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Malaysia's Evolving Rare Disease Ecosystem: Challenges, Interventions & System Imperatives

Meow-Keong Thong^{1,2}, Teguh Haryo Sasongko^{3,4}, Nadiyah Hanim Abdul Latif⁵

Introduction

Rare diseases (RDs) collectively constitute a significant yet often overlooked component of national public health systems. The World Health Organization (WHO) defines a rare disease (RD) as any disease which affects a small percentage of the general population.¹ EURORDIS (European Alliance of Rare Disease Patient Organizations) defines RDs as conditions affecting 5 in 10,000 of the general population² while in Malaysia, it was first recognised as a disease entity with the opening of the first genetic service in Universiti Malaya Medical Centre (UMMC) in 1995. A modification made was to amend the definition of RD as a condition with a prevalence of 1 in 4,000 of the general population (<http://www.mrds.org.my>) which was subsequently adopted by Ministry of Health (MOH) Malaysia in 2018/2019.³ As of March 2023, the MOH has identified nearly 500 such RD conditions nationwide.⁴ Although each RD is individually rare, collectively they number over 6,000 types and the RD community makes up 3.5 – 5.9% of world population. RDs may happen to anyone regardless of race, gender, age, or socio-economic background. Over seventy percent of RD are genetic in origin; and 30% of the patients passed away by the age of five years, unfortunately.⁵ The survivors with RDs often need long term medical care. RDs are non-communicable diseases (NCDs) but due to the lack of registry, there is little data on their epidemiology in Malaysia. The United Nations General Assembly in 2021 approved a resolution on addressing the

challenges of persons living with a RD and their families.⁶ Yet, patients with RDs face stigmatisation and arduous “diagnostic odysseys” – delayed treatment due to late diagnosis, low awareness by members of the public and healthcare professionals, limited access to genetic services and reduced access to life-saving medicines.

For families with children or adults living with RDs, the healthcare system must provide lifelong and comprehensive support. This includes early detection, continuous clinical management, access to specialised medicines and therapeutic interventions, and psychosocial assistance for patients and caregivers. A holistic and life-course approach is essential to ensure equitable quality of life and to prevent undue emotional, financial, and logistical burdens on families. The ecosystem surrounding RD care comprising geneticists, genetic counsellors, diagnostic laboratories, rehabilitation services, non-governmental organisations (NGOs), and patient support groups, is inherently interconnected. Each component plays a vital role in facilitating early diagnosis, treatment continuity, emotional well-being, and social inclusion.

A central driver enabling this ecosystem to function effectively is sustainable and continuous financing. Without predictable funding for diagnostics, medicines, rehabilitative services, and community-based support systems, RD patients risk falling through systemic gaps. Strengthened awareness

¹ Genetics and Metabolism Unit, Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

² M Kandiah Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Kajang, Selangor, Malaysia

³ Institute for Research, Development, and Innovation (IRDI), IMU University, Kuala Lumpur, Malaysia

⁴ Department of Human Biology, School of Medicine, IMU University, Kuala Lumpur, Malaysia

⁵ Malaysian Rare Disorders Society, Bangunan Sultan Salahuddin Abdul Aziz Shah, Petaling Jaya, Selangor, Malaysia

Corresponding author:

Professor Dr Meow-Keong Thong

Genetics and Metabolism Unit, Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Email: thongmk@um.edu.my

across the general public, health professionals, and policymakers at national, regional, and global levels, is also indispensable. Crucially, societal perceptions of the RD community must evolve. RD patients should be regarded not as passive recipients of welfare but as citizens entitled to equitable access to healthcare, education, employment, and dignified living conditions. With increased visibility and resources, Malaysia implemented key transformative strategies, such as developing a national RD registry, enhancing inter-ministerial coordination, and empowering patient advocacy networks to support individuals from birth to end-of-life culminating in a landmark National Policy on Rare Diseases launch in August 2025.⁷

Key Challenges Faced by Rare Disease Patients and Families

Although Orphanet's 2020 estimates suggest that 3.5 – 5.9% of the global population may be affected by an RD,⁵ equivalent to at least one million Malaysians affected, public perception continues to frame RD as a marginal issue. This contrasts sharply with the attention given to more common NCDs, such as cardiovascular diseases, diabetes mellitus, and cancer. Given their high population burden and chronic, debilitating nature, RDs should be conceptualised as a major NCD subgroup within national health planning.

The longstanding neglect of RD in public health policy stems partly from insufficient knowledge and awareness among healthcare professionals. Malaysia faces a significant shortage of geneticists, with only

15 to 18 specialists serving the entire country, and genetic counselling remains unrecognised in the public service scheme. This limits the availability of early diagnostic services and contributes to delayed or inappropriate clinical management. Moreover, genetic clinics are not present in every state, creating geographical inequities in access.

Financial constraints further exacerbate these challenges. National RD funding remains inadequate and is often restricted to known patients, leaving limited provisions for new diagnoses or family support. Expanded newborn screening is still not implemented nationwide in Malaysia. While conditions such as inborn errors of metabolism, primary immunodeficiencies, endocrine disorders, and lysosomal storage diseases can often be treated effectively if detected early, current newborn screening available in Malaysia includes only G6PD deficiency, congenital hypothyroidism, and hearing loss.

Equally concerning is the lack of harmonised planning across key ministries – including MOH, the Ministry of Women, Family and Community Development (KPWKM), the Ministry of Education (MOE), the Ministry of Higher Education (MOHE), Ministry of Finance (MOF), Ministry of Home Affairs, Ministry of Youth and Sports, and the Ministry of Human Resources, including their implementing agencies (such as Department of Social Welfare or Jabatan Kebajikan Malaysia (JKM), National Population and Family Development Board (or Lembaga Penduduk dan Pembangunan Keluarga Negara, LPPKN, higher learning institutions, etc). Fragmented governance

results in a disjointed continuum of care, hindering RD patients' access to inclusive education, social services, and employment opportunities.

Importance and Impact of the Rare Disease in Malaysia

Delayed diagnosis can lead to irreversible physical complications and missed therapeutic windows, compromising long-term health outcomes. Insufficient clinical expertise may result in misdiagnosis, inappropriate treatment, and psychological distress for families. The financial burden of RD including but not limited to, medical expenses, frequent hospitalisation, and loss of income due to caregiving, further exacerbates household vulnerability. A fragmented, non-integrated system undermines continuity of care and leaves patients navigating multiple uncoordinated services. Moreover, broader societal and economic consequences arise when caregivers are forced to leave the workforce or when untreated RD leads to lifelong disability. If unresolved, these will widen health inequities, increase long-term healthcare costs, and dampen Malaysia's progress toward inclusive health policies that reflect the needs of all communities. This will also negatively affect national productivity and economic growth by increasing losses of disability-related workforce and long-term dependency, ultimately placing additional strain on Malaysia's gross domestic product (GDP). International estimates indicate that the exclusion of persons with disabilities from the labour market may reduce national economic output by several percentage points of GDP (approximately 3 – 7%),

through a combination of lost productivity, reduced labour participation, and increased long-term dependency (ILO 2009).

Intervention Approaches and Methods of Care

Effective management of rare diseases typically involves a combination of interventions tailored to the patient's specific condition. These include early diagnosis, specialised therapies, targeted medicines (orphan drugs), genetic counselling, and long-term monitoring delivered through multi-disciplinary teams.

Genetic Clinics and Diagnostic Services in Malaysia

Malaysia's genetic healthcare services span several ministries, including MOH, MOHE, Ministry of Defence Malaysia (MINDEF), and Ministry of Home Affairs (MHA). Recognising the need for research into RD, the first dedicated Genetic Medicine unit in Malaysia was established in UMMC in 1995, and scored many "firsts": first to treat lysosomal diseases (Gaucher in 1994, Pompe disease in 2007 and mucopolysaccharidosis type VI) with enzyme replacement therapy; first to offer genetic counselling and to train genetic counsellors to enable board-certification in 2003; first to establish a Malaysia Rare Disorders Society (MRDS); first public hospital to start newborn screening programme for RDs in 2015 and to offer next generation sequencing for undiagnosed malformation syndromes. Extensive research and collaborations with national and international institutions were conducted on RDs which many were hitherto unknown in the Malaysian population.

Over 120 academic journal publications were published on RDs and hereditary conditions in Malaysia, as well as pamphlets on various rare conditions. Three books on RD were published, including a compilation on patients' narratives entitled "Rare Journeys of Love",⁸ numerous book chapters on various RDs including the Oxford Monograph in Medical Genetics⁹ and The Institute for Democracy and Economic Affairs (IDEAS) White Paper policy document entitled "Rare Diseases in Malaysia".¹⁰ Recent progress includes clinical drug trials for genetic therapeutics and policy development for RDs in Malaysia. Gene therapy was successfully used in Southeast Asia for the first time in 2020 for six UMMC patients with spinal muscular atrophy type 1, a rare genetic neuromuscular condition. Due to the efforts of first few clinical geneticists, Clinical Genetics was accepted as a paediatric subspeciality in 2006 in the National Specialist Registry. In addition to the MRDS set up as a lay support group, the Genetic Counselling Society of Malaysia, as well as Medical Genetics Society of Malaysia were established for the various professionals and genetic healthcare providers.

Clinical Genetics Service at the MOH began later in 1999 when the Genetic & Metabolic Unit was established at the Institute of Paediatrics, Hospital Kuala Lumpur (IPHKL) as one of the subspecialties in paediatrics. Since then, more paediatricians have been trained and have qualified as clinical geneticists. The Blueprint for Genetic Service was prepared by the MOH's Medical Development Division in 2008 following a series of discussions with clinical geneticists and relevant stakeholders.

The policy paper titled "Restructuring of Genetic Services in Hospital Kuala Lumpur (HKL)" was presented and accepted at the Special Meeting by the Director-General of Health on 16 December 2008. The Department of Clinical Genetics of HKL was officially established on 1 September 2009 and in Hospital Pulau Pinang (HPP) in 2019. In addition to the two MOH's Clinical Genetic Departments, a few teaching hospitals including Tunku Ampuan Besar Tuanku Aishah Rohani (Hospital Pakar Kanak-Kanak Universiti Kebangsaan Malaysia, HUKM) and Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, also offer clinical genetic services.

As of July 2025, genetic clinics operate in six major hospitals, led by an estimated 15 to 18 geneticists nationwide. The Institute of Paediatrics, HKL, functions as the national referral centre. Other key institutions include HPP, UMMC, HUKM, HUSM, and the Universiti Sultan Zainal Abidin Teaching Hospital. Several other specialist hospitals also play significant roles in RD management.

Diagnostic capacity remains limited. While the Institute for Medical Research (IMR) and Hospital Tunku Azizah of MOH offer specialised diagnostic services, including Whole Exome Sequencing and biochemical and genetic testing for inborn errors of metabolism, genetic and genomic tests are not routinely available in teaching hospitals and other parts of the country, requiring samples to be sent overseas. This creates a significant financial barrier, particularly for the B40 group, as costs are often borne by families. Although hospitals, NGOs, and

welfare units may offer partial assistance, coverage is inconsistent and insufficient, leaving many patients undiagnosed. For families who cannot afford genetic testing, the lack of diagnosis delays or prevents access to targeted treatment and clinical management. In 2015, UMMC started the first expanded newborn screening for inherited metabolic diseases in a public hospital in Malaysia, but such initiatives remain rare and have not been scaled nationally.

Supportive and Medical Interventions

Supportive therapies such as physiotherapy, occupational therapy, and speech therapy are widely available but may lack sufficient frequency due to resource constraints. Community-Based Rehabilitation centres supplement hospital services by fostering social integration and enhancing functional independence.

Access to orphan drugs remains limited due to high costs and restricted financing despite the existence of MOH's technical review mechanisms and the publication of a national Rare Disease List. Even for the majority of RDs without approved orphan drugs, long-term care remains intensive and costly. Patients may require corrective surgeries, growth hormone therapy, bone marrow transplantation, specialised medical foods, assistive devices, and regular specialist follow-ups. The MOH support treatment of RDs to the tune of RM25 million in 2024.

Genetic and Psychosocial Counselling

Genetic counselling supports families in understanding inheritance patterns, assessing risks, interpreting diagnostic options, and navigating long-term planning. Psychosocial counselling is equally critical due to the emotional strain of chronic caregiving, frequent hospitalisation, financial pressure, and concerns about long-term care, including "Who will care for my child when I am no longer here?". Counselling services help build resilience, address stigma, and support mental well-being across the life course.

To build local expertise in supporting patients with genetic conditions, the first core group of genetic counsellors were trained in UMMC in conjunction with the Human Genetics Society of Australasia in 2003. In 2016, UKM started the Master of Science (Genetic Counselling) programme. However, graduates face significant constraints because the MOH does not currently recognise "Genetic Counsellor" as an official position within the public healthcare system. As a result, many graduates work in research, academia, or private healthcare settings rather than in government hospitals, limiting their direct impact on clinical services for RD patients. Despite these challenges, genetic counsellors play an important role in improving awareness, providing pre- and post-test counselling, and guiding families through complex decisions related to genetic testing and disease management. Their expertise helps bridge communication gaps between clinicians and patients, supports informed consent for genomic testing, and advocates for better integration of genetic services into Malaysia's healthcare system.

Role of NGOs and Support Groups

NGO-led support groups were started by parents in the mid-2000 and since then, there are currently 21 registered NGOs dedicated to issues related to RD. They provide vital emotional, informational, and advocacy support systems. They connect families, disseminate care practices, facilitate access to resources, and advocate for inclusive policies in education, healthcare, and employment. These groups help reduce isolation and strengthen community mobilisation.

Regular Monitoring and Research

Continuous health monitoring ensures timely adjustments to treatment and early detection of complications. Research on RDs, including clinical trials for gene therapy and biologics, is critical but remains underfunded due to a prevailing perception that RD lacks commercial value.

Drawing on a systematic literature network analysis of RD research in Malaysia (manuscript in draft), the national research and development (R&D) landscape appears unevenly developed, with a strong historical concentration around a small number of conditions – most notably thalassaemia – where sustained research has translated into screening programmes, clearer care pathways, and population-level impact. It is noteworthy that thalassaemia is included in the Malaysian Rare Disease List 2023 due to the relatively high birth prevalence of 1 in 2000, highlighting that the research literature has been shaped by legacy public health and genetic priorities and does not, on its own, fully capture the contemporary RD

profile in Malaysia. In contrast, research on many conditions that meet the RD definition, such as metabolic, neuromuscular, and multisystem genetic disorders, remains fragmented, low-density, and largely descriptive, with limited integration across diagnostics, therapeutics, and health system domains. Emerging themes such as enzyme replacement therapies and broader “rare disease” discourse are visible but still weakly connected to national data infrastructure, implementation research, or financing mechanisms. Consequently, translation of R&D outputs to bedside care has occurred selectively and disease-specifically, rather than systemically, reflecting gaps in registries, genomic service integration, trial readiness, and RD – specific health technology assessment.

Institutional Consolidation and the Deepening of Expertise: Evolution

Malaysia's institutional landscape for RDs remains relatively young, but progress is evident. As tertiary centres formalised their RD units, institutional governance and clinical protocols matured. Several hospitals established dedicated metabolic laboratories, newborn screening programmes, and molecular diagnostic units, though coverage remains inconsistent across states. Academic institutions have played a central role in advancing RD education. Universities have expanded postgraduate training in genetics, metabolic medicine, and child neurology. Despite ongoing workforce shortages, the number of specialists is gradually increasing, contributing to more balanced distribution of expertise nationwide.

Parallel to institutional growth, patient and caregiver knowledge has expanded. Civil society organisations such as MRDS and various condition-specific associations have undertaken large-scale awareness campaigns, educational workshops, and policy dialogues. Their advocacy has improved public understanding, normalised RD discourse, and reduced stigma surrounding genetic conditions, as well as advocated for non-health issues such as access to employment with dignity, child rights and protection and inclusive education.⁶

Although formal registries remain limited, clinicians have accumulated rich tacit knowledge from years of treating rare conditions. This tacit expertise, while insufficient as a standalone evidence base, has been instrumental in shaping clinical practice guidelines and informing policy discussions.

Policy Development and Governance Dynamics

Malaysia's policy environment for RDs is characterised by incrementalism, pilot initiatives, and gradual institutionalisation rather than sweeping legislative reform. Early progress emerged through the MOH's development of the National Strategic Plan for Rare Diseases (NSPRD), which identified priorities in diagnostics, training, research, and patient care. However, implementation has faced obstacles due to limited dedicated funding, governance fragmentation, and the absence of binding statutory mandates.

Governance Structures

The MOH, MOHE and academic hospitals share overlapping responsibilities for RD services. While this multi-agency system can amplify resource distribution, it often results in bureaucratic delays and inconsistencies across states. Public-private collaboration is emerging, particularly in diagnostics and enzyme replacement therapies, but remains largely ad hoc.

One notable development is the increased use of working groups comprising clinicians, MOH officers, patient representatives, and pharmacists, to standardise clinical pathways and advise on high-cost treatments. These committees have begun developing criteria for funding prioritisation, although transparency and coverage remain limited.

Financing Mechanisms

The financing of RD treatments remains the most challenging policy barrier. Treatment can be broadly divided into two groups. The first group involve specific genetic or pharmacological therapeutics. Currently, it is estimated that only about 5% of RDs have a specific pharmacological agents approved. Due to the high cost of R&D of these therapeutics and the relatively small number of patients, the treatment costs are high, ranging from hundreds of thousands to millions of ringgits every year for each patient. The second group consists of non-pharmacological treatment such as specific medical foods, rehabilitation services, surgical treatment and other forms of treatments. Many of these young families have limited resources and having to cope with "out-of-pocket" expenses, thus, exacerbating the financial crises.¹⁰

Current funding models rely on:

- (i) MOH discretionary funding,
- (ii) zakat and charitable funds,
- (iii) corporate social responsibility (CSR) contributions from pharmaceutical companies,
- (iv) occasional Parliament-approved allocations.

While these mechanisms provide life-saving support for some patients, they produce inequities, unpredictability, and long waiting times. A sustainable, ring-fenced national funding mechanism has yet to be established. A number of other innovative funding mechanisms are currently under considerations and beyond the scope of this review.

Regulatory and Data Infrastructure

Malaysia lacks a comprehensive RD registry, relying instead on disease-specific lists curated by clinicians. There is also no formalised national newborn screening policy beyond congenital hypothyroidism, hearing loss and G6PD deficiency. Diagnostic delays remain common, partly due to limited genomic sequencing access outside major centres.⁹

Nonetheless, incremental progress is visible: digital health systems under development may enable the integration of RD modules, and genetic services typically initiated their hospital-based local patient databases to monitor patients' diagnosis and treatment outcomes.

Synergy Between Clinical Networks and Policy Reform

Despite structural constraints, Malaysia's RD progress

is driven by increasing synergy between clinical, institutional, and policy ecosystems. Clinical networks generate evidence and guidelines, patient groups amplify needs and lobby for resources, and policymakers respond through targeted reforms. These interactions produce: (i) improved diagnostic pathways – as Multi Disciplinary Teams (MDTs) streamline referrals and shorten diagnostic odysseys; (ii) enhanced access to therapies – as committees evaluate high-cost drugs based on accumulated clinical evidence; (iii) greater public legitimacy – as patient groups contribute to policymaking dialogues; (iv) policy experimentation – including pilot funding models, state-level newborn screening expansions, and pharmaceutical access partnerships.

Although progress is uneven, this ecosystemic synergy reflects Malaysia's shift from fragmented service provision toward coordinated governance.

Malaysia in the Asia-Pacific Context

Comparatively, Malaysia is positioned in the intermediate tier of Asia-Pacific RD development. Countries such as Japan¹¹, Taiwan¹², Australia¹³, and South Korea¹⁴ have enacted comprehensive RD laws, national insurance coverage, and advanced registries, giving them structural advantages. Meanwhile, lower-middle-income countries in Southeast Asia often lack formal RD frameworks.

Malaysia's strengths include: (i) well-developed tertiary centres with subspecialty expertise; (ii) growing advocacy infrastructure; (iii) increasing policy engagement; and (iv) regional partnerships that enhance clinician training.

However, major gaps remain in financing, statutory protections, disability classification, and genomic research integration. Addressing these gaps is essential for Malaysia to converge with regional leaders.

Future Directions and Strategic Recommendations

Malaysia's recent policy trajectory reflects an unprecedented alignment with global momentum on RDs. In May 2025, the World Health Assembly adopted a landmark Resolution on Rare Diseases, formally recognising rare conditions as a global public health priority and urging member states to strengthen national strategies, coordinated research, and cross-border cooperation. This resolution provides an international mandate for countries – especially those in the Global South – to embed RDs within universal health coverage, research systems, and long-term health financing reforms.

Building on this global shift, Malaysia launched its National Policy for Rare Diseases (2025), the country's first comprehensive framework to articulate national commitments across early detection, diagnostics, genomic integration, workforce development, data governance, and access to therapies. The policy offers a unifying national direction for what was previously a fragmented landscape of small-scale initiatives. It also establishes the governance mechanisms needed to integrate RDs into broader health planning, including research and innovation agendas.

This momentum is further reflected in Malaysia's health research ecosystem. For the first time, RDs have been included in the deliberations for the 13th Malaysia Plan Health Research Priorities (2026–2030). While the formal document has not yet been released, the stakeholder engagement process led by the MOH has emphasised that RDs form part of the country's emerging research concerns. The consultative technical discussions spanning clinicians, researchers, policymakers, and patient groups, signal a significant normative shift: RDs are no longer viewed as marginal, but increasingly recognised as a legitimate component of national research planning. Any reference to RDs in the forthcoming priority list should, however, be interpreted cautiously until the official document is published.

At the regional level, Malaysia has signalled its intention to play a leadership role in advancing RD policy within Southeast Asia. During the Southeast Asia Rare Disease (SEA-RD) Policy Forum, Malaysia publicly committed to spearheading the development of an ASEAN Rare Disease Declaration, positioning RDs as a shared regional health and equity concern rather than a series of isolated national challenges. This commitment reflects an emerging recognition that coordinated policy frameworks, cross-border data sharing, and collective advocacy are essential to addressing the structural disadvantages faced by people living with RDs across the ASEAN region (The Star 2025).

To sustain progress, Malaysia's RD ecosystem requires structural reforms across five domains which were outlined in the NPRD:

1. **Legislative and Policy Consolidation:** A dedicated Rare Disease Act, as practised in Japan and Taiwan, would strengthen rights-based access, financing continuity, and multi-agency accountability.
2. **Comprehensive National Funding Mechanism:** A ring-fenced RD fund, financed through blended models (government budget, social insurance, public-private partnerships), is critical for equitable access to high-cost therapies.
3. **National Rare Disease Registry and Genomic Integration:** A unified registry supported by genomic sequencing platforms would generate high-quality epidemiological data and inform precision-medicine-based policy decisions.
4. **Expansion of Newborn Screening:** Scaling newborn screening beyond the existing limited panel would reduce long-term morbidity, lower economic burden, and improve survival for treatable metabolic disorders.
5. **Strengthening the Workforce Pipeline:** Developing specialised training tracks, fellowships, and regional rotations would expand the talent pool in genetics, metabolic medicine, dietetics, and genetic counselling.

Conclusion

Malaysia's ecosystem of RD care reflects both significant progress and persistent structural challenges. While diagnostic, clinical, and community-based resources exist, systemic gaps particularly in financing, inter-ministerial coordination, public awareness, and research investment, remain a hindrance to equitable access to care. Strengthening nationwide newborn screening, expanding genetic services, recognising genetic counselling, increasing funding for orphan drugs, and establishing a national RD registry are essential steps toward a more inclusive and responsive healthcare system. Ultimately, reframing the RD community not as passive beneficiaries of welfare but as citizens entitled to equal rights and human dignity is fundamental for building a society where no individual is left behind.

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Bridging Realism and Risk: Confederates in Simulation-Based Education

Khairunniza Gharib

Introduction

Simulation-based education provides healthcare professionals with a psychologically and physically safe environment to repeatedly practise both technical and non-technical skills without placing patients at risk.¹ It represents a modern approach to healthcare education that aligns closely with the goals of Education 4.0.² While high fidelity manikins and simulated patients are widely used, the pedagogical value of confederates has received less attention and remains underexplored in literatures.

In healthcare simulation, a confederate is defined as “*an individual other than the patient who is scripted in a simulation to provide realism, additional challenges, or additional information for the participant*”.³ In other words, a confederate is someone who is “in on” the scenario, playing a scripted role such as a nurse, family member, or colleague, to guide or shape the learning experience without being a learner themselves. Unlike simulated patients who primarily portray patients, confederates often represent healthcare professionals, relatives, or team members.^{4,5,6}

Research on healthcare confederates in Malaysia remains limited; however, existing insights into simulation-based education within the country reveal potential areas where confederates could be integrated.⁷ This commentary discusses both the potential benefits and the challenges of employing confederates in simulation, emphasising their role in enhancing healthcare education. It ultimately calls for the broader use of confederates in simulation-based education and highlights the importance of

structured training programmes to ensure they are well-prepared, effective, and consistent in their roles.

Benefits of Confederates in Simulation-Based Education

Incorporating confederates enhances the social realism of simulations⁵ by enacting emotional responses, complex interpersonal interactions, and professional roles, thereby creating learning contexts that cannot be reproduced by manikins or task trainers alone.⁸ For instance, in a simulation of breaking bad news, a confederate playing the role of a distressed family member can display grief, anger, or denial – an emotional response that manikins cannot provide. Such portrayals challenge learners to practise empathy and refine their communication skills in a realistic context.

Similarly, in a team-based emergency scenario, a confederate acting as a nurse may question clinical decisions or introduce a medication error, prompting learners to demonstrate leadership, teamwork, and error management within a dynamic clinical environment. For learners, confederates not only enhance engagement but also deepen immersion⁵ and strengthen the perceived authenticity of simulation scenarios.⁹ They support the development of essential skills such as communication, teamwork, and situational awareness, all of which are critical for safe clinical practice.

Confederates also introduce unpredictability that mirrors real-world interactions, fostering learner resilience and adaptability.¹⁰ For example, in a simulated ward round, a confederate portraying a

Clinical Skills & Simulation Centre, IMU University, Seremban Clinical Campus, Seremban, Negeri Sembilan, Malaysia

Corresponding author:

Khairunniza Gharib

Address: Clinical Skills & Simulation Centre, IMU University, Seremban Clinical Campus, 70300 Seremban, Negeri Sembilan, Malaysia

Email: khairunniza_gharib@imu.edu.my Tel: +6019-2367432

junior doctor might interrupt with an urgent concern, while another, playing a patient's relative, raises emotional questions about care. These unexpected interactions draw learners deeper into the scenario, compelling them to communicate clearly, collaborate effectively, and remain situationally aware. The unpredictability of such encounters closely resembles real clinical practice, helping learners cultivate the flexibility and coping skills necessary for safe patient care.

Beyond realism and unpredictability, confederates can subtly help guide the scenario flow to ensure that key learning objectives are addressed without breaking immersion.⁹ They offer a cost-effective complement to high-fidelity manikins and simulated patients,^{10,11} while their versatility allows them to take on diverse roles across multiple scenarios. Importantly, confederates can also provide valuable feedback on learner performance,^{4,9} offering unique insights from their perspective within the scenario. Such feedback, when incorporated into debriefing, enriches reflection and helps learners better understand how their behaviours and communication are perceived by others.

While challenges exist, confederates significantly enhance learner experiences, emphasising the need for their structured training and deliberate use in simulation. By bridging technical fidelity with human realism, confederates enrich the educational value of simulation and prepare learners more effectively for the complexities of clinical practice.

Challenges in the Use of Confederates in Simulation-Based Education

Alongside their educational value, confederates also present a range of challenges that must be carefully considered. Incorporating confederates into simulations requires thoughtful planning by scenario designers, simulation leaders, and the confederates themselves. Confederates require thorough training to maintain role authenticity, ensure consistency across sessions, balance realism with educational purpose, and minimise bias in learner assessment.^{4,8,12} Acting also does not come easily to every confederate, as some may mix personal and scenario roles, which can mislead learning.

One challenge arises when experienced clinicians are assigned the role of a novice within their own specialty. While this may appear straightforward, it can be difficult for experts to authentically portray a beginner, as their clinical reasoning, management strategies, and other skills have become deeply inherent and automatic. For example, an experienced intensive care nurse may be asked to take on the role of a newly graduated nurse during a simulation on medication administration. While the expectation is to demonstrate hesitancy with dosage calculations and to rely more heavily on protocols or peer support, the senior nurse may instinctively recall drug interactions, anticipate complications, or administer medications with a level of efficiency that unintentionally reflects their expertise rather than the uncertainty of a novice.

In a similar way, junior clinicians may be tasked with portraying a more senior colleague, yet the expected fluency in clinical actions and professional language often exceeds their current level of competence.

For instance, a newly qualified junior doctor may be asked to portray a senior registrar leading a trauma resuscitation. The role requires authoritative leadership, advanced clinical reasoning, and confident communication with the multi-disciplinary team. However, the junior doctor may struggle to convincingly display the decisiveness and fluency characteristic of a more experienced colleague, as these skills are still developing in their own practice.

Another challenge relates to the resources required for effective use of confederates. Recruiting, training, and rehearsing with confederates can be time-consuming and resource-intensive,^{8,13} which may limit their sustainability in settings with constrained staff or budgets.⁵ Even with training, consistency can be difficult to achieve, as different confederates may deliver the same role in slightly different ways, introducing variation in learner experience and potentially influencing assessment outcomes. Furthermore, confederates who are also educators or clinical staff may face role conflict, as their instinct to guide or support learners can inadvertently interfere with the authenticity of the scenario.

In addition, ethical concerns arise when confederates are required to provoke stress, deliver bad news, or portray conflict,¹⁴ as such roles may risk psychological discomfort for both learners and confederates if not carefully managed.⁹ For example, an ethical concern is evident in simulations where a confederate plays an angry family member following a patient's sudden deterioration, a scenario that can produce emotional stress for learners and unease for the confederate. Ethical considerations also extend to maintaining confidentiality, where confederates must refrain from

discussing or revealing how well or poorly learners performed during the simulation.¹⁵ Upholding confidentiality protects learner trust, supports a psychologically safe learning environment, and reinforces the educational integrity of the simulation process.¹⁵

Proposed Structured Preparation Framework for the Use of Confederates in Simulation-Based Education

A structured preparation plan can help overcome challenges related to training, authenticity, resources, and ethics when using confederates in simulation-based education. The process begins with a comprehensive orientation⁹ session, where confederates are introduced to the purpose of simulation, learning objectives, role expectations, confidentiality, and ethical considerations. In this stage, they are also familiarised with the simulation environment, available equipment, and the roles of other participants.

This is followed by a detailed role briefing⁹ which provides a clear understanding of the scenario, expected behaviours, and boundaries for improvisation to maintain authenticity and consistency. Confederates are provided with a written role description that outlines the scenario context, background of the character, expected emotional tone, and verbal or non-verbal behaviours. Adequate orientation and role briefing helps improve performance and realism.⁹

A role play rehearsal¹³ session is then conducted to allow confederates to practice their parts, receive facilitator feedback, and refine their performance for realism and accuracy. Rehearsing beforehand is the

key to running simulation cases well.¹³ The rehearsal can include mock simulations, peer observations, or video recording to allow facilitators to provide targeted feedback on timing, communication style, and authenticity of the portrayal.

On the day of the simulation, a short pre-simulation briefing¹⁶ ensures coordination between facilitators and confederates where the confederates are reminded of the objectives, key cues, and ethical boundaries, including the need to avoid overacting or revealing scenario details prematurely.

Finally, a structured debriefing⁹ is conducted not only for learners but also for confederates. This reflection allows confederates to discuss their experience, share observations about learner behaviour, and express any emotional or ethical challenges faced during the simulation, hence, promoting continuous learning and emotional support, reinforcing their value as integral members of the simulation team.

Additionally, a post-simulation review involving facilitators and confederates helps evaluate the effectiveness of the whole preparation process, identify areas for improvement, and plan for ongoing training or resource optimisation. Regular review meetings also serve as a platform for continued professional development, helping build a pool of skilled, confident, and ethically aware confederates.

Conclusion

Confederates bring unique value to simulation-based education by adding human realism that supports communication, teamwork, and adaptability – skills manikins alone cannot provide. Their use, however, presents challenges in training, authenticity, resources, and ethics. Addressing these through structured preparation, thoughtful scenario design, and institutional support will ensure their meaningful contribution. Future work, particularly in Malaysia, should build evidence and best practices for training and role assignment so that confederates can be integrated more effectively, enriching the realism and impact of healthcare simulation.

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Quality Appraisal of Clinical Guidelines for Vulvar Disorders Using the AGREE II Instrument

Samuel Jun Hao Chau¹, Zheng Yi Ooi¹, Jun Yi Ng¹, Ji Chao Leong¹, Sasikala Devi Amirthalingam², Sivalingam Nalliah³

Introduction

This systematic review aims to appraise clinical practice guidelines and consensus statements on the management of common benign vulvar disorders using the AGREE II checklist.

Methods

A systematic search for articles was conducted employing PubMed, EMBASE, Cochrane, and Science Direct from 1 January 2013 to 31 December 2023. The quality of eighteen practice guidelines was independently assessed by four appraisers using the AGREE II checklist.

Results

Of the eighteen guidelines assessed, one was classified as “recommended”, sixteen were designated as “recommended with modifications” and one as “not recommended”.

Conclusion

All guidelines proposed similar management strategies for the selected vulvar disorders with only minor variations. Medical practitioners are encouraged to treat patients in accordance with evidence-based recommendations in these guidelines.

Keywords: *vulvar disorders, practice guidelines, and consensus, quality appraisal*

Introduction

Common benign chronic vulvar conditions include genitourinary syndrome of menopause (formerly called vulvovaginal atrophy), lichen sclerosus, lichen

planus, lichen simplex chronicus, and vulvodynia.¹ These conditions require effective management guided by up-to-date clinical practice guidelines advocating a multi-disciplinary approach to treatment.² The Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument serves as a valuable tool for assessing the methodological quality of these guidelines across various domains. Systematic evaluations are essential to identify gaps in guideline quality and ensure that general practitioners and gynaecologists can provide optimal care and improvement of quality of life. The objective of this review is to analyse the methodological quality of practice guidelines and consensus on selected vulvar disorders through the application of the AGREE II Instrument.³

Methods

This systematic review adopted the PRISMA 2020 guidelines in searching for clinical practice guidelines related to the management of vulvar disorders (Figure 1). The literature search encompassed multiple databases, including PubMed, EMBASE, Cochrane, and Science Direct, as well as organisational websites, from 1 January 2013, to 31 December 2023. Adopting established reporting standards, this review aims to enhance transparency and rigor in the assessment of clinical guidelines, ultimately contributing to improved patient care.

The MeSH terms used were: “vulvar disorders”, “lichen planus”, “lichen sclerosus”, “lichen simplex chronicus”, “vulvodynia”, “vulval intraepithelial neoplasia”, “practice guideline”, and “consensus”.

¹ School of Medicine, IMU University, Clinical Campus, Seremban, Negeri Sembilan, Malaysia

² Department of Family Medicine, School of Medicine, IMU University, Clinical Campus, Seremban, Negeri Sembilan, Malaysia

³ Department of Obstetrics and Gynaecology, School of Medicine, IMU University, Clinical Campus, Seremban, Negeri Sembilan, Malaysia

Corresponding author:

Dr Sasikala Devi Amirthalingam

Department of Family Medicine, School of Medicine, IMU University, Clinical Campus, Seremban, Negeri Sembilan, Malaysia

Email: SasikalaDevi@imu.edu.my Tel: +6013-3513435

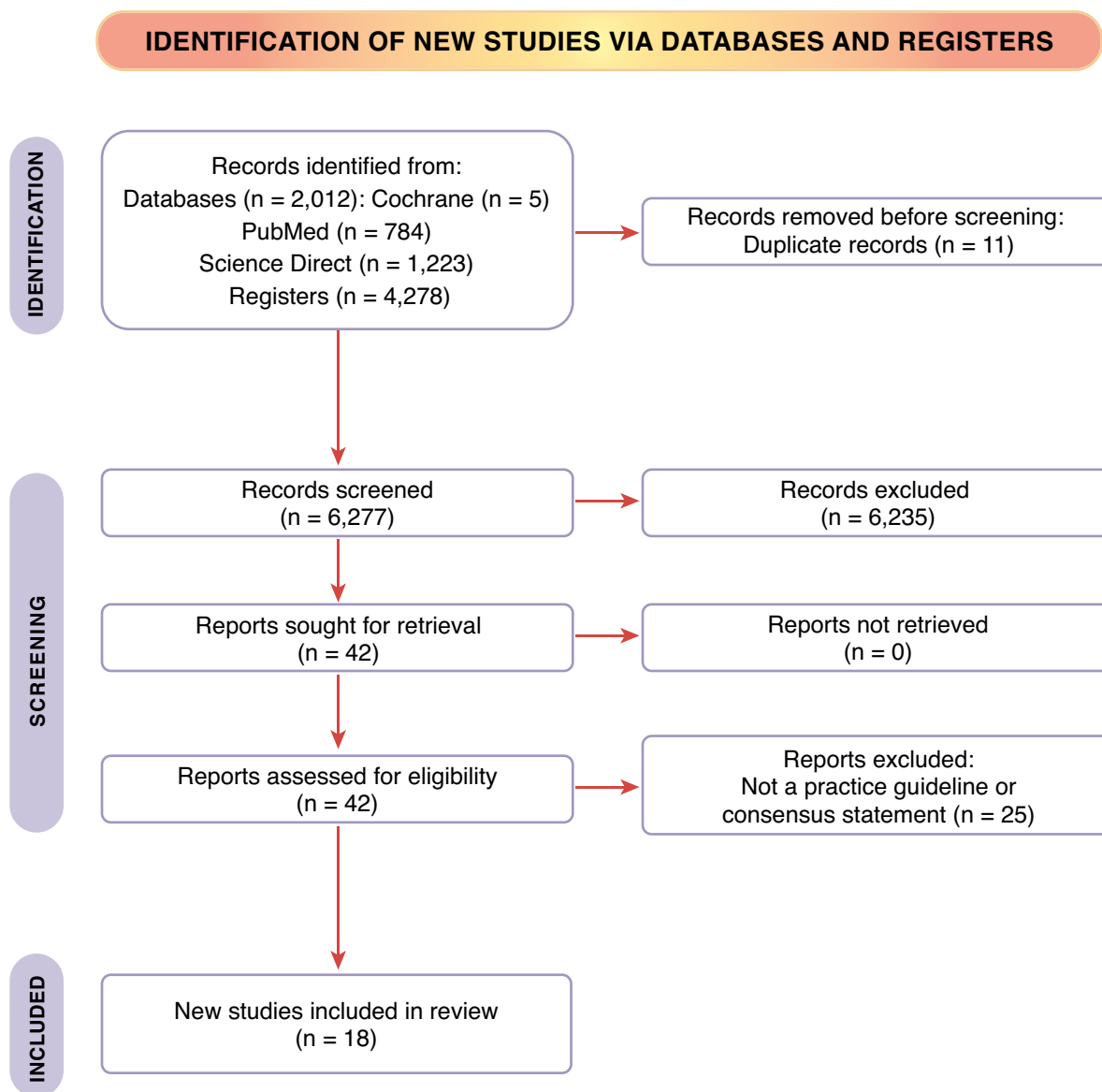


Figure I
PRISMA 2020 Flow Chart for Selection of Clinical Practice Guidelines.
 PRISMA ~ Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020).

Four authors (SJHC, JCL, JYN, ZYO) independently retrieved and reviewed the full-text version of the guidelines and consensus which fulfilled the inclusion criteria.

Inclusion criteria

- i. A practice guideline or consensus bulletin on vulvar disorders that includes at least one of the following conditions: vulvar lichen sclerosus, vulvar lichen planus, vulvar lichen simplex chronicus, vulvodynia, and vulvar intraepithelial neoplasia.
- ii. The selected guideline or consensus statement has been developed, reviewed, or revised between 2013 – 2023.

Exclusion criteria

- i. A translated version of a practice guideline or consensus.
- ii. A guideline intended for patients' reference.
- iii. A brief version or summary of a practice guideline or consensus.
- iv. Guidelines for local institutional practice.

Four authors (SJHC, JCL, JYN, and ZYO) consulted with two subject matter experts (SLN, SDA) employed AGREE II, which has six domains, to assess the methodological quality of the practice guidelines. Each item in AGREE II is rated on a seven-point scale, with a score of 1, strongly disagree, and 7, being strongly agree, while scores of 2–6 indicating that the full criteria are not met. The domain scores were

calculated by scaling the total scores of all items in each domain as a percentage of the maximum possible score for the domain.

It was agreed, by consensus, that a domain score of 50% or higher would be classified as high quality, aligning with findings from similar studies.^{4,5}

Three categories were developed, ie.

- i. Overall score:
50%
Recommended (R)
- ii. Overall score:
30% – 49%
Recommended with modifications (RwM)
- iii. Overall score:
0% – 29%
Not recommended (NR)

Cohen's kappa coefficient was employed to determine the overall concordance and significance with kappa value ranging from 0.00 – 1.00 indicating the level of agreement. A kappa value of 0.00 signifies poor agreement while 1.00 indicates near perfect agreement.

The key characteristics of each guideline appraised are shown in Table I, while the level of evidence and grading of recommendations are summarised in Table II.

Table I
Key Characteristics of Clinical Practice Guidelines.

| NO. | YEAR | COUNTRY | ORGANISATION | TITLE | EVIDENCE-BASED GRADING SYSTEM | EVIDENCE-BASED GRADING TASKFORCE |
|------|------|----------------|--|---|--|--|
| I | 2014 | United Kingdom | British Association for Sexual Health and HIV (BASHH) | 2014 UK National Guideline on the Management of Vulval Conditions | Studies: Ia, Ib, IIa, IIb, III, IV Recommendation: A-C | N/A |
| II | 2021 | Australia | Australasian College of Dermatologists (ACD) | Vulval lichen sclerosis: An Australasian management consensus | N/A | N/A |
| III | 2014 | Spain | Spanish Menopause Society (SMS) | Spanish consensus on vulvar disorders in postmenopausal women | | Grading of Recommendations, Assessment, Development and Evaluation (GRADE) |
| IV | 2018 | United Kingdom | British Association of Dermatologists (BAD) | British Association of Dermatologists guidelines for the management of lichen sclerosis, 2018 | Recommendation: strong, weak, no recommendation | Guideline Development Group (GDG) |
| V | 2023 | United Kingdom | British Gynaecological Cancer Society (BGCS) | British Gynaecological Cancer Society (BGCS) Vulval Cancer Guidelines: Recommendations for Practice | Studies: 1++, 1+, 1-, 2++, 2+, 2-, 3, 4 Recommendation: A-D | Guideline Committee (GC) |
| VI | 2015 | Japan | Japan Society of Gynecologic Oncology (JSGO) | Japan Society of Gynecologic Oncology guidelines 2015 for the treatment of vulvar cancer and vaginal cancer | Studies: I, II, III, IV Recommendation: A, B, C1, C2, D | Guidelines Formulation Committee and Evaluation Committee |
| VII | 2022 | European | The European Society of Gynaecological Oncology (ESGO), the International Society for the Study of Vulvovaginal Disease (ISSVD), the European College for the Study of Vulval Disease (ECSVD) and the European Federation for Colposcopy (EFC) | The European Society of Gynaecological Oncology (ESGO), the International Society for the Study of Vulvovaginal Disease (ISSVD), the European College for the Study of Vulval Disease (ECSVD) and the European Federation for Colposcopy (EFC) consensus statements on pre- invasive vulvar lesions | N/A | N/A |
| VIII | 2021 | European | European Academy of Dermatology and Venereology (EADV1) | 2021 European guideline for the management of vulval conditions | N/A | N/A |

| NO. | YEAR | COUNTRY | ORGANISATION | TITLE | EVIDENCE-BASED GRADING SYSTEM | EVIDENCE-BASED GRADING TASKFORCE |
|------|------|--------------------------|---|---|---|--|
| IX | 2020 | United States of America | American College of Obstetricians and Gynecologists (ACOG1) | Diagnosis and Management of Vulvar Skin Disorders: ACOG Practice Bulletin, Number 224 | Studies: I, II-1, II-2, II-3, III Recommendation: A-C | US Preventive Services Task Force |
| X | 2020 | European | European Academy of Dermatology and Venereology (EADV2) | European S1 guidelines on the management of lichen planus: a cooperation of the European Dermatology Forum with the European Academy of Dermatology and Venereology | N/A | N/A |
| XI | 2015 | European | European Academy of Dermatology and Venereology (EADV3) | Evidence-based (S3) Guideline on (anogenital) Lichen sclerosis | Studies: 1++, 1+, 1-, 2++, 2+, 2-, 3, 4 Recommendation: A, B, C, D, D(GPP) | Grading of Recommendations, Assessment, Development and Evaluation (GRADE) |
| XII | 2012 | European | European Menopause and Andropause Society (EMAS) | EMAS clinical guide: Vulvar lichen sclerosis in peri and postmenopausal women | N/A | N/A |
| XIII | 2022 | China | | Chinese expert consensus on the clinical applications of aminolevulinic acid-based photodynamic therapy in female lower genital tract diseases (2022) | N/A | N/A |
| XIV | 2021 | North America | North American Society of Paediatrics and Adolescent Gynaecology (NASPAG) | NASPAG Clinical Opinion: Diagnosis and Management of Lichen Sclerosis in Paediatric and Adolescent Patients | Studies: I, II-1, II-2, II-3, III | US Preventive Services Task Force |

| NO. | YEAR | COUNTRY | ORGANISATION | TITLE | EVIDENCE-BASED GRADING SYSTEM | EVIDENCE-BASED GRADING TASKFORCE |
|-------|------|--------------------------|--|---|--|---|
| XV | 2015 | Germany | German Society for Gynecology and Obstetrics (DGGG) and German Cancer Society (DKG) | Diagnosis, Therapy and Follow-up Care of Vulvar Cancer and its Precursors. Guideline of the DGGG and DKG (S2k-Level, AWMF Registry Number 015/059, November 2015) | Consensus strength: +++, ++, +, - | N/A |
| XVI | 2019 | Multiple countries | International Continence Society (ICS) and International Society for the Study of Vulvovaginal Disease (ISSVD) | The Clinical Role of LASER for Vulvar and Vaginal Treatments in Gynecology and Female Urology: An ICS/ISSVD Best Practice Consensus Document | Studies: 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5 Recommendation: A-D | Centre of Evidence-Based Medicine, American Society of Plastic Surgeons |
| XVII | 2016 | United States of America | American College of Obstetricians and Gynaecologists (ACOG2) | Committee Opinion No 673: Persistent Vulvar Pain | N/A | N/A |
| XVIII | 2016 | United States of America | American College of Obstetricians and Gynaecologists (ACOG3) | Committee Opinion No.675: Management of Vulvar Intraepithelial Neoplasia | N/A | N/A |

Table II
Summary of Evidence and Recommendations.

| | BASHH | SMS | BAD | BGCS | JSGO | EADV1 | ACOG1 | NASPAG | DGGG, DKG | ISSVD, ICS |
|---------------------------------|-----------|-----|-------------------|-------------|-----------|-------------|-------------------|------------------|-----------|--------------|
| Level of Evidence | | | | | | | | | | |
| Strong | Ia, Ib | 1 | - | 1++, 1+, 1- | I | 1++, 1+, 1- | I | I | +++ | 1a, 1b, 1c |
| Moderate | Ila, I Ib | - | - | 2++, 2+, 2- | II | 2++, 2+, 2- | II-1, II-2, II-32 | II-1, II-2, II-3 | ++, + | 2a, 2b, 2c |
| Weak | III, IV | 2 | - | 3,4 | III, IV | 3,4 | III | III | - | 3a, 3b, 4, 5 |
| Grade of Recommendations | | | | | | | | | | |
| Strongly recommended | A | A | Strong | A | A | A | A | - | - | A |
| Recommended | B | B | Weak | B | B | B | B | - | - | B |
| Recommended with discretion | C | C | No recommendation | C, D | C1, C2, D | C, D | C | - | - | C, D |

Numbering based on Table I

- I. BASHH ~ British Association for Sexual Health and HIV.
- III. SMS ~ Spanish Menopause Society.
- IV. BAD ~ British Association of Dermatologists.
- V. BGCS ~ British Gynaecological Cancer Society.
- VI. JSGO ~ Japan Society of Gynecologic Oncology.
- VIII. EADV1 ~ European Academy of Dermatology and Venereology.
- IX. ACOG1 ~ American College of Obstetricians and Gynecologists.
- XIV. NASPAG ~ North American Society of Paediatrics and Adolescent Gynaecology.
- XV. DGGG ~ German Society for Gynecology and Obstetrics; DKG ~ German Cancer Society.
- XVI. ISSVD ~ International Society for the Study of Vulvovaginal Disease; ICS ~ International Continence Society.

Results

Eighteen English language practice guidelines and consensus documents from 2013 to 2023 have been analysed, based on the inclusion criteria. These covered lichen planus (refer to Table I – Guideline I, V, VIII, IX, X), lichen sclerosus (I, II, IV, VIII, IX, XI, XII, XIII, XIV, XVI), lichen simplex chronicus (I, VIII, IX), vulvodynia (I, III, VIII, XVI, XVII) and vulvar intraepithelial neoplasia (VIN) (III, V, VI, VII, VIII, XIII, XV, XVIII).

Table I shows the key characteristics of clinical practice guidelines. The summary of evidence and recommendations are shown in Table II. Table III shows the total score for each domain and overall quality of the guidelines.

Scope and Purpose

In this domain, the average score was 51.1%. BAD¹² and EADV1⁸ achieved the highest score (80.6%).

Stakeholder Involvement

This domain focused on a diverse group of professionals in ensuring expertise and viewpoints. Additionally, the views and preferences of the target population, including patients and the public, must be actively sought. The average score in stakeholder involvement was 46.5%, with EADV2¹⁰ at 72.2%.

Rigour of Development

This important phase in the development of CPGs assesses the methodological quality and transparency involved, minimising bias and adhering to rigorous methodological standards. This ensures the CPG is reliable and evidence based. The overall mean score of 37.0% is low; ESGO²¹ scored the highest (67.7%). Six guidelines were below 30%.

Clarity of Presentation

Clear presentation of management options with identifiable key recommendations are essential components in this domain. This domain had a mean score of 75.3% and BGCS⁷ scored highest at 94.4%.

Applicability

In the AGREE II framework, “Applicability” relates to implementation of CPGs in the real world. Issues like barriers to its application, resource implications and monitoring of its effectiveness relates to usability and ease of adoption by practitioners.

The overall score of 27.9 % is low. The BAD¹² guideline had a score of 50%.

Editorial Independence

Editorial independence in the AGREE II framework refers to the extent to which clinical practice guidelines are free from influence by funding bodies or conflicts of interest. The analysis showed an overall average score of 53.2% with ESGO²¹ at 87.5%.

Overall Score

The BAD¹² guideline achieved the highest overall score (64.9%) and exceeded 50% in all domains. Others scored 30-50%, categorised as “recommended with modifications”.

Table III
Scores Across Domains Using the AGREE II instrument.

| Guideline | Scope and Purpose | Stakeholder Involvement | Rigour of Development | Clarity of Presentation | Applicability | Editorial Independence | Guideline Overall Score | Recommendation |
|---------------------------------|--------------------|-------------------------|-----------------------|-------------------------|--------------------|------------------------|-------------------------|----------------|
| BASHH (Mean) (Domain scores) | 38.9% 20 (6-42) | 44.4% 22 (6-42) | 28.1% 43 (16-112) | 66.7% 30 (6-42) | 20.8% 18 (8-56) | 58.3% 18 (4-28) | 38.0% 151 (46-322) | RwM |
| ACD | 38.9% 20 (6-42) | 41.7% 21 (6-42) | 25.0% 40 (16-112) | 86.1% 37 (6-42) | 27.1% 21 (8-56) | 50.0% 16 (4-28) | 39.5% 155 (46-322) | RwM |
| SMS | 41.7% 21 (6-42) | 33.3% 18 (6-42) | 26.0% 41 (16-112) | 72.2% 32 (6-42) | 25.0% 20 (8-56) | 75.0% 22 (4-28) | 39.1% 154 (46-322) | RwM |
| BAD | 80.6% 35 (6-42) | 55.6% 22 (6-42) | 60.4% 74 (16-112) | 83.3% 36 (6-42) | 50.0% 32 (8-56) | 75.0% 22 (4-28) | 64.9% 225 (46-322) | R |
| BGCS | 58.3% 27 (6-42) | 13.9% 11 (6-42) | 32.3% 47 (16-112) | 94.4% 40 (6-42) | 45.8% 30 (8-56) | 0.0% 4 (4-28) | 40.9% 155 (46-322) | RwM |
| JSGO | 63.9% 29 (6-42) | 55.6% 26 (6-42) | 26.0% 41 (16-112) | 58.3% 27 (6-42) | 41.7% 28 (8-56) | 83.3% 24 (4-28) | 46.7% 175 (46-322) | RwM |
| ESGO | 66.7% 30 (6-42) | 50.0% 24 (6-42) | 67.7% 81 (16-112) | 75.0% 33 (6-42) | 18.8% 17 (8-56) | 87.5% 25 (4-28) | 59.4% 210 (46-322) | RwM |
| EADV1 | 11.1% 10 (6-42) | 27.8% 16 (6-42) | 36.5% 51 (16-112) | 91.7% 39 (6-42) | 39.6% 27 (8-56) | 83.3% 24 (4-28) | 43.8% 167 (46-322) | RwM |
| ACOG1 | 63.9% 29 (6-42) | 41.7% 21 (6-42) | 42.7% 57 (16-112) | 88.9% 38 (6-42) | 18.8% 17 (8-56) | 54.2% 17 (4-28) | 48.2% 179 (46-322) | RwM |
| EADV2 | 69.4% 31 (6-42) | 61.1% 28 (6-42) | 39.6% 54 (16-112) | 86.1% 37 (6-42) | 22.9% 19 (8-56) | 75.0% 22 (4-28) | 52.5% 191 (46-322) | RwM |
| EADV3 | 80.6% 35 (6-42) | 72.2% 32 (6-42) | 39.6% 54 (16-112) | 91.7% 39 (6-42) | 18.8% 17 (8-56) | 62.5% 19 (4-28) | 54.3% 196 (46-322) | RwM |
| EMAS | 41.7% 21 (6-42) | 30.6% 17 (6-42) | 32.3% 47 (16-112) | 72.2% 32 (6-42) | 25.0% 20 (8-56) | 66.7% 20 (4-28) | 40.2% 157 (46-322) | RwM |
| China | 47.2% 23 (6-42) | 47.2% 23 (6-42) | 33.3% 48 (16-112) | 47.2% 23 (6-42) | 10.4% 13 (8-56) | 45.8% 15 (4-28) | 35.9% 145 (46-322) | RwM |
| NASPAG | 55.6% 26 (6-42) | 63.9% 29 (6-42) | 53.1% 67 (16-112) | 75.0% 33 (6-42) | 29.2% 22 (8-56) | 50.0% 16 (4-28) | 53.3% 193 (46-322) | RwM |
| DGGG, DKG | 50.0% 24 (6-42) | 63.9% 29 (6-42) | 49.0% 63 (16-112) | 58.3% 27 (6-42) | 35.4% 25 (8-56) | 8.3% 6 (4-28) | 46.4% 174 (46-322) | RwM |
| ICS, ISSVD | 61.1% 28 (6-42) | 36.1% 19 (6-42) | 45.8% 60 (16-112) | 50.0% 24 (6-42) | 25.0% 20 (8-56) | 83.3% 24 (4-28) | 46.7% 175 (46-322) | RwM |
| ACOG2 | 27.8% 16 (6-42) | 58.3% 27 (6-42) | 13.5% 29 (16-112) | 80.6% 35 (16-42) | 20.8% 18 (8-56) | 0.0% 4 (4-28) | 30.1% 129 (46-322) | RwM |
| ACOG3 | 22.2% 14 (6-42) | 38.9% 20 (6-42) | 14.6% 30 (16-112) | 77.8% 34 (16-42) | 27.1% 21 (8-56) | 0.0% 4 (4-28) | 27.9% 123 (46-322) | NR |

Numbering based on Table I

- I. BASHH ~ British Association for Sexual Health and HIV.
- II. ACD ~ Australasian College of Dermatologists.
- III. SMS ~ Spanish Menopause Society.
- IV. BAD ~ British Association of Dermatologists.
- V. BGCS ~ British Gynaecological Cancer Society.
- VI. JSGO ~ Japan Society of Gynecologic Oncology.
- VII. ESGO ~ European Society of Gynaecological Oncology.
- VIII. EADV1 ~ European Academy of Dermatology and Venereology.
- IX. ACOG1 ~ American College of Obstetricians and Gynecologists.
- X. EADV2 ~ European Academy of Dermatology and Venereology.
- XI. EADV3 ~ European Academy of Dermatology and Venereology.
- XII. EMAS ~ European Menopause and Andropause Society.
- XIII. China ~ Chinese expert consensus.
- XIV. NASPAG ~ North American Society of Paediatrics and Adolescent Gynaecology.
- XV. DGGG ~ German Society for Gynecology and Obstetrics; DKG ~ German Cancer Society.
- XVI. ISSVD ~ International Society for the Study of Vulvovaginal Disease; ICS ~ International Continence Society.
- XVII. ACOG2 ~ American College of Obstetricians and Gynecologists.
- XVIII. ACOG3 ~ American College of Obstetricians and Gynecologists.

RwM ~ Recommended with Modifications.

R ~ Recommended.

NR ~ Not Recommended.

Practice Recommendations

Lichen Planus

The treatment of lichen planus by five guidelines (refer to Table I – Guideline I, V, VIII, IX, X) prioritise ultra-potent topical steroids like clobetasol propionate as the primary treatment. Guidelines (I, VIII, X) recommend transitioning to weaker steroids or less frequent applications for maintenance, along with careful monitoring and long-term care, especially for erosive forms. BASHH⁶ also recommends the addition of antibacterial or antifungals together with ultra-potent topical corticosteroids. Guidelines (VIII, IX, X) further introduce alternative treatments, such as topical calcineurin inhibitors and suggest intravaginal corticosteroids combined with vaginal dilators for severe cases. Both EADV1⁸ and ACOG1⁹

acknowledge the potential need for surgical intervention in cases of significant scarring.

Lichen Sclerosus

Ten guidelines were eligible for treating lichen sclerosus. ACOG1⁹ advises against using CO2 laser due to insufficient evidence, while BAD¹² provides a comprehensive approach for patients. EADV3¹³ offers strong evidence-based guidance on managing the condition. EMAS¹⁴ and NASPAG¹⁶ agree that topical androgens and progesterone offer no benefits. Chinese experts suggest photodynamic therapy as an option.¹⁵ BAD¹² does not recommend topical calcineurin inhibitors and oral retinoids due to inadequate evidence, but these treatments are mentioned in other studies as alternatives to steroids. Oral retinoids pose a high risk of teratogenicity, requiring a pregnancy

avoidance period of at least 2 years.^{6,8,14} Surgical intervention is limited to cases with coexisting vulvar intraepithelial neoplasia, squamous cell carcinoma, or tissue fusion.⁶

Lichen Simplex Chronicus

Guidelines (I, VIII, IX) address the management of lichen simplex chronicus (LSC), emphasising vulvar care, itch and scratch control, and treating inflammation with topical corticosteroids.^{6,8,9} All recommend avoiding irritants and using mild soap for vulvar self-care, with ACOG⁹ offering more detailed guidance.^{6,8,9} ACOG1⁹ suggests prescribing different potencies of topical corticosteroids based on LSC severity.¹² Additionally, all three guidelines (I, VIII, IX) recommend using anxiolytic antihistamines to effectively manage itching.^{6,8,9}

Vulvodynia

This study includes four clinical guidelines on treating vulvodynia. Guidelines (I, VIII, XVII) stress the importance of vulvar care to minimise irritation, advising practices like avoiding irritants, using mild soaps, applying emollients after showering, and ensuring lubrication during intercourse. For pain management, all four guidelines (I, VIII, IX, III) suggest topical anaesthetics like 5% lidocaine ointment and oral pain modifiers such as low-dose amitriptyline and gabapentin. Non-pharmacological options include physical therapy techniques like pelvic floor muscle feedback and vaginal TENS. Additionally, psychosexual interventions, including cognitive behavioral therapy and counselling, are recommended to help manage pain during sexual activity. Surgical options, such as vestibulectomy, should be considered only after other treatments fail.

Vulvar Intraepithelial Neoplasia (VIN)

Overall, eight clinical guidelines covering vulvar intraepithelial neoplasia highlighted the need for individualised treatment approaches and consistent monitoring to manage recurrence and prevent progression to vulvar cancer. For low-grade VIN (LSIL), JSGO²⁰ recommended periodic monitoring without invasive treatment. For high-grade VIN (HSIL), seven guidelines suggested options including surgical excision or ablation, with DGGG/DKG²² favoring laser ablation while JSGO²⁰ and ACOG3²³ recommending wide local excision if invasive disease is suspected. Topical treatments like imiquimod cream and cidofovir gel were alternatives in six guidelines (III, V, VI, VIII, XV, XVIII). Photodynamic therapy with 5-aminolevulinic acid was recommended by guidelines VII and XIII. Prophylactic HPV vaccination was widely endorsed by six guidelines (V, VI, VIII, XV, XVI, XVIII) to reduce the risk of VIN. For differentiated VIN (dVIN), four guidelines (VI, VII, VIII, XV) emphasised surgical excision with clear margins, rejecting ablation or pharmacological treatments. Reconstructive techniques were advised for extensive surgeries to minimise impairment. Due to the high recurrence rates of HSIL and dVIN, long-term follow-up was advised by all guidelines except China,¹⁵ with varied schedules ranging from biannual to lifelong surveillance.

Discussion

Eighteen practice guidelines and consensus statements on managing vulvar disorders were evaluated using the AGREE II protocol.³ The British Association of Dermatologists guideline (BAD¹²) ranked highest with an overall score of 64.9%, meeting satisfactory criteria

across all six domains. Guidelines VII, X, XI and XIV surpassed the 50% threshold in quality assessment but exhibited notable shortcomings. Domain 4 (Clarity of presentation) scored highest at 75.3%, while Domain 5 (Applicability) had the lowest average score of 27.9%, due to insufficient identification of barriers and monitoring criteria in most guidelines, indicating the need for improvement. Domain 1 (Scope and purpose) was generally well-defined, except in some cases where guidelines lacked details about the target population. Domain 2 (Stakeholder involvement) was satisfactory overall, with most guidelines involving relevant professional groups; however, few considered patients' perspectives during its development. Domain 3 (Rigour of development) scored an average of 37%, with most guidelines using systematic evidence collection and clear recommendation processes. Lastly, Domain 6 (Editorial independence) was well-established, with most guidelines disclosing funding sources and managing potential conflicts of interest. Overall, while the guidelines showed strengths in clarity and stakeholder involvement, significant gaps in applicability and specific patient considerations highlight areas for enhancement to ensure comprehensive and practical management of vulvar disorders.

While the evaluated guidelines demonstrate strengths in clarity and stakeholder involvement, they exhibit gaps in applicability and specific patient considerations. These deficiencies are to be addressed in future revisions of CPGs in management of vulvar disorders. There is a limitation in the applicability domain concerning the local population. The prevalence of vulvar disorders, such as lichen sclerosus, may vary among the ethnic groups in Malaysia.

However, the lack of local CPGs, and the absence of recommendations stratified by ethnic groups, make it difficult to provide comments that apply to the local population. Access to vulvoscopy, colposcopy, and histopathological services in primary care settings is a common challenge in resource-limited countries. Consequently, clinicians in primary care often rely on clinical criteria; adopting this as an alternative diagnostic approach could broaden the applicability of this domain. Additionally, care-seeking behaviour for vulvar disorders in the local population is often delayed or limited. We recommend incorporating culturally sensitive educational strategies into CPGs to address these issues. Another concern is the gap in training availability for providers in the examination and diagnosis of common vulvar disorders. Since most vulvar disorders are chronic, and significantly affect the quality of life, locally relevant CPGs should incorporate these considerations and ensure clear monitoring indicators for affected individuals, as well as adherence to treatment strategies.

Implications

The main implication from this systematic review is that, there needs to be an agreed definition of the list of vulvar disorders that should be included in every clinical guideline. This will allow for better comparability and applicability among different medical practitioners internationally. Moreover, it will ensure that all patients with vulvar disorders can receive the most optimal care based on evidence from research. Management strategies for the varied vulvar disorders clearly require a standardised classification agreed upon by different medical specialties such as primary care, dermatology and gynecology to enhance comparability and applicability of treatment

strategies. Many of the disorders necessitate a multidisciplinary approach, emphasising the need for improved communication among stakeholders for effective evidence-based recommendations.

Limitations

While the AGREE II tool offers a comprehensive user manual outlining the criteria for assessing each domain, it falls short in providing sufficient explanations and examples of what constitutes an appropriate score. The research team implemented a consensus-building approach to address this issue, especially when the score for one item differed by more than three points.

Conclusion

Medical practitioners managing vulvar disorders will find the European Guideline for the Management of Vulval Conditions (EADV⁸) as the most

comprehensive clinical guideline available, encompassing all five vulvar disorders discussed in this systematic review.

The Guidelines for the Management of Lichen Sclerosus by BAD¹² achieved satisfactory scores in all domains, and is the only guideline recommended without modifications.

Clearly, a consensus definition of common vulvar disorders is essential for optimising patient care. Additionally, regular reviews and updates of practice guidelines are necessary, as many of the guidelines reviewed were published prior to 2020.

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Students' Satisfaction and Learning Outcomes with Virtual and Light Microscopy in Undergraduate Pathology: A Randomised Cross-Over Trial

Thin Thin Win¹, Saint Nway Aye¹, Sunil Pazhayanur Venkateswaran¹, Purushotham Krishnappa¹, Dhanashri Kshitij Panse¹, Arun Kumar Basavaraj²

Introduction

Virtual microscopy (VM) has emerged as a valuable adjunct to light microscopy (LM) in medical education, enabling remote access to high-quality histopathological images. While many studies report improved satisfaction and comparable better learning outcomes with VM, effectiveness in student performance was not properly studied. This study evaluated students' satisfaction and effectiveness of VM compared to LM in undergraduate pathology teaching of a Malaysia private institution.

Methods

A randomised cross-over trial was conducted among Year 1 and Year 2 medical students. Pre- and post-tests consisting of 10 one-best-answer (OBA) questions, mapped to the histopathology slides used in pathology practical sessions, were used to analyse effectiveness of VM and LM. After crossover swapping the groups, students completed pre-validated 5-point Likert scale questionnaires to assess the satisfaction on both methods.

Results

A majority ($\geq 65\%$) expressed satisfaction with both LM and VM; however, VM scored higher for ease of use, time efficiency, and image quality. Group (B) with VM followed by LM had higher mean pre-test scores (6.85 ± 1.80) than Group A with LM followed by VM (5.92 ± 2.29), suggesting possible baseline differences. Post-test scores improved significantly in both groups ($p < 0.001$). Although Group B's post-test mean was

higher (9.13 ± 1.19) than Group A's (8.61 ± 1.63), this may reflect initial group performance rather than VM superiority alone.

Conclusion

Although the reliability statistics of tests could not be analysed, this study concluded that VM is a reliable adjunct tool to replace traditional LM in teaching learning. However, differences in baseline performance between groups highlight the need for cautious interpretation when comparing modalities. Integration of VM into e-learning platforms may enhance blended pathology education.

Keywords: *Virtual microscopy; Light microscopy; Histopathology; Undergraduate medical education; Student satisfaction; Learning outcomes.*

Introduction

Pathology teaching plays a pivotal role in bridging the gap between basic sciences and clinical practice. In addition to understanding the aetiopathogenesis and pathophysiology of diseases, medical students must develop the ability to recognise and interpret morphological features, both gross and microscopic, to arrive at accurate diagnoses and support patient management.^{1,2} Histopathology, therefore, remains a cornerstone of undergraduate medical curricula.

Observing and studying typical histology and histopathology slides are integral aspects of pathology education in an undergraduate medical programme. Traditionally, histopathology teaching has relied

¹ Department of Pathology and Pharmacology, School of Medicine, IMU University, 126 Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

² Newcastle University Medicine Malaysia (NUMed Malaysia) DULN005(J), No. 1 Jalan Sarjana 1, Kota Ilmu, EduCity@Iskandar, 79200 Iskandar Puteri, Johor, Malaysia

Corresponding author:

Dr Thin Thin Win

Department of Pathology and Pharmacology, School of Medicine, IMU University, 126 Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia
E-mail: thinthinwin@imu.edu.my

on light microscopy (LM) in supervised laboratory sessions. While LM offers direct visualisation of glass slides, it requires substantial resources, including high-quality slides, functional microscopes, and skilled faculty able to provide close guidance.³ Maintaining microscope functionality and replenishing slide collections pose additional logistical challenges.⁴

The digitisation of histopathological slides has introduced virtual microscopy (VM) as an innovative teaching tool. VM enables high-resolution whole-slide imaging that can be navigated on digital platforms, allowing simultaneous access for unlimited students regardless of location.^{5,6} Studies have shown that VM can enhance student engagement, promote self-directed learning, and offer consistent image quality.^{7,8,9} Reported satisfaction rates with VM are often higher than with LM, particularly for accessibility and convenience.⁸ Student satisfaction with VM in a study of an undergraduate medical school was reported as 89% compared with 53% of traditional light microscopic studies.⁸ VM has been shown to enhance student learning experiences, and an unlimited number of students can study digital slides at the same time.^{9,10}

The medicine programme employs a problem-based learning (PBL) curriculum, students must integrate histopathology into their understanding of disease mechanisms despite the lack of discipline-specific teaching blocks. Increasing student numbers, along with difficulties in obtaining certain histopathological slides, have created challenges in organising small-group LM sessions. VM offers a potential solution to these limitations by reducing dependence on physical

slides and equipment while enhancing access to rare cases.

As few medical schools in Malaysia including our institution have initiated the application of VM in medicine programme teaching, we would like to explore the students' satisfaction and effectiveness in LM and VM in pathology teaching learning in an undergraduate medical course. Most of the research studies on VM were done with students' satisfaction by using questionnaire survey; however, effectiveness of VM has not been studied properly especially in Malaysia. Although a few systematic reviews on the efficacy of VM in pathology education were conducted, the heterogeneity was high with the included articles which did not permit outlining a specific method of performance evaluation.^{11,12}

Therefore, to fill up the research gap, this study was designed to compare students' satisfaction and learning outcomes when using VM and LM for histopathology in undergraduate pathology teaching. To answer the research question on the students' satisfaction and effectiveness on LM and VM in pathology teaching learning of an undergraduate medical course, we conducted a randomised cross-over trial to evaluate both modalities in the context of respiratory and gastrointestinal pathology teaching, aiming to provide balanced insights into their strengths, limitations, and applicability in blended learning environments.

Methods

Study Design and Participants

This randomised cross-over trial was conducted among Year 1 and Year 2 undergraduate medical

students enrolled in Semester 2 and Semester 3 at the IMU University (Formerly International Medical University), Malaysia. A total of 88 students participated voluntarily after a briefing on the study's objectives and procedures. Written informed consent was obtained from all participants. The study received ethical approval from the IMU Joint Committee on Research and Ethics (Ethical Approval Code: IMU 469/2000).

Randomisation and Group Allocation

Students were assigned into two groups by simple randomisation:

- Group A: LM session first, followed by VM session.
- Group B: VM session first, followed by LM session.

Group A consisted of 49 students (24 from Semester 2, 25 from Semester 3), while Group B comprised 39 students (20 from Semester 2, 19 from Semester 3).

Teaching Content and Materials

Two modules from the pathology curriculum were selected:

1. Respiratory System (Semester 2)
2. Gastrointestinal System (Semester 3)

For each module, histopathology slides relevant to key teaching points were used. The same cases were prepared for both LM and VM sessions to ensure comparability.

- Respiratory pathology (6 slides): Tuberculous lymphadenitis, miliary tuberculosis, acute pneumonia, chronic pneumonia, squamous cell carcinoma of the lung, anthracosis.

- Gastrointestinal pathology (5 slides): Acute appendicitis, colonic adenomatous polyp, colonic adenocarcinoma, signet ring cell carcinoma, squamous cell carcinoma of the oesophagus.

Virtual Microscopy Preparation

Glass slides were scanned using the 3DHISTECH PANNORAMIC Midi II automatic digital slide scanner¹³ and viewed using Case Viewer software. VM images were identical in content to the LM glass slides.

Orientation and Viewing Procedure

All students received a 15-minute standardised orientation before the practical session to familiarise them with the assigned modality:

- For LM, instructions on focusing, magnification adjustment, and slide handling were provided.
- For VM, navigation tools, zoom functions, and annotation features were demonstrated.

Viewing was conducted individually at dedicated workstations to ensure equal access and prevent group bias. Each session lasted one hour under identical environmental conditions (quiet laboratory, same lighting, temperature, and seating arrangement).

Assessment of Learning Outcomes

Effectiveness was measured using pre-test and post-test scores:

- Format: 10 one-best-answer (OBA) questions for each module.
- Content: Questions were mapped directly to the histopathological features visible in the assigned

slides. The questions were blueprinted on the relevant learning outcomes of the curriculum.

- Sample questions: Provided in Appendices 1 and 2.
- Administration: The pre-test was conducted immediately before the session, and the post-test immediately after. Tests were supervised, with a fixed time allocation for all students.

After the crossover, students did not repeat the OBA tests but completed satisfaction questionnaires for the second modality. The details of the study are shown in Figure I.

Assessment of Student Satisfaction

Two separate pre-validated questionnaires (for LM and VM) with 11 items each were adopted from published literature, after seeking permission from the original

authors to use and modify the questions.^{14,15,16} Each used a 5 point Likert scale (Strongly agree to Strongly disagree) to assess ease of use, effectiveness, time efficiency, image quality, and technical challenges.

Statistical Analysis

Data were analysed using SPSS version 29.0 (IBM Corp, Armonk, NY, USA). Pre- and post-test scores within each group were compared using the Wilcoxon signed-rank test to compare two related samples if the assumption of normality for the dependent t-test were not met. Satisfaction data were expressed as percentages of students selecting “Strongly agree” or “Agree” for each item. Statistical significance was set at $p < 0.05$.

A flowchart for the detailed conduct of the study is shown in Figure I.

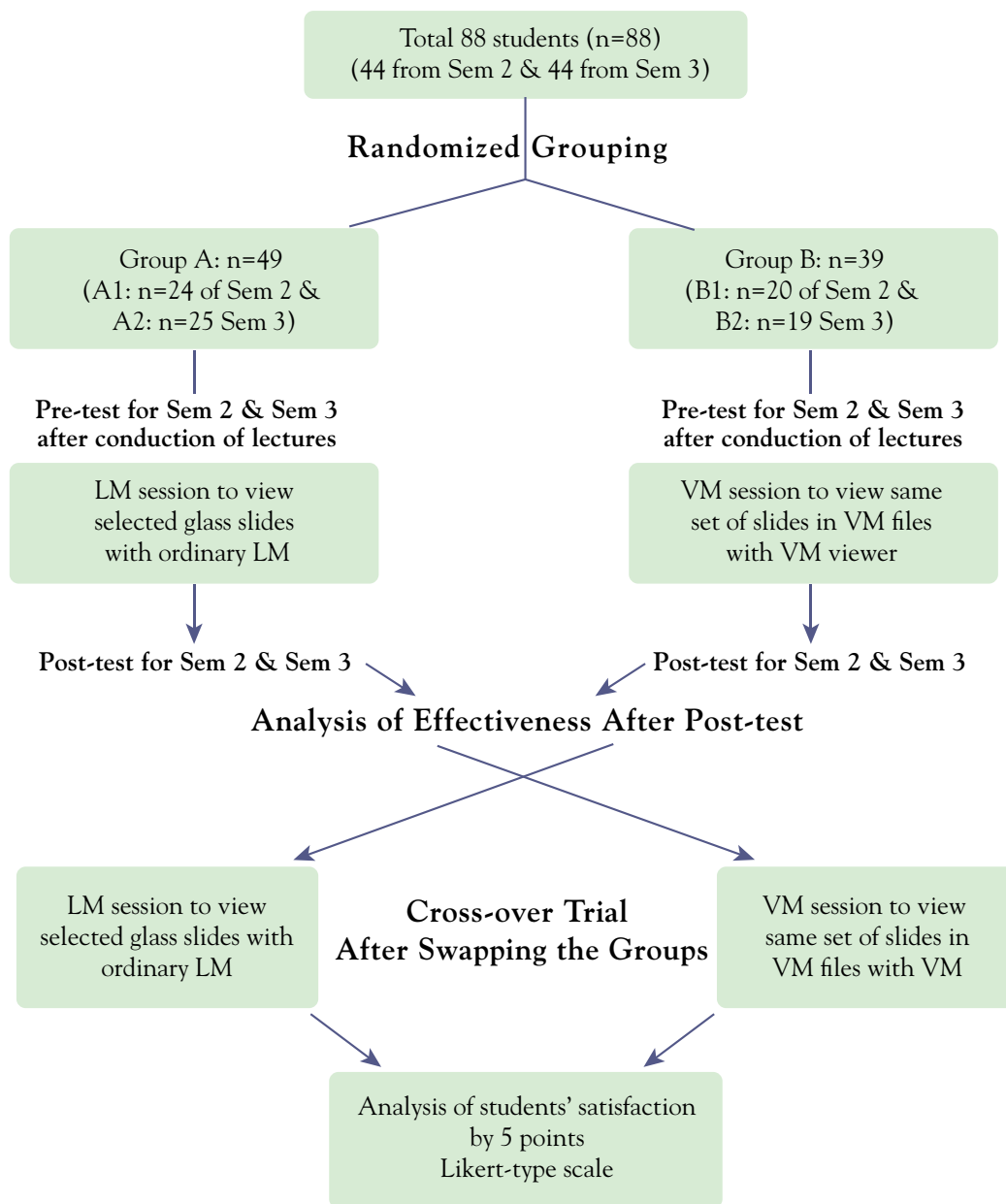


Figure 1: A flowchart for the conduct of the study. (Sem: Semester).

Results

Participant Flow and Completion

Eighty-eight students (44 from Semester 2 and 44 from Semester 3) completed all study components, including the pre-test, post-test, and both satisfaction questionnaires. No participants were excluded after randomisation.

Student Satisfaction with Light Microscopy (LM)

Table I summarises student responses to the LM questionnaire. A total of 65% of students agreed or strongly agreed that LM was user-friendly and easy to use. Most agreed that LM was effective for the course (71.5%) and provided adequate image quality

(59.5%). However, fewer students agreed that LM saved time (42.5%) or allowed them to view all slides at the required magnification in the allocated time (63%).

Student Satisfaction with Virtual Microscopy (VM)

Table II presents responses to the VM questionnaire. Over 90% of students agreed or strongly agreed that VM was user-friendly, effective for the course, and time-saving. Students consistently rated VM higher than LM in ease of access (93.5%), time efficiency (92.5%), and image quality (95%). Technical problems with VM were reported by only 13.5% of students, though some noted navigation challenges (18%).

Table I: Student’s responses (in percentage) to the survey questionnaires regarding the use of light microscopy.

| No | Statements | Strongly agree (%) | Agree (%) | Neutral (%) | Disagree (%) | Strongly disagree (%) |
|----|--|--------------------|-----------|-------------|--------------|-----------------------|
| 1 | Light microscopy (LM) is user-friendly and easy to use. | 30 | 34.5 | 29 | 6.5 | 0 |
| 2 | LM is effective for the purpose of the course. | 39 | 32.5 | 22.5 | 4 | 2 |
| 3 | The access to view the glass slides is quick. | 31 | 32.5 | 25.5 | 9 | 2 |
| 4 | LM allows time saving. | 20 | 22.5 | 33.5 | 16 | 8 |
| 5 | The quality of the images of the glass slides is adequate under LM. | 27 | 32.5 | 28.5 | 10 | 2 |
| 6 | LM has the required magnification for identification of tissue detail. | 27 | 35 | 25.5 | 6.5 | 6 |
| 7 | I had problems with the magnification of LM. | 7 | 20 | 14.5 | 42.5 | 16 |
| 8 | Instructions to use LM are clearly understood by the students. | 38.5 | 33.5 | 17.5 | 8 | 2.5 |
| 9 | I can view all glass slides at the required magnification in the allocated time. | 35 | 28 | 21.5 | 10.5 | 5 |
| 10 | LM can facilitate overall learning of the students. | 32.5 | 32 | 24 | 6.5 | 5 |
| 11 | I did not face any technical problems using LM. | 23 | 30.5 | 31.5 | 13 | 2 |

Table II: Student's responses (in percentage) to the survey questionnaires regarding the use of virtual microscopy.

| No | Statements | Strongly agree (%) | Agree (%) | Neutral (%) | Disagree (%) | Strongly disagree (%) |
|----|--|--------------------|-----------|-------------|--------------|-----------------------|
| 1 | Virtual microscopy (VM) is user-friendly and easy to use. | 62.5 | 31.5 | 6 | 0 | 0 |
| 2 | VM is effective for the purpose of the course. | 62 | 36.5 | 0 | 1.5 | 0 |
| 3 | The access to the virtual slides is quick and it allows time saving | 65.5 | 28 | 5.5 | 1 | 0 |
| 4 | VM allows time saving. | 71 | 21.5 | 6.5 | 1 | 0 |
| 5 | The quality of the images of the virtual slides is adequate. | 58.5 | 36.5 | 4 | 1 | 0 |
| 6 | VM has the required magnification for identification of tissue detail. | 64 | 29.5 | 6.5 | 0 | 0 |
| 7 | I had problems with the navigation of VM. | 9 | 9 | 14 | 29.5 | 38.5 |
| 8 | Instructions to use VM are clearly understood by the students. | 56 | 22.5 | 16 | 4 | 1.5 |
| 9 | I can view all virtual slides at the required magnification in the allocated time. | 57.5 | 24 | 14.5 | 4 | 0 |
| 10 | VM can facilitate overall learning of the students. | 62.5 | 25.5 | 12 | 0 | 0 |
| 11 | I did not face any technical problems using virtual microscopes. | 45.5 | 32 | 18.5 | 4 | 0 |

Pre- and Post-Test Performance

Group A (LM → VM):

- Pre-test mean score: 5.92 ± 2.29
- Post-test mean score: 8.61 ± 1.63
- The improvement was statistically significant ($p < 0.001$).

Group B (VM → LM):

- Pre-test mean score: 6.85 ± 1.80
- Post-test mean score: 9.13 ± 1.19
- The improvement was statistically significant ($p < 0.001$).

Although Group B achieved higher pre-test and post-test means than Group A, this difference may partly reflect the baseline variation in student performance rather than the teaching modality alone.

Pre-test and Post-test to Assess the Effectiveness of LM and VM

In group A (LM followed by VM), mean scores of pre-tests and post-tests were 5.92 ± 2.29 and 8.61 ± 1.63 respectively (Figure II). The Wilcoxon signed ranks test showed that the performance of Group A between pre-tests and post-tests was statistically significant with $p < 0.001$ (Table III).

In Group B (VM followed by LM), mean scores of pre-tests and post-tests were 6.85 ± 1.80 and 9.13 ± 1.19 respectively (Figure III). The Wilcoxon signed ranks test showed that the performance of Group B between the pre-tests and post-tests was also statistically significant with $p < 0.001$ (Table IV).

Both groups scored more in the post-test. However, the mean scores of both pre-test and post-tests of Group B (VM followed by LM) were higher than Group A (LM followed by VM).

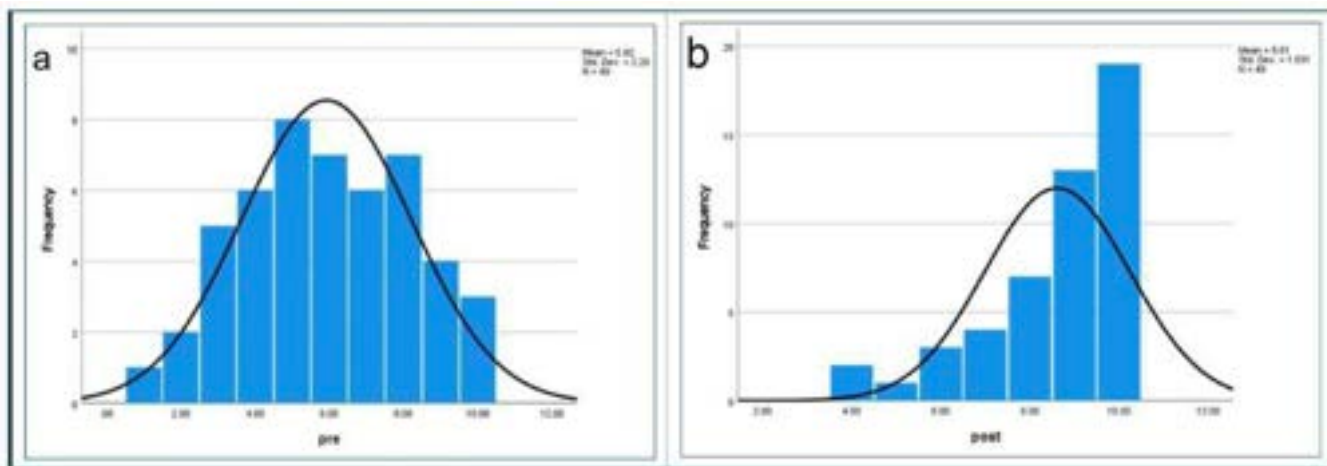


Figure II: Analysis of performance of pre-test (a) and post-test (b) of group A (LM followed by VM).

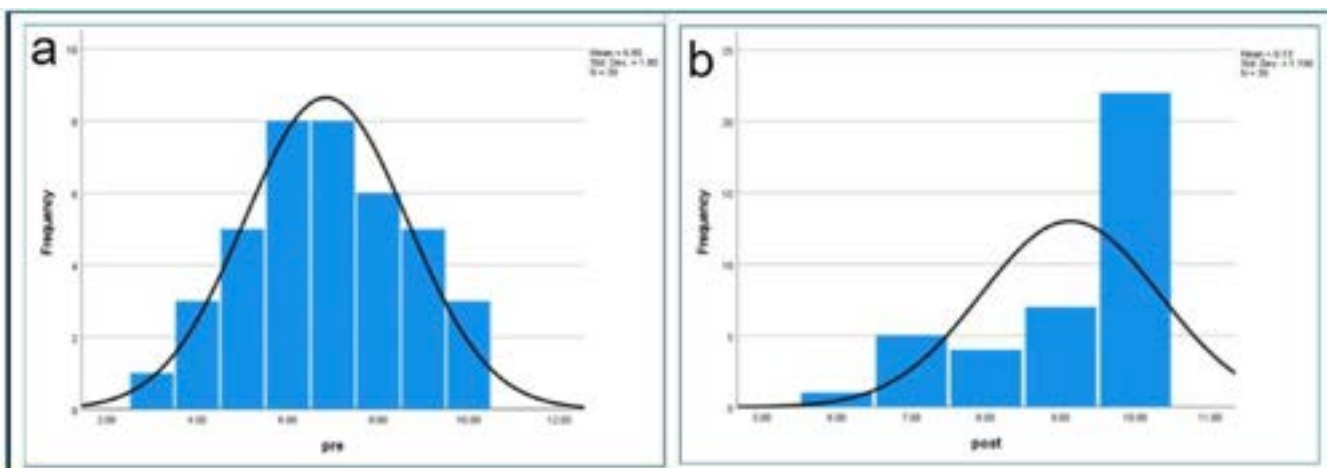


Figure III: Analysis of performance of pre-test (a) and post-test (b) of group B (VM followed by LM).

Table III: Wilcoxon signed ranks test and test statistics on the analysis of performance of pre-test and post-test of group A (LM followed by VM).

| | | N | Mean Rank | Z | P value |
|------------|----------------|-----------------|-----------|--------|---------|
| Post - Pre | Negative Ranks | 0 ^a | .00 | -5.467 | <.001 |
| | Positive Ranks | 39 ^b | 20.00 | | |
| | Ties | 10 ^c | | | |

^a post < pre ^b post > pre ^c post = pre

Table IV: Wilcoxon signed ranks test and test statistics on the analysis of performance of pre-test and post-test of group B (VM followed by LM).

| | | N | Mean Rank | Z | P value |
|------------|----------------|-----------------|-----------|--------|---------|
| Post - Pre | Negative Ranks | 0 ^a | .00 | -4.647 | <.001 |
| | Positive Ranks | 28 ^b | 14.50 | | |
| | Ties | 11 ^c | | | |

^a post < pre ^b post > pre ^c post = pre

Summary of Findings

- Both LM and VM sessions were associated with significant improvements in test scores.
- VM received consistently higher ratings for ease of use, accessibility, image quality, and time efficiency.
- LM was still valued by many students for its tactile and traditional approach.
- The higher performance of Group B in both pre- and post-tests indicates a possible influence on prior knowledge or ability level, which must be considered when interpreting modality effectiveness.

Discussion

This randomised cross-over trial compared students' satisfaction and learning outcomes between virtual microscopy (VM) and light microscopy (LM) in undergraduate pathology teaching. Both modalities led to significant improvements in post-test scores, indicating that either approach can support histopathology learning when combined with prior lectures. VM, however, consistently received higher ratings for accessibility, image quality, and time efficiency.

With the advent of digitalisation, the education sector has taken new strides to adapt and evolve in the changing times. Professionals and institutions have turned over to more digital solutions that are remotely accessible. Digitalisation of histopathological slides also employs a broad range of pathological learning to educate both undergraduate and postgraduate students through continuous professional development and external quality assurance.¹⁷ It is also now being used for diagnosis in clinical pathology practice at some diagnostic centres.¹⁸

VM has been introduced as an adjunct tool to teach histology and histopathology in medical schools for more than a decade.¹⁹ Many studies on VM have reported both advantages and limitations, especially in undergraduate medical teaching. In our study, based on the results of the survey questionnaires regarding LM and VM, the majority of the students preferred VM due to various reasons, such as it being user-friendly, timesaving, ease of navigation, easy magnification in identification of the tissue histopathology details, better quality of histological images and less technical problems compared to LM. Most of the students indicated that the quality of images and magnification were more satisfactory compared to LM. Most of the

students did not have any problems with navigation or any technical problems with using VM. Therefore, our study confirmed the students' satisfaction with VM in histopathology teaching and learning. These findings from our study are consistent with the studies of the use of VM in anatomy teaching and learning.^{15,16,20,21}

In the assessment of effectiveness of LM and VM by using the pre-test and post-test OBAs, both groups scored more marks in the post-tests. As the pre-tests were done before the start of the pathology practical sessions, the mean scores of the pre-tests were less than the post-tests for both groups. Although the post-test scores of both groups were not statistically comparable, the mean post-test score of Group B (VM followed by LM) was higher than that of Group A (LM followed by VM). This finding indicated that VM is more effective in learning histopathological images and understanding of students' histopathological identification. This finding is also comparable with some other studies on the effectiveness of VM.^{20,21}

VM has been emerging into anatomy and pathology teaching in medical schools, especially during the COVID-19 pandemic. Pathology teaching around the world has largely shifted towards remote delivery, and whole courses need to be re-designed to fit the online environment. VM is one of the methods of teaching histology and histopathology via a synchronous remote delivery approach.^{22,23,24} However, just like any other teaching tool, it has both its strengths and limitations.²⁵

One of the advantages of VM is its convenience, flexibility, lesser distraction and engagement, and student's academic performance were satisfactory

in general.²³ These advantages are also reported in some of the studies on learning oral histology for a dentistry programme.²⁶ It improves accessibility to slides and promotes self-directed learning.²¹ VM also reduces the challenges of the availability of quality histopathological slides for teaching histopathology. In our institution, some of the histopathological slides are difficult to obtain nowadays such as pneumonia and some other rare diseases. By digitising the slides, deterioration of the staining quality can be avoided and maintained for the future. There are other advantages of VM, especially during the COVID-19 pandemic and the post-COVID pandemic period. VM can reduce the risk of contamination and transmission of infectious diseases among the users, whereas cleaning and sanitisation of light microscopes after every use is challenging.

Most of the challenges in our study using VM were the installation of the software to view the VM files and its compatibility with some laptops, especially those made by Macintosh (Apple™). Technical issues with compatibility and the operating system of Mac laptops were also reported by other studies on VM.¹⁵ Apart from these issues, VM does not have any reported major issues in histology and histopathology teaching of undergraduate medical programmes. However, using VM in postgraduate pathology training reported some challenges in the interpretation of histopathology slides such as fuzzy images, poor screen colour and freezing of the screen, etc.²⁷

Nowadays, the availability of numerous free online VM resources has helped global access to educational materials geared towards learning of normal histology of human tissue and histopathological features of

various human diseases.²⁸ Facilities of whole slide imaging (WSI) and digitisation of the slides have provided valuable support in medical education, training, and diagnosis.²⁹ Some of the institutions are using a cloud-based library of high-resolution biomedical histology images for the students to study histology and histopathology.^{30,31} A systematic review of 39 studies on the outcomes of VM concluded that VM provided stimulated learning, improved student satisfaction and an overall better learning experience.¹²

VM is not only beneficial to undergraduate pathology teaching, but also efficient and reliable tools in postgraduate pathology teaching and assessments.⁵ Whole slide imaging has emerged as the digital pathology platform of choice for teaching in recent years. Some of the postgraduate examination boards are utilising VM with Web-based extended multiple-choice examination along with virtual slides and minimal clinical information to resident trainees.^{5,24} As VM is enhancing proficiency testing and quality of education, it is now being widely used in external quality assurance in histopathology, haematopathology and microbiology.^{31,32} Since VM allows students to actively explore slides, annotate, and compare cases, it supports competency-based education. Greater flexibility and accessibility of VM support blended or hybrid learning models and flipped classrooms, where students review slides before class and discuss cases during tutorials. This can influence the curriculum design of postgraduate pathology training.³³ VM also can be integrated into assessment, especially for objective structural practical examination (OSPE). Some of the medical institutions have initiated using VM in undergrad

examinations, especially starting during COVID-19 pandemic time.³⁴

The benefits of VM are not only for the students but also for the educators in medical and health sciences education. The implementation of an online VM viewer can enhance teaching and learning and be beneficial to the students and faculties as it allows personalised education and increases accessibility of learning materials.³⁵ A study on VM exploring the perception of health and earth science university teachers reported that VM learning activities promote higher-order thinking skills in both online and face-to-face teaching sessions.³⁶

Interpretation of Findings

Our results aligned with previous studies which reported high student satisfaction with VM.^{7,8,14,16} The ability to access slides quickly, navigate with ease, and zoom without optical limitations likely contributed to its appeal. Students also valued the time efficiency of VM, which eliminates the need for manual focusing and repositioning of glass slides.

However, the finding that 65% of students also rated LM positively underscores that traditional microscopy retains an important role in pathology education. LM provides tangible, hands-on experience that some students find more engaging for skill development, particularly in focusing techniques and slide handling.

The higher pre- and post-test scores in Group B (VM first) compared with Group A (LM first) may reflect pre-existing differences in student knowledge or aptitude rather than the inherent superiority of VM. Similar observations have been reported in

other cross-over designs, where baseline performance influenced apparent modality effectiveness.³⁷ This underlines the importance of interpreting VM–LM comparisons with caution. Some strategies to mitigate baseline differences in interpretation of the results such as stratified randomisation should be considered in future studies.

Technical Limitations of VM

While VM offers numerous advantages, its effectiveness is dependent on technical factors. High-resolution images require substantial file sizes and reliable hardware for smooth navigation. Viewing performance can be affected by device processing speed, screen resolution, and network stability. Some students in our study reported navigation challenges, and compatibility issues were noted with certain laptop operating systems, particularly macOS which are consistent with prior reports.^{14,18} Image quality, although generally superior in VM, can be compromised if slides are poorly prepared before digitisation, or if colour calibration is inconsistent across displays. These considerations are critical when implementing VM in resource-limited or mixed-device environments.

Relevance in Blended and Remote Learning

VM has gained prominence during the COVID-19 pandemic, enabling continuity of histopathology teaching through remote access.^{19,20} Its integration into e-learning platforms supports asynchronous learning and provides a scalable solution for large student cohorts. However, a balanced approach combining VM for accessibility and LM for hands-on skills may provide the most comprehensive training experience.

Strengths and Limitations of this Study

Strengths include the cross-over design, which allowed all students to experience both modalities, and the use of identical histopathology content for fair comparison. The study also employed pre-validated questionnaires and matched teaching conditions across groups.

Limitations include the small number of OBA test items (10 per module), which restricted the ability to assess reliability metrics such as Cronbach's alpha. Effectiveness was measured immediately after each session, without long-term retention testing. Baseline differences in group performance could not be fully controlled despite randomisation. Technical aspects of VM, such as file loading time and device compatibility, were not formally quantified, though they were reported anecdotally.

Implications for Future Practice

Future studies should include larger question banks, long-term follow-up assessments, and detailed evaluation of the technical performance of VM systems. Institutions planning to adopt VM should consider device standardisation, adequate server capacity, and integration with existing learning management systems to maximise benefits. Challenges in conducting VM sessions could be overcome if VM application can be merged into the e-learning platform to provide easy access to educational content. Future research studies also should consider long-term retention and maintenance or cost-effective analysis.

Conclusion

Both virtual microscopy (VM) and light microscopy (LM) effectively supported learning in undergraduate histopathology teaching, with significant improvements in student performance following either modality. VM was rated more highly for ease of use, accessibility, image quality, and time efficiency, but LM remained valued for its hands-on experience and traditional diagnostic approach. Differences in baseline performance between groups highlight the need for cautious interpretation when comparing modalities. While VM offers clear advantages in scalability and integration into e-learning platforms, optimal pathology training may be achieved through a blended approach that leverages the strengths of both VM and LM.

For the educators, development of structured teaching learning guides along with the training should be considered. Development of institutional level policy for the use of VM and funding may enhance the digital literacy and innovation in teaching learning.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

This study received ethical approval from the IMU Joint Committee on Research and Ethics (Reference number: 4.3/JCM-195/2020) and Project ID: IMU 469/2020).

Authors' Contribution

- Research concept and design: TTW, SNA, SPV.
- Conduct of the study: TTW, SNA, SPV, PK, AKB, DKP.
- Data analysis: TTW, SNA.
- Drafting the manuscript: TTW.
- Final approval of manuscript: TTW, SNA, SPV, PK, AKB, DKP.

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PHARMACOVIGILANCE AND ADR REPORTING IN PERAK

Muhammad Muqri Bin Barudinsah¹, Khalid Ahmad Ali AL Sunaidar¹

Background: Healthcare professionals, particularly pharmacists, play a crucial role in adverse drug reaction (ADR) reporting and pharmacovigilance activities. Despite retail pharmacies being the most accessible point of care for the patients to report mild ADRs, ADR reporting by community pharmacists in Malaysia remains low. Hence, increasing reporting rate among community pharmacists is crucial to promote medication safety. **Objective:** This study aimed to assess the knowledge, attitudes, and barriers related to ADR reporting and pharmacovigilance among community pharmacists in Perak, Malaysia, and explore associations between their sociodemographic characteristics with their good knowledge, positive attitudes and high barriers level. **Methods:** A cross-sectional study design was employed through both physical and online survey, involving 179 community pharmacists in Perak. Data were collected using a 38-item self-administered online structured questionnaire. Statistical analyses were subsequently conducted. **Results:** This study revealed that community pharmacists exhibited good knowledge (82.1%), positive attitudes (68.7%) and low barriers (86.1%) towards ADR reporting and pharmacovigilance. However, several significant barriers hindered their reporting efforts, including the time-consuming nature of the reporting process (37.4%) and doubts about the causality of ADRs (29.7%). Remarkably, gender and CPD programmes participation were associated with good knowledge. While female gender, younger age and recent pharmacovigilance course exposure were associated with positive attitudes, higher education level was inversely associated with positive attitudes. **Conclusion:** Despite possessing good knowledge and

positive attitudes, several barriers prevent community pharmacists in Perak from effectively reporting ADRs. Targeted interventions are necessary to address these barriers and improve ADR reporting rates among community pharmacists.

Keywords: ADR, adverse drug reactions, attitude, barriers, community pharmacists, knowledge, pharmacovigilance.

Introduction

The acceptance of Malaysia as the 30th member of the International Drug Monitoring Programme (PIDM) marked the establishment of the first Malaysian World Health Organization (WHO)-endorsed pharmacovigilance centre called National Centre for Adverse Drug Reaction Monitoring (NPRM, 2019). Pharmacovigilance (PV) refers to the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems (World Health Organization, 2002). The benefits of PV extend from detecting and preventing adverse drug reactions (ADRs) that may not be identified in pre-marketing trials to providing evidence-based information for healthcare professionals, patients, and policymakers on drug safety (Trifirò & Crisafulli, 2022; WHO, 2002). PV relies on collaboration from many types of healthcare professionals, including community pharmacists who are often first points of contact for patients. Pharmacists' active participation in ADR reporting is crucial, yet community pharmacists frequently submit few reports. For

¹ Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Health Sciences, Royal College of Medicine Perak, Universiti Kuala Lumpur (RCMP UniKL), 30450 Ipoh, Perak, Malaysia

Corresponding author:

Dr Khalid Ahmad Ali AL Sunaidar

Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Health Sciences, Royal College of Medicine Perak, Universiti Kuala Lumpur (RCMP UniKL), 30450 Ipoh, Perak, Malaysia

instance, in Malaysia only 0.97% of ADR reports in 2020 originated from community pharmacists (NPRA, 2020). Studies in other countries like Sudan, Nigeria and Lithuania also show similarly low reporting by community pharmacists, underscoring a regional trend of underreporting (Mohammed Tahir & Hussein, 2020; Usifoh, *et al*, 2018; Valinciute-Jankauskiene & Kubiliene, 2021). Despite the rising needs of community pharmacists in PV in Malaysia, very little is known regarding their current knowledge, attitudes and barriers towards PV and ADR reporting which may explain such low level of ADR reporting practice.

In Malaysian landscapes, a cross-sectional survey in Selangor circa 2015 found that while community pharmacists demonstrated sufficient knowledge and positive attitudes to report ADR, the practice of ADR reporting was low (Zin, *et al*, 2019). They highlighted barriers such as inadequate clinical knowledge hindered them from reporting ADR. Another Malaysian study in northern region of Malaysia reinforced this narrative, revealing a lack of awareness among pharmacists regarding PV activities (Elkalmi, *et al*, 2014). The low reporting rate further highlighted barriers, including a lack of knowledge on reporting procedures and the unavailability of reporting forms. This study will address crucial gaps in understanding the current knowledge, attitudes, and barriers related to PV and ADR reporting among community pharmacists in Perak, Malaysia. The findings can inform interventions, educational programmes, and policy changes, empowering community pharmacists as vigilant guardians of patient safety and optimising healthcare resources. Additionally, the study findings

could serve to align Malaysian pharmacovigilance practices with international standards.

Therefore, this work aimed to evaluate the knowledge, attitudes and barriers of PV and ADR reporting among community pharmacists in Perak, Malaysia and explore the potential association between their sociodemographic characteristics with the level of knowledge, attitude and barriers toward PV and ADR reporting.

Methods

This cross-sectional study employed convenience sampling to assess the knowledge, attitudes, and barriers related to PV and ADR reporting among community pharmacists in Perak, Malaysia, from March to May 2024. The study targeted pharmacists with a valid license in Malaysia, must work as community pharmacists in the state of Perak, at least one year of experience, and proficiency in English. The population size was estimated at 331, aligning with the number of registered retail pharmacies in the state (*Program Perkhidmatan Farmasi*, 2020). The required sample size, calculated using Raosoft software at a 95% confidence level and a 5% margin of error, was 179 participants (Raosoft, 2004). All participants who meet the inclusion criteria were recruited into the study. Participants who do not satisfy the inclusion criteria or fulfil the defined exclusion criteria were excluded from participation. The defined exclusion criteria are as follows; a) Participants who do not possess a valid license to practise as a pharmacist in Malaysia, b) Participants who practise in settings other than community pharmacy, c) Participants who work as community pharmacists but do not practise in

the state of Perak, Malaysia, d) Participants with less than one year of practice experience, e) Participants who are not able to read and understand English language.

Data were collected via a self-administered online questionnaire using Google Form distributed through e-mail, social media, and physical visits. The questionnaire, adapted from various sources (Alam, *et al*, 2021; Alnawaiseh & AL-Oroud, 2022; Alsaleh, *et al*, 2017; Elkalimi, *et al*, 2014; Mustafa, *et al*, 2021; Syed, *et al*, 2018), consisted of five sections: sociodemographic characteristics, knowledge of PV and ADR reporting, attitudes towards PV, barriers to reporting, and recommendations for improvement. The first section comprised six questions, with one multiple selection answer question. The second section comprised ten multiple choice questions. The third and fourth section consisted of ten closed-ended statements, structured on a 5-point Likert scale. The fifth section concluded with one open-ended question. Questions were adapted from validated Knowledge, Attitude, Practice & Barriers (KAPB) studies in similar contexts. The specific adaptation process was guided by relevance to Malaysian community pharmacy practice. The complete final questionnaire is included as an Appendix for reference.

The content validity of the questionnaire was rigorously evaluated by three expert panels from Universiti Kuala Lumpur Royal College of Medicine Perak with extensive expertise in the fields of pharmacovigilance and pharmacy practice. A pilot test with ten pharmacists verified its reliability, achieving a Cronbach's alpha of 0.84, indicating strong internal consistency (Bujang, *et al*, 2018). Since the pilot study

respondents met all inclusion criteria and only minor revisions were made to the questionnaire, their data were included in the main study. Ethical approval was granted by the Universiti Kuala Lumpur Royal College of Medicine Perak (UniKL-RCMP) Ethical Committee (UniKLRCMP/MREC/MARCH-JULY 2024/FPHS/BACH.PHARM/FYP-010).

The scoring system in knowledge, attitudes and barriers evaluation sections (second, third and fourth sections) was aligned with the categorisation based on Bloom's cut-off points: 80.0%-100.0% for good/positive/high knowledge/attitudes/barriers; 60.0%-79.0% for moderate/neutral knowledge/attitudes/barriers; 0.0%-59.0% for poor/negative/low knowledge/attitudes/barriers, respectively (Alzahrani, *et al*, 2022).

For the section assessing the knowledge of community pharmacists toward PV and ADR reporting, a binary scoring system was applied. A score of 1 was assigned for each correct answer, while a score of 0 was given for incorrect/uncertain responses (Mutagonda, *et al*, 2022). The maximum total score for this section was ten, indicating a perfect knowledge score, and the minimum was 0. To enhance interpretability, the total scores for this section are trichotomised into three levels: Poor Knowledge (<6); Moderate Knowledge (6 – 7); Good Knowledge (>7).

Meanwhile, the attitude evaluation utilising 5-point Likert scale was transformed to binary scale using established methods from other past studies (Mouhieddine, *et al*, 2015; Mutagonda, *et al*, 2022; Zajmi, *et al*, 2017). Each positive response (agree or strongly agree) was assigned a score of one, while

each negative response (neutral, disagree, or strongly disagree) was given a score of 0 (Mutagonda, *et al*, 2022). There were two negative statements provided, hence the positive response (in this case, strongly disagree, or disagree) is assigned a score of one, while each negative response (neutral, agree, or strongly agree) is given a score of 0. The maximum score for this section is ten, indicating a highly positive attitude. The scoring breakdown is as follows: Positive Attitude (>7); Neutral Attitude (6 – 7); Negative Attitude (<6). The same scoring system was applied to barriers evaluation section.

Data analysis for this study was conducted using IBM SPSS version 29 (IBM Corp, Armonk, NY, USA). Descriptive analysis was conducted to evaluate knowledge, attitudes, and barriers, with categorical variables presented in frequencies and percentages. Median and interquartile ranges were calculated for continuous variables as they were not normally distributed. For bivariate analyses, pharmacists were categorised into “good” vs “not good” knowledge

(combining moderate and poor knowledge categories) and “positive” vs “not positive” attitudes (combining neutral and negative attitude categories) for chi-square tests, due to small cell counts in lower categories. Similarly, they were also categorised into “high” and “not high” barriers (combining moderate and low barrier categories). Associations between good knowledge, positive attitudes, and high barriers levels with sociodemographic characteristics were assessed using Pearson’s Chi-squared or Fisher’s Exact Test when appropriate, with Phi and Cramer’s V Test applied in cases of significant associations to express the strength of existing association (Akoglu, 2018; Kim, 2017). We interpret the strength of association results from the Cramer’s V values as suggested by Akoglu (2018), see Table I. The Spearman correlation test was used to examine the relationship between the outcomes of knowledge and attitude levels, with statistical significance set at $p < 0.05$.

Table I: Interpretation of Phi and Cramer’s V Value.

| Phi and Cramer’s V value | Interpretation |
|--------------------------|-----------------|
| More than 0.250 | Very strong |
| 0.151 – 0.250 | Strong |
| 0.101 – 0.150 | Moderate |
| 0.051 – 0.100 | Weak |
| 0 – 0.050 | No or very weak |

(Akoglu, 2018)

Results

A total of 179 community pharmacists completed the survey and were analysed (no participants were excluded). Table II presents the sociodemographic characteristics of the respondents, including gender, age, highest education level, length of practice, participation in CPD programmes (in hours), and exposure to a PV course within the past one year. As these data are categorical variables, they are represented using frequencies and percentages.

Table II: Community Pharmacists' Sociodemographic Information.

| Variable | Category | Frequency (N) | Percent (%) |
|---|--|---------------|-------------|
| Gender | Male | 73 | 40.8 |
| | Female | 106 | 59.2 |
| Age | 21 – 30 years | 91 | 50.8 |
| | 31 – 40 years | 48 | 26.8 |
| | 41 – 50 years | 28 | 15.6 |
| | ≥ 51 years | 12 | 6.7 |
| Education Level | Undergraduate (Bachelor's degree) | 165 | 92.2 |
| | Postgraduate (Master's degree or PhD) | 14 | 7.8 |
| Length of practice as a community pharmacist (in years) | ≤ 5 | 106 | 59.2 |
| | 6 – 10 | 31 | 17.3 |
| | 11 – 15 | 14 | 7.8 |
| | 16 – 20 | 14 | 7.8 |
| | ≥ 21 | 14 | 7.8 |
| Participation in CPD programmes per year (in hours) | None | 14 | 7.8 |
| | 1 – 5 | 34 | 19.0 |
| | 6 – 10 | 55 | 30.7 |
| | ≥ 11 | 76 | 42.5 |
| Exposure in pharmacovigilance course or seminar for the last one year | No | 134 | 74.9 |
| | Yes | 45 | 25.1 |

Note: N=179

A slight majority of the participants were female (106 respondents; 59.2%), while males constituted 40.8% (73 respondents). The age distribution indicated that more than half of the respondents were between 21–30 years old (91 respondents; 50.8%), with the smallest group being those older than 50 years (12 respondents; 6.7%). A substantial majority of the respondents were undergraduates (165 respondents; 92.2%), with postgraduates representing only 7.8% (14 respondents). Since majority of the respondents are among younger demographic, most respondents (106; 59.2%) had less than five years of practice, and a minority (14; 7.8%) had more than 21 years of experience. 42.5% (76 respondents) participated in more than 11 hours of CPD programmes annually, while 7.8% (14 respondents) did not participate in CPD programmes at all. Lastly, 74.9% (134 respondents) had not attended any PV courses or seminars in the past one year, whereas 25.1% (45 respondents) had such exposure.

Knowledge, Attitudes and Barriers Domains

The knowledge domain comprised ten questions as presented in Figure I. For the first question defining “Pharmacovigilance”, 81% (145 respondents) answered correctly, while 19% (34 respondents) were uncertain or answered wrongly. The second question regarding the purpose of PV saw 92.2% (165 respondents) responding accurately. Defining an ADR was correctly done by 84.4% (151 respondents), whereas 15.6% (28 respondents) were uncertain or answered incorrectly. Identifying reportable ADR examples was achieved by 87.7% (157 respondents),

while 12.3% (22 respondents) failed to identify the correct answer. Recognising the existence of an ADR reporting system in Malaysia was known by 94.4% (169 respondents). When asked about the channel of ADR reporting in Malaysia through email, 38% (68 respondents) answered incorrectly, making only 62% (111 respondents) able to choose the correct answer. For the seventh question, 95.5% (171 respondents) correctly identified the ADR form as a channel to report ADRs in Malaysia. The existence of an official standardised form to report ADRs was known by 88.8% (159 respondents). The ninth question about reporting side effects like headache, fever, and vomiting had 63.1% (113 respondents) answering correctly. Lastly, 91.1% (163 respondents) correctly identified Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) as the reporting organisation in Malaysia.

The preferred source of information about PV and ADR reporting is presented in Figure II. This question accepted multiple answers from each respondent. The main source of information was social media/internet (n=100; 37.9%), followed by university courses (n=68; 25.8%) and CPD programmes (n=68; 25.8%). Journals were the least preferred source of information (n=8; 3%), with others (n=20; 7.6%). Among those selected “Other” sources of information, no further details were provided as the participants were not able to specify others. The total number of answers collected was 264.

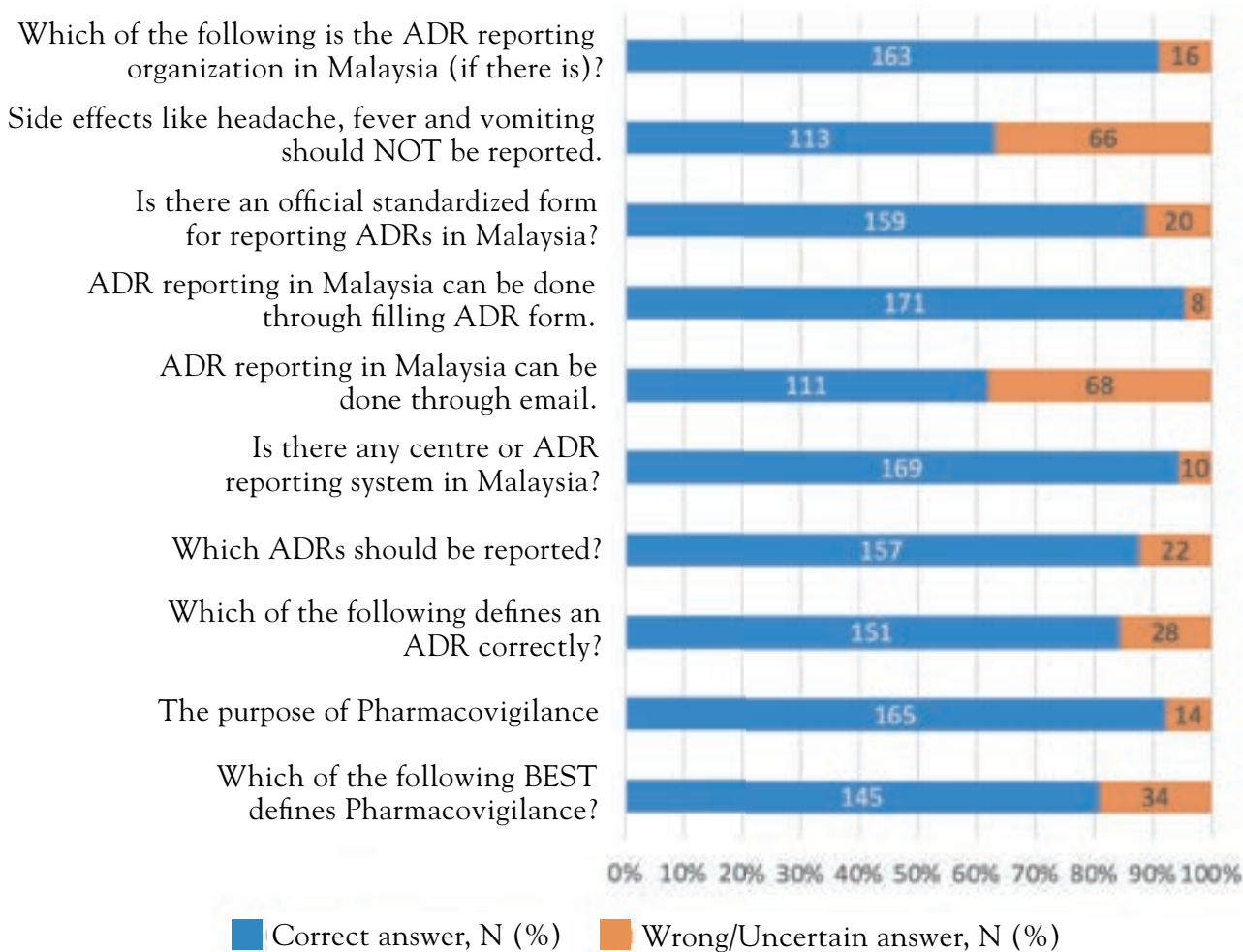


Figure I: Responses of the community pharmacists on knowledge domain about PV and ADR Reporting.

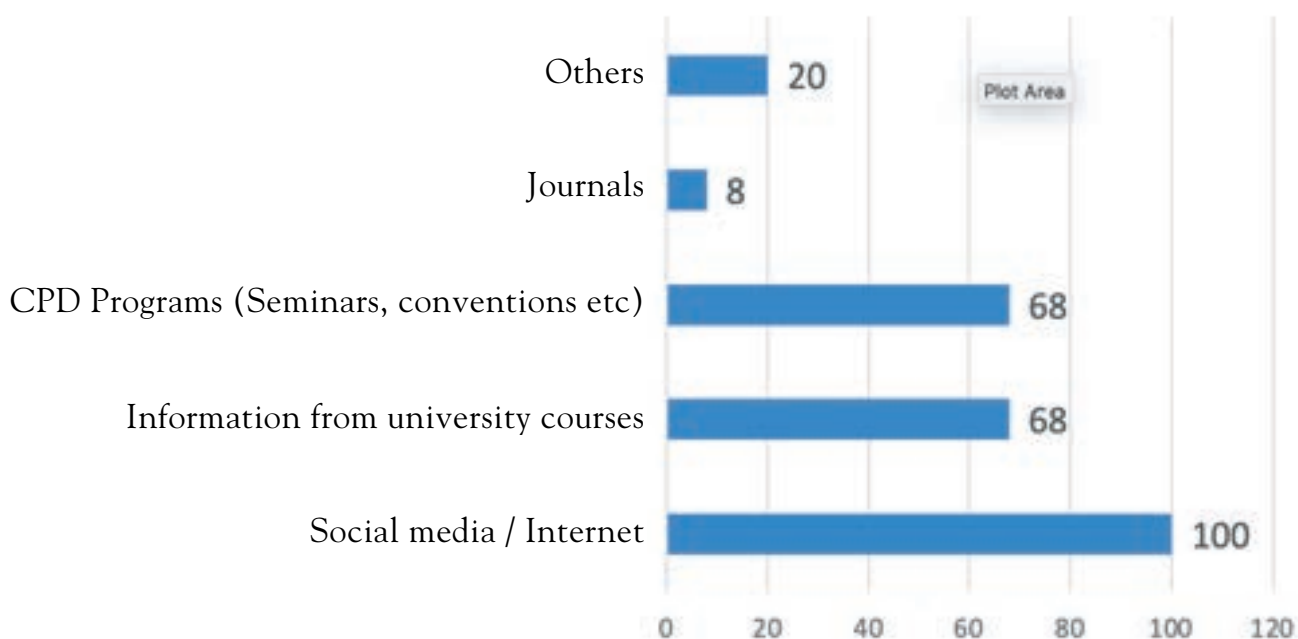


Figure II: Sources of information about PV and ADR reporting.

Figure III presents data related to attitude. Regarding attitudes towards ADR reporting, 93.3% (167 respondents) believed it to be part of a pharmacist's duty, and 94.4% (169 respondents) considered monitoring drug safety as important. Only a small minority (7.8%; 14 respondents) did not think it necessary to confirm an ADR's relation to a specific drug before reporting. The necessity to report ADRs related to OTC products was acknowledged by 76% (136 respondents). Additionally, 93.3% (167 respondents) recognised the importance of reporting ADRs leading to hospitalisation, and 85.5% (153 respondents) deemed reporting life-threatening ADRs as important. Discussing ADRs with a trained physician or academician was considered important by 76.5% (137 respondents), while 62% (111 respondents) believed that non-serious adverse reactions should be reported.

Table III exhibits data related to barriers. The majority (72 respondents; 40.2%) strongly disagreed that the unavailability of reporting forms was a barrier. The complexity of the reporting form was strongly disagreed upon by 32.4% (58 respondents). Although 32.4% (58 respondents) were neutral on the time-consuming nature of reporting ADRs, 20.1% (36 respondents) agreed, and 17.3% (31 respondents) strongly agreed it was time-consuming. Besides, confidential handling of reports was not seen as a barrier by 34.6% (62 respondents). Furthermore, insufficient clinical knowledge was strongly disagreed upon as a barrier by 38% (68 respondents), meanwhile lack of knowledge on how to report ADRs was strongly disagreed upon by 43.6% (78 respondents). Finally, while 29.1% (52 respondents) were neutral on being not convinced that the ADR is caused by the drug as a barrier to report ADRs, 29.7% (53 respondents) collectively agreed or strongly agreed it was ... (truncated?)

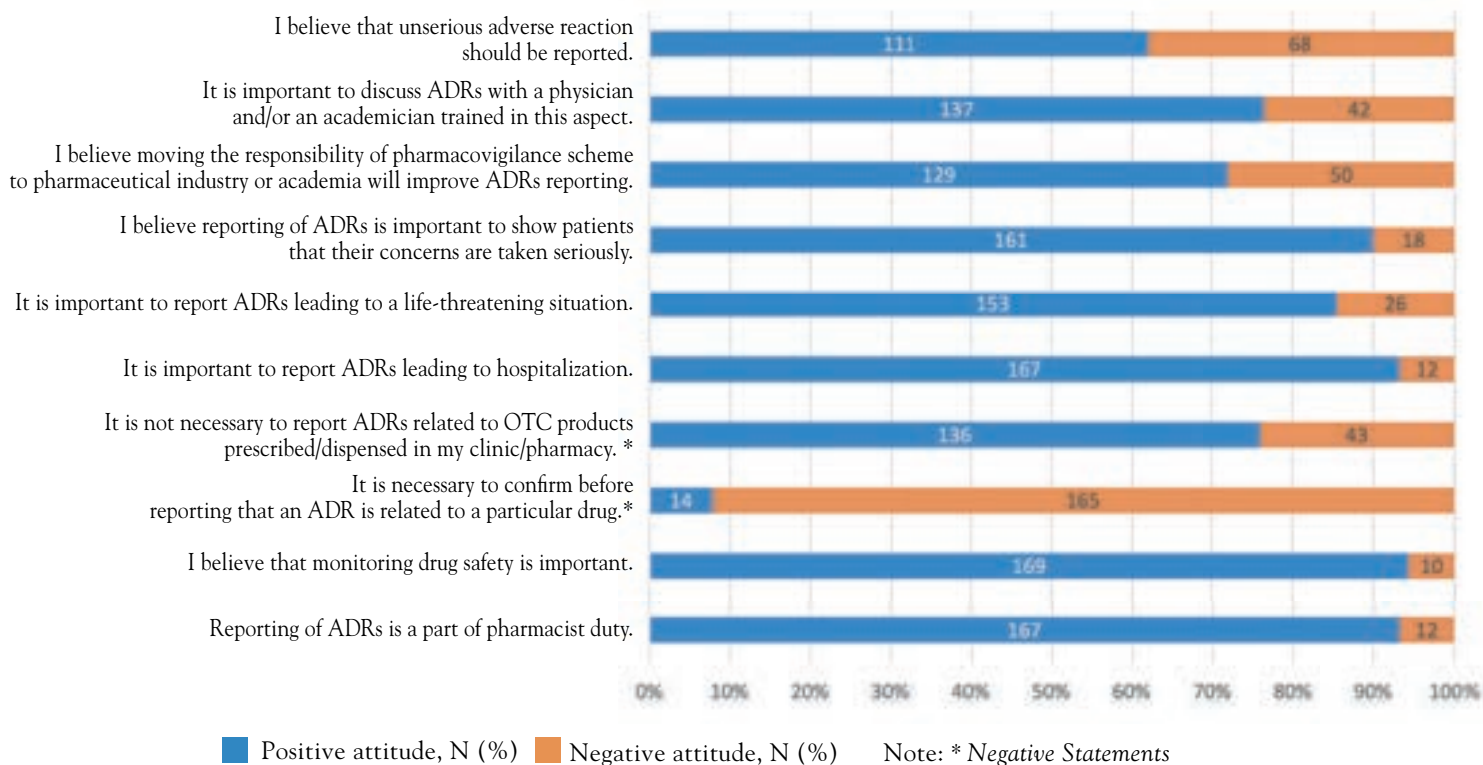


Figure III: Responses of the community pharmacists on attitude domain about PV and ADR Reporting.

Table III: Barriers on Pharmacovigilance and ADR Reporting (N=179).

| Statement | Strongly Disagree | | Disagree | | Neutral | | Agree | | Strongly Agree | |
|--|-------------------|------|----------|------|---------|------|-------|------|----------------|------|
| | N | % | N | % | N | % | N | % | N | % |
| I don't report ADRs because reporting form is not available. | 72 | 40.2 | 40 | 22.3 | 38 | 21.2 | 14 | 7.8 | 15 | 8.4 |
| The reporting form is too complicated. | 58 | 32.4 | 26 | 14.5 | 54 | 30.2 | 20 | 11.2 | 21 | 11.7 |
| Reporting ADRs is time consuming. | 22 | 12.3 | 32 | 17.9 | 58 | 32.4 | 36 | 20.1 | 31 | 17.3 |
| I don't report ADRs because I am not convinced about the confidential handling of the reports. | 62 | 34.6 | 60 | 33.5 | 46 | 25.7 | 4 | 2.2 | 7 | 3.9 |
| I don't report ADRs because I fear it may harm the confidence of my patients. | 66 | 36.9 | 54 | 30.2 | 34 | 19.0 | 10 | 5.6 | 15 | 8.4 |
| I don't report because I find it difficult to admit that the patients have been harmed. | 54 | 30.2 | 60 | 33.5 | 34 | 19.0 | 14 | 7.8 | 17 | 9.5 |
| I don't report because I fear legal liability for the reported ADRs. | 66 | 36.9 | 52 | 29.1 | 42 | 23.5 | 8 | 4.5 | 11 | 6.1 |
| I don't report because I have insufficient clinical knowledge. | 68 | 38.0 | 50 | 27.9 | 32 | 17.9 | 18 | 10.1 | 11 | 6.1 |
| I don't report because I don't know how to report ADRs. | 78 | 43.6 | 44 | 24.6 | 32 | 17.9 | 14 | 7.8 | 11 | 6.1 |
| I don't report because I am not convinced the ADR is caused by the drug. | 36 | 20.1 | 38 | 21.2 | 52 | 29.1 | 18 | 10.1 | 35 | 19.6 |

The median knowledge score was 9 (IQR: 8-9). The attitude scores were similarly analysed, with the median score being 8 (IQR: 7-9). The median barriers score was found to be 0 (IQR: 0-3). The summarisation of knowledge and attitude levels among the respondents is detailed in Table IV.

Table IV: Summary of the knowledge, attitude and barrier level of the community pharmacists.

| Variable (median, IQR) | Categories | N | % |
|----------------------------------|------------|-----|-------|
| Knowledge (Median 9, IQR 8–9) | Poor | 6 | 3.4% |
| | Moderate | 26 | 14.5% |
| | Good | 147 | 82.1% |
| Attitude (Median 8, IQR 7–9) | Negative | 20 | 11.2% |
| | Neutral | 36 | 20.1% |
| | Positive | 123 | 68.7% |
| Barrier (Median 0, IQR 0–3) | Low | 155 | 86.1% |
| | Moderate | 18 | 10.0% |
| | High | 7 | 3.9% |

Association between sociodemographic characteristics and good knowledge, positive attitudes and high barriers

Gender was significantly associated with knowledge with 88.7% of females and 72.6% of males had good knowledge ($\chi^2=7.61$, $p=0.006$, Cramer's $V=0.206$). A Cramer's V of 0.206 corresponds to a small-to-moderate effect size (Akoglu, 2018). In addition, those who had not participated in CPD programs showed the least percentage of good knowledge level (28.6%), with 82.4%, 85.5%, and 89.9% of 1–5 hour(s), 6–10 hours, and more than ten hours CPD programmes groups showed good knowledge level, respectively.

Hence, the Chi-square Test revealed significant result ($\chi^2(1) = 30.561$, $p = <0.001$, $V = 0.413$). These results shows that there is a significant association between annual CPD programmes and good knowledge level, indicating moderate association. Participation in CPD programmes was also significantly associated with knowledge ($\chi^2=30.56$, $p<0.001$, $V=0.299$), indicating a moderate effect size. Furthermore, 82.4% of the pharmacists in the age bracket of 21-30 years old had good knowledge level. Likewise, 79.2%, 92.9% and 66.7% of the pharmacists demonstrated good knowledge level in the age bracket of 31-40, 41-50 and ≥ 51 years old respectively. The Chi-

square Test yielded no significant result ($\chi^2(3) = 4.441, p = 0.218$). Despite obvious differences, these results imply that there is no significant association between age and good knowledge level, possibly due to small numbers in some age groups. Education level (undergraduate 81.8% vs postgraduate 85.7%) also showed no significant association ($p=1.000$, Fisher's Exact). The association between PV course exposure and knowledge was not significant ($p=0.069$).

Meanwhile, relationship between sociodemographic characteristics and high barriers level showed no significant association for all characteristics except for length of practice and participation in CPD programmes ($p = 0.038, V = 0.219$ and $p < 0.001, V = 0.299$, respectively) as stipulated in Table V.

Table V: Sociodemographic characteristics and their correlation with good knowledge, positive attitudes and high barriers.

| Characteristics | Good Knowledge | | | | Positive Attitudes | | | | High Barriers | | | |
|--------------------------------------|----------------|---------------------|---------|------------------------|--------------------|---------------------|---------|------------------------|---------------|---------------------|---------|------------------------|
| | % | χ^2 value (df) | p-value | Phi & Cramer's V value | % | χ^2 value (df) | p-value | Phi & Cramer's V value | % | χ^2 value (df) | p-value | Phi & Cramer's V value |
| Gender | | | | | | | | | | | | |
| Male | 72.6 | 7.610 | 0.006 | 0.206 | 53.4 | 13.407 | <0.001 | 0.274 | 4.1 | - | 0.062* | - |
| Female | 88.7 | (1) | | | 79.2 | (1) | | | 3.8 | | | |
| Age (years) | | | | | | | | | | | | |
| 21–30 | 82.4 | | | | 69.2 | | | | 3.3 | | | |
| 31–40 | 79.2 | 4.441 | 0.218 | - | 83.3 | 13.515 | 0.004 | 0.275 | 8.3 | - | 0.121* | - |
| 41–50 | 92.9 | (3) | | | 57.1 | (3) | | | 0.0 | | | |
| ≥ 51 | 66.7 | | | | 33.3 | | | | 0.0 | | | |
| Education Level | | | | | | | | | | | | |
| Undergraduate | 81.8 | | 1.000* | - | 70.9 | | 0.038* | -0.162 | 4.2 | - | 0.518* | - |
| Postgraduate | 85.7 | - | | | 42.9 | - | | | 0.0 | | | |
| Length of practice (in years) | | | | | | | | | | | | |
| ≤ 5 | 81.1 | 4.577† | 0.331† | - | 71.7 | 5.924† | 0.197† | - | 3.8 | - | 0.038* | 0.219 |
| 6–10 | 80.6 | | | | 74.2 | | | | 9.7 | | | |
| 11–15 | 100.0 | | | | 57.1 | | | | 0.0 | | | |
| 16–20 | 85.7 | | | | 71.4 | | | | 0.0 | | | |
| ≥ 21 | 71.4 | | | | 42.9 | | | | 0.0 | | | |

| CPD programmes per year (in hours) | | | | | | | | | | | | |
|---|------|--------|--------|-------|------|-------|-------|-------|------|---|---------|-------|
| None | 28.6 | | | | 57.1 | | | | 0.0 | | | |
| 1–5 | 82.4 | 30.561 | <0.001 | 0.413 | 70.6 | 1.174 | 0.759 | – | 11.8 | – | <0.001* | 0.299 |
| 6–10 | 85.5 | (3) | | | 67.3 | (3) | | | 1.8 | | | |
| ≥ 11 | 89.5 | | | | 71.1 | | | | 2.6 | | | |
| Pharmacovigilance course or seminar for the last one year | | | | | | | | | | | | |
| No | 79.1 | 3.308 | 0.069 | – | 64.2 | 5.102 | 0.024 | 0.169 | 4.5 | – | 0.140* | – |
| Yes | 91.1 | (1) | | | 82.2 | (1) | | | 2.2 | | | |

Note:

* Fisher–Freeman–Halton Exact Test

† Fisher’s Exact Test for cases when more than 20% of the cells have expected count less than 5

Spearman’s correlation revealed a significant positive correlation (Spearman’s rho = 0.288, p < 0.001) between the knowledge and attitudes domains as stipulated in Table VI. In contrast, attitudes and barriers domains noted no significant correlation.

Table VI: Spearman’s correlation across knowledge, attitude and barrier scores.

| Variable | Spearman's rho | Knowledge | Attitude | Barrier |
|-----------------|----------------|---------------|---------------|---------|
| Knowledge Score | Correlation | 1.000 | 0.288* | 0.037 |
| | Coefficient | – | < 0.001 | 0.624 |
| | p-value | | | |
| Attitude Score | Correlation | 0.288* | 1.000 | -0.053 |
| | Coefficient | < 0.001 | – | 0.478 |
| | p-value | | | |
| Barrier Score | Correlation | 0.037 | -0.053 | 1.000 |
| | Coefficient | 0.624 | 0.478 | – |
| | p-value | | | |

Note: * Correlation is significant at the 0.01 level (2-tailed).

Finally, the community pharmacists recommended a few significant measures to improve PV and ADR reporting through the provided open-ended question. These include provide training and exposure to PV, enforcing law, improvising reporting system, establishing guidelines or standard operating procedures, incentive system, instillation in undergraduate syllabus and making ADR forms available in all retail pharmacy stores.

Discussion

In the current study, we examined the knowledge, attitude, and barriers related to PV and ADR reporting among community pharmacists in the state of Perak, Malaysia. Our findings shed light on current knowledge and attitude levels and also barriers faced by pharmacists in ensuring drug safety and highlight areas for improvement in the reporting system.

Overall pharmacists' knowledge and attitude

Overall, our findings revealed that community pharmacists demonstrated a good understanding of PV and ADR reporting. Majority of the participants (82.1%) answered more than two third of the questions correctly, with an average score (median) of 9 (IQR 8-9). Additionally, most of the participants (68.7%) exhibited a positive attitude toward PV and ADR reporting. This aligns with previous research conducted in Selangor in 2015, which also indicated sufficient knowledge among community pharmacists (Zin, *et al*, 2019). Globally, community pharmacists in Saudi Arabia, South Africa and Yemen also appeared to have good knowledge with positive attitudes comparable to our findings (Abdulsalim, *et al*, 2023; Alsheikh & Alasmari, 2022; Gordhan & Bangalee, 2022).

Knowledge Domain

Furthermore, in knowledge domain, almost a quarter (19%) of our participants wrongly defined PV. Meanwhile, a previous study in Malaysia reported only 11.6% were able to define pharmacovigilance, suggesting that the knowledge on pharmacovigilance term had fairly improved over the years (Zin, *et al*, 2019). Furthermore, 91.1% were able to identify MADRAC as ADR reporting organisation in Malaysia. This notes a higher leap of percentage compared to other past studies done in Malaysia, possibly due to more outreach programmes done by MADRAC along the time (Elkalmi, *et al*, 2014; Zin, *et al*, 2019). Most of the source of information about PV and ADR reporting of the studied community pharmacists were from social media or internet. This proves the proactive role of relevant agencies in reaching the pharmacists. MADRAC annual bulletin on the internet might evident that internet plays a big role in disseminating PV information.

Attitude Domain

A substantial majority of our respondents believed that reporting ADR is a part of pharmacist duty, showing positive attitude. This finding is coherent with another study in Selangor, Malaysia where our finding showed an increase in percentage for the positive responses, indicating the increased awareness on PV role of pharmacists (Zin, *et al*, 2019). Subsequently, our study found a gap in attitude of the community pharmacists who underestimated the importance to report unserious ADRs. Unserious suspected ADRs should still be reported to establish causality relationship between the drugs and ADRs for an improved intervention. On the other hand, unlike

many studies, our study found that huge majority (92.2%) believed that it is necessary to confirm the causality between drugs and ADRs before reporting. In fact, any suspicion should be enough to report ADRs as the analysis of the causality would be performed by MADRAC instead. This finding is contradictory to a study in Lagos State which most of the community pharmacists showed positive attitude (Olugbake OA, *et al*, 2023). It is fair to note that our method utilising Likert scale has superior approach due to its ability to evaluate the degree of their attitudes in which the above contradicting study only utilised agree/disagree answer choices.

Barriers Domain

As for the barriers of ADR reporting, our study found that a noticeable amount of the respondents identified the inability to be convinced that ADRs was caused by the drug as a barrier to report ADRs. This barrier is coherent with the finding of a similar study in Malaysia (Elkalmi, *et al*, 2014). This underscores a widespread misconception. ADR reporting is encouraged even on suspicion alone, since causality assessment is handled by regulatory agency. More interventions should be done to instil awareness to the community pharmacists to ascertain them that there is no requirement to validate the causality before reporting ADRs. Future research should further explore the underlying reasons for this reluctance, such as lack of confidence, fear of inaccuracy or limited training to design more effective educational and policy interventions. Furthermore, the most significant barrier found from our study is ADR reporting was deemed to be time-consuming. The same finding was reported by several studies in Malaysia, Wales, United Kingdom, and Saudi Arabia

(Alsheikh & Alasmari, 2022; Hughes & Weiss, 2019; Zin, *et al*, 2019). More significant approach needs to be done to reduce the time consumption of ADR reporting. A study in Wales had found that by centralising the reporting forms with dispensing software would be great facilitator to report ADRs among community pharmacists (Hughes & Weiss, 2019).

Association between sociodemographic characteristics and good knowledge, positive attitudes and high barriers

Consistent with past studies in another region in Malaysia and Poland, our study found that knowledge about PV and ADR reporting is not significantly influenced by the length of practice of the pharmacists (Elkalmi, *et al*, 2014; Zimmermann, *et al*, 2016). This suggests that CPD might be more critical than years of experience alone. Related to that, a very strong association was found in our study between CPD programmes and good knowledge. This highlights the critical role of CPD in enhancing pharmacists' knowledge about PV and ADR reporting. While CPD programmes are effective in enhancing knowledge, they may not directly influence attitudes based on our study findings. Hence, more CPD programmes on PV should be implemented with inclusion of components that address attitudes and evoke motivation to report ADRs as suggested by previous studies (Valinciute-Jankauskiene & Kubiliene, 2021; Zin, *et al*, 2019). For instance, offering CPD points for each ADR report submitted could be an effective incentive to translate their knowledge into practice. On the other hand, interestingly, an inversely related association was found where pharmacists with undergraduate

degrees had more positive attitudes than those with postgraduate degrees, possibly due to more recent curricular exposure to pharmacovigilance. This suggests the need to reinforce pharmacovigilance education consistently across both undergraduate and postgraduate levels. Further research, particularly qualitative or comparative studies, is needed to explore the reasons behind this inverse relationship. Finally, the findings from our study revealed that exposure to PV courses is strongly associated with positive attitude, suggesting that targeted educational interventions can effectively improve the community pharmacists' attitudes towards these critical practices (Al-Worafi, *et al*, 2017). Meanwhile, no significant association was identified between sociodemographic characteristics and high barriers, likely due to pooled number of subjects who exhibited low barriers level. Less participants (n=7) with high barriers causes the differences between each characteristic difficult to appear in statistical tests. However, lower practice length and lower CPD programmes are associated with higher barriers, indicating that interventions like providing CPD programmes may lower the barriers to report ADRs.

Correlation across knowledge, attitude and barriers scores

Furthermore, our study found significant positive correlation between knowledge and attitude domains among community pharmacists. This finding aligns with a study in Yemen, highlighting that enhanced knowledge likely contributes to more favourable attitudes (Al-Worafi, *et al*, 2017). Therefore, comprehensive education and training programmes are crucial for fostering positive attitudes and

improving ADR reporting rates, ultimately enhancing patient safety and drug monitoring. Various recommendations were provided by the pharmacists to improve PV and ADR reporting, with the most recommended for training and exposures. This can be achieved through CPD programmes and exposure through internet. Besides, incentives system (which should not always be in monetary but could also be in the form of CPD points reward per report submitted) was also reported, consistent with several studies (Elkalmi, *et al*, 2011; Hughes & Weiss, 2019).

Karuppannan, *et al* (2022) reported that while most hospital and clinical pharmacists recently encountered ADRs, 81% of hospital/clinic pharmacists who encountered so reported the event compared to only 40% of community pharmacists. This disparity highlights that community pharmacists face distinct barriers to reporting and supports the need for previously discussed interventions tailored to the community setting.

Conclusion

The community pharmacists in Perak, Malaysia, exhibited good knowledge and positive attitudes towards PV and ADR reporting despite low ADR reporting rates. We found that the good knowledge and positive attitudes did not translate into practice due to several identified barriers. The barriers include the complexity and time-consuming nature of the reporting process and many of the retail pharmacists were not convinced that ADRs were caused by the drug. We also found a big misconception among community pharmacists where most believed that causality between drug and ADR is a prerequisite for

ADR reporting, when in fact causality assessment should only be done by the regulatory agency. This highlights the need for interventions to overcome the barriers between their knowledge and attitude with their ADR reporting behaviour.

Strengths and Limitations

Strengths of this study include achieving the pre-calculated sample size (n=179), use of a validated and pilot-tested questionnaire with good internal consistency (Cronbach's $\alpha=0.84$) and comprehensive assessment of knowledge, attitudes and barriers in the defined population. While this study provides valuable insights into the knowledge base, there are several limitations. The data collected were based on self-reported responses, which may be subject to response bias. Respondents might provide socially desirable answers regarding their attitudes and barriers. Besides that, the cross-sectional design of the study provides only a snapshot of the current state of knowledge, attitudes, and barriers. Longitudinal studies are needed to assess changes over time and the impact of interventions. Furthermore, the use of convenience sampling may limit the generalisability of the

findings, as the respondents may not fully represent the broader population of community pharmacists in Perak or Malaysia. Potential confounding variables (age, length of practice) may influence both exposures (CPD programmes participation) and outcomes (knowledge and attitudes). As the analysis relied primarily on bivariate tests, residual confounding cannot be excluded and should be considered when interpreting associations. Due to the cross-sectional design and small counts in some categories, analysis used bivariate methods. Future studies with larger samples should apply multivariable regression to adjust for potential confounders.

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Conflict of Interest

The authors declare no conflict of interest. No sponsorship was received to conduct this study.

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Meta-IMU: A R Shiny App to Conduct Meta-Analysis in Systematic Review and Umbrella Reviews

Ket Li Ho¹, Teguh Haryo Sasongko², Sook Han Ng³, Pei Kuan Lai⁴, Lay Cheng Lim⁵ & Sook Yee Gan⁶

Many tools exist for conducting meta-analyses in systematic reviews, but they are often expensive or difficult for beginners to use. This challenge arises because most tools either fail to address all aspects of meta-analysis comprehensively or lack sufficient guidance for navigating their features. To address these limitations, we developed Meta-IMU, a free R-based Shiny application tailored specifically for beginners. Unlike many existing tools that focus solely on standard systematic reviews, Meta-IMU supports both systematic reviews and umbrella reviews, offering a more versatile approach. To ensure accessibility, Meta-IMU includes built-in instructional videos that guide users step by step, from navigating the application to interpreting the results produced. This guidance ensures users can confidently perform analyses without prior expertise. Meta-IMU encompasses a comprehensive range of features covering key aspects of meta-analysis, such as defining review questions, developing search terms, retrieving studies from various databases, assessing risk of bias, creating tables and plots, analysing small-study effects, performing meta-regression and subgroup analyses, conducting sensitivity analyses, assessing the certainty of evidence, summarizing findings, and generating PRISMA checklist reports. By integrating these functionalities into a single platform, Meta-IMU provides a user-friendly, all-in-one solution. In summary, Meta-IMU is a comprehensive, free application designed to simplify the process of meta-analysis for both systematic reviews and umbrella reviews, making advanced analytical techniques accessible to researchers at any level of experience.

Keywords: *Systematic review, umbrella review, meta-analysis, R, Shiny*

Introduction

Systematic reviews aim to comprehensively identify, evaluate, and summarise all available studies addressing a specific research question, whereas Umbrella review (also known as overviews of reviews) aims to summarise evidence across multiple systematic reviews on related topics. Both approaches employ meta-analysis, a statistical technique that integrates the results of multiple studies to generate a comprehensive conclusion. Conducting meta-analyses efficiently requires specialised software. Researchers are offered a wide range of tools, each with its own advantages, challenges, and limitations. However, these tools often vary significantly in terms of ease of use, features, and statistical capabilities, which can impact the accuracy and efficiency of the meta-analytic process. A brief overview of the most prominent existing tools used in meta-analytic research is provided below.

1.0 A Brief Overview of Existing Tools in Systematic Review and Meta-analysis

(a) RevMan

RevMan, developed by the Cochrane Collaboration, is one of the most widely used software tools for conducting systematic reviews and meta-analyses. It offers a comprehensive environment for managing the entire review process, including data extraction, statistical analysis, and manuscript preparation.¹

^{1,3,5,6} School of Pharmacy, IMU University, Malaysia

^{2,4} Institute for Research, Development & Innovation (IRDI), IMU University, Malaysia

Corresponding author:

Dr Ket Li Ho

School of Pharmacy, IMU University, Malaysia

Email: hoketli@imu.edu.my

Despite its popularity, RevMan's statistical functionality is relatively limited, as it mainly supports standard fixed-effect and random-effects models. More advanced methods, such as meta-regression or multivariate meta-analysis, are not easily accommodated. Furthermore, RevMan is primarily designed for systematic reviews of primary studies and therefore does not natively support umbrella reviews, which require the synthesis of results from multiple systematic reviews. Its design is also largely tailored to the structure of Cochrane reviews, which may limit flexibility for non-Cochrane applications.

(b) R

R is a powerful statistical computing environment that offers several valuable packages for meta-analysis, such as meta and metafor. These packages support various effect size measures, subgroup analyses, sensitivity analyses, and produce graphical outputs like forest and funnel plots. Their high level of customisation and flexibility makes them popular among statisticians and researchers experienced with R.^{2,3} However, effective use of R requires a solid understanding of statistical methods and proficiency in R programming, which can be a significant hurdle for beginners. While R does not offer packages specifically designed for Umbrella review, its versatility allows researchers to generate the necessary outputs, such as credibility plot by using other general-purpose packages such as ggplot2.

(c) Comprehensive Meta-Analysis (CMA)

Comprehensive Meta-Analysis (CMA) is a widely used standalone software that offers an intuitive, graphical user interface to facilitate the meta-analysis process. It supports a wide range of study types and effect size calculations, making it a versatile choice

for meta-analysts.⁴ One of its key advantages is its ease of use, requiring little to no programming knowledge. However, CMA is a proprietary tool, requiring paid licenses, which may limit access for some researchers, particularly those in resource-constrained settings. Besides, CMA does not integrate well with other software tools (eg, R, Stata), thus it is difficult to extend or automate outside of the CMA environment.

(d) Microsoft Excel

Several Excel-based tools (eg Meta-Essentials, MetaXL and MetaEasy) have been developed to perform meta-analyses, leveraging the familiarity and accessibility of Excel as a platform. These tools support a variety of effect size measures and models, providing users with a simple, yet powerful tool for basic meta-analytic calculations.⁵⁻⁸ However, these tools lack the advanced statistical features of more specialised software.

(e) Statistical Package for the Social Sciences (SPSS)

SPSS, a general-purpose statistical software, includes meta-analysis functionalities as part of its broader suite of statistical tools. It is particularly popular in the social sciences, where SPSS is widely used for data analysis.⁹ SPSS's meta-analysis capabilities are somewhat limited compared to specialised software, and conducting meta-analyses within SPSS requires a solid understanding of both meta-analytic methods and SPSS syntax.¹⁰ While it can handle basic tasks, more advanced features like meta-regression are not as fully developed. Besides, SPSS does not have the flexibility to easily integrate with other open-source meta-analysis libraries, such as R's metafor, restricting its extensibility.

(f) Stata

Stata is a powerful statistical software package that offers extensive support for meta-analysis through built-in commands and user-contributed packages.¹¹ Stata is particularly known for its flexibility and ability to handle complex data structures, making it an excellent choice for advanced meta-analyses and meta-regressions. It is favored by economists and medical researchers who require high-level statistical tools. However, its steep learning curve and the need for licensing fees can be barriers for new users or those working in resource-limited settings.¹² The interface and coding-based analysis may be overwhelming for users new to statistical analysis, requiring significant time to learn and apply effectively.

(g) MetaWin

MetaWin is another tool for meta-analysis, often used in ecological and environmental sciences. It provides a wide range of options for conducting meta-analyses, including different statistical models, permutation tests, and resampling techniques.¹³ Although MetaWin is less commonly used in medical and social science fields, its application to ecological data sets and flexibility in handling non-parametric data make it a valuable tool for researchers in these domains. As MetaWin is tailored for ecological and environmental sciences, its applicability to other research fields, such as medicine or social sciences is limited. The software does not support advanced techniques such as multivariate meta-analysis or network meta-analysis, making it unsuitable for complex data structures.

(h) R-based App

Several free, R-based applications for meta-analysis are available, such as JASP and jamovi. While these tools are open-source and provide robust statistical analysis capabilities, they function primarily as statistical software rather than comprehensive systematic review workflow managers. Consequently, they do not guide researchers through the full review process. Users are expected to already possess knowledge of systematic review and meta-analysis methodology, including the ability to formulate research questions using the PICOS framework (Population, Intervention, Comparator, Outcomes, Setting) and to develop appropriate search strategies. Additional software is required to complement JASP and jamovi, as they lack features such as automated preparation of PRISMA flow diagrams or implementation of GRADE assessments. Moreover, they do not support umbrella reviews; therefore, outputs such as redundancy tables and credibility plots cannot be generated natively within these platforms.

The pros and cons of the above-mentioned tools are summarised in Table I. Given the limitations of previously mentioned meta-analysis tools, there is a clear need for a free, comprehensive platform that provides a one-stop solution for meta-analysis, particularly for beginners. To address this gap, we developed Meta-IMU, a new R Shiny application designed to simplify the process of conducting meta-analyses for both systematic and umbrella reviews.

Table I: Pros and Cons of Existing Tools for Systematic Review and Meta-Analysis.

| Tool | Pros | Cons |
|---|--|---|
| RevMan | <ul style="list-style-type: none"> • Widely used, especially within Cochrane. • Comprehensive platform for managing systematic reviews (data extraction, analysis, manuscript preparation). | <ul style="list-style-type: none"> • Limited statistical methods. • Not suitable for Umbrella reviews. • Less flexible for non-Cochrane work. |
| R (meta, metafor, etc) | <ul style="list-style-type: none"> • Highly flexible and customisable. • Supports advanced analyses. • Strong graphical capabilities. • Open-source and free. | <ul style="list-style-type: none"> • Steep learning curve, requires R programming skills. • No dedicated umbrella review packages (requires custom coding). • Not user-friendly for beginners. |
| Comprehensive Meta-Analysis (CMA) | <ul style="list-style-type: none"> • Intuitive GUI, easy to learn. • Supports wide range of study types and effect sizes. • Does not require programming. | <ul style="list-style-type: none"> • Proprietary licenses. • Poor integration with other tools (R, Stata). • Limited automation and extensibility. |
| Microsoft Excel (Meta-Essentials, MetaXL, MetaEasy) | <ul style="list-style-type: none"> • Widely available and familiar interface. • Free or low-cost add-ins. • Useful for basic meta-analytic calculations. | <ul style="list-style-type: none"> • Limited advanced statistical functions. • Dependent on Excel environment. • Less intuitive user interface. |
| SPSS | <ul style="list-style-type: none"> • Popular and widely used in social sciences. • Provides some built-in meta-analysis capabilities. • Familiar interface for existing SPSS users. | <ul style="list-style-type: none"> • Proprietary licenses. • Limited meta-analysis functions compared to specialised tools. • Requires good knowledge of SPSS syntax. |
| Stata | <ul style="list-style-type: none"> • Powerful statistical package. • Extensive support for advanced meta-analysis and meta-regression. • Flexible and suitable for complex data structures. • Strong academic/clinical reputation. | <ul style="list-style-type: none"> • Proprietary licenses. • Steep learning curve (code-based workflow). • May overwhelm new users. |

| | | |
|---|--|--|
| <p>MetaWin</p> | <ul style="list-style-type: none"> • Specialised for ecological and environmental sciences. • Supports permutation tests and resampling methods. • Flexible for non-parametric data. | <ul style="list-style-type: none"> • Less applicable outside ecology/environmental fields. • Limited adoption in medicine and social sciences. |
| <p>R-based Apps (JASP, jamovi)</p> | <ul style="list-style-type: none"> • Free, open-source, and user-friendly. • GUI-based, lowering entry barrier vs R. • Good for basic statistical meta-analysis. • Cross-platform support. | <ul style="list-style-type: none"> • Not a full systematic review manager. • Users must already know PICOS/ search strategy design. • Lack PRISMA flowchart, GRADE, umbrella review support. • Cannot produce redundancy tables or credibility plots natively. |

2.0 Meta-IMU

Meta-IMU is an R-based Shiny app developed by IMU University, Malaysia, and is available as freeware to the public (Copyright number: LY2024W05922). Shiny provides an interactive and user-friendly web interface while R provides computational and flexibility in data analysis. This combination ensures that complex analysis can be performed while still being accessible for users who are not proficient in R programming. Besides, as Meta-IMU is developed in line with internationally recognised standards and guidelines such as Cochrane Handbook, it ensures that the workflows and outputs produced are robust, transparent and adhere to global standards.

2.1 Software Development

Meta-IMU was written in R, using various packages such as shiny, shinythemes, dplyr, tidyverse, ggplot2, gridExtra, readxl, shinyscreenshot, meta, iNZightTools, metasens, syn, robvis, shinyjs, shinycssloaders, etc.

2.2 System Requirement

Meta-IMU can be used on both Microsoft Windows and macOS. Even though it may function on other operating systems supported by R and RStudio as well, this has not been verified. Besides, it is preferable that the computer has at least 16GB of RAM (random access memory). While a system with 8GB of RAM may run the application, some tasks may be slow or unresponsive.

2.3 Installation

The installation of Meta-IMU requires several preparatory steps. R and RStudio (available at <https://posit.co/download/rstudio-desktop/>) must first be installed as the computational environment. A spreadsheet programme such as Microsoft Excel, capable of editing .csv, .xlsm, and .xlsx files, is also necessary. Access to the Meta-IMU package is obtained by completing a registration form on the IMU University IRDI website (<https://imu.edu.my/irdi/meta-analysis>). Following registration, an email containing the download link to the Meta-IMU zip file is provided. Because the software is continuously

updated, the most current version should be used whenever a new project is initiated.

Once the required files and software are prepared, a new RStudio project is created to establish a working directory, which functions as the default folder for reading and saving files. The Meta-IMU zip file is then extracted, and its contents placed in this directory. Opening the app.R file in RStudio loads the application code into the source panel (Figure 1). To enable the full range of functionalities, the application should be executed by selecting the “Run external” option in RStudio. Thereafter, clicking “Run app” launches Meta-IMU in the web browser.

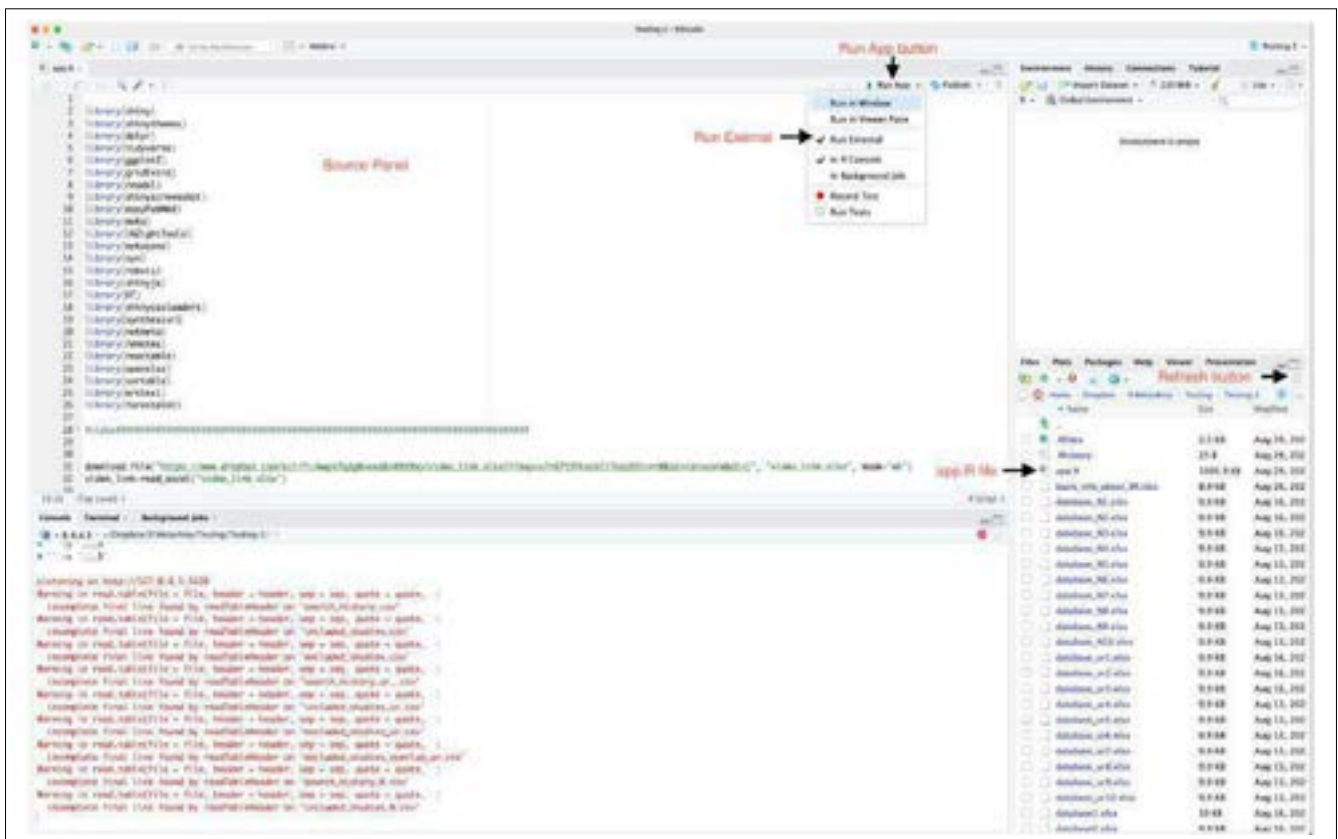


Figure 1: RStudio interface highlighting the key buttons relevant to the installation process.

2.4 General User Interface (UI)

The Meta-IMU user interface is organised into four main components (Figure II). The *side panel* provides access to key functionalities, including options to save user inputs with or without refreshing the application, capture screenshots, and specify the type of review (systematic or Umbrella). It also contains advanced settings for defining summary measures in forest plots

and adjusting plot dimensions when large numbers of studies are included, as well as a reference section. The *step selection panel* adapts dynamically to the chosen review type, displaying 13 steps for systematic reviews and 12 steps for Umbrella reviews. Each step is supported by an *instructional video* that guides users through the relevant procedures. Finally, the *main panel* serves as the primary workspace, where analyses are conducted and results are reviewed.



Figure II: General User Interface (UI) for Meta-IMU.
 (a) Side Panel (b) Step Selection Panel (c) Instructional Video (d) Main Panel

2.5 Data Input for Systematic Review

Meta-IMU structures the conduct of a systematic review into sequential, interdependent steps, with each stage building on the preceding one. The process requires users to complete the following steps:

Step 1: Define Review Question

The review question is formulated using the PICO framework, in which 'P' denotes the patients, population, or problem; 'I' the intervention; 'C' the comparator; 'O' the outcome; and 'S' the setting.

Step 2: Define Search Term

Relevant MeSH terms, serving as synonyms for the PICO elements, are identified using the NCBI MeSH database (<https://www.ncbi.nlm.nih.gov/mesh>). These terms are then entered into the corresponding fields in Meta-IMU to generate search terms.

Step 3a: Option 1 – Search Study from Various Databases

Users should choose Option 1 if they are yet to finalise the list of included studies and plan to search across multiple databases. In Meta-IMU, database searching can be performed using one of two methods. Method 1 is suitable for most databases including Scopus, Cochrane library and ClinicalTrials. The search term generated in Step 2 is entered into the database, and the results are exported in *.ris* format with abstracts included. The downloaded *.ris* file is then processed within Meta-IMU using the appropriate upload option, which generates a processed *.xlsx* file. The resulting data are copied, excluding the

header, into the designated database spreadsheet (eg, *database1.xlsx*).

Method 2 applies to databases such as PubMed, Semantic Scholar, and OpenAlex. This approach requires the installation of the Publish or Perish software (<https://harzing.com/resources/publish-or-perish>), which enables searches across a wide range of databases. The search term is entered into the software, and results are exported in *.ris* format. As Publish or Perish imposes a limit of 1,000 records per search, broad queries may need to be refined to remain within this threshold. The *.ris* file is then processed to generate an *.xlsx* file, which is transferred into the corresponding database spreadsheet (eg, *database2.xlsx*).

Once database-specific files have been prepared, Meta-IMU needs to be reloaded to integrate the data. The platform supports up to ten databases simultaneously. Duplicate records are automatically identified, and a summary table indicates both the total number of duplicates and the databases from which they were removed. This information may be requested by journal editors and is retained for transparency. A consolidated dataset of de-duplicated studies is subsequently generated.

Titles and abstracts of de-duplicated studies are screened to identify potentially eligible studies. These records are transferred into a "potential studies" table. Full-text articles for these studies should then be obtained and assessed in detail. Following this review, eligible studies are moved into the "included studies" table, while those deemed unsuitable are recorded in the "excluded studies" table along with reasons for exclusion.

To ensure rigor, lists of included and excluded studies generated by independent authors are compared, and discrepancies are resolved by consensus. Authors may add or remove studies from either list during this reconciliation process.

Step 3a: Option 2 – Import Included Studies Directly

Option 3 is intended for cases in which the list of included studies has already been finalised, particularly when other software such as Covidence has been used for screening. In this approach, the study title, year of publication, and first author's last name are entered into the *included_studies.csv* file within the working directory. After refreshing Meta-IMU, Step 3b can be bypassed, and the process continues directly with Step 4.

Step 3b: Generate PRISMA Flow Diagram

A PRISMA flow diagram can be generated within Meta-IMU through an embedded online application developed by Haddaway, *et al.*¹⁴

Step 4: Assigning Studies to Outcomes

Once the list of included studies has been established, the next step involves determining which outcomes each study contributes to. Individual studies may contribute to one or more outcomes. Meta-IMU accommodates up to six outcomes per project; additional outcomes require the initiation of a new project.

Meta-IMU supports eight types of meta-analyses depending on the number of groups and data structure: (i) compare two groups-continuous outcomes, (ii) compare two groups – binary/dichotomous outcomes, (iii) compare two groups-incidence rate outcomes,

(iv) single group – correlation, (v) single group – mean, (vi) single group – proportion, (vii) single group – incidence rate, and (viii) generic outcomes. Each type of analysis requires extraction of different data elements from the studies.

For each outcome, studies are assigned by entering their index number, as listed in the included studies table. Meta-IMU then generates a *data_outcome.csv* file for each outcome, which is saved in the working directory. These files are automatically populated with the study label and publication year, while the remaining columns must be completed with data extracted from the studies. Once populated, these files form the basis for subsequent analyses.

Step 5: Risk of Bias Assessment

The reliability of evidence in a systematic review can be influenced by the risk of bias in the included studies. To account for this, Meta-IMU provides six risk-of-bias assessment tools tailored to different study designs: ROB-1, ROB-2, ROB-2-Cluster (for cluster randomised trials), ROB-2-Crossover (for crossover trials), ROBINS-I (for non-randomised interventions), and ROBINS-E (for non-randomised exposure studies). Once the appropriate risk-of-bias tool is assigned to each outcome, Meta-IMU will generate a corresponding *rob_outcome.xlsm* file for each outcome.

Risk-of-bias assessment requires independent evaluation by at least two authors. Following independent assessments, reviewers compare results, discuss discrepancies, and resolve disagreements through consensus or, if necessary, consultation with a third reviewer. Once the risk of bias for all outcomes have been assessed, the *rob_outcome.xlsm* file should be filled up.

Step 6: Forest Plot

Figure III shows a sample of Forest plot generated by Meta-IMU. Users can customise various features, including the names of the treatment and control groups, the lower and upper limits of the x-axis, and the measures of effect. For details about the interpretation of Forest plot, please refer to the article from Chang, *et al* (2022).¹⁵

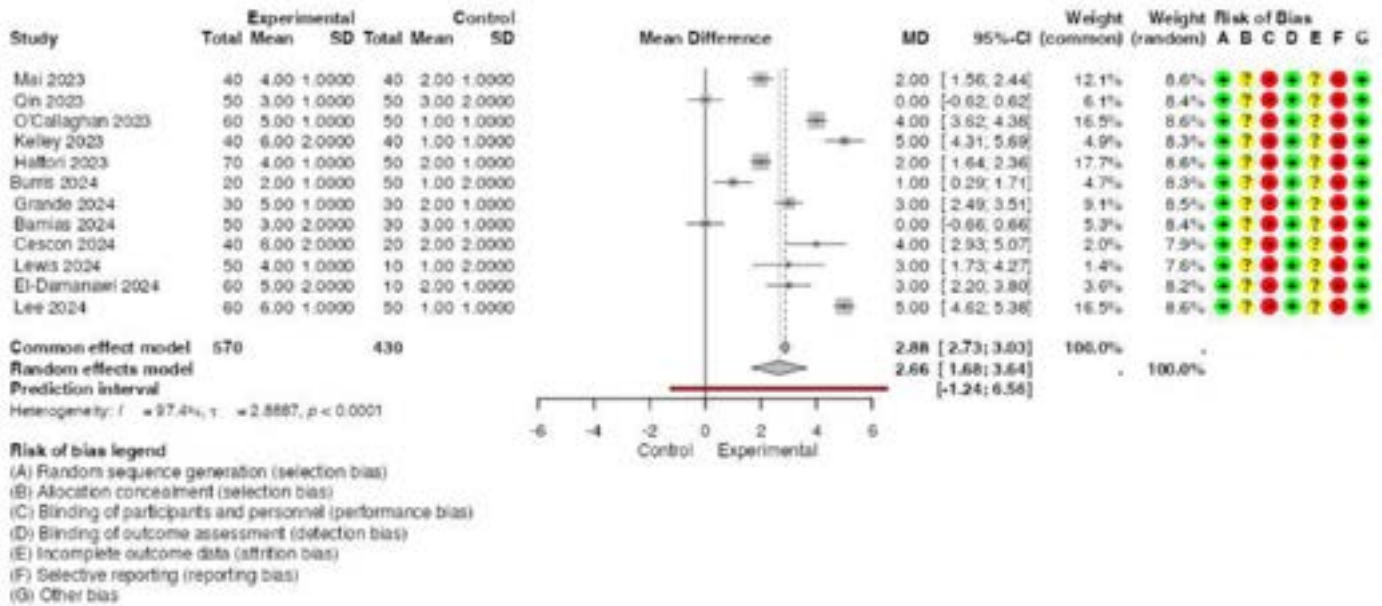


Figure III: Forest plot with risk of bias.

Step 7: Small-Study Effects

Small-study effects refer to the phenomenon where smaller studies tend to report larger effects (or stronger associations) than larger studies, which can bias the overall meta-analysis and lead to an overestimation of the true effect size. To assess and mitigate these potential biases, Meta-IMU provides

Funnel plots, trim-and-fill adjusted Funnel plots, and Radial plots for each outcome (examples shown in Figure IV). Statistical tests for Funnel plot asymmetry are also available, including the Begg, Egger, Thompson, Harbord, Macaskill, Peters, Schwarzer, and Pustejovsky tests, which can only be performed if at least ten studies are included for a given outcome.¹⁶

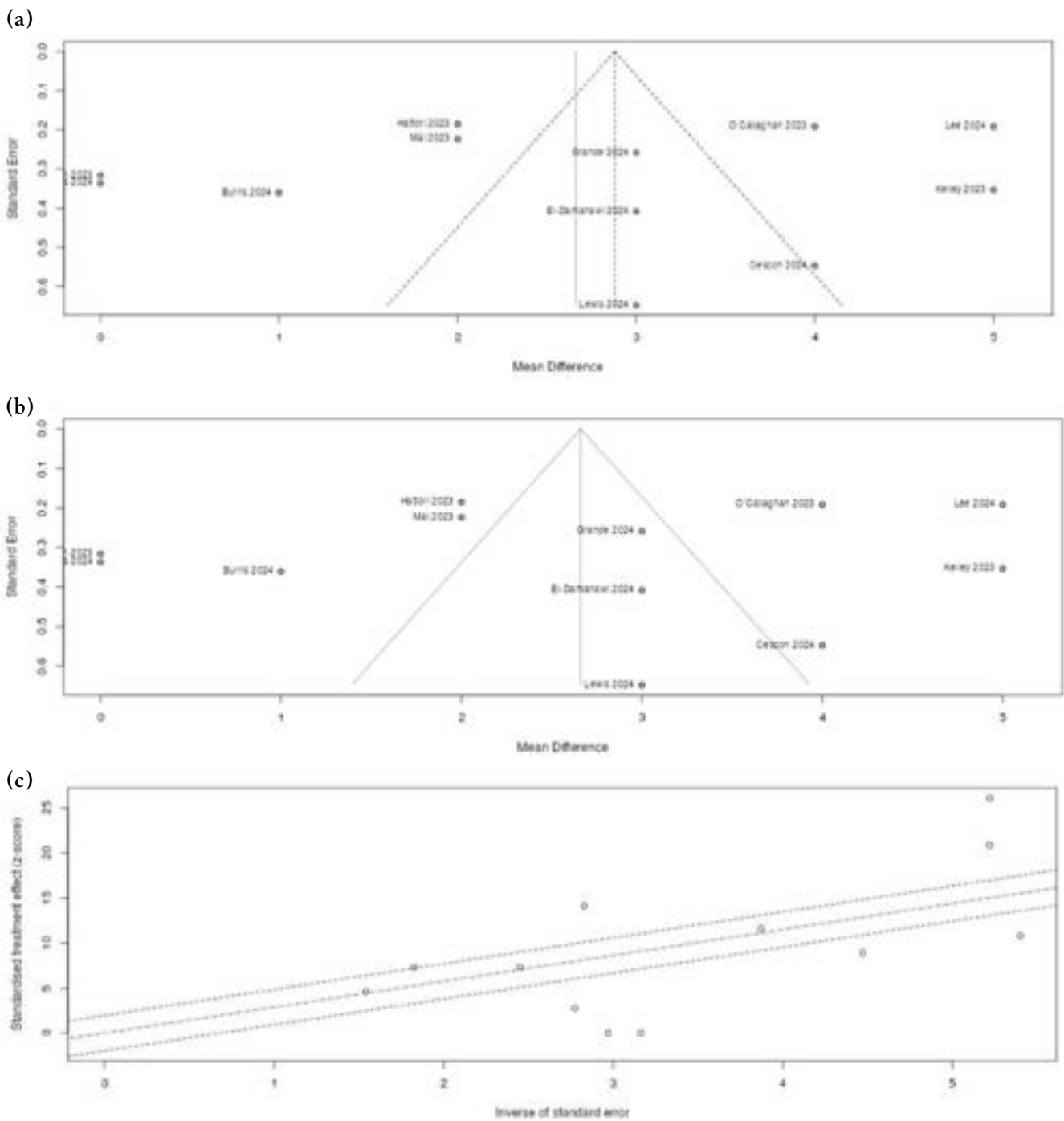


Figure IV: Small-study Effects. (a) Funnel Plot (b) Trim-and-fill Funnel Plot (c) Radial Plot.

Step 8: Meta-regression/Subgroup Analysis

Meta-regression is a statistical technique used in meta-analysis to examine the relationship between study-level characteristics – such as participant demographics, intervention features, or study design – and the observed effect sizes across individual studies. Subgroup analysis represents a specific form of meta-regression, allowing the exploration of whether particular groups respond differently to an intervention. For example, while a Forest plot may show no overall intervention effect, subgroup analysis may reveal that a specific age group benefits significantly.

In Meta-IMU, users can conduct meta-regression and subgroup analyses with up to two covariates. For each outcome, the process begins by generating the corresponding *data_regression_outcome.csv* files, which are then populated with covariate data. Covariates can represent categorical or continuous variables. For instance, studies may be grouped by patient age (eg, Age 1, Age 2, Age 3) or by sex (eg, male = 1, female = 2). Once covariates are entered, the files are saved and the application is refreshed to proceed.

Meta-IMU supports several estimation methods for meta-regression, including restricted maximum likelihood (REML), DerSimonian–Laird (DL), maximum likelihood (ML), Hunter–Schmidt (HS), Sidik–Jonkman (SJ), Hedges (HE), and empirical Bayes (EB). The fitted model provides estimates of residual heterogeneity (τ^2), the proportion of unexplained variability between studies (I^2), and the proportion of variance explained by the included predictors (R^2). A test of moderators is also provided; a statistically significant p-value ($p < 0.05$) indicates that the covariate meaningfully influences effect sizes.

Outputs also include Forest plots stratified by subgroups, and bubble plots that visualise regression slopes. In bubble plots, each bubble represents a study, with size proportional to its weight in the analysis. Subgroup Forest plots allow visual comparison of intervention effects across predefined categories, and their display can be adjusted within the application for clarity. Examples of meta-regression results, including bubble plots and subgroup Forest plots, are presented in Figure V.¹⁷

(a)

```
Mixed-Effects Model (k = 12; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):    3.3898 (SE = 1.7587)
tau (square root of estimated tau^2 value):           1.8409
I^2 (residual heterogeneity / unaccounted variability): 97.39%
H^2 (unaccounted variability / sampling variability):  38.25
R^2 (amount of heterogeneity accounted for):          0.00%

Test for Residual Heterogeneity:
QE(df = 8) = 298.6939, p-val < .0001

Test of Moderators (coefficients 2:4):
QM(df = 3) = 1.3711, p-val = 0.7123

Model Results:

```

| | estimate | se | zval | pval | ci.lb | ci.ub | |
|---------------------------|----------|--------|---------|--------|---------|--------|-----|
| intrcpt | 3.6986 | 1.0939 | 3.3811 | 0.0007 | 1.5546 | 5.8426 | *** |
| .subgrouplight smoking | -1.0370 | 1.5357 | -0.6753 | 0.4995 | -4.0468 | 1.9728 | |
| .subgroupmoderate smoking | -1.3907 | 1.5423 | -0.9017 | 0.3672 | -4.4136 | 1.6321 | |
| .subgroupno smoking | -1.6864 | 1.5320 | -1.1008 | 0.2710 | -4.6891 | 1.3162 | |

```

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Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

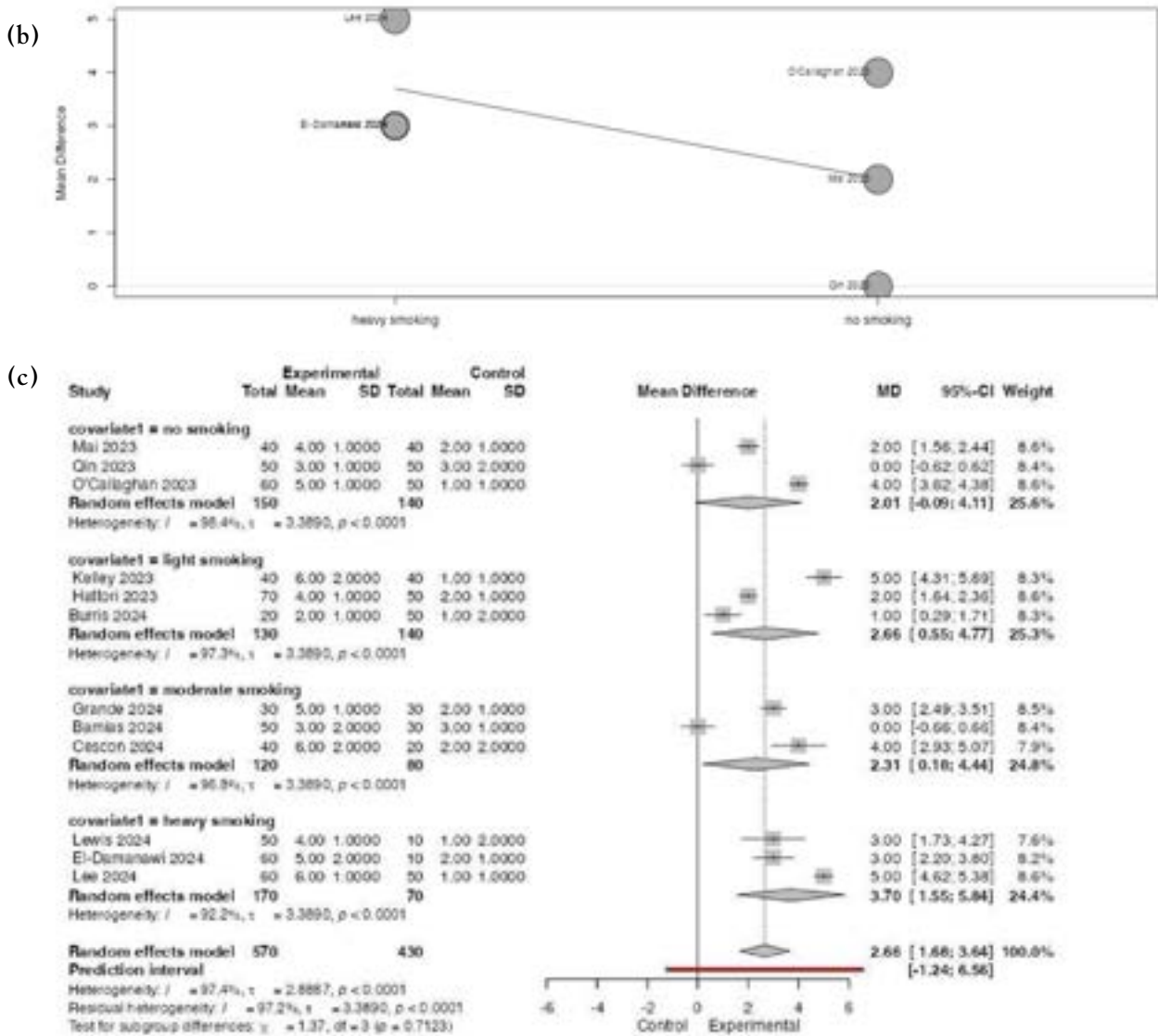


Figure V: Meta-regression. (a) Meta-regression Based on REML (b) Bubble Plot (c) Forest Plot with Subgroup Analysis.

Step 9: Sensitivity analysis

Sensitivity analysis in a systematic review is a method used to evaluate the robustness and reliability of the results by examining how changes in the analysis influence the conclusions drawn from the data.

Additionally, by conducting sensitivity analysis, researchers can identify whether specific studies have a disproportionate impact on the overall results. Meta-IMU conducts sensitivity analysis using leave-one-out and cumulative meta-analysis methods (sample shown in Figure VI).

In the leave-one-out approach, each study is removed individually from the analysis, and the remaining studies are synthesised to estimate the effect size. This process is repeated for each study, yielding a series of effect size estimates that can be compared to the original estimate, which includes all studies. If the effect size remains relatively consistent across all iterations, it suggests that the results of the meta-analysis are robust and not heavily influenced by any single study. Conversely, if the effect size varies

significantly when individual studies are excluded, it may indicate that the results are sensitive to those specific studies.

Cumulative method is used to assess how evidence evolves over time. In a cumulative meta-analysis, studies are added in chronological order, and the cumulative effect size is recalculated after each addition. This method helps visualise how the results of the meta-analysis change as more evidence becomes available.

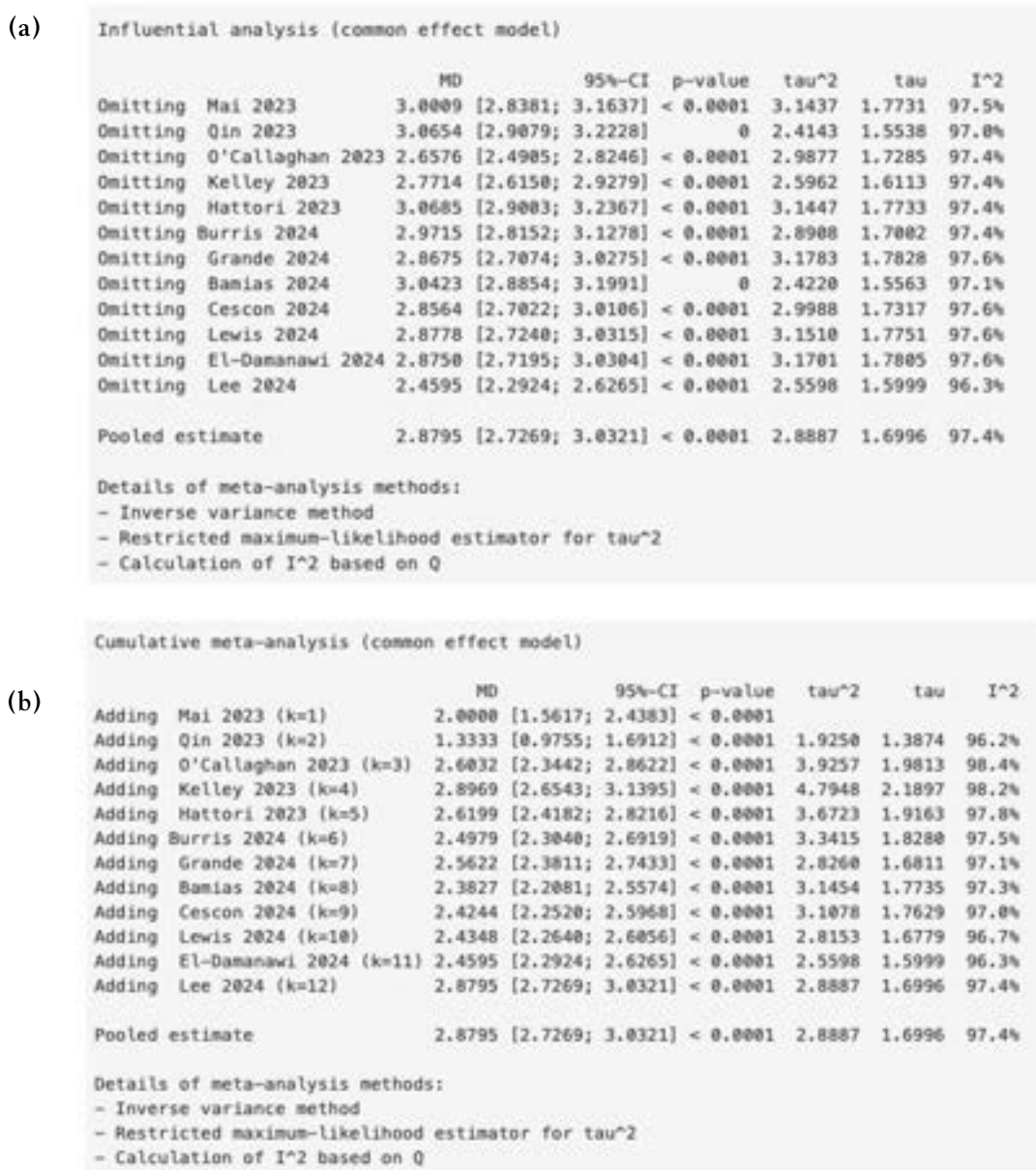
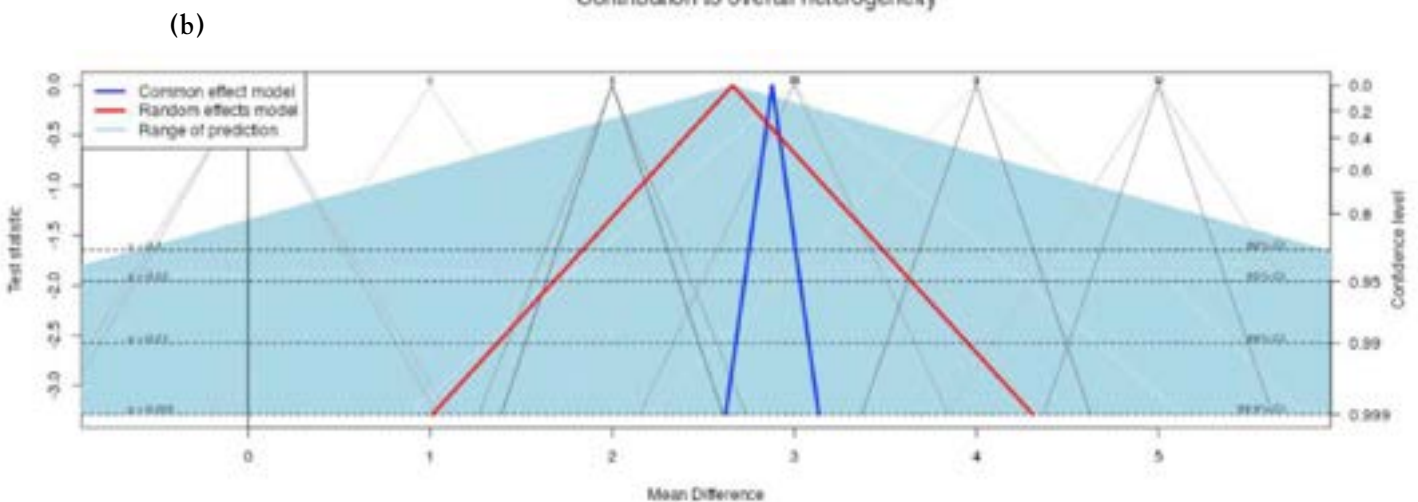
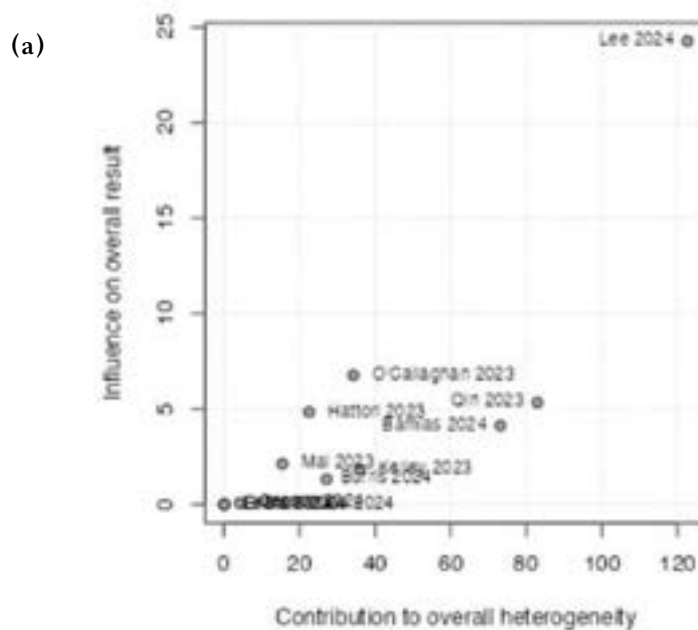


Figure VI: Sensitivity Analysis. (a) Leave-one-out Method (b) Cumulative Method.

Step 10: (Additional figures)

Meta-IMU offers several types of plots that are less commonly used in meta-analysis but can still be quite useful. Figure VII shows Baujat plots, drapery plots and L'Abbé plot. Baujat plot is a visualisation tool to assess heterogeneity, special attention should be paid to studies located at the far right or at the top of the plot, as these may skew the results of the meta-analysis. The drapery plot can complement the forest plot. One advantage of the drapery plot is that confidence intervals for individual studies and pooled estimates can be directly read for any confidence level,

whereas the forest plot displays only one confidence level at a time. However, a limitation of the drapery plot is that it may be difficult to identify individual studies if the number of studies is large. L'Abbé plot is only applicable for binary data. The points on the solid diagonal line represent studies where the event rates did not differ between the intervention and control groups. Points below this line indicate studies where the event rates were lower in the treated group compared to the control group. The dashed line represents the estimated effect based on the fitted model, and larger points correspond to more precise estimates.



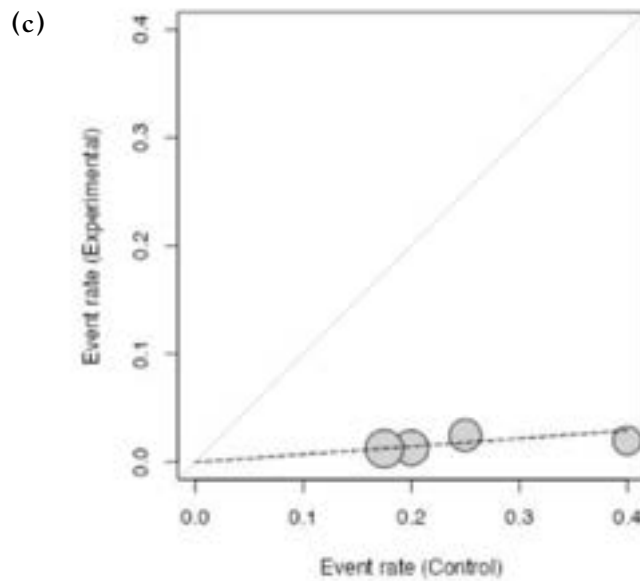


Figure VII: (a) Baujat Plot (b) Drapery Plot (c) L'Abbé plot.

Step 11: Certainty of Evidence

In the final stage of evidence synthesis, the effect size for each outcome is categorised as “trivial or no effect,” “small but important,” “moderate,” or “large.” This assessment is followed by a series of structured “yes” or “no” questions that evaluate the certainty of the evidence. These judgments are then integrated to generate concise, one-sentence conclusions summarising the findings for each outcome. The process ensures that both the magnitude of effect and the strength of supporting evidence are explicitly considered, thereby enhancing the interpretability

and applicability of results. Ultimately, these outcome-specific conclusions are incorporated into a summary of findings table, providing a transparent and accessible synthesis to support decision-making in clinical and policy contexts.

Step 12: Summary of Findings

A sample of the summary of findings is displayed in Figure VIII. Please note that this table is quite generic, and it should be further tailored to the specific study.

| Outcomes | Plain language statement | Number of studies | Estimated overall effect (Common model) | Standard error of overall effect (Common model) | P value for overall effect (Common model) | Lower confidence limit (Common model) | Upper confidence limit (Common model) | Estimated overall effect (Random model) | Standard error of overall effect (Random model) | P value for overall effect (Random model) | Lower confidence limit (Random model) | Upper confidence limit (Random model) | Certainty of the evidence |
|---------------|--|-------------------|---|---|---|---------------------------------------|---------------------------------------|---|---|---|---------------------------------------|---------------------------------------|---------------------------|
| incident rate | The evidence is very uncertain about the effect of treatment on outcome! | 3 | -0.03 | 0.03 | 0.35 | -0.09 | 0.03 | -0.08 | 0.08 | 0.30 | -0.24 | 0.07 | very low |

Figure VIII: Summary of Findings.

Step 13: PRISMA Checklist

A PRISMA checklist report can be generated via an embedded online app developed by Page, *et al* (2021).¹⁸

2.6 Data Input for Umbrella Review

Meta-IMU breaks down the procedures for Umbrella review into sequential steps. Each step is interrelated and builds upon the previous one. Users need to perform the following steps:

Step 1: Suitability of Umbrella Review

This step helps users confirm whether their research question is best addressed by an Umbrella review rather than a systematic review. Users need to answer a series of questions. After completing this, a response will be given by Meta-IMU. If it says “Do not carry out an umbrella review”, users should perform a standard meta-analysis instead. But if it says “Proceed to step 2”, then the umbrella review is the right approach.

Step 2 – Step 4b

These procedures are identical to those described in Steps 1–3b of the systematic review process outlined above, with the distinction that all files requiring modification in the working directory carry the suffix *_ur*, which indicates Umbrella review.

Step 5: Redundancy Table

Overlapping studies occur when different systematic reviews include the same primary studies, which may lead to redundancy and potential bias in evidence synthesis. To address this, Pollock, *et al*, provides a decision tool to guide whether overlapping reviews should be retained or excluded, based on

factors such as recency, quality, relevance, and comprehensiveness.¹⁹ A *primary_study_list.csv* file can be generated, where study labels for each primary study are entered by replacing placeholder values. This allows identification of shared primary studies across systematic reviews. This allows the generation of a redundancy table, which facilitates cross-referencing to determine which reviews overlap. Where overlap is identified, a specific review can be excluded by entering the corresponding index number and providing justification (eg, removal of an older or redundant review due to overlapping primary studies). Excluded reviews remain documented in a separate table and can be reinstated if necessary. Importantly, all subsequent analyses (Step 6 onwards) are based solely on the updated set of included studies, ensuring that the synthesis reflects deliberate and transparent decisions regarding study overlap.

Step 6: RoB Assessment Using AMSTAR2 Tool

The reliability of an umbrella review is closely linked to the methodological quality of the systematic reviews it includes, and this is commonly evaluated through risk of bias assessment. In this study, the AMSTAR 2 tool was applied to assess the methodological quality of the included systematic reviews. Data for this evaluation were entered into a structured spreadsheet (*rob_ur.xlsx*), with items completed according to the accompanying AMSTAR 2 guidance. The completed assessments were then summarised in tabular form, providing an overview of the risk of bias across reviews. Importantly, each systematic review was assigned an overall confidence rating, which served as a critical input for subsequent stages of the analysis.²⁰

Step 7: RoB Assessment Using ROBIS Tool

The ROBIS tool is used to evaluate the risk of bias.²¹

Step 8: Descriptive Characteristics

Descriptive characteristics of the included systematic reviews is documented using a structured data extraction file (*basic_info_about_SR.xlsx*). Relevant information is entered across all predefined columns, capturing key attributes of each review. The completed dataset is then processed to generate summary table, which provides an overview of the characteristics of the included systematic reviews.

Step 9: Assign Study to Outcome

This step involves determining the outcomes to which each study contributes. Each included study may contribute data to one or more predefined outcomes. Meta-IMU can accommodate up to six outcomes within a single project. If more than six outcomes are of interest, a new project must be initiated.

The type of effect size needs to be specified for each outcome, followed by assigning studies to outcomes. Once assignments are completed, the *data_outcome_ur.xlsx* file is generated and stored in the working directory. Each generated file already contains pre-populated columns for *studlabel* and *year*, the remaining fields must be completed with data extracted directly from the included studies:

- *AMSTAR2* values are selected from a dropdown menu, using the table generated in Step 6 as guidance;
- *Nstudies* refers to the number of primary studies included in the systematic review;

- *Npart* denotes the total number of participants across all primary studies;
- *I²* indicates heterogeneity;
- *Effect* represents the pooled effect size;
- *Lower and Upper* indicate the lower and upper bounds of the confidence interval, respectively.

Step 10: Forest Plot

Based on the data provided in Step 9, the corresponding forest plots are automatically generated. In the event that the plots fail to appear despite completion of the preceding steps, Meta-IMU should be refreshed. The Forest plot comprises a tabulated summary of the included studies on the left and the main graphical display on the right. Users may modify the x-axis labels through the designated text box. The default plot width is relatively narrow; however, both the width and height of the plot can be adjusted using the slider controls located in the side panel.

Step 11: Credibility Plot

In this visualisation, each study is depicted as a bubble, with bubble size proportional to the number of participants included (Figure IX). Bubble color indicates the assigned credibility class, based on the predefined classification standards. Users may also modify the label of the X-axis if alternative terminology is preferred.

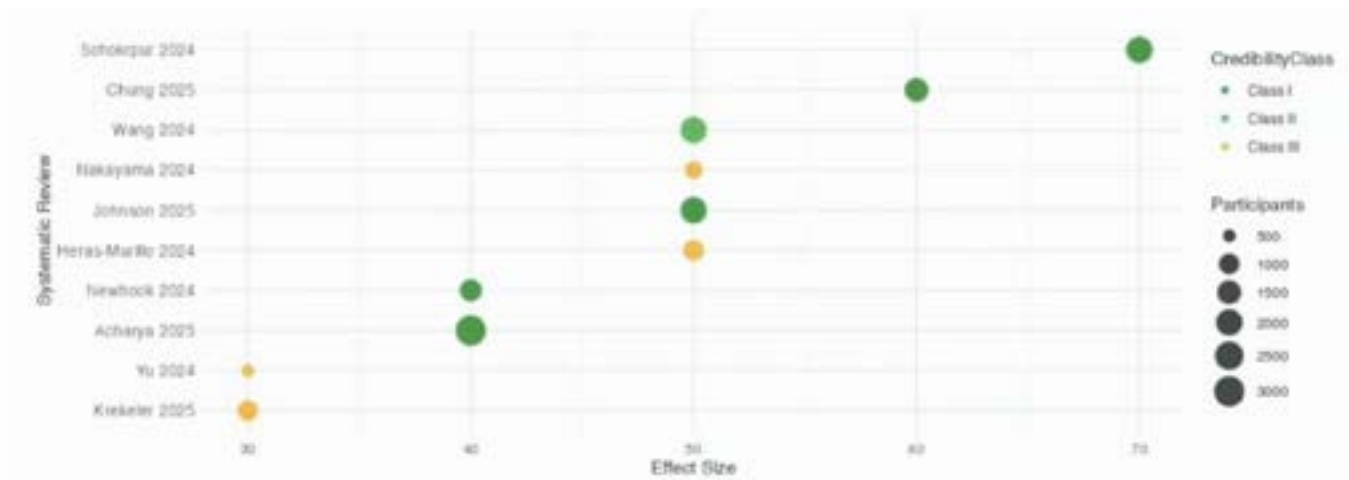


Figure IX: Credibility Plot.

3.0 Discussion and Conclusion

Meta-IMU integrates an intuitive interface with advanced statistical functionalities, offering an accessible yet powerful platform for conducting systematic reviews and meta-analyses. Its step-by-step guidance, comprehensive feature set, and embedded instructional resources make it particularly valuable for researchers with varying levels of methodological expertise. Beyond supporting conventional meta-analysis, Meta-IMU extends its functionality to umbrella reviews, thereby broadening its applicability and addressing a gap in existing tools that often lack versatility or ease of use.

The significance of Meta-IMU lies in lowering the entry barrier for novice researchers while simultaneously providing advanced options for experienced analysts, effectively bridging the gap between usability and methodological rigor. Compared with traditional software, Meta-IMU enhances transparency, learning support, and

methodological flexibility, thereby contributing to improved quality and reproducibility of evidence synthesis.

Nevertheless, some limitations should be acknowledged. The current version depends on stable internet connectivity, may have computational constraints for extremely large datasets, and requires further validation across a wider range of complex analytic scenarios. Future developments will aim to optimise performance, incorporate additional statistical modules, and ensure seamless integration with external databases. Recognising these limitations provides a balanced appraisal and underscores the potential of Meta-IMU as a valuable contribution to the evolving ecosystem of evidence synthesis tools.

Acknowledgement

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