, and other mental health issues in adulthood.[5] The African region exhibited the highest prevalence of SI at 21.0%, while the Asian region had the lowest prevalence at 8.0%.[6] In a 2016 study conducted in Brazil, which involved 674 students from public and private schools, the rate of students who experienced SI was 7.9%.[7] Another research conducted in Ontario, Canada, with 1,922 students in grades 7-12, reported that 10.8% of the students had SI, while 3.0% indicated having attempted suicide in the past 12 months.[8] A study of 1,517 high school students aged 15 to 17 in Tabriz City, Iran, showed that 4.1% of students had SI.[9] According to the results of the Malaysia National Health and Morbidity Survey 2022, the rate of SI among adolescents aged 13 to 17 years increased from 10% in 2017 to 13.1% in 2022. Similarly, suicide attempt rates rose from 6.9% in 2017 to 9.5% in 2022.[10] In Vietnam, an assessment of the Survey and Assessment of Vietnamese Youth (SAVY I), conducted from 2003 to 2004, and SAVY II, carried out from 2009 to 2010, demonstrated that the rate of suicidal behavior among adolescents aged 14 to 19 years was 5.28% and 12.21%, respectively.[11] According to data reported by the WHO for Vietnam in 2019, the prevalence of students with SI in the last 12 months was 15.61%, with rates of 11.89% for males and 18.35% for females.[12]

Evidence shows that suicide does not have a single cause; rather, it is a complex outcome influenced by various psychological, social, biological, cultural, and environmental factors.[9,13] Research has indicated a link between suicide and mental disorders, as many suicides occur impulsively during times of crisis when individuals struggle to cope with life and stressors such as financial problems, broken relationships, or chronic pain and illness.[3] A study conducted among adolescents in 41 low- and middle-income countries found that being bullied was one of the stressors that lead to suicide in adolescents, while factors such as lack of sleep and body weight were also identified as contributing factors.[14] Research conducted in India revealed that the likelihood of SI was higher among adolescents who were frequently exposed to mass media, adolescents whose mothers had experienced physical abuse, or those who had experienced sexual abuse.[13] A study involving 5,852 adolescents from 37 middle schools in 5 provinces in China demonstrated a relationship between abuse, neglect, and suicide in adolescents.[15] Research conducted in the Philippines has identified several factors that increase the risk of attempted suicide, including the female gender, physical attacks, bullying,

loneliness, poor sleep, limited close friends, smoking, alcohol use, low physical activity, amphetamine or methamphetamine use, and low parental supervision.[16] In a study by Chan YY et al., which examined 2,789 school-going adolescents aged 16-17 in Malaysia, the findings revealed that the female gender, feelings of loneliness and anxiety, a lack of close friends and peer support, engagement in sexual intercourse, and involvement in fights were associated with a higher risk of SI.[17]

In light of the rising suicide mortality rates globally and the limited information available on SI among adolescents in Haiphong, Vietnam, this study aims to investigate the prevalence of SI and identify associated risk factors in this population. Therefore, the findings of this study will provide valuable insights for schools, families, and policymakers, facilitating the development of timely and effective strategies and public health interventions to address this urgent issue.

METHODS

Study Participants and Site

The participants in this study were high school students from grades 10, 11, and 12 at a high school in Ngo Quyen District, Haiphong, located in northeastern Vietnam. Students who voluntarily agreed to participate in the study met the inclusion criteria, and those absent or suffered an acute illness during the study period met the exclusion criteria.

Study Design and Sample Size

The sample size for the study was determined using the formula for estimating the sample size for a proportion: $N = Z^2_{(1-\alpha/2)} P(1 - P)/(\varepsilon P)^2$. Here, Z: The level of confidence (for a confidence level of 95%, Z = 1.96). P: The estimated proportion of adolescents having SI (P = 0.11).[18] ε: The relative error (ε = 0.15). The minimum sample size was calculated to be 1,381 participants. An additional 15% (N = 244) was added to account for potential errors in completing the questionnaire. The expected percentage of non-respondents was 10% (N = 154), resulting in a target sample size of 1,779 participants. However, during the data collection period, only 1,270 participants were included in the sample.

A self-reported questionnaire was utilized to gather data in a classroom environment. The researcher explained the study's objective before distributing the questionnaire to the participants. Subsequently, an online questionnaire was created using Google Forms and sent to a total of 1,865 participants enrolled at the school. The response rate obtained during the data collection period from February 15, 2021, to March 30, 2021, was approximately 68%.

Instrument

A self-reported questionnaire was administered to collect data in a classroom setting. The questionnaire was developed based on the Global School-based Student Health Survey (GSHS), designed by the WHO in collaboration with the United Nations International Children's Emergency Fund (UNICEF), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the Joint United Nations Programme on HIV and AIDS (UNAIDS), and the Centers for Disease Control and Prevention (CDC).[19] The questionnaire was translated into Vietnamese (the local language). It comprised a total of 30 closed-ended questions (see Supplementary S1).

Dependent variable: Participants's SI was measured using the question Q11: "During the past 12 months, did you ever seriously consider suicide ideation?"

Participants who answered "yes" were categorized as having SI.

Independent variables: The demographic variables (gender, age, grade level, weight, height) (Q1-Q5), individual factors (physical attack, bullying, and personal emotions), health risk behaviors (tobacco use, alcohol use, drug use, sexual intercourse, and physical activities), and experiences at school and home (going hungry, relationships with friends and parents/guardians) were included. Self-reported weight and height were collected to calculate the Body Mass Index (BMI); participants were considered overweight/ obese if their BMI was ≥ 25 kg/m^2.

Five questions (Q6-Q10) were used to measure the individual factors. Participants were considered not to have experienced being physically attacked, bullied, feeling lonely, worried, or having difficulty focusing on homework if they selected the response option '0' or 'Never.'

The health risk behaviors of the participants were assessed using eight questions (Q12-Q19). If participants responded with '0' or 'no,' it indicates that they did not engage in smoking cigarettes, alcohol consumption, drug use, sexual intercourse, or physical activity.

Participants were asked 11 questions (Q20-Q30) regarding their school and home experiences. Participants were asked about the number of close friends, with response options of 0, 1, 2, and 3 or more (Q20). Participants who selected the '0' option were categorized as not having close friends. Participants were asked how many days they missed classes or school without permission in the last 30 days (Q21). Those who selected the "0" option were considered to have not missed any classes or school. Nine questions assessed participants' experiences of going hungry and their relationships with friends, parents/guardians in the last 30 days (Q22-Q30). The response options for these questions were 'never/rarely/sometimes/ most of the time/always.' Participants who selected 'rarely/sometimes/most of the time/always' for Q22, Q24, Q25, Q26, and Q28, and 'never' for Q23, Q27, Q29, and Q30 were considered to have positive relationships with their friends, parents/guardians during the last 30 days.

Statistical Analysis

The statistical analysis was conducted using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Qualitative data were presented using frequencies and percentages. The Chi-square test was used to compare the difference in SI percentage and factors. We conducted univariate and multivariate logistic regression analyses to identify factors associated with SI. To eliminate confounding effects, independent variables related to SI with a significance level of $p < 0.25$ in the univariate analysis were included in the multivariable logistic regression models using the enter method. Statistical significance was determined at $p < 0.05$.

Ethical Approval

The research protocol was approved by the Scientific Council of Hai Phong University of Medicine and Pharmacy, Vietnam, under Decision No. 265/QĐ-YDHP, dated February 5, 2021. The survey was anonymous, and no identifying information was collected. All the data collected were kept confidential to ensure the participants' privacy.

RESULTS

Table 1 shows the distribution of SI by participant demographic characteristics. Overall, 214 (16.9%) participants reported seriously considering SI in the past 12 months. The percentage of males having SI was slightly higher than that of females, at 17.1% and 16.7%, respectively. Among the participants, 11th-grade students reported the highest SI rate (20.1%). Furthermore, the percentage of overweight/obese participants experiencing SI was 24.7%.

Table 1. Distribution of suicidal ideation by demographic characteristics of participants (N = 1,270)

Variables	Having suicidal ideation		Total
	Yes (N, %)	No (N,%)	N (%)
Gender			
Male	78 (17.1)	378 (82.9)	456 (35.9)
Female	136 (16.7)	678 (83.3)	814 (64.1)
Age (year)			
15 years old	17 (14.3)	102 (85.7)	119 (9.4)
16 years old	64 (15.5)	348 (84.5)	412 (32.4)
17 years old	106 (17.8)	489 (82.2)	595 (46.9)
≥ 18 years old	106 (17.8)	38 (82.2)	144 (11.3)
Grade level			
10	65 (14.7)	378 (85.3)	443 (34.9)
11	81 (20.1)	322 (79.9)	403 (31.7)
12	68 (16.0)	356 (84.0)	424 (33.4)
Overweight/obese			
No	172 (15.6)	928 (84.4)	1100 (86.6)
Yes	42 (24.7)	128 (75.3)	170 (13.4)
Overall	214 (16.9)	1056 (83.1)	1270 (100)

The risk factors for SI are presented in Table 2. A total of 151 (11.9%) participants stated that they had been physically attacked during the past 12 months, while 81 (6.4%) participants reported being bullied within the past 30 days. Furthermore, 966 (76.1%) participants frequently experienced loneliness in the last 12 months. The percentages of participants who reported being worried, not sleeping at night, and having difficulty focusing on homework in the last 12 months were 63.1% and 85.3%, respectively. Additionally, 3.5% and 22% of the participants reported tobacco use and alcohol use in the last 30 days, respectively. The percentages of participants who stated that they had ever used drugs, marijuana, amphetamine/methamphetamine, and had engaged in sexual intercourse were 1.7%, 2.5%, 1.8%, and 4%, respectively. Moreover, 11% of the participants had no close friends, and 95.7% of the students reported that most students in school were kind and helpful. The percentages of participants whose parents/guardians regularly checked homework, understood the problems and worries of the students, and provided advice and guidance in the last 30 days were 62.4%, 86.8%, and 92.6%, respectively.

Table 2. The risk factors for suicidal ideation (N = 1,270)

Variables	N	%
Physical attacked and bullied		
Physically attacked in the last 12 months	151	11.9
Bullied in the last 30 days	81	6.4
Individual emotions		
Often felt lonely in the last 12 months	966	76.1
Worried and could not sleep at night in the last 12 months	801	63.1
Hard to focus on homework in the last 12 months	1083	85.3
Health risk behaviors		
Tobacco use in the last 30 days	45	3.5
Alcohol use in the last 30 days	280	22.0
Have ever used drugs	22	1.7
Have ever used marijuana	32	2.5
Have ever used amphetamine or methamphetamine	23	1.8
Had sexual intercourse	51	4.0
Less physical activity in the last 7 days	276	21.7
Not attended physical education class	37	2.9
Experiences at school and at home		
No close friends	140	11.0
Missed classes or school without permission in the last 30 days	112	8.8
Most of the students in school kind and helpful	1215	95.7
Gone hungry because not enough food in the last 30 days	539	42.4
Parents/guardians regularly checked homework in the last 30 days	792	62.4
Parents/guardians understood student's problems and worries in the last 30 days	1102	86.8
Parents/guardians known what student were doing in free time in the last 30 days	1093	86.1
Parents/guardians have gone through things without the student's approval in the last 30 days	883	69.5
Parents/guardians regularly gave advice and guidance in the last 30 days	1176	92.6
Parents/guardians often expected students too much	142	11.2
Parents/guardians often disrespected students	629	49.5

The results of the multivariate logistic regression analysis, which examined the factors associated with SI, are presented in Table 3. The analysis revealed several statistically significant factors related to SI. These factors include being bullied during the past 30 days (AOR= 2.15, 95%CI: 1.23-3.77), often feeling lonely in the last 12 months (AOR= 1.95, 95%CI: 1.10-3.44), worried and inability to sleep at night in the last 12 months (AOR= 4.40, 95%CI: 2.64-7.34), tobacco use in the last 30 days (AOR= 3.76, 95%CI: 1.66-8.54), alcohol use in the last 30 days (AOR= 1.83, 95%CI: 1.26-2.65), having no close friends (AOR= 2.03, 95%CI: 1.30-3.17), parents/guardians not regularly checking homework in the last 30 days (AOR= 1.57, 95%CI: 1.09-2.25), parents/guardians not understanding problems and worries of students in the last 30 days (AOR= 3.32, 95%CI: 2.04-5.42) and parents/guardians often displaying disrespect in the last 30 days (AOR= 1.63, 95%CI: 1.13-2.36).

Table 3. Factors associated with suicidal ideation: Univariate and Multivariate Logistic Regression Analysis (N,%)

Variables	Suicidal ideation		Univariate	Multivariate
	No	Yes	OR (95%CI)	AOR (95%CI)
	N = 1056	N = 214		
Overweight/obese				
No	928 (84.4)	172 (15.6)	1	1
Yes	128 (75.3)	42 (24.7)	**1.15** (0.81-1.62)**	1.03 (0.65-1.63)
Physically attacked in the last 12 months				
No	924 (82.6)	195 (17.4)	1	1
Yes	132 (87.4)	19 (12.6)	0.68 (0.41-1.13)	0.66 (0.38-1.15)
Bullied in the last 30 days				
No	1007 (84.7)	182 (15.3)	1	1
Yes	49 (60.5)	32 (39.5)	**3.61***(2.25-5.80)**	**2.15**(1.23-3.77)**
Often feeling lonely in the last 12 months				
No	285 (93.8)	19 (6.3)	1	1
Yes	771 (79.8)	195 (20.2)	**3.79***(2.32-6.19)**	**1.95*(1.10-3.44)**
Worried and could not sleep at night in the last 12 months				
No	443 (94.5)	26 (5.5)	1	1
Yes	613 (76.5)	188 (23.5)	**5.23***(3.41-8.02)**	**4.40***(2.64-7.34)**
Hard to focus on homework in the last 12 months				
No	174 (93.0)	13 (7.0)	1	1
Yes	882 (81.4)	201 (18.6)	**3.05***(1.70-5.47)**	0.73 (0.36-1.49)
Tobacco use in the last 30 days				
No	1032 (84.2)	193 (15.8)	1	1
Yes	24 (53.3)	21 (46.7)	**4.68***(2.55-8.57)**	**3.76**(1.66-8.54)**
Alcohol use in the last 30 days				
No	854 (86.3)	136 (13.7)	1	1
Yes	202 (72.1)	78 (27.9)	**2.43***(1.76-3.33)**	**1.83**(1.26-2.65)**
Have ever used marijuana				
No	1035 (83.6)	203 (16.4)	1	1
Yes	21 (65.6)	11 (34.4)	**2.67**(1.27-5.63)**	0.66 (2.05-2.12)
Had sexual intercourse				
No	1023 (83.9)	196 (16.1)	1	1
Yes	33 (64.7)	18 (35.3)	**2.85***(1.57-5.16)**	1.04 (0.46-2.35)
Having close friend				
Yes	963 (85.2)	167 (14.8)	1	1
No	93 (66.4)	47 (33.6)	**2.91***(1.98-4.29)**	**2.03**(1.30-3.17)**
Less physical activity in the last 7 days				
Yes	843 (84.8)	151 (15.2)	1	1
No	213 (77.2)	63 (22.8)	**1.65**(1.19-2.30)**	1.43 (0.97-2.10)
Attended physical education class				
Yes	1032 (83.7)	13 (35.1)	1	1
No	24 (64.9)	13 (35.1)	**2.78**(1.39-5.55)**	1.40 (0.57-3.45)

Variables	Suicidal ideation		Univariate	Multivariate
	No	Yes	OR (95%CI)	AOR (95%CI)
	N = 1056	N = 214		
Missed classes or school without permission in the last 30 days				
No	972 (83.9)	186 (16.1)	1	1
Yes	84 (75.0)	28 (25.0)	**1.74*(1.10-2.75)**	0.95 (0.54-1.68)
Most of the students in school are kind and helpful				
Yes	1021 (84.0)	194 (16.0)	1	1
No	35 (63.6)	20 (36.4)	**3.01***(1.70-5.32)**	1.38 (0.64-2.96)
Gone hungry because there was not enough food in the last 30 days				
No	629 (86.0)	102 (14.0)	1	1
Yes	427 (79.2)	112 (20.8)	**1.62**(1.20-2.17)**	0.99 (0.71-1.40)
Parents/guardians did regularly check homework in the last 30 days				
Yes	690 (87.1)	102 (12.9)	1	1
No	366 (76.6)	112 (23.4)	**2.07***(1.54-2.79)**	**1.57*(1.09-2.25)**
Parents/guardians understood student's problems and worries in the last 30 days				
Yes	954 (86.6)	148 (13.4)	1	1
No	102 (60.7)	66 (39.3)	**4.17***(2.93-5.95)**	**3.32***(2.04-5.42)**
Parents/guardians known what student were doing in free time in the last 30 days				
Yes	937 (85.7)	156 (14.3)	1	1
No	119 (67.2)	58 (32.8)	**2.93***(2.05-4.18)**	1.33 (0.82-2.17)
Parents/guardians have gone through things without student's approval in the last 30 days				
No	329 (85.0)	58 (15.0)	1	1
Yes	727 (82.3)	156 (17.7)	1.22(0.88-1.69)	1.05 (0.69-1.60)
Parents/guardians gave regularly advice and guidance in the last 30 days				
Yes	993 (84.4)	183 (15.6)	1	1
No	63 (67.0)	31 (33.0)	**2.67***(1.69-4.22)**	0.89 (0.44-1.76)
Parents/guardians often disrespected students in the last 30 days				
No	565 (88.1)	76 (11.9)	1	1
Yes	491 (78.1)	138 (21.9)	**2.09***(1.54-2.84)**	**1.63**(1.13-2.36)**

Abbreviation: *OR: Odds Ratio, AOR: Adjusted Odds Ratio*, *CI: Confidence Interval*
Notes: *Bolded numbers are significant at p < 0.05 (*<0.05, **<0.01, ***<0.001)*

DISCUSSION

Prevalence of Suicidal Ideation

This cross-sectional study examined the prevalence and associated factors of SI among 1,270 high school students. The findings revealed that 16.9% of the participants reported having SI in the past 12 months. This prevalence was higher than that reported in previous research conducted in Vietnam, such as studies in Hanoi in 2006,[20] and across four regions of Vietnam during 2016 and 2017.[18] It was also slightly higher than the mean proportion of 15.61% reported by the WHO for adolescents in Vietnam in 2019.[12] This difference can be explained by the variation in research subjects. Our study focused on high school students aged 15 to 18, whereas the research conducted in Hanoi in 2006 targeted adolescents aged 15 to 24. Additionally, the research conducted from 2016 - 2017 in four regions of Vietnam encompassed secondary and high school students. These findings highlight an increasing trend of SI among Vietnamese adolescents, raising concerns for parents and guardians. Compared to research conducted in other countries, our findings showed a higher prevalence of SI. For instance, our results were higher than those reported in previous studies conducted by

Ziaei R et al. in Iran,[9] McCallum SM et al. in Australia,[21] a study conducted in China,[22] and a study conducted in Thailand.[23] Our findings were similar to the results of the study conducted in Taiwan,[20] and lower compared to the results of a study conducted in Ghana.[24] These comparisons provide insights into the varying prevalence rates of SI among adolescents across different countries. We found that male students had slightly higher rates of SI than female students, similar to the research results in Malaysia.[25] This can be explained by the fact that women are more likely than men to share and discuss their feelings with friends, seek feedback, and receive advice.[26]

Associated Factors with Suicidal Ideation

In our study, we discovered a significant association between being bullied in the past 30 days and SI among high school students. This finding is consistent with previous research conducted by Tran QA et al., which involved 6,407 students across four geographical regions in Vietnam,[18] a study conducted by Bao W et al. on 41 low- and middle-income countries,[14] and the research findings of Lagman JG et al. in the Philippines.[16] Furthermore, our study identified additional factors significantly associated with SI. These factors include experiencing feelings of loneliness and worry in the past 12 months and lacking close friends. These findings are in agreement with the research results of Chan YY et al. on adolescents in Malaysia, highlighting the consistent association between these psychosocial factors and an elevated risk of SI.[17]

The results of our study are in line with previous findings regarding the association between smoking and SI.[27,28] While it's important to note that this association does not imply a cause-and-effect relationship, our study suggests that smoking prevention and cessation should be incorporated into suicide prevention programs.[29] The findings of our study are consistent with previous research, indicating that participants who reported alcohol use in the past 30 days had a higher prevalence of SI.[16,30,31] Alcohol use is one of the most common risk factors for SI.[32] This association can be attributed to the impact of alcohol on neurotransmitters that regulate mood, potentially contributing to an increase in SI.[33]

In our study, we found that participants who reported a lack of parental attention and care, including infrequent checking of homework, limited understanding of student's problems and worries, and a lack of respect for relevant student matters, were associated with an increased risk of SI. These findings indicate that parental care and concern play a significant role in protecting adolescents against SI, and are consitent with previous research studies.[16,18,34,35]

Communication campaigns addressing school violence, promoting awareness of health-risk behaviors, and enhancing the role of parents or guardians are crucial. Equipping students with the necessary skills to cope with psychological and emotional challenges in relationships is essential. Furthermore, school health programs should include mental health education in the official curriculum to promote student well-being.

LIMITATION

This study has several limitations. Firstly, this is a cross-sectional study that does not allow the establishment of causality for any of the factors involved. Secondly, the study was conducted at a high school in Haiphong and may not represent adolescents from other areas of Haiphong or non-school-going participants. Thirdly, it is important to note that the GSHS

questionnaire used in this study has not been validated specifically for use in Vietnam. As a result, the validity and reliability of the questionnaire as a measurement tool in this context cannot be assessed. Finally, although the survey was anonymous, the participants may not have answered accurately because of the sensitivity of the research topic.

CONCLUSION

In the present study, the percentage of participants who reported having SI was high. Individual factors, health risk behaviors, and experiences at school and home were found to be significantly associated with suicidal ideation.

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CONFLICTS OF INTERESTS

The authors declares no conflict of interest in this study.

AUTHORS' CONTRIBUTION

TTTH and PTM designed the study; TTTH and PTM conducted research; CMD analyzed data; CMD wrote the manuscript. TTTH, CMD had primary responsibility for the final content. All authors have read and agreed to the published version of the manuscript.

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