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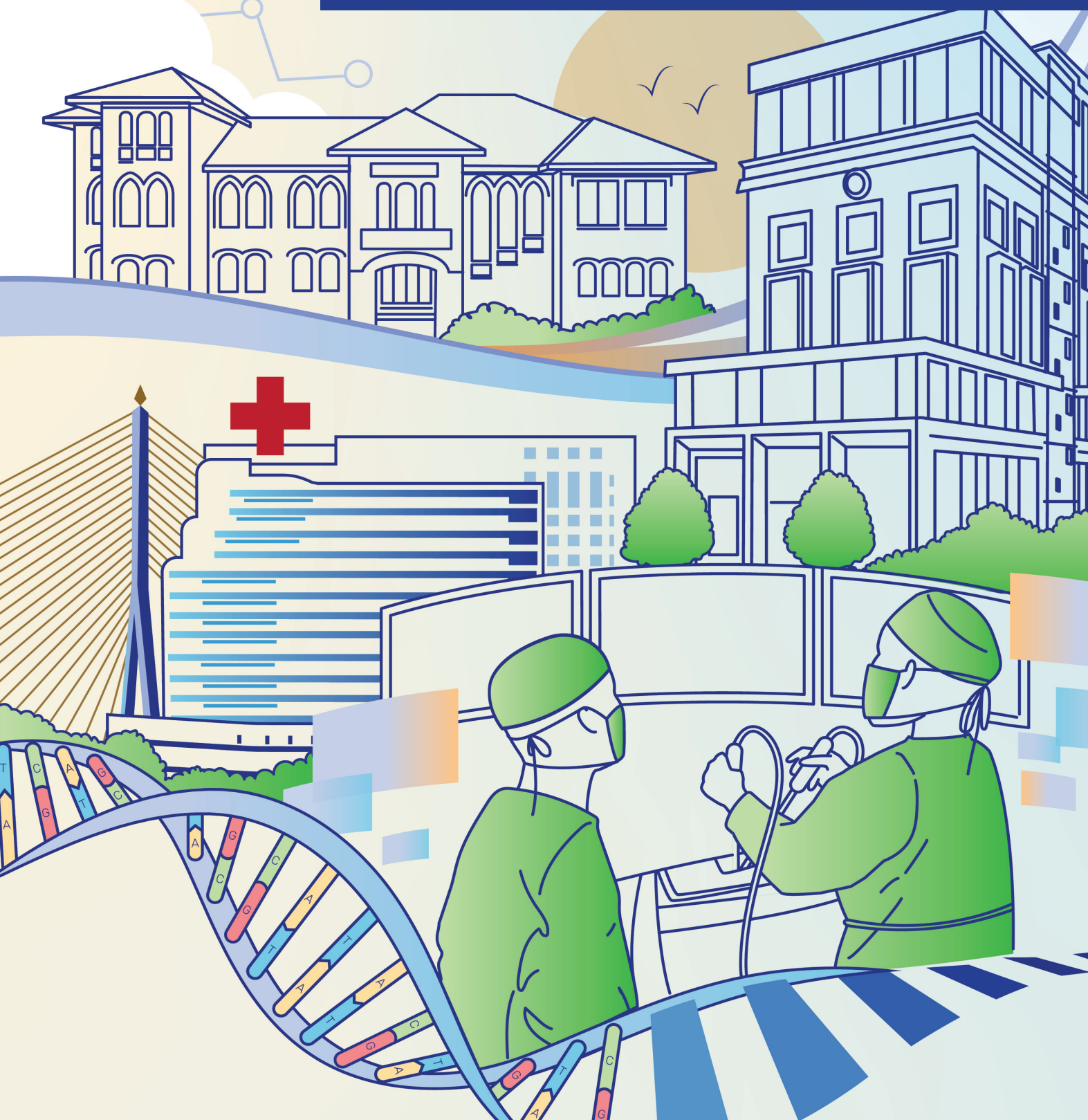

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ORIGINAL ARTICLES

REVIEW ARTICLES

Original Article

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A Decade of Invasive Candida Infection in Neonates: A Retrospective Study at a Tertiary Neonatal Intensive Care Unit in Thailand (2008–2018)

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ABSTRACT

OBJECTIVE: To determine the epidemiology of invasive candida infection in the neonatal intensive care unit (NICU) at a tertiary care center in Thailand over 10 years.

METHODS: A retrospective descriptive study was conducted. Participants were enrolled from all neonates diagnosed with invasive candidiasis infection (ICI) in Vajira Hospital between 2008 and 2018. Demographic data, microbiological results, and neonatal outcomes were reviewed.

RESULTS: During the study period, 9,031 neonates were admitted to the NICU. A total of 14 neonates were diagnosed with ICI, giving a prevalence of 1.5 cases per 1,000 infants admitted to the level II and III NICU. The median (IQR) gestational age and birth weight were 28.5 weeks (27.0, 31.0) and 1,053 g (850.0, 1,586.5), respectively. In all, 10 (71.4%) and 8 (57.1%) neonates had positive blood and urine cultures, respectively. All infants had negative cerebrospinal fluid cultures. Among 14 neonates diagnosed with ICI, 7 (50.0%) neonates had positive cultures for *Candida albicans*. The overall mortality rate of neonates with ICI was 21.4%.

CONCLUSION: ICI exhibits a low incidence rate within Vajira Hospital. This occurrence is demonstrably associated with prematurity, extremely low birth weight infants, and a demonstrably high mortality rate.

KEYWORDS: invasive candida infection, neonates, neonatal intensive care unit

INTRODUCTION

Invasive candidiasis infection (ICI) is a significant cause of sepsis in neonatal units, particularly in neonatal intensive care units (NICUs)[1-2]. ICI is associated with increased morbidity and mortality rates[1,3-4]. Its morbidity includes long-term developmental and neurological sequelae, such as cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia[5-8]. The incidence of ICI in neonates varies substantially between hospitals[5, 9-16]. Established risk factors for neonatal ICI include prematurity, extremely low birth weight (ELBW), invasive procedures such as central venous catheterization (CVC), and broad-spectrum antibiotic exposure[2,5,9,16-19]. For units with an ICI incidence exceeding 10%, the Infectious Diseases Society of America (IDSA) recommends implementing fluconazole prophylaxis in all NICU infants born weighing less than 1,000 grams[20]. This highlights the crucial role of individual unit-level NICU ICI

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incidence data in guiding fluconazole prophylaxis decisions. The aim of this study was to determine the epidemiology of invasive candida infection in the NICU at a tertiary care center in Thailand over 10 years.

METHODS

This retrospective descriptive study was conducted in the level II and III NICU at Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. Vajira Hospital is a 900-bed university hospital with approximately 2,000 deliveries per year. We reviewed the medical records of infants diagnosed with candida infection based on the International Classification of Diseases, 10th Revision (ICD-10) codes (B370, 371, 372, 374, 375, 377, 378, 379, and P375). The inclusion criteria included being born at Vajira Hospital between January 2008 and December 2018, and diagnosed with ICI confirmed by the positive isolation (aerobic culture) of *Candida species (spp.)* from blood, cerebrospinal fluid (CSF), or urine obtained via catheterization or suprapubic aspiration. Retrospective data were collected anonymously using a designated form.

Maternal and infant characteristics documented included sex, gestational age (GA), birth weight (BW), delivery route, maternal antenatal care, maternal chorioamnionitis, and Apgar scores. Outcomes data collected included age at diagnosis, source of Candida isolation and species identified, length of hospital stay, and in-hospital mortality. Treatment data included type and duration of antifungal and antibiotic use, ventilation support duration, invasive procedures (e.g., CVC, urethral catheterization), total parenteral nutrition administration, and history of surgery. Ethical approval for the study protocol was granted by the Institutional Review Board of the Vajira Hospital Faculty of Medicine, Navamindradhiraj University (COA093/62).

ICI is defined as an infection confirmed by the isolation of *Candida spp.* from the blood, CSF, or urine, collected through either urethral catheterization or suprapubic aspiration, with microbiology laboratory confirmation. Disseminated candidiasis is defined as more than 1 site of infection confirmed by the isolation of *Candida spp.*

Very low birth weight (VLBW) and ELBW infants are defined as those with a BW less than 1,500 g, and 1,000 g, respectively. Level II NICU (step down or special care baby unit) is defined as units that can take care of infants without advanced respiratory support who need mild support for their immaturity or transitional illness (those on supplemental oxygen or gastric tubing). Level III NICU 3 (tertiary care or Intensive Care) is defined as units that can take care of infants with critical illness, or those on advanced respiratory support.

Descriptive statistics were calculated using the Statistical Package for Social Science software version 22.0 (SPSS Inc., Chicago, IL, USA). Numerical data were analyzed using the mean and standard error of the mean or the median and interquartile range, depending on the distribution of the data. Categorical data were analyzed using percentages.

RESULTS

Between January 1, 2008, and December 31, 2018, 9,031 newborns were admitted to the Vajira Hospital level II and III NICU. Of these, 102 infants were diagnosed with candida infection based on ICD-10 codes. However, only 16 were diagnosed with neonatal ICI confirmed by culture. Two infants' medical records were missing; therefore 14 neonates ultimately met the study inclusion criteria (figure 1). Ten (71.4%) were male, the median GA was 28.5 weeks (27.0, 31.0), and the median BW was 1,053 g (850.0, 586.5). Of these infants, 12 (85.7%) were preterm, 9 (64.3%) were VLBW, and 6 (42.9%) were ELBW (table 1).

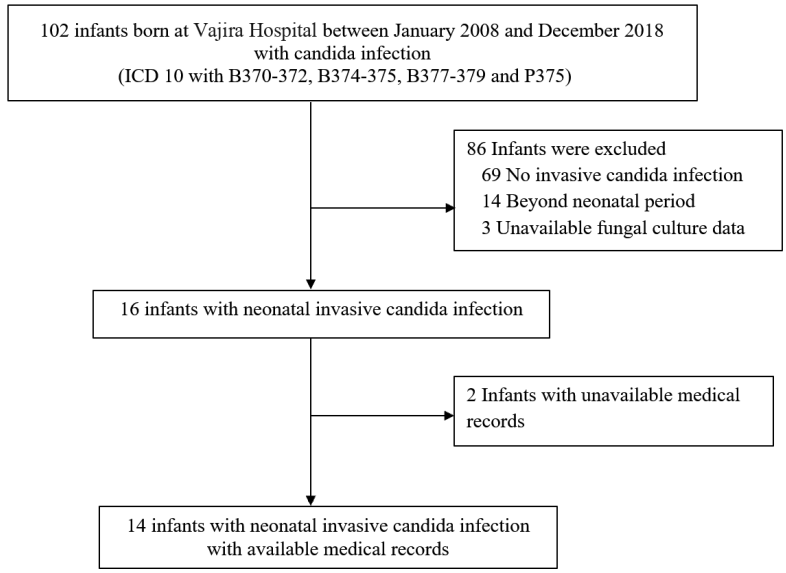

Figure 1 Flowchart demonstrating selection of study

The prevalence of neonatal ICI was 1.5 per 1,000 infants admitted to the level II and III NICU. Among neonates diagnosed with ICI, positive cultures were obtained from only blood in 6 cases (42.9%), only urine in 4 cases (28.6%)–4 cases (28.6%) had both candida septicemia and urinary tract infection. Notably, no infants were diagnosed with candida meningitis. The median age at diagnosis of ICI was 31.5 days (19.0, 44.3) (table 1).

Positive cultures were obtained from blood in 10 cases (71.4%), urine in 8 cases (57.1%), and sputum in 3 cases (21.4%). Of the isolates, 7 (50.0%) were identified as *Candida albicans*, while 7 (50.0%) were *non-Candida albicans species*, (*Candida parapsilosis*, 4 (28.6%); *Candida tropicalis*, 1 (7.1%); unspecified 2 (14.2%). Notably, no positive cultures were obtained from CSF, and no infants were infected with more than one type of *Candida spp.* All *Candida parapsilosis* infections (28.6%) were identified between 2016 and 2018 (table 1).

Nine mothers received antenatal care. Six deliveries were vaginal, while two occurred before arrival at the hospital. One mother was diagnosed with chorioamnionitis (table 1). The infants with ICI were diagnosed with several comorbidities. Necrotizing enterocolitis was present in 5 cases (35.7%), respiratory distress syndrome in 9 cases (64.3%), and bronchopulmonary dysplasia in 10 cases (71.4%) (table 2). All infants received intubation and were administered intravenous medications through a variety of catheters, including umbilical catheters, peripherally inserted central catheters (PICC), and double-lumen CVC (table 1). Additionally, 12 (85.7%) infants were treated with a third-generation cephalosporin and carbapenem (table 2).

Infants diagnosed with ICI received various antifungal regimens: 10 (71.4%) received fluconazole monotherapy, 2 (14.3%) received a combination of fluconazole and amphotericin B, and 2 (14.3%) received amphotericin B monotherapy. The median antifungal therapy duration was 13.0 days (12.0, 14.0) and median hospitalization duration was 89.5 days (42.5, 110.5) (table 2). The mortality rate of infants with ICI was 21.4% (3/14). All fatal cases involved VLBW infants diagnosed with disseminated intravascular coagulopathy (DIC) and septic shock. Two infants (66.7%) who died were ELBW infants (table 2).

Table 1 Maternal and neonatal characteristics with neonatal invasive candida infection (n = 14)

Characteristics	n (%)
Maternal data	
Antenatal care	9 (64.3)
Chorioamnionitis	1 (7.1)
Birth before arrival	2 (14.3)
Vaginal delivery	6 (42.9)
Apgar scores at 5 minutes < 7	3 (21.4)
Neonatal data	
Male gender	10 (71.4)
GA, weeks	28.5 (27.0, 31.0)
BW, g	1,053 (850.0, 586.5)
≥ 1,500	5 (35.7)
1,000-1,499	3 (21.4)
< 1,000	6 (42.9)
Clinical characteristics	
Age at diagnosis of ICI, days	31.5 (19.0, 44.3)
Diagnosis	
Candida septicemia only	6 (42.9)
Candida urinary tract infection only	4 (28.6)
Candida septicemia + urinary tract infection	4 (28.6)
Specimen of positive culture*	
Blood	10 (71.4)
Urine	8 (57.1)
CSF	0 (0)
Sputum	3 (21.4)
Species	
Candida albicans	7 (50.0)
Non-*albicans Candida*	
Candida parapsilosis	4 (28.6)
Candida tropicalis	1 (7.1)
Candida glabrata	0 (0)
Non-specifies	2 (14.2)
Intubation	14 (100.0)
Umbilical vein catheter	14 (100.0)
Central venous catheter (double lumen)	4 (28.6)
Peripherally inserted central catheter	1 (7.1)

Abbreviations: BW, birth weight; CSF, cerebrospinal fluid; g, grams; GA, Gestational age; ICI, invasive candida infection; n, number
Data reported as number and percentage or median and interquartile range.
* Some infants had ≥ 1 specimens of positive culture.

Table 2 The treatment and outcomes of infants with neonatal invasive candida infection (n = 14)

Neonatal outcomes	n (%)
Co-morbidity	
Necrotizing enterocolitis	5 (35.7)
Respiratory distress syndrome	9 (64.3)
Bronchopulmonary dysplasia	10 (71.4)
Antifungal drugs	
Fluconazole only	10 (71.4)
Fluconazole + amphotericin B	2 (14.3)
Amphotericin B only	2 (14.3)
Duration of antifungal treatment, days	13.0 (12.0, 14.0)
Postnatal steroid	1 (7.1)
Total parenteral nutrition	13 (92.8)
Antibiotics use	
3rd generation cephalosporin use	12 (85.7)
Carbapenem use	12 (85.7)
Length of stay, day	89.5 (42.5, 110.5)
Mortality	3 (21.4)

Abbreviations: n, number
Data reported as number and percentage or median and interquartile range (IQR).

DISCUSSION

ICI is a leading cause of mortality and significant complications in neonates. ICI incidence varies between hospitals and is influenced by factors such as GA and BW. This study showed a lower prevalence of ICI (0.15%) in neonates admitted to the level II and III NICU compared with reported rates in European studies (1.1%–3%)[12,21-22] and the United States (0.3%–0.45%)[13,23]. Notably, the incidence of invasive fungal infection in Thai neonates was reported to be 0.8%, with *Candida spp.* identified in 80–90% of cases[16]. This study observed a lower prevalence of ICI among neonates admitted to level II and III NICUs. This finding may be partially explained by the relatively low proportion of VLBW infants admitted to these units in Vajira Hospital. Notably, prematurity and VLBW are established risk factors for ICI development. Therefore, there is no clear justification for fluconazole prophylaxis in all infants with a BW under 1,000 g admitted to Vajira Hospital level II and III NICU.

No cases of candida meningitis were identified among neonates diagnosed with ICI. This observation may be partially attributed to the potential for false-negative CSF cultures. The timing of lumbar punctures in these infants could have been suboptimal, potentially leading to negative results. Notably, antifungal treatment was initiated prior to lumbar puncture procedures, further contributing to the possibility of negative CSF cultures. This practice likely stems from the institutional policy of avoiding lumbar punctures during the intubation process.

Most infants in this study were preterm (85.7%), VLBW (64.3%), and ELBW (42.9%). This finding aligns with a study from tertiary centers in Thailand[10,16], 58.3% premature infants and 63.8% VLBW, but showed a lower prevalence of prematurity (85.7%) and VLBW (64.3%) compared with studies from Europe (87.8% premature infants and 87.8% VLBW) and the United States (94.4% premature infants and 83.1% VLBW)[13,22].

Premature and VLBW infants are at high risk for ICI because of several factors, including candida colonization, impaired gastrointestinal, skin, and immune function, and the virulence of *Candida spp*[24]. Additionally, they are subject to more invasive procedures.

Multiple studies have identified risk factors for intubation, intravenous catheterization, parenteral nutrition, and the use of broad-spectrum antibiotics[2,5,9,16-19,25]. This study observed a trend suggesting a potential association between a higher proportion of infants with ICI and the presence of these factors. However, a tertiary referral center in southern Thailand found a significantly different risk factor: a history of cefoperazone/sulbactam use[16]. In this study, 57.1% (8/14) of infants with ICI had received this medication.

Candida albicans was the most isolated fungal species in this study (50.0%), in line with studies in Asia, Europe, and the United States[10,13,16,22,26]. Notably, all *Candida parapsilosis* infections (28.6%) were identified between 2016 and 2018, similar to report highlighting a recent increase in the prevalence of this species[14,21-22,27-30]. A 2013 study by Pammi et al., reported a 27% prevalence of *Candida parapsilosis* in neonates after 2000[27]. The association of *Candida parapsilosis* with intravenous catheterization, parenteral nutrition, and biofilm formation may contribute to its increased virulence and emergence as a significant pathogen in this population[28,31].

Fluconazole was the most administered antifungal drug in this study, aligning with recommendations from the IDSA[20,32]. Other studies have also reported successful treatment with fluconazole[15] or fluconazole combined with amphotericin B[10,21]. The median duration of antifungal therapy in this study was 13.0 (12.0, 14.0) days, which is shorter than that reported from China and the United States, where it was 21.5 (5.0, 69.0) days and 23 ± 14 days, respectively[14-15]. While no definitive evidence currently exists for optimal antifungal treatment duration[24], IDSA guidance from 2009 and 2016 recommends 3 weeks of therapy after culture sterilization[20,33]. Therefore, the shorter treatment duration observed in our study warrants investigation and may inform guideline development for managing invasive candidiasis in neonates.

In this study, two ELBW infants (< 26 weeks' gestation) succumbed to candida septicemia complicated by septic shock and DIC. This highlights the importance of early detection and intervention for ICI in this vulnerable population. The specific causes of death in these infants, and the role of antifungal drug administration, warrant further investigation to inform strategies for preventing and promptly identifying ICI in ELBW infants.

This study possesses several limitations that restrict the generalizability of its findings. Firstly, the retrospective analysis conducted at a single tertiary medical center limits the applicability of the results to broader populations. Secondly, the data lack crucial details regarding CVC practices, such as the utilization and duration of PICC lines and CVC, as well as their removal following the detection of catheter-related infections. This information is vital for understanding and optimizing catheter management strategies to minimize the risk of ICI in neonates. Additionally, the absence of data on further investigations, including abdominal imaging for the detection of intraabdominal abscesses, hinders the comprehensive assessment of prognosis and management plans for ICI. Furthermore, details regarding treatment, such as organism eradication and the timing of antibiotic and antifungal administration, are missing, limiting insights into potential therapeutic challenges. Moreover, the study lacks data on long-term outcomes, such as growth and development, which are crucial considerations for understanding the full impact of ICI on neonates. Finally, the descriptive study design inherently limited the analysis of factors associated with ICI. The lack of data on infants who did not receive a diagnosis of ICI within the NICU setting precludes the identification of risk factors and comparative analysis. Additionally, the relatively small sample size might have restricted the ability to detect statistically significant associations between variables.

Nevertheless, the study's 10-year timeframe offers valuable insights into the incidence, characteristics, and outcomes of ICI in neonates. It has informed the development of improved neonatal care guidelines for quality improvement, with an emphasis on preventing ICI and facilitating faster diagnosis, through methods beyond symptom-based approaches and culture results, and timely and appropriate treatment.

CONCLUSION

The prevalence of neonatal ICI is low in Vajira Hospital. This occurrence is demonstrably associated with prematurity, ELBW infants, and a demonstrably high mortality rate. While *Candida albicans* remains the most prevalent fungal isolate in ICI, the emergence of non-albicans Candida species is a growing concern.

CONFLICT OF INTEREST

The authors report 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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Correlation between Various Factors and Pain in Gynecological Cancer Patients within the First 24 Hours Post-Operation: A Study in an Urban-Based Tertiary Medical Center

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ABSTRACT

OBJECTIVE: To investigate various pain factors in patients with gynecological cancer who have undergone different types of elective hysterectomy.

METHODS: In this retrospective study, data on pain assessment were collected from gynecological cancer patients who underwent elective total abdominal hysterectomy or total laparoscopic hysterectomy surgeries (with associated surgery) between January 2019 and December 2022 at Vajira Hospital. The data were gathered starting from 24 hours after the procedures.

RESULTS: The pain assessment was evaluated using the Numerical Rating Scale (ranging from 0 to 10, representing low to severe pain) during the first 24 hours after the surgery. The results revealed that several factors, such as cancer location, prior surgical history, and body weight, influenced the intensity and onset of pain. However, different types of surgery did not have a significant impact on pain assessment. Moreover, patients with cancer lesions in the endometrium experienced an early onset of severe pain. Additionally, patients without previous surgical experience and those who are obese should receive additional attention in terms of pain management.

CONCLUSION: This study sheds light on evidence-based factors that influence pain intensity and/or pain onset, including cancer location, prior surgical history, and body mass index. Understanding these factors can contribute to more effective pain management strategies for gynecological patients' post-surgery.

KEYWORDS: gynecological cancer, pain, pain factor, pain management

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INTRODUCTION

Cancer has become the second leading cause of death worldwide in recent years[1]. According to a 2020 report, cervical and ovarian cancers ranked as the second and sixth most prevalent cancers among Thai women, respectively[2]. Both cancers fall under the category of gynecological cancer, which typically involves multiple organs such as the vagina, cervix, uterus, fallopian tubes, and ovaries. Fortunately, these cancers are largely manageable, with hysterectomy being a commonly employed treatment method[3].

Hysterectomy can be performed through various approaches, including transabdominal hysterectomy (TAH) or open abdominal surgery, transvaginal hysterectomy (TVH), or laparoscopic surgery with a laparoscope (TLH) (with associated surgery). TVH and TLH (with associated surgery) are less invasive procedures that result in minimal postoperative pain and faster recovery. However, major hysterectomies are typically performed using TAH due to better disease visibility and procedural simplicity[4-7]. As a result, TAH surgeries typically last one to two hours. It is important to note that patients undergoing TAH may experience moderate to severe postoperative pain, which typically occurs within the first 24 hours after the procedure[8]. Postoperative pain in this context is primarily somatic nociceptive inflammatory pain, which occurs when nociceptors are activated by inflammatory stimuli released by injured cells and local white blood cells at the surgical site. The degree of pain experienced is also influenced by the nature and duration of the operation[9-10].

To assess pain levels, this study utilized the Numerical Rating Scale (NRS), which ranges from 0 to 10 and represents no pain to severe pain. The NRS takes into account various factors such as patient knowledge, pain characteristics, location, onset, duration, and intensity[11]. When the pain score exceeds three (threshold > 3), common treatment options include non-pharmacological therapies or drug administration, such as nonsteroidal anti-inflammatory drugs or opioids. Therefore, understanding postoperative pain and examining its influencing factors is crucial[12-13].

Previous studies have suggested that several factors may contribute to moderate to severe postoperative pain in patients, including high intraabdominal pressure (> 12 mmHg), longer surgery duration (> 3 hours), advanced age (65 years), body mass index, and adequate postoperative analgesia. Non-pain-related variables may include previous surgical experiences, type of surgery, preoperative prolonged pain, analgesic prophylaxis, and the patient's physical condition under anesthesia. However, there is still controversy surrounding the key factors contributing to postoperative pain, particularly within the first 24 hours following surgery, leaving significant gaps in information[8,14-17].

The present study aims to investigate the parameters that influence postoperative pain in patients who undergo gynecological surgery within the initial 24-hour period. The findings of this study provide valuable information for the effective management of postoperative pain.

METHODS

This retrospective study received approval from the institutional review board of the Faculty of Medicine Vajira Hospital (COA 024/2565). Data on pain assessment were collected from 162 gynecological cancer patients who underwent elective TAH or TLH surgery between January 2019 and December 2022 at the Faculty of Medicine Vajira Hospital in Bangkok, Thailand. Exclusion criteria were applied, including incomplete patient information, lack of pathological diagnosis confirmation, and absence of nursing care records.

The NRS, ranging from 0 to 10, was utilized in this study to assess pain levels at four-hour intervals during the first 24 hours following surgery. A score of "0" indicates the absence of pain, while a score of "10" represents the worst possible or most severe pain experienced by patients.

Pain levels were analyzed based on various patient factors, including age, body mass index (BMI), type and duration of hysterectomy (with associated surgery), histological findings, pain onset, and previous surgery history. Data analysis was conducted using SPSS version 24.0 for Windows OS. To fulfill the analytical objectives, the following statistical tests were employed: simple t-test, Mann-Whitney U test, Kruskal Wallis test, Chi-Square test, and correlation coefficient test. Numerical data were presented as mean ± SD or median (25^{th} and 75^{th} percentile), while qualitative data were described in terms of frequency and percentage. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The study included a total of 162 female patients with a mean age of 56 ± 14.38 years. The average BMI indicated a normal weight for most patients, with an average value of approximately 26. However, around 30% of patients were classified as overweight, while approximately 17% were categorized as obese. The majority of patients (80%) underwent TAH, with an average surgery duration of approximately four hours. The most common cancer sites among patients were the endometrium, cervix, and ovary, accounting for 45.7%, 32.7%, and 21.6% of cases, respectively. Regarding previous surgical history, 43.2% of patients had never undergone surgery, while the remaining patients had undergone procedures under either local or general anesthesia in the past.

Based on the pain assessment records, the majority of patients experienced their initial pain response approximately 130 minutes (2 hours) after surgery, with a pain score of "3 out of 10" on the pain scale. Subsequently, most patients reported their worst pain scores of "5 out of 10" approximately 267 minutes (4.45 hours) following the surgery. Morphine was administered to alleviate pain in all patients. Each patient had 6 to 8 pain response records (see table 1 for more details).

Regarding the different types of procedures, there was no significant difference in the first pain onset (127.5 and 137.5 minutes, p = 0.533) or worst pain onset (270 and 250 minutes, p = 0.880) between patients who underwent elective TAH or TLH. Additionally, the pain scores between the TAH and TLH groups did not differ significantly at the first pain onset (3 out of 10 in both groups, p = 0.130) or worst pain onset (5 vs. 4 score, p = 0.180) during this observation (table 2).

To examine the relationship between the locations of cancer, pain onset, and pain score, we compared patients with cancer in three different locations. The findings revealed no statistically significant differences in pain onset or score. However, patients with endometrial cancer experienced their initial pain sooner than those with ovarian cancer and cervical cancer. Conversely, the worst pain onset was significantly delayed in the cervical cancer group compared to the ovarian cancer group (435 vs. 195 minutes, respectively), with a p-value less than 0.05. Furthermore, the cervix cancer group had the highest pain score among the different locations, scoring 7 out of 10 compared to 4.5 to 5 out of 10 in the other locations. Detailed data can be found in Table 3.

The relationship between past surgical history and pain perception is believed to have an impact. In this study, patients were categorized into three groups based on their surgical history: 1) those who had no prior surgery, 2) those who had surgery under local anesthesia, and 3) those who had surgery under general anesthesia. Interestingly, patients who had undergone surgery with local anesthesia had significantly lower pain scores (3 out of 10) compared to patients who had surgery under general anesthesia (5 out of 10) and patients who had no previous surgery (6 out of 10) (p < 0.05 and p = 0.001, respectively). However, there were no significant differences in the onset time of pain among these patient groups. Detailed information can be found in Table 4.

Table 1 Patient demographic data

Variable	Value (%)
Age (year)	54.56 ± 14.38
Weight (kg) and Height (cm)	61.58 ± 14.46 and 155.41 ± 6.25
Body Mass Index	25.48 ± 5.78
Underweight	13 (8.0)
Normal weight	71 (43.8)
Overweight	50 (30.9)
Obesity	28 (17.3)
Duration procedure (min)	250.70 ± 86.09
Procedure	
Transabdominal hysterectomy (with associated surgery)	130 (80.2)
Laparoscopic hysterectomy (with associated surgery)	32 (19.8)
Site of cancer	
Cervix	35 (21.6)
Endometrium	74 (45.7)
Ovary	53 (32.7)
Histologic type	
Cervix, Squamous cell carcinoma	22 (13.6)
Cervix, Adenocarcinoma	9 (5.6)
Cervix, Adenosquamous carcinoma	4 (2.5)
Endometrium, endometrioid carcinoma	60 (37.0)
Endometrium, serous carcinoma	6 (3.7)
Endometrium, clear cell carcinoma	4 (2.5)
Endometrium, carcinosarcoma	5 (3.1)
Endometrial stromal sarcoma	2 (1.2)
Ovary, clear cell carcinoma	16 (9.9)
Ovary, endometrioid carcinoma	7 (4.3)
Ovary, serous carcinoma	19 (11.7)
Ovary, other	8 (4.9)
Time of onset after surgery (min)	130 (105 , 170)
First pain score (0 to 10)	3 (3, 5)
Time of worst-pain onset (min)	267.50 (133.75, 712.50)
Maximal pain score (0 to 10)	5 (3, 8)
Surgery history	
No previous surgery	70 (43.2)
Local anaesthesia	27 (16.7)
General anaesthesia	65 (40.1)
Morphine use	162 (100.0)
Pain at others site of body	10 (6.2)
Frequency of pain assessment after surgery	7 (6, 8)

Abbreviations: cm, centimeter; kg, kilogram; min, minute
Data were represented based on type of data. Numerical data were represented by mean ± SD or median (25^{th} and 75^{th} percentile). Qualitative data were described by frequency and percentage.

Table 2 Surgical procedure and pain reflexion

Pain assessment	Procedure		P-value
	TAH	TLH	
First pain onset (min)	127.50 (105.00, 166.25)	137.50 (106.25, 180.00)	0.533
Score at first onset	3 (3, 5)	3 (2.25, 3.75)	0.126
Worst pain onset (min)	270.00 (127.50, 720.00)	250.00 (153.75, 675.00)	0.880
Score at worst pain	5 (3, 8)	4 (3, 7)	0.180

Abbreviations: min, minute; TAH, transabdominal hysterectomy; TLH, hysterectomy with laparoscope
Data were analysed by Mann-Whitney U test and represented by median (25th and 75th percentile).

Table 3 Cervical cancer site and pain reflexion

Pain assessment	Site of cancer			P-value		
	Cervix	Endometrium	Ovary	Cervix vs. Endometrium	Cervix vs. Ovary	Endometrium vs. Ovary
Time (min)						
First pain onset	140 (105, 180)	127.5 (105, 170)	130 (105, 175)	0.449	0.635	0.858
Worst pain onset	435 (165, 900)	257.5 (143, 656)	195 (120, 627.5)	0.092	0.047	0.514
Pain score (0 to 10)						
Score at first onset	3 (2, 5)	3 (2.75, 5)	3 (3, 5)	0.957	0.359	0.264
Score at worst pain	7 (3, 10)	4.5 (3, 7.25)	5 (3, 7)	0.101	0.090	0.759

Abbreviation: min, minute
Data were analysed by Mann-Whitney U test and represented by median (25th and 75th percentile).
P-value ≤ 0.05 is considered as statistical significance.

Table 4 Surgical history and pain reflexion

Pain assessment	Surgical history			P-value		
	None	LA	GA	None vs. LA	None vs. GA	LA vs. GA
Time (min)						
First pain onset	127.5 (105, 180)	145 (110, 180)	125 (105, 168)	0.366	0.497	0.159
Worst pain onset	325 (134, 713)	205 (145, 690)	225 (130, 728)	0.442	0.449	0.871
Pain score (0 to 10)						
Score at first onset	3 (3, 5)	3 (2, 4)	3 (3, 5)	0.069	0.762	0.050
Score at worst pain	6 (4, 8)	3 (3, 6)	5 (3, 7)	0.001	0.088	0.030

Abbreviations: GA, patient with past surgery with general anesthesia under their procedure; LA, patient with past surgery with local anesthesia under their procedure; min, minute
Data were analysed by Mann-Whitney U test and represented by median (25th and 75th percentile).

Body weight and height can be factors that impact postoperative pain management. Patients classified as obese had significantly higher pain scores at the onset of pain compared to both underweight and overweight groups (p = 0.026 and p = 0.007, respectively). They also showed a trend towards statistical significance when compared to the normal BMI group (p = 0.058). Furthermore, patients classified as obese experienced their initial discomfort more quickly than those who were overweight (p = 0.027). However, there were no significant differences in the onset and severity of worst pain among the different BMI groups. Detailed information can be found in Table 5.

Despite our efforts, this observation did not yield any significant factors that exhibited a strong correlation with pain score. However, we did identify a negative correlation between patient age and the severity of worst pain experienced (correlation coefficient = -0.220, p = 0.005, data not shown).

DISCUSSION

This study aimed to report the pain scores and associated factors during the first 24 hours following elective hysterectomy (with associated surgery) in gynecological cancer patients. The overall pain scores based on the NRS were 3 out of 10 (indicating low pain) at initial pain onset and 5 out of 10 (indicating moderate pain) at worst pain onset (table 1). These findings are consistent with previous reports on postoperative pain after elective gynecological, orthopedic, and general surgeries[14,18].

The use of morphine in all patients after surgery limited the pain intensity to mild-to-moderate levels. Morphine acts by binding to mu-opioid receptors in the central and peripheral nervous systems, activating descending inhibitory pathways and reducing pain transmission[18-20]. The analysis of pain-associated factors revealed that the type of surgery (TAH and TLH (with associated surgery)) did not affect pain scores or pain onset duration in this study (table 2). A similar report also demonstrated no significant difference in pain scores between these two types of operations[21]. However, the presence of diverse cancer lesions in different locations may play a role in pain perception, rather than the specific surgical procedures. This study revealed that patients with ovarian cancer experienced the worst pain onset earlier than those with cervical cancer and endometrial cancer. The worst pain in patients with ovarian cancer occurred approximately 3 hours after surgery, while in other cancer sites, it occurred between 4 and 7 hours post-surgery. However, there was no difference in the level of pain intensity among patients with various cancer locations in this observation (table 3). Additionally, pain levels may be associated with various factors specific to different cancer sites, such as etiology, individual symptoms, and pathological mechanisms[22-23].

Patients' previous surgical experiences emerged as a significant contributing factor to pain in this study. Patients with no prior surgical experience had the highest worst pain scores, particularly when compared to patients who had previous surgery with local anesthesia (pain scores of 6 and 3 out of 10, respectively). Moreover, patients with prior surgical experiences also exhibited different pain scores between the groups who had undergone procedures with local anesthesia and general anesthesia (pain scores of 3 and 5 out of 10, respectively). However, the timing of first pain onset and worst pain onset did not differ significantly (table 4). Thus, previous surgical history may influence pain scores, especially in patients with no prior surgical experience who may develop pre-surgery anxiety or stress, which can affect pain responses[17,24].

The weight and height of patients were also analyzed to assess their impact on pain scores and pain onset. Patients were categorized based on their BMI. The results indicated that patients with obesity had higher pain scores at the onset of pain compared to the overweight and underweight groups. However, the worst pain scores did not differ significantly among the various BMI groups (table 5). Several studies have also demonstrated that obesity is associated with increased self-reported pain intensity and severity compared to individuals with normal BMI[25-26]. Additionally, another study showed that patients with obesity exhibited increased pain sensitivity after surgery[27].

Other factors, including surgery duration and histological type, did not significantly impact pain intensity or pain onset. Furthermore, a negative correlation between age and pain scores was observed, although the limited number of patients in each category based on diverse factors can be considered a limitation of this study.

Table 5 BMI and pain reflexion

Pain assessment	BMI				P-value					
	Underweight (A)	Normal (B)	Overweight (C)	Obesity (D)	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Time (min)										
First pain onset	120 (100, 150)	120 (105, 170)	145 (118, 200)	120 (90, 166)	0.487	0.124	0.857	0.118	0.289	0.027
Worst pain onset	195 (115, 558)	280 (150, 690)	257.5 (143, 724)	292.5 (120, 818)	0.373	0.535	0.709	0.689	0.677	0.872
Pain score (0 to 10)										
Score at first onset	3 (2, 3.5)	3 (3, 5)	3 (2, 4)	4 (3, 7)	0.193	0.560	0.026	0.226	0.058	0.007
Score at worst pain	3 (2.5, 8)	5 (3, 8)	4.5 (3, 7)	6 (4, 8.75)	0.322	0.730	0.249	0.215	0.499	0.103

Abbreviations: BMI, body mass index; min, minute
Data were analysed by Mann-Whitney U test and represented by median (25^{th} and 75^{th} percentile).
P-value ≤ 0.05 is considered as statistical significance.

CONCLUSION

This study aimed to identify evidence-based factors that influence pain intensity and onset, including cancer location, previous surgical experience, and BMI. Understanding these factors is crucial for effectively managing postoperative pain in gynecological patients.

CONFLICT OF INTEREST

The authors declare no competing interests.

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DATA AVAILABILITY STATEMENT

The datasets are available from the corresponding author on reasonable request.

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Original Article

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Prevalence of Problematic Internet Use and Related Factors in Children with Attention Deficit Hyperactivity Disorder and Non-Attention Deficit Hyperactivity Disorder

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ABSTRACT

OBJECTIVE: To compare the prevalence of problematic internet use (PIU) in attention deficit hyperactivity disorder (ADHD) and non-ADHD children and explore the related factors and effects of PIU in children.
METHODS: A cross-sectional study was done. ADHD and non-ADHD participants aged 7-15 years old with current internet use were enrolled. A self-report questionnaire collected child and parental demographic data, internet use, and related data. An internet addiction scale was used.
RESULTS: A total of 127 participants were enrolled, including 56 ADHD participants and 71 non-ADHD participants. The rate of possible PIU and PIU (possible PIU/PIU) in the ADHD group was 60.7% and 61.5% in the non-ADHD group. In the ADHD group, internet usage time ≥ 21 hours per week was a significant related factor to possible PIU/PIU (adjusted odd ratio 27.08, 95% confidence interval 2.35 – 312.04). Male was significant related factor to possible PIU/PIU in the non-ADHD group (adjusted odd ratio 4.25, 95% confidence interval 1.25 - 14.47). School level, grade, online gaming or social media exposure, and parental internet restriction were non-significant related factors in both groups. Children with possible PIU/PIU had significantly more positive depressive symptoms than the normal internet use group (p = 0.006).
CONCLUSION: The results indicate a higher rate of possible PIU/PIU in both groups and a significant relation with depressive symptoms. In routine practice, we should clarify this issue and provide education to families and children with or without ADHD to prevent internet related problems.

KEYWORDS: attention deficit hyperactivity disorder, internet addiction, problematic internet use, social media exposure

INTRODUCTION

Problematic internet use (PIU), or internet addiction (IA) is a condition of over and uncontrollable internet use that affects a person's function. Previous studies found that some online users were becoming addicted to the internet similar to drug or alcohol addiction, which resulted in academic, relationship, financial, and occupational impairment[1-2]. The negative impacts of excessive internet use or IA can include difficulty to complete homework assignments[1], sleep problems[1,3-4], or psychiatric problems[5-7]. There is no definite consensus for a diagnostic criterion of PIU, but previous studies have used some instruments to measure or describe PIU such as the IA test, the compulsive internet use scale, or the Chen IA scale. Prevalence of PIU or IA was 1.5- 47.4 %, and a high prevalence was shown in southeast Asia country[3,5-6,8-9].

In Thailand, the National Statistical Office Thailand reported the incremental use of

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information technology among children aged 6 years and above. In 2004, the proportion of children using the internet and a mobile phone were 11.9% and 28.2%[10] and gradually increased to 52.9% and 88.1%, respectively, in 2015[11]. In 2021, the proportion of children aged 6-11 years who used internet was 92.6%, while 92.9% had a mobile phone[12]. The most common online activity is social networking, including the use of Facebook, Twitter, Line, and Instagram (88.6%), downloading pictures, music, movies, games, and playing online games (87.4%), uploading pictures or video (59.1%), and emailing (44.6%). A previous study found that the prevalence of PIU in secondary school children in Chiangmai was 3.7%[13].

The factors increasing the risk of PIU are being male[14-15], school achievement[14], exposure time[7,13,16], psychological disorders including depression, anxiety, and attention deficit hyperactivity disorder (ADHD)[5-6,14-15,17-18], and family factors, especially socioeconomic status[4,6,8,14,19-20]. Previous research reported primary school children who were diagnosed with ADHD had behaviors that were similar to PIU 33%[18]. The prevalence of PIU in ADHD children was 21.7-32% and were significantly greater than non-ADHD children[21]. A previous review and meta-analysis showed a moderate association between IA and ADHD. The authors pointed out that ADHD children were easily bored, did not wait for rewards, and the internet responded fast enough for them. Due to the lack of dopamine secretion in the dopamine circuit, playing online games resulted in the activation of dopamine secretion. The poor self-control and organization factors of ADHD also lead to PIU[15,18].

In the current situation, most children use internet via mobile phone or tablet in routine activities and there are scanty of studies about the prevalence of PIU, especially in ADHD children. This study aimed to explore the prevalence of PIU among ADHD and non-ADHD children and compare the related factors and effects of PIU in children.

METHODS

This study was approved by the institutional review board of the Faculty of Medicine Vajira Hospital (certificate of approval 19/2560). In accordance with the declaration of Helsinki, all caregivers and participants provided a written inform consent or/and assent form.

This was a cross-sectional study. We invited and enrolled two groups of participants: ADHD and non-ADHD participants, aged 7-15 years old with current internet use. Participants with ADHD were enrolled from the Vajira Growth and Developmental Clinic. Non-ADHD participants were enrolled from a public primary school near the hospital. In the non-ADHD group, researchers contacted the school principal for permission and explained the research process to the teachers. The teachers then distributed research information and questionnaires to interested parents. Exclusion criteria included autism, mental retardation or intellectual disability, major neurological disabilities such as cerebral palsy, epilepsy, congenital malformation or abnormalities such as Down syndrome, and current or history of depression or anxiety disorder. Participants with a history of ADHD diagnosis or ADHD medication use were excluded from the non-ADHD group. Variables were assessed by a self-reported questionnaire that included child and parental demographic data, internet use, and related data and utilized an internet addiction scale (IAS) and childhood depression screening. The child psycho-emotional effects were collected by parental response (yes/no); examples of the statement: "Associated with child internet using: 1. He/she has any physical effects. (headache, visual disturbance, myalgia, sleep disturbance, over or underweight). 2. He/she has any emotional effects. (easily frustrated, easily annoyed, verbal or physical aggression). 3. He/she .... with family members. (fun to talk, deny talking, spend more time, spend less time, easily fighting or argue).

PIU or addictive internet use was assessed by the IAS which was developed in the Thai language by Wanajak[13]. The IA questionnaire contained 20 items indicating how often the child engaged in the behavior, with responses using a 5 point-Likert scale. The response ranged from "never" = 1 to "always" = 5. Total scores of 70

or higher were classified as PIU (addictive internet use), scores 40-69 were classified as frequent internet use or possible PIU, and scores below 40 were classified as normal internet use. Childhood depression was assessed by the children's depression inventory, which is a self-reported questionnaire with 27 items. The item scores were as follows: 0, 1, and 2 with a total score of 0-54. A score > 15 is associated with depression. Sensitivity and specificity of the test are 78.8 % and 91.3%.

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 22. Continuous variables were expressed as means and standard deviation or median and interquartile range if the data had a non-normal distribution. Categorical variables were presented as count and percentages. Logistic regression analysis was used to compare the related factors for PIU and presented as odd ration with 95% confidence interval. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 127 participants were enrolled, with 56 participants in the ADHD group and 71 participants in the non-ADHD group. Table 1 presents the participants' characteristic data. Of the ADHD participants, males accounted for 69.6%, studying in primary school was 69.6%, and 33.9% had internet usage time ≥ 21 hours/week. Non-ADHD participants were 43.7% male, 74.6% were studying in secondary school, and 73.2% were able to access internet at school. Of the 127 participants, only two participants in the ADHD group had an IA score classified at the PIU level (prevalence rate equal 3.5%). The mean IA score of both groups were 43.9 and 43.4, indicating heavy internet usage. The rate of possible PIU/PIU in the ADHD and non-ADHD groups were 60.7% and 60.5%, respectively. The ADHD group were 1.01 times more likely to have possible PIU/PIU than the non-ADHD group, which is not statistically significant (table 2).

Table 1 Participant demographic data (n = 127)

	ADHD (n = 56)	Non-ADHD (n = 71)
	n (%)	n (%)
Sex		
Male	39 (69.6)	31 (43.7)
Female	17 (30.4)	40 (56.3)
School level		
Primary school	39 (69.6)	18 (25.4)
Secondary school	17 (30.4)	53 (74.6)
School performance		
Grade < 3.5 or < 85 %	9 (16.1)	37 (52.1)
Grade ≥ 3.5 or ≥ 85%	47 (83.9)	34 (47.9)
Free time activities[a]		
Game online/social media	23 (41.1)	49 (69.0)
Exercise	20 (35.7)	18 (25.4)
Book reading/music	18 (32.1)	35 (49.3)
Television watching	28 (50.0)	40 (56.3)
Cooking	16 (28.6)	22 (30.9)
Others	9 (16.1)	13 (18.3)
Caregiver characteristics		
Primary caregiver as		
father or mother	37 (66.1)	61 (85.9)
others	19 (33.9)	10 (14.1)

Table 1 Participant demographic data (n = 127) (coutinued)

	ADHD (n = 56)	Non-ADHD (n = 71)
	n (%)	n (%)
Family income		
≤ 50,000 Baht/month	9 (16.1)	35 (49.3)
> 50,000 Bath/month	47 (83.9)	36 (50.7)
Parental internet usage ≥ 2 hours/day	21 (37.5)	31 (43.7)
< 2 hours/day	35 (62.5)	40 (56.3)
Internet usage character		
Access internet via[b]		
Computer/notebook	28 (50.0)	46 (64.8)
Tablet	12 (21.4)	25 (35.2)
Mobile phone	50 (89.3)	66 (93.0)
Internet time limited by		
Parents	45 (80.4)	46 (64.8)
No parents	11 (19.6)	25 (35.2)
Internet access at school		
Able to access	30 (53.6)	52 (73.2)
Unable to access	26 (46.4)	19 (26.8)
Internet usage time ≥ 21 hours/week	19 (33.9)	40 (56.3)
< 21 hours/week	37 (66.1)	31 (43.7)

Abbreviations: ADHD, attention deficit hyperactivity disorder; n, number
[a,b] Participants can respond to more than one choice.

Table 2 Internet addiction scale data of ADHD and non-ADHD participants.

	ADHD n (%)	Non-ADHD n (%)	OR (95%CI)	P-value
Possible PIU /PIU	34 (60.7)	43 (61.5)	1.0 (0.5-2.1)	0.986
Normal internet use	22 (39.3)	28 (39.4)		
Mean internet addiction score ± SD	43.9 ± 12.2	43.4 ± 14.0		

Abbreviations: ADHD, attention deficit hyperactive disorder; PIU, problematic internet use; n, number; SD, standard deviation
Statistical significance: p-value < 0.05

The researchers analyzed relating factors of possible PIU/PIU in both groups, as shown in Table 3. Accessing the internet at school was associated with possible PIU/PIU in the non-ADHD group. In the ADHD group, internet usage time ≥ 21 hours/week were significantly associated with possible PIU/PIU. When controlling for other factors, this association was still significant.

Table 4 compares psycho-emotional effects between the possible PIU/PIU group with the normal internet use group, with the result indicating that 34.5% of the possible PIU/PIU participants (n=19) had depressive scores and a significantly higher proportion of depressive participants than the normal internet use group (p = 0.020).

Table 3 Univariable and multivariable analysis of factors relating with possible PIU/PIU in ADHD and non-ADHD group

Variables	ADHD (n = 56)		Non-ADHD (n = 71)	
	OR (95% CI)	Adj.OR (95% CI)	OR (95% CI)	Adj.OR (95% CI)
Sex				
Male	2.3 (0.7-7.2)	1.9 (0.5-7.4)	2.2 (0.8-5.9)	4.2* (1.3-14.5)
Female	Ref		Ref	
School level				
Secondary school	5.57* (1.3–23.9)	2.26 (0.28–18.3)	1.8 (0.51–6.3)	-
Primary school	Ref		Ref	
School performance				
Grade < 3.5 or < 85%	1.3 (0.3-5.4)	-	1.10 (0.4-2.9)	-
Grade ≥ 3.5 or ≥ 85%	Ref		Ref	
Free time activities				
Free time-game online/social media	2.7 (0.8-8.5)	1.4 (0.4-5.4)	2.5 (0.9-6.9)	3.5 (0.9-12.4)
Free time–no game online/social media	Ref		Ref	
Free time - Exercise	1.3 (0.4-4.1)	-	0.6 (0.2-1.7)	-
Free time–no exercise	Ref		Ref	
Parental internet usage				
≥ 2 hours/day	1.5 (0.5-4.6)	-	1.3 (0.5-3.5)	-
< 2 hours/day	Ref		Ref	
Internet time limited by				
Parents	1.9 (0.5-8.3)	-	1.6 (0.6-4.6)	-
No parents	Ref		Ref	
Internet access at school				
Able to access	1.7 (0.6-5.1)	-	3.9* (1.3-11.6)	5.6* (1.5-20.7)
Unable to access	Ref		Ref	
Internet usage time				
≥ 21 hours/week	23.6** (2.9-196.0)	27.1** (2.4-312.0)	2.5 (0.9-6.6)	2.6 (0.8-8.1)
< 21 hours/week	Ref		Ref	

Abbreviations: ADHD, attention deficit hyperactive disorder; Adj.OR, adjusted odd ratio; CI, confidence interval; n, number; OR, odd ratio; PIU, problematic internet use; Ref, reference; SD, standard deviation
Statistical significance: *p-value < 0.05, **p-value significant ≤ 0.001

Table 4 Comparing psycho-emotional effects between possible PIU/PIU with average internet use for children with ADHD and non-ADHD

Effects	Possible PIU/PIU (n=77) n (%)	Normal internet use (n=50) n (%)	P-value
Physical health problems	23 (29.9)	20 (40.0)	0.239
Aggressive/easily frustration	32 (41.6)	17 (34.0)	0.393
Sleep disturbance/insomnia	19 (24.7)	12 (24.0)	0.931
Decreased family relationship	33 (42.9)	22 (44.0)	0.899
Depression (CDI score > 15)	25 (34.7)	5 (11.6)	0.006*

Abbreviations: CDI, childhood depression index; n, number; PIU, problematic internet use
Statistical significance: *p-value < 0.05

DISCUSSION

This study found the prevalence of PIU to be around 3.5%, all PIU participants had ADHD. Comparing the prevalence of possible PIU/PIU, 60.7% in ADHD group and 61.5% in non-ADHD group, there were no statistical differences (p = 0.986). In non-ADHD group, there was high percentage of using internet ≥ 21 hours per week and playing online games or social media during free time, this may be the reasons for having the prevalence of possible PIU/PIU in non-ADHD equal as ADHD group. Our result for the PIU prevalence was in line with Dib et al. which found that 4.5% had severe internet use[16], but our finding is lower than other studies, especially studies from Southeast Asia countries[3,7-9]. Because we classified possible PIU with a lower score than other studies (IAS ≥ 40 vs ≥ 50), the possible PIU/PIU prevalence in this study was higher than the previous studies which found 7.4-46.4% [3, 17, 20].

Like other studies, we found internet exposure time was significantly associated with possible PIU/PIU in the ADHD group. For example, a 2021 study among university students showed internet time exposure was a risk for having PIU (OR 1.3, 95% CI 1.1-1.3)[7], while another study revealed using the internet ≥ 5 hours/day was significantly associated with PIU (OR 4.8, 95% CI 2.0-11.6)[16]. However, the exposure time was not a significant associated-factor for internet addict-gamers (IAS ≥ 71)[22].

In the non-ADHD group, a significant risk factor for possible PIU/PIU was the ability to access the internet at school. As we knew, the exposure time was the one of risk factors for PIU, when the child used internet at school, the internet exposure time and frequency of internet use was expanded. In this point, future case-control studies should explore the robustness of this factor. However, our results did not show a relation between gender, school performance, or parental internet restriction with possible PIU/PIU in both groups, like previous studies[19-20].

We analyzed the psycho-emotional effects of possible PIU/PIU compared with normal internet use, and our results were similar to previous studies[7,17] that participants in the possible PIU/PIU group had a significantly higher percentage of depression than normal internet users (34 % vs 11.6%, p 0.006). Sleep disturbance/ insomnia did not show a significant effect like in the literature[3-4]. The previous studies stated the PIU had greater anxiety than the non-PIU group[7,16], but this issue was not explored in the present study.

This study presents the prevalence, associated factors, and psycho-emotional effects of internet use in both ADHD and non-ADHD groups among Thai school-aged children. There are several limitations such as only current internet users were enrolled, so this prevalence cannot be generalized in normal population and the recall bias of measurement by self-reported questionnaire, may be result in over or underestimated of outcomes. Finally, due to the study design, it is not possible to identify the causes and effect of the psychological outcome. Further studies should include family socioeconomic status to adjust the outcomes or explore anxiety effects in a cohort or case-control design.

CONCLUSION

The present study showed a high prevalence of possible PIU/PIU. The highest risk factor for the ADHD group was exposure time more than time ≥ 21 hours/week and for the non-ADHD was the ability to access internet at school. In the digital era, families and schools should be educated about internet exposure time limiting and signs of depression should be evaluated in possible PIU/PIU children.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Review Article

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Global Warming and Parasitic Infection in Urban Communities: A Systematic Review

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ABSTRACT

Global climate change is an important global issue; it influences not only the environment but also human health. Parasitic infection is one of the most recognized infectious diseases generally observed in rural areas of developing countries in tropical and subtropical zones of all continents. Interestingly, there are few reports on parasitic infections in the temperate zone; however, climate change provides a wide warming area optimal for the survival of several parasites. This situation leads to the spread of parasitic pathogens and their vectors in other zones around the world that they lack access to optimal healthcare. Moreover, the urban community shares a lot of the population in several developed and developing countries, which generally have a better sanitary system when compared with rural areas. Furthermore, there could have been a slight chance of parasitic infections in the past in these urban communities. For several reasons, the association between climate change and parasitic infection in urban areas has caught research interest. Hence, this systematic review proves the increased prevalence of parasitic infections in urban areas worldwide in the last decade. The most prevalent parasites were vector-borne parasites, which directly suggests their relationship with climate change. Our findings can benefit healthcare providers and governors who must address this situation. In conclusion, parasitic infections in urban areas should be an increasing concern given their increased likelihood because of climate change.

KEYWORDS: climate change, parasitic infection, urban communities

INTRODUCTION

Global climate change, particularly global warming, refers to the most recent emergency crisis worldwide because of the widespread impact effects of several social elements and not only the environment. El Niño and La Niña, which form heatwaves, storms, and melting polar ice, represent the enormous impacts of climate change on humans[1]. Several organizations have been collaborating to halt or at least delay climate change. The recent COP28 UN climate change conference released the United Arab Emirates consensus on agreement signals, "beginning of the end of the fossil fuel era" at the end of 2023 to accelerate climate action through reduction in fossil fuel usage and levels of greenhouse gases[2]. This action is a crucial step that must be considered by communities around the world.

Regarding the health impact, the direct effects of an increase in ground temperature include discomfort and occasional death caused by heatwaves; moreover, the increment in global temperature can lead to changes in infectious environments, which can only expand from limited areas[1,3]. Vector-borne diseases are the best example of this alteration in global temperature.

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Global warming has expanded the geographic distribution of mosquito vectors from tropical to temperate zones. This spread in geographic distribution has increased the likelihood of mosquito-borne diseases, such as malaria, dengue, and yellow fever, in regions that have never experienced such a situation before, which leads to endemic expansion[4-5].

Parasitic infection poses a most concerning health issue worldwide, especially in rural areas of low- and middle-income countries in tropical zones[6]. The World Health Organization and previous studies estimated that > 3.5 billion people are at risk of parasitic infections, including those caused by helminths, protozoa, and ectopic parasites, worldwide[6-8]. Although most endemic areas remain in the same regions, global climate change can increase the prevalence of parasitic infections worldwide[9-10]. In this review, we focused on the reports on parasitic infections in urban areas, where sound sanitary systems and good waste management are not only found in developing countries but also in developed countries around the world. The parasitic infection in the urban areas can be referred to the effects of global climate change on the infectious diseases due to it change the habitat of the organisms, which will be the sign for anxious situation in the future.

SEARCH STRATEGY AND DATABASES

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guideline for systematic review and meta-analysis[11]. All procedures were conducted in accordance with the checklist and applied at all stages of this study. The search keywords were "parasite infection" OR "parasitic infection" OR "parasite-infection" OR "parasitic-infection", "urban community" OR "urban communities" OR "urban", and "climate change" OR "global warming". Three investigators used these keywords to search three databases, including PubMed, Scopus, and Google Scholar, until January 11, 2024.

ELIGIBILITY CRITERIA

The PICO method (P: population, I: intervention, C: comparators, O: outcome) was used to identify studies that met the inclusion criteria: Data on each part were as follows: P: data on parasitic infection in urban communities coupled with climate change; I: none; C: data on parasitic infection in urban communities without climate change evidence; O: the prevalence or proportion of parasitic infection in urban communities under climate change conditions. This work included all studies published in English and reported parasitic infection in urban areas related to climate change, including case reports and series. However, the following types of research were excluded: (1) those that did not report parasitic pathogens, (2) those that reported parasitic infections in rural areas, (3) those that reported parasitic infections without evidence of climate change, (4) review articles, and (5) conference abstracts.

IDENTIFICATION OF KEYWORDS

Parasitic infection refers to infectious diseases caused by parasitic organisms, including protozoa and helminths (nematodes, trematodes, cestodes, and acanthocephalan). Furthermore, infections caused by ectopic parasites, including acari and insects, are considered parasitic infections. The urban area relates to the community characteristics that form a town or city. The climate change discussed in this review refers to long-term shifts in temperatures and weather patterns[12].

DATA SELECTION AND EXTRACTION

This study considered publications that met the criteria and were published in the last 20 years (2004–2023). Duplicate publications, publications generated from automation, and those published in unreliable journals were removed. Published articles were screening thoroughly. Non-research articles were withdrawn at this step, and only retrieved articles were included. Research on nonparasitic pathogens,

noninvolvement of urban communities, and climate change were filtered out at the final screening step. All stages of data extraction were performed using EndNote version 20 (Stanford, CT, USA).

QUALITY ASSESSMENT AND BIAS REDUCTION

This review focused on studies with several research designs, including prevalence, retrospective cross-sectional, comprehensive, spatiotemporal modeling, and intercomparison modeling studies and case reports. Given the different natures of study designs, comparison of the quality of articles was impossible. Therefore, no quality assessment was performed in this systematic review. Three independent searches by different searchers reduced the selection bias. All included articles were pooled, decisions on selected publications were discussed, and a final consensus decision was made.

EXPLANATION OF FINDINGS

In the first stage, 307 articles were obtained from all databases by limiting the search. In total, 61 duplicate articles were removed, and the other 213 were removed for different reasons, such as those generated by automation tools, published in unreliable journals or databases, and nonrelevant research. Then, 96 articles were included in the screening step, and 41 review articles were removed afterward. Attempts were made to retrieve the full texts of 55 research articles from the databases. Four articles could not be retrieved. In the final step of screening, 13 articles were removed as they were concerned with research on other pathogens, e.g., viruses and bacteria. Next, 8 nonrelevant articles on urban communities were removed, and another 14 were removed for the lack of direct involvement with climate change. Figure 1 illustrates the study flow diagram, and Table 1 shows all the studies included in this review.

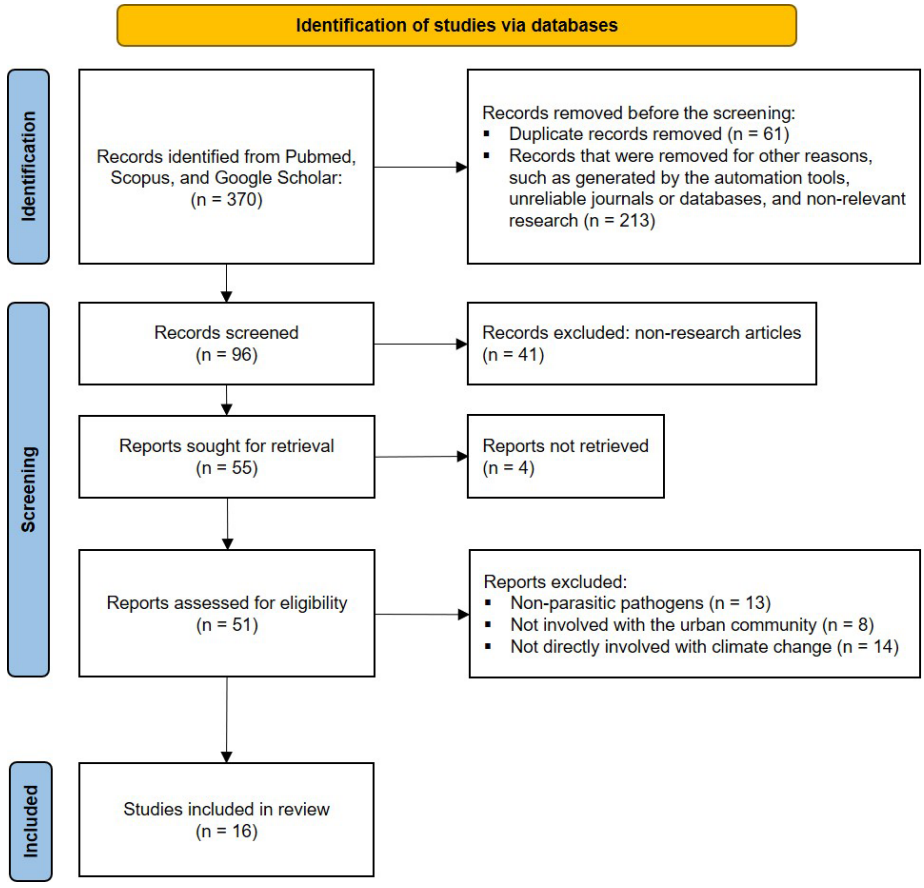

Figure 1 PRISMA flowchart diagram of systematic review process used in this study

Table 1 The publications included in this systematic review at the final selection step

No.	Title	Authors	Journal	Parasite	Country/ Continent	Year
1	Quantifying climatic and socioeconomic drivers of urban malaria in Surat, India: a statistical spatiotemporal modelling study	Santos-Vega M, et al.[33]	Lancet Planet Health	Malaria	India	2023
2	*Toxoplasma gondii* in small mammals in Romania: the influence of host, season and sampling location	Kalmár Z, et al.[21]	BMC Vet Res	*Toxoplasma gondii*	Romania	2023
3	Climate change and cutaneous leishmaniasis in the province of Ghardaïa in Algeria: a model-based approach to predict disease outbreaks	Saadene Y, et al.[36]	Ann Saudi Med	cutaneous leishmaniasis	Algeria	2023
4	Identification of a triatomine infected with *Trypanosoma cruzi* in an urban area of the state of Veracruz, Mexico: a comprehensive study	Ochoa-Martínez P, et al.[28]	Zoonoses Public Health	*Trypanosoma cruzi*	Mexico	2023
5	Data-driven predictions of potential *Leishmania* vectors in the Americas	Vadmal GM, et al.[29]	PLoS Negl Trop Dis	*Leishmania* vectors	Americas	2023
6	Molecular epidemiological study of *Trichomonas gallinae* focusing on central and southeastern Europe	Tuska-Szalay B, et al.[22]	Front Vet Sci	*Trichomonas gallinae*	Europe	2022
7	Synergies between environmental degradation and climate variation on malaria re-emergence in southern Venezuela: a spatiotemporal modelling study	Fletcher IK, et al.[30]	Lancet Planet Health	Malaria	Venezuela	2022
8	The neglected role of relative humidity in the interannual variability of urban malaria in Indian cities	Santos-Vega M, et al.[34]	Nat Commun	Malaria	India	2022
9	A comparative spatial and climate analysis of human granulocytic anaplasmosis and human babesiosis in New York state (2013-2018)	O'Connor C, et al.[31]	J Med Entomol	*Anaplasma Babesia*	USA	2021
10	One Health approach to zoonotic parasites: molecular detection of intestinal protozoans in an urban population of Norway rats, *Rattus norvegicus*, in Barcelona, Spain	Galán-Puchades MT, et al.[23]	Pathogens	Intestinal parasites	Norway	2021
11	Effects of climate change and heterogeneity of local climates on the development of malaria parasite (*Plasmodium vivax*) in Moscow megacity region	Mironova V, et al.[24]	Int J Environ Res Public Health	Malaria	Russia	2019
12	Risk factors for schistosomiasis in an urban area in northern Côte d'Ivoire	M'Bra RK, et al.[37]	Infect Dis Poverty	*Schistosoma*	Côte d'Ivoire	2018
13	Phleboviruses detection in Phlebotomus perniciosus from a human leishmaniasis focus in South-West Madrid region, Spain	Remoli ME, et al.[25]	Parasit Vectors	*Leishmania*	Spain	2016
14	The increase of exotic zoonotic helminth infections: the impact of urbanization, climate change and globalization	Gordon CA, et al.[38]	Adv Parasitol	Helminths	Global	2016
15	*Angiostrongylus cantonensis* infection in molluscs in the municipality of São Gonçalo, a metropolitan area of Rio de Janeiro, Brazil: role of the invasive species *Achatina fulica* in parasite transmission dynamics	Oliveira AP, et al.[32]	Mem Inst Oswaldo Cruz	*Angiostrongylus cantonensis*	Brazil	2015
16	Visceral leishmaniasis-associated mortality in Bangladesh: a retrospective cross-sectional study	Huda MM, et al.[35]	BMJ Open	*Leishmania*	Bangladesh	2014

The number of publications in the last 20 years has increased. Our review demonstrated that most included articles were published in 2019–2023 (11 articles, 68.75%), followed by those published in 2014–2018 (5 articles, 31.25%), whereas no publications in 2004–2013 were included (table 2 and figure 2A). Notably, most of the published articles were conducted in Europe and America (5 articles, 31.25% for each continent), followed by those in Asia (3 articles, 18.75%) and Africa (2 articles, 12.50%), and 1 article that was conducted at the global scale (6.25%) (table 2). Among infective parasites, *Plasmodium* spp. (malaria) and *Leishmania* spp. were the two most prevalent (4 articles, 25.00% for each parasite). The other parasites, including *Toxoplasma* spp., *Schistosoma* spp., *Trypanosoma* spp., *Angiostrongylus* spp., *Trichomonas* spp., intestinal parasites, helminths (unclassified), and other protozoa, were observed at the same proportions (1 article, 6.25% for each parasite) (table 2 and figure 2B). The model-based approach was the most used study procedure (7 articles, 43.75%), followed by comprehensive and epidemiological (3 articles, 18.75% for each study method), spatiotemporal modeling (2 articles, 12.50%), and cross-sectional (1 article, 6.25%) (table 2) studies.

Table 2 The data analysis from all publications used in this systematic review

Parameters	No. of study	Percentage (%)
Published year		
2004 – 2008	0	0.00
2009 – 2013	0	0.00
2014 – 2018	5	31.25
2019 – 2023	11	68.75
Study area		
Global	1	6.25
America	5	31.25
Europe	5	31.25
Asia	3	18.75
Africa	2	12.50
Parasite		
Malaria	4	25.00
Leishmania	4	25.00
Toxoplasma	1	6.25
Schistosoma	1	6.25
Trypanosoma	1	6.25
Angiostrongylus	1	6.25
Trichomonas	1	6.25
Intestinal parasites	1	6.25
Helminth (unclassified)	1	6.25
Other protozoa	1	6.25
Study method		
spatiotemporal modelling study	2	12.50
model-based approach	7	43.75
comprehensive study	3	18.75
epidemiological study	3	18.75
cross-sectional study	1	6.25

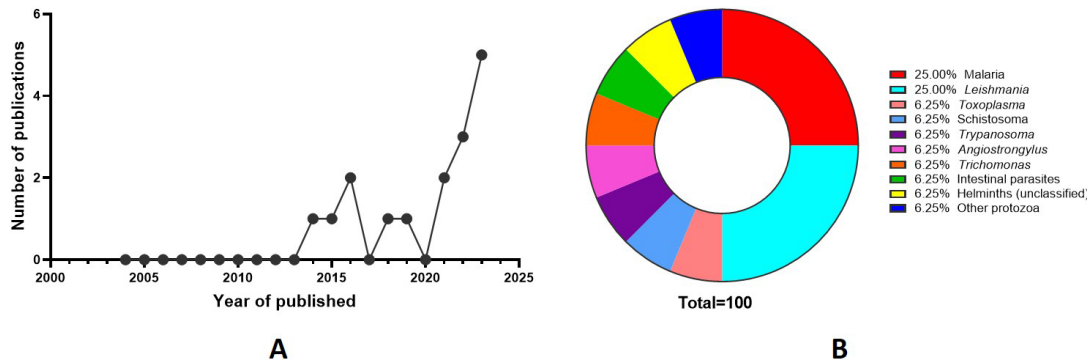

Figure 2 (A) The trend of publications in the parasitic infection in urban areas related to climate change, (B) The proportion of parasites found in this review during 2004 – 2023.

CONSIDERATION OF FINDINGS

This systematic review demonstrated the trends of parasitic infection in urban communities involved with global climate change published in the last 20 years. Our results reveal the increment in published articles, which reached up to twofold of the previous period (2004–2013), especially in the past decade (2014–2023). This finding suggests the effects of climate change on parasitic infection in urban areas of several countries. Furthermore, this result agrees with those of several previous reviews and reports that indicated the association between climate change and increased likelihood of parasitic infections[13-17]. Comparably, this trend is the same as that observed for other pathogenic organisms, which are increasingly reported in relation to climate change[18-20].

Our review revealed that the highest prevalence of parasitic infection was observed in Europe and the Americas. In Europe, where high sanitary standards are implemented, the reported parasites were *Toxoplasma gondii*, *Trichomonas gallinae*, intestinal protozoans, malaria parasites, and *Leishmania*, which were reported from Romania, Spain, Russia, and central and southeastern Europe[21-25]. *Toxoplasma gondii*, *Trichomonas gallinae*, and intestinal protozoans can spread through direct contact and consumption of contaminated foods and beverages; however, a supportive solid evidence of their association with climate change is lacking. In contrast, malaria and *Leishmania* were vector-borne parasites. This result indicates that the vectors of these parasites, namely, *Anopheles* mosquitoes and sandflies, can be increasingly found in Europe. This situation directly affects climate change because the normal habitat of these insects includes the tropical and subtropical zones[26-27]. In the Americas, the reported parasites included *Trypanosoma cruzi*, *Leishmania* spp., malaria parasites, *Anaplasma* spp., *Babesia* spp., and *Angiostrongylus cantonensis*, which were noted from the urban areas of USA, Mexico, Brazil, and Venezuela[28-32]. Publications from the Latin Americas were obtained because these countries are in tropical and subtropical zones; however, *Anaplasma* spp. and *Babesia* spp. were unexpectedly observed in New York City[31]. In general, these parasites are rarely observed in humans. Still, an article suggested an association between parasites and climate change via a comparative spatial analysis; the results revealed that the spread of parasites was indirectly associated with house locations, which were neither close nor far from forests[31]. Asia and Africa have fewer reports of parasitic infections in urban areas. These areas have a high number of parasitic cases, and reports focusing on climate change are very few. Regarding Asia, our review included two reports from India and one from Bangladesh[33-35]. Malaria and *Leishmania* were parasites that have been reported along with the burden involved with climate change. However, humidity was the only specific reason for the increase in malaria cases[34]. Two reports from Africa included in our review demonstrated that climate change promoted cutaneous leishmaniasis and schistosomiasis in urban areas[36-37]. These studies indicate that the inflation risk of these parasites is related to climate change worldwide[38]. However, more investigation is still required for a definite conclusion when getting more reports in the future.

CONCLUSION

This systematic review provided a specific discussion topic focusing on climate change, which can affect human life by increasing the chance of parasitic infections. Our study revealed the increased trend of parasitic infections in urban areas, where sanitary conditions are better than those in other communities reported worldwide. The most reported parasites were malaria parasites and *Leishmania*, which can be considered effects of climate change owing to the biology of their vectors. In conclusion, climate change can be associated with parasitic infection in urban areas. This finding can be used for further prevention and precautionary campaigns.

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Review Article

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The Past and Present Situation of *Opisthorchis viverrini* Infection in Thailand

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ABSTRACT

Opisthorchis viverrini, a major foodborne trematode, remains a major public health concern in Thailand, particularly in the northern and northeastern provinces. *O. viverrini* can be transferred to people and reservoir hosts through the consumption of uncooked cyprinid fish with metacercariae. Chronic infection with *O. viverrini* can lead to a severe condition known as cholangiocarcinoma (CCA). According to the Nationwide Hospital Admission Database, Thailand has experienced the highest incidence of CCA globally in recent years. Particularly, between 2009 and 2013, there was an incidence rate of 14.6 cases per 100,000 individuals within the population and a corresponding mortality rate (MR) of 14%. In addition, high incidence rates of CCA were reported in Khon Kaen Province from 1989 to 2018, with a rate of 36.1 per 100,000 person-years in men and 14.4 per 100,000 person-years in women. Despite the reduction in the overall prevalence of *O. viverrini* at the national level, several studies have indicated that the infection remains highly prevalent in some communities in the northeastern and northern regions. Some communities have demonstrated a prevalence of *O. viverrini* exceeding 20%, and rates reaching as high as 45.7%. Therefore, in populations with a high prevalence, programs to control this parasite should be implemented, including monitoring eating habits. This review article provides a comprehensive overview of the current distribution of *O. viverrini* in Thailand, outlining its pathophysiology, background, and preventive and control strategies. In addition, this review suggests that individuals in high-risk communities should act to eradicate liver fluke, as this is crucial for the overall health of the community.

KEYWORDS: cholangiocarcinoma, foodborne trematode, *Opisthorchis viverrini*, prevalence

INTRODUCTION

Human liver flukes, including *Opisthorchis viverrini, Clonorchis sinensis,* and *Opisthorchis felineus,* belong to the family Opisthorchiidae, class Trematode, subclass Digenea, and phylum Pathyhelminthis[1]. *O. viverrini* is highly prevalent in Southeast Asia, including Thailand, Lao People's Democratic Republic (Lao PDR), Cambodia, Myanmar, and southern Vietnam[2-3]. *C. sinensis* is mostly found in some regions of northern Vietnam, southern China, and Korea[2], whereas *O. felineus* is widely distributed over eastern Europe and many regions of Russia[4]. Early infections of *O. viverrini, C. sinensis*, and *O. felineus* (clonorchiasis and opisthorchiasis) are usually asymptomatic; however, some patients present symptoms of abdominal pain, nausea, vomiting, diarrhea, and obstructive jaundice[5-7].

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Additionally, early symptoms seem to occur more often in patients with *O. felineus* infections than in patients with *O. viverrini* and *C. sinensis* infections[8]. In chronic infection, the clinical manifestations are associated with obstructive jaundice, cholangitis, cholelithiasis, cholecystitis, periportal fibrosis, and cholangiocarcinoma (CCA)[6-7].

A recent study in 2018 indicated that in critically endemic countries in Southeast Asia, a total of 12.39 million individuals have been reported to have acquired *O. viverrini* infections. Specifically, the total number of documented cases in Thailand was 6.71 million, Lao PDR accounted for 2.45 million, Vietnam reported 2.07 million, and Cambodia documented 1.00 million cases[9]. In Myanmar, the first formal survey of *O. viverrini* infection in humans was performed on 364 fecal samples and reported at 9.3% in three regions of Lower Myanmar[10]. In Thailand, the risk factor for *O. viverrini* infection is the consumption frequency of Koi Pla, or chopped raw fish salad, a traditional dish consumed by people in northeastern and northern Thailand. Other risk factors for opisthorchiasis include age, gender, occupation, endemic area, and raw food consumption attitude. However, a recent research indicated that education was not considered a major risk factor[3]. Although infection with *O. viverrini* affects people of all ages, there is an increased risk among the older population, and men are at a higher risk than women due to their frequent ingestion of Koi Pla with alcohol. To date, there are many prevention campaigns can effectively prevent *O. viverrini* infection and CCA; however, current studies on the approaches for preventing liver fluke are of poor quality. Nevertheless, it is important to understand the overall positive impact of health education in preventing infection. Therefore, in order to plan prevention and control programs, it is crucial to understand the epidemiology and distribution of *O. viverrini*, as they directly affect parasite populations, host dynamics, and human behaviors.

GEOGRAPHIC DISTRIBUTION OF *O. VIVERRINI* IN THAILAND

O. viverrini is a common species of human liver flukes that is highly prevalent in Thailand. In 1955, the initial report documented the significant prevalence of *O. viverrini* infection in Thailand, indicating that certain areas in the northern region of the country had a prevalence approaching 100%[11]. After three decades, a study of *O. viverrini* infection targeting 1,651, 1,585, and 1,447 individuals in 1980, 1981, and 1982 was conducted in several villages in Khon Kaen Province. The total prevalence of *O. viverrini* infection was reported to be 89.5% in 1980, 92.5% in 1981, and 88.6% in 1982, indicating Khon Kaen Province is the main endemic region for this parasite[12]. The first nationwide survey of *O. viverrini* infection was done from 1980-1981 and reported the prevalence at 14% (figure 1),

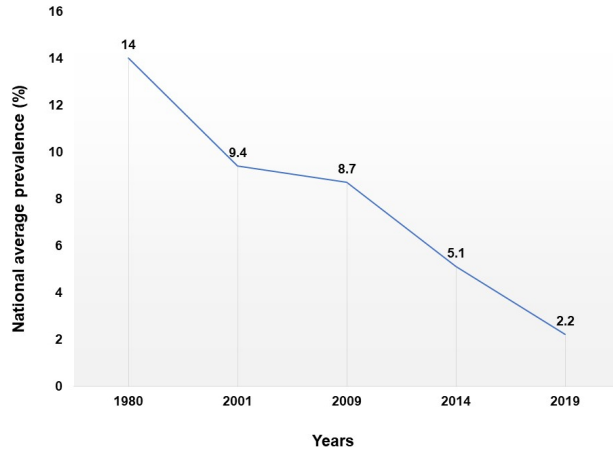

Figure 1 The average national prevalence of *Opisthorchis viverrini* infection in Thailand from 1980 to 2019

including 34.6% in the northeastern, 6.3% in the central, 5.6% in the northern, and 0.01% in the southern regions of the country[13]. In the average national survey of *O. viverrini* infection, the prevalence had decreased to 9.4% in 2001 due to continued and intensive control programs and public health campaigns. Notably, the prevalence of *O. viverrini* infection varied regionally, with rates of 0% observed in the South, 19.3% in the North, 15.7% in the Northeast, and 3.8% in the Central[13]. In 2009, the average national infection rate of *O. viverrini* was reduced to 8.7% from a survey including 15,555 people, of whom 1,351 cases were positive[14]. Furthermore, the average national prevalence of *O. viverrini* infection demonstrated a decline to 5.1% by the year 2014, exhibiting prevalence rates of 9.2% in the Northeast, 5.2% in the North, 0.9% in the Central, and 0% in the South. Following numerous preventative campaigns, the prevalence of *O. viverrini* has markedly reduced to 2.2% on a national level, as reported by the most recent National Helminthiasis Surveillance data in 2019 (figure 1), exhibiting a prevalence of 9.2% in the Northeast, 5.2% in the North, 0.9% in the Central, and 0% in the South[15]. The five national average surveys conducted between 1980 and 2019 provided evidence that Thailand has achieved significant progress in controlling opisthorchiasis over the last four decades. Consequently, the following aims are to eradicate *O. viverrini* and decrease the occurrence of CCA in Thailand.

Moreover, based on fecal screening for *O. viverrini* infection conducted in Khon Kaen Province between 1990 and 2001, the overall prevalence of *O. viverrini* infection was recorded at 24.5%, with variations observed across different districts ranging from 2.1% to 70.8%. Additionally, infection rate was higher among males (27.6%) than among women (21.4%)[16]. In 2010 and 2015, the results of surveillance that included 17 community-based surveys demonstrated a high prevalence of > 20%, and the highest prevalence (45.7%) was observed in a community in the northeastern region[17]. In 2023, the prevalence of *O. viverrini* in Chaiyaphum Province, northeastern Thailand, was 7.15%, which was higher than that in the national surveillance conducted in 2019, which reported a prevalence of only 2.2%[18]. Despite a decline in the overall prevalence at the national level, many studies have indicated that the infection rate of *O. viverrini* remains high in several communities within the northeastern areas[17-18].

Between 2013 and 2019, the prevalence of *O. viverrini* in 20 provinces in the northeastern regions was increased and recently reported to be 32.4%[19]. The above information indicates that the recent prevalence of *O. viverrini* in the northeastern region is still higher than the total national prevalence, especially in rural communities. Moreover, co-infection between *O. viverrini* and minute intestinal flukes (MIFs) is commonly found in Thailand, because they share a second intermediate host. In particular, the rate of co-infection of both parasites is high in northern Thailand. In northern Thailand, most foodborne trematode species are MIFs, and co-infection occurs between *O. viverrini* and MIFs in the genus *Haplorchis* spp., such as *Haplorchis taichui* and *Haplorchis yokogawai*[20-21]. Recently, reports have indicated that the total distribution of co-infection of *O. viverrini* and *H. taichui* was 37.2% and the total distribution of *O. viverrini* in residents of northern Thailand was 47.7% in Chiang Mai Province[21]. Due to immigration and environmental changes, a high prevalence of *O. viverrini* species has recently been found in nonendemic areas such as central Thailand. For example, in Chachoengsao Province, the incidence of *O. viverrini* infection was 21.4/100 person-years, and the prevalence of *O. viverrini* was 9.6%[22]. Moreover, cross-sectional studies were carried out in non-endemic regions of Thailand, demonstrating *Opisthorchis*-like egg infection prevalence ranging from 8.4% to 16.8% in high-risk districts[23-24]. Data on the epidemiology of *O. viverrini* infection indicate that some areas in rural communities still have a high prevalence of this parasite. Therefore, to reduce transmission and infection of this parasite in these endemic areas, control programs must be applied continually.

LIFE CYCLE OF *O. VIVERRINI*

O. viverrini has a complex life cycle and requires two intermediate hosts (i.e., freshwater snails and freshwater fish) and one definitive host (humans). Beginning with humans as the definitive host, adult worms reside inside the bile ducts and release fully developed eggs through feces. The eggs must have fallen into the water and been consumed by their first intermediate host, a freshwater snail of the genus *Bithynia*. After being eaten by a suitable snail, miracidiae undergo several stages of transformation into sporocysts, rediae, and cercariae. The cercariae are produced via an asexual reproduction process that involves germinal cells within the cercariae. About 21 to 30 days after infection, the free-living cercariae emerge from the snail and then penetrate the skin of freshwater fish. After penetrating the fish skin, the cercariae undergo a waiting period of 21 days before they transform into infective metacercariae. In addition, cats and dogs can be reservoir hosts of this liver fluke (figure 2). Approximately 18 species of fish belonging to the *Cyprinidae* family can be the second intermediate host (figure 3). Consumption of raw or undercooked fish containing metacercariae can infect humans, cats, and dogs. The metacercariae excyst in the duodenum of the definitive or reservoir host and then migrate upward through the bile ducts, developing into adult worms in approximately 1 or 2 months. After 3 to 4 weeks, these adult worms begin the process of egg deposition (figure 2).

During a thorough surveillance of *O. viverrini* infection in cyprinid fish, a total of 640 fish from 32 different regions in Nakhon Ratchasima Province in northeastern Thailand were subjected to investigation for *O. viverrini* metacercariae infection between the years 2010 and 2011[25]. The study revealed an infection rate of 12.3% (79 out of 640 fish), with *Cyclocheilichthys armatus*,

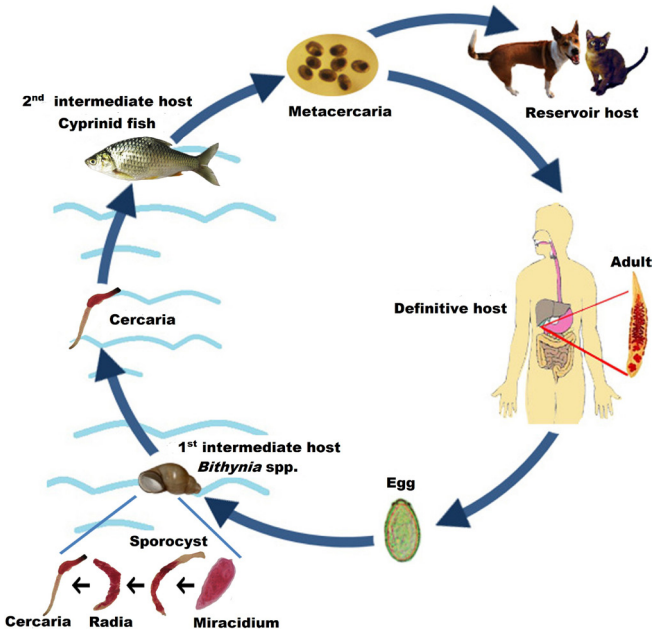

Figure 2 The life cycle of *Opisthorchis viverrini* requires a first intermediate host (*Bithynia* spp.) and a second intermediate host (freshwater fish of the *Crypinidae* family). Humans are the parasite's definitive hosts, whereas cats and dogs act as reservoir hosts.

Figure 3 The second intermediate host of *Opisthorchis viverrini* is freshwater fish in the family *Crypinidae*, also known as cryprinid fish.

Cyclocheilichthys repasson, *Hampala dispar*, *Puntioplites proctzysron*, and *Hampala macrolepitota* being the predominant infected species[25]. Subsequently, from 2011 to 2012, a study was conducted to assess the distribution of *O. viverrini* in cyprinid fish across 20 provinces in northeastern Thailand, encompassing various aquatic environments such as rivers, dams, ponds, and lakes. During this period, six species were identified as harboring *O. viverrini* metacercariae: *C. armatus*, *P. proctozysron*, *P. orphoides*, *H. dispar*, *Henicorhynchus siamensis*, and *Osteochilus hasselti*, with an infection rate of 24.3%[26]. In addition, during the surveillance period from 2019 to 2021, metacercariae of *O. viverrini* were detected in freshwater fish across 20 districts in the upper regions of northeastern Thailand, and infection rates of *O. viverrini* in fish ranged between 3.9% and 21.1% with the average prevalence of 7.1%[27]. Moreover, *O. viverrini* metacercariae were detected in five different fish species, with the following prevalence rates: 13.7% in *H. siamensis*, 12.7% in *Cyclocheilichtys* spp., 8.1% in *Hampala* spp., 6.9% in *Systomus* spp., and 5% in *Barbonymus goniatus*[27]. From 2018 to 2019, a total of 2,149 freshwater fish, consisting of 20 different species, were examined for the prevalence of *O. viverrini* metacercariae across five districts in Nakhon Phanom Province, northeastern Thailand. The species most frequently found infected with *O. viverrini* metacercariae were *H. dispar* and *Anematichthys repasson*, with an average of 0.23 metacercaria per fish. Furthermore, the prevalence displayed district-level variation, with rates ranging from 0.07 to 0.52[28].

The geographical distribution of *Bithynia* spp., the first intermediate host of *O. viverrini*, varies by region, including *Bithynia funiculata* in the north, *Bithynia siamensis goniomphalos* in the northeast, and *Bithynia siamensis siamensis* in central Thailand[29-30]. A previous study demonstrated that the prevalence of *O. viverrini* in *Bithynia* spp. was generally < 1% which was significantly lower than that observed in cyprinid fish[31-34]. For example, a study performed between 2008 and 2011 in 48 locations in northeastern Thailand and Lao PDR indicated that the average prevalence of *O. viverriini* in *B. siamensis goniomphalos* was 0.73% (42/5,790) in northeastern Thailand and 1.08% (63/5,848) in Lao PDR[32]. In addition, seasonal prevalence of *O. viverrini* in *B. siamensis goniomphalos* in northeastern Thailand showed significant variations from 2012 to 2013, with rates of 0.31%, 1.05%, and 0.37% during rainy, cold, and hot seasons, respectively[33]. Another study in Bangkok's canal network from 2018 to 2019 found a total prevalence of *O. viverrini* infection of 0.05% (4/7473) in *B. siamensis*[34].

For a study on the prevalence of *O. viverrini* infection in reservoir hosts, Aunpromma et al. conducted a study in Khon Kaen Province from 2007 to 2009, revealing a high prevalence of *O. viverrini* infection in cats (35.51%, or 76/214), compared to dogs (0.37%, or 3/821). In addition, cats with severe infections showed gall bladder wall thickening and hyperechoic liver parenchyma on ultrasound, indicating cats act as the main reservoir for human opisthorchiasis in this endemic area[35]. Another study in 2016 around Ubolratana Dam found higher infection rates in cats (30.92%, or 77/249) than dogs (0.20%, or 2/1,018), especially in raw fish-eating cats, were more likely to develop risk factors as potential disease transmitters[36]. Therefore, the epidemiology of *O. viverrini* in secondary hosts should be considered for improved control and education programs. Interestingly, the study of *O. viverrini* infection in fish-eating animals in northeastern Thailand, including monkeys, rodents, small domestic mammals, and avian species, revealed the absence of *O. viverrini* infection, suggesting these animals are unlikely to act as reservoir hosts for *O. viverrini* in these endemic areas[37].

CLINICAL MANIFESTATIONS AND PATHOGENESIS OF *O. VIVERRINI* INFECTION

The primary symptoms of opisthorchiasis and arise from inflammation and damage to the bile ducts. Symptoms may not be evident during

early-stage infections. However, long-term infections can cause liver and bile duct inflammation, formation of gallstones, periductal fibrosis, and CCA, subsequently damaging the liver and bile ducts[5,38]. At 2 to 4 weeks after infection, initial pathological alterations involve a rapid inflammatory response in the first- and second-order bile ducts and the connective tissue surrounding the portal. In addition, localized coagulation necrosis is observed in the liver lobules and more cells in the bile ducts[39]. At 12 weeks after infection, adult worms cause chronic pathological changes, including hyperplasia, adenomatous changes, granuloma formation, and thickening fibrous tissue around the bile ducts, resulting in the obstruction and gradual enlargement of the bile ducts[39-40]. In addition, in a hamster model, the biliary epithelium demonstrated inflammation and fibrosis along its entire length, leading to tumorigenesis and development of CCA[39,41]. Periductal fibrosis observed in animals with persistent infection was similar to that observed in humans, as evaluated by ultrasonography[42]. In addition, in patients with chronic opisthorchiasis, a strong association was detected between the severity of *O. viverrini* infection and the increased occurrence of advanced periductal fibrosis, which is also associated with a higher incidence of CCA[6]. Cholangiocarcinogenesis associated with *O. viverrini* infection is a complicated process that is triggered by several factors. Initially, the sucking activity during feeding and the movement of adult worms result in mechanical damage to the ductal epithelial cells. In addition, *O. viverrini* produces proteases, including cathepsin F and cathepsin B1, which contribute to tissue damage via the breakdown of extracellular proteins[38]. In addition, the excretory secretory products of *O. viverrini* stimulate proinflammatory responses, resulting in an increase in Toll-like receptors and interleukins 6 and 8, which activate downstream chemokines and promote CCA development[43]. In addition, *O. viverrini* induces persistent damage to the bile duct tissue by the actions of reactive oxygen species (ROS). produced by phagocytic cells, leading to DNA damage and mutagenesis, which increases the risk of CCA. Moreover, cell proliferation during development of CCA is promoted by the activation of mitogenic and antiapoptotic factors[44]. Similarly, by increasing cell proliferation, stimulation of mitogenic and antiapoptotic proteins enhances the formation of CCA[45]. Finally, the degradation of tissue by cathepsin F and cathepsin B1 can change the surrounding extracellular matrix environment, leading to the collapse of the basement membrane and the invasion and spread of CCA, which is characterized by high invasiveness, rapid development, high spreading potential, and a very poor prognosis[5,7]. To date, the chronic infection of *O. viverrini* can cause CCA; *C. sinensis* has also been strongly reported to be associated with CCA; and both liver flukes are classified as Type 1 carcinogens[6,8,46]. For *O. felineus* infection, there are a few studies related to CCA. For example, one epidemiological study from Russia suggested an increased incidence of CCA in areas endemic to *O. felineus*[47]. Additionally, some animal models revealed that CCA is a sequalae of *O. felineus* infection[48]. However, there is less research on *O. felineus* associated with CCA than on *C. sinensis* and *O. viverinni*; therefore, it is difficult to explain the association between *O. felineus* infection and CCA, despite the fact that such a correlation seems to exist.

INCIDENCE OF CCA IN THAILAND

CCA is a rare cancer that develops and arises from bile duct epithelium cells. However, CCA is more commonly observed in Thailand, where its incidence is relatively high. In addition, high incidences of CCA have been reported in Thailand's northern and northeastern regions, which are geographically associated with widespread *O. viverrini* infection[6,13]. As from many researches, *O. viverrini* has been categorized as a group 1 carcinogenic agent, which is a major risk factor for CCA[46]. Moreover, the top 10 provinces in Thailand with the highest CAA MR

were published in 2005. The highest CCA MR was observed in Sakol Nakhon Province, northeastern Thailand, at 61.4 per 100,000 people, followed by Prae Province in northern Thailand, at 55.8 per 100,000 population. In addition, the remaining provinces with high MRs were found in the northeastern region of Thailand, particularly in Roi-Et Province (MR = 54.8), Nongbua Lamphoo Province (MR = 54.1), Kalasin Province (MR = 50.9), Amnat Charoen Province (MR = 47.8), Mahasarakham Province (MR = 44.9), Udon Thani Province (MR = 44.3), Nakhon Phanom Province (MR = 40.3), and Yasothorn Province (MR = 39.9) (figure 4)[7]. Between 1988 and 2012, the age-standardized rate of liver cancer and bile duct cancer in Thailand ranged from 40.5 to 33.9 per 100,000 in males and 16.3 to 12.9 per 100,000 in females. According to Green et al., the prevalence of CCA in Khon Kaen Province in 1988 was 135.4 per 100,000 for males and 43.0 per 100,000 for females[49]. For individuals older than 35 years, there was a threefold increase in prevalence of 317.6 cases per 100,000 person-years. Furthermore, as reported by Banales et al.[50]. There was a significant decrease from 1989 to 2018 in the incidence of CCA among males and females in Khon Kaen Province. The reduction in CCA incidence can be attributed to the low birth rate in this population[51]. According to the predicted data, the age-standardized rate for men in 2028 is estimated to be 7.6 per 100,000 individuals, whereas it is projected to be 3.6 per 100,000 for females. Since the incidence rates of CCA decreased in Khon Kaen Province between 1989 and 2018 and will continue to decline until 2028, the five-year relative survival analysis for CCA was only 10.9%, indicating the survival of the patients remains low[51]. Therefore, the survival rate of patients with CCA is a major obstacle in achieving positive patient treatment outcomes.

DIAGNOSIS OF *O. VIVERRINI*

MICROSCOPIC EXAMINATION

Conventional techniques for diagnosing *O. viverrini* infection consist of the direct, simple smear technique; the Kato–Katz technique; and the formalin–ethyl acetate concentration technique (FECT) for detecting parasite eggs in feces[52-53]. In addition, the Mini Parasep® stool kit was recently developed to identify parasite eggs in feces, including liver fluke eggs. However, the use of only microscopic examination for detecting *O. viverrini* will result in false positives with MIF eggs, because these eggs are very similar and difficult to distinguish under a light microscope.

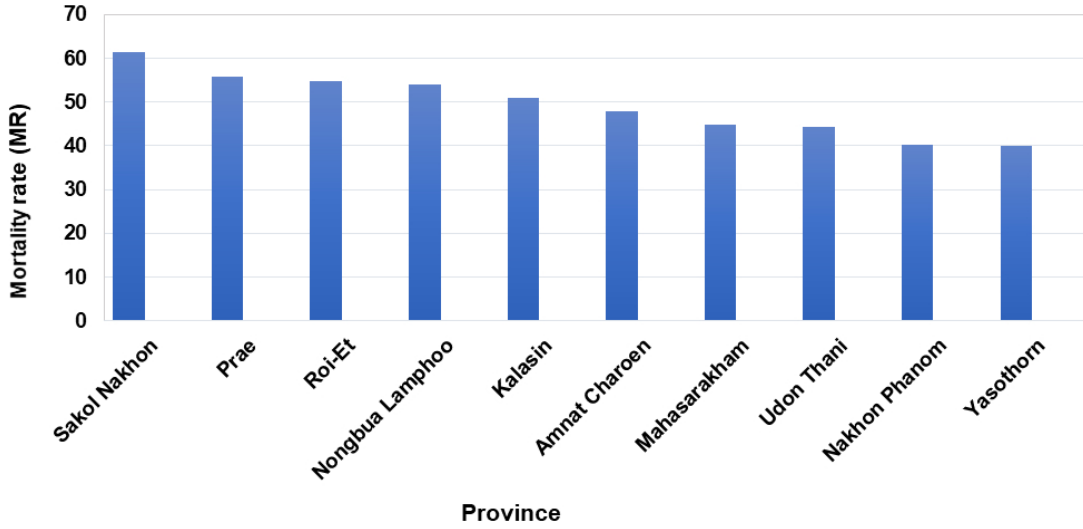

Figure 4 The top province with mortality rates of cholangiocarcinoma in Thailand. The mortality rate is per 100,00 people[7].

Furthermore, it has been shown that when there are fewer than 20 adult worms of *O. viverrini*, no eggs could be found in the feces. As compared with the sensitivity of diagnostic techniques, the direct, simple smear; Kato–Katz; FECT; and stool kits (Mini Parasep Kit) had sensitivity values of 12.4%, 68.3%, 91.0%, and 32.4%, respectively[52]. Moreover, one study demonstrated that FECT, Kato–Katz, and stool kits (Mini Parasep Kit) had diagnostic sensitivity values of 75.5%, 66.0%, and 67.3%, respectively, for detecting *O. viverrini* eggs[53]. Therefore, FECT provides higher sensitivity for detecting *O. viverrini* in feces than other diagnostic methods[53].

SEROLOGICAL DIAGNOSIS

Antibody detection assays are preferred for the detection of *O. viverrini*. However, there were limitations due to the cross-reactivity of antigens, and positive results may not always indicate active parasite infection. For example, crude antigens (17-18 kDa) of *O. viverrini* were employed in ELISA, exhibiting sensitivities of 91% -92% across diverse subject groups, including opisthorchiasis patients, those with mixed infections of *O. viverrini*, individuals with other parasitic infections, and healthy individuals[54]. However, specificity ranged from 70% to 80%, with noted cross-reactions in individuals infected with parasites such as *Paragonimus heterotremus*, *Schistosoma* spp., *Ascaris lumbricoides*, and others[54]. In 2001, Wongsaroj et al. successfully extracted the oval antigen of *O. viverrini* using monoclonal antibodies, achieving 100% sensitivity, specificity, and accuracy in detecting *O. viverrini* infection via dot-ELISA[55]. This method is ideal for mass screening, especially in newly endemic regions. In 2007, an ELISA study using crude *O. viverrini* antigen found sensitivities ranging from 23.1% to 99.2% and specificities from 29.6% to 93.0%. This study revealed a correlation between the *O. viverrini* egg count in feces and specific IgG and IgG_4 levels in serum and urine[56]. A lateral flow immunochromatographic (ICT) kit, using soluble *O. viverrini* worm extract and colloidal-gold-labeled IgG antibody conjugates, was developed and tested on 347 simulated whole-blood samples[57]. The ICT kit exhibited diagnostic outcomes of a sensitivity of 95.5%, a specificity of 87.0%, a positive predictive value of 80.5%, a negative predictive value of 97.2%, and an overall accuracy of 90.1% in diagnosing opisthorchiasis.

Additionally, the assay demonstrated the ability to detect clonorchiasis, yielding a sensitivity of 85.7%, a specificity of 87.0%, a positive predictive value of 53.6%, a negative predictive value of 97.2%, and an overall accuracy of 86.8%[57]. Moreover, a rapid ICT was recently developed to detect anti-*O. viverrini* IgG and IgG4 subclass antibodies in the serum of CCA patients. Among the 36 CCA patients tested, 61.1% were positive for IgG antibodies and 41.6% for IgG_4 antibodies. In comparison, IgG ICT and IgG_4 ICT assays were positive in 25.5% and 27.7%, respectively, of patients with liver cirrhosis and other malignancies. The patients diagnosed with CCA exhibited a 6.53-fold higher positivity rate for anti-*O. viverrini* IgG antibody and a 3.27-fold increase in positivity for anti-*O. viverrini* IgG_4 antibody compared to the non-CCA group[58]. Therefore, this ICT shows potential for developing a diagnostic biomarker for predicting CCA risk linked to *O. viverrini* infection. A recently developed lateral flow ICT kit demonstrated high sensitivity and specificity for diagnosing opisthorchiasis and detecting co-infections with clonorchiasis, offering potential for field surveys in endemic areas[58]. Recently, a urine *O. viverrini* antigen-based rapid diagnostic test (OV-RDT) was developed in 2023 using an ICT technique. This OV-RDT revealed a high sensitivity of 94.2% and a high specificity of 93.2% in comparison to the commonly used FECT for detecting 423 urine specimens. Furthermore, the urinary OV-RDT had a low 2% of cross-reactions with other helminth infections, indicating that it might be beneficial for large-scale screening campaigns targeting opisthorchiasis in fields due to the simplicity of collecting urine samples[59].

MOLECULAR DIAGNOSIS

As compared with microscopic examination, the molecular-based polymerase chain reaction (PCR) technique has a higher specificity and sensitivity for detecting *O. viverrini* eggs in fecal samples. In 2001, Wongratanacheewin et al. developed a PCR assay to detect as little as 2×10^{-17} ng of *O. viverrini* genomic DNA in fecal samples. When the numbers of eggs per gram were > 1,000, > 200, and < 200, the sensitivity of the assay was 100%, 68.2%, and 50%, respectively[60]. In addition, multiplex PCR was used to identify *C. sinensis* and *O. viverrini* infections by targeting the mitochondrial NADH dehydrogenase subunit 2 (*nad2*) gene; this technique was able to detect one egg of *O. viverrini* and two eggs of *C. sinensis* in a fecal sample[61]. Because the egg morphologies of *O. viverrini* and MIFs are very similar, a PCR assay was developed to discriminate between these parasites using internal transcribed spacer (ITS)1 and ITS2 as targets with 76.2% sensitivity for ITS1 and 95.2% for ITS2[62]. Moreover, conventional PCR and real-time quantitative PCR were also developed to detect and discriminate between *O. viverrini* and *H. taichui* by amplification of mitochondrial cytochrome c oxidase subunit I (*cox1*) genes, demonstrating 100% sensitivity for the detection of *Opisthorchis*-like eggs[63]. Moreover, *O. viverrini* is considered to be a species complex consisting of at least two siblings, one in Thailand and the other in Lao PDR, using multilocus enzyme electrophoresis. Furthermore, to study the genetic structure and genetic variation of *O. viverrini*, mitochondrial DNA sequencing of subunit 1 of the NADH dehydrogenase gene (*nad1*) and the cytochrome oxidase gene (*cox1*) were used, which indicated the monophyletic group of this parasite[23,64-65]. In addition, random amplified polymorphic DNA was used to study *O. viverrini* from northeastern Thailand and Lao PDR, and the results suggested that this parasite is composed of different genotypes[66]. In a recent study, microsatellite DNA analysis was used to assess the genetic diversity and population structure of *O. viverrini* across various geographical regions. The findings revealed genetic variation in the population of *O. viverrini* at a localized level, with corresponding patterns observed at a broader scale[67]. Since 2007, the use of multilocus enzymes to study systematics and genetic variation in *O. viverrini* populations has revealed a species complex, termed "*O. viverrini* sensu lato," which includes cryptic species in Thailand and Lao PDR wetlands[68-69]. Subsequently, genetic variation in mitochondrial genes, specifically *cox1* and *nad1* nucleotide sequences, was observed in *O. viverrini* sensu lato across Thailand and Lao PDR, with variations ranging from 0% to 0.3% for *nad1* and 0% to 0.5% for *cox1* in *O. viverrini*[64]. Furthermore, a novel cryptic *O. viverrini* sensu lato population was identified in Pangkon district, Sakon Nakhon Province, exhibiting distinctive genetics compared to other isolates based on *nad1*, *cox1*, cathepsin F gene (CF-int6), paramyosin gene (Pm-int9), ITS2, and 28S rDNA sequence analysis[70]. Additionally, the random amplified polymorphic DNA analysis also showed genetic differences between *O. viverrini* populations in northeastern Thailand and Lao PDR[66]. At present, microsatellite DNA marker analysis conducted on four neighboring villages in Khon Kaen Province revealed genetic variation and distinct alleles, along with sub-structuring within the *O. viverrini* population across these areas in Thailand[67]. Additionally, Namsanor et al. (2020) identified a cryptic species of *O. viverrini* sensu lato in Sakon Nakhon Province, northeastern Thailand, using microsatellite DNA, nuclear DNA, and mitochondrial DNA markers[71]. Moreover, genetic studies revealed co-evolution between *O. viverrini* sensu lato and *Bithynia* spp., the first intermediate host, with at least three distinct genetic groups. Population genetics of *O. viverrini* indicated complex species across Thailand and Lao PDR[68,72-73]. As the distribution of *O. viverrini* infection continues to spread in new regions of Thailand, the evolutionary association between *O. viverrini*

and *Bithynia* spp. remains unclear. Future studies should focus on evaluating genetic diversity and population dynamics in endemic areas, using microsatellite DNA markers. Additionally, it is essential to conduct thorough investigations into the genetic characterization of *O. viverrini* infections in cyprinid fish, which serve as the secondary intermediate host, in order to enhance our understanding of their life cycle and transmission dynamics.

PREVENTION AND CONTROL OF *O. VIVERRINI* INFECTION

Since 1987, national control strategies for *O. viverrini* have been initiated to eradicate *O. viverrini* infection[74]. First, the strategies were used to control liver fluke, including identifying infected individuals through stool examination and following treatment with praziquantel to eliminate *O. viverrini* in humans and reservoir hosts[75]. Second, as an important prevention step against infection, promoting health education programs emphasizing the consumption of cooked fish is crucial. This should be followed by attempts to enhance sanitary defecation habits by promoting hygiene behaviors for feces disposal, such as the use of latrines at the household level and rice paddies to effectively reduce environmental contamination with *O. viverrini* eggs. In addition, human consumption of raw or unprocessed freshwater fish is the main factor contributing to the persistence of liver flukes in rural areas. Therefore, health education is required to change the eating habits of people in endemic areas, which could also reduce the future prevalence and incidence of CCA. However, prevention and control programs have not been successful in some endemic areas. In Thailand, the major strategies for prevention and control are fecal examination to detect parasite infection and praziquantel treatment to eliminate adult worms in human hosts. However, some patients become reinfected with *O. viverrini* in some areas at a rate of approximately 10.9%[76]. Therefore, to reduce the transmission and distribution of *O. viverrini* infection in Thailand, an effective prevention and control program is still required.

CONCLUSION

O. viverrini remains an important trematode in Thailand, with a high prevalence in northeastern and northern Thailand. Although the total national prevalence is decreasing, the prevalence remains high in some areas. Moreover, *O. viverrini*–associated CCA results from by multiple factors, including parasite factors, host immunological responses to parasites, and exogenous or endogenous nitrosamine. All of these factors are derived from chronic infection with *O. viverrini*. In addition, CCA is a malignancy with a poor prognosis and a high MR; therefore, it is necessary to eradicate this parasite to reduce the incidence of CCA in Thailand. As an example, implement ongoing campaigns to discourage raw fish consumption and provide health education on *O. viverrini* infections at community and school levels to alter eating habits, particularly in high-prevalence endemic regions of northern and northeastern Thailand. Additionally, an effective control strategy involves reducing infection prevalence by screening individuals via fecal examination, treating infected humans, and treating reservoir animals (such as cats and dogs) to minimize transmission and act as primary prevention for CCA. Additionally, suspected CCA patients should undergo ultrasonography screening for periductal fibrosis to determine the need for CCA monitoring, then a diagnosis and suitable treatment.

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Review Article

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Preventive Dentistry in Children with Special Needs: Narrative Review

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ABSTRACT

Children with special healthcare needs face a high prevalence of dental and oral health problems due to unique challenges in maintaining oral hygiene. Preventive dentistry, which encompasses practices and strategies aimed at maintaining optimal oral health and preventing dental caries, periodontal disease, and other oral conditions, is therefore of utmost importance for this vulnerable group. This narrative review compiles the dental health concerns commonly encountered in these children and outlines preventive strategies to address them. Common dental issues encountered in this population include dental caries, gingival inflammation, tooth erosion, and attrition. Factors contributing to these problems range from motor impairments limiting brushing ability, food preferences, bruxism, gastroesophageal reflux disease, and side effects of certain medications. Effective preventive measures involve early dental visits, appropriate oral hygiene routines, judicious use of fluoride toothpaste and supplements, dietary modifications, and cessation of nighttime bottle-feeding. Specific recommendations are provided for caregivers, such as selecting the right toothbrush, maintaining proper brushing techniques, and monitoring fluoride intake based on age and risk factors. Interdisciplinary collaboration between pediatricians, dentists, and other healthcare professionals is crucial in identifying potential dental issues and providing tailored preventive care for children with special needs.

KEYWORDS: children with special needs, dental caries, disabilities, oral hygiene, preventive dentistry

INTRODUCTION

Children with special needs are children with intellectual, physical, or mental disabilities. Their physical, psychological, and social abilities are inadequate[1]. The disabilities could stem from a wide range of conditions, including cognitive impairment (such as global developmental delay (GDD), autism spectrum disorder (ASD)), motor disorders (e.g., cerebral palsy (CP) and brain abnormalities), behavioral and emotional problems (including attention deficit hyperactivity disorder (ADHD)), and sensory impairments (visual and auditory impairments)[2].

Because oral care is difficult for them, children with special needs often have oral health problems. According to a study by Obeidat et al. (2022), 20.3% of children with special needs had oral health needs compared to 12.2% of normal children[3]. The most commonly reported problems in children with special needs are dental caries (16.7%), bleeding gums (3.5%), and toothache (7.2%)[3]. A study by da Silva et al. (2016)

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found that the prevalence of dental caries and periodontal disease in children and adolescents with ASD was as high as 60.6% and 69.4%, respectively[4]. According to studies by Makkar et al. (2019)[5] and Roberts et al. (2016)[6], children with intellectual disabilities (ID) had a high prevalence of dental caries and gingival diseases, as high as 86% and 69%, respectively. A meta-analysis study by Zemene et al. (2024) found that the prevalence of dental caries in children with CP was 42.4%-64%[7]. Table 1 summarizes the prevalence of various dental health problems among children with different special needs, highlighting the conditions of most concern for each group.

Collectively, these data indicate that dental and oral health problems are major concerns for children with special healthcare needs. If left untreated, these children may experience difficulties with eating, sleepless nights, abscess formation, systemic infection, and poor quality of life[8].

The American Academy of Pediatrics has guidelines for children's oral and dental health care[9], yet children with special needs face significant barriers to accessing these services. These challenges arise from factors related to the children, their families, and public health systems[8,10]. Behavioral difficulties, sensory processing issues, and conditions such as ASD, ID, and ADHD often result in disruptive behaviors, poor cooperation, and difficulty following instructions during dental procedures[11]. Furthermore, impaired communication abilities hinder these children from effectively expressing their dental needs or discomfort during treatment[12].

Children with sensory processing disorders often experience heightened anxiety during dental visits, affecting their cooperation[13]. Financial constraints and inadequate insurance coverage limit access to specialized dental care while scheduling and transportation challenges further impede dental screenings and treatment[14]. Additionally, many dental professionals lack the training or experience necessary to manage the unique needs of these children, complicating the provision of appropriate care[15].

Therefore, it is crucial for pediatricians and other healthcare professionals to recognize the increased risk of dental problems in children with special needs and provide guidance on primary oral care for this population. This narrative review aims to discuss dental health concerns, management strategies, and evidence-based recommendations for promoting good oral hygiene and preventing dental problems in children with special healthcare needs.

METHODS

This narrative review synthesizes available literature on preventive dentistry approaches for children with special healthcare needs. A comprehensive search was conducted using multiple electronic databases, including PubMed, Scopus, and Google Scholar, from 2004 to 2024. The following search terms were used in various combinations: "children with special needs", "disabled children", "preventive dentistry", "oral hygiene", "dental caries", and related keywords. In addition to the database searches, the reference lists of relevant articles were manually screened to identify any additional pertinent studies.

Table 1 The prevalence of dental health problems in children with special needs

Special needs category	Prevalence of dental caries	Prevalence of periodontal disease	Prevalence of other notable conditions
Autism spectrum disorder (ASD)	60.6%	69.4%	Not specified
Intellectual disabilities (ID)	86%	69%	Not specified
Cerebral palsy (CP)	42.4-64%	Not specified	Not specified
General special needs	16.7%	Not specified	Bleeding gums 3.5% Toothache 7.2%

Abbreviations: ASD, autism spectrum disorder; CP, cerebral palsy; ID, intellectual disabilities

Studies were included if they provided information on dental health concerns, risk factors, and preventive strategies for children with special healthcare needs or disabilities. Preference was given to recent systematic reviews, meta-analyses, and clinical practice guidelines when available. Given the broad scope of this narrative review, both original research articles and review articles were considered for inclusion.

DENTAL HEALTH PROBLEMS AND MANAGEMENT IN CHILDREN WITH SPECIAL HEALTH CARE NEEDS

Children with special needs require specialized oral and dental health care, as outlined in Table 2.

Table 2 Dental health condition and initial management in children with special healthcare needs

Special healthcare needs	Health condition	Dental problems	Initial management
Cerebral palsy	Poor hand dexterity	Limited brushing ability	- Modified toothbrushes with larger handles or built-up grips to provide a better grasp - Using mouth opening kit to keep the mouth open and allow better access for brushing and cleaning - Caregivers may need to provide hands-on assistance with brushing for children with severe manual dexterity limitation
	Esophageal reflux	Erosion	- Regular brushing with a fluoride toothpaste to help remineralization and protect tooth enamel from acid erosion - Keeping the child in an upright position during and after feeding to prevent reflux
	Bruxism	Broken tooth attrition	- Custom-made occlusal splints or mouth guards - Dental restorations - Botulinum toxin injections into the masseter muscles in severe cases
	Drug-induced sialorrhea	Increased risk of dental caries	- Frequent wiping of the mouth and teeth with a clean, soft cloth or gauze - Encouraging adequate water intake to dilute and wash away saliva - Limiting sugary and acidic foods and beverages to reduce the cariogenic potential of saliva - Regular brushing, flossing, and use of fluoride toothpaste to protect against dental caries
Autism spectrum disorder	Food preferences	Dental caries due to preference for starches and snack foods	- Avoid cariogenic foods
	Hypersensitivity	Difficult oral hygiene practices	- Use toothbrushes with different bristle textures (e.g., soft, extra-soft) - Minimize distractions and sensory stimuli during oral care routines
	Drug-induced xerostomia	Increased risk of dental caries and periodontal disease	- Encouraging frequent sipping of water - Use saliva substitutes or saliva stimulants in severe cases - Topical fluoride treatments to strengthen tooth enamel and provide additional protection against caries
Global developmental delay/ intellectual disability	Bruxism	Broken tooth attrition	- Custom-made occlusal splints or mouth guards - Dental restorations - Botulinum toxin injections into the masseter muscles in severe cases
Epilepsy	Drug-induced gingival hyperplasia	Gingival hyperplasia	- Meticulous oral hygiene practices - Topical fluoride treatments to strengthen tooth enamel and provide additional protection against caries - Use the antimicrobial mouth rinses to reduce plaque levels and prevent gingivitis

Children with CP are physically unable to clean the inside of their mouths, and it is difficult for caregivers to do so because the children cannot open their mouths wide enough[16]. In addition to physical therapy, a modified toothbrush and mouth-opening kit can help resolve this restriction[17].

Children with CP are also prone to gastroesophageal reflux disease due to poor muscle control in the lower esophageal sphincter and swallowing difficulties. This condition can cause tooth erosion[18]. Fluoride treatment helps reduce surface microhardness loss and mineral loss in enamel and dentin[19]. The study by Mazzoleni et al. (2023)[20] found that children using fluoride-containing toothpaste had a significantly lower mean surface roughness (0.82 ± 0.12 μm) of their teeth after a second acid attack compared to children using non-fluoride toothpaste (1.06 ± 0.18 μm). Therefore, children with CP should be encouraged to use fluoride-containing toothpaste to prevent demineralization after acid attacks in their oral cavity.

Children with ASD often prefer foods containing sugar, starch, and dairy products. These foods are cariogenic and should be avoided to prevent tooth decay in these children[21]. In addition, hypersensitivity to certain textures, sounds, or sensations in the mouth can make routine oral hygiene practices challenging. Toothbrushes designed for oral hypersensitivity and minimizing distractions and sensory stimuli during oral care routines help to manage this condition[13].

Bruxism, which is the grinding of teeth, is a common cause of tooth damage among children with CP and GDD. In cases where bruxism is not causing dentin damage, using an occlusal splint can prevent tooth attrition. However, dental restoration may be necessary in severe cases where tooth attrition has occurred. Additionally, Botulinum toxin injections may reduce muscle spasms in the mouth and alleviate symptoms. Three months after receiving Botox injections into the masseter and temporalis muscles, there was a reduction in the Miami Bruxism Score, which measures bruxism severity, from 19 (severe) to 6 (mild)[22].

Some children with special health care needs also have epilepsy. Some antiepileptic drugs (such as phenytoin, sodium valproate, phenobarbitone, and vigabatrin) can induce gingival hyperplasia and lead to periodontitis and tooth decay[23-24]. Antipsychotics, such as risperidone, olanzapine, and clozapine, are frequently prescribed to children with ASD, ID, and other neurodevelopmental disorders. These medications can cause dry mouth (xerostomia) as a side effect, which increases the risk of dental caries, periodontal disease, and oral infection[25]. Children with CP or neuromuscular disorders may be prescribed muscle relaxants like baclofen or tizanidine, which can cause excessive drooling (sialorrhea), leading to perioral skin irritation, halitosis, and increased risk of dental caries and infections[26]. To mitigate these risks, healthcare providers need to be aware of the side effects of these medications and provide appropriate preventive measures[27], as shown in Table 2.

RECOMMENDATION FOR PROMOTING GOOD DENTAL HEALTH IN CHILDREN WITH SPECIAL HEALTHCARE NEEDS

Because children with special healthcare needs have a higher risk of dental health problems, healthcare providers and caregivers need to collaborate in preventing these issues, as shown in Table 3. The fundamental principles for promoting good dental health in children with special healthcare needs are as follows:

Table 3 The roles of caregivers and healthcare providers in promoting good dental health in children with special healthcare needs

Principles for promoting good dental health	Caregiver's roles	Healthcare provider's roles
Regular dental checkups	- Take children for their first dental visit when the first tooth emerges - Follow the recommended schedule for regular dental check-ups, typically every 6 months or more frequently based on the child's risk factors	- Emphasize the importance of regular dental visits, starting with the first tooth eruption - Provide appropriate referrals to dental professionals
Routine oral care	- Use appropriate toothbrushes and toothpaste based on the child's age and risk factors - Assist children with brushing their teeth, especially those with severe motor disabilities - Monitor and limit dietary fluoride intake based on age and fluoride levels in drinking water	- Educate caregivers on proper oral hygiene techniques, including positioning, brushing, and flossing - Recommend suitable toothbrushes, toothpaste concentrations, and dental cleaning aids based on the child's needs - Advise on appropriate fluoride supplementation based on age, risk factors, and drinking water fluoride levels
Diet & eating behavior	- Avoid frequent consumption of starchy, sugary, and acidic foods and beverages - Stop nighttime bottle-feeding before the child reaches 18 months of age	- Provide dietary counseling and recommendations for limiting cariogenic foods and beverages - Advise on the appropriate timing for cessation of nighttime bottle-feeding

Regular dental checkups

Parents must take their children to the dentist when they get their first tooth to learn how to care for their child's teeth and what to monitor[28]. In addition, regular dental visits are essential. The American Academy of Pediatric Dentistry recommends that children with special needs should receive comprehensive oral evaluations and preventive dental care every 6 months, or more frequently if indicated by their risk factors or specific conditions[29]. Based on the research of Ardenghi et al. (2012)[28], an essential factor related to children's first dental visit before the age of 3 is that parents have a better perception of their children's oral health (OR=1.38, 95% CI: 1.01-1.89). Therefore, healthcare providers who have the opportunity to take care of pediatric patients should encourage primary caregivers to recognize the importance of children's oral and dental health. Especially for caregivers who need to take care of children with special medical needs, they are at high risk of dental and oral health issues.

Some children with special needs fear dental health services. Parents can prepare them by telling stories related to dentistry, role-playing a visit to the dentist, watching videos of actual dental visits, and showing the dental care process[30-32]. The study by Bagattoni et al. (2022)[30] found that children whose parents used preparatory tools exhibited less disruptive behavior during the dental appointment than children who did not receive any preparatory material before their visit (p-value = 0.013). Furthermore, the study by Murshid et al. (2017) revealed that the percentage of children with ASD exhibiting positive behavior during dental treatment significantly increased, rising from 47.5% before utilizing the book to 80% after employing the book ($p < 0.001$). Therefore, the preparatory process before a dental visit can help shape positive dental experiences and behaviors in children with special healthcare needs. Children taking medications to alleviate behavioral and emotional problems, such as antipsychotics and psychostimulants, should continue taking them during dental procedures[33]. For children with ASD who often have auditory hypersensitivity, parents may prepare equipment such as noise-canceling headphones[31-32].

Routine oral care

Toothbrushes for children should be designed to fit in their hands, as shown in Figure 1. The bristles should have a straight cross-section and be soft enough to clean between the teeth properly without injuring the gums. The appropriate toothbrush size that fits the child's mouth size is also essential, especially for children with limited mouth-opening capability[17].

The appropriate fluoride concentration in toothpaste is also a crucial factor in reducing the risk of tooth decay. Fluoride strengthens the tooth surface, making it more resilient to acidic substances that can cause decay, and it reduces the buildup of dental plaque[34]. The 2019 study by Walsh et al. concluded that for children and adolescents, using a fluoride toothpaste containing 1,000-1,500 ppm fluoride can reduce caries increments when compared to non-fluoridated toothpaste (standard mean difference of -0.28 to -0.36 (95% CI: -0.43 to -0.25)[34]. However, using toothpaste with excessive fluoride may increase the risk of developing dental fluorosis[35]. Therefore, the American Academy of Pediatric Dentistry recommends using a concentration of fluoride and an amount of toothpaste as shown in Table 4 and Figure 2[36].

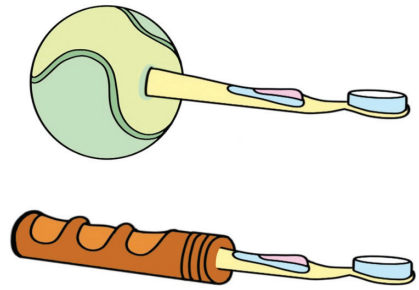

Figure 1 Examples of modified toothbrushes

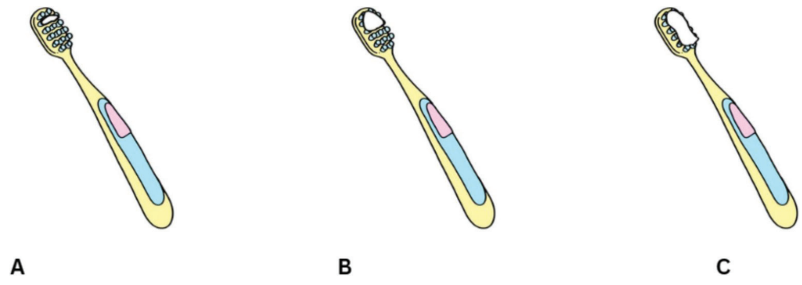

Figure 2 The amount of toothpaste recommended for different age groups.
For newborns up to 3 years old, use rice grain sized toothpaste (2A). For 3-6 years old, use corn grain sized toothpaste (2B). For children over 6, use toothpaste equal to the length of the brush (2C).

Table 4 Appropriate amount of fluoride in toothpaste

Child's age	Recommended amount of toothpaste	Recommended concentration of fluoride in toothpaste	Other additional suggestions
First tooth eruption – 3 years old	Just wet bristles (as much as a grain of rice)	1,000 ppm (1,500 ppm in cases with a high risk of tooth decay)	Parents should brush their children's teeth and wipe off foam after brushing
3 - 6 years old	Equal to brush width (equal to a corn kernel)	1,000 ppm (1,500 ppm in cases with a high risk of tooth decay)	Parents assist in squeezing toothpaste, brushing their child's teeth, and reminding them to spit out foam
6 years old and above	Equal to brush length	1,500 ppm	If a child brushes on their own, the parent should check again

Abbreviation: ppm, parts per million

For children who do not cooperate with brushing their teeth, oral fluoride supplements may be considered. According to a study by Tubert-Jeannin et al. (2011), dietary fluoride supplements can reduce permanent tooth caries by 24%[37]. However, the effectiveness of fluoride supplement for reducing caries, tooth extraction, and fillings in primary teeth is still unclear[38]. Furthermore, using systemic fluoride during the first six years of life increases the risk of developing dental fluorosis[39]. Consequently, dietary fluoride supplements are not recommended for children under 6 years old. Furthermore, fluoride supplements should be based on the fluoride level in the drinking water. Therefore, for children aged 6-16 years, it is recommended that 1 mg/day of fluoride supplement should be used if the fluoride concentration in drinking water is under 0.3 ppm. 0.5 mg/day of fluoride supplement should be used if the fluoride concentration in drinking water is 0.3-0.5 ppm. No supplement is needed if the fluoride content in water exceeds 0.5 ppm[40].

Children with severe motor disabilities require caregiver assistance for effective dental care, including tooth brushing. Caregivers should support the child's back and head while opening their lips to clean their teeth properly (figure 3)[41]. For children with oromotor dysfunction, cleaning around the cheek bulges is essential to remove food residue[41]. Triple-headed toothbrushes are more effective at plaque removal than single-headed ones[42], while the effectiveness of electric toothbrushes compared to traditional ones remains unclear[43].

Figure 3 Position for cleaning teeth of a child with severe motor disability

Dental sealants are another essential technique for preventing dental caries in these children. Dental sealants are thin, protective coatings applied to the chewing surfaces of the molars and premolars. They act as a physical barrier, protecting the tooth enamel from plaque accumulation and acid attacks that can lead to the development of dental caries. A study by Williams et al. (2018) found that after one year 74% of sealants were fully retained without caries present[44]. Moreover, a 14-year follow-up study of Balian found that dental sealants were 90.44-93.6% effective at preventing tooth decay[45].

Diet & eating behavior

Children who frequently consume starchy and sugary foods are at a higher risk of developing dental problems. Streptococcus mutans and Lactobacilus species on dental plaque decompose sugar, producing organic acid. Decreasing the pH on the tooth surface leads to demineralization and eventually causes dental caries[46-47]. Therefore, avoiding foods and beverages with added sugars is especially important in children with limited ability to clean their mouths and teeth.

In addition, nighttime bottle-feeding can lead to tooth decay due to the prolonged presence of milk sugar on the teeth. A 2014 study by Olatosi and Sote revealed that children who were bottle-fed were 4.5 times more likely to suffer from tooth decay compared to those who were not[48]. As a result, it is now recommended that parents stop bottle-feeding their children before they reach 18 months of age to help prevent tooth decay[49].

Finally, effectively providing comprehensive oral health care and early detection of dental health problems requires interdisciplinary collaboration between pediatricians, dentists, and caregivers of children with special healthcare needs. Appropriate dental health care leads to good quality of life, which is the goal of holistic treatment for these children.

DENTAL HEALTHCARE SERVICES FOR CHILDREN WITH SPECIAL HEALTHCARE NEEDS IN THAILAND

Accessing appropriate preventive dental care is crucial for maintaining good oral health in children with special healthcare needs. In Thailand, dental services are available at primary and secondary care levels to support this population.

Primary Care Dental Services[50]

At the community level, primary care units and health centers often provide essential dental services focused on prevention and early intervention. These services may include:

- Distribute complimentary toothbrushes and fluoride toothpaste to promote good oral hygiene practices from an early age.
- General dental check-ups and screenings to identify potential issues like tooth decay or gum disease.
- Educational programs that teach proper brushing and flossing techniques are designed for children and their caregivers.
- Provide guidance on reducing the intake of foods and drinks that can cause tooth decay.

Secondary Care Dental Facilities[50]

For children requiring more specialized dental treatment, secondary care facilities like community hospitals and dental clinics can offer additional preventive and restorative services such as:

- Applying dental sealants to the chewing surfaces of permanent molars helps prevent cavities.
- Provision of custom-fitted mouth guards for children at risk of tooth damage from bruxism or trauma.
- Comprehensive oral rehabilitation under general anesthesia when necessary for severe cases.
- Access to pediatric dentists with specialized training in managing the dental needs of children with disabilities or complex medical conditions.

Utilizing these available healthcare services can significantly benefit children with special needs by promoting preventive oral care, early detection of dental problems, and timely intervention when required. Enhancing awareness of such local resources empowers parents and general pediatricians to better advocate for and ensure optimal dental health outcomes.

CONCLUSION

Children with special health care needs are at higher risk of experiencing dental problems such as dental caries, attrition, and broken teeth. The common causes of dental health issues in these children include poor hand dexterity, esophageal reflux, food preferences, bruxism, and the side effects of medications. To maintain good oral health care in children, following up with a dentist as soon as their first tooth emerges is crucial. Parents should establish an appropriate oral care routine, limit the consumption of foods that promote tooth decay, and cease bottle-feeding before the child reaches 18 months of age. By taking these measures, parents can help ensure their children maintain healthy teeth and oral hygiene.

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