Borneo Journal of Medical Sciences

Volume 19, Issue 2, May 2025







PENERBIT UNIVERSITI MALAYSIA SABAH Kota Kinabalu • Sabah • Malaysia http://www.ums.edu.my 2024 A Member of the Malaysian Scholarly Publishing Council (MAPIM)



Journal of the Faculty of Medicine and Health Sciences Universiti Malaysia Sabah

EDITORIAL BOARD 2025

Editor-in-Chief

Dr. Kamruddin Ahmed

Professor Department of Pathobiology and Medical Diagnostics, *Director* Borneo Medical and Health Research Centre Faculty of Medicine and Health Sciences Universiti Malaysia Sabah, Malaysia **Areas of Expertise:** Virology, Molecular epidemiology, Emerging infectious diseases, Diagnostics https://www.scopus.com/authid/detail. uri?authorld=7202086359

International Advisor

Dr. Hidekatsu Iha Associate Professor Department of Microbiology Faculty of Medicine Oita University, Japan Areas of Expertise: Oncogenic virus, Molecular biology https://www.scopus.com/authid/detail. uri?authorld=6701805654

Dr. Richard Culleton

Professor Division of Molecular Parasitology Proteo-Science Center Ehime University, Japan **Areas of Expertise:** Parasitology, Malariology https://www.scopus.com/authid/detail. uri?authorld=7801604688

Dr. Kimberly Fornace

Associate Professor Saw Swee Hock School of Public Health National University of Singapore, Singapore Areas of Expertise: Malariology, Epidemiology https://www.scopus.com/authid/detail. uri?authorld=24472918000

Dr. Gulendam Bozdayi

Professor Department of Medical Microbiology Faculty of Medicine Gazi University, Turkey **Area of Expertise:** Medical virology https://www.scopus.com/authid/detail. uri?authorld=6505967744

Dr. Hanan I. Malkawi

Professor Department of Biological Sciences /Yarmouk University. Irbid - Jordan. Areas of Expertise: Microbiology & Molecular biology

https://www.scopus.com/authid/detail.

uri?authorId=6603849618

Editors

Dr. Aminur Rahman

Deputy Executive Director & Director International Drowning Research Centre Bangladesh Centre for Injury Prevention and Research, Bangladesh Areas of Expertise: Public health, Drowning prevention

Dr. Mohammad A. Karim

Research Associate Phoenix VA Health Care System. Arizona Veterans Research and Education Foundation. Phoenix, Arizona, USA. **Areas of Expertise:** Human genetics, Genotype-phenotype relationship, Neurogenetics https://www.scopus.com/authid/detail. uri?authorld=7202145316

Dr. Mya Myat Ngwe Tun

Assistant Professor Center for Vaccines and Therapeutic Antibodies for Emerging Infectious Diseases, Shimane University, Japan **Area of Expertise:** Virology https://www.scopus.com/authid/detail. uri?authorld=56053235800

Dr. Andee Dzulkarnaen Zakaria

Professor School of Medical Sciences Universiti Sains Malaysia, Kubang Kerian, Malaysia **Areas of Expertise:** General and Colorectal Surgery https://www.scopus.com/authid/detail. uri?authorld=55570987200

Dr. Irfan bin Mohamad

Professor School of Medical Sciences Universiti Sains Malaysia, Kubang Kerian, Malaysia Areas of Expertise: Otorhinolaryngology https://www.scopus.com/authid/detail. uri?authorld=57201594554

Dr. Mohd Rohaizat Bin Hassan

Professor Epidemiology at the Department of Public Health Medicine, Faculty of Medicine, National University of Malaysia. Areas of Expertise: Infectious disease epidemiology focusing on neglected tropical diseases, emerging re-emerging diseases, vector-borne and zoonotic diseases https://www.scopus.com/authid/detail.

uri?authorId = 55259986300

Ts. Dr. Pasupuleti Visweswara Rao

Professor Director, International Relations, and Research Collaborations Associate Dean, School of Applied and Allied Health Sciences, REVA University, Bangalore, India **Areas of Expertise:** Biomedical Sciences, Metabolic Diseases, Nanobiotechnology, Natural Product Research https://www.scopus.com/authid/detail. uri?authorld=55904825600

Dr. Matloob Husain

Associate Professor Department of Microbiology and Immunology University of Otago, New Zealand Areas of Expertise: Virology https://www.scopus.com/authid/detail. uri?authorld=7201522843

Dr. Md Iqbal Alam

Professor and Head of Department Department of Physiology Hamdard Institute of Medical Sciences & Research, Jamia Hamdard, Hamdard Nagar, New Delhi-110062, India **Areas of Expertise:** Cardiovascular Physiology, Vascular physiology https://www.scopus.com/authid/detail. uri?authorld=7401493175

Managing Editors

Dr Mohd Firdaus Bin Mohd Hayati

Associate Professor Department of Surgical Based Discipline Faculty of Medicine and Health Sciences Universiti Malaysia Sabah, Malaysia **Areas of Expertise:** Carcinogenesis, surgery https://www.scopus.com/authid/detail. uri?authorld=57194659096

Dr Sadia Choudhury Shimmi

Senior Lecturer Department of Biomedical Science Faculty of Medicine and Health Sciences Universiti Malaysia Sabah, Malaysia **Areas of Expertise:** Physiology, complementary and alternative medicine, renal system, hepatobiliary system, cardiovascular system https://www.scopus.com/authid/detail. uri?authorld=57215409368

Dr Fong Siat Yee @ Alison

Senior Lecturer Department of Biomedical Science Faculty of Medicine and Health Sciences Universiti Malaysia Sabah, Malaysia **Areas of Expertise:** Molecular biology, natural products https://www.scopus.com/authid/detail. uri?authorld=57191264120

Ts. Jaeyres Jani Lecturer Department of Biomedical Science

Faculty of Medicine and Health Sciences Universiti Malaysia Sabah, Malaysia **Areas of Expertise:** Bioinformatic, Genetic Information https://www.scopus.com/authid/detail. uri?authorld=57193361113

Secretariat

Bernard Tzing Ziang Vui

Senior Science Officer Faculty of Medicine and Health Sciences Universiti Malaysia Sabah, Malaysia

Dayang Katija

Medical Laboratory Technologist Faculty of Medicine and Health Sciences Universiti Malaysia Sabah, Malaysia



Volume 19, Issue 2, May 2025

CONTENTS

Orio	inal	Artia	oloe
Ully	IIIai		109

•	Designing a PCR-Based Genotyping Technique for the LEP A19G Polymorphism: Method Development and Optimization	63
	Hartini Yusof, Alya Syuhada Safawi, Umi Nabiha Mohd Azli, Azrina Begam Mohd Ali, Zana Jamal Kareem, Fazleen Haslinda Mohd Hatta	
•	Factors Influencing Occupational Health Practices and Hypertension Among Security Personnel in a Public University Noor Fatimah Mutahar, Khamisah Awang Lukman, Mohd Faizal Madrim, Pravina Deligannu	75
•	Educational Experiences and Career Aspirations of Final-Year Nursing Students at International Islamic University Malaysia Siti Azuna Abu Bakar, Khin Thandar Aung, Mashitah Aqilah Fauzi	84
•	Prevalence of Dental Anomalies in Cleft Lip and Palate Patients Referred for Orthodontic Treatment Jin Han Lee	96
•	Prospective, Non-randomized Study of Clinical Outcome in Patients With Primary Versus Delayed Ureteroscopy for Proximal Ureteric Stone (PRIDE Study) Kian Joo Sun, Shankaran Thevarajah	104
Re	view Article	
•	Exploring the Bacteriophage in Malaysia: An Overview of Applications and Challenges Nur Nashyiroh Izayati Mastor, Mohammad Zahirul Hoque, Vijay Kumar Subbiah	110
•	Overview of Exercise Addiction - Early Detection for Early Intervention Khairun'naim Khairuddin, Muhammad 'Adil Zainal Abidin, Hazwani Hanum Hashim, Azwanis Abdul Hadi	123
•	Vehicles for antibiotic formulation in endodontic treatment: A narrative review Nor Hazwani Jamaludin, Nurul Ain Ramlan, Afiq Azizi Jawami, Nurul Aida Ngah	130
Ca	se Reports	
•	From paralytic ileus to Guillain-Barre Syndrome: A diagnostic puzzle Kong Meng Tung, Bradley Avery Noelle Bachi, Yen Lik Chia, Chiew Yen Haw	140
•	Metastatic Breast Carcinoma Masquerading as Eyelid Swelling: A Case Report Muhammad Fauzan Shamsuddin, Patricia Ann John	145

BJMS Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Designing a PCR-Based Genotyping Technique for the LEP A19G Polymorphism: Method Development and Optimization

Hartini Yusof¹, Alya Syuhada Safawi¹, Umi Nabiha Mohd Azli¹, Azrina Begam Mohd Ali², Zana Jamal Kareem^{3,4}, Fazleen Haslinda Mohd Hatta⁵*

- ¹ Centre for Medical Laboratory Technology Studies, Faculty of Health Sciences, Universiti Teknologi MARA (UiTM), Selangor Branch, Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia
- ² Apical Scientific Sdn Bhd, No. 7-1 to 7-4, Jln S/ P2/7, Taman Serdang Perdana, Seksyen 2 Seri Kembangan, 43300 Seri Kembangan, Selangor, Malaysia
- ³ Faculty of Health Science, Qaiwan International University (QIU), Slemani Heights, Sulaymaniyah, Iraq
- ⁴ Kurdistan Institution for Strategic Studies and Scientific Research (KISSR), 335 Shorsh St, Iraq
- ⁵ Department of Pharmaceutical Pharmacology and Chemistry, Faculty of Pharmacy Universiti Teknologi MARA Selangor Branch, Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia
- *Corresponding author's email: fazleen@uitm.edu.my

Received: 21 JUNE 2024

Accepted: 25 October 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.5485

Keywords: A19G, Polymorphism, Leptin, Appetite, Genotyping



Borneo Journal of Medical Sciences @ 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

The LEP gene is a protein-encoding gene for the satiety hormone called leptin, which stimulates appetite, impeding food intake and anorexigenic peptide upregulation. This research aims to develop a genotyping method to detect the LEP gene variant A19G, known for its association with appetite and eating preference. Convenience random sampling was performed by disseminating the subject's recruitment on social media among the students of Faculty of Health Sciences, Universiti Teknologi MARA. A total of 51 undergraduates (mean age, 23.20 (Standard Deviation, SD 1.56) years old; 41 females, 10 males) from the faculty were recruited. Questionnaires have been provided to assess the subjects' meal preferences and food intake frequency. A19G genotyping was performed using polymerase chain reaction (PCR) and subsequent agarose gel electrophoresis (AGE). The analysis confirmed the successful development of the A19G genotyping method. The variant allele frequency (VAF) for A19G was 0.13. This approach provides a reliable genotyping tool for LEP A19G in future investigations despite data suggesting that A19G may not be a marker for appetite differences in this subject group. Further research with a larger, more diverse population is warranted to confirm these results and explore the influence of other LEP gene variants on appetite and eating preferences.

INTRODUCTION

A healthy and balanced food intake would protect individuals from malnutrition and diet-related noncommunicable diseases (NCDs) such as stroke, diabetes, cancer, and heart disease (WHO, 2019). Healthy diet practices recommended by the World Health Organization (WHO) include terminating saturated and industrially manufactured trans fats from the diet, opting for unsaturated fats consumption, balancing calorie intake and output, and limiting salt and sugar consumption. An unhealthy diet is the leading global challenge in the health sector. Even though people living in urban areas have easy access to clean, healthy, and adequate food, a trend of satisfying sweet and fatty food cravings has been incorporated into an urbanised lifestyle. Appetite is an intricate concept. It is regarded as the inner urge to look for, choose, and consume food from a biological standpoint (de Graaf et al., 2004). In the broader context, appetite is an interrelated process of physiological, psychological, and environmental factors that regulate an individual's quotidian eating pattern (Halford & Blundell, 2000). The correlation between appetite and eating patterns is evident, as an intricate interplay of hormonal and neural factors governs appetite. This regulatory mechanism aims to maintain a balanced energy intake that adequately metabolic needs. This system sustains stimulates eating behavior by starvation, hedonic sensations, and food cravings (Das & Roy, 2017). Comprehending food choice preference, meal timing, and frequency of food intake is imperative in tackling the epidemics of cardiovascular diseases, obesity, and diabetes. According to the National Health and Morbidity Survey, diabetes, hypertension, or hypercholesterolemia affects at least onethird of the Malaysian population (NIH, 2020).

Based on Noncommunicable Diseases Country Profiles 2018, 74% of overall deaths in Malaysia were accounted for NCDs, with cardiovascular diseases recorded as high as 35%, where salt intake, diabetes, and obesity are some risk factors for mortality due to NCDs (WHO, 2018). Leptin is a hormone that comprises 167 amino acids and is released by the hypothalamus to regulate food intake (Facey et al., 2017). The leptin (LEP) gene is located at chromosome 7q31.3, the short arm of chromosome 7, and encompasses approximately 20kb length of 3 exons (Isse et al., 1995), which is responsible for encoding for the 16-kDa leptin hormone.

The leptin receptor is a transmembrane protein from the class I cytokine family receptor, and by binding to this receptor, only leptin can carry out its physiological function (Fan & Say, 2014). Variations in genes of digestive neuroendocrine hormones and enzymes such as cholecystokinin (CCK), leptin, fat mass and obesity (FTO), and glutamic acid decarboxylase (GAD) have been observed to increase the risk of obesity by regulating satiety and hunger (Grimm & Steinle, 2011). Variants in CCK and leptin hormone contribute to imprudent meal size and excessive snacking behaviour, respectively (de Krom et al., 2007).

Meanwhile, FTO gene variants are associated with increased caloric intake (Tanofsky-Kraff et al., 2009), and increased carbohydrate intake behaviour is observed in individuals with GAD gene variants (Choquette et al., 2009). Polymorphism of LEP and LEPR genes that encode for leptin hormone is usually assessed for dietary deficiency-related problems such as obesity. A19G is one of the leptin gene alleles typically assessed for its polymorphisms in other research studies. The A19G polymorphism showed no significant association as a potential obesity-predisposing marker in Malaysian populations (Wan Rohani et al., 2018). A study reported that single nucleotide polymorphisms (SNPs) of the leptin gene in Malaysia were associated with ethnicity rather than body mass index (BMI) and gender (Fan & Say, 2014).

In addition, more investigations are needed on the association between A19G polymorphisms and appetite; hence, future research and genotypic data are limited. Therefore, this study aims to develop a method to detect the LEP gene corresponding to the variant A19G. We studied the relationship between A19G polymorphism on the LEP gene and appetite among the Faculty of Health Sciences, Universiti Teknologi MARA students, to understand the association between appetite and A19G polymorphism.

MATERIALS AND METHODS

Subject Recruitment

This study comprised of 51 undergraduate students from the Faculty of Health Sciences, Universiti Teknologi MARA whose ages ranged from 18 to 30 years, recruited by convenience sampling. Recruitment of participants was done using social media. We excluded students from other faculties, participants whose blood failed to be extracted, and participants with low DNA quality. The selected participants were willing to follow the research instructions, free from chronic and blood-borne diseases, and ready to sign informed consent forms. Participants will not be recruited if they refuse to participate.

Data and Blood Sample Collection

The study was approved by the Research Ethics Committee of Universiti Teknologi MARA with reference number REC/662/19, and informed consent was obtained from all participants. Participants were briefed about the research procedure, and their height and weight were measured. Participants' information on demographic data and appetite was collected through written interviews. The assessment questions consisted of the subjects' eating preferences such as whether food was taken during the indicated eating time and where the food was consumed, with a scale of frequency of food consumption. The questionnaire was adapted from validated questionnaires which include the Adult Eating Behaviour Questionnaire (AEBQ) (Hunot, et al., 2016), Self-Regulation of Eating Behaviour Questionnaire (SREBQ) (Kliemann, et al., 2016) and Adolescents' Food Habits Checklist (AFHC) (Johnson, et al., 2002). Participants' venous blood was collected by qualified personnel into a 5ml ethylenediaminetetraacetic acid (EDTA) blood collection tube. The blood was frozen at -80°C during collection and appropriately thawed before DNA extraction.

Genotyping

Blood DNA was extracted utilising the EZ-10 Spin Column DNA Cleanup Minipreps Kit (Bio Basic Inc., USA). The DNA extraction was done according to the kit's manual. The gene was subsequently amplified using two sets of designed primers. The sequence of the leptin A19G nucleotides was determined using the National Center for Biotechnology Information (NCBI) website, which is accessible at https:// www.ncbi.nlm.nih.gov. The leptin A19G accession number was NM_000230.3 (Homo sapiens). The primer was created using the Primer-BLAST website, and the NCBI website's FASTA sequence was used as a reference. After the Primer-BLAST generated primer sequences, the primer pair of interest was chosen from the detailed primer reports as depicted in Table 1. Determination of primer specificity was assessed employing the BLAST (https://blast.ncbi.nlm.nih.gov). application The validated primer sequence was procured from a primer synthesis company.

Primer	Sequence	Melting tempera- ture (°C)
LEP Common Forward	5'-GAG CTG GCG CTA GAA ATG C	59.4
LEP Common Reverse	5'-TGC CAA GAA AGA CCA GCA GA	58.4
LEP 19G (wild-type)	5'-GCG GTT GCA AGG TAA GGC	59.0
LEP 19A (mutant)	5'-TAG GAA TCG CAG CGC CAA	59.0

Table 1: Primer sequences and meltingtemperature.

Leptin A19G genotypes were identified through polymerase chain reaction (PCR) in a 25µl amplification mixture. The mixture comprised specific primers for both wild-type and alternative alleles. LEP common forward and reverse primers (0.2µM each) and 0.1µM of LEP 19G wild-type primers were used in the wild-type tube. Meanwhile, 0.2µM each of LEP common forward and reverse primers, along with 0.1µM of LEP 19G mutant primers, were employed in the alternative allele tube. The amplification mixture also included 12.5µl of 2X Tag Master Mix from Vivantis Technologies (Malaysia) and double-distilled water to reach a total volume of 25µl. The amplification process was carried out using the MyCyclerTM Thermal Cycler from Bio-Rad (USA). It is important to note that this is a double-tube reaction, where one tube represents the wild-type allele, and the other represents the alternative allele for each sample. The mixture was made to ensure an internal control of the common PCR band resulting from the amplification of both the common primers pairing was present regardless of the genotype state, indicating that there was DNA and that the PCR was working.

PCR began with 5 min of 95°C denaturation, followed by 32 cycles of 30 sec each of denaturation, annealing, and fragment extension at 95°C, 61°C, and 72°C, respectively. The cycle was terminated with a subsequent elongation for 2 min at 72°C. The PCR was set to retain the temperature at 20°C before collecting the PCR products. Before amplifying the samples, a temperature gradient was performed to determine the optimal primer annealing temperature empirically. In line with the PCR program and the predetermined PCR parameters, five PCR reaction mixtures with identical DNA samples were run at five different temperatures per the PCR program and PCR parameters set. The temperatures mentioned ranged from 55°C to 65°C. Ultimately, 61°C was the best annealing temperature based on the amplicon band thickness and lack of an unspecific band of the observed agarose gel.

PCR amplification products were detected using the agarose gel electrophoresis (AGE) method. The AGE method necessitated agarose powder, Tris-borate-EDTA (1X TBE) buffer, and SafeGreen gel stain. The first and last wells were loaded with a 1.5µL VC 50bp DNA ladder (Vivantis, Malaysia). The remaining wells were loaded with 10µL of PCR products. The gel was electrophoresed with 90V power for 28 min. Subsequently, the AGE product was visualized using ImageQuant LAS 500 (GE Healthcare Bio-Sciences AB, Sweden), an automated gel documentation system. The gel was placed onto the provided DNA tray, and an orange filter was inserted for fluorescence detection. DNA stain imaging was automated, and image analysis output was viewed using the ImageQuant TL v8.1 software.

To evaluate the normality of genotypic distribution in the study, the Hardy-Weinberg Equation was assessed using the formula as follows:

> p2 + 2pq + q2 = 1.....(3.3)p = frequency of dominant allele<math>q = frequency of mutant allele

The Hardy-Weinberg Equilibrium formula was derived from allelic frequencies tabulated in a Punnet square. By plugging in p=43/51 and q=8/51 derived from genetic counting, the Hardy-Weinberg Equilibrium was calculated as follows:

(86/102)2 + 2([86/102] [16/102]) + (16/102)2 = 1

Capillary Sequencing

Samples from each genotype group obtained from the PCR experiment were sent for capillary sequencing. This step was vital to endorse the primers in targeting the correct sequence of the DNA genome, concomitantly verifying the results obtained. Before sending for capillary sequencing, the polymorphic bands were eluted and purified using the EZ-10 Spin Column DNA Cleanup Minipreps Kit (Bio Basic Inc., USA). The company's capillary sequencing results were viewed using Chromas version 2.6.6 DNA sequencing software (Technelysium Pty Ltd, Australia).

Statistical Analysis

Statistics analyses were executed using the Statistical Package for Social Sciences (SPSS) version 28 (SPSS Inc, Chicago, IL, USA). Numerical data were described as mean (\pm Standard Deviation, SD), while categorical data were expressed as frequency (%). Genotype and allele frequencies were assessed using gene counting, and the Hardy-Weinberg Equilibrium value was calculated for the genotype distribution of the LEP A19G. The association between A19G polymorphism regarding eating preference and frequency of food consumption was assessed using the Chisquare (χ 2) test. p-value <0.05 was considered statistically significant.

RESULTS

Development of PCR Method for Detection of A19G Polymorphism

The PCR temperature gradient was done using MyCyclerTM Thermal Cycler (Bio-Rad, US) and DNA extracted from a blood sample to establish the optimal annealing temperature for the primers. This step was essential to ensure appropriate primer-to-template integration. As outlined on the specification sheet, the calculated annealing temperature for the common forward and reverse primers was 56.7°C and 56.8°C, respectively. Therefore, the optimal temperature was empirically determined from 48°C to 62°C. Five different temperatures were run for the DNA sample to determine the outcomes of the gel electrophoresis band. As a result, the PCR procedure was run for 32 cycles with an optimized annealing temperature of 61°C, which was higher than the predicted temperature for both primers. The difference in calculated annealing temperature from the actual annealing temperature was probably influenced by magnesium (Mg2+) and potassium (K+) concentrations (Porta & Enners, 2012) in the buffer.

A19G Polymorphism Detection

A wild-type allele was visualized as a 130bp band, while an 80bp band represented a mutant allele. Gene carrying both alleles produced DNA bands at 130bp and 80bp. The A19G polymorphism detection products are shown in Figure 1. The DNA band bases were relatively compared to the 50bp ladder on lanes 1 and 8. The upper and lower columns were electrophoresed PCR products of wild-type and mutant primers, respectively. The combination of wild type and mutant electrophoresed on the upper and lower lanes gave the genotype for each sample. Samples 302, 304, 306, and 307 indicated homozygous wild type. Sample 303 was shown to be carrying both heterozygous, wild-type and mutant alleles, while sample 305 was genotyped as a homozygous mutant.



Figure 1: Genotyping result for samples 302-307.

Subjects' Demographics, A19G Genotypic Frequencies and Distribution

Among the 51 participants, there were 10 males (19.6%) and 41 females (80.4%), with a mean age of 23.20 (SD1.56) years old and a mean body mass index (BMI) of 22.74 (SD 4.91) kg/m2. This data was also represented by native (Bumiputra) ethnics, especially Malays, as Universiti Teknologi MARA was established to cater specifically to native ethnics' needs for academic studies and professional

Chi-square (χ 2) test presented in Table 2.

The findings of the Fisher-Freeman-Halton Exact test were interpreted because the predicted frequencies for the study were not fulfilled.

Validation of A19G Polymorphism Detection Results

The results of polymorphism detection by the second person were assessed and compared to the results previously obtained by the method.

Breakfast	Skip n (%)	At home n (%)	At café n (%)	X2	p-value ^a
Wild-type Heterozygous Mutant	9(24.3) 3(25.0) 1(50.0)	14(37.8) 4(33.3) 1(50.0)	14(37.8) 5(41.7) 0(0.0)	1.843	0.916
Lunch	At home n (%)	Fast food/ cafe/ restaurant n (%)	Pace lunch prepared at home n		
Wild-type Heterozygous Mutant	4(10.8) 1(8.3) 0(0.0)	33(89.2) 10(83.3) 1(50.0)	0(0.0) 1(8.3) 1(50.0)	8.227	0.064
Supper	At home n (%)	Fast food/ cafe/restaurant n (%)			
Wild-type Heterozygous Mutant	28(75.7) 10(83.3) 2(100.0)	9(24.3) 2(16.7) 0(0.0)		0.537	0.822

Table 2: The relationship between A19G polymorphism and eating preference at breakfast, lunch, and supper (n=51).

^a Fisher-Freeman-Halton Exact test

development (Universiti Teknologi MARA, 2020). The subjects' mean BMI was $22.74(\pm 4.91)$ kg/m2, categorized as normal weight based on global WHO recommendations (WHO, 2010) The most significant percentage of overall A19G genotype distribution was weighed by homozygous wild-type genotype with over 37 (72.5%), followed by heterozygous mutant genotype with 12 (23.5%) and homozygous s mutant genotype with 2 (3.9%). The wild-type allele was assigned as G, while A was mutant.

Association between A19G Polymorphism and Eating Preference

Further analysis was performed to assess the association between A19G polymorphism and the eating preference of the subjects using the

The polymorphism detection was observed in Figure 1. Capillary sequencing results delivered by the sequencing companies were viewed and interpreted. The base composing the gene mutation point was regarded to determine the polymorphism. After the 5'-GCCA-3' sequence in the genome, the guanine (G) base was dominant, while the adenine (A) base was regarded as recessive. Table 3 outlines the capillary sequencing results. The chromatogram revealed that guanine composed the mutation point for samples 301 and 311, while 305 bases comprised adenines. Peaks of guanine and adenine were observed for samples 127 and 319.

DISCUSSION

Robust detection of minute DNA samples has been established with PCR. Optimizing the protocol is critical in yielding amplicons with high fidelity. Yields' performance relied on parameters such as DNA template, buffer condition, PCR cycle number, and primer sequences (Porta & Enners, 2012). First and foremost, DNA was extracted from venous blood. The blood sample has a high yield of DNA templates and can be kept for a long in a proper storage condition in case of delayed molecular testing. An efficient buffer condition was ensured with the appropriate concentration of DNA polymerase, magnesium

Table 3: Capillary sequencing of polymorphic PCR products.

Sample number	Chromatogram	Base at mutation point	A19G polymorphism
301	MMM	Guanine (G)	Homozygous wild-type
311		Guanine (G)	Homozygous wild-type
127		Guanine (G) > Adenine (A	Heterozygous mutan
319		Guanine (G) > Adenine (A)	Heterozygous mutant



chloride (MgCl2), and deoxynucleoside triphosphate (dNTPs). Also, the PCR cycle number plays a pivotal role in producing excellent yields. Setting the cycle number too high would be time-consuming. Initial PCR was done with 30 cyclical reactions during optimization but failed to visualize any bands on the electrophoresed agarose gel. Optimal 32-cycle PCR succeeded in observing bright and distinct bands.

It took specific complementary primers only to amplify the specified target product. Using the Primer-BLAST software, the right flanking area on the genome sequence could be easily identified. To prevent self-annealing and nonspecific primer binding, a universal primer concentration of 0.2 M was employed (Sachse, 2003). In this study, the primer generated the correct bands at 180, 130, and 80 bp.

The A19G genotypic distribution among the subjects was in Hardy-Weinberg equilibrium to indicate no deviation of the genotypic distribution of the expected results from the previous generation and studies. A19G genotype of the homozygous wild type was predominant, followed by heterozygous mutant and homozygous mutant. The frequency trend was similar to several studies in Malaysia (Fan & Say, 2014; Wan Rohani et al., 2018). However, contradicting genotype frequencies can be observed (Liew et al., 2009), where the heterozygous mutant was predominant, followed by the homozygous mutant and homozygous wild type.

Based on gender stratification, males and females have the highest frequencies of homozygous wild-type genotypes. The frequency of A19G genotypic distribution followed the trend of the Malaysian suburban population in Perak (Fan & Say, 2014). Still, it contradicted Mestizos in western Mexico (Partida-Pérez et al., 2011) and the Italian population (Lucantoni et al., 2000). The variation in trend can be attributed to various ethnicities (Fan & Say, 2014). In this study, A19G polymorphism was higher in female subjects than in males. Some studies disclosed that the polymorphism was unrelated to gender (Fan & Say, 2014; Mizuta et al., 2008). The gender difference in polymorphism distribution might arise due to the small sample number and female subjects predominating the sample. Leptin hormone was also reported to be positively associated with estradiol and negatively associated with testosterone, leading to gender dimorphism of the A19G polymorphism (Lagiou et al., 1999).

Based on the Fisher's Exact test, there was no significant association between A19G polymorphism and breakfast (p=0.916), lunch (p=0.064), and supper (p=0.822) preferences among the subjects. As no correlation was reported in the literature related to the A19G polymorphism, little was known about the association between the polymorphism and eating preference. Nevertheless, some studies have provided insights into the association between meal intake and leptin hormone encoded by the LEP gene (Dashti et al., 2021; Forester et al., 2018; Paz-Filho et

al., 2012; Whincup et al., 2005). Whincup PH indicated a significant association of leptin levels between young pupils consuming home-cooked meals and school dinners (Whincup et al., 2005). Contrary to the current findings, a previous report found that leptin hormone levels tended to be elevated in breakfast-skipper subjects than in breakfasteater subjects (Forester et al., 2018). Other authors reported that elevated insulin levels (Forester et al., 2018; Paz-Filho et al., 2012) may have caused the high leptin levels since insulin boosted the leptin hormone. Another study also supports this statement, where high morning leptin level was distinguished in subjects who were partial to late dinner eating, suppressing their morning appetite (Dashti et al., 2021). Socioeconomic status and food availability might explain an insignificant association between A19G polymorphism preference. Students with and eating unsatisfied life inclined to skip breakfast and dinner (Schnettler et al., 2015). Low dietary restraint was associated with fat-free mass changes (Finlayson et al., 2012). The intake of convenient takeaway meals was evident in university students being away from family (Papadaki et al., 2007). These findings suggest that restrictions in low socioeconomic status and food variations restricted students' means to choose healthful eating and hindered the consumption of food the students craved.

Research indicates that the A19G mutation may influence leptin mRNA translation, potentially altering serum leptin levels (Zhang et al., 2021). Some studies suggest that individuals with the A19G mutation might exhibit different leptin levels compared to those without the mutation, which could affect their appetite regulation and susceptibility to obesity (Liu et al., 2014). However, the evidence is mixed, with some research finding no significant association between this polymorphism and leptin levels or obesity traits (Fan et al., 2014). This suggests that the relationship between the LEP A19G mutation and leptin levels is complex and

may be influenced by other genetic and environmental factors.

Besides genetic factors, different environments provide various sensory cues that can significantly affect appetite. For instance, the sight and smell of food in a restaurant can stimulate hunger and increase food intake, even if one is not particularly hungry. Bright lighting and vibrant colors in fast-food restaurants are designed to encourage quick eating and turnover, often leading to overeating. Conversely, a calm and quiet dining environment, such as a homecooked meal in a cozy kitchen, can promote slower eating and better recognition of satiety signals. Additionally, social settings, like dining with friends or family, can lead to longer mealtimes and increased consumption due to social interactions and the enjoyment of shared experiences. These sensory cues, whether visual, olfactory, or social, play a crucial role in influencing our eating behaviors and overall appetite. We found that the eating habit of our subjects are mostly the same when dietary intake and eating behaviors are controlled or consistent across subjects, it could affect genetic factors, such as the LEP A19G mutation, on obesity. This consistency minimizes the influence of environmental and behavioral variables, making it easier to observe the direct impact of the mutation on body weight and appetite regulation.

Our research had some limitations. The sample size was small, so future studies should include larger-scale sampling. The convenience sampling method might cause dimorphism and mono-ethnic gender distribution among the subjects. We propose sampling subjects from all ethnicities and ages with balanced gender stratification. This study relied on self-reports from the subjects, which might result in recall bias as they might incorrectly gauge their actual food intake. Thus, deviation from accurate results is plausible. Furthermore, this study did not consider anthropometric measures or leptin

hormone levels, which might give an essential insight into the results.

CONCLUSION

In this study, we have successfully developed a PCRscreening method for A19G polymorphism. However, polymorphism was not associated with the frequency of meal preferences and food intake among Faculty of Health Sciences students. This variant allele was lower than the average Malaysian population variant allele frequencies. The A19G polymorphism may not be a marker in different appetite regulation among the subjects. An insignificant association between A19G polymorphism and appetite might be attributed to students' education, socioeconomic status, and lifestyle.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We want to thank everyone from the Faculty of Health Science, UiTM, who participated in the research. We want to express our gratitude to all the respondents.

FUNDING

This research was funded by Geran Penyelidikan Khas (GPK) (600-RMC/GPK 5/3 (026/2020)).

REFERENCES

- Choquette, A. C., Lemieux, S., Tremblay, A., Drapeau, V., Bouchard, C., Vohl, M.-C., & Pérusse, L. (2009). GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec family study. Physiology & Behavior, 98(4), 505–510. https://doi.org/10.1016/j. physbeh.2009.08.004
- Das, D., & Roy, T. (2017). Chapter 34 A Practical Approach to Loss of Appetite. Progress in Medicine, 181-186.
- Dashti, H. S., Gómez-Abellán, P., Qian, J., Esteban, A., Morales, E., Scheer, F. A., & Garaulet,

M. (2021). Late eating is associated with cardiometabolic risk traits, obesogenic behaviors, and impaired weight loss. The American Journal of Clinical Nutrition, 113(1), 154–161. https://doi.org/10.1093/ajcn/ngaa264

- de Graaf, C., Blom, W. A., Smeets, P. A., Stafleu, A., & Hendriks, H. F. (2004). Biomarkers of satiation and satiety. The American Journal of Clinical Nutrition, 79(6), 946–961. https://doi. org/10.1093/ajcn/79.6.946
- de Krom, M., van der Schouw, Y. T., Hendriks, J., Ophoff, R. A., van Gils, C. H., Stolk, R. P., Grobbee, D. E., & Adan, R. (2007). Common genetic variations in CCK, leptin, and leptin receptor genes are associated with specific human eating patterns. Diabetes, 56(1), 276– 280. https://doi.org/10.2337/db06-0473
- Facey, A., Dilworth, L., & Irving, R. (2017). A review of the leptin hormone and the association with Obesity and diabetes mellitus. Journal of Diabetes & Metabolism, 08(03). https://doi. org/10.4172/2155-6156.1000727
- Fan, S. H., & Say, Y. H. (2014). Leptin and leptin receptor gene polymorphisms and their association with plasma leptin levels and obesity in a multi-ethnic Malaysian suburban population. Journal of Physiological Anthropology, 33(1). https://doi.org/10.1186/1880-6805-33-15
- Finlayson, G., Cecil, J., Higgs, S., Hill, A., & Hetherington, M. (2012). Susceptibility to weight gain. eating behaviour traits and physical activity as predictors of weight gain during the first year of university. Appetite, 58(3), 1091–1098. https://doi.org/10.1016/j. appet.2012.03.003
- Forester, S. M., Widaman, A. M., Krishnan, S., Witbracht, M. G., Horn, W. F., Laugero, K. D., & Keim, N. L. (2018). A clear difference emerges in hormone patterns following a standard midday meal in young women who regularly eat or skip breakfast. The Journal of Nutrition, 148(5), 685–692. https://doi.org/10.1093/jn/ nxy020
- Grimm, E. R., & Steinle, N. I. (2011). Genetics of eating behavior: Established and emerging concepts. Nutrition Reviews, 69(1), 52–60. https://doi.org/10.1111/j.1753-4887.2010.00361.x
- Halford, J. C., & Blundell, J. E. (2000). Separate Systems for serotonin and leptin in appetite control. Annals of Medicine, 32(3), 222–232. https:// doi.org/10.3109/07853890008998829
- Hunot, C., Fildes, A., Croker, H., Llewellyn, C.H., Wardle, J., Beeken, R.J. (2016). Appetitive traits and relationships with BMI in adults:

Development of the adult Eating Behaviour Questionnaire. Appetite 105, 356–363. https://doi.org/10.1016/j.appet.2016.05.024

- Isse, N., Ogawa, Y., Tamura, N., Masuzaki, H., Mori, K., Okazaki, T., Satoh, N., Shigemoto, M., Yoshimasa, Y., Nishi, S., Hosoda, K., Inazawa, J., & Nakao, K. (1995). Structural Organization and chromosomal assignment of the human obese gene. Journal of Biological Chemistry, 270(46), 27728–27733. https:// doi.org/10.1074/jbc.270.46.27728
- Johnson, F., Wardle, J., & Griffith, J. (2002). The Adolescent Food Habits Checklist: Reliability and validity of a measure of healthy eating behaviour in adolescents. European Journal of Clinical Nutrition, 56(6), 644-649. https:// doi.org/10.1038/sj.ejcn.1601371
- Kliemann, N., Beeken, R. J., Wardle, J., & Johnson, F. (2016). Development and validation of the Self-Regulation of Eating Behaviour Questionnaire for adults. International Journal of Behavioral Nutrition and Physical Activity, 13(1), 87. https://doi.org/10.1186/ s12966-016-0414-6
- Lagiou, P., Signorello, L. B., Mantzoros, C. S., Trichopoulos, D., Hsieh, C., & Trichopoulou, A. (1999). Hormonal, lifestyle, and dietary factors in relation to leptin among elderly men. Annals of Nutrition and Metabolism, 43(1), 23–29. https://doi.org/10.1159/000012763
- Liew, S. F., Chuah, H. S., Lau, C. L., Lee, C. H., & Say, Y. H. (2009). Prevalence of the leptin and leptin receptor gene variants and obesity risk factors among Malaysian University students of Setapak, Kuala Lumpur. Asian Journal of Epidemiology, 2(3), 49–58. https://doi. org/10.3923/aje.2009.49.58
- Liu, P., Shi, H., Huang, C., Shu, H., Liu, R., Yang, Y., Gong, J., Yang, Y., & Cai, M. (2014). Association of LEP A19G polymorphism with cancer risk: a systematic review and pooled analysis. Tumor Biology. 35, 8133–8141. https://doi. org/10.1007/s13277-014-2088-5
- Lucantoni, R., Ponti, E., Berselli, M. E., Savia, G., Minocci, A., Calò, G., De Medici, C., Liuzzi, A., & Di Blasio, A. M. (2000). The A19G polymorphism in the 5 untranslated region of the human obese gene does not affect leptin levels in severely obese patients. The Journal of Clinical Endocrinology & Metabolism, 85(10), 3589–3591. https://doi. org/10.1210/jcem.85.10.6860
- Mizuta, E., Kokubo, Y., Yamanaka, I., Miyamoto, Y., Okayama, A., Yoshimasa, Y., Tomoike, H., Morisaki, H., & Morisaki, T. (2008). Leptin gene and leptin receptor gene polymorphisms

are associated with sweet preference and obesity. Hypertension Research, 31(6), 1069–1077. https://doi.org/10.1291/ hypres.31.1069

- National Institutes of Health (NIH). (2020). National Health and Morbidity Survey (NHMS) 2019: Non-communicable diseases, healthcare demand, and health literacy - Key Findings.
- Papadaki, A., Hondros, G., A. Scott, J., & Kapsokefalou, M. (2007). Eating habits of university students living at, or away from home in Greece. Appetite, 49(1), 169–176. https://doi. org/10.1016/j.appet.2007.01.008
- Partida-Pérez, M., de la Luz Ayala-Madrigal, M., Peregrina-Sandoval, J., Macías-Gómez, N., Moreno-Ortiz, J., Leal-Ugarte, E., Cárdenas-Meza, M., Centeno-Flores, M., Maciel-Gutiérrez, V., Cabrales, E., Cervantes-Ortiz, S., & Gutiérrez-Angulo, M. (2010). Association of LEP and ADIPOQ common variants with colorectal cancer in Mexican patients. Cancer Biomarkers, 7(3), 117–121. https:// doi.org/10.3233/cbm-2010-0154
- Paz-Filho, G., Mastronardi, C., Wong, M. L., & Licinio, J. (2012). Leptin therapy, insulin sensitivity, and glucose homeostasis. Indian journal of endocrinology and metabolism, 16(Suppl 3), S549–S555. https://doi.org/10.4103/2230-8210.105571
- Porta, A. R., & Enners, E. (2012). Determining annealing temperatures for polymerase chain reaction. The American Biology Teacher, 74(4), 256–260. https://doi. org/10.1525/abt.2012.74.4.9
- Sachse K. (2003). Specificity and performance of diagnostic PCR assays. Methods in Molecular Biology (Clifton, N.J.), 216, 3–29. https://doi. org/10.1385/1-59259-344-5:03
- Schnettler, B., Miranda, H., Lobos, G., Orellana, L., Sepúlveda, J., Denegri, M., Etchebarne, S., Mora, M., & Grunert, K. G. (2015). Eating habits and subjective well-being. A typology of students in Chilean State Universities. Appetite, 89, 203–214. https://doi. org/10.1016/j.appet.2015.02.008
- Tanofsky-Kraff, M., Han, J. C., Anandalingam, K., Shomaker, L. B., Columbo, K. M., Wolkoff, L. E., Kozlosky, M., Elliott, C., Ranzenhofer, L. M., Roza, C. A., Yanovski, S. Z., & Yanovski, J. A. (2009). The FTO gene RS9939609 obesityrisk allele and loss of control over eating. The American Journal of Clinical Nutrition, 90(6), 1483–1488. https://doi.org/10.3945/ ajcn.2009.28439
- Universiti Teknologi MARA. (2020). Discover UiTM – History. Retrieved January 5, 2023, https://

uitm.edu.my/index.php/en/discover-uitm/ history

- Wan Rohani, W. T., Aryati, A., & Amiratul Athirah, S. (2018). Haplotype analysis of leptin gene polymorphisms in obesity among Malays in Terengganu, Malaysia population. The Medical Journal of Malaysia, 73(5), 281–285.
- Whincup, P. H., Owen, C. G., Sattar, N., & Cook, D. G. (2005). School dinners and markers of cardiovascular health and type 2 diabetes in 13-16 Year Olds: Cross Sectional Study. BMJ, 331(7524), 1060–1061. https://doi. org/10.1136/bmj.38618.540729.ae
- World Health Organization (WHO). (2010). A healthy lifestyle - who recommendations. World Health Organization. Retrieved December 27, 2022, from https://www.who.int/europe/ news-room/fact-sheets/item/a-healthylifestyle---who-recommendations
- World Health Organization. (2018). Noncommunicable diseases country profiles 2018. Retrieved December 1, 2022, from World Health Organization. https://iris.who. int/handle/10665/274512
- World Health Organization (WHO). (2019). Healthy Diet. WHO Regional Office for the Eastern Mediterranean. Retrieved from, https://apps.who.int/iris/bitstream/ handle/10665/325828/EMROPUB_2019_ en_23536.pdf
- Zhang, A., Wang, S., Zhang, F., Li, W., Li, Q., & Liu, X. (2021). The prognosis of Leptin rs2167270 G > A (G19A) polymorphism in the risk of cancer: A meta-analysis. Frontiers in Oncology, 11, 754162. https://doi.org/10.3389/ fonc.2021.754162

BJMS Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Factors Influencing Occupational Health Practices and Hypertension Among Security Personnel in a Public University

Noor Fatimah Mutahar¹, Khamisah Awang Lukman^{1,2*}, Mohd Faizal Madrim¹, Pravina Deligannu¹

- ¹ Department of Public Health Medicine, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
- ² Centre for Occupational Safety and Health, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
- * Corresponding author's email: khamisah@ums.edu.my

Received: 25 March 2024

Accepted: 30 September 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.6095

Keywords: Security personnel, Occupational health practices, cardiovascular screenings, Cancer screenings, Hypertension



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

Introduction: The noncommunicable disease has emerged as a major epidemic for decades and hypertension has been reported as a disease that has a high association with the occupational factors of security personnel. The duty routines of security personnel such as doing patrols, post-guards and the need to stay alert have made them vulnerable to occupational health and safety hazards. Therefore, this study aimed to identify the factors influencing occupational health practices and hypertension among security personnel in a public university in Kota Kinabalu, Sabah. Methodology: A crosssectional study was conducted among the security personnel of a public university in Kota Kinabalu, Sabah, using a convenient sampling technique. Questionnaires adapted from NHMS 2019 have been distributed among the security personnel of the selected public university. Data analysis was conducted by using the SPSS version 28. Descriptive analysis and cross-tabulations were conducted. Pearson Chi-square/Fisher exact test was used to find the association. Statistical significance was considered at p<.05. Results: Of the total respondents, 77.7% were male and 22.3% of them were female. The mean age of the respondents was 35.5 years with a standard deviation of 8.5. The proportion of annual cardiovascular screenings was 68%, and type of residence (p=.013) and previous employment factors (p=.013) were found

to be statistically significant. Alternately, the proportion of recent cancer screenings was 16.5%, and gender (p=<.001), marital status (p=.004) and year of services (p=.034) were found to be statistically significant. The prevalence of hypertension was 21.4%, and age (p=.001) and year of services (p=.010), were found to be statistically significant. **Conclusion:** Early detection of underlying disease will contribute to the prevention of cardiovascular diseases such as hypertension and diabetes mellitus. Subsequently, annual health screening activities are essential in guaranteeing the guality of health and a life sustenance fundamental practice among security personnel.

INTRODUCTION

The noncommunicable diseases (NCDs) had exerted a heightening trend of morbidity and major cause of mortality across the globe and Malaysia to date (National Institute of Health, 2020; World Health Organization, 2013; World Health Organization, 2023). In particular, the cardiovascular diseases (CVDs), such as hypertension and diabetes mellitus had topped rank other NCDs (Budreviciute et. al, 2020; National Institute of Health, 2020; World Health Organization, 2013; World Health Organization, 2023).

The good and bad effects of urban living were better job prospects but unhealthy lifestyles. The unhealthy lifestyle had further subjected the population living the urban lives to the development of NCDs. In addition, demographic aging, gradual and rapid urbanization and globalization of unhealthy lifestyles have led to a shift in the trends of epidemiologic transcended humankinds, in particular, the NCD (Kumar et. al, 2023; Budreviciute et. al, 2020; National Institute of Health, 2020; World Health Organization, 2023).

Factors associated with occupational health (OH) practices were indicated by

measures taken to maintain a good health status. In order to maintain good health, the security personnel should be aware of their health status in the first place. As described by Chauhan et. al, 2022, focus on law enforces health status and timely intervention rather important in order to maintain good health.

Various studies have shown the association of occupational factors of police duty natures with the prevalence of hypertension (Arredondo, 2019; Parkash et. al, 2019; Hussain & Ajuwon, 2020; Chauhan et. al, 2022; Kumar et. al, 2023). There was also an association of sociodemographic factors with the incidences of hypertension among police types of occupations (Kumar et. al, 2023; Hussain & Ajuwon, 2020). The findings mentioned above had shown inconsistencies in the prevalence of hypertension in various abroad regions as indicated in their studies, in which in the Indian regions, hypertension among policemen indicated higher prevalence (Parkash et. al, 2019; Chauhan et. al, 2022; Kumar et. al, 2023), when compared to the study conducted among policemen in Mexico (Arredondo, 2019).

The above-mentioned phenomenon raised interest in the current study setting and population, in which the sociodemographic and occupational factors of the study population would have predisposed them to the infliction of hypertension. This led to insights that present ranked position, job scopes, duty shifts, working hours, year of service and previous employment were the occupational factors that had contribute to the development of hypertension among security personnel of the study population.

Whereas, the significant influences of occupational factors on humankind were that occupants in various broad cultures of occupation tended to be developing or inculcating various modes of dietary patterns, socializing norms and within-society adaptation (Parkash et. al, 2019). This led to the insights that non-modifiable risk factors such as the gender, age, race, marital status, level of education and type of residence would have caused the infliction of hypertension among the security personnel of this study setting.

Hypertension had been identified to be highly associated with security nature of occupations (Chauhan et. al, 2022; Hussain & Ajuwon, 2020; Parkash et. al, 2019). The need to stay alert and highly vigilante had imposed them to the infliction of hypertension (Chauhan et. al, 2022; Hussain & Ajuwon, 2020; Parkash et. al, 2019). This correlated with the duty scopes of security personnel which demanded them to be in highly vigilante mode and concentrations while doing postguards in their designated post locations.

In this particular study, the main study population and settings involved a public university security division, which was registered as auxiliary police of the University but profoundly known as security personnel. The classification of their duty roles would resemble the duty forces of both the security and police forces. Nevertheless, this study aimed to investigate factors associated with occupational health practices and hypertension among the security personnel in Kota Kinabalu, Sabah.

MATERIALS AND METHODS

Study Design, Setting and Participants

A cross-sectional study was conducted from September 2022 to July 2023 among the security personnel of a public university security division, in Kota Kinabalu, Sabah. All eligible study participants who consented to participate in this research activity received a hard copy of an anonymous questionnaire. This included an explanatory opening paragraph reporting the purpose of the study, advising that there was no obligation to complete the questionnaire, and reassuring that the information obtained would remain confidential. The return of the ended question was considered as written consent to participation. Pre-tested questionnaires adapted from NHMS 2019 were self-administered in the security division office setting and in every zone post location in the university compound. It contained three sections which were: I socio-demographic factors, and occupational factors and II the self-reported medical histories of known hypertension. The final section assessed their practice of substantial OH elements which consisted of the annual cardiovascular and recent cancer screenings.

Dependent Variables

Annual cardiovascular/medical check-ups/ screenings were the thorough body checkups conducted and medical reports that had been validated by medical doctors and could be used as proof of the designated worker's health condition (National Institute of Health, 2020). Whereas, cancer screenings were the pre-cancer screenings conducted based on the most recent period within this study implementation. Collectively, colorectal, breast, PAP smear and mammogram were jointly grouped in this variable (National Institute of Health, 2020). Meanwhile, the known hypertension was defined as selfreported as being told to have hypertension by a doctor or assistant medical officer, in the past twelve months of this study duration (National Institute of Health, 2020).

Independent Variables

The socio-demographic variables were gender, age, marital status, type of residence and level of education. Residence is defined as security personnel who temporarily resided within the university compound due to duty purposes and non-residence are those living outside the university compound and needed to travel back and forth for duty purposes.

The occupational variables were present ranked position, job scopes, working hours, duty shifts, year of service and previous employment factors. Junior ranked position referred to every ranking order below ranking grades 41, and senior referred to ranking grades 41 and above. The administration duty scopes comprised desk job, administrative, and accounting type duties and attached in the security division main office and worked in Non-shift mode of working (daily office hours). Meanwhile, operational duty scope entitled to doing regular patrols, zone post guards and supervising and working in shift mode. Previously unemployed/self-working referred to as security personnel who were not affiliated in other working sectors. Whilst, the previously employed security personnel were those affiliated in another working sector before joining the security division of Universiti Malaysia Sabah (UMS).

Sample Size Calculation and Sampling Technique

A convenient sampling technique was used to select study units and the sample size was calculated using the Krejcie & Morgan (1970) sample size formulae (Chua, 2020). Thus, with a population of 170, the sample size was determined as 118.

Inclusion Criteria

Serving security personnel aged between 20 and 60 years old and were willing to participate were included in the study.

Exclusion Criteria

The security personnel of the university setting who were on sick and personal leaves were excluded from the study.

Data Analysis

Data were compiled and analyzed using SPSS version 28.0. Descriptive analysis and Crosstabs were used to evaluate association between groups of the categorized variables. p-value <.05 was considered statistically significant. Whereas Pearson Chi Square and Fisher Exact test were used to determine the significant association between independent and dependent variables.

Ethical Approval

The ethics approval for research activities had been given by the medical committee of the Faculty of Medicine and Health Sciences, UMS. The approval code was JKEtika 1/23 (13). In addition, research activity consent was also submitted and approved by the university setting security division.

RESULTS

A total of 103 respondents were obtained throughout the study. Of the 103 respondents, 68 (66%) of them were identified to have conducted yearly cardiovascular health screenings and 17 (16.5%) of them have conducted cancer screenings. Male security personnel, between 31 and 40 years of age, Sabahan, married and with secondary level of education, junior ranked, having operational duty scope, having 1 to 5 years of services and previously employed in other working sectors made up the majority of respondents to have conducted annual cardiovascular and cancer screenings. Whereas, type of residences (p=.013) and previous employment factors (p=.013) were identified to have significant association with the prevalence of yearly conducted cardiovascular screenings. Besides, gender (p=<.001), marital status (p=.004) and year of services (p=.034) were identified to have significant association with the prevalence of cancer screenings. All information was shown in Table 1.

On the other hand, 22 (21.4%) of them were identified to have known hypertensive. The age factor (p=0.002) and year of services were identified to have significant association with the prevalence of known hypertension (p=.010). Meanwhile, sociodemographic factors such as race, marital status, education and type of residences and occupational factors such as the present rank position, duty scopes, shift hours and previous employment factors had no significant association with the prevalence of known hypertension. All information was shown in Table 2.

Table	1.	The	Asso	ciation	of	socio	-dem	ographic	and	occupational	factors	with	the	prevalence	of
annua	l ca	rdio	vasci	ular an <mark>c</mark>	d ca	ncer s	creen	ings.							

Variable (n=103)	Annual Cardiovascular Check-ups n (%)	p-value	Cancer Screenings n (%)	p-value
	68 (66)		17 (16.5)	
Gender Male Female	51 (49.5) 17 (16.5)	Fisher's exact test used: .259	2 (11.8) 15 (88.2)	Fisher's exact test used: <.001
Age (Years) 20 to 30 31 to 40 41 and above	23 (33.8) 30 (44.1) 15 (22.1)	χ2 val- ue=.060; df=2; p=.970	6 (35.3) 7 (41.2) 4 (23.5)	χ2 value=.101; df=2; p=.951
Race Malay Sabahan Sarawakian	3 (2.9) 63 (61.2) 2 (1.9)	χ2 val- ue=2.705; df=2; p=.259	1 (5.9) 16 (94.1) -	χ2 val- ue=1.104; df=2; p=.602
Marital Status Unmarried Married Divorce/Widow/Widower	16 (15.5) 51 (49.5) 1 (1)	χ2 val- ue=3.323; df=2; p=.190	5 (29.4) 9 (53) 3 (17.6)	χ2 val- ue=11.166; df=2; p=.004
Level of Education Secondary Level Tertiary Level Higher Level	47 (45.6) 13 (12.6) 8 (7.8)	χ2 val- ue=.380; df=2; p=.827	11 (64.7) 5 (29.4) 1 (5.9)	χ2 val- ue=1.305; df=2; p=.521
Type of Residences Residence Non-Residence	9 (8.7) 59 (57.3)	Fisher's exact test used: .013	1 (5.9) 16 (94.1)	Fisher's exact test used: .281
Present Ranked Position Junior Senior	61 (59.2) 7 (6.8)	Fisher's exact test used: .541	17 (100) -	Fisher's exact test used: .150
Job Scope Administration Operation	17 (16.5) 51 (49.5)	Fisher's exact test used: .259	1 (5.9) 16 (94.1)	Fisher's exact test used: .063
Duty Shift Yes No	60 (88.2) 8 (11.8)	Fisher's exact test used: .448	16 (94.1) 1 (1)	Fisher's exact test used: .424
Year of Services New Intake 1 to 5 Years 6 to 10 Years 11 Years and above	11 (10.7) 22 (21.4) 18 (17.5) 17 (16.5)	χ2 val- ue=6.661; df=3; p=.084	1 (5.9) 11 (64.7) 1 (5.9) 4 (23.5)	χ2 val- ue=8.657; df=3; p=.034
Previous Employment Factors Unemployed/ Self-Working Employed	15 (22.1) 53 (77.9)	Fisher's exact test used: .013	7 (41.2) 10 (58.8)	Fisher's exact test used: .209

Table 2. The association of socio-demographic and occupational factors with the prevalence of known hypertension.

Variable (n=103)	Known Hypertension n (%)	p-value
	22 (21.4)	
Gender Male Female	18 (22.5) 4 (3.8)	Fisher's exact test used: .418

Age (Years) 20 to 30 31 to 40 41 and above	1 (4.5) 11 (50) 10 (45.5)	χ2 value=13.744; df=2; p=.001
Race Malay Sabahan Sarawakian	1 (1) 21 (20.4)	χ2 value=.800; df=2; p=.670
Marital Status Unmarried Married Divorce/Widow/Widower	3 (2.9) 19 (18.4) -	χ2 value=3.211; df=2; p=.201
Level of Education Secondary Level Tertiary Level Higher Level	15 (14.6) 5 (4.9) 2 (1.9)	χ2 value=.143; df=2; p=.931
Type of Residences Residence Non-Residence	4 (3.8) 18 (17.5)	Fisher's exact test used: .345
Present Ranked Position Junior Senior	20 (19.4) 2 (1.9)	Fisher's exact test used: .638
Job Scope Administration Operation	7 (6.8) 15 (14.6)	Fisher's exact test used: .178
Duty Shift Yes No	21 (20.4) 1 (1)	Fisher's exact test used: .268
Year of Services New Intake 1 to 5 Years 6 to 10 Years 11 Years and above	6 (5.8) 5 (4.9) 11 (10.7)	χ2 value=11.409; df=3; p=.010
Previous Employment Factors Unemployed/ Self-Working Employed	9 (8.7) 13 (59.1)	Fisher's exact test used: .162

DISCUSSION

The OH practices would symbolize the importance of maintaining appropriate health practices while at work, for employees' longterm well-being (World Health Organization, 2002). The occupational health hazards could be broadly classified as biological, chemical, physical, ergonomic, and psychological agents, and accidents (Mehrdad, 2020; Canadian Centre for Occupational Health and Safety, 2021). In relation to this, factors associated with OH included mitigation and identification of health risks and hazards, improved productivity, efficiency and improved employee relations and morale, reduced costs associated with accidents or injuries which resulted from fewer workplace

incidents and workers' compensation claims (World Health Organization, 2002).

Since the 9th Malaysia Plan in 2006, the focus has changed from illness to wellness and many policies and programs have been introduced and implemented to encourage regular health screenings (National Institute of Health, 2020). The notable recent one is the PEKA B40 health screening initiative for the low-income B40 group aged 40 years and above which had been related to cardiovascular (CVD) screenings.

The annual cardiovascular screenings comprised of blood pressure, full blood count, lipid profile and glycated hemoglobin test. This was the basic package in the yearly medical check-ups conducted as for health and also occupational demands for contract renewal purposes.

In Malaysian settings, the prevalence of health screening or medical check-ups within the past 12 months (prior to the period of this survey conducted through NHMS 2019) was 49.0% (95% Cl: 47.03, 50.94). The prevalence was higher among older age groups, with 77.3% (95% Cl: 74.36, 79.95) among adults aged 60 years and above. Females also reported having a higher prevalence compared to males. Widowers and divorcees had a higher uptake of medical check-ups, as well as among retirees.

Among the socio-demographic factors assessed in this study, type of residence showed a significant association with the prevalence of yearly medical screenings. Non-residence turned out showing higher prevalence and was highly significant in having conducted the yearly medical screenings as compared with residents. Whereas in terms of occupational factors, previous employment factor was shown to be significantly associated with a high prevalence of yearly conducted medical screenings, in which previously employed in other working sectors were highly prevalent in comparison with those previously unemployed or self-worked.

Other than CVD risk screenings, Malaysia also has a national cancer screening program for breast cancer, cervical cancer, and colorectal cancer (National Institute of Health, 2020). Such notions should be highly encouraged, but the actual uptake of health screening practices among Malaysians is still vastly unknown (National Institute of Health, 2020).

As reported in NHMS 2019, breast cancer was the most common cancer among women in Malaysia. Breast self-examination, clinical breast examination, and mammogram screening were several methods suggested for early detection of breast lumps. Mammogram screening did exhibit a reduction of breast cancer mortality by approximately 15% for women aged 39 to 49 years old. As reviewed in NHMS 2019, the most significant barriers to mammograms among Malaysian women in the general population were lack of time, lack of knowledge, unawareness of the facilities to run the test, and the fear of knowing the test result.

On the other hand, cervical cancer is the most common cancer among women worldwide. As per the report, in Malaysia, cervical cancer was the third most common cancer in women, with an incidence rate of 6.3 per 100,000 (National Institute of Health, 2020). The pap smear screening program was introduced in Malaysia by the MOH in 1969. Moreover, women aged between 30 and 65 years and who were sexually active were recommended to undergo pap smear screening.

In addition, colorectal cancer (CRC) was the most prevalent cancer among males (14.8%) and second most common among females (11.1%), according to the Malaysia Cancer Registry Report 2012 to 2016. Evidence exists that reductions in CRC mortality could be achieved through the detection and treatment of early-stage CRCs. In Malaysia, the CRC screening program was implemented using the WHO stepwise approach in 2014. The target group was asymptomatic males and females aged 50 to 75 years old. The screening method was using the immunological Faecal Occult Blood Test (iFOBT), followed by colonoscopy for those who were found to be positive for iFOBT. The objective of the colorectal screening program in Malaysia was to detect the pre-cancerous lesion and to detect cancer at the earliest stage possible (National Institute of Health, 2020).

It showed that the female gender and married status had significant association with the prevalence of the yearly conducted cancer screenings. These findings show inter relation as the fact that the type of cancer screenings being assessed, such as breast cancer, PAP smear test and mammogram were gender preference over female and that requirements of doing were mainly associated with the marital status of females, for instance, the PAP smear test.

The occupational factors revealed that the year of services had a significant association with the prevalence of cancer screenings. Duration of 1 to 5 years of services had the highest prevalence of having conducted the cancer screenings shown interrelation with the fact that female aged 18 years and above were encouraged to do breast screening. Whereas mammograms and PAP smear test were advised to be conducted among those having symptoms, married female respondents and gotten advice of doing by medical practitioners.

The annual health screening activity would suggest its importance to be maintained and promoted of doing not only due to occupational demands but also in concern with one's health. Hypertension seemed to be taken lightly with the circulating stigma that every aging individual would have developed high blood pressure due to age factors without knowing the fact that hypertension is a risk factor for occurrences of other serious health problems.

The age had significant association with hypertension in this study (p=.002), and similar findings was also observed in similar study (Parkash et. al, 2019). Most of the hypertensive respondents had completed Malaysian secondary level of education and were married. Yet, these findings fluctuated with other literature findings (Chauhan et. al, 2022; Hussain & Ajuwon, 2020; Kumar et. al, 2023; Parkash et. al, 2019).

The operational duty scope was the highest and duty patrols confined within

operational duty scopes had shown to have significant association with the prevalence of hypertension (Chauhan et. al, 2022). Yet, these findings deflected with the current study conducted. Every security personnel, regardless of position rankings were inscribed with total of eight hours shift of working and had been found to have significant association with the prevalence of hypertension (p=.010) and had been reported in other similar studies (Chauhan et. al, 2022; Kumar et. al, 2023; Parkash et. al, 2019).

CONCLUSION

Overall findings revealed that the current study settings had practiced moderately good OH practices. Nonetheless, OH practices such as the yearly activity of health screenings needed to be continuously maintained in every working community to maintain good health.

ACKNOWLEDGEMENT

Warmest thanks and deepest feelings of gratefulness to our research project leader and co-supervisors who made our work possible. Last but not least, very heartfelt gratefulness to the university for having funded this research project.

FUNDING

This study was funded by UMS Grant SDK 0108-2019.

CONFLICT OF INTEREST

There was no conflict of interest.

REFERENCES

Arredondo, G. P. (2019). Incidence of hypertension in a high-risk workgroup (Police officers) – Observational study. Annals of Clinical Hypertension, 3, 052-058. doi: 10.29328/ journal.ach.1001020.

Budreviciute, A., Damiati, S., Sabir, D. K., Onder,

K., Schuller-Goetzburg, P., Plakys, G., Katileviciute, A., Khoja, S., & Kodzius, R. (2020). Management and prevention strategies for non-communicable diseases and their risk factors. Frontiers in Public Health, 8, 574111. doi: 10.3389/fpubh.2020.574111

- Canadian Centre for Occupational Health and Safety (CCOHS). (2021). Occupations and Workplaces. https://www.ccohs.ca/ oshanswers/occup_workplace
- Chauhan, V. S., Bansal, M., Sharma, V., & Gupta, R. (2022). Prevalence and risk factors of hypertension among police personnel of district Gwalior – A cross sectional study. Indian Journal of Community Medicine, 47, 379-385.
- Chua, Y. P. (2020). Mastering research methods. (3rd ed.). McGraw-Hill Education Malaysia.
- Hussain, O. J. & Ajuwon, A. J. (2020). Prevalence, knowledge and preventive practices against hypertension among police officers in Ibadan. Annals of Ibadan Postgraduate Medicine, 18, 114-121.
- Kumar, A., Gautam, P. B., & Pore, P. (2023). Prevalence of hypertension and its associated risk factors among police personnel of a metropolitan city. Asian Journal of Medical Sciences, 14, 122-129. doi: 10.3126/ajms.v14i3.50019
- Mehrdad, R. (2020). Introduction to occupational health hazards. International Journal of Occupational and Environmental Medicine, 11, 59-60.
- National Institute of Health. (2020). National health and morbidity survey (NHMS) 2019: Vol. I: NCDs – Non-communicable diseases: Risk factors and other health problems (NIH Publication No. MOH/S/IKU/144.20(TR)-e). Ministry of Health Malaysia. https://iku.moh. gov.my/images/IKU/Document/REPORT/ NHMS2019/Report_NHMS2019-NCD_v2.pdf
- Parkash, J., Kalhan, M., Singhania, K., Punia, A., Kumar, B., & Kaushal, P. (2019). Prevalence of hypertension and its determinants among policemen in a City of Haryana, India. International Journal of Applied & Basic Medical Research, 9, 143-147. doi: 10.4103/ ijabmr.IJABMR_356_18
- World Health Organization. (2002). Good practice in occupational health services: A contribution to workplace health (EUR/02/5041181). https://iris.who.int/handle/10665/107448
- World Health Organization. (2013). A global brief on hypertension. https://www.who.int/ publications-detail-redirect/a-global-briefon-hypertension-silent-killer-global-publichealth-crisis-world-health-day-2013

World Health Organization. (2023). Noncommunicable diseases. https://www. who.int/en/news-room/fact-sheets/detail/ noncommunicable-diseases

BJMS Borneo Journal of Medical Sciences

CASE REPORT

Educational Experiences and Career Aspirations of Final-Year Nursing Students at International Islamic University Malaysia

Siti Azuna Abu Bakar¹, Khin Thandar Aung^{1*}, Mashitah Aqilah Fauzi²

- ¹ Critical Care Nursing Department, Kulliyyah of Nursing, International Islamic University Malaysia, 53100 Selangor, Malaysia
- ² Aurelius Hospital Pahang, Pahang, Malaysia
- * Corresponding author's email: khin_ta@iium.edu.my
- Received: 20 August 2024
- Accepted: 3 December 2024
- Published : 2 May 2025
- DOI: https://doi.org/10.51200/bjms.v19i2.6099

Keywords: Clinical placements, Career aspirations, Specialization in nursing, Nursing Education, Professional development



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

Recognizing the career aspirations of nursing students is essential for designing educational programs that develop skilled healthcare practitioners. Personal choices in career fields, development opportunities, and education all influence these aspirations. This study explores final-year nursing students' educational experiences and career aspirations at the International Islamic University Malaysia (IIUM). A qualitative descriptive approach was employed to conduct personal interviews with purposefully selected participants from the Kulliyyah of Nursing. The findings reveal that while students are keen to specialise in paediatrics and critical care, they encounter challenges such as academic pressure and a lack of clinical practice hours. Mentorship and clinical placements play a vital role in shaping their professional aspirations. Participants stressed the necessity for enhanced clinical practice and academic support to better equip them for their future roles. These findings underscore the importance of aligning nursing education with students' career goals and addressing their challenges to improve their readiness for specialised healthcare positions. This study enhances the literature on nursing education by emphasising the importance of robust mentorship programmes that support students in their academic and professional growth. By focusing on these elements, nursing curricula can be refined to facilitate specialisation, thereby advancing the field of nursing education.

INTRODUCTION

Career goals play a crucial role in shaping nursing students' educational journeys and future career choices. Nursing is a dynamic and rapidly evolving profession that offers numerous opportunities for advancement and specialisation. Thus, nursing students need well-rounded educational preparation. Historically, how well a nursing school or department trains its students has been linked with subsequent clinical and professional success (Aller, 2020; Qonitatin et al., 2023; Younas et al., 2019). To ensure that students are well-prepared to take up roles in the future, it is important to understand their education history and aspirations for a career.

Increasing literature identifies the need to examine career choice and development among nursing determinants students (Matarese et al., 2019; Tosunöz et al., 2019). In this sense, by investigating these factors, educators can provide a learning environment which can support learners from their growth, and specialisation until their careers (Fontanilla et al., 2023; Sari, 2020). However, the study of Vujicic et al. (2023) provides strong support for the intrinsic motivators that influence people to participate in nursing, including professional fulfilment and responsibility as well as interpersonal relationships. Yet, this investigation only partially compromised nursing students' foundational training and professional desires.

The nursing sector in Malaysia has evolved over the past decade, placing a greater emphasis on specialised knowledge and skills. The International Islamic University Malaysia (IIUM) nursing programme uniquely integrates Islamic values with contemporary healthcare practices, offering students an exceptional learning experience. This is important to ensure that the local curriculum better reflects the local skill needs and also international requirements while understanding these experiences and their impact on career aspirations.

The determinants impacting students' career choices were grouped into three main domains: clinical environment, education and individual. It can promote particular specialities over others in a nursing curriculum. This study provides an understanding of the motivating and demotivating factors that influence students' future career choices and how to motivate/remind them towards less-preferred nursing specialities (Anyango et al., 2024).

Kulliyyah of Nursing at IIUM encompasses a comprehensive four-year course which is supplemented by significant clinical placements in relevant institutions like Hospital Tengku Ampuan Afzan and Hospital Sultan Ahmad Shah. The university focuses that it gives on the importance of Islamic values, and ethical conduct, and these placements create a different learning opportunity for students' eyes regarding their career goals as compared to any other University.

Although the literature on the career aspirations and motivations of nursing students is growing, few studies examine the perceptions of final-year nursing students regarding their course experiences concerning their future careers and specialisation options. Focusing solely on final-year students is important, as this stage represents a critical transition from being a student to becoming a practitioner. Students are ideally positioned at this point, well past the majority of academic and clinical training yet still planning for their future careers, to take stock of how their education has prepared them for any desired career paths. Furthermore, finalyear students are in the process of making career-related decisions such as specialization and future employment opportunities and therefore represent an important group for understanding nursing career aspirations

(Anyango et al., 2024).

There is a notable scarcity of literature specifically addressing final-year nursing students, who are in a transitional phase between education and practice. As these students approach the end of their clinical rotations, they often reflect on where they envision starting their careers. However, not much is known about their opinions on how their educational experiences have influenced these decisions, especially in the context of Malaysian Islamic higher education.

Because there exists a lack of empirical research to investigate this area, therefore this study was designed to answer this phenomenon by exploring final-year nursing students' experiences and expectations towards the profession at the International Islamic University Malaysia (IIUM). This understanding will assist the study in developing targeted interventions to enhance nursing education and support students in their career paths.

Thesefactors will establish the theoretical framework for understanding how different perceptions of educational preparation influence students' expectations for their professional careers. This knowledge will inform appropriate curriculum development and career counselling initiatives, ensuring that future nurses are well-equipped to thrive in an evolving and dynamic healthcare landscape.

MATERIALS AND METHODS

Research Design

A qualitative research design was utilized to gather in-depth insights into the experiences and aspirations of the students. This approach is appropriate for comprehending the nuances of individual perceptions and behaviours (Tang et al., 2020). Qualitative research provides rich, detailed data that quantitative methods might not be able to capture by allowing for a thorough exploration of participants' thoughts, feelings, and experiences (Cadena, 2019).

Setting and Samples

Stratified random sampling was employed to choose final-year nursing students from the Kulliyyah of Nursing at IIUM Kuantan. The eligibility criteria included final-year nursing students with at least one year of clinical practice experience. The study took place in formal classrooms and practical experience areas at the IIUM Kuantan Campus. This setting was advantageous for obtaining an overall understanding of the student's educational background. Several factors support the choice of IIUM as the study location. First, IIUM is a prominent institution with a diverse student population, offering a comprehensive nursing curriculum that integrates both theoretical and practical components. This environment is ideal for exploring the educational experiences and career aspirations of nursing students. Furthermore, IIUM emphasises Islamic values in its educational framework, adding a unique cultural and ethical dimension to the students' learning experiences. This focus on valuesbased education, coupled with the university's strong emphasis on clinical training, provides an enriching context for investigating students' readiness for professional practice. Additionally, the Kulliyyah of Nursing at IIUM is well-regarded for its clinical placements, offering students hands-on experience in various healthcare settings. These placements are crucial for shaping students' career goals, making IIUM's environment particularly relevant for a study exploring the link between educational experiences, clinical exposure, and career aspirations. Finally, the university's commitment to producing competent healthcare professionals aligns with the objectives of this research, further validating the selection of IIUM as the setting for this study.

In qualitative research, there is no predetermined sample size, and it should

depend on the required information or research objectives (Polit & Beck, 2019). Previous qualitative studies have used a sample size of 16 participants (Monique & Kaiser, 2022). However, for this study, the sample was limited to 10 participants, and data saturation was reached during the 8th interview. Details such as the date and time of the last interview and the participant identification number 9 indicated that data saturation had been achieved. The interviews were concluded when no additional information could be identified, and no more codes could be generated for this study. This occurred after a total of nine interviews, and the data became saturated.

Data Collection

The study was conducted in the year 2024, with a duration of four months, from February to June. Data were collected through faceto-face semi-structured interviews. The interviews were conducted in English and Malay, depending on the participants' preference. Each interview lasted between 30 and 60 minutes. The interview guide consisted of open-ended questions that allowed participants to freely express their thoughts and experiences. The questions focused on educational experiences, clinical placements, career aspirations, and factors influencing career choices. The interviews were transcribed verbatim and analysed using thematic analysis to identify key themes. This method involves coding the data, identifying recurring patterns, and synthesizing the findings to provide a comprehensive understanding of the students' experiences and aspirations.

Data analysis

The data processing process began by transcribing the interviews conducted in the participants' language using Microsoft Word. The transcripts were reviewed multiple times to familiarize the researcher with the participants' accounts and establish an initial understanding of their narratives. Before coding, a comprehensive analysis of the transcripts was conducted using the thematic analysis method to determine overarching themes.

Braun and Clarke (2006) propose a sixstep framework for thematic analysis, which includes becoming familiar with the data, generating initial codes, identifying themes, reviewing themes, defining and naming the themes, and finally, writing the report (Naeem et al., 2023). The first step involved examining the structure of the narratives to understand their chronological flow. The second step focused on the content of the narratives to uncover the meaning. The researcher then proceeded with coding, independently coding at least two transcripts to generate initial codes. The data were then categorized by identifying more general categories or themes from these initial codes. In the final step of the analysis, the objective was to identify recurring patterns in the participants' decision-making processes. To ensure the development of emerging themes, the authors engaged in a recursive dialogue, reaching a consensus on the themes while preserving the participants' voices. Any discrepancies were resolved by reviewing the typed interview notes and tapes or consulting the field notes. Although some quotes may have been translated from Malay into English for documentation purposes, the meaning closely resembled the source language to accurately reflect the participants' accounts.

Trustworthiness/rigor:

Dependability and confirmability in this study were ensured by maintaining an audit trail, as recommended by Braun and Clarke, 2006 (Naeem et al., 2023). The audit trail recorded and monitored the actions and choices made throughout the process of gathering, analyzing, interpreting, and formulating conclusions from the data. Detailed documentation was kept in a research journal, documenting observations on the research procedure, interactions with participants, and the researcher's thoughts, emotions, and analyses. Consistent with the criteria outlined by Braun and Clarke, 2006 and Naeem et al (2023), it was important to prioritize transparency in interpreting the data. The analysis of the results was based on a thorough examination of the data, including interview transcripts, audio recordings, reflective journals, and field notes. Additionally, regular consultations with three experts in qualitative research and a thorough examination of relevant literature guided the analytical process.

The importance of transparency in narrative research, states that describing how interpretations were obtained allows readers to evaluate the study's thoroughness (Campbell et al., 2019). Therefore, the interpretations provided in this context are based on a comprehensive analysis of the data and scholarly discussions, confirming the researcher's commitment to ensuring the accuracy and reliability of the results.

Although member-checking is commonly used to enhance the credibility of qualitative research, its use in this study was reevaluated due to the extensive audit trail and strong engagement with the data. Conversely, the study highlights the importance of providing detailed and comprehensive descriptions, as well as purposefully selecting samples, to improve the applicability of the findings to different situations (Hiebl, 2021).

Ethical Considerations

Before the commencement of the study, ethical approval was obtained from the appropriate authority, specifically the IIUM Ethical Committee, under reference number IREC 2024-KON/CCN1. Participation in the study was entirely voluntary, and informed consent was obtained from all participants before their involvement. To protect participants' identities, pseudonyms were assigned during the transcription and analysis phases of the study, ensuring that no identifiable information was linked to the data. Additionally, any identifying details in the interviews, such as specific references to individuals or locations, were removed to maintain confidentiality. The anonymity and confidentiality of the data were diligently maintained throughout the research process, and all data were stored securely in password-protected files accessible only to the research team.

RESULTS

A total of 9 final-year nursing students aged between 23 and 24 participated in this study, of which 7 were female and 2 were male. The findings are presented under four major themes: learning experience, clinical placement, career aspiration, and factors influencing career choices.

Theme 1: Learning Experience

Participants reported that their learning experience had been profoundly affected by the transition to online learning due to the COVID-19 pandemic. This shift made it challenging for students to remain motivated and engaged, especially in the absence of hands-on activities. One participant shared, "When the classroom changed to online, it was a difficult transition. It was much harder to stay motivated and engaged since we couldn't do hands-on activities." (Participant 1).

The study was conducted in 2024, after the COVID-19 pandemic. However, the participants faced challenges during their second and third years. Despite these difficulties, students noted that the support and mentorship they received from faculty members significantly contributed to their growth. One participant highlighted the value of their mentor, stating, "My mentor was very encouraging. Her support helped me overcome many obstacles and inspired me to pursue a career in paediatric nursing." (Participant 2).

Theme 2: Clinical Placement

Clinical placements were regarded as vital for developing practical skills and boosting confidence in real-life healthcare settings. Participants shared experiences from various placements, which influenced their career perspectives. For instance, one student said, "Working in the ICU was an enlightening experience. It was very busy, but I learned a lot about patient care and teamwork." (Participant 3, 8). Another participant noted how their time in the oncology ward reignited their passion for working with cancer patients, stating, "The experience on the oncology ward reignited my passion for working with cancer patients." (Participant 4).

Theme 3: Career Aspiration

Several students expressed a desire to pursue specialities in areas such as paediatrics, critical care, and emergency. As the participants advanced through their education, their career aspirations became more defined. Initially, many students expressed broad interests, but clinical placements helped narrow their focus. For example, one participant shared, "At first, I was confused about my career choice, but after my rotations, I knew I wanted to specialise in Emergency Nursing." (Participant 5).

Theme 4: Factors Influencing Career Choices

The participants identified personal interest, family influence, and role modelling as key factors shaping their career decisions. They expressed gratitude for their family's support, saying, "My family always gave me the confidence to pursue nursing as my career, and without them, it would not have been possible." (Participant 6, 7). Furthermore, mentorship played a critical role in helping students gain confidence and pursue their aspirations. One participant remarked, "Having a mentor who believes in you can make all the difference in the world. You feel confident to pursue your dreams." (Participant 9).

In summary, the interviews conducted with nine nursing students revealed significant insights into the multifaceted experiences that shape their educational journeys and career aspirations. The transition to online learning during the COVID-19 pandemic presented considerable challenges, particularly in maintaining engagement and motivation without hands-on practice. However, mentorship from professors and clinical instructors emerged as a crucial element of support, facilitating both professional development and resilience.

Consistently, clinical placements were identified as pivotal in enhancing practical skills and building professional confidence. These experiences not only equip students with essential knowledge and skills but also play a decisive role in shaping their career interests and specialization choices. Participants' career aspirations evolved, influenced by their clinical rotations and the guidance they received, leading many to focus on specific nursing specialities such as paediatrics, emergency nursing, and critical care.

Furthermore, the study highlighted the profound impact of personal motivations, familial support, and mentorship on the participants' career choices. The combination of these factors emphasizes the importance of a supportive and nurturing environment in the development of a strong professional identity and the pursuit of career goals in nursing. Overall, the findings suggest that targeted support through mentorship, diverse clinical experiences, and a conducive learning environment are essential for cultivating the next generation of nurses who are both confident and committed to their chosen specialities. Future research could further explore how these factors interact throughout a nursing student's education and their longterm impact on professional development.

DISCUSSION

Learning Experience

Relevant ideas were found from the study results which are appropriate to clarify the experiences and professional growth of nursing students. They found these concepts throughout the presentation and have expanded upon them. The sudden transition to online learning because of the COVID-19 pandemic presented significant challenges. This sudden change disrupted the in-person clinical opportunities for students in the spring of 2020 due to global health challenges (Head et al., 2022; Pologruto et al., 2021). According to the studies (Kalanlar, 2022; Kang, 2021), students could not experience continuous engagement and implement theoretical knowledge due to a lack of practical training opportunities. In addition, students struggle to maintain motivation and interest when there are no experiential opportunities (Kinsey, 2020). The discussion section explains the reasons behind these findings, as well as more information related to the interruption of actual patient care. The findings of this study provide critical evidence to help inform nursing education policy and curriculum development in response to the challenges posed by COVID-19. Online learning did not allow for critical in-person clinical experiences essential to the nursing education process whereby real practice occurs and practical experience is gained. Such a disruption called into question the need for a more adaptive and resilient educational system. According to Kalanlar (2022) and Kang (2021), completeness of clinical competence development can not only be from online learning. Nursing education policy must better plan for the mixed-mode model of education that integrates theory with simulations in virtual space so that the translation into clinical practice can continue when physical clinical placements are scarce. According to Pologruto et al. (2021) stimulated understanding of the virtual simulation programmes retains significant competence when in-person clinical training is not feasible. Additionally, the difficulties caused by the pandemic highlighted the need for mentorship in nursing higher education. Supported by Heffernan (2020), and Dahlberg & Byars-Winston (2019) that addressed the importance of rethinking mentorship as a means of making connections between theory and application, to help students manage academic or

professional life when challenges appear. Policies should promote that established mentorship programmes are integrated into the nursing curriculum to support nursing students with experience during their clinical placements. These programmes will ideally improve the performance, satisfaction and career understanding of the students (Enyan et al., 2021).

Clinical Placement

Clinical placements in the education and training of competent healthcare professionals are an essential component (Aryuwat et al, 2024). As recently documented by Younas and Maddigan (2019), this anticipation is reinforced by the needs of students who greatly value the developed practice skills, as well as fortified confidence in applying these skills in actual healthcare settings. Students will be able to advance their technical skills and be able to provide care to patients, give medications and perform medical procedures under the auspices of experts. It enables them to be flexible in the changing environment of health care (Rojo et al., 2020). Clinical placements are not just a means to gain skills, they also foster critical thinking, problem-solving and choices that require ethical decisionmaking (Aryuwat et al., 2024). This approach is based on exposing students to real-world problems that need solutions. Clinical practice is a formative process, and the guidance and advice of experienced healthcare providers are crucial to guiding students through complex clinical situations while developing their professional identities. In addition, clinical placements are integral to the socialisation of practice-oriented skills of collaboration and communication (Cant et al., 2021) during interdisciplinary episodes in healthcare. Contact with different populations develops more empathy, resilience and patientcentredness. These experiences influence graduates' job choices because participants receive first-hand experience in different specialities, impacting students' future career directions (Bobbo & Lázzaro, 2018). To sum it up, clinical placements are the bridge from theory to practice and enable students to gain the essential skills and practical experiences that prepare them for their future practice as healthcare professionals.

Career Aspiration

Career ambitions are deeply rooted in clinical experiences Many students said that their ambitions were clarified and refined as they took courses, gained experience, and received more direct advice. This result is consistent with previous studies (Abbas et al., 2019; Boston-Fleischhauer, 2019), which have shown a strong connection between clinical placements and specialization choices. The complex landscape of modern healthcare has led students to select specific fields. Clinical experiences, personal motives, family support and mentorship work together to be essential in career decision-making for students. This study builds upon existing literature (Bugaj et al., 2016; Kelly et al., 2017; Khan & Parveen, 2020) that outlines the important role of a supportive environment, including peers and institutional support services, in facilitating access to academic success and the development of skills needed for professional success. To summarize, students' career trajectories are shaped at the intersection of practical experience, individual characteristics, and a supportive environment.

Whiletacklingsomeverypertinentissues, this study affirms the importance of resilience and adaptability in nursing education. The findings concur with Ching & Cheung (2021) in that resilience, is key to overcoming obstacles such as those presented during the pandemic. Resilience training should be included in existing nursing curricula as part of their stress, coping and crisis leadership preparation to enhance student preparedness for healthcare challenges such as global health crises.

This study, which supports Kelly et al. Eenhoorn, Faber and Roodbol (2017); and Khan & Parveen (2020) have highlighted the role of self-motivation which is very crucial in this regard and suggest that nursing should provide supportive environments to develop individuals both personally and professionally. Support structures from family and peers strengthen resiliency and success for students. Thus, educational institutions should offer services such as a cademic advising, counselling, and career services to help students cope with individual and academic challenges (Bugaj et al., 2016). These systems are important to help students connect their experiences in school with their future childhood goals.

Factors Influencing Careers

As nursing students endure a challenging academic and clinical course of study, crucial to their success is support from others. Support from family is indispensable; it can provide financial support, emotional comfort and physical assistance. Families play a critical role in bolstering the resilience of students by acknowledging their commitments and investing in the faith that they will perform (Kelly et al., 2017; Khan & Parveen, 2020).

Guidance, knowledge and networking support from more experienced nursing professionals Having a mentor leads to the development of critical thinking skills among students and also facilitates their navigating through clinical challenges, thereby hastening their professional growth (Barker & Kelley, 2020; Nowell, 2018). Peer encouragement motivates creating a community space of collaboration and togetherness which enhances the role of a supportive learning environment (Jafarian-Amiri et al., 2020). These systems are supplemented by educational institutions providing counselling, academic advising services and student organizations (Bugaj et al., 2016). They provide the student's well-being and academic planning as well as work-life balance.

This study demonstrated the multiple levels of family support, mentorship, peer
relationships and institutional resources interact to contribute towards nursing student success. Together, this holistic framework fosters a space to grow personally and professionally in an intellectually vibrant environment; we produce educated but also humane healthcare providers.

Implications for practice and future research

The results of this study highlight the etch on clinical placement opportunities have on nursing students' practice pathways. Nursing educators and clinical preceptors should strive to optimize the benefits of placements by facilitating varied rotations, developing effective mentorship programs, creating supportive learning environments and including holistic career counselling alongside clinical experience. Targeted approaches such as these can facilitate students to widen their scope of discovery into other specialities, benefit from invaluable mentorship led by experienced nurses over decades, and develop competencies around collaboration, and the various aspects of career planning and decision-making.

The findings further have policy and practice implications for nursing education concerning future curriculum development practices as a solution to COVID-19 pandemic challenges. Nursing education may need to increase their preparedness for future emergencies by adapting blended learning approaches and providing organized mentorship programs together with options that offer flexibility in clinical placements as well as resilience elements. Not only will these changes foster student engagement and skill attainment, but they will also make certain that nursing graduates have the knowledge and stamina to survive progressive movements in our volatile climate. According to Abbas et al. According to Kane and Boston-Fleischhauer (2019), these changes will develop a nursing workforce that is more competent, agile, and specialized to be prepared for the evolving healthcare demands of today.

Future longitudinal studies should also examine the enduring impacts of school experiences on career paths. Although nursing students within a particular educational system may differ, comparing student outcomes between schools in differing countries may provide valuable information about trends or best practices on an international level. Indepth gualitative investigations that explore the complex pathways between economic conditions and career choice, together with studies that examine the intersection of student-level variables including technology with aspirations and professional development can inform new teaching and learning designs. Answering such research questions allows the nursing field to better understand students' lived experiences to create more effective support systems for training future healthcare providers.

Limitations

Limitations of this qualitative study First, the use of stratified random sampling in this study may restrict the generalization of results to a wider population of nursing students. Participants were primarily selected for their specific conditions, limiting the findings to a generalization of that cohort only. Secondly, the low number of participants in this study could limit the reach and depth of data gathered. The gualitative approach enables deep exploration into the experiences of participants; however, the small number of participants may not provide adequate perspectives and experiences by members representing that group. Third, while the qualitative nature of this study renders the rich data collection process possible, it may also expose researcher bias. Findings may also be biased due to subjective conclusions drawn by the researcher based on the interpretations and analysis of the data. This speaks to the need for continued reflexivity, and triangulation of diverse data. Lastly, the specific focus on nursing students from IIUM only could also restrict the generalisation of findings to other institutions as well as cultural contexts. Nursing students in IIUM are stated to be different from others, due to the nature of IIUM with its religious engagement and specific unique programs offered. The limitations of this study could be addressed in future research in terms of the sample size and diversity, multiple data collection methods and methodological rigour that would improve generalizability.

CONCLUSION

This research investigated final-year nursing students' educational experiences and career ambitions at the International Islamic University Malaysia (IIUM). The study aimed to enhance nursing education by examining the determinants of profession selection and assessing the perceived sufficiency of educational preparation. The results indicated that while students are motivated to pursue specialisation, they face obstacles such as academic pressure and limited clinical practice opportunities. These findings underscore the need for nursing programmes to modify and enhance their curricula to better align with the evolving requirements of students and the healthcare sector. Future initiatives may include establishing structured mentorship programmes, increasing clinical placement opportunities, and incorporating resilience training into the curriculum to prepare students for the complexities of contemporary healthcare effectively. Additionally, continuous monitoring and feedback systems must be implemented to consistently assess these interventions' effectiveness. By focusing on these areas, nursing education can better align with professional expectations, thereby cultivating a more proficient and versatile nursing workforce capable of addressing the challenges of the healthcare environment.

CONFLICT INTEREST

The authors have not declared any conflict of interest.

ACKNOWLEDGEMENTS

We would like to express our sincere gratitude to the participants for their invaluable contributions to this study.

REFERENCES

- Abbas, M., Nabavi, F. H., Afshar, L., Yazdani, S., Pouresmail, Z., & Hoseinpour, Z. (2019). The
- Comparison of professional confidence in nursing students and clinical nurses: A cross-sectional study. International Journal of Nursing and Midwifery, 24(4), 261-261. https://doi. org/10.4103/ijnmr.ijnmr_102_17
- Aller, L. (2020). A contemporary model for undergraduate nursing education. Nurse Educator, 46, 250-
- 254. https://doi.org/10.1097/ NNE.0000000000933
- Anyango, E., Adama, E., Brown, J., & Ngune, I. (2024). The impact of final-year clinical placements
- on nursing students' career planning for the graduate year and beyond. Nurse education in practice, 76, 103944. https://doi. org/10.1016/j.nepr.2024.103944
- Aryuwat, P., Holmgren, J., Asp, M., Radabutr, M., & Lövenmark, A. (2024). Experiences of nursing
- Students regarding challenges and support for resilience during clinical education: A qualitative study. Nursing Reports, 14(3), 1604-1620. https://doi.org/10.3390/ nursrep14030120
- Barker, J., & Kelley, M. (2020). The impact of mentorship on clinical outcomes in nursing students.
- Journal of Nursing Education, 59(2), 150-155.
- Bobbo, N., & Lázzaro, S. (2018). Nursing students' future employment preferences and the real
- demands of patients using the health services: A qualitative study on a group of final-year students at the University of Padua. In Nursing Education: Research and Practice (pp. 315-326). Firenze University Press. https://doi.org/10.36253/978-88-6453-672-9.37
- Boston-Fleischhauer, C. (2019). Confronting clinical rotations. Nursing2019, 49(1), 6-8.
- https://doi.org/10.1097/nna.0000000000000699
- Bugaj, T. J., Cranz, A., Junne, F., Erschens, R., Herzog, W., & Nikendei, C. (2016). Psychosocial
- burden in medical students and specific prevention strategies. Medical Humanities, 4(1), 24-30. https://doi.org/10.1016/j.mhp.2015.12.003

- Cadena, S. (2019). Qualitative research: Interactions and experiences. MedUNAB.
- https://doi.org/10.29375/01237047.3746
- Campbell, M., Katikireddi, S., Sowden, A., & Thomson, H. (2019). Lack of transparency in reporting
- narrative synthesis of quantitative data: A methodological assessment of systematic reviews. Journal of Clinical Epidemiology, 105, 1-9. https://doi.org/10.1016/j. jclinepi.2018.08.019
- Cant, R., Ryan, C., Hughes, L., Luders, E., & Cooper, S. (2021). What helps, what hinders?
- Undergraduate nursing students' perceptions of clinical placements based on thematic svnthesis of literature. а SAGE Nursing, https://doi. Open 7. org/10.1177/23779608211035845
- Ching, S. S. Y., & Cheung, K. (2021). Factors affecting resilience of nursing, optometry, radiography,
- and medical laboratory science students. International Journal of Environmental Research and Public Health, 18(8), 3867. https://doi.org/10.3390/ijerph18083867
- Dahlberg, M. L., & Byars-Winston, A. (2019). The science of mentoring relationships: What is
- mentorship? The Science of Mentoring Relationships.
- https://www.ncbi.nlm.nih.gov/books/NBK552775/
- Enyan, N. I. E., Boso, C. M., & Amoo, S. A. (2021). Preceptorship of student nurses in Ghana: A
- descriptive phenomenology study. Hindawi Publishing Corporation, 2021, 1-8. https:// doi.org/10.1155/2021/8844431
- Fontanilla, D., Rebollido, C., Anacito, A., Algar, C., Cruz, J., Herrera, M., Palcon, M., Lim, A., &
- Apolinar, H. (2023). Reasons for the choice of nursing as a career among students in a private university in Manila, Philippines. International Journal of Advanced Research. https://doi.org/10.21474/ijar01/17437
- Head, M. L., Acosta, S., Bickford, E. G., & Leatherland, M. A. (2022). Impact of COVID-19 on
- undergraduate nursing education: Student perspectives. Academic Medicine, 97(3S), S49-S54. https://doi.org/10.1097/ acm.000000000004530
- Heffernan, T. (2020). Academic networks and career trajectory: There's no career in academia without
- networks. Higher Education Research & Development, 40, 981-994. https://doi.org/1 0.1080/07294360.2020.1799948
- Hiebl, M. (2021). Sample selection in systematic literature reviews of management research.
- Organizational Research Methods, 26, 229-261. https://doi.org/10.1177/1094428120986851

- Jafarian-Amiri, S. R., Zabihi, A., & Qalehsari, M. Q. (2020). The challenges of supporting nursing
- students in clinical education. Journal of Education and Health Promotion, 9(1), 216. https://doi. org/10.4103/jehp.jehp_13_20
- Kalanlar, B. (2022). Nursing education in the pandemic: A cross-sectional international study. Nurse
- Education Today, 108, 105213. https://doi. org/10.1016/j.nedt.2021.105213
- Kang, J. (2021). Introduction to the special issue: "Nursing education and research in the remote era".
- Advances in Nursing Research, 15(5), 327-328. https://doi.org/10.1016/j.anr.2021.06.002
- Kelly, A., & Parveen, S. (2017). The role of family support in the academic success of nursing students.
- Journal of Nursing Education, 56(1), 45-50.
- Khan, S., & Parveen, S. (2020). The impact of family support on the mental health of nursing students.
- Journal of Advanced Nursing, 76(1), 123-132. https://doi.org/10.1111/jon.15187
- Matarese, M., Lommi, M., Piredda, M., Marchetti, A., & Marinis, M. (2019). "Where would I prefer to
- work after graduation?" Career preferences of students attending Italian nursing schools. Nurse Education Today, 83, 104204. https:// doi.org/10.1016/j.nedt.2019.104204
- Monique, H., & Kaiser, B. N. (2022). Sample sizes for saturation in qualitative research: A systematic
- review of empirical tests. Social Science & Medicine, 292, 114523. https://doi.org/10.1016/j. socscimed.2021.114523
- Naeem, M., Ozuem, W., Howell, K., & Ranfagni, S. (2023). A step-by-step process of thematic analysis
- to develop a conceptual model in qualitative research. International Journal of Qualitative Methods, 22. https://doi. org/10.1177/16094069231205789
- Nowell, J. (2018). The role of mentorship in the development of nursing students. Nurse Education
- Today, 65, 123-128. https://doi.org/10.1016/j. nedt.2018.02.017
- Polit, D., & Beck, C. (2019). Nursing research. Wolters Kluwer Health.
- https://books.google.com.my/ books?id=RTXDDwAAQBAJ
- Pologruto, P., Jewell, J., & Cruz, L. (2021). Students' perceptions of clinical education during a global
- pandemic. Journal of Health and Allied Sciences NU.

https://doi.org/10.1055/s-0041-1736282

- Qonitatin, N., Sawitri, D., & Dewi, E. (2023). The role of culture in students' career aspirations: A
- preliminary study. In Proceedings of International Conference on Psychological Studies (ICPsyche). https://doi.org/10.58959/ icpsyche.v4i1.28
- Rojo, J., Ramjan, L., Hunt, L., & Salamonson, Y. (2020). Nursing students' clinical performance issues
- and the facilitator's perspective: A scoping review. Nurse Education in Practice, 48, 102890. https://doi.org/10.1016/j.nepr.2020.102890
- Sari, N. (2020). Career choices among nursing students: Differences between freshmen and interns.
- Jurnal Pendidikan Keperawatan Indonesia, 6(1), 17-25. https://doi.org/10.17509/jpki.v6i1.18758
- Tang, H., Hite, S., Hite, J., Boren, D., & Randall, E. (2020). Challenges and achievements in student
- learning experiences in a business school's at-home internationalization programs in China. Journal of International Business Education, 15, 1-22. https://doi.org/10.1108/jieb-04-2020-0026
- Tosunöz, İ., Eskimez, Z., & Öztunç, G. (2019). Factors affecting the career choices of nursing students.
- Kocaeli Üniversitesi Sağlık Bilimleri Dergisi. https:// doi.org/10.30934/kusbed.532097
- Younas, A., & Maddigan, J. (2019). Proposing a policy framework for nursing education for fostering
- compassion in nursing students: A critical review. Journal of Advanced Nursing, 75(1), 123-132. https://doi.org/10.1111/jan.13946

BJMS Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Prevalence of Dental Anomalies in Cleft Lip and Palate Patients Referred for Orthodontic Treatment

Jin Han Lee*

Department of Orthodontics, Queen Elizabeth II Hospital, Sabah, Malaysia.

* Corresponding author's email: jinjinhlee@yahoo.com

Received: 6 August 2024

Accepted: 6 November 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.5488

Keywords: Dental anomalies, cleft lip palate, hypodontia, peg lateral, impacted, supernumerary



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

In Malaysia, cleft lip and palate (CLP) prevalence varies, and dental anomalies increase the patients' need for dental care and orthodontic treatment. This cross-sectional study aimed to assess the prevalence of dental anomalies in CLP patients referred for orthodontic treatment at a government clinic in Kota Kinabalu. Demographic data, patterns of CLP, and dental anomalies from 85 dental records in 2010-2021 were reviewed retrospectively and analysed descriptively. The gender and the dental anomalies differences were tested using Fisher's exact test. The mean age of the patients at the time of referral was 12.12 ± 0.48 years. There were 84 (98.82%) patients presented with at least one dental anomaly. More than one-third of the patients presented with more than one type of dental anomaly (45.88%). The most common dental anomalies were hypodontia (68.24%), pegshaped lateral incisor (34.12%), impacted teeth (31.76%), supernumerary (11.76%), and transposition (9.41%). Almost all patients with hypodontia had missing lateral incisors (98.28%). 66.67% of patients with impacted teeth had impacted canine. In conclusion, almost all CLP patients referred for orthodontic treatment had at least one dental anomaly, with a prevalence of 98.82%. Multiple dental anomalies affected more than one-third of the patients. Hypodontia was the most common dental anomaly, with lateral incisors most prevalent. Other dental anomalies were

peg-shaped lateral incisors, impacted teeth, mostly impacted canine, supernumerary, and transposition. Early identification of dental anomalies in CLP patients is very important in treatment planning to allow timely referral to the multidisciplinary team.

INTRODUCTION

In Malaysia, the prevalence of cleft lip and palate (CLP) was varying in different regions of the country; 0.76 (Noraihan et al., 2005), 1.24 (Boo & Arshad, 1990), and 1.69 (Thong et al., 2005) per 1000 live births. The Chinese had the highest prevalence (1.9 per 1000 deliveries), while the Malay had the lowest prevalence (0.98 per 1000 deliveries) (Boo & Arshad, 1990). Unilateral cleft palate was the most common (Boo & Arshad, 1990; Shah et al., 2015), with the left side being more affected (Chai et al., 2013; Shah et al., 2015). It was more prevalent in females compared to males (Shah et al., 2015). However, based on a pilot epidemiological study in Sabah, cleft lip with or without cleft palate, was more prevalent among the males (Chai et al., 2013).

CLP patients experience aesthetic, speech, hearing, dental, and psychological complications (Haque & Alam, 2015). The findings of dental anomalies were higher in CLP patients compared to the normal population (Ai Jamal et al., 2010; Lehtonen et al., 2015; Paradowska-Stolarz & Kawala, 2023; Wong et al., 2012). More than 90% of CLP patients have at least one dental anomaly (Akcam et al., 2010; Nicholls, 2016), while 34% have more than one dental anomaly (Nicholls, 2016). Common dental anomalies associated with CLP were hypodontia, supernumerary, morphological anomalies, delayed teeth development and eruption, and microdontia (Hague & Alam, 2015). The lateral incisor was the most affected tooth (Paradowska-Stolarz & Kawala, 2023).

The management of CLP patients started from birth till adulthood by a multidisciplinary

team of paediatrics, plastic surgery, oral and maxillofacial surgery, otolaryngology, orthodontics, genetics, prosthodontics, psychology, social work, speech therapy, and nursing (Shetye, 2016). Knowledge of the prevalence of dental anomalies in CLP patients is important because the malocclusion is complicated due to the presence of multiple dental anomalies. Dental anomalies increase the patients' need for dental care (Namdar et al., 2021) and orthodontic treatment (Sander et al., 2022).

Therefore, this study aimed to assess the prevalence of dental anomalies in CLP patients referred for orthodontic treatment at a government clinic in Kota Kinabalu, specifically to evaluate the prevalence of hypodontia, impacted teeth, supernumerary teeth, and other dental anomalies in CLP patients. This clinic received referrals within Sabah state and from the Federal Territory of Labuan and Limbang, Sarawak.

MATERIALS AND METHODS

All dental records of written case notes, relevant radiographs, and study models that fulfilled the inclusion criteria were selected and assessed retrospectively. Ethical approval to conduct this study was acquired from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia and registered with the National Medical Research Register (NMRR-20-1736-56007). The sample was the CLP patients referred for orthodontic treatment at a government clinic in Kota Kinabalu from 2010 to 2021.

The sample size was calculated using the prevalence formula (Naing et al., 2022). The inclusion criteria were patients who presented with cleft lip and/or cleft palate. The exclusion criteria were patients with other congenital craniofacial syndrome, and incomplete dental records to diagnose the dental anomalies. A total of 89 dental records of cleft lip and/ or cleft palate patients were taken and assessed. However, all four cleft lip-only or cleft palateonly patients (one cleft lip-only patient and three cleft palate-only patients) were not included in the analysis as there was no dental anomaly among them, leaving 85 cleft lip and palate patients for data analysis.

Data included were demographic details (age, gender, and ethnic group), pattern of CLP, and types of dental anomalies. Only dental anomalies on the upper arch (maxilla) were taken. A standardised data collection form was used to record the data. All variables were analysed descriptively using Stata 15. Fisher's exact test was used to evaluate the differences between the proportions of the dental anomalies in males and females. The level of significance was 5% (p < 0.05).

RESULTS

The mean age of the CLP patients at the time of referral was 12.12 ± 0.48 years. More than half of the patients were males (n=47, 55.29%). Most of the patients were Bumiputera Sabah; Kadazan Dusun (n=29, 34.12%), Bumiputera Sabah lain (n=19, 22.35%) and Bajau (n=11, 12.94%), followed by Chinese (n=12, 14.12%), Malay (n=7, 8.23%), and other ethnic groups (Indian, Bisaya, Bumiputera Sarawak, Iban, and Kedayan) (n=7, 8.23%) (Table 1).

Table 1: Demographic profile of the patients(n=85)

Variables		n (%)	Mean ± SE
Age			12.12 ± 0.48
Gender	Male	47 (55.29)	
	Female	38 (44.71)	
Ethnic groups	Bumi- putera Sabah	59 (69.41)	
	Chinese	12 (14.12)	
	Malay	7 (8.23)	
	Others	7 (8.23)	

Nearly two-thirds of the patients had unilateral CLP (n=54, 63.53%). Left side unilateral CLP (n=35, 41.18%) almost doubled right side unilateral CLP (n=19, 22.35%). More than one-third of the patients had bilateral CLP (n=31, 36.47%) (Figure 1).



Unilateral CLP (left) Bilateral CLP Unilateral CLP (right)

Figure 1: Pattern of CLP among the patients (n=85)

There were 84 (98.82%) CLP patients presented with at least one dental anomaly, while one (1.18%) CLP patient had no dental anomaly. More than half of the patients presented with one type of dental anomaly (n=45, 52.94%). More than one-third of the patients presented with two types of dental anomalies (n=30, 35.29%), while there was about one-tenth of the patients presented with more than two types of dental anomalies (n=9, 10.59%) (Figure 2).



One dental anomaly Two dental anomalies More than two dental anomalies No dental anomaly

Figure 2: Frequency of dental anomalies among the patients (n=85)

The most common dental anomalies were hypodontia (n=58, 68.24%), peg-shaped lateral incisor (n=29, 34.12%), impacted teeth (n=27, 31.76%), supernumerary (n=10, 11.76%), and transposition (n=8, 9.41%) (Figure 3).



Figure 3: Prevalence and types of dental anomalies among the patients (n=85)

Almost all of the patients presented with hypodontia had missing lateral incisors (n=57, 98.28%). More than one-quarter had a missing second premolar (n=15, 25.86%), followed by a missing central incisor (n=3, 5.17%), missing first premolar (n=3, 5.17%), and missing canine (n=1, 1.72%) (Figure 4).



Figure 4: Prevalence and types of missing teeth among patients presented with hypodontia (n=58)

Meanwhile, two-thirds of the patients presented with impacted teeth had impacted canine (n=18, 66.67%), followed by impacted second premolar (n=8, 29.63%), impacted lateral incisor (n=7, 25.93%), and impacted first premolar (n=1, 3.70%) (Figure 5).





The prevalence of hypodontia in females was higher than in males. Meanwhile, the prevalence of impacted teeth, supernumerary, and transposition in males was higher than in females, with the prevalence of transposition in males more than twice compared to females. The prevalence of peg-shaped lateral incisors was about the same in males and females. There were no significant differences between males and females for each type of dental anomaly, p > 0.05 (Table 2).

Table 2: Prevalence and types of dentalanomalies between the genders (n=85)

	Males, n (%)	Females, n (%)	p-value
Hypodontia	31 (65.96)	27 (71.05)	0.647
Peg-shaped lateral incisor	16 (34.04)	13 (34.21)	1.000
Impacted teeth	17 (36.17)	10 (26.32)	0.359
Supernumer- ary	6 (12.77)	4 (10.53)	1.000
Transposition	6 (12.77)	2 (5.26)	0.288

DISCUSSION

In Sabah, CLP were among the common congenital craniofacial anomalies referred for orthodontic consultation and treatment. In this study, CLP were more prevalent in males, supporting the finding of a previous study in Sabah (Chai et al., 2013). The majority of the CLP patients were Bumiputera Sabah ethnicity. Some of the patients were from the Federal Territory of Labuan and Limbang, Sarawak because the government orthodontic clinic in Kota Kinabalu was more accessible to them during the period of the year 2010 to 2021.

The mean age of the patients referred for orthodontic consultation showed delayed referrals as the mean age of pre-alveolar bone graft orthodontic treatment was 8.72 ± 0.70 years (Chang et al., 2022). Early referrals are important for diagnosis and treatment planning as an alveolar bone graft is needed to assist timely eruption of the teeth at the cleft. Unilateral CLP occurred more frequently than bilateral CLP, with the left side more affected (Jamilian et al., 2016; Namdar et al., 2021). This was because the embryonic fusion of the palate on the right side lasted longer and occurred later in development (Paradowska-Stolarz & Kawala, 2014).

The prevalence of dental anomalies in this study showed almost all CLP patients had at least one type of dental anomaly. For patients at CLP centres, the prevalence of dental anomalies was lower, 80.6% (Ezzeldin et al., 2023). This gave the impression that dental anomalies might be among the main reasons for orthodontic referrals for CLP patients. There were no significant gender differences in the prevalence of dental anomalies, which agrees with other studies (Al-Kharboush et al., 2015; Namdar et al. 2021; Ousehal et al., 2024). Dental anomalies occurred more frequently on the side of the cleft (Camporesi et al., 2010) and increased with the severity of the cleft (Lasota, 2021). Therefore, in patients with cleft lip only or cleft palate only, dental anomalies were relatively lower. The prevalence of hypodontia was 34.14%, while supernumerary was only 2.43% among complete cleft palate patients. Furthermore, the prevalence of hypodontia supernumerary reduced and among incomplete cleft palate patients (Schwartz et al., 2014).

In this study, patients with cleft lip only or cleft palate only were not included in the analysis as there was no dental anomaly among them. The arch of their maxilla was not affected, and dental anomalies were least apparent. A study found that surgical trauma due to primary periosteoplasty, decreased blood supply associated with palatal defects, and absence of early orthopaedic treatment significantly increased the prevalence of dental anomalies (Korolenkova et al., 2019). Patients with cleft lip only or cleft palate only might not require orthodontic treatment (Sharma et al., 2021).

Hypodontia was the most common dental anomaly in this study, with more than two-thirds prevalence, similar to a study in Saudi Arabia (Al-Kharboush et al., 2015; Pradhan et al., 2020). This was higher than a study in Hong Kong, that found half of the CLP children had hypodontia, 57.6% (Wong et al., 2012) but lower than a study in Nepal, 77.9% (Pradhan et al., 2020). Missing lateral incisor at the side of the cleft was highest, same as other studies (Chang et al., 2022; Germec Cakan et al., 2018; Jamilian et al., 2016; Muller et al., 2021; Pradhan et al., 2020). The theories behind frequently missing lateral incisors at the cleft site were mesenchyme deficiency, multiple genetic and environmental factors, and the direct effect of the cleft on the primordial tissues related to the development of the tooth (Ross & Johnston, 1972). The clinical implications of hypodontia were aesthetic and functional disturbances for the patients. Implant placement was often not possible, especially at the cleft site due to decreased bone (Lasota, 2021). Therefore, a bridge or removable denture might be more suitable for the patients to replace the missing teeth.

The prevalence of peg-shaped lateral incisors in this study was lower than in other studies, 45.6% (Al-Kharboush et al., 2015). The cause of the formation of peg-shaped lateral incisors might be associated with primary periosteoplasty surgery and decreased blood supply (Korolenkova et al., 2019). The clinical implications of the smaller size of the pegshaped teeth were tooth size to arch length discrepancy and dental asymmetry. Following orthodontic alignment, usually, restorative treatment to build up the teeth will be needed to improve the aesthetic appearance.

The prevalence of impacted teeth in this study was higher compared to a similar study, 12.5% (Al-Karboush et al., 2015). Teeth most often affected were the canine at the cleft. The causes for the impaction were the constricted maxilla, insufficient bone, and lack of space for eruption. Timely orthodontic expansion and alveolar bone graft could assist these teeth in erupting by providing bone volume and space. In this study, the prevalence of supernumerary was close to other studies (Al-Kharboush et al., 2015; Pradhan et al., 2020; Wong et al., 2012). During cleft formation, fragmentation of the dental lamina might form supernumerary (Watted et al., 2014). The clinical complications of supernumerary are interference to alveolar bone graft (Lasota, 2021) and often preventing eruption of adjacent teeth by obstructing the path of eruption.

Transposition was due to the displacement of tooth germs due to the constricted maxilla. In this study, transposition occurred often between the canine and first premolar. Management of transposition depends on the level of transposition. In true transposition, it is best to accept the transposed positions without intervention (Lasota, 2021) to prevent complicated and prolonged treatment and to avoid iatrogenic damage such as root resorption to the teeth.

In this study, multiple dental anomalies affected more than one-third of the CLP patients. The prevalence of certain dental anomalies was not the same in other similar studies.This could be the differences in ethnicity and environmental backgrounds. These patients required multiple dental treatments of orthodontic, restorative, prosthodontic, paediatric, and oral surgery attention. Good clinical outcomes could be achieved with a comprehensive multidisciplinary approach and regular reviews (Pastuszak et al., 2020), hence improving the quality of life of the patients (Ousehal et al., 2024).

Undoubtedly, there were limitations in this retrospective study. Data collection was fully dependent on the dental records, whilst clinical examination could provide more accurate information on the severity of the cleft and enamel hypoplasia. Meanwhile, the absence of some CLP patients due to poor socioeconomic status or difficulty accessing healthcare services could also influence the prevalence of dental anomalies. In addition, advanced statistical analyses might be helpful to check correlations between the severity of cleft and specific dental anomalies. Future studies were recommended to include the whole state of Sabah to investigate the differences in dental anomalies with specific ethnic and geographic backgrounds. Multicentre studies might provide more accurate prevalence.

CONCLUSIONS

Almost all the CLP patients referred for orthodontic treatment had at least one dental anomaly, with a prevalence of 98.82%. Multiple dental anomalies affected more than onethird of the patients. Hypodontia was the most common dental anomaly, with lateral incisors most prevalent. Other dental anomalies were peg-shaped lateral incisors, impacted teeth, mostly impacted canine, supernumerary, and transposition. Early identification of dental anomalies in CLP patients is very important in treatment planning to allow timely referral to the multidisciplinary team.

CONFLICT OF INTERESTS

The author declared no conflict of interest in this research.

ACKNOWLEDGEMENTS

The author would like to thank the Director General of Health Malaysia and the Principal Director of the Oral Health Programme for the permission to publish this article.

REFERENCES

- Ai Jamal, G.A., Hazza'a, A.M., & Rawashded, M.A. (2010). Prevalence of dental anomalies in a population of cleft lip and palate patients. The Cleft Palate-Craniofacial Journal; https:// doi.org/10.1597/08-275.1
- Akcam, M.O., Evirgen, S., Uslu, O., & Memikoglu, U.T. (2010). Dental anomalies in individuals with cleft lip and / or palate. European Journal of Orthodontics; 32(2): 207-213.
- Al-Kharboush G.H., Al-Balkhi, K.M., & Al-Moammar, K. (2015). The prevalence of specific dental anomalies in a group of Saudi cleft lip and palate patients. The Saudi Dental Journal; 27: 75-80.
- Boo, N.Y., & Arshad, A.R. (1990). A study of cleft lip and palate in neonates born in a large Malaysian maternity hospital over a 2-year period. Singapore Medical Journal; 31(1): 59-62.
- Camporesi, M., Baccetti, T., Marinelli, A., Defraia, E., & Franchi, L. (2010). Maxillary dental anomalies in children with cleft lip and palate: a controlled study. International Journal of Paediatric Dentistry; 20(6): 442-450.
- Chai, S.C., Jimeno, Z.K.L., Sasidaran, R., & Sergius, A. (2013). Pilot epidemiological study of cleft lip and / or palate in Kota Kinabalu, Sabah. Asian Journal of Medical Sciences; 4(3): 86-91.
- Chang, C.H., Chang, C.H., Lai, J.P., Lin, S.S., & Chang, Y.J. (2022). Prevalence of Dental Anomalies in Taiwanese Children with Cleft Lip and Cleft Palate. Journal of Personalized Medicine; 12(10):1708. https://doi.org/10.3390/ jpm12101708
- Ezzeldin, M., Gee, S., Curtis, J., Clark, V.J., Smallridge, J., & Collard, M. (2023). Dental anomalies in cleft lip and / or palate children at age 10- a retrospective review across three cleft centres: Part 1. British Dental Journal; 234: 926-930.
- Germec Cakan, D., Nur Yilmaz, R.B., Bulut, F.N., & Aksoy, A. (2018). Dental anomalies in different types of cleft lip and palate: is there any relation? The Journal of Craniofacial Surgery; 29(5): 1316-1321.
- Haque, S., & Alam, M.K. (2015). Common dental anomalies in cleft lip and palate patients. Malaysian Journal of Medical Sciences; 22(2):

55-60.

- Jamilian, A., Lucchese, A., Darnahal, A., Kamali, Z., & Perillo, L. (2016). Cleft sidedness and congenitally missing teeth in patients with cleft lip and palate patients. Progress in Orthodontics; 17:14.
- Korolenkova, M.V., Starikova, N.V., & Udalova, N.V. (2019). The role of external aetiological factors in dental anomalies in non-syndromic cleft lip and palate patients. European Archives of Paediatric Dentistry; 20(2): 105-111.
- Lasota, A. (2021). Dental anomalies in children with cleft lip with or without cleft palate. Journal of Pre-Clinical and Clinical Research; 15(1): 46-49.
- Lehtonen, V., Anttonen, V., Ylikontiola, L.P., Koskinen, S., Pesonen, P., & Sándor, G.K. (2015). Dental anomalies associated with cleft lip and palate in Northern Finland. European Journal of Paediatric Dentistry; 16(4): 327-332.
- M ller, L.S., Pradel, W., Gedrange, T., & Botzenhart, U.U. (2021). Prevalence of hypodontia and supernumerary teeth in a German cleft lip with/ without palate population. BMC Oral Health; 21:60.
- Naing, L., Nordin, R.B., Abdul Rahman, H., & Naing, Y.T. (2022). Sample size calculation for prevalence studies using Scalex and ScalaR calculators. BMC Medical Research Methodology; 22: 209. https://doi.org/10.1186/s12874-022-01694-7.
- Namdar, P., Mesgarani, A., & Shiva, A. (2021). Prevalence of maxillary dental anomalies and related factors in children with cleft lip and palate in Sari. International Journal of Pediatric; 9(10): 14600-14607.
- Nicholls, W. (2016). Dental anomalies in children with cleft lip and palate in Western Australia. European Journal of Dentistry; 10(2): 254-258.
- Noraihan, M.N., Raja, R., & Symonds, E.M. (2005). Audit of birth defects in 34,109 deliveries in a tertiary referral centre. Medical Journal of Malaysia; 60(4): 460-468.
- Ousehal, L., Sair, S., & Lazraq, A. (2024). Prevalence of dental anomalies among cleft lip and palate patients: a cross-sectional study. Open Access Library Journal; 11(4): doi:10.4236/ oalib.1111385.
- Paradowska-Stolarz, A., & Kawala, B. (2023). Dental Anomalies in Maxillary Incisors and Canines among Patients with Total Cleft Lip and Palate. Applied Sciences; 13(11):6635. https://doi.org/10.3390/app13116635.
- Paradowska-Stolarz, A., & Kawala, B. (2014). Occlusal disorders among patients with total clefts

of lip, alveolar bone, and palate. Biomed Research International; http://dx.doi. org/10.1155/2014/583416.

- Pastuszak, P., Dunin-Wilczyńska, I., & Lasota, A. (2020). Frequency of additional congenital dental anomalies in children with cleft lip, alveolar and palate. Journal of Clinical Medicine; 9: 3813: doi:10.3390/jcm9123813.
- Pradhan, L., Shakya, P., Thapa, S., Nakarmi, K.K., Maharjan, A., Sagtani, R.A., & Rai, S.M. (2020). Prevalence of dental anomalies in the patient with cleft lip and palate visiting a tertiary care hospital. Journal of Nepal Medical Association; 58(228): 591-6.
- Ross, R.B, & Johnston, M.C. (1972). Cleft lip and palate. Baltimore, Md: Williams and Wilkins Co; 81-82.
- Sander, A.K., Grau, E., Bartella, A.K. et al. (2022). Dental anomalies and their therapeutic implications: retrospective assessment of a frequent finding in patients with cleft lip and palate. BMC Oral Health; 22, 553. https://doi. org/10.1186/s12903-022-02606-3.
- Schwartz, J.P., Somensi, D.S., Yoshizaki, P., Reis, L.L.S., Lauris, R.C.M.C., Silva Filho, O.G., Dalbén, G., & Garib, D.G. (2014). Prevalence of dental anomalies of number in different subphenotypes of isolated cleft palate. Dental Press Journal of Orthodontics; 19(1): 55-9.
- Shah, S.Y.A., Rahman, Z.A.A., Mirani, S.A., Shaikh, M.L., Khattak, M.N., & Sahito, M.A. (2015). Demographic data on the characterization of oral clefts in Malaysia. Pakistan Oral & Dental Journal; 35(1): 108-110.
- Sharma, P., Khera, A.K., & Raghav, P. (2021). Role of orthodontists in cleft lip and palate. Journal of Oral Health and Craniofacial Science; 6: 008-015.
- Shetye, P.R. (2016). Orthodontic management of patients with cleft lip and palate. APOS Trends of Orthodontics; 6: 281-6.
- Thong, M.K., Ho, J.J., & Khatijah, N.N. (2005). A population-based study of birth defects in Malaysia. Annals of Human Biology; 32(2): 180-187.
- Watted, N., Abdulgani, A., & Abu-Hussein, M. (2014). Supernumerary teeth in permanent dentition in patients with cleft lip and palate. International Journal of Dental and Health Sciences; 1(3): 410-418.
- Wong, H.M., Lai, M.C., & King, N.M. (2012). Dental anomalies in Chinese children with cleft lip and palate. Dentistry; 2 (3): 127. Doi: 10.4172/2161-1122.1000127.

BJMS Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Prospective, Non-randomized Study of Clinical Outcome in Patients With Primary Versus Delayed Ureteroscopy for Proximal Ureteric Stone (PRIDE Study)

Kian Joo Sun*, Shankaran Thevarajah

Urology Unit, Queen Elizabeth Hospital, 88586 Kota Kinabalu, Sabah, Malaysia

* Corresponding author's email: sunkianjoo@gmail.com

Received: 15 July 2024

Accepted: 9 October 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.6370

Keywords: Primary ureteroscopy, Delayed ureteroscopy, Urolithiasis, Proximal ureteric stone



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

Introduction: Conventionally, proximal ureteric stone is managed with stenting followed by a definitive delayed treatment. This approach requires multiple hospital visits. Primary ureteroscopy has been employed to expedite the treatment as a single-stage procedure. Methodology: This prospective, non-randomized, cohort study assessed the efficacy and safety of primary (P-URS) versus delayed ureteroscopy (D-URS) in the management of proximal ureteric stone. A total of 176 consecutive patients with unilateral proximal ureteric stone >3mm were included in the final data analysis (95 P-URS and 81 D-URS). The decision to proceed with P-URS or D-URS was based on initial presentation and surgeon's expertise. Stone free was defined as no visible residual fragments on the kidney, ureter and bladder (KUB) radiograph which was performed 6 weeks post-operatively. Primary outcome was stone free rate. Secondary outcomes include operative duration, length of hospital stay and rate of complications. **Results:** D-URS had a higher stone free rate (96.3%) compared to P-URS (74.7%) but overall operative duration, length of stay and rate of complications were comparable between these 2 groups. All complications from D-URS were UTI-related (8.6%) Conclusion: P-URS for proximal ureteric stone is a safe and feasible option accepting the lower stone free rate compared to D-URS.

INTRODUCTION

Urolithiasis, or urinary tract stone is a major health problem worldwide. There has been a stone forming belt stretching across the West Asia, Southeast Asia, South Asia as well as several developed countries, including South Korea and Japan, with prevalence ranging from 5% to 19.1% (Liu et al., 2018). Unfortunately, the Borneo part of Malaysia (Sarawak and Sabah) is not spared from this "stone-belt". A recent epidemiological study of urolithiasis in Sarawak found a prevalence of 4.4%, with the commonest age group being 24 –64 years (Perumal et al., 2023). Another study in Sabah revealed that ureteric stone alone (excluding multiple sites) accounts for 18% of all urolithiasis (Cheema et al, 2022). Intervention on ureteric stones poses a significant burden on healthcare cost and national economy, both directly and indirectly through follow-up appointments and absence from work.

Conventionally, ureteric stone is managed firstly with stenting followed by a definitive treatment later such as delayed ureteroscopy (D-URS) or extracorporeal shock wave therapy (ESWL). However, this approach requires multiple hospital visits and thus, exacerbating the burden on individual and healthcare system. Increasingly, primary ureteroscope (P-URS) has been employed to expedite the definitive management of ureteric stone as a single-stage procedure.

While distal and mid ureteric stones are deemed easy to access using ureteroscope, proximal ureteric stone remains a challenge for most endourologists, even the most experienced ones. A number of studies have looked at the role of P-URS (Arcaniolou et al., 2017), but none was specific to proximal ureteric stone. This prospective, nonrandomized, cohort study is the first study in modern literature to assess the efficacy and safety of primary versus delayed ureteroscopy in the management of proximal ureteric stone.

MATERIALS AND METHODS

Between March 2022 and December 2023, 178 consecutive patients from a tertiary urological referral center were recruited in a prospective but non-randomized manner, where they were diagnosed with unilateral proximal ureteric stone >3mm requiring surgical intervention. Proximal stone was defined as a stone above the upper border of pelvic brim. Children <18 years old, pregnant ladies and patients with ongoing active infection were excluded from this study. Two patients were excluded from final data analysis due to pyonephrosis upon stone fragmentation. The decision to proceed with primary or delayed ureteroscopy was based on initial presentation (severe colic or infection would mandate drainage first) and surgeon's expertise. Sample size was calculated based on previous similar study (Elderwy et al., 2018) where stone free rate for P-URS and D-URS were 0.75 and 0.87 respectively. Using formula for comparative study (Sharma et al., 2020), the sample size needed to achieve 95% confidence level with a power of 80% was 162 patients with 81 in each group. Final data analysis included 176 patients in total (95 for P-URS and 81 for D-URS).

This study was approved by MREC (Medical Research and Ethics Committee) of Ministry of Health Malaysia (NMRR ID-22-01294-KA2).

Initial non-contrasted computed tomography (CT) scans and kidney, ureter and bladder (KUB) radiography were performed for all patients to determine the size and location of ureteric stone. KUB radiography-radiolucent stones were excluded from this study. All procedures were performed by a urologist or a senior trainee under supervision of a single consultant urologist. All patients underwent the procedure either under spinal or general anesthesia based on anesthetist's experience and clinical judgement. Ureteroscope used was a Richard-Wolf 6.5/7Fr semi-rigid ureteroscope. Stone fragmentation was performed with

low power Holmium:YAG laser (Jena Surgical Multipulse Ho 35W). The decision to leave a stent post operatively was left to surgeon's discretion. Duration of operation and length of hospital stay post operatively were noted.

Stone free status was defined as no visible residual fragments on the KUB radiography which was performed 6 weeks after operation. Any post-operative complications were noted.

Data analysis was done using SPSS version 24 (SPSS, Chicago, IL, USA). Categorical data were assessed using χ^2 and Fisher's exact test. Continuous data were analyzed using the independent t-test assuming that the data were normally distributed. The statistical significance level was set at 0.05.

RESULTS

A total of 176 patients were included in the final data analysis. Among these 176 patients, 95 underwent P-URS and 81 underwent D-URS. Mean age of patients for P-URS was 52 years (SD 12) compared to 54 years (SD 13) in D-URS group. Both groups had similar proportion of male and female patient. P-URS had 47 male (49%) while D-URS had 44 male (54%) (p=0.411). P-URS had 45 right-sided stone (47%) while D-URS had 41 right-sided stone (51%) (p=0.185). The mean stone size for P-URS group was 13.31mm (SD 4.31) compared to D-URS which was 13.23mm (SD 5.48) (p=0.924) (Table 1).

URS for Ure- teric Stone (n=176)	Primary (n=95) ± SD	Delayed (n= 81) ±SD	95% Confidence Interval (p-val- ue=0.05)
Mean age, years	52±12	54±13	0.217 (-6.272 to 1.434)
Gender	Male=47 Female=48	Male=44 Female=37	0.411
Location	Right=45 Left=50	Right=41 Left=40	0.185
Stone Size (mm)	13.31±4.31	13.23±5.48	0.924 (-1.387 to 1.528)

Table 1: Patient and stone demographics.

In terms of stone outcomes, D-URS had performed better with a stone free rate (SFR) of 96.3% (78 patients) compared to 74.7% (71 patients) for P-URS. These results were statistically significant (p=0.000) (Table 2).

URS for Ure- teric Stone (n=176)	Primary (n=95) ± SD	Delayed (n= 81) ±SD	95% Confidence Interval (p-val- ue=0.05)	
Stone Free Rate, (100%)	Yes=71 (74.7%) No=24 (25.3%)	Yes=78 (96.3%) No=3 (3.7%)	15.648 (p=0.000)	
Operation duration (min)	47.47±18.31	48.40±18.78	0.743 (-0.921 to 2.802)	
Stay duration (hours)	22.48±10.72	29.20±31.14	0.05 (-13.441 to 0.015)	
Stenting	Yes=95 (100%) No=0 (0%)	Yes=73 (90.1%) No=8 (9.9%)	7.685 (p=0.002)	
Complica- tions	Yes=5 (5.3%) No=90 (94.7%)	Yes=7 (8.6%) No=74 (91.4%)	0.786 (p=0.55)	
Severity (Clavien-Din- do Grading)	No=90 (94.7%) Grade 2 (UTI)=1 (1.1%) Grade 2 (Stent- Irritation)=1 (1.1%) Grade 1 (Irrigation)=2 (2.1%) Grade 2 (Transfu- sion)=1 (1.1%)	No=74 (91.4%) Grade 2 (UTI)=7 (8.6%)	9.004 (p=0.016) 8.369 (p=0.018)	
Unsuccessful Reason	No=71 (74.7%) Impacted=5 (5.3%) Retropul- sion=14 (14.7%) Difficult Maneuver=5 (5.3%)	No=78 (96.3%) Impacted=2 (2.5%) Retropul- sion=1 (1.2%)	16.874 (p=0.000) 17.545 (p=0.000)	

Table 2: Operative outcomes.

In terms of operative outcomes, both P-URS and D-URS had similar mean operative duration (minutes) which was 47.47 (SD 18.31) and 48.40 (SD18.78) respectively (p=0.743). Patients from P-URS group had a mean post-operative length of stay (hours) of 22.48 (SD 10.72) compared to D-URS group which was 29.20 (SD 31.14) (p=0.05). 100% of P-URS patients had stenting post-operatively compared to 90.1% of D-URS patients (Table 2).

In terms of complications, P-URS group had 5 cases (5.3%) while D-URS group had 7 cases (8.6%) (p=0.786). These results were statistically not significant. All 7 cases with complications from D-URS group were urinary tract infection (UTI) compared to only 1 case from P-URS group. All of the complications were minor (Clavien-Dindo grade 2 and below). The most common unsuccessful reason for P-URS was retropulsion of stone (14 cases) (Table 2).

In terms of efficacy of different level of surgeon, both trainee and specialist groups had achieved similar SFR (85.6% for trainee and 83.1% for specialist) (p=0.199). The differences were not statistically significant (Table 3).

Table 3: Level of surgeon.

URS for Ure- teric Stone (n=176)	Primary (n=95) ± SD	Delayed (n= 81) ±SD	95% Confidence Interval (p-val- ue=0.05)
Stone Free Rate, (100%)	Yes=95 (85.6%) No=16 (14.4%)	Yes=54 (83.1%) No=11 (16.9%)	0.199 (p=0.670)

DISCUSSION

Our prospective, non-randomized study has shown that P-URS for proximal ureteric stone had a lower stone free rate (SFR) compared to D-URS, with similar operative duration, length of hospital stay and rate of complication. Another study conducted in UK looking at P-URS versus D-URS for ureteric stone at all locations had shown similar results with comparable SFR (Mckay et al., 2021). Data from a retrospective study in New Zealand had also shown that emergency P-URS is a feasible approach in managing acute ureteric colic for stones in all locations with a success rate of 72% (Zargar-Shostari et al., 2015).

As far as we know this is the first study to focus on ureteroscopic management of proximal ureteric stone. Unstented patients especially young female and proximal ureteric stone were the least likely to be accessed primarily (Fuller et al., 2016). In our study, there were total of 24 unsuccessful cases for P-URS (14 cases due to retropulsion, 5 cases due to stone impaction and 5 cases due to difficult maneuver). These results reflected the challenges that endourologists had to face during manipulation of proximal ureteric stone. The risk of proximal fragment migration is influenced by the pressure of the irrigant fluid, type of energy source used for intracorporeal lithotripsy, site and degree of calculus impaction, and degree of proximal ureteral dilatation (Hendlin et al., 2008). A stone could be deployed to reduce the risk of proximal stone retropulsion (Bastawisy et al., 2011). Pre-operative alpha blockers could improve ureteroscopic outcome based on a recent meta-analysis (Bhojani et al, 2024). With the advent of smaller, flexible ureteroscopes and better LASER equipment, we have a reason to believe that the stone free rate for P-URS would be improved in the near future.

Both P-URS and D-URS in our study have shown similar complications rates (5.3% versus 8.6%) and all complications were considered minor. This is in concordance with other larger studies (de la Rosette et al., 2014). Another study reported a lower rate of complication (2.83%) with proximal stone ureteroscopy, but ureteral access sheath (UAS) was used in 22% of the patients (Lazarovich et al., 2023). UAS was not used in our study due to extra cost and risk of ureteric perforation. Most complications included transient hematuria and urinary tract infection (UTI) which resolved with conservative management. Surprisingly, in our study, the complications from D-URS were all UTI-related. This was probably associated with prolonged indwelling stent. A recent study had shown that preoperative stenting was

significantly associated with post-URS urinary tract infection (16.9% versus 7.1%) (Pereira et al., 2023). Female gender, preoperative positive urine cultures and stone recurrence were significant risk factors (Pereira et al., 2023). Another study has demonstrated that a stent dwelling time of more than two months was associated with an increased risk of postureteroscopic febrile UTI (Geraghty et al., 2022). We advise to obtain pre-operative cultures prior to ureteroscope and treat accordingly in case of prolonged indwelling stent.

Our study has shown that there was no difference in terms of SFR for different level of surgeon. The slight reduction for SFR in specialist group was probably due to selection bias as specialist would have taken on more challenging cases based on pre-operative imaging. However, it should be safe to say that P-URS could be performed by trainee with equivalent outcome to specialist.

P-URS could have positive impact on patient's quality of life, total work-day loss and healthcare expenses. P-URS avoided the initial admission for pre-stenting and stent-related complications during the waiting period for definitive operation especially in public hospital. The stent post P-URS could be easily removed during outpatient visit in 2 weeks. On cost evaluation, a UK study has shown that average total treatment cost for emergency stenting (delayed intervention) was 5900 Euro compared to 4450 Euro for P-URS group (Wani et al., 2021). In long run, P-URS could be the most cost-effective option to deal with ureteric stones provided that facilities and suitable endourological experience are available.

The placement of indwelling stent has variable degree of impact across all general health domains. Many patients report fatigue, dependence to perform daily activities, and even reduce their social life while presenting symptoms associated with the stent (Bargues-Balanza et al., 2022). P-URS totally avoided the stent-irritation symptoms during the waiting period for D-URS.

CONCLUSION

Primary URS for proximal ureteric stone is a safe and feasible option accepting the lower SFR compared to delayed URS. Primary URS avoided the stent-irritation symptoms during the waiting period for D-URS. Primary URS should be attempted provided that the facilities and expertise are available. Further studies are required to identify patients that are not favorable for primary URS in the setting of proximal ureteric stone.

CONFLICT OF INTEREST

The authors declared no conflicts of interest.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Urology team in Hospital Queen Elizabeth for contributing to data collection and Dr (PhD) Loh YC for statistical analysis.

REFERENCES

- Arcaniolo, D., De Sio, M., Rassweiler, J., Nicholas, J., Lima, E., Carrieri, G., Liatsikos, E., Mirone, V., Monga, M., & Autorino, R. (2017). Emergent versus delayed lithotripsy for obstructing ureteral stones: a cumulative analysis of comparative studies. Urolithiasis, 45(6), 563-572. https://doi.org/10.1007/s00240-017-0960-7
- Bargues-Balanzá, M., Ordaz-Jurado, G., Budía-Alba, A., & Boronat-Tormo, F. (2022). Ureteral Stents. Impact on Patient's Quality of Life. In F. Soria, D. Rako & P. de Graaf (Eds.), Urinary Stents (pp.49-58). Springer, Cham. https:// doi.org/10.1007/978-3-031-04484-7_5
- Bastawisy, M., Gameel, T., Radwan, M., Ramadan, A., Alkathiri, M., & Omar, A. (2011). A comparison of Stone Cone versus lidocaine jelly in the prevention of ureteral stone migration during ureteroscopic lithotripsy. Therapeutic Advances in Urology, 3(5), 203-210. https:// doi.org/10.1177/1756287211419551
- Bhojani, N., Chew, B. H., Bhattacharyya, S., Krambeck, A. E., Ghani, K. R., & Miller, L. E. (2024). Effect of preoperative alpha-blockers on ureteroscopy

Prospective, Non-randomized Study of Clinical Outcome in Patients With Primary Versus Delayed Ureteroscopy for Proximal Ureteric Stone (PRIDE Study)

outcomes: A meta-analysis of randomised trials. BJUI Compass, 5(7), 613-620. https://doi.org/10.1002/bco2.358

- Cheema, J. & Thevarajah, S. (2022). Descriptive profile of urolithiasis cases in a tertiary hospital in Sabah. Borneo Journal of Medical Sciences, 16(2), 15–22. https://doi.org/10.51200/bjms. vi.3310
- de la Rosette, J., Denstedt, J., Geavlete, P., Keeley, F., Matsuda, T., Pearle, M., Preminger, G., & Traxer O. (2014) CROES URS Study Group. The clinical research office of the endourological society ureteroscopy global study: indications, complications, and outcomes in 11,885 patients. Journal of Endourology, 28(2), 131-139. https://doi.org/10.1089/end.2013.0436
- Elderwy, A. A., Gadelmoula, M., Elgammal, M. A., Hameed, D. A., Behnsawy, H. M., Osman, M. M., & Kurkar, A. (2018). Primary versus deferred ureteroscopy for management of calculus anuria: a prospective randomized study. Central European Journal of Urology, 71(4):462-466. https://doi.org/10.5173/ ceju.2018.1768
- Fuller, T. W., Rycyna, K. J., Ayyash, O. M., Ferroni, M. C., Mitchell, C. R., Ohmann, E., Wollin, D. A., Shah, O., Miller, N. L., & Semins, M. J. (2016). Defining the rate of primary ureteroscopic failure in unstented patients: A multi-institutional study. Journal of Endourology, 30(9), 970-974. https://doi.org/10.1089/end.2016.0304
- Geraghty, R. M., Pietropaolo, A., Villa, L., Fitzpatrick, J., Shaw, M., Veeratterapillay, R., Rogers, A., Ventimiglia, E., & Somani, B. K. (2022) postureteroscopy infections are linked to preoperative stent dwell time over two months: Outcomes of three European endourology centres. Journal of Clinical Medicine, 11(2), 310. https://doi.org/10.3390/jcm11020310
- Hendlin, K., Weiland, D., & Monga, M. (2018). Impact of irrigation systems on stone migration. Journal of Endourology, 22(3):453-458. https://doi.org/10.1089/end.2007.0260
- Lazarovich, A., Haramaty, R., Shvero, A., Zilberman, D. E., Dotan, Z. A., Winkler, H., & Kleimann, N. (2023). Primary ureteroscopy without pre-stenting for proximal ureteral stones – Is it feasible? Life, 13(10), 2019. https://doi. org/10.3390/life13102019
- Liu, Y., Chen, Y., Liao, B., Luo, D., Wang, K., Li, H., & Zeng, G. (2018) Epidemiology of urolithiasis in Asia. Asian Journal of Urology, 5(4), 205-214. https://doi.org/10.1016/j.ajur.2018.08.007
- Mckay, A., Somani, B. K., Pietropaolo, A., Geraghty, R., Whitehurst, L., Kyriakides, R., & Aboumarzouk, O. M. (2021). Comparison of primary and

delayed ureteroscopy for ureteric stones: A prospective non-randomized comparative study. Urologia Internationalis, 105(1-2), 90-94. https://doi.org/10.1159/000510213

- Paulino, P. L. J., Kums, A. C. M., Beck, J. J. H., & Pauline, M. L. H. (2023). The influence of indwelling double-J stent duration prior to URS on postoperative complicated urinary tract infections. Tijdschrift voor Urologie, 13, 76–82. https://doi.org/10.1007/s13629-023-00378-1
- Perumal, K. R., Chua, R. H. B., Teh, G. C., & Lei, C. C. M. (2023). Prevalence of urolithiasis in Sarawak and associated risk factors: An ultrasonagraphy-based cross-sectional study. BJUI Compass, 4(1), 74-80. https://doi. org/10.1002/bco2.152
- Sharma, S. K., Mudgal, S. K., Thakur, K., & Gaur, R. (2020). How to calculate sample size for observational and experimental nursing research studies? National Journal of Physiology, Pharmacy and Pharmacology, 10(1), 1-8. https://doi.org/10.5455/ njppp.2020.10.0930717102019
- Wani, M., Burki, J., Melhem, M., Gilani, S., Ghumman, F., & Masood, S. (2021) Is primary ureteroscopy an alternative to emergency stenting in terms of quality and cost? Central European Journal of Urology, 74(3), 446-450. https:// doi.org/10.5173/ceju.2021.0029.R1
- Zargar-Shoshtari, K., Anderson, W., & Rice, M. (2015) Role of emergency ureteroscopy in the management of ureteric stones: Analysis of 394 cases. BJU International, 115(6), 946-950. https://doi.org/10.1111/bju.12841

BJMS Borneo Journal of Medical Sciences

REVIEW ARTICLE

Exploring the Bacteriophage in Malaysia: An Overview of Applications and Challenges

Nur Nashyiroh Izayati Mastor^{1,2}, Mohammad Zahirul Hoque³, Vijay Kumar Subbiah^{1*}

- ¹ Biotechnology Research Institute, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
- ² Borneo Marine Research Institute, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
- ³ Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
- * Corresponding author's email: vijay@ums.edu.my

Received: 8 March 2024

Accepted: 9 October 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.6172

Keywords: *Bacteriophages, applications, Antimicrobial-resistant, AMR, Malaysia*



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

Antibiotic resistance is a worldwide concern as more drugs are losing efficacy and fewer candidates are being developed in the pipeline. As a result, there is growing attention towards alternative applications of microbial control, and bacteriophages have come to the forefront of research. However, there is limited data and experimental studies in Malaysia. The well-documented use of these viruses to overcome the problem of antimicrobial resistance and multi-drug resistance is still scarce in the country and warrants exploration. Here, we discuss the potential of bacteriophage applications in healthcare, animal husbandry, aquaculture and agriculture in Malaysia. The challenges faced in doing so and reception among the country's researchers, clinicians and healthcare authorities are also discussed. Although the use of bacteriophages in this capacity is just beginning to unfold, it is hoped that there will be a shift in perception towards a positive reception, especially with the looming threat of antibiotic resistance.

INTRODUCTION

Antimicrobial resistance is a public health concern in Malaysia as it is in many countries. Recently, in April 2021, the World Health Organization (WHO) published a report on the diminishing effectiveness of antibiotics available for clinical use and the lack of new candidates being developed (WHO, 2021a). The misuse and overuse of antibiotics, together with the slow pace of new drug development, have exacerbated the problem of resistance, forcing researchers to focus on alternative antimicrobial therapeutics. Many ASEAN countries, including Malaysia, have begun exploring ways to combat antimicrobial resistance, and bacteriophage research is one of the promising options (Binte et al., 2020; Chu et al., 2022). Mostly comprising large DNA-bearing viruses, bacteriophages need to infect a specific bacteria host to replicate and survive. Upon activation of the lytic cycle, the virus progeny will form and be released into the environment through rupture of the bacterial cell wall which will destroy the host in the process. Phage therapy and antibiotic therapy differ in their modes of action and dose administration. Antibiotics target broad bacterial processes, often affecting both harmful and beneficial bacteria, which can lead to resistance. In contrast, phage therapy uses bacteriophages that specifically infect and lyse certain bacterial strains, minimizing the impact on the microbiota and evolving alongside bacteria to reduce resistance. While antibiotics are administered in fixed doses, phages replicate at the infection site, potentially reducing the need for repeated doses.

With its abundance in the environment, the only challenge is to isolate the most effective phages to destroy pathogens without affecting the functions of human and animal cells. Bacteriophages potentially have a variety of applications, and some of them have been approved by the United States Food and Drug Administration. They include medicine (to treat wound infection), agriculture (to control plant pathogens) and food safety (to control contamination).

Anti-Microbial Resistance

Poor monitoring and rampant misuse of antibiotics in ASEAN countries are resulting in a huge public health threat: the rise of antimicrobial-resistant (AMR) and multidrugresistant (MDR) bacteria. This may be demonstrated by the persistent increase in tuberculosis (TB) infections known as MDR-TB in the region (WHO, 2021b). Worldwide pathogen monitoring has recorded a rise in the prevalence of such bacteria against a number of antibiotics, including sulfonamides and phenicols (Hendriksen et al., 2019). The global prevalence of single-drug resistance and cross-resistance in bacterial species varies significantly across ASEAN countries, influenced by local healthcare practices, antibiotic usage, and surveillance systems (Vilaichone et al., 2018; Chua et al., 2021). In Malaysia, the antibiotic prescription rate in hospitals and primary care settings remains high (between 70 % and 80 %), which results in higher mortality, morbidity and treatment cost as common pathogens begin to develop resistance (Akhtar et al., 2020).

According to the 2017 Malaysian National Surveillance of Antibiotic Resistance (NSAR) study, there has been an alarming rise in the spread of antimicrobial-resistance and multidrug-resistance genes (Institute for Medical Research, 2020). These genes confer microbes the ability to neutralise the active site of antibiotics or an enhanced efflux of drugs. For example, resistance to all antibiotics in Acinetobacter baumanii has increased by 42.4 % in 2021 compared to the year before. In many public hospitals, the rise of extended spectrum beta-lactamase (ESBL) feature in Enterobacteriaceae species has become a major problem. Klebsiella pneumoniae, one of the most common nosocomial pathogens, has been found to have increased resistance towards cefotaxime and ceftazidime (a thirdgeneration cephalosporin introduced in the 1980s) from 22.6 % and 20.6 % in 2020 to 24.5 % and 22.5% in 2021. Resistance to cefotaxime in Escherichia coli has also increased from 15 % in 2010 to 23.4 % in 2016. The presence of the New Delhi metallo-B-lactamase-1 (NMD-1) gene in carbapenem-resistant K. pneumoniae (CRKP) was identified at a Malaysian hospital in 2010. Since then, its prevalence has increased

dramatically from 0.3 % in 2011 to 2.8 % in 2015. The increasing usage of carbapenems in Malaysia has led to a steady rise of carbapenem resistance, as these antibiotics are advised for the treatment of ESBL infections (Paterson et al., 2004; Institute for Medical Research, 2020). Vancomycin-resistant Enterococcus faecium also reportedly increased from 8.7 % in 2012 to 14.9 % in 2016.

The indiscriminate use of antimicrobials in animal husbandry and poultry production is another key contributor to the spread of antimicrobial resistance in Malaysia. Many current antibiotics used in human healthcare are also being used in veterinary production, including third and fourth generation cephalosporins, macrolides, fluoroquinolones, aminoglycosides and penicillin. They are frequently used to stimulate growth or to prevent infection in livestock and poultry kept in congested and unsanitary conditions. These antimicrobial residues accumulate in muscle tissues, blood and internal organs (Hossain et al., 2022), which may be passed on via the food chain, potentially resulting in foodborne infections that cannot be treated with routinely used antibiotics. E. coli and K. pneumoniae are two common bacteria found in farm animals and are usually resistant to a range of antibiotics (Brennan et al., 2016; Harada et al., 2016). Cases of Salmonella, Campylobacter, Methicillin-resistant Staphylococcus aureus (MRSA) and Vancomycin-resistant S. aureus (VRSA) are also on the rise in food animals, with serious consequences for public health (Friese et al., 2013; Schmithausen et al., 2015; Hassali et al., 2019; Gahamanyi et al., 2020; Grant et al., 2016).

The excessive use of antibiotics has added pressure on the national healthcare system, where precious resources have to be allocated to control the spread of AMR and MDR bacteria, besides increasing treatment cost for patients. Antimicrobial resistance is expected to surpass all other causes of death by 2050, so it is critical to find a safe and effective solution to mitigate this impending threat.

Potential Applications in Malaysia

Bacteriophages, which are viruses that selectively kill bacteria, offer an effective alternative for treating drug-resistant bacterial infections. Phages can be found anywhere where there is an abundance of host bacteria, and this has made them a potentially rich resource for the discovery of new antibacterial agents to complement existing treatments (Derensinski et al., 2009). Phages have demonstrated their potential as a viable alternative to antibiotics. However, the adoption of phage therapy and its research vary by country and may be influenced by healthcare infrastructure, legislation, funding and reception among clinicians. Although the boom of synthetic antibiotics in the mid-20th century had somewhat diminished interest in phage therapy, some researchers, particularly those in Eastern Europe, had continued to explore its potential. In Malaysia, there is very little interest and research in the use of bacteriophage, even for non-human applications. This indicates that the country's healthcare, research and industry players still have many alternatives to deal with bacterial infection and may rather avoid the manipulation of viruses due to safety fears.

Phage therapy is indeed difficult to develop as the high specificity of the virus requires it to be used as a cocktail that is tailormade for the host population. This means a "phage bank" has to be established to produce the cocktail of different bacteriophages to treat the same disease, as pathogen components may vary between patient and location. The host pathogen needs to be studied to determine if they bear receptors that allow the correct bacteriophage to infect them. Furthermore, bacteria can evolve and change their receptors, allowing the host pathogen to develop resistance against phage infection just like antimicrobials (Dimitriu et al., 2022; Oechslin et al., 2018; Labrie et al., 2010).

This requires the phage bank to be regularly updated so it can expand its collection and maintain the effectiveness of its viruses in treating infections. The maintenance of the virus bank, together with constant regulatory tests for safety, require a heavy investment. In a developing country like Malaysia, where funding is limited and broad economical methods are in top demand, the government and industry players have little to no appetite in establishing complicated healthcare facilities like a phage bank.

The safety aspect is also a challenge, especially when the country lacks knowledge and researchers to utilise phage therapy. Unlike Western countries that have been studying bacteriophage therapy for the past 100 years, there is still very little literature on the subject produced by Malaysian scientists. Bacteriophage research in Malaysia is still developing, with studies such as those on bacteriophages from water samples effective against Vibrio cholerae (Al-Fendi et al., 2014) and those targeting colibacillosis in broiler chickens (Lau et al., 2010) marking important contributions. However, the overall scope of research in this area remains limited compared to more established fields of microbiology or regions with a longer tradition of bacteriophage studies. Basically, the bacteriophage used in a therapy only infect prokaryotes and does not infect the patients' eukaryotic cells. However, bacteriophage can have potential concerns related to the human immune response. For example, the human immune response may recognize bacteriophages as foreign entities and may produce antibodies against it. In addition to this, as with any foreign substance injected into the human body, some people may develop allergic reactions to phage preparations. These allergic reactions might range from mild skin irritation to lifethreatening complications.

Despite the concerns, phage therapy has mostly been observed to be safe and effective. Most reported complications like fever, diarrhoea, nausea and inflammation among patients are attributed to endotoxins formed by the rupturing and lysis of bacterial cell walls in the lytic phase and it is a transient response indicating that the therapy is working (Ujmajuridze et al., 2018; Ooi et al., 2019). These conditions were often milder and less common than the side-effects observed in antibiotic-treated patients.

Although there are many challenges in bacteriophage research, the number of local researchers who are interested in the field is growing, with the primary goal of isolating and characterising viruses against key AMR and MDR pathogens, such as Salmonella spp., K. pneumonia and Enterococcus spp. (El-Telbany et al., 2021; Bager et al., 2021) (Table 1). The recent alarming report on the rise of antimicrobial resistance in ASEAN countries has begun to open the eyes of scientists and stakeholders on the importance of developing novel agents and therapeutic strategies that not only overcome the cases, but also prevent their rise in the first place (Center for Disease Dynamic, Economics and Policy, 2021).

Phage as Anti-Bacterial Therapy

Phage therapy is the use of phages or their derivatives as bioagents to cure or prevent infectious diseases caused by bacteria (Matsuzaki et al., 2005). Despite the low enthusiasm in the medical community, efforts are still made to consider applying phage as a treatment option. Sourcing for bacteriophage is never a problem as they may be found in abundance where their hosts reside, such as in jungles, dairy products, seafood, vegetables, meat samples and sewage (Tan et al., 2021; Premaratne et al., 2017; Thung et al., 2017).

Although Malaysia has not approved any clinical trials on phage therapy, in vivo pre-clinical investigations have been reported. For example, an intraperitoneal phage administration study was reported to be efficient in reducing Burkholderia pseudomallei infection in mice experiment

Phage Application	Phage strain	Phage family	Isolation source	Host pathogen	Reference
Clinical	vB_ZEFP	Podoviridae	Hospital wastewater plant	Enterococcus faecalis	(El-Telbany et al., 2021)
	КР	Podoviridae Myoviridae Siphoviridae	Sewage water and cockles	Klebsiella pneumonia	(Baqer et al., 2021)
	C34	Myoviridae	Sea water	Burkholderia pseudomallei	(Guang-Han et al., 2016)
	ΦNUSA-1	Myoviridae	Raw sewage wate	Staphylococcus aureus	(Tan et al., 2020)
	Φ NUSA-10	Siphoviridae			
Agriculture	No strain name	Not reported	Sewage and soil sample	Escherichia coli	(Tan and Tony, 2014)
	pPM_01	Siphoviridae	Sewage treatment facility	Proteus mirabilis	(Wirjon et al., 2016)
	NΦ-1 and NΦ-3	Podoviridae	Termite infected rice	<i>Xanthomonas oryzae</i> In rice	(Liu et al., 2021)
	ΦKpaV03 ΦKpaVa10 and ΦKpaV12	Myoviridae	Domestic sewage facility	Klebsiella pneumoniae	(Paran et al., 2020)
	ФКраV03 and ФКраVa10	Podoviridae			
Livestock	SE07	Podoviridae	Retail chicken meat	Salmonella Enteritidis	(Thung et al., 2017)
	SE01-SE14 ST01-ST04 CJ01-CJ04 VP01 and VP02 EC01-EC05	Not reported	Various food types and sewage water	Salmonella Enteritidis SalmonellaTyphimurium Camphylobacter Jejuni Vibrio parahymolyticus Escherichia coli	(Thung et al., 2017) (Thung et al., 2020)
	ΦLM1-ΦLM05 ΦEC1-ΦEC3 ΦSA1 and ΦSA2 ΦMRSA1 ΦCC1 ΦCj1-ΦCJ5	Not reported	Food product (Beef, chicken, vegetable, clam, cockles and shrimps) and environ- mental samples (water and sewage)	Camphylobacter jejuni, Escherichia coli, Staphylococcus aureus, Listeria monocytogenes	(Premarathne et al., 2017)
	EC1	Not reported	Chicken faeces	Escherichia coli	(Lau et al., 2010)
	VPUSM	Myoviridae	Environmental water samples: rivers, lakes, sewage, fish farms, ditches, ponds	Vibrio cholerae	(Al-Fendi et al., 2014)
	CJ01	Myoviridae	Retail chicken meat	Camphylobacter jejuni and Camphylobacter lari	(Thung et al., 2020)
Aquaculture	Vp33, Vp22, Vp21, Vp02 Vp08 and Vp11	Podoviridae Siphoviridae	Seafood samples	Vibrio parahaemolyticus	(El-Telbany et al., 2021)
	vB_Sags-UPM1	Siphoviridae	Infected tilapia	S. agalactiae	(Megat et al., 2023)
	VpKK5	Siphoviridae	Coastal sand sediment	Vibrio parahaemolyticus	(Lal et al., 2016)
	VhKM4	Myoviridae	A diseased culture Barramundi Perch Lates calcarifer	Vibrio harveyi and Vibrio parahemolyticus	(Taylor and Reeder, 2020)

Table 1: The list of bacteriophages studies in Malaysia included in this article.

(Guang-Han et al., 2016). Although the formulation is tolerable to mice, the safe dose and immunological interactions have yet to be properly characterised in humans. Using the agar overlay method, Tan et al. (2021) tested the lytic activity of multiple phages against S. aureus strains recovered from sewage (Tan et al., 2021). Excitingly, they discovered that two phages from the Myoviridae and Siphoviridae families had an extraordinarily broad host range against >80 % of methicillin-resistant S. aureus (MRSA) and its susceptible counterpart Because of their broad (MSSA). and outstanding antibacterial properties, these phages have been proposed as a potential novel therapeutic option for S. aureus clinical infection (Tan et al., 2020).

Another study by Wirjon et al. (2016) found that Phage pPM 01 isolated from a sewage treatment facility in Penang was a good candidate to treat Proteus mirabilis, which caused urinary tract infection in humans (Wirjon et al., 2016). This was due to the phage's high lytic capabilities and virulence against P. mirabilis. The genome analysis showed neither virulence factors nor potentially known toxins were present in the phage pPM_01 genome (Wirjon et al., 2016). Another host-specific phage C34 belonging to the Myoviridae family was isolated from a seawater sample and found to be potent against clinical B. pseudomallei (Guang-Han et al., 2016). The efficacy of C34 phages had been evaluated an in vivo model, resulting in significant reduction of bacterial burden in B. pseudomallei-infected mice compared with untreated control. Phage therapy for melioidosis is currently being reviewed in clinical trials, but it has not yet been licensed for industrial use. The findings of phage C34 and several other phages reported elsewhere (Kvitko et al., 2012; Wang et al., 2022) strongly implied their potential to be developed as a therapeutic agent for melioidosis.

Another study by Paran et al. (2020) used a lytic bacteriophage cocktail isolated

from a domestic sewage plant to treat clinical K. pneumoniae (Paran et al., 2020). The phage was observed to lyse a gentamycin-resistant strain of the bacteria. Significantly, because mono-phage treatment is more personalised and time demanding, this discovery sheds light on the effectiveness of using phage cocktail treatments (Paran et al., 2020).

Phage in the Livestock and Aquaculture

The use of bacteriophages is not confined to human healthcare. It may be used in livestock and poultry protection to reduce animal mortality. The aquaculture is rapidly growing industry and livestock farming is a significant part of the economy in ASEAN regions. The traditional reliance on antibiotic has led to rising concerns on antibiotic resistance and threatens the sustainability of the industry. Studies on the effectiveness of phage in controlling pathogens such as Vibrio and Aeromonas which are responsible for significant mortality in shrimp and fish population have been reported. For example, a study demonstrated that phage treatment significantly protected shrimp from Acute Hepatopancreatic Necrosis Disease (AHPND) caused by Vibrio parahaemolyticus (Jun et al., 2018). Additionally, the isolation of specific phages, like vB_AdhS_M4 against Aeromonas dhakensis, indicates the feasibility of targeted phage therapy for biocontrol in aquaculture (Sawaengwong et al., 2023).

Malaysia's livestock industry is growing, and it includes both ruminants and nonruminant animals, such as dairy, poultry and porcine (Rosali et al., 2015). Population and wealth growth have increased demand for meat and poultry, which resulted in farms overusing antibiotics to enhance the growth of animals and supply stock in the fastest time possible. As a result, increasing levels of AMR and MDR bacteria and residual antibiotics have been detected in dairy and poultry products (Hassali et al., 2018; Geidam et al., 2012). Intensive livestock farming can facilitate disease transmission as these animals often have low genetic diversity and are reared in large and dense populations (WHO, 2016). Campylobacter spp., Salmonella spp., Listeria spp. and E. coli are examples of food-borne pathogens frequently associated with the livestock industry (WHO, 2016). Bacteriophages may thus be utilised to prevent and controlling pathogenic bacterial growth and proliferation in these animals.

While many studies have isolated phage against MDR pathogens and investigate their efficacy in vitro, local researchers are screening for potential bacteriophages to tackle the degree of antimicrobial resistance in the food chain (Lisha et al., 2017; Mohammad Jajere et al., 2020). Recently, phage against Campylobacter jejuni and Salmonella which are common food pathogens have been isolated by local scientists (Thung et al., 2017; Thung et al., 2020). Some of these phages may act as a biocontrol agent to selectively reduce or eliminate pathogen-susceptible organisms from animal environments (e.g., Intestinal flora).

A local study at Universiti Putra Malaysia has also reported the isolation of phages specific for C. jejuni, E. coli, S. aureus and Listeria monocytogenes from various environments to combat food-borne diseases (Thung et al., 2017). The study suggested that people do frequently ingest phages in their food and can be isolated from food products. Previously, Lau et al. (2010) documented the efficiency of bacteriophage isolated from chicken faeces in combating pathogenic strains of E. coli that caused colibacillosis in chickens (Lau et al., 2010). They demonstrated that the phage could reduce the severity of E. coli infection, bacterial loads (septicaemia) and mortality rate in farmed chickens. In another Malaysian study, Al-Fendi et al. (2014) successfully recovered 11 vibrio-phages from a variety of sources, including rivers, lakes, sewage, fish farms, ditches and ponds (Al-Fendi et al., 2014). They went on to characterise three of them, three of which were lytic phages with a narrow

host range and recommended them as good candidates for use as biological control agents against cholera (Tan and Tony, 2014).

The use of phage in aquaculture has also been proposed, especially to control water-borne pathogens. Vibrio spp. and A. hydrophila are two frequent bacterial diseases affecting the aquaculture industry, causing not only high mortality rates but also significant economic losses. Methods to control these pathogens are similar to the livestock industry, which is the use of antibiotics. Tan et al. (2021) reported six bacteriophages isolated from seafood samples (blood clams, prawns, and surf clams) that demonstrated a narrow host specificity, infecting only the V. parahaemolyticus strains, which was commonly found in a variety of seafood (Tan et al., 2021). The isolation of Myoviridae and Siphoviridae phage against Vibrio harveyi were also done in Universiti Malaysia Sabah (Lal et al., 2017; Lal et al., 2016). This bacterium is known to cause gastroenteritis, which is frequently manifested in humans as bouts of abdominal pain, diarrhoea, fever and nausea. A temperate phage was recently reported and employed against Streptococcus agalactiae infection in tilapia fish (Megat et al., 2023). The phage endolysin is observed to destroy two strains of S. agalactiae with variable degrees of efficiency.

Phage in Agriculture

The use of bacteriophage to control plant pathogens has caught the interest of the agricultural industry. With millions of hectares of fertile land, the Malaysian economy is still partially dependent on agricultural production, particularly commodities like rubber and palm oil. Agriculture is also an important industry as the country tries to achieve food security by producing robust crops with better yield and disease resistance. The country's tropical climate is both a blessing and a curse because the warm and humid environment is not only suitable to promote the growth of plants, but it also stimulates the growth of phytopathogens (plant bacteria) like Xanthomonas spp., Dickeya spp. and Ralstonia spp.

The extent of antibiotic use in agricultural production in low- and middleincome countries was recently revealed more extensive than most of the literature reported (Taylor & Reeder, 2020). According to their findings, antibiotics were routinely used in the production of more than 100 crops, with rice topping the list as the most commonly treated product. Five antibiotics are most commonly reported in plant agriculture: streptomycin (the most widely used antibiotic globally), oxytetracycline, kasugamycin, oxolinic acid (OA), and gentamicin (McManus, 2014; Sundin & Wang, 2018; Miller et al., 2022). In Malaysia, a study found that 62.4 % of farms used antibiotics, with broiler chicken being the most treated (78 %) (Teo et al., 2023) and colistin sulphate (a reserved antibiotics) was noted 3.6 % of cases, raising concerns of the resistance.

Although the use of bacteriophage has not been approved for any application in Malaysia, researchers have discovered several phages that can infect common phytopathogens that harm plantations in order to mitigate the heavy dependency on antibiotics and to be applied in agriculture as biocontrol agent. Xanthomonas oryzae pv. oryzae (Xoo), for example, causes bacterial leaf blight (BLB) disease, and it is one of the most destructive pathogens of paddy crops in Malaysia. Two isolated Podoviridae phages from termites found in rice-growing areas were identified and sequenced (Liu et al., 2021). These phages have a short latent period with high burst size, indicating that they are specifically active against a large number of host strains. The detailed analysis of the phage genome showed that the presence of two important genes; holin and lysin, were responsible for bacterial host lysis. Similarly, the suitability of incorporating phage cocktails with fertiliser to treat tomato bacterial wilt caused by Ralstonia solanacearum, and soft rot disease in pitaya (dragon fruit) caused by Xanthomonas campestris, was evaluated (Tan & Tony, 2014). The findings revealed that 80 % of the tomato plants exhibited no wilting symptoms, and disease spread was successfully limited in pitaya plants.

Additionally, recent studies highlight the increasing adoption of bacteriophages as a biocontrol method against phytopathogens in ASEAN countries (Nawaz et al., 2023; Wang et al., 2024). A study in China reported that increasing the frequency of phage significantly applications can reduce the density of pathogens like Ralstonia solanacearum, leading to lower incidences of diseases such as bacterial wilt in crops (Wang et al., 2024). Similarly, the researchers at university in Jember, Indonesia had recently isolated phages from soybean soil against Pseudomonas syringae pv. glycenia that cause several destructions on the soybean stem, leaf and pod. Their study showed all the phages have double stranded deoxyribonucleic acid (dsDNA) with different propagation ability in the bacterial host (Addy & Wahyuni, 2016).

Phage Challenges and Limitations in Malaysia

The limitation and challenges of bacteriophage application can vary from country to country. Among the major challenges in Malaysia is the availability of financial resources for infrastructure development. The experimental and clinical trials conducted for phage therapy can be costly and time-consuming. Phage therapy exhibits notable host specificity, primarily targeting specific bacterial strains, which contrasts with the broader action of traditional antibiotics. In terms of dose administration, repeated intravenous (IV) doses have been shown to lead to faster phage clearance, activating host immune responses without significant toxicity (Tan et al., 2023; Spek & Smithyman. 2016). Therefore, a sustainable infrastructure is a pressing need for the phage development in clinical, animal husbandry, and agriculture. Laboratories,

research facilities and phage banks are needed to develop standardized protocols and their successful execution. Phage applications may require isolation, characterisation, and selection of specific phages to target particular bacterial strains by expertise for its effective use.

The lack of extensive data and inconsistent outcomes have impeded the broader acceptance among the public, medical community and regulatory agencies. For example, the direct influence of phage has not been comprehensively investigated particularly in the context of its application and very few reported by local researchers. The concerns about the safety of phage on the human immune response such as allergic response has prevented phage therapy from becoming a mainstream medical treatment and create hesitation to adopt phage therapy in animal husbandry and food production. Furthermore, the scarcity of comprehensive genetic data on phages limits the ability to accurately predict their behaviour and effectiveness against specific bacterial strains, which is essential for developing personalised treatment strategies (Culqui Molina et al., 2024).

The journey to bringing phage therapy to the forefront in Malaysia and combating pathogenic bacteria with AMR and MDR properties is indeed lengthy and challenging. However, with concerted efforts in research, regulation, public awareness, and collaboration, phage therapy has the potential to play a significant role in addressing the global health challenge posed by drugresistant bacteria.

CONCLUSION

To summarise, a phage revolution targeting pathogenic bacteria with AMR and MDR properties in Malaysia is indeed a significant endeavour that will be the key for bringing phage therapy out of the shadow. The growing involvement of dedicated local scientists in phage research has make it a promising avenue and it is of the utmost importance because they will play the role of pioneers and lay the foundation for such applications. Phage therapy will be futile in the region without the input of these experts. It is anticipated that there will be more scientific publications covering phage biology, systematics and anti-MDR organism potential as more phage experts emerge. Eventually, there will also be more clinical trials focusing on the use of phage against MDR organisms.

The development of phage interest may be increased by creating an inaugural conference on phage and phage-derived technologies or phage consortium, such as the recent Protein Engineering and Phage Display Conference in Malaysia, as a source of continuing education and providing an avenue where the exchange of ideas and knowledge can occur. It is also critical to hone the complementing skills in the implementation of phage therapy, such as electron microscopy, whole genome sequencing, phage formulation procedures and delivery methods. The molecular characterisation of phages is crucial in designing an effective therapy, i.e., the range of bacterial strains the viruses can target and understanding the molecular basis of bacterial resistance mechanisms, such as CRISPR-Cas systems or surface receptor mutations.

The existing facilities, such as universitybased phage collections or current virological institutes may be utilised as the foundation for the development of crucial phage facilities, such as phage banks and testing centres. These existing collaborations can be revisited and modified using the regulatory models from other countries; after these changes, regulatory agencies can accommodate more investigational and personalised therapeutic options. Therefore, the sooner the region begins discussing the issue, the sooner policymakers may begin implementing phage therapy to bring the problem of AMR and MDR cases under control.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

The authors are grateful for the resources and literature that contributed to the development of this review.

REFERENCES

- Addy, H. S. & Wahyuni, W. S. (2016). Nucleic acid and protein profile of bacteriophages that infect Pseudomonas syringae pv. glycenia, bacterial blight on Soybean. Agriculture and Agricultural Science Procedia, 9, 475-481.
- Akhtar, A., Khan, A. H., Zainal, H., Ahmad Hassali, M. A., Ali, I., & Ming, L. C. (2020). Physicians' perspective on prescribing patterns and knowledge on antimicrobial use and resistance in Penang, Malaysia: A qualitative study. Frontiers in Public Health, 8, 601961.
- Al-Fendi, A., Shueb, R. H., Ravichandran, M., & Yean, C. Y. (2014). Isolation and characterization of lytic vibriophage against Vibrio cholerae O1 from environmental water samples in Kelantan, Malaysia. Journal of Basic Microbiology, 54, 1036-1043. doi: 10.1002/ jobm.201300458
- Baqer, A. A., Wai, Y. C., Adnan, S. N. A., & Md Nor, N. S. (2021). Morphology characterization of ten lytic bacteriophages from different family targeting Klebsiella pneumoniae. Malaysian Journal of Microscopy, 17(1), 1-20.
- Binte Muhammad Jai, H. S., Dam, L. C., Tay, L. S., Koh, J. J. W., Loo, H. L., Kline, K. A., & Goh, B.C. (2020). Engineered lysins with customized lytic activities against Enterococci and Staphylococci. Frontiers in Microbiology, 11, 574739. doi: 10.3389/fmicb.2020.574739
- Brennan, E., Martins, M., McCusker, M. P., Wang, J., Alves, B. M., Hurley, D., El Garch, F., Woehrlé, F., Miossec, C., McGrath, L., Srikumar, S., Wall, P., & Fanning, S. (2016). Multidrug-resistant Escherichia coli in bovine animals, Europe. Emerging Infectious Diseases, 22, 1650-1652. doi: 10.3201/eid2209.160140
- Center for Disease Dynamics, Economics and Policy. (2021). Resistance Map. Available at: https://resistancemap.cddep.org/ AntibioticResistance.php

- Chua, A., Verma, M., Hsu, L. Y., Legido-Quigley, H., & Legido-Quigley, H. (2021). An analysis of national action plans on antimicrobial resistance in Southeast Asia using a governance framework approach. Lancet Regional Health Western Pacific, 23(7), 100084.doi:10.1016/J.LANWPC.2020.100084
- Chu, J. J. K., Poh, W. H., Hasnuddin, N. T. B., Hew, E. Y., Dam, L. C., Sahili, A. E., Rice, S. A., & Goh, B.
 C. (2022). Novel phage lysin Abp013 against Acinetobacter baumannii. Antibiotics (Basel), 11(2), 169. doi: 10.3390/antibiotics11020169. PMID: 35203772; PMCID: PMC8868305
- Culqui Molina, W. P., Pinta Riofrio, M. D., Jiménez Espinosa, P. M., & Suárez Jurado, M. A. (2024). Phage therapy against multiresistant bacteria. Interamerican Journal of Health Sciences, 4. doi: 10.59471/ijhsc202491
- Deresinski, S. (2009). Bacteriophages therapy: exploiting smaller fleas. Clinical Infectious Diseases, 48(8), 1096-101. doi: 10.1086/597405.
- Dimitriu, T., Kurilovich, E., Lapinska, U., Severoniv, K., Pagliara, S., Szczelkun, M. D., & Westra, E.R. (2022). Bacteriostatic antibiotics promote CRISPR-Cas adaptive immunity by enabling increased spacer acquisition. Cell Host & Microbe. 30, 31-40.
- El-Telbany, M., El-Didamony, G., Askora, A., Ariny, E., Abdallah, D., Connerton, I. F., & El-Shibiny, A. (2021). Bacteriophages to control multi-drug resistant Enterococcus faecalis infection of dental root canals. Microorganisms, 9, 517.
- Friese, A., Schulz, J., Laube, H., von Salviati, C., Hartung, J., & Roesler, U. (2013). Faecal occurrence and emissions of livestock-associated methicillin-resistant Staphylococcus aureus (laMRSA) and ESbl/AmpC-producing E. coli from animal farms in Germany. Berl Munch Tierarztl, 126,175–180. 10.2376/0005-9366-126-175
- Gahamanyi, N., Mboera, L. E. G., Matee, M. I., Mutangana, D., & Komba, E. V. G. (2020). Prevalence, risk factors, and antimicrobial resistance profiles of thermophilic campylobacter species in humans and animals in sub-saharan Africa: A systematic review. International Journal of Microbiology, 1–12. 10.1155/2020/2092478
- Geidam, Y. A., Zakaria, Z., Abdul Aziz, S., Bejo, S. K., Abu, J., & Omar, S. (2012). High prevalence of multi-drug resistant bacteria in selected poultry farms in Selangor, Malaysia. Asian Journal of Animal and Veterinary Advances, 7, 891-897.

Grant, A., Hashem, F., & Parveen, S. (2016). Salmonella

and campylobacter: antimicrobial resistance and bacteriophage control in poultry. Food Microbiology, 53, 104–109. 10.1016/j. fm.2015.09.008

- Guang-Han, O., Leang-Chung, C., Vellasamy, K. M., Mariappan, V., Li-Yen, C., & Vadivelu, J. (2016). Experimental phage therapy for Burkholderia pseudomallei infection. PLoS One, 11, e0158213. doi: 10.1371/journal. pone.0158213
- Harada, K., Shimizu, T., Mukai, Y., Kuwajima, K., Sato, T., Usui, M., Tamura, Y., Kimura, Y., Miyamoto, T., Tsuyuki, Y., Ohki, A., & Kataoka, Y. (2016). Phenotypic and molecular characterization of antimicrobial resistance in Klebsiella spp. isolates from companion animals in Japan: clonal dissemination of multidrug-resistant extended-spectrum β-lactamase-producing Klebsiella pneumoniae. Frontiers in Microbiology, 7, 1021. 10.3389/fmicb.2016.01021
- Hassali, M. A. A., Yann, H. R., Verma, A. K., Hussain, R. & Sivaraman, S. (2018). Antibiotic use in food animals: Malaysia overview. Penang, Malaysia: University Science Malaysia, School of Pharmaceutical Sciences.
- Hendriksen, R. S., Munk, P., Njage, P., van Bunnik, B., McNally, L., Lukjancenko, O., Röder, T., Nieuwenhuijse, D., Pedersen, S. K., Kjeldgaard, J., Kaas, R. S., Clausen, P. T. L. C., Vogt, J. K., Leekitcharoenphon, P., van de Schans, M. G. M., Zuidema, T., de Roda Husman, A. M., Rasmussen, S., Petersen, B.; Global Sewage Surveillance project consortium; Amid, C., Cochrane, G., Sicheritz-Ponten, T., Schmitt, H., Alvarez, J. R. M., Aidara-Kane, A., Pamp, S. J., Lund, O., Hald, T., Woolhouse, M., Koopmans, M. P., Vigre, H., Petersen, T. N., & Aarestrup, F. M. (2019). Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nature Communications, 10(1), 1124. doi: 10.1038/s41467-019-08853-3
- Hossain, M. M. K., Islam, M. S., Uddin, M. S., Rahman, A. T. M. M., Ud-Daula A., Islam, M. A., Rubaya, R., Bhuiya, A. A., Alim, M. A., Jahan, N., Li, J., & Alam, J. (2022). Isolation, identification and genetic characterization of antibiotic resistant Escherichia coli from frozen chicken meat obtained from supermarkets at Dhaka City in Bangladesh. Antibiotics (Basel), 12(1), 41. doi: 10.3390/antibiotics12010041
- Institute for Medical Research. 2020. National surveillance of antimicrobial resistance, Malaysia. Available at https://www.imr.gov. my/en/component/content/article/75-

english-content/national-collabration/1469nsar-main.html. [Accessed 11 August 2024].

- Jun, J. W., Han, J. E., Giri, S. S., Tang, K. F. J., Zhou, X., Aranguren, L. F., Kim, H. J., Yun, S., Chi, C., Kim, S. J., & Park, S. C. (2018). Phage application for the protection from acute hepatopancreatic necrosis disease (AHPND) in Penaeus vannamei. Indian Journal of Microbiology, 58(1), 114-117. doi: 10.1007/S12088-017-0694-9
- Kvitko, B. H., Cox, C. R., DeShazer, D., Johnson, S. L., Voorhees, K. J., & Schweizer, H. P. (2012). X216, a P2-like bacteriophage with broad Burkholderia pseudomallei and B. malleistrain infectivity. BMC Microbiology, 12, 289.
- Labrie, S. J., Samson, J. E., & Moineau S. (2010). Bacteriophage resistance mechanisms. Nature Reviews Microbiology, 8, 317–327. doi: 10.1038/nrmicro2315
- Lal, T. M., Sano, M., & Ransangan, J. (2017). Isolation and characterization of large marine bacteriophage (Myoviridae) VhKM4 infecting Vibrio harveyi. Journal of Aquatic Animal Health, 29(1), 26-30. doi: 10.1080/08997659.2016.1249578
- Lal, T. M., Sano, M., & Ransangan, J. (2016). Genome characterization of a novel vibriophage Vpkk5 (Siphoviridae) specific to fish pathogenic strain of Vibrio parahaemolyticus. Journal of Basic Microbiology, 56, 872–888. doi: 10.1002/jobm.201500611
- Lau, G. L., Sieo, C. C., Tan, W. S., Hair-Bejo, M., Jalila, A., & Ho, Y. W. (2010). Efficacy of a bacteriophage isolated from chickens as a therapeutic agent for colibacillosis in broiler chickens. Poultry Science, 89(12), 2589-2596.
- Lisha, V., New, C. Y., Nishibuchi, M., & Son, R. (2017). Rapid genetically modified organism (GMO) screening of various food products and animal feeds using multiplex polymerase chain reaction (PCR). Food Research, 1, 1-6.
- Liu, J., Chia, S. L., & Tan, G. H. (2021). Isolation and characterization of novel phages targeting Xanthomonas oryzae: Culprit of bacterial leaf blight disease in rice. Phage (New Rochelle), 2(3), 142-151. doi: 10.1089/phage.2021.0009
- McManus, P. S. (2014). Does a drop in the bucket make a splash? Assessing the impact of antibiotic use on plants. Current Opinion in Microbiology, 19, 76–82. doi: 10.1016/j. mib.2014.05.013
- Matsuzaki, S., Rashel, M., Uchiyama, J., Sakurai, S., Ujihara, T., Kuroda, M., Ikeuchi, M., Tani, T., Fujieda, M., Wakiguchi, H., & Imai, S. (2005). Bacteriophage therapy: A revitalized therapy

against bacterial infectious diseases. Journal of Infection and Chemotherapy, 11, 211-219. doi: 10.1007/s10156-005-0408-9

- Megat Mazhar Khair, M. H., Tee, A. N., Wahab, N. F., Othman, S. S., Goh, Y. M., Masarudin, M. J., Chong, C. M., In, L. L. A., Gan, H. M. Song, A. A. (2023). Comprehensive Characterization of a Streptococcus agalactiae Phage Isolated from a Tilapia Farm in Selangor, Malaysia, and Its Potential for Phage Therapy. Pharmaceuticals, 16, 698. doi: 10.3390/ ph16050698
- Miller, S. A., Ferreira, J. P., & Lejeune, J. T. (2022). Antimicrobial use and resistance in plant agriculture: A one health perspective. Agriculture, 12, 1–27. doi: 10.3390/ agriculture12020289
- Mohammed Jajere, S. Hassan, L., Zakaria Z, Abu, J., & Abdul Aziz, S. (2020). Antibiogram profiles and risk factors for multidrug resistance of Salmonella enterica recovered from village chickens (Gallus gallus domesticus Linnaeus) and other environmental sources in the Central and Southern Peninsular Malaysia. Antibiotics (Basel), 9(10), 701.
- Nawaz, A., Zafar, S., Shahzadi, M., & Ullah Shah Bukhari, S. M. A. (2023). Bacteriophages: An overview of the control strategies against phytopathogens. Egyptian Journal of Biological Pest Control, 33, 108. doi: 10.1186/ s41938-023-00751-7
- Oechslin, F. (2018). Resistance Development to bacteriophages occurring during bacteriophage therapy. Viruses, 10(7), 351. doi: 10.3390/v10070351
- Ooi, M. L., Drilling, A. J., Morales, S., Fong, S., Moraitis, S., Macias-Valle, L., Vreugde, S., Psaltis, A. J., & Wormald, P. J. (2019). Safety and tolerability of bacteriophage therapy for chronic rhinosinusitis due to Staphylococcus aureus. JAMA Otolaryngol Head Neck Surgery, 145(8), 723-729.
- Paran, A. K., Mamora, D., Fong, G. K. Y., Lihan, S., Zulkarnain, A., & Tan, C. S. (2020). Evaluation of the efficacy of a phage cocktail against gentamicin-resistant Klebsiella pneumoniae. Journal of Sustainability Science and Management, 15(3), 86-100.
- Premarathne, J. M. K. J. K., Thung, T. Y., New, C. Y., Huat, J. T. Y., Basri, D. F., Rukayadi, Y., Nakaguchi, Y., Nishibuchi, M., & Son, R. (2017). Distribution of bacteriophages in food and environment samples. International Food Research Journal, 24(2), 888-896.
- Rosali, H. S., & Mohammad Nor, N. A. (2015). The development and future direction

of Malaysia's livestock industry. FFTC Agricultural Policy Platform (FFTC-AP). https://ap.fftc.org.tw/article/960

- Sawaengwong, T., Sunthornthummas, S., Surachat, K., Atithep, T., Rangsiruji, A., Sarawaneeyaruk, S., & Pringsulaka, O. (2023). Isolation and characterization of lytic bacteriophages against Aeromonas dhakensis isolated from water in Thailand. Journal of Current Science and Technology, 13(3), 551-563. doi: 10.59796/jcst.V13N3.2023.932
- Schmithausen, R. M., Schulze-Geisthoevel, S. V., Stemmer, F., El-Jade, M., Reif, M., Hack, S., Meilaender, A., Montabauer, G., Fimmers, R., Parcina, M., Hoerauf, A., Exner, M., Petersen, B., Bierbaum, G., & Bekeredjian-Ding I. (2015). Analysis of transmission of MRSA and ESBL-E among pigs and farm personnel. PLoS One, 10(9), e0138173 doi: 10.1371/journal. pone.0138173
- Speck, P., & Smithyman, A. (2016). Safety and efficacy of phage therapy via the intravenous route. FEMS Microbiology Letters, 363(3), fnv242. doi: 10.1093/femsle/fnv242
- Sundin, G. W., & Wang, N. (2018). Antibiotic resistance in plant-pathogenic bacteria. Annual Review of Phytopathology, 56, 161– 180. doi: 10.1136/pgmj.48.558.216
- Tan, X., Chen, K., Jiang, Z., Liu, Z., Wang, S., Ying, Y., Zhang, J., Yuan, S., Huang, Z., Gao, R., Zhao, M., Weng, A., Yang, Y., Luo, H., Zhang, D., & Ma, Y. (2023). Phage administration with repeated intravenous doses leads to faster phage clearance in mammalian hosts. bioRxiv. doi: 10.1101/2023.03.10.532150
- Tan, C. S., Aqiludeen, N. A., Tan, R., Gowbei, A., Mijen, A. B., Santhana Raj, L., & Ibrahim, S. F. (2020). Could bacteriophages isolated from the sewage be the solution to methicillinresistant Staphylococcus aureus? Medical Journal of Malaysia, 75(2), 110-116. PMID: 32281590
- Tan, G. H., & Tony, P. S. H. (2014). Disease control of Ralstonia solanacaerum in tomato and Xanthomonas campestris in pitaya using bacteriophage. Direct Research Journal of Agriculture and Food Science, 2(10), 147– 155.
- Tan, C. W., Rukayadi, Y., Hasan, H., Abdul-Mutalib, N-A., Jambari, N.N., Hara, H., Thung, T.Y., Lee, E., & Radu, S. (2021). Isolation and characterization of six Vibrio parahaemolyticus lytic bacteriophages from seafood samples. Frontiers Media S.A., 12, 616548. doi: 10.3389/fmicb.2021.616548
- Taylor, P., & Reeder, R. (2020). Antibiotic use on crops

in low and middle-income countries based on recommendations made by agricultural advisors. CABI Agriculture and Bioscience, 1, 1. doi: 10.1186/s43170-020-00001-y

- Thung, T. Y., Siti Norshafawatie, B. M., Premarathne, J.
 M., Chang, W. S., Loo, Y. Y., Kuan, C. H., New, C.
 Y., Ubong, A., Ramzi, O. S., Mahyudin, N. A., & Dayang, F. B. (2017). Isolation of food-borne pathogen bacteriophages from retail food and environmental sewage. International Food Research Journal, 24(1), 450–454.
- Thung, T. Y., Lee, E., Mahyudin, N. A., Wan Mohamed Radzi, C. W. J., Mazlan, N., Tan, C. W., & Radu, S. (2020). Partial characterization and in vitro evaluation of a lytic bacteriophage for biocontrol of Campylobacter jejuni in mutton and chicken meat. Journal of Food Safety. 40(2), e12770. doi: 10.1111/jfs.12770
- Ujmajuridze, A., Chanishvili, N., Goderdzishvili, M., Leitner, L., Mehnert, U., Chkhotua, A., Kessler, T. M., & Sybesma, W. (2018). Adapted bacteriophages for treating urinary tract infections. Frontiers in Microbiology, 9, 1832. doi: 10.3389/fmicb.2018.01832
- Vilaichone, R. K., Quach, D. T., Yamaoka, Y., Sugano, K., & Mahachai, V. (2018). Prevalence and pattern of antibiotic resistant strains of Helicobacter Pylori infection in ASEAN. Asian Pacific Journal of Cancer Prevention, 19(5), 1411-1413. doi: 10.22034/APJCP.2018.19.5.1411
- Wang, Y., Li, X., Dance, D. A. B., Xia, H., Chen, C., Luo, N., Li, A., Li, Y., Zhu, Q., Sun, Q., Wu, X., Zeng, Y., Chen, L., Tian, S., & Xia Q. (2022). A novel lytic phage potentially effective for phage therapy against Burkholderia pseudomallei in the tropics. Infectious Diseases of Poverty, 11(1), 87.
- Wang, X., Wang, S., Huang, M., He, Y., Guo, S., Yang, K., Wang, N., Yang, H., Yang, T., Xu, Y., Shen, Q., Friman, V-P., & Wei, Z. (2024). Phages enhance both phytopathogen density control and rhizosphere microbiome suppressiveness. Mbio, 15(6), e0301623. doi: 10.1128/ mbio.03016-23
- Wirjon, I. A., Lau, N. S., & Arip, Y. M. (2016). Complete genome sequence of Proteus mirabilis Phage pPM_01 isolated from raw sewage. Intervirology, 59(5-6), 243-253. doi: 10.1159/000468987
- World Health Organization. (2021a). Global shortage of innovative antibiotics fuels emergence and spread of drug-resistance. https://www. who.int/news/item/15-04-2021-globalshortage-of-innovative-antibiotics-fuelsemergence-and-spread-of-drug-resistance. [Accessed 6 August 2024].

- World Health Organization. (2021b). Global Tuberculosis Report. The Thirteenth Meeting of the South-East Asia Regional MDR-TB Advisory Committee (SEA RGLC) (who.int)
- World Health Organization. (2016). Burden of foodborne diseases in the South-East Asia region. World Health Organization, Regional Office for South-East Asia. https://apps.who .int/iris/handle/10665/332224

BJMS Borneo Journal of Medical Sciences

REVIEW ARTICLE

Overview of Exercise Addiction - Early Detection for Early Intervention

Khairun'naim Bin Khairuddin¹, Muhammad 'Adil Zainal Abidin³, Hazwani Hanum Binti Hashim¹, Azwanis Binti Abdul Hadi²*

- ¹ Department of Community and Family Medicine, Faculty of Medical and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
- ² Department of Family Medicine, Kulliyyah of Medicine, Universiti Islam Antarabangsa Malaysia Kampus Kuantan, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia
- ³ Department of Community Medicine, Kulliyyah of Medicine, Universiti Islam Antarabangsa Malaysia Kampus Kuantan, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia
- * Corresponding author's email: azwanis@iium.edu.my

Received: 6 February 2024

Accepted: 9 October 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.6372

Keywords: *Exercise, Addiction, Screening, EDS21, EAI*



Borneo Journal of Medical Sciences @ 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

Exercise has been proven to have many significant positive physical, mental and social effects. It makes our body healthier, reduces stress levels and improves relationships with others. However, not much is known about the negative effects of exercise as the benefits of exercise are more visible. In excess, some people who could develop one of the substantial negative effects of exercise called exercise addiction. The complications of exercise addiction can be seen in the form of injuries, stress, anxiety and social relationship problems. Early detection of a person with high risk of exercise addiction can prevent its complications by instituting an early intervention. This review aims to examine the available literature on exercise addiction as well as to elicit available psychometric tools that can be used to detect exercise addiction.

INTRODUCTION

Similar to many other developing countries, there has been an increase in awareness among Malaysians of the importance of a healthy lifestyle, due to the heavy promotion of its benefits. In WHO's Global Action Plan (2018) for physical activity, a minimum of 150 minutes of moderate-intensity exercise or 75 minutes of high-intensity exercise per week is recommended for adults aged 18 to 64 years in order to maintain physical and mental health. As a result, exercise has emerged as a popular and even trendy pastime. The National Health and Morbidity Survey (NHMS) 2019 showed a steep increase in physical activity among the Malaysian population, to 74.9% from 64.3% in 2011 and 64.5% in 2015. Nik Nasir et al. (2022) showed that the prevalence of active Malaysians was 66%. Many Malaysians devote much of their time to exercise, and some, to the point of addiction.

An electronic search of available literature was conducted using ResearchGate, Google Scholar and Scopus. The following keywords were used: Exercise, Addiction, Dependency and Screening from year 1994 to 2023 for the available literature on exercise addiction. Further searches for psychometric exercise addiction screening tools were made using the keywords X, Y and Z. A total of 132 articles were found. Thirty-two articles were included and synthesized in this review.

Exercise Addiction and its Complications

American Psychiatric Association (APA) (2022) defines addiction as a biopsychosocial disorder characterized by a state of psychological and/or physical dependence on a persistent and intense urge to use a drug or engage in behavior that produces natural reward, despite substantial harm and other negative consequences. Exercise is a repetitive behavior and it may develop into an addiction. People exercise for a healthy lifestyle, but may then find themselves unable to stop, even though their exercising has caused injury and disruption to their social lives, leading to psychological problems. This is a manifestation of exercise addiction. Exercise and sports can positively impact physical and mental health, but only when performed in moderation.

The rewarding effect of exercise can increase the intention effect. Satisfaction and pleasure-seeking can cause a person to do more than intended (Dishman & O'Connor, 2009). This can lead to over-exercising, thereby using time that was supposed to be used for other things. Consequently, it may result in a lack of self-control. Unable to reduce the amount of stimulation required to achieve satisfaction, the addict will develop a persistent craving or be unable to cut down or control the amount and intensity of the exercise.

The outcome of addiction can be evaluated in its influence on time and other social activities. Time will be prioritized for exercise by sacrificing or ignoring other needs. A great deal of time will be spent on activities necessary to obtain the desired effect. In the context of exercise, this is shown as exercise satisfaction, at the expense of social, occupational, or recreational needs (De La Vega et al., 2016). Such behavior can lead to problems in relationships, especially with family and friends. Excessive exercise can also interrupt formal work due to the loss of concentration and fatigue. An exercise addict will continue to exercise excessively, despite knowing that it is harmful to him. Feeling unwell or sustaining injuries is not a good enough reason to stop him from continuing to exercise and in rare instances, this addiction might lead to death.

Injuries happen when people overexercise and fail to take heed of the warning signs that their bodies have reached their limits. An addict may continue to exercise despite their injuries, as seen in cases of stress fracture and joint problems among the elderly. Jones et al. (1994) stated that the risk of injury increases substantially with the amount of exercise. This is supported by Overgaard et al. (2015), with the additional finding that there is no optimal dose for exercise to prevent injury. Therefore, as a safety precaution, a person should not exercise beyond their limit and must take safety measures while exercising.

Social relationships can also be impaired by exercise addiction. A person who is addicted to exercise would devote most of their time to their exercises, thus neglecting all other activities. This could mean sacrificing their social needs to the point of jeopardizing their relationships with family and friends, their work, or their studies (Derevensky, 2019). Their thoughts would always be focused on exercise instead of their work or other, more pressing needs.

Psychologically, an exercise addict would yearn for a certain level of intensity, length of time, or frequency in their exercise to obtain satisfaction (Samadzadeh et al., 2011). Problems arise when these targets are not achieved, for example during illness or when work or family matters prevent them from exercising. Problems also occur when these desired levels are so high that they become difficult to achieve. A characteristic of exercise addiction is the satisfaction of achieving the exercise target. Therefore, when they fall short, satisfaction fails to be achieved because the addict has developed a tolerance for satiety. Consequently, this can lead to psychological problems, such as stress and anxiety.

Exercise addiction can present with or without a combination of other behavioral or mental health problems. Various studies have shown the correlation between exercise addiction and other behavioral issues or addiction to other things, such as tobacco, alcohol, illicit drugs, eating, gambling, the Internet, love, sex, work, or shopping (Szabo et al., 2017). A study by Sussman et al. (2011) showed that 15% of exercise addicts were also dependent on alcohol, cigarettes, or illegal drugs, while 25% might have other addictions. Exercise addiction also positively correlates with body dysmorphic disorder (BDD) (Trott et al., 2021). Eating disorders, for instance, are shown to correlate with exercise addiction. With the concurrence of other behavioral problems such as eating disorders, an exercise addict is likely to suffer extreme weight loss on top of poor health. A comparative metaanalysis by Levit et al., (2018) showed that the prevalence of exercise addiction among those with eating disorders was three times higher than among those without eating disorders.

Prevalence of Exercise Addiction

Obsessive passion and dedication to exercise can be considered strong predictors of exercise addiction. It can, therefore, be presumed that the prevalence of exercise addiction is different in different categories of people. A study by Szabo et al. (2015) showed that between 7% and 42% of the athletic population were exercise addicts and around 3% of non-competitive leisure exercisers were addicted to exercise. The high variation seen among athletes depends on the type of sport involved, seen higher. Lichtenstein et al. (2018) also conducted a study on the prevalence of exercise addiction in different groups of respondents. The study showed that the prevalence rate of exercise addiction among school athletes was 4%, among fitness attendees it was 8% and among people with eating disorders, the rate was 21%. Another study by Trott et al. (2021) obtained a similar finding of 5.5% among university students and 8.1% among general exercisers. In a separate study, Corazza et al. (2019) revealed a high prevalence of exercise addiction among athletes (e.g., runners, and triathletes). Furthermore, Szabo et al. (2017) showed that the prevalence of exercise addiction among regular exercisers was 10.3%. In Asia, only Korea has conducted a study to ascertain the prevalence of the high risk of addiction to exercise. A total of 15.4% out of the 408 respondents in their sample had a high risk of exercise addiction (Shin & You, 2015).

Pathophysiology of Exercise Addiction

Exercise addiction has been a subject of worldwide debate among scholars. There are no specific guidelines or criteria to diagnose exercise addiction. The American Psychiatric Association (APA) recognizes only gambling as a behavioral addiction at this moment, which is classified under 'Substance-Related and Addictive Disorders'. Although there is no clear organic substance involved in behavioral addiction, the effect is similar to the effect of substance addiction. This is pathologically explained using the reward and relief pathways, which can be seen in both behavioral addiction and substance abuse (Dishman et al., 2009).

Exercise increases the release of opiatelike substances, such as beta-endorphins. Leuenberger (2006) believed that this hormone induces happiness by creating a reward pathway in the brain and reducing pain. The person will develop a feeling that is best described as satisfaction, a state of sheer joy, euphoria, inner harmony, limitless energy, feelings of well-being, and a reduced perception of pain. From the psychological aspect, exercise relieves stress. People who use physical activity to alleviate their stress will have trouble refraining from their exercise routines. They turn to exercise to avoid their stress instead of addressing the source of the stress. Antunes et al. (2016) found that exercise addicts experienced withdrawal symptoms when they stopped exercising, especially in the form of mood changes. Additionally, it was found that their beta-endorphin levels dropped when they stopped exercising. It is this euphoria-seeking and stress-relieving behavior through exercise that can lead to addiction. The endorphins released by exercise influence the dopamine reward system in a way that is similar in effect to substances such as cocaine. Robison et al. (2018) and Paungmali et al. (2018) showed that aerobic exercise could reduce cocaine-seeking behavior. It is, therefore, suggested that exercise can allay the withdrawal effects of cocaine. This is supported by Wang et al. (2014) who showed that exercise could effectively treat substance abuse.

Screening for Exercise Addiction

Screening for warning signs is a proactive way to identify people who are at risk of addiction so that early intervention can be applied to prevent unnecessary complications. A good and validated tool that can screen psychometrically needs to be employed for early detection of the addiction. Two common screening methods have been validated and are now widely used to evaluate the risk of exercise addiction. They are the Exercise Dependence Scale 21 (EDS-21) and the Exercise Addiction Inventory (EAI). The EDS-21 has 21 items while the EAI has 6 items. The EDS-21 has been translated and validated in eleven different languages (French, Hungarian, Korean, Danish, Swedish, Italian, Spanish, Estonia, German, Chinese and Greek) (Szabo et al., 2013; Sicilia & González-Cutre, 2011; Müller et al., 2013; Shin & You, 2015; Yang et al., 2021). Both tools were developed based on the substance addiction domain in DSM IV (2000). The EDS-21 covers all domains of addiction, consisting of tolerance, withdrawal, intention effect, lack of control, time, reduction of other activities and continuance (Hausenblas & Downs, 2002). Both are accepted as tools for screening exercise dependency levels. The exercise dependency level can be used as a guide to screen for exercise addiction.

Both tools used a dependency scale that was developed based on multiple domains that can fall under substance addiction. For example, under tolerance, the person needs to increase the amount of exercise in order to achieve the desired effect. The person also needs to have more stimulation to achieve the same effect. Withdrawal is a domain that can be easily assessed and evaluated. A person with an addiction will show organic symptoms once the behavior is stopped, as found by Antunes et al. (2016). The addict will display signs resembling withdrawal symptoms, such as anxiety, fatigue and insomnia.

In EDS21, all these domains can be reflected in the 21 questions. The questions refer to current exercise beliefs and behaviors that have occurred in the past 3 months (Hausenblas & Downs, 2002). EDS-21 requires approximately 5 minutes to complete. The level of dependencies will be assessed from the analysis of the result. Responses on a Likert scale anchored at the extremes with never (1) and always (6). The total of mean score will be calculated for every domain. EDS-21 already

	Domain with mean 5 or 6 score	Domain with mean 3 or more score	Domain with mean 2 or less score
At-Risk For Exercise Dependence	3 or more domain	-	-
Nondependent-Symptomatic	Less than 3 domains	3 or more domain	-
Nondependent-Asymptomatic	Less than 3 domains	Less than 3 domains	-

Table 1: Exercise Dependence Scale 21 Scoring.

have its SPSS Syntax that can automatically compute the total and subscale mean scores. The result will be in 3 outcomes that are atrisk for exercise dependence, nondependentsymptomatic, and nondependentasymptomatic.

For EAI, it only uses 6 questions with a Likert scale to cover all the addiction domains (Terry et al., 2004). The total scores are calculated and used to reflect the level of exercise dependencies. The result is either atrisk of exercise dependencies or no exercise dependencies as shown in Table 1. The person with the result of at-risk for exercise addiction from both psychometric tools needs to be referred to an addiction specialist for further evaluation. This questionnaire is used only as a screening method and not as confirmatory. Therefore, it is preferable to use EAI as a simpler screening tool compared to EDS-21 which is more complicated.

Mónok et al. in 2012, compared both tools using a total of 474 leisure exercisers and showed a good fit in Confirmatory Factor Analysis (CFA) for both tools. The results were CFI = 0.971, TLI = 0.952, and RMSEA = 0.052 for EAI and CFI = 0.938, TLI = 0.922; RMSEA = 0.049. The correlation between the two tools was high (r = 0.79). A similar result was seen in a study by Granziol et al. in 2021 with a total of 1011 athletes showed both instruments revealed good fit in indexes, even across genders. The study also shows that EDS21 was much better than EAI as the CFAs on EAI scores showed some violations of measurement invariance across the competition level ($\Delta CFI=$ 0.03; $\Delta RMSEA = 0.02$). On the contrary, CFAs on EDS21 scores did not show invariance violations across the competition level (Δ CFI= <0.01; Δ RMSEA= < 0.01). Therefore, both tools are good psychometric tools for screening of exercise dependency but EDS21 can be consider more reliable compared to EAI.

With the availability of psychometric assessments to detect the risk of exercise addiction, we can nip the problem in the bud and address it early enough to avoid severe consequences. Treatments, such as psychotherapy and psychoeducation, can be useful to help an addict. Screening can be performed in high-risk groups, such as athletes and patients with other behavioral problems.

CONCLUSION

This narrative review shows that exercise addiction can have a negative influence on a person physical, mental, and social health. Exercise addiction was rarely heard of in the past, but with the growing number of exercise enthusiasts in Malaysia, this could become a real problem. The earlier intervention can prevent permanent problems and improve the outcome. The availability of psychometric tools can help in detecting patients with a high risk of exercise addiction. Most of the data regarding exercise addiction are from the Western population. There is no local data regarding psychometric tools for exercise addiction screening that can be explored in future studies.

ACKNOWLEDGMENT

We thank all the researchers whose work has contributed to this review. Special thanks to Department of Family Medicine, IIUM for their
support.

FUNDING

This narrative review is self-funded.

CONFLICT INTEREST

None to declare.

REFERENCES

- Antunes, H. K. M., Leite, G. S. F., Lee, K. S., Barreto, A. T., Santos, R. V. T. D., De Sá Souza, H., Tufik, S., & De Mello, M. T. (2016). Exercise deprivation increases negative mood in exerciseaddicted subjects and modifies their biochemical markers. Physiology & Behavior, 156, 182–190. https://doi.org/10.1016/j. physbeh.2016.01.028
- American Psychiatric Association. (2022). Diagnostic and statistical manual of mental disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), 5(5). https://doi.org/10.1176/appi. books.9780890425787
- Corazza, O., Simonato, P., Demetrovics, Z., Mooney, R., Van De Ven, K., Román-Urrestarazu, A., Rácmolnár, L., De Luca, I., Cinosi, E., Santacroce, R., Marini, M., Wellsted, D., Sullivan, K., Bersani, G., & Martinotti, G. (2019). The emergence of exercise addiction, body dysmorphic disorder, and other imagerelated psychopathological correlates in fitness settings: A cross sectional study. PLOS ONE, 14(4), e0213060. https://doi. org/10.1371/journal.pone.0213060
- De La Vega, R., Parastatidou, I. S., Ruíz-Barquín, R., & Szabó, A. (2016). Exercise addiction in athletes and leisure exercisers: The moderating role of passion. Journal of Behavioral Addictions, 5(2), 325–331. https:// doi.org/10.1556/2006.5.2016.043
- Derevensky, J. L. (2019). Behavioral addictions: Some developmental considerations. Current Addiction Reports, 6(3), 313–322. https://doi. org/10.1007/s40429-019-00257-z
- Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR). (2000). In American Psychiatric Association eBooks. https://doi.org/10.1176/ appi.books.9780890423349
- Dishman, R. K., & O'Connor, P. J. (2009). Lessons in exercise neurobiology: The case of

endorphins. Mental Health and Physical Activity, 2(1), 4–9. https://doi.org/10.1016/j. mhpa.2009.01.002

- Granziol, U., Zorzi, A., Cardaioli, F., Cipriani, A., D'Ascenzi, F., Firth, J., Stubbs, B., Trott, M., & Solmi, M. (2021). Exercise addiction in athletes: Comparing two assessment instruments and willingness to stop exercise after medical advice. Psychological Assessment, 33(4), 326–337. https://doi. org/10.1037/pas0000987
- Hausenblas, H. A., & Downs, D. S. (2002). How Much is Too Much? The Development and Validation of the Exercise Dependence Scale. Psychology & Health, 17(4), 387–404. https:// doi.org/10.1080/0887044022000004894
- Jones, B. H., Cowan, D. N., & Knapik, J. J. (1994). Exercise, training and injuries. Sports Medicine, 18(3), 202–214. https://doi. org/10.2165/00007256-199418030-00005
- Leuenberger, A. (2006). Endorphins, exercise, and addictions: A review of exercise dependence. Impulse: The Premier Undergraduate Neuroscience Journal. https://doaj.org/articl e/124cfe5128584718876f3e1c0672bb9a
- Levit, M., Weinstein, A., Weinstein, Y., Tzur-Bitan, D., & Weinstein, A. (2018). A study on the relationship between exercise addiction, abnormal eating attitudes, anxiety and depression among athletes in Israel. Journal of Behavioral Addictions, 7(3), 800–805. https://doi.org/10.1556/2006.7.2018.83
- Lichtenstein, M. B., Nielsen, R. O., Gudex, C., Hinze, C. J., & Jørgensen, U.G. (2018). Exercise addiction is associated with emotional distress in injured and non-injured regular exercisers. Addictive Behaviors Reports, 8, 33–39. https://doi.org/10.1016/j.abrep.2018.06.001
- Mónok, K., Berczik, K., Urbán, R., Szabó, A., Griffiths, M. D., Farkas, J., Mägi, A., Eisinger, A., Kozma, T., Kökönyei, G., Kun, B., Paksi, B., & Demetrovics, Z. (2012). Psychometric properties and concurrent validity of two exercise addiction measures: A population wide study. Psychology of Sport and Exercise, 13(6), 739–746. https://doi.org/10.1016/j. psychsport.2012.06.003
- Müller, A., Claes, L., Smits, D., Gefeller, O., Hilbert, A., Herberg, A., Müller, V., Hofmeister, D., & De Zwaan, M. (2013). Validation of the German version of the exercise dependence scale. European Journal of Psychological Assessment, 29(3), 213–219. https://doi. org/10.1027/1015-5759/a000144
- Nik-Nasir, N. M., Md-Yasin, M., Ariffin, F., Mat-Nasir, N., Miskan, M., Abu-Bakar, N., & Yusoff, K. (2022).

Physical activity in Malaysia: Are we doing enough? Findings from the REDISCOVER Study. International Journal of Environmental Research and Public Health, 19(24), 16888. https://doi.org/10.3390/ijerph192416888

- Overgaard, K., Aagaard, P. G., Andersen, L. J., Grønbæk, M., Lichtenstein, M. B., Nielsen, R. Ø., Pedersen, B. K., & Roos, E. (2015). Supermotionisme og helbred [High volume exercise can be unhealthy]. Ugeskrift for laeger, 177(30), V11140611.
- Paungmali, A., Joseph, L., Punturee, K., Sitilertpisan, P., Pirunsan, U., & Uthaikhup, S. (2018). Immediate effects of core stabilization exercise on B-Endorphin and cortisol levels among patients with chronic nonspecific low back pain: a randomized crossover design. Journal of Manipulative and Physiological Therapeutics, 41(3), 181–188. https://doi. org/10.1016/j.jmpt.2018.01.002
- Robison, L. S., Alessi, L., & Thanos, P. K. (2018). Chronic forced exercise inhibits stress-induced reinstatement of cocaine conditioned place preference. Behavioural Brain Research, 353, 176–184. https://doi.org/10.1016/j. bbr.2018.07.009
- Samadzadeh, M., Abbasi, M., & Shahbazzadegan, B. (2011). Comparison of sensation seeking and self-esteem with mental health in professional and amateur athletes, and nonathletes. Procedia - Social and Behavioral Sciences, 15, 1942–1950. https://doi. org/10.1016/j.sbspro.2011.04.032
- Shin, K., & You, S. (2015). Factorial validity of the Korean version of the exercise Dependence Scale–Revised. Perceptual and Motor Skills, 121(3), 889–899. https://doi. org/10.2466/03.08.pms.121c27x8
- Sicilia, Á., & González-Cutre, D. (2011). Dependence and physical exercise: Spanish validation of the Exercise Dependence Scale-Revised (EDS-R). Spanish Journal of Psychology, 14(1), 421–431. https://doi.org/10.5209/rev_ sjop.2011.v14.n1.38
- Sussman, S., Lisha, N. E., & Griffiths, M. D. (2011). Prevalence of the addictions: A problem of the majority or the minority? Evaluation & the Health Professions, 34(1), 3–56. https:// doi.org/10.1177/0163278710380124
- Szabo, A., Griffiths, M. D., Høglid, R. A., & Demetrovics, Z. (2017). Drug, nicotine, and alcohol use among exercisers: Does substance addiction co-occur with exercise addiction? Addictive Behaviors Reports, 7, 26–31. https://doi. org/10.1016/j.abrep.2017.12.001
- Szabo, A., Griffiths, M. D., de La Vega Marcos,

R., Mervó, B., & Demetrovics, Z. (2015). Methodological and conceptual limitations in exercise addiction research. Yale Journal of Biology and Medicine, 88(3), 303–308.

- Szabo, A., De La Vega, R., Ruíz-Barquín, R., & Rivera, O. (2013). Exercise addiction in Spanish athletes: Investigation of the roles of gender, social context and level of involvement. Journal of Behavioral Addictions, 2(4), 249–252. https:// doi.org/10.1556/jba.2.2013.4.9
- Terry, A., Szabó, A., & Griffiths, M. D. (2004). The Exercise Addiction Inventory: a new brief screening tool. Addiction Research & Theory, 12(5), 489–499. https://doi.org/10.1080/160 66350310001637363
- Trott, M., Jackson, S. E., Firth, J., Jacob, L., Grabovac, I., Mistry, A., Stubbs, B., & Smith, L. (2021). A comparative meta-analysis of the prevalence of exercise addiction in adults with and without indicated eating disorders. Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity, 26(1), 37–46. https:// doi.org/10.1007/s40519-019-00842-1
- Wang, D., Wang, Y., Wang, Y., Li, R., & Zhou, C. (2014). Impact of physical exercise on substance use disorders: A meta-analysis. PLOS ONE, 9(10), e110728. https://doi.org/10.1371/journal. pone.0110728
- World Health Organization. Global Action Plan on Physical Activity 2018–2030: More Active People for a Healthier World. WHO; Geneva, Switzerland: 2018.
- Yang, P., Yu, Q., Montag, C., Becker, B., Cheval, B., Herold, F., Delphine, C., Li, J., Szabo, A., & Zou, L. (2021). Validation of the Chinese Version of the Exercise Dependence Scale-Revised (EDS-R). International Journal of Mental Health and Addiction. https://doi. org/10.1007/s11469-021-00654-4

BJMS Borneo Journal of Medical Sciences

REVIEW ARTICLE

Vehicles for Antibiotic Formulation in Endodontic Treatment: A Narrative Review

Nor Hazwani binti Jamaludin¹, Nurul Ain binti Ramlan¹*, Afiq Azizi bin Jawami¹, Nurul Aida binti Ngah²

- ¹ Centre of Study for Comprehensive Care, Faculty of Dentistry, Universiti Teknologi MARA Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia
- ² Centre of Oral & Maxillofacial Surgery Studies, Faculty of Dentistry, Universiti Teknologi MARA Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia
- * Corresponding author's email: ainramlan@uitm.edu.my

Received: 25 July 2024

Accepted: 14 November 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.5546

Keywords: Drug vehicles, Regenerative endodontic, Triple antibiotic

ABSTRACT

Triple antibiotic paste (TAP) has been widely utilized in endodontic therapy to treat bacterial infections within the root canal system. The efficacy and biocompatibility of TAP largely depend on the choice of vehicle used for its preparation. This narrative review aims to provide a comprehensive overview of the various vehicles employed in TAP formulations and their impact on clinical outcomes, effective dissolution, uniform distribution within the paste, and long-term stability. Propylene glycol, macrogol (polyethylene glycol), chlorhexidine, and antibiotic-eluting fibers are among the used vehicles for TAP preparation. Each vehicle possesses unique properties affecting the paste's antimicrobial activity, physical characteristics, and biocompatibility. The choice of vehicle in TAP formulations should be guided by considerations such as antimicrobial spectrum requirements, paste consistency preferences, and patient-specific factors. Optimal treatment outcomes with minimal side effects can be achieved when clinicians carefully consider the benefits and drawbacks of each vehicle. Further research exploring the comparative efficacy and safety profiles of different TAP vehicles is warranted to refine clinical guidelines and enhance treatment protocols in endodontic therapy.



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

Borneo Journal of Medical Sciences 19 (2) May, 2025: 130 - 139

INTRODUCTION

TThe microorganisms present in the root canal can potentially invade the surrounding periapical tissue, causing both pulpal and periapical diseases (Kakehashi et al., 1965; Sundqvist, 1993). The affected tooth may require endodontic treatment, which could involve one or more visits depending on criteria such as the complexity of the case and the severity of the infection. The utilization of an intracanal medicament has been shown to significantly improve the process of disinfection after chemomechanical procedures (Alsubait et al., 2020). Intracanal medicament is a chemical agent sealed within the root canal system and used between appointments as an anodyne and/or antimicrobial agent ("Glossary of Endodontic Terms 10th Ed," 2020). Calcium hydroxide, antibiotic paste, and corticosteroid base material are examples of intracanal medicament (Hasselgren et al., 1988; Hoshino et al., 1996; Negm, 2001).

Regenerative endodontic procedures (REP) have shown favorable results in treating an immature tooth diagnosed with pulpal necrosis or apical periodontitis. These procedures have shown potential for increasing root length, root wall thickness, as well as potentially restoring the tooth vitality responses (Hargreaves et al., 2021). REP requires the administration of an intracanal medication that possesses antibacterial qualities (Lovelace et al., 2011; Murray et al., 2007). Subsequently, bleeding is induced to establish a matrix that facilitates the development of new dentalpulpal tissue within the root canal space (Xie et al., 2021). The objective of this review is to analyze and examine the characteristics of vehicles employed in the formulation of triple antibiotic paste (TAP) for intracanal administration.

Properties of Ideal Intracanal Medicaments in Endodontics

Microorganisms from the root canal space may invade the periapical tissue and progress

to pulp and periapical disease (Sundqvist, 1993) and the development and progression endodontically-induced of periapical lesions are associated with the presence of microorganisms in the root canal system (Taneja et al., 2010). Chemomechanical debridement is used to eliminate bacteria from the root canal system. Nevertheless, the utilization of instrumentation and irrigation do not completely eliminate germs from the root canal (Sjögren et al., 1997). The root canal cannot be precisely disinfected by mechanical cleansing alone, as bacteria can conceal themselves in areas that are difficult to access, such as the isthmus, dentinal tubules, and apical delta (Bystrom & Sundqvist, 1985). The usage of interappointment medicament has demonstrated a significant improvement in disinfection following chemomechanical operations (Alsubait et al., 2020). Intracanal medicaments are used for root canal treatment as multiple-visit root canal medication. One of the most often used intracanal drugs is calcium hydroxide (CaOH) (Mohammadi & Dummer, 2011). Hermann introduced the intracanal medicament to dentistry in 1920, and it became popular for root canal therapy in the 1970s and it is today considered one of the first choices for multiple-visit root canal medication (Kumar et al., 2019). An important property of an intracanal medicament is the antimicrobial properties (Doran & Radtke, 1998; Kumar et al., 2019). While the exact modes of action remain unclear, it appears that CaOH raises pH in aquatic environments via the release of hydroxyl ions that lead to harmful effect to most of pathogenic bacteria as they cannot survive this kind of environment. Additionally, CaOH has some protein denaturizing effects that can aid in the dissolution of pulp tissue (Rahimi et al., 2014; Sirén et al., 2004). CaOH requires a carrier substance to achieve the right consistency before being placed into the canal. Normal saline, lidocaine, and chlorhexidine are commonly used for this purpose (Silveira et al., 2011).

Another important property of an

intracanal medicament is the biocompatibility and stability. CaOH has been determined as suitable for use as an intracanal medicament as it is stable for long periods, harmless to the body, and the bactericidal effect only in a limited area. It induces hard tissue formation and is effective for stopping inflammatory exudates (Kawashima et al., 2009).

Apart from CaOH, Grossman first discussed the use of polyantibiotic paste as an intracanal medicament in weeping canals or where there was continuous drain from the pulp space. Mixture of ciprofloxacin, metronidazole and minocycline is useful for sterilization of infected root dentine, at only a low dose of the mixture is required (Sato et al., 1996). The mixed antibacterial drugs are also effective against bacteria in periodontal pockets and dental plaque (Ando & Hoshino, 1990) suggesting that this drug combination may also be useful in the treatment of endodontic-periodontal diseases (Sato et al., 1996).

The intracanal medicaments, such as calcium hydroxide or antibiotic formulation, should possess a consistency that is effective in carrying a maximum number of active component particles (Kumar et al., 2019). For example, when the intracanal medicament is prepared with the usage of gel as the vehicle, it was able to clean the root canal walls and their anatomic complexities effectively due to the viscosity of the gel (International Standard ISO 6876:2001, n.d.). The usage of chlorhexidine gel as the vehicle increases in the viscosity of intracanal medicament, resulting in reduced flowability and may prolonged contacts between particles and the tooth structure, facilitating the antibacterial effect (Al-Sabawi, 2020).

A narrative review on the ideal properties of intracanal medicaments in modern endodontics recommend the following (Kumar et al., 2019):

1. Effective antimicrobial agent

- 2. Nonirritating to the periradicular tissues
- 3. Remain stable in solution
- 4. Prolonged antimicrobial effect
- 5. Active in the presence of blood, serum, and protein derivatives of tissues
- 6. Low surface tension
- 7. Not interfere with the repair of periradicular tissues
- 8. Not stain tooth structure
- 9. Not induce a cell-mediated immune response

Thus, intracanal to ensure an medicament exhibits maximum efficacy, it is crucial to prepare it with a suitable vehicle that aligns with its physicochemical properties. Selecting an appropriate vehicle for an intracanal medicament is essential for maximizing its therapeutic properties. The vehicle should be chosen based on the specific needs of the treatment, considering factors such as stability, viscosity, biocompatibility, and antimicrobial activity. By doing so, the effectiveness of the intracanal medicament in disinfecting the root canal system can be significantly enhanced.

Triple Antibiotic Paste (TAP)

An intracanal medication with an effective antibacterial action is recommended to predictably eliminate bacteria from the entire root canal system (Chong & Ford, 1992). Since its first use by Hoshino and the team, TAP combination metronidazole, ciprofloxacin, and minocycline (Sato et al., 1996) has been the most widely used intracanal medicament in endodontic regeneration and recommended by American Association of Endodontists (American Association of Endodontists, 2021). TAP showed the antibacterial efficacy on bacteria of carious and endodontic lesions of human deciduous teeth, showing carious and endodontic lesions can be sterilized by the mixed drugs in situ (Sato et al., 1993). In the study, ciprofloxacin, metronidazole, plus a third antibiotic; amoxicillin, cefaclor, cefroxadine, fosfomycin, or rifamycin were used. Later it was reported that ciprofloxacin, metronidazole, and minocycline can inhibit the growth of bacteria in the deep layers of root canal dentine in situ (Sato et al., 1996). High success rates have been observed in regenerative endodontic procedure (REP) with the usage of triple antibiotic paste as the intracanal medicament. TAP containing cefaclor, ciprofloxacin, and metronidazole was used in a clinical study, which included 28 immature permanent teeth with necrotic pulps. The study reported a 100% resolution of periapical radiolucencies, 93% clinical success score and 96.4% survival rate (Chan et al., 2017).

In terms of concentration of triple antibiotic to be used for the treatment, only at concentrations of 0.1-0.01 mg/mL, there was no negative impact on the viability of stem cells from the apical papilla (SCAP) (Ruparel et al., 2012). TAP concentrations of 0.01, 0.1, 1, 10, and 100 mg/mL were applied to SCAP and results indicated that at concentrations of 10-100 mg/mL less than 20% of the stem cells remained viable, at concentrations of 1 mg/ mL, 33-56% of the stem cells remained viable when TAP was used. Another concentration study reported that TAP with a concentration of 0.125 mg/ml showed significant antibacterial effects with no cytotoxic effects when it was tested on dental pulp stem cells (DPSCs) (Sabrah et al., 2015).

The usage of the triple antibiotic formulation was shown to have the desired outcome and lesser cytotoxicity when it is prepared with macrogol and propylene glycol (PG) in comparison to water. TAP prepared with water showed to have lower pH and higher toxicity (Faria et al., 2018). The form of antibiotic being used is reported to have different levels of pH and cytotoxicity value, as the United States Pharmacopeia (USP) grade antibiotics showed lower pH and were more toxic in comparison with the tablet/capsule (T/C) type of antibiotic (Faria et al., 2018).

Drug Vehicles

Drug carriers are biocompatible tools for the transport of molecules for pharmaceutical, cosmetic, and nutraceutical applications. The delivery of active pharmaceutical substances to patients is significantly facilitated by the utilization of vehicles, which serve as a vital mechanism for delivering medicine into the body. The choice of vehicles is crucial since it can significantly influence the effectiveness/ potency of drug formulation (Allen et al., 2011). A localized medication delivery system is utilized to provide a precise and focused effect, especially in restricted regions. A localized drug delivery system is an approach to administering medication to a targeted site, intending to reduce movement and enhance absorption into the circulatory system (Rolfes et al., 2012). A number of the most popular vehicles are ointments, creams, gels, and lotions (Barnes et al., 2021).

Drug Vehicles in Regenerative Endodontics Procedure (REP)

The use of vehicles in TAP preparation for endodontic therapy is a critical factor that will impact the characteristics and efficacy of the paste. TAP to be used in REP, require the mixing of the antibiotics and a vehicle in which will be mix into a paste form, and later will be placed within the root canal of the tooth. The selection of a vehicle holds significance for multiple reasons, one of which is its biocompatibility. The chosen vehicle must exhibit biocompatibility with pulp tissue, hence avoiding any potential adverse responses or disruptions to the healing process. Another thing to consider is the convenience of handling, as qualities that are easier to handle will facilitate the mixing and delivering of the paste during the treatment procedure. Furthermore, the antibiotic must possess stability and solubility to ensure effective dissolution, uniform distribution within the paste, and long-term stability. Propylene glycol, macrogol (polyethylene glycol), antibiotic-eluting fibers are among the used vehicles for TAP. Each vehicle possesses unique properties affecting the paste's antimicrobial activity, physical characteristics, and biocompatibility.

Macrogol and Propylene Glycol

Macrogols, also known as polyethylene glycols (PEG) and propylene glycol (PG) are synthetic substances that are used as vehicles in a variety of cosmetic and medical products. Macrogol is commonly used in the treatment of constipation, particularly when first-line treatments such as education and lifestyle modifications do not yield the desired results. regenerative endodontics procedure In (REP), PEG is the most widely used as it is antimicrobial effective and easily manipulated. PEG is a polyether compound derived from petroleum with many applications, from industrial manufacturing to medicine. PEG, often referred to as polyethylene oxide (PEO) or polyoxyethylene (POE), is named differently based on its molecular weight. It is readily soluble in water, ethanol, acetone, glycols, and chloroform. PEGs that present mostly as hydrophilic, they are favorably used as penetration enhancers, example in topical dermatological preparations (Becker et al., 2017).

PG is a clear, colorless, viscous, practically odorless liquid with a density of 1.038 g/cm³ at 20°C and a molecular weight of 76.095. It is an alcohol that is soluble in water and is a well-known pharmaceutical excipient that is used for several purposes in a wide range of pharmaceutical dosage forms. For example, 15% of the PG been used as humectant in topicals, 15 to 30% as a preservative in solutions, 10–25% as a co-solvent in aerosols, and 5 to 80% in topicals application (European Medicines Agency, 2017). PG is mainly used in medication formulation to increase the solubility of hydrophobic compounds (Co & Gunnerson, 2019).

Both PEG and PG are considered biologically inert and safe by the United States Food and Drug Administration (US FDA). However, the toxicity linked to PG arises from its metabolism by alcohol and aldehyde dehydrogenase in the liver, resulting in the production of lactic and pyruvic acids. This can cause different levels of anion gap metabolic acidosis and impairment of liver function. PG is excreted in the urine without undergoing any changes, which can worsen toxicity in patients with acute renal injury due to the accumulation of the substance (Lim et al., 2014). Research has suggested that propylene glycol is likely to be toxic at concentrations exceeding 25 mg/dL (Barnes et al., 2006). There is increasing data indicating that over 72% of the population, who have never been treated with PEGylated medications, have measurable levels of anti-PEG antibodies (Yang et al., 2016). The identification of an allergy to PEG typically occurs after a diagnosis of an allergy to a growing array of apparently unrelated goods, such as processed foods, cosmetics, medications, and other substances that either include PEG or were produced using PEG (Wenande & Garvey, 2016).

In dentistry, PEG have been used to address periodontitis by encapsulating stem cells in the gel, which promotes healing in the gums. The gel with encapsulated stem cells was to be injected into the site of disease and crosslinked to create the microenvironment required for the stem cells to function (Ma et al., 2017). In REPs, both PEG and PG play roles in facilitating the disinfection of the root canal space, delivering medicaments to promote tissue regeneration, and creating an environment conducive for healing. In a study, the utilization of carriers such as PEG and PG has been proposed as a means to enhance the permeation of antibiotics and facilitate their transportation into the dentinal tubules. In turn, it contributes to the efficient elimination of microbial burden (Cruz et al., 2002) a critical factor in the treatment of REPs. Moreover, preparing this TAP with PEG and PG has been demonstrated to yield the desired outcome with less cytotoxicity, in comparison when the TAP was prepared with water, it was demonstrated to have a lower pH and greater toxicity (Faria et al., 2018).

Antibiotic-Eluting Fibers

As technology continues to evolve, the integration of TAP components into electros pun small-sized biodegradable polymeric fibers has been suggested as a potentially more cellular-friendly methodology on account of the significantly reduced antibiotic content (Karczewski et al., 2018). Antibiotic-eluting fibers are a type of biomaterial designed to release antibiotics gradually over time. These fibers are typically made from biocompatible polymers that can be impregnated or coated with antibiotics. Study reported that the use of TAP-eluting nanofibers for the disinfection of biofilm-infected dentin samples showed similar antimicrobial activity as compared to TAP (Albuquerque et al., 2017). Apart from that, the use of TAP-eluting nanofibers resulted in less tooth discoloration compared to the use of TAP, indicating a lower concentration of antibiotics in the TAP-eluting nanofibers (Albuquerque et al., 2017). These antibioticeluting fibers represent a valuable strategy for localized drug delivery in medical and dental practice, offering controlled release of antibiotics to effectively manage infections and promote tissue healing.

Hydrogels

Hydrogels are the material that provides a three-dimensional (3-D) scaffold that mimics extracellular matrix. Examples of these materials are chitosan, gelatin, and hyaluronic acid. These hydrogels are important components in drug delivery as they can control the release of drugs over time and deliver them in a targeted manner, enhancing the effectiveness of treatments while minimizing side effects. The bioactive components of the drug delivery have the capacity to interact with biological systems, including the living tissues (Leveque et al., 2023). A variety of bioactive materials were already designed and proposed to improve interactions between cells and tissues, triggering processes such as cell adhesion, proliferation, differentiation, and the promotion of tissue regeneration. In endodontics, the bioactive components are incorporated into this hydrogel such as antibiotics, peptides, or nanoparticles thus making them bioactive (Ribeiro et al., 2022). Bioactive endodontic hydrogels could be considered as advanced and innovative materials for REPs that were specifically designed to promote and enhance dental pulp regeneration.

Most of the hydrogel used in endodontic is in injectable forms as it is more convenient to the operator (Leveque et al., 2023). Several parameters such as porosity, mechanical strength, or biocompatibility of the hydrogel could strongly promote or reduce its properties and changes in the endodontic environment may result in the ability of the hydrogel to change in its shape, its degradation over time, the efficiency of active components, and variations when in contact with fluids (Leveque et al., 2023). As in periapical environments, inflammation of the tissue potentially influences the local pH and therefore the ionization state of bioactive molecules, thus modifying the solubility, resulting in the release of bioactive materials in hydrogels.

White Petrolatum

White petrolatum, also known as white soft paraffin and petroleum jelly, is a semisolid mixture of hydrocarbons that is composed of a white to yellowish color and is dewaxed from paraffinic residual oil. The carbon numbers of the hydrocarbons are primarily greater than C25 (Bao et al., 2020). The major constituents inside the white petrolatum are n-paraffin, isoparaffin, and naphthene (Barry & Grace, 1971). White petrolatum differs from petrolatum as it is the purified form of petrolatum or petroleum jelly, and it is highly refined. It is commonly used in cosmetic and pharmaceutical applications, including skincare products, ointments, and lip balms. In comparison, petrolatum is the original, unrefined form of petrolatum and it is used mainly in industrial applications and certain less refined products. It has properties of the present in semi-solid consistency at

room temperature, melting point ranges from 36-60°C therefore the ointment viscosity will decrease following application (Greaves et al., 1993) hydrophobic, colorless, translucent (Bao et al., 2017), inert and non-reactive with other substances. A randomized control trial reported that white petrolatum is safe and effective wound care ointment, and it possesses an equally low infection rate and minimal risk of induction allergy (Smack, 1996). White petrolatum has been used in the medical field for many functions one of which is as a moisturizer (Purnamawati et al., 2017). In addition, white petrolatum is much utilized as an eye ointment, serving as an excipient/vehicle in the formulation (Bao et al., 2017; Bao et al., 2020). The advantages of this material are ease of application and ease of manipulation. This material has been used in the field of dentistry as a vehicle in which in the year 1990, white petrolatum has been used as a vehicle in preparation with tetracycline to be used in the treatment of periodontal disease (Eckles et al., 1990). Besides, a study reported that white petrolatum does not show direct relation with antimicrobial effect, which is it only modulates the antimicrobial effect in topical application usage for the prevention of skin infection (Czarnowicki et al., 2016). This is an important property as when the white petrolatum is used as a vehicle with triple antibiotic, the antibacterial effect is modulated by the antibiotic itself. This potentiates white petrolatum to be used as a vehicle in the preparation of triple antibiotic paste for regenerative endodontic procedures.

CONCLUSION

In conclusion, the choice of vehicle for TAP formulations in endodontic therapy plays a crucial role in determining the treatment's efficacy, safety, and clinical outcomes. While this narrative review provides valuable insights into the properties and applications of different TAP and intracanal medicaments vehicles, further research is needed to address the remaining gaps in knowledge. Comparative studies evaluating the efficacy and safety profiles of various TAP formulations could enhance our understanding, and white petrolatum is a potential vehicle for use in the preparation of TAP for regenerative endodontic procedures following the guide in evidence-based clinical practice.

CONFLICT OF INTEREST

The authors affirm that they have no conflicts of interest, whether financial or of any other nature..

REFERENCES

- Albuquerque, M. T. P., Nagata, J., & Bottino, M. C. (2017). Antimicrobial efficacy of triple antibiotic-eluting polymer nanofibers against multispecies biofilm. Journal of Endodontics, 43(9), S51–S56. https://doi. org/10.1016/j.joen.2017.06.009
- Allen L. V., Popovich N. G., & Ansel H. C. (2011). Ansel"s pharmaceutical dosage forms and drug delivery systems (9th ed.). Philadelphia: Lippincott Williams & Wilkins.
- Al-Sabawi, N. (2020). Physical, chemical, and antimicrobial properties of chlorhexidine combine with calcium hydroxide as intracanal medicament. Al-Rafidain Dental Journal, 13(3), 388–395. https://doi.org/10.33899/ rden.2020.165358
- Alsubait, S., Alsaad, N., Alahmari, S., Alfaraj, F., Alfawaz, H., & Alqedairi, A. (2020). The effect of intracanal medicaments used in endodontics on the dislocation resistance of two calcium silicate-based filling materials. BMC Oral Health, 20(1), 57. https://doi. org/10.1186/s12903-020-1044-6
- American Association of Endodontists. (2021). Clinical considerations for a regenerative procedure. https://www.aae.org/specialty/ wpcontent/uploads/sites/2/2021/08/ ClinicalConsiderationsApprovedByREC06292 1.pdf
- Ando, N., & Hoshino, E. (1990). Predominant obligate anaerobes invading the deep layers of root canal dentine. International Endodontic Journal, 23(1), 20–27. https://doi. org/10.1111/j.1365-2591.1990.tb00798.x
- Bao, Q., Jog, R., Shen, J., Newman, B., Wang, Y., Choi, S., & Burgess, D. J. (2017). Physicochemical attributes and dissolution testing of ophthalmic ointments. International Journal

of Pharmaceutics, 523(1), 310–319. https:// doi.org/10.1016/j.ijpharm.2017.03.039

- Bao, Q., Morales-Acosta, M. D., & Burgess, D. J. (2020). Physicochemical attributes of white petrolatum from various sources used for ophthalmic ointment formulations. International Journal of Pharmaceutics, 583, 119381. https://doi.org/10.1016/j. ijpharm.2020.119381
- Barnes, B. J., Gerst, C., Smith, J. R., Terrell, A. R., & Mullins, M. E. (2006). Osmol gap as a surrogate marker for serum propylene glycol concentrations in patients receiving lorazepam for sedation. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 26(1), 23–33. https://doi. org/10.1592/phco.2006.26.1.23
- Barnes, T. M., Mijaljica, D., Townley, J. P., Spada, F., & Harrison, I. P. (2021). Vehicles for drug delivery and cosmetic moisturizers: Review and comparison. Pharmaceutics, 13(12), 2012. https://doi.org/10.3390/ pharmaceutics13122012
- Barry, B.W., & Grace, A.J. (1971). Structural, rheological and textural properties of soft paraffins. Journal of Texture Studies, 2(3), 259–279. https://doi.org/10.1111/j.1745-4603.1971. tb01004.x
- Becker, L. C., Bergfeld, W. F., Belsito, D. V., Hill, R. A., Klaassen, C. D., Liebler, D. C., Marks Jr, J. G., Shank, R. C., Slaga, T. J., Snyder, P. W., & Gill, L. J. (2017). Amended safety assessment of PEG propylene glycol derivatives as used in cosmetics. Cosmetic Ingredient Review. https://www.cir-safety.org/sites/default/ files/pegpge122016rep.pdf
- Bystrom, A., & Sundqvist, G. (1985). The antibacterial action of sodium hypochlorite and EDTA in 60 cases of endodontic therapy. International Endodontic Journal, 18(1), 35–40. https://doi. org/10.1111/j.1365-2591.1985.tb00416.x
- Chan, E. K. M., Desmeules, M., Cielecki, M., Dabbagh, B., & Ferraz dos Santos, B. (2017). Longitudinal cohort study of regenerative endodontic treatment for immature necrotic permanent teeth. Journal of Endodontics, 43(3), 395–400. https://doi.org/10.1016/j. joen.2016.10.035
- Chong, B. S., & Ford, T. R. P. (1992). The role of intracanal medication in root canal treatment. International Endodontic Journal, 25(2), 97–106. https://doi. org/10.1111/j.1365-2591.1992.tb00743.x
- Co, I. N., & Gunnerson, K. J. (2019). latrogenic and poison-derived acid base disorders. In C. Ronco, R. Bellomo, J. A. Kellum, Z. Ricci (Eds.),

Critical Care Nephrology (pp. 417-423.e2). Elsevier. https://doi.org/10.1016/B978-0-323-44942-7.00071-6

- Cruz, E. V., Kota, K., Huque, J., Iwaku, M., & Hoshino, E. (2002). Penetration of propylene glycol into dentine. International Endodontic Journal, 35(4), 330–336. https://doi.org/10.1046/ j.1365-2591.2002.00482.x
- Czarnowicki, T., Malajian, D., Khattri, S., Correa da Rosa, J., Dutt, R., Finney, R., Dhingra, N., Xiangyu, P., Xu, H., Estrada, Y. D., Zheng, X., Gilleaudeau, P., Sullivan-Whalen, M., Suaréz-Fariñas, M., Shemer, A., Krueger, J. G., & Guttman-Yassky, E. (2016). Petrolatum: Barrier repair and antimicrobial responses underlying this "inert" moisturizer. Journal of Allergy and Clinical Immunology, 137(4), 1091-1102.e7. https://doi.org/10.1016/j. jaci.2015.08.013
- Doran, M. G., & Radtke, P. K. (1998). A review of endodontic medicaments. General Dentistry, 46(5), 484–488; quiz 489–490.
- Eckles, T. A., Reinhardt, R. A., Dyer, J. K., Tussing, G. J., Szydlowski, W. M., & DuBous, L. M. (1990). Intracrevicular application of tetracycline in white petrolatum for the treatment of periodontal disease. Journal of Clinical Periodontology, 17(7), 454–462. https://doi. org/10.1111/j.1600-051X.1990.tb02344.x
- European Medicines Agency. (2017). Questions and answers on propylene glycol used as an excipient in medicinal products for human use. https://www.ema.europa. eu/en/documents/scientific-guideline/ questions-and-answers-propylene-glycolused-excipient-medicinal-products-humanuse_en.pdf
- Faria, G., Rodrigues, E. M., Coaguila-Llerena, H., Gomes-Cornélio, A. L., Neto Angéloco, R. R., Swerts Pereira, M. S., & Tanomaru Filho, M. (2018). Influence of the vehicle and antibiotic formulation on cytotoxicity of triple antibiotic paste. Journal of Endodontics, 44(12), 1812–1816. https://doi.org/10.1016/j. joen.2018.09.009
- Glossary of Endodontic Terms 10th ed. (2020). American Association of Endodontists (AAE).
- Greaves, J. L., Wilson, C. G., & Birmingham, A.T. (1993). Assessment of the precorneal residence of an ophthalmic ointment in healthy subjects. British Journal of Clinical Pharmacology, 35(2), 188–192.
- Hargreaves K.M, Berman L.H, Rotstein I, & Cohen S. (2021). Cohen's Pathways of the Pulp (12th ed.). St. Louis. International Standard ISO 6876:2001. (n.d.).

- Kakehashi, S., Stanley, H. R., & Fitzgerald, R. J. (1965). The effects of surgical exposures of dental pulps in germ-free and conventional laboratory rats. Oral Surgery, Oral Medicine, Oral Pathology, 20(3), 340–349. https://doi. org/10.1016/0030-4220(65)90166-0
- Karczewski, A., Feitosa, S. A., Hamer, E. I., Pankajakshan, D., Gregory, R. L., Spolnik, K. J., & Bottino, M. C. (2018). Clindamycinmodified triple antibiotic nanofibers: A stain-free antimicrobial intracanal drug delivery system. Journal of Endodontics, 44(1), 155–162. https://doi.org/10.1016/j. joen.2017.08.024
- Kawashima, N., Wadachi, R., Suda, H., Yeng, T., & Parashos, P. (2009). Root canal medicaments. International Dental Journal, 59(1), 5–11.
- Kumar, A., Tamanna, S., & Iftekhar, H. (2019). Intracanal medicaments – Their use in modern endodontics: A narrative review. Journal of Oral Research and Review, 11(2), 94. https://doi.org/10.4103/jorr.jorr_3_19
- Leveque, M., Bekhouche, M., Farges, J.-C., Aussel, A., Sy, K., Richert, R., & Ducret, M. (2023). Bioactive endodontic hydrogels: From parameters to personalized medicine. International Journal of Molecular Sciences, 24(18), 14056. https:// doi.org/10.3390/ijms241814056
- Lim, T. Y., Poole, R. L., & Pageler, N. M. (2014). Propylene glycol toxicity in children. The Journal of Pediatric Pharmacology and Therapeutics, 19(4), 277–282. https://doi. org/10.5863/1551-6776-19.4.277
- Lovelace, T. W., Henry, M. A., Hargreaves, K. M., & Diogenes, A. (2011). Evaluation of the delivery of mesenchymal stem cells into the root canal space of necrotic immature teeth after clinical regenerative endodontic procedure. Journal of Endodontics, 37(2), 133–138. https://doi.org/10.1016/j.joen.2010.10.009
- Ma, Y., Ji, Y., Zhong, T., Wan, W., Yang, Q., Li, A., Zhang, X., & Lin, M. (2017). Bioprinting-based PDLSC-ECM screening for in vivo repair of alveolar bone defect using cell-laden, injectable and photocrosslinkable hydrogels. ACS Biomaterials Science & Engineering, 3(12), 3534–3545. https://doi.org/10.1021/ acsbiomaterials.7b00601
- Mohammadi, Z., & Dummer, P.M.H. (2011). Properties and applications of calcium hydroxide in endodontics and dental traumatology. International Endodontic Journal, 44(8), 697–730. https://doi.org/10.1111/j.1365-2591.2011.01886.x
- Murray, P. E., Garcia-Godoy, F., & Hargreaves, K. M. (2007). Regenerative endodontics: A review

of current status and a call for action. Journal of Endodontics, 33(4), 377–390. https://doi. org/10.1016/j.joen.2006.09.013

- Purnamawati, S., Indrastuti, N., Danarti, R., & Saefudin, T. (2017). The role of moisturizers in addressing various kinds of dermatitis: A review. Clinical Medicine & Research, 15(3–4), 75–87. https://doi.org/10.3121/ cmr.2017.1363
- Rahimi, S., Janani, M., Lotfi, M., Shahi, S., Aghbali, A., Vahid Pakdel, M., Salem Milani, A., & Ghasemi, N. (2014). A review of antibacterial agents in endodontic treatment. Iranian Endodontic Journal, 9(3), 161–168.
- Ribeiro, J. S., Münchow, E. A., Bordini, E. A. F., Rodrigues, N. S., Dubey, N., Sasaki, H., Fenno, J. C., Schwendeman, S., & Bottino, M. C. (2022). Engineering of injectable antibiotic-laden fibrous microparticles gelatin methacryloyl hydrogel for endodontic infection ablation. International Journal of Molecular Sciences, 23(2), 971. https://doi.org/10.3390/ ijms23020971
- Rolfes, C., Howard, S., Goff, R., & laizzo, A., P. (2012). Localized drug delivery for cardiothoracic surgery. In L. Cagini (Ed.), Current Concepts in General Thoracic Surgery. InTech. https:// doi.org/10.5772/48577
- Ruparel, N. B., Teixeira, F. B., Ferraz, C. C. R., & Diogenes, A. (2012). Direct effect of intracanal medicaments on survival of stem cells of the apical papilla. Journal of Endodontics, 38(10), 1372–1375. https://doi.org/10.1016/j. joen.2012.06.018
- Sabrah, A. H. A., Yassen, G. H., Liu, W.-C., Goebel, W. S., Gregory, R. L., & Platt, J. A. (2015). The effect of diluted triple and double antibiotic pastes on dental pulp stem cells and established Enterococcus faecalis biofilm. Clinical Oral Investigations, 19(8), 2059–2066. https://doi. org/10.1007/s00784-015-1423-6
- Sato, I., Ando-Kurihara, N., Kota, K., Iwaku, M., & Hoshino, E. (1996). Sterilization of infected root-canal dentine by topical application of a mixture of ciprofloxacin, metronidazole and minocycline in situ. International Endodontic Journal, 29(2), 118–124. https:// doi.org/10.1111/j.1365-2591.1996.tb01172.x
- Sato, T., Hoshino, E., Uematsu, H., & Noda, T. (1993). In vitro antimicrobial susceptibility to combinations of drugs of bacteria from carious and endodontic lesions of human deciduous teeth. Oral Microbiology and Immunology, 8(3), 172–176. https://doi. org/10.1111/j.1399- 302X.1993.tb00661.x
- Silveira, C. F., Cunha, R. S., Fontana, C. E., de Martin,

A. S., Gomes, B. P., Motta, R. H., & da Silveira Bueno, C. E. (2011). Assessment of the antibacterial activity of calcium hydroxide combined with chlorhexidine paste and other intracanal medications against bacterial pathogens. European Journal of Dentistry, 5(1), 1-7.

- Sirén, E. K., Haapasalo, M. P. P., Waltimo, T. M. T., & Ørstavik, D. (2004). In vitro antibacterial effect of calcium hydroxide combined with chlorhexidine or iodine potassium iodide on Enterococcus faecalis. European Journal of Oral Sciences, 112(4), 326–331. https://doi. org/10.1111/j.1600-0722.2004.00144.x
- Sjögren, U., Figdor, D., Persson, S., & Sundqvist, G. (1997). Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. International Endodontic Journal, 30(5), 297–306. https://doi.org/10.1046/j.1365-2591.1997.00092.x
- Smack, D. P. (1996). Infection and Allergy incidence in ambulatory surgery patients using white petrolatum vs bacitracin ointment. JAMA, 276(12), 972. https://doi.org/10.1001/ jama.1996.03540120050033
- Sundqvist, G. (1993). Pathogenicity and virulence of black-pigmented Gram-negative anaerobes. FEMS Immunology & Medical Microbiology, 6(2–3), 125–138. https://doi.org/10.1111/ j.1574-695X.1993.tb00315.x
- Taneja, S., Kumari, M., & Parkash, H. (2010). Nonsurgical healing of large periradicular lesions using a triple antibiotic paste: A case series. Contemporary Clinical Dentistry, 1(1), 31. https://doi.org/10.4103/0976-237X.62519
- Wenande, E., & Garvey, L. H. (2016). Immediate-type hypersensitivity to polyethylene glycols: a review. Clinical & Experimental Allergy, 46(7), 907–922. https://doi.org/10.1111/cea.12760
- Yang, Q., Jacobs, T. M., McCallen, J. D., Moore, D. T., Huckaby, J. T., Edelstein, J. N., & Lai, S. K. (2016). Analysis of pre-existing IgG and IgM antibodies against polyethylene glycol (PEG) in the general population. Analytical Chemistry, 88(23), 11804–11812. https://doi. org/10.1021/acs.analchem.6b03437

BJMS Borneo Journal of Medical Sciences

CASE REPORT

From paralytic ileus to Guillain-Barre Syndrome: A diagnostic puzzle

Kong Meng Tung*, Bradley Avery Noelle Bachi, Yen Lik Chia, Chiew Yen Haw

Department of Internal Medicine, Queen Elizabeth Hospital, 88586 Kota Kinabalu, Sabah, Malaysia

* Corresponding author's email: kongrocks90@gmail.com

Received: 18 September 2024

Accepted: 27 December 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.5486

Keywords: Paralytic ileus, Guillain-Barre syndrome, Diagnostic puzzle, Peripheral neuropathy, Gastrointestinal motility



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

Guillain-Barre Syndrome (GBS) is a rare, acute neuro-immunological disorder that affects the peripheral nerves, characterised by rapid, ascending symmetrical limb weakness and sensory deficits. Autonomic dysfunction is reported in 40-45% of GBS cases, typically manifesting in the later stages. However, it is uncommon for paralytic ileus to be the initial presenting symptom before motor and sensory deficits become apparent. We report a case of GBS in a young man who had paralytic ileus as his primary presenting complaint. The patient was managed supportively but showed minimal improvement. A subsequent neurological assessment revealed proximal myopathy of 4 limbs with generalised areflexia. A nerve conduction study showed electrophysiological evidence of diffuse sensory motor axonal neuropathy affecting the lower limb more than the upper limb. He underwent plasma exchange therapy, in his fourth week of illness. With plasma exchange, his abdominal symptoms resolved, but neurological recovery remained partial. The delayed diagnosis likely affected his outcome, highlighting the importance of early GBS recognition for timely treatment to achieve better recovery.

INTRODUCTION

Guillain-Barre Syndrome (GBS) is an immunemediated neuropathy affecting the peripheral nerves, typically presenting with ascending weakness and non-length-dependent sensory symptoms. Autonomic dysfunction, which may manifest as cardiac arrhythmias, blood pressure fluctuations, constipation, diarrhoea or ileus, and urinary retention, often occurs in the later stages of GBS when motor and sensory symptoms are already prominent (Bellanti & Rinaldi, 2024).

Paralytic ileus refers to the inability of the bowel to move its contents forward due to impaired motility, without the presence of a mechanical obstruction. Common symptoms include nausea, vomiting, abdominal distension, constipation and inability to pass flatus. This condition can result from various factors, including dysmotility of the bowel musculature, post-abdominopelvic surgery, certain medications, infections, and endocrine metabolic disturbances (Weledeii,2020).

There were literature reports of Guillain-Barre Syndrome (GBS) with predominant gastrointestinal dysfunction autonomic symptoms preceding the onset of motor weakness. Typically, in adult cases, the onset of motor weakness was reported within two weeks of the onset of the gastrointestinal symptoms. In our case, we present a young gentleman who was admitted to our centre with a one-week history of abdominal symptoms and was initially diagnosed with paralytic ileus, in which the initial neurology examination was normal. Subsequently, motor weakness was detected on day 10 of admission (day 17 from the onset of abdominal symptoms). Cerebrospinal fluid analysis and nerve conduction studies were performed and a diagnosis of Guillain-Barre Syndrome was made. In this case, it is suggested that the onset of motor symptoms following paralytic ileus may be varied and may take longer than previously reported. Therefore, it posed significant challenges in achieving the correct diagnosis.

A 37-year-old gentleman was admitted to the Emergency Department with a oneweek history of constipation, vomiting and intolerance to food. Over the past four days, he developed abdominal distension, and on the day of admission, he began experiencing shortness of breath. He was previously healthy, with no prior weight loss, abdominal surgery or hematochezia. However, he had an upper respiratory tract infection three weeks before admission. On examination, his vital signs were notable for a blood pressure of 118/65mmHg, heart rate of 130 beats per minute, and febrile with a temperature of 38.1 oC. He was tachypnoeic, with a respiratory rate of 34 breaths per minute, and oxygen saturation of 90% on room air. The abdomen was grossly distended with generalised tenderness but without guarding or rebound tenderness. Bowel sounds were sluggish. The lung examination was unremarkable. Muscle strength and tendon reflexes were intact and normal.

Blood investigations showed a white cell count of 25 x 103/uL with neutrophil predominance. Procalcitonin level was elevated at 32.80 ng/mL. He also had hyponatremia (sodium 114 mmol/L), hypokalemia (potassium 2.9 mmol/L) and hypocalcemia (calcium 1.97 mmol/L). Thyroid function tests were normal. All these electrolyte' abnormalities were consistent with gastrointestinal loss (vomiting) and the loss of appetite. Contrast-enhanced computed tomography (CECT) of the abdomen showed diffuse large bowel dilatation, with a maximum diameter of 8.9 cm at the transverse colon, a prominent ileocecal junction, and terminal ileum (Figure 1). There was also short segment dilatation of the ileum, measuring up to 3.9 cm likely due to obstruction, but no mass lesions were identified to account for the obstruction.

DISCUSSION

The patient was diagnosed with pneumonia

CASE PRESENTATION



Figure 1: Contrast-enhanced abdominal computed tomography (axial view), arrows show dilated colons with air-fluid levels.

and intra-abdominal sepsis complicated by ileus, precipitated by electrolyte imbalances. He was on a high-flow nasal cannula (HFNC). Abdominal decompression was achieved with a nasogastric tube, and broad-spectrum antibiotics were initiated, along with intravenous fluids and electrolyte correction. Total parenteral nutrition was administered temporarily. The patient's electrolytes were normalised by day four of treatment. Ten days after admission, the patient was able to wean off supplemental oxygen. However, his ileus symptoms only partially resolved; he had minimal bowel output despite regular laxatives, and his abdomen remained mildly distended but non-tender. A colonoscopy was done, revealing a normal large bowel.

The patient was then allowed to eat orally. However, it was observed that he was unable to sit unassisted and fumbled while attempting to use a spoon independently. A neurological examination revealed proximal myopathy of the upper limbs, flaccid paralysis of the lower limbs, reduced sensations, and generalised areflexia. A nerve conduction study showed electrophysiological evidence of diffuse sensorimotor axonal neuropathy, with greater involvement of the lower limbs than the upper limbs. A lumbar puncture was performed, revealing a cerebrospinal fluid (CSF) cell count of 0 and elevated protein at 0.64g/L, suggestive of cytoalbuminologic dissociation. Based on these findings, a diagnosis of Guillain-Barre Syndrome (GBS), an Acute Motor Sensory Axonal Neuropathy (AMSAN) variant, was made. Ileus, tachycardia and fever were the evidence of dysautonomia in this case.

The patient exhibited no facial muscle involvement. Creatine kinase (CK) levels were normal. Both blood and stool cultures were negative. Serum ganglioside antibody testing, including anti-GM1 and anti-GQ1B, returned negative results. Additional tests showed normal levels of vitamin B12 and folate, negative HIV serology and a negative antinuclear antibody (ANA) test.

The patient received plasma exchange therapy for Guillain-Barre Syndrome (GBS) in the fourth week of his illness. A total of five sessions were completed. While this treatment led to the complete resolution of his abdominal symptoms, neurological improvement was only partial. His muscle power showed some progress, with an improvement to a Medical Research Council (MRC) scale of 4 in the upper limbs (previously 3) and 3 in the lower limbs (previously 2). There was no involvement of the respiratory or bulbar muscles, he remained on room air and was able to tolerate feeding. Upon discharge, his mobility was dependent on a wheelchair.

In our case, we were initially considering ileus due to sepsis, electrolyte imbalance and pseudo-obstruction as a result of lack of mobility. However, with standard treatment of ileus, which includes abdominal decompression, electrolytes correction, fluid replacement and total parenteral nutrition, ileus symptoms are only partially resolved. With the completion of the plasma exchange after the diagnosis of Guillain-Barre Syndrome (GBS), the abdominal symptoms completely resolved suggestive of the relation of ileus to Guillain-Barre Syndrome (GBS).

DISCUSSION

Guillain-Barre syndrome (GBS) is an immunemediated neurological condition that affects the peripheral nerve and causes progressive paralysis of the autonomic, bulbar, and respiratory systems (Bellanti & Rinaldi, 2024).

GBS is classified into four subtypes: acute inflammatory demyelinating polyradiculoneuropathy (AIDP) which accounts for 85% of the cases, followed by, acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and lastly, Miller-Fisher syndrome (MFS) at 5% of the cases (Torres-Vásquez et al., 2020).

addition to motor weakness, In autonomic nervous system involvement can be prominent during GBS. Autonomic manifestations are thought to arise from either failure or overactivity of the sympathetic and parasympathetic systems. These symptoms may include labile blood pressure and heart rates, abnormal hemodynamic responses to medications, sweating and pupillary abnormalities, and bladder or bowel dysfunction. Notably, autonomic involvements have been associated with an increased risk of clinical deterioration, suggesting that these clinical features may indicate more severe disease progression (Chakraborty et al., 2019).

Normal physiology of gastrointestinal motility is regulated by both intrinsic and extrinsic neural control. Extrinsic parasympathetic input to the stomach, small intestine, and much of the colon are mediated by the vagus nerve, while parasympathetic innervation of the distal colon comes from sacral parasympathetic fibres. Sympathetic input to the stomach, small intestine, and colon are provided by the splanchnic and lumbar colonic nerves (Spencer & Hu, 2020).

It is believed that early-onset ileus in GBS results from an imbalance between sympathetic and parasympathetic tone due to immune-mediated damage. This is supported by autopsy findings, which have demonstrated mononuclear inflammatory cell infiltration and demyelination of somatic, parasympathetic, and sympathetic fibers (Shahrizaila et al., 2021).

Paralytic ileus in GBS is typically seen in the advanced stages of the disease. However, it is rarely reported as the initial symptoms before the onset of motor weakness Nowe et al. (2008) first reported a case involving a 74-yearold man who presented with paralytic ileus as the initial symptom, followed by paraparesis 4 days later. There was a similar case of a 34-yearold man, with symptoms of paralytic ileus and only to develop progressive limb weakness 5 days later. (Man & Fu, 2014). There were two severe GBS cases (a 28-month-old girl and a 54-year-old man) reported subsequently, both starting with bowel dysfunction. Both patients eventually required intubation and invasive mechanical ventilation. (Lee et al., 2019; Lee SH & Lee KH, 2017)) All the cases involved an episode of upper respiratory tract infection occurring 5 days to 3 weeks before the onset of GBS symptoms. From the previous literature, the onset of weakness was detected within 2 weeks of ileus symptoms and all were given intravenous immunoglobulin (IVIG) most of them achieved complete resolution of ileus and some degree of neurological recovery except the 54-year-old man who passed on. In our case, the motor weakness was detected on day 10 of admission (17 days after the onset of ileus symptoms) suggesting that the onset of motor weakness following paralytic ileus may be varied and may take longer than previously documented. As for our case, since the diagnosis of GBS is made in the 4 weeks from initial symptoms, plasma exchange therapy was initiated

CONCLUSION

In summary, although paralytic ileus is generally seen in the later stages of GBS, its occurrence as an early isolated symptom is rare but noteworthy. These cases highlighted the need for clinicians to remain vigilant when encountering unexplained gastrointestinal dysfunction. In such scenarios, especially with a recent history of upper respiratory infection, GBS should be considered as a differential diagnosis to ensure timely and appropriate intervention to prevent irreversible neurological damage.

CONFLICT OF INTEREST

The authors do not have any conflict of interest

CONSENTS

Written informed consent was obtained from the patient to publish the case with its related pictures. A copy of the written consent is available for review by the Editor in Chief.

ACKNOWLEDGEMENTS

All authors are appreciated to the patient who agreed to publish the case.

REFERENCES

- Bellanti, R., & Rinaldi, S. (2024). Guillain-Barré syndrome: A comprehensive review. European Journal of Neurology, 31(8). https://doi.org/10.1111/ene.16365
- Chakraborty, T., Kramer, C. L., Wijdicks, E. F. M., & Rabinstein, A. A. (2019). Dysautonomia in Guillain–Barré Syndrome: prevalence, clinical spectrum, and outcomes. Neurocritical Care, 32(1), 113–120. https://doi.org/10.1007/ s12028-019-00781-w
- Lee, K., Ho, T., Lee, J., Lin, L., Chang, W., Shih, C., & Yang, F. (2019). Paralytic ileus as the presenting symptom for Guillain–Barré syndrome: a case report. Journal of International Medical Research, 48(4), 030006051989316. https:// doi.org/10.1177/0300060519893169
- Lee, S. H. & Lee, K.H. (2017). A Child with Guillain-Barré Syndrome Presenting Paralytic Ileus. Journal of the Korean Child Neurology Society, 25(3), 191–194. https://doi. org/10.26815/jkcns.2017.25.3.191
- Man, B. L., & Fu, Y. P. (2014). Intestinal pseudoobstruction as a presenting symptom of Guillain-Barre syndrome. BMJ Case Reports, bcr2014205155. https://doi.org/10.1136/

bcr-2014-205155

- Nowe, T., Hüttemann, K., Engelhorn, T., Schellinger, P. D., & Köhrmann, M. (2008). Paralytic ileus as a presenting symptom of Guillain-Barré syndrome. Journal of Neurology, 255(5), 756–757. https://doi.org/10.1007/s00415-008-0783-0
- Shahrizaila, N., Lehmann, H. C., & Kuwabara, S. (2021). Guillain-Barré syndrome. The Lancet, 397(10280), 1214–1228. https://doi. org/10.1016/s0140-6736(21)00517-1
- Spencer, N. J., & Hu, H. (2020). Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. Nature Reviews Gastroenterology & Hepatology, 17(6), 338– 351. https://doi.org/10.1038/s41575-020-0271-2
- Torres-Vásquez, M., Chávez-Bosquez, O., Hernández-Ocaña, B., & Hernández-Torruco, J. (2020). Classification of Guillain–Barré Syndrome Subtypes Using Sampling Techniques with Binary Approach. Symmetry, 12(3), 482. https://doi.org/10.3390/sym12030482
- Weledji, E. P. (2020). Perspectives on paralytic ileus. Acute Medicine & Surgery, 7(1). https://doi. org/10.1002/ams2.573

BJMS Borneo Journal of Medical Sciences

CASE REPORT

Metastatic Breast Carcinoma Masquerading as Eyelid Swelling: A Case Report

Muhammad Fauzan Shamsuddin, Patricia Ann John*

Department of Ophthalmology, Segamat Hospital, Johor, Malaysia

* Corresponding author's email: patriciarathnam@gmail.com

Received: 30 July 2024

Accepted: 11 JNovember 2024

Published : 2 May 2025

DOI: https://doi.org/10.51200/bjms.v19i2.5544

Keywords: Breast, Carcinoma, Metastasis, Eyelid, Swelling



Borneo Journal of Medical Sciences © 2025 The Authors is licensed under CC BY-NC 4.0 (https://creativecommons.org/ licenses/by-nc/4.0/)

ABSTRACT

Eye metastases are rare, with breast carcinoma being the most prevalent primary tumour among all metastatic tumours of the eye. Eyelid metastases have been very rarely reported. This case report details the presentation of a 51-year-old Malay woman with underlying diabetes mellitus, presented with persistent left lower eyelid swelling for two months. Initially resembling a small pimple, it progressively increased in size, accompanied by erythema. Previous consultations with a private ophthalmologist were treated as preseptal cellulitis. Notably, the patient had a one-year history of progressive swelling of the right breast; but had never sought medical attention. Examination of the left eye revealed a lower lid mass, moderate to firm in nature and erythematous nasally. Breast examination revealed a right breast lump, firm to hard consistency, adhered to the underlying chest wall and overlying skin, peau d'orange skin changes, with nipple retracted. Contrast enhanced computed topography orbit demonstrated features suggestive of eyelid malignancy. An incisional biopsy was done, and histopathological results revealed metastatic carcinoma, likely of breast origin, subsequently planned for chemotherapy. Patients presenting with eyelid swelling should be evaluated for possible metastases. Systemic examination is necessary for establishing the diagnosis. Initiating early treatment enhances patient outcomes and quality of life.

INTRODUCTION

Eye metastases are rare, with breast carcinoma being the most prevalent primary tumour among all metastatic tumours to the eye (Wickremasinghe et al.,2007). The choroid, orbit, and ciliary body are the most commonly affected tissues (Ferry et al.,1974). Eyelid metastases are very rarely reported, accounting for less than 1% of all malignant eyelid lesions. (Aurora et al., 1970; Arnold et al., 1985; Bianciotto et al., 2009). Only 12 to 31% of patients present with eye metastases as the first sign of malignant disease. We present a rare case of metastatic breast carcinoma that masqueraded as eyelid swelling as the first presentation.

CASE PRESENTATION

AA 51-year-old Malay woman with a history of diabetes mellitus, presented with persistent swelling of the left lower eyelid over two months. Initially resembling a small pimple, the swelling progressively increased in size, involving the lower eyelid, accompanied by erythema (Figure 1). Previous consultations with a private ophthalmologist resulted in a diagnosis of preseptal cellulitis, which was treated with several antibiotics, yet the swelling persisted. Subsequently, the patient was referred to our facility for further evaluation. Notably, the patient also reported a one-year history of progressive swelling of the right breast with skin dimpling, yet she did not seek medical attention for this concern.

Ocular examination revealed a visual acuity of 6/9.5 in both eyes, with no relative afferent pupillary defect and normal extraocular muscle movement. Examination of the left eye revealed a lower lid mass measuring 5 cm x 1.5 cm in size, characterised as moderate to firm in nature, erythematous nasally, and adherent to the overlying skin. The mass was immobile, non-tender, with no punctum, nor warm to touch. There was no madarosis, telangiectasia or ulceration noted. The anterior and posterior segments of both eyes were otherwise unremarkable.

Breast examination identified a 10 cm x 15 cm mass encompassing the entire right breast. The mass was firm to hard, adhered to both the underlying chest wall and the overlying skin, and exhibited peau d'orange changes with a retracted nipple. No discharge was present. Bilateral axillary, supraclavicular, infraclavicular, and cervical nodes were not palpable. Examination of the left breast was unremarkable.

Blood investigations were performed, but results were unremarkable. Further imaging with contrast enhanced computed topography (CECT) orbit demonstrated an illdefined homogenously enhancing soft tissue lesion involving skin and subcutaneous tissue in the lower eyelid measuring 0.8 cm x 0.2 cm x 1.0 cm with no intra-orbital extension.



Figure 1: Swelling of the left lower eyelid, accompanied by erythema. A. Eye opened B. Eye closed



Figure 2: CECT orbit demonstrated an ill-defined homogenously enhancing soft tissue lesion involving skin and subcutaneous tissue at the lower eyelid with no intra-orbital exten-

Radiological interpretation suggested features consistent with eyelid malignancy (Figure 2).CECT of the thorax, abdomen and pelvis revealed right breast malignancy with metastasis to the spine, 1st rib, axillary lymph nodes as well as the brachial plexus. A mammogram showed thickened skin with diffuse subcutaneous oedema, and a large heterogenous mass occupying the entire right breast with increased colour Doppler signal. The patient was subsequently referred to the oculoplastic team for an incisional biopsy. Histopathological examination confirmed metastatic carcinoma. Microscopy showed malignant cells arranged in infiltrative cords, singly dispersed and occasional small nests infiltrating skeletal muscle bundles and fibrocollagenous tissue. The cells displayed moderate pleomorphic hyperchromatic nuclei, with small to inconspicuous nucleoli moderate cytoplasm. Rare mitosis and present. Immunohistological studies was demonstrated the malignant cells were positive for cytokeratin AE1/AE3, GAIA 3 and estrogen receptor (ER), favouring primary breast origin. A trucut biopsy of the right breast was done, and histopathological results confirmed invasive examination lobular carcinoma. Microscopy demonstrated breast tissues infiltrated by tumour cells arranged in linear cords and clusters, with mild to moderate nuclear pleomorphism and Immunohistochemistry dense chromatin.

showed positive for estrogen receptor (ER) as well as progesterone receptor (PR). The HER-2 receptor was equivocal, hence the dual in situ hybridization status was submitted and came back as negative.

The patient's care was subsequently co-managed by both the oncology and surgical teams. The ophthalmology team opted for conservative management as there was no intraorbital involvement. The patient had undergone 6 cycles of chemotherapy with Paclitaxel, and oral Letrozole post chemotherapy until disease progression. A follow up CECT of the thorax, abdomen and pelvis was scheduled to assess for disease progression. No surgical intervention was planned for the patient.

DISCUSSION

Eye metastases are generally rare, and breast carcinoma remains the most prevalent primary malignancy, accounting for 28.5% to 58.8% of all cases of eye metastases followed by lung cancer (24%) and skin melanoma (14%) (Ahmad et al. 2007; Wickremasinghe et al. 2006). Eyelid metastasis is even rarer. Among malignant eyelid lesions, eyelid metastasis accounts for less than 1% of all cases, with basal cell carcinoma being the most common (80.4%), followed by squamous cell carcinoma (7%), malignant melanoma (5.1%), and sebaceous carcinoma (3.3%) respectively (Aurora et al., 1970; Arnold et al., 1985; Bianciotto et al., 2009). Moreover, a review by Bianciotto et al., 2009 stated that ocular metastatic disease is significantly more prevalent with only 1.1% of patients having eyelid metastasis.

Studies have shown that it is not uncommon to misdiagnose an eyelid metastasis as the case varies from patient to patient. Patients may present with painless nodules, diffuse eyelid swelling, ulcerative lesions, and even inflammatory nodules often mistaken for chalazion (Arnold et al., 1985). Involvement of lid epidermal and surfaces of conjunctiva has also been reported (Hood et al., 1973). In our case, the patient presented with persistent swelling of the left lower eyelid, resembling a pimple and was misdiagnosed as preseptal cellulitis. While eye metastasis is usually detected in patients with known breast cancer, in 12 to 31% of cases, similar to our case, metastasis can present as the first sign of an undiagnosed breast malignancy (Muhd et al., 2020). Therefore, detecting metastasis is more difficult in the absence of primary malignancy. Moreover, as per Ferry et al., 1974, the latency period between primary carcinoma and the development of orbital metastasis may range from 4 to 6.5 years.

Imaging will aid in determining whether a mass is malignant or benign, as well as assessing the extent of the mass. In our patient, orbital imaging revealed an eyelid malignancy and helped identify the spread of the disease. Histopathological examination from biopsy remains the gold standard in making a diagnosis. The main biopsy techniques in eyelid tumours are excisional, incisional, punch, snip, curette, and shave biopsies (Wu et al., 2019). Choice of biopsy is selected based on lesion characteristics, possible diagnosis, location, and surgeon preference (Wu et al., 2019). For our patient, an incisional biopsy of the left lower eyelid was performed. Studies suggest that incisional biopsy had a 95% accuracy rate in diagnosing eyelid tumours (Rice et al., 2003). Subsequently, a trucut biopsy was done over the right breast, revealing invasive lobular carcinoma. Contrary to general statistics, invasive ductal carcinoma would have been more common (Saad et al., 2022).

Management of eyelid metastases is largely dependent on the tumour's clinical features, such as the shape, number, and site of metastases, as well as systemic features. Treatment options are excisional biopsy, external beam radiation therapy (EBRT), systemic chemotherapy or immunotherapy, and observation (Bianciotto et al., 2009). An excisional biopsy is performed for small, solitary nodular lesions. Generally, EBRT is done for patients with multiple eyelid metastases or recurrent lesions. Systemic chemotherapy or immunotherapy is indicated for patients with widespread systemic disease and is administered based on the tumour's response. For terminal patients who are not undergoing systemic treatment, general observation is the approach taken (Bianciotto et al., 2009).

Regardless of treatment, the prognosis in patients with multiple metastases is much poorer. With regards to our patient, who was diagnosed with right breast lobular carcinoma, T4bN1M1, metastases to bone and lung. Systemic chemotherapy was chosen by the surgical team due to the extensive systemic involvement. The patient is being monitored for tumour response to chemotherapy; however, the patient defaulted Ophthalmology clinic follow up.

CONCLUSION

Patients presenting with eyelid swelling should be evaluated for possible metastases, a detailed systemic examination is necessary for establishing the diagnosis. Initiating early treatment enhances patient outcomes and quality of life.

CONFLICT INTEREST

The authors declare that they have no

competing interests in publishing this case.

CONSENTS

Written consent was obtained from patient. A copy of the written consent is available for review by the Editor-in-chief.

REFERENCES

- Ahmad, S. M., & Esmaeli, B. (2007). Metastatic tumors of the orbit and ocular adnexa. Current opinion in ophthalmology, 18(5), 405-413. Ovid Technologies (Wolters Kluwer Health). https://doi.org/10.1097/ icu.0b013e3282c5077c
- Arnold, A. C., Bullock, J. D., & Foos, R. Y. (1985). Metastatic eyelid carcinoma. Ophthalmology, 92(1), 114-119. Elsevier BV. https://doi. org/10.1016/s0161-6420(85)34072-1
- Aurora, A. L., & Blodi, F. C. (1970). Lesions of the lids: A clinicopathologic study. Surv Ophthalmol, 15
- Bianciotto, C., Demirci, H., Shields, C. L., Eagle, R. C., & Shields, J. A. (2009). Metastatic tumors to the eyelid: report of 20 cases and review of the literature. Archives of Ophthalmology, 127(8), 999-1005. American Medical Association (AMA). https://doi.org/10.1001/ archophthalmol.2009.120
- Ferry, A. P. (1974). Carcinoma metastatic to the eye and orbit. I. A clinicopathologic study of 227 cases. Arch Ophthalmol., 92, 276-286. American Medical Association (AMA). https://doi.org/10.1001/ archopht.1974.01010010286003
- Hood, C. I., Font, R. L., & Zimmerman, L. E. (1973). Metastatic mammary carcinoma in the eyelid with histiocytoid appearance. Cancer, 31(4), 793-800.Wiley.https://doi.org/10.1002/1097-0142(197304)31:4<793:: a i d cncr2820310406>3.0.co;2-a
- Muhd, H., Zuhaimy, H., Ismail, M. F., Arshad, F., Azmi, S. N. M., & Sahak, N. H. (2020). Orbital metastasis as the initial presentation of breast cancer. Malaysian Family Physician: the Official Journal of the Academy of Family Physicians of Malaysia, 15(3), 74.
- Rice, J. C., Zaragoza, P., Waheed, K., Schofield, J., & Jones, C. A. (2003). Efficacy of incisional vs punch biopsy in the histological diagnosis of periocular skin tumours. Eye, 17(4), 478-481. Springer Science and Business Media LLC. https://doi.org/10.1038/sj.eye.6700383
- Saad, E. S. P., Bakri, H. M., Rayan, A., Barakat, D., &

Khalel, M. M. (2022). Eye metastasis in breast cancer: case report and review of literature. ecancermedicalscience, 16. Ecancer Global Foundation. https://doi.org/10.3332/ ecancer.2022.1353.

- Wickremasinghe, S., Dansingani, K. K., Tranos, P., Liyanage, S., Jones, A., & Davey, C. (2007). Ocular presentations of breast cancer. Acta Ophthalmologica Scandinavica, 85(2), 133-142. Wiley. https://doi.org/10.1111/j.1600-0420.2006.00737.x.
- Wu, A., Huilgol, S. C., & Selva, D. (2019). Biopsy Techniques for Eyelid Tumours. Surgical Ophthalmic Oncology: A Collaborative Open Access Reference, 11-14. Springer International Publishing. https://doi. org/10.1007/978-3-030-18757-6_2