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ORIGINAL ARTICLES

REVIEW ARTICLE

Original Article

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A Comparative Analysis of Interest in Advanced Care Planning and Organ Donation Following Exposure to Video or Pamphlet Media

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ABSTRACT

OBJECTIVE: To compare the increase in interest in engaging in advance care planning between two groups: those receiving information via video media and those receiving information via pamphlets.

METHODS: A randomized controlled trial was conducted with 100 participants aged 18 to 60 years, who understood Thai and had no diagnosed psychiatric disorders or neurological conditions affecting consciousness, nor were they considered legally incompetent. The participants visited the Family Medicine Clinic at Vajira Hospital in 2024. The participants were screened using inclusion and exclusion criteria. The sample was divided using simple random sampling into two groups: 50 participants receiving information through a video and 50 participants receiving information through a pamphlet. Participants were asked to complete a questionnaire regarding their interest in engaging in advance care planning and organ donation. The level of interest was assessed using a five-point Likert scale, where a score of 5 indicates "very interested" and a score of 1 indicates "not interested". The content validity of the questionnaire was evaluated by three medical experts, demonstrating an index of item objective congruence of 0.85. Afterward, they either watched the video or read the pamphlet and then immediately completed the same questionnaire.

RESULTS: There were no significant differences in the basic characteristics of both groups. The average score of interest in creating an advance directive and organ donation significantly increased in the experimental group (by 1.4 and 0.82 points, respectively) compared with the control group (by 0.38 and 0.16 points, respectively) ($p < 0.001$).

CONCLUSION: Providing information through video media was more effective in increasing interest in advance care planning and organ donation compared with providing information through pamphlets.

KEYWORDS: advance care planning, advance directives, organ donation, pamphlets, video media

INTRODUCTION

Advance care planning allows individuals to plan for future health care decisions in the event they become unable to make their own decisions[1]. It helps ensure that end-of-life care aligns with patients' needs[2], reduces patient anxiety and fear of the care team, allows patients to plan for future affairs, and prevents conflicts between family and relatives over treatment decisions. In addition, it can help reduce unnecessary health care costs and resource use[3]. Thailand's National Health Act of 2007, section 12, upholds the right of citizens to create advance directives to refuse life-sustaining treatments or

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to end suffering from illness. Since advance care planning and advance directives serve as important communication tools, Thailand has developed a tool that provides a standard form for patients or those interested in completing it[4,5]. Currently, advance care planning and advance directives are provided in different ways across institutions. At Vajira Hospital, advance care planning and advance directives are discussed with patients in the terminal stage, as well as with those who request this information.

In a study conducted among patients who received outpatient services at the Family Medicine Department, Vajira Hospital, only 3% of patients had engaged in advance care planning[6]. Research conducted by Canny and colleagues on public awareness of advance care planning worldwide from 2015 to 2021 consistently showed that a lack of knowledge was the main factor leading to low rates of advance care planning[7]. Other factors included fear, the belief that advance care planning brings bad luck, and feelings of sadness that distress both the patient and family. In addition, there was a lack of trust in family members to make decisions on the patient's behalf, misunderstandings, confusion over whether advance care planning needs to be performed at the end of life, and misconceptions about treatments such as cardiopulmonary resuscitation or intubation, thinking they would cure the underlying illness. There was also an expectation that medical personnel would initiate discussions about advance care planning; however evidence suggests that doctors do not have enough time to initiate the conversations[7]. A qualitative study using in-depth interviews in Australia also found that the lack of knowledge was a significant factor contributing to low rates of advance care planning. Participants expressed comments such as, "I've never heard of it before," "I don't know what it is," "I didn't know advance care planning existed," and "I don't know where to get information about it[8]." An experimental study conducted among older adult patients compared those who received information about advance care planning through a video with those who received standard advice at a healthy aging clinic at Chulalongkorn Hospital[9]. The group who watched the video showed more interest in creating advance directives than the group receiving standard advice did, despite being given the same amount of time for guidance. In Taiwan, patients in the geriatrics department watched a video on advance care planning, and at 2-week follow-up after hospital discharge, those who watched the video were found to complete advance directives more frequently than those who received standard advice (33.3% vs. 9.3%). In addition, the group who watched the video had increased knowledge and interest in advance care planning[10]. In a study conducted in the general population in Korea, the authors reported that those who watched a video had greater intentions to engage in advance care planning and gained better knowledge about palliative care compared with those who read a pamphlet[11].

The mortality rate of the Thai population has increased. According to public health statistics from 2017 to 2021, the mortality rate among the Thai population aged 20 to 59 years was as high as 28.6% to 30.3%, which is almost one-third of the mortality rate across all age groups[12]. In 2022, there were 6,279 individuals on the waiting list for organ transplants, whereas 303 deceased individuals donated organs, equating to 4.6 donors per million population. There were 105,743 individuals registered as organ donors, which is a decrease of 29,876 from 2021[13]. Organ donation can be arranged by completing an advance directive, which may be done in conjunction with advance care planning.

As a result, advance care planning is considered to be a beneficial procedure for maintaining autonomy and providing future medical information from the patient's perspective to their family and health care professionals. Currently, the health education media available to patients at Vajira Hospital consists of paper and screen-based media. Each media supports patients in different ways. Screen-based media

could provide information, examples, and scenarios, printed materials offer detailed information[14].

The provision of information through video media significantly increases interest in advance care planning and the creation of advance directives, particularly among the older adult population[9-11]. However, beyond older adults, advance care planning can be conducted by individuals of all ages and genders. Therefore, in this study, we aim to examine the provision of advance care planning and organ donation information through video media as compared with through traditional pamphlets to a population aged 18 to 60 years. We hypothesized that providing information on advance care planning through video media will increase interest in creating in advance directives and/or organ donation more than providing information via pamphlets would. The results of this study will be used to plan for providing information to the public in the future.

METHODS

This study was a randomized controlled trial comprising 100 participants who attended the Family Medicine Clinic at Vajira Hospital between April 2024 and June 2024. Sample size calculations for the randomized controlled trial with binary outcome formula shown in Figure 1[9, 15-17] indicated that each group should consist of at least 29 individuals to account for potential incomplete data collection.

$$m_{trt} = \frac{n_{trt}}{4}\left(1+\sqrt{1+\frac{2(r+1)}{n_{trt}r|p_2-p_1|}}\right)^2$$

$$n_{trt} = \left[\frac{z_{1-\frac{\alpha}{2}}\sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)}+z_{1-\beta}\sqrt{p_1q_1+\frac{p_2q_2}{r}}}{\Delta}\right]^2$$

$$p_1 = P(outcome|treatment), q_1 = 1-p_1$$

$$p_2 = P(outcome|control), q_2 = 1-p_2$$

$$\bar{p} = \frac{p_1+p_2r}{1+r}, \bar{q} = 1-\bar{p}, r = \frac{n_{con}}{n_{trt}}$$

Figure 1 The sample size formula

The sample size calculation for a randomized controlled trial with a binary outcome was conducted using n4Studies software. The parameters used for the calculation included a treatment group outcome probability of P(outcome | treatment) = 0.980 and a control group outcome probability of P (outcome | control) = 0.670, with a treatment-to-control ratio of 1.00. The significance level (α) was set at 0.05, with a Z value of 1.959964 for a 97.5% confidence interval, and the power (1 - β) was set at 80% (β = 0.20), with a Z value of 0.841621. Based on these inputs, the calculated sample size without a continuity correction was 23 participants per group (treatment and control). Additionally, applying a continuity correction resulted in an increased sample size of 29 participants per group.

Consequently, we recruited 50 individuals per group, resulting in a total of 100 participants. Inclusion criteria were individuals aged 18 to 60 years who were able to listen, speak, and read Thai. The exclusion criteria were individuals diagnosed with psychiatric disorders or neurologic conditions affecting consciousness or those considered legally incompetent.

The primary objective of the study was to compare the interest in creating advance directives between two groups: one group receiving information through video media and the other receiving information via pamphlets. The secondary objective was to compare interest in organ donation between these two groups.

The research tools consisted of three components. First, the educational materials were either a video or pamphlet, and both media types provided information on advance care planning and organ donation. They included topics such as the definition of advance care planning, relevant laws, benefits, who should consider it, procedural steps, eligibility for organ donation, the types of organs that can be donated, the donation process, and a simulated scenario (for the video) depicts a young adult man was involved in a traffic accident and received life support through an endotracheal tube,

after which he was admitted to the ICU. Despite medical intervention, his condition did not improve, and the doctors determined that he had suffered brain death. His mother, deeply saddened and distressed by the situation, recalled that her son had previously expressed his wishes regarding his healthcare. He had communicated that he did not want to be resuscitated in the event of a vegetative state, poor quality of life, or loss of human dignity. Additionally, he had expressed a desire to donate his organs to help others in need of a transplant. In light of this, his mother, although grieving, found solace in respecting his wishes and made the decision to honor his wishes for organ donation. These materials were reviewed and validated by three family medicine specialists. Second, the data recording form contained demographic information with 9 questions including age, gender, marital status, education, religion, income, underlying disease, and whether participants had relatives or close individuals receiving palliative care or needing organ donation. Third, a questionnaire was applied to assess participants' interest in advance care planning and organ donation with 4 questions including the baseline level of interest in engaging in advance care planning, the baseline level of interest in organ donation, the level of interest in engaging in advance care planning following the intervention, and the level of interest in organ donation following the intervention. The questionnaire was developed based on the literature review. Then, its content validity was analyzed by three experts, demonstrating an index of item objective congruence of 0.85. Participants rated their opinions on a 5-point Likert-type scale (with a minimum of 1 and a maximum of 5) before and after receiving the educational information. The cut-off point is 3; a score of 3 or higher indicates interest, while a score below 3 indicates no interest.

After recruiting participants who met the eligibility criteria, the researcher explained the study's objectives, research procedures, potential risks, and the option to withdraw from the study and obtained informed consent. Participants were randomly assigned via simple randomization by a random number generator into two groups: an experimental group (video media) and a control group (pamphlet) allocating that each day participants will be receiving the same intervention at the Family Medicine Clinic. All participants completed a questionnaire assessing their interest in advance care planning and organ donation. The control group was instructed to read the pamphlet, which took approximately 10 minutes, whereas the experimental group watched an 8-minute video. Afterward, participants completed the same questionnaire again to assess their interest in advance care planning and organ donation. The video was not disseminated elsewhere, and the study was conducted on separate days for the control and experimental groups to ensure that the control group received information from only the pamphlet and was not influenced by the video content.

Statistical data analysis was conducted using STATA version 13.0 (Stata Corporation, College Station, TX, USA). We calculated the descriptive data, including gender, marital status, education, religion, average monthly income, underlying disease, whether the participant had relatives or close individuals receiving palliative care, and whether the participant had relatives or close individuals who needed organ donation, as percentages. Comparisons were made using the Chi-square test, Mann–Whitney U test, and Fisher's exact test, as appropriate for the data. Quantitative data, including age, and interest scores were reported as the mean and standard deviation (mean ± SD). Comparisons were made using the Mann–Whitney U test and Chi-square test, as appropriate. We used multilevel mean difference regression with random intercepts and random effect to analyze the mean difference in interest scores from baseline to after the intervention in both the video and pamphlet groups and to compare the mean difference in interest scores at baseline between

the two groups and between each participant (intercept) at baseline. Multivariable analysis adjusted for interest scores in creating advance directives at baseline. The Ethics Committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, approved this study, with the research project number 194/66 E on January 2, 2024.

RESULTS

We collected data from 100 participants at the Family Medicine Clinic, Vajira Hospital divided into two groups: 50 participants in the video group and 50 in the pamphlet group. The basic characteristics collected included average age, gender, marital status, education, religion, income, underlying diseases, whether the participant had relatives or close individuals receiving palliative care, and whether the participant had relatives or close individuals who required organ donation. As shown in Table 1, there were no statistically significant differences between the groups.

Table 1 Baseline characteristics of participants in Video media and Pamphlet groups

Characteristic	Video media (n = 50)	Pamphlet (n = 50)	P-value*
Age (median (IQR))	46 (34-52)	43 (35-50.5)	0.666*
Female (n, %)	36, 72	34, 68	0.663
Marital Status (n, %)			0.693**
Single	22, 44	18, 36	
Married	23, 46	28, 56	
Widowed/Divorced/Separated	5, 10	4, 8	
Education (n, %)			0.548
Under Bachelor	26, 52	23, 46	
Bachelor or higher	24, 48	27, 54	
Religious (n, %)			0.617**
Buddhist	49, 98	47, 94	
Christian	0, 0	1, 2	
Islam	1, 2	2, 4	
Monthly Income (n, %)			0.320
Less than 5,000 THB	6, 12	7, 14	
5,000 to 10,000 THB	1, 2	2, 4	
10,001 to 20,000 THB	24, 48	16, 32	
More than 20,000 THB	19, 38	25, 50	
Underlying disease (n, %)			0.056
No underlying disease	12, 24	21, 42	
Has underlying disease	38, 76	29, 58	
Having Relatives or Close Individuals Receiving Palliative Care (n, %)			1.000
Yes	6, 12	6, 12	
No	44, 88	44, 88	
Having Relatives or Close Individuals in Need of Organ Donation (n, %)			1.000
Yes	0, 0	1, 2	
No	50, 100	49, 98	

Abbreviations: IQR, interquartile range; n, number; SD, standard deviation; THB, Thai Baht
The data were analyzed using the Chi-square test, *Mann-Whitney U test, and **Fisher's exact test.
* Significant level at $p < 0.05$, Chi-square test or Fisher's exact test & Independent t-test or Mann-Whitney U test were used to compared characteristics between video media and pamphlet group.

The group who received information via video media had an average baseline score for interest in creating advance directives of 2.34 ± 1.349 points, whereas the group who received information via pamphlet had an average baseline score of 2.86 ± 1.161 points. This difference was statistically significant (p = 0.037). However, to assess the effectiveness of the intervention, this difference was controlled using multilevel linear regression. After the intervention, the group who received information via video media had an average score of 3.74 ± 0.986 points, whereas the group receiving information via pamphlet had an average score of 3.24 ± 0.797 points. This difference was statistically significant (p < 0.001). The average interest scores in creating advance directives, both before and after receiving information via video media compared with the pamphlet, are shown in Figure 2 and detailed in Table 2.

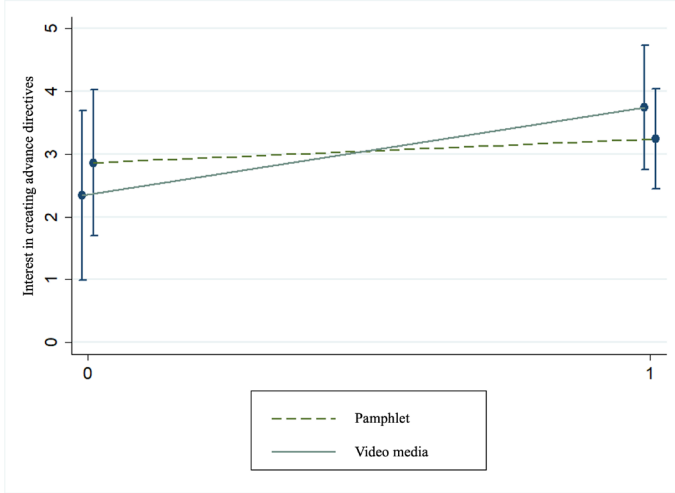

Figure 2 Mean with standard deviation of interest scores in creating advance directive from baseline to post intervention in intervention group and control group

Table 2 Multilevel mean difference regression analysis with random intercepts and random effect for interest score in creating advance directives and organ donation of participants from baseline to post intervention

Endpoint of interested	Video group	Pamphlet group	Mean difference of scores from baseline to post-intervention in Video group	P-value*	Mean difference of scores from baseline to post-intervention in Pamphlet group	P-value*	Difference of change between two group	P-value†
Interest in creating advance directives								
at baseline	2.34 ± 1.349	2.86 ± 1.161	Ref.		Ref.			
at post-intervention	3.74 ± 0.986	3.24 ± 0.797	1.40 (1.068 to 1.732)	0.000	0.38 (0.478 to 0.712)	0.025	1.02 (0.550 to 1.490)	0.000
Interest in organ donation								
at baseline	2.74 ± 1.259	3.08 ± 1.158	Ref.		Ref.			
at post-intervention	3.56 ± 1.072	3.24 ± 0.960	0.82 (0.537 to 1.103)	0.000	0.16 (-0.123 to 0.443)	0.267	0.66 (0.260 to 1.060)	0.001

* Multilevel mean difference regression with random intercepts and random effect was used to analyze mean difference in interest scores from baseline to post intervention both video and pamphlet group and to compare mean difference in interest scores at baseline between two group and between each participant (intercept) at baseline. Multivariable analysis adjusted for interest scores in creating advance directives at baseline.

† Multilevel risk difference regression with random intercepts and random effects was used to calculate mean difference in effect over time (slope) on interest score at post intervention between video and pamphlet group. Multivariable analysis adjusted for interest scores in creating advance directives at baseline.

‡ Multilevel mean difference regression with random intercepts and random effect was used to analyze mean difference in interest score at baseline between video and pamphlet group.

With regard to interest in organ donation, the group who received information via video media had an average baseline score of 2.74 ± 1.259 points, whereas the group who received information via pamphlet had an average baseline score of 3.08 ± 1.158 points. This difference was not statistically significant (p = 0.203). After the intervention, the group who received information via video media had an average score of 3.56 ± 1.072 points, whereas the group who received information via pamphlet had an average score of 3.24 ± 0.960 points. This difference was statistically significant (p = 0.038). The average interest scores in organ donation, both before and after receiving information via video compared with pamphlet, are shown in Figure 3 and detailed in Table 2.

The calculations of the increase in interest scores at baseline and post-intervention demonstrated that the video group showed a significantly greater increase in interest in both creating advance directives and organ donation compared with the pamphlet group (p = 0.000 and 0.0012, respectively). The mean difference in scores from baseline to post-intervention for the video group was 1.40 points in interest in creating advance directives, whereas the pamphlet group showed a mean difference of 0.38 points. For organ donation, the video group demonstrated a mean difference of 0.82 points, while the pamphlet group had a mean difference of 0.16 points, as shown in Table 2.

DISCUSSION

In this study, we examined the increased interest in creating advance directives and organ donation in participants who received information via video media compared with those receiving information through pamphlets at the Family Medicine Clinic, Vajira Hospital. The questionnaire measured interest both before and after the intervention, using a 5-point Likert scale, with scores ranging from 1 to 5. The study found no significant difference in the baseline characteristics between the two groups. Although at baseline prior to receive the advance care plan information, the pamphlet group showed greater interest in creating advance directives compared with the video group. After controlling for this factor, we found that the video group had a statistically significant increase in interest. In video group, interest in creating advance directives increased by 1.4 points (from 2.34 to 3.74, p = 0.000), and interest in organ donation increased by 0.82 points (from 2.74 to 3.56, p = 0.000). The difference in the increase in interest between the two groups was also statistically significant (p = 0.000 and 0.001, respectively). These findings are consistent with the results of a study conducted in Thailand

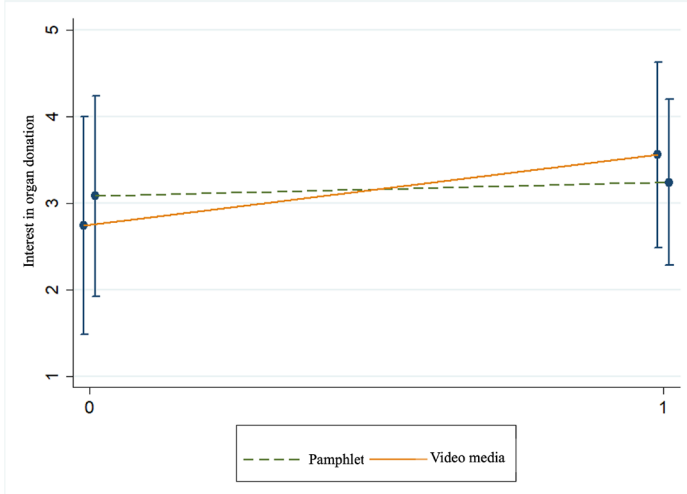

Figure 3 Mean with standard deviation of interest scores in organ donation from baseline to post intervention in intervention group and control group

among older participants[9]. The effectiveness of video as a medium may stem from its ability to engage multiple senses-sight, hearing, and reading short key phrases simultaneously-creating content that is more visual, easier to understand, and able to more effectively capture attention in a short period compared with audio or reading alone[9]. This is also similar to studies conducted in Taiwan and South Korea, where cultural similarities may play a role and video was found to be a highly engaging medium[10,11].

Although the video significantly increased participants' interest in creating advance directives and in organ donation compared to the pamphlet alone, the educational material in the pamphlet also provided detailed information, allowing participants to spend time outside the clinic reading independently. The video effectively captured attention and presented case scenarios that helped to illustrate key concepts, enhancing participants' understanding. Combining these two methods may work synergistically to further enhance participants' interest.

This study's limitations are that it evaluated the interest of participants immediately after they received the information and did not follow up for long-term assessment. In addition, some research participants had vision problems, which posed a barrier to reading the pamphlets. However, the researcher ensured that the participants were capable of reading. In the future, those who receive this information may have personal experiences, such as their own illness or other of their family and friends, that could lead them to consider whether advance care planning is in place, benefiting those who received the information to some extent.

Because participants may become more interested or decide to create advance directives or increase organ donation after discussing the information with family members, future research should include longitudinal studies. It may also be beneficial to gather data from those who engage in advance care planning or create advance directives to identify the factors influencing their decisions, with the expectation that prior information will positively affect their planning decisions.

Furthermore, palliative care has been promoted by the National Health Commission, and the Ministry of Public Health supports the development of health systems for end-of-life care, promoting policies and organizing various activities to endorse the knowledge and understanding of the topic to individuals and the public. Continuous information could be provided through video media to enhance comprehension and familiarity, reduce fear, and normalize discussions on these topics, similar to financial planning, health care, work, or retirement planning. This could lead to greater societal acceptance and interest in advance care planning.

CONCLUSION

In summary, advance care planning remains a concept that is not widely recognized by the public. Providing information through video media could more effectively enhance interest in advance care planning and organ donation than pamphlets could. In addition, video is a convenient and engaging media that well captures attention and is resource efficient.

Further studies could investigate the combination of video and pamphlet interventions to increase interest and awareness of creating advance directives. Additionally, future interventions could incorporate a holistic health education program that combines these two methods to provide a more comprehensive approach.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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DATA AVAILABILITY STATEMENT

The research data are presented in this article. For additional information, please contact the corresponding author.

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Original Article

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Chief Complaints, Clinical Characteristics, and Outcomes of Emergency Department Visit among Pediatric Cancer Patients: A Single-Center Experience

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ABSTRACT

OBJECTIVE: The aim of this study was to examine the chief complaints and clinical characteristics, outcomes, and associated factors of pediatric cancer patients who present at the emergency department (ED).

METHODS: A retrospective, single-center study was conducted on children less than 18 years old with active cancer treatment at the Department of Pediatrics, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand from January 2017 to September 2023. The chief complaints, and clinical characteristics of ED encounter were captured. The outcomes of the patients were categorized into those from admitted patients and those from the discharged group, before the potential risk factors were analyzed.

RESULTS: A total of 91 ED encounters were documented among fifty cancer patients, representing 0.2% of total pediatric ED visits. Sixty-three (69.2%) ED visits met the inclusion criteria. The most common cancer was acute lymphoblastic leukemia. The common ED chief complaints were fever, gastrointestinal complaints, and respiratory complaints. Our results show that most pediatric cancer patients presenting at the ED were hospitalized (84.1%). There were no deaths at ED, and no patient died within 48 hours of ED visits. Seventy-seven percent of patients sought care within one day of developing emergency conditions. Fever as a chief complaint ($p = 0.016$), and levels 1 and 2 of emergency severity index (ESI) were the risk factors associated with cancer ED visits resulting in hospitalization (odds ratio = 5.64; 95% confidence intervals 1.09-29.14).

CONCLUSION: ED visits were common among children with cancer. The most frequent chief complaints were fever, gastrointestinal complaints, and respiratory complaints. Approximately 80% of ED visits resulted in hospitalization. Having fever as the chief compliant, especially in patients with high body temperature, and levels 1 and 2 of ESI, were associated with an increased likelihood of admission. This study provides valuable baseline information to enhanced the quality of emergency care for pediatric cancer patients.

KEYWORDS: cancer, chief complaint, emergency, fever, pediatric

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INTRODUCTION

The incidence of childhood cancer has increased over the past decade[1,2]. Despite improvements in cancer treatments, childhood cancer is one of the major causes of death among children and adolescents worldwide[3]. Cancer patients can develop emergency conditions related to diseases, treatment-associated adverse effects, general acute illnesses, or end-of-life care[4-6]. These emergency situations significantly impact use of healthcare and mortality[7-9]. Recently, Christodoulou et al.[10] reported a higher frequency of emergency department (ED) visits and mortality rate among children with cancer than that in the pediatric population without cancer.

A chief complaint represents a patient's concise statement of symptom or reason for seeking medical care[11,12]. Previous studies reported a chief compliant leading ED visit among cancer patients[6,8,13]. The common chief complaints among patients visiting the ED include the following: pain (such as chest pain, back pain, and extremity pain), gastrointestinal symptoms (such as bloating, loss of appetite, diarrhea, nausea, vomiting, and abdominal pain), respiratory complaints (such as dyspnea, shortness of breath, and coughing), neurologic complaints (such as alteration of conscious, dizziness, and seizures), fever, injuries, bleeding, fatigue or malaise, seeking for medication refill, dehydration, abnormal blood test, and hypertension. The management approach and outcomes varied across studies. Focusing on pediatric cancer population, admission rate ranged from 44% to 62.5% in the USA[5,8,10,14]. Prior hospitalization within four weeks, and the chief complaint of fever were the risk factors associated with high admission rate[8]. However, there is much less data on ED visits among pediatric populations in low-income and middle-income countries than in high-income countries[15]. No such data for the pediatric population in Thailand. Therefore, this study aimed to retrospectively explore the chief complaints related to ED visits, outcomes, and associated clinical features among children and adolescent with cancer in Thailand. Findings of this study were envisaged to assist in planning the optimum emergency services and providing better care for pediatric cancer patients at ED.

METHODS

We conducted a retrospective chart review using the electronic hospital information system of ED encounters. We included children and adolescent with cancer aged less than 18 years who received active cancer treatment at the Department of Pediatrics, Faculty of Medicine Vajira Hospital, Bangkok, Thailand from January 1, 2017 to September 30, 2023. Pediatric patients with cancer were identified based on information from clinical records of pediatric cancer care maintained by the Division of Pediatric Hematology and Oncology, Department of Pediatrics, and inpatient encounters that included an International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) code for cancer (140.x-209.x, 235.x-239.x), as described previously[10,16].

The ED at Vajira Hospital is an urban level 1 trauma center that provides services for about 30,000 children who accounted for 53,396 ED visits during the study period. We excluded ED visits of a new diagnosis of cancer or before cancer diagnosis, referral visits, and scheduled visits for appointments related to a treatment plan. In this cohort, the primary outcomes focused on ED complaints, and clinical characteristics of ED visits. The secondary outcomes included the outcomes of ED visits, including mortality and, ED disposition status; admission rate, and factors related to hospitalization.

The study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand. (COA 022/2567)

The cohort included 50 consecutive pediatric patients with cancer who had been treated during study periods. Data was extracted from the electronic medical record database. For eligible patients, we collected demographic data, including age, gender, comorbidity and cancer diagnosis, and number of ED visits. The treatment-related data regarding treatment protocol, and disease status were recorded. For all the identified ED visits, we collected data on ED chief complaints and characteristics, including emergency severity index (ESI) acuity measured at five levels (level 1 = crisis condition, immediate life-saving intervention required, level 2 = emergency condition, level 3 = urgent condition, multiple resources needed to stabilize the patient, level 4 = less urgent condition, and level 5 = non-urgent illness)[17], vital signs, sepsis based on 2020 surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children[18], febrile neutropenia[19], unplanned revisit within 48 hours, and clinical outcomes.

Data analyses were performed using the PASW statistical software version 28 (SPSS, Chicago, IL, USA). Descriptive statistics were expressed as mean, standard deviation (SD), median, interquartile range, frequency and percentages. Statistical comparisons were performed using the independent t-test, Chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the six-year study period, we identified 50 pediatric cancer patients who were involved in 91 episodes of ED visits, which accounted for 0.17% of all pediatric ED visits. Sixty-three (69.2%) ED visits met the inclusion criteria, whereas 22 (24.2%) of the ED visits were new diagnoses for cancer, and 6 (6.6%) of them were referral visits. Patient characteristics are summarized in Table 1. There were almost equal proportions of males and females in the cohort. The most common cancers were acute lymphoblastic leukemia (21%), solid tumor (18%)-including osteosarcoma (n = 3), rhabdomyosarcoma (n = 2), hepatoblastoma (n = 2), Ewing sarcoma (n = 1), and germ cell tumor (n = 1)-lymphoma (12%), and brain tumor (12%), such as medulloblastoma (n = 4), central nervous system (CNS) germ cell tumor (n = 2). The median age was 7.94 years (range, 0.3-13.7 years). Most of the cancer patients had at least one ED visit (80%).

Table 1 Patient characteristics and clinical features of emergency department visits

Characteristics	n = 50
Median of age at baseline, years (range)	7.94 (0.34-13.75)
Male: Female	25: 25
Cancer diagnosis, n (%)	
Acute lymphoblastic leukemia	21 (42)
Solid tumor	9 (18)
Lymphoma	6 (12)
Brain tumor	6 (12)
Acute myeloid leukemia	4 (8)
Chronic myeloid leukemia	2 (4)
Histiocytic disease	2 (4)
Patients with any ED visits, n (%)	40 (80)
Frequency of ED visits per individual, n (%)	
1-2	25 (50)
3-4	12 (24)
≥ 5	3 (6)

Table 1 Patient characteristics and clinical features of emergency department visits (continued)

Characteristics			n = 50
Comorbid, n (%)			
Invasive pulmonary aspergillosis			2 (4)
Epilepsy			1 (2)
Renal tubular acidosis			1 (2)
Deep vein thrombosis			1 (2)
Total number of ED visits by cancer patients			n = 63
Number of chief complaints per visit		1	37 (58.7)
		2	20 (31.7)
		3	3 (4.8)
		4	3 (4.8)
Duration of symptoms before ED visit		≤ 1 day	49 (77.8)
		> 1 day	14 (22.2)
ED chief complaints	Fever		41 (65.1)
	Gastrointestinal complaints		12 (19.0)
	Respiratory		12 (19.0)
	Pain		11 (17.5)
	Bleeding		6 (9.5)
	Fatigue/ malaise		3 (4.7)
	Dehydration/ poor intake		3 (4.7)
	Rash		3 (4.7)
	Injury		2 (3.2)
	Cardiovascular complaints		2 (3.2)
	Neurological complaints		1 (1.6)
	Abnormal lab		1 (1.6)
ESI status	1 (crisis)		2 (3.2)
	2 (emergency)		31 (49.2)
	3 (urgent)		28 (44.4)
	4 (less urgent)		2 (3.2)
Sepsis			9 (14.3)
Disease status	Newly cancer diagnosis on therapy		53 (84.1)
	Relapsed disease on therapy		6 (9.5)
	Palliative		3 (4.8)
	Off therapy for less than 6 months		1 (1.6)
Recent admission in prior 4 weeks			57 (90.5)
Unplanned revisit (within 48 hours)			20 (31.7)
Inpatient			15 (23.8)
Outpatient			5 (7.9)
Diagnosis before time to ED visit		< 6 months	28 (44.4)
		6-12 months	23 (36.5)
		> 12 months	12 (19.0)
Status	Discharged		10 (15.9)
	Admission		53 (84.1)
	Ward		48 (76.2)
	ICU		5 (7.9)

Abbreviations: ED, emergency department; ESI, emergency severity index; ICU, intensive care unit; n, number

The clinical features of the ED visits are summarized in Table 1. Most of the visits occurred within the first six months of cancer diagnosis (44.4%), followed by 6 to 12 months (36.5%), and more than 12 months (19%) after cancer diagnosis. Overall, 58.7% of ED visits had only one chief complaint, whereas 31.7% of ED visits had two chief complaints. More than 75% of the ED cancer visits were by patients who had the presenting symptom or chief complaint for less than one day. Fever was the most common (65.1%) ED chief complaint; followed by gastrointestinal complaints (19%), respiratory complaints (19%), and pain (17.5%). Fever was the most common ED chief complaint of all cancer types except in patients with brain tumors, whose most frequent ED complaint was bleeding (Figure 1). Absolute neutrophil count was evaluated in 97.5% of fever visits (40/41). Only 17 (41.5%) visits had febrile neutropenia, whereas 23 (56.1%) febrile episodes occurred in patients with absolute neutrophil count of more than 1,000 cells/mm^3. The most common triage status was ESI level 2 (49.2%), followed by level 3 (44.4%), level 1 (3.2%), and level 4 (3.2%). Regarding the time of ED visits, over half of the patients (58.7%) visited during the night (from 6:00 PM to 6:00 AM), and the remaining patients came during daytime (from 6:00 AM to 6:00 PM). Twenty ED encounters (31.7%) were unplanned revisits, including visits by patients who had recently been discharged from wards or outpatient departments for less than 48 hours. Approximate 90% of ED visited had a history of admission with the past 4 weeks. The mean body temperature was 38.0°C (SD = 0.14). Severe sepsis was observed in 14.3% of the cancer patients.

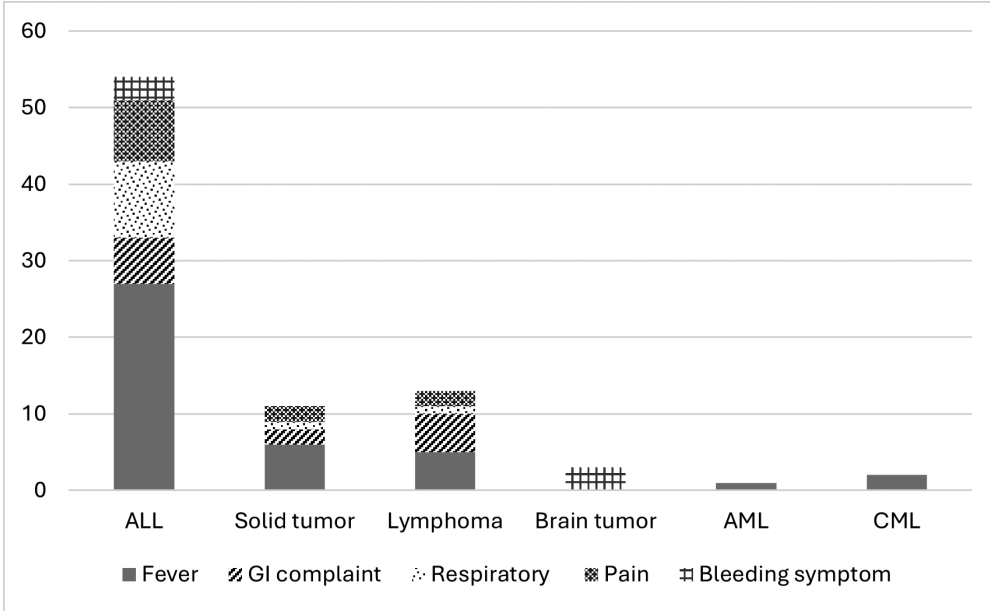

Figure 1 The most common chief complaints at ED by cancer diagnosis
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ED, emergency department; GI, gastrointestinal

Among the patients who visited the ED, 53 (84.1%) patients were admitted to the ward (48; 76.2%) and pediatric intensive care unit (ICU) (5; 7.9%), and 10 (15.9%) patients were discharged without any unplanned ED revisit within 48 hours. There were no deaths at ED, and no patient died within 48 hours of ED visits. A comparison of the clinical characteristics between patients admitted from the ED and outpatients are shown in Table 2.

There were significant demographic differences between the hospitalized group and the discharged group; the former had fever as a presenting chief complaint, and had higher body temperature and level 1 and 2 of ESI. ED visits with fever as the chief complaint had higher odds of admission (odds ratio (OR) = 5.91; 95% confidence intervals (CI) 1.35-25.93). High likelihood of being admitted was associated with levels 1 and 2 of ESI (OR = 5.64; 95%CI 1.09-29.14). The mean temperature was higher in hospitalized patients (38.2°C ± 1.1°C) than in patients who were treated under outpatient settings (37.1°C ± 0.8°C); the differences between the two groups were significant (p = 0.005). Discharged patients were older (7.5 ± 3.9 vs 8.8 ± 3.4 years old, p = 0.33) than those who were admitted. We also observed no significant difference in median duration between the time of diagnosis and the ED visit, as well as prior admission within the previous 4 weeks. The median duration from cancer diagnosis to the ED visit was 7.1 months (range, 0.26-30.6 months) in the admitted group, compared to 10.8 months (range, 0.79-40.9 months) in the discharged group (p = 0.075).

In this cohort, five patients with severe features requiring ICU admission presented to the ED with fever along with others chief complaints. All patients were diagnosed with febrile neutropenia accompanied by septic shock. The clinical data of patients requiring ICU admission are summarized in Table 3. Notably, patient with severe conditions tended to present to the ED with multiple complaints, and 60% of severe case visits requiring ICU admission occurred in the patient who sought ED care more than one day after the onset of an emergency condition (p = 0.074).

Table 2 Clinical characteristics of patients presenting to ED by admission status (Independent t-test and Chi-squared test)

Characteristics	Admitted (n = 53)	Discharged (n = 10)	P-value
Duration of symptoms before ED visit less than 1 day	39 (73.6)	10 (100.0)	0.100
ED chief complaints			
Fever	38 (71.7)	3 (30.0)	0.016
Gastrointestinal complaints	11 (20.8)	1 (10.0)	0.671
Respiratory complaints	10 (18.9)	2 (20.0)	1.000
Pain	8 (15.1)	3 (30.0)	0.360
ESI 1-2	31 (58.5)	2 (20.0)	0.038
Mean age (years old ± SD)	7.5 ± 3.9	8.8 ± 3.4	0.329
Mean body temperature (°C ± SD)	38.2 ± 1.1	37.1 ± 0.8	0.005
Median duration from cancer diagnosis (months, min-max)	7.1 (0.26-30.6)	10.8 (0.79-40.9)	0.075
Sepsis	9 (17.0)	0	0.332
Unplanned re-visit (within 48 hours)	16 (30.2)	4 (40.0)	0.713
Recent admission in prior 4 weeks	49 (92.5)	8 (80.0)	0.240

Abbreviations: °C, celsius; ED, emergency department; ESI, emergency severity index; n, number; SD, standard deviation

Table 3 Clinical courses of ED cases with severe feature requiring intensive care

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (year)	10.8	12.3	1	13.7	8.3
Sex	Male	Male	Female	Female	Female
Diagnosis	ALL	Diffuse large B lymphoma	AML	Ewing sarcoma	ALL
Treatment protocol/ phase of treatment	TPOG ALL1303/ augmented consolidation	TPOG BL-13HR/ maintenance	TPOG AML-1302/ consolidation	TPOG-EWS-13SR	TPOG ALL1303/ maintenance
Comorbid	None	None	None	None	None
Number of chief complaints; details	4; fever, GI, fatigue, pain	4; fever, GI, pain, fainting	1; fever	3; fever, pain, dehydration	2; fever, GI
Duration from cancer diagnosis (days)	91	224	86	137	499
Onset >1 day	Yes	No	Yes	Yes	No
Sepsis	Yes	Yes	Yes	Yes	Yes
Diagnosis	Febrile neutropenia, SARS-CoV-2 infection	Febrile neutropenia	Febrile neutropenia	Febrile neutropenia	Febrile neutropenia, relapsed disease
Reason for ICU	Septic shock	Septic shock, severe dehydration	Septic shock	Septic shock	Septic shock
Outcome	Discharge, recovery	Discharge, recovery	Discharge, recovery	Discharge, recovery	Discharge, palliative care

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BL, B-cell non-Hodgkin lymphoma; ED, emergency department; EWS, Ewing sarcoma; GI, gastrointestinal; HR, high risk; ICU, intensive care unit; SR, standard risk; TPOG, Thai Pediatric Oncology group

DISCUSSION

In this retrospective cohort study, the proportion of pediatric cancer patients visiting ED averaged 0.17% of the total pediatric patient ED visits. These patients may present to the ED for the management of symptomatic cancer, treatment-related complications, acute conditions, or palliative care needs. This study reported that fever was the most common ED chief compliant, followed by gastrointestinal complaints, and respiratory symptoms. Additionally, the vast majority of pediatric cancer patients presenting to the ED were subsequently hospitalized.

Acute leukemia, solid tumors, and lymphoma, being the most prevalent cancers in the study population and accounted for the majority of ED encounters. Our study found that fever was the most common chief complaint among cancer-related ED visits. These findings are similar to previous studies conducted in USA and Ethiopia, which also identified fever as the most common ED chief complaint among pediatric and adolescent patients with cancer[6,8,20]. However, some previous studies report that in adult cancer population, the most common ED chief complaints are pain, gastrointestinal symptoms, respiratory system symptoms, and fever[6,13]. The reasons for this discrepancy might be differences in primary cancer type and treatment between the population groups. Cancer ED visits tended to be from patients within the first six months of cancer diagnosis (44.4%). Most ED visits could be associated with aggressive nature of cancers and treatment-related toxicities of intensive chemotherapy during the initial period of their treatment[21].

In a previous study with a large study population, Christodoulou et al.[10] reported a mortality of 1.2% among pediatric patients with cancer presenting to the ED. Our study demonstrated favorable outcomes, with no deaths

reported in the ED, or within 48 hours of presentation. This observation may be attributed to the tendency of patients in this cohort to seek medical care promptly, typically within less than one day of experiencing an emergency or urgent conditions. However, due to the limited sample size in this study, we could not identify a significant association between delayed ED encounter and severe clinical conditions necessitating intensive care. Notably, a high admission rate was observed. Our findings revealed that 84.1% of pediatric cancer patients presenting to the ED were admitted, which is higher than in previous reports. In the US, hospitalization rates have ranged from 44% to 62.5% depending on the study population[5,8,10,14]. This difference might be attributed to variations in the emergency care system between developing and developed countries, including the lack of specific risk-stratified approach to the management of fever and follow-up systems, particularly for non-neutropenic fever[22], which constituted a significant proportion of fever episodes in this study.

A previous study reported that factors associated with hospitalization following ED presentation included prior hospitalization within 4 weeks, and a chief complaint of fever[8]. In the current study, we also identified significant variability in hospitalization, particularly regarding fever as the chief complaint, especially in patients with high body temperature, and levels 1 and 2 of ESI. However, in contrast to that previous study, prior hospitalization within 4 weeks was not identified as a significant factor for hospitalization. This may be attributed to differences in chemotherapy management and health care system in Thailand, as most patients tended to be admitted for chemotherapy.

This study provides a better understanding of the emergency conditions of pediatric cancer patients in the ED settings. It emphasizes the need for medical providers, pediatricians, and oncologists to be adequately prepared to address common emergency chief complaints and improve the quality of emergency management. Future research should focus on developing risk-stratified treatment guidelines for fever management, and enhancing multidisciplinary care systems, particularly by improving the ability of patients or caregivers to promptly detect emergency conditions, as well as strengthening follow-up systems, and referral services in resource-limited settings to reduce unnecessary hospitalization and mortality.

This study had some limitations. First, the retrospective analysis may lead to lack of document more specific ED chief compliant. Second, data in hospital databases might exclude patients who died at home before documentation of the ED revisit episodes. Third, with a small sample size, single-center patients might not be representing the diversity of patients in other institutions in terms of volume and spectrum of cancer diagnosis. Therefore, further prospective studies incorporating multiple centers should be considered.

CONCLUSION

ED visits were common among children with cancer. The most common chief complaints were fever, gastrointestinal complaints, and respiratory complaints. No deaths were observed in the ED or within 48 hours after the visit. The majority of patient tended to visit ED within one day of developing emergency conditions. Most of the pediatric cancer patients who visited the ED were hospitalized. Having a chief compliant of fever, especially in patients with high body temperature, and levels 1 and 2 of ESI were associated with high chances of admission. This study enhanced the understanding of emergency conditions in pediatric cancer patients in the ED, which may assist healthcare providers in preparing for the management of common emergency complaints, and improve quality of ED care in the future.

CONFLICT OF INTEREST

None

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This study was approved by the ethics committee on human rights related to research to research involving human subjects, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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Original Article

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Musculoskeletal Disorders among Medical School Staff in an Urban Tertiary Care Academic Hospital in Thailand

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ABSTRACT

OBJECTIVE: This study aimed to assess the prevalence of musculoskeletal disorders (MSDs) and explore related factors among medical school workers.

METHODS: A cross-sectional study was conducted among workers at a medical school in Bangkok, Thailand (n = 152). Data were collected via online questionnaires, which gathered general information, sleep quality, working conditions, ergonomics, psychological factors, and the presence of MSDs. Sleep quality was measured using the Thai version of the Pittsburgh Sleep Quality Index. The prevalence of MSDs and psychological factors were measured using the standardized Nordic questionnaire for 12 body parts and the Depression Anxiety and Stress Scale, respectively. The Chi-square test was utilized to evaluate the association between related factors and MSDs. Additionally, binary logistic regression was performed to examine the relationship among sleep quality, ergonomics, psychological factors, and specific body pain.

RESULTS: Out of 152 workers, a significant majority (95.5% in females and 75.0% in males) reported experiencing MSDs in one or more body regions. The highest prevalence of MSDs was observed in the shoulder, with 74.3% reporting discomfort in the past seven days and 69.1% in the past 12 months. Nearly all participants reporting MSDs also experienced depression (97.0%) and anxiety (97.4%). Ergonomics (e.g., twisted postures and repetitive movements) and psychological factors (e.g., depression and anxiety) were significantly associated with the occurrence of MSDs. Repetitive movements (odds ratio (OR) = 2.50; 95% confidence interval (CI) = 1.19-5.25), depression (OR = 3.39; 95% CI = 1.48-7.79), anxiety (OR = 4.22; 95% CI = 1.88-9.50), and stress (OR = 5.40; 95% CI = 1.97-14.81) were significantly linked to shoulder pain.

CONCLUSION: There is a high prevalence of MSDs among medical school workers, with several individual, work-related, ergonomic, burnout-related, and psychological factors being key contributing factors. The findings suggest that both physical and psychological health should be addressed to prevent MSDs in this population.

KEYWORDS: anxiety, depression, musculoskeletal disorders, stress

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INTRODUCTION

Musculoskeletal disorders (MSDs) are among the most significant health-related issues in the workplace, leading to physiological and psychological health problems[1-3]. Long-term MSDs can reduce work activity, increase sick leave absences, result in chronic occupational disability, and diminish the quality of life[1,4]. Over the past decade, there has been a high prevalence of MSDs among working populations worldwide, with contributing factors including personal factors such as gender, age, body mass index (BMI)[5], sleep quality[6], work-related factors, and psychological factors[7-10]. Studies have identified a significant correlation between sleep quality and MSDs, suggesting that sleep quality is a more robust predictor of MSDs than pain is of sleep quality[11,12]. Individuals with musculoskeletal abnormalities exhibit a reduction in sleep quality by up to 86% compared to those without such conditions[13]. A study of medical staff indicated that 57% of them suffered from poor sleep quality, which was associated with high levels of musculoskeletal pain and stress[14].

Work-related factors, particularly ergonomic issues, are key determinants of MSDs. Studies have shown that increased working hours per week raise the odds of low back pain, knee pain, and shoulder pain[7]. Ergonomic factors such as twisted posture, repetitive movements, heavy lifting, improper lifting techniques, prolonged sitting or standing, and awkward postures are also associated with MSDs[1,5,7,15-18]. Additionally, psychological factors play a significant role in MSDs. A study examining both physical and psychosocial factors on body pain symptoms found that workers exposed to high physical demands combined with high psychosocial risk factors had increased odds of experiencing body pain. In contrast, this association was not observed in those exposed to high physical demand and low psychosocial risk factors[1].

Several studies have reported high incidences of MSDs among healthcare professionals, particularly those employed in hospital settings such as nurses[19-21] and physical therapists[8,22,23] with the lower back, neck, and thighs being identified as the most commonly affected regions[7]. In Thailand, healthcare workers report facing to occupational hazards, including ergonomics (e.g., moving heavy materials over 20 kg, standing for prolonged periods) and MSDs affecting various part of the body. Neck pain is most commonly reported by surgical staff (36%), while shoulder pain is highest among nutrition service workers (50%)[24]. A study among dental workers found that musculoskeletal symptoms interfering with daily activities within 12 months were most common in shoulder (47.5%), neck (38.7%) and lower back (31.5%), respectively[25]. Additionally, an investigation into musculoskeletal abnormalities among nursing personnel revealed a 47.8% incidence rate of withdrawals attributed to these disorders[26]. Working in medical schools may further increase the likelihood of suffering from MSDs due to several unique occupational factors. Medical school staff often engage in prolonged standing during lectures and demonstrations, which can strain the lower back and legs, while repetitive movements involved in teaching procedures and laboratory work contribute to repetitive strain injuries. The frequent need to adopt awkward postures during these activities further exacerbates the risk. For those without teaching roles, administrative tasks and prolonged computer use can also lead to MSDs due to poor ergonomic setups and extended periods of sitting. Moreover, the high-stress nature of working in a tertiary hospital, coupled with academic responsibilities, increases the overall physical and mental strain on staff. A study conducted in a tertiary hospital found MSDs among the staff in at least one body region, with the highest prevalence observed in the lower back and knees. This study indicated that psychosocial factors were associated with the incidence of MSDs[7].

Given these occupational challenges, one key objective of this study was to investigate the prevalence of MSDs among medical school staff,

as understanding how widespread these conditions are within this specific occupational group can provide valuable insights into the unique challenges they face. Although most of the existing research on MSDs has concentrated on the physical aspects, the impact of psychological factors on MSDs has not been extensively studied. Previous studies have indicated that both physical and psychosocial factors are related to MSDs. However, the specific links between psychological factors such as depression, anxiety, and stress and the incidence of MSDs remain inadequately explored. Thus, the purpose of this study was to examine the relationship between these psychological factors and the occurrence of MSDs among medical school staff in Thailand. The study also aimed to explore the relationship between various factors (i.e., individual, work-related, ergonomic, burnout-related, and psychological) and MSDs among medical school staff. By focusing on a group that is particularly vulnerable to both physical and mental stressors, this research intended to offer a more comprehensive understanding of MSDs. The results could lead to the creation of more holistic intervention strategies that address both the physical and psychological dimensions of workplace health, ultimately enhancing the quality of life and well-being of medical school staff.

METHODS

A cross-sectional survey was conducted on medical school staff in Bangkok, Thailand over three months from January to March 2023. This study was approved by the Ethics Committee of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand (approval no. COA: 014/2566).

The medical school encompasses a tertiary hospital, the Faculty of Medicine, and office services. Participants in this study were medical school staff working in the hospital, educational, or service sectors. The sample size was estimated using the formula for calculating the sample size for an infinite population proportion[27], $n = z^2_{0.975}p(1-p)/d^2$, where d is the margin of error, which was set to 10% and p is the proportion or prevalence of MSDs. Based on a reported prevalence of MSDs at 57.1%[28], the calculated sample size was 95 participants. To account for uncertainty or incomplete data, we increased the sample size by 10%, resulting in a minimum requirement of 105 participants. The actual sample collected was 152 participants, which exceeds the minimum requirement and is considered sufficient.

The inclusion criteria for this study were (a) being a medical school staff member working for more than three months, (b) being either female or male aged 18 or older, (c) being able to understand Thai, and (d) being willing to participate. On the other hand, the exclusion criteria included (a) individuals who had undergone musculoskeletal surgery on any part of the body, (b) those not residing in Bangkok, and (c) pregnant women.

The questionnaire was divided into three sections. The first section collected data regarding individual factors such as age, sex, BMI, underlying disease, exercise habits, and sleep quality. Sleep quality was assessed using the Thai version of the Pittsburgh Sleep Quality Index, which has a sensitivity of 89.1, specificity of 86.5, and Cronbach's alpha coefficient of 0.836[29]. Additionally, this section addressed work-related factors such as work position, working hours, patient contact, and ergonomics. Ergonomic factors were assessed with a dichotomous scale (yes/no) that inquired about working posture, including twisted posture (frequent twisting or turning of the body), repetitive movements (tasks requiring repetitive use of the hands or arms, maintaining the same posture or movement pattern continuously, or performing rapid repetitive motions with a cycle time of less than 30 seconds), prolonged sitting (working in a seated position for more than half of the total working hours), and prolonged standing (working in a standing position for more than half of the total working hours).

The second section collected information on burnout and psychological factors. Burnout was measured using the Thai version of the Copenhagen Burnout Inventory (T-CBI), originally developed by Kristensen et al.[30] and adapted in Thai by Phuekphan with a reported reliability of 0.96[31]. The T-CBI consists of three distinct subscales: personal, work-related, and client-related burnout[26]. First, personal burnout refers to the physical and mental fatigue individuals experience throughout the day. Second, work-related burnout refers to the degree of exhaustion caused by job demands. Finally, client-related burnout refers to the exhaustion resulting from interactions with clients (e.g., patients). In addition to burnout, psychological factors were assessed using the Depression Anxiety and Stress Scale, which is a validated self-reporting scale that measures levels of depression, anxiety, and stress, with Cronbach's alpha coefficient 0.82, 0.78, 0.69, respectively[32].

The third section addressed the Standardized Nordic Musculoskeletal Questionnaires, which is commonly used to assess MSDs over the previous seven days and 12 months. The questionnaires consist of 12 body parts, namely, neck, shoulder, upper back, lower back, upper arm, elbows, lower arm, wrist, hip, knee, calf, and ankle/feet. The participants were asked about the pain they had experienced in each body part (with the potential answer being either "yes" or "no")[33,34]. Those who answered "yes" were classified into the "pain" group, while those who answered "no" were placed in the "no pain" group for the corresponding body part and specific period.

Data were collected using online questionnaires generated with Google Forms. The link and QR code were shared via organization email and social media using an accidental sampling technique. The first page provided an invitation and details about the research, including information on inclusion and exclusion criteria. Participants were required to review the inclusion criteria and indicate 'yes' or 'no.' If they selected 'No,' the online form automatically closed. If they selected 'yes,' they proceeded to the next section. Informed consent was requested on the subsequent page, and participants who did not provide consent were automatically exited from the form. Participants were required to answer all questions. An incomplete form could not be submitted. Thus, there was no missing data.

Statistical analyses were performed using SPSS version 29.0.0.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables such as age were summarized using the median (interquartile range), while categorical variables such as sex were reported as frequencies and proportions. To test significant differences between groups with and without MSDs, the Chi-square test and Fisher's exact test were used for categorical variables, while Mann-Whitney U-test was used for continuous variables. Univariate binary logistic regression analyses were conducted to calculate the crude odds ratios for each independent variable, identifying associations with pain in specific body regions. Statistical significance was determined using a 95% confidence interval and a p-value threshold of 0.05.

RESULTS

This study aimed to investigate the prevalence of MSDs and the factors associated with MSDs among medical school staff in Bangkok, Thailand. As Table 1 shows, the prevalence of MSDs within seven days significantly varied across several individual, work-related, sleep quality, ergonomic, burnout, and psychological factors. Individual factors included age, sex, and BMI. Staff members more likely to report experiencing MSDs were under 50 years old, female, and not overweight. Ergonomic factors, including having a twisted posture and engaging in repetitive movements, were associated with a higher likelihood of experiencing an MSD. Burnout factors included personal, work-related, client-related, and total burnout. Those reporting medium to high levels of these burnout

factors were more likely to have an MSD. Psychological factors included depression and anxiety, with affected staff members more likely to experience an MSD.

Similarly, as Table 1 shows, the prevalence of MSDs within 12 months also demonstrated significant variation across several individual, ergonomic, burnout, and psychological factors, as well as a work-related factor. In addition to age, sex, and BMI, having an underlying disease was negatively associated with experiencing MSDs. Among burnout factors, only personal burnout and total burnout were significantly associated with experiencing an MSD. Similar to the seven-day prevalence, both depression and anxiety were significantly associated with MSDs within 12 months. Moreover, patient contact, a work-related factor, was also related to MSDs within 12 months.

Table 1 Individual factors, work-related factors, sleep quality, ergonomic factors, burnout, psychological disorders, and MSDs among medical school staff (n = 152)

Factors	MSDs within 7 days		P-value	MSDs within 12 months		P-value
	Pain	No pain		Pain	No pain	
Individual factors						
Age (%)			0.015[b]			0.013[a]
< 50 years	100 (94.3)	6 (5.7)		98 (92.5)	8 (7.5)	
≥ 50 years	37 (80.4)	9 (19.6)		36 (78.3)	10 (21.7)	
(Median (IQR))	38.00 (30.0–52.0)	50.00 (39.0–58.0)	0.027[c]	38.00 (30.0–52.0)	50.00 (40.5–58.0)	0.025[c]
Sex (%)			< 0.001[b]			0.008[b]
Male	30 (75.0)	10 (25.0)		30 (75.0)	10 (25.0)	
Female	107 (95.5)	5 (4.5)		104 (92.9)	8 (7.1)	
BMI (%)			0.009[a]			0.043[a]
Underweight	60 (98.4)	1 (1.6)		57 (93.4)	4 (6.6)	
Normal	55 (87.3)	8 (12.7)		56 (88.9)	7 (11.1)	
Overweight - Extremely obese	22 (78.6)	6 (21.4)		21 (75.0)	7 (25.0)	
Underlying Disease (%)			0.100			0.042[a]
Have	44 (84.6)	8 (15.4)		42 (80.8)	10 (19.2)	
Not have	93 (93.0)	7 (7.0)		92 (92.0)	8 (8.0)	
Exercise (%)			0.149			0.053
Yes	92 (87.6)	13 (12.4)		89 (84.8)	16 (15.2)	
No	45 (95.7)	2 (4.3)		45 (95.7)	2 (4.3)	
Sleep quality			0.027[a]			0.363
Good	51 (83.6)	10 (16.4)		52 (85.2)	9 (14.8)	
Poor	86 (94.5)	5 (5.5)		82 (90.1)	9 (9.9)	
Work-related factors						
Work position (%)			0.658			0.931
Health care worker	63 (91.3)	6 (8.7)		61 (88.4)	8 (11.6)	
Non-health care worker	74 (89.2)	9 (10.8)		73 (12.0)	10 (12.0)	
Working hours (%)			0.741			1.000
≤ 8 hours	108 (90.8)	11 (9.2)		105 (88.2)	14 (11.8)	
> 8 hours	29 (87.9)	4 (12.1)		29 (87.9)	4 (12.1)	
Patient contact (%)			0.210			0.017[a]
Not contact	69 (93.2)	5 (6.8)		70 (94.6)	4 (5.4)	
Contact	68 (87.2)	10 (12.8)		64 (82.1)	14 (17.9)	

Table 1 Individual factors, work-related factors, sleep quality, ergonomic factors, burnout, psychological disorders, and MSDs among medical school staff (n = 152) (continued)

Factors	MSDs within 7 days		P-value	MSDs within 12 months		P-value
	Pain	No pain		Pain	No pain	
Ergonomics						
Twist posture			0.006[a]			0.005[a]
No	59 (83.1)	12 (16.9)		57 (80.3)	14 (19.7)	
Yes	78 (96.3)	3 (3.7)		77 (95.1)	4 (4.9)	
Repetitive movement			0.014[a]			0.006[a]
No	47 (82.5)	10 (17.5)		45 (78.9)	12 (21.1)	
Yes	90 (94.7)	5 (5.3)		89 (93.7)	6 (6.3)	
Burnout						
Personal burnout (%)			0.006[a]			0.014[a]
Low	50 (82.0)	11 (18.0)		49 (80.3)	12 (19.7)	
Medium to high	87 (95.6)	4 (4.4)		85 (93.4)	6 (6.6)	
Work-related burnout (%)			0.044[a]			0.104
Low	63 (85.1)	11 (14.9)		62 (83.8)	12 (16.2)	
Medium to high	74 (94.9)	4 (5.1)		72 (92.3)	6 (7.7)	
Client burnout (%)			0.037[a]			0.059
Low	45 (83.3)	9 (16.7)		44 (81.5)	10 (18.5)	
Medium to high	92 (93.9)	6 (6.1)		90 (91.8)	8 (8.2)	
Total Burnout (%)			0.005[a]			0.012[a]
Low	49 (81.7)	11 (18.3)		48 (80.0)	12 (20.0)	
Medium to high	88 (95.7)	4 (4.3)		86 (93.5)	6 (6.5)	
Psychological disorders						
Depression (%)			0.013[a]			0.015[a]
No	73 (84.9)	13 (15.1)		71 (82.6)	15 (17.4)	
Yes	64 (97.0)	2 (3.0)		63 (95.5)	3 (4.5)	
Anxiety (%)			0.002[a]			0.010[a]
No	62 (82.7)	13 (17.3)		61 (81.3)	14 (18.7)	
Yes	75 (97.4)	2 (2.6)		73 (94.8)	4 (5.2)	
Stress (%)			0.052			0.066
No	84 (86.6)	13 (13.4)		82 (84.5)	15 (15.5)	
Yes	53 (96.4)	2 (3.6)		52 (94.5)	3 (5.5)	

Abbreviations: BMI, body mass index; IQR, interquartile range; MSDs, musculoskeletal disorders; n, number
Percentages are calculated within each row.
[a] Chi-square test, significant level at $p < 0.05$
[b] Fisher's exact test, significant level at $p < 0.05$
[c] Mann–Whitney U-test, significant level at $p < 0.05$

As Figure 1 illustrates, the most frequently experienced MSDs were neck, shoulder, upper back, and lower back pain, both within seven days and within 12 months. Specifically, within seven days, neck pain was reported by 68.4% of staff, shoulder pain by 74.3%, upper back pain by 65.1%, and lower back pain by 66.4%. Within 12 months, neck pain was reported by 65.1%, shoulder pain by 69.1%, upper back pain by 62.5%, and lower back pain by 63.2%. Other notable MSDs included wrist/arm pain (57.9% within seven days and 55.9% within 12 months) and hip pain (55.3% within seven days and 46.1% within 12 months).

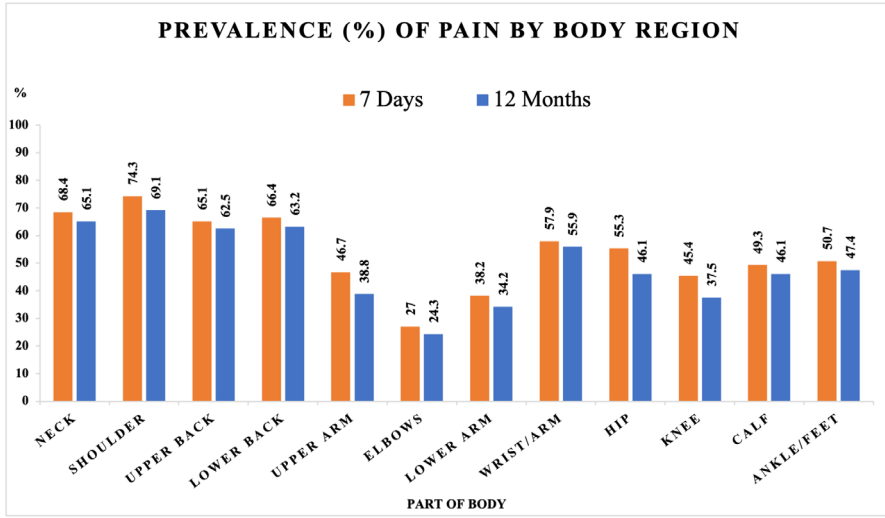

Figure 1 MSDs prevalence both within seven days and within 12 months

In addition to exploring the prevalence, individual, work-related, ergonomic, burnout, and psychological disorder factors that were predictive of MSDs within seven days were examined. The analysis focused on the top four frequently reported MSDs, including neck pain, shoulder pain, upper back pain, and lower back pain, for brevity. These body regions accounted for the highest number of reported cases, making them the most relevant for identifying risk factors and informing targeted interventions. Factors related to MSDs within the past 12 months were not analyzed due to the similarity between the seven-day and 12-month pain reports (i.e., participants who reported pain in the past seven days also reported pain in the past 12 months; see Figure 1). Additionally, the 12-month recall period is more prone to bias. Therefore, we focused on the seven-day results for greater validity.

As Table 2 shows, factors that significantly predicted neck pain included BMI (OR = 2.81, p = 0.030), personal burnout (odds ratio (OR) = 3.43, p < 0.001), work-related burnout (OR = 4.49, p < 0.001), client burnout (OR = 2.47, p = 0.012), depression (OR = 2.43, p = 0.017), anxiety (OR = 5.84, p < 0.001), and stress (OR = 2.90, p = 0.009).

Table 2 Factors associated with neck pain within seven days among medical school staff in urban area Bangkok, Thailand (n = 152)

Factors	Neck pain within 7 days		Crude OR (95%CI)	P-value
	Pain n (%)	No pain n (%)		
BMI				
Overweight - Extremely obese	14 (50.0)	14 (50.0)	1	
Normal	45 (71.4)	18 (28.6)	2.50 (1.00–6.28)	0.051
Underweight	45 (73.8)	16 (26.2)	2.81 (1.10–7.16)	0.030*
Personal burnout				< 0.001*
Low	32 (52.5)	29 (47.5)	1	
Medium to high	72 (79.1)	19 (20.9)	3.43 (1.68–7.01)	
Work-related burnout				< 0.001*
Low	39 (52.7)	35 (47.3)	1	
Medium to high	65 (83.3)	13 (16.7)	4.49 (2.12–9.50)	

Table 2 Factors associated with neck pain within seven days among medical school staff in urban area Bangkok, Thailand (n = 152) (continued)

Factors	Neck pain within 7 days		Crude OR (95%CI)	P-value
	Pain n (%)	No pain n (%)		
Client burnout				0.012*
Low	30 (55.6)	24 (44.4)	1	
Medium to high	74 (75.5)	24 (24.5)	2.47 (1.22–5.00)	
Depression				0.017*
No	52 (60.5)	34 (39.5)	1	
Yes	52 (78.8)	14 (21.2)	2.43 (1.17–5.05)	
Anxiety				< 0.001*
No	38 (50.7)	37 (49.3)	1	
Yes	66 (85.7)	11 (14.3)	5.84 (2.67–12.78)	
Stress				0.009*
No	59 (60.8)	38 (39.2)	1	
Yes	45 (81.8)	10 (18.2)	2.90 (1.31–6.43)	

Abbreviations: BMI, body mass index; CI, confidence interval; n, number; OR, odd ratio
Percentages are calculated within each row.
1 = reference group
* P-value by binary logistic regression, significant level at p < 0.05

As Table 3 shows, age (OR = 0.45, p = 0.038), sex (OR = 0.46, p = 0.048), sleep quality (OR = 2.46, p = 0.018), prolonged sitting (OR = 4.42, p < 0.001), repetitive posture (OR = 2.50, p = 0.016), personal burnout (OR = 3.82, p < 0.001), work-related burnout (OR = 3.71, p = 0.001), client burnout (OR = 3.28, p = 0.002), depression (OR = 3.39, p = 0.004), anxiety (OR = 4.22, p < 0.001), and stress (OR = 5.40, p = 0.001) were significant predictors of shoulder pain.

Table 3 Factors associated with shoulder pain within seven days among medical school staff in an urban area in Bangkok, Thailand (n = 152)

Factors	Shoulder pain within 7 days		Crude OR (95%CI)	P-value
	Pain n (%)	No pain n (%)		
Age				0.038*
< 50 years	84 (79.2)	22 (20.8)	1	
≥ 50 years	29 (63.0)	17 (37.0)	0.45 (0.21–0.96)	
Sex				0.048*
Female	88 (78.6)	24 (21.4)	1	
Male	25 (62.5)	15 (37.5)	0.46 (0.21–0.995)	
Sleep quality				0.018*
Good	39 (63.9)	22 (36.1)	1	
Poor	74 (81.3)	17 (18.7)	2.46 (1.17–5.16)	
Prolonged sitting				< 0.001*
No	14 (48.3)	15 (51.7)	1	
Yes	99 (80.5)	24 (19.5)	4.42 (1.88–10.38)	
Repetitive movement				0.016*
No	36 (63.2)	21 (36.8)	1	
Yes	77 (81.1)	18 (18.9)	2.50 (1.19–5.25)	

Table 3 Factors associated with shoulder pain within seven days among medical school staff in an urban area in Bangkok, Thailand (n = 152) (continued)

Factors	Shoulder pain within 7 days		Crude OR (95%CI)	P-value
	Pain n (%)	No pain n (%)		
Personal burnout				< 0.001*
Low	36 (59.0)	25 (41.0)	1	
Medium to high	77 (84.6)	14 (15.4)	3.82 (1.78–8.21)	
Work-related burnout				0.001*
Low	46 (62.2)	28 (37.8)	1	
Medium to high	67 (85.9)	11 (14.1)	3.71 (1.68–8.19)	
Client burnout				0.002*
Low	32 (59.3)	22 (40.7)	1	
Medium to high	81 (82.7)	17 (17.3)	3.28 (1.54–6.96)	
Depression				0.004*
No	56 (65.1)	30 (34.9)	1	
Yes	57 (86.4)	9 (13.6)	3.39 (1.48–7.79)	
Anxiety				< 0.001*
No	46 (61.3)	29 (38.7)	1	
Yes	67 (87.0)	10 (13.0)	4.22 (1.88–9.50)	
Stress				0.001*
No	63 (64.9)	34 (35.1)	1	
Yes	50 (90.9)	5 (9.1)	5.40 (1.97–14.81)	

Abbreviations: CI, confidence interval; n, number; OR, odd ratio
Percentages are calculated within each row.
1 = reference group
* P-value by binary logistic regression, significant level at p < 0.05

As Table 4 shows, predictors of upper back pain included age (OR = 0.45, p = 0.029), sex (OR = 0.31, p = 0.002), BMI (OR = 3.36, p = 0.013), prolonged standing (OR = 2.56, p = 0.26), prolonged sitting (OR = 4.11, p = 0.001), repetitive posture (OR = 3.96, p < 0.001), personal burnout (OR = 2.86, p = 0.003), work-related burnout (OR = 3.40, p < 0.001), client burnout (OR = 4.08, p < 0.001), depression, anxiety (OR = 4.88, p < 0.001), and stress (OR = 6.19, p < 0.001).

Table 4 Factors associated with upper back pain within seven days among medical school staff in urban area Bangkok, Thailand (n = 152)

Factors	Upper back pain within 7 days		Crude OR (95%CI)	P-value
	Pain n (%)	No pain n (%)		
Age				0.029*
< 50 years	75 (70.8)	31 (29.2)	1	
≥ 50 years	24 (52.2)	22 (47.8)	0.45 (0.22–0.92)	
Sex				0.002*
Female	81 (72.3)	31 (27.7)	1	
Male	18 (45.0)	22 (55.0)	0.31 (0.15–0.66)	
BMI				
Overweight - Extremely obese	14 (50.0)	14 (50.0)	1	
Normal	38 (60.3)	25 (39.7)	1.52 (0.62–3.73)	0.360
Underweight	47 (77.0)	14 (23.0)	3.36 (1.30–8.69)	0.013*

Table 4 Factors associated with upper back pain within seven days among medical school staff in urban area Bangkok, Thailand (n = 152) (continued)

Factors	Upper back pain within 7 days		Crude OR (95%CI)	P-value
	Pain n (%)	No pain n (%)		
Prolonged standing				0.026*
No	65 (59.6)	44 (40.4)	1	
Yes	34 (79.1)	9 (20.9)	2.56 (1.12–5.86)	
Prolonged sitting				0.001*
No	11 (37.9)	18 (62.1)	1	
Yes	88 (71.5)	35 (28.5)	4.11 (1.77–9.59)	
Repetitive movement				< 0.001*
No	26 (45.6)	31 (54.4)	1	
Yes	73 (76.8)	22 (23.2)	3.96 (1.95–8.02)	
Personal burnout				0.003*
Low	31 (50.8)	30 (49.2)	1	
Medium to high	68 (74.7)	23 (25.3)	2.86 (1.44–5.70)	
Work-related burnout				< 0.001*
Low	38 (51.4)	36 (48.6)	1	
Medium to high	61 (78.2)	17 (21.8)	3.40 (1.68–6.88)	
Client burnout				< 0.001*
Low	24 (44.4)	30 (55.6)	1	
Medium to high	75 (76.5)	23 (23.5)	4.08 (2.00 – 8.30)	
Depression				< 0.001*
No	46 (53.5)	40 (46.5)	1	
Yes	53 (80.3)	13 (19.7)	3.55 (1.69–7.43)	
Anxiety				< 0.001*
No	36 (48.0)	39 (52.0)	1	
Yes	63 (81.8)	14 (18.2)	4.88 (2.38–10.17)	
Stress				< 0.001*
No	51 (52.6)	46 (47.4)	1	
Yes	48 (87.3)	7 (12.7)	6.19 (2.55–15.02)	

Abbreviations: BMI, body mass index; CI, confidence interval; n, number; OR, odd ratio
Percentages are calculated within each row.
1 = reference group
* P-value by binary logistic regression, significant level at p < 0.05

Finally, as Table 5 shows, factors significantly predicting lower back pain included sex (OR = 0.44, p = 0.31), BMI (OR = 2.66, p = 0.042), prolonged standing (OR = 2.85, p = 0.017), work-related burnout (OR = 2.09, p = 0.035), depression (OR = 3.23, p = 0.002), and anxiety (OR = 2.58, p = 0.008).

Overall, factors that were consistently related to neck pain, shoulder pain, upper back pain, and lower back pain were work-related burnout, depression, and anxiety. These findings suggest that psychological factors are crucial in predicting the experience of pain in certain parts of the body.

Table 5 Factors associated with lower back pain within seven days among medical school staff in urban area Bangkok, Thailand (n = 152)

Factors	Lower back pain within 7 days		Crude OR (95%CI)	P-value
	Pain n (%)	No pain n (%)		
Sex				0.031*
Female	80 (71.4)	32 (28.6)	1	
Male	21 (52.5)	19 (47.5)	0.44 (0.21–0.93)	
BMI				
Overweight - Extremely obese	15 (53.6)	13 (46.4)	1	
Normal	40 (63.5)	23 (36.5)	1.51 (0.61–3.72)	0.373
Underweight	46 (75.4)	15 (24.6)	2.66 (1.03–6.83)	0.042*
Prolonged standing				0.017*
No	66 (60.6)	43 (39.4)	1	
Yes	35 (81.4)	8 (18.6)	2.85 (1.21–6.73)	
Work-related burnout				0.035*
Low	43 (58.1)	31 (41.9)	1	
Medium to high	58 (74.4)	20 (25.6)	2.09 (1.05–4.16)	
Depression				0.002*
No	48 (55.8)	38 (44.2)	1	
Yes	53 (80.3)	13 (19.7)	3.23 (1.54–6.77)	
Anxiety				0.008*
No	42 (56.0)	33 (44.0)	1	
Yes	59 (76.6)	18 (23.4)	2.58 (1.28–5.17)	

Abbreviations: BMI, body mass index; CI, confidence interval; n, number; OR, odd ratio
Percentages are calculated within each row.
1 = reference group
* P-value by binary logistic regression, significant level at $p < 0.05$

DISCUSSION

MSDs are significant health-related issues in the workplace, particularly among medical school staff. This study aimed to investigate the prevalence of MSDs and the factors contributing to their occurrence among medical school employees. The findings revealed that 90% and 88% of the participants experienced MSDs in at least one body region within the past seven days and 12 months, respectively. These results are consistent with previous studies that report a high prevalence of MSDs within seven days[7] and 12 months[5,35]. This study also found that the most frequently experienced MSDs were neck, shoulder, upper back, and lower back pain, both within seven days and within 12 months. The highest MSDs prevalence within seven days among medical school staff was 74.3% in the shoulder, which was higher than that reported in studies of healthcare professionals (35.2%)[7], nurses (37.8%)[5], and dermatologists (63.1%)[36]. Furthermore, the highest MSDs prevalence within 12 months was 69.1% in the shoulder, which was higher than that reported in studies of physiotherapists (35%)[35], and nurses (37.8%)[5]. However, it was comparable to the rates reported for dermatologists (63.1%)[36], dental personnel in a dental school (72.1%)[4], and occupational therapists (67.2%)[37]. The high prevalence of MSDs in the upper body, particularly in the neck, shoulder, upper back, and lower back, may attributed to both physical and psychological factors, as reported in previous studies[1,2,10]. The demanding nature of jobs held by staff in this study, which include both service duties in an urban tertiary hospital and academic responsibilities for medical students, likely contributes to this prevalence. Medical school staff in this study also reported

awkward postures such as twisted postures, repetitive movements, prolonged sitting, and standing, which are recognized as contributing factors for body pain[5,9]. Additionally, previous studies in this setting have reported high levels of burnout[38] and poor quality of sleep[39].

This study also attempted to investigate the relationships between various factors (i.e., individual, work-related, ergonomic, burnout-related, and psychological) and MSDs among medical school staff in Thailand. Due to potential recall bias associated with reporting MSDs over a 12-month period, the study focused on the presence of MSDs within the past seven days. The results suggested that age and sex were related to certain common MSDs, including shoulder and upper back pain, within the past seven days. This aligns with the findings of previous research, which identified age and sex as determinants of MSDs. Older individuals often have joint and muscle wear and tear, making them more prone to pain[7]. Furthermore, differences in musculoskeletal pain between sexes have been observed, likely due to physiological and hormonal variations, as well as the types of tasks typically performed by each sex[7,9]. Consistent with previous research, women in tertiary hospital experienced more body pain than men[7]. Additionally, sex was found to be related to lower back pain, which is attributed to these physiological differences and task variations. BMI also showed significant relationships with neck, upper back, and lower back pain within seven days. Surprisingly, overweight staff tended to report fewer MSDs compared to underweight staff, which is inconsistent with previous studies[5,21]. One possible explanation is that underweight individuals may experience a higher workload. In performing the same tasks, they may require greater muscle force, potentially leading to increased muscle strain and injury compared to their overweight counterparts.

Poor sleep quality was linked to shoulder pain. This may be because poor sleep quality, which affects the body's ability to repair and recover, can contribute to musculoskeletal pain and is a critical factor in overall health. Studies by Haack and Miettinen provide evidence supporting this link, highlighting the importance of good sleep hygiene and effective sleep management as part of a comprehensive approach to managing musculoskeletal health and preventing the progression of related chronic conditions[40,41]. Moreover, prolonged standing and sitting were related to upper back pain, with prolonged standing also being related to shoulder pain. Prolonged standing can lead to muscle fatigue and strain, particularly in the back and shoulders, as the body must constantly work to maintain an upright position. Similarly, prolonged sitting can contribute to poor posture and muscle imbalances, leading to discomfort and pain in the upper back[5].

Ergonomic factors, including twisted posture and repetitive movement, were associated with the presence of any MSDs within seven days, with repetitive movement also linked to shoulder and upper back pain. These findings are consistent with previous research, which has demonstrated the link between poor ergonomic practices and the development of MSDs[15,17]. It is possible to lower the risk of MSDs by more than 30% by regularly switching between sitting and standing or walking during the workday[42].

Finally, the associations between various forms of burnout, depression, anxiety, stress, and MSDs highlight the significant impact of mental health on physical health. Personal, work-related, and client burnout were linked to neck, shoulder, and upper back pain, while work-related burnout was additionally associated with lower back pain. Further, depression and anxiety were related to the top four MSD areas, while stress was specifically related to neck, shoulder, and upper back pain. One possible explanation is psychological hazards may increase muscle tension and blood flow to muscle[43,44]. Additionally, 80.9% of participants in this study reported working in a seated position for more than half of their working hours, which could contribute to

upper body pain. Reports indicate high stress among medical staff[45-47] and psychological factors have been found to contribute to MSDs[48,49]. A study in a tertiary hospital found a relationship between stress and MSDs, specifically in the lower back, knee, and shoulder[7]. Our findings are consistent with those of previous research that reported an association between depressive symptoms and neck and shoulder pain[50]. Additionally, psychosocial factors have been reported as causally related to neck, shoulder, and lower back pain in review studies[9]. Previous studies also suggest that mental health conditions can amplify the perception of pain and contribute to chronic pain conditions through physiological and psychological mechanisms[51,52].

The findings of this study have several practical implications. Employers and healthcare providers should consider integrated approaches that address both the physical and psychological aspects of MSDs. Ergonomic interventions, mental health support, and targeted strategies for high-risk groups (e.g., older individuals) could mitigate the burden of MSDs. For example, in addition to annual physical health check-ups, their should also provide mental health screening. Additionally, promoting healthy lifestyle choices, such as ensuring quality sleep, could further reduce the risk of MSDs.

However, this study also has several limitations that should be acknowledged. First, the cross-sectional design limits the ability to establish causation and the direction of relationships between variables. For example, although several studies suggest that mental health problems lead to MSDs, findings from this study cannot confirm this direction or the reverse. Second, this study focused only on significant results. Non-significant findings do not necessarily imply a lack of effect but may instead reflect a small effect size that could not be detected with the current sample size. Future research could address these factors with larger sample sizes to provide more robust insights. Third, the findings may not be generalizable to all medical school employees or other occupational groups, as the study was conducted within a specific context and population. Fourth, the use of self-reported data introduces the potential for reporting inaccuracies. Finally, The information obtained from Google form may not be fully representative of all medical staff, as the distribution was limited by the sampling method used. Future studies could address these issues by employing experimental designs, using different samples, and incorporating more objective measures of the variables studied.

CONCLUSION

This study highlights the high prevalence of MSDs among medical school staff, particularly shoulder pain, neck pain, and back pain. Several individual, work-related, ergonomic, burnout-related, and psychological factors are significantly associated with MSDs. The findings underscore the influence of both physical and psychological factors, emphasizing the need for a comprehensive approach to the prevention and management of MSDs in medical school settings, which combine healthcare and academic environments.

CONFLICT OF INTEREST

The authors have declared that that they have no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data sets generated and analyzed during the current study are not publicly available due to information but are available from the corresponding author on reasonable request answering the survey.

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Original Article

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Survival and Related Prognostic Factors for Patients with Superior Vena Cava Syndrome in Palliative Settings

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ABSTRACT

OBJECTIVE: The safety of upfront systemic treatment without radiation is questionable in patients with superior vena cava (SVC) syndrome. Whether steroids or loop diuretics can improve patients' outcomes is unclear. This study aimed to evaluate the prognostic factors affecting overall survival (OS).

METHODS: Data of patients with SVC syndrome caused by neoplasm and treated with palliative intent were retrospectively collected. Cox proportional hazard regression was used to analyze the associations between variables and time until death.

RESULTS: A total of 104 patients were identified. The median follow-up time was 81 days. The mean age was 56.4 years (standard deviation (SD) 16.5 years). Among the patients, 22.1% received systemic therapy as an upfront treatment. Steroids and loop diuretics were administered in 50% and 34.6% of patients, respectively, and 7.7% were intubated. Multivariable analysis revealed intubation as an only significant independent factor for OS (hazard ratio 3.47; 95% confidence interval 1.2–10.05). Intubated and nonintubated patients had 1-year OS rates of 12.5% and 17.6%, respectively, and their median OS values were 6 and 86 days, respectively (p-value 0.02). For patients treated with radiotherapy and systemic treatment, 1-year OS rates were 17.1% and 17.4% (median survival of 86 and 71 days) (p-value 0.8). Symptomatic improvement was reported in 8 and 27 patients after receiving systemic therapy and radiation with mean duration of 9.4 (SD 5.4), and 8.2 (SD 4.7) days.

CONCLUSION: Intubation is a poor prognostic factor. No difference in OS was observed between the patients who received systemic treatment and radiotherapy as upfront therapy. Neither steroids nor loop diuretics showed any benefit in terms of survival.

KEYWORDS: intubation, radiotherapy, superior vena cava syndrome, systemic treatment

INTRODUCTION

Superior vena cava (SVC) syndrome is a group of signs and symptoms following blood flow obstruction in the SVC, leading to elevated venous pressure in the upper body. Approximately 15,000 cases per year are reported in the United States, and its incidence ranges from 1 in 650 to 1 in 3,100 patients[1]. The most common etiology is malignancy. Infection, particularly syphilitic aortic aneurysm

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and tuberculosis, can also cause the syndrome; however, because of the improvements in antibiotics, infection is rarely the origin of this disease nowadays. The use of intravascular devices, such as catheters and pacemakers, is another cause and could result in thrombus obstructing SVC. Other etiologies include aortic aneurysm and fibrosing mediastinitis. For SVC syndrome secondary to cancer, most of the cases resulted from non-small cell lung cancer (NSCLC) (50%), followed by small cell lung cancer (SCLC) (22%), lymphoma (12%), and metastatic diseases (9%), which mostly arise from breast cancer[2]. Meanwhile, 1.7% of NSCLC cases were reported to have SVC syndrome at diagnosis[3]. Lung cancer is the second most and most common type of cancer in Thailand and worldwide, accounting for 12.4% and 11.4%, respectively. Most patients with NSCLC are initially diagnosed at an advanced stage. In 2017, the proportion of patients with stage IV and I cancer at diagnosis was 44.1% and 29%, respectively, according to the United States Cancer Statistics database[4].

As compared to skeletal metastases, visceral metastases are significantly associated with worse overall survival (OS) due to the deterioration of the organ function. Similarly, brain metastases lead to neurological deficit and increase mortality risk in cancer patients. In addition intraluminal tumors were reported to be a poor prognostic factor, compared to extrinsic compression[5]. The management of SVC syndrome involves cancer treatment and supportive care. For patients with locally advanced cancer located in the chest and presenting with SVC syndrome, curative treatment is indicated. Patients with advanced stage disease are typically treated with upfront systemic treatment. However, in palliative settings, the necessity of upfront radiation prior to systemic therapy for patients with SVC syndrome remains controversial. In addition, the benefit of steroids and loop diuretics for these patients is yet to be proven. This study aimed to explore the prognostic factors affecting OS and evaluate the survival of patients with SVC syndrome.

METHODS

Information of patients with SVC syndrome in palliative settings who were treated between January 2012 and August 2022 was reviewed. The inclusion criteria were patients with radiological findings of SVC obstruction and histologically or cytologically confirmed neoplasm and who underwent either systemic therapy (including chemotherapy, targeted therapy, and immunotherapy) or radiotherapy as upfront treatment. Palliative treatment was defined as interventions other than curative therapy[6-8]. A chart review was performed to collect the patients' information. Death certificates were obtained when survival details were not sufficiently reported. Patients were excluded if they had SCLC and hematologic malignancy as a cause of SVC syndrome and their data were incomplete. This study was approved by the institutional review board (COA 111/2565).

After the diagnosis of SVC syndrome, a radiation oncologist and a medical oncologist were consulted to determine the suitable management for the patients. Unless neoplasm was pathologically confirmed as the cause of the disease, the tissue diagnosis proceeded. For patients with life-threatening conditions requiring immediate cancer treatment, either systemic treatment or radiation was administered before a definite diagnosis of the neoplasm in accordance with the attending physicians' discretion.

For radiotherapy, the technique and dose depended on machine availability at the time of treatment, patient's performance status, and preference of the radiation oncologist. Two radiation techniques, 2D and 3D conformal radiation (3DCRT), were adopted. The treatment fields for the 2D technique were typically the anterior–posterior/posterior–anterior fields.

The treatment planning of 3DCRT was based on target volume delineation. For the systemic treatment, the regimen was based on the histopathology and molecular markers of the tumor, patient's performance status, previous systemic treatments, and attending physician's choice.

The primary objective was to assess the OS, which was calculated from the initiation of cancer treatment for SVC syndrome, either systemic therapy or radiation, to death from any cause. Significance level of 0.05 and power of 0.8 were determined for sample size estimation. Given the survival rate difference of 0.148[9], the calculated sample size was 90. Overall response was defined by RECIST 1.1 using images from chest X-ray and computed tomography (CT) scan of the chest approximately 3 months after the last treatment. Symptomatic response was evaluated based on SVC syndrome grade[10]. Recurrence was defined as the time from the last treatment to the recurrence of signs and symptoms[2] and radiological findings of SVC syndrome. Age cutoff of 65 years was adopted because it is commonly used in oncology studies and frequently applied to define the elderly. Patients without any events were censored at their date of the last follow-up. Survival curves were drawn using the Kaplan–Meier method. Differences between survival curves were analyzed by the log-rank test and Cox regression (univariable and multivariable analyses). Other outcomes were analyzed using the Cox proportional hazards model. The effect of prognostic factors on survival was examined using the Cox regression model. Statistical significance was set at p-value ≤ 0.05. Predictive Analytics SoftWare Statistics (SPSS) 28.0 (SPSS Inc., Chicago, IL., USA) was used for the analysis.

RESULTS

A total of 156 patients were assessed for eligibility. The number of excluded patients was 52 (13 for diagnosis of lymphoma, 17 for diagnosis of SCLC, 11 for incomplete data, 9 for receiving curative treatment, and 2 for no cancer treatment given). Therefore, 104 patients matched the eligibility criteria, including 80 with lung cancer, 4 with breast cancer, 3 with cervical cancer, 2 with osteosarcoma, 3 with soft tissue sarcoma, 4 with thymic cancer, 3 with thymoma, 1 with hepatocellular carcinoma, 1 with gastric cancer, 1 with rectal cancer, 1 with nasopharyngeal cancer, and 1 with nonseminoma. The mean age of the patients was 56.4 years (standard deviation (SD) 16.5). Among them, 25% were female, 75% had an Eastern Cooperative Oncology Group score of at least 2, and nearly 60% had a history of smoking. Before or at the diagnosis of SVC syndrome, 24, 68, and 20 patients had visceral, brain, and bone metastases, respectively. SVC syndrome grade 2[8] was specified in almost 80% of the patients. Prior to the diagnosis of SVC syndrome, nonmetastatic diseases were treated with surgery, systemic treatment, and radiotherapy in 8.7%, 11.5%, and 6.7% of the patients, respectively. Previous treatment for metastatic diseases was performed as systemic treatment in 28 patients and radiation in 5 patients. Only one patient underwent an operation for a metastatic lesion. SVC thrombus and thrombus distal to SVC were found in 20 and 26 patients, respectively, and tumor thrombus was depicted in 15 patients. All of the patients had NSCLC as the cause of SVC syndrome. In total, 50%, 34.6%, and 15.4% of the patients were administered with steroids, loop diuretics, and anticoagulants, respectively, and 7.7% were intubated. Twenty-three patients were treated with upfront systemic therapy (22.1%). Only one patient received targeted therapy for lung cancer, while the rest were administered with chemotherapy. Radiation was used as an initial treatment for the syndrome in 81 patients. Table 1 shows the treatment characteristics of the eligible patients.

Table 1 Characteristics of the Patients at Baseline

Characteristics	(n = 104)
Age ≥ 65 years	29 (27.9)
Male	78 (75)
Smoking history	60 (57.7)
ECOG score	
0	6 (5.8)
1	20 (19.2)
2	45 (43.3)
3	25 (24)
4	8 (7.7)
Non-lung cancer	24 (23.1)
Visceral metastases	68 (65.4)
Brain metastases	3 (2.9)
Bone metastases	20 (19.2)
SVC syndrome grade	
0	7 (6.7)
1	8 (7.7)
2	82 (78.8)
3	4 (3.8)
4	3 (2.9)
SVC thrombus	20 (19.2)
Thrombus distal to SVC	26 (25)
Tumor thrombus	15 (14.4)
Previous surgery for non-metastatic disease	9 (8.7)
Previous systemic therapy for non-metastatic disease	12 (11.5)
Previous radiotherapy for non-metastatic disease	7 (6.7)
Previous surgery for metastatic disease	1 (1)
Previous systemic treatment for metastatic disease	28 (26.9)
Previous radiotherapy for metastatic disease	5 (4.8)
Intubation	8 (7.7)
Cancer treatment	
Systemic therapy	23 (22.1)
Radiotherapy	81 (77.9)
8 Gy single fraction	2 (1.9)
17 Gy in 2 fractions weekly	6 (5.8)
20 Gy in 5 fractions daily	10 (9.6)
30 Gy in 10 fractions daily	63 (60.6)
Steroids	52 (50)
Loop diuretics	36 (34.6)
Anticoagulants	16 (15.4)

Abbreviations: ECOG, eastern cooperative oncology group; Gy, Gray; n, number; SVC, superior vena cava
Note: Gray (Gy) is a unit of radiation dose, expressed as absorbed energy per unit mass of tissue.

The median follow-up time was 81 days. Symptomatic improvement was reported in 35 patients (8 for systemic therapy and 27 for radiation). The mean duration from initiation of the treatment to symptomatic improvement was 8.4 (SD 4.8), 9.4 (SD 5.4), and 8.2 (SD 4.7) days for the overall cohort, systemic treatment group, and radiation group, respectively. Eight patients reported their symptoms to be resolved (two for systemic therapy and six for radiation). The mean duration from the initiation of the treatment to the resolution of symptoms was 18.1 (SD 6.9), 21 (SD 0), and 17.2 (SD 7.9) days, respectively. Thirty-four patients underwent imaging 3 months after their last treatment. Among them, nine had

chest X-rays and 25 had CT scans of the chest. In addition, 6 and 28 received systemic treatment and radiotherapy, respectively. RECIST 1.1 revealed that for the radiotherapy group, 48.1%, 44.4%, and 7.4% had partial response (PR), stable disease, and progressive disease (PD), respectively. In the systemic therapy group, three, one, and two patients exhibited PR, stable disease, and PD, respectively. Three patients reported the recurrence of SVC syndrome with a disease-free interval from the last treatment ranging from 6 days to 169 days. Two patients with lung cancer received upfront radiation, and one patient with thymoma received chemotherapy. Cause of death was recorded in 28 patients, and chemotherapy-related death was the cause of death in one patient (infection). No grade 5 radiation toxicity was recorded. Sepsis due to urinary tract infection was the cause of death for one patient. One patient died due to chronic obstructive pulmonary disease, and the rest had tumor-related deaths.

Univariable analysis revealed intubation to be significantly associated with increased mortality (hazard ratio (HR) 2.29; 95% confidence interval (CI) 1.1–4.77). In multivariable analysis, the independent factor was intubation (HR 3.47; 95%CI 1.2–10.05). No treatment during SVC syndrome was significantly associated with survival (HR 1.28; 95%CI 0.72–2.28 for systemic therapy, HR 0.60; 95%CI 0.4–1.19 for steroids, HR 0.8; 95%CI 0.46–1.37 for loop diuretics, and HR 0.73; 95%CI 0.3–1.77 for anticoagulants) (Table 2).

Table 2 Univariable and multivariable analyses

Characteristics	Univariable analysis	P-value	Multivariable analysis	P-value
	HR (95% CI)		HR (95% CI)	
Age ≥ 65 years	1.14 (0.73-1.78)	0.56	0.96 (0.57-1.63)	0.96
Male	1.48 (0.92-2.38)	0.1	1.28 (0.67-2.43)	0.46
Smoking history	1.18 (0.78-1.77)	0.43	1.32 (0.72-2.42)	0.37
ECOG score > 1	1.48 (0.93-2.36)	0.1	1.54 (0.89-2.66)	0.12
Non-lung cancer	0.72 (0.44-1.16)	0.18	0.74 (0.34-1.65)	0.47
CNS metastases	1.74 (0.54-5.55)	0.35	2.65 (0.53-13.26)	0.24
Visceral metastases	1 (0.66-1.54)	0.97	0.93 (0.57-1.52)	0.77
Bone metastases	1.23 (0.73-2.06)	0.44	1.16 (0.62-2.17)	0.64
SVC syndrome grade > 2	1.25 (0.58-2.71)	0.57	1.22 (0.37-3.98)	0.75
SVC thrombus	0.68 (0.39-1.16)	0.16	2.2 (0.93-5.21)	0.07
Thrombus distal to SVC	1.05 (0.65-1.7)	0.83	0.52 (0.23-1.18)	0.12
Tumor thrombus	0.6 (0.33-1.11)	0.1	0.48 (0.21-1.14)	0.1
Previous surgery for non-metastatic disease	0.72 (0.35-1.48)	0.37	1.05 (0.4-2.81)	0.93
Previous systemic therapy for non-metastatic disease	0.72 (0.38-1.36)	0.31	0.42 (0.09-1.93)	0.26
Previous radiotherapy for non-metastatic disease	0.73 (0.34-1.59)	0.43	3.11 (0.58-16.62)	0.19
Previous surgery for metastatic disease	0.58 (0.08-4.15)	0.58	0.41 (0.04-4.14)	0.45
Previous systemic treatment for metastatic disease	1.49 (0.94-2.38)	0.09	1.4 (0.8-2.46)	0.24
Previous radiotherapy for metastatic disease	1.09 (0.44-2.69)	0.86	0.82 (0.25-2.72)	0.74
Intubation	2.29 (1.1-4.77)	0.03	3.47 (1.2-10.05)	0.02
Cancer treatment				
Systemic therapy	1.02 (0.64-1.69)	0.88	1.28 (0.72-2.28)	0.4
Radiotherapy	1		1	
Steroids	1.02 (0.69-1.54)	0.89	0.69 (0.4-1.19)	0.18
Loop diuretics	0.88 (0.58-1.36)	0.58	0.8 (0.46-1.37)	0.41
Anticoagulants	0.89 (0.5-1.58)	0.69	0.73 (0.3-1.77)	0.49

Abbreviations: CI, confidence interval; CNS, central nervous system; ECOG, eastern cooperative oncology group; HR, hazard ratio; SVC, superior vena cava

The 1-year OS for the whole cohort was 17.3%, and the median survival was 80 days (Figure 1). The intubated and nonintubated patients had 1-year OS rates of 12.5% and 17.6%, respectively, and their median survival values were 6 and 86 days, respectively (p-value 0.02) (Figure 2). The 1-year OS rates of patients who were treated with radiotherapy and systemic treatment were 17.1% and 17.4%, with median survival of 86 and 71 days, respectively (p-value 0.8).

DISCUSSION

No significant difference in OS was found between systemic treatment and radiation as an initial therapy for patients suffering from SVC syndrome. Neither steroid nor loop diuretic administration could enhance their survival. For these patients, intubation was the only independent factor. These findings provide additional evidence supporting the use of systemic treatment, especially chemotherapy, as a primary therapy for patients with SVC syndrome. Additionally, overall response, together with symptomatic improvement and resolution between upfront treatments were not significantly different.

The indication for endotracheal tube insertion due to SVC syndrome or their comorbidities is that the patient must be in a critical condition, which could lead to mortality or fatal morbidity. As a consequence, intubation was associated with a poor prognosis. Therefore, strategies to prevent intubation, such as avoiding treatment delay, should be adopted to improve the survival of these patients.

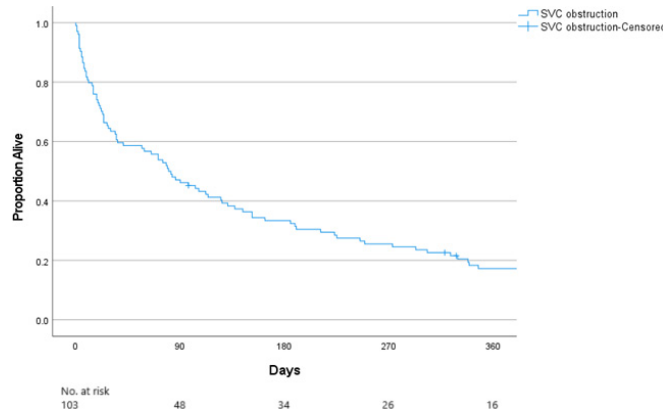

Figure 1 Overall survival among patients with SVC syndrome

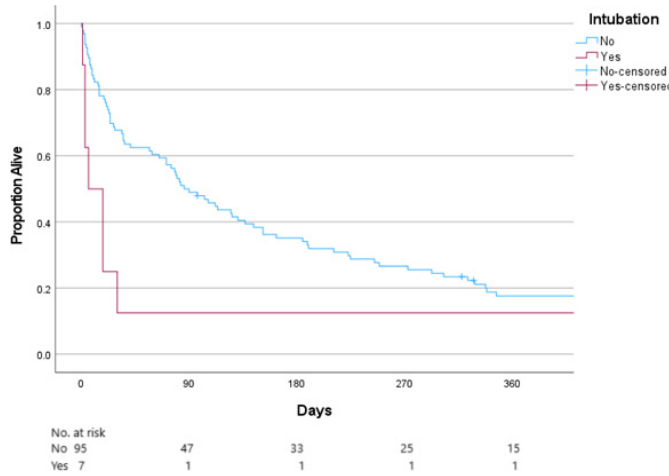

Figure 2 Overall survival among patients treated with and without intubation

Few randomized controlled trials compared upfront chemotherapy versus radiotherapy. First, in 1938, Spiro and colleagues[11] compared chemotherapy with and without radiotherapy in SVC syndrome due to SCLC and demonstrated no difference in terms of OS. Second, in 1969, Levitt et al.[12] randomized 28 patients with SVC syndrome to either nitrogen mustard and subsequent radiation or radiation alone. Most patients in this study had lung cancer; only two had lymphoma and one had malignant thymoma. No advantage of nitrogen mustard prior to radiotherapy was observed[12]. Third, in 1999, Pereira et al.[9] compared neoadjuvant chemotherapy with subsequent radiotherapy to radiotherapy alone in patients with NSCLC and SVC syndrome. Owing to the large number of treatment-related deaths in the chemotherapy arm, the study was terminated before the accrual target was reached. No significant survival benefit was observed in the patients receiving neoadjuvant chemotherapy[9]. Consistent with the present study and the improved safety profile of chemotherapy regimens in the current practice, no survival difference was observed between systemic therapy and radiotherapy. Hence, both could be used interchangeably as an upfront treatment for these patients.

Although the effectiveness of steroids has been widely explored, the limitation in recording the performance status became an apparent methodological issue. In this study, steroid administration showed no benefit in improving the survival of patients with SVC syndrome. Loop diuretics have been used as a supportive treatment for SVC syndrome for decades. Nevertheless, limited evidence supports their benefit. A mechanism of this drug that alleviates the symptoms is believed to be the reduction of venous return to the right atrium by decreasing preload, which relieves the increased venous pressure distal to the obstruction. However, this supportive treatment did not increase patient survival in this study. Therefore, the administration of these medications for symptomatic improvement is not required if cancer treatment can be performed immediately after the diagnosis of SVC syndrome.

A Japanese study found that patients with extrinsic compression (198.6 days) had better survival than those with intraluminal tumors (44.9 days)[5]. This finding was inconsistent with the current results, in which no difference was demonstrated among the patients with and without SVC thrombus (HR 2.2; 95%CI 0.93–5.21) and with thrombus distal to SVC (HR 0.52; 95%CI 0.23–1.18). The reason might be that only 14.4% of the patients in the present study had a tumor thrombus. In addition, most of the patients were at an advanced stage, and mortality from the increased risk of hematogenous spreading due to the thrombus was impossible. Therefore, SVC thrombus and thrombus distal to SVC were not determined as independent factors.

Even though a retrospective study is valuable in certain contexts, a range of drawbacks must be considered when interpreting the results and drawing conclusions and could possibly affect the reliability and validity of the findings. Selection bias, which potentially prevents the included patients to represent the general population, complicates the results and limits their generalizability. In addition, missing data, including medication dosage, variability in data collection, and uncontrolled confounding variables could substantially influence the outcomes. Apart from the study design, the heterogeneity of the primary tumor could affect the results' generalizability.

CONCLUSION

In terms of upfront treatment in palliative settings, no difference in OS was found between patients suffering from SVC syndrome who received systemic treatment and radiotherapy. Loop diuretics and steroids showed no benefit in enhancing patient survival. Intubation was identified as a poor prognostic factor.

CONFLICT OF INTEREST

None

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DATA AVAILABILITY STATEMENT

The data underlying this article were provided by a third party by permission. Data will be shared on request to the corresponding author with permission of a third party.

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Original Article

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Exploring Factors Associated with Intolerance of Helmet Noninvasive Ventilation in High-Risk Postextubation Patients

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ABSTRACT

OBJECTIVE: Studies on the use of helmet noninvasive ventilation (NIV) to prevent postextubation respiratory failure in high-risk patients are limited compared with other types of NIV. Only one randomized controlled trial (RCT) has reported that patients may have high helmet NIV intolerance. This study aimed to determine the prevalence of helmet NIV intolerance among high-risk postextubation patients and identify factors associated with this intolerance.

METHODS: This retrospective cohort study included patients at high risk of postextubation failure between June 2022 and June 2023. This study was based on an RCT that included 114 patients at high risk of postextubation failure. A subgroup analysis was performed on patients who received helmet NIV. The primary outcome was the prevalence of helmet NIV intolerance. The secondary outcome was factors associated with helmet NIV intolerance.

RESULTS: Of the 114 patients, 57 received helmet NIV. Of the 57 patients, 43 (75.4%) exhibited intolerance. A higher prevalence of cancer was observed among patients with helmet NIV intolerance, along with lower initial heart rates and higher partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratios. No significant differences in the etiology of respiratory failure or severity scores, including Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores, were observed between the two groups. Additionally, the 48-h extubation success rate was comparable. Multivariate analysis revealed that a lower heart rate was a significant factor associated with helmet NIV intolerance.

CONCLUSION: During the postextubation period in high-risk patients, helmet NIV use was significantly associated with a high rate of intolerance. However, no differences in extubation success were observed. Lower initial heart rate was a significant factor associated with helmet NIV intolerance.

KEYWORDS: extubation success, helmet noninvasive ventilation, high-risk extubation failure, noninvasive ventilation intolerance

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INTRODUCTION

Noninvasive ventilation (NIV) plays a crucial role in preventing postextubation respiratory failure[1-4]. NIV is superior to conventional oxygen therapy in reducing the reintubation rate, particularly in patients at high risk of extubation failure[5-7]. Age > 65 years, preexisting cardiac or pulmonary disease, acute physiology and chronic health evaluation II (APACHE II) score > 12, body mass index (BMI) > 30 kg/m^2, difficult or prolonged weaning for >7 days, and Charlson comorbidity index > 2 on the day of extubation are risk factors associated with a high risk of extubation failure[5,8-10]. NIV mitigates the risk of respiratory failure by optimizing gas exchange, reducing the work of breathing, and enhancing alveolar recruitment[2].

The face mask is the most common NIV interface used to prevent postextubation respiratory failure. However, face mask NIV has certain limitations, including improper mask fit, which leads to air leakage and ineffective pressure delivery, thereby reducing its efficacy. The helmet is an alternative NIV interface that has gained prominence during the COVID-19 pandemic. Helmet NIV has proven effective in reducing the intubation rate in patients with hypoxemic respiratory failure[11]. Additionally, helmet NIV has been reported to be associated with lower in-hospital mortality and reintubation rates than face mask NIV[12-14].

Despite these advantages, studies on helmet NIV use among high-risk postextubation patients are limited. Only one randomized controlled trial (RCT) has compared helmet with face mask NIV in patients at high risk of extubation failure. The finding revealed no significant difference in extubation success[15]. Additionally, this trial reported a high rate of helmet NIV intolerance, a finding that is inconsistent with previous studies showing the efficacy of helmet NIV[16-19]. This discrepancy highlights the need for further investigation.

Therefore, this study aimed to assess the prevalence of helmet NIV intolerance in high-risk postextubation patients based on data from an RCT and investigate factors associated with this intolerance.

METHODS

This was a retrospective cohort study including patients at high risk of extubation failure who received helmet NIV at King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, between June 2022 and June 2023.

Written informed consent was obtained from all patients or their relatives before inclusion. A retrospective analysis was then conducted based on the initial results from an RCT comprising 114 patients entitled "Comparison of extubation success between prophylactic helmet NIV and facemask NIV in high-risk postextubation patients: a randomized controlled trial". This trial was approved by the Institutional Review Board of the Faculty of Medicine Vajira Hospital (IRB number 186/66E or COA number 197/2566) (TCTR20240731006).

A subgroup analysis was performed on patients at high risk of extubation failure who received helmet NIV. The inclusion criteria were age > 65 years, chronic cardiac or lung disease, APACHE II score > 12, BMI > 30 kg/m^2, difficult or prolonged weaning for > 7 days, and Charlson comorbidity index > 2 on the day of extubation. Preexisting cardiac disease was defined as left ventricular dysfunction (left ventricular ejection fraction < 45% from any cause), history of cardiogenic pulmonary edema, documented ischemic heart disease, or permanent atrial fibrillation. Preexisting chronic pulmonary diseases included chronic obstructive pulmonary disease, obesity hypoventilation syndrome, and restrictive lung disease from any cause[5,8-10]. The exclusion criteria were long-term NIV use, chronic neuromuscular disease, traumatic brain injury requiring intubation, accidental or self-extubation, do-not-resuscitate status after extubation, and contraindications to NIV.

During the study, either a helmet or face mask interface was used with a critical care ventilator. The initial ventilator settings were standardized, with a positive end-expiratory pressure (PEEP) set at 5 centimeter of water (cmH_2O), which was gradually increased by 2–3 cmH_2O to achieve oxygen saturation > 90% with a fraction of inspired oxygen (FiO_2) < 0.6. Pressure support was applied above PEEP level of at least 4 cmH_2O, which was gradually increased by 2–3 cmH_2O to maintain a respiratory rate below 30 breaths/min. Both interfaces were used in each group for 24 h after extubation. Apart from interface differences, both groups received identical standard treatment, nursing care, and management according to the protocol. A 4-h break, with a maximum of 60 min per session, was provided to the helmet NIV and facemask NIV. During the break, an oxygen cannula with a flow rate of 1–5 L/min was used to maintain oxygen saturation above 90%. The total duration of NIV use was at least 18 h. After NIV, an oxygen cannula delivering 1–5 L/min was used to maintain oxygen saturation above 90%.

The primary outcome was the prevalence of helmet NIV intolerance, which was defined as patient discomfort after adapting to a standardized ventilator setting without signs or symptoms of postextubation respiratory failure. For patients who experienced NIV intolerance, a high-flow nasal cannula set to a flow rate of 50 L/min with FiO_2 adjusted to maintain an oxygen saturation of at least 92% was used. The secondary outcome was factors associated with helmet NIV intolerance.

Demographic data and the prevalence of helmet NIV intolerance were analyzed using descriptive statistics, including percentages, means, and standard deviations. The Chi-square test, Fisher's exact test, Independent t-test as well as Mann-Whitney U test were used for statistical analyses. Medians and interquartile ranges were used for nonnormally distributed data. Factors associated with helmet NIV intolerance were assessed using combined and multivariate regression analyses. In the univariate analysis, crude odds ratios and 95% confidence intervals were used to evaluate the strength of the association. Factors with a p-value < 0.20 were included in the multiple logistic regression model. A p-value < 0.05 was considered statistically significant. Adjusted odds ratios with 95% confidence intervals were calculated to determine the strength of the association. All statistical analyses were performed using Stata 16.

RESULTS

A total of 114 patients were included in this study. Among them, 57 received helmet NIV immediately after extubation (Figure 1). The prevalence of helmet NIV intolerance during the postextubation period was 75.4% (Figure 2). Table 1 shows the baseline characteristics of the helmet NIV group. General baseline characteristics, including age, gender, BMI, and underlying diseases, were comparable between the tolerance and intolerance groups. The prevalence of cancer was significantly higher in the intolerance group. No differences in the severity of the current disease, preexisting comorbidities, initial vital signs, gas exchange, weaning parameters, weaning time, volume status, etiologies of respiratory failure, duration of mechanical ventilation, NIV settings, and extubation success were observed between the two groups. However, the intolerance group exhibited a lower heart rate, higher partial pressure of oxygen in arterial blood (PaO_2)/FiO_2 ratio, and shorter NIV duration. No differences in the reintubation rate within 7 days, etiologies of reintubation, adverse events during NIV, or hemodynamic and gas exchange parameters at 30 min, 2 h, 24 h, and 48 h were observed between the two groups. However, the helmet NIV intolerance group exhibited a lower heart rate 30 min after extubation (Table 2).

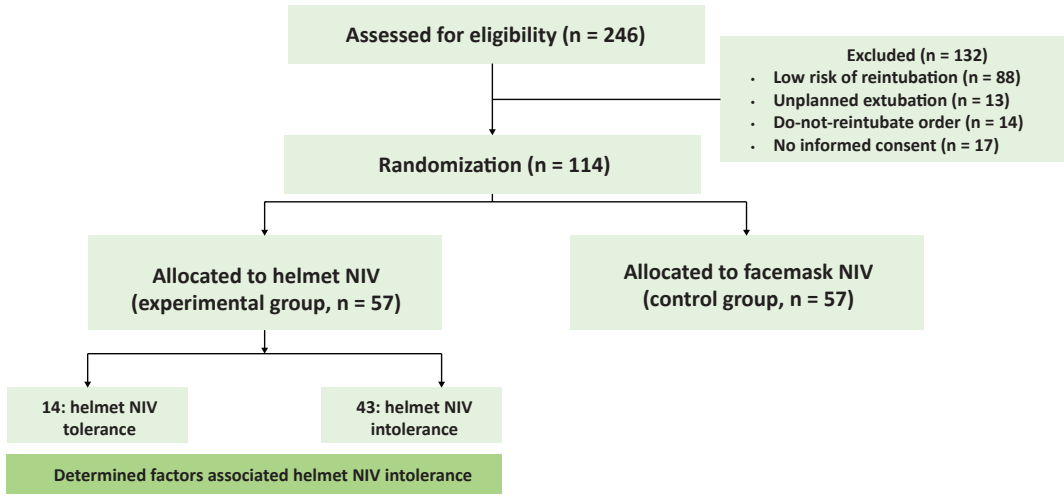

Figure 1 Flowchart of participants in the study

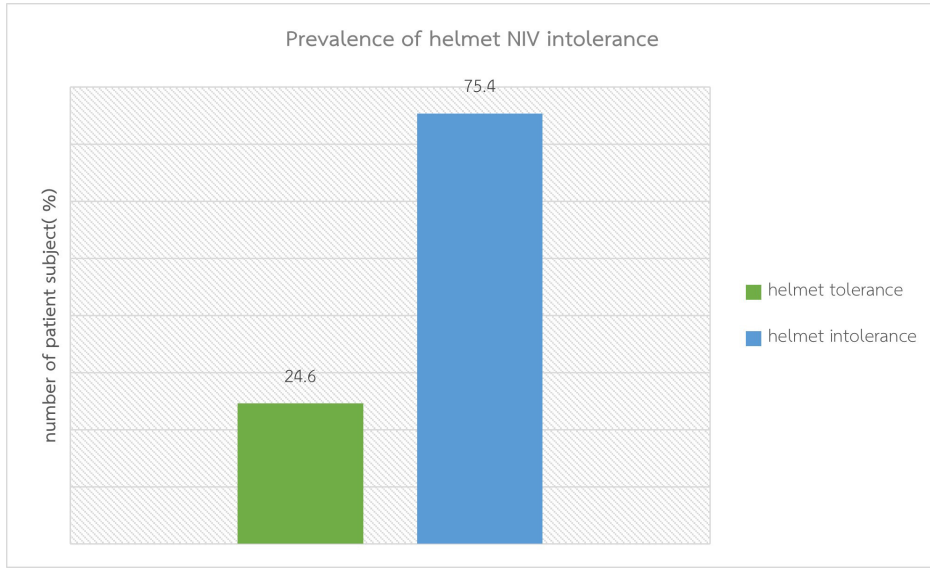

Figure 2 Prevalence of helmet NIV intolerance

Table 1 Patient's baseline characteristic

Baseline characteristics	Helmet NIV tolerance (n = 14)	Helmet NIV intolerance (n = 43)	P-value
Gender Male, n (%)	5 (35.71)	21 (48.84)	0.39
Age (years), mean ± SD	56 ± 18.32	65.93 ± 15.74	0.06
BMI (kg/m^2), mean ± SD	23.88 ± 5.93	24.4 ± 5.58	0.77
Underlying diseases, n (%)			
Hypertension	7 (50.00)	32 (74.42)	0.11
Diabetes mellitus	9 (64.29)	26 (60.47)	0.80
Congestive heart failure	5 (35.71)	15 (34.88)	0.99
Renal impairment	11 (78.57)	22 (51.16)	0.07
Conservative treatment	3 (21.43)	14 (32.56)	0.51
Renal replacement therapy	8 (57.14)	9 (20.93)	0.01

Table 1 Patient's baseline characteristic (continued)

Baseline characteristics	Helmet NIV tolerance (n = 14)	Helmet NIV intolerance (n = 43)	P-value
Cirrhosis	0 (0)	8 (18.60)	0.18
Airway diseases			
COPD	2 (14.29)	5 (11.63)	0.99
Asthma	0 (0)	1 (2.33)	0.99
Bronchiectasis	0 (0)	2 (4.65)	0.99
Tracheobronchomalacia	0 (0)	1 (2.33)	0.99
Cancer	0 (0)	13 (30.23)	0.03*
Disease status of cancer			
Former	0 (0)	4 (9.30)	0.57
Current	0 (0)	9 (20.93)	0.10
Type of malignancy			
Solid organ malignancy			
CNS tumor	0 (0)	1 (2.33)	0.99
Lung cancer	0 (0)	2 (4.65)	0.99
Gastrointestinal malignancy	0 (0)	2 (4.76)	0.99
Gynecologic malignancy	0 (0)	2 (4.65)	0.99
Breast cancer	0 (0)	1 (2.33)	0.99
Hematologic malignancy	0 (0)	5 (11.63)	0.32
Connective tissue disease	1 (7.14)	1 (2.33)	0.43
The severity of the current disease and pre-existing comorbidities			
Charlson Comorbidity Index, median [Q1, Q3]	4.5 (3,7)	5 (3,8)	0.64
APACHE II, mean ± SD	14.21 ± 3.38	14.07 ± 2.76	0.87
SOFA score, median [Q1, Q3]	3 (2,6)	3 (2,4)	0.69
Vital signs			
RR (rpm), mean ± SD	18.07 ± 3.32	19.16 ± 2.96	0.25
MAP (mmHg), mean ± SD	90.07 ± 12.49	84.67 ± 11.34	0.14
HR (bpm), mean ± SD	95.64 ± 16.62	83.47 ± 12.29	0.005*
Gas exchange			
PaO_2/FiO_2, mean ± SD	339.33 ± 43.56	383.79 ± 84.26	0.014*
SaO_2/FiO_2, mean ± SD	357.32 ± 60.95	350.11 ± 68.25	0.73
pCO_2 (mmHg), mean ± SD	32.37 ± 4.96	32.66 ± 6.94	0.89
pH, mean ± SD	7.44 ± 0.05	7.45 ± 0.04	0.67
Weaning parameters			
Work of breathing score, median [Q1, Q3]	1 (1,2)	1 (1,2)	0.29
RSBI, mean ± SD	83.61 ± 10.41	79.07 ± 13.1	0.24
CPF (LPM), mean ± SD	190.71 ± 27.02	190.93 ± 29.79	0.98
NIF (cmH_2O), mean ± SD	-23.61 ± 4.33	-23.28 ± 3.38	0.77
Weaning time (minutes), mean ± SD	43.93 ± 10.14	48.09 ± 14	0.31
Volume status			
Net fluid (mL), median [Q1, Q3]	305 (-3681,1392)	476 (-566,1245)	0.34
Causes of respiratory failure, n (%)			
Pulmonary causes	10 (71.43)	30 (69.77)	0.99
Pneumonia	5 (35.71)	15 (34.88)	0.99
Aspiration	0 (0)	1 (2.33)	0.99

Table 1 Patient's baseline characteristic (continued)

Baseline characteristics	Helmet NIV tolerance (n = 14)	Helmet NIV intolerance (n = 43)	P-value
ARDS	3 (21.43)	2 (4.65)	0.09
Bronchospasm	1 (7.14)	6 (13.95)	0.67
DAH	0 (0)	1 (2.33)	0.99
Pulmonary edema	6 (42.86)	13 (30.23)	0.52
Extra-pulmonary causes	8 (57.14)	20 (46.51)	0.49
Sepsis	6 (42.86)	17 (39.53)	0.83
Metabolic acidosis from other causes	5 (35.71)	7 (16.28)	0.14
Comatose status	1 (7.14)	6 (13.95)	0.67
Hemorrhagic shock	0 (0)	5 (11.63)	0.32
Duration of mechanical ventilation before extubation (days), median [Q1, Q3]	5 (3,7)	5 (3,7)	0.74
NIV settings			
PEEP (cmH_2O), mean ± SD	6.43 ± 1.28	6.05 ± 1.46	0.39
PS (cmH_2O), mean ± SD	13 ± 1.75	12.05 ± 2.33	0.17
VTi (mL), mean ± SD	1184.29 ± 182.58	1147.3 ± 170.27	0.49
VTe (mL), mean ± SD	1060.14 ± 169.89	1033.74 ± 161.44	0.60
FiO_2, mean ± SD	0.29 ± 0.05	0.29 ± 0.05	0.74
% Leakage, median [Q1, Q3]	10.25 (8,12)	10 (8,12)	0.58
NIV duration (hours), median [Q1, Q3]	24 (24,24)	4 (2,9)	< 0.001*
Extubation success	14 (100)	35 (81.4)	0.18

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index; bpm, beats per minute; cmH_2O, centimeter of water; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPF, cough peak flow; DAH, diffuse alveolar hemorrhage; FiO_2, fraction of inspired oxygen; HR, heart rate; kg/m^2, kilogram per square meter; LPM, litres per minute; MAP, mean arterial pressure; mL, milliliter; mmHg, millimeters of mercury; n, number of patients; NIF, negative inspiratory force; NIV, non-invasive ventilation; PaO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; pH, positive potential of the hydrogen ions; PS, pressure support; Q1, 25% quartile; Q3, 75% quartile; rpm, respirations per minute; RR, respiratory rate; RSBI, rapid shallow breathing index; SaO_2, saturation of oxygen in arterial blood; SD, standard deviation; SOFA, sequential organ failure assessment; VTe, expired tidal volume; VTi, inspired tidal volume
*, significant

Table 2 Patient's baseline characteristics

Baseline characteristics	Helmet NIV tolerance (n = 14)	Helmet NIV intolerance (n = 43)	P-value
Reintubation rate within 7 days, n (%)	1 (7.14)	10 (23.26)	0.26
Time to reintubation (days), median [Q1, Q3]	0 (0,3.5)	0 (0,6)	0.25
Comfort score#, mean ± SD	5.5 ± 2.28	6.79 ± 2.18	0.06
Adverse events			
Pressure sore score, mean ± SD	0 (0,1)	0 (0,2)	0.92
Hot air, n (%)	0 (0)	8 (18.6)	0.18
Noise, n (%)	8 (57.14)	32 (74.42)	0.31
Asynchrony, n (%)	0 (0)	3 (6.98)	0.57
Others, n (%)	1 (7.14)	1 (2.33)	0.43
Parameter during extubation			
30 minutes after extubation			
RR (rpm), mean ± SD	19.21 ± 2.81	20.84 ± 1.91	0.06
MAP (mmHg), mean ± SD	88.57 ± 11.44	85.35 ± 11.57	0.37
HR (bpm), mean ± SD	94.29 ± 15.18	85.65 ± 12.49	0.038*
SaO_2/FiO_2, mean ± SD	354.32 ± 62.18	354.86 ± 63.26	0.98

Table 2 Patient's baseline characteristics (continued)

Baseline characteristics	Helmet NIV tolerance (n = 14)	Helmet NIV intolerance (n = 43)	P-value
% Leakage, median [Q1, Q3]	11 (8,15)	10 (5,15)	0.19
WOB score, median [Q1, Q3]	1 (1,2)	2 (1,2)	0.15
2 hours after extubation			
RR (rpm), mean ± SD	19.86 ± 2.21	20.72 ± 1.87	0.16
MAP (mmHg), mean ± SD	90 ± 11.64	85.81 ± 10.7	0.22
HR (bpm), mean ± SD	93.21 ± 13.73	85.67 ± 12.78	0.07
SaO_2/FiO_2, mean ± SD	364.21 ± 53.08	364.58 ± 65.05	0.98
PaO_2/FiO_2, mean ± SD	395.01 ± 88.71	406.78 ± 82.78	0.65
pCO_2 (mmHg), mean ± SD	33.44 ± 6.24	32.6 ± 6.51	0.67
pH, mean ± SD	7.45 ± 0.04	7.45 ± 0.03	0.87
% Leakage, median [Q1, Q3]	8 (5,12)	10 (5,15)	0.48
WOB score, median [Q1, Q3]	1 (1,2)	1 (1,2)	0.48
24 hours after extubation			
RR (rpm), mean ± SD	18.64 ± 2.34	19.91 ± 2.04	0.06
MAP (mmHg), mean ± SD	88.14 ± 11.71	84.14 ± 10.02	0.22
HR (bpm), mean ± SD	88.86 ± 12	85.14 ± 11.9	0.32
SaO_2/FiO_2, mean ± SD	365.21 ± 54.57	365.91 ± 64.87	0.97
PaO_2/FiO_2, mean ± SD	416.8 ± 100.58	405.17 ± 84.95	0.67
pCO_2 (mmHg), mean ± SD	31.71 ± 4.85	33.28 ± 6.07	0.25
pH, mean ± SD	7.46 ± 0.04	7.44 ± 0.03	0.38
% Leakage, median [Q1, Q3]	8 (5,12)	10 (5,15)	0.48
WOB score, median [Q1, Q3]	1 (1,2)	1 (1,2)	0.43
48 hours after extubation			
RR (rpm), mean ± SD	18.79 ± 1.37	19.44 ± 1.88	0.23
MAP (mmHg), mean ± SD	87.36 ± 10.58	83.81 ± 9.31	0.24
HR (bpm), mean ± SD	87.86 ± 12.49	84.16 ± 11.75	0.32
SaO_2/FiO_2, mean ± SD	362.69 ± 53.27	368.79 ± 61.38	0.74
PaO_2/FiO_2, mean ± SD	383.55 ± 67.03	380.11 ± 75.03	0.88
pCO_2 (mmHg), mean ± SD	31.64 ± 4.25	33.74 ± 5.95	0.23
pH, mean ± SD	7.45 ± 0.03	7.45 ± 0.03	0.96
WOB score, median [Q1, Q3]	1 (1,2)	1 (1,2)	0.31
Reasons of reintubation within 7 days, n (%)			
Pulmonary cause	1 (7.14)	7 (16.28)	0.66
Pneumonia	1 (7.14)	3 (6.98)	0.99
Aspiration	0 (0)	2 (4.65)	0.99
Secretion obstruction	1 (7.14)	3 (6.98)	0.99
Pulmonary edema	0 (0)	2 (4.65)	0.99
Extra-pulmonary cause	0 (0)	3 (6.98)	0.57
Sepsis	0 (0)	3 (6.98)	0.57
Metabolic acidosis from other causes	0 (0)	1 (2.33)	0.99

Abbreviations: bpm, beats per minute; cmH_2O, centimeter of water; FiO_2, fraction of inspired oxygen; HR, heart rate; MAP, mean arterial pressure; mmHg, millimeters of mercury; n, number of patients; NIV, non-invasive ventilation; PaO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; pH, positive potential of the hydrogen ions; Q1, 25% quartile; Q3, 75% quartile; rpm, respirations per minute; RR, respiratory rate; SaO_2, saturation of oxygen in arterial blood; SD, standard deviation; WOB score, work of breathing score
#, the higher score, the more discomfort; *, significant

Table 3 shows factors associated with helmet NIV intolerance using univariate and multivariate regression analyses. In the univariate analysis, age, renal impairment, heart rate, PaO_2/FiO_2 ratio, and comfort score had a p-value < 0.2. After multicollinearity was checked, factors with a p-value < 0.2 were included in the multivariate analysis. The analysis revealed that heart rate was significantly associated with helmet NIV intolerance (p < 0.05).

DISCUSSION

This study demonstrated that the use of helmet NIV during the postextubation period in patients at high risk of postextubation respiratory failure was associated with a higher rate of NIV intolerance. However, no significant difference in extubation success was observed. Even after adjusting for well-protocolized pressure support and PEEP settings in the NIV mode, patients in the intolerance group experienced discomfort, which may be due to the device itself and the median duration of use of 4 h.

We hypothesized that helmet NIV might offer better tolerability due to reduced air leakage and more effective ventilation, which is consistent with many guidelines that recommend helmet NIV over face mask NIV when patients experience intolerance to face mask NIV[18,20]. This study showed a higher rate of helmet NIV intolerance. These findings are inconsistent with those of other studies[16,17]. These discrepancies may be due to differences in study populations, as this study focused on the postextubation period. Conversely, other studies have been conducted on patients with hypoxemic respiratory failure to prevent intubation[17,19].

Helmet NIV intolerance was more prevalent among patients with malignancy, those with a lower initial heart rate before helmet NIV use, and those with higher baseline PaO_2/FiO_2 ratios. Therefore, caution should be exercised when using helmet NIV after extubation for patients with malignancy. However, scientific data supporting the association between lower initial heart rate and high PaO_2/FiO_2 ratios and intolerance are lacking. Although a statistical difference was observed, no clinical difference was observed due to the lack of differences between the etiologies of respiratory failure and gas exchange parameters during the device use. This study focused on the postextubation period,

Table 3 Factors associated with helmet NIV intolerance using univariate and multivariate logistic regression analyses

Factors	Univariate analysis		Multivariate analysis	
	Crude Odds ratio (95% CI)	P-value	Adjusted Odds ratio (95% CI)	P-value
Gender: Male	1.72 (0.49 - 5.97)	0.39	1.35 (0.20 - 9.28)	0.76
Age (years)	1.04 (1.00 - 1.08)	0.06	1.06 (0.98 - 1.14)	0.13
BMI (kg/m^2)	1.02 (0.91 - 1.14)	0.76	1.01 (0.86 - 1.20)	0.88
Renal impairment	0.29 (0.07 - 1.17)	0.08	0.05 (0 - 1.14)	0.06
Charlson comorbidity index	1.07 (0.88 - 1.30)	0.51	0.91 (0.61 - 1.36)	0.63
APACHE II	0.98 (0.79 - 1.21)	0.87	1.33 (0.77 - 2.30)	0.31
SOFA score	0.96 (0.73 - 1.26)	0.76	1.18 (0.58 - 2.37)	0.64
HR (bpm)	0.93 (0.89 - 0.98)	0.01	0.93 (0.87 - 0.99)	0.04*
PaO_2/FiO_2	1.01 (1.00 - 1.02)	0.07	1.02 (1.00 - 1.03)	0.07
Pulmonary causes of respiratory failure	0.92 (0.24 - 3.49)	0.90	1.03 (0.04 - 24.47)	0.98
Extra-pulmonary causes of respiratory failure	0.65 (0.19 - 2.20)	0.49	0.66 (0.05 - 9.56)	0.76
Comfort score	1.31 (0.98 - 1.75)	0.06	1.41 (0.92 - 2.17)	0.11

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; BMI, body mass index; bpm, beats per minute; CI, confidence interval; FiO_2, fraction of inspired oxygen; HR, heart rate; kg/m^2, kilogram per square meter; PaO_2, partial pressure of oxygen; SOFA, sequential organ failure assessment
*, significant

which may explain the higher PaO_2/FiO_2 ratios in this study than in other studies. Even in a study that focused on the treatment of postoperative hypoxemia, the PaO_2/FiO_2 ratios were lower than those in our study[16].

Multivariate analysis revealed a positive association between lower heart rate and helmet NIV intolerance. To the best of our knowledge, this is the first study to report on hemodynamic and gas exchange parameters during helmet NIV use. Although this correlation was statistically significant, it may not be clinically significant because the observed lower heart rate was not low enough to cause hemodynamic instability. However, caution should be exercised when using helmet NIV in patients with a low initial heart rate. A low heart rate might be due to medications administered, which are not included in the data collection. Further studies are needed to explore and validate this correlation.

This study has some limitations. This was a retrospective cohort study conducted at a single center, raising the possibility that it might be underpowered, limiting the generalizability of the findings to other healthcare settings. Despite these limitations, this is the first study to identify factors associated with helmet NIV intolerance in the postextubation period among high-risk patients. Improving helmet use among the Thai population requires. Moreover, the prevalence of chronic obstructive pulmonary disease is slightly higher in the intolerance group, but the difference is not statistically significant. Further studies are needed to confirm this finding. Enhancing the learning curve and educating the medical team are crucial to increasing the use of helmet NIV, improving outcomes, and reducing the rate of intolerance[21].

CONCLUSION

Noninvasive respiratory support, particularly the use of helmet NIV during the postextubation period in high-risk patients,was associated with a high rate of NIV intolerance. However, no differences in extubation success were observed. Patients with malignancy, lower initial heart rates, and higher PaO_2/FiO_2 ratio were more likely to experience helmet NIV intolerance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. The authors will consider any reasonable requests for additional data case-by-case basis.

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Review Article

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A Review of the Beneficial Effects of Hesperidin on Urban Diseases

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ABSTRACT

The urban environment is increasingly recognized as a key determinant of health, influencing lifestyles that can either promote or hinder well-being. This review aims to summarize recent studies (2020-2024) on the potential therapeutic effects of hesperidin, a flavonoid derived from citrus fruits, in addressing urban-related diseases worsened by pollution, sedentary habits, poor nutrition, and chronic stress. These health conditions include cardiovascular diseases respiratory issues, metabolic disorders, neurodegenerative diseases, mental health challenges, infectious diseases, and cancer. Hesperidin's anti-inflammatory, antioxidant, and immunomodulatory properties have shown promise in improving cardiovascular health, reducing oxidative stress, enhancing insulin sensitivity, protecting against neurodegeneration, alleviating mental health symptoms, reducing respiratory inflammation, and inhibiting cancer cell growth. While preclinical studies show encouraging results, clinical evidence remains limited, underscoring the need for further research to validate its safety, efficacy, and optimal dosage for urban health interventions.

KEYWORDS: antioxidant, flavonoid, hesperidin, urban diseases

INTRODUCTION

Urban-associated diseases are illnesses that become either more common or more severe due to urban living or are projected to rise due to future urbanization trends[1]. Urban diseases encompass a range of health conditions, including diseases of immune dysfunction such as allergies, asthma, and autoimmune disorders; lifestyle and chronic diseases such as cardiovascular disease and obesity; and infectious diseases such as respiratory infections. Together, these conditions constitute a significant portion of the global health burden[1].

In recent times, bioactive compounds, phytochemicals naturally found in edible plants and food, have gained significant importance in drug discovery and disease treatment. Technological advancements and global collaboration have driven research into the anti-inflammatory, antimicrobial, and antioxidant properties of plant extracts. Techniques such as chromatography, spectroscopy, and genomic tools are extensively employed to identify bioactive compounds and investigate phytochemical biosynthesis[2]. Plant extracts are increasingly utilized in the management of chronic conditions such as diabetes, cancer, and neurodegenerative diseases (NDGDs). These natural substances and their active compounds have been shown to mitigate oxidative stress and inflammation, while also aiding in the management of cardiovascular and neurological disorders[3-7]. Therefore, medicinal plants offer a promising alternative to conventional medicine, often with fewer side effects, and continue to be a key focus in high-impact research.

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Hesperidin, a naturally occurring flavonoid mainly found in citrus fruit peels and other citrus plants, has been reported to have beneficial health effects[8]. Hesperidin has been incorporated into traditional Chinese medicine for the treatment of various health conditions[9]. These citrus plants are widely available and easy to include in daily diets, making them a practical source of hesperidin beneficial for all ages. Apart from citrus fruits, hesperidin has been discovered in mint plants (*Mentha*), honeybush (Cyclopia maculata), and aromatized tea[10]. Hesperidin possesses diverse pharmacologic properties, including antioxidative and anti-inflammatory effects[11]. It has been reported to improve neurologic disorders, including NDGDs, mental disorders, demyelinating diseases, and ischemic–reperfusion and brain injury[12]. In addition, hesperidin has shown effective anticancer properties through the regulation of a variety of cell-signaling molecules. Hesperidin's anticancer effect is evidenced by its effect on inflammation, cell-cycle regulation, apoptosis, and angiogenesis[13]. However, there are currently no studies gathering data on the effects of hesperidin on urban-associated diseases. Therefore, this review aims to summarize the underlying biological mechanisms and potential therapeutic benefits of hesperidin in these conditions.

THE EFFECT OF HESPERIDIN ON URBAN DISEASES

Allergies and asthma

Urban environments typically have higher levels of pollutants, including vehicle emissions, industrial waste, and environmental smoking exposure, which can exacerbate respiratory conditions[14]. In addition, the consumption of fast foods and fried meats is common in densely populated cities, contributing to the increased prevalence of allergy. Studies have shown that children and adults in urban settings are at a higher risk of developing and experiencing more severe symptoms of allergies and asthma compared with those in rural areas[15,16]. Hesperidin has shown significant potential in the management of allergies and asthma, largely due to its anti-inflammatory properties. Various experimental models have shown hesperidin to alleviate airway inflammation and hyperresponsiveness, which are common symptoms of asthma. These effects are mediated through its influence on nuclear factor kappa B (NF-κB), which reduces the production of proinflammatory cytokines and chemokines, thus mitigating the inflammatory cascade that exacerbates asthma symptoms[17]. A recent study demonstrated that hesperidin in three different doses effectively mitigated the effects induced by mechanical ventilation. This was evidenced by the reduced infiltration of inflammatory cells into the airways, decreased levels of inflammatory markers, and diminished oxidative damage, all of which are involved in asthma development[18]. Hesperidin notably reduced the increase in transforming growth factor–beta (TGF-β), tumor necrosis factor–alpha (TNF-α), interleukin-5 (IL-5), and immunoglobulin E levels in ovalbumin (OVA)–induced bronchial asthma. Moreover, it attenuated cellular infiltration, mitigated damage to alveolar sacs, decreased disruption of the bronchiole walls, and reduced neuronal cell nucleus pyknosis. These effects suggest that hesperidin, potentially through its anti-inflammatory and immunoregulatory effects, may offer protection against OVA-induced asthma[19]. Overall, recent research underscores hesperidin's potential as a complementary treatment for managing allergies and asthma, primarily through its action on the TGF-β, TNF-α, and NF-κB pathway associated with the production of proinflammatory cytokines. These findings highlight the importance of further clinical studies to establish the efficacy and safety of hesperidin in human populations.

Autoimmune and inflammatory diseases

Autoimmune and inflammatory diseases in urban areas are influenced by various

environmental factors including pollution and lifestyle habits in urban settings[20]. These factors can contribute to the increased incidence and severity of conditions such as rheumatoid arthritis[21] and inflammatory bowel disease[20]. Hesperidin exhibits potent anti-inflammatory and antioxidant properties, which are crucial in modulating inflammatory responses. In rats with collagen-induced arthritis, hesperidin was shown to be effective in reducing the severity of rheumatoid arthritis by lowering the arthritic score, arthritis index, and serum levels of TNF-α, IL-6, IL-17A, and C-reactive protein[22]. In addition, hesperidin exhibited an antiarthritic property by reducing scavenging free radicals and inhibiting glycation processes[23], modulating serum interferon gamma and IL-4 levels, and providing protection against oxidative damage[11]. Furthermore, the administration of hesperidin in rats with cyclosporine A–induced nephrotoxicity reduced the expressions of TNF-α, B-cell lymphoma-2 (Bcl-2)–associated X protein, and NF-κB, resulting in the attenuation of pathological kidney damage with an increase in nuclear factor erythroid 2–related factor 2 (Nrf2) expression in the kidney[24]. Thus, these findings suggest the role of hesperidin as an immunomodulatory agent.

LIFESTYLE AND CHRONIC DISEASES

Cardiovascular disease

Previous study indicated that cardiovascular diseases are the leading cause of mortality in urban areas and worldwide[25]. Recent studies have explored various aspects of the effects of urban living on cardiovascular health. In urban areas, patients with ST-elevation myocardial infarction exposed to high concentrations of nitrogen dioxide (NO_2) and particles with a diameter of 10 microns or less (PM_{10}) experience a greater risk of readmission for heart failure[26]. Nevertheless, individual factors such as dietary habits, educational level, and physical activity influence the prevalence of cardiovascular disease. Hesperidin has garnered attention for its potential cardiovascular benefits. Previous studies suggested that hesperidin exhibits antioxidant, anti-inflammatory, and antiapoptotic effects, which contribute to its protective effects against cardiotoxicity[27]. Similarly, hesperidin prevents cardiotoxicity via modulation of the gene expression levels of the Phosphoinositide 3-kinase/ Protein kinase B (Akt)/ mammalian target of rapamycin (mTOR) signaling pathway[28], and proapoptotic Bcl-2-associated X protein and caspase-3, and it also improves the expression of the pathway proteins p62 and Nrf2[29]. Hesperidin also enhances cholesterol reverse transport by increasing the upregulation of adenosine triphosphate-binding cassette protein A1 (ABCA1)[30] which is a crucial factor in the development and progression of cardiovascular disease. Hesperidin also prevented vascular alterations induced by L-NG-Nitroarginine Methyl Ester in rats, possibly by suppressing the activation of the renin-angiotensin system, inhibiting TGF-β1 expression, and reducing oxidative stress[5]. It also improved symptoms of metabolic syndrome and cardiac dysfunction in a rat model of diet-induced metabolic syndrome, likely through the insulin receptor substrate/ Akt/Glucose transporter type 4 signaling pathway[4]. In addition, hesperidin protected against varenicline-enhanced oxidized low-density lipoprotein uptake in RAW 264.7 cells by blocking the upregulation of cluster of differentiation 36 (CD36) and lectin-like oxidized low-density lipoprotein receptor-1 scavenger receptors and preventing the downregulation of ABCA1 and adenosine triphosphate-binding cassette sub-family G member 1 cholesterol efflux transporters[31], further reducing the risk of atherosclerosis and related cardiovascular events. Therefore, hesperidin provides substantial cardiovascular protection via its antioxidant, anti-inflammatory, and antiapoptotic properties by modulating key signaling pathways, lowering blood pressure, enhancing lipid profiles, and safeguarding against cardiotoxicity, metabolic syndrome, and atherosclerosis.

Neurodegenerative diseases

Air pollution in urban areas poses a serious threat to public health and the environment. The major sources of air pollution include vehicle emissions, industrial discharges, and construction activities, leading to elevated levels of PM, carbon dioxide, and NO_2[32]. These pollutants contribute to cardiovascular diseases as well as NDGDs[33]. Air pollution is increasingly recognized as a significant contributor to NDGDs such as Alzheimer's disease (AD) and Parkinson's disease (PD). Pollutants such as PM and heavy metals can trigger neuroinflammation and oxidative stress, leading to neuronal damage. Data from a recent review indicated that individuals in polluted areas face a higher risk of NDGDs, highlighting the critical need for strategies to reduce air pollution and protect brain health[34]. There has been a growing interest in recent studies on NDGDs and the potential therapeutic effects of hesperidin, with evidence suggesting that hesperidin may offer neuroprotective benefits. NDGDs, such as AD, PD, and amyotrophic lateral sclerosis, are characterized by the progressive degeneration of the nervous system, leading to cognitive and motor impairments. Hesperidin has been shown to exhibit antioxidant, anti-inflammatory, and neuroprotective properties, which could potentially help in mitigating the underlying mechanisms of neurodegeneration[35,36]. Recent research highlighted the role of hesperidin in improving cognitive functions and reducing amyloid beta aggregation, α-synuclein aggregation[37] and decreasing oxidative/nitrosative stress[38], which are key features in AD. In addition, researchers also reported dopaminergic neuronal protection and stabilization of cellular calcium homeostasis by hesperidin, suggesting its potential role as a complement treatment for PD[39,40]. Moreover, hesperidin has been shown to affect several signaling pathways involved in neuronal survival, making it a promising candidate for drug development[41, 42]. Although preclinical studies have shown promising results regarding the neuroprotective effects of hesperidin, additional clinical trials are necessary to confirm its efficacy in human populations and to optimize treatment protocols. Continued investigation into hesperidin's mechanisms of action and its therapeutic potential could pave the way for novel interventions in the management of NDGDs, ultimately improving patient outcomes and quality of life.

Cancer

The incidence of cancer in urban areas has been a growing concern, particularly because of the interplay of environmental and lifestyle factors prevalent in densely populated regions. Residents of urban environments are often exposed to higher levels of air pollution, which has been linked to an increased risk of lung cancer and other respiratory malignancies[43]. In many Asian cities, including Bangkok, urban air pollution from traffic is a significant issue. This pollution mainly arises from incomplete fossil fuel combustion and includes carcinogenic compounds such as polycyclic aromatic hydrocarbons and benzene. It has been reported that Bangkok schoolchildren are exposed to total polycyclic aromatic hydrocarbons at levels 3.5 times higher than children in rural areas are, while their exposure to benzene is about twice as high as that of schoolchildren in rural regions[44]. In addition, a previous study reported high incidences of other types of cancer in urban areas, including ovarian cancer[45], thyroid and colorectal cancers, lung cancer, prostate cancer, kidney cancer, bladder cancer, lymphoma, and leukemia[46]. However, variations in individual lifestyle factors, such as diet, exercise, and the prevalence of smoking and alcohol consumption, also influence the risk of developing cancer.

In the past few years, various studies have reported the promising anticancer properties of hesperidin, which exerts its effects through multiple mechanisms including antioxidant activity, modulation of inflammatory pathways, and induction of apoptosis in cancer cells. In the preclinical setting, hesperidin was shown to

abolish the growth and metastasis of breast cancer[47], prostate cancer[48], lung cancer[49], oral cancer[50], intrahepatic cholangiocarcinoma[51], leukemia cancer[52], and colorectal cancer[53]. Furthermore, hesperidin also inhibited cancer cell progression via modulation of the p53 signaling pathway[54], inhibition of the Mitogen-Activated Protein Kinase Kinase Kinase 2 (MEKK2)/Mitogen-Activated Protein Kinase Kinase 5 (MEK5)/Extracellular-signal-regulated kinase 5 (ERK5) signaling pathway activation[51], and inhibition of programed death ligand 1 expression via downregulation of Akt and NF-κB signaling[55]. In addition, hesperidin also suppressed the phosphorylated signal transducer and activator of transcription 1 and signal transducers and activators of transcription 3, leading to cell-cycle arrest in cancer cells[50]. Hesperidin also promotes apoptotic cancer cell death via reactive oxygen species (ROS)–driven cell necrosis[48] and targeting of the microRNA-132/zinc finger Ebox binding homeobox 2 signaling pathway[49].

A recent study demonstrated that a combined treatment with hesperidin and chlorogenic acid produced a synergistic effect by regulating mitochondria and production of adenosine triphosphate through the estrogen receptor pathway in breast cancer cells. This finding suggests that, when used alongside chemotherapy drugs, hesperidin and chlorogenic acid could be effective as adjunctive therapies for breast cancer patients[56]. Moreover, hesperidin also enhances the efficacy of conventional therapies such as chemotherapy, potentially by protecting normal cells from treatment-induced damage[57]. Overall, hesperidin represents a potent bioactive compound with significant potential in cancer prevention and treatment. The compound's antioxidant and anti-inflammatory properties further contribute to its protective effects against cancer. Despite promising preclinical findings, more clinical trials are needed to confirm the safety, optimal dosage, and therapeutic potential of hesperidin in cancer treatment.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterized by chronic inflammation and irreversible airflow obstruction, primarily caused by long-term exposure to irritants such as cigarette smoke and air pollutants[58]. Inflammation is a pervasive factor in numerous respiratory diseases, such as COPD[59]. Hesperidin, a prominent polyphenol, has been shown to inhibit key transcription factors and regulatory enzymes involved in the mediation of inflammation, including NF-κB, inducible NO synthase, and cyclooxygenase-2. Moreover, hesperidin enhances cellular antioxidant defenses via the activation of the ERK/Nrf2 signaling pathway, suggesting its potential therapeutic utility in managing the inflammatory aspects of respiratory diseases[17]. The effect of hesperidin on COPD currently remains unclear. Nevertheless, a recent study demonstrated that hesperidin effectively mitigated inflammation and oxidative stress in mice with COPD induced by cigarette smoke extract. This beneficial effect is likely mediated through the modulation of the sirtuin 1/peroxisome proliferator-activated receptor gamma coactivator 1-alpha/NF-κB signaling pathway[60]. This suggests that hesperidin might be a potential therapeutic option for managing COPD.

Obesity and diabetes mellitus

Obesity and diabetes mellitus (DM) are common in the urban areas of developing countries[61]. Previous studies have highlighted hesperidin's potential benefits in managing obesity and DM due to its anti-inflammatory, antioxidant, and lipid-lowering properties, resulting in improvements in metabolic profiles and insulin resistance[62,63]. An in-silico study showed that the administration of hesperidin significantly improved leptin and insulin resistance in a high-fat diet (HFD)–induced obese experimental animal model[62]. Moreover, researchers also reported a substantial reduction in serum amylase and lipase activities,

a significant increase in insulin levels, and improvement in the pancreatic antioxidant defense system in cadmium-induced pancreatitis rats[64]. Moreover, several lines of evidence have suggested the antidiabetic effects of hesperidin. In HFD-fed rats, the administration of hesperidin improved blood glucose, insulin level, liver enzymes, lipid profile, and oxidative profile[65] and normalized the expression levels of insulin signaling and glucose metabolism–related genes in the liver[63]. In rats fed an obesogenic diet, hesperidin supplementation decreased total cholesterol, low-density lipoprotein cholesterol, and free fatty acids[66]. In addition, the highest dose of hesperidin used in this study also improved blood pressure and insulin sensitivity and reduced markers of arterial stiffness and inflammation. A recent study in patients with gestational DM and obesity showed that hesperidin significantly inhibited the autophagy proteins and m6A level in LPS and glucose-induced human villous trophoblasts isolated from these patients[67]. Overall, the evidence from recent studies suggests that hesperidin could be a valuable component of therapeutic strategies aimed at managing obesity and diabetes, promoting overall metabolic health, and reducing the risk of associated complications.

Mental health

Urban environments present a unique set of challenges that can contribute to the development and exacerbation of depression among residents. Several factors such as social isolation and environmental stressors including noise and pollution contribute to mental health conditions[68], which can exacerbate and lead to physical diseases that diminish the overall quality of life. Hesperidin has been reported to effectively slow the progression of mental health conditions, especially depression. Hesperidin administration in chronic unpredictable mild stress (CUMS) depressed mice significantly alleviated depressive symptoms and expression levels of key components in the proptosis pathway including caspase 1, IL-18, IL-1β, and nucleotide-binding and oligomerization domain-like receptor protein 3[69]. A similar effect was observed when hesperidin was administered to CUMS-induced rats[70]. Moreover, hesperidin could ameliorate depression and anxiety-like behaviors in diabetic rats by enhancing glyoxalase-1, potentially via the activation of the Nrf2/ antioxidant responsive element (ARE) pathway[71]. Researchers have also reported the protective role of hesperidin against depression. Pretreatment with hesperidin significantly reduced depressive behavior; increased the levels of CD4, CD25, forkhead box P3, IL-10, dopamine, serotonin, and neurotrophin-3; and improved the motor function of OVA-induced bronchial asthma rats, suggesting its protective roles against OVA-induced asthma and depression[19]. It also exerted anxiolytic-like and antidepressant-like effects in the neurotoxin 6–hydroxydopamine model of PD by modulating cytokine production, neurotrophic factor levels, and dopaminergic innervation in the striatum[72]. In addition, hesperidin has shown antidepressant effects in animal models of posttraumatic stress disorder by decreasing the 5-hydroxyindoleacetic acid/5-hydroxytryptamine ratio, monoamine oxidase A activity, and tryptophan hydroxylase-1 expression[73]. In the clinical setting, coronary artery bypass graft patients who had mild depression exhibited a reduction in depressive symptoms after 12 weeks of 200 mg/day hesperidin[74]. Overall, these results indicate that hesperidin is a promising therapeutic option for treating depressive disorders.

Infectious diseases

Urban areas, which are characterized by high population density and frequent social interactions, are particularly vulnerable to the rapid spread of infectious diseases. Studies have shown that a high density of people and frequent social contact contribute to an increased risk of a range of infections, including respiratory illnesses such as coronavirus disease 2019 (COVID-19) and influenza, as well as vector-borne diseases[75,76].

Hesperidin has been demonstrated to exert its antiviral and anti-inflammatory effects, particularly in relation to COVID-19 and other infectious diseases, through a variety of mechanisms. It inhibits viral replication by modulating key viral proteins and cellular signaling pathways. For instance, hesperidin has been reported to interfere with the entry of severe acute respiratory syndrome coronavirus 2 into host cells by affecting the interaction between the virus spike protein and angiotensin-converting enzyme 2[77,78]. In addition, an in-silico study showed that the combination of hesperidin with zinc oxide nanoparticles exhibited high antiviral activity against mRNA hepatitis A virus, indicating that this combination might be a promising candidate for the treatment of COVID-19[79]. In nonvaccinated patients with COVID-19, 1,000 mg of hesperidin daily for 14 days could reduce the key symptoms of COVID-19, such as fever, shortness of breath, cough, and anosmia. Although it slightly alleviated anosmia, the most persistent symptom, further research with longer treatment periods or higher doses is required[80]. Hesperidin also exhibited strong inhibitory effects on the Chikungunya virus[81] and hepatitis C virus nonstructural protein 3 protease[82] with half-maximal inhibitory concentration values of 10 and 11.34 μg/mL, respectively.

Moreover, infectious diseases can also be caused by bacterial infection. A recent study reported hesperidin's antivirulence effects against *Aeromonas hydrophilia* (*A. hydrophilia*), a rod-shaped, gram-negative bacterium present predominantly in drinking water, wastewater, sewage, and food. The transmission of *A. hydrophilia* from fish to humans via the consumption of raw seafood can cause diseases such as gastroenteritis, septicemia, and skin diseases. Hesperidin methylchalcone decreased the development of biofilm and the production of the virulence factor of *A. hydrophilia*, suggesting its role as a possible treatment for *A. hydrophilia*–related infections in humans[83]. These findings suggest the potential role of hesperidin as a supportive therapeutic agent in the management of viral and bacterial infections. Although the current results are promising, further studies are needed to establish the comprehensive efficacy and safety profiles of hesperidin. Longer treatment periods, higher doses, and diverse experimental conditions should be conducted to evaluate its effectiveness and optimal usage.

CONCLUSION

In this review based on studies conducted from 2020 to 2024, we have highlighted the possible mechanisms and therapeutic benefits of hesperidin as a promising treatment for urban diseases (Table 1). Hesperidin demonstrates multiple mechanisms that can address various urban diseases. It inhibits key inflammatory pathways, particularly by modulating NF-κB signaling. This reduces the production of proinflammatory cytokines (such as TNF-α, IL-6, IL-1β) and chemokines, which are crucial in conditions like asthma, COPD, and autoimmune diseases. It also acts as an antioxidant by activating the Nrf2 pathway, which helps combat oxidative stress in cardiotoxicity. In metabolic syndrome, hesperidin improves cardiac function by influencing insulin receptor substrate/Akt/insulin-responsive glucose transporter signaling pathway. It also enhances insulin sensitivity and regulates glucose metabolism in diabetes and obesity. Hesperidin stabilizes calcium homeostasis, prevents amyloid beta aggregation, and decreases dopaminergic neuronal damage. These effects are beneficial for conditions like PD and AD. Its anticancer properties are linked to the regulation of cell progression through p53, and MEKK2/MEK5/ERK5 signaling pathway pathways. Regarding mental health, hesperidin reduced depressive symptoms in CUMS mice and rats by lowering proptosis markers. It also improved depression and anxiety in diabetic rats via the Nrf2/ARE pathway and showed antidepressant effects in post-traumatic stress disorder models

by reducing key biochemical markers. In infectious diseases, hesperidin inhibits viral replication and bacterial virulence factors. Hesperidin inhibits the entry of viruses like SARS-CoV-2 into host cells. This is done by modulating the interaction with the angiotensin converting enzyme-2 receptor. Its broad mechanisms position hesperidin as a potential therapeutic agent for managing urban-related diseases. While preclinical studies have demonstrated promising results, further clinical research is needed to fully validate the therapeutic efficacy and safety of hesperidin in humans. Additionally, optimal dosing regimens and long-term effects require further investigation. Nonetheless, hesperidin holds considerable promise as a natural therapeutic option for managing a variety of urban-associated health challenges, offering a potential complementary approach to current medical treatments and preventative health strategies.

Table 1 The major targets of hesperidin and their associated signaling pathways on urban diseases

Diseases	The major targets and possible mechanism of action	Model	References
Allergies and asthma	Decreased levels of TNF-α, IL-5, and IgE	OVA-induced bronchial asthma in rats	19
Autoimmune and inflammatory diseases	Reduced TNF-α, IL-6, IL-17A, and C-reactive protein	Collagen-induced arthritis in rats	22
	Reduced serum TNF-γ and IL-4 levels	Complete Freund's adjuvant-induced arthritic rats	11
	Suppressed TNF-α, Bcl-2–associated X protein, and NF-κB, upregulated Nrf2 expression	Cyclosporine-induced nephrotoxicity in rats	24
Cardiovascular disease	Upregulated IRS/Akt/GLUT4	HFD-induced MS in rats	4
	Decreased renin-angiotensin system activation and TGF-β1 expression	L-NAME rats	5
	Modulated PI3K/Akt/mTOR signaling pathway, inflammatory parameters (Beclin 1, LC3A, LC3B, NF-κB, IL-1β, TNF-α), and apoptotic genes (caspase-3, -6, -9, Bax, Bcl-2, p53, cytochrome c)	Sodium fluoride-induced cardiotoxicity in rats	28
	Increased p62-Keap1-Nrf2 signaling pathway	Cisplatin-induced cardiotoxicity in mice	29
	Increased ABCA1 upregulation	Apoe-deficient mice	30
	Decreased CD36 and LOX-1 scavenger receptors upregulation, but increased ABCA1 and ABCG1 cholesterol efflux transporters upregulation	Apoe KO mice	31
Neurodegenerative diseases	Reduced beta amyloid and α-synuclein	*In vitro* model of AD	37
	Reduced NOx and protein carbonyl levels	Streptozotocin-induced AD rat model	38
	Stabilized cellular calcium homeostasis	SH-SY5Y cellular model of Parkinson disease	39
	Decreased Fe levels	Parkinson-like disease in Drosophila melanogaster	40
Cancer	Increased miR-132 expression and decreased ZEB2 expression	Non-small cell lung cancer	49
	Inhibited MEKK2/MEK5/ERK5 signaling pathway activation	Intrahepatic cholangiocarcinoma	51
	Modulated p53 signaling pathway	Breast cancer stem cells	54

Table 1 The major targets of hesperidin and their associated signaling pathways on urban diseases (continued)

Diseases	The major targets and possible mechanism of action	Model	References
	Downregulated Akt and NF-κB signaling	Breast cancer cells	55
	Inactivated STAT1 and STAT3 signaling molecules	Oral cancer cells	50
	Induced ROS–driven cell necrosis	Prostate cancer cells	48
Chronic obstructive pulmonary disease	Modulated SIRT1/PGC-1α/NF-κB signaling pathway	COPD mice	60
Obesity and diabetes mellitus	Increased insulin-mediated phosphorylations of Akt and GSK3β	PA-treated HepG2 cell	63
	Normalized expression levels of hexokinase-II, enolase-1, and PI3 kinase p110δ	HFD-induced obese mice	63
	Decreased iNOS, NF-κB, IL-6 and TNF–α levels	Cadmium-induced pancreatitis rats	64
	Suppressed autophagy proteins and m6A levels	LPS and glucose-induced human villous trophoblasts	67
Mental health	Regulated the NLRP3 pathway	Chronic unpredictable mild stress depressed mice	69, 70
	Activated Nrf2/ARE/Glyoxalase 1 pathway	Diabetic rats	71
	Modulated cytokine production, neurotrophic factor levels, and dopaminergic innervation	6-OHDA Parkinson's model	72
	Decreased 5-HIAA/5-HT ratio, MAO-A activity, and tryptophan hydroxylase-1 expression	Animal model of post-traumatic stress disorder	73
Infectious diseases	Interfered the binding of the SARS-CoV-2 S protein to the ACE2 receptor	in silico methods	77
	Decreased the interaction between the spike protein and ACE2, as well as ACE2 and TMPRSS2 expression	VeroE6 cells	78

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; ABCA1, ATP-binding cassette transporter A1; ABCG, ATP binding cassette subfamily G member; ACE2, angiotensin-converting enzyme 2; AD, Alzheimer's disease; Akt, protein kinase B; ApoE, apolipoprotein E; ARE, arrestin-related protein; Bax, Bcl-2-associated X protein; Bcl2, anti-apoptotic protein; CD36, cluster of differentiation 36; COPD, chronic obstructive pulmonary disease; ERK5, extracellular signal-regulated kinase 5; Fe, iron; GLUT4, glucose transporter type 4; GSK3β, glycogen synthase kinase 3 beta; HepG2, human hepatoblastoma cell line; HFD, high fat diet; IgE, immunoglobulin E; IL, interleukin; iNOS, inducible nitric oxide synthase; IRS, insulin receptor substrate; Keap1, Kelch-like ECH-associated protein; KO, knock out; LC, microtubule-associated protein light chain; L-NAME, N-nitro-L-arginine methyl ester; LOX-1, elctin-like oxidized low-density lipoprotein receptor 1; LPS, lipopolysaccharide; MAO-A, monoamine oxidase A; MEK5, mitogen-activated protein kinase kinase 5; MEKK2, mitogen-activated protein kinase kinases kinase 2; miR, microRNA; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-kappa B; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; NOx, nitrogen oxides; Nrf2, nuclear factor erythroid 2-related factor 2; OHDA, 6-hydroxydopamine; OVA, ovalbumin; PA, palmitate; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; ROS, proto-oncogene tyrosine-protein kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SH-SY5Y, a thrice-cloned subline of the human neuroblastoma cell line SK-N-SH; SIRT1, sirtuin 1; STAT, signal transducers and activators of transcription; TGF-β1, transforming growth factor beta 1; TMPRSS2, transmembrane serine protease 2; TNF-α, tumor necrosis factor-alpha; TNF-γ, tumor necrosis factor-gamma; ZEB2, zinc finger E-box binding homeobox 2

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