ORIGINAL RESEARCH

Invasive Meningococcal Disease Remains a Health Threat in Vietnam People's Army

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Objective: Despite strict surveillance, *Neisseria meningitidis* still causes life-threatening invasive meningococcal disease (IMD). The study aimed to describe the prevalence, clinical and subclinical features, and treatment outcomes of IMD among young soldiers of the Vietnam People's Army.

Methods: A prospective, population-based surveillance study was conducted in all Vietnamese military hospitals from January 2014 to June 2021. The presence of *Neisseria meningitidis* was confirmed by PCR or culture from blood or/and CSF. Epidemiological indices (incidence, serogroups, and distribution of cases by length of service), medical history, clinical and subclinical features, and treatment outcomes were documented and analyzed.

Results: There were 69 IMD cases (91% serogroup B) documented, mainly in conscripts (91%). The highest annual incidence was 3.33/100,000 soldiers per year. Of these cases, 44% were meningitis (n=30), 19% septicemia (n=13), and 38% meningococcemia (n=26). The most common clinical symptoms were neck stiffness (61 cases, 88%), petechial rash (51%), and shock (20 cases, 29%). Laboratory findings showed leukocytosis in 96% of IMD cases, PCT >0.05 (ng/mL) in 100%, elevated leukocyte count (>1,000/mm3) in 71%, and high protein >1 g/L in 70%. The overall mortality rate was 9%. Two cases were found to be resistant to ceftriaxone. Prognostic factors of severity included petechial rash (OR = 9.82, p < 0.001), septicemia (OR = 5.83, p < 0.001), meningococcemia (OR = 6.22, p < 0.001), low platelet count, prolonged prothrombin time; high PCT (AUC = 0.84, p < 0.001), and increased creatinine (AUC = 0.86, p < 0.001).

Conclusion: IMD remains a health threat in the armed forces in Vietnam, especially among new recruits. To the best of our knowledge, this is the first study in Vietnam describing ceftriaxone resistance in *Neisseria meningitidis* and suggests the need to reconsider standard empiric therapy for IMD.

Keywords: meningitis, *Neisseria meningitidis*, sepsis

Introduction

Neisseria meningitidis (NM) is one of the most common causes of life-threatening bacterial meningitis worldwide.[1] These Gram-negative diplococci colonize the naso-pharyngeal mucosa of about 10% of the healthy population.[2] These pathogens can occasionally cause invasive meningococcal disease (IMD), which can lead to meningitis, septicemia or meningosepticemia with case fatality rates (CFRs) ranging from 4.1% to 20.0%, depending on age and pathogen strain.[3] Appropriate and continued monitoring is critical for accurate case management.[4] After an outbreak of IMD serogroup C between 1977 and 1979,[5] only a few sporadic cases have been reported,[6–8] noting the increasing number of NM serogroup B,[9] while the efficacy of

current licensed meningococcal B vaccines in the Asian population remains controversial.[10]

Young children, adolescents, and young adults are the most vulnerable age groups.[3,11] In Vietnam, high rates of meningococcal infection have been reported among new military recruits, which are associated with a higher risk of developing IMD. Surveys of military units in northern Vietnam revealed high asymptomatic transmission rates of 39%, but only 25 cases of IMD were documented between 2008 and 2014 (5 deaths) (unpublished data). IMD can lead to a fulminant course within a few hours, early treatment, including administration of an appropriate antibiotic, was considered the most effective measure.[12] Strains with reduced susceptibility to penicillin (PEN) have been reported worldwide,[13–16] but resistance to third-generation cephalosporins and ciprofloxacin (CIP) was considered rare.[15–17] Data from Vietnam show a few sporadic cases with NM strains resistant to CIP (0.19 mg/L) and PEN (0.25 mg/L),[9] whereas resistance to ceftriaxone – a commonly prescribed empiric antibiotic – has not been reported.

The aim of this study was to systematically investigate the prevalence, clinical and subclinical features, and treatment outcomes of IMD and to determine prognostic factors for the severity of this devastating infection in young soldiers of the Vietnamese People's Army.

Materials and Methods
Designs
A prospective, military population-based surveillance study was conducted in the Vietnam people's army, by the Department of Military Medicine from January 2014 to June 2021.

Inclusion Criteria
Case definition (Ministry of Health 2012) was used to include appropriate patients in the study. Enrolled patients were arranged in groups based on where NM was detected. In detail, the detection of NM (either by culture or PCR) only in CSF indicated meningitis; confirmation of NM only in blood (either by culture or PCR) indicated septicemia, and detection of NM in both CSF and blood by PCR or culture indicated meningococcemia.[18,19]

Severe disease was defined as having shock or coma or the need for invasive mechanical ventilation or the need for renal replacement therapy.

Data Collection
Epidemiological indices (incidence, serogroups, and distribution of cases by service time), medical history, clinical and laboratory findings; treatment (antibiotics, supportive measurements), and outcomes (death, survival, time to defervescence) were collected.

Specimen Collection and Laboratory Testing
Cerebral spinal fluid (CSF), serum and culture isolates were collected and sent to the Department of Microbiology – Military Institute of Preventive Medicine and 108 Military central Hospital for confirmatory testing and molecular typing.

Gram stain followed by microscopy was used to detect Diplococcic bacteria from clinical samples.

Blood and CSF samples were cultured using BACTEC FX TOP automation systems. The positive bottles were transferred to media agars for conventional culture. In detail, primary cultures were aerobically grown on Blood agar, Chocolate agar and MacConkey agar (Merck, Kenilworth, New Jersey, USA). Once growth of bacteria was detected, bacterial colonies were selected for species' identification using the VITEK MS system and Maldi Tof Vitek MS.

Serogroup was determined by real-time PCR as previously described.[20]

Antibiotic susceptibility was tested using E-test strip (bioMerieux, France) following manufacturer's guidelines. The diameters of the inhibited zones were measured and interpreted following CLSI guidelines. There were no interpretation guidelines for ceftriaxone resistance based on disk diffusion test, therefore, in this study, the diameter of N.meningitidis below 34mm was considered an indication of resistance.

Statistical Analysis
Annual number of active military personnel of 450,000 was used as denominator for calculation of incidence of IMD.[21] All statistical analyses were computed with R software (version 4.0.5). Where applicable, 95% confidence intervals are given and a two-sided p-value of <0.05 was considered statistically significant. In descriptive analysis: mean ± standard deviation (SD) was calculated for variables with normal distribution. Chi-squared test was used to compare the frequency of petechial rash, meningitis, septicemia; and Mann–Whitney test was used where applicable to show the difference between groups of severe and non-severe patients.

Univariable analysis was used to calculate Odds Ratio (OR). Area Under Curve (AUC) was used to determine the correlation between variables and severity of IMD patients. Variable with AUC > 0.9 was scaled excellent; from 0.8 to 0.9 was good and from 0.7 to 0.8 was fairly good.[22]

Results

Epidemiology

From 2014 to 2021, there were 69 cases of invasive meningococcal disease (IMD) recorded with mostly meningococcal serotype B (63 cases 91.3%). The average annual incidence was 1.9/100,000. The incidence was highest with 3.33/100,000 in 2016. The lowest incidence was 0.22/100,000 in 2021.

The overall death rate was 8.69% (6/69). The number of deaths was highest in 2016, then declined with no deaths recorded over the last 3 years (2019–2021).

The distribution of IMD cases by army service time and geographical distribution was described in Figures 1 and 2. Nearly half of the cases were new recruits whose service time in military was shorter than 6 months (Figure 1).

There was 65.2% (45/69) of the cases recorded in the Northern Units with the highest number of cases documented in the spring months while in the Southern Units, number of cases was highest in the first months of the rainy season.

Clinical Manifestation and Laboratory Characteristics

Mean disease onset to hospitalization was 2 ± 0.9 days. The most common forms of IMD were meningitis and meningococcemia with 30 (43.5%) and 26 (37.7%) cases,
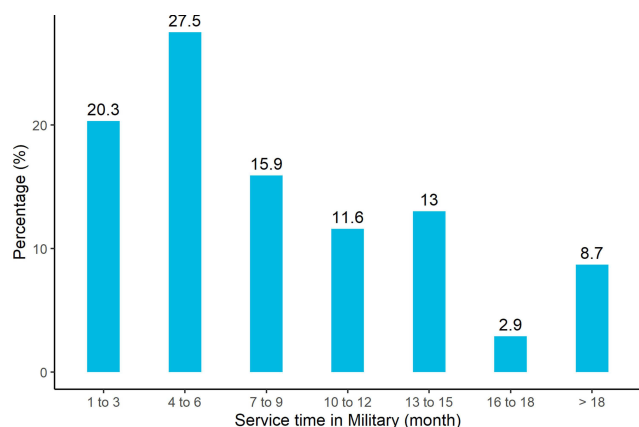

Figure 1 Distribution of IMD cases by army service time.

respectively, while the least common one was septicemia with 13 (18.8%) cases.

Neck stiffness was observed in 61 cases (88.4%), most frequently in meningitis group (100%) and meningococcemia group (96.2%), but less commonly found in septicemia group (46.2%). Altered mental status was documented in 72.5% of the cases with the highest number in meningococcemia (84%) followed by septicemia (69.2%) and meningitis (63.3%). Other neurological symptoms including coma (18.8%), seizure (13%), and urinary incontinence (11.6%) were most commonly documented in septicemia group (30.8%, 23.1%, and 15.4, respectively).

Petechial rash was found in 50.7% of IMD cases with the highest number documented in septicemia group (92.3%) compared to that in meningococcemia group (88.5%). In meningitis group, there were no cases with petechial rash. Shock was described in 20 cases (29%) in septicemia group.

95.7% of IMD cases had WBC > 10 G/L, 3 cases (23.1%) in septicemia group had normal or decreased WBC. The majority of IMD cases had PCT level > 10 (ng/mL) with 62.5%, 90.9%, and 66.7% in meningitis, septicemia and meningococcemia group, respectively.

Thrombocytopenia (platelets < 100 G/L) was documented in 37.7% of IMD cases, with the highest number documented in septicemia group (69.2%). There was no case with platelets < 100 G/L in meningitis group. Prolonged prothrombin time was found in two thirds of IMD cases with the highest number documented in meningococcemia group (81.8%).

Elevated serum bilirubin (> 17 μmol/L) was documented in 50%, 34.8%, and 48% of IMD cases in septicemia, meningitis and meningococcemia group, respectively. Renal failure (serum creatinine > 120 μmol/L) was found in one third of IMD cases with the highest number documented in septicemia group (76.9%) followed by meningococcemia group (26.9%) and only 1 case (3.3%) in meningitis group.

Elevated WBC count (> 1,000/ mm3) was found in 70.6% of IMD case; high protein level (> 1 g/L) was documented in 70% of cases; low CSF glucose level (glucose CSF/glucose serum <0.6) was found in 80% of cases.

Treatment and Outcomes

About one third of patients were treated with intravenous (IV) 3rd generation cephalosporin before admission and carbapenem was empirically given to 3 cases (4.3%).

Antibiotic susceptibility tests were done for 8 isolates and revealed 2 cases with resistance to ceftriaxone (first line to treat IMD).
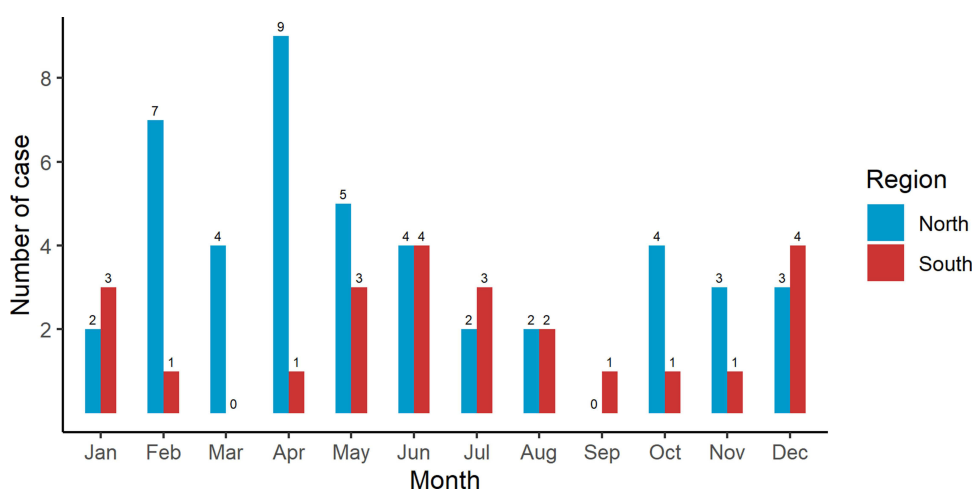
Figure 2 Number of IMD cases.

One third of the patients needed central catheter insertion with the highest number documented in meningococcemia group (50%). 13% of cases needed mechanical ventilation. Renal replacement therapy was done for 8.7% of cases.

Overall, there were 6 deaths (8.69%) due to IMD.

Petechial rash (OR = 9.82), septicemia (OR = 5.83), meningococcemia (OR = 6.22), low platelet count, prolonged prothrombin time, high PCT level (AUC = 0.84), increased creatinine (AUC = 0.86) were shown to be significant prognostic factors for severe IMD (Table 1).

Discussion

This study, the first of its kind in Vietnam, provides comprehensive insight into the prevalence and burden of invasive meningococcal disease in the military. Overall, the average annual incidence of IMD was 1.9/100,000 (Table 2). This is higher compared to what was reported in European countries (0.7/100,000), the United States (0.12/100,000), and Canada (0.3/100,000) and some other countries: China, Taiwan, Japan, South Korea.[11]

The highest IMD incidence was documented in 2016 with 3.33 cases per 100,000 soldiers and 2 deaths (Table 2). In response to this rising threat of IMD, the

Table 1 Common Prognostic Factors in IMD

Variables	Non-Severe (N=42)	Severe (N=27)	p	
Petechial rash	13 (31%)	22 (81.5%)	<0.001*	OR = 9.82
Meningitis	26 (61.9%)	4 (14.8%)	<0.001*	OR = 1
Septicemia	3 (7.1%)	10 (37%)		OR = 5.83
Meningococcemia	13 (31%)	13 (48.1%)		OR = 6.22
WBC (G/L)	20.9 [10.4–38.6]	21.3 [1.36–50.1]	0.7962#	
Bilirubin (µmol/L)	13.9 [4.1–44.6]	19.6 [2.9–47.4]	0.1174#	
Platelets (G/L)	144 [14–305]	37 [18–171]	<0.001#	AUC = 0.15
Prothrombin (%)	62 [8–96]	25 [11–38]	<0.001#	AUC = 0.20
Creatinine (µmol/L)	83 [60–199]	170 [56–491]	<0.001#	AUC = 0.86
PCT (ng/mL)	24.465 [0.08–102]	100 [100–200]	<0.001#	AUC = 0.84

Notes: *Chi-squared test; #Mann–Whitney test.
Abbreviations: WBC, white blood count; PCT, procalcitonin.

Table 2 Incidence, Serogroup, and Mortality

Year	Case					Mortality
	Number	**Incidence***	**Serogroup**			
			B	**W135**	**NA**	
2014	9	2	08	01		
2015	8	1.78	08		01	2
2016	15	3.33	13	01	02	2
2017	12	2.67	12		01	1
2018	12	2.67	11			1
2019	9	2	09			
2020	03	0.67	03			
2021	1	0.22	1			
Sum (%)	69 (100%)	1.92	63 (91.30%)	02 (2.90%)	04 (5.80%)	6 (8.69%)

Notes: *Incidence (cases/100,000 soldiers/year); NA (serogroup was not identified).

Department of Military Medicine released a new guideline for management of suspected cases of IMD. Thereafter, the number of cases decreased gradually and the lowest number of cases – 0.22 per 100,000 soldiers – was documented in 2021, with only 1 death in the four most recent years (Table 2). The lowest incidence of IMD recorded in the last 2 years of the study time overlapped with the occurrence of the Covid-19 pandemic when people, especially military men, are being asked to wear facemasks and strictly follow sanitation guidelines. These control measures were believed to limit the spread of airborne pathogens including Neisseria meningitidis.[23] Our data suggest that, in low-income settings with limited access to vaccines, using facemasks and practicing hand hygiene regularly could be practical and efficient to prevent invasive meningococcal disease.

The number of cases was high in the first 3-months group (Figure 1), when newly recruited soldiers gathered in military units, lived in crowded conditions,[24,25] and were exposed to Neisseria meningitis. The number of IMD cases was lower in other groups of subjects: 16–18 months of service (2.9%) and more than 18 months of service (8.7%) (Figure 1) whose protective immunity against Neisseria meningitis was demonstrated to be more sufficient.[26] This annual trend of prevalence and incidence is similar to what was reported elsewhere[24] and suggests the prevention strategy should focus on the youngest cohort as the first priority.

Mild IMD manifestations can progress to severe symptoms rapidly with mean duration from the first symptom

onset to hospitalization of 2 ± 0.9 days, and even shorter in septicemia group (1.8 ± 0.8 days) (Table 3). Similar rapid progression was documented in a cohort of 752 patients in the Netherlands.[27] Therefore, early diagnosis of IMD and hourly monitoring of severe signs and symptoms, even if the patient initially looks well at the onset of IMD, are crucial for optimal treatment and to minimize number of deaths.

Shock was documented in 29% (20/69) of the cases (Table 3), higher than that reported in another study,[27] but lower than data from a cohort study of IMD in young adults in the US during the 1990s (117/278 cases).[28] Shock in meningococcal sepsis is caused by hypovolemia (result of capillary leak syndrome),[29] myocardial dysfunction,[30] altered vasomotor tone and adrenal insufficiency in some cases.[31] Shock was one of the factors that defined severe disease (Table 1) and was associated with higher mortality.[18,27]

Classical symptoms remain highly common in IMD despite the low specificity for bacterial meningitis.[32] Neck stiffness is the most common symptom (61 cases, 88.4%) appearing in 100% of cases in meningitis group and noticeably in 46.2% of cases in septicemia group (Table 3).

Altered mental status (72.5%) and other neurological symptoms including seizure (13%), and urinary incontinence (11.6%) are less common (Table 3). Laboratory findings including elevated WBC count and PCT level (Table 4) are valuable parameters that, together with classical symptoms, help establish the diagnosis of IMD. Petechial skin rash is frequently observed in IMD[32,33] and could possibly lead to

Table 3 Clinical Manifestation of IMD

	Meningitis N = 30 (43.5%)	Septicemia N = 13 (18.8%)	Meningococcemia N = 26 (37.7%)	Sum 69 (100%)
Admission	1.9 ± 0.9	1.8 ± 0.8	2.2 ± 0.8	2 ± 0.9
AMS	19 (63.3%)	9 (69.2%)	22 (84%)	50 (72.5%)
Coma	4 (13.3%)	4 (30.8%)	5 (19.2%)	13 (18.8%)
Neck stiffness	30 (100%)	6 (46.2%)	25 (96.2%)	61 (88.4%)
Seizure	4 (13.3%)	3 (23.1%)	2 (7.7%)	9 (13%)
Incontinence	4 (13.3%)	2 (15.4%)	2 (7.7%)	8 (11.6%)
Shock	0	10 (76.9%)	10 (38.5%)	20 (29%)
Petechial rash	0	12 (92.3%)	23 (88.5%)	36 (50.7%)

Notes: Admission: time from onset to hospitalization (days); incontinence: urinary incontinence.
Abbreviation: AMS, altered mental status.

Table 4 Laboratory Findings

Variables		Meningitis N = 30	Septicemia N = 13	Meningococcemia N = 26	Sum N = 69
Blood analysis					
WBC (G/L) (N = 65)	< 4	0	1 (7.7%)	0	1 (1.4%)
	4–10	0	2 (15.4%)	0	2 (2.9%)
	>10	30 (100%)	10 (76.9%)	26 (100%)	66 (95.7%)
	Mean	22.3 ± 6.3	18.9 ± 11.5	24.2 ± 9	22.4 ± 8.6
PCT (ng/mL) (N = 34)	≤0.05	0	0	0	0
	>0.05–2	5 (20.8%)	1 (9.1%)	2 (8.3%)	8 (13.6%)
	>2–10	4 (16.7%)	0	6 (25%)	10 (16.9%)
	>10	15 (62.5%)	10 (90.9%)	16 (66.7%)	41 (69.5%)
PLT count < 100 G/L		0	9 (69.2%)	17 (65.4%)	26 (37.7%)
Prothrombin < 70%		10 (47.6%)	8 (80%)	18 (81.8%)	36 (67.9%)
Bilirubin > 17 µmol/L		8 (34.8%)	5 (50%)	12 (48%)	25 (43.1%)
Creatinine > 120 µmol/L		1 (3.3%)	10 (76.9%)	7 (26.9%)	18 (26.1%)
CSF analysis					
WBC (G/L)	<500	1 (3.3%)	6 (100%)	5 (19.2%)	12 (19.4%)
	500–1000	3 (10%)	0	2 (7.7%)	5 (8.1%)
	>1000	26 (88.7%)	0	19 (73.1%)	45 (72.6%)
Neutrophilia		26 (89.7%)		22 (84.6%)	48 (87.3%)
Protein (g/L)	<1	5 (16.7%)	6 (100%)	7 (29.2%)	18 (30%)
	1–3	12 (40%)	0	9 (37.5%)	21 (35%)
	>3	13 (43.3%)	0	8 (33.3%)	21 (35%)
Glucose ratio < 0.6		27 (90%)	0	21 (87%)	48 (80%)

Notes: Neutrophilia: neutrophil percentage > 70%, glucose ratio (glucose in CSF/glucose in serum).
Abbreviations: WBC, white blood cell count; PCT, procalcitonin; PLT, platelet; CSF, cerebrospinal fluid.

Table 5 Treatment and Outcomes

Variables	Meningitis N = 30 (43.5%)	Septicemia N = 13 (18.8%)	Meningococcemia N = 26 (37.7%)	Sum 69 (100%)
3GC	9 (30%)	3 (23.1%)	9 (34.6%)	21 (30.4%)
Carbapenem	0	2 (15.4%)	1 (3.8%)	3 (4.3%)
Central line	4 (13.3%)	6 (46.2%)	13 (50%)	23 (33.3%)
Arterial line	0	0	1 (3.8%)	1 (1.4%)
CRRT	0	2 (15.4%)	4 (15.4%)	6 (8.7%)
MV	1 (3.3%)	2 (15.4%)	6 (23.1%)	9 (13%)
FFP transfusion	1 (3.3%)	2 (15.3%)	1 (3.8%)	4 (5.8%)
PLT transfusion	0	1 (7.7%)	1 (3.8%)	2 (2.9%)
Amputation	0	2 (15.4%)	0	2 (2.9%)
Mortality	0	4 (30.8%)	3 (11.5%)	6 (8.7%)
Defervescence	4 ± 1.9	6 ± 4.5	4.9 ± 2.8	4.7 ± 2.8

Abbreviations: 3GC, 3rd Generation Cephalosporin use before admission; CRRT, continuous renal replacement therapy; MV, mechanical ventilation; FFP, fresh frozen plasma transfusion; PLT transfusion, platelet transfusion.

misdiagnosis, for instance, with Dengue hemorrhagic fever in this cohort. This could consequently lead to delayed antibiotic treatment and increased mortality. The primary pathophysiology causing meningococcal petechial rash is disorders of coagulation.[29,31,34] Thrombocytopenia (platelets < 100 G/L) and prolonged prothrombin time are common disorders (Table 4) and are associated with severe disease (Table 1).[35,36]

Renal failure is most frequently found in septicemia cases and related to the severity of shock[29] which may require continuous renal replacement therapy (CRRT) (Table 5).

The preferred empirical treatment of IMD includes ceftriaxone.[18] However, the low availability of this drug in infirmary of all military units in Vietnam[6] may be related to its limited use before hospitalization (Table 5). In addition, due to an increasing prevalence of antimicrobial resistance in Vietnam, carbapenem is empirically recommended for treatment of severe cases at admission to central hospitals,[37] as exemplified by 3 cases in our cohort (Table 5).

Susceptibility assay revealed two culture isolates with ceftriaxone resistant NM. These two cases were successfully treated with a combination of ceftriaxone and IV ciprofloxacin (ceftriaxone use was prolonged upon decision of clinician). This is of great concern because to the best of our knowledge, isolates with reduced susceptibility to third generation cephalosporin are rare.[14–17] Another study in civil patients in Southern Vietnam revealed 3 out of 11 isolates

were resistant and 5 out of 8 isolates intermediated to CIP (0.19 mg/L) and PEN (0.25 mg/L), respectively.[9] We assumed the efficacy of the treatment was maintained by ciprofloxacin.

In conclusion, IMD remains a health threat in the military in Vietnam especially in new military recruits. To the best of our knowledge, this is the first study to describe ceftriaxone-resistant Neisseria meningitidis in Vietnam, however, further studies are needed to investigate this phenomenon.

Ethics Approval

The study was approved by the Ethical Committee of 108 Military Central Hospital (No 432/ HĐĐĐ). The consent obtained from conscious patients or legal guardians of unconscious patients was written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the

article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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