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EDITORIAL

Artificial Intelligence in Medical Education: Preparing Future Physicians for an AI-Driven Healthcare System

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Artificial intelligence (AI) is a transition from an old speculative idea to a new comprehensive idea that is a vital element for healthcare and medical education. AI is either generative or assistive, strengthening the field of study. The most popular generative AI platform, ChatGPT, along with other language models, has been widely used by medical students to access information, solve problems, develop clinical reasoning, and prepare for examinations. On the other hand, educators are searching for AI-assisted technologies for assessment and evaluation design, feedback generation, curriculum development, teaching methods and strategies, and various research. This notable evolution presents huge opportunities while also raising concerns about ethical practice, data privacy, learners' professionalism and dependency, writing individuality, academic integrity, and professional accountability.

In the evolution and development of science and technology, medical education has evolved historically. There is extensive incorporation of machine-based learning, simulation-based learning, digital anatomy platforms, virtual patients and simulation, electronic medical records, and electronic mannequins that demonstrate and facilitate the learning process and underscore the importance of innovation in learning. AI enhances the future phase of this evolution. Generative AI not only disseminates information but also supports original writing, summarisation, formulation of clinical cases, and problem-solving and decision-making.

However, medical schools face challenges in whether to incorporate AI into the education system and how to ensure that incorporation maintains the integrity and core values of the medical profession.

Opportunities for Transforming Medical Education

AI brings remarkable opportunities to intensify learning in both undergraduate and postgraduate medical education. The most significant is individual learning. In traditional medical teaching, the same materials are delivered to every student, while AI offers the opportunity to tailor content to individual needs, allowing students to learn at their own pace and create content according to their requirements. This system also helps students understand their own weaknesses and strengths. Therefore, this adaptive learning approach directs the self-directed learning that is the part and parcel of lifelong learning in medicine.

Generative AI is used as a learning helper for students. By using AI, students can improve their ability to understand complex physiological mechanisms, prepare revision notes, summarise lecture notes or book reviews, prepare clinical case problems and scenarios, and practise exam questions related to the topic. These tools promote active learning and understanding according to students' level. Traditional classroom teaching only provides notes and understanding within a defined time; an AI-powered virtual tutor supports them indefinitely and guides them to explain and give feedback when used properly and effectively.

Moreover, medical educators benefit from AI-assisted technologies. Educators can use AI to prepare daily lessons, learning objectives or outcomes for classes, prepare quizzes for in-class activities, construct multiple-choice questions, modified essay questions, and short-answer questions, create objective structured clinical examinations (OSCE) and objective structured practical examinations (OSPE), and draft lecture

materials. Administrative work can be less time-consuming by using AI, such as mentoring students, assisting clinical reasoning, and nurturing professionalism.

AI application is promising in another aspect of medical education, that is, simulation-based education. AI enhances virtual patient encounters with realistic clinical conversations, stimulating students to practice history-taking, physical examination, diagnosis, and clinical decision-making in a realistic, in-house clinical environment. Though this innovation is expensive to support students, it provides real patient scenarios where limited patient availability allows students to practice as long as they can.

Challenges That Cannot Be Ignored

When there are pros, there are also cons. AI advantages are significant, but it has educational risks as well. Firstly, most language models contain unscientific, fabricated, and inaccurate information that can give students wrong guidelines. Medicine deals with human beings, not machines. Therefore, any wrong information that students learn directly has an impact on patient care, which can have serious consequences. Educators and students should be careful to verify information before applying it to patients. On the other hand, AI should collect and deliver information through evidence and recognised sources.

Secondly, academic integrity is another major concern. Assignments, essay writing, reflective writing and question answers can be produced directly by generative AI. Previous traditional methods could detect students' understanding, writing ability and patterns of answers. But due to AI assistance, it is difficult to evaluate this performance. Though it is difficult to stop using AI and it has beneficial effects also, therefore, medical schools should redesign the assessment techniques, in-class activities, physical examinations, oral examinations, work-based assessments, clinical performance and practical-oriented evaluations rather than written assessments outside the supervisor's settings.

Another concerning issue is independent clinical reasoning. Medical education is not just about providing knowledge to students but also about training them to communicate with empathy to patients, interpret uncertainty, and balance patient preferences with professional judgement. Unfortunately, higher-order thinking and interpersonal competencies cannot be possible with AI tools. Therefore, students might lack training in analysing complex situations and dealing with patient empathy.

Integrating AI into medical education is complicated by ethical considerations. It is very challenging to address copyright, patient confidentiality, informed consent, transparency, and so on. Students might not know how to use AI ethically or when it should not be used. Proper and ethical use of AI that adheres to professional ethics and clinical decisions, not for algorithms, which are the backbone of healthcare professionals.

AI Literacy as a Core Competency

Although AI has many beneficial effects and provides guidance to students, medical schools should emphasise AI literacy as a core competency. They must train students in the ethical considerations of AI, its appropriate applications in clinical and educational settings, and its limitations.

Medical graduates with AI training must have sufficient knowledge about AI-generated information. They should be able to understand potential biases and inaccuracies, patient confidentiality, evidence-based information and decision-making skills. They should know AI is for assistance, not to replace their knowledge and skills, clinical reasoning, professionalism and ultimate patient care.

Moreover, Faculty need to play vital roles in the effective use of AI. Most faculty members do not have an idea about the use of AI in teaching, assessment and evaluation. Therefore, faculty must arrange workshops or training for faculty members to effectively use AI in teaching, learning, assessment and evaluation. This will help them train students and apply AI effectively (Figure 1).

Implications for Medical Schools in Malaysia and Southeast Asia

The incorporation of AI in medical education in Malaysia and other Southeast Asian countries is appropriate. In this region, medical schools have digital learning platforms, simulation-based education and blended-learning methodologies. However, AI implementation cannot be fully effective because of faculty expertise, lack of technological infrastructure and institutional policies. Therefore, complete coordination is essential to incorporate AI in medical education and provide students with



Figure 1: Framework of responsible AI integration in medical education.

AI-enhanced educational opportunities.

AI incorporation in medical education is therefore not limited to a single lecture but needs to be considered in the curriculum as longitudinal incorporation for both undergraduate and postgraduate students. To train healthcare students about AI, the fundamentals of AI, ethical considerations, data governance, algorithms, critical appraisal, and clinical decision support should be integrated into the core competency curriculum.

In addition, faculty development is also important. Educators must know the uses and limitations of generative AI and how to incorporate this tool into their teaching, assessment, and evaluation practices. Therefore, the train-the-trainers method can be used to train the educators. Continuous professional development can build their practical knowledge and skills related to AI use, assessment redesign, incorporating students in class, evaluating students using AI, and ethical digital professionalism.

Moreover, medical schools must have clear institutional policies for AI use. These guidelines should properly mention brainstorming, formative learning, revision summarisation, as well as inappropriate techniques and misuse of AI. Clear guidelines and transparent policies can provide educators and students with a clear understanding of AI use.

Keeping Humanity at the Centre of Medical Education

Despite rapidly evolving technology, the basics of medicine remain deeply human. Compassion, ethics, professionalism, cultural sensitivity, effective communication, and, most of all, empathy are the fundamentals of medicine that cannot be entrusted to AI. Diagnosis is not the only strategy for the patient; rather, it is a health practitioner-patient relationship that includes reassurance, trust and shared decision-making.

Therefore, AI is not a substitute for educators or clinicians; rather, it is an educational partner. Future physicians will

know how to integrate theoretical and practical knowledge to critically assess AI-generated information, communicate uncertainty, acknowledge algorithm limitations, and make context-sensitive clinical decisions. Medical education should include AI technologies, and graduates should have the confidence to use them through lifelong learning, reflective practice, and fostering curiosity.

Educators have opportunities to incorporate AI in assessment methods. Not only can AI be used to assess, but it can also be used to evaluate, such as assessing clinical reasoning, ethical judgment, teamwork, communication, patient-oriented problem-solving, and clinical decision-making. AI techniques can support humanisation techniques.

Recommendations for Medical Schools

To effectively prepare future physicians, medical schools should consider several strategic initiatives:

1. Integrate AI literacy as a core competency for both undergraduate and postgraduate students.
2. Institutional guidelines for the implementation of AI in teaching, learning, assessment and evaluation should be established.
3. Assessment strategies should be redesigned for clinical reasoning, professionalism and workplace-based competency.
4. Curriculum review in faculty to incorporate AI-assisted teaching, learning and assessment.
5. Train the students to critically assess AI-generated answers by using evidence-based clinical guidelines.
6. Interdisciplinary collaboration among clinicians, medical educators, policy makers, data scientists, and ethicists to ensure safe and sound integration of AI in healthcare education (Figure 2).

AI is the most innovative transformation in medical education. It significantly contributes

OPPORTUNITIES	CHALLENGES	KEY RECOMMENDATIONS
 Personalised and adaptive learning	 AI hallucinations and inaccuracies	 Teach AI literacy and critical appraisal skills
 Intelligent tutoring and instant feedback	 Academic misconduct and integrity issues	 Redesign assessment (authentic, workplace-based)
 Simulation and virtual patients	 Bias and inequity in AI outputs	 Ensure fairness, diversity in data and outputs
 Clinical decision support and learning tools	 Privacy and data security concerns	 Strengthen data governance and confidentiality
 Efficiency in curriculum and assessment design	 Overreliance and erosion of critical thinking	 Promote human oversight and balance technology with human judgement
 Research assistance and evidence synthesis	 Lack of transparency and explainability	 Use explainable AI and require transparency of AI use

Figure 2: Opportunities, challenges and key recommendations for AI in medical education.

to self-learning, increases educational efficiency, supports simulation-guided training, and promotes self-motivated learning, offering valuable opportunities for both students and educators. In addition to these benefits, there are challenges related to accuracy, bias, academic integrity, professionalism, and ethical considerations. To train the future physicians, there is now a demand to prepare them for an AI-driven healthcare landscape to adopt AI-related technologies. Every medical school should prepare future graduates who can critically, responsibly and ethically utilise these AI technologies while keeping the humanistic values that are the backbone of the medical profession. Therefore, the aim is not to produce healthcare professionals who simply accept or rely on AI, but rather to produce physicians who understand when, how, why, and where to apply AI for patient care and needs, while maintaining clinical judgment, professionalism, and compassion.

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ORIGINAL ARTICLE

Healthcare Utilisation Inequality and the Hidden Burden of Out-of-Pocket Expenditures in Sabah

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ABSTRACT

Malaysia has made significant progress in reducing financial hardship from out-of-pocket (OOP) health expenditures, aligning with Sustainable Development Goal 3.8.2 on universal health coverage. However, persistent income inequality, particularly in Sabah, where nearly one in five families live below the poverty line, continues to hinder equitable access to healthcare. The objectives of this study are to describe the patterns of healthcare utilisation and associated inequalities in Sabah, and the patterns of catastrophic and impoverishing health expenditures using the capacity-to-pay approach. This study utilises data from the National Health and Morbidity Surveys (NHMS, 1996 - 2023) and the Household Income and Expenditure Surveys (HIES, 2014 - 2022). Analyses were conducted using STATA v18. NHMS data were used to evaluate disparities in service use, while HIES data captured catastrophic and impoverishing health expenditures. Catastrophic expenditure was defined as health spending exceeding 40% of household capacity-to-pay, and impoverishment as OOP payments that pushed households below the basic needs threshold. Inequality was assessed using the concentration index (CI), where negative values indicate a pro-poor and positive values indicate a pro-rich distribution. In 2023, inpatient care remained concentrated in the public sector, while outpatient services were more evenly utilised across industries. CIs indicated rising pro-rich inequalities. Between

2.41% and 3.10% of households experienced catastrophic payments. Households impoverished by healthcare costs increased (from 0.1% in 2014 to 0.3% in 2022), whereas those further impoverished declined (from 2.4% to 1.7%). Targeted and inclusive financial protection strategies are crucial for closing these gaps and achieving equitable health coverage.

INTRODUCTION

Globally, socioeconomic status is a key determinant of health, influencing both disease burden and access to healthcare services (Nasirin & Lionardo, 2021; National Association of Chronic Disease Directors & Centres for Disease Control and Prevention, 2024). In many low- and middle-income countries, out-of-pocket (OOP) expenditures often constitute a significant share of healthcare financing, exposing households to financial hardship (World Health Organisation & World Bank, 2023). These expenditures can lead to catastrophic health expenditure (CHE), where a substantial portion of household income is spent on healthcare, or impoverishing health expenditure (IHE), which pushes households below the poverty line.

In Malaysia, these global patterns are reflected, particularly in the socioeconomically disadvantaged state of Sabah. Despite nationwide improvements in health outcomes and a well-established public healthcare system, Sabah consistently lags, with persistent poverty and stark health inequities. In 2019, Sabah's poverty rate stood at 19.7%, the highest in the country (Department of Statistics Malaysia, 2022). These economic challenges intersect with health disparities, where poorer households face disproportionate barriers to accessing healthcare and a greater likelihood of forgoing necessary care (National Association of Chronic Disease Directors & Centres for Disease Control and Prevention, 2024).

The health outcomes in Sabah further highlight these disparities. The state continues to report some of the nation's highest rates

of infant, toddler, and maternal mortality (Khazanah Research Institute, 2020; Ministry of Health Malaysia, 2021). Communicable diseases, such as tuberculosis and malaria, remain significant public health challenges. Meanwhile, the prevalence of chronic non-communicable diseases (NCDs) has shown modest changes over time. Between 2011 and 2023, the prevalence of diabetes decreased slightly from 9.0% to 8.8%, while hypercholesterolemia increased from 31.1% to 32.1%, and hypertension dropped from 29.1% to 25.5% (Ministry of Health Malaysia, 2011, 2024).

Behavioural risk factors further influence socioeconomic and health inequities in Sabah (Hamsah et al., 2025). The state exhibits one of the highest smoking rates in Malaysia, with 24.9% of individuals aged 15 years and older smoking (Ministry of Health Malaysia, 2024). Additionally, 74.8% of adults aged 18 and above engage in binge drinking, the highest prevalence in the country (Ministry of Health Malaysia, 2019). These risky behaviours add to the effects of poverty and social problems, making health issues harder to manage.

In Sabah, the rising cost of healthcare has raised concerns, yet data on catastrophic and impoverishing health spending remain limited. This study addresses that gap by using data from two national surveys to examine both inequalities in healthcare use and the financial impact of OOP spending. The capacity-to-pay (CTP) method estimates the financial burden based on a household's resources after meeting its basic needs. This provides a more accurate picture of economic hardship, particularly among low-income groups in Sabah (Cylus et al., 2018). The objectives of this study are to describe the patterns of healthcare utilisation and associated inequalities in Sabah, as well as the patterns of catastrophic and impoverishing health expenditures using the capacity-to-pay approach. These objectives focus on identifying gaps in healthcare access and financial protection challenges in Sabah.

MATERIALS AND METHODS

A Study design and study location

This was a cross-sectional study, which utilised data from the National Health and Morbidity Surveys (NHMS, 1996-2023) and the Household Income and Expenditure Surveys (HIES, 2014-2022). Data were extracted between January and April 2024. Subsequent data analysis and interpretation were performed from May to July 2024.

Sabah is the country's second-largest state, with a population of almost 3.8 million, located on the northern part of the island of Borneo (Department of Statistics Malaysia, 2025; Kerajaan Negeri Sabah, 2025). Sabah's population is ethnically and culturally diverse, consisting of more than 30 ethnic groups (Kerajaan Negeri Sabah, 2025). Healthcare in Sabah is part of Malaysia's dual system, comprising a heavily subsidised public sector and a growing private sector. The Ministry of Health Malaysia (MOH) oversees the provision of public healthcare, which serves as the leading provider across the state.

Data source

National Health & Morbidity Survey (NHMS)

Healthcare utilisation data for Sabah were taken from the NHMS, a nationwide household survey that has been running since 1986. It plays a central role in monitoring population health in Malaysia. While some changes to the questionnaire over the years may affect comparisons across rounds, consistent state-level data for Sabah have been available since 1996. Most rounds used face-to-face interviews, except in 2023, when computer-assisted telephone interviews (CATI) were introduced. The MOH publishes more details on the survey design (Ministry of Health Malaysia, 2024)

Household Income and Expenditure Survey (HIES)

HIES data were used to assess patterns in catastrophic (CHE) and impoverishing health expenditure (IHE). HIES is conducted

nationwide twice every 5 years by Malaysia's Department of Statistics (DOSM). It provides detailed household spending information, including health expenses. More information about how the survey can be found in DOSM's official reports (Department of Statistics Malaysia, 2023).

Measurement of living standards

Depending on the available data, socioeconomic status (SES) is typically measured using household income, expenditure, or consumption standards (C Anuranga et al., 2013). Among these, expenditure and consumption data are often preferred because they better reflect living standards and are more stable.

In the NHMS, income data were collected in the 1996, 2006, and 2023 rounds, whereas expenditure or consumption data were used in 2011, 2015, and 2019. The choice between income and expenditure data depended on the survey's design and data collection method. For example, the 2023 NHMS utilised CATI, which limited the collection of detailed expenditure data.

Adjustments were made to allow fairer comparisons between different household types by accounting for differences in household size and composition. When making comparisons, a single household with an income of MYR 40,000 annually can be compared to the same income for a household with two adults and two children by adjusting for their differing needs. This approach, known as the adult equivalent (AE) method, is widely used by the Organisation for Economic Co-operation and Development (OECD) (Organisation for Economic Co-operation and Development, 2008). The formula is as follows:

$$AE_h = (A_h + \alpha K_h)^\theta$$

where,

AE_h is the adult equivalent of the household h
 A_h is the number of adults in the household h
 K_h is the number of children 0-14 years old
 α (value is 0.5) is the "cost of children" and
 θ (value is 0.75) reflects the degree of economies of scale

After adjustment, households are ranked and grouped into quintiles. The lowest quintile represents the bottom 20% of households, while the highest quintile represents the top 20%.

Healthcare utilisation

Healthcare utilisation was assessed based on self-reported data. Outpatient care was measured by the number of visits to any healthcare facility, while inpatient care was measured by the number of admissions. The recall periods were two weeks for outpatient visits and one year for inpatient care. The data were further divided by type of provider, distinguishing between public and private services.

Catastrophic Health Expenditure (CHE)

CHE happens when a household spends more than 40% of its CTP on healthcare (Cylus et al., 2018). CTP is the amount a household has left after paying essentials like food, housing, and utilities. It's calculated using the Normative Spending on Food, Housing, and Utilities method (Cylus et al., 2018). This method takes the average spending from households in the 25th to 35th percentile range of their total expenses. According to Cylus et al. (2018), this group represents typical basic spending patterns without extremes, making it a practical benchmark. The formula to calculate CTP for each household is as follows:

$$CTP_i = EXP_i - SE_{25-35i}$$

where,

CTP_i is the capacity to pay in the household i
 EXP_i is the total expenditure in the household i
 SE_{25-35i} is the average subsistence expenditure in the 25th to 35th percentile of the i^{th} household

Impoverishing Health Expenditure (IHE)

A household is considered impoverished if healthcare payments force its spending below the poverty line. Here, the poverty line is measured by a household's CTP. IHE shows how medical expenses reduce what families have left to spend on basic needs. Households already below the poverty line before paying

medical costs are categorised as "further impoverished," reflecting the added hardship these families experience. These households are already struggling financially, and health expenses push them even deeper into poverty. Some families might not yet be poor, but their remaining resources after healthcare expenses put them dangerously close to 120% of the poverty line. They are at risk of falling into poverty because of these expenses (World Health Organisation & World Bank, 2023).

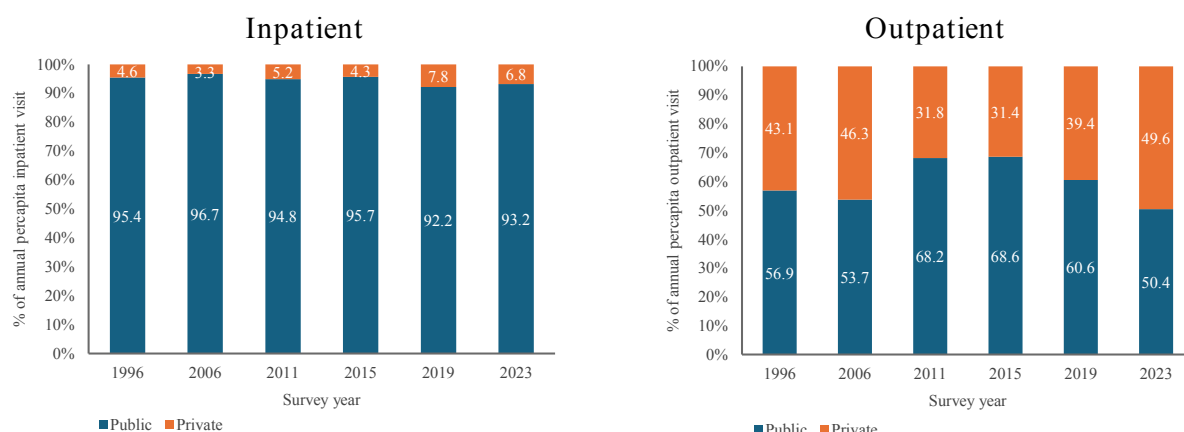
Data Analysis

Descriptive statistics were used to examine overall healthcare utilisation across different SES groups. The distribution of healthcare utilisation across SES segments was assessed for relative inequalities using the Concentration Index (CI). Ranging from -1 to $+1$, the CI indicated both the direction and magnitude of concentration. Negative values suggested that healthcare utilisation was more concentrated among the poor (pro-poor), while positive values indicated that it was more concentrated among the wealthy (pro-rich). A CI value of 0 represented an equal distribution of utilisation across all SES groups. Descriptive statistics were also applied to analyse the incidence of CHE and IHE across the survey year. The analysis measured the proportion of households that experienced CHE or IHE. Data analysis was conducted using STATA v18.0.

RESULT

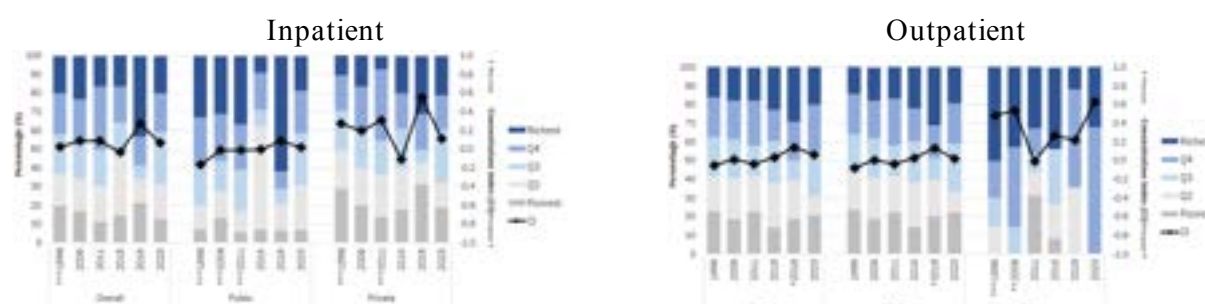
Trends of Healthcare Utilisation

The public sector consistently provided the majority of inpatient visits, though its share declined slightly, ranging from 95.4% in 1996 to 93.2% in 2023, as the private sector's share increased slightly from 4.6% to 6.8% (Figure 1). In contrast, the distribution of outpatient visits between public and private sectors showed greater variation. The public sector's share declined from 56.9% in 1996 to 50.4% in 2023, reflecting a gradual shift toward private outpatient care, whose share increased from 43.1% to 49.6% during the same period.



Note: Inpatient estimates are based on the distribution of inpatient admissions.

Figure 1: Composition of healthcare utilisation by public and private sectors, NHMS 1996-2023



Notes:

1. Significance of difference of the Concentration Index (CI) indicated by * $0.05 \leq p < 0.1$, ** $0.01 \leq p < 0.05$, *** $p < 0.01$
2. Survey design can differ across surveys, so comparisons are not strictly comparable.

Figure 2: Distribution of inpatient and outpatient (visits) by socioeconomic quintiles, NHMS 1996-2023

Inpatient visits by socioeconomic quintiles

Figure 2 shows the distribution of inpatient visits by socioeconomic quintiles, overall and by sectors, across all survey years. In 2019, the distribution of overall inpatient visits was pro-rich (CI = 0.142). Public inpatient visits, initially pro-poor in 1996 (CI = -0.079), shifted towards pro-rich in 2019 (CI = 0.135). In contrast, private inpatient visits were consistently pro-rich in earlier years, with CI values increasing from 0.478 in 1996 to 0.538 in 2006, indicating a widening gap during that period, with poorer groups increasingly underserved.

In public facilities, the poorest quintile's share fell slightly, and the richest quintile's share increased. For private facilities, the richest quintile consistently accounted for most visits. The overall distribution of inpatient visits by socioeconomic quintiles is presented in Table 1.

Outpatient visits by socioeconomic quintiles

The distribution of outpatient visits also evolved (Figure 2). Outpatient visits showed a pro-rich distribution in 1996 (CI = 0.025). Public outpatient visits consistently demonstrated a pro-poor distribution in earlier years, with the CI shifting from -0.164 in 1996 to -0.009 in 2011. In contrast, private outpatient visits remained pro-rich, with CI values ranging from 0.274 to 0.308 throughout the same period.

Over time, the poorest quintile's share of overall outpatient visits decreased, while the richest quintile's share remained relatively stable. In public facilities, the shares of both the poorest and wealthiest quintiles declined. Conversely, in private facilities, the share of the poorest quintile dropped slightly; however, the share of the wealthiest quintile nearly doubled, indicating a pro-rich pattern. This highlights the importance of public services in providing access for poorer households, as private care remains largely inaccessible to

Table 1: Distribution of inpatient visits by socioeconomic quintiles, NHMS 1996-2023

Survey Year	Overall						Public						Private					
	Quintile					CI	Quintile					CI	Quintile					CI
	Poorest	Q2	Q3	Q4	Richest		Poorest	Q2	Q3	Q4	Richest		Poorest	Q2	Q3	Q4	Richest	
1996	22.7	19.3	20.6	21.3	16.1	-0.054	23.8	19.4	20.8	21.4	14.6	-0.079**	0.0	14.2	16.0	19.5	50.3	0.478***
2006	18.4	21.9	21.0	20.6	18.1	0.014	19.0	21.7	21.1	20.3	17.7	0.005	0.0	0.0	14.3	42.9	42.9	0.538**
2011	22.8	19.2	15.7	24.3	17.9	-0.035	22.4	19.5	16.1	24.9	17.1	-0.037	31.2	12.8	9.3	13.7	33.1	-0.008
2015	14.2	23.6	22.5	16.6	23.2	0.036	14.4	23.9	22.1	17.4	22.2	0.026	8.3	18.4	29.3	0.0	43.9	0.265
2019	18.7	20.6	10.7	20.5	29.6	0.142*	20.3	19.4	11.6	17.7	31.1	0.135*	0.0	35.4	0.0	52.5	12.1	0.219
2023	20.5	10.3	23.9	25.0	20.3	0.063	22.0	11.1	25.7	21.8	19.4	0.022	0.0	0.0	0.0	67.8	32.2	0.631

Notes:

1. Significance of difference indicated by * $0.05 \leq p < 0.1$, ** $0.01 \leq p < 0.05$, *** $p < 0.01$
2. Survey design can differ across surveys, so comparisons are not strictly comparable.
3. CI: Concentration Index

Table 2: Distribution of outpatient visits by socioeconomic quintiles, NHMS 1996-2023

Survey Year	Overall						Public						Private					
	Quintile					CI	Quintile					CI	Quintile					CI
	Poorest	Q2	Q3	Q4	Richest		Poorest	Q2	Q3	Q4	Richest		Poorest	Q2	Q3	Q4	Richest	
1996	19.6	17.1	21.2	21.9	20.2	0.025***	7.3	12.7	20.9	26.1	33.0	-0.164***	28.9	20.5	21.4	18.8	10.5	0.274***
2006	17.0	17.1	18.8	23.7	23.4	0.086	13.3	14.4	16.0	25.1	31.2	-0.010***	20.2	19.4	21.3	22.5	16.7	0.199
2011	11.3	19.0	19.5	33.6	16.6	0.092	5.9	10.9	22.3	24.1	36.8	-0.009***	13.8	22.8	18.2	38.0	7.2	0.308***
2015	14.7	31.9	17.6	19.4	16.5	-0.035	7.3	54.9	9.0	19.8	9.0	-0.001	18.1	21.4	21.5	19.1	19.9	-0.109
2019	21.5	12.3	7.6	15.5	43.1	0.272	6.7	13.7	8.2	9.7	61.7	0.088	31.1	11.4	7.2	19.3	31.0	0.555
2023	13.0	18.3	28.1	20.7	19.9	0.065	6.8	23.8	27.9	23.0	18.5	0.017	19.1	12.9	28.4	18.3	21.3	0.114

Notes:

1. Significance of difference indicated by * $0.05 \leq p < 0.1$, ** $0.01 \leq p < 0.05$, *** $p < 0.01$
2. Survey design can differ across surveys, so comparisons are not strictly comparable.
3. CI: Concentration Index

them. The overall distribution of outpatient visits by socioeconomic quintiles is presented in Table 2.

Capacity-to-pay (CTP)

Table 3 shows the trends in household expenditure, subsistence costs, and CTP from 2014 to 2023. Overall household expenditure rose steadily from MYR 1934.82 in 2014 to MYR 2778.32 in 2023. Similarly, subsistence expenditure increased from MYR 647.14 to MYR 844.12 over the same period. The CTP, representing available income after basic needs, grew from MYR 1287.68 to MYR 1934.19. OOP health expenditure also saw a significant rise, from MYR 23.29 in 2014 to MYR 71.65 in 2023.

Trend of Catastrophic Health Expenditure

Figure 3 shows the proportion of households whose OOP health spending exceeded 40% of their CTP from 2014 to 2022. The share rose from about 3% in 2014 to just over 4% in 2016, before falling to around 2% by 2022



Figure 3: Population with OOP Exceeding 40% of CTP, HIES 2014-2022

Figure 4 shows the proportion of households experiencing OOP health expenditures exceeding 40% of their CTP, by income quintile, for 2014, 2016, 2019, and 2022. From 2014 to 2022, catastrophic OOP expenditure was consistently concentrated among the poorest households (Q1), where it was 5–7 times more likely. While the overall prevalence fluctuated between 3–4% in 2014–2019, before dropping to about 2% in 2022, Q1 households showed much higher percentages, remaining around

one in five in 2016 and 2019 before reducing to 11.8% in 2022. In contrast, the higher-income quintiles (Q2–Q5) recorded negligible proportions and very minimal changes across all years. This shows that, despite some improvements, the poorest remain disproportionately burdened compared to other groups.

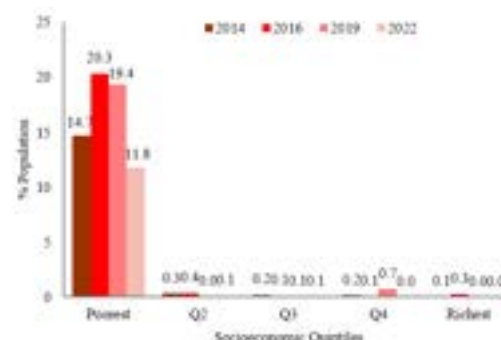


Figure 3: Population with OOP Exceeding 40% of CTP, HIES 2014-2022

Figure 5 illustrates the distribution of households by risk of impoverishment due to OOP health expenditures from 2014 to 2022. The proportion of households that were further impoverished due to healthcare costs decreased, while the percentage of households that were impoverished remained low, ranging from 0.1% to 0.4%. The proportion of households at risk of impoverishment declined substantially from 29.0% in 2014 to 5.1% in 2022. Over the same period, the proportion of households not at risk of impoverishment steadily increased from 65.5% to 90.5%, indicating a marked improvement in financial protection. The percentage of households incurring no OOP payments remained relatively stable, fluctuating between 3.0% and 3.8%, with a slight decrease to 2.4% in 2022.

DISCUSSION

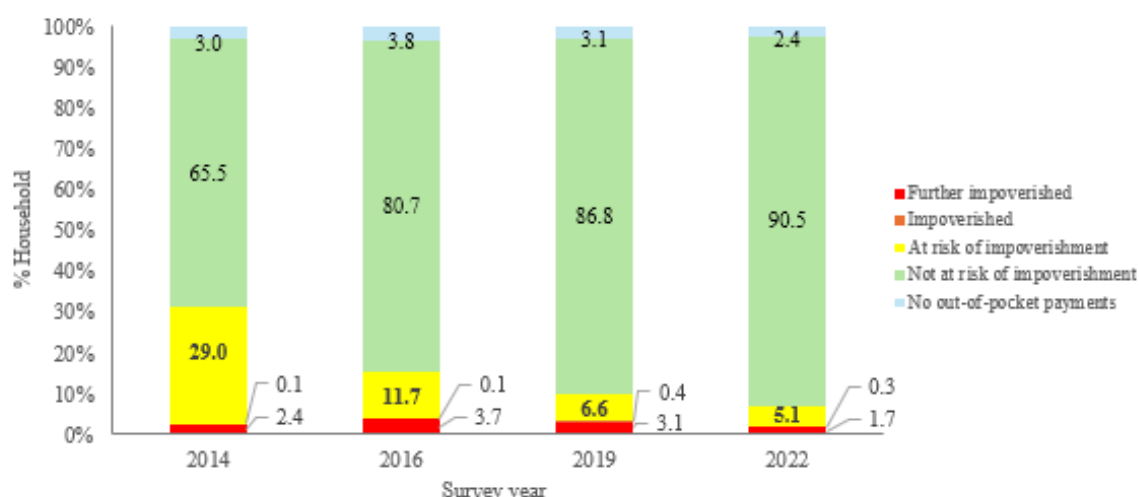
The findings from this study describe the patterns of healthcare utilisation in Sabah shifting over the years towards the private sector for outpatient services (56.9% in 1996 to 50.4% in 2023), whilst inpatient services

Table 3: Monthly Household Expenditure, Subsistence Costs, and Capacity-to-Pay, HIES 2014-2022

Expenditure Type	HIES 2014 (MYR)		HIES 2016 (MYR)		HIES 2019 (MYR)		HIES 2022 (MYR)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Overall expenditure	1934.82	1891.53 - 1978.11	2123.62	2053.84 - 2193.39	2275.66	2228.72 - 2322.60	2778.32	2715.57 - 2841.06
Subsistence expenditure	647.14	636.69 - 657.58	704.44	692.07 - 716.80	720.77	708.63 - 732.91	844.12	831.73 - 856.51
Capacity-to-pay	1287.68	1245.08 - 1330.29	1419.18	1351.92 - 1486.44	1554.89	1509.96 - 1599.82	1934.19	1873.10 - 1995.28
Out-of-pocket health expenditure	23.29	21.42 - 25.16	29.58	22.08 - 37.07	39.37	37.19 - 41.55	71.65	68.47 - 74.82

Notes:

1. Overall expenditure, subsistence expenditure, and capacity-to-pay are adjusted for household size and composition.
2. Overall expenditure figures are adjusted for imputed rent, which represents the economic value of the housing services homeowners use, equivalent to the rent they would pay if they rented their home. This adjustment provides a more accurate measure of the household's proper economic resources (Cylus et al., 2018)
3. MYR: Malaysian Ringgit; CI: Confidence Intervals



Note: The risk of impoverishment occurs when total spending, after out-of-pocket payments, exceeds 120% of the poverty line. The poverty line is a relative measure that reflects basic needs for food, housing, and utilities.

Figure 5: Breakdown of population by the risk of impoverishing health expenditure, HIES 2014-2022.

are predominantly still public-centric. This is consistent with the recent NHMS 2023 finding that showed 51.1% of outpatient visits were now in private facilities, whereas 74.7% of inpatient admissions were in public hospitals (Ministry of Health Malaysia, 2024). This shift in outpatient visits is potentially driven by perceptions of better service quality and shorter waiting times in the private sector (Kamarohim et al., 2013; Rasiah et al., 2009). This apparent shift presents an opportunity to leverage public-private partnerships by curating well-structured partnerships that optimise the efficiency and perceived quality the private sector provides while maintaining affordability.

In Sabah, partly due to the state's unique geography, healthcare delivery can be especially challenging, as many rural and remote communities are spread across mountains, islands, and forested regions. Urban centres like Kota Kinabalu benefit from a more developed health infrastructure, which includes a robust range of private facilities. For rural populations, the public sector is often the only feasible option in hard-to-reach areas (Abd Samad et al., 2024; Naing et al., 2020). While outpatient care is shifting

nationally toward private providers, Sabah's rural population remains reliant on the public sector. The financial dimension adds another layer of complexity to healthcare access, as the burden of OOP payments, though declining over time, remains particularly concerning for low-income households. Sabah's rural poverty rate stands at 19.5%, starkly higher than the 5.5% in urban areas (Department of Statistics Malaysia, 2022). High poverty rates among these households may drive them to rely on public services, as they often prioritise basic needs over healthcare costs (Department of Statistics Malaysia, 2022; Goroh et al., 2020; UN Human Rights, 2019).

However, systemic limitations in the public sector, such as understaffing, long waiting times, and limited resources, may push patients to seek private care despite the higher costs. (Abd Samad et al., 2024; Atun et al., 2016). According to NHMS 2019, outpatient OOP spending ranged from MYR 18 to MYR 508 over two weeks, while inpatient care costs ranged from MYR 404 to MYR 1,526 a year (Ministry of Health Malaysia, 2019). These costs increase the risk of CHE and impoverishment, particularly among poorer households. Our findings on healthcare utilisation by

socioeconomic quintiles show that the private sector has consistently been pro-rich across survey years, while public sector use, which was pro-poor in the 1990s, has been shifting dynamically towards a more even distribution across income groups in the recent NHMS 2023 cycle. These patterns demonstrate that the richer population remains the primary driver of private-sector use.

In contrast, the public sector has been moving away from a pro-poor safety net to a more universal provider over the years, consistent with previous analyses of NHMS data (Abu Bakar et al., 2019). In India, a similar shift was observed with the introduction of health policies to benefit people with low incomes, as the public sector became progressively less pro-rich. At the same time, private-sector services remained dominated by the rich (Selvaraj et al., 2021).

Indirect costs, such as transportation costs, are an essential challenge to healthcare access for lower-income households (Syed et al., 2013). This is amplified amongst those requiring regular follow-ups, such as those with dialysis, cancer, or mental health conditions (Lee et al., 2024). These expenses often result in forgone care, perpetuating cycles of poor health and financial strain ('Allocate More Resources for Mental Health Care in Sabah', 2023; Ansiung, 2024; Leong et al., 2007; Shoesmith & Pang, 2016). Additionally, Sabah's large migrant population (around 24%) also faces low financial protection (Department of Statistics Malaysia, 2024). Barriers related to legal status and limited insurance make this group especially vulnerable, highlighting the need for inclusive approaches to basic healthcare (Lasimbang et al., 2016).

Government programmes such as the Bantuan Prihatin Rakyat (BPR) and the Economic Stimulus Package have helped reduce OOP spending for people experiencing poverty (Ministry of Economy, 2023; Ministry of Finance, 2021). However, policies must go beyond temporary financial aid to strengthen long-term financial protection by expanding health coverage and improving insurance

options. This is especially critical in rural areas of Sabah, where the physical and systemic barriers are especially intensified. Focused action, such as expanding healthcare facilities in rural areas, improving access to primary and specialist care, partnering with non-governmental organisations, and retaining trained healthcare workers in underserved areas, is critical and can be implemented. Established services such as the Flying Doctor Service and mobile health teams have addressed some geographic barriers, but newer approaches such as telemedicine and mobile clinics should be considered as a practical way to scale up to reach geographically isolated populations (Falcon, 2019; Manual et al., 2024; Naserrudin et al., 2023; Thangiah et al., 2020). By addressing inequities stemming from poverty, geography, or migrant status, a more inclusive and equitable healthcare system in Sabah can be achieved, ensuring that all experience universal health coverage.

Limitations and future research directions

This study offers valuable insights into healthcare use and financial strain among households in Sabah. However, it has some limitations. Given that the NHMS data were self-reported, they are subject to recall bias. Additionally, using healthcare utilisation as a proxy for access may not accurately reflect actual healthcare needs, as low utilisation among the poorer population could indicate unmet needs rather than improved health status. Future research should explore complementary measures of health demand and unmet healthcare needs to strengthen these findings.

Furthermore, qualitative research would yield insights into patient narratives and lived experiences, particularly among underserved groups such as rural and migrant communities. Research is also needed to assess how current government programmes affect access to care and whether new policies are helping to reduce healthcare gaps. More work is required on forgone care, especially in rural areas where distance and cost limit

access. Understanding why people skip or delay care will help guide better solutions. It is also essential to study how expanded financial protection, including universal health coverage, can lower the risk of catastrophic spending in Sabah. This evidence will be valuable for shaping future policies.

CONCLUSION

Rising gaps in healthcare access and financial hardship in Sabah highlight the need for stronger, targeted policies to support health equity. Government efforts have improved access and reduced poverty for many, but challenges remain. Rural communities, low-income families, and migrants continue to face serious barriers to care. Tangible measures, such as expanding primary care services and leveraging partnerships with the private sector or non-governmental organisations, could help improve healthcare utilisation and reduce financial hardship.

CONFLICT OF INTEREST

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest. Most of the authors are affiliated with the Ministry of Health, Malaysia, and the study was conducted in accordance with institutional policies and guidelines.

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ORIGINAL ARTICLE

***TP53* Downregulation in Non-melanoma Skin Cancer Cells Treated with *Citrus limon* (Cl) Essential Oil**

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ABSTRACT

Citrus limon essential oil (CLEO) is rich in bioactive compounds, exhibit various therapeutic properties, including anticancer potential. Non-melanoma skin cancers, such as squamous cell carcinoma, are commonly associated with *TP53* mutations, leading to uncontrolled cell proliferation. This study investigates the cytotoxic effects of CLEO on normal human foreskin fibroblast cells (HFF1) and human squamous carcinoma cells (A431) by analysing morphological changes, p53 protein secretion, and *TP53* gene expression. HFF1 and A431 cells were treated with CLEO at concentrations of 125, 250, and 500 µg/mL for 24 hours. Morphological changes were observed using an inverted light microscope, while p53 protein secretion was analysed via Western blot. *TP53* gene expression was assessed using quantitative real-time PCR. Mild structural changes were observed in HFF1 cells at higher CLEO concentrations (250 and 500 µg/mL), whereas A431 cells exhibited significant membrane blebbing and detachment at all concentrations (125, 250, and 500 µg/mL). p53 protein secretion in the culture media increased in HFF1 cells following CLEO treatment, while A431 cells exhibited a dose-dependent reduction in p53 secretion. Additionally, *TP53* gene expression was notably downregulated in A431 cells at 125 and 500 µg/mL CLEO concentrations, suggesting the presence of alternative cytotoxic mechanisms. CLEO shows stronger cytotoxicity against A431 squamous carcinoma cells than against normal

HFF1 fibroblasts, suggesting therapeutic potential. The modulation of p53 protein secretion and *TP53* gene expression suggests that p53 operates through both dependent and independent mechanisms. Further studies, including in vivo and clinical investigations, are needed before its application in cancer therapy can be considered.

INTRODUCTION

Citrus limon (CL), also known as lemon, belongs to the genus *Citrus*, a part of the Rutaceae family. It is widely used in the food, cosmetic and cleaning products industries. The fruits are the primary raw material used to extract juice and essential oil (EO). While CL juice is rich in flavonoids, phenolic acids and vitamins, CL essential oil (CLEO) contains monoterpenoids, furanocoumarins and polymethoxylated flavones. Limonene is the most dominant monoterpene in CLEO (Klimek-szczykutowicz et al., 2020). It exhibits numerous health benefits due to its bioactive properties. It has been shown to have cytotoxic, antioxidant, antibacterial, antifungal, neuroprotective and anti-inflammatory activities (Dosoky & Setzer, 2018b, 2018a). Hence, CLEO is preferred in pharmaceutical contexts due to its efficacy in various therapeutic applications.

Non-melanoma skin cancer (NMSC) is the most common form of skin cancer. It primarily includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), both originating from the epidermal layer of the skin (Hedberg et al., 2022). Despite a lower metastatic potential than melanoma, NMSC can cause significant local tissue damage if left untreated. Like other cancers, NMSC arises due to genetic mutations and environmental factors that disrupt normal cellular processes, including cell division, differentiation, and apoptosis. Commonly disrupted regulatory genes in cancers include tumour suppressor genes like *TP53*, proto-oncogenes such as *RAS*, and DNA repair genes, for example, *BRCA1* and *BRCA2* (Sinkala, 2022). Among these, the *TP53* gene plays a pivotal role as a tumour suppressor

by regulating the cell cycle, inducing apoptosis, and maintaining genomic stability (Zhu et al., 2020). The *TP53* gene encodes the p53 protein, a tumour suppressor. One of the key functions of p53 protein is detecting DNA damage, halting the cell cycle, initiating DNA repair and triggering apoptosis of extensively damaged cells which are beyond repair (Benjamin & Ananthaswamy, 2007; Marei et al., 2021; Page et al., 2016). On the other hand, these protective roles are impaired in mutated or inactivated p53 proteins. It is important to note that *TP53* are very sensitive to ultraviolet (UV), and mutated *TP53* is a common finding in NMSC (Benjamin & Ananthaswamy, 2007; Paulo et al., 2019). In this circumstance, the skin cells can no longer repair the defective DNA or undergo apoptosis; instead, they continue the cell cycle and proliferate, resulting in cancer (Benjamin & Ananthaswamy, 2007).

Currently, there are various treatments offered for those diagnosed with NMSC, including surgical excision, chemotherapy, radiotherapy and immunotherapy. Nevertheless, current therapies have their own limitations and undesirable effects, such as anaemia, infections, fatigue and others (Sol et al., 2024). Therefore, natural remedies have become a point of interest for researchers seeking to develop treatments for skin cancer. Exposure to EO may affect the activity and expression of p53, potentially reducing tumour cell proliferation and promoting apoptosis, making it an important target for cancer treatment. A study showed that CLEO had cytotoxic effects on human skin, gastric, and brain cancer cells, indicating its anti-proliferative activity (Manjunath & Mahurkar, 2021). Tea tree EO used in previous studies has also been shown to successfully induce apoptosis in human melanoma and squamous cell carcinoma cells by upregulating p53 gene expression (Ramadan et al., 2019). Although direct studies on the effects of CLEO on p53 expression in NMSC are limited, the general anti-cancer mechanisms of citrus EO suggest a possible interaction with pathways involving p53. However, to date, no commercial drugs

based on CLEO have been explicitly approved for the treatment of skin cancer.

The objective of this study is to evaluate the cytotoxic effects of CLEO in NMSC. Specifically, the study seeks to evaluate the morphological changes, p53 protein expression and secretion, and *TP53* gene expression in NMSC treated with CLEO. The findings of this study would contribute to understanding the anticancer effects of CLEO in normal and cancerous skin cells, thereby exploring its potential anticancer role in skin cancer.

MATERIALS AND METHODS

Materials

Reagents and chemicals used in this study were procured from Sigma-Aldrich (St. Louis, MO, United States).

Cell Culture

Human foreskin fibroblast cells (HFF1) and human epidermoid squamous carcinoma cells (A431) were acquired from Shanghai iCell Biotechnology Co., Ltd. These cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Biosera, France) with 10% fetal bovine serum (FBS) (Biosera, France) and 100 IU/mL penicillin-streptomycin (Thermo-Fisher Scientific, USA) in a 75 cm² culture flask. The cells were grown in a humidified incubator at 37°C and 5% CO₂. Once they were 80-90% confluent, the cells were subcultured in new flasks following the standard cell culture protocols (Anuar et al., 2024).

Cell morphology study and cell harvesting

The HFF1 and A431 cells were seeded at a density of 3.0×10^5 cells per well in 6-well plates. The cells were then incubated under the conditions described earlier. After 72 hours of incubation, the cells were treated with CLEO dissolved in dimethyl sulfoxide (DMSO) for 24 hours. The cells were treated with 125, 250, and 500 µg/mL CLEO, with each treatment performed in triplicate (three wells per group). The final DMSO concentration was maintained

at 0.1% across all treatment groups. Cells treated with 0.1% DMSO (vehicle-treated) served as the negative control. To prepare the CLEO treatment, CLEO was first mixed with DMSO, and the mixture was vortexed until homogenised. A single batch of CLEO was used throughout the study to ensure reproducibility. The 24-hour treatment period is chosen because it provides sufficient time to observe the initial apoptotic response in many cell lines. It was reported that the increase in caspase-3 and cytochrome c levels in ovarian cancer cells, indicative of early apoptotic events, was evident within 24 hours of treatment with resveratrol and nutlin-3 (Marimuthu et al., 2011). Similarly, the cytotoxic effects of dieckol on prostate cancer cells were manifested within 24 hours of treatment, as shown by reactive oxidative species generation and increased apoptotic signals (Karupaiya et al., 2024).

Next, the cells' morphological changes were qualitatively assessed. Images were captured at 10- to 20-times magnification using an inverted light microscope (Olympus, Japan). Morphological assessment was based on established hallmarks of apoptosis. Apoptotic HFF1 cells were characterised by observable cell rounding compared to their original elongated, spindle-like shape, detachment and a partial loss of cell clustering. On the other hand, apoptotic A431 cells exhibited loss of their original polygonal shape, detachment, and reduced clustering.

After imaging, adherent cells were harvested using TRIzol reagent (Thermo Scientific, USA) and mechanical scraping (Biosera, France). Lastly, the cell lysates were stored at -20°C for subsequent protein and gene expression analyses, and the culture media were preserved at -20°C for protein secretion studies.

Total RNA and protein expression extraction from cell lysate

Firstly, total RNA was extracted from the cell lysates in TRIzol reagent (Thermo Scientific, USA) using the innuPREP RNA Mini Kit (Analytik

Jena) according to the manufacturer's instructions. Then, the extracted RNA was eluted in 30 µl of elution buffer and stored it at -80°C. Protein was isolated from the second filtrate obtained during the RNA extraction process using a cold acetone precipitation method. Lastly, the resulting protein pellets were dissolved in 30 µl of RIPA extraction and lysis buffer, and stored at -20°C for further analysis.

Protein extraction from conditioned media

The collected culture media were mixed with four volumes of 100% cold acetone and incubated at -20°C for 1 hour. Next, the mixture was centrifuged at 13,000 g in an ultracentrifuge (Beckman Coulter Life Sciences, USA) according to the protocol (Mohd Radzuan, 2020). After centrifugation, the resulting protein pellets were air-dried. Then, the pellets were resuspended in 200 µl of RIPA extraction and lysis buffer (Thermo Scientific, USA). The resuspended protein was stored at -20°C for further analysis.

Western blot

Cytosolic protein expression was analysed separately from protein in the media for protein secretion assays. A431 cells treated with 125 µg/mL cisplatin served as the positive control group. The cytosolic and secreted protein extract concentrations were quantified using a Protein Assay BCA Kit (Nacalai Tesque, Japan). For analysis, 50 µg of denatured protein samples were loaded in 2x Laemmli (BioRad, USA) onto a 10% acrylamide gel (BioRad, USA) along with a protein molecular weight marker (BioRad, USA) in the first well. Normalisation to a housekeeping protein was not performed, as conventional intracellular loading controls are absent from the secretome under non-lytic conditions. Electrophoresis was conducted at 100V for 10 minutes, followed by 120V for 1 hour.

After electrophoresis, the protein band on the gel was transferred to a PVDF membrane using the Trans-Blot Turbo Kit (BioRad, USA) at 13V for 20 minutes. Subsequently, the

membrane was blocked with 1% bovine serum albumin (BSA) at room temperature for 1 hour. For the protein expression assay, the membrane was cut between 42 and 53 kDa, corresponding to the protein molecular weight marker. Next, the membranes were incubated overnight at 4°C with p53 antibody (sc-263, Santa Cruz Biotechnology, USA) and *ACTB* antibody (C4, Santa Cruz Biotechnology, USA) at a 1:1000 dilution. The following day, the membranes were incubated with a secondary antibody (m-IgG2a BP-HRP: sc-542731, Santa Cruz Biotechnology, USA) at a 1:25 dilution at room temperature for 1 hour. Finally, the protein bands were detected using the Chemi-Lumi One Series for HRP (Nacalai Tesque, Japan). The signals were captured and quantified using the ChemiDoc Imaging System Machine and ChemiDoc XRS software (BioRad, USA).

cDNA conversion

The total RNA concentration for each sample was measured using a NanoDrop 1000 Spectrophotometer (Thermo Scientific, USA). Then, one µg of RNA was used to synthesise 20 µl of cDNA with the SensiFAST™ cDNA Synthesis Kit (BioLine, UK). Finally, the resulting cDNA was stored at -20°C until further analysis.

Gene expression study

First, gene expression analysis was performed using predesigned primers and probes for the *TP53* and *ACTB* genes (IDT DNA, USA). The primer sequences used were as follows: *ACTB*-F (ACAGAGCTCGCCTTTG), *ACTB*-R (CCTTGACATGCCGGAG), *ACTB* probe (/56-FAM/TCATCCATG/ZEN/GTGAGCTGGCGG/3IABkFQ/); *TP53*-F (CAAGCAGTCACAGCACATGA), *TP53*-R (AATACTCCACACGCAAATTTCC), and *TP53* probe (56-FAM/CCTCCTCAG/ZEN/CATCTTATCCGAGTGGA/3IABkFQ/).

Next, a 10 µL PCR reaction mixture was prepared by mixing 20x primers and probes, PrimeTime™ Gene Expression Master Mix 2x (IDT DNA, USA), cDNA diluted 1:10, and RNase-free water. Each sample was run in

duplicates. Amplification was carried out using the CFX96 Touch Real-Time PCR Detection System (BioRad, USA) under the following conditions: polymerase activation at 95°C for 3 minutes, denaturation at 95°C for 15 seconds, and annealing/extension at 58°C for 1 minute, repeated for 50 cycles. Data from two biological replicates are presented as mean ± SEM.

Statistical analyses

The CFX Manager™ software (Bio-Rad, USA) was used to calculate relative gene expression (fold-change) in gene expression ($\Delta\Delta C_q$). For this analysis, the fold-change data from three independent biological replicates (each with technical duplicates) were analysed using a one-way ANOVA followed by Tukey’s post-hoc test (comparing all treatments to the vehicle control). A p-value < 0.05 was considered significant.

RESULTS

Effect of CLEO on Cell Morphology

In the morphologic study, untreated and DMSO-treated HFF1 cells exhibited typical fibroblast-like morphology, with elongated spindles and intact cellular structures (Figure 1, A-B). However, treatment with CLEO at concentrations of 125 µg/mL and 250 µg/mL for 24 hours induced observable morphological changes (Figure 1, C-E). At these concentrations, some cells showed slight rounding and reduced adherence. Despite these changes, the majority of cells retained their overall structure, and the alterations were less pronounced compared to those observed in cancerous A431 cells.

In contrast, A431 cells showed noticeable changes following CLEO treatment. The untreated control and DMSO-treated

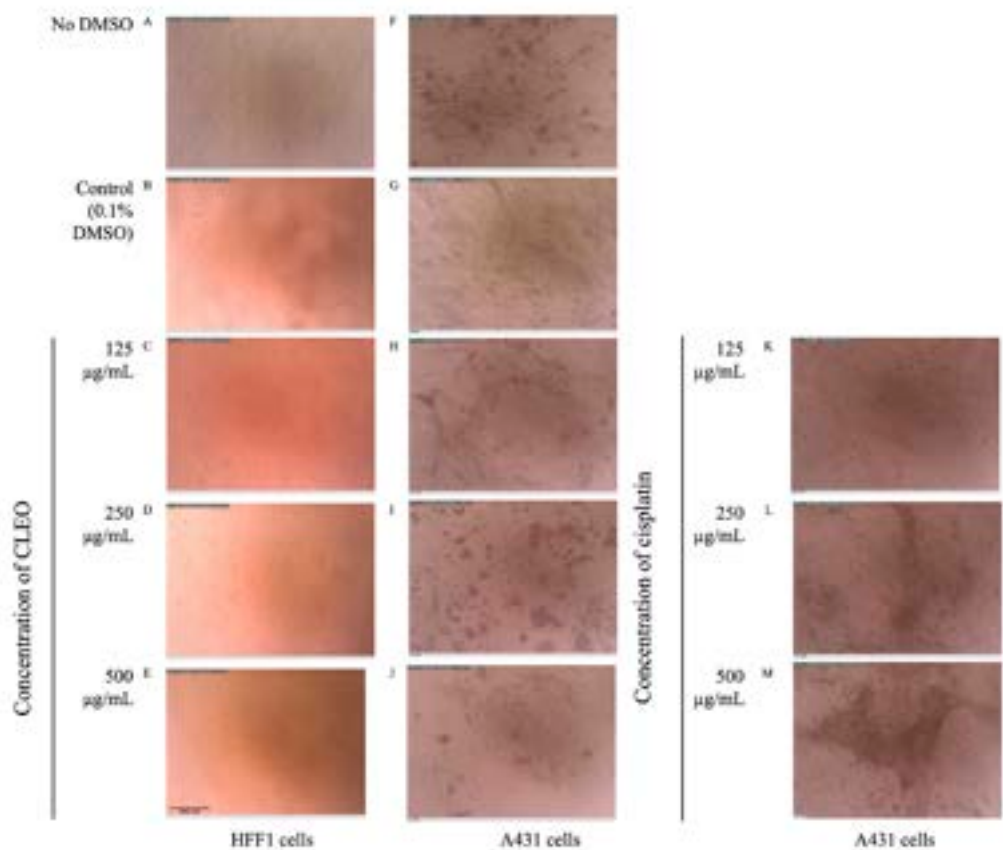


Figure 1: The overall morphological impact of CLEO treatment on cell density and confluence at a population level in HFF1 cells (A-E) and A431 cells (F-J) after 24 h of treatment with CLEO, and cisplatin (K-M). Cells were observed under 20x magnification. CLEO = Citrus lemon essential oil. Scale bar: 500 µm (based on standard 20x field of view).

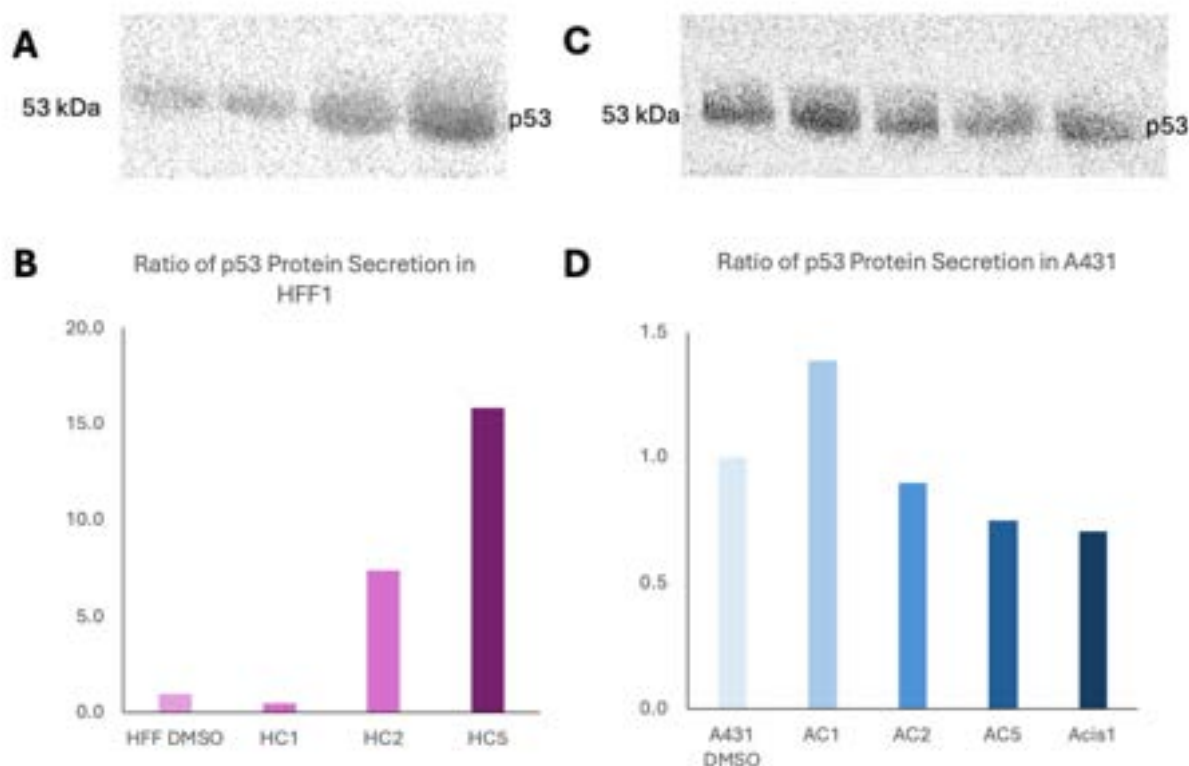


Figure 2: Analysis of (secreted) p53 protein levels in cell culture media. A) Western blot image of p53 protein secretion in HFF1 cells of different treatments (vehicle (0.1% DMSO) as control, 125 µg/mL CLEO, 250 µg/mL CLEO, and 500 µg/mL CLEO) and B) its densitometric ratio compared to control (vehicle-treated), normalised to equal volume loading. C) Western blot image of p53 protein secretion in A431 cells of different treatments (vehicle (0.1% DMSO) as control, 125 µg/mL CLEO, 250 µg/mL CLEO, 500 µg/mL CLEO and 125 µg/mL cisplatin) and D) its densitometric ratio compared to control (vehicle-treated), normalised to equal volume loading. Equal volumes of concentrated conditioned media were loaded for all samples; normalisation to a housekeeping protein was not applicable for secretome analysis. Acis1 = A431 cells treated with 125 µg/mL cisplatin; A431DMSO = A431 cells treated with 0.1% DMSO; AC1 = A431 cells treated with 125 µg/mL CLEO; AC2 = A431 cells treated with 250 µg/mL CLEO; AC5 = A431 cells treated with 500 µg/mL CLEO; HFF1DMSO = HFF1 cells treated with 0.1% DMSO; HC1 = HFF1 cells treated with 125 µg/mL CLEO; HC2 = HFF1 cells treated with 250 µg/mL CLEO; HC5 = HFF1 cells treated with 500 µg/mL CLEO.

cells displayed typical epithelial morphology with high cell density and intact structures (Figure 1, F-G). However, treatment with CLEO and cisplatin at concentrations of 125, 250, and 500 µg/mL for 24 hours resulted in significant morphological alterations, including cell shrinkage, membrane blebbing, and detachment, particularly at higher concentrations (Figure 1, H-M).

Effect of CLEO on p53 Protein Expression and Secretion

Cytosolic protein concentrations for HFF1 and

A431 cells were below the detection threshold for reliable quantification. Western blot analysis for p53 protein secretion was performed. Due to sample availability constraints, this analysis was conducted on a single biological replicate per condition. The data are therefore presented as observed fold-changes and should be considered preliminary. HFF1 cells treated with 500 µg/mL CLEO had the highest secreted p53 (16-fold), followed by 250 µg/mL (7.5-fold), and 125 µg/mL (0.5-fold) (Figure 2, A-B).

Meanwhile, A431 cells treated with

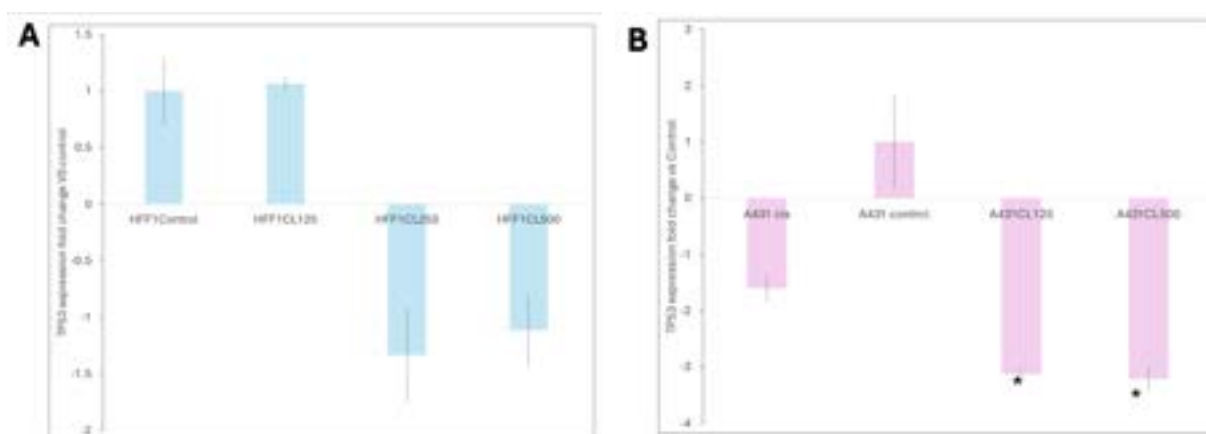


Figure 3: Relative *TP53* expression fold change vs control in A) HFF1 cells and B) A431 cells after treatment with CLEO at 125, 250 and 500 µg/mL for 24 h. * indicates significant $p < 0.05$ compared to control. A431 cis = A431 cells treated with 125 µg/mL cisplatin; A431Control = A431 cells treated with 0.1% DMSO; A431CL125 = A431 cells treated with 125 µg/mL CLEO; A431CL500 = A431 cells treated with 500 µg/mL CLEO; HFF1CL125 = HFF1 cells treated with 125 µg/mL CLEO; HFF1CL250 = HFF1 cells treated with 250 µg/mL CLEO; HFF1CL500 = HFF1 cells treated with 500 µg/mL CLEO; HFF1Control = HFF1 cells treated with 0.1% DMSO.

125 µg/mL CLEO showed the highest secretion of p53 protein, followed by control, 250 µg/mL CLEO, and 500 µg/mL CLEO (Figure 2, C-D). A431 cells treated with 125 µg/mL CLEO showed a 1.4-fold increase compared to the control (1-fold). For A431 cells treated with 250 µg/mL CLEO, the CLEO concentration was 0.5-fold, and for A431 cells treated with 500 µg/mL CLEO, the CLEO concentration was 0.75-fold compared to the control.

Effect of CLEO on *TP53* Gene Expression

There were no significant changes in *TP53* gene expression in CLEO-treated HFF1 cells compared to control (Figure 3A). In contrast, analysis of the *TP53* gene in A431 treated with 125 and 500 µg/mL of CLEO exhibited a significant downregulation compared to control ($p < 0.001$, respectively) (Figure 3B). RNA yield in A431 cells treated with 250 µg/mL of CLEO was below the detection threshold for reliable quantification of *TP53* gene expression.

DISCUSSION

Citrus limon is extensively utilised across diverse industries due to its versatile applications. CLEO, previously shown to have various health benefits, was studied in depth to assess its potential for treating cancers, including skin cancer. This study examined

cell morphology, p53 protein secretion, and *TP53* gene expression to better understand the cytotoxic mechanisms by which CLEO differentially affects normal and cancerous skin cells.

We observed that higher concentrations of CLEO caused mild morphological changes in normal HFF1 cells. The morphological changes are suggestive of early signs of cellular stress or cytotoxicity. In contrast, A431 cancer cells treated with CLEO showed significant morphological changes, including loss of the original polygonal shape, cell detachment, and reduced clustering. These observed changes were dose-dependent, with more pronounced changes at higher CLEO concentrations. The changes in the cellular morphology are highly likely due to the oxidative stress and disrupted membrane integrity, induced by the bioactive compounds present in CLEO, for example, limonene and citral (Gautam et al., 2014; Manjunath & Mahurkar, 2021). It is noteworthy that HFF1 cells showed greater resilience to CLEO than A431 cells. A plausible mechanism is that the further insult by the CLEO bioactive compounds on top of the defective or dysfunctional *TP53* genes in A431 cells triggers another mechanism leading to cell apoptosis or necrosis (Cordani et al., 2016; Ozaki & Nakagawara, 2011). Meanwhile,

normal HFF1 cells with functional *TP53* could repair DNA more effectively, leading to less cell death than A431 cancer cells. Hence, HFF1 demonstrated superior resistance to cellular stress. Nevertheless, it is important to optimise the CLEO dose to minimise adverse effects on normal cells. We acknowledged that, in future studies, a formal, blinded scoring system should be employed to assess morphological changes and reduce bias in assessment and improve objectivity.

The second objective of this study was to evaluate the effect of CLEO on p53 secretion and *TP53* expression in skin cancer cells. There was a contrasting trend in these parameters between the normal HFF1 and A431 cancer cell lines. In normal HFF1 cells, there was higher p53 protein secretion in cells treated with higher CLEO concentrations. One possible inference is that higher p53 secretion could be a stress response to cellular insults induced by the CLEO. The bioactive compounds in CLEO are foreign to cells, thereby triggering inflammatory responses and leading to apoptosis or senescence (Hafner et al., 2019; Yu et al., 2006). Surprisingly, the cancerous A431 cells had reduced p53 protein secretion at higher CLEO concentrations in contrast to HFF1 cells. As explained earlier, A431 cells are likely to have a defective *TP53* gene and a reduced capacity to cope with cellular stress. Further insult and oxidative damage from exposure to CLEO may cause a greater degree of damage, destabilisation, and defects in the p53 proteins (Møller et al., 2007). Another plausible explanation for this observation is that the p53 antibody used in the Western Blot in this study is designed to bind wild-type p53 rather than the defective p53 synthesised by A431 cells. At higher CLEO concentrations, there was further damage to the cells' DNA, leading to a lower amount of normal, functional p53 proteins being secreted. CLEO may induce oxidative damage and impair *TP53* gene expression and p53 protein stability via multiple mechanisms. For example, oxidation of cysteine and methionine residues can disrupt p53 structural integrity and zinc binding (Nomura et al., 2009;

Scotcher et al., 2013). Additionally, oxidative stress modulates MDM2 activity and promotes post-translational modifications such as phosphorylation and crotonylation, further influencing p53 degradation (Lee et al., 2008; Liao et al., 2020). Natural compounds may also directly interact with the p53-MDM2 pathway or induce reactive oxygen species, altering p53 stability in a context-dependent manner (Qin et al., 2018; Ramli et al., 2024).

Furthermore, downregulation of *TP53* gene expression was observed in CLEO-treated A431 cells at 125 and 500 µg/mL. However, a notable limitation in the dose-response analysis in this study was insufficient RNA yield from A431 cells treated with the intermediate CLEO concentration of 250 µg/mL, preventing reliable quantification. As a result, a complete assessment of the concentration-dependent effect was not possible. Despite this gap, the consistent downregulation at the two effective concentrations, 125 and 500 µg/mL, suggests a potential role for p53 in CLEO's mechanism of action in A431 cells. This effect appears to be cell-type-specific since it was not observed in HFF1 cells, which remained unaffected at all CLEO doses. This observation points to the selective targeting of CLEO to cancer cells, a desirable characteristic for a potential therapeutic agent. Overall, our findings were contrary to the expected upregulation as observed in previous studies. We proposed that CLEO could have induced other alternative p53-independent pathways that eventually lead to apoptosis of the cancer cells, as suggested by previous studies (Srivastava et al., 2012; Yoon et al., 2024). This warrants further studies to investigate the possible pathways affected by CLEO.

Our current qPCR data measure steady-state mRNA levels. At this level, it is not possible to distinguish whether the low mRNA level is due to transcriptional repression or to mRNA degradation. The observed downregulation of *TP53* mRNA and reduced extracellular p53 levels at higher CLEO concentrations in A431 cells certainly raises important mechanistic questions. This observed CLEO effect is unlikely

to be due solely to cytotoxicity, as it was also apparent at concentrations that had only modest effects on cell morphology. Moreover, it was not evident in the equally sensitive HFF1 cells. Possible reasons include CLEO-induced repression of *TP53* transcription or promotion of *TP53* mRNA degradation. Furthermore, CLEO could have induced post-translational modifications, destabilising the p53 protein, which eventually renders it a target for proteasomal degradation. To uncover the underlying mechanisms of CLEO's cell-type-specific effects on *TP53*/p53 dynamics, future studies should employ nuclear run-on assays, mRNA stability analyses, and analysis of p53 protein half-life. Although significant cell death at higher concentrations could be a major confounding factor, our data suggest that cell death is not the sole explanation for *TP53* downregulation in A431 cells treated with a higher CLEO concentration. The non-malignant HFF1 cells showed no significant change in *TP53* expression despite the highest concentrations. This suggests that the downregulation in A431 cells is not merely a general consequence of cell death but may involve a mechanism specific to the cancer cell line. Further studies to clarify the molecular pathways are warranted by analysing the apoptotic and autophagic markers and p53 mutational status in these CLEO-treated cells.

CONCLUSION

CLEO is cytotoxic towards in vitro skin cancer cells in a dose-dependent manner. While it activates p53 mechanisms in normal skin cells, CLEO activates alternative p53-independent cytotoxic mechanisms in skin cancer cells. Overall, this study suggests the potential of CLEO, a natural compound, as a complementary therapy for non-melanoma skin cancer, targeting cancer cells with minimal toxicity to normal cells. However, further investigations are needed to elucidate the precise molecular pathways involved in CLEO-induced cytotoxicity in skin cancer cells. This is essential for optimising the therapeutic

application of CLEO while minimising its impact on normal cells.

CONFLICT OF INTEREST

There was no conflict of interest.

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ORIGINAL ARTICLE

Bridging the Theory - Practice Divide in Cardiopulmonary Resuscitation: Knowledge and Readiness Among Trainees at ILKKM Kota Kinabalu

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ABSTRACT

Cardiopulmonary resuscitation (CPR) is a critical life-saving skill formally embedded within the curriculum of healthcare training programmes in Malaysia. At the Training Institute Ministry of Health Malaysia Kota Kinabalu (ILKKM KK), CPR instruction is a mandatory component of both the Diploma in Medical and Health Sciences (DMHS) and Diploma in Nursing (DPNS) programmes. Although theoretical content is consistently delivered, concerns remain regarding the extent to which trainees are practically ready to perform CPR in real-life emergencies. This study aimed to assess the levels of CPR knowledge and practical readiness among ILKKM KK trainees and to examine the relationship between these two domains. A cross-sectional study was conducted involving 120 trainees (stratified random sampling) who had completed the CPR module. Data collection was carried out using a structured questionnaire administered through Google Forms. The instrument assessed knowledge using multiple-choice questions and practical readiness through self-reported behavioural indicators on a three-point frequency scale. Descriptive statistics summarised participants' performance, while chi-square and independent t-tests were used to determine associations and group differences. The findings showed that 63 of 120 trainees (52.5%) demonstrated high levels of CPR knowledge ($M = 13.5$, $SD = 0.8$), while 42 of 120 trainees (35.0%) reported high readiness to perform the procedure ($M = 25.5$, $SD =$

3.2). A statistically significant association was identified between knowledge and readiness levels, $\chi^2(4, N = 120) = 27.06, p < 0.001$, Cramér's $V = 0.34$, indicating a moderate relationship. There were no statistically significant differences in CPR knowledge or readiness scores between DMHS and DPNS trainees. These results highlight a critical disconnect between theoretical knowledge and applied readiness, despite the mandatory inclusion of CPR in the academic syllabus. Strengthening CPR education through structured simulations, continuous reinforcement, and psychological preparedness may help ensure that trainees are not only knowledgeable but capable of responding confidently and competently in emergencies.

INTRODUCTION

Cardiopulmonary resuscitation (CPR) is a critical, time-sensitive intervention that significantly improves the chances of survival in individuals experiencing cardiac or respiratory arrest. Survival following out-of-hospital cardiac arrest (OHCA) depends strongly on early recognition and prompt, high-quality CPR (Panchal et al., 2020; Kleinman et al., 2015). In Malaysia, recent emergency medical services data from Sarawak, Penang and the Klang Valley showed that 38% of OHCA cases received bystander CPR, while only 4.76% survived to hospital admission (Sarah Shaikh Abdul Karim et al., 2025). These findings highlight continuing gaps in early community response and the importance of ensuring that future healthcare personnel are adequately prepared to respond to cardiac emergencies.

Within Malaysian health training programmes, cardiopulmonary resuscitation is incorporated as a core competency guided by national resuscitation training standards, including the Ministry of Health Malaysia Basic Life Support Training Manual (Ministry of Health Malaysia, 2023). Evidence from the Malaysian context has shown that structured CPR education can significantly improve knowledge and attitudes towards resuscitation

(Rahman et al., 2013). At the Training Institute Ministry of Health Malaysia Kota Kinabalu (ILKKM KK), CPR instruction is embedded in both the Diploma in Medical and Health Sciences (DMHS) and the Diploma in Nursing (DPNS) programmes. While DMHS trainees are introduced to CPR in the context of emergency medical response and prehospital care, DPNS students receive CPR instruction as part of broader nursing competencies within acute, chronic and emergency care modules. Despite this inclusion, retention of CPR knowledge and technical performance remains an important educational concern. Evidence from CPR retention studies supports the need for repeated practice and appropriately scheduled refresher training to sustain performance over time (Sand et al., 2021; Oermann et al., 2022). Similar gaps in knowledge, attitude and perceptions towards basic life support training have also been reported among university students in the Malaysian context (Fariduddin & Siau, 2021).

The gap between theoretical learning and practical readiness may also be influenced by psychological and behavioural factors. Stress, anxiety and self-efficacy can influence nursing students' performance during simulated CPR (Mauriz et al., 2021), while attitude, subjective norms and self-efficacy have been associated with nursing students' intention to perform bystander CPR (Wati et al., 2021). Simulation-based resuscitation education offers an important means of addressing these gaps. Studies among nursing students have demonstrated improvements in CPR knowledge, practical performance and self-confidence following simulation-based training (Demirtas et al., 2021), while simulation-based advanced life support education has also been associated with greater knowledge, performance and self-efficacy than lecture-based education alone (Kim et al., 2020). However, limited data exist on Malaysian health trainees, particularly regarding readiness after formal instruction. Comparative evidence across academic programmes also remains limited.

This study was conceptually informed by Bloom's Taxonomy, particularly its cognitive domain for interpreting CPR knowledge (Bloom, 1956), and Kirkpatrick's Four-Level Training Evaluation Model (Kirkpatrick, 1994). CPR knowledge represented the cognitive learning component, while self-reported readiness reflected perceived preparedness and willingness to translate learning into practice.

Within Kirkpatrick's framework, the study primarily assessed Level 2 learning, while readiness was interpreted as a potential precursor to Level 3 behavioural application rather than a direct measure of behaviour change. Integrating these frameworks offers a theoretically grounded approach for interpreting the relationship between knowledge and readiness and informs the need for instructional interventions that support deeper learning, skill retention, and confidence in real-time application.

This study aimed to evaluate CPR knowledge and practical readiness among Malaysian healthcare trainees, addressing a gap in national-level data on readiness outcomes and informing curricular improvements across allied health education. It further sought to explore the association between knowledge and readiness and to examine whether programme affiliation influences these competencies. The findings are intended to inform CPR education strategies that go beyond knowledge transmission to foster confident, real-time clinical performance.

MATERIALS AND METHODS

A cross-sectional study was conducted to evaluate CPR knowledge and practical readiness among trainees at ILKMM KK. Sample size was calculated using the Raosoft calculator for a finite population of 150 eligible trainees, with a 95% confidence level and 5% margin of error, yielding a minimum required sample of 109 (Raosoft, 2004). A total of 120 trainees were recruited to enhance statistical power. The study was carried out between January

and March 2024 and focused on two academic programmes in which CPR instruction is formally embedded: the Diploma in Medical and Health Sciences (DMHS) and the Diploma in Nursing (DPNS).

The study population comprised trainees from both programmes who had completed the CPR module as part of their coursework. Stratified random sampling was employed to ensure proportional representation across programmes and semesters. Trainees who had not yet received CPR instruction were excluded to maintain baseline uniformity in training exposure.

Data were collected using a structured, self-administered questionnaire distributed through Google Forms. The instrument comprised three sections: demographic information, theoretical CPR knowledge and readiness to perform CPR. The knowledge domain consisted of 15 multiple-choice questions developed with reference to the Basic Life Support Training Manual published by the Ministry of Health Malaysia (2023). Knowledge scores were categorised as high (≥ 12), moderate (8–11) and low (≤ 7) out of a maximum of 15 points. The readiness domain included 15 items measured using a three-point frequency scale scored as Never = 0, Sometimes = 1 and Always = 2, yielding a total score ranging from 0 to 30. Readiness scores were categorised as high (≥ 24), moderate (12–23) and low (≤ 11). These categories were used for descriptive interpretation of the study outcomes. All responses were anonymised at the point of collection and stored securely.

Data were analysed using IBM SPSS Statistics version 27. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were used to summarise participant characteristics and outcome variables. Internal consistency of the questionnaire was evaluated using Cronbach's alpha, yielding good reliability for the knowledge domain ($\alpha = 0.82$) and excellent reliability for the readiness domain ($\alpha = 0.88$).

The association between CPR knowledge and readiness levels was analysed

using the chi-square test of independence. Independent t-tests were used to compare knowledge and readiness scores between DMHS and DPNS trainees. Statistical significance was set at $p < .05$. The study received ethical approval from the Institutional Ethics Committee of ILKKM Kota Kinabalu. Informed consent was obtained from all participants prior to enrolment. Confidentiality and anonymity were strictly maintained throughout data collection and analysis.

RESULTS

A total of 120 trainees participated in the study, equally distributed between the Diploma in Medical and Health Sciences (DMHS) and Diploma in Nursing (DPNS) programmes. The gender distribution was balanced, with 60 male (50%) and 60 female (50%) participants. Most trainees ($n = 87$, 72.5%) were between 18 and 22 years old, and the majority had completed secondary education as their highest academic qualification ($n = 116$, 96.7%). Selected demographic characteristics are presented in Table 1.

CPR knowledge

In terms of CPR knowledge, 63 trainees (52.5%) demonstrated high knowledge ($M = 13.5$, $SD = 0.8$), 45 (37.5%) had moderate knowledge ($M = 8.0$, $SD = 1.2$), and 12 (10.0%) had low knowledge ($M = 3.5$, $SD = 1.5$) as shown in Figure 1. When disaggregated by programme, 33 of 60 DMHS trainees (55.0%) demonstrated high knowledge, compared to 30 of 60 DPNS trainees (50.0%). The mean knowledge score

was slightly higher among DMHS trainees ($M = 10.80$, $SD = 3.31$) than DPNS trainees ($M = 10.08$, $SD = 3.90$), although the difference was not statistically significant, $t(118) = 1.10$, $p = .274$, 95% CI $[-0.58, 2.03]$.

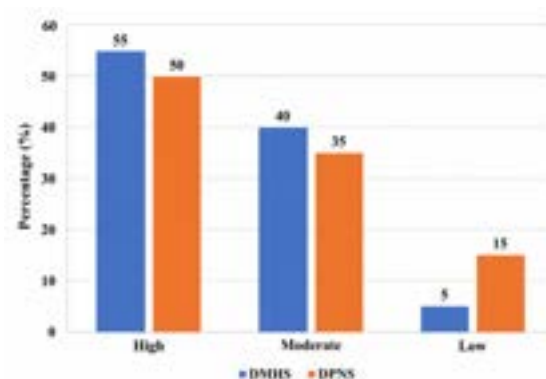


Figure 1: CPR knowledge level by programme.

CPR readiness

Regarding CPR readiness, 42 trainees (35.0%) reported high readiness ($M = 25.5$, $SD = 3.2$), 60 (50.0%) demonstrated moderate readiness ($M = 15.5$, $SD = 2.8$), and 18 (15.0%) reported low readiness ($M = 5.0$, $SD = 2.5$). High readiness was slightly more prevalent among DMHS trainees (40.0%) compared to DPNS trainees (30.0%). Mean readiness scores were slightly higher among DMHS trainees ($M = 17.93$, $SD = 7.73$) than DPNS trainees ($M = 16.93$, $SD = 7.30$), with no statistically significant difference, $t(118) = 0.73$, $p = .468$, 95% CI $[-1.72, 3.72]$. Detailed readiness results are shown in Table 2 and Figure 2. Differences in knowledge and readiness between DMHS and DPNS trainees are presented in Table 3.

Table 1: Demographic characteristics (N=120).

Variable	Category	Frequency (Percentage)
Gender	Male	60 (50.00%)
	Female	60 (50.00%)
Programme	DMHS	60 (50.00%)
	DPNS	60 (50.00%)
Highest Academic Qualification	Secondary Education	116 (96.70%)
	Tertiary Education (Diploma)	4 (3.30%)
	Tertiary Education (Degree)	0 (0.00%)

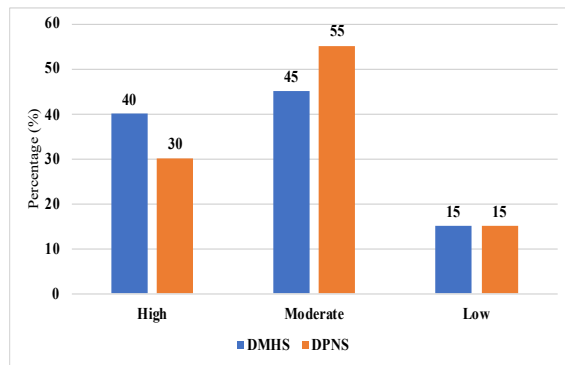


Figure 2: CPR readiness level by programme.

Association between knowledge and readiness

A chi-square test of independence revealed a statistically significant association between CPR knowledge and readiness levels, $\chi^2(4, N = 120) = 27.06$, $p < .001$, indicating a moderate effect size (Cramér's $V = .34$). Trainees with higher knowledge levels were more likely to report high readiness. The association between CPR knowledge and readiness levels is presented in Table 4.

DISCUSSION

Cardiopulmonary resuscitation (CPR) remains a cornerstone intervention in the management of cardiac arrest, with its timely administration pivotal in improving survival outcomes (Merchant et al., 2020). This study evaluated the level of CPR knowledge and practical readiness among trainees enrolled in the Diploma in Medical and Health Sciences (DMHS) and Diploma in Nursing (DPNS) programmes at the Training Institute Ministry of Health Malaysia Kota Kinabalu (ILKMM KK). The findings offer a holistic view of CPR preparedness among these future healthcare professionals, highlighting both competencies achieved and critical areas for pedagogical enhancement.

The assessment of CPR knowledge revealed that a majority of trainees demonstrated high levels of theoretical understanding, although a substantial proportion remained within the moderate and low knowledge categories. This finding suggests that formal curricular exposure alone may not produce uniform levels of knowledge

Table 2: Distribution of CPR knowledge and readiness levels by programme (N = 120).

Variable	DMHS	DPNS	Total
Knowledge Level			
High Knowledge, n (%)	33 (55.0%)	30 (50.0%)	63 (52.5%)
Moderate Knowledge, n (%)	24 (40.0%)	21 (35.0%)	45 (37.5%)
Low Knowledge, n (%)	3 (5.0%)	9 (15.0%)	12 (10.0%)
Readiness Level			
High Readiness, n (%)	24 (40.0%)	18 (30.0%)	42 (35.0%)
Moderate Readiness, n (%)	27 (45.0%)	33 (55.0%)	60 (50.0%)
Low Readiness, n (%)	9 (15.0%)	9 (15.0%)	18 (15.0%)

Table 3: Comparison of CPR knowledge and readiness scores between DMHS and DPNS trainees (N = 120).

	DMHS Mean $\pm$ SD	DPNS Mean $\pm$ SD	Mean Difference	t(df)	p-value	95% CI
CPR Knowledge Score	10.80 $\pm$ 3.31	10.08 $\pm$ 3.90	0.73	1.10 (118)	.274	-0.58 to 2.03
CPR Readiness Score	17.93 $\pm$ 7.73	16.93 $\pm$ 7.30	1.00	0.73 (118)	.468	-1.72 to 3.72

Table 4: Association between CPR knowledge and readiness levels (N = 120).

Knowledge Level	Low Readiness	Moderate Readiness	High Readiness	Total	χ^2	p	Cramér's V
Low Knowledge	5	6	1	12	$\chi^2 (4, N=120) = 27.06$	< .001	0.34
Moderate Knowledge	6	32	7	45			
High Knowledge	7	22	34	63			
Total	18	60	42	120			

across trainees. Variability in CPR knowledge, attitude and practice has also been reported among healthcare professionals in Malaysia (Mughni, 2024). Similar concerns have been observed internationally. Mohammed et al. (2020), for example, reported adequate CPR knowledge among only 31.7% of junior doctors and 6.2% of medical students despite generally positive attitudes towards CPR training. Retention is another important consideration. Aqel and Ahmad (2014) found that although high-fidelity simulation improved CPR knowledge and skill acquisition and retention compared with traditional instruction, significant deterioration in both knowledge and skills was evident three months after training. These findings reinforce the importance of continued reinforcement rather than reliance on a single episode of CPR instruction.

Readiness to perform CPR, as captured in this study, extends beyond cognitive understanding to include willingness, perceived preparedness and confidence in responding to an emergency. A substantial proportion of trainees reported only moderate or low readiness despite relatively favourable knowledge levels, suggesting that knowledge alone may not translate directly into willingness to act. Evidence from nursing students supports this distinction. Wati et al. (2021) found that attitudes, subjective norms and self-efficacy were significantly associated with intention to perform bystander CPR. Similarly, Mao et al. (2021) reported that behavioural attitudes, subjective norms and perceived behavioural control were significant predictors of willingness to perform bystander CPR among university students. These findings support the view that readiness is influenced

by cognitive, psychological and behavioural factors rather than knowledge alone.

Several factors may contribute to the observed readiness gap. Limited opportunities for repeated practice, insufficient exposure to realistic resuscitation scenarios and psychological responses during emergencies may affect a trainee's ability to translate knowledge into action. Mauriz et al. (2021) demonstrated that stress, anxiety and socio-emotional factors are relevant to nursing students' clinical performance during simulated CPR. Simulation may help address some of these challenges. Demirtas et al. (2021) reported improvements in CPR knowledge, practical skills and self-confidence following simulation-based CPR training, while Takhdad et al. (2022) found higher CPR knowledge retention and self-efficacy following high-fidelity simulation compared with case-based learning. Repeated simulation experience has also been associated with improved perceived self-efficacy among nursing students (Al Gharibi et al., 2021). Collectively, these findings support educational strategies that combine cognitive learning with repeated experiential practice.

The significant association observed between knowledge and readiness in this study supports the interrelated nature of cognitive and behavioural components of CPR education. Trainees with higher knowledge levels were more likely to report greater readiness, although the moderate effect size (Cramér's $V = .34$) indicates that knowledge does not fully explain readiness. Self-efficacy and behavioural intention may contribute to this relationship, as demonstrated among nursing students by Wati et al. (2021). Training frequency and instructional format may also

influence longer-term competence. Oermann et al. (2022) demonstrated that the spacing and scheduling of CPR practice influenced subsequent skill retention, while Takhdar et al. (2022) showed that high-fidelity simulation supported both knowledge retention and self-efficacy. These findings suggest that the relationship between knowledge and readiness should be interpreted within the wider context of training exposure, psychological preparedness and opportunities for repeated practice.

The comparative analysis between DMHS and DPNS trainees revealed no statistically significant differences in CPR knowledge or readiness scores. Although minor variations were observed between the programmes, programme affiliation was not associated with meaningful differences in these outcomes. This may reflect comparable exposure to core CPR content across both programmes. Nevertheless, contextual factors such as instructional approaches, opportunities for skills practice and clinical exposure may warrant further investigation. Examining these factors in future cohorts could help determine whether differences in educational experience influence subsequent CPR competence and readiness.

The findings have important implications for CPR education. Regular reinforcement should form part of efforts to sustain CPR competence, as skill retention is influenced by both the frequency and spacing of training (Sand et al., 2021; Oermann et al., 2022). Simulation-based learning should therefore be considered a longitudinal educational strategy rather than a one-time activity. High-fidelity simulation has demonstrated benefits for CPR knowledge and skill acquisition and retention (Aqel & Ahmad, 2014), while simulation-based advanced life support education has improved nursing students' knowledge, performance and self-efficacy (Kim et al., 2020). More recent evidence also indicates that both mannequin-based and virtual simulation approaches can improve nursing students' CPR learning outcomes (Abbasi et al., 2024).

Repeated simulation may further support self-efficacy and provide opportunities for learners to identify and correct performance gaps (Al Gharibi et al., 2021). Tucker et al. (2023) similarly found improved resuscitation self-efficacy following simulation, although rapid cycle deliberate practice did not provide a significant additional advantage over standard simulation. Psychological preparedness should therefore be addressed alongside technical competence, particularly because stress, anxiety and self-efficacy can influence performance during simulated CPR (Mauriz et al., 2021).

These findings carry significant implications for health education policy, particularly regarding the standardisation of CPR curricula and the reinforcement of instructor training strategies across academic programmes. The variability in CPR knowledge and readiness levels, even within structured institutional syllabi, supports the need for formal integration of recurring CPR instruction throughout the academic cycle. National guidelines should prioritise longitudinal simulation-based assessments rather than limiting CPR evaluation to a single module. Institutions such as the Ministry of Health and the Malaysian Qualifications Agency may consider endorsing policies that embed repeated exposure to high-fidelity simulations and practical assessments throughout healthcare training. Additionally, CPR instructor training should extend beyond technical skills to include pedagogical strategies that strengthen learners' confidence, reduce psychological barriers, and enhance real-time decision-making. Competency frameworks for educators may include modules on emotional preparedness, scenario-based debriefing, and cognitive-behavioural facilitation techniques. Institutionalising these enhancements will strengthen CPR education quality and support national objectives to improve early response rates and survival outcomes in cardiac emergencies.

Despite its strengths, this study is not without limitations. The cross-sectional design

restricts causal inference, and the reliance on self-reported readiness introduces potential for social desirability bias. Future research should incorporate objective skill assessments, behavioural simulations, and longitudinal follow-up to evaluate the evolution of CPR competence over time. Triangulating quantitative data with qualitative insights from students and instructors may also provide a more nuanced understanding of what facilitates or impedes CPR readiness in the academic environment.

In conclusion, this study contributes critical insight into the interdependence of CPR knowledge and readiness among healthcare trainees in Malaysia. While theoretical instruction appears effective in imparting foundational knowledge, readiness to act remains a multifactorial challenge that requires curricular innovation. Embedding refresher courses, simulation-based practice, and psychological readiness training into CPR education can help bridge the theory-practice divide. Preparing future healthcare professionals for real-time cardiac emergencies demands more than knowledge and requires confidence, competence and readiness to respond without hesitation.

CONCLUSION

The findings suggest a need to strengthen CPR curriculum guidelines through structured refresher training, simulation-based assessments, and reinforcement of readiness beyond theoretical instruction. Incorporating confidence-building strategies and repeated hands-on practice within national academic frameworks may improve trainee preparedness. Future curriculum revisions should prioritise practical readiness and consider standardising instructor development to ensure consistent delivery across institutions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. No financial or external support was received that

could have influenced the design, conduct, or reporting of this study. The research was conducted independently as part of academic work within the Training Institute Ministry of Health Malaysia Kota Kinabalu.

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ORIGINAL ARTICLE

Prevalence of Psychotropics Used and Occurrence of falls among older patients with Parkinson's disease

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ABSTRACT

Older patients diagnosed with Parkinson's disease (PD) often experience a range of both motor and non-motor symptoms, including psychiatric issues. Managing these patients effectively typically requires a combination of medications, which raises concerns about potential side effects, such as an increased risk of falls. This study aims to explore the prevalence of psychotropic medication use and the occurrence of falls among PD patients aged 65 years and older at a quaternary care center in Malaysia. This retrospective cohort study included all idiopathic PD patients aged 65 years and above who were under follow-up at the interdisciplinary geriatric unit in Hospital Kuala Lumpur from 1st January to 31st December 2023. A total of 42 patients were eligible in this study. We collected baseline demographic data, information on psychiatric conditions (e.g., duration, management, and types of psychotropic medications prescribed), and the incidence of falls during the study period. The median age of participants was 75 years (IQR 10), with slightly more males (52%). The mean duration of PD was 6 years (SD 5), and 50% of patients were in stages 1 to 3 of the Hoehn and Yahr scale. All participants had comorbidities and were on polypharmacy. Sixty-two percent were diagnosed with a psychiatric disorder, and 77% were prescribed psychotropic medications. The most common psychotropic medications were antidepressants (75%), followed by antipsychotics (15%), anxiolytics (5%), and



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hypnotics (5%). None had psychotropic polypharmacy. This study highlights the high prevalence of psychiatric disorders, psychotropic medication use, and fall incidents in this population. Regular medication reviews and fall assessments should be integral to the comprehensive geriatric evaluation for PD patients.

INTRODUCTION

Parkinson's disease (PD) is a progressive movement disorder of the nervous system. It causes nerve cells (neurons) in parts of the brain to weaken, become damaged, and die, leading to symptoms that include problems with movement, tremor, stiffness, impaired balance and non-motor symptoms that significantly impair quality of life (Tanner & Ostrem, 2024).

It is a neurological disorder that causes significant physical and mental complications (Tysnes & Storstein, 2017). Older individuals diagnosed with PD frequently experience a range of both motor and non-motor symptoms including psychiatric issues. Among the various non-motor symptoms, psychiatric disorders such as depression, anxiety, and hallucinations are common and often treated with psychotropic medications (Weintraub, 2020). Cognitive decline is another significant non-motor symptom in PD, with the development of Parkinson's disease dementia (PDD) being a concerning long-term outcome (Aarsland et al., 2017). As a result, the need for anti-dementia treatment is often required.

Effective management of these patients requires a combination of multiple medications. Pharmacological treatment with psychotropic drugs (i.e. antipsychotics, anxiolytics, hypnotics, and antidepressants) and anti-dementia medication is usually the standard intervention and provision of psychotherapy is scarce in this age group (Resnick et al., 2023). While these medications offer therapeutic benefits, their use in older individuals, particularly those with PD, raises concerns due to the potential for side effects,

including an increased risk of falls.

Falls are a significant concern in individuals with Parkinson's disease, as they can lead to severe complications such as fractures, disability, and even death. The use of psychotropic drugs, including antidepressants, antipsychotics, and benzodiazepines, has been implicated in exacerbating this risk, potentially by affecting motor control, cognitive function, and balance (Muench & Hamer, 2010). Despite the growing prevalence of both PD and psychotropic medication use, there remains limited comprehensive data on the relationship between psychotropic drug use and the occurrence of falls in this vulnerable population.

Studies in Malaysian aged-care facilities indicate that between 68% and 74% of older residents are prescribed at least one fall risk increasing drug (FRID) (Fujita et al., 2023), but there is a lack of data specifically focusing on psychotropic use among older PD patients. Given Malaysia's unique demographic profile, healthcare delivery system, and prescribing practices, local data are crucial to quantify the magnitude of this problem and guide safer pharmacotherapy and fall prevention strategies. Therefore, this study aims to determine the prevalence of psychotropic use and its association with falls among older patients with PD in Malaysia. By understanding these dynamics, we can better inform clinical decision-making and improve patient care strategies to minimize fall-related injuries and enhance the quality of life for individuals living with PD.

MATERIALS AND METHODS

The retrospective observational study was conducted at Hospital Kuala Lumpur, a 2,700-bed government-owned tertiary care hospital located in the capital city of Malaysia. The hospital's geriatric unit provided a list of all patients aged 65 years and older with a diagnosis of idiopathic PD, as determined by a geriatrician and documented using ICD-10 codes. These patients were under follow-up at

the interdisciplinary geriatric clinic between 1st January and 31st December 2023. Only patients who were actively followed up at the interdisciplinary geriatric unit during the study period were included. Inclusion criteria encompassed all individuals aged 65 years and above with a confirmed diagnosis of idiopathic PD within the specified timeframe. Patients were excluded if they were younger than 65 years, diagnosed outside the study period, had missing data, or were diagnosed with Parkinson-plus syndromes.

A total of 42 patients were eligible for this study during the specified period. As this was a retrospective observational study, all patients who met the inclusion criteria and were followed up at the interdisciplinary geriatric clinic in Hospital Kuala Lumpur during the study period were included. Therefore, a formal sample size calculation was not required. The sample represents the full population of eligible patients during the study period, helping to reduce selection bias. Although exploratory, the study offers meaningful insights based on real-world clinical data. Data was collected by a single researcher using an agreed data collection tool by investigators. Findings were presented as numbers and percentages for categorical data and either median with interquartile range (IQR) or mean with standard deviation (SD) based on the parametric distribution of the data using Kolmogorov-Smirnov test. Missing values will be regarded as missing, and analysis will be performed on available data. All analyses were performed using SPSS version 26.

In February 2025, the Malaysia Research Ethics Committee (MREC) of the Ministry of Health reviewed and approved the study under registration number NMRR ID-25-00738-9EG (IIR). Access to the data was restricted to the principal investigators, and the data were solely used for research purposes. The study adhered to the ethical guidelines outlined in the Malaysian Good Clinical Practice Guidelines and the Declaration of Helsinki.

RESULTS

Among the 42 patients, the median age was 75 years (IQR 10), with a slight male predominance (52%) and the majority being of Chinese ethnicity (59%). The mean duration of PD was 6 years (SD 5). Half of the patients were in stages 1 to 3 of the Hoehn and Yahr scale. All patients had multi-comorbidity (≥ 2 long-term health conditions) (Harrison et al., 2021) and were on polypharmacy (≥ 5 medications) (Masnoon et al., 2017) (Table 1).

Table 1: Demographic characteristics of the PD patients.

	Total (n = 42)
Age (Median, IQR) years	75 (10.0)
Gender (Count, %)	
Male	2.8 mg/L
Female	0.11 ng/mL
Race (Count, %)	
Malay	9 (21.4)
Chinese	25 (59.5)
Indian	8 (19.1)
Other	0 (0.0)
Multi-morbidity (Count, %) ^a	
Yes	42 (100.0)
No	0 (0.0)
Polypharmacy (Count, %) ^b	
Yes	42 (100.0)
No	0 (0.0)
Duration of PD (Mean, SD) years	6 (5.0)
PD Hoehn and Yahr Stage (Count, %)	
1	2 (4.8)
2	7 (16.7)
3	12 (28.5)
4	17 (40.5)
5	4 (9.5)
Diagnosed with psychiatric disorder (Under DSM-V) (Count, %)	
Yes	26 (61.9)
No	16 (38.1)
Diagnosed to have dementia (Count, %)	
Yes	19 (45.2)
No	23 (54.8)

^a Multi-morbidity: ≥ 2 long-term health conditions
^b Polypharmacy: ≥ 5 medications

Of the patients, 62% had been diagnosed with a psychiatric disorder, and 45% had dementia. A total of 77% were prescribed psychotropic medications, while 32% were on anti-dementia medications.

Antidepressants were the most commonly prescribed psychotropics (75%), followed by antipsychotics (15%), anxiolytics (5%), and hypnotics (5%). Notably, none of the patients were prescribed psychotropic polypharmacy (the use of two or more psychiatric medications in the same patient) (Kingsbury et al., 2001) (Table 2).

Table 2: PD patients with psychiatric disorders.

	Total (n = 26)
Duration of psychiatric disorders (Median, IQR) years	1 (2.0)
Management of psychiatric disorders (Count, %)	
Non-Pharmacological	6 (23.1)
Combination (Non-Pharmacological and Pharmacological)	20 (76.9)
Types of psychotropic medications used (Count, %)	20 (76.9)
Anti-depressant	15 (75.0)
Anti-psychotic	3 (15.0)
Anxiolytic	1 (5.0)
Hypnotic (Zolpidem, Melatonin)	1 (5.0)
Psychotropic polypharmacy (Count, %) ^c	
Yes	0 (0)
No	20 (100)
Cognitive enhancer (Count, %)	
Yes	6 (31.6)
No	14 (68.4)
Fall post initiation of psychotropic medications (Count, %)	
Yes	15 (75.0)
No	5 (25.0)

^c Psychotropic polypharmacy: ≥ 2 psychiatric medications

Among those on psychotropic medications, 75% experienced falls. PD patients on psychotropic medications, especially those with concurrent dementia, had an increased risk of falls (Table 3).

DISUCSSION

This is the first study looking into the prevalence of psychotropics used and occurrence of falls among older patients with PD in the Malaysia hospital setting. A significant proportion of PD patients studied had psychiatric disorders, were on psychotropic medications and experienced at least a fall during the period of the study (75%). PD often leads to comorbid psychiatric conditions such as depression, anxiety, and hallucinations (Dorsey et al., 2018). To manage these, psychotropic drugs such as antidepressants, antipsychotics, hypnotics, and mood stabilizers are frequently prescribed. While these medications are essential for managing psychiatric symptoms, they often come with significant side effects that could exacerbate the motor symptoms of PD, such as dizziness, sedation, or motor impairment. They can also increase the risks of various PD-related complications, including drug-drug interactions, increased all-cause mortality, cognitive impairments, and an elevated likelihood of falls (Csoti et al., 2019). These factors highlight the need for careful management and monitoring of psychotropic drug use in this patient group to minimize potential adverse outcomes.

Older patients with PD are particularly vulnerable to polypharmacy (Bhagavathula et al., 2022), and in this study, all patients experienced it, which presents several challenges. A primary concern is the risk of drug interactions, which can either reduce the effectiveness of Parkinson's medications or cause adverse reactions. Additionally,

Table 3: Occurrence of PD patients on psychotropic medication with at least a fall.

Characteristics	Fall		No (n = 5)
	Yes (n = 15)	No (n = 5)	
Age (Count, %)			
Less than 75 years old	7 (100.0)	0 (0.0)	0.058
75 years old and more	8 (61.5)	5 (38.5)	
Dementia (Count, %)			
Yes	10 (100.0)	0 (0.0)	0.010
No	5 (50.0)	5 (50.0)	
Cognitive enhancer (Count, %)			
Yes	4 (66.7)	2 (33.3)	0.197
No	11 (78.6)	3 (21.4)	

managing and monitoring complex medication regimens can be difficult, especially for older patients who may experience cognitive decline or struggle with medication adherence. Polypharmacy also heightens the risk of medication errors (Savva et al., 2022), potentially leading to hospitalization or exacerbated symptoms (Gradalski, 2019). The complexity of medication schedules can result in confusion and missed doses, further diminishing treatment effectiveness. To mitigate these risks, it is crucial to implement careful monitoring, personalized treatment plans, and regular medication reviews. In some cases, non-pharmacological approaches such as physical therapy, cognitive rehabilitation, and support groups can help alleviate the burden of polypharmacy.

This study found that PD patients on psychotropic medications concomitant with dementia have an increased risk of falls. This finding is consistent with previous studies that have examined the relationship between psychotropic medication use and falls or fall-related injuries in community-dwelling older people with cognitive impairment (Hart et al., 2019; Santiago Martinez et al., 2023). Dementia may amplify this risk through several mechanisms. Cognitive decline can impair attention, judgment, and hazard perception, making it more difficult for individuals to recognize and respond appropriately to environmental risks (Sturnieks et al., 2025). In addition, dementia often reduces the ability to maintain postural stability and dual-tasking, further compromising balance and coordination (Zhong et al., 2025). Psychotropic medications, particularly sedatives, antidepressants, and antipsychotics, can exacerbate these deficits by causing drowsiness, delayed reaction time, and orthostatic hypotension, thereby increasing the overall sedative burden. Moreover, individuals with dementia may have difficulties adhering to safety precautions, further elevating their vulnerability to falls. Several studies have emphasized the detrimental effects of psychotropic drugs on

fall risk, underscoring the potential benefits of deprescribing these medications in individuals with PD and dementia. By carefully managing medication use, healthcare providers may be able to reduce the risk of falls, improve patient safety, and enhance overall quality of life for these individuals.

The findings of this study have important clinical implications for the management of fall risk among older patients with PD who are prescribed psychotropic medications. Given the association between psychotropic drug use, cognitive impairment, and increased fall risk, clinicians should adopt a proactive and multifaceted approach to mitigate these risks. Regular medication reviews and deprescribing where appropriate are essential strategies to minimize sedative burden and reduce exposure to medications known to increase fall risk. Whenever feasible, non-pharmacological interventions should be integrated into the care plan, including physiotherapy to improve gait and balance, cognitive rehabilitation to strengthen attention and executive function, and caregiver education to enhance environmental safety and support. Additionally, incorporating routine fall risk assessments into comprehensive geriatric care can facilitate early identification of high-risk individuals and timely implementation of targeted interventions. Such a multidisciplinary approach not only enhances patient safety but may also improve functional outcomes, quality of life, and reduce healthcare burden associated with fall-related injuries in this vulnerable population.

There were limitations associated with this study. Important factors that could have influenced PD patients' falls were not analyzed, such as frailty, disability, morbidity and illness severity. This would support targeting attention on factors associated with high risk of falls. In addition, the study involved a relatively small sample size, which may limit the statistical power to detect significant associations and increases the possibility of errors. The findings were also derived from a single urban hospital, which restricts the external validity and

generalizability of the results to broader or more diverse populations. Furthermore, the retrospective study design meant that data accuracy and completeness were entirely dependent on existing clinical notes and electronic health records, which may be prone to recall bias, missing data, and inconsistent documentation. These limitations should be carefully considered when interpreting the results and planning future prospective, multicenter studies with larger sample sizes.

Further research into the factors influencing falls in PD patients at this stage could offer valuable insights into what clinicians consider when making decisions and the reasoning behind those choices. Additionally, risk stratification to identify characteristics and factors linked to high-risk falls would enable clinicians and stakeholders to target interventions more effectively. A deeper understanding of these factors would help optimize care organization and improve the delivery of high-quality services to meet the healthcare needs of an aging population. Future work should build on these findings to offer a clearer, locally relevant picture for our healthcare system.

CONCLUSION

A significant proportion of PD patients studied had psychiatric disorders, were on psychotropic medications and experienced at least a fall during the period of the study. Regular review of the ongoing need for these medications and a fall assessment should therefore be central to the comprehensive geriatric assessment in this cohort.

Given the complexity of PD, a tailored approach to fall prevention is essential. Although general strategies are commonly applied to older adults, individuals with PD face distinct challenges stemming from impaired motor coordination, postural instability, and autonomic dysfunction. To address these specific risks, future prospective multicenter studies involving larger cohorts and standardized fall assessment tools are

needed to develop and validate targeted interventions for this population.

As the first study of its kind in a Malaysia hospital setting, these findings provide valuable local insight. Nonetheless, they highlight the urgent need for context-specific strategies to improve care and outcomes for older adults living with PD.

ACONFLICT OF INTEREST

None

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REVIEW ARTICLE

Anaemia in Pregnancy in Sabah, Malaysia: A Challenge

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antenatal care.*

ABSTRACT

Anaemia in pregnancy represents a critical maternal health concern in Malaysia, especially in the state of Sabah. Frequently discussed causes include intensifying the burden in Sabah relative to other states in Malaysia, limited access to healthcare, poor socioeconomic conditions, and geographic isolation. This article explores the epidemiological patterns, contributing factors, health consequences, and strategic responses to anaemia in pregnancy among Sabah's diverse communities. A few major contributing factors that are specific to Sabah include inadequate nutrition, early and multiple pregnancies, poverty, and cultural dietary restrictions. Anaemia in pregnancy increases the risk of complications for both mother and baby, such as preterm birth, low birth weight, and maternal mortality. A thorough Set of National and local health policies and interventions has been tailored, including routine haemoglobin assessments, iron-folic acid supplementation, and nutrition education. Even a good strategy will fail if not properly implemented. Promising results from case studies, such as the reduction in anaemia cases at Klinik Kesihatan Penampang, underscore the importance of tailored and aggressive implementation and intervention. A conclusion can be made that by aggressive implementation of the recommendation, such as actionable access to antenatal care, enhanced diagnostics, and promoting culturally sensitive health education to reduce anaemia in pregnancy and improve maternal and child outcomes in Sabah.



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INTRODUCTION

Globally, anaemia in pregnancy poses a significant health concern, especially in developing countries. Anaemia in pregnancy, by definition, is a pregnant mother with a haemoglobin level below 11 g/dL. Anaemia significantly affects maternal and foetal health, which can lead to morbidity and mortality (WHO, 2023). Among Malaysian states, Sabah stands out for its high anaemia prevalence, attributed to regional disparities, nutritional deficiencies, and limited healthcare access (MOH, 2020). Another factor contributing to this problem in Sabah is the high prevalence of the Thalassemia trait. Sabah comprises fewer than 38 principal ethnic groups. Ethnic groups with the highest numbers of thalassemia and thalassemia trait carriers are Kadazan Dusun, Rungus, Bajau, and Murut (MOH, 2020; Mohd Ibrahim, 2020). This article examines the challenges of anaemia in pregnancy, particularly in Sabah, and identifies its contributing factors. This can help develop or implement strategies to improve (Abd Rahman et al., 2022; WHO, 2023).

METHOD

An electronic search of the available literature was conducted using ResearchGate, Google Scholar, and Scopus. The following keywords were used: Anaemia in Pregnancy, Iron Deficiency Anaemia, Iron Supplementation, and Sabah's health services from 2000 to 2025, for the available literature on anaemia in pregnancy in Sabah. A total of 38 articles were found. Thirty articles were included and synthesised in this review.

RESULT AND DISCUSSION

Anaemia in pregnancy in Sabah

Malaysia's anaemia prevalence during pregnancy ranges from 19.3% to 57.4%, depending on access to healthcare and regional differences, with the highest rates in Sabah (Abd Rahman et al., 2022; Neliti, 2020).

Sabah is the second-largest state in Malaysia, characterised by vast rural areas and rugged terrain that limit accessibility. The limited availability of healthcare resources, along with the population's low socioeconomic status, contributes to higher rates than in other states, with some districts reporting prevalence rates exceeding 40% (Foo et al., 2004). A retrospective study involving 3,374 antenatal mothers registered with government clinics in Kota Kinabalu in 2021 showed that 43.3% had anaemia (Ling et al., 2022). Research from Kudat, in northern Sabah, found a higher rate of iron-deficiency anaemia (IDA) among schoolchildren than the national average. This condition, attributable primarily to widespread nutritional inadequacies, persists into adulthood (Annan et al., 2021; Roslie et al., 2019). These deficiencies extend to reproductive health, highlighting intergenerational effects (Yilmaz et al., 2018; Jack et al., 2022). Therefore, anaemia impacts not just the pregnant mother but also extends beyond.

Anaemia in pregnancy increases risks for both mother and child. Mothers with anaemia often experience fatigue, shortness of breath, palpitations, and dizziness, and they face higher chances of complications such as gestational hypertension, preeclampsia, prolonged labour, and postpartum haemorrhage (Haniff et al., 2007; Mahmood et al., 2019). These morbidities are compounded by diminished oxygen-carrying capacity, impairing uterine muscle contraction and increasing the likelihood of caesarean delivery and blood transfusions. Anaemia in pregnant mothers significantly increases the risk of delivery-related complications, chiefly postpartum haemorrhage during childbirth. Pre-delivery anaemia has been shown to double the risk of post-partum haemorrhage (PPH). A meta-analysis reports an odds ratio for post-partum haemorrhage ranging from 1.45 to 3.28 depending on anaemia severity (Tura et al., 2021). Specifically, severe anaemia is linked to a sevenfold higher risk of PPH-related mortality, with each 1g/dL

reduction in haemoglobin concentration correlating with higher PPH risk. Empirical studies further confirm that women with moderate-to-severe anaemia (haemoglobin < 9 g/dL) experience significantly greater blood loss during vaginal delivery and the postpartum period (Samsuriati et al., 2024; Tura et al., 2021). Consequently, anaemic mothers are more likely to require blood transfusions intrapartum or postpartum. One extensive cohort study reported transfusion rates of 5.1 per 1,000 in non-anaemic women, compared with 21 per 1,000 in women with moderate anaemia. Taken together, these data underscore the vital importance of early anaemia detection, optimised prenatal iron management, and targeted labour monitoring to reduce haemorrhagic risks during delivery (WOMAN-2, 2023).

For the foetus, maternal anaemia is strongly associated with prematurity, intrauterine growth restriction, low birth weight, low Apgar scores, neonatal asphyxia, and even early neonatal death (Azizah et al., 2022). One study reported a nearly threefold increase in the risk of low birth weight, with an odds ratio of 3.42 (95% confidence interval, 1.85-6.34). Moreover, maternal anaemia can impair placental development and reduce neonatal iron stores, heightening the risk of infant anaemia and potentially causing long-lasting neurodevelopmental delays (Sifakis, 2000).

Severe anaemia (<7 g/dL) in pregnancy can compromise oxygen delivery to the foetus and often requires blood transfusions. The situation is exacerbated by the fact that blood transfusions are not always readily available in Sabah's remote areas (Abd Rahman et al., 2022; Benson et al., 2022). There are still many areas in Sabah without access to health services or that are far from services. Some individuals must travel for several hours to reach the nearest health facility, which may not be equipped to address complications that arise during delivery. Taken together, it can be concluded that the importance of managing anaemia in pregnancy lies in preventing

complications during delivery, particularly in areas with limited or no access to health services. Managing anaemia in pregnancy is easier compared to managing complications that can arise.

The causes of anaemia in pregnancy in Sabah are complex and interrelated. Iron deficiency is the leading cause of anaemia in pregnancy, primarily due to poor dietary intake and increased iron requirements during pregnancy (Jack et al., 2022; NH Nik et al., 2012; Wong et al., 2024). Additional causes include folate and B12 deficiency, parasitic infections, and genetic blood disorders such as thalassemia (Abd Rahman et al., 2022; Thirukkane et al., 2010). A few factors have been recognised that can contribute to the high cases of anaemia in pregnancy in Sabah. Inadequate nutrition is the most prominent cause. Many families in rural areas consume plant-based diets that are low in bioavailable iron (Foo et al., 2004; Nurnaningsih, 2022). Financial hardship limits access to nutritious food and supplements, thereby worsening iron replenishment (Milman, 2015; Yuen et al., 2023).

Additionally, very young mothers and frequent pregnancies contribute to the problem. Sabah has a high number of early motherhood and problems with pregnancy spacing. Closely spaced births reduce maternal iron reserves (Abd Rahman et al., 2022). This may also be due to a lack of awareness and contraceptive accessibility. Cultural beliefs also contribute to iron-deficiency anaemia in pregnancy. In some communities, dietary restrictions are being practised for pregnant mothers. Sabah's population includes diverse ethnic groups, including Kadazan-Dusun, Bajau, and Murut. Cultural food practices may contribute to iron-deficiency anaemia among pregnant women. For example, some traditions discourage the consumption of meat and eggs, exacerbating nutritional deficiencies (NH Nik et al., 2012).

Limited coverage of health services also contributes to the high prevalence of anaemia in pregnancy. Some rural areas in

Sabah have rugged terrain, making access to healthcare difficult. This hinders early diagnosis and treatment, as the patient presents to the clinic late in pregnancy or with fewer visits than necessary. There is also a lack of availability of haemoglobin level checks required for diagnosis and treatment monitoring. Underdiagnosis or delayed diagnosis can delay treatment and exacerbate this problem. Delayed or missed antenatal care (ANC) visits are common due to transportation issues, language barriers, and low health literacy (Abd Kadir et al., 2021). All these factors are closely related, so a holistic approach is required.

Strategies and Interventions

The Malaysian government has already implemented a few national strategies through the Ministry of Health to combat anaemia in pregnancy. Current ongoing programmes are making 'haemoglobin testing' become a standard during ANC visits, supplying iron-folic acid supplements for all pregnant women (Rahman et al., 2022), giving health education to every pregnant woman on iron-rich diets, and infection control, such as deworming and malaria prevention programs in high-risk zones (WHO, 2023).

The government should place greater emphasis on health staff training. Training is a crucial factor in reducing anaemia in pregnancy. By equipping healthcare providers with up-to-date knowledge and practical skills, they can better identify, manage, and prevent anaemia among pregnant women. Training should cover topics such as nutritional counselling, iron and folic acid supplementation, screening protocols, and effective communication strategies. Malaysia's government health clinics, which are known as Klinik Kesihatan, have well-trained staff, a necessity in combating anemia in pregnancy. They can ensure early detection of anaemia, provide timely treatment, and educate expectant mothers about a healthy diet and adherence to supplementation (Abd Manaf et al., 2022). Strengthening health staff training at both urban and rural levels is essential

to improve maternal health outcomes and reduce the risks associated with anaemia in pregnancy across the country.

The Ministry of Health has established a method to measure and monitor the intervention's effectiveness by setting an improvement target, which is tracked through the annual Key Performance Indicator (KPI). The KPI is the percentage of pregnant women at 36 weeks with anaemia. The targets set by the Ministry of Health for Sabah in 2023 are lower than the national target of 5% (PKKP, 2024). A conclusion that Sabah is far behind other states in Malaysia can be drawn from this large discrepancy in targets alone.

There will be a significant improvement if all the national strategies are well implemented. In Sabah, an exemplary case of significant improvement is evident at Klinik Kesihatan Penampang, a government clinic. Multiple significant efforts have been implemented to address anaemia in pregnancy, primarily focusing on improved nutrition and supplementation. The supplementation includes aggressive escalation of the iron dose and earlier initiation of IV iron therapy in cases that fail to improve haemoglobin after oral iron therapy. In addition to a static health clinic, mobile outreach services were launched to improve access and ensure that health services reach most rural areas (Rahman et al., 2022). Klinik Kesihatan Penampang demonstrated success by reducing the prevalence of anaemia among pregnant women from 12.1% to 5.7% within a year through more aggressive iron supplementation (Daily Need Group, 2023; PKKP, 2024). A similar improvement is also observed in other high-prevalence areas, primarily through reinforcing the pregnant mother's diet and supplementation.

Sabah requires additional government health clinics or infrastructure improvements to enhance health access. However, at present, this solution is not feasible due to limited government resources. To further address anaemia in pregnancy in Sabah, there is a need to expand health services, particularly antenatal care coverage, by mobilising mobile

clinics with the assistance of community health workers (Abd Rahman et al., 2022). The availability of a haemoglobin point-of-care machine is also important. Every health clinic should be equipped with hemoglobinometers and ferritin tests (Benson et al., 2022). All health staff need adequate knowledge of anaemia and its health education tailored to the local culture. Culturally relevant health education materials should be developed and distributed to specific local communities. Strengthening surveillance through effective data collection can guide interventions and their outcomes (Neliti, 2020). The current target set by the Sabah Health Authority for anaemia in pregnancy at 36 weeks is less than 6%, which is commendable, as every health worker has a target to meet. However, it is well above the national target of 5% or less.

CONCLUSION

Anaemia in pregnancy in Sabah remains a significant issue for pregnant women, but it can be solved with the proper implementation of the National Strategies. The main issues to be resolved are regarding access to health services and iron supplementation. Other than that, recognising anaemia in pregnancy has multifactorial causes, ranging from nutritional and cultural factors to systemic healthcare barriers, and thus implementing targeted strategies can achieve significant improvements in maternal and neonatal health.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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CASE REPORT

An Unexpected Site: Pleomorphic Adenoma in the Nasal Septum

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ABSTRACT

Pleomorphic adenoma is the most frequent benign neoplasm of the major salivary glands, but it may also originate from minor salivary glands, particularly within the hard and soft palate. Its occurrence inside the nasal cavity is rare; when present, about 80% arise from the nasal septum, with the rest involving the lateral nasal wall or turbinates. We describe a 49-year-old woman with a year-long history of left-sided epistaxis, gradually worsening nasal blockage, and a painless swelling over the left lateral alar region for six months. Rigid zero-degree nasoendoscopy revealed a large, smooth-surfaced polypoid lesion in the left anterior nasal cavity. Histopathological evaluation of a biopsy was consistent with pleomorphic adenoma. Computed tomography of the paranasal sinuses demonstrated a well-enhancing lesion confined to the left nasal cavity. The mass was successfully removed endoscopically, and the patient has remained disease-free on follow-up. This case underscores the importance of recognising intranasal pleomorphic adenoma as a rare differential diagnosis and highlights the value of early identification with prompt surgical removal.

INTRODUCTION

Pleomorphic adenoma is the most frequently encountered benign tumour of both major and minor salivary glands, with the parotid gland being the most common site of origin.

While major glands are most often involved, the tumour can also develop in minor salivary glands, including those located in the palate, lips, and, in rare instances, the upper respiratory tract, particularly the nasal cavity (Ejeil, 2018; Kajiyama, 2019). Intranasal pleomorphic adenomas account for only about 0.4% of all pleomorphic adenomas reported worldwide (Kajiyama, 2019). Among these intranasal tumours, approximately 80-90% originate from the nasal septum, with fewer arising from the lateral nasal wall or nasopharynx (Karlighiotis, 2020; Sciandra, 2008). Interestingly, despite the lateral wall containing a greater number of seromucinous glands, septal tumours are more frequently found, a pattern that remains poorly explained.

CASE PRESENTATION

A 49-year-old woman, otherwise healthy, was referred to our clinic with a one-year history of left-sided epistaxis, nasal discharge, and nasal obstruction. She also reported a painless swelling over the left lateral nasal area that had gradually developed over six months. Clinical examination revealed bilateral obliteration of the nasofacial sulcus, more pronounced on the left side. The swelling was non-tender and exhibited a soft to firm consistency on palpation (Figure 1). Rigid zero-degree nasoendoscopy demonstrated a smooth, pinkish, vascularised, non-pulsatile mass in the left anterior nasal cavity. The precise site of origin could not be determined because of the obstructive nature of the mass, and no bleeding was noted upon gentle probing. A punch biopsy was taken, and histopathological analysis suggested pleomorphic adenoma.



Figure 1: Physical examination: obliteration over the left nasofacial sulcus (Arrow)

Computed tomography (CT) of the paranasal sinuses demonstrated an enhancing soft-tissue mass at the proximal left nasal cavity, measuring $2.4 \times 1.8 \times 2.7$ cm, with associated thinning of the adjacent left nasal bone (Figure 2).

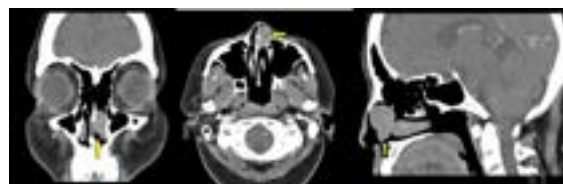


Figure 2: Computed tomography of the paranasal sinus showed an enhancing soft tissue density lesion at the proximal left nasal cavity, measuring $2.4 \times 1.8 \times 2.7$ cm with thinning of the adjacent left nasal bone (Arrows)

The lesion was excised via a transnasal endoscopic approach. Intraoperatively, the lesion was identified as originating from the left superior nasal septum near the roof and extending posteriorly to the posterior septum, measuring approximately 1.5×2.5 cm (Figure 3), without involvement of the lateral nasal wall or nasal floor. An anterior incision was made over the septum, and the mucoperichondrium was elevated to facilitate complete excision of the lesion. Histopathology confirmed pleomorphic adenoma, comprising predominantly epithelial and myoepithelial cells, with clear resection margins posteriorly.



Figure 3: Left septal mass post excision.

The patient was discharged in good condition and reviewed two weeks later for nasal splint removal. Follow-up nasoendoscopic examination revealed minimal crusting and a well-healed left nasal septal mucosa (Figure 4). Ongoing reviews

were initially conducted monthly and later extended to every three months. There has been no evidence of recurrence or residual disease at three years post-operatively.

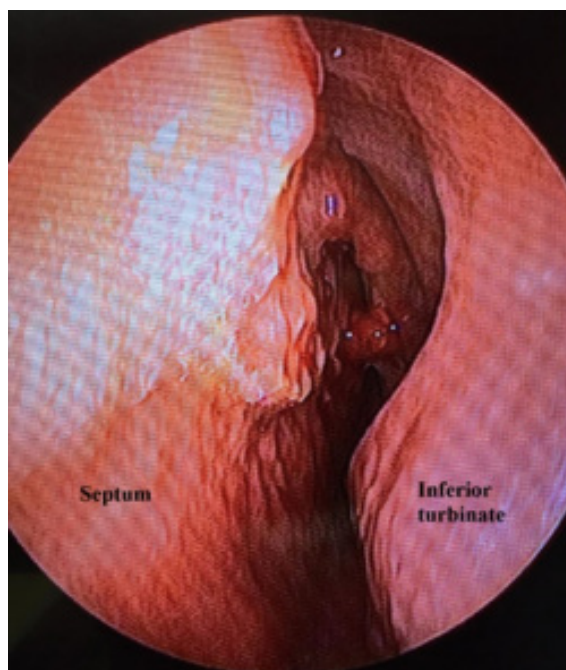


Figure 4: Nasoendoscopic view of left nostril after two weeks post-excision, showing well-healed nasal septal mucosa and no new lesion seen.

DISCUSSION

Pleomorphic adenoma, sometimes termed benign mixed tumour, is the most frequently diagnosed salivary gland neoplasm, arising from both epithelial and myoepithelial components (Mc Loughlin,2019). While the parotid gland is the predominant site, the tumour may also arise in the submandibular or minor salivary glands. Occurrence in the nasal cavity, maxillary sinus, or nasopharynx is distinctly uncommon(Ejeil,2018; Kajiya,2019; Sciandra,2008). Among intranasal cases, approximately 80% involve the septum, with the remainder occurring in the lateral wall or turbinates. Pleomorphic adenomas most commonly occur in females between the ages of 30 and 60, which is consistent with the demographic profile of our patient.

The origin of pleomorphic adenomas within the nasal septal mucosa remains

debatable. Matthew et al. proposed that these tumours may arise from displaced embryonic epithelial cells embedded in the septal mucosa during development. Alternatively, Stevenson suggested that remnants of the vomeronasal organ could be the source. In contrast, Evans and Cruickshank argued that such tumours originate exclusively from the epithelial components of mature salivary glands, rather than from embryological remnants (Compagno,1977).

Common presenting symptoms of intranasal pleomorphic adenoma include unilateral nasal obstruction, epistaxis, and occasionally pain. Patients may develop external nasal deformities or septal deviation in more advanced cases. On rigid nasoendoscopy, the lesion typically appears as a unilateral, smooth-surfaced, pale greyish to whitish mass. In our case, the patient presented with left-sided nasal obstruction, rhinorrhoea, and external nasal swelling. Endoscopic examination revealed a smooth, pinkish, vascularised mass occupying the left anterior nasal cavity. The mass was obstructive, which limited visualisation of its point of origin. However, gentle probing during endoscopy did not elicit any bleeding. Definitive diagnosis is established through tissue biopsy, often complemented by imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). These modalities are critical in preoperative planning, as they assist in delineating the tumour's extent and excluding aggressive features or local invasion (Sciandra,2008). On CT, these tumours often appear as well-defined, lobulated lesions displacing the septum, and can also highlight areas of calcification or adjacent bony changes (Ozturk,2008). However, in this case, the exact origin was indeterminate on imaging and was only confirmed intraoperatively.

The preferred treatment modality is complete surgical excision with tumour-free margins. While open approaches such as lateral rhinotomy, transpalatal access, and midfacial degloving have been described, the transnasal endoscopic approach is increasingly

preferred due to its minimally invasive nature, reduced morbidity, and favourable cosmetic outcomes (Case,2022). Complete resection is crucial, as pleomorphic adenomas risk recurrence and malignant transformation. Malignant change—referred to as carcinoma ex pleomorphic adenoma—has been reported in approximately 4% of cases, with a 2.4% malignancy rate specifically among nasal tumours. Postoperative recurrence has also been reported in up to 8.8% of cases (Kajiyama, 2019).

Extended surveillance is necessary to enable early recognition of recurrence or malignant transformation (Sciandra,2008). This typically involves periodic endoscopic examinations and, where indicated, repeat imaging with CT or MRI. Our patient's follow-up nasoendoscopy up to three years postoperatively showed no signs of recurrence or complications, and imaging was deferred without clinical concern.

CONCLUSION

Although intranasal pleomorphic adenoma is rare, it should remain a consideration in patients with unilateral nasal obstruction and epistaxis, particularly when a nasal mass is identified on examination. Timely recognition and appropriate surgical management are essential to prevent complications and ensure favourable outcomes. Owing to the risk of recurrence or malignant transformation, prolonged follow-up is advisable. This case emphasises the importance of maintaining a broad diagnostic perspective when evaluating unilateral nasal lesions..

CONFLICT OF INTEREST

None of the authors has any conflicts of interest to disclose in this case report..

CONSENTS

Written informed consent was obtained from the patient. A copy of the consent form is available for review by the Editor-in-Chief.

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CASE REPORT

Severe Bickerstaff Brainstem Encephalitis in a Young Adult Male: Delayed Recovery Despite Early Immunotherapy

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ABSTRACT

Bickerstaff brainstem encephalitis (BBE) is a rare post-infectious autoimmune disorder within the anti-GQ1b antibody spectrum, commonly presenting with ophthalmoplegia, ataxia, and impaired consciousness. Diagnosis is typically delayed because early symptoms are non-specific, and initial imaging often appears normal. We report a case of a 19-year-old male who initially presented with fever, limb weakness, and slurred speech. Within days, he deteriorated rapidly, requiring intubation. Initial imaging and cerebrospinal fluid analysis (CSF) were inconclusive. However, later serological studies revealed the presence of anti-GQ1b antibodies. Although MRI results were normal, the clinical picture was consistent with BBE. He underwent plasma exchange in the third week of illness. His recovery was complicated by hospital-acquired infection and barotrauma. His neurological recovery was slow. At the time plasma exchange was initiated (Day 21 of admission), the patient remained unresponsive with a Glasgow Coma Scale (GCS) of E1VTM1. By the sixth week of admission, his GCS had improved to E4V5M6, reflecting significant neurological recovery. With multidisciplinary rehabilitation, he eventually regained the ability to ambulate independently within 6 months. This case highlights the importance of considering BBE early in young patients presenting with acute brainstem dysfunction, even when initial imaging is unremarkable.



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INTRODUCTION

Bickerstaff brainstem encephalitis (BBE) is a rare autoimmune neurological condition that mainly affects the brainstem. The typical clinical manifestations include ophthalmoplegia, ataxia and altered consciousness (Zoghaib et al., 2021). It is considered part of the anti-GQ1b antibody-associated spectrum of post-infectious disorders, which also includes Miller Fisher syndrome and Guillain-Barré syndrome (Nayak et al., 2024). It often follows a viral illness and may present with subtle or even normal neuroimaging findings, making diagnosis challenging (Abide et al., 2023). Other reports described cases with initially normal neuroimaging, only later to reveal subtle midbrain or pontine signal changes on repeat MRI, reinforcing the importance of serological testing in the diagnostic process (Mathur et al., 2023).

There are several case reports highlighting the diagnostic and therapeutic challenges of BBE. In some patients, presentations mimicked brainstem stroke or infectious meningoencephalitis, leading to delayed recognition until anti-GQ1b antibodies were identified (Hamza Ahmed et al., 2025). Although many patients respond to treatment, outcomes can vary significantly, and patients may experience delayed neurological improvement despite early immunotherapy. Severe presentations requiring mechanical ventilation have also been documented. In such cases, immunotherapy with intravenous

immunoglobulin (IVIG) or plasma exchange has been associated with gradual recovery, although the timeline varies across individuals (Giaccari et al., 2024). These reports collectively emphasise the heterogeneity of BBE in its clinical course and in treatment response, making timely recognition and tailored management crucial.

CASE PRESENTATION

A 19-year-old previously healthy male, who recently completed pre-university studies, presented to Labuan Hospital with a two-day history of fever, generalised body weakness, and slurred speech. On admission, his neurological examination revealed hyperreflexia and a positive Romberg sign, but no cranial nerve deficits. Initial laboratory investigations revealed a mildly elevated white cell count of $14 \times 10^3/\mu\text{L}$, with otherwise regular renal and liver function tests (Table 1). A diagnosis of possible central nervous system infection or inflammatory demyelinating disorder was considered.

On the third day of admission (July 12, 2024), the patient experienced a sudden drop in consciousness, with GCS declining from E4V2M6 to E2V2M5, necessitating intubation for airway protection. Bilateral lower limb jerky movements were observed at the time, suggestive of seizure activity, although these were not aborted by diazepam and did not recur. A CT scan of the brain and a subsequent contrast-enhanced CT scan of the brain

Table 1: Key laboratory investigations during admission.

Test	Result	Reference	Comment
WBC	$13.7 \times 10^9/\text{L}$	4.0 – 10.0	Mild leukocytosis
Sodium	131 mmol/L	135 – 145	Mild hyponatremia
CRP	2.8 mg/L	<5	Not elevated
Procalcitonin	0.11 ng/mL	<0.5	Not elevated
Serology	HIV, HBsAg, Anti-HCV, dengue, leptospira all negative		
Blood cultures	No growth	-	Negative
Anti-ganglioside antibodies (serum)	Positive GQ1b IgG	Negative	Supports diagnosis of BBE

were reported as usual. A lumbar puncture performed on day 4 revealed an opening pressure of 34 cmH₂O, with cerebrospinal fluid (CSF) protein of 0.6 g/L and glucose of 3.89 mmol/L (glucose ratio: 0.62) (Table 2). Cultures and viral PCR screening were negative.

Even after stopping sedation on day 5, he remained unresponsive with a GCS of E1VTM1. He was transferred to Queen Elizabeth Hospital, Kota Kinabalu, for neurology input. A repeat lumbar puncture on day 16 showed a normal opening pressure, clear and acellular CSF (Table 2). Importantly, serum tested positive for anti-GQ1b IgG antibodies, confirming Bickerstaff brainstem encephalitis (Islam et al., 2024). An MRI brain scan performed on day 15 showed no abnormalities or contrast enhancement (Figure 1). However, the clinical picture and serological findings supported a diagnosis of autoimmune brainstem encephalitis (Giacconi et al., 2024). No follow-up MRI was performed, as the patient demonstrated progressive neurological recovery following treatment.

Between day 21 and day 29, he received five sessions of plasma exchange (PLEX) every

other day. Each session replaced approximately 2.4 L of his plasma with 5% human albumin and 0.5% saline, along with pre- and post-treatment calcium gluconate infusions. During this time, he developed features of sepsis, with elevated inflammatory markers. A diagnosis of hospital-acquired pneumonia was made, and blood cultures were negative. He was treated with intravenous piperacillin-tazobactam followed by amoxicillin-clavulanate. CSF culture revealed the presence of *Acinetobacter baumannii* and *Bacillus altitudinis*, both of which were sensitive to appropriate antibiotics and were successfully treated.

On day 22, a CT pulmonary angiogram was performed to investigate persistent tachypnea and rising ventilator settings, with markedly elevated D-dimer. The scan excluded pulmonary embolism but incidentally revealed pneumomediastinum, pneumopericardium, and left dominant pneumothorax. These findings were attributed to barotrauma secondary to mechanical ventilation. Cardiothoracic and respiratory input recommended conservative management.

Table 2: Key laboratory investigations during admission.

Parameter	First LP (13/07/2024)	Second LP (25/07/2024)	Reference Range	Remarks
Appearance	Clear, colourless	Clear, colourless	Clear	Normal both
WCC	0 cells/mm ³	0 cells/mm ³	0-5 cells/mm ³	No pleocytosis
Glucose (CSF:serum ratio)	3.9 mmol/L (0.62)	5.3 mmol/L (0.62)	Ratio >0.6	Normal
Protein	0.61 g/L	0.70 g/L	0.15 – 0.45 g/L	Mild elevation both
Gram stain/ Culture	No growth	<i>Acinetobacter baumannii</i> & <i>Bacillus altitudinis</i>	Negative	Likely contaminants (no pleocytosis)
AFB smear	Negative	Negative	Negative	Tuberculosis excluded
Cryptococcal Ag	Negative	-	Negative	Excluded
Viral PCR (JE, HSV)	Negative	-	Negative	Excluded
Autoimmune (NMDAR)	Negative	-	Negative	Excluded

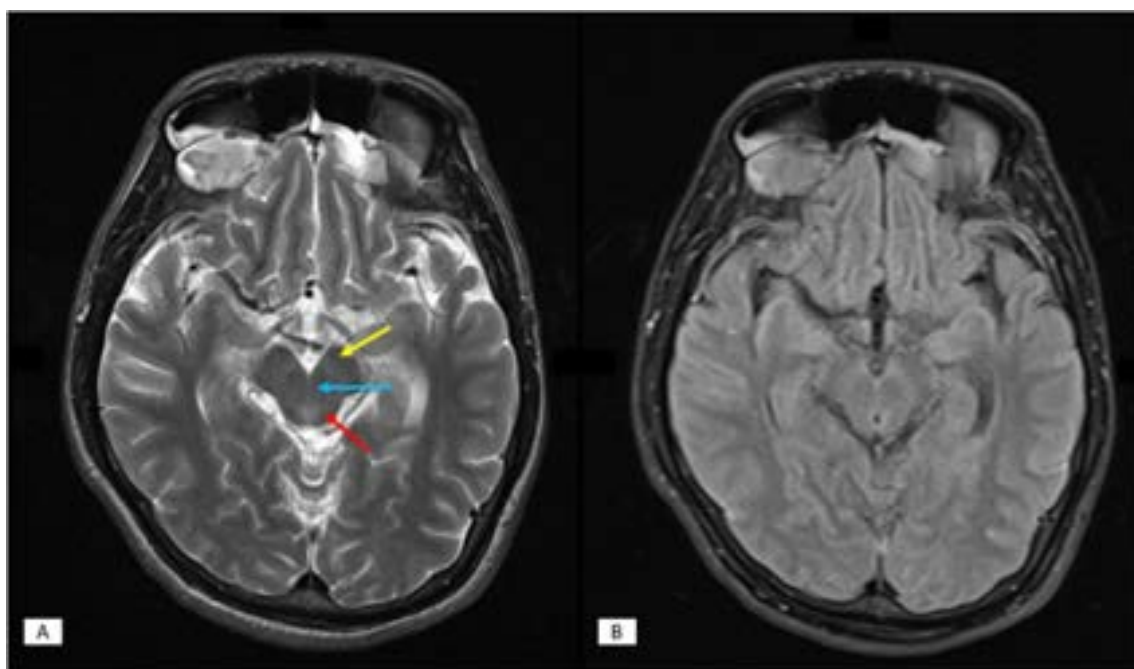


Figure 1: Axial MRI brain at the level of the midbrain (A) T2-weighted TSE, showing the left cerebral peduncle (yellow), the aqueduct of Sylvius (blue), and the left superior colliculus (red). (B) Corresponding FLAIR sequence. Both sequences demonstrate no abnormal signal changes in the brainstem or surrounding structures.

On day 31, he had a surgical tracheostomy and was gradually weaned off the ventilator. By week 7, his GCS improved to E4VTM6. Neurological examinations showed bilateral lower motor neuron facial weakness, upper limb power of 4/5, and lower limb power of 2/5. Physiotherapy, occupational therapy, and dietary support were initiated. He required wheelchair mobility and nasogastric tube feeding and was referred to social welfare services for home support.

A follow-up neurology outpatient assessment approximately 6 months after admission (January 13, 2025) showed remarkable progress. He was alert, cognitively intact, and communicating well despite persistent dysarthria. His facial weakness was improving. Upper limb strength had returned to normal, and lower limb strength improved to 3–4/5. Although still using a wheelchair, he was able to stand with assistance and was undergoing intensive neurorehabilitation. His tracheostomy was successfully closed 9 weeks post-tracheostomy, in October 2024. Further plans included ENT follow-up and orthotic support for bilateral foot drop.

DISCUSSION

BBE is a post-infectious autoimmune encephalitis characterised by brainstem dysfunction and strongly associated with anti-GQ1b antibodies. While usually self-limiting, its symptoms can range from mild ophthalmoplegia to deep coma (Lee et al., 2024). The presence of anti-GQ1b antibodies is a key diagnostic feature, particularly when neuroimaging is inconclusive (Koga et al., 2020). These antibodies are particular for BBE and related anti-GQ1b spectrum disorders (Giaccari et al., 2024).

Similar findings were reported by Cabral et al. (2023), who demonstrated that patients with classical BBE symptoms, such as drowsiness, ataxia, and ophthalmoplegia, frequently had normal imaging studies. This reinforces the importance of testing for anti-GQ1b antibodies in suspected cases, even when MRI findings are non-revealing.

Other differentials, including acute disseminated encephalomyelitis (ADEM), were considered, given the preceding fever

and altered consciousness. However, ADEM seemed unlikely due to the absence of multifocal demyelinating lesions on MRI and no inflammatory cells in the CSF (Finsterer & Iranpoor, 2022).

The patient's prolonged unconsciousness and slow initial response to treatment are less typical, though they have been reported before. Larger studies of BBE and overlapping syndromes have documented delayed recovery despite immunotherapy (Islam et al., 2024). Although IVIG remains the primary treatment, evidence supports plasma exchange as an effective alternative, particularly in severe presentations (Ban et al., 2022). Prior to PLEX, neither corticosteroids nor intravenous immunoglobulin (IVIG) were administered. In this case, the decision to initiate PLEX as the first-line immunotherapy on day 21 of admission was guided by the patient's prolonged unresponsiveness despite cessation of sedation. While IVIG is more commonly used in Bickerstaff encephalitis, PLEX was selected due to its potential to expedite the clearance of circulating pathogenic antibodies, such as anti-GQ1b, especially in severe presentations (Giaccari et al., 2024). This approach is supported by reports of PLEX being effective in severe or delayed presentations of Guillain-Barré spectrum disorders.

A similar case by Czempik et al. (2025) involved a 32-year-old man who developed Bickerstaff brainstem encephalitis following a febrile illness due to Influenza A. He rapidly deteriorated with impaired consciousness requiring intubation. His brain MRI was unremarkable, and he received five sessions of plasma exchange, with complete recovery reported at follow-up. While both patients had similar treatments and disease severity, our patient faced additional complications, including secondary infections and respiratory complications. In our case, the slow recovery and residual foot drop may be attributed to several contributing factors. Like other reports, this illustrates how BBE can vary significantly

and that routine imaging does not necessarily rule out severe brain involvement. Plasma exchange and supportive care demonstrate that substantial recovery is possible even after prolonged periods of unconsciousness.

CONCLUSION

In summary, although Bickerstaff brainstem encephalitis typically presents with altered consciousness and cranial nerve problems, its onset may be subtle and imaging findings may be normal. This case highlights the importance of considering BBE in the differential diagnosis when evaluating patients with acute neurological deterioration following a febrile illness. Early serological testing for anti-GQ1b IgG antibodies is crucial, especially when conventional imaging is inconclusive. Although the patient's GCS remained low despite starting immunotherapy early, his eventual recovery shows that prolonged unconsciousness does not necessarily indicate a poor prognosis. Complications such as ventilator-associated pneumonia and barotrauma highlight the importance of supportive treatment throughout the disease course.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

CONSENTS

Written informed consent was obtained from the patient's guardian for publication of this case report and any accompanying images.

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