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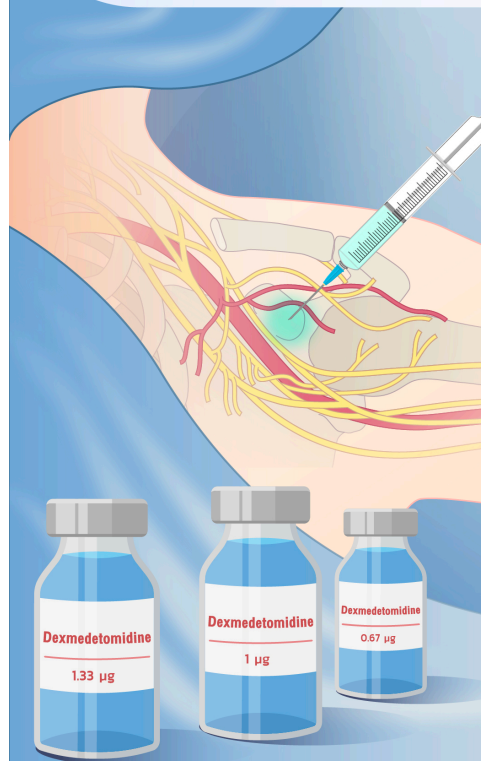
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MONTHLY

ORIGINAL ARTICLE **CORRIGENDUM**

Optimal dose of dexmedetomidine for infraclavicular block (ICB)



69 Patients



Upper limb surgery distal to elbow

Ultrasound-guided ICB

35 mL of lidocaine 1%-bupivacaine
0.25% with epinephrine (5 µg/mL)
and perineural dexamethasone (2 mg)

A randomized trial



Comparing 3 doses of
perineural dexmedetomidine
(0.67 µg/kg vs 1 µg/kg vs 1.33 µg/kg) for ICB

Conclusion



1 and 1.33 mcg/kg
may constitute
the optimal dose of
dexmedetomidine:
compared with 0.67 µg/kg



Shorter onset time



Longer duration
of motor block

SCAN FOR
FULL TEXT



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ORIGINAL ARTICLE

- 725** Comparative Effectiveness of Endoscopic Sinus Surgery Versus Medical Therapy on Olfactory Function in Chronic Rhinosinusitis: A Systematic Review and Meta-Analysis
Nur Alma Aulia, Widia Isa Aprillia Sujana
- 735** Development and Evaluation of an Interactive Online Game-Based Learning Program on Knowledge, Attitudes, Subjective Norms, Perceived Behavioral Control, and Intention to Use E-Cigarettes among Lower Secondary School Students
Pramote Thangkratok, Thepwinphan Theppitak, Panasun Ngamsirijit, Natchaya Palacheewa, Pornpimol Apartsakun, Supavit Manusook, Chatpeerat Songsoontorn, Watcharin Satjamukda, Phattharaphon Udson, Atiphan Rattanakarn
- 748** Effect of the Grasp and Grow Program on Fine Motor Development Among Preschool Children in Pathum Thani Province, Thailand
Ploypailin Chomphu, Phitchasuda Dechboon, Nattaphon Thepee, Rujira Seepa, Aphitsara Seehamat, Aoranuch Saekue, Apichet Jumneansuk, Rattanaporn Arsa
- 759** A Randomized Comparison among 0.67 µg/kg, 1 µg/kg and 1.33 µg/kg of Perineural Dexmedetomidine for Ultrasound-guided Infraclavicular Block
Samita Pirotasak, Daniah Ghareeb Dhaifallah, Mohamed Alem, Anas Alkhoutani, Alexander Amir, Karoll Rodelo, Juan Francisco Asenjo, Roderick J Finlayson, Julián Aliste, De Q Tran
- 771** Supercharged Colonic Interposition for Total Oesophageal Reconstruction: Technical Refinements, Perioperative Protocol, and Functional Outcomes
Sarut Chaisrisawadisuk, Pornchanit Karanthakarn, Sirin Apichonbancha, Nutcha Yodrabum, Jirawat Swangsri
- 780** Antimicrobial Susceptibility and Multidrug Resistance among *Streptococcus pneumoniae* Isolates from Predominantly Non-Sterile Respiratory Specimens in Children Hospitalized with Pneumonia or Suspected Bacteremia in the Mekong Delta, Vietnam, 2022–2024: A Hospital-Based Cross-Sectional Study
Nghia Quang Bui, Khai Quang Tran, Le Thi Nhu Tran, Long Duy Phun, Duy Khanh Nguyen, Duong Thai Bach, No Thi Tran, Tram Ngoc Ly, Thinh Nguyen, Hien Thi Nguyen
- 793** Restoring Culturally Essential Floor-Sitting in Transfemoral Prosthesis Users: A Six-Week Pilot Randomized Within-Subject Trial
Natthawan Sutthison, Nang Myat Myat Moe, Yasmin Nutchamlong, Marisa Amattayakul, Mathurin Rairat, Woratee Dacharux, Gary Guerra, Kazuhiko Sasaki
- 805** Effects of a Home-Based Fall Prevention Program in Older Lower Limb Prosthesis Users: A Randomized Controlled Trial
Prawina Sakulkosol, Pieter U Dijkstra, Kazuhiko Sasaki, Gary Guerra, Jutamanee Poonsiri

CORRIGENDUM

- 816** Survival and Factors Predictive of Survival in Patients with Thymic Carcinoma
Suparauk Geanphun, Pranya Sakiyalak



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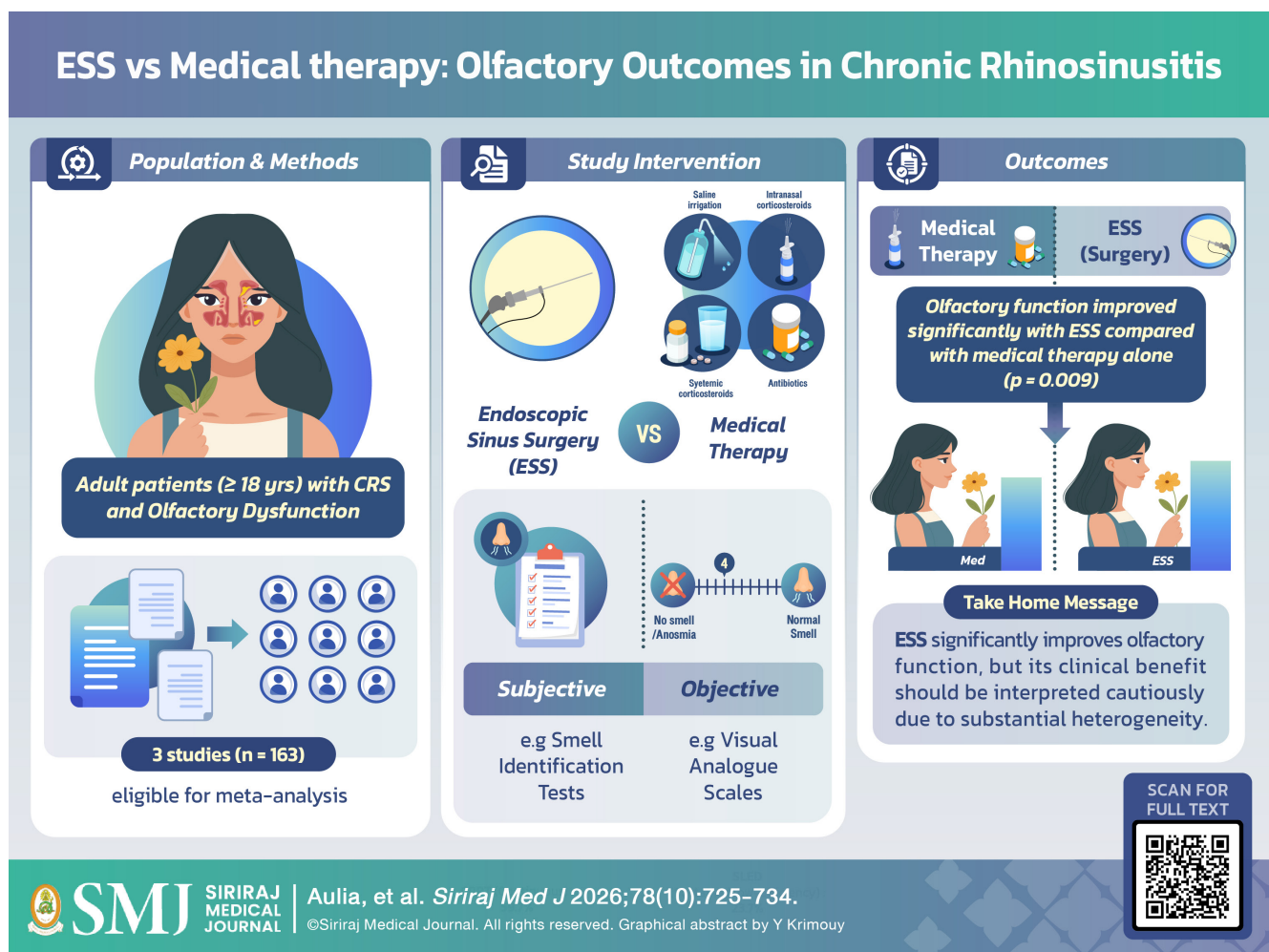
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Comparative Effectiveness of Endoscopic Sinus Surgery Versus Medical Therapy on Olfactory Function in Chronic Rhinosinusitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This study aimed to compare the effectiveness of ESS versus medical therapy in improving olfactory function among adult patients with CRS.

Materials and Methods: A systematic review and meta-analysis were conducted using PubMed, Cochrane Library, and ScienceDirect. Comparative studies evaluating ESS and medical therapy with reported olfactory outcomes were included. Standardized mean differences (SMD) were calculated using a random-effects model. Outcomes were oriented such that higher values indicated better olfactory function.

Results: Four studies were included in the qualitative synthesis, with three studies ($n = 163$) eligible for quantitative meta-analysis. The pooled analysis demonstrated a statistically significant improvement favoring ESS over medical therapy alone (SMD = 1.02, 95% CI: 0.26 to 1.78; $p = 0.009$), though substantial statistical heterogeneity was observed ($I^2 = 75\%$). Individual studies showed variable results across outcome metrics. Despite this statistical difference, the comparative clinical efficacy remains highly uncertain due to high risk of bias, small study numbers, and differences between objective psychophysical testing and subjective self-reported measures.

Conclusion: Evidence regarding the comparative effectiveness of ESS versus medical therapy in improving olfactory function remains highly uncertain. Given the methodological limitations of current data, further high-quality, well-phenotyped trials are required to clarify relative treatment efficacy.

Keywords: Chronic rhinosinusitis; endoscopic sinus surgery; medical therapy; olfactory dysfunction; meta-analysis (Siriraj Med J 2026;78(10):725-734)

INTRODUCTION

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disease affecting 5% to 12% of the global population.¹⁻³ While its classical symptoms include mucopurulent discharge, nasal obstruction and facial pressure, olfactory dysfunction has increasingly been recognized as one of its most distressing and impactful manifestations.^{2,4}

Olfactory impairment in CRS represents a critical determinant of patient-reported outcomes. Loss or reduction of smell has been consistently associated with diminished quality of life, impaired taste, reduced appetite, and heightened safety risks from environmental hazards.⁴⁻⁶ As such, restoration of olfactory function has emerged as a central therapeutic objective alongside the control of inflammation and sinonasal symptoms.

The underlying mechanisms of olfactory loss in CRS involve both conductive and sensorineural components. Conductive impairment arises from physical obstruction of the olfactory cleft by mucosal edema, polyps, or secretions, limiting odorant access to the epithelium.^{5,7,8} In parallel, chronic type 2 inflammation driven by eosinophilic infiltration and cytokine dysregulation can directly damage the neuroepithelium, leading to persistent or irreversible dysfunction.^{8,9} These mechanisms are prominent in CRSwNP, where olfactory loss is typically more severe and treatment resistant.^{8,9} Consequently, effective management requires therapeutic strategies

that address both structural obstruction and underlying inflammatory pathways.

Current CRS management follows a stepwise approach, beginning with maximal medical therapy including intranasal corticosteroids and saline irrigation, and, when indicated, short courses of systemic corticosteroids or antibiotics.^{2,3} While effective in controlling general disease activity by reducing inflammation and improving sinonasal patency, its impact on olfactory recovery is still unpredictable and often suboptimal, particularly in patients with longstanding disease or extensive polyp burden.^{6,10} Improvements in olfaction are transient and may diminish after cessation of systemic therapy, highlighting the limitations of medical management alone.^{6,10}

For patients with refractory CRS, endoscopic sinus surgery (ESS) is commonly considered as the next line of treatment. ESS restores sinus ventilation and drainage by removing obstructive tissue, enlarging sinus ostia, and enhancing the penetration of topical therapies to the sinonasal mucosa, potentially improving long-term disease control.^{1,3} From a mechanistic perspective, ESS may offer advantages in restoring olfactory function by addressing both conductive barriers and reducing inflammatory load within the olfactory cleft.^{6,7} Nevertheless, the extent to which these theoretical benefits translate into meaningful clinical improvement in olfaction remains a matter of ongoing discussion.

Existing literature comparing the effectiveness

of ESS and continued medical therapy in improving olfactory outcomes has yielded inconsistent findings. Some studies suggest that surgical intervention results in greater improvement in olfactory function, particularly in CRSwNP patients or severe baseline impairment.^{6,7} Conversely, other studies reported comparable results, especially when using objective measures.^{4,10} These discrepancies may be explained by variations in study design, patient selection, baseline disease severity, and the type of outcome measures used. Indeed, heterogeneity in olfactory assessment tools, ranging from objective tests such as the Brief Smell Identification Test (B-SIT) and Sniffin' Sticks to subjective patient-reported scales, challenges the synthesis of evidence across studies.^{4,5}

Furthermore, recent advances in CRS endotypes and the emergence of targeted biologic therapies have complicated the treatment landscape, particularly for CRSwNP.⁸ Although biologics demonstrate promising results in improving olfactory function, their high cost and limited accessibility necessitate continued evaluation of conventional modalities like ESS and medical therapy.^{8,9} Therefore, clarifying the comparative effectiveness of these established interventions remains highly relevant, especially in resource-limited settings.

However, given the critical role of olfactory function in overall disease burden, a comprehensive synthesis of evidence is warranted to address outcome measurement variability. Therefore, this systematic review and meta-analysis aims to evaluate and compare the effectiveness of endoscopic sinus surgery versus medical therapy in improving olfactory function among adult populations diagnosed with chronic rhinosinusitis.

MATERIALS AND METHODS

Study design

This study was designed as a systematic review and meta-analysis to evaluate the comparative effectiveness of endoscopic sinus surgery (ESS) versus medical therapy in improving olfactory function among adult patients with chronic rhinosinusitis (CRS). This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A protocol was not prospectively registered for this review.

Eligibility criteria

Study selection was performed using predefined inclusion and exclusion criteria based on the Population, Intervention, Comparator, and Outcomes (PICO) framework.

Studies were selected based on the PICOS framework.

We included studies evaluating adult patients (≥ 18 years) diagnosed with chronic rhinosinusitis (CRS), with or without nasal polyps, according to the EPOS 2020 diagnostic criteria. Eligible studies compared endoscopic sinus surgery (ESS) with medical therapy consisting of intranasal/systemic corticosteroids and/or nasal saline irrigations for a minimum of 4 weeks.

Outcomes of interest were olfactory function changes evaluated using validated objective instruments (smell identification tests) or subjective assessment tools (Visual Analog Scale). Studies required a minimum follow-up duration of 3 months post-treatment. When outcomes were reported at multiple post-treatment time points, data from the primary reported endpoint or the longest follow-up time point closest to 12 months were selected for quantitative synthesis.

Only full-text, peer-reviewed comparative studies published in English were included. Case reports, editorials, conference abstracts, pediatric studies (< 18 years), and studies with non-extractable outcome data were excluded.

The intervention of interest was endoscopic sinus surgery (ESS) followed by standard postoperative medical therapy, reflecting a treatment strategy of surgery with postoperative medical management. The comparator was continued medical therapy without surgery, with regimens varying across studies and including saline irrigation, intranasal corticosteroids, systemic corticosteroids, and/or antibiotics. Accordingly, the target estimand was the comparative effect of an ESS-based treatment strategy (ESS plus postoperative medical therapy) versus continued medical therapy alone, rather than the isolated effect of surgery itself.

The primary outcome was improvement in olfactory function, assessed using either objective measures (e.g., smell identification tests) or subjective patient-reported outcomes (e.g., visual analogue scales). Studies that did not report olfactory outcomes separately or did not report adequate data for quantitative extraction were excluded from the meta-analysis and instead considered for qualitative synthesis.

Furthermore, eligible study designs included randomized controlled trials and observational comparative studies. Case reports, case series without comparator groups, editorials, review articles, and conference abstracts were excluded from analysis.

Information sources and search strategy

A comprehensive literature search was conducted across three electronic databases (PubMed, Cochrane Library, and ScienceDirect) from inception to April 4, 2026. The strategy combined MeSH terms and free-

text keywords covering three main domains: chronic rhinosinusitis, endoscopic sinus surgery versus medical therapy, and olfactory function. In accordance with PRISMA 2020 and PRISMA-S guidelines, the complete, line-by-line search strategies for each database including exact field tags, Boolean operators, and applied filters are provided in [Supplementary Material 1](#).

The search strategy targeted comparative studies evaluating ESS and medical therapy for olfactory outcomes in CRS. To complement database searching, reference lists of included articles and relevant systematic reviews were manually screened to identify additional studies. Primary database selection was limited to PubMed, Cochrane Library, and ScienceDirect based on institutional accessibility. Across all databases, the search yielded a total of 828 records.

Study selection

Record screening and selection were conducted independently and in duplicate by the two authors at both the title/abstract and full-text evaluation stages. Reference management, deduplication, and title/abstract screening were performed using Microsoft Excel. Full-text articles of potentially eligible studies were retrieved and independently assessed against the predefined inclusion criteria. Disagreements between the two reviewers were resolved through structured re-evaluation of the study data against the eligibility criteria and joint discussion until full consensus was achieved.

The duplicate records were identified and removed before the full-text screening. The disagreements in study selection were resolved through discussion and consensus. The complete study selection process is presented in the PRISMA flow diagram.

Data extraction

Data were extracted independently in duplicate by both authors using a standardized form. Variables extracted included study characteristics, demographics, CRS subtypes, intervention protocols, olfactory instruments, follow-up durations, and quantitative outcomes (means, SDs, sample sizes). Study characteristics and qualitative findings are summarized in [Table 1](#). The complete extraction form and raw quantitative dataset used for meta-analysis are provided in [Fig 2](#). Disagreements were resolved by consensus, and primary authors were contacted via email for missing data.

Continuous outcome data reported as medians and interquartile ranges (Zhang et al., 2024) were transformed into estimated means and standard deviations using validated statistical formulas. No standard deviations

were borrowed or imputed across studies. Detailed transformation parameters for each study are provided in [Supplementary Material 2](#). To test the robustness of the primary findings, a sensitivity analysis was performed by excluding transformed data (Zhang et al., 2024) and retaining only studies with directly reported mean and standard deviation values (Smith et al., 2011; DeConde et al., 2014).

Risk of bias assessment

Risk of bias was evaluated independently in duplicate by both authors using RoB 2 for the randomized trial (Ragab et al., 2004) and ROBINS-I for non-randomized cohort studies (Smith et al., 2011; DeConde et al., 2014; Zhang et al., 2024). Disagreements were resolved by consensus. The RCT was judged as having “some concerns” (due to unblinded outcome assessment), while non-randomized studies were categorized as “moderate risk of bias” (due to potential selection bias and confounding). Detailed domain-level evaluations and justifications are provided in [Supplementary Material 3](#).

Statistical analysis

To address construct heterogeneity among outcome measures, continuous olfactory data were synthesized separately. Outcome instruments were categorized into objective psychophysical olfactory tests and subjective patient-reported olfactory outcomes. Standardized mean differences (SMDs) with 95% confidence intervals were calculated separately within each construct subgroup using random-effects models. Pooling across non-equivalent constructs was strictly avoided.

All of the outcomes were oriented so that higher values indicated better olfactory function. For studies in which higher scores represented worse symptoms, values were reversed before the analysis.

Quantitative synthesis used inverse-variance random-effects models with DerSimonian–Laird variance estimation (τ^2) and Hedges’ g correction for small-sample bias. Heterogeneity was assessed using I^2 (>50% indicating substantial heterogeneity). Given $k=3$, Knapp–Hartung adjustments and fixed-effects sensitivity analyses were applied to verify stability, with results interpreted cautiously. Prediction intervals were omitted due to $k < 10$.

All analyses were conducted using Review Manager (RevMan, version 5.4.1), with statistical significance set at $p < 0.05$. The primary synthesis evaluated olfactory outcomes at the 6-month follow-up (range: 3–12 months). Post-treatment endpoint scores (mean $\pm$ SD) were defined as the primary input data; where change scores were reported, endpoint values were reconstructed per

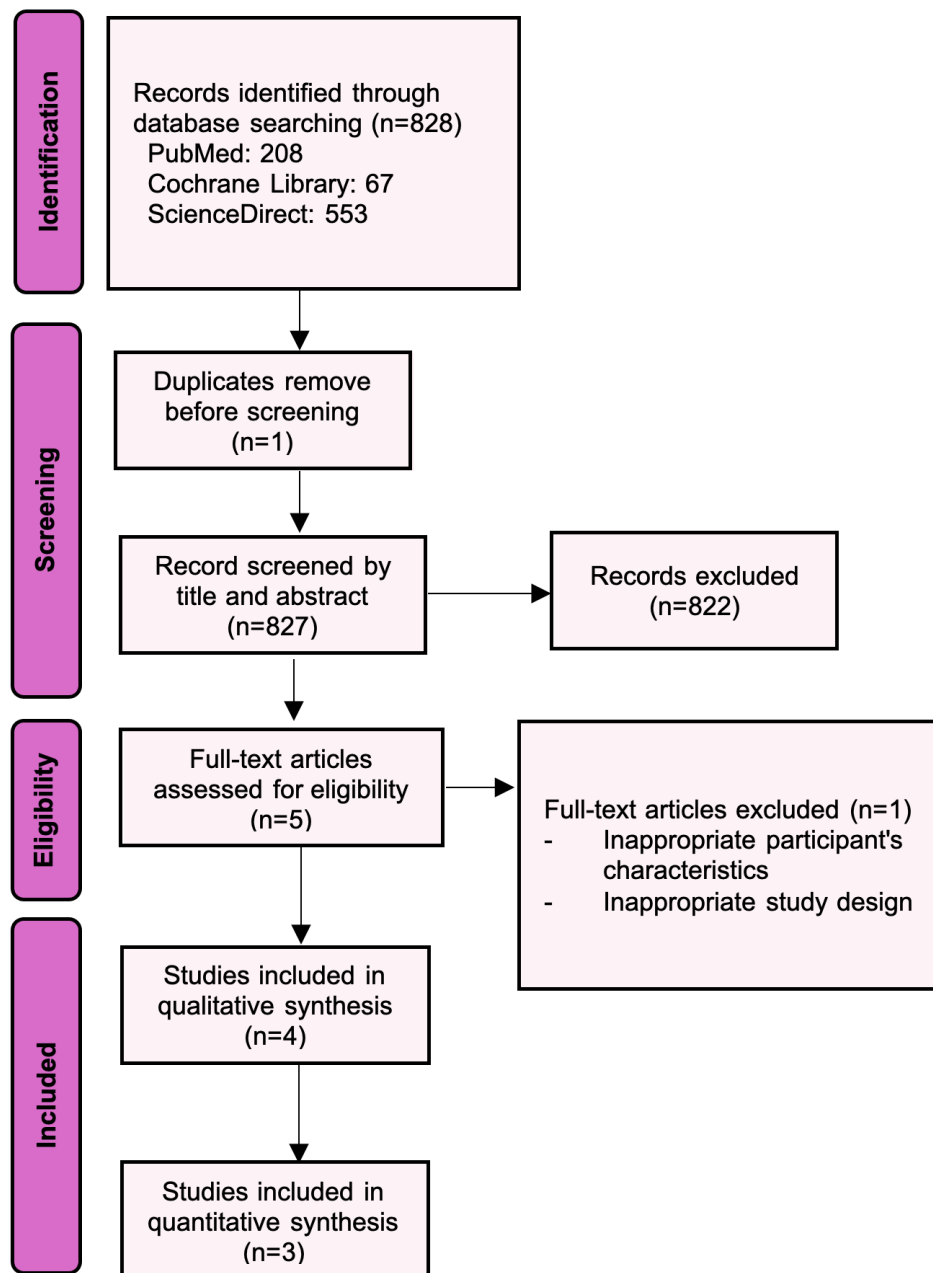


Fig 1. Diagram flow of literature search strategy for this systematic review.

Quantitative Synthesis (Meta-analysis of Olfactory Outcomes)

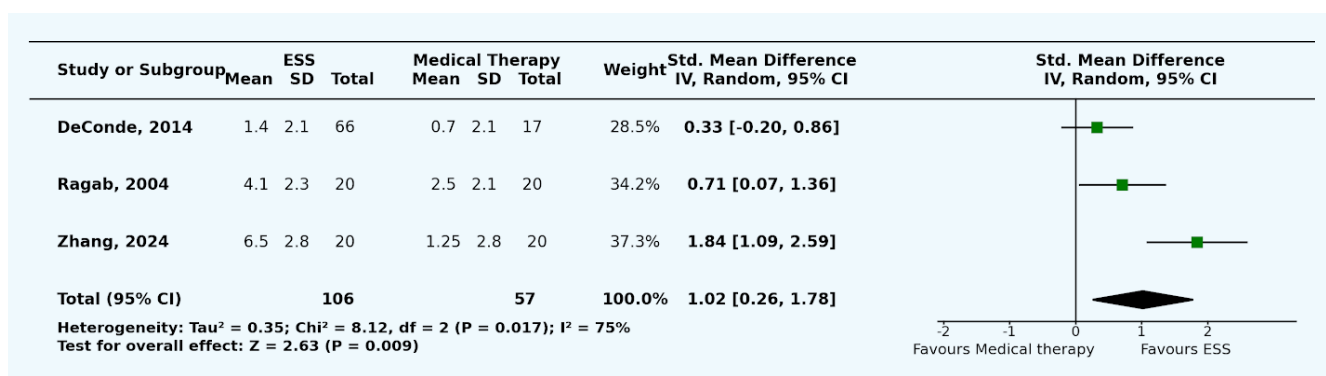


Fig 2. Pooled result for olfactory outcome.

TABLE 1. Characteristics and results of the included studies.

First Author (Year)	Country / Setting	Study Design	Population (Inclusion Criteria)	Sample Size (ESS / Medical)	Mean Age (ESS / Medical)	Male (%)	CRS Type (CRSwNP / CRSsNP)	Baseline Olfactory Status	Intervention Details (ESS + postop therapy)	Comparator (Medical Therapy)	Olfactory Measurement Tool	Follow-up Duration	Key Results	Summary of Findings	Risk of Bias
Smith et al. (2011) ¹¹	USA (multi-institutional: OHSU, NWU, MUSC, UPenn)	Prospective non-randomized cohort	Adults ≥18 years with CRS who failed initial medical therapy	75 / 55 (analyzed at 6 months)	44.1 / 51.5	52.5% / 43.2%	Mixed CRS (polyps present ~39% ESS vs 33% medical)	Not reported	ESS + continued medical therapy based on clinician judgment	Continued medical therapy (antibiotics, steroids, etc.)	Not reported (QOL-based: RSDI, CSS)	6 months	ESS showed significantly greater improvement in QOL (RSDI, CSS) and reduced antibiotic/steroid use and missed days	ESS superior to medical therapy in improving disease-specific outcomes	Low
Zhang et al. (2024) ¹²	China (single-center, Beijing Tongren Hospital)	Prospective cohort	Adults with CRSwNP nonresponsive to intranasal corticosteroids	20 / 20	43.6 / 42.2	50% / 60%	CRSwNP only	Worse in steroid group (VAS olfactory median 9.90 vs 9.30, p=0.0225)	ESS + postoperative intranasal corticosteroids	Oral corticosteroids (methylprednisolone taper) + intranasal steroids	VAS (olfactory function, 0–10 scale)	3 months	Both groups improved, but ESS showed significantly greater improvement in olfactory function	ESS provides superior olfactory improvement vs oral corticosteroids	Low
DeConde et al. (2014) ¹³	USA (multi-institutional: Oregon, South Carolina, Stanford)	Prospective cohort (non-randomized)	Adult CRS patients refractory to initial medical therapy	222 / 58 (total analyzed n=280)	51.9 vs 50.3	53.6% vs 39.7%	CRSwNP + CRSsNP	29.6% impaired olfaction at baseline	ESS + postoperative medical therapy	Continued medical therapy (antibiotics, steroids)	B-SIT (0–12)	≥6 months (mean ~ 12 months)	Both groups improved B-SIT significantly; no difference between groups	ESS and medical therapy yield comparable olfactory improvement	Low
Ragab et al. (2004) ¹⁴	UK (Royal National Throat, Nose and Ear Hospital, London)	Randomized Controlled Trial	Adults with CRS refractory to initial medical therapy (≥8 weeks symptoms + CT changes)	45 / 45 (total n=90)	43 ± 13	50% male	CRSwNP + CRSsNP	Included (olfactory disturbance part of VAS)	ESS + postoperative medical therapy (macrolide, steroid, douche)	Continued medical therapy (erythromycin + steroid + douche)	VAS (subjective; includes olfactory domain)	6 months & 12 months	Significant improvement in both groups; no significant difference between ESS and medical therapy	ESS and medical therapy show comparable improvement in CRS outcomes including olfactory symptoms	Low

Cochrane guidelines. To prevent multiplicity bias, only one primary olfactory scale was extracted per study. Full input data and exact parameters are documented in Fig 2 for complete plot reproducibility.

RESULTS

Study selection

A total of 828 records were identified through database searches (PubMed: 208; Cochrane Library: 67; ScienceDirect: 553). Prior to screening, 1 duplicate record was removed, leaving 827 unique records for screening. Title and abstract screening resulted in the exclusion of 822 records due to irrelevance to the study question. Five full-text articles were sought and retrieved for full eligibility assessment. One full-text article was excluded due to inappropriate participant characteristics and non-eligible study design. Ultimately, four studies were included in the qualitative synthesis. Of these, three studies provided isolated, quantitative olfactory outcome data and were included in the quantitative meta-analysis.

Study characteristics

The four included studies consisted of one randomized controlled trial and three prospective cohort studies, encompassing adult patients with chronic rhinosinusitis (CRS), with or without nasal polyps. Sample sizes varied across studies, with the largest cohort reported by DeConde et al. (2014), while Zhang et al. (2024) included the smallest sample.^{12,13} Interventions consisted of endoscopic sinus surgery (ESS) followed by standard postoperative medical therapy, compared with continued medical therapy alone, which typically included corticosteroids and/or antibiotics.

Eligibility was strictly limited to studies reporting isolated olfactory outcomes. DeConde et al. (2014) provided objective psychophysical data (B-SIT),¹³ while Ragab et al. (2004) and Zhang et al. (2024) provided subjective olfactory ratings (VAS).^{12,14} Smith et al. (2011) was excluded from quantitative synthesis due to a lack of discrete olfactory endpoints. For Zhang et al. (2024), continuous data presented as medians and IQRs were converted to means and SDs using validated transformation formulas per Cochrane guidelines. To address potential selection bias and transformation uncertainty in Zhang et al., an exclusion sensitivity analysis was performed.

Following a comprehensive data audit against the primary reports, three studies were included in the quantitative meta-analysis, evaluating a reconciled total of 163 participants (ESS group vs. medical therapy group). DeConde et al. (2014) contributed objective

B-SIT outcomes from the olfaction-impaired cohort ($n = 66$ ESS, $n = 17$ Medical). Subjective olfactory outcomes (VAS) were contributed by Ragab et al. (2004) ($n = 20$ ESS, $n = 20$ Medical) and Zhang et al. (2024) ($n = 20$ ESS, $n = 20$ Medical). Smith et al. (2011) was excluded from quantitative olfactory synthesis due to the absence of an isolated olfactory endpoint.

The pooled random-effects estimate yielded a standardized mean difference (SMD) of 1.02 (95% CI: 0.26 to 1.78; $Z = 2.63$, $p = 0.009$). Patients receiving endoscopic sinus surgery (ESS) demonstrated higher olfactory improvement scores compared to those receiving medical therapy alone. Substantial statistical heterogeneity was observed across studies ($I^2 = 75\%$, $p = 0.017$).

Individually, Zhang et al. (2024) reported a substantial improvement favoring ESS (SMD = 1.84; 95% CI: 1.09 to 2.59), and Ragab et al. (2004) similarly demonstrated a significant benefit in subjective olfactory VAS scores favoring ESS over medical therapy (SMD = 0.71; 95% CI: 0.07 to 1.36). In contrast, DeConde et al. (2014) showed a positive direction of effect favoring ESS in the olfaction-impaired subgroup, though this difference did not reach statistical significance (SMD = 0.33; 95% CI: -0.20 to 0.86).

Heterogeneity and consistency

Considerable statistical heterogeneity was identified across the included studies ($I^2 = 75\%$, $\tau^2 = 0.35$, $P = 0.01$). Given the small number of pooled studies ($k = 3$), empirical meta-regression or subgroup analyses to establish the exact sources of heterogeneity were not feasible. Methodologically, this variability may reflect differences in outcome measurement instruments (objective psychophysical testing vs. subjective VAS), patient clinical profiles (CRSwNP vs. mixed CRS populations), and study designs. Due to the limited number of studies ($k = 3$), a formal 95% prediction interval could not be reliably calculated, as variance estimators for between-study variance are highly unstable with fewer than four studies.

Overall interpretation of findings

While individual studies demonstrated variable degrees of olfactory recovery, the pooled quantitative synthesis indicated that endoscopic sinus surgery (ESS) yields a statistically significant improvement in olfactory function compared with medical therapy alone. However, the substantial statistical heterogeneity reflects notable methodological variability in outcome instruments and patient characteristics across the included trials.

Thus, these findings suggest that while ESS may offer potentially important improvements in selected patients,

particularly those with more severe or refractory disease, its overall advantage in restoring olfactory function compared with medical therapy alone demonstrates a large statistical effect size. However, because included studies utilized heterogeneous outcome tools without a standardized anchor-based minimally important difference (MID), the precise clinical magnitude of this improvement warrants cautious interpretation.

DISCUSSION

Principal findings

The pooled quantitative analysis demonstrated that ESS provides a statistically significant improvement in olfactory outcomes compared with medical therapy alone. These findings suggest that ESS offers potentially important benefits in restoring olfactory function, though substantial clinical and methodological heterogeneity across studies warrants cautious interpretation.

This observation was particularly relevant when considered alongside the current understanding of CRS as a multifactorial inflammatory disease. While ESS effectively restored sinus ventilation and removed obstructive tissue, olfactory recovery is not solely dependent on anatomical factors but is also strongly influenced by persistent mucosal inflammation and potential damage to the olfactory neuroepithelium.^{2,6,15} Therefore, the statistically significant superiority of ESS over medical therapy may reflect the synergistic impact of combining structural clearance with ongoing inflammatory control in reversing olfactory dysfunction.

Comparison with existing literature

The findings of this study were consistent with previous evidence indicating that both surgical and medical interventions can lead to meaningful improvements in CRS-related symptoms, including olfactory dysfunction.^{1,3} Several studies have shown that corticosteroid-based medical therapy can significantly improve olfactory outcomes, particularly in patients with type 2 inflammatory endotypes, thereby narrowing the expected advantage of surgical intervention.^{5,16}

Conversely, other reports suggested that ESS may offer superior improvement in olfaction, especially in patients with nasal polyps or more severe baseline impairment.^{4,5} This apparent inconsistency across studies may be attributed to variations in the study populations, baseline disease severity, and outcome measurement methods. Importantly, patients selected for surgery are often those with refractory disease, which may predispose them to greater relative improvement compared to those managed medically.¹⁶

Objective versus subjective olfactory outcomes

A key finding in this analysis was the divergence between objective and subjective measures of olfactory function. Studies employing objective assessments, such as smell identification tests, generally showed comparable outcomes between ESS and medical therapy. In contrast, subjective measures, including visual analogue scales, more frequently indicated greater improvement following surgical intervention.

This discrepancy may be explained by the influence of overall symptom relief on patient perception. Improvement in nasal airflow and reduction of obstruction following ESS may enhance the subjective experience of smell without corresponding changes in measurable olfactory performance.⁴ Additionally, objective tests may not fully capture subtle functional improvements or the multidimensional nature of olfactory perception.⁷ These findings highlighted the importance of integrating both objective and patient-reported outcomes in future studies.

Role of CRS phenotype and inflammation

The heterogeneity observed in treatment response was likely influenced by differences in CRS phenotype and underlying inflammatory pathways. CRSwNP, characterized by type 2 inflammation and eosinophilic predominance, is associated with more severe olfactory dysfunction and may respond differently to treatment modalities.^{1,3}

While ESS can effectively reduce polyp burden and improve airflow, persistent inflammation may limit long-term recovery of olfactory function.¹⁷ In recalcitrant CRS, osteitis represents a key hallmark of persistent mucosal inflammation and tissue remodeling, which is associated with severe disease states and reduced responsiveness to standard therapies.¹⁸ In contrast, medical therapies, particularly corticosteroids and emerging biologic agents, target inflammatory pathways more directly and may play a critical role in restoring olfactory function at the cellular level.^{3,15} This supports the concept that optimal management of CRS requires a combined approach addressing both structural and inflammatory components.^{1,10,15–17}

Clinical implications

From a clinical standpoint, these findings suggest that ESS should not be universally regarded as superior to medical therapy for the improvement of olfactory function alone. Instead, treatment decisions should be individualized based on disease severity, phenotype, prior response to therapy, and patient preferences.^{6,8}

Medical therapy remains a fundamental component

of chronic rhinosinusitis (CRS) management and may be sufficient to achieve meaningful olfactory improvement in selected patients.^{6,8} ESS continues to be an important option for patients with refractory disease or significant anatomical obstruction; however, clinicians should provide realistic expectations regarding the extent of olfactory recovery following surgery.^{2,10}

Limitations

Several critical limitations must be considered when interpreting these findings. First, the small number of included studies ($k = 3$) limits statistical power and precision, yielding a very low overall certainty of evidence. Second, substantial heterogeneity ($I^2 = 75\%$) was identified, driven by combining distinct outcome constructs namely objective psychophysical tests and subjective self-reported measures alongside variations in CRS subtypes and baseline disease severity. Third, methodological constraints in primary studies introduce potential risk of bias, including non-randomized treatment selection, unexplained subgroup sample sizes, imputed standard deviations for incomplete statistical reporting, and potential selective outcome inclusion. Finally, the absence of a pre-registered review protocol limits methodological transparency.

Future directions

Future research should prioritize well-designed randomized controlled trials with standardized olfactory outcome measures to improve comparability across studies. The use of validated objective tools combined with patient-reported outcomes will be essential to provide a comprehensive assessment of treatment effects.⁷

Additionally, further investigation into the role of CRS phenotypes and inflammatory endotypes in predicting treatment response is warranted. Emerging therapies targeting specific inflammatory pathways, including biologic agents, may offer new opportunities for improving olfactory outcomes and should be explored in future comparative studies.^{15,16,19,20}

CONCLUSIONS

Current evidence regarding the comparative effectiveness of endoscopic sinus surgery (ESS) versus medical therapy for olfactory restoration in chronic rhinosinusitis remains highly uncertain. Although the pooled quantitative synthesis indicated a statistically significant improvement favoring ESS, this finding is limited by substantial statistical heterogeneity, a small number of included studies, wide confidence intervals, and a high risk of methodological bias. Consequently,

no definitive clinical practice recommendations can be made from this analysis. Well-designed, randomized controlled trials employing standardized, objective olfactory assessments are needed to establish the true comparative efficacy of these interventions.

Data Availability Statement

No primary data were generated for this study. This systematic review and meta-analysis were conducted using secondary data extracted from previously published studies. All studies included in the analysis are cited in the reference list.

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DECLARATIONS

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Conflict of Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Registration Number of Clinical Trial

Not applicable. This manuscript is a systematic review and meta-analysis, not a primary clinical trial.

Author Contributions

Conceptualization and methodology, N.A.A and W.I.A.S; Formal analysis, N.A.A and W.I.A.S; Visualization and writing – original draft, N.A.A ; Writing – review and editing, N.A.A and W.I.A.S. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

During the preparation of this manuscript, the authors used Grammarly solely for language editing, grammar correction, and improving structural readability. No artificial intelligence tools were used in the conception, database literature search (PubMed, Cochrane Library, ScienceDirect), screening, data extraction, risk of bias assessment, or statistical meta-analysis conducted via RevMan 5.4.1. The authors reviewed and edited the final manuscript and take full responsibility for the content of this publication.

Institutional Review Board Statement

Ethical approval was not required for this study, as it is a systematic review and meta-analysis based entirely on previously published literature and does not involve direct human subjects or biological samples.

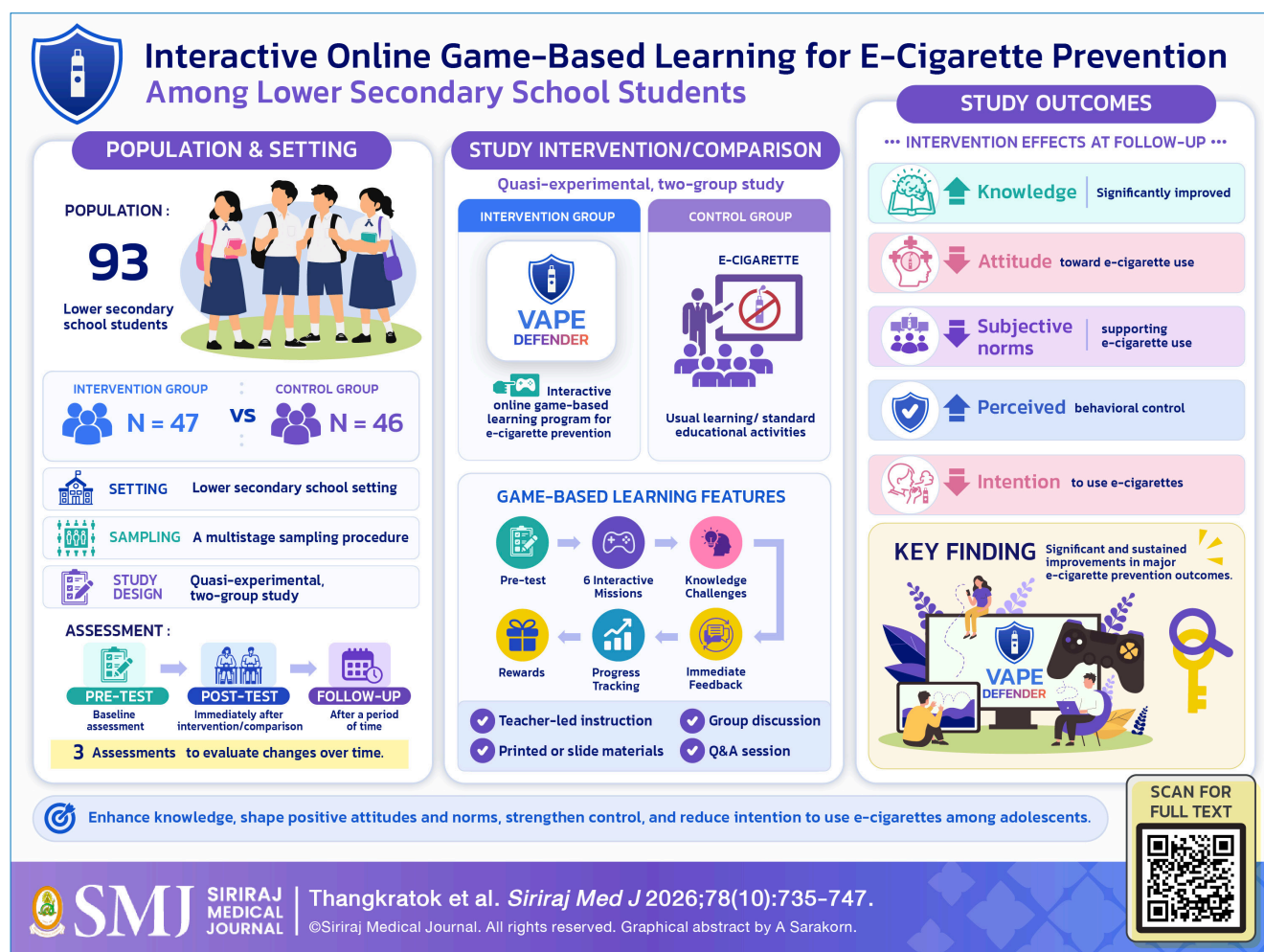
REFERENCES

- Rombaux P, Huart C, Levie P, Cingi C, Hummel T. Olfaction in Chronic Rhinosinusitis. *Curr Allergy Asthma Rep.* 2016;16(5):41.
- Soler ZM, Hyer JM, Ramakrishnan V, Smith TL, Mace J, Rudmik L, et al. Identification of chronic rhinosinusitis phenotypes using cluster analysis. *Int Forum Allergy Rhinol.* 2015;5(5):399–407.
- Yang SK, Cho S-H, Kim DW. Interpretation of Clinical Efficacy of Biologics in Chronic Rhinosinusitis With Nasal Polyps via Understanding the Local and Systemic Pathomechanisms. *Allergy Asthma Immunol Res.* 2022;14(5):465.
- Rimmer RA, Mace JC, Gill A, Alt J, Detwiler K, Geltzeiler M, et al. Association of statins with quality of life and olfaction in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2022;12(2):237–9.
- Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol.* 2019;276(3):719–28.
- Orlandi RR, Kingdom TT, Smith TL, Bleier B, DeConde A, Luong AU, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol.* 2021;11(3):213–739.
- Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. *Rhinol Suppl.* 2017;54(26):1–30.
- Michalik M, Krawczyk B. Chronic Rhinosinusitis—Microbiological Etiology, Potential Genetic Markers, and Diagnosis. *Int J Mol Sci.* 2024;25(6):3201.
- Hopkins C. Chronic Rhinosinusitis with Nasal Polyps. *N Engl J Med.* 2019;381(1):55–63.
- Benninger MS, Sindwani R, Holy CE, Hopkins C. Early versus Delayed Endoscopic Sinus Surgery in Patients with Chronic Rhinosinusitis. *Otolaryngol Head Neck Surg.* 2015;152(3):546–52.
- Smith TL, Kern RC, Palmer JN, Schlosser RJ, Chandra RK, Chiu AG, et al. Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study. *Int Forum Allergy Rhinol.* 2011;1(4):235–41.
- Zhang J, Sima Y, Shao S, Zheng M, Zhao Y, Gao F, et al. Cost-utility and clinical outcome analysis of surgery or oral corticosteroids treatment in patients with chronic rhinosinusitis with nasal polyps. *Asia Pac Allergy.* 2024;14(4):174–82.
- DeConde AS, Mace JC, Alt JA, Schlosser RJ, Smith TL, Soler ZM. Comparative effectiveness of medical and surgical therapy on olfaction in chronic rhinosinusitis: a prospective, multi-institutional study. *Int Forum Allergy Rhinol.* 2014;4(9):725–33.
- Ragab SM, Lund VJ, Scadding G. Evaluation of the Medical and Surgical Treatment Of Chronic Rhinosinusitis: A Prospective, Randomised, Controlled Trial. *Laryngoscope.* 2004;114(5):923–30.
- Zhu H, Qu S, Gong M, Xiang Y, Gan S, Teng Y, et al. Mechanisms, diagnosis, and treatment of olfactory dysfunction in rhinosinusitis. *Eur J Med Res.* 2025;30(1):474.
- Lane AP, Mullol J, Hopkins C, Fokkens WJ, Lee SE, Msihid J, et al. Dupilumab improves sense of smell and clinical outcomes in patients with severe chronic rhinosinusitis with nasal polyps with anosmia. *Curr Med Res Opin.* 2025;41(1):53–9.
- Kohli P, Naik AN, Farhood Z, Ong AA, Nguyen SA, Soler ZM, et al. Olfactory Outcomes after Endoscopic Sinus Surgery for Chronic Rhinosinusitis. *Otolaryngol Head Neck Surg.* 2016;155(6):936–48.
- Hadi W, Sujana WIA. Osteitis in Chronic Rhinosinusitis: A State-of-the-Art Review. *Siriraj Med J.* 2025;77(7):533–42.
- Hernandez AK, Wendler O, Mayr S, Iro H, Hummel T, Mueller SK. Predictors of olfactory improvement after endoscopic sinus surgery in chronic rhinosinusitis with nasal polyps. *J Laryngol Otol.* 2023;137(5):524–31.
- Briner HR, Jones N, Simmen D. Olfaction after endoscopic sinus surgery: long-term results. *Rhinology.* 2012;50(2):178–84.

Development and Evaluation of an Interactive Online Game-Based Learning Program on Knowledge, Attitudes, Subjective Norms, Perceived Behavioral Control, and Intention to Use E-Cigarettes among Lower Secondary School Students

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ABSTRACT

Objective: This study aimed to examine the effectiveness of an interactive online game-based learning program on knowledge, attitudes, subjective norms, perceived behavioral control, and intention to use e-cigarettes among lower secondary school students.

Materials and Methods: A quasi-experimental study was conducted in two lower secondary schools, with one school assigned to the intervention condition and the other to the comparison condition. Ninety-three students participated (intervention, $n = 47$; comparison, $n = 46$). Knowledge, attitudes, subjective norms, perceived behavioral control, and intention to use e-cigarettes were assessed at pretest, posttest, and follow-up. Longitudinal changes were analyzed using repeated-measures models. Because each condition included only one school, between-group findings were considered exploratory and may reflect school-level effects.

Results: Compared with the comparison school, students in the intervention school showed greater improvements in knowledge at posttest and follow-up. Attitudes, subjective norms, and intention scores decreased at both assessments, indicating less favorable attitudes toward e-cigarette use, lower perceived social pressure to use e-cigarettes, and lower intention to use e-cigarettes. Perceived behavioral control showed little immediate change but increased at follow-up.

Conclusion: Participation in the interactive online game-based learning program was associated with favorable changes in knowledge and psychosocial determinants related to e-cigarette use. However, the observed differences cannot be separated from school-level effects. Studies involving multiple schools in each condition are needed to confirm intervention effectiveness.

Keywords: Electronic nicotine delivery systems; vaping; adolescents; students; prevention program; intention (Siriraj Med J 2026;78(10):735-747)

INTRODUCTION

Over the past decade, the use of electronic cigarettes (e-cigarettes) among Thai youth has shown a continuous upward trend.^{1,2} Although the sale of e-cigarettes remains illegal in Thailand, these products are still easily accessible through online platforms.³ This issue is particularly concerning among lower secondary school students, who are at a developmental stage characterized by identity formation, a strong desire for peer acceptance, and exploratory behaviors.⁴ E-cigarettes have become increasingly attractive to adolescents due to their modern appearance, appealing flavors, and aggressive online marketing strategies.⁵ The proportion of students who had experimented with or were currently using e-cigarettes increased compared with previous years.⁶ Most adolescents obtained misleading information regarding the safety of e-cigarettes through social media and were also influenced by peers who used these products.³ This situation highlights the urgent need for preventive measures and age-appropriate educational interventions to promote accurate understanding of the harmful effects of e-cigarettes, particularly among lower secondary school students.

Despite various measures implemented to prevent and reduce e-cigarette use among Thai youth, these interventions have not adequately addressed the behavioral patterns and

social contexts of the digital era.⁷ Government agencies, including the Ministry of Public Health, have enforced bans on the importation and sale of e-cigarettes in Thailand and have launched public awareness campaigns regarding the dangers of e-cigarette use.⁸ Educational activities and training programs have also been conducted in schools, particularly at the secondary school level. However, many campaigns still rely on traditional communication methods, such as lectures, brochures, and informational videos, which may not effectively engage contemporary adolescents or significantly influence their attitudes and behaviors.^{9,10} Many young people continue to receive misleading information and persuasive advertising about e-cigarettes through social media, particularly messages portraying e-cigarettes as a “safer alternative” to conventional cigarettes.³

Although attempts have been made to educate adolescents about the harmful effects of e-cigarettes, there remains a lack of innovative educational approaches integrating digital technologies, such as educational games and interactive learning systems, that align with adolescents’ learning preferences. Many existing programs focus primarily on providing information and knowledge, while insufficient attention has been paid to behavioral psychology principles, including intrinsic

motivation, critical thinking, and rational decision-making. Furthermore, most educational media and learning materials are developed by adults or experts without directly involving adolescents in identifying their needs or preferences, resulting in a mismatch between the content provided and the interests of the target audience. The development of positive knowledge and attitudes should involve collaboration among schools, teachers, parents, and peers, all of whom represent influential social groups in adolescents' lives.¹¹ However, many interventions continue to operate independently and lack systematic continuity and integration.

Traditional learning approaches that focus solely on providing information may be insufficient to effectively change adolescents' behaviors. In contrast, the design of Interactive Game-Based Learning programs has considerable potential to enhance learner engagement, memory retention, and decision-making processes.¹² A systematic review of digital games used for the prevention, assessment, and treatment of substance use, as well as for promoting positive youth development, found that approximately half of the reviewed studies (50%) reported that digital games were effective in reducing substance use behaviors. Regarding attitudes toward substance use, 65% of the studies demonstrated statistically significant improvements in attitudes, while studies focusing on positive youth development showed effectiveness in 35.7% of cases. These findings suggest that digital games have strong potential as educational and intervention tools capable of both reducing risky substance-use behaviors and promoting positive life skills among adolescents.¹²

Furthermore, a pilot study evaluating the short-term effects of an interactive video game on changes in knowledge, beliefs, risk perception, and intentions to use e-cigarettes, cigarettes, and other tobacco products employed a one-group pretest–posttest design. Participants engaged in four 60-minute gameplay sessions over a four-week period. The results showed increased knowledge of e-cigarettes and other tobacco products, greater perceived risks associated with cigarette and e-cigarette use, and more favorable beliefs regarding tobacco prevention. However, no significant change was observed in intentions to use tobacco products. Nevertheless, the findings suggested that brief exposure to an interactive gaming intervention—a total of four hours over four weeks—may have the potential to improve adolescents' knowledge and promote attitudes supportive of tobacco-use prevention, particularly regarding e-cigarettes.¹³

The Theory of Planned Behavior (TPB) was used as the conceptual framework for both intervention design and outcome evaluation. According to the TPB, behavioral

intention is determined by attitudes toward the behavior, subjective norms, and perceived behavioral control.¹⁴ In this study, activities addressing the health, legal, and social consequences of e-cigarette use were designed to reduce favorable attitudes; peer-pressure and social-influence simulations targeted subjective norms; and refusal-skills and decision-making exercises were intended to strengthen perceived behavioral control. Intention to use e-cigarettes was specified as the proximal behavioral outcome. Knowledge was included as an additional cognitive outcome because accurate understanding of health risks and legal consequences may support less favorable attitudes and more informed decisions. The hypothesized pathway was that the game-based program would improve knowledge, attitudes, subjective norms, and perceived behavioral control, thereby reducing intention to use e-cigarettes.

Preliminary observations revealed that most students had acquired knowledge regarding the harmful effects of e-cigarettes from multiple sources, including classroom instruction, educational activities conducted by school personnel, peer warnings from senior students, and exposure to media content.¹⁵ However, such awareness remains influenced by personal and environmental factors, individuals' ability to critically evaluate information, and peer pressure, all of which may shape attitudes and behaviors related to e-cigarette use. Therefore, the development of educational tools that promote a deeper understanding of the harmful effects of e-cigarettes, while simultaneously strengthening decision-making skills and rational coping strategies for dealing with social pressure, is highly important. This is particularly relevant when educational media are designed in formats that are accessible, engaging, and aligned with adolescents' digital lifestyles, such as interactive online game-based learning programs.¹⁶ Such programs may enhance learner participation and contribute to long-term changes in attitudes and behaviors. Consequently, this study aimed to evaluate the effectiveness of an interactive online game-based learning program by comparing knowledge regarding e-cigarettes, attitudes toward e-cigarette use, subjective norms, perceived behavioral control, and intention to use e-cigarettes between the intervention and control groups at baseline, posttest, and follow-up. A secondary objective was to evaluate satisfaction with the program among students in the intervention group.

MATERIALS AND METHODS

This study employed a quasi-experimental research design with an intervention group and a comparison group. Data were collected at three time points: before the

intervention (T0: pretest), immediately after completion of the program (T1: posttest), and 2 weeks after T1 (T2: follow-up). The pretest, intervention, and posttest were conducted on May 15, 2026, with the posttest administered immediately after completion of the program. The follow-up assessment was completed on May 29, 2026, 2 weeks after the posttest. The study was registered with the Thai Clinical Trials Registry (TCTR20260505009). Ethical approval was obtained from the Human Research Ethics.

Study population

The target population consisted of lower secondary school students enrolled in private secondary schools under the Office of the Private Education Commission in Dusit District, Bangkok. Eligible participants were students studying in Grades 7–9 (Matthayom 1–3), aged 12–17 years, who were able to use a smartphone or computer with internet access, had obtained parental consent and provided student assent, and were willing to participate in the study. The age range of 12–17 years was specified to accommodate variation in age within the eligible grade levels, including students who entered school later or had repeated a grade.

Eligibility regarding e-cigarette use was assessed before enrollment using a confidential self-administered screening form. Students who self-reported regular e-cigarette use or nicotine dependence at baseline were excluded; biochemical verification was not performed. After enrollment and assignment according to school, inability to complete the intervention or follow-up assessments was treated as attrition rather than as an exclusion criterion.

Sample size determination

An initial participant-level sample size calculation was performed using G*Power (F tests: repeated-measures ANOVA, between–within interaction) assuming a medium effect size ($f = 0.25$), $\alpha = 0.05$, power = 0.80, two groups, three measurement occasions, a correlation of 0.50 among repeated measures, and $\epsilon = 1.00$. This calculation yielded an estimated minimum of approximately 80 students. Allowing for approximately 15% attrition, the recruitment target was increased to 94 students. However, this initial calculation did not account for the school-level allocation or intracluster correlation. Because the actual design included only two schools, with one school assigned to each study condition, the intervention condition was completely confounded with school and the effective number of independent allocation units was two rather than the number of participating students. Therefore, the originally specified 80% statistical power does not apply

to the estimation of a school-level intervention effect. The present study should be regarded as an exploratory two-cluster quasi-experimental study, and the participant-level sample size was used to guide student recruitment rather than to establish adequate power for confirmatory intervention-effect inference.

Sampling procedure

A multistage sampling procedure was used. First, Dusit District, Bangkok, was purposively selected as the study area because it includes several private secondary schools under the Office of the Private Education Commission. A sampling frame was then constructed comprising seven private schools offering lower secondary education in the district. Two schools were selected using probability proportional to size (PPS) sampling based on student enrollment, with reserve schools identified in case a selected school declined participation.

After the two participating schools agreed to participate, the schools were randomly assigned at the school level, with one school allocated to the intervention condition and the other to the comparison condition. Thus, the study included two school-level clusters, with one school representing each study condition.

Within each participating school, students in Grades 7–9 (Mathayom 1–3) who met the predefined eligibility criteria were purposively recruited. Parental consent and student assent were obtained before enrollment. Recruitment continued until the planned number of participants was reached, resulting in 47 students from the intervention school and 46 students from the comparison school.

Because only one school was allocated to each study condition, school and study condition were completely confounded, and there was no independent replication at the level of allocation. Consequently, comparisons between students in the two schools were considered exploratory and descriptive and were not interpreted as confirmatory estimates of an intervention effect.

Intervention

The intervention consisted of an interactive online game-based learning program, “Vape Defender”, developed to prevent e-cigarette use among lower secondary school students. The program was delivered by the researchers through a web-based interactive learning platform. Participants completed one structured session lasting approximately 25–30 minutes using an internet-enabled device.

The program was guided by the Theory of Planned Behavior and comprised six interactive game missions

designed to address knowledge, attitudes, subjective norms, perceived behavioral control, and intention related to e-cigarette use prevention. The six missions were: (1) Item Scanner, which introduced participants to e-cigarette devices, components, and related products; (2) Toxic Vapor, which focused on harmful substances and the health consequences of e-cigarette use; (3) Bomb Disposal, which used problem-solving activities to reinforce recognition of e-cigarette-related risks and consequences; (4) Decode, which challenged participants to interpret and evaluate information related to e-cigarettes; (5) Face-Off, which presented simulated situations involving peer and social influences and allowed participants to practice decision-making and refusal skills; and (6) Spread the Message, which reinforced prevention messages and encouraged participants to communicate knowledge and attitudes supportive of avoiding e-cigarette use. Gamification features, including scores, achievement feedback, rewards, and progress tracking, were incorporated to promote active participation and engagement.

Participants in the comparison school did not receive the Vape Defender interactive game-based program during the study period and continued with the usual health education and routine learning activities provided by the school. No additional game-based intervention was provided by the researchers to the comparison group. The comparison condition was not specifically

matched to the intervention condition for contact time or attention.

Outcomes in both schools were assessed at three time points: before the intervention (T0: pretest), immediately after completion of the program (T1: posttest), and 2 weeks after T1 (T2: follow-up).

Research instruments

The research instruments used in this study consisted of several questionnaires designed to assess knowledge, attitudes, subjective norms, perceived behavioral control, intentions regarding e-cigarette use, and participant satisfaction with the program.

The e-cigarette knowledge questionnaire consisted of 10 multiple-choice items assessing knowledge of the health effects, harmful substances, addictive properties, and legal issues related to e-cigarettes. The questionnaire was adapted from relevant literature and existing evidence on e-cigarette prevention among adolescents.² Each correct response was scored 1 and each incorrect or “do not know” response was scored 0, yielding a total score ranging from 0 to 10, with higher scores indicating greater knowledge about e-cigarettes.

The attitude toward e-cigarette use questionnaire was adapted from the Electronic Cigarette Attitudes Survey developed by Alduraywish et al. (2023).¹⁷ The instrument consisted of 10 items rated on a five-point Likert scale

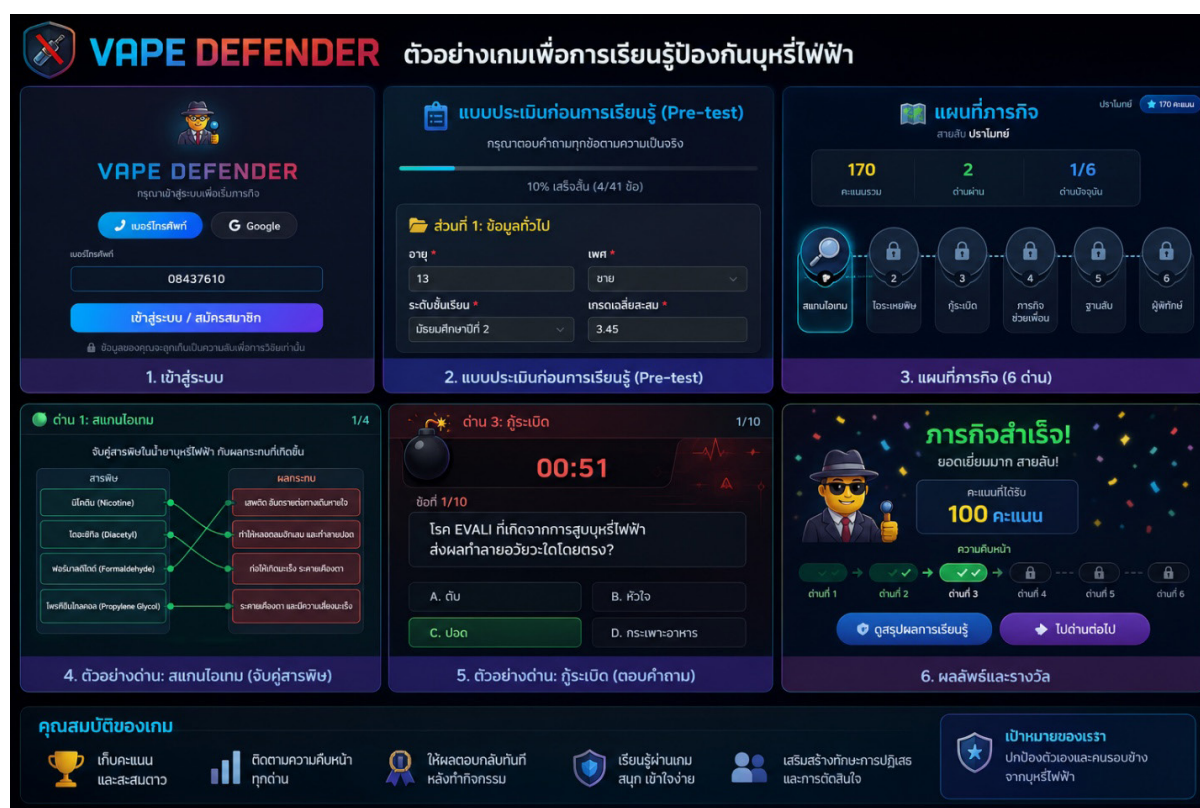


Fig 1. User interface screens of the interactive online game-based learning program.

ranging from strongly disagree (1) to strongly agree (5). Items 4 and 7 were reverse-coded before calculation of the scale score. After reverse coding, an item mean score was calculated across the 10 items, yielding a possible range of 1.00–5.00. Higher mean scores indicated more favorable attitudes toward e-cigarette use, whereas lower mean scores indicated less favorable or more negative attitudes toward e-cigarette use.

The subjective norm questionnaire regarding e-cigarette use was developed based on the Theory of Planned Behavior and relevant literature.^{2,14} The questionnaire consisted of six items assessing perceived social influence from significant others and social sources, including peers, family members, celebrities, and online media, regarding e-cigarette use. Each item was rated on a five-point Likert scale ranging from 1 to 5. An item mean score was calculated across the six items, yielding a possible range of 1.00–5.00. Higher mean scores indicated stronger perceived social influence or pressure supporting e-cigarette use, whereas lower mean scores indicated weaker perceived social influence supporting e-cigarette use.

The perceived behavioral control questionnaire was developed based on the Theory of Planned Behavior and relevant literature.^{2,14} The instrument consisted of six items assessing participants' perceived ability and confidence to resist or avoid e-cigarette use in situations in which they might encounter opportunities or social pressure to use e-cigarettes. Each item was rated on a five-point Likert scale ranging from 1 to 5. All items were scored in the same direction so that higher values consistently represented greater perceived behavioral control. An item mean score was calculated across the six items, yielding a possible range of 1.00–5.00. Higher mean scores indicated greater perceived behavioral control over avoiding e-cigarette use, whereas lower scores indicated lower perceived behavioral control.

The intention to use e-cigarettes questionnaire was developed by the researchers based on the Theory of Planned Behavior and relevant literature.^{2,14} The instrument consisted of five items assessing participants' intentions to try or use e-cigarettes at present, within the next six months, or if an opportunity to use e-cigarettes arose. Each item had three response options: "No" (1 point), "Maybe" (2 points), and "Yes" (3 points). An item mean score was calculated across the five items, yielding a possible range of 1.00–3.00. Higher mean scores indicated stronger intention to use e-cigarettes, whereas lower mean scores indicated weaker intention to use e-cigarettes.

Participants' experiences and satisfaction with the intervention program were assessed using a five-item

satisfaction questionnaire rated on a five-point Likert scale ranging from 1 (very low satisfaction) to 5 (very high satisfaction). A mean item score was calculated across the five items, yielding a possible range of 1.00–5.00, with higher scores indicating greater satisfaction. Mean scores were interpreted using equal-width intervals as follows: 1.00–1.80, very low; 1.81–2.60, low; 2.61–3.40, moderate; 3.41–4.20, high; and 4.21–5.00, very high satisfaction.

All research instruments were evaluated for content validity by three experts with expertise in adolescent health, e-cigarette prevention, and behavioral research. Item-Objective Congruence (IOC) values ranged from 0.67 to 1.00. The instruments were subsequently pilot-tested with 30 adolescents who had characteristics similar to those of the target population but were not included in the main study.

For the 10-item dichotomously scored knowledge questionnaire, internal consistency was assessed using the Kuder–Richardson Formula 20 (KR-20), yielding a coefficient of 0.80. Cronbach's alpha coefficients in the pilot sample were 0.93 for attitude, 0.93 for subjective norm, 0.89 for perceived behavioral control, 0.92 for intention to use e-cigarettes, and 0.80 for program satisfaction.

Data collection procedures

Before data collection, the researchers and research assistants were trained in the study protocol, including participant recruitment, parental consent and student assent, questionnaire administration, operation of the online learning platform, data recording, confidentiality, and protection of participants' privacy. The instruments and study procedures were pilot-tested with 30 adolescents who were not included in the main study to assess questionnaire comprehension, completion time, procedural clarity, and instrument reliability. Necessary equipment and internet access were prepared before implementation.

Eligible students were screened according to the predefined eligibility criteria. The study objectives, procedures, potential benefits and risks, confidentiality safeguards, and voluntary nature of participation were explained to students and their parents or guardians. Written parental consent and student assent were obtained before enrollment. At baseline (T0), participants completed demographic questions and measures of e-cigarette knowledge, attitude, subjective norm, perceived behavioral control, and intention to use e-cigarettes. Research personnel provided standardized instructions and checked submitted questionnaires for completeness.

After the baseline assessment, students in the intervention school participated in the Vape Defender

interactive online game-based learning program delivered by the researchers. The program consisted of six interactive game missions and was completed in one session lasting approximately 25–30 minutes. Implementation information, including attendance, completion of the game activities, duration of participation, and technical problems, was recorded to assess intervention fidelity. Students in the comparison school continued their usual school-based health education and routine learning activities and did not receive the Vape Defender program during the study period. The comparison condition was not specifically matched to the intervention condition for contact time or attention.

The posttest (T1) was administered immediately after completion of the intervention using the same outcome measures as at baseline. The follow-up assessment (T2) was conducted 2 weeks after T1. The same assessment schedule was applied to participants in the comparison school. Participant completion and missing outcome data were documented at each assessment point. After completion of the T2 assessment, participants in the comparison school were offered access to the Vape Defender program; data collected after this access were not included in the primary analyses.

Data analysis

Descriptive statistics were used to summarize participant characteristics and outcomes. The prespecified primary outcome was intention to use e-cigarettes; knowledge, attitude, subjective norm, and perceived behavioral control were secondary outcomes. Longitudinal patterns across T0, T1, and T2 were examined using mixed-effects models with participant-specific random intercepts and adjustment for age and GPA.

Because only one school represented each study condition, school and intervention condition were completely confounded; therefore, between-school comparisons were interpreted as exploratory rather than confirmatory intervention effects. Secondary-outcome analyses were also considered exploratory because of multiple comparisons.

Outcome distributions were examined for ceiling and floor effects. Given the pronounced floor effect in intention and ceiling effect in knowledge, robust and non-parametric sensitivity analyses were conducted. These analyses assessed the robustness of the observed patterns but did not resolve school-level confounding.

RESULTS

A total of 94 students were enrolled in the study. One participant did not complete the follow-up (T2) questionnaire and was excluded from the final analysis. Thus, 93 students were included in the analysis, comprising 47 students in the intervention group and 46 students in the control group. Complete outcome data were available for these 93 participants at T0, T1, and T2.

Baseline characteristics are presented descriptively in Table 1. The intervention and comparison schools had similar observed distributions of age, GPA, knowledge, attitude, subjective norm, and perceived behavioral control. Baseline intention scores were lower in the intervention school than in the comparison school (1.17 ± 0.48 vs. 1.40 ± 0.53). Because each study condition was represented by only one school, baseline differences may reflect school-level contextual characteristics rather than study condition. Accordingly, subsequent changes in intention were interpreted descriptively and may also be influenced by baseline differences and regression to the mean.

TABLE 1. Baseline characteristics of participants by group.

Variable	Intervention school (n = 47)	Comparison school (n = 46)
Age, mean $\pm$ SD	14.28 $\pm$ 1.14	14.28 $\pm$ 1.07
GPA, mean $\pm$ SD	3.46 $\pm$ 0.49	3.44 $\pm$ 0.44
Knowledge, mean $\pm$ SD	7.28 $\pm$ 1.83	6.87 $\pm$ 2.15
Attitude, mean $\pm$ SD	2.67 $\pm$ 1.04	2.72 $\pm$ 0.97
Subjective norm, mean $\pm$ SD	2.34 $\pm$ 1.27	2.63 $\pm$ 1.25
Perceived behavioral control, mean $\pm$ SD	4.11 $\pm$ 1.02	4.07 $\pm$ 0.87
Intention, mean $\pm$ SD	1.17 $\pm$ 0.48	1.40 $\pm$ 0.53

Descriptive results showed that students in the intervention school had increased knowledge scores from pretest to follow-up, whereas those in the comparison school showed relatively little change. Attitude, subjective norm, and intention scores decreased over time in the intervention school, indicating less favorable attitudes toward e-cigarette use, weaker perceived social influence supporting e-cigarette use, and lower intention to use e-cigarettes, respectively. Perceived behavioral control remained relatively stable at posttest and increased at follow-up, indicating greater perceived ability to avoid e-cigarette use. These patterns are interpreted descriptively because school and study condition were completely confounded.

Exploratory linear mixed-effects models were used to examine longitudinal patterns in the five outcomes. Models included group, time, and group-by-time interaction terms, with participant-specific random intercepts and adjustment for age and GPA. Because one school represented each study condition, the interaction estimates reflect differences in change between the two schools and should not be interpreted as causal intervention effects. Students in the intervention school showed greater increases in knowledge than those in the comparison school at posttest ($\beta = 1.10$, 95% CI [0.50, 1.70]) and follow-up

($\beta = 2.36$, 95% CI [1.75, 2.96]). Greater reductions were also observed in attitude at posttest ($\beta = -0.49$, 95% CI [-0.88, -0.11]) and follow-up ($\beta = -0.46$, 95% CI [-0.85, -0.08]), and in subjective norm at posttest ($\beta = -0.64$, 95% CI [-1.05, -0.24]) and follow-up ($\beta = -0.99$, 95% CI [-1.40, -0.59]). Perceived behavioral control showed little between-school difference in change at posttest ($\beta = 0.04$, 95% CI [-0.38, 0.46]) but was higher at follow-up ($\beta = 0.80$, 95% CI [0.38, 1.23]). For the prespecified primary outcome, intention to use e-cigarettes, greater reductions were observed in the intervention school at posttest ($\beta = -0.23$, 95% CI [-0.38, -0.09]) and follow-up ($\beta = -0.47$, 95% CI [-0.62, -0.33]). Given the baseline imbalance and pronounced floor effect in intention at follow-up, these findings should be interpreted descriptively and cautiously.

Overall, the exploratory analyses showed favorable changes in knowledge, attitude, subjective norm, perceived behavioral control, and intention among students in the intervention school relative to those in the comparison school. Larger between-school differences were observed at follow-up for several outcomes; however, these findings should not be interpreted as evidence of sustained or strengthened intervention effects because no direct posttest-versus-follow-up contrast with valid cluster-

TABLE 2. Descriptive statistics of outcomes by group and time point.

Outcome	School	Pretest	Posttest	Follow-up
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Knowledge, total score (0–10)	Intervention	7.28 $\pm$ 1.83	8.72 $\pm$ 1.46	9.91 $\pm$ 0.46
	Comparison	6.87 $\pm$ 2.15	7.22 $\pm$ 2.12	7.15 $\pm$ 2.19
Attitude, mean item score (1–5)	Intervention	2.67 $\pm$ 1.04	2.17 $\pm$ 1.08	2.24 $\pm$ 0.55
	Comparison	2.72 $\pm$ 0.97	2.72 $\pm$ 0.89	2.75 $\pm$ 0.85
Subjective norm, mean item score (1–5)	Intervention	2.34 $\pm$ 1.27	1.71 $\pm$ 1.06	1.38 $\pm$ 0.55
	Comparison	2.63 $\pm$ 1.25	2.63 $\pm$ 1.19	2.66 $\pm$ 1.14
Perceived behavioral control, mean item score (1–5)	Intervention	4.11 $\pm$ 1.02	4.08 $\pm$ 1.41	4.76 $\pm$ 0.60
	Comparison	4.07 $\pm$ 0.87	4.00 $\pm$ 0.85	3.91 $\pm$ 0.76
Intention, mean item score (1–3)	Intervention	1.17 $\pm$ 0.48	1.06 $\pm$ 0.22	1.00 $\pm$ 0.00
	Comparison	1.40 $\pm$ 0.53	1.52 $\pm$ 0.51	1.70 $\pm$ 0.51

Note: Knowledge was reported as a total score ranging from 0 to 10, with higher scores indicating greater knowledge. Attitude, subjective norm, and perceived behavioral control were reported as mean item scores ranging from 1 to 5. Lower attitude scores indicated less favorable attitudes toward e-cigarette use, and lower subjective norm scores indicated weaker perceived social influence supporting e-cigarette use. Higher perceived behavioral control scores indicated greater perceived ability to avoid e-cigarette use. Intention was reported as a mean item score ranging from 1 to 3, with lower scores indicating weaker intention to use e-cigarettes.

TABLE 3. Exploratory group-by-time interaction estimates from linear mixed-effects models.

Outcome	Group-by-time interaction	β	SE	95% CI	p-value
Knowledge	Intervention $\times$ Posttest	1.10	0.31	0.50 to 1.70	<.001
	Intervention $\times$ Follow-up	2.36	0.31	1.75 to 2.96	<.001
Attitude	Intervention $\times$ Posttest	-0.49	0.20	-0.88 to -0.11	.013
	Intervention $\times$ Follow-up	-0.46	0.20	-0.85 to -0.08	.019
Subjective norm	Intervention $\times$ Posttest	-0.64	0.21	-1.05 to -0.24	.002
	Intervention $\times$ Follow-up	-0.99	0.21	-1.40 to -0.59	<.001
Perceived behavioral control	Intervention $\times$ Posttest	0.04	0.21	-0.38 to 0.46	.864
	Intervention $\times$ Follow-up	0.80	0.21	0.38 to 1.23	<.001
Intention (primary outcome)	Intervention $\times$ Posttest	-0.23	0.07	-0.38 to -0.09	.002
	Intervention $\times$ Follow-up	-0.47	0.07	-0.62 to -0.33	<.001

Note: Models included participant-specific random intercepts and were adjusted for age and GPA. The comparison school and pretest were the reference categories. β represents the estimated difference in change over time between students in the intervention and comparison schools. Negative coefficients for attitude, subjective norm, and intention indicate greater reductions in the intervention school, whereas positive coefficients for knowledge and perceived behavioral control indicate greater increases. Intention to use e-cigarettes was the prespecified primary outcome; the remaining outcomes were secondary and interpreted exploratorily. Because only one school represented each study condition, school and study condition were completely confounded. Accordingly, confidence intervals and nominal p-values should be interpreted descriptively and not as confirmatory evidence of an intervention effect.

level inference was performed. The observed patterns may also reflect maturation, school-level contextual differences, contamination, regression to the mean, and ceiling or floor effects. In particular, intention reached the minimum possible score at follow-up in the intervention school (1.00 ± 0.00), indicating a complete floor effect and requiring cautious interpretation.

Table 4 presents students' satisfaction toward the interactive online game-based learning program among participants in the experimental group ($N = 47$). Overall, students reported a very high level of satisfaction with the program, with an overall mean score of 4.66 ± 0.47 . The item with the highest mean score was "Learning through games helped me understand the content better"

TABLE 4. Satisfaction toward the interactive online game-based learning program ($N = 47$).

Satisfaction Items	Mean $\pm$ SD	Interpretation
The games or activities in the program were interesting.	4.71 ± 0.52	Very high
The content within the games was easy to understand and appropriate.	4.62 ± 0.58	Very high
The game system was convenient, fast, and easy to use.	4.55 ± 0.63	Very high
Learning through games helped me understand the content better.	4.74 ± 0.49	Very high
Learning through games encouraged greater participation.	4.68 ± 0.54	Very high
Overall satisfaction	4.66 ± 0.47	Very high

Note: Satisfaction items were rated on a five-point Likert scale ranging from 1 (very low) to 5 (very high). Mean item scores were interpreted using equal-width intervals: 1.00–1.80 = very low, 1.81–2.60 = low, 2.61–3.40 = moderate, 3.41–4.20 = high, and 4.21–5.00 = very high satisfaction.

(4.74 ± 0.49), followed by “The games or activities in the program were interesting” (4.71 ± 0.52) and “Learning through games encouraged greater participation” (4.68 ± 0.54). In addition, students rated the content within the games as easy to understand and appropriate at a very high level (4.62 ± 0.58), while the convenience, speed, and ease of use of the game system also received a very high rating (4.55 ± 0.63). These findings indicate that the interactive online game-based learning program was well accepted by lower secondary school students and was perceived as engaging, understandable, user-friendly, and supportive of active participation and learning.

DISCUSSION

The findings showed favorable changes in knowledge and psychosocial factors related to e-cigarette use among students in the intervention school compared with those in the comparison school. These observed patterns suggest the potential usefulness of interactive online game-based learning for e-cigarette prevention; however, they should be interpreted cautiously because school and study condition were completely confounded.

Adolescents may be influenced by social media, peers, the modern appearance of e-cigarette products, attractive flavors, and misleading information regarding the safety of e-cigarettes.¹⁸ In this context, preventive activities relying solely on lectures or printed materials may be insufficient to engage adolescents in the digital era. Interactive online game-based learning may provide a more engaging and accessible approach by promoting active participation and connecting prevention-related knowledge with situations relevant to adolescents' everyday lives.¹⁹⁻²¹

The greater increase in e-cigarette-related knowledge observed among students in the intervention school may be related to the interactive nature of the program, which incorporated game-based activities, matching exercises, quizzes, simulations, and problem-solving tasks. These activities addressed e-cigarette types and components, addictive mechanisms, health effects, legal consequences, and social impacts. Previous studies have highlighted adolescents' exposure to misleading information about e-cigarettes through social media, including perceptions that e-cigarettes are safer than conventional cigarettes.¹⁸ Interactive game-based learning may therefore provide opportunities for students to actively evaluate information, correct misconceptions, and receive immediate feedback.²² However, the substantial ceiling effect in knowledge scores at follow-up and the confounding between school and study condition warrant cautious interpretation of these observed changes.

Regarding attitudes toward e-cigarette use, students in the intervention school showed a decrease in attitude scores, indicating less favorable attitudes toward e-cigarette use. This pattern may be related to the program's emphasis on health risks, addiction, effects on learning, social and family consequences, and legal implications. Previous studies have shown that e-cigarettes may be portrayed to adolescents as modern, attractive, and socially acceptable through online marketing, flavors, and product imagery.⁵ Interactive activities that encouraged students to evaluate persuasive messages and potential consequences may have supported more critical perceptions of e-cigarette use. This observed pattern is consistent with the Theory of Planned Behavior, in which less favorable attitudes toward a behavior may be associated with lower behavioral intention.¹⁴ However, the findings should be interpreted cautiously because school and study condition could not be separated in the present design.

Regarding subjective norms, students in the intervention school showed lower scores over time, indicating weaker perceived social influence supporting e-cigarette use. This pattern is consistent with previous evidence that early adolescence is a period in which peer acceptance is highly valued and adolescents may be particularly influenced by peers and social groups.²³ The program addressed persuasion, peer pressure, and simulated situations involving responses to offers of e-cigarettes. Such interactive activities may provide opportunities for students to recognize social influences, practice refusal skills, and consider more independent health-related decisions. However, the observed changes cannot be attributed solely to the program because school-level contextual influences could not be separated from the study condition.

For perceived behavioral control, students in the intervention school showed little change immediately after the program but higher scores at follow-up. The program included scenario-based activities and decision-making tasks that provided opportunities to practice refusal skills and responses to social pressure. Such experiential activities may support confidence in managing situations involving e-cigarette use.²⁴ This approach is consistent with prevention strategies that extend beyond knowledge provision to include decision-making, self-regulation, and coping with social influences.^{24,25} However, the greater change observed at follow-up should not be interpreted as evidence of a delayed or strengthened intervention effect, as maturation, school context, and other unmeasured factors may also have contributed to the observed pattern.

Furthermore, the lower intention to use e-cigarettes

observed among students in the intervention school is consistent with the Theory of Planned Behavior, which proposes that attitudes, subjective norms, and perceived behavioral control are related to behavioral intention.¹⁴ The observed reductions in intention occurred alongside less favorable attitudes toward e-cigarette use, weaker perceived social influence supporting e-cigarette use, and higher perceived behavioral control. These patterns are consistent with the theoretical framework underlying the program. However, the present study did not test mediation or causal pathways among attitudes, subjective norms, perceived behavioral control, and intention; therefore, the observed change in intention cannot be attributed to changes in these factors.

Satisfaction was a prespecified secondary outcome. Students reported high satisfaction with the program, indicating favorable perceptions of its content, usability, and learning activities. This finding is consistent with previous work suggesting that adolescent e-cigarette prevention may benefit from accessible and engaging approaches aligned with adolescents' digital lifestyles.^{26,27} High acceptability may support engagement with school-based prevention activities. When implementing similar programs, consideration should be given to device and internet availability, teacher support, and measures to minimize contamination between study groups. Recent studies have documented persistent misconceptions about e-cigarettes among Thai young adults and highlighted the respiratory and airway harms associated with vaping, underscoring the importance of accurate risk communication in prevention programs.^{28,29} For school-based implementation, consideration should also be given to device and internet availability, teacher support, and strategies to minimize contamination between study conditions.

Strengths and limitations

This study has several strengths. The intervention was guided by the Theory of Planned Behavior and incorporated interactive online game-based learning relevant to adolescents' digital learning environments. Outcomes were assessed at three time points and included knowledge, attitude, subjective norm, perceived behavioral control, and intention to use e-cigarettes.

The principal limitation is the allocation of only one school to each study condition. With no independent replication at the school level, school and intervention condition were completely confounded, making it impossible to distinguish intervention-related differences from underlying school-level differences. Consequently, participant-level P values and confidence intervals from

the longitudinal models do not provide valid confirmatory tests of an intervention effect and should be regarded as exploratory and interpreted cautiously.

Additional limitations include the recruitment of students from private schools in one district of Bangkok, which limits generalizability; reliance on self-reported measures, which may be subject to social desirability and reporting bias; the short follow-up period; baseline differences in intention; and substantial ceiling and floor effects in some outcomes. In addition, the study assessed psychosocial outcomes and behavioral intention rather than actual e-cigarette use. Future studies should include multiple independently allocated schools in each study condition, longer follow-up periods, and behavioral outcomes to establish intervention effectiveness.

CONCLUSION

The findings suggest that interactive online game-based learning may be a feasible and promising approach for e-cigarette prevention among lower secondary school students. Students in the intervention school showed favorable changes in knowledge, attitudes, subjective norms, perceived behavioral control, and intention to use e-cigarettes; however, these changes cannot be attributed solely to the program because only one school represented each study condition. The findings therefore provide preliminary evidence for feasibility and hypothesis generation rather than confirmation of intervention effectiveness. Future studies should employ multi-school cluster-randomized designs with adequate school-level replication, larger and more diverse samples, longer follow-up periods, and measures of actual e-cigarette use to determine the effectiveness and sustainability of the program.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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DECLARATION

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Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this study. No financial or personal relationships influenced the design, conduct, analysis, interpretation, or reporting of the research.

Registration Number of Clinical Trial

Thai Clinical Trials Registry (TCTR) identification number is TCTR20260505009 (<https://www.thaiclinicaltrials.org/show/TCTR20260505009>).

Author Contributions

Conceptualization, P.T., T.T., and P.N.; Methodology, P.T., T.T., P.N., and P.A.; Investigation, P.T., T.T., P.N., P.A., S.M., C.S., W.S., P.U., and A.R.; Formal analysis and interpretation, P.T., T.T., P.N., P.A., S.M., C.S., W.S., P.U., and A.R.; Writing – original draft, P.T. and T.T.; Writing – review and editing, P.T., T.T., and N.P.; Funding acquisition and resources, T.T., P.N., and P.A. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

Artificial intelligence-assisted tools were used to support language editing, grammar checking, and improvement of manuscript clarity. The authors carefully reviewed, verified, and revised all AI-assisted outputs. The authors take full responsibility for the accuracy, integrity, originality, and final content of the manuscript. No AI tool was used as an author, and no AI tool was responsible for study design, ethical approval, data collection, data interpretation, or final scientific conclusions.

Institutional Review Board Statement

This study was conducted in accordance with the ethical principles for research involving human participants. The study was registered with the Thai Clinical Trials Registry under the identification number TCTR20260505009. Data collection was conducted from May 15, 2026, to May 31, 2026. Ethical approval was

obtained from the Human Research Ethics Committee of the Srisavarindhira Thai Red Cross Institute of Nursing, Thailand, with the Certificate of Approval No. 005/2026 and IRB-STIN 038/2568. Participation was voluntary, and participants were informed that they could withdraw from the study at any time without penalty. All data were kept confidential and used only for research purposes. No personal identifying information was reported in this manuscript. The authors confirm that the conduct of the study complied with institutional research ethics requirements and relevant national ethical guidelines.

REFERENCES

1. Sakboonyarat B, Poovieng J, Jongcherdchootrakul K, Hempatawee N, Hatthachote P, Mungthin M, et al. Emerging trends and determinants of electronic cigarette use among young Thai men, 2022–2024. *BMC Public Health*. 2025;25(1):3842.
2. Palacheewa N, Thangkratok P. Exploring the intention to use e-cigarettes and its influencing factors among Thai non-formal education students: a cross-sectional study. *Tob Prev Cessat*. 2026:12.
3. Seeherunwong A, Tipayamongkhogul M, Angsukiattitavorn S, Muangsakul W, Singkhon O, Junda S, et al. Association between socioecological factors and electronic cigarette use among Thai youth: an institution-based cross-sectional study. *BMJ Open*. 2023;13(7).
4. Nakju S, Tanapek S, Assawamaitree S, Nitikorn K. Prevalence and factors associated with intention to use e-cigarettes among lower secondary school students in Bangkok: a cross-sectional study. *Tob Induc Dis*. 2026:24.
5. Zhou X, Hao X, Chen Y, Deng H, Fang L, Zhang L, et al. Social media marketing strategies for electronic cigarettes: content analysis of Chinese Weibo accounts. *J Med Internet Res*. 2024;26:e51594.
6. Patanavanich R, Aekplakorn W, Glantz SA, Kalayasiri R. Use of e-cigarettes and associated factors among youth in Thailand. *Asian Pac J Cancer Prev*. 2021;22(7):2199–207.
7. Vittaporn S, Kanthajaem K, Coothongkul A, Pooseesod K. Effectiveness of an intervention program to develop e-cigarette control leaders at the University in Lampang Province, Thailand. *Tob Prev Cessat*. 2024:10.
8. Patanavanich R, Glantz S. Successful countering of tobacco industry efforts to overturn Thailand's ENDS ban. *Tob Control*. 2021;30(e1)–e19.
9. Chen Y, Chen J, Wang Z, Zhao X, Gao R, Cai Y, et al. Effective features of e-cigarette prevention videos: a qualitative study with primary school students. *Tob Induc Dis*. 2025:23.
10. Kong G, Schott AS, Lee J, Dashtian H, Murthy D. Understanding e-cigarette content and promotion on YouTube through machine learning. *Tob Control*. 2023;32(6):739–46.
11. Al-Hassan SM, Duell N, Lansford JE, Dodge KA, Gurdal S, Liu Q, et al. Parents' learning support and school attitudes in relation to adolescent academic identity and school performance in nine countries. *Eur J Psychol Educ*. 2024;39(4):3841–66.
12. Lee S, Kim J, Bockhold S, Lee J, Chun J, Yu M. Game-based digital interventions for enhancing positive development and addressing substance use in adolescents: a systematic review. *Children*. 2024;11(12):1554.

13. Pentz MA, Hieftje KD, Pendergrass TM, Brito SA, Liu M, Arora T, et al. A videogame intervention for tobacco product use prevention in adolescents. *Addict Behav.* 2019;91:188–92.
14. Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process.* 1991;50(2):179–211.
15. Dienlin T, Johannes N. The impact of digital technology use on adolescent well-being. *Dialogues Clin Neurosci.* 2020;22(2):135–42.
16. Maeneja R, Rato J, Ferreira IS. How is the digital age shaping young minds? A rapid systematic review of executive functions in children and adolescents with exposure to ICT. *Children.* 2025; 12(5):555.
17. Alduraywish SA, Aldakheel FM, Alsuhailani OS, Jabaan ADB, Alballa RS, Alrashed AW, et al. Knowledge and attitude toward e-cigarettes among first year university students in Riyadh, Saudi Arabia. *Healthcare.* 2023;11(4):502.
18. Marques P, Piqueras L, Sanz MJ. An updated overview of e-cigarette impact on human health. *Respir Res.* 2021;22(1):151.
19. Zimmermann E, Tomczyk S. Using social media to promote life skills among adolescents: a debate on opportunities, challenges, and implications for health and education. *J Prev.* 2025;46(2): 201–11.
20. Mancone S, Corrado S, Tosti B, Spica G, Diotaiuti P. Integrating digital and interactive approaches in adolescent health literacy: a comprehensive review. *Front Public Health.* 2024;12:1387874.
21. Moreno MA, Binger K, Zhao Q, Eickhoff J, Minich M, Uhls YT. Digital technology and media use by adolescents: latent class analysis. *JMIR Pediatr Parent.* 2022;5(2).
22. Tavares N. The use and impact of game-based learning on the learning experience and knowledge retention of nursing undergraduate students: a systematic literature review. *Nurse Educ Today.* 2022;117:105484.
23. Slagter SK, Gradassi A, van Duijvenvoorde ACK, van den Bos W. Identifying who adolescents prefer as source of information within their social network. *Sci Rep.* 2023;13(1):20277.
24. Antikchi M, Heydari S, Bakhshi F. The effect of game-based scenario writing on the clinical reasoning of internship nursing students in cardiovascular emergencies and critical care units. *BMC Med Educ.* 2025;25(1):597.
25. Lin W, Wang JY, Yueh HP. Learning information ethical decision making with a simulation game. *Front Psychol.* 2022;13:933298.
26. Haddock A, Ward N, Yu R, O'Dea N. Positive effects of digital technology use by adolescents: a scoping review of the literature. *Int J Environ Res Public Health.* 2022;19(21):14009.
27. Raeside R. Advancing adolescent health promotion in the digital era. *Health Promot Int.* 2025;40(2).
28. Songsin N, Wannapaschaiyong P, Loylib P, Dampueak W, Kingkaew WMM, Siladlao S, et al. Perception and attitude towards electronic cigarettes among rural Thai young adults. *Siriraj Med J.* 2024;76(9):604–10.
29. Simanjuntak AM, Putra MRE, Amalia NP, Hutapea A, Suyanto, Siregar IE. Lung and airway disease caused by e-cigarette (vape): a systematic review. *Siriraj Med J.* 2024;76(5):325–32.

Effect of the Grasp and Grow Program on Fine Motor Development Among Preschool Children in Pathum Thani Province, Thailand

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ABSTRACT

Objective: This study aimed to evaluate the effect of the Grasp and Grow program on fine motor development among preschool children (Kindergarten 2) in Pathum Thani Province, Thailand, compared with routine art instruction.

Materials and Methods: A two-group pretest-posttest design was implemented, with one school allocated to each condition (single-cluster-per-arm) at two government primary schools in Pathum Thani, Thailand, between July and September 2025. Ninety-two Kindergarten 2 children (age 4-5 years) were allocated by school-level lottery to an experimental group (n=46), receiving an 8-week, classroom-delivered program of seven structured art-based activities grounded in Gesell's Maturation Theory, or a comparison group (n=46) receiving routine art instruction. Fine motor development was assessed using a 20-item structured observation instrument covering four domains; single-covariate ANCOVA was conducted post hoc as the primary between-group analysis, selected after baseline imbalance became apparent.

Results: Baseline fine motor scores were lower in the experimental group (28.63 vs. 33.63, $p < 0.001$). At posttest, the experimental group scored higher (48.43 vs. 37.00, Cohen $d = 2.14$, $p < 0.001$). The ANCOVA-adjusted between-group difference was 12.98 points (95% CI: 10.74-15.22), $F(1, 89) = 132.66$, Cohen $d = 2.59$, $p < 0.001$. Three analyses (the primary analysis and two additional sensitivity analyses) showed a consistent direction (Cohen's d range: 2.49-2.59), though this consistency does not establish a causal effect given shared design limitations.

Conclusion: In this exploratory, single-cluster-per-arm study, children receiving the Grasp and Grow program showed significantly greater fine motor improvement than those receiving routine art instruction. Given the unreplicated school-level allocation, this finding should be treated as hypothesis-generating rather than evidence of a causal program effect. Given its low cost, the program may offer schools in resource-limited settings a feasible option pending confirmation through a teacher-led, cluster-randomized trial.

Keywords: Motor skills; child; preschool; child development; hand strength (Siriraj Med J 2026;78(10):748-758)

INTRODUCTION

Fine motor delay is more than a classroom problem. Children who struggle with basic hand tasks such as dressing, using utensils, or holding a pencil often fall behind their peers in ways that affect confidence and emotional well-being. Lower self-esteem and anxiety have both been documented in children with poor fine motor proficiency.¹ Left unaddressed, these difficulties can persist into school-age and affect daily participation in ways that matter to health.

At kindergarten entry, fine motor skills predict academic achievement alongside executive function.² A review of 29 studies identified preschool-based programs, along with age, gender, and physical activity, as positive determinants of motor skill development in children aged 3 to 6.³ Schools may therefore serve as a practical setting for fine motor intervention, rather than only a place where delay is first noticed.

In Thailand, fine motor and gross motor skills are recognized as part of the physical movement and health competency that early childhood should acquire.⁴ According to the Director of the National Institute for Child and Family Development, approximately 47% of Thai preschoolers show suspected delay in the combined fine motor and intelligence domain under national developmental surveillance.⁵ However, province-specific

data for Pathum Thani were not identified, representing a gap that this study begins to address.

Despite a growing evidence base, several gaps remain. A scoping review mapping 45 motor skill intervention studies for preschool-aged children found that only two were conducted in low- and middle-income countries, while 24 were conducted in the United States alone.⁶ The same scoping review found that occupational therapists and physiotherapists delivered the majority of interventions, with classroom teachers serving as the primary facilitator in only seven of the 45 studies mapped.⁶ Iivonen and Sääkslahti (2014) identified parent- and family-related factors as one of four categories of potential determinants for fine motor development, although evidence for this category was limited to a small number of studies³, yet structured home-based components remain uncommon in published intervention programs. In Thailand, creative art activities have been shown to improve fine motor development among Kindergarten children⁷, but comparative evaluation of structured programs against such routine activities remains limited in this setting. A teacher-deliverable, low-cost program with evidence behind it could give schools a practical option for supporting fine motor development in typically developing children without relying on specialist services that are often unavailable.

This study aimed to evaluate the effect of the Grasp

and Grow program on fine motor development among Kindergarten 2 children in Pathum Thani Province, Thailand. The program is a structured, classroom-delivered intervention grounded in Gesell's Maturation Theory, using low-cost everyday materials and sequencing seven activities by motor demand across four fine motor domains. To isolate the program's specific contribution, fine motor outcomes were compared against active art instruction rather than a non-active condition.

MATERIALS AND METHODS

Ethics statement

This study was approved by the Valaya Alongkorn Rajabhat University under the Royal Patronage Institutional Review Board (COA No. 0055/2568; REC No. 0043/2568; 21 July 2025) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all guardians prior to enrollment.

Study design

A two-group pretest-posttest design was employed, with allocation at the school level (one school per condition) to prevent within-school contamination. As this constitutes a single-cluster-per-arm design, the treatment condition is fully confounded with school; findings should be interpreted as hypothesis-generating rather than confirmatory of a causal program effect. Data were collected between 28 July and 25 September 2025 at two small government primary schools in Klongsong Subdistrict, Khlongluang District, Pathum Thani Province, Thailand. Formal school- or class-level characteristics (e.g., enrollment size, teacher-to-student ratio, resource level) were not systematically measured or compared; observed baseline differences in fine motor scores and family structure between groups (Table 2) suggest the two schools and their enrolled populations were not equivalent.

Sample size

Sample size was calculated using G*Power 3.1.⁸ An effect size of $d = 0.80$ was specified.⁹ Alpha was set at 0.05 and power = 0.95, yielding a minimum of 84 participants. A 10% allowance for attrition produced a final target of 92 participants (46 per group). This calculation was based on individual-level power analysis and did not account for the study's actual single-cluster-per-arm allocation; see Limitations

Participants

Children were eligible if enrolled in Kindergarten 2 (age 4–5 years), able to communicate in Thai, and

accompanied by a parent or guardian who provided written informed consent. Children were excluded if they had a diagnosed intellectual disability, previously identified developmental delay, attention-deficit/hyperactivity disorder, or any condition directly affecting fine motor function.

Sampling

A multi-stage sampling approach was used. Khlongluang District and Klongsong Subdistrict were purposively selected as a peri-urban area with multiple small government primary schools offering Kindergarten 2 classes. Two schools were then selected by simple random sampling (lottery) from seven eligible schools within the subdistrict (opaque-envelope procedure; allocation concealment maintained until draw). A second independent lottery assigned one school to the experimental condition and the other to the comparison condition. All Kindergarten 2 children enrolled at each allocated school who met the eligibility criteria were invited to participate, constituting a census of the eligible population at each site. At the comparison school, 48 children met eligibility criteria; two guardians declined participation, yielding 46 consenting children (identical to the experimental school's 46). The two non-consenting children remained present in the classroom throughout all activity sessions to avoid social exclusion but were directed to an unrelated activity during the Week 1 and Week 8 assessment sessions and contributed no outcome data. As only one school was allocated to each condition, the treatment condition is fully confounded with school; findings should be interpreted as hypothesis-generating rather than confirmatory of a causal program effect.

Intervention program

The program was developed through four stages: theoretical grounding, activity selection, expert validation, and pilot testing.

In Stage 1, Gesell's Maturation Theory was selected as the theoretical framework on the basis that it explicitly addresses the biologically sequenced progression of motor development in early childhood, predicting that fine motor control develops in a proximal-to-distal and simple-to-complex direction. This sequencing principle was used as a practical organizing framework for activity design rather than as a claim that the program accelerates innate maturation; consistent with contemporary motor-learning evidence that fine motor skills require active teaching and reinforcement rather than developing through maturation alone¹⁰, the program provided structured, progressively demanding practice. This progression

principle provided the organizing logic for sequencing program activities from lower to higher motor control demands across 8 weeks.

In Stage 2, seven activities were selected through a narrative review to target all four fine motor domains using low-cost classroom materials without specialist equipment. Activities were sequenced from foundational control tasks (tracing) through grip modulation and bilateral coordination tasks (paper collage, nature printing, sensory bag filling, bead threading) to whole-hand integration tasks (drawing, creative cutting). A consolidated review session in Week 8 reinforced all four domains, consistent with the distributed practice principle in motor skill acquisition.¹¹ Full activity-level details and theoretical linkage are provided in Table 1.

In Stage 3, the program manual was submitted for content validation to three experts (early childhood education, public health, and pediatric occupational therapy). Content Validity Index was 0.89 (≥ 0.80 threshold).

Expert suggestions were incorporated prior to finalization.

In Stage 4, the program was piloted with 15 Kindergarten 2 children at a non-study school. All activities were confirmed executable within 60 minutes using low-cost materials. Minor bead size adjustments were made to reduce choking risk. No changes to the activity sequence or framework were required.

Design rationale

Activity design followed two criteria. First, sequencing and difficulty progression were grounded in Gesell's Maturational Theory, ordering activities from lower to higher motor control demand across the 8-week period (Table 1). Second, all materials were selected for low cost and ready availability in the Thai context (leaves, beads, rope, recycled paper, and similar everyday items), so that the program could be feasibly adopted by government schools operating with limited budgets.

TABLE 1. Grasp and grow program.

Week	Activity	Materials	Targeted Domain(s)	Gesell's Principle
1	Tracing tasks	Tracing sheets, pencils, crayons	Control; Hand-eye coordination	Proximal-to-distal; simple-to-complex
2	Paper collage (precision tearing)	Newspapers, coloured paper, glue sticks	Control	Bilateral-to-unilateral hand differentiation
3	Nature printing (Eco Print)	Leaves, flowers, ink pads, paper	Control <i>Flexibility*</i>	Proximal-to-distal grip modulation
4	Sensory bag filling	Zip-lock bags, sand, rice, beans, fabric	Dexterity; Hand-eye coordination <i>Flexibility*</i>	Progressive finger-wrist refinement
5	Bead threading/ stringing	Beads, pasta, string or shoelace	Control; Dexterity; Hand-eye coordination	Pincer grasp maturation; distal control
6	Drawing and painting	Paper, crayons, watercolors, brushes	Control; Dexterity; Hand-eye coordination	Proximal stability with distal dexterity
7	Creative cutting	Child-safe scissors, paper, cardboard	Control; Dexterity; Hand-eye coordination	Complex bilateral coordination
8	Consolidated review	All materials from Weeks 1–7	All four domains	Spiraling repetition; consolidation

Note: Activities are sequenced from Week 1 (lowest motor control demand) to Week 7 (highest motor control demand) in accordance with Gesell's Maturational Theory principle of simple-to-complex developmental progression. Week 8 is a consolidated review session covering all four domains.

*Domain inferred from the physical demands of the activity (e.g., grip-pressure modulation in Eco Print, finger flexion/extension in bag tying) rather than stated as an explicit objective in the original protocol.

Procedure: grasp and grow program

Activities were ordered by motor demand across all four domains (Table 1). Sessions were 60 minutes, delivered weekly for 8 weeks by research team members, with the classroom teacher present throughout. All materials were low-cost (leaves, beads, rope, paper). Attendance and fidelity (adherence to the designed activity protocol) were independently recorded in parallel by two research team members and cross-checked for agreement. All 46 children attended every session (fidelity: 100.0%). The Week 8 posttest assessment was conducted before the consolidated review session, to avoid inflated performance from immediate rehearsal of aligned tasks.

Program dissemination

Upon completion of the Week 8 session, a pre-planned dissemination phase was implemented at both schools. Each school received a teacher manual, and each enrolled family received a home exercise workbook and parent guide to support independent replication and continued home practice. Materials were distributed to both schools to ensure equity of access. No outcome data were collected after the Week 8 posttest.

Comparison group

The comparison group received routine art instruction (drawing, block assembly, clay modeling, cutting, collage) without structured sequencing, following the school's existing curriculum plan. Sessions were delivered weekly for 60 minutes by the two classroom teachers routinely present in each classroom, without additional training; the research team had gathered information on the school's existing art curriculum prior to intervention design but did not deliver or supervise comparison-group sessions directly. Attendance was recorded by the classroom teacher each session. Materials were comparable in type but not systematically quantified or matched in quantity to the experimental group. Researchers assessed at Week 1 and Week 8 only.

Measurement tool

The primary outcome was the total fine motor score at posttest (maximum 60 points). Fine motor development was assessed using a 20-item structured observation instrument adapted from Noiniam¹² used in this study in its original form, without modification, under the developer's CC BY-NC-ND 4.0 open-access license with full attribution, covering four domains (5 items each). Each item was scored 0–3 based on the quantity of the task completed within a fixed time limit specified for that item: 3 = full quantity completed within the time limit;

2 = more than half completed; 1 = less than half completed; 0 = unable to complete or did not attempt (maximum total: 60). The complete instrument, including item-level time limits and materials, is provided in Supplementary Table S1. Content validity was confirmed by three experts (CVI = 0.89), and internal consistency tested with a pilot sample of 30 children (Cronbach's α = 0.87). A comparable content-validation and reliability-testing approach has been applied in developing motor-function assessment tools for Thai children in other clinical contexts.¹³

Assessment was conducted by research team members, independent of the classroom teacher. A pre-collection calibration session standardized scoring among assessors. Assessors were not blinded to group allocation, and the same research team members who delivered the intervention also conducted the outcome assessments; this overlap in role represents a substantial source of potential detection bias that could not be mitigated through role separation. Inter-rater reliability was good (ICC = 0.88, 95% CI: 0.82–0.93).¹⁴ Each child was independently scored by two research team assessors; when scores diverged, the child was asked to repeat the task so both assessors could re-observe and reach an agreed score. Assessments were not video-recorded, precluding independent blinded re-rating.

Bias

Potential biases were addressed systematically. Selection bias was partially mitigated through school-level lottery and predefined eligibility criteria; residual baseline imbalances were addressed via post hoc ANCOVA sensitivity analyses. Performance bias was unavoidable given the visible intervention. Detection bias was substantial: assessors were not blinded, and the same research team members who delivered the intervention also conducted assessments, with role overlap only partially offset by a pre-collection calibration session. Attrition bias was absent (100% retention). Criterion contamination is expected to have favored the experimental group to some degree: the intervention's activities were organized around the same four domain labels used by the outcome instrument, and at least one activity (bead threading, Week 5) closely resembled a specific instrument item (macaroni threading), whereas the comparison group's routine activities overlapped with instrument items only incidentally and to a lesser extent. This asymmetry is likely to have inflated the between-group effect size in a specific, non-neutral direction, though the degree of item-level overlap varied across the program's activities and was not uniform, motivating substantial caution in interpreting the effect size's magnitude and the use of standardized, non-aligned instruments in future studies.

Statistical analysis

Descriptive statistics (frequency, percentage, mean $\pm$ SD) were computed for baseline characteristics. Baseline comparability was examined using chi-square and independent t-tests. Within-group change was assessed by paired t-test; between-group posttest comparison used independent t-test. Cohen's d^9 was reported as the effect size index, interpreted as: small (≥ 0.20), medium (≥ 0.50), large (≥ 0.80), and very large (≥ 1.20).¹⁵ Change scores (post-pre) were calculated to supplement between-group interpretation.

Given the significant baseline difference in fine motor scores, single-covariate ANCOVA (pretest score as covariate) was conducted post hoc as the primary between-group analysis, selected after baseline imbalance became apparent. An independent t-test on posttest scores was retained for descriptive comparison. Additional sensitivity analyses comprised: (i) an independent t-test on change scores; and (ii) two-covariate ANCOVA (pretest score and family structure). Statistical significance was set at $\alpha = 0.05$. (Data were analyzed using SPSS version 29.0.1 [IBM Corp.].) Levene's test indicated unequal variances between groups at baseline ($p < 0.001$) and posttest ($p = 0.037$); given equal group sizes ($n = 46$ per group), this is expected to have minimal impact on the validity of ANCOVA and t-test results. Reported t-tests used pooled variance; Welch's correction yielded an essentially identical result ($t = 10.248$, $p < 0.001$ for both). ANCOVA assumption checks indicated adequate homogeneity of regression slopes ($p = 0.211$), normally distributed residuals (Shapiro-Wilk $p = 0.988$), and 8 of 92 observations (8.7%) exceeding the conventional Cook's distance threshold. Linearity was weaker in the experimental group ($r = 0.10$, ns) than the comparison group ($r = 0.46$, $p = 0.001$). Heteroscedasticity-robust (HC3) standard errors yielded a similar 95% CI (10.60–15.37) to the original (10.74–15.22).

RESULTS

Participant flow

Ninety-two children were enrolled (experimental: $n = 46$; comparison: $n = 46$), following school-level (two-cluster) allocation in which one entire school was assigned to each condition; guardian consent was obtained prior to this allocation, so recruitment was not influenced by knowledge of group assignment. No withdrawals occurred; all completed both assessments. Intervention fidelity was complete: all eight sessions were delivered as planned with all 46 experimental group children attending every session (100.0%). No adverse events were recorded in either group. (Fig 1)

Baseline characteristics

Table 2 presents baseline characteristics. The groups did not differ significantly in sex, age, or screen time (all $p > 0.05$). Statistically significant differences were observed in family structure ($p = 0.029$), with more intact two-parent families in the experimental group (97.8% vs. 78.3%). Baseline fine motor scores differed significantly between groups (28.63 vs. 33.63, $p < 0.001$), an imbalance addressed through post hoc sensitivity analyses.

Within-group comparisons

The experimental group improved from 28.63 ± 4.07 to 48.43 ± 4.23 (+19.80 points, +69.2%; $d = 3.56$). The comparison group improved from 33.63 ± 7.88 to 37.00 ± 6.28 (+3.37 points, +10.0%; $d = 0.45$).

Between-group comparison

The primary analysis (single-covariate ANCOVA) yielded adjusted posttest means of 49.21 (experimental) and 36.23 (comparison), a between-group difference of 12.98 points (95% CI: 10.74–15.22), $F(1, 89) = 132.66$, $d = 2.59$, $p < 0.001$, calculated as the adjusted mean difference divided by the residual standard deviation (5.01). These estimates assume independence among children and do not account for school-level clustering, given the single-cluster-per-arm design. The unadjusted posttest difference was also significant (48.43 vs. 37.00; $d = 2.14$). The experimental group's change score (+19.80) was 5.9 times greater than the comparison group's (+3.37), despite commencing from a lower baseline.

Domain-level analysis

All four domains showed significant between-group differences at posttest (all $p < 0.001$; Cohen's d range: 1.34–1.56), consistent with the primary outcome. These analyses were exploratory, not corrected for multiplicity, and subject to the same design limitations (single-cluster-per-arm, criterion contamination) as the primary outcome.

Sensitivity analysis

Additional sensitivity analyses are presented in Table 4. The two-covariate ANCOVA (pretest score and family structure) yielded $d = 2.55$ ($p < 0.001$), and the change score t-test yielded $d = 2.49$ ($p < 0.001$). All estimates exceeded the unadjusted $d = 2.14$. However, this consistency does not confirm a causal intervention effect, given the shared limitations of a single school per condition, criterion contamination favoring the experimental group, and non-blinded assessment. These estimates are compatible with, but do not establish, the

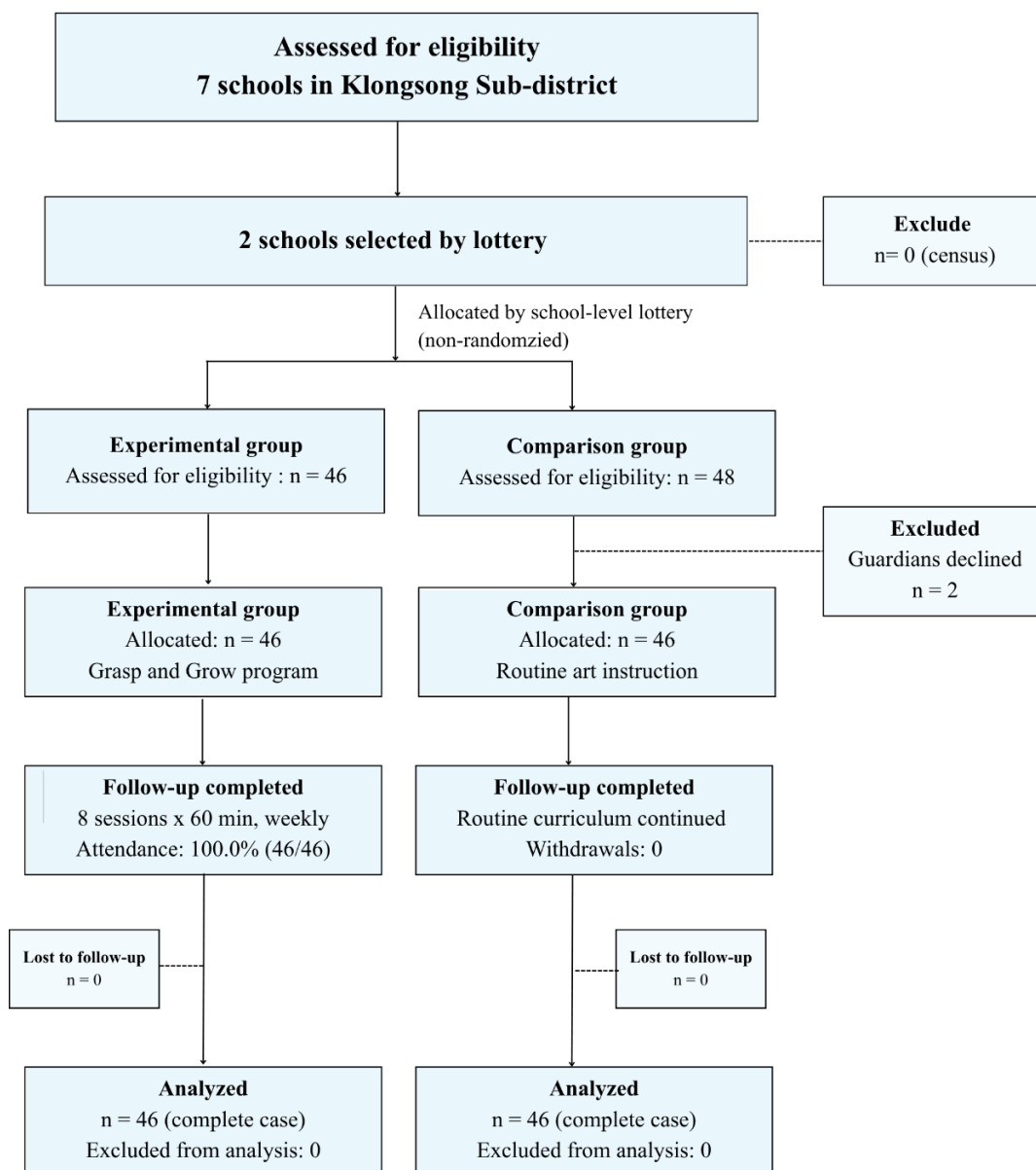


Fig 1. Participant flow diagram (TREND format for non-randomized designs).

Allocation occurred at the school level (two-cluster allocation); one entire school was assigned to each condition, and individual children were not independently randomized. Two schools were selected by lottery from seven eligible school; a second lottery assigned one school to each condition. Of 94 eligible children across both schools, 92 were enrolled (46 at the experimental school; 46 of 48 eligible at the comparison school, where 2 guardians declined participation). No withdrawals or losses to follow-up occurred among enrolled participants; all 92 were included in the final analysis.

TABLE 2. Baseline characteristics and group comparability (n = 92).

Characteristic	Total (n=92)	Experimental (n=46)	Comparison (n=46)	p-value
Sex: male, n (%)	48 (52.2)	23 (50.0)	25 (54.3)	0.68
Age (years), mean ± SD	4.71 ± 0.46	4.72 ± 0.45	4.69 ± 0.47	0.762
Screen time >2 h/day, n (%)	56 (60.9)	31 (67.4)	25 (54.3)	0.187
Two-parent family, n (%)	81 (88.0)	45 (97.8)	36 (78.3)	0.029*
Baseline fine motor score, mean ± SD	31.13 ± 6.72	28.63 ± 4.07	33.63 ± 7.88	<0.001***

* $p < 0.05$.

TABLE 3. Between-group comparison at posttest and change score analysis.

Outcome	Total (n=92)	Experimental (n=46)	Comparison (n=46)	t	95% CI	p	d
Posttest score, mean $\pm$ SD	42.72 $\pm$ 7.83	48.43 $\pm$ 4.23	37.00 $\pm$ 6.28	10.25	9.22, 13.65	<0.001***	2.14 (95% CI: 1.62, 2.65)
Change score, mean	11.59 $\pm$ 10.55	+19.80 $\pm$ 5.56	+3.37 $\pm$ 7.50	-	-	-	-

t-test used pooled variance (Welch's *t* = 10.248, *p* < 0.001, nearly identical).
Exact *p*-values reported; no asterisks.

TABLE 4. Sensitivity analyses: change score comparison and ANCOVA-adjusted posttest means.

Analysis	Experimental	Comparison	t(90)	p-value	Cohen's d
Change score (mean $\pm$ SD)	+19.80 $\pm$ 5.56	+3.37 $\pm$ 7.50	11.94	<0.001***	2.49
ANCOVA-adjusted posttest mean ¹	49.21	36.23	-	<0.001***	2.59
Two-covariate ANCOVA ²	49.12	36.32	-	<0.001***	2.55

¹ Post hoc primary analysis (pretest as covariate), conducted after baseline imbalance was identified.

² Pretest and family structure as covariates. **p* < 0.05

interpretation that baseline imbalance suppressed rather than inflated the apparent effect.

DISCUSSION

Summary of main findings

This study found that the Grasp and Grow program produced a substantially larger improvement in fine motor skills than routine art instruction, an effect that was consistent across multiple sensitivity analyses accounting for baseline imbalances between groups. Improvement was observed across all four assessed fine motor domains. The comparison group also improved, though to a smaller degree, indicating that routine classroom art activities are not without benefit, but that structured, theory-grounded sequencing provided meaningfully more support for fine motor development.

Interpretation and relevance

The program was grounded in Gesell's Maturational Theory¹⁶, with activities sequenced from foundational wrist and finger control through grip modulation and bilateral coordination to tool-guided precision cutting,

an ordering absent from the comparison group's routine curriculum. The program also incorporated progressive difficulty, drawn directly from this sequencing logic, and distributed exposure across varied activity contexts in the Week 8 review session, consistent with literature on the benefits of spaced over massed practice.¹¹ This theoretical grounding offers one plausible explanation for why a structured, sequenced program outperformed unstructured routine art activities covering similar materials.

These findings carry practical relevance for early childhood settings, particularly in resource-limited government schools, where access to specialist occupational therapy is often limited. A structured but low-cost, classroom-deliverable program of this kind offers a feasible option for supporting fine motor development in typically developing children, addressing a concern flagged at the national level for several consecutive years. Beyond the immediate skill gain, fine motor proficiency in early childhood has downstream relevance: it has been linked to later academic performance^{17,18} and, in at least one large cohort, to behavioral health outcomes extending well beyond the skill domain itself.¹⁹

This suggests that early, low-cost fine motor support may carry value beyond the immediate outcome measured here, though this study was not designed to test those downstream pathways directly.

Comparison with other studies

The direction of this study's findings is broadly consistent with that study's conclusion that structured motor skill interventions are, on average, moderately effective for improving fine motor outcomes in young children²⁰, and with another meta-analysis concluding that fundamental movement skills require active teaching and reinforcement rather than developing through maturation alone.¹⁰ However, the magnitude of effect observed in this study was considerably larger than what is typically reported in that body of literature. Several factors plausibly explain this gap: the present comparison group received an active alternative (routine, unstructured art instruction) rather than no intervention, which should, if anything, narrow rather than widen an observed difference; conversely, the experimental group's low starting score left more room for improvement, and the assessment instrument's close alignment with the trained activities raises the possibility of criterion contamination, which other studies using more generic standardized instruments would not share to the same degree.

Strengths

This study's strengths include a statistical analysis plan that appropriately addressed the observed baseline imbalance between groups (though selected post hoc rather than pre-specified, as noted in the Limitations), an active comparison condition rather than a no-treatment control (allowing isolation of the program's specific contribution beyond general classroom engagement), complete retention with no missing data, and a structured four-stage intervention development process including expert content validation and pilot testing prior to the main trial.

Limitations

Several limitations require acknowledgement. Criterion contamination is expected to have favored the experimental group specifically, given that the intervention's activities were organized around the same four domain labels as the outcome instrument, whereas the comparison group's routine activities overlapped only incidentally; this asymmetry likely inflated the between-group effect in a specific, non-neutral direction rather

than merely inflating within-group change. Assessors were not blinded to group allocation, and the same research team members who delivered the intervention also conducted assessments, representing a substantial source of potential detection bias; assessments were not video-recorded, precluding independent blinded re-rating. Additionally, the experimental group's sessions involved research team members delivering the program with the classroom teacher present, while the comparison group's sessions were delivered by classroom teachers alone; this difference in provider composition introduces a potential attention/provider confound that cannot be separated from the program's specific content using the current design. The baseline fine motor imbalance and the family structure difference between groups represent threats to internal validity that were addressed but not eliminated by sensitivity analyses; while all adjusted estimates exceeded the unadjusted estimate, this pattern is compatible with, but does not establish, suppression of the effect by baseline imbalance, given the limitations noted above. The study was confined to two schools in one sub-district, limiting generalizability, and sessions were delivered by research team members rather than classroom teachers, which limits inference about real-world scalability under ordinary school conditions.

Future research

A cluster-randomized trial with baseline-matched groups and blinded assessors would address the principal limitations identified here. A fully teacher-led effectiveness trial under ordinary classroom conditions, without research-team delivery, is needed to establish real-world scalability. Future work should also incorporate a standardized, independently validated fine motor instrument not aligned with the specific trained activities, to rule out criterion contamination as an explanation for effect size.

CONCLUSIONS

The Grasp and Grow program produced significantly greater fine motor improvement than routine art instruction in this exploratory, single-cluster-per-arm study of Thai preschool children. Given its low cost and minimal personnel requirements, the program may offer schools in resource-limited settings a feasible option for supporting fine motor development, pending confirmation through a teacher-led, cluster-randomized trial.

Data Availability Statement

The datasets are not publicly available but are available from the corresponding author upon reasonable request.

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DECLARATIONS

Grants and Funding Information

This study received no external funding.

Conflict of Interest

The authors declare no conflicts of interest related to the content of this manuscript.

Registration Number of Clinical Trial

The study was retrospectively registered with the Thai Clinical Trials Registry (TCTR20260409005; 9 April 2026).

Author Contributions

Conceptualization: P.C., P.D., N.T., R.S., A.Se., and A.Sa.; Methodology: all authors; Software: P.D., A.J., and R.A.; Validation: P.D., A.J., and R.A.; Formal analysis and data interpretation: all authors; Investigation: P.C., P.D., N.T., R.S., A.Se., A.Sa., and A.J.; Resources: all authors; Data Curation: P.C., P.D., N.T., R.S., A.Se., and A.Sa.; Writing – original draft: P.C., P.D., and N.T.; Writing – review & editing: P.D.; Visualization: P.D.; Project administration: P.D. All authors read and approved the final manuscript.

Use of Artificial Intelligence

The authors used AI-assisted tools (Claude Sonnet 4.6, Anthropic) to support language editing and manuscript formatting. All intellectual content, research design, data collection, analysis, and interpretation were conducted by the authors. The authors take full responsibility for the accuracy and integrity of the work.

Institutional Review Board Statement

This study was approved by the Valaya Alongkorn Rajabhat University under the Royal Patronage Institutional Review Board (COA No. 0055/2568; REC No. 0043/2568; July 21, 2025) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all guardians prior to enrollment. Given the young age of participants (4–5 years), separate child assent was not obtained; guardian consent served as the

basis for enrollment, consistent with standard practice for research involving preschool-aged children.

REFERENCES

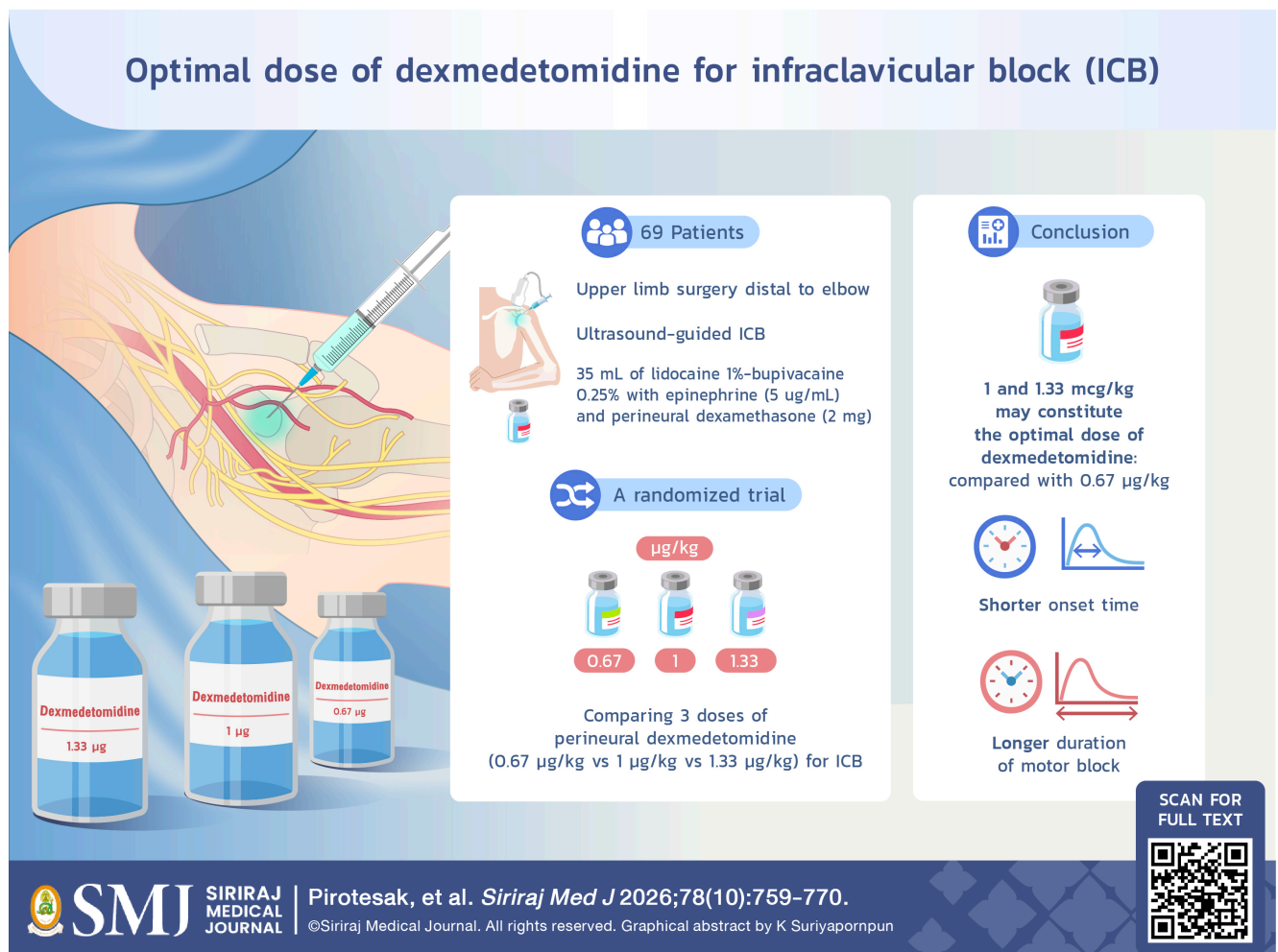
- Gaul D, Issartel J. Fine motor skill proficiency in typically developing children: on or off the maturation track? *Hum Mov Sci.* 2016; 46:78–85.
- Cameron CE, Brock LL, Murrah WM, Bell LH, Worzalla SL, Grissmer D, et al. Fine Motor Skills and Executive Function Both Contribute to Kindergarten Achievement. *Child Dev.* 2012;83(4): 1229–44.
- Iivonen S, Sääkslahti AK. Preschool children's fundamental motor skills: a review of significant determinants. *Early Child Development and Care.* 2014; 184(7):1107–26.
- Office of the Education Council, Ministry of Education. Competency of early childhood development for ages 3–5 years: guidelines for teachers and caregivers. 1st ed. Bangkok: Office of the Education Council, Ministry of Education; 2009. 116p.
- Matichon. Department of Health reports 1 in 4 Thai preschoolers show developmental delay in language and fine motor/intelligence post-COVID-19 [Internet]. 2022 Nov 1 [cited 2025 Jan 19]. Available from: https://www.matichon.co.th/weekly/pr/article_622847
- van der Walt J, Plastow NA, Unger M. Motor skill intervention for pre-school children: a scoping review. *Afr J Disabil.* 2020; 9:747.
- Thongsut P, Palintorn N. The development of fine-motor of early childhood students Kindergarten 2 by using creative arts activities. *J Buddhist Stud MCU Ubon Ratchathani.* 2023;5(1): 141–50.
- Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39(2): 175–91.
- Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale (NJ): Lawrence Erlbaum Associates; c1988. 567 p.
- Logan SW, Robinson LE, Wilson AE, Lucas WA. Getting the fundamentals of movement: a meta-analysis of the effectiveness of motor skill interventions in children. *Child Care Health Dev.* 2012;38(3):305–15.
- Donovan JJ, Radosevich DJ. A meta-analytic review of the distribution of practice effect: now you see it, now you don't. *J Appl Psychol.* 1999;84(5):795–805.
- Noiniam P. The ability in using fine motor of children aged 4–5 years through creative soil art activities [master's thesis]. Bangkok: Graduate School, Srinakharinwirot University; 2013. Available from: <https://hdl.handle.net/20.500.14740/41076>
- Wangthomrong L, Boonsinsukh R, Wannapakhe J. Developing Cerebral Palsy Screening of Functional Abilities in School (CPS-FAS). *Siriraj Med J.* 2024;76(8):497–503.
- Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* 2016;15(2):155–63.
- Sawilowsky SS. New effect size rules of thumb. *J Mod Appl Stat Methods.* 2009 ;8(2):597–9.
- Gesell A, Amatruda CS. The embryology of behavior: the beginnings of the human mind. New York: Harper & Brothers; 1945. 289p.

17. Luo Z, Jose PE, Huntsinger CS, Pigott TD. Fine motor skills and mathematics achievement in East Asian American and European American kindergartners and first graders. *Br J Dev Psychol.* 2007;25(4):595-614.
18. Pitchford NJ, Papini C, Outhwaite LA, Gulliford A. Fine motor skills predict maths ability better than they predict reading ability in the early primary school years. *Front Psychol.* 2016;7:783.
19. Butler E, Clarke M, Spirtos M. Do motor difficulties in infancy predict 7-year-olds' behavioural health? Findings from the Avon Longitudinal Study of Parents and Children. *J Pediatr Clin Pract.* 2025;17:200167.
20. Strooband KFB, de Rosnay M, Okely AD, Veldman SLC. Systematic review and meta-analyses: motor skill interventions to improve fine motor development in children aged birth to 6 years. *J Dev Behav Pediatr.* 2020;41(4):319-31.

A Randomized Comparison among 0.67 µg/kg, 1 µg/kg and 1.33 µg/kg of Perineural Dexmedetomidine for Ultrasound-guided Infraclavicular Block

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ABSTRACT

Objective: This randomized trial compared three doses of perineural dexmedetomidine for ultrasound-guided infraclavicular block: 0.67 µg/kg (**D1**), 1 µg/kg (**D2**), and 1.33 µg/kg (**D3**), using an identical admixture of 35 mL of lidocaine 1%- bupivacaine 0.25%- epinephrine 5 µg/mL- perineural dexamethasone (2 mg). We hypothesized a stepwise 15% increase in motor block duration from D1 to D2 to D3.

Materials and Methods: Sixty-nine subjects were randomized to three dexmedetomidine doses. The primary outcome was motor block duration. Secondary outcomes included block onset, surgical anesthesia, analgesia and sensory block duration, and dexmedetomidine-related adverse events.

Results: Motor block duration was longer with D2 and D3 than D1 by omnibus ANOVA/post-hoc testing [18.6 (3.8) vs. 15.8 (3.8) hours, $P = 0.028$; and 18.6 (4.2) vs. 15.8 (3.8) hours, $P = 0.027$, respectively]. However, Kaplan-Meier log-rank analysis showed no intergroup difference ($P = 0.078$). No other differences were observed in sensorimotor block or analgesia duration. Onset was shorter with D2 and D3 than D1 (15 [15-20] vs. 20 [20-25] minutes; $P = 0.012$; and 15 [15-20] vs. 20 [20-25] minutes; $P = 0.007$, respectively), with no difference between D2 and D3. Surgical anesthesia and adverse event rates were similar.

Conclusion: With this ICB regimen, 1 and 1.33 µg/kg dexmedetomidine may statistically prolong motor block and shorten onset compared with 0.67 µg/kg. Given inconsistent statistical findings and the secondary outcome of onset, these results are exploratory. Further studies should examine perineural dexmedetomidine for other local anesthetic molecules, injectates, and doses greater than 1.33 µg/kg.

Keywords: Dexmedetomidine; brachial plexus block (Siriraj Med J 2026;78(10):759-770)

List of Abbreviations

ASA = American Society of Anesthesiologists

ICB = infraclavicular brachial plexus block

LA = local anesthetic

US = ultrasound

INTRODUCTION

The combination of perineural dexamethasone and perineural dexmedetomidine provides a valuable adjunct to local anesthetic (LA) for ultrasound (US)-guided infraclavicular block (ICB). In a previous trial, we found that, compared with perineural dexamethasone (2 mg) alone, combined perineural dexamethasone (2 mg)-dexmedetomidine (50 µg) results in a 26%-longer duration of sensorimotor block for ICB performed with adrenalized lidocaine 1%- bupivacaine 0.25%.¹ The optimal dose of perineural dexamethasone has been demonstrated to be 2 mg.² However, the optimal dose of dexmedetomidine (when combined with dexamethasone) remains unknown.

Consequently, in this randomized trial, we compared three different doses (0.67 µg/kg vs. 1 µg/kg vs. 1.33 µg/kg) of perineural dexmedetomidine for US-guided ICB performed with adrenalized lidocaine 1%- bupivacaine 0.25%- perineural dexamethasone (2 mg). We selected the duration of motor block as the primary outcome. Our research hypothesis was that the 1.33 µg/kg dose (**group D3**) would provide a 15%-longer duration of

motor block than the 1 µg/kg dose (**group D2**), which in turn would result in a 15%-longer motor block than the 0.67 µg/kg dose (**group D1**).

MATERIAL AND METHODS

The protocol used in the current study was identical to the one employed in our two previous trials.^{1,2} Prior to the submission of the project to the Ethics committee approval, an initial No Objection Letter (May 23, 2025) was obtained from Health Canada for the off-label use of perineural dexamethasone and perineural dexmedetomidine. After securing its approval (see below), we obtained an amended NOL from Health Canada (November 10, 2025).

Ethics committee approval (Research Ethics Board, McGill University Health Center) was secured on September 30, 2025. The protocol was registered on November 18, 2025 at www.ClinicalTrials.gov (NCT07249827) prior to patient recruitment. Sixty-nine patients undergoing upper limb surgery distal to the elbow were enrolled. The first subject was recruited on December 29, 2025. Written informed consent was obtained from all

participants. Inclusion criteria were: age between 18 and 75 years, American Society of Anesthesiologists (ASA) physical status I to III and body mass index between 18 and 35 kg/m². Exclusion criteria were: inability to consent to the study, coagulopathy, sepsis, hepatic or renal failure, pregnancy, breastfeeding, allergy to LA or dexmedetomidine, exposure to dexmedetomidine during the previous 48 hours preceding the study, chronic pain condition requiring the intake of opioids at home, prior surgery in the infraclavicular region, and pre-existing neuropathy.

After arrival in the induction room, standard ASA monitors were applied throughout the procedure. Patients were positioned supine with the surgical extremity by the side of the body. After skin disinfection and draping, the US transducer (3-12 MHz, Sonosite PX, Fuji Film), covered by a sterile sheath, was placed in a sagittal position medial to the coracoid process in order to obtain a short-axis image of the axillary artery. The skin and subcutaneous tissues were infiltrated with LA (3 mL of 1% lidocaine). Subsequently, a 21-gauge block needle (SonoPlex® 100 mm, Pajunk) was advanced until the tip was positioned dorsal to the axillary artery.^{1,2} The LA solution consisted of 35 mL of lidocaine 1%-bupivacaine 0.25% with epinephrine (5 µg/mL) and perineural dexamethasone (2 mg). In addition, a computer-generated randomization sequence was prepared by a research assistant who was not involved in the intervention or outcome assessment. Participants were allocated according to this sequence. Allocation concealment was maintained using sequentially numbered, sealed, opaque, and tamper-evident envelopes. The envelopes were opened by the same independent research assistant only after participant enrollment and allocation had been completed. Patients were randomized to receive the following doses of perineural dexmedetomidine: 0.67 µg/kg (D1); 1 µg/kg (D2); and 1.33 µg/kg (D3). We selected these doses because they correspond to 50 µg, 75 µg and 100 µg, respectively, for an average 75 kg-patient and are commonly used for brachial plexus blocks.³⁻⁵ The injectate was prepared by an investigator not otherwise involved in patient care nor patient assessment. Consequently, all the anesthesiologists, surgeons, nursing personnel and patients remained blinded to the dose of dexmedetomidine administered. Furthermore, all primary and secondary outcomes were recorded by blinded investigators.

Measurement of Primary Outcome

Similarly to our two previous trials,^{1,2} we selected the duration of motor block as the main outcome. Motor block duration was defined for patients with complete

sensorimotor blocks at 30 minutes (see below) as the temporal interval between the end of LA injection through the block needle and the return of movement to the hand and fingers.

Measurement of Secondary Outcomes

During the performance of the ICB, an investigator recorded the imaging time (defined as the temporal interval between the contact of the US transducer with the patient and the acquisition of a satisfactory picture) and the needling time (defined as the temporal interval between the skin infiltration and the end of LA injection through the block needle). Performance time was defined as the sum of imaging and needling times.^{1,2} The same investigator recorded the number of needle passes. The initial needle insertion counted as the first pass. Any subsequent needle advancement that was preceded by a retraction of at least 10 mm counted as an additional pass.⁶ The investigator also documented all complications occurring during the performance of the block (e.g., vascular puncture, paresthesia, pneumothorax, LA toxicity).

After the performance of the ICB, assessment of sensorimotor block was performed every 5 minutes (for 30 minutes) in the territories of the musculocutaneous, median, radial, and ulnar nerves. Sensory block was graded according to a 3-point scale using a cold stimulus: 0=no block, 1=analgesia (can feel touch, but not cold), 2=anesthesia (feels neither cold nor touch). Sensory blockade of the musculocutaneous, median, radial and ulnar nerves was assessed on the lateral aspect of the forearm, the volar aspect of the thumb, the lateral aspect of the dorsum of the hand and the volar aspect of the fifth finger, respectively.^{1,2} Motor block was also graded according to a 3-point scale: 0=no block (normal mobility and strength), 1=paresis (can move against gravity, but not against resistance), 2=paralysis (unable to move), using elbow flexion (musculocutaneous nerve), thumb abduction (radial nerve), thumb opposition (median nerve), and thumb adduction (ulnar nerve).^{1,2} A complete block was defined as a minimum composite score of 14 points (out of a maximum of 16 points) provided the sensory score was at least 7 out of 8 points. Thus, the onset time was defined as the time required to achieve a complete block. In turn, total anesthesia-related time was defined as the sum of performance and onset times. Furthermore, the level of procedural pain felt by the patient during the ICB was also recorded using an 11-point scale (0=no pain; 10=worst imaginable pain). Thirty minutes after the performance of ICB, the investigator documented possible side effects related to dexmedetomidine as follows: bradycardia (defined as a heart rate less than 50 beats

per minute), hypotension (defined as a mean arterial pressure less than 60 mm Hg), desaturation (defined as an oxygen saturation less than 90% on room air). The level of sedation was also evaluated using a 6-point Ramsay sedation scale.

During the surgery, an investigator recorded the presence of surgical anesthesia, defined as the ability to proceed with surgery without the need for intravenous narcotics, general anesthesia, rescue blocks or LA infiltration by the surgeon. However, in case of anxiety (as voiced by patients or determined by the treating anesthesiologists), subjects received a propofol infusion (25-75 µg/kg/min) intraoperatively, provided response to verbal stimulus was maintained.^{1,2} In patients with a failed block, the choice of anesthesia management was at the discretion of the anesthesiologist in charge. Depending on the clinical situation, management included an additional isolated nerve block (e.g., ulnar nerve block), administration of additional LA by the surgeon, or conversion to general anesthesia.

Postoperatively, patients were monitored in the Post Anesthesia Care Unit for two hours; all possible side effects related to dexmedetomidine (see above) were documented. Using a data sheet, patients with complete ICBs (i.e., minimum composite score ≥ 14 points at 30 minutes) were asked to record the duration of the sensory block (defined as the temporal interval between the end of LA injection through the block needle and the return of sensation to the hand and fingers), motor block (see above), and analgesia (defined as the temporal interval between the end of LA injection and the appearance of pain at the surgical site).^{1,2}

On postoperative day 2, an investigator collected the data sheet in person (inpatients) or by phone (outpatients). If the patient reported no pain after the block wore off, the investigator did not record an analgesic duration. Similarly, if the sensory or motor block wore off during the patient's sleep, the investigator did not record a sensory or motor block duration.

On postoperative day 7, an investigator contacted study subjects to enquire about persistent sensory (numbness) or motor (weakness) deficits.

Other recorded data

The medical chart was reviewed to collect demographic data (sex, age, weight, height, type of surgery) as well as experience level of the operator who performed the ICB. Independently of their status, operators were considered experts if, prior to the start of the study, they possessed an experience level equal or superior to 60 US-guided ICBs. Otherwise, they were considered trainees.⁷

Sample size calculation

Our experience with combined perineural dexamethasone (2 mg)- perineural dexmedetomidine (50 µg) for US-guided ICB reveals a motor block duration of 21.5 hours (SD = 2.7 hours).¹ The available literature suggests that perineural dexmedetomidine (without dexamethasone) may provide a dose-dependent prolongation in sensorimotor blockade.³⁻⁵ Thus, for the current study, we hypothesized that the D3 group (1.33 µg/kg) would provide a 15%-longer duration of motor block than the D2 group (1 µg/kg), which in turn would result in a 15%-longer motor block than the D1 group (0.67 µg/kg). A calculated sample size of 17 patients per group was required to provide a statistical power of 0.90 and a type I error of 0.05 (one-way ANOVA, GPowerMac version 3.1.9.6). Since block duration can only be calculated for successful blocks and since we anticipated a 90%-success rate with a 35 mL-volume,⁸ 19 subjects needed to be enrolled per group to account for block failure. Furthermore, since the duration of motor block cannot be accurately measured if blocks wear off during the patient's sleep (approximately 20% of cases), a total of 23 patients per group was enrolled to account for potential dropout. Therefore, the total sample size was 69 patients.

Statistical analysis

The statistical analysis was performed with the SPSS statistical software version 28 (IBM, Amonk, New York). For continuous data, the normality was first assessed with the Lilliefors test. Subsequently, the one-way ANOVA test was used to examine normal data and post hoc testing used Fisher's LSD. Data that did not have a normal distribution was analyzed with the Kruskal-Wallis and Dunn post-hoc test. In addition, to examine a possible dose-response relationship, formal tests of trend were utilized. Specifically, a Jonckheere-Terpstra test for trend was applied to non-normally distributed data, and a linear polynomial contrast within a one-way ANOVA was utilized for normally distributed continuous data. Categorical data was analyzed with the Chi square or Fisher's exact test and P values derived from these tests were adjusted using the Bonferroni method for multiple comparisons. While the one-way ANOVA was used to examine the primary outcome (duration of motor blockade), a secondary analysis was undertaken using Kaplan-Meier curves and log-rank tests. All P values presented are two-tailed and those less than 0.05 are considered significant.

RESULTS

The 69 patients were recruited from December 29, 2025 to June 10, 2026 (Fig 1). Demographic data and types of surgery are presented in Table 1.

The D2 and D3 group resulted in longer durations of motor block than the D1 group [18.6 (3.8) vs. 15.8 (3.8) hours; $P = 0.028$; and 18.6 (4.2) vs. 15.8 (3.8) hours; $P = 0.027$, respectively] as per (primary) the omnibus ANOVA/post-hoc test but not as per the (secondary) Kaplan-Meier log-rank test ($P = 0.078$). No other statistical differences were found amongst the three groups in terms of the duration of motor block, sensory block or analgesia (Table 2; Fig 2-4).

There were no intergroup differences in block performance (i.e., imaging/ needling/ performance times; procedural pain; number of needle passes; incidences

of vascular puncture/ pleural puncture/ paresthesia/ LA toxicity) (Table 2). Furthermore, parameters of block success (i.e., proportion of patients with a complete block at 30 minutes; incidence of surgical anesthesia) were also similar for the 3 groups (Table 2; Fig 5). However, both D2 and D3 groups resulted in shorter onset times (15 [15-20] vs. 20 [20-25] minutes; $P = 0.012$; and 15 [15-20] vs. 20 [20-25] minutes; $P = 0.007$, respectively) as well as shorter total anesthesia-related times [22.6 (6.1) vs. 27.3 (5.4) minutes; $P = 0.011$ and 23.4 (5.9) vs. 27.3 (5.4) minutes; $P = 0.033$, respectively) compared with the D1 group. No statistical differences were found between the D2 and D3 groups (Table 2).

For adverse events possibly related to dexmedetomidine, no intergroup differences were found in terms of bradycardia, hypotension, oxygen desaturation or level of sedation

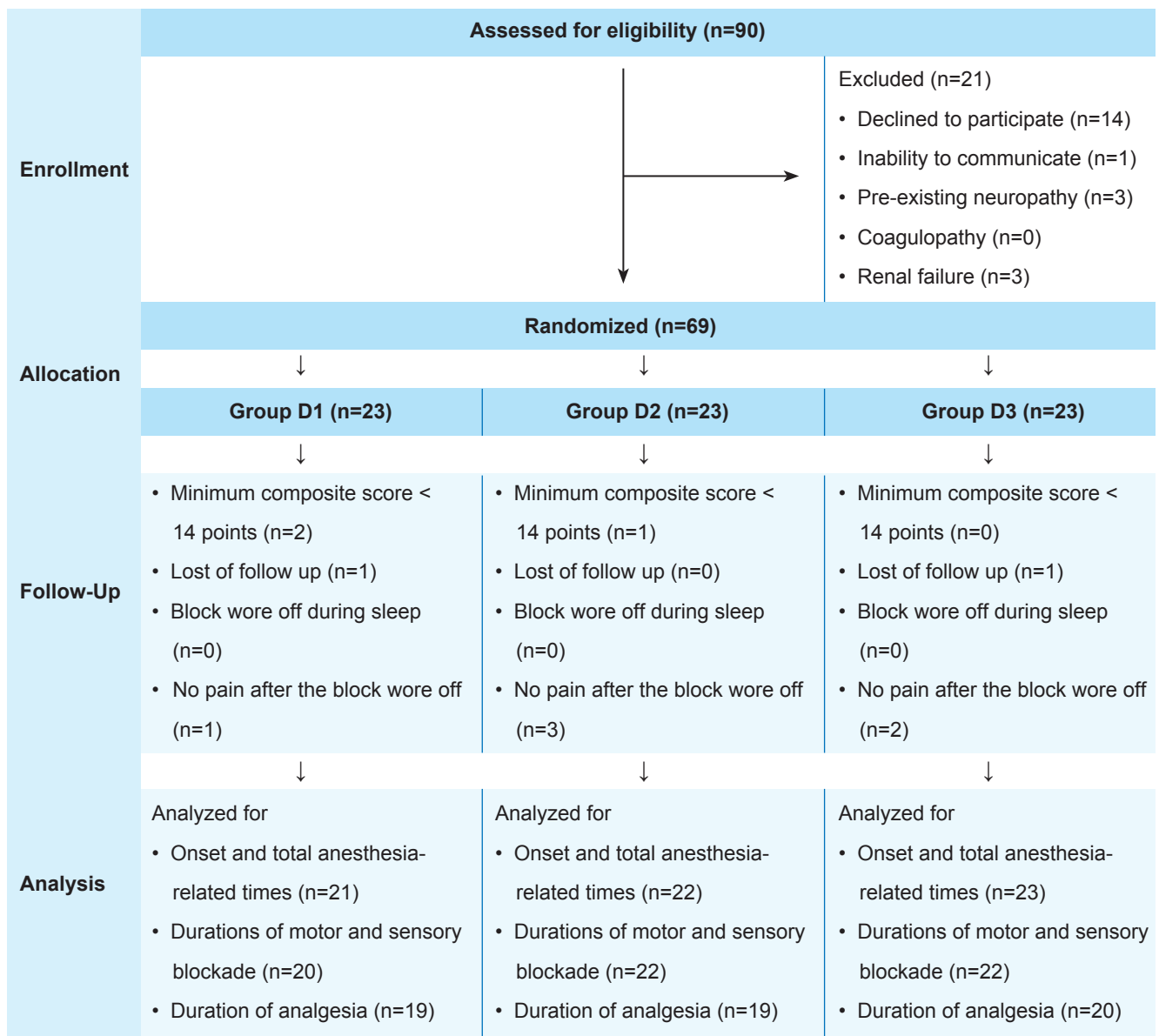


Fig 1. CONSORT diagram of the patient flow through the study.

TABLE 1. Patient characteristics and type of surgery.

	Group D1 (0.67 µg/kg, n=23)	Group D2 (1.0 µg/kg, n=23)	Group D3 (1.33 µg/kg, n=23)
Age in years, mean (SD)	42.3 (16.3)	46.1 (14.2)	49.2 (16.6)
Sex, n (%)			
Male	17 (73.9)	14 (60.9)	14 (60.9)
Female	6 (26.1)	9 (39.1)	9 (39.1)
BMI in kg/m², mean (SD)	25.6 (3.8)	27.6 (4.3)	25.2 (3.9)
ASA physical status, n (%)			
I	7 (30.4)	10 (43.5)	4 (17.4)
II	15 (65.2)	9 (39.1)	15 (65.2)
III	1 (4.3)	4 (17.4)	4 (17.4)
Type of surgery, n (%)			
Hand	21 (91.3)	14 (60.9)	15 (65.2)
Wrist	2 (8.7)	5 (21.7)	5 (21.7)
Forearm	0 (0.0)	4 (17.4)	3 (13.0)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

TABLE 2. Block performance data, onset time, durations of sensorimotor block and postoperative analgesia, and side effects.

	Group D1 (n=23)	Group D2 (n=23)	Group D3 (n=23)	Omnibus testing* P values	Pairwise testing† P values	Test of trend‡ P values
Imaging time in seconds, median [IQR]	55 [26–108]	30 [24–60]	30 [15–58]	0.073		
Needling time in minutes, median [IQR]	4.1 [3.2–4.9]	3.9 [3.1–5.8]	4.6 [4.0–5.5]	0.240		
Performance time in minutes, median [IQR]	5.0 [4.2–6.6]	4.4 [3.9–6.8]	5.5 [4.4–5.9]	0.601		
Onset time in minutes, median [IQR]	20.0 [20.0–25.0] n=21	15.0 [15.0–20.0] n=22	15.0 [15.0–20.0] n=23	0.003	1 vs. 2 p=0.012 1 vs. 3 p=0.007	0.003
Total anesthesia-related time in minutes, mean (SD)	27.3 (5.4) n=21	22.6 (6.1) n=22	23.4 (5.9) n=23	0.025	1 vs. 2 p=0.011 1 vs. 3 p=0.033	0.033
Blocks with a minimum composite score of 14 points, n (%)	21 (91.3)	22 (95.7)	23 (100.0)	0.768		

TABLE 2. Block performance data, onset time, durations of sensorimotor block and postoperative analgesia, and side effects. (Continued)

	Group D1 (n=23)	Group D2 (n=23)	Group D3 (n=23)	Omnibus testing* P values	Pairwise testing† P values	Test of trend‡ P values
Surgical anesthesia, n (%)	23 (100.0)	22 (95.7)	22 (95.7)	>0.999		
Intraoperative sedation requirement, n (%)				0.249		
Propofol sedation	19 (82.6)	20 (87.0)	16 (69.6)			
No additional sedation	4 (17.4)	2 (8.7)	6 (26.1)			
Number of needle passes, median [IQR]	1 [1–2]	1 [1–2]	2 [1–2]	0.145		
Block-related pain (NRS 0–10), median [IQR]	2 [1–4]	2 [0–3]	2 [2–3]	0.590		
Operator's experience level, n (%)				0.922		
Expert	2 (8.7)	2 (8.7)	3 (13.0)			
Trainee	21 (91.3)	21 (91.3)	20 (87.0)			
Duration of motor block in hours, mean (SD)	15.8 (3.8) n=20	18.6 (3.8) n=22	18.6 (4.2) n=22	0.041	1 vs. 2 p=0.028 (-5.22 to -0.31) ^ε 1 vs. 3 p=0.027 (-5.23 to -0.33) ^ε	0.027
Duration of sensory block in hours, mean (SD)	17.7 (3.9) n=20	18.5 (4.7) n=22	19.5 (4.4) n=22	0.435		
Duration of analgesia in hours, mean (SD)	19.3 (5.0) n=19	22.4 (4.6) n=19	20.6 (4.5) n=20	0.138		
PACU Ramsay sedation score, median [IQR]	2 [2–2]	2 [2–2]	2 [2–2]	0.539		
Vascular puncture, n (%)	0 (0)	2 (8.7)	2 (8.7)	0.536		
Paresthesia, n (%)	0 (0)	3 (13.0)	2 (8.7)	0.357		
Pneumothorax, n (%)	0 (0)	0 (0)	0 (0)	>0.999		
LA systemic toxicity, n (%)	0 (0)	0 (0)	0 (0)	>0.999		
Bradycardia, n (%)	1 (4.3)	0 (0)	1 (4.3)	>0.999		
Hypotension, n (%)	3 (13.0)	5 (21.7)	5 (21.7)	0.740		
95% CI	(2.7-33.6)	(7.5-43.7)	(7.5-43.7)			

TABLE 2. Block performance data, onset time, durations of sensorimotor block and postoperative analgesia, and side effects. (Continued)

	Group D1 (n=23)	Group D2 (n=23)	Group D3 (n=23)	Omnibus testing* P values	Pairwise testing† P values	Test of trend‡ P values
Desaturation, n (%)	0 (0)	0 (0)	0 (0)	>0.999		
7-day non-surgical neurological deficit, n (%)	0 (0) n=22	0 (0) n=23	0 (0) n=21	>0.999		

Onset and total anesthesia-related times could only be tabulated for patients displaying a minimum sensorimotor composite score of 14 points. Thus, the exact sample size is listed in each corresponding cell.

Durations of sensorimotor block could only be tabulated for patients displaying a minimum sensorimotor composite score of 14 points, whose blocks did not recede during their sleep. Thus, the exact sample size is listed in each corresponding cell.

Duration of analgesia could only be tabulated for patients displaying a minimum sensorimotor composite score of 14 points who experienced pain when the block receded. Thus, the exact sample size is listed in each corresponding cell.

Residual neurological deficit was assessed at the 7-day follow-up; the number of patients assessed is listed in each corresponding cell.

Ramsay sedation scale: 1, anxious, agitated or restless; 2, cooperative, oriented and tranquil; 3, responsive to commands only; 4, brisk response to a light glabellar tap or loud auditory stimulus; 5, sluggish response to a light glabellar tap or loud auditory stimulus; 6, no response to a light glabellar tap or loud auditory stimulus.

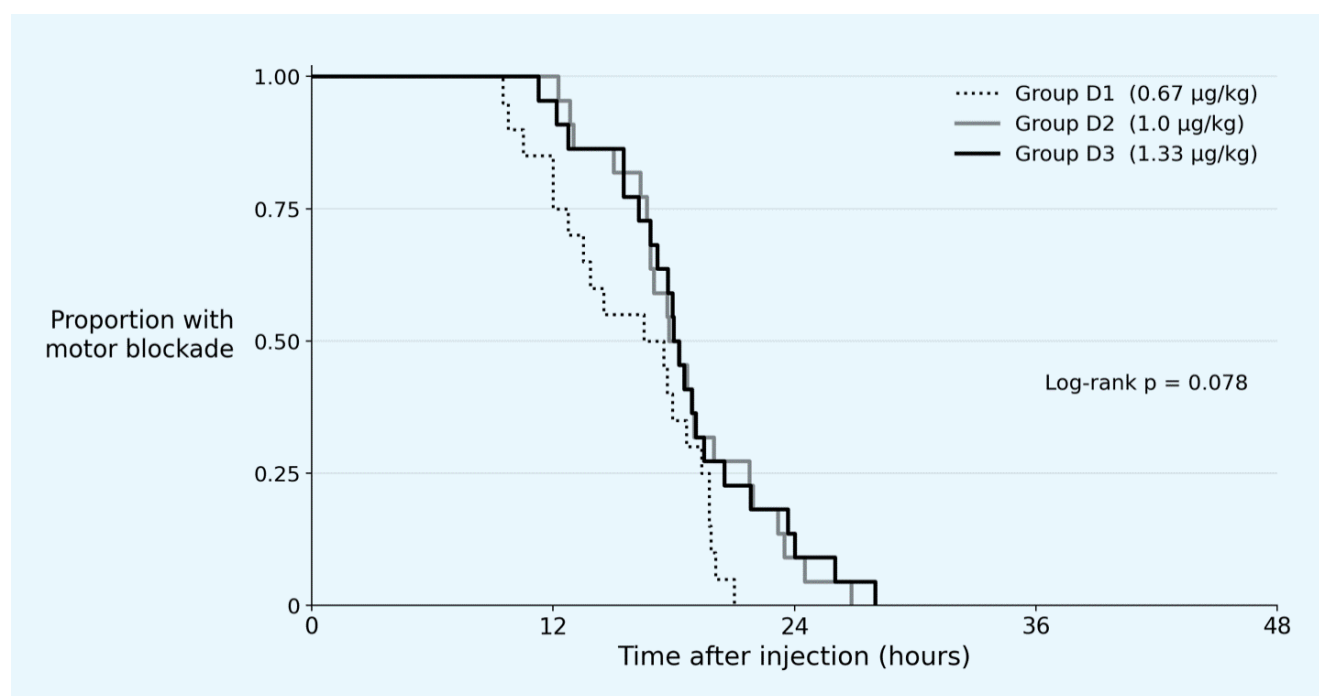
PACU, post-anesthesia care unit.

*One-Way ANOVA or Kruskal-Wallis test

†Dunn's test or Fisher's LSD

‡Linear polynomial contrast within a one-way ANOVA or Jonckheere-Terpstra test for trend

£ 95% confidence interval for the difference of the means

**Fig 2.** Kaplan-Meier survival plot for the duration of motor block. $p = 0.078$ (log-rank test)

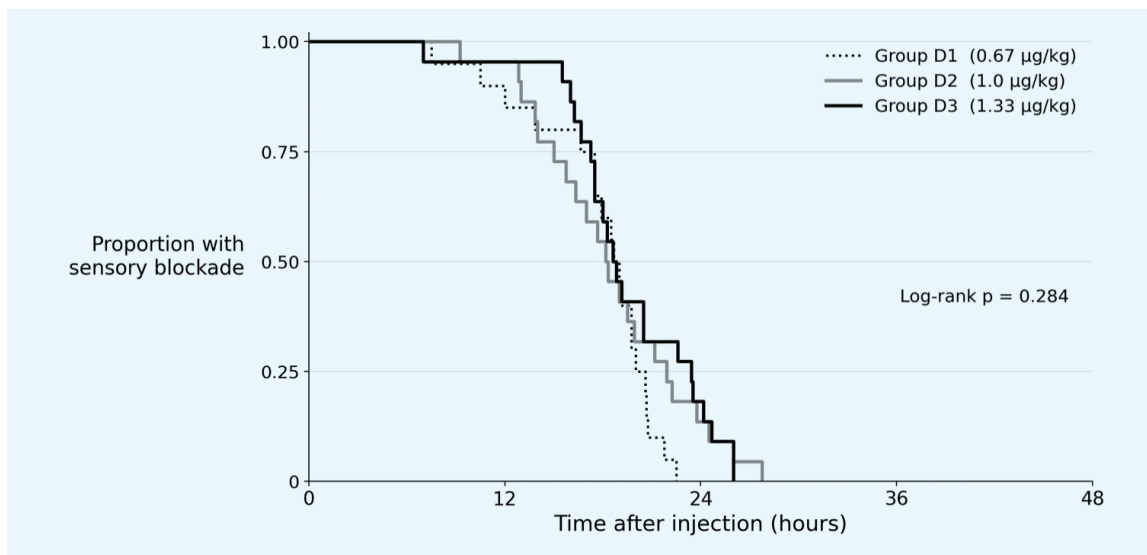


Fig 3. Kaplan-Meier survival plot for the duration of sensory block. $p = 0.284$ (log-rank test)

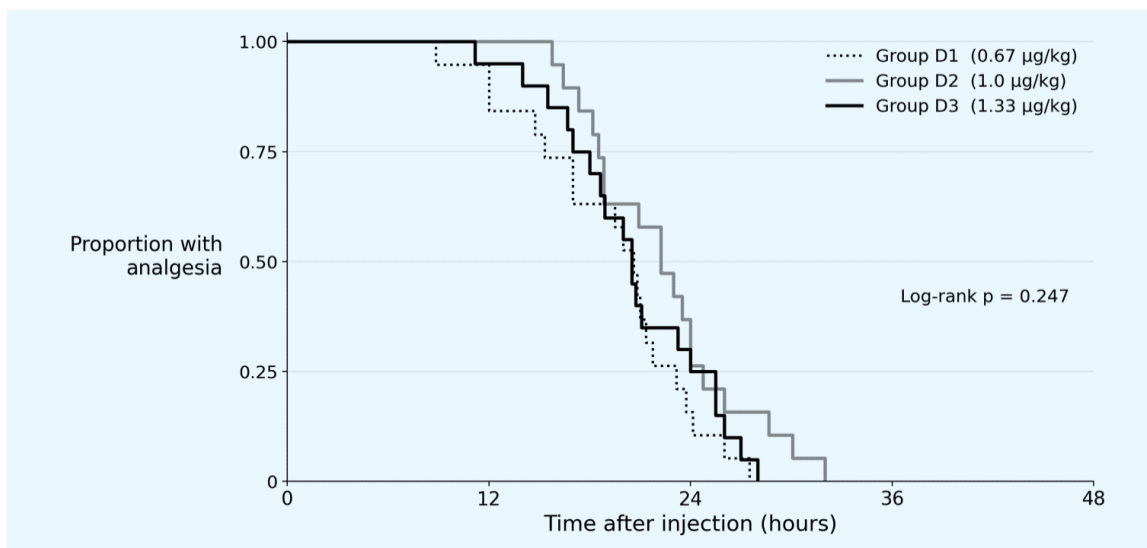


Fig 4. Kaplan-Meier survival plot for the duration of postoperative analgesia. $p = 0.247$ (log-rank test)

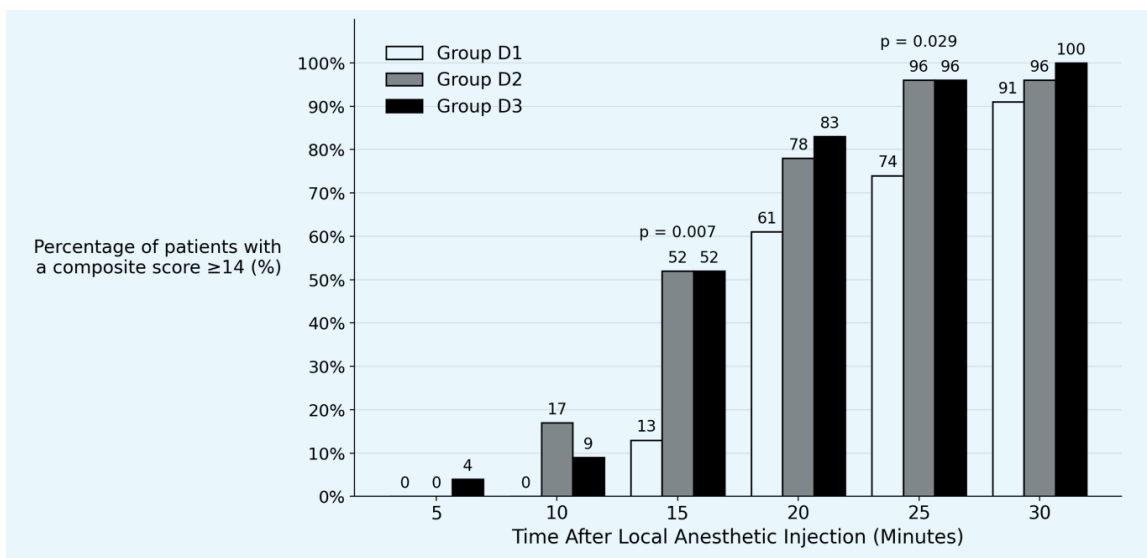


Fig 5. Percentage of patients with a minimum composite score of 14 points according to time, by group (D1, 0.67 µg/kg; D2, 1.0 µg/kg; D3, 1.33 µg/kg). Significant chi-square tests (exploratory analysis, unadjusted p values) for 15 min ($p = 0.007$) and 25 min ($p = 0.029$).

(Table 2). None of the subjects who displayed hypotension were symptomatic. The decrease in blood pressure was easily treated with 5 mg- boluses of intravenous ephedrine (until the mean arterial pressure was above 60 mmHg). No patient reported sensory or motor deficits at 7 days.

DISCUSSION

In this randomized trial, we compared three doses of perineural dexmedetomidine (0.67 µg/kg; 1 µg/kg and 1.33 µg/kg) for US-guided ICB performed with 35 mL of lidocaine 1%- bupivacaine 0.25%- epinephrine 5 µg/mL- dexamethasone 2 mg. We did not find a 15% stepwise increase in motor block duration among the three doses. Consequently, our research hypothesis was not demonstrated. Although the 1 µg/kg and 1.33 µg/kg doses did result in a statistically longer motor block than the 0.67 µg/kg dose as per the omnibus ANOVA/post-hoc test (Table 2), the Kaplan-Meier log-rank test for the same outcome fails to detect a significant difference ($P=0.078$, Fig 2). Thus, the differences in motor block duration (D2-D3 groups vs. D1 group) may not be robust across analytic approaches and should therefore be considered hypothesis-generating. Moreover, our results suggest that 1 µg/kg provides a similar onset to 1.33 µg/kg and a shorter onset time than 0.67 µg/kg. Because onset time constituted a secondary outcome, this finding should be considered exploratory for the time being.

Our choice of primary outcome deserves special mention. Similarly to our two previous trials,^{1,2} we selected motor block duration instead of sensory block or analgesic duration as the primary outcome because we reasoned that it best reflects the perineural action of dexmedetomidine. Analgesic duration inherently depends on the patient's consumption of pain killers and, more importantly, on the level of postoperative pain associated with the surgical procedure. For instance, in a recent trial, Samerchua et al⁹ observed that, in 21% of cases, patients undergoing forearm, wrist or hand surgery experienced no pain after the brachial plexus receded. From a methodological standpoint, the duration of sensory block may be less reliable if confounded by the presence of injury to small cutaneous nerves (e.g., superficial branches of the radial nerve at the level of the anatomical snuff box). In contrast, the duration of motor block remains independent of surgical procedure, analgesics and injury to cutaneous nerves.

The differences in block duration between the D1 group and the intervention group in our previous study¹ require discussion (Table 3). The senior investigators (JA, RJF, DQT) have authored both studies. In both protocols,

the doses of perineural dexmedetomidine (50 µg for the previous trial; and 0.67 µg/kg for patients whose average weight is 77.6 kg, i.e., 52 µg, in the current study) were similar. Furthermore, the LA admixture (35 mL of lidocaine 1%- bupivacaine 0.25%- epinephrine- dexamethasone 2 mg), the ICB technique (single-injection dorsal to the axillary artery), and the research methodology (including the definitions of onset time, complete block, surgical anesthesia, and analgesic/ sensorimotor duration) were also identical. Thus, the different block durations between the D1 group and the intervention group of our previous trial¹ could be explained by the fact that perhaps the absolute magnitude of the “dexmedetomidine effect” is variable. An alternative (untested) explanation stems from a difference in clinical practice. The two studies were conducted in different centers, i.e., Hospital Clínico Universidad de Chile (for the previous study) vs. the Montreal General Hospital (for the current trial). At the Montreal General Hospital, all patients were discharged the same day (vs. 70% for Hospital Clínico Universidad de Chile). Thus, we speculate that the difference between the two sets of results stems from the subjective recall of analgesic/ sensorimotor block resolution, which was perhaps less optimal in the current trial due to the outpatient status of all our study patients, and not from actual block performance. Our hypothesis is supported by the fact that all parameters that were recorded in the hospital (i.e., performance time; proportion of complete block/ surgical anesthesia; onset and total anesthesia-related times) are virtually identical between the two studies (Table 3). Consequently, the shortened onset time associated with the D2 and D3 groups remains reliable findings.

The incidence of hypotension also needs to be highlighted. Although we found no statistical differences amongst the three groups, the D2 and D3 groups both resulted in a 22%-incidence of hypotension, which was higher than one associated with the D1 group (13%). Consequently, we cannot rule out the possibility that the absence of statistical differences may stem from an underpowered sample size to detect said difference rather than a true absence of clinical effect.

Our protocol contains some limitations. First, our findings are specific to a LA admixture consisting of lidocaine 1%- bupivacaine 0.25%- epinephrine 5 µg/mL- dexamethasone 2 mg. Future trials should investigate if they apply to other LA molecules (e.g., bupivacaine 0.5% or ropivacaine 0.5%). Second, our results also depend on the LA volume (35 mL). Future studies are required to determine if they hold true for smaller (or larger) injectates. Third, in our study, trainees performed 87%-91% of the

TABLE 3. Comparison between the current and previous trials for infraclavicular block using 35 mL of lidocaine 1% – bupivacaine 0.25% – epinephrine 5 µg/mL – dexamethasone 2 mg – dexmedetomidine 50–52 µg.

	Current Trial N = 23	Previous Trial (Aliste et al. 2022) N = 25
Performance time (min)	Median [IQR] = 5.0 [4.2–6.6]	Mean (SD) = 5.6 (2.7)
Onset time (min)	Median [IQR] = 20.0 [20.0–25.0]	Mean (SD) = 20.0 (5.8)
Total anesthesia-related time (min)	Median [IQR] = 27.7 [23.8–31.2]	Mean (SD) = 25.4 (6.3)
Complete block, n (%)	21 (91)	23 (92)
Surgical anesthesia, n (%)	23 (100)	23 (92)
Number of passes	1 [1–2]	2 [1–3]
Procedural pain, NRS (0–10)	2 [1–4]	3 [0–7]
Operator's level of experience (expert/trainee)	2 / 21	1 / 24
Duration of motor block (hours)	15.8 (3.8)	21.5 (2.7)
Duration of sensory block (hours)	17.7 (3.9)	21.6 (3.6)
Duration of analgesia (hours)	19.3 (5.0)	25.5 (9.4)

Current trial corresponds to the 0.67 µg/kg dexmedetomidine group. Continuous data are median (IQR) or mean (SD); categorical data are n (%).

Abbreviation: NRS, numerical rating scale

ICBs. Thus, we cannot rule out the possibility that our results might have differed had experienced operators carried out 100% of the blocks. Finally, we only investigated 0.67 µg/kg, 1 µg/kg and 1.33 µg/kg of dexmedetomidine. Consequently, our findings should not be extrapolated to other doses of perineural dexmedetomidine, such as 1.5 µg/kg or 2 µg/kg.¹⁰ Further investigation is required to determine if doses > 1.33 µg/kg provide incremental benefits in terms of decreased onset time or increased block duration.

CONCLUSION

For ICB performed with 35 mL of lidocaine 1%-bupivacaine 0.25%- epinephrine 5 µg/mL- perineural dexamethasone (2 mg), 1 µg/kg and 1.33 µg/kg doses may result in a statistically longer motor block than the 0.67 µg/kg dose. Because this difference may not be robust across analytic approaches, this finding should be considered hypothesis-generating. Similarly, although 1 µg/kg 1.33 µg/kg provide a shorter onset time than 0.67 µg/kg, this finding should be considered exploratory

because onset time constituted a secondary outcome. Consequently, further investigation is required to confirm the increased motor block duration with the 1 µg/kg-1.33 µg/kg doses. Future studies should also examine perineural dexmedetomidine for other LA molecules, injectates, and doses greater than 1.33 µg/kg.

Data Availability Statement

The de-identified datasets supporting the findings of this study are not publicly deposited, as the informed consent obtained does not cover open data sharing. They are available from the corresponding author upon reasonable request and with the approval of the McGill University Health Centre Research Ethics Board. The trial was prospectively registered at ClinicalTrials.gov (NCT07249827; <https://clinicaltrials.gov/study/NCT07249827>).

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DECLARATIONS

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None of the authors received funding for this study.

Conflict of Interest

The authors declare no competing interest.

Registration number of clinical trial

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Author Contributions

Conceptualization and methodology, J.A., D.T., and R.J.F.; Validation, J.A., D.T., and R.J.F.; Formal analysis, J.A., D.T., and R.J.F.; Investigation, J.A., D.T., S.P., D.G.D., M.A., A. Alkhoutani, A. Amir, K.R., and J.F.A.; Resources, J.A., D.T., R.J.F., S.P., D.G.D., M.A., A. Alkhoutani, A. Amir, K.R., and J.F.A.; Data curation, J.A., D.T., R.J.F., S.P., D.G.D., M.A., A. Alkhoutani, A. Amir, K.R., and J.F.A.; Writing – original draft, J.A., D.T., R.J.F., S.P., and D.G.D.; Writing – review and editing, J.A., D.T., R.J.F., and S.P.; Visualization, J.A., D.T., and S.P.; Supervision, J.A. and D.T.; Project administration, J.A. and D.T. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

The authors declare that no artificial intelligence was used in this manuscript.

Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of Research Ethics Board, McGill University Health Center (Approval No. 2025-11084, approved on September 30, 2025).

Key Messages

• **What is already known on this topic** – Infraclavicular block with 35 mL of adrenalized lidocaine 1%- bupivacaine 0.25%- epinephrine 5 µg/mL- perineural dexamethasone (2 mg)- perineural dexmedetomidine results in a long-acting block.

The optimal dose of perineural dexmedetomidine remains unknown.

• **What this study adds** – This randomized trial compared 3 doses of perineural dexmedetomidine (0.67 µg/kg vs. 1 µg/kg vs. 1.33 µg/kg) for infraclavicular block. Our findings suggest that 1 µg/kg may constitute the optimal dose of dexmedetomidine: it results in a similar onset

to 1.33 µg/kg and provides a shorter onset time than 0.67 µg/kg.

How this study might affect research, practice, or policy

–A local anesthetic admixture containing lidocaine 1%- bupivacaine 0.25%- epinephrine 5 µg/mL- dexamethasone (2 mg)- dexmedetomidine (1 µg/kg) provides a useful strategy for infraclavicular blocks.

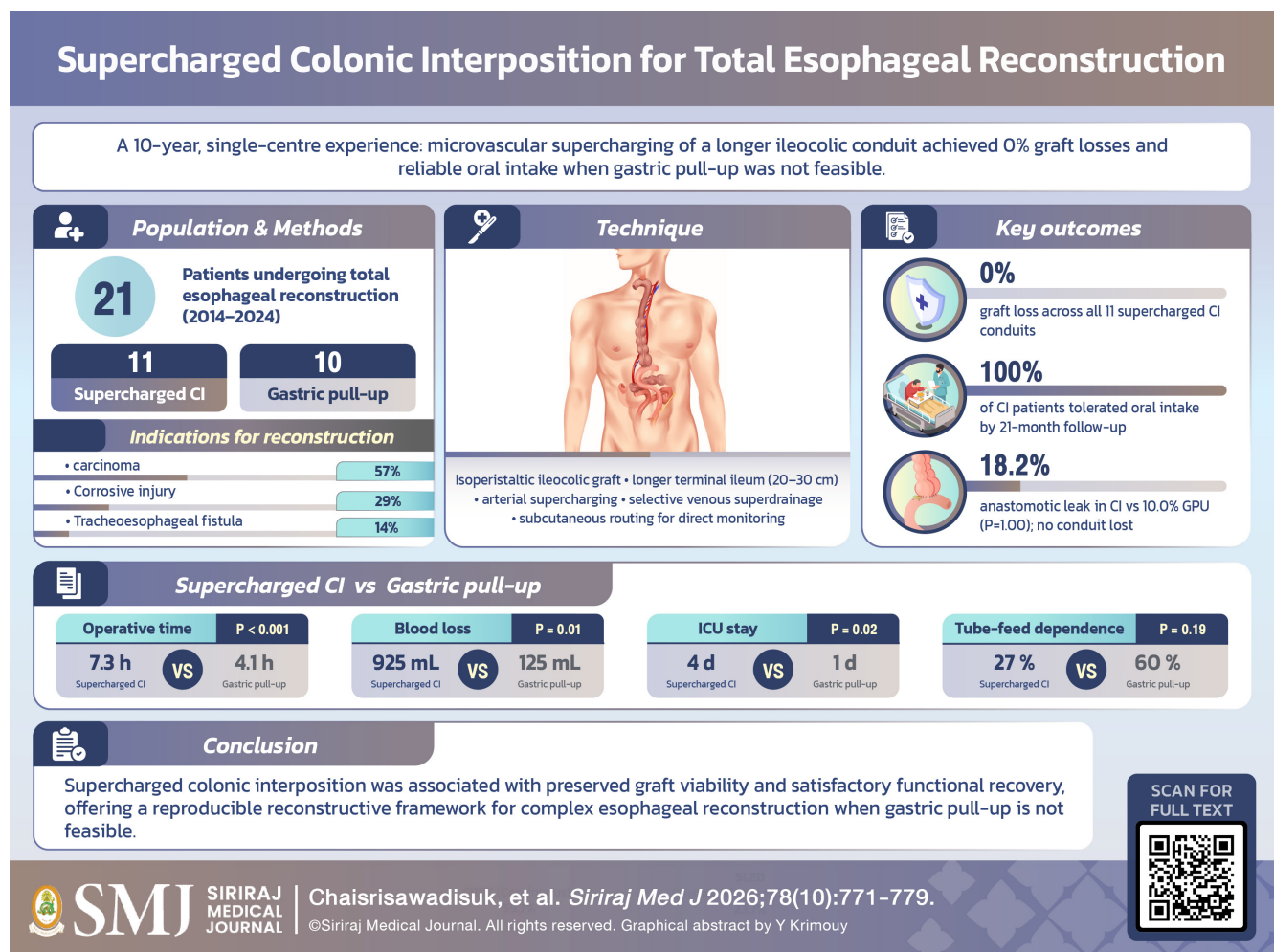
REFERENCES

1. Aliste J, Layera S, Bravo D, Aguilera G, Erpel H, García A, et al. Randomized comparison between perineural dexamethasone and combined dexamethasone- dexmedetomidine for ultrasound-guided infraclavicular block. *Reg Anesth Pain Med.* 2022;47: 554-9.
2. Bravo D, Aliste J, Layera S, Fernández D, Leurcharusmee P, Samerchua A, et al. A multicenter, randomized comparison between 2, 5, and 8 mg of perineural dexamethasone for ultrasound-guided infraclavicular block. *Reg Anesth Pain Med.* 2019;44:46-51.
3. Shaika S, Singh J, Ghimire A, Shrestha B. Supraclavicular brachial plexus block: Comparison of varying doses of dexmedetomidine with ropivacaine. *Kathmandu Unive Med J (KMJ).* 2021;19: 345-50.
4. Ghazaly HF, Aly AAA, Zaher ZZ, Hassan MM, Mahmoud AA. Comparison of the efficacy of two doses of dexmedetomidine as an adjunct to levobupivacaine in infraclavicular brachial plexus block: Prospective double blinded randomized controlled trial. *BMC Anesthesiol.* 2022;22(1):338.
5. Akshara P, Govindan DK, Govindasamy J, Arif M, Sethuraman RM. Comparing different doses of dexmedetomidine combined with ropivacaine for ultrasound-guided supraclavicular brachial plexus block for upper limb surgeries: A prospective randomized controlled trial. *Anesth Essays Res.* 2022;16:94-7.
6. Casati A, Danelli G, Baciarello M, Corradi M, Leone S, Di Cianni S, et al. A prospective, randomized comparison between ultrasound and nerve stimulation guidance for multiple injection axillary brachial plexus block. *Anesthesiology.* 2007;106:992-6.
7. Konrad C, Schupfer G, Wietlisbach M, Gerber H. Learning manual skills in Anesthesiology: Is there a recommended number of cases for anesthetic procedures? *Anesth Analg.* 1998; 86: 635-9.
8. Tran DQ, Dugani S, Diachenko A, Correa JA, Finlayson RJ. Minimum effective volume of lidocaine for ultrasound-guided infraclavicular block. *Reg Anesth Pain Med.* 2011;36: 190-4.
9. Samerchua A, Supphapipat K, Leurcharusmee P, Moolsan S, Promfang P, Finlayson RJ, et al. Perineural dexmedetomidine decreases the onset time of bupivacaine 0.5%- epinephrine-dexamethasone for infraclavicular block: A randomized controlled trial. *Reg Anesth Pain Med.* 2026; Jun 2:rapm-2026-107917. doi: 10.1136/rapm-2026-107917. Online ahead of print.
10. Jung HS, Seo HK, Kang JH, Jeong JY, Kim YS, Han NR. Optimal dose of perineural dexmedetomidine for interscalene brachial plexus block to control postoperative pain in patients undergoing arthroscopic shoulder surgery: A prospective, double-blind, randomized controlled study. *Medicine (Baltimore).* 2018;97:e0440.

Supercharged Colonic Interposition for Total Oesophageal Reconstruction: Technical Refinements, Perioperative Protocol, and Functional Outcomes

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ABSTRACT

Objective: We report a 10-year experience with supercharged colonic interposition (CI) for total oesophageal reconstruction, focusing on technical refinements and functional outcomes.

Materials and Methods: A retrospective review of patients undergoing total oesophageal reconstruction (2014–2024) was conducted. A modified, supercharged CI was performed using a longer terminal ileal segment of 20–30 cm. Conduits were routed subcutaneously, and arterial supercharging—usually to the transverse cervical artery—was performed selectively. When congestion persisted, venous superdrainage was additionally implemented. Outcomes were compared with a contemporaneous gastric pull-up (GPU) cohort.

Results: Twenty-one patients underwent reconstruction (11 CI, 10 GPU). No graft failures occurred after supercharged CI. Anastomotic leakage occurred in 18.2% of CI and 10.0% of GPU patients ($P=1.00$) and was managed without conduit loss. Stricture was more frequent after CI (36.4% vs. 10.0%, $P=0.31$) and was successfully treated endoscopically. At a median follow-up of 21 months, all CI patients tolerated oral intake (45.5% solid, 45.5% soft diet); feeding tube dependence was 27.3% after CI vs. 60.0% after GPU ($P=0.19$).

Conclusions: Supercharged colonic interposition was associated with preserved graft viability and satisfactory functional recovery in patients requiring complex total oesophageal reconstruction. A defined selection algorithm, standardised technique, subcutaneous routing, and structured perioperative care offer a reproducible framework for complex oesophageal reconstruction when gastric pull-up is not feasible.

Keywords: Oesophageal reconstruction; colonic interposition; supercharged flap; microvascular augmentation; visceral reconstruction; swallowing function (Siriraj Med J 2026;78(10):771-779)

INTRODUCTION

Oesophageal reconstruction is among the most technically demanding procedures in reconstructive surgery. Loss of oesophageal continuity from malignancy, corrosive injury, stricture, or tracheoesophageal fistula severely impairs swallowing, nutrition, and quality of life.¹ Gastric pull-up (GPU) is the preferred conduit when feasible, owing to its dependable vascular supply and technical simplicity,^{2,3} but prior gastrectomy, compromised gastric vascularity, or long-segment defects often preclude its use. Colonic interposition (CI) is the principal alternative, offering adequate length, orthodromic peristalsis, and reservoir capacity,^{4,5} but its marginal vascular supply—particularly at the proximal graft segment—has historically predisposed to anastomotic leakage and graft compromise.^{6,7}

Microvascular supercharging augments arterial inflow, and when needed, venous outflow, to reinforce the conduit at its most vulnerable segment. Published series^{8–11} demonstrate improved graft viability with augmentation, but few define the clinical criteria that should trigger it, and technical algorithms for patient selection, conduit routing, and monitoring remain inconsistent.

We report a 10-year single-centre experience with supercharged CI for total oesophageal reconstruction, focusing on technical refinements that extend safe conduit reach, our rationale for a monitoring-oriented subcutaneous routing strategy, and a structured perioperative protocol. Functional outcomes, including a descriptive comparison

with a contemporaneous GPU cohort, support this technical framework, which we intend as a reproducible model for centres managing complex oesophageal reconstruction when GPU is not feasible.

MATERIALS AND METHODS

Study design and setting

We retrospectively reviewed patients undergoing total oesophageal reconstruction at the Faculty of Medicine Siriraj Hospital from January 2014 to December 2024, using a prospectively maintained institutional database. This study was approved by the Siriraj Institutional Review Board (Si 048/2025).

Patient selection

Patients undergoing total oesophageal reconstruction for oesophageal carcinoma, corrosive injury, benign stricture, or tracheoesophageal fistula were included; those undergoing partial reconstruction or with incomplete records were excluded. Demographic, operative, and hospitalisation variables were collected, including age, sex, body mass index, smoking and alcohol history, prior gastric surgery, and preoperative chemoradiation. Postoperative outcomes included surgical and medical complications, dietary tolerance, feeding tube dependence, time to oral intake and to a regular diet, and survival status.

Conduit selection algorithm

GPU was used when the stomach was viable with adequate vascular supply; CI was chosen for patients with prior gastrectomy, compromised gastric vascularity, long-segment defects, or when gastric reconstruction was otherwise not feasible. Colon lumen and vascular arcades were routinely evaluated preoperatively to confirm conduit suitability.

Operative technique: modified supercharged CI

All conduits were isoperistaltic ileocolic grafts based on the terminal ileum and right colon, mobilised while preserving the middle colic vessels as the primary pedicle. A longer segment of terminal ileum (20-30 cm proximal to the ileocecal valve), rather than further transverse colon mobilisation, provided sufficient length while avoiding tension on the transverse mesentery and yielded a narrower-calibre segment for the cervical anastomosis. Arterial perfusion was assessed by direct visualisation and transillumination, supplemented by indocyanine green angiography in selected cases. Arterial supercharging-typically between terminal ileal branches and the transverse cervical artery-was performed under microscope before the proximal oesophageal anastomosis. (Fig 1) Venous superdrainage was added only when venous congestion of the conduit tip developed after arterial supercharging; when needed, the external jugular vein or a tributary was used. The proximal ileal segment was hand-sewn to the cervical oesophageal stump, in selected cases just distal to the pyriform sinus. Distally, the conduit was anastomosed to the gastric remnant or

a Roux-en-Y jejunal limb, and a feeding jejunostomy was routinely placed.

Route selection: rationale for the subcutaneous pathway

All conduits were routed subcutaneously rather than through the posterior mediastinum, retrosternal space, or chest. Because a supercharged conduit's viability depends on a single microvascular anastomosis, we prioritised a route allowing continuous visual and Doppler surveillance and prompt salvage-an advantage the posterior mediastinal route, which conceals the conduit, cannot offer. This route also avoided dissection through a mediastinum or pleural space scarred by prior treatment and improved access for the cervical microvascular anastomosis. We accept that this route requires a longer conduit and has been linked to delayed emptying.¹²

Postoperative management

Patients received 7 days of antibiotic prophylaxis, proton pump inhibitors when a cologastric anastomosis was present, and routine prokinetic agents. The conduit was monitored via an externalised segment or Doppler ultrasound every 2 hours for the first 24 hr. Endoscopy was performed meticulously on postoperative day 1 to assess patency of the oesophageal anastomosis and viability of the ileo-colic graft. Oral intake was withheld 7-10 days pending a contrast esophagogram to exclude leakage, then advanced from liquids to a post-gastrectomy diet as tolerated. Vitamin D levels (deficiency if < 30 ng/ml) were checked after surgery throughout the postoperative period.

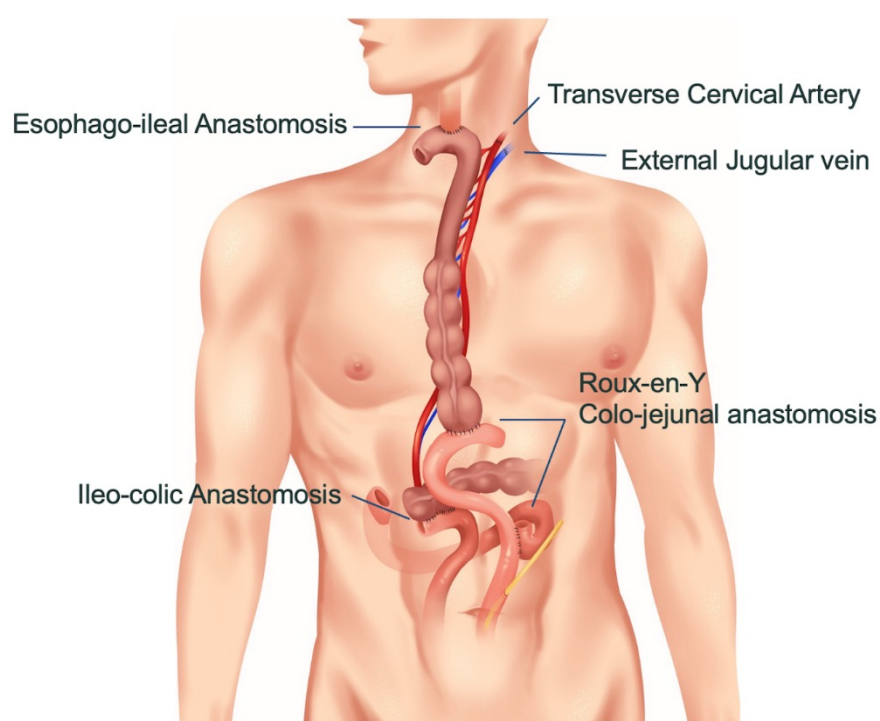


Fig 1. Surgical technique of supercharged colonic interposition. A longer segment of terminal ileum is used for cervical oesophageal reconstruction. The transverse cervical artery is anastomosed to the terminal ileal artery; if conduit congestion is observed, the external jugular vein is additionally anastomosed to the terminal ileal vein.

Statistical analysis

Continuous variables are reported as mean (SD) or median (range), and categorical variables as frequencies, with between-group comparisons by t test, Mann-Whitney U test, or Fisher exact test as appropriate ($P < 0.05$ considered significant). Given the small, non-randomized samples and the absence of a power calculation, comparisons with GPU are exploratory rather than confirmatory.

RESULTS

Patient characteristics

Between 2014 and 2024, 21 patients underwent total oesophageal reconstruction: 11 (52.4%) with supercharged CI and 10 (47.6%) with GPU (Table 1). Mean age was 53.1 (SD 12.9) years, and 71.4% were male. Mean body mass index was 17.81 (SD 3.18) kg/m². Diagnoses included carcinoma (57.1%), corrosive injury (28.6%), and tracheoesophageal fistula (14.3%).

Operative outcomes

Table 2 demonstrates the outcomes after supercharged CI. The terminal ileal artery was the pedicle in all cases; the

transverse cervical artery was the most common recipient artery (81.8%) and the external jugular vein the most common recipient vein (54.5%). Venous superdrainage was unnecessary in 2 patients (18.2%). All conduits were routed subcutaneously.

Median operative time (7.3 vs 4.1 hours, $P < 0.001$), blood loss (925 vs 125 mL, $P = 0.01$), and ICU stay (4 vs 1 day, $P = 0.02$) were greater for CI than GPU; total hospitalisation did not differ significantly (24 vs 18.5 days, $P = 0.29$) (Table 3).

No graft failures occurred in either group (Table 4). Anastomotic leakage occurred in 18.2% of CI and 10.0% of GPU patients and was managed without conduit loss. Stricture was the most frequent late CI complication (36.4% vs 10.0%) and was successfully treated endoscopically in all cases. Vitamin D deficiency was more common after CI (45.5% vs 10.0%). However, those showed no statistical difference.

Functional outcomes

At a median follow-up of 21 months, all CI patients tolerated oral intake, with 45.5% achieving a solid and

TABLE 1. Patient characteristics.

	All patients (<i>n</i> = 21)	Supercharged colonic interposition (<i>n</i> = 11)	Gastric pull-up (<i>n</i> = 10)	<i>P</i> value
Age, years; mean (SD)	53.1 (12.9)	51.1 (11.7)	55.4 (14.4)	0.45
BMI, kg/m ² ; mean (SD)	17.81 (3.18)	18.40 (4.07)	17.17 (1.79)	0.39
Sex, <i>n</i> (%)				
Male	15 (71.4)	7 (63.6)	8 (80)	0.63
Female	6 (28.6)	4 (36.4)	2 (20)	
Preoperative chemoradiation, <i>n</i> (%)	4 (19%)	0 (0%)	4 (40%)	0.03
Diagnosis, <i>n</i> (%)				
Corrosive ingestion with esophageal stricture	6 (28.6)	5 (45)	1 (10)	0.11
Carcinoma	12 (57.1)	4 (36.4)	8 (80)	
Tracheoesophageal fistula	3 (14.3)	2 (18.2)	1 (10)	
Smoking status				
Former, <i>n</i> (%)	7 (33.3)	2 (18.2)	5 (50)	0.18
Alcohol status				
Former, <i>n</i> (%)	3 (14.3)	1 (9.1%)	2 (20%)	0.58

Abbreviations: BMI, body mass index; SD, standard deviation.

TABLE 2. Operative data: supercharged colonic interposition.

Variable		n (%)
Recipient artery	Transverse cervical artery	9 (81.1)
	Internal mammary artery	0
	Superior thyroid artery	1 (9.1)
	Inferior thyroid artery	1 (9.1)
Recipient vein	External jugular vein	6 (54.5)
	Internal jugular vein	1 (9.1)
	Facial vein	1 (9.1)
	Inferior thyroid vein	1 (9.1)
	None	2 (18.2)
Pathway	Subcutaneous	11 (100)

TABLE 3. Operative data by surgical procedure.

	Supercharged colonic interposition (n = 11)	Gastric pull-up (n = 10)	P value
Operative time, h; median (range)	7.3 (5.3–15)	4.1 (3–7)	< 0.001
Estimated blood loss, mL; median (range)	925 (100–2000)	125 (50–500)	0.01
Length of ICU stay, days; median (range)	4 (3–8)	1 (0–10)	0.02
Hospitalization, days; median (range)	24 (14–115)	18.50 (5–58)	0.29

Abbreviation: ICU, intensive care unit.

TABLE 4. Complications, by surgical procedure.

	All patients (n = 21)	Supercharged colonic interposition (n = 11)	Gastric pull-up (n = 10)	P value
Medical complications, n (%)				
Pulmonary	6 (28.6)	4 (36.4)	2 (20)	0.63
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	
Vitamin D deficiency	6 (28.6)	5 (45.5)	1 (10)	0.14
Surgical complications, n (%)				
Anastomosis leak/fistula	3 (14.3)	2 (18.2)	1 (10.0)	1.00
Wound infection/dehiscence	2 (9.5)	1 (9.1)	1 (10)	1.00
Stricture	5 (23.8)	4 (36.4)	1 (10)	0.31
Gastroparesis, pyrospasm	1 (4.8)	0 (0.0)	1 (10)	0.47
Bowel obstruction	0 (0.0)	0 (0.0)	0 (0.0)	NA†
Dysphagia	1 (4.8)	0 (0.0)	1 (10)	NA†
Reflux	0 (0.0)	0 (0.0)	0 (0.0)	0.47

† “NA” indicates that the *P* values for bowel obstruction and dysphagia were not calculable due to zero events.

45.5% a soft diet. Tube feeding dependence was 27.3% in CI group vs 60.0% after GPU (Tables 5&6). Time to regular diet was longer after CI (median 50 vs 35 days). Overall survival at last follow-up was 71.4%, with deaths attributable to disease progression rather than surgical complications.

DISCUSSION

Selecting the optimal conduit for total oesophageal reconstruction remains a central challenge in upper gastrointestinal surgery, balancing operative complexity, vascular reliability, and long-term functional outcome.

Successful reconstruction requires not only restoration of gastrointestinal continuity but also preservation of functional swallowing and long-term nutritional status.¹ In this study, we describe our institutional experience with supercharged CI over a 10-year period, focusing on technical strategy, perioperative management, and functional outcomes. Our findings demonstrate that with a structured operative approach and multidisciplinary perioperative management, supercharged CI can achieve reliable graft viability and satisfactory functional recovery. Our current surgical technique modifies the traditional CI by using a longer ileal segment, typically 20–30 cm

TABLE 5. Summary of outcomes, by surgical procedure.

	Supercharged colonic interposition	Gastric pull-up	<i>P</i> value
Mortality, <i>n</i> (%)			
Mortality within 30 days	0 (0.0)	0 (0.0)	NA†
Mortality within 90 days	0 (0.0)	0 (0.0)	NA†
Time to oral intake, days; median (range)	20.5 (7–90)	7 (7–32)	0.76
Time to regular diet, days; median (range)	50 (18–480)	35 (20–180)	0.84
Length of follow-up, months; median (range)	21 (13–73)	9.5 (6–37)	0.03

† “NA” indicates that the *P* values for mortality within 30 days and 90 days were not calculable due to zero events.

TABLE 6. Functional outcomes, by surgical procedure.

	All patients (<i>n</i> = 21)	Supercharged colonic interposition (<i>n</i> = 11)	Gastric pull-up (<i>n</i> = 10)	<i>P</i> value
Diet at last follow-up, ≥ 6 months; <i>n</i> (%)				
NPO	2 (9.5)	0 (0.0)	1 (10.0)	0.23
Liquid	3 (14.3)	1 (9.0)	3 (30.0)	
Soft	7 (33.3)	5 (45.5)	2 (20.0)	
Solid	9 (42.9)	5 (45.5)	4 (40.0)	
Tube feed dependence, <i>n</i> (%)	9 (42.9)	3 (27.3)	6 (60.0)	0.19
Survival status, <i>n</i> (%)				
Alive	15 (71.4)	9 (81.8)	8 (80.0)	0.64
Dead from disease	6 (28.6)	2 (18.2)	2 (20.0)	

Abbreviation: NPO, nothing by mouth (nil per os).

from the IC valve of the terminal ileum, for oesophageal reconstruction (Fig 1). This approach facilitates microvascular blood augmentation through the supercharged technique. The longer ileal segment offers several advantages: First, its smaller size compared to the ascending colon in the neck improves aesthetic outcomes and results in no perceptible peristalsis, enhancing patient confidence. Second, using a longer terminal ileum segment avoids mobilising the transverse colon, which could compromise the blood supply. Third, in cases with severe intra-abdominal scarring from previous surgery, or when the right side branch of the middle colic artery limits colon conduit use, the longer ileal segment with supercharging overcomes these limitations. Lastly, a longer ileal segment can be anastomosed at the very proximal cervical level. In some cases, we performed the esophago-ileal anastomosis just distal to the pyriform sinus.

A key challenge in CI is maintaining adequate vascular perfusion of the conduit. The marginal blood supply of the colon, particularly at the proximal graft segment, has historically been associated with an increased risk of anastomotic leakage and graft necrosis.^{6,7} Microvascular supercharging has therefore been proposed to augment arterial inflow and improve conduit perfusion. Previous reports have demonstrated that vascular augmentation may reduce ischemia-related complications and improve graft survival.^{9–11} In our series, arterial supercharging was performed in all CI cases, as we increasingly preferred using the transverse cervical artery. This artery is located in the lower cervical area, usually away from the zone of previous oesophagostomy—typically performed in corrosive ingestion cases—and near where the donor vessels hang after ileo-esophagogastric anastomosis. A prior report from Thailand recommended using this artery as a long pedicle in a stable position for harvesting.¹³ When intraoperative congestion was observed, we also performed selective venous superdrainage. Notably, there were no instances of graft loss in our cohort, indicating that careful conduit selection combined with vascular augmentation may contribute to reliable conduit perfusion. The choice of conduit is another critical factor influencing outcomes in oesophageal reconstruction. GPU remains the most widely used reconstructive option due to its relative simplicity and dependable vascular supply.³ However, this technique may not be feasible in patients with prior gastrectomy, compromised gastric anatomy, or extensive oesophageal defects. In such cases, CI provides several physiological advantages, including adequate conduit length, orthodromic peristalsis, and reservoir capacity.^{4,5} In our institutional practice, CI is primarily reserved for patients in whom gastric reconstruction is

not possible. A structured conduit selection algorithm and careful operative planning enabled consistent functional outcomes, with all patients ultimately tolerating oral intake.

Another notable aspect of our technique is the subcutaneous route for conduit placement. Although the posterior mediastinal route has traditionally been used in oesophageal reconstruction, the subcutaneous pathway offers several practical advantages. This route facilitates postoperative monitoring of the conduit and allows early detection of graft compromise through clinical inspection.^{1,14} In addition, the subcutaneous route provides improved accessibility for microvascular anastomosis and may reduce operative complexity in patients with prior thoracic surgery or extensive mediastinal scarring. Our experience suggests that this approach is safe and allows reliable postoperative surveillance of the reconstructed conduit.

Despite favourable graft viability, postoperative complications remain a concern in complex oesophageal reconstruction. In our series, pulmonary complications were the most common early postoperative medical complication. Anastomotic leakage occurred in a minority of patients (2/11 CI and 1/10 GPU) but was managed without conduit loss. Oesophageal stricture was the most frequent late complication in the CI group; however, all strictures were successfully managed with endoscopic dilation. These findings are consistent with previous reports demonstrating that although strictures may occur following CI, most cases can be effectively treated with endoscopic intervention.⁴

Functional outcomes are an important measure of success following oesophageal reconstruction. In our cohort, all patients who underwent CI ultimately achieved oral intake, and a substantial proportion tolerated soft or solid diets at long-term follow-up. Although some patients required continued enteral supplementation, swallowing function was restored in most cases. These findings support previous studies demonstrating that colonic conduits can provide satisfactory long-term swallowing function and acceptable quality-of-life outcomes.^{5,12}

Nutritional considerations also represent an important aspect of postoperative care following oesophageal reconstruction. Patients undergoing complex gastrointestinal reconstruction may develop micronutrient deficiencies owing to altered absorption and gastrointestinal physiologic changes. Prior studies have reported deficiencies in vitamin B12, iron, calcium, and fat-soluble vitamins following oesophageal reconstruction.^{15,16} In our experience, we observed vitamin D deficiency in several patients following CI, and they required supplements, highlighting the

importance of long-term nutritional surveillance and appropriate supplementation. A more well-organised study should be conducted to explore this issue further. This study has several limitations. First, it is a retrospective, single-centre experience with a relatively small cohort. Second, conduit selection was influenced by underlying disease characteristics and prior surgical history, which introduces selection bias and precludes a direct head-to-head comparison between the two conduits. Third, functional outcomes were assessed primarily through routine clinical follow-up rather than standardised quality-of-life instruments. Despite these limitations, the series provides a detailed account of the technical strategy and perioperative management of supercharged CI within a structured institutional framework. Future multicentre studies with larger cohorts and longer follow-up are needed to refine patient-selection criteria and standardise outcome assessment with validated quality-of-life instruments.

CONCLUSIONS

In this 10-year experience, supercharged colonic interposition was associated with preserved graft viability and satisfactory functional recovery in patients requiring complex total oesophageal reconstruction.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request, in accordance with institutional data-sharing policies and patient confidentiality requirements.

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Conflict of Interest

The authors declare no conflicts of interest relevant to this manuscript.

Registration Number of Clinical Trial

Not applicable.

Author Contributions

Conceptualisation and methodology, S.C, P.K., N.Y., J.S. ; Investigation, S.C., N.Y., J.S. ; Data curation, S.C., P.K., S.A., N.Y., J.S. ; Formal analysis, S.C., P.K., S.A., N.Y., J.S. ; Writing - original draft, S.C., P.K., S.A., N.Y., J.S. ; Writing - review and editing, S.C., J.S. ; Supervision, J.S. ; Project administration, J.S. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

The author declares that no AI was used to produce the manuscript.

Institutional Review Board Statement

This study was approved by the Siriraj Institutional Review Board (Si 048/2025).

REFERENCES

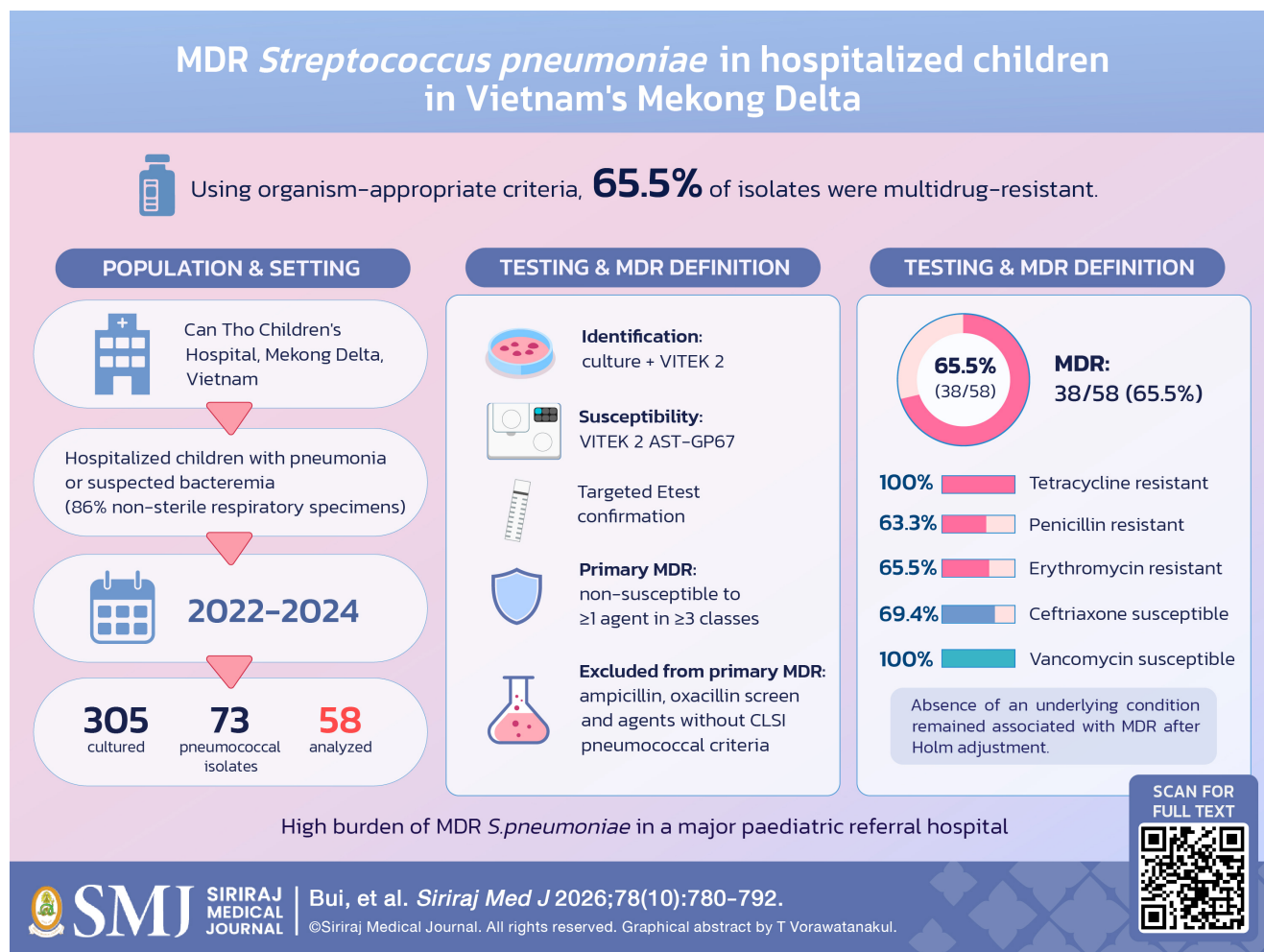
1. Markar S, Gronnier C, Duhamel A, Bigourdan JM, Badic B, du Rieu MC, et al. Pattern of postoperative mortality after esophageal cancer resection according to center volume: results from a large European multicenter study. *Ann Surg Oncol*. 2015;22(8):2615-23.
2. Abdel-Latif MM, O'Riordan J, Windle HJ, Carton E, Ravi N, Kelleher D, et al. NF-κB activation in esophageal adenocarcinoma: relationship to Barrett's metaplasia, survival, and response to neoadjuvant chemoradiotherapy. *Ann Surg*. 2004;239(4):491-500.
3. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies: changing trends, lessons learned. *Ann Surg*. 2007;246(3):363-74.
4. Irino T, Tsekrekos A, Coppola A, Scandavini CM, Shetye A, Lundell L, et al. Long-term functional outcomes after replacement of the esophagus with gastric, colonic, or jejunal conduits: a systematic literature review. *Dis Esophagus*. 2017;30(12):1-11.
5. Hamai Y, Hihara J, Emi M, Aoki Y, Okada M. Esophageal reconstruction using the terminal ileum and right colon in esophageal cancer surgery. *Surg Today*. 2012;42(4):342-50.
6. O'Rourke IC, Threlfall GN. Colonic interposition for oesophageal reconstruction with special reference to microvascular reinforcement of graft circulation. *Aust N Z J Surg*. 1986;56(10):767-71.
7. Shirakawa Y, Naomoto Y, Noma K, Sakurama K, Nishikawa T, Nobuhisa T, et al. Colonic interposition and supercharge for esophageal reconstruction. *Langenbecks Arch Surg*. 2006;391(1):19-23.
8. Marchi F, Kang SC, Cheong DCF, Hung SY, Wang SH, Chiu TH, et al. The benefits of the supercharged ileocolic flap in patients who underwent total esophagectomy and gastrectomy. *J Reconstr Microsurg*. 2021;37(6):475-85.
9. Mays AC, Yu P, Hofstetter W, Liu J, Xue A, Klebuc M, et al. The supercharged pedicled jejunal flap for total esophageal reconstruction: a retrospective review of 100 cases. *Plast Reconstr Surg*. 2019;144(5):1171-80.

10. Barzin A, Norton JA, Whyte R, Lee GK. Supercharged jejunum flap for total esophageal reconstruction: single-surgeon 3-year experience and outcomes analysis. *Plast Reconstr Surg*. 2011; 127(1):173-80.
11. Chen HC, Tang YB, eds. *Microsurgical reconstruction of the esophagus*. Semin Surg Oncol. 2000; Wiley Online Library.
12. Greene CL, DeMeester SR, Augustin F, Worrell SG, Oh DS, Hagen JA, et al. Long-term quality of life and alimentary satisfaction after esophagectomy with colon interposition. *Ann Thorac Surg*. 2014;98(5):1713-20.
13. Awsakulsutthi S. Result of esophageal reconstruction using supercharged interposition colon in corrosive and Boehave's injury: Thammasat University Hospital experience. *J Med Assoc Thai*. 2010;93 Suppl 7:S303-6.
14. Chung JH, Lee SH, Yi E, Jung JS, Han JW, Kim TS, et al. A non-randomized retrospective observational study on the subcutaneous esophageal reconstruction after esophagectomy: is it feasible in high-risk patients? *J Thorac Dis*. 2017;9(3):675.
15. Blonk L, Gooszen J, Fakkert R, Eshuis WJ, Rietveld SCM, Wierdsma NJ, et al. Micronutrient deficiencies and anemia in the follow-up after gastroesophageal cancer surgery. *Dis Esophagus*. 2024;37(11):doae053.
16. Gonggetyai G, Techalertsuwan N, Nampoolsuksan C, Parakonthun T, Swangsri J, Methasate A, et al. Frailty and Upper Gastrointestinal Surgery: Initial Findings from Thailand's First Surgical Frailty Study. *Siriraj Med J [Internet]*. 2025 Aug. 1 [cited 2026 Sep. 12];77(8):574-82.

Antimicrobial Susceptibility and Multidrug Resistance among *Streptococcus pneumoniae* Isolates from Predominantly Non-Sterile Respiratory Specimens in Children Hospitalized with Pneumonia or Suspected Bacteremia in the Mekong Delta, Vietnam, 2022–2024: A Hospital-Based Cross-Sectional Study

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ABSTRACT

Objective: To characterize antimicrobial susceptibility and multidrug resistance (MDR) among *Streptococcus pneumoniae* isolates from children hospitalized with pneumonia or suspected bacteremia in Vietnam's Mekong Delta and explore factors associated with MDR.

Materials and Methods: This cross-sectional study included children aged 2 months–15 years with culture-confirmed *S. pneumoniae* and susceptibility results at a tertiary pediatric hospital during 2022–2024. Identification used conventional methods and VITEK 2 Compact; susceptibility testing used VITEK 2 AST-GP67, Etest when indicated, and contemporaneous CLSI M100 criteria. MDR was defined as non-susceptibility to ≥ 1 agent in ≥ 3 classes with an independent pneumococcal CLSI criterion; screening tests and non-independent results (including surrogate ampicillin) were excluded. Associations were explored using Fisher's exact test with Holm adjustment.

Results: Among 58 children, 38 (65.5%, 95% CI 52.7–76.4) had MDR isolates. Resistance was 100% to tetracycline, 65.5% to erythromycin, 63.3% to penicillin, and 52.2% to cefepime. Ceftriaxone was susceptible in 25/36 isolates (69.4%); all 58 isolates were vancomycin-susceptible. MDR occurred in 5/8 blood isolates and 33/50 nasopharyngeal aspirate isolates, reported descriptively. Absence of an underlying condition was associated with MDR after Holm adjustment (adjusted $P=0.020$); vaccination was not (adjusted $P=0.367$). Risk-factor analyses were exploratory and underpowered (20 non-MDR isolates).

Conclusion: MDR *S. pneumoniae* was common in this referral population. Because most isolates came from non-sterile respiratory specimens and testing was clinically directed, the 65.5% estimate should be interpreted as institution-level surveillance conditional on the observed testing panel rather than an unbiased population prevalence.

Keywords: *Streptococcus pneumoniae*; Drug resistance, multiple, bacterial; Child, hospitalized; Pneumococcal vaccines; Vietnam (MeSH terms) (Siriraj Med J 2026;78(10):780-792)

INTRODUCTION

Streptococcus pneumoniae remains one of the leading bacterial causes of pneumonia, bacteremia, and meningitis in children worldwide, and it was the leading pathogen attributed to lower respiratory infection deaths in children younger than 5 years in the Global Burden of Disease Study 2021.¹ Antimicrobial resistance in this organism has narrowed the range of reliable empirical options and is recognized by the World Health Organization as a medium-priority pathogen for research and development and surveillance in the 2024 Bacterial Priority Pathogens List.²

Because pneumococcal resistance is driven by locally circulating clones, local antimicrobial pressure, and the composition of the referral population, resistance profiles differ substantially between countries, between hospitals within a country, and between time periods.³ Institution-level surveillance is therefore not a duplication of national data but a prerequisite for rational empirical prescribing at the bedside. Vietnamese national hospital-based surveillance through VINARES likewise documented high and heterogeneous antimicrobial resistance across 13 hospitals in 2016–2017, including pneumococcal resistance indicators.⁴ These national data predate the present study period and do not substitute for contemporary

institution-level pediatric *S. pneumoniae* surveillance in the Mekong Delta.

Vietnam carries a heavy pediatric pneumonia burden, and throughout the 2022–2024 observation period the pneumococcal conjugate vaccine (PCV) was not part of the national Expanded Program on Immunization; PCV10 and PCV13 were obtainable only through fee-based private immunization services from 2014 and 2019, respectively, resulting in low and socially patterned coverage.⁵ Phased public-sector introduction has been initiated only after the period covered by this study, so our findings describe a wholly PCV-naïve programmatic context. Contemporary hospital-level susceptibility data from the Mekong Delta, a region of approximately 17 million people served by a single tertiary pediatric referral center, remain scarce. The most recent dataset from this region was restricted to children with severe pneumonia⁶ and Vietnamese studies that formally quantify multidrug-resistant (MDR) *S. pneumoniae* and examine its correlates are few.^{7,8}

We therefore conducted a hospital-based cross-sectional study with two objectives: (i) to describe the antimicrobial susceptibility profile and the prevalence of MDR among *S. pneumoniae* isolated from children hospitalized at the study hospital between 2022 and 2024;

and (ii) to explore, in a hypothesis-generating manner, demographic and clinical characteristics associated with MDR status.

MATERIALS AND METHODS

This study was approved by the Biomedical Research Ethics Committee of Can Tho University of Medicine and Pharmacy (approval no. 23.101.SV/PCT-HĐĐĐ, 25 December 2023; study code 23.KY.042) and was authorized by the Director of Can Tho Children's Hospital. It was conducted at Can Tho Children's Hospital, the tertiary pediatric referral center for the Mekong Delta region of southern Vietnam. Case ascertainment combined a retrospective phase (1 January 2022 to 31 December 2023), based on review of laboratory and medical records, and a prospective phase (1 January to 31 December 2024), during which eligible children were enrolled at the time of culture confirmation. The ethics approval explicitly covered retrospective review of medical and laboratory records and of stored isolate data for the 2022–2023 period; no retrospective record was accessed before the date of approval. The requirement for individual informed consent was waived for the retrospective component on the grounds that the data were de-identified and the research posed no more than minimal risk. For the prospective component, written informed consent was obtained from a parent or legal guardian of every child, and age-appropriate assent was obtained from children aged 7 years and older. The study is reported in accordance with the STROBE statement for cross-sectional studies⁹, supplemented, where applicable, by the STROBE-AMS extension for epidemiological studies of antimicrobial resistance¹⁰; a completed STROBE-AMS checklist is provided as Supplementary Material.

During 2022–2024, no pneumococcal outbreak, pneumococcus-specific infection-control change, formal hospital-wide antimicrobial stewardship program, antimicrobial restriction policy, or formulary change was identified; routine standard precautions remained unchanged throughout the study period.

Participants

Using total population sampling, we included every hospitalized child aged 2 months to 15 years with (i) a clinical diagnosis of pneumonia or suspected bacteremia assigned by the treating pediatric team at admission, (ii) a culture-confirmed *S. pneumoniae* isolate from any specimen source, and (iii) an available antimicrobial susceptibility result. Diagnostic syndrome and microbiological specimen source were recorded independently. Suspected bacteremia denoted the clinical syndrome prompting blood-culture

collection and did not require a subsequently positive culture; only 4 of the 12 children with suspected bacteremia had *S. pneumoniae* recovered from blood, whereas the remaining 8 had the organism recovered only from a respiratory specimen. Children with a documented primary or secondary immunodeficiency, and those receiving immunosuppressive therapy, were excluded. This exclusion was prespecified because immunosuppression is an established risk factor for carriage of resistant pneumococci and we sought to characterize resistance in the general pediatric inpatient population; we acknowledge that it reduces the representativeness of a tertiary referral series and is likely to bias the MDR estimate downward. Only the first isolate per child was analyzed.

Both diagnoses were assigned by attending pediatric specialists (Specialist Level I or II, or Master of Pediatrics). Pneumonia was diagnosed according to Vietnam Ministry of Health pediatric guidance (Decision 4239/QĐ-BYT) together with WHO clinical-radiographic criteria³, requiring acute respiratory symptoms, age-specific tachypnea or chest indrawing, crackles on auscultation, and chest-radiographic parenchymal infiltrate or consolidation. Suspected bacteremia was defined under the hospital systemic-infection work-up protocol by fever $\geq 38.5^{\circ}\text{C}$ or hypothermia $< 36.0^{\circ}\text{C}$ together with systemic inflammatory or impaired-perfusion signs (including capillary refill > 2 s), lethargy, unusual irritability, or poor feeding, accompanied by elevated C-reactive protein or procalcitonin; meeting these criteria prompted blood-culture collection and did not itself establish culture-confirmed bacteremia.

No a priori sample-size calculation governed recruitment. All eligible isolates identified during the study period were included, and statistical precision is reported post hoc as 95% confidence intervals for all proportions.

Microbiological methods

Respiratory specimens were nasopharyngeal aspirates (NPA); the term “nasotracheal aspirate” used in the original submission was incorrect and has been corrected after verification with the Microbiology Department. NPA was obtained by passing a sterile flexible suction catheter (6–8 Fr) through the nostril to the posterior nasopharynx, using the nostril-to-earlobe distance as the insertion guide, at a suction pressure of approximately 80–120 mmHg with gentle catheter rotation, and collecting the aspirate into a sterile specimen trap. Blood was collected by sterile venipuncture. Sampling was prioritized before the first antimicrobial dose administered at the study hospital; antimicrobial treatment received at a referring facility was documented in the admission

record. Specimen adequacy was assessed by direct Gram stain at low-power examination (10× objective; 100× total magnification) using modified Bartlett/Murray–Washington criteria. A specimen was accepted for culture only when it contained <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per low-power field. Specimens failing either criterion were rejected before culture and repeat sampling was requested; therefore, all respiratory isolates included in the study derived from specimens meeting these criteria. Because rejection occurred before culture and study eligibility, the number of rejected specimens was not captured and cannot be reconstructed. Pneumococcal growth was considered clinically relevant when *S. pneumoniae* was recovered in pure culture or as clearly predominant growth and was concordant with Gram-positive diplococci or short chains and inflammatory cells on the original smear. Where investigated, viral co-pathogens (respiratory syncytial virus, influenza, adenovirus, rhinovirus) and bacterial co-pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*) were recorded separately using multiplex real-time PCR and/or parallel culture.

Isolates were identified by Gram stain, colony morphology on 5% sheep blood agar, optochin susceptibility, and the VITEK 2 Compact system (bioMérieux, Marcy-l'Étoile, France). Routine antimicrobial susceptibility testing was performed with the VITEK 2 AST-GP67 card (bioMérieux). Quantitative minimum inhibitory concentration (MIC) confirmation by gradient diffusion (Etest, bioMérieux) was performed for penicillin and for cefotaxime or ceftriaxone when the oxacillin 1 µg screening zone diameter was <20 mm, and for other clinically important isolates requiring confirmatory MIC assessment. Oxacillin 1 µg disk diffusion was used solely as a screen for penicillin non-susceptibility: a zone diameter <20 mm was recorded as a positive screen requiring confirmatory penicillin MIC testing and was never interpreted as oxacillin resistance. Results were interpreted using the Clinical and Laboratory Standards Institute (CLSI) M100 edition current in each study year, 32nd edition for 2022, 33rd edition for 2023, and 34th edition for 2024¹¹, applying parenteral non-meningitis criteria for penicillin (susceptible ≤2, intermediate 4, resistant ≥8 µg/mL) and for cefotaxime and ceftriaxone (susceptible ≤1, intermediate 2, resistant ≥4 µg/mL), because no child had meningitis and no cerebrospinal fluid isolate was included; oral penicillin V criteria were not applied to any isolate. This is also the convention recommended by WHO for pneumococcal surveillance reporting, in which non-meningitis breakpoints are applied when isolates are interpreted without a meningitis

designation.³ *Streptococcus pneumoniae* ATCC 49619 served as the quality-control strain. Quality control for disk and gradient diffusion was performed weekly once satisfactory performance had been documented on 20–30 consecutive days, and each new VITEK 2 card lot underwent lot-to-lot verification. Quality-control records for 2022–2024 are retained by the laboratory. The CLSI M100 Table 2G criterion, measurement, breakpoint, and study-year edition applied to each reportable agent are documented in [Supplementary Table S4](#). The original quantitative measurements, however, could not be retrieved for this analysis: neither numerical MIC values nor inhibition-zone diameters were transferred to the study database, and only the categorical interpretations issued by the clinical laboratory at the time of testing — susceptible, intermediate or resistant, and screen-positive or screen-negative for oxacillin — were available. These categorical data are therefore treated as legacy laboratory reports rather than a re-verifiable primary-data susceptibility dataset: they derive from contemporaneous interpretations made under the CLSI edition in force in each study year, and retrospective re-interpretation or independent re-derivation from raw measurements was not possible. [Supplementary Table S2](#) summarizes the testing workflow, interpretive standard, and quality-control procedures by study year.

The panel comprised 16 agents and was selected by the treating team according to clinical syndrome and specimen type; consequently, not every isolate was tested against every agent, and susceptibility proportions are reported with agent-specific denominators and 95% confidence intervals. CLSI M100 does not provide applicable *S. pneumoniae* interpretive criteria for ceftazidime, gentamicin, ciprofloxacin, or ofloxacin in the editions used; oxacillin is a 1 µg screening test for penicillin non-susceptibility rather than a therapeutic susceptibility category. These legacy outputs have therefore been removed from the main susceptibility analysis and are retained only as non-interpretive audit labels in [Supplementary Table S3](#). Ampicillin was also excluded from the independently interpretable panel and primary MDR algorithm because its categorical result was a surrogate interpretation derived from penicillin rather than an independent pneumococcal breakpoint; its historical surrogate labels are reported only for audit purposes in [Supplementary Table S3](#).

Definitions and variables

MDR was defined as non-susceptibility (intermediate or resistant) to at least one agent in three or more antimicrobial classes with recognized antipneumococcal activity and an independent applicable CLSI *S. pneumoniae* interpretive

criterion. The ≥ 3 -class threshold follows the resistant-only convention used in the multinational ANSORP pneumococcal surveillance study, in which MDR was defined as resistance to at least three antibiotic classes¹², and is consistent with a subsequent pneumococcus-specific synthesis defining MDR as resistance to three or more antimicrobial classes.¹³ Our primary definition deliberately broadens that resistant-only convention by counting intermediate results as non-susceptible; the resistant-only definition is therefore reported separately as a sensitivity analysis. The consensus definition of Magiorakos et al. cited in the original submission was not applied because it does not provide an organism-specific classification scheme for pneumococci. The seven evaluable classes were penicillins (penicillin only), extended-spectrum cephalosporins (cefuroxime, cefotaxime, ceftriaxone, cefepime), macrolides (erythromycin), lincosamides (clindamycin), phenicols (chloramphenicol), tetracyclines (tetracycline), and glycopeptides (vancomycin). Ampicillin, the oxacillin screen, ceftazidime, gentamicin, ciprofloxacin, and ofloxacin were excluded from the primary MDR algorithm.

A class not tested for a given isolate was treated as missing and was never imputed as susceptible. Isolates with fewer than three evaluable classes would have been excluded from the MDR analysis; no isolate met this criterion. Testing intensity and the complete isolate-level classification for all 58 isolates are provided in [Supplementary Table S1](#). Classification as MDR is robust once ≥ 3 non-susceptible evaluable classes are observed, but classification as non-MDR is conditional on the observed panel because additional untested classes could have been non-susceptible. This verification bias can therefore miss MDR but cannot create a false MDR classification; the primary prevalence is presented as a conservative floor conditional on the clinically directed testing panel, not as an unbiased population prevalence. Four prespecified sensitivity analyses were examined: (1) intermediate results counted as susceptible; (2) the broader nine-category protocol definition; (3) isolates tested against < 5 of the seven evaluable classes reclassified as indeterminate; and (4) non-MDR status accepted only when the observed non-susceptible classes plus all untested classes could not reach the three-class threshold.

Explanatory variables were extracted from medical records using a standardized form: age group, sex, admitting ward (respiratory medicine versus intensive/critical care), presence of any underlying condition, documented antibiotic use in the 30 days before admission, and prior pneumococcal vaccination. Vaccination status

was ascertained from the immunization record when available and otherwise from caregiver report, and was analyzed dichotomously (any documented or reported PCV dose versus none); vaccine product, dose number, dates and schedule completeness were not systematically recorded. Documented antimicrobial exposure in the 30 days before admission was abstracted from the medical record, including treatment documented before referral or transfer where available. Length of hospital stay was defined as the interval in days from admission to discharge, and duration of antimicrobial therapy was recorded separately as the number of days of in-hospital antimicrobial treatment.

Statistical analysis

Categorical variables are summarized as counts and percentages, and continuous variables as medians with interquartile ranges (IQR). Proportions are presented with 95% Wilson score confidence intervals. Associations between candidate variables and MDR status were assessed using Fisher's exact test, with unadjusted odds ratios (OR) and 95% confidence intervals (CI) estimated by the Woolf method with the Haldane–Anscombe correction where a cell contained zero. Length of hospital stay and duration of antimicrobial therapy were compared using the Mann–Whitney U test because subgroup sizes were small and distributions were skewed. Because six comparisons were performed, P values were additionally adjusted for multiplicity using the step-down Holm procedure computed from full-precision (unrounded) P values, and interpretation is based on the adjusted values. With only 20 non-MDR isolates, multivariable modeling was not attempted; all association analyses are exploratory, unadjusted for confounding, and hypothesis-generating rather than confirmatory. Analyses were performed in IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study flow

During the study period the microbiology register identified 305 children who underwent respiratory or blood culture, of whom 73 had a culture-confirmed *S. pneumoniae* isolate. Fifteen children were excluded: repeat isolates from the same treatment episode ($n = 8$), documented immunodeficiency or immunosuppressive therapy ($n = 5$), and incomplete susceptibility results ($n = 2$); no child was excluded because the medical record was unavailable. Fifty-eight children, each contributing a single isolate, formed the analytic sample ([Fig 1](#)).

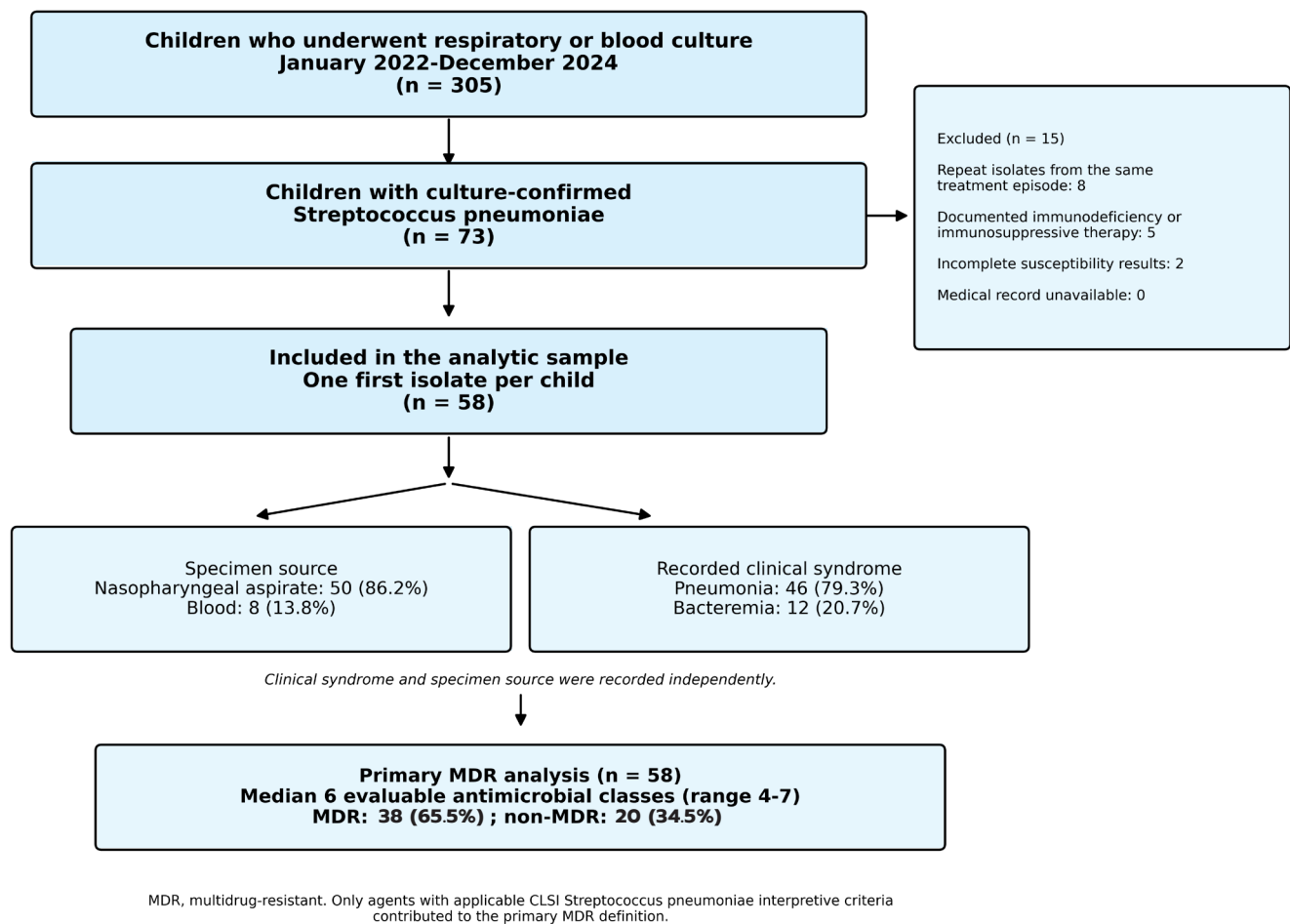


Fig 1. Study flow diagram showing participant selection and primary multidrug-resistance classification of the analytic sample (n = 58)

Characteristics of the study population

Fifty-eight children met the eligibility criteria (Table 1). The median age was 31 months (IQR 14–60); 26 children (44.8%) were younger than 2 years, and 33 (56.9%) were male. Pneumonia accounted for 46 cases (79.3%) and suspected bacteremia for 12 (20.7%); fifty isolates (86.2%) were recovered from nasopharyngeal aspirates and 8 (13.8%) from blood. Clinical syndrome and specimen source were recorded independently and were not concordant: four children with pneumonia had a positive blood culture, representing bacteremic pneumococcal pneumonia, whereas only 4 of the 12 children with suspected bacteremia (33.3%) had a positive blood culture; the remaining 8 had *S. pneumoniae* recovered only from a respiratory specimen and did not have culture-confirmed bacteremia. Five children (8.6%) had an underlying condition (congenital heart disease, n = 3; malnutrition, n = 2), 16 (27.6%) had received an antibiotic in the 30 days before admission, 17 (29.3%) had a history of pneumococcal vaccination, and 14 (24.1%) were admitted to intensive or critical care. Median length

of hospital stay was 10 days (IQR 7–14) and median duration of antimicrobial therapy 9.5 days (IQR 7–12).

Antimicrobial susceptibility

Resistance was frequent across most classes with applicable interpretive criteria (Table 2). Because the testing panel was selected by the treating team according to clinical syndrome and specimen type rather than applied uniformly to every isolate, agent-specific denominators varied widely (range 21–58 isolates tested), and estimates from different agents are not directly comparable. All 32 isolates tested against tetracycline were resistant (100%). Resistance was also frequent for erythromycin (36/55, 65.5%), penicillin (31/49, 63.3%), and cefepime (12/23, 52.2%). Surrogate ampicillin labels, the oxacillin screen, and historical outputs for agents without applicable pneumococcal interpretive criteria are reported only in Supplementary Table S3 and were excluded from the primary MDR classification.

Among cephalosporins with established CLSI interpretive criteria, ceftriaxone was susceptible in 25

TABLE 1. Baseline characteristics of the 58 children with a culture-confirmed *Streptococcus pneumoniae* isolate.

Characteristic	Total group (n = 58)
Age, months, median (IQR)	31 (14–60)
<2 years	26 (44.8)
2–5 years	18 (31.0)
>5 years	14 (24.1)
Male sex	33 (56.9)
Clinical syndrome: pneumonia	46 (79.3)
Clinical syndrome: suspected bacteremia	12 (20.7)
Specimen: nasopharyngeal aspirate	50 (86.2)
Specimen: blood	8 (13.8)
Pneumonia with positive blood culture	4 (6.9)
Suspected bacteremia with positive blood culture (confirmed)	4 (6.9)
Suspected bacteremia without positive blood culture (clinical only)	8 (13.8)
Underlying condition present	5 (8.6)
Congenital heart disease	3 (5.2)
Malnutrition	2 (3.4)
Prior pneumococcal vaccination	17 (29.3)
Antibiotic use within 30 days before admission	16 (27.6)
Admission to intensive/critical care unit	14 (24.1)
Length of hospital stay, days, median (IQR)	10 (7–14)
Duration of antimicrobial therapy, days, median (IQR)	9.5 (7–12)

Percentages are based on $n = 58$ unless otherwise indicated. Clinical syndrome (pneumonia vs suspected bacteremia) and specimen source (nasopharyngeal aspirate vs blood) were recorded independently and are not interchangeable; suspected bacteremia was microbiologically confirmed by a positive blood culture in only 4 of 12 cases (33.3%).

Abbreviation: IQR, interquartile range

of 36 isolates (69.4%, 95% CI 53.1–82.0), cefuroxime in 30 of 47 (63.8%, 95% CI 49.5–76.0), cefotaxime in 7 of 21 (33.3%), and cefepime in 10 of 23 (43.5%). Because these agents were tested in different, clinically selected subsets rather than a common panel, these are agent-specific descriptive estimates and do not support a cross-agent ranking of activity. Chloramphenicol resistance was 32.0% (8/25), clindamycin resistance was 39.7% (23/58), and all 58 isolates tested against vancomycin were susceptible.

Multidrug resistance and associated factors

Isolates were tested against a median of 11 antimicrobial agents (range 6–15), corresponding to a median of 6

evaluable classes (range 4–7) under the primary definition. Thirty-eight of 58 isolates (65.5%, 95% CI 52.7–76.4) met the primary MDR definition; this estimate is conditional on the observed testing panel and should be regarded as a conservative floor. MDR prevalence was 62.1% (36/58; 95% CI 49.2–73.4) when intermediate results were counted as susceptible and 89.7% (52/58; 95% CI 79.2–95.2) under the broader nine-category protocol definition (Table 4). When the 4 isolates tested against fewer than five of the seven evaluable classes were reclassified as indeterminate, prevalence among the remaining 54 isolates was 70.4% (38/54; 95% CI 57.2–80.9). Under the stricter logical criterion, 9 isolates were definitively non-MDR and 11 were indeterminate; restricting the denominator to the

TABLE 2. Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates, 2022–2024.

Antimicrobial agent	No. tested	Susceptible, n (%)	Intermediate, n (%)	Resistant, n (%)
A. Reportable susceptibility results — agents with applicable CLSI <i>S. pneumoniae</i> interpretive criteria				
Penicillin	49	18 (36.7)	0 (0.0)	31 (63.3)
Cefuroxime	47	30 (63.8)	0 (0.0)	17 (36.2)
Cefotaxime	21	7 (33.3)	6 (28.6)	8 (38.1)
Ceftriaxone	36	25 (69.4)	0 (0.0)	11 (30.6)
Cefepime	23	10 (43.5)	1 (4.3)	12 (52.2)
Erythromycin	55	14 (25.5)	5 (9.1)	36 (65.5)
Clindamycin	58	31 (53.4)	4 (6.9)	23 (39.7)
Chloramphenicol	25	17 (68.0)	0 (0.0)	8 (32.0)
Tetracycline	32	0 (0.0)	0 (0.0)	32 (100.0)
Vancomycin	58	58 (100.0)	0 (0.0)	0 (0.0)
B. Screening test — not a therapeutic susceptibility category				
Oxacillin 1 µg screen	45	Screen-negative: 7 (15.6)		Screen-positive: 38 (84.4)

Denominators vary because testing was clinically directed; percentages are based on the number tested, and agent-specific estimates are descriptive and not directly comparable. Table 2 includes only agents with an independent applicable CLSI *S. pneumoniae* interpretive criterion plus the oxacillin screening test. Surrogate ampicillin labels and historical outputs for ceftazidime, gentamicin, ciprofloxacin, and ofloxacin are reported only in Supplementary Table S3 and were excluded from primary MDR classification. For vancomycin, CLSI provides only a susceptible MIC breakpoint (≤ 1 µg/mL); intermediate and resistant categories are not applicable.

TABLE 3. Susceptibility and multidrug resistance by specimen source.

Outcome	Blood isolates (n = 8)	Nasopharyngeal aspirate isolates (n = 50)
MDR, primary definition	5 (62.5)	33 (66.0)
Penicillin susceptible	3/6 (50.0)	15/43 (34.9)
Ceftriaxone susceptible	4/6 (66.7)	21/30 (70.0)
Erythromycin susceptible	3/8 (37.5)	11/47 (23.4)
Vancomycin susceptible	8/8 (100.0)	50/50 (100.0)

Denominators vary by agent because testing was clinically directed. Blood isolates (n = 8) are presented descriptively only; no comparative inference or claim of equivalence is made from this subgroup.

Abbreviation: MDR, multidrug-resistant

TABLE 4. Prevalence of multidrug resistance under the primary definition and prespecified sensitivity analyses (n = 58).

MDR definition	MDR / total	Prevalence, %	95% CI
Primary: non-susceptibility to ≥ 3 classes with an independent applicable pneumococcal criterion	38/58	65.5	52.7–76.4
Sensitivity 1: intermediate counted as susceptible	36/58	62.1	49.2–73.4
Sensitivity 2: broader nine-category scheme used in the original protocol	52/58	89.7	79.2–95.2
Sensitivity 3: isolates tested against < 5 of 7 evaluable classes reclassified as indeterminate	38/54	70.4	57.2–80.9
Sensitivity 4: definitive non-MDR only where untested classes could not alter the call	38/47	80.9	67.5–89.6

Wilson 95% CIs are shown. Penicillins contribute to the primary definition through penicillin only; surrogate ampicillin results, the oxacillin screen, ceftazidime, aminoglycosides, and fluoroquinolones are counted only in the broader protocol sensitivity analysis. In Sensitivity 3, four isolates tested against fewer than five of seven evaluable classes were reclassified as indeterminate. In Sensitivity 4, non-MDR status required that observed non-susceptible classes plus all untested classes could not reach three; 9 isolates were non-MDR and 11 were indeterminate. Isolate-level classifications are provided in Supplementary Table S1.

Abbreviations: CI, confidence interval; MDR, multidrug-resistant

47 determinate isolates yielded 80.9% MDR (38/47; 95% CI 67.5–89.6).

MDR occurred in 5 of 8 blood isolates (62.5%) and 33 of 50 nasopharyngeal aspirate isolates (66.0%) (Table 3). These results are presented descriptively only; with only eight blood isolates, no comparative inference or claim of equivalence is made. Median length of hospital stay was 9.5 days (IQR 7–14) in children with MDR isolates and 10 days (IQR 7.5–13) in those with non-MDR isolates ($P = 0.95$); median duration of antimicrobial therapy was 8.5 days (IQR 7–12) and 10 days (IQR 7–11), respectively ($P = 0.91$).

In exploratory unadjusted analyses (Table 5), absence of a documented underlying condition was the only characteristic associated with MDR status after Holm correction for the six comparisons. None of the five children with an underlying condition had an MDR isolate, compared with 38 of 53 children without one (OR 0.04, 95% CI 0.002–0.70; unadjusted $P = 0.0034$; Holm-adjusted $P = 0.020$). This estimate is fragile because it is anchored by a zero cell in a group of only five children. Pneumococcal vaccination was not associated with MDR after correction (8/17 vs 30/41; OR 0.33, 95% CI 0.10–1.06; unadjusted $P = 0.073$; Holm-adjusted $P = 0.367$). Age

group, sex, admitting ward, and antibiotic use in the preceding 30 days were not associated with MDR status.

DISCUSSION

In this three-year, single-center series of *S. pneumoniae* isolates from hospitalized children in the Mekong Delta, approximately two in three isolates were multidrug-resistant under an organism-appropriate definition restricted to agents with an independent pneumococcal interpretive criterion, resistance to tetracycline was universal, and resistance to penicillin and erythromycin each exceeded 60%. Vancomycin retained complete in vitro activity. A central methodological finding is that the MDR estimate moved from 89.7% under the broader protocol definition to 65.5% under the primary definition when surrogate and non-interpretable results were excluded, underscoring the importance of a transparent organism-specific MDR algorithm.

The resistance profile for penicillin, oxacillin, and erythromycin is broadly consistent with earlier Vietnamese data and with reports from elsewhere in East and Southeast Asia, a region that has long carried among the highest pneumococcal resistance burdens globally.^{6,14–18} The MDR prevalence of 65.5% falls within the range of published

TABLE 5. Exploratory unadjusted analysis of characteristics associated with multidrug-resistant status (n = 58).

Characteristic	MDR, n (%)	Non-MDR, n (%)	Unadjusted OR (95% CI)	P value	Holm-adjusted P
Age ≤5 years (vs >5 years)	29 (65.9)	15 (34.1)	1.07 (0.31–3.78)	1.000	1.000
Male sex (vs female)	24 (72.7)	9 (27.3)	2.10 (0.70–6.30)	0.265	1.000
Respiratory ward (vs ICU)	29 (65.9)	15 (34.1)	1.07 (0.31–3.78)	1.000	1.000
Underlying condition (vs none)	0 (0.0)	5 (100.0)	0.04 (0.00–0.70)	0.003	0.020
Antibiotic use ≤30 days (vs none)	11 (68.8)	5 (31.2)	1.22 (0.36–4.19)	1.000	1.000
Pneumococcal vaccination (vs none)	8 (47.1)	9 (52.9)	0.33 (0.10–1.06)	0.073	0.367

Percentages are row percentages. ORs compare each category with the reference shown in parentheses; Haldane–Anscombe correction was used for zero cells. P values are from two-sided Fisher exact tests; Holm-adjusted values use the step-down Holm procedure for six comparisons computed from full-precision (unrounded) P values. The association involving underlying condition is anchored by a zero cell in only five children and should be interpreted cautiously; no other association remained significant after multiplicity adjustment.

Abbreviations: CI, confidence interval; ICU, intensive/critical care unit; MDR, multidrug-resistant; OR, odds ratio

estimates from the region, although direct comparison is limited by differences in isolate selection and susceptibility panels. Three explanations are plausible and mutually compatible. First, as the sole tertiary referral center for the region, our hospital receives children who have often failed community treatment, enriching the sample for resistant organisms. Second, antimicrobials remain widely available without prescription in Vietnam, and more than a quarter of our patients had documented antibiotic exposure in the preceding month. The same pattern has been described in neighbouring Thailand, where antimicrobial dispensing by drug stores outside formal prescription is common and frequently directed at self-limiting illnesses, and where short courses of antimicrobials in primary care have been shown to select for resistance in the treated individual for up to a year.¹⁹ Third, the highly resistant clones and serotypes described across the region, notably 19A and 19F, are known to circulate in Vietnam.^{5,17,20} None of these mechanisms was measured directly here, and our estimate should be read as descriptive rather than explanatory. Comparison with previously published Vietnamese estimates approaching 100% must also be made with caution, because those series applied broader and largely undocumented agent panels; the incomparability is itself a finding that argues for a standardized surveillance panel. The same problem is documented at global scale: among countries reporting to the WHO Global Antimicrobial Resistance and Use

Surveillance System, both the isolates selected for testing and the agents included vary widely, which limits the comparability of resistance estimates between settings.³

Two aspects of the susceptibility profile carry stewardship implications, framed here as surveillance and laboratory-practice observations rather than treatment guidance. No vancomycin non-susceptibility was detected; this finding does not establish an empirical-treatment recommendation. Ceftazidime has no applicable *S. pneumoniae* interpretive criterion in the CLSI M100 editions used.¹¹ Accordingly, as a laboratory-stewardship measure, routine ceftazidime testing or interpretation for *S. pneumoniae* should be avoided, and its continued presence in local pneumococcal panels should be reconsidered by the laboratory.

Ceftriaxone susceptibility was 69.4% (25/36; 95% CI 53.1–82.0). This agent-specific estimate is not directly comparable with the other cephalosporin percentages because the agents were tested in different, clinically selected subsets. We deliberately refrain from translating it into an empirical-therapy recommendation. Susceptibility testing was clinically directed rather than protocol-driven, and 22 of 58 isolates were not tested against ceftriaxone; empirical regimen selection also requires consideration of clinical syndrome, disease severity, dosing, the possibility of meningitis, and current national and institutional guidance, none of which this study was designed to evaluate.

Fewer MDR isolates were recovered from previously vaccinated children (8/17, 47.1%) than from unvaccinated children (30/41, 73.2%), but this association did not survive multiplicity adjustment (OR 0.33, 95% CI 0.10–1.06; Holm-adjusted $P = 0.367$) and is not presented as a positive finding. A protective direction is biologically coherent because conjugate vaccines target serotypes disproportionately represented among resistant lineages^{21,22}, and Vietnamese evidence supports direct PCV protection against invasive pneumococcal disease despite low private-sector coverage.⁵ Nevertheless, the estimate is sparse and unadjusted; vaccination in a setting where PCV was privately purchased may also mark household income, health literacy, and access to care. Vaccination status was partly caregiver-reported, without vaccine product or dose number, and no serotyping or molecular resistance testing was performed. Because this case-only hospital series had no disease-free comparison group, it cannot estimate vaccine effectiveness or support inference about vaccination policy.

The direction of this association is not universal. A multicenter study in Bogotá following PCV10 introduction and a study of immunocompromised patients in Tunisia receiving PCV13 both reported higher resistance among vaccinated individuals^{23,24}, consistent with serotype replacement by resistant non-vaccine types where vaccine pressure has been sustained. Our finding should therefore be treated as setting-specific and hypothesis-generating, not as evidence that vaccination reduces resistance.

This study has several limitations. It was conducted at a single center, which constrains generalizability. Most isolates (50/58) were recovered from nasopharyngeal aspirates rather than a sterile site; because *S. pneumoniae* colonizes the nasopharynx, some may represent colonization rather than the causative pathogen, and only the 8 blood isolates represent unequivocally invasive disease.²⁵ Eight children with a clinical diagnosis of suspected bacteremia had no positive blood culture, so their syndrome classification was clinical rather than microbiological. Viral co-pathogens were not systematically ascertained: multiplex testing for respiratory syncytial virus, influenza, adenovirus, and rhinovirus was performed only when clinically requested, SARS-CoV-2 was not part of the routine panel, and viral results were not captured as a structured study variable; therefore, unmeasured viral co-infection may have contributed to clinical outcomes independently of pneumococcal resistance. The susceptibility panel was clinically directed rather than standardized, so selective-testing verification bias remains; incomplete testing can miss MDR among isolates classified as non-MDR, making the primary 65.5% estimate conditional on the observed

panel. Numerical MIC values and inhibition-zone diameters could not be retrieved, so the categorical results are legacy laboratory reports that cannot be independently re-derived or re-interpreted under another CLSI edition. Trimethoprim–sulfamethoxazole was not included in the panel, which may further bias the MDR estimate downward. The sample was small, with only 20 non-MDR isolates, so association analyses were underpowered and unadjusted for confounding; the sole adjusted association (absence of an underlying condition) rests on a zero cell in five children. Finally, no serotyping or molecular characterization was performed.

Set against these constraints, the study has genuine strengths: laboratory confirmation of *S. pneumoniae* recovery in every included child, a single unchanged laboratory workflow across three years, inclusion of all eligible children rather than a convenience subset, and public deposition of the anonymized dataset together with a full isolate-level classification that allows the MDR outcome to be independently reconstructed. The institutional context was stable: no pneumococcal outbreak or change in pneumococcus-specific infection-control or formal hospital-wide antimicrobial-stewardship policy occurred during the study period.

CONCLUSION

Among hospitalized children in the Mekong Delta of Vietnam, *S. pneumoniae* showed frequent antimicrobial resistance, with 65.5% of isolates meeting the primary MDR definition restricted to agents with an independent applicable pneumococcal criterion; this is a conservative estimate conditional on the observed testing panel. Because 50 of 58 isolates were recovered from nasopharyngeal aspirates and only 4 of 12 clinically suspected bacteremia cases were confirmed by a positive blood culture, the findings should be interpreted as institution-level surveillance of clinically obtained *S. pneumoniae* rather than a resistance profile restricted to confirmed invasive disease. Agent-specific susceptibility percentages should not be ranked because testing subsets differed. As a laboratory-stewardship measure, ceftazidime should not be tested or interpreted for *S. pneumoniae* under the CLSI framework used. Absence of an underlying condition was the only characteristic associated with MDR after Holm adjustment, but that finding depends on a zero cell in five children and is hypothesis-generating; pneumococcal vaccination and the remaining characteristics were not associated after multiplicity adjustment. Standardized, organism-appropriate susceptibility panels are needed for more reliable MDR surveillance.

Data Availability Statement

The anonymized dataset supporting the findings of this study is publicly available in the Zenodo repository at <https://doi.org/10.5281/zenodo.21600133>, under a Creative Commons Attribution 4.0 International license. The deposited file contains categorical susceptibility interpretations only, together with a codebook defining every variable and value code; numerical MIC values and inhibition-zone diameters were not retrievable and are therefore not included. All prevalence estimates, odds ratios, confidence intervals, and multiplicity-adjusted P values reported in this manuscript are reproducible from the deposited dataset.

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Conflict of Interest

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this article.

Registration Number of Clinical Trial

Not applicable.

Author Contributions

Conceptualization and methodology, N.Q.B. and H.T.N.; Investigation, K.Q.T., L.T.N.T. and L.D.P.; Data curation, D.K.N., D.T.B., N.T.T., T.N.L. and T.N.; Formal analysis, N.Q.B.; Writing — original draft, N.Q.B.; Writing — review and editing, D.K.N., D.T.B., N.T.T., T.N.L., T.N. and H.T.N.; Supervision and project administration, K.Q.T., L.T.N.T., L.D.P. and H.T.N. All authors have read and agreed to the published version of the manuscript.

Use of Artificial Intelligence

During the preparation of this work the authors used Grammarly (Grammarly Inc.) and Claude (Anthropic) to improve language, readability, and manuscript formatting.

These tools were not used to generate, analyze, or interpret data, or to draw scientific conclusions. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Institutional Review Board Statement

This study was approved by the Biomedical Research Ethics Committee of Can Tho University of Medicine and Pharmacy (approval no. 23.101.SV/PCT-HĐĐĐ, 25 December 2023; study code 23.KY.042) and was authorized by the Director of Can Tho Children's Hospital. The approval covered retrospective review of 2022–2023 records and stored isolate data with a waiver of individual consent; written informed consent from a parent or legal guardian, and age-appropriate assent, were obtained for the prospective 2024 component. All procedures were conducted in accordance with the ethical standards of the responsible institutional committee and with the 1964 Declaration of Helsinki and its later amendments.

REFERENCES

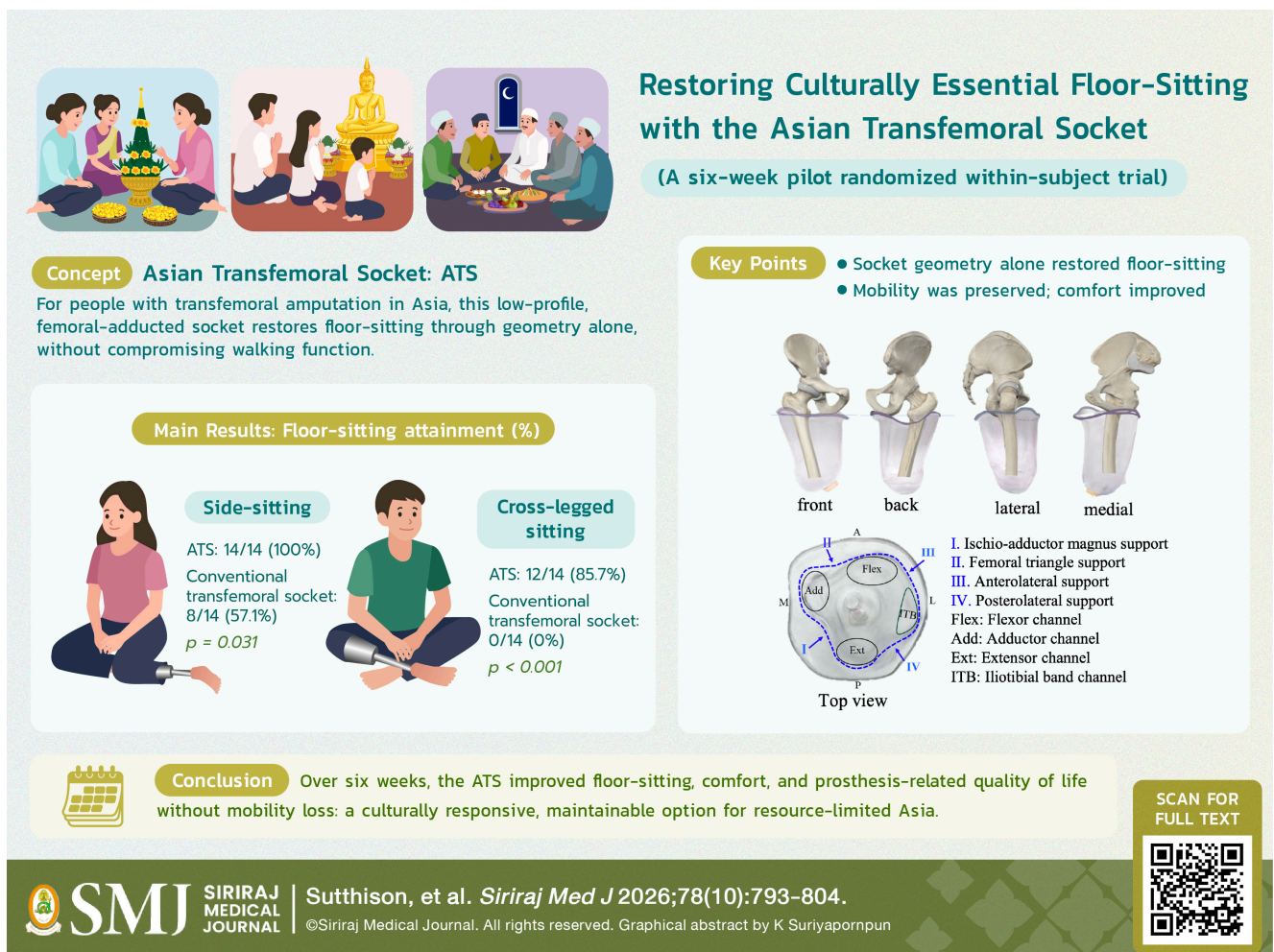
1. GBD 2021 Lower Respiratory Infections and Antimicrobial Resistance Collaborators. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Infect Dis.* 2024;24(9):974–1002.
2. World Health Organization. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: World Health Organization; 2024.
3. World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report 2021. Geneva: World Health Organization; 2021.
4. Vu TVD, Choisy M, Do TTN, Nguyen VMH, Campbell JI, Le TH, et al. Antimicrobial susceptibility testing results from 13 hospitals in Viet Nam: VINARES 2016–2017. *Antimicrob Resist Infect Control.* 2021;10(1):78.
5. Truong HC, Pham QD, Phan TV, Vo DTT, Nguyen PD, Nguyen HT, et al. Effectiveness of pneumococcal conjugate vaccines against invasive pneumococcal disease in Vietnamese children prior to national introduction: a matched case-control study. *Vaccine.* 2026;77:128349.
6. Tran-Quang K, Nguyen-Thi-Dieu T, Tran-Do H, Pham-Hung V, Nguyen-Vu T, Tran-Xuan B, et al. Antibiotic resistance of *Streptococcus pneumoniae* in Vietnamese children with severe pneumonia: a cross-sectional study. *Front Public Health.* 2023;11:1110903.
7. Bui AS, Duong DC, Le THH, Do NA. Frequency of *erm(B)* and *mef(A)* genes among macrolide-resistant *Streptococcus pneumoniae* strains isolated from children under 5 years with pneumonia in Nghe An province, 2019–2021. *Vietnam J Sci Technol.* 2023;65(2): 9–13. Vietnamese.
8. Wambugu P, Shah MM, Nguyen HA, Le KA, Le HH, Vo HM,

- et al. Molecular epidemiology of *Streptococcus pneumoniae* detected in hospitalized pediatric acute respiratory infection cases in Central Vietnam. *Pathogens*. 2023;12(7):943.
9. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-7.
10. Tacconelli E, Cataldo MA, Paul M, Leibovici L, Kluytmans J, Schröder W, et al. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. *BMJ Open*. 2016;6(2):e010134.
11. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 32nd, 33rd and 34th eds. CLSI supplement M100. Wayne (PA): Clinical and Laboratory Standards Institute; 2022, 2023, 2024.
12. Song JH, Jung SI, Ko KS, Kim NY, Son JS, Chang HH, et al. High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP study). *Antimicrob Agents Chemother*. 2004;48(6):2101-7.
13. Kim L, McGee L, Tomczyk S, Beall B. Biological and epidemiological features of antibiotic-resistant *Streptococcus pneumoniae* in pre- and post-conjugate vaccine eras: a United States perspective. *Clin Microbiol Rev*. 2016;29(3):525-52.
14. Cai K, Wang Y, Guo Z, Xu X, Li H, Zhang Q. Clinical characteristics and antimicrobial resistance of pneumococcal isolates of pediatric invasive pneumococcal disease in China. *Infect Drug Resist*. 2018;11:2461-9.
15. Nguyen TH, Nguyen VA, Pham TL, Le HLH. Antibiotic resistance status of *Streptococcus pneumoniae* causing respiratory infections in children under 6 years at Duc Giang General Hospital, 2023. *Vietnam Med J*. 2024;541(3):339-43. Vietnamese.
16. Oh H, Heo ST, Kim M, Kim YR, Yoo JR. Antimicrobial susceptibility trends of *Streptococcus pneumoniae* by age groups over recent 10 years in a single hospital in South Korea. *Yonsei Med J*. 2021;62(4):306-14.
17. Pan F, Han L, Huang W, Tang J, Xiao S, Wang C, et al. Serotype distribution, antimicrobial susceptibility, and molecular epidemiology of *Streptococcus pneumoniae* isolated from children in Shanghai, China. *PLoS One*. 2015;10(11):e0142892.
18. Zhao W, Pan F, Wang B, Wang C, Sun Y, Zhang T, et al. Epidemiology characteristics of *Streptococcus pneumoniae* from children with pneumonia in Shanghai: a retrospective study. *Front Cell Infect Microbiol*. 2019;9:258.
19. Thamlikitkul V. STOP antimicrobial resistance: everybody's business. *Siriraj Med J*. 2014;66(6):234-40.
20. Peng S, Ren H, Deng J, Zhao N, Li Y, Li M, et al. Genotypic and phenotypic characteristics of *Streptococcus pneumoniae* from community-acquired pneumonia patients and healthy asymptomatic participants in Sichuan province, China. *BMC Infect Dis*. 2021;21(1):1030.
21. Song JY, Nahm MH, Moseley MA. Clinical implications of pneumococcal serotypes: invasive disease potential, clinical presentations, and antibiotic resistance. *J Korean Med Sci*. 2013;28(1):4-15.
22. Marimon JM, Ardanuy C. Epidemiology of pneumococcal diseases in Spain after the introduction of pneumococcal conjugate vaccines. *Enferm Infecc Microbiol Clin*. 2021;39(3):142-50.
23. Gutiérrez-Tobar IF, Londoño-Ruiz JP, Mariño-Drews C, Beltrán-Higuera S, Camacho-Moreno G, Leal-Castro AL, et al. Epidemiological characteristics and serotype distribution of culture-confirmed pediatric pneumococcal pneumonia before and after PCV10 introduction: a multicenter study in Bogotá, Colombia, 2008-2019. *Vaccine*. 2022;40(20):2875-83.
24. Raddaoui A, Simões AS, Baaboura R, Félix S, Achour W, Ben Othman T, et al. Serotype distribution, antibiotic resistance and clonality of *Streptococcus pneumoniae* isolated from immunocompromised patients in Tunisia. *PLoS One*. 2015;10(10):e0140390.
25. Bogaert D, De Groot R, Hermans PWM. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis*. 2004;4(3):144-54.

Restoring Culturally Essential Floor-Sitting in Transfemoral Prosthesis Users: A Six-Week Pilot Randomized Within-Subject Trial

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ABSTRACT

Objective: Floor-sitting, including cross-legged and side-sitting, is culturally essential in many Asian societies but is often prevented by conventional transfemoral sockets. The Asian Transfemoral Socket (ATS) is a low-profile, femoral-adducted design that aims to restore floor-sitting through socket geometry rather than costly add-on components.

Materials and Methods: In a pilot randomized within-subject trial, 14 community walkers with unilateral transfemoral amputation were assessed with the ATS after six weeks of use and with their own socket, in randomized order. The primary outcome was floor-sitting attainment (cross-legged and side-sitting); secondary outcomes were socket comfort (SCS), prosthesis-related quality of life (PEQ), walking capacity (6MWT), dynamic balance (4SST), and daily step count. Outcomes were analyzed using Wilcoxon signed-rank and McNemar tests, with rank-biserial correlations as effect sizes.

Results: Cross-legged was attained by 12 participants with the ATS ($p < 0.001$) and side-sitting by 6 additional participants ($p = 0.031$). The ATS showed large effect sizes on comfort and quality of life, significant on two of four SCS ratings and two of three PEQ scales, whereas walking, balance, and activity did not differ (6MWT $r = 0.09$; 4SST $r = 0.29$; steps $r = -0.05$).

Conclusion: The ATS was associated with better floor-sitting and patient-reported outcomes. No statistically supported mobility difference was detected (paired median differences: 6MWT +0.4 m [95% CI -3.5 to 11.3], 4SST -0.21 s [-0.44 to 0.21], steps/day -23 [-449 to 521]); clinically important harm cannot be excluded. Cost, fabrication time, training, maintenance, and service delivery were not evaluated; findings are limited to this Thai center.

Keywords: Transfemoral prosthesis; socket design; floor-sitting; quality of life; resource-limited setting (Siriraj Med J 2026;78(10):793-804)

INTRODUCTION

Floor-sitting is routine and culturally embedded in many Asian societies.¹ Cross-legged sitting and side-sitting are used during meals, family gatherings, social interaction, and religious ceremonies, and may recur repeatedly throughout daily life.²⁻⁴ For transfemoral prosthesis users, inability to floor-sit is linked to body function, activity, and participation under the International Classification of Functioning, Disability and Health (ICF) framework.⁵⁻⁷

Conventional transfemoral sockets such as quadrilateral and ischial-containment designs were primarily developed to provide stability, load transfer, and control during standing and walking.⁸⁻¹⁰ However, they restrict the combined hip flexion, abduction, and rotation required for floor-sitting because of their high proximal trim lines and pelvic enclosure.^{11,12} Mechanical rotation adapters integrated into the prosthesis between the transfemoral socket and knee may facilitate controlled axial rotation of the prosthetic limb and increase sitting mobility; however, they add cost and weight, increase the mechanical complexity of the prosthetic system and the need for technical adjustment, and impose a maintenance burden, which limits feasibility in resource-limited Asian settings.^{6,13,14} Low-profile socket designs, such as the Marlo Anatomical Socket (MAS) or Sub-ischial socket, may improve hip motion, comfort, or function.

However, MAS depends principally on specialized casting, rectification, and fitting expertise, and its implementation may require specialized clinician training. Sub-ischial sockets typically require silicone gel liners, vacuum unit systems, and greater maintenance.^{8,15-17}

We designed the Asian Transfemoral Socket (ATS), a low-profile, femoral-adducted transfemoral socket for Asian transfemoral prosthesis users living in floor-sitting cultures. The ATS aims to restore culturally essential floor-sitting through socket geometry and anatomical load distribution rather than costly add-on components. The ATS has lowered proximal trim lines, a reduced ischial containment region, a subtrochanteric lateral contour, and approximately 6 degrees of socket adduction (Fig 1).¹⁸ In this way it permits greater hip motion during floor-sitting while maintaining sufficient support for walking. This pilot randomized within-subject study analyzed effects of ATS compared with the own socket of the participant after six weeks of daily use. Study outcomes were floor-sitting attainment, socket comfort, prosthesis-related quality of life, walking capacity, dynamic balance, and daily step count.

MATERIALS AND METHODS

Asian Transfemoral Socket

The ATS uses lowered proximal trim lines, with the lateral wall reduced to a level below the greater trochanter,

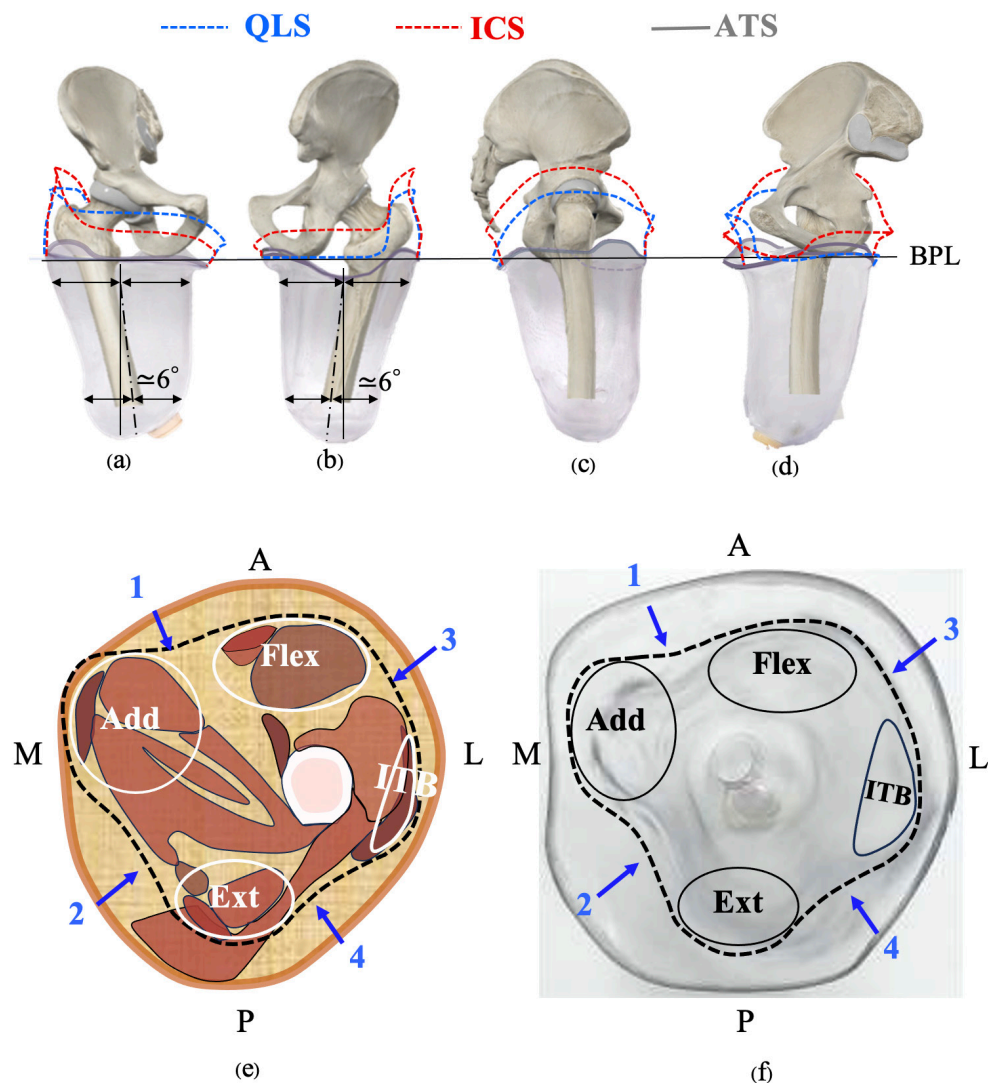


Fig 1. Asian Transfemoral Socket (ATS): (a) anterior, (b) posterior, (c) lateral, and (d) medial views; (e) cross-sectional view of the ATS and residual limb; and (f) cross-sectional view showing biomechanical forces. In (a–d), the blue dashed line represents the quadrilateral socket (QLS), and the red dashed line represents the ischial containment socket (ICS). In (a,b), the black dash-dot line indicates approximately 6° of socket adduction. In (e,f), the black dashed line indicates the contour 25 mm distal to the Below Pelvic Level (BPL). 1, femoral triangle support; 2, ischio-adductor magnus support; 3, anterolateral support; 4, posterolateral support.

Abbreviations: ATS, Asian Transfemoral Socket; QLS, quadrilateral socket; ICS, ischial containment socket; Flex, flexor channel; Add, adductor channel; Ext, extensor channel; ITB, iliotibial band channel.

aiming to facilitate hip motion during floor-sitting while reducing mechanical interference with the floor surface and peri-pelvic soft tissues. Rather than enclosing the ischium within a high proximal wall, it distributes load through anatomical support regions of the pelvis and thigh and through an inclined ischial support that contains the ischial ramus without raising a proximal wall, reducing perineal compression during the hip flexion, abduction, and external rotation of cross-legged sitting. In the frontal plane, the socket was aligned at approximately 6 degrees of adduction, based on Köhler et al.,¹⁸ to support frontal-plane stability during gait. The ATS thus integrates the hip mobility required for floor-sitting with the stability required for standing and walking (Fig 1).

Study

The study was conducted at the Sirindhorn School of Prosthetics and Orthotics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, and was approved by the Siriraj Institutional Review Board (COA no. Si 703/2022; 4 October 2022). Written informed consent was obtained from all participants. Enrollment occurred from 6 October 2022 to 24 March 2024. The trial was retrospectively registered with the Thai Clinical Trials Registry (TCTR20260619005; <https://www.thaiclinicaltrials.org/show/TCTR20260619005>) because clinical-trial registration was temporarily suspended when enrollment began. No protocol deviations relevant to this trial occurred.

Participants

Individuals with a unilateral transfemoral amputation were recruited via a poster at the SSPO clinic. Interested individuals received verbal and written study information from co-investigators (Y.N. and M.R.) and provided written informed consent before enrollment. Inclusion criteria were adult (≥ 18 years) unilateral transfemoral prosthesis user with a well-fitted current prosthesis; at least six months of prosthetic use; Medicare Functional Classification Level K2 or higher, able to walk independently on level ground without a walking aid; a residual limb more than 15 cm; body mass index 17-25 kg/m²; and ability to communicate in Thai. Exclusion criteria were comorbidities precluding the physical outcome tests; bilateral major lower-limb amputations; surgery on the non-amputated side; limited hip range of motion on both sides; a manual-muscle-test grade below four in either lower limb; residual-limb edema, wounds, or allergy to socket plastics; and difficulties in comprehension or communication. Because the protocol required exclusive ATS use during its six-week period, participants were required to refrain from using their own socket to avoid mixed-device exposure during assessment. The own socket of the participant was held in safekeeping and returned on request, on withdrawal, or if the ATS became unsuitable. Participants who wished to continue using the ATS after the study could keep it free of charge; this IRB-approved option was disclosed during informed consent and was not conditional on study completion. The authors had no financial or intellectual-property interest in the ATS.

Study design

In this single-center, two-period, two-sequence randomized crossover trial, we compared the ATS with the own socket of the participant. After eligibility was confirmed, participants were assigned 1:1 to the own-socket-first or ATS-first sequence using a pre-generated block-randomized sequence with a fixed block size of 2. The first author enrolled participants; sequence assignment was made after written informed consent according to chronological enrollment order. No separate allocation-concealment mechanism was used. In the own-socket-first sequence, outcomes were assessed at baseline from the established everyday use of each participant, after which participants used the ATS for a six-week daily-use period and were reassessed. In the ATS-first sequence, no outcome assessment was performed at baseline; participants used the ATS for six weeks and were assessed, then resumed their own socket use and were reassessed after a further six weeks. The ATS condition, therefore,

always comprised a six-week ATS use period, whereas the own-socket condition reflected the normal everyday use of each participant. A common pre-randomization outcome assessment was not included in the original design, and no formal washout was used. Because own-socket assessment timing differed by sequence, period and sequence effects were examined in exploratory crossover models; residual learning, accommodation, or carryover cannot be excluded. A six-week ATS use period was chosen because the Prosthesis Evaluation Questionnaire (PEQ) requires at least four weeks of use. Two weeks after the start of ATS use, socket fit was reassessed and safety checks were performed. If no fitting problems were identified, participants continued using the ATS for the remaining four weeks, completing a total of six weeks of ATS use before assessment.

Socket casting, fabrication, and alignment standardization

All sockets were single-wall suction sockets fabricated without gel liners or vacuum assistance, using a standardized casting and rectification protocol targeting approximately 6 degrees of socket adduction.^{15,19} Two prosthetists fabrication and fitting the ATS sockets using an identical protocol. To avoid component-related confounding, the own prosthetic components of each participant were transferred unchanged to the ATS, and alignment was standardized so that the ATS load line and the static socket-knee-foot relationship matched those of the existing prosthesis of the participant. Because the ATS was readily distinguishable from the own socket of each participant, blinding was not feasible. Therefore, fabrication and fitting (K.S. and N.M.), outcome assessment (Y.N., M.A., and M.R.), and data processing (N.S.) were performed by different persons. Before analysis, socket-condition labels were replaced with neutral alphanumeric codes by co-investigators (Y.N. and N.M.).

Outcome measurements

Wear compliance and fitting-related complications were monitored by telephone at Week 1. Daily ambulatory activity was recorded continuously by a small pedometer fixed in a protective capsule on the prosthetic shank. The pedometer could neither be read nor adjusted by the participant. Outcomes are reported throughout in the following order, beginning with the most important: floor-sitting attainment (primary), socket comfort (Socket Comfort Score, SCS), prosthesis-related quality of life (Prosthesis Evaluation Questionnaire, PEQ), walking capacity (Six-Minute Walk Test, 6MWT), dynamic balance (Four-Square Step Test, 4SST), and daily step count. Each outcome, with its measurement properties, is

described below. As an exploratory acceptability outcome, we asked the participant at the end of the ATS period whether they wished to keep the ATS or resume using their own socket.

Floor-sitting attainment was the primary outcome domain, assessed separately for cross-legged and side-sitting; neither posture was designated as a separate co-primary endpoint. The same prespecified 10-s criteria were applied by one unblinded assessor. Any attempt that did not satisfy all stated attainment criteria was scored as not attained. Because this test was developed for the present study, no published reliability or validity estimates are available; no repeated-rating reliability estimate or video-adjudication result is available. This is consistent with the reported lack of psychometrically established outcome measures for culturally important floor-sitting activities in people with lower-limb absence.²⁰

The SCS measures self-reported socket comfort on an 11-point numerical rating scale (0-10, higher = better); in an expanded administration, participants rated current comfort plus their best, worst, and average comfort over the preceding week. It has acceptable test-retest reliability and construct validity in lower-limb prosthesis users.²¹

The PEQ measures prosthesis-related quality of life; the Utility, Residual Limb Health, and Ambulation scales (0-100, higher = better) were administered at six weeks. These scales have acceptable test-retest reliability and construct validity in this population.²²

The 6MWT measures submaximal walking capacity as the distance walked in six minutes.²³ It has established validity and test-retest reliability in people with lower-limb amputation.^{24,25}

The 4SST measures dynamic balance as the time taken to step over four quadrants in both directions; it was performed twice and the faster trial was retained. It has high test-retest and inter-rater reliability,^{26,27} and discriminates multiple fallers after amputation.²⁸

Daily step count measures habitual ambulatory activity and was recorded continuously using a tri-axial accelerometer pedometer (H-235 Daily Partner, Dretec, Japan) mounted on the prosthetic shank. The manufacturer specifies $\pm 3\%$ step-count accuracy under vibration testing; prosthesis-mounted accelerometer monitors have demonstrated criterion validity, although accuracy may decrease at slow walking speeds.²⁹

Floor-sitting evaluation

Floor-sitting was assessed in two postures common in Thai daily life. Cross-legged sitting evaluated the combined external rotation, flexion, and abduction of

the prosthetic-side hip; attainment required the sound and prosthetic lower legs to cross in front of the pelvis with the foot of each leg contacting the opposite lower leg (Fig 2a,b; a failed attempt is shown in Fig 2e,f). The sound limb was positioned inward first, and the prosthetic foot was then placed in front of the sound lower leg, so that any hip-motion restriction on the prosthetic side did not affect the movement of the sound side. Side-sitting evaluated the combined internal rotation, flexion, and abduction of the prosthetic-side hip; attainment required the sound foot and the prosthesis to be in contact after the participant had assumed the posture (Fig 2c,d; a failed attempt is shown in Fig 2g,h). Participants were permitted to use their hands while moving into each position; once seated, they held both hands at chest level and maintained the posture for 10 s without arm support. Satisfying the posture condition and holding it for 10 s without arm support was scored 1 (attained); requiring arm support was scored 0 (not attained).

Sample size

As an exploratory pilot, sample size was selected pragmatically. Whitehead et al.³⁰ informed pilot planning but did not provide power justification for the paired binary primary outcome; no formal progression criteria were prespecified.

Analysis

Floor-sitting attainment, the primary outcome domain, was summarized as the number and percentage of participants attaining each posture in each socket condition, with Clopper-Pearson exact binomial 95% confidence intervals, and between-socket paired comparisons were performed using the exact two-sided McNemar test. The secondary outcomes were then analyzed in the same fixed order: socket comfort, prosthesis-related quality of life, walking capacity, dynamic balance, and daily step count. Within-subject comparisons between the ATS and the own socket of the participant were summarized as medians with interquartile ranges (IQR) and tested using the Wilcoxon signed-rank statistic with exact sign-permutation *p* values; zero differences were excluded and ties received midranks. Effect sizes were calculated as matched-pairs rank-biserial correlations (*r*) from the same signed-rank statistics, with positive *r* values indicating ATS superiority. For the 4SST, the difference sign was reversed so that faster times yielded positive *r* values. The 95% confidence intervals were estimated by paired bootstrap resampling of participants using 10,000 resamples and the bias-corrected and accelerated (BCa) method. Effect-sizes were interpreted as negligible

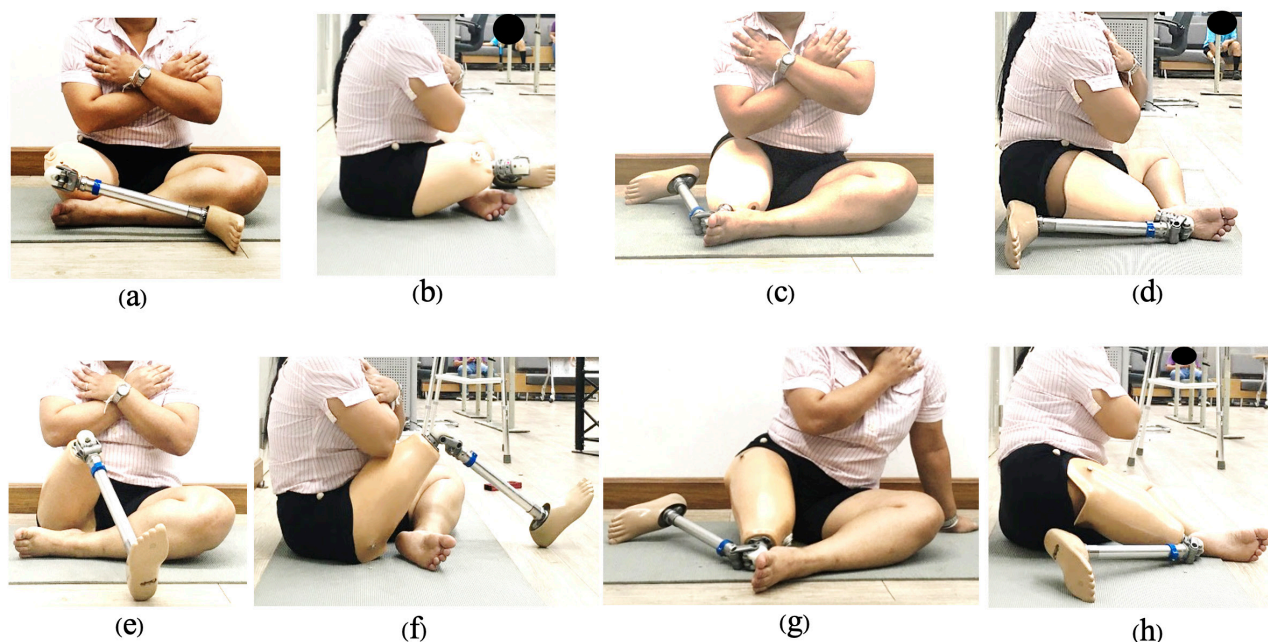


Fig 2. Floor-sitting task outcomes. Panels (a,b) and (c,d) show attained cross-legged sitting and side-sitting; panels (e,f) and (g,h) show failed attempts. Within each pair, the first panel shows the frontal view, and the second shows the lateral view. A posture was scored as attained when held for 10 s without arm support; full attainment criteria are given in the Methods section.

(< 0.10), small (< 0.30), medium (< 0.50), and large (≥ 0.50). No multiplicity adjustment was prespecified; secondary *p* values were treated as descriptive and interval estimates were emphasized. All analyses were performed in R 4.6.1 using the stats and boot (1.3-32) packages, with figures produced in ggplot2. Exploratory crossover models included treatment, period, and sequence with participant-clustered standard errors (Supplementary Table S1). Additional crossover analyses were performed in Python 3.13.5 using statsmodels 0.14.6.

RESULTS

Seventeen individuals with a unilateral transfemoral amputation were assessed for eligibility. Two participants were excluded before randomization: one had an extremely short residual limb that did not meet the length criterion, and one used an exoskeletal prosthesis that precluded safe standardization of the distal components. The remaining 15 participants were randomized: seven to the own-socket-first sequence and eight to the ATS-first sequence. One participant in the ATS-first sequence developed transient pruritus and erythema after contact with suction-valve materials and talcum powder, together with suspension problems, during the first two weeks after randomization and discontinued ATS use. Symptoms resolved within a few hours without medication or hospitalization; severity was not formally graded. All 15 randomized participants were included in safety reporting. The remaining 14 participants (13 men, 1 woman) completed both conditions

and contributed paired efficacy data (complete-case estimand), leaving seven completers in each sequence (Table 1 and Fig 3). Of the 14 completers, six habitually used a quadrilateral socket and eight an ischial containment socket, and all used suction suspension (Supplementary Table S2). No serious adverse event occurred. In a worst-case primary-outcome sensitivity analysis coding the missing participant as ATS failure and own-socket success, cross-legged attainment remained statistically supported (McNemar $p = .003$), whereas side-sitting did not ($p = .125$). Floor-sitting attainment, the median values, effect sizes, and confidence intervals for the continuous and ordinal outcomes are presented in Table 2. Self-reported comfort and quality-of-life estimates generally favored the ATS, whereas no statistically supported difference was detected in objective walking or activity measures.

Floor-sitting attainment

Cross-legged sitting and side-sitting were significantly more often attained when using the ATS compared to when using their own socket (Table 2).

Socket comfort and prosthesis-related quality of life

SCS and PEQ findings are exploratory (Table 2). Nominal *p* values were .049 for SCS Worst, .035 for SCS Today, .048 for PEQ Residual Limb Health, and .003 for PEQ Ambulation; other SCS/PEQ comparisons had $p = .057-.072$. After the final outcome assessment, before data analysis or disclosure of results, participants were

TABLE 1. Baseline characteristics of all randomized participants by sequence (N = 15).

Characteristic	Own-socket-first (n=7)	ATS-first (n=8)	Total (N=15)
Continuous variables, median (IQR)			
Age, years	44.0 (43.0-48.0)	53.0 (44.8-62.8)	49.0 (43.0-58.5)
Body mass, kg	59.5 (56.5-65.5)	62.5 (58.8-69.8)	62.0 (56.5-68.5)
BMI, kg/m ²	22.4 (20.6-24.2)	23.1 (20.3-24.5)	23.1 (20.1-24.5)
Residual limb length, cm	24.5 (23.0-27.8)	20.5 (18.5-21.6)	21.8 (19.5-24.3)
Femur length, cm	21.5 (20.3-23.5)	18.3 (16.9-20.3)	20.0 (17.0-21.3)
Time since amputation, years	22.0 (6.5-27.5)	27.0 (12.0-29.3)	26.0 (10.0-28.5)
Categorical variables, n (%)			
Sex			
Male	6 (85.7)	8 (100.0)	14 (93.3)
Female	1 (14.3)	0 (0.0)	1 (6.7)
Amputation side			
Right	4 (57.1)	4 (50.0)	8 (53.3)
Left	3 (42.9)	4 (50.0)	7 (46.7)
Cause of amputation			
Trauma	4 (57.1)	6 (75.0)	10 (66.7)
Cancer	1 (14.3)	2 (25.0)	3 (20.0)
Infection	2 (28.6)	0 (0.0)	2 (13.3)
Medicare Functional Classification Level			
K2	2 (28.6)	0 (0.0)	2 (13.3)
K3	5 (71.4)	8 (100.0)	13 (86.7)

Note. Values are median (IQR) or n (%). The participant who discontinued ATS after randomization is included in the ATS-first baseline column. Residual limb length is measured from the ischial tuberosity to the distal end of the residual limb. BMI, body mass index; K2/K3, Medicare Functional Classification Level.

asked whether they wished to keep the ATS or resume their own socket. Neither choice involved study-related cost; 12 of 14 (85.7%) chose the ATS.

Functional capacity and daily activity

No statistically supported difference was detected for 6MWT, 4SST, or step count (Table 2). In exploratory crossover models, the ATS treatment estimate was +1.71 SCS points for Worst (95% CI 0.52 to 2.91) and +9.89 PEQ Utility points (2.76 to 17.02). Period effects were also present for these outcomes, whereas sequence terms

were not statistically supported (Supplementary Table S1). These model-based estimates are exploratory.

DISCUSSION

This trial tested whether a low-profile, femoral-adducted transfemoral socket can restore culturally important floor-sitting without sacrificing walking function. Over six weeks of real-life use, the ATS tended to improve floor-sitting attainment, socket comfort, and prosthesis-related quality of life, while functional capacity and habitual activity remained unchanged, suggesting

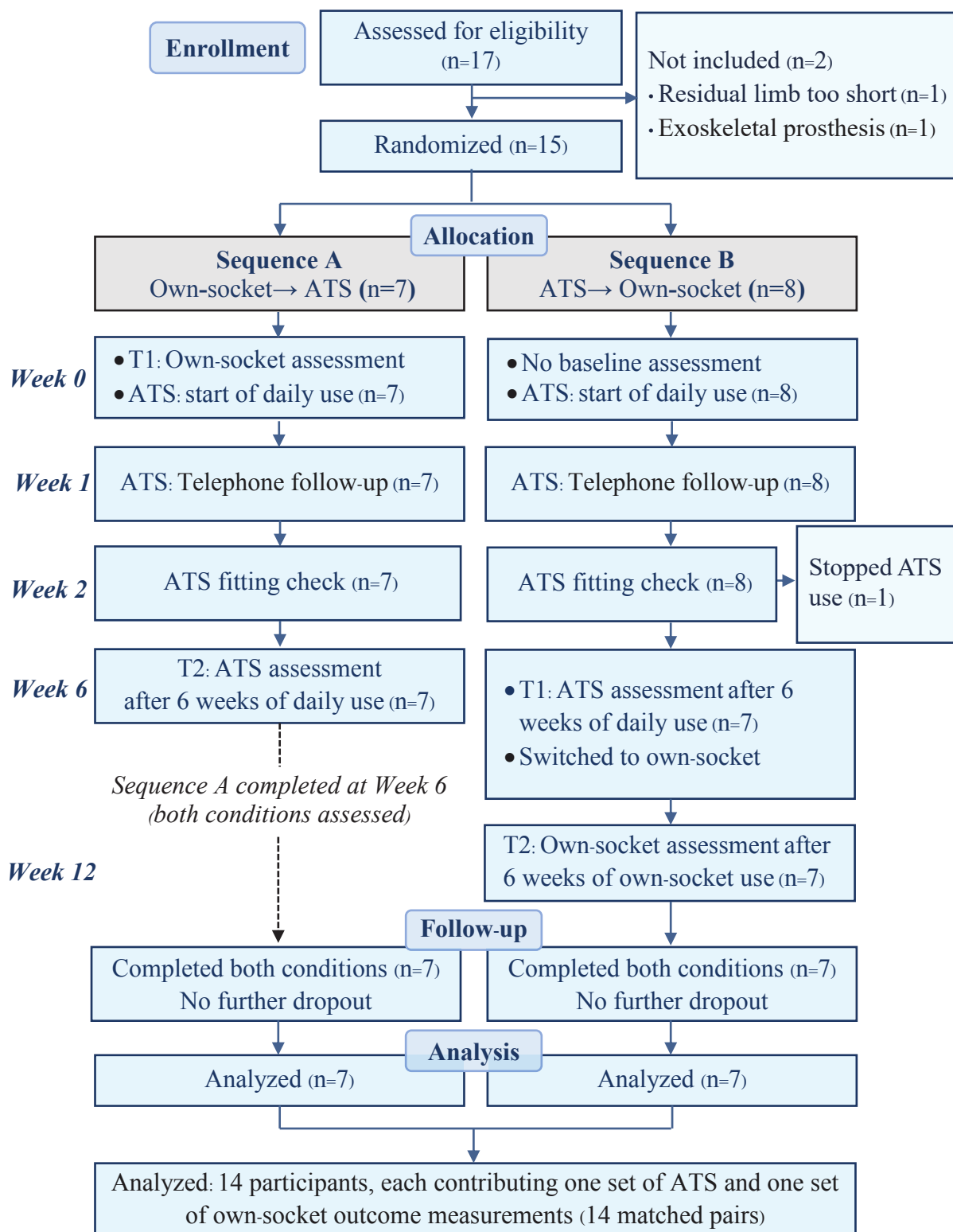


Fig 3. CONSORT flow diagram of the randomized within-subject trial. T1: first outcome measurements; T2: second outcome measurements
Abbreviation: ATS: Asian Transfemoral Socket

TABLE 2. Within-subject comparison of the ATS and the own socket of the participant across postural attainment, socket comfort, self-reported outcomes, functional capacity, and daily activity ($N = 14$).

Posture	ATS	Own socket	ATS % [95% CI]	Own socket % [95% CI]	<i>p</i>
	<i>n/N</i>	<i>n/N</i>			
Cross-legged sitting	12/14	0/14	85.7 [57.2, 98.2]	0.0 [0.0, 23.2]	< .001
Side-sitting	14/14	8/14	100.0 [76.8, 100.0]	57.1 [28.9, 82.3]	.031
Outcome	ATS Median (IQR)	Own socket Median (IQR)	Effect size <i>r</i> [95% CI]	<i>p</i>	
Socket comfort					
SCS: Best	9.0 (8.2-10.0)	9.0 (8.0-9.0)	0.67 [0.00, 1.00]	.072	
SCS: Worst	8.5 (6.2-9.0)	6.5 (5.0-7.8)	0.63 [0.02, 0.92]	.049	
SCS: Average	9.0 (8.1-10.0)	8.0 (7.0-9.0)	0.60 [-0.05, 0.92]	.057	
SCS: Today	9.0 (8.2-10.0)	8.5 (8.0-9.0)	0.80 [-0.14, 1.00]	.035	
Quality of life (Self-reported)					
PEQ: UT	87.8 (82.6-89.7)	80.2 (72.1-85.8)	0.55 [-0.10, 0.90]	.070	
PEQ: RLH	84.6 (69.6-90.5)	77.3 (71.0-82.2)	0.60 [-0.09, 0.98]	.048	
PEQ: AB	94.7 (87.9-96.7)	87.1 (83.2-91.8)	0.85 [0.26, 1.00]	.003	
Functional capacity and daily activity					
6MWT	350.6 (314.6-384.6)	353.9 (318.9-379.0)	0.09 [-0.52, 0.66]	.808	
4SST	10.4 (9.2-11.4)	10.2 (9.6-11.7)	0.29 [-0.35, 0.77]	.365	
Step count	2690 (1074-4720)	1993 (1027-5505)	-0.05 [-0.62, 0.54]	.903	

Note. Floor-sitting values are *n/N* (%) with Clopper-Pearson 95% CIs and exact McNemar *p* values. Continuous/ordinal values are median (IQR); *r* is matched-pairs rank-biserial correlation with BCa 95% CI. Wilcoxon *p* values are exact sign-permutation values. Non-zero pairs for SCS Best, Worst, Average, and Today were 10, 13, 13, and 9; all PEQ scales, 6MWT, 4SST, and step count had 14. Secondary *p* values are descriptive because multiplicity was not adjusted. For 4SST, positive *r* indicates faster ATS performance.

Abbreviation: ATS, Asian Transfemoral Socket; SCS, Socket Comfort Score; PEQ, Prosthesis Evaluation Questionnaire; UT, Utility; RLH, Residual-Limb Health; AB, Ambulation; 6MWT, Six-Minute Walk Test; 4SST, Four-Square Step Test.

that the benefit for floor-sitting was not gained at the cost of walking.

Floor-sitting, comfort, and quality of life

Floor-sitting showed the largest and most clinically relevant differences. Cross-legged sitting was not achieved by any participant in their own socket, whereas 12 of 14 participants achieved it with the ATS. This result is consistent with earlier reports that cross-legged sitting is extremely difficult for transfemoral prosthesis users whereas it is a valued determinant of quality of life.^{6,7} The fact that side-sitting was already attainable for 8

participants yet improved further to 14 with the ATS fits the interpretation that side-sitting can be partly achieved through compensatory pelvic tilt. Cross-legged sitting depends more directly on hip external rotation which a conventional high lateral wall and ischial brim obstruct. SCS estimates generally favored the ATS but were imprecise: $r = 0.67$ [0.00, 1.00] for Best, 0.63 [0.02, 0.92] for Worst, 0.60 [-0.05, 0.92] for Average, and 0.80 [-0.14, 1.00] for Today (BCa 95% CIs). PEQ Ambulation showed the clearest six-week estimate ($r = 0.85$ [0.26, 1.00]); these unblinded subjective outcomes remain exploratory.

Functional capacity and daily activity

A potential concern with lowering the proximal trim lines is reduced mediolateral control during gait. No statistically supported between-socket difference was detected for 6MWT, 4SST, or step count. Median paired differences (ATS-own socket) were +0.4 m (95% CI -3.5 to 11.3), -0.21 s (-0.44 to 0.21), and -23 steps/day (-449 to 521), respectively. Because this pilot was not a non-inferiority study and the intervals remain wide, clinically important mobility changes cannot be excluded; preserved mediolateral control was not established. Prior biomechanical evidence suggests that removing ischial containment may not substantially affect frontal-plane hip moments, lateral trunk lean, step width, or walking speed.^{16,17} Frontal-plane stability may also depend on socket adduction alignment. Köhler et al. reported that adduction of approximately 6 degrees reduced compensatory lateral trunk lean during prosthetic-side stance.¹⁸ Because the ATS combines this adduction with distal femoral centralization,¹⁹ proximal support may be redistributed through alignment and anatomical load-sharing rather than being simply reduced. Increased rotational freedom may be a further mechanism but, with transverse-plane motion unmeasured, remains hypothetical. The divergence between subjective and objective outcomes is not necessarily contradictory: the objective tests captured short, supervised capacity, where a well-aligned conventional socket and the ATS may perform similarly, whereas the self-reported measures reflected a week of habitual use including floor-sitting. The fact that worst- and average-comfort ratings improved over the week, not only on the day-of rating, also argues against a purely novelty effect.

Cultural sustainability and rehabilitation relevance

Framed within the ICF, the results trace a coherent path from body function to participation. By releasing the combined hip motion that floor-sitting demands (body function), the ATS restored cross-legged and side-sitting (activity), the postures through which meals, social gatherings, and religious ceremonies are conducted in many Asian communities (participation).¹ This path reframes socket design as a participation-oriented, culturally responsive rehabilitation goal, consistent with inclusive, equitable rehabilitation for under-served populations.^{13,14} Importantly, the ATS achieves its intended function through socket geometry and alignment rather than additional components such as rotation adapters, vacuum suspension systems, or specialized prosthetic liners, which may reduce component-related costs and maintenance requirements in resource-limited settings. However, formal cost data were not collected in this study.

Limitations

Several limitations should be considered. First, this was a small, single-center study of 14 predominantly male participants, which limits statistical power and generalizability. In addition, participants had medium to long residual limbs, longer than 15 cm, and therefore the findings may not be directly generalizable to short or very short residual limbs. The within-subject design reduced between-participant variability, but a fully placebo-controlled crossover trial was not feasible because prosthetic sockets must be individually fabricated, aligned, and accommodated, and the ATS was visibly different from the own socket of the participants. Consequently, blinding was not possible, and self-reported comfort, PEQ scores, and device preference may have been influenced by expectation, novelty, or the option to keep the ATS after the study. Second, the six-week follow-up was sufficient to assess short-term accommodation and daily use but not long-term durability, maintenance burden, residual-limb volume change, skin tolerance, or sustained satisfaction. Third, floor-sitting was evaluated as binary attainment rather than by three-dimensional kinematics or interface-pressure measurement; therefore, the proposed mechanisms linking lowered trim lines to improved hip motion remain inferential. In addition, the floor-sitting attainment test was developed for this study, so its reliability and validity have not been formally established, although a priori criteria and a single rater were used to limit measurement error. Larger, multicenter, longer-term studies with biomechanical assessment are needed to confirm or refute effectiveness, clarify mechanisms, and evaluate clinical sustainability in routine practice.

CONCLUSION

This six-week randomized within-subject trial suggests that the Asian Transfemoral Socket improves culturally important floor-sitting, socket comfort, and prosthesis-related quality of life without any evident short-term reduction in walking capacity, balance, or daily activity.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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DECLARATIONS

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Conflict of Interest

No potential conflict of interest was reported by the authors.

Registration Number of Clinical Trial

The Thai Clinical Trials Registry (TCTR20260619005).

Author Contributions

Conceptualization and methodology, N.S., K.S., G.G., W.D. ; Investigation, N.M., Y.N., M.A., M.R., K.S. ; Formal analysis, N.S., G.G. ; Visualization and writing – original draft, N.S. ; Writing – review and editing, N.S., K.S., G.G. ; Funding acquisition, N.S., K.S. ; Supervision, K.S., G.G., W.D. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

The authors declare no use of artificial intelligence.

Institutional Review Board Statement

The study was conducted at the Sirindhorn School of Prosthetics and Orthotics (SSPO), Faculty of Medicine Siriraj Hospital, Mahidol University, approved by the Siriraj Institutional Review Board (COA no. Si 703/2022), carried out in accordance with the Declaration of Helsinki, with written informed consent from all participants.

REFERENCES

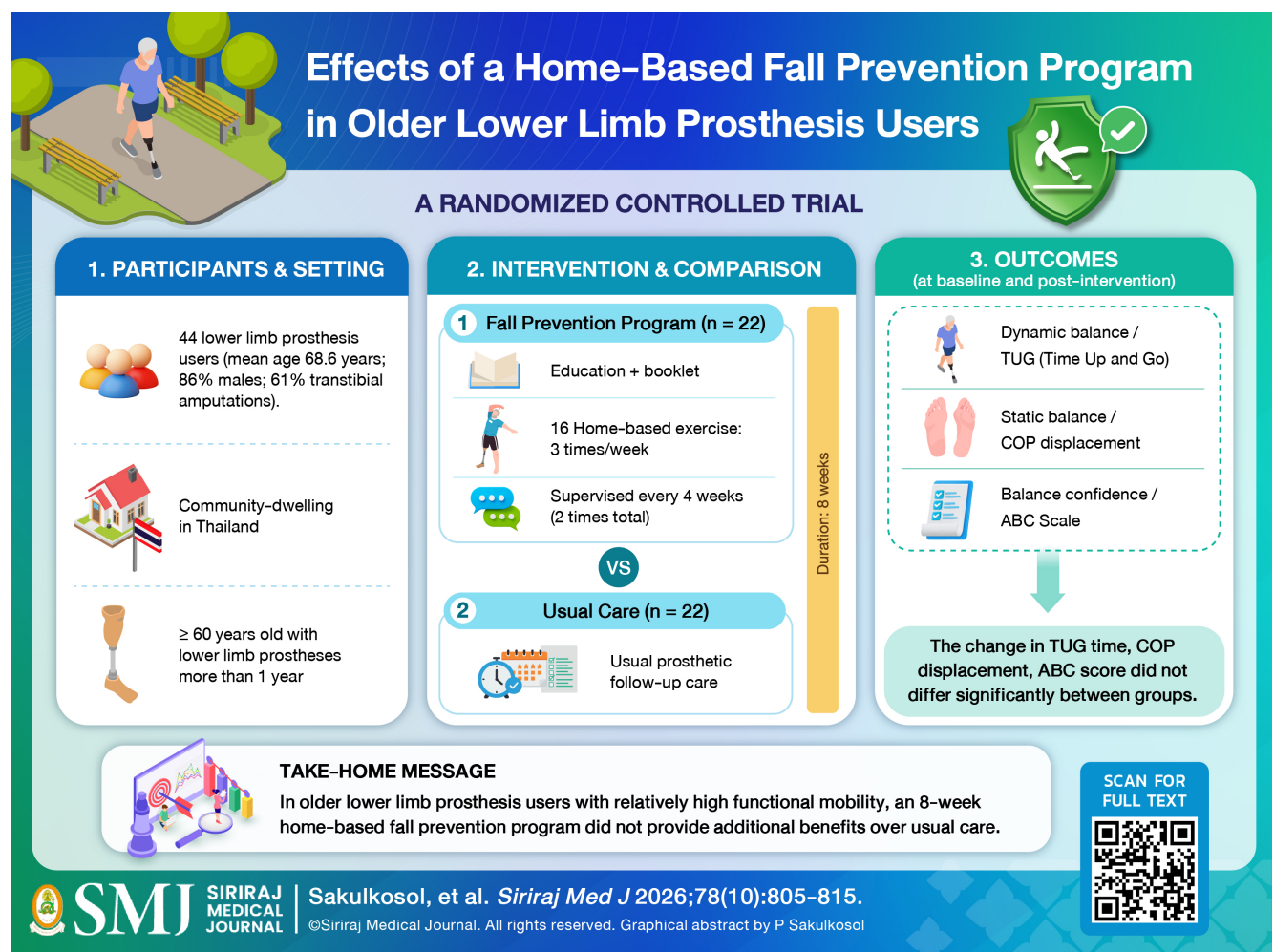
- Hewes GW. World distribution of certain postural habits. *Am Anthropol*. 1955;57(2):231–44.
- Kapoor A, Mishra SK, Dewangan SK, Mody BS. Range of movements of lower limb joints in cross-legged sitting posture. *J Arthroplasty*. 2008;23(3):451–3.
- Zhou H, Liu A, Wang D, Zeng X, Wei S, Wang C. Kinematics of lower limbs of healthy Chinese people sitting cross-legged. *Prosthet Orthot Int*. 2013;37(5):369–74.
- Ganokroj P, Chaowalitwong J, Kerdsonnuek P, et al. Three-dimensional motion analysis of ten common Asian sitting positions in daily living and factors affecting range of hip motions. *BMC Musculoskelet Disord*. 2021;22:618.
- World Health Organization. International Classification of Functioning, Disability and Health: ICF. Geneva: World Health Organization; 2001.
- Cavuto ML, Chun M, Kelsall N, et al. Design of mechanism and preliminary field validation of low-cost transfemoral rotator for use in the developing world. In: *Proceedings of the ASME 2016 International Design Engineering Technical Conferences*; 2016 Aug 21–24; Charlotte, NC, USA. V05AT07A035.
- Horgan O, MacLachlan M. Psychosocial adjustment to lower-limb amputation: a review. *Disabil Rehabil*. 2004;26(14–15):837–50.
- Brodie M, Murray L, McGarry A. Transfemoral prosthetic socket designs: A review of the literature. *J Prosthet Orthot*. 2022;34(2):e73–e92.
- Radcliffe CW. Functional considerations in the fitting of above-knee prostheses. Berkeley (CA): Biomechanics Laboratory, University of California; 1955.
- Sabolich J. Contoured adducted trochanteric-controlled alignment method (CAT-CAM): Introduction and basic principles. *Clin Prosthet Orthot*. 1985;9(4):15–26.
- Hagberg K, Häggström E, Uden M, Brånemark R. Socket versus bone-anchored transfemoral prostheses: Hip range of motion and sitting comfort. *Prosthet Orthot Int*. 2005;29(2):153–63.
- Klotz R, Colobert B, Botino M, Permentiers I. Influence of different types of sockets on the range of motion of the hip joint by the transfemoral amputee. *Ann Phys Rehabil Med*. 2011;54(7):399–410.
- Harkins CS, McGarry A, Buis A. Provision of prosthetic and orthotic services in low-income countries: A review of the literature. *Prosthet Orthot Int*. 2013;37(5):353–61.
- Craig J. Prosthetic feet for low-income countries. *J Prosthet Orthot*. 2005;17(Suppl):S47–S49.
- Gusev MG, Lein GA, Alzoba SV. Advantages of the Marlo anatomical socket (MAS) for transfemoral prosthesis. *Genij Ortopedii*. 2020;26(3):359–63.
- Fatone S, Caldwell R. Northwestern University Flexible Subischial Vacuum Socket for persons with transfemoral amputation–Part 1: Description of technique. *Prosthet Orthot Int*. 2017;41(3):237–45.
- Fatone S, Caldwell R. Northwestern University Flexible Subischial Vacuum Socket for persons with transfemoral amputation–Part 2: Description and preliminary evaluation. *Prosthet Orthot Int*. 2017;41(3):246–50.
- Köhler TM, Blumentritt S, Braatz F, Bellmann M. The impact of transfemoral socket adduction on pelvic and trunk stabilization during level walking—a biomechanical study. *Gait Posture*. 2021;89:169–77.
- Schuch CM. Modern above-knee fitting practice (a report on the ISPO workshop on above-knee fitting and alignment techniques, May 15–19, 1987, Miami, USA). *Prosthet Orthot Int*. 1988;12(2):77–90.
- Tan JM, Halford GRJ, Lukin M, Kohler F. Recommendations from the ISPO lower-limb COMPASS: patient-reported and performance-based outcome measures. *Prosthet Orthot Int*. 2023;47(1):13–25.
- Hanspal RS, Fisher K, Nieveen R. Prosthetic socket fit comfort score. *Disabil Rehabil*. 2003;25(22):1278–80.
- Legro MW, Reiber GD, Smith DG, del Aguila M, Larsen J, Boone D. Prosthesis evaluation questionnaire for persons with lower limb amputations: Assessing prosthesis-related quality of life. *Arch Phys Med Rehabil*. 1998;79(8):931–8.

23. ATS Statement. Guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–7.
24. Resnik L, Borgia M. Reliability of outcome measures for people with lower-limb amputations: distinguishing true change from statistical error. *Phys Ther*. 2011;91(4):555–65.
25. Balk EM, Gazula A, Markozannes G, Kimmel HJ, Saldanha IJ, Resnik LJ, et al. Lower limb prostheses: measurement instruments, comparison of component effects by subgroups, and long-term outcomes. Comparative Effectiveness Review No. 213. Rockville (MD): Agency for Healthcare Research and Quality; 2018. AHRQ Publication No. 18-EHC017-EF.
26. Dite W, Temple VA. A clinical test of stepping and change of direction to identify multiple falling older adults. *Arch Phys Med Rehabil*. 2002;83(11):1566–71.
27. Sawers A, Kim J, Balkman G, Hafner BJ. Interrater and test-retest reliability of performance-based clinical tests administered to established users of lower limb prostheses. *Phys Ther*. 2020; 100(7):1206–16.
28. Dite W, Connor HJ, Curtis HC. Clinical identification of multiple fall risk early after unilateral transtibial amputation. *Arch Phys Med Rehabil*. 2007;88(1):109–14.
29. Ramstrand N, Nilsson KA. Validation of a patient activity monitor to quantify ambulatory activity in an amputee population. *Prosthet Orthot Int*. 2007;31(2):157–66.
30. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res*. 2016; 25(3):1057–73.

Effects of a Home-Based Fall Prevention Program in Older Lower Limb Prosthesis Users: A Randomized Controlled Trial

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ABSTRACT

Objective: To analyze the effects of a home-based fall prevention program on dynamic and static balance and balance confidence in older lower limb prosthesis (LLP) users.

Materials and Methods: In this randomized controlled trial, 44 older LLP users were randomly assigned to either a control group receiving usual care or an intervention group receiving a fall prevention program consisting of education and 16 home-based exercises performed three times per week for eight weeks. Dynamic balance was measured using the Timed Up and Go (TUG) test, static balance using center of pressure displacement, and balance confidence using the Activities-specific Balance Confidence scale. Outcomes were assessed at baseline and post-intervention.

Results: Forty-one of 44 randomized participants completed the study. Among the 44 randomized participants, the mean age was 68.6 ± 6.7 years; 86% were male; 61% had transtibial amputations; 66% had traumatic amputation. The change in TUG time did not differ significantly between groups (median (inter-quartile range) change: -0.6 ($-1.5, 0.4$) seconds in the intervention group and -0.4 ($-1.2, 0.3$) seconds in the control group; $p = 0.584$, $r = 0.09$). No significant between-group differences were observed in static balance or balance confidence. No falls were reported during the study.

Conclusion: A combined fall prevention education and eight-week home-based exercise program did not result in significantly greater improvements than usual care in dynamic balance, static balance, or balance confidence among older LLP users with relatively high functional mobility. The findings should be interpreted with consideration of the unblinded outcome assessment.

Keywords: Fall prevention; older adult; amputee; lower limb; prosthesis (Siriraj Med J 2026;78(10):805-815)

INTRODUCTION

Following a lower limb amputation (LLA), individuals have a reduced ability to correct balance disturbances due to the loss of proprioceptive information from the amputated limb.¹ As a result, balance in both the anteroposterior and mediolateral directions is significantly reduced.² When people with LLA age, their ability to correct balance declines further, thereby increasing their risk of falling.³ Falls in this population are common, and approximately 40 to 60% of those who fall sustain fall-related injuries.⁴ Such falls often lead to severe injuries, including fractures,⁵ brain injury,⁶ and residual limb injuries,⁷ leading to hospitalization and increased healthcare costs.⁸ Beyond their physical consequences, falls are associated with decreased balance confidence and increased fear of falling,^{9,10} which may contribute to activity restriction and reduced social participation among individuals with LLA.^{9,10}

Fall risk among older lower limb prosthesis (LLP) users is multifactorial, resulting from a combination of age-related and amputation-specific factors.⁴ Although exercise-based fall prevention interventions have shown improvements in physical performance among individuals with LLA, most have adapted established fall prevention models developed for older adult population and have focused on supervised, high-intensity, or task-specific training in relatively younger or mixed-age cohorts.¹¹ A recent meta-analysis demonstrated significant improvements

in gait speed, 2-minute walk test performance, and Timed Up and Go (TUG) test performance in favor of exercise interventions compared with usual care.¹² Additionally, randomized controlled trials have demonstrated reduction in fall incidence and improvements in gait speed following individualized training.³ Nevertheless, current evidence specifically targeting fall prevention exercise programs for older LLP users, particularly those delivered through a home-based approach, remains limited.

Fall prevention education is an important component of multifactorial fall prevention programs for older adults. Previous systematic reviews have shown that educational interventions improve fall-related knowledge and preventive behaviors, particularly when combined with exercise.¹³ However, the effectiveness of such educational approaches in older LLP users has not yet been established.

Although previous studies have implemented exercise-based fall prevention interventions for LLP users, these programs have mainly focused on physical training components, with limited incorporation of educational elements.³ According to the World Health Organization's Falls Prevention for Active Aging model, effective fall prevention strategies should integrate education to increase awareness of fall risk, promote safe behaviors, and enhance adherence to exercise.¹⁴ Moreover, home-based interventions extend rehabilitation support into the home environment and offer advantages in accessibility, feasibility, cost-effectiveness, and long-term sustainability.

These programs are particularly suitable for individuals who are unable to attend supervised sessions.¹⁵ Therefore, developing a program that integrates education with strength and balance exercises tailored to the functional demands of older LLP users may provide a practical approach to fall prevention in this population. However, evidence regarding the combined effects of fall prevention education and home-based exercise on balance outcomes specifically in older LLP users remains limited.

Therefore, the aim of this randomized controlled trial was to analyze the effects of a home-based program combining fall prevention education and exercise on dynamic and static balance and balance confidence in older LLP users. It was hypothesized that participants receiving the combined fall prevention education and home-based exercise program would demonstrate greater improvements in dynamic balance, static balance, and balance confidence than those receiving usual care.

MATERIALS AND METHODS

This study was conducted at the clinic of the Sirindhorn School of Prosthetics and Orthotics (SSPO) after receiving approval from the Institutional Review Board of the Faculty of Medicine Siriraj Hospital (COA no. Si 776/2024) (Thai Clinical Registry, ID no. TCTR20250525005, on May 25th, 2025).

Participants

The inclusion criteria were LLP users aged at least 60 years who had used a prosthesis for more than one year, were able to walk daily with the prosthesis for at least eight hours a day without pain,¹⁶ and were able to speak and read Thai. The exclusion criteria were cognitive impairment, a history of severe depression, or other mental disorders. Cognitive impairment was screened using the Montreal Cognitive Assessment (MoCA), and participants with a score below 26 were not included.¹⁷ During the recruitment interview participants were asked if they had a history of a diagnosed psychiatric disorder, including severe depression.

Procedure

Data collection was conducted between June and October 2025. The participants were recruited through an invitation poster distributed by the researcher (PS). Individuals who expressed interest contacted the researcher and underwent eligibility screening. Eligible participants received a detailed explanation of the study procedures using a participant information sheet before providing written informed consent.

Participants were randomly assigned to either the

intervention group or the control group, which received usual care, in a 1:1 ratio. The allocation sequence was generated by a statistician using block randomization with mixed block sizes. Sequentially numbered, sealed opaque envelopes containing the allocation were prepared by the researcher according to the allocation sequence. After enrollment, the envelope was provided to the participant sequentially and opened to reveal the group allocation. One researcher conducted participant recruitment, intervention delivery, follow-up, and outcome assessments and was therefore not blinded to group allocation.

Baseline assessments were performed before the intervention, and all outcome measures were reassessed after the 8-week intervention period.

Intervention group: Fall prevention education and exercise program

The conceptual framework of this study was adapted from the World Health Organization's Falls Prevention for Active Aging model at the individual level and comprised of education to raise awareness of fall prevention, pre-post assessment of fall risk (dynamic and static balance and perceived balance confidence), as well as an evidence-based exercise program.¹⁴

Participants in the intervention group attended a 1-hour face-to-face education session delivered by the researcher. Additionally, they received a fall prevention booklet¹⁸ specifically developed for older LLP users. The education session included verbal instruction on falls and their consequences, risk factors for falls, fall prevention strategies, environmental safety, the benefits of exercise, exercise principles and precautions and guidance on the home-based strength and balance exercise program. Participants were also given a demonstration of the exercises and practiced them during the session to ensure correct and safe performance.

The home-based exercise program was adapted from the Otago Exercise Program.¹⁹ It consisted of 16 exercises: five strengthening exercises (knee extensor, knee flexor, hip abductor, calf raises, and toe raises) and 11 balance retraining exercises (knee bends, backwards walking, walking and turning around, sideways walking, tandem stance, tandem walking, heel walking, toe walking, backward heel-toe walking, sit-to-stand, and stair walking). Participants were instructed to follow the sequence presented in the booklet.¹⁸ Although no structured progression of exercise intensity or resistance was used, upper-limb support during balance exercises was reduced according to the ability of the participants. Walking was not prescribed as a separate aerobic exercise component of the program. Participants were instructed to perform the exercises

three times per week for eight weeks.¹⁹ Each exercise session lasted approximately 30 minutes and could be divided into three 10-minute sessions throughout the day. Participants recorded exercise completion in a logbook. To support adherence, participants received weekly telephone follow-up calls throughout the study period²⁰ and visited the clinic at week 4 to review exercise performance. During this visit, participants practiced the exercises under the researcher's supervision to ensure correct and safe performance. Exercise compliance was assessed only in the intervention group using participant-completed logbooks and was calculated as the mean number of prescribed exercise sessions completed during the eight-week program.

Control group:

Usual prosthetic care at the clinic includes a routine follow-up visit approximately one month after prosthesis delivery. During this visit, participants received standard verbal instructions regarding residual limb care, care of the remaining limb, prosthesis maintenance, and general safety instructions. They were also provided with a pamphlet on self-care and prosthesis maintenance. During the 8-week study period, control-group participants continued their usual prosthetic care and received no structured exercise training or additional follow-up calls.

To minimize contamination between groups, appointments for intervention and control groups were scheduled at different times, and all clinicians at the clinic were informed about this study to avoid contamination. Fall occurrence was assessed by participant self-report in both groups at weeks 4 and 8. At the end of the study, control-group participants were asked whether they had engaged in any exercise during the study period.

Outcome measures

Primary outcome: Dynamic balance

Dynamic balance was assessed using an inertial sensor (G-Walk, BTS Bioengineering, Milan, Italy) during the TUG test.²¹ Prior to the TUG test, the G-Walk inertial measurement unit (IMU) sensor was placed at the lower back at waist level. Participants were instructed to stand up from a chair, walk three meters at a self-selected comfortable walking speed, turn around, walk back to the chair, and sit down. One practice trial was performed before data collection.²² The TUG test was then performed three times, and the mean time (in seconds) of the three trials was used for analysis. In older adults, a TUG time of ≥ 13.5 seconds is associated with an increased risk of falling,²³ whereas in people with a LLA, a TUG time of ≥ 19.0 seconds is associated with an increased risk of multiple falls.²⁴

Secondary outcome: Static balance and balance confidence

Static balance was assessed by measuring GRAIL-derived center of pressure (COP) displacement as an exploratory measure while standing on an instrumented split-belt treadmill (GRAIL, Motek Medical B.V., Houten, Netherlands). COP signals were sampled at 100 Hz. Participants stood with their hands at their sides and adopted a self-selected comfortable base of support on the GRAIL. All assessments were performed using the participants' usual prosthesis alignment and footwear. Measurements were obtained under two conditions: eyes open (three trials, 30 seconds each) and eyes closed (three trials, 30 seconds each).²⁵ During the eyes-open condition, participants were instructed to focus on a black wall at a distance of 1.5 meters at eye level to minimize external disturbances during testing.²⁶ The COP outcomes included mean COP displacement, maximal sway amplitude in the anteroposterior and mediolateral directions, and sway velocity. COP variables were recorded for each trial, and the mean of the three trials was used for analysis. For each trial, the first 100 frames (1 s) were excluded, and the subsequent 3,000 frames (30 s) were used for analysis. No additional filtering was applied to the exported COP data. COP displacement between consecutive samples was calculated as the Euclidean distance, $d_i = \sqrt{(Cx_i - Cx_{i-1})^2 + (Cy_i - Cy_{i-1})^2}$, where Cx and Cy represent the mediolateral and anteroposterior COP coordinates, respectively. Total sway path was calculated as the sum of consecutive COP displacements, and mean distance was calculated as the mean of these displacements. Maximum sway amplitudes in the mediolateral and anteroposterior directions were calculated as the difference between the maximum and minimum Cx and Cy coordinates, respectively. Sway velocity was calculated by dividing the total sway path by the 30-second analysis duration. Trials in which participants stepped or were unable to complete the assessment were excluded and repeated. Greater mean distance, sway amplitude, and sway velocity indicated poorer static balance.

Balance confidence was assessed using the Activities-specific Balance Confidence Scale (ABC scale), which measures fall-related self-efficacy and perceived confidence in performing daily activities without losing balance.²⁷ Participants rated their balance confidence in performing 16 activities on a scale from 0 (no confidence) to 100 (complete confidence). In the original study, older adults with high mobility demonstrated a mean ABC score of approximately 80%.²⁸ Previous studies in community-dwelling older adults have suggested that ABC scores below 67% are associated with an increased risk of falling.²⁷

Sample size calculation

The sample size was calculated using nQuery Advisor based on an independent-samples *t*-test. Because no previous intervention studies in older LLP users reporting TUG outcomes were available at the time of study planning, the sample size calculation was based on data of a study considering most similar in older adults using a 12-week Otago exercise program.²⁹ The expected post-intervention TUG times at 8 weeks for the intervention and control groups were 9.0 and 10.9 seconds, respectively, corresponding to an expected between-group difference of 1.9 seconds, with an assumed standard deviation of 2.0 seconds.²⁹ With a two-sided significance level of 0.05 and 80% power, 19 participants per group were required. A 15% dropout was added, resulting in 22 participants in each group.

Data analysis

Statistical analyses were performed using SPSS Statistics (version 31) (IBM, Armonk, NY, USA). Descriptive statistics were used to summarize participant characteristics at baseline. Continuous variables were presented as mean and standard deviation (SD) or median and inter-quartile range, depending on data distribution, which was assessed using the P-P plots and the Shapiro–Wilk test. Categorical variables were reported as frequencies and percentages.

For all outcome measures, change scores were calculated as the difference between post-intervention and baseline values. Because the dynamic and static balance outcomes were non-normally distributed, between-group comparisons were conducted using the Mann–Whitney U test and are presented as median (inter-quartile range). Effect sizes were calculated as $r = Z/\sqrt{N}$. Balance confidence, which met normality assumptions, was analyzed using the independent-samples *t*-test. Both per-protocol and an intention-to-treat analyses were performed for the primary outcome (TUG). Secondary outcomes were analyzed using a per-protocol approach. For participants with missing post-intervention TUG data, the baseline TUG value was carried forward as the post-intervention value using the last observation carried forward method, resulting in a change score of zero. All randomized participants were included in the intention-to-treat analysis. All statistical tests were two-tailed, and statistical significance was set at $p \leq 0.05$.

RESULTS

A total of 69 individuals were assessed for eligibility, and 44 participants were randomized. Three participants were lost to follow-up, two in the intervention group and one in the control group, because they were unable to attend the second appointment (Fig 1).

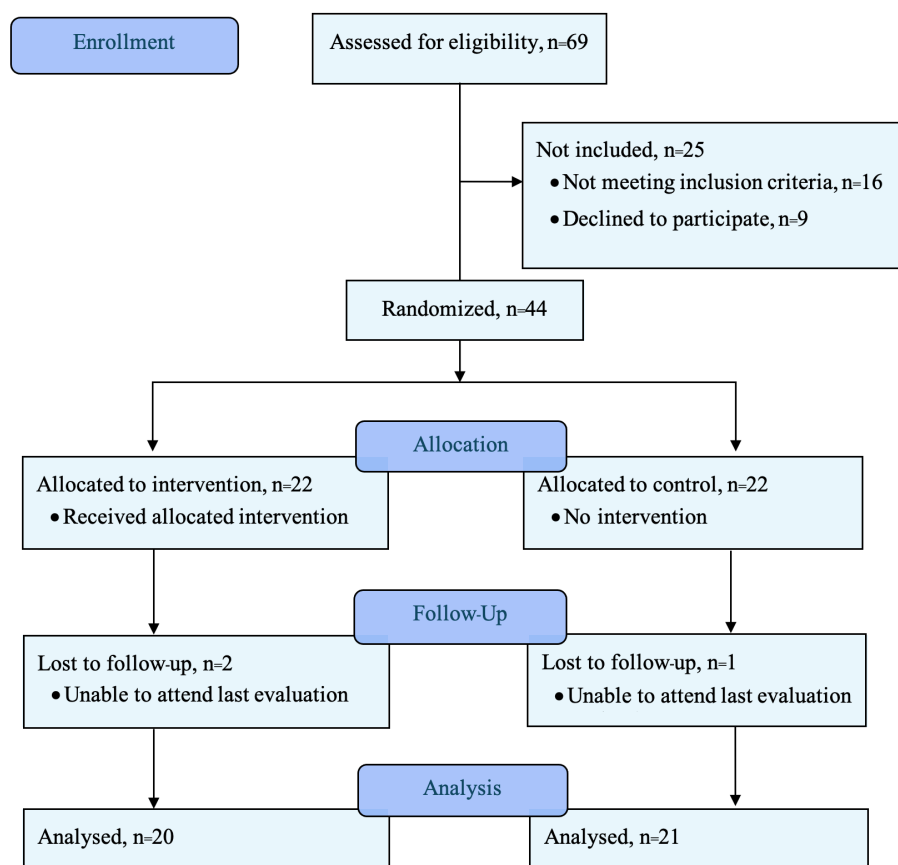


Fig 1. Flow diagram of the randomized controlled trial

Baseline and clinical characteristics were similar between the groups (Table 1). In the intervention group, the median (inter-quartile range) exercise compliance was 24 (12, 24) of the prescribed 24 sessions. No participants in the control group reported engaging in additional exercise during the study period, apart from their usual daily walking activities.

The per-protocol analysis revealed no significant between-group difference in the change in TUG time (Table 2). The intention-to-treat analysis yielded similar nonsignificant results (Mann–Whitney U test, $p = 0.606$ ($r = 0.08$)).

Changes in COP mean distance, maximal sway amplitude in both directions, and sway velocity under

TABLE 1. Participant characteristics ($n=44$).

	Total ($n = 44$)	Intervention group ($n = 22$)	Control group ($n = 22$)	p -value
Age (years), mean (SD)	68.6 (6.7)	69.2 (7.2)	68.0 (6.3)	0.572 ^a
Gender (male), n (%)	38 (86)	20 (91)	18 (82)	0.664 ^b
Weight (kilograms), mean (SD)	62.9 (11.0)	63.6 (10.7)	62.1 (11.5)	0.657 ^c
Height (centimeters), mean (SD)	164.0 (7.6)	164.8 (6.0)	163.2 (9.0)	0.507 ^c
Level of amputation, n (%) *				0.391 ^d
PF	1 (2)	1 (5)	-	
AD	2 (5)	-	2 (9)	
TT	27 (61)	14 (64)	13 (59)	
KD	1 (2)	-	1 (5)	
TF	13 (30)	7 (32)	6 (27)	
Cause of amputation, n (%) *				0.570 ^d
Traumatic	29 (66)	13 (59)	16 (73)	
Diabetes	4 (9)	2 (9)	2 (9)	
Infected wound	5 (11)	4 (18)	1 (5)	
Other	6 (14)	3 (14)	3 (14)	
Type of prosthetic foot, n (%) *				0.391 ^d
SACH foot	27 (61)	14 (64)	13 (59)	
Single-axis foot	13 (30)	6 (27)	7 (32)	
Dynamic-response foot	1 (2)	1 (5)	0 (0)	
Pirogoff foot	2 (5)	0 (0)	2 (9)	
Custom-made foot	1 (2)	1 (5)	0 (0)	
Education, n (%)				0.318 ^d
No education	1 (2)	-	1 (5)	
Primary	20 (45)	9 (41)	11 (50)	
Secondary	13 (30)	9 (41)	4 (18)	
College level or higher	10 (23)	4 (18)	6 (27)	
Number of falls in the previous year, median (IQR)	0 (0;1)	1 (0;2)	0 (0;1)	0.079 ^a
Number of falls during the study period, median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	NA
Completed exercise sessions (out of 24), median (IQR)	-	24 (12;24)	-	

* The sum of percentages isn't equal to 100 because of rounding.

Exercise compliance was applicable to the intervention group only.

The total number of falls reported during the previous year was 29 in the intervention group and 16 in the control group.

Abbreviations: SD = standard deviation, IQR = inter-quartile range, PF = partial foot, AD = ankle disarticulation, TT = transtibial, KD = knee disarticulation, TF = transfemoral.

^aMann–Whitney U, ^bFisher's Exact Test, ^cIndependent Sample T-Test, ^dPearson Chi-square.

NA = not applicable because no participant experienced a fall during the study period.

TABLE 2. Dynamic and static balance outcomes at two time points, and between-group comparisons of change scores with effect sizes (per-protocol analysis).

Outcome	Pre (n=22)	Intervention Post (n=20)	Change (n=20)	Pre (n=22)	Control Post (n=21)	Change (n=21)	p-value	Effect size
Dynamic balance (TUG)								
Total time (s)	14.2 (13.1;16.3)	14.3 (12.3;16.4)	-0.6 (-1.5;0.4)	14.9 (14.7;17.2)	16.1 (14.4;18.2)	-0.4 (-1.2;0.3)	0.584	$r = 0.09$
Static balance (COP displacement)								
Eyes-opened								
Mean distance (mm)	3.4 (2.8;4.2)	3.9 (2.9;4.3)	0.3 (-0.7;1.1)	3.8 (3.1;4.5)	3.0 (2.7;4.6)	-0.2 (-0.9;0.5)	0.355	$r = 0.15$
Sway maximal amplitude (mm)								
Anteroposterior	33.4 (26;38.6)	33.5 (26.8;39.9)	1.1 (-1.9;4.8)	27.9 (25.0;33.8)	29.2 (27.1;34.4)	-1.3 (-3.2;2.4)	0.461	$r = 0.12$
Mediolateral	17.6 (14.9;22.5)	18.7 (16.3;24.5)	1.5 (-0.9;4.1)	16.4 (13.0;22.2)	16.9 (14.7;18.5)	0.2 (-2.3;3.8)	0.495	$r = 0.11$
Sway velocity (mm/s)	337.7 (281.9;415.5)	394.6 (287.6;428.2)	30.6 (-65.7;110.4)	380.1 (309.2;447.1)	296.2 (265.4;463.1)	-22.3 (-90.6;43.5)	0.383	$r = 0.14$
Eyes-closed								
Mean distance (mm)	3.2 (2.8;4.5)	3.7 (2.5;4.4)	-0.4 (-1.1;1.1)	3.8 (3.1;4.6)	3.6 (2.5;4.7)	-0.3 (-0.6;0.5)	0.938	$r = -0.02$
Sway maximal amplitude (mm)								
Anteroposterior	37.4 (33.4;45.0)	40.7 (35.6;47.3)	0.4 (-2.1;5.7)	41.7 (31.8;44.9)	37.0 (32.1;45.1)	2.2 (-6.3;9.0)	0.729	$r = 0.06$
Mediolateral	22.1 (18.0;26.0)	22.7 (17.3;25.5)	0.2 (-4.1;2.8)	24.2 (16.2;27.6)	20.8 (17.5;24.7)	-2.2 (-3.4;2.4)	0.863	$r = -0.03$
Sway velocity (mm/s)	321.7 (287.7;455.5)	388.6 (265.5;442.5)	-31.4 (-91.5;100.9)	390.9 (311.4;459.4)	399.1 (249.2;500.0)	-30.5 (-59.3;53.2)	0.840	$r = -0.04$
Balance confidence (ABC)	81.4 (12.0)	83.8 (12.3)	2.4 (9.4)	79.8 (14.8)	83.1 (13.4)	3.3 (8.1)	0.750	$d = 0.10$

Values are presented as median (inter-quartile range), except for balance confidence (ABC), which is presented as mean (SD).

Change scores were calculated for each participant as the post-intervention value minus the baseline value and included only participants with data available at both time points.

Effect sizes are reported as r for Mann-Whitney U tests and Cohen's d for the independent-samples t -test.

Abbreviations: TUG = Timed-up-and-go, COP = center of pressure, ABC = Activities-specific Balance Confidence, mm = millimeter, mm/s = millimeter/second.

eyes-open and eyes-closed conditions did not differ significantly between the intervention and control groups (all p values > 0.05 , r ranged from -0.04 to 0.15 , Table 2).

Balance confidence, measured using the ABC Scale, also did not differ significantly between groups (Table 2). The between-group mean difference in change was -0.9% (95% CI = -6.46 to 4.66 ; independent samples t -test, $p = 0.750$; Cohen's $d = 0.10$). Analyses of the ABC scale were based on complete-case data. No falls were reported during the training period in the intervention group or the control group (Table 1).

DISCUSSION

No significant between-group differences were observed in dynamic balance (TUG), static balance (COP displacement under eyes-open and eyes-closed conditions), or balance confidence (ABC scale) following the eight-week intervention. Although TUG time showed a slight reduction in the intervention group, baseline TUG values were well below the established fall-risk threshold for individuals with LLA (≥ 19 s).²⁴ Our participants had relatively high functional mobility, as reflected by their baseline TUG performance, low fall incidence, and moderate-to-high balance confidence ($\sim 80\%$). The sample was also composed predominantly of individuals with transtibial amputations (mean age 68.6 ± 6.7 years; predominantly transtibial amputees). Given that a transtibial amputation is generally associated with better mobility outcomes than more proximal levels,³⁰ these characteristics may have limited the potential for improvement with a short-term exercise intervention. Greater effects may require a more individualized and progressively challenging training approach.

Multicomponent exercise, incorporating different exercise modalities such as balance, functional, and resistance training, is recommended for fall prevention in older adults. Exercise intensity and progression should be individualized according to functional capacity and comorbidities.³¹ Systematic reviews have shown that structured exercise programs can improve physical performance in individuals with LLA.^{12,32} In a meta-analysis a significant pooled improvement in TUG time was found (weighted mean difference = -2.01 s, 95% CI = -3.90 to -0.13) in favor of exercise interventions.¹² However, many of the included studies enrolled relatively younger participants (often in their 50s to early 60s) and individuals with mixed amputation levels compared to participants in the current study.^{3,12,33} These differences in participant characteristics may partly explain the smaller treatment effects observed in our

study, as older LLP users with relatively high functional mobility may require more intensive, longer-duration, or progressively challenging interventions to achieve measurable balance adaptations.¹² Previous studies have incorporated supervised progressive resistance training, treadmill-based perturbation training, task-specific gait training, and structured progression of exercise intensity or complexity.¹¹ Given the relatively high functional mobility of participants in the present study, a greater emphasis on progressive resistance and progressively challenging balance exercises may have provided a more appropriate training stimulus. In contrast, the present program was primarily home-based, included only two supervised sessions, and did not incorporate structured progression, progressive overload, or perturbation-based components. Furthermore, walking was not prescribed as a separate aerobic exercise component. Although several exercises involved walking tasks, these were designed primarily as balance exercises rather than aerobic training. Considering the relatively high functional mobility of the participants, the intervention focused primarily on strength and balance exercises; however, the absence of a structured aerobic component may have limited the overall training stimulus. The intervention intensity was intentionally designed to be moderate and feasible for older LLP users to ensure safety and promote adherence. However, this conservative approach may have limited the magnitude of balance improvements observed. Although exercise adherence was acceptable, with a median (inter-quartile range) of 24 (12, 24) completed sessions, variability in completion of specific exercises was observed. In particular, some participants did not perform the stair-ascending and stair-descending task due to environmental constraints (e.g., absence of stairs at home) or fear of stair negotiation. Because stair ambulation represents a higher-level, task-specific balance challenge, reduced exposure to this component may have attenuated the overall training stimulus and limited potential functional gains.

Additionally, structural and prosthetic factors, including socket fit, prosthetic alignment, and prosthetic foot characteristics, are known to influence center of pressure displacement and postural steadiness during quiet standing.^{34,35} As these biomechanical determinants were not modified or controlled in the present study, changes in static balance measures may have been limited despite participation in the exercise program. Balance confidence may also be less responsive to short-term physical training alone because psychosocial factors contribute substantially to self-perceived stability.^{36,37}

Taken together, the small effect sizes across all outcomes indicate that the intervention did not produce measurable benefits beyond usual care.

These findings suggest that an eight-week program consisting primarily of fall prevention education and home-based exercise program did not result in statistically significant improvements in older LLP users with relatively high functional mobility. More intensive, longer-duration, or task-specific interventions may be required to elicit clinically meaningful improvements.

Limitations

Several limitations should be considered when interpreting the results of this study. Although exercise adherence was generally acceptable, variability in session completion may have influenced individual responses to the intervention. In addition, exercise adherence was assessed using self-reported logbooks, which may have introduced information bias due to inaccurate or incomplete recording.

Although exercise completion was monitored using participant logbooks and weekly follow-up calls, actual exercise performance and quality of execution could not be objectively verified. Therefore, variability in adherence to the prescribed exercises may have influenced the effectiveness of the intervention. However, the consistency between the complete-case and intention-to-treat sensitivity analyses suggests that the study findings were not substantially influenced by the small number of dropouts.

Furthermore, the relatively high functional mobility of the participants may limit generalizability of the findings to individuals with lower baseline mobility, or a higher risk of falls. In addition, the predominantly male composition of the sample should be considered when interpreting the applicability of these findings to female older LLP users.

Moreover, participant recruitment, intervention delivery, follow-up, and outcome assessments were conducted by the same unblinded researcher, which may have introduced performance and detection bias, particularly for timed and self-reported outcomes. The intervention group also received more frequent contact through weekly telephone calls and a supervised visit at week 4, whereas the control group did not receive matched attention. This differential contact represents a potential co-intervention and may have influenced participant engagement and self-reported outcomes. Adverse events were not systematically collected, which limited the assessment of potential intervention-related harms.

Future research should consider stratifying participants according to baseline functional level or fall history to better target individuals at higher risk of falls, as well as examining whether amputation level and prosthetic characteristics influence intervention outcomes. Studies should also investigate the effects of progressive, task-specific balance challenges and extended interventions and follow-up periods.

CONCLUSIONS

A fall prevention education and exercise program consisting of verbal instruction on fall prevention supported by a booklet and an eight-week program of 16 strength and balance exercises did not result in significantly greater improvements than usual care in dynamic balance, static balance, or balance confidence in older LLP users with relatively high functional mobility. These findings suggest that a longer duration of training or a higher-intensity, progressively challenging exercise program may be required to produce meaningful changes in balance performance in this population.

Data Availability Statement

The data that support the findings of this study are available from the first author upon reasonable request.

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DECLARATIONS

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Conflict of Interest

The authors report no conflicts of interest.

Registration Number of Clinical Trial

Thai Clinical Registry (ID no. TCTR20250525005) on May 25th, 2025.

Author Contributions

Conceptualization and methodology, P.S., P.U.D., K.S., G.G., and J.P. ; Investigation, P.S. ; Formal analysis, P.S. and J.P. ; Visualization, P.S. ; Writing – original draft,

P.S., P.U.D. and J.P. ; Writing – review and editing, P.S., P.U.D., K.S., G.G. and J.P. ; Funding acquisition, P.S. and J.P. ; Supervision, P.U.D., K.S., G.G. and J.P. ; All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

The authors declare they have not used artificial intelligence.

Institutional Review Board Statement

This study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si 776/2024) on October 3rd, 2024. Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the protocol approved by the Siriraj Institutional Review Board.

REFERENCES

- Kanade R, Van Deursen RWM, Harding KG, Price PE. Investigation of standing balance in patients with diabetic neuropathy at different stages of foot complications. *Clin Biomech.* 2008; 23(9):1183–91.
- Buckley JG, O'Driscoll D, Bennett SJ. Postural sway and active balance performance in highly active lower-limb amputees. *Am J Phys Med Rehabil.* 2002;81(1):13–20.
- Schafer ZA, Perry JL, Vanicek N. A personalised exercise programme for individuals with lower limb amputation reduces falls and improves gait biomechanics: a block randomised controlled trial. *Gait Posture.* 2018;63:282–9.
- Hunter SW, Batchelor F, Hill KD, Hill AM, Mackintosh S, Payne M. Risk factors for falls in people with a lower limb amputation: a systematic review. *PM R.* 2017;9(2):170–80.e1.
- Lewallen R, Johnson E Jr. Fractures in amputation stumps: review of treatment of 16 fractures. In: *Mayo Clinic Proceedings*; 1981.
- Kulkarni J, Wright S, Toole C, Morris J, Hirons R. Falls in patients with lower limb amputations: prevalence and contributing factors. *Physiotherapy.* 1996;82(2):130–6.
- Behar T, Burnham S, Johnson G Jr. Major stump trauma following below-knee amputation. Outcome and recommendations for therapy. *J Cardiovasc Surg.* 1991;32(6):753–6.
- Mundell B, Maradit Kremers H, Visscher S, Hoppe K, Kaufman K. Direct medical costs of accidental falls for adults with transfemoral amputations. *Prosthet Orthot Int.* 2017;41(6):564–70.
- Miller WC, Deathe AB, Speechley M, Koval J. The influence of falling, fear of falling, and balance confidence on prosthetic mobility and social activity among individuals with a lower extremity amputation. *Arch Phys Med Rehabil.* 2001;82(9):1238–44.
- Miller WC, Speechley M, Deathe B. The prevalence and risk factors of falling and fear of falling among lower extremity amputees. *Arch Phys Med Rehabil.* 2001;82(8):1031–7.
- Clemens S, Doerger C, Lee SP. Current and emerging trends in the management of fall risk in people with lower limb amputation. *Curr Geriatr Rep.* 2020;9(3):134–41.
- Chang S, Yan JX, Mu L. Effects of exercise on physical performance and quality of life in individuals with limb amputation: a systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2025;26(1):965.
- Ong MF, Soh KL, Saimon R, Wai MW, Mortell M, Soh KG. Fall prevention education to reduce fall risk among community-dwelling older persons: a systematic review. *J Nurs Manag.* 2021;29(8):2674–88.
- World Health Organization. WHO global report on falls prevention in older age. Geneva: World Health Organization; 2008.
- McDonough CM, Harris-Hayes M, Kristensen MT, Overgaard JA, Herring TB, Kenny AM, et al. Physical therapy management of older adults with hip fracture. *J Orthop Sports Phys Ther.* 2021; 51(2):1–81.
- Klute GK, Berge JS, Orendurff MS, Williams RM, Czerniecki JM. Prosthetic intervention effects on activity of lower-extremity amputees. *Arch Phys Med Rehabil.* 2006;87(5):717–22.
- Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695–9.
- Sakulkosol P, Dijkstra PU, Sasaki K, Guerra G, Poonsiri J. Development and evaluation of a patient education booklet on fall prevention exercises for older lower limb prosthesis users. *Siriraj Med J.* 2026;78(2):87–95.
- Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM. Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. *BMJ.* 1997;315(7115):1065–9.
- Simek EM, McPhate L, Haines TP. Adherence to and efficacy of home exercise programs to prevent falls: a systematic review and meta-analysis of the impact of exercise program characteristics. *Prev Med.* 2012;55(4):262–75.
- Mangano GR, Valle MS, Casabona A, Vagnini A, Cioni M. Age-related changes in mobility evaluated by the timed up and go test instrumented through a single sensor. *Sensors.* 2020;20(3):719.
- Podsiadlo D, Richardson S. The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* 1991;39(2):142–8.
- Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther.* 2000;80(9):896–903.
- Dite W, Connor HJ, Curtis HC. Clinical identification of multiple fall risk early after unilateral transtibial amputation. *Arch Phys Med Rehabil.* 2007;88(1):109–14.
- Quijoux F, Vienne-Jumeau A, Bertin-Hugault F, Zawieja P, Lefevre M, Vidal PP, et al. Center of pressure displacement characteristics differentiate fall risk in older people: a systematic review with meta-analysis. *Ageing Res Rev.* 2020;62:101117.
- Tjernström F, Björklund M, Malmström EM. Romberg ratio in quiet stance posturography—test to retest reliability. *Gait Posture.* 2015;42(1):27–31.
- Lajoie Y, Gallagher S. Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg Balance Scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers. *Arch Gerontol Geriatr.* 2004;38(1):11–26.
- Powell LE, Myers AM. The activities-specific balance confidence

- (ABC) scale. *J Gerontol A Biol Sci Med Sci.* 1995;50A(1):M28-34.
29. Khumpaneid N, Phoka T, Khongprasert S. Effects of modified-Otago exercise program on four components of actual balance and perceived balance in healthy older adults. *Geriatrics.* 2022; 7(5):88.
30. Fortington LV, Rommers GM, Geertzen JH, Postema K, Dijkstra PU. Mobility in elderly people with a lower limb amputation: a systematic review. *J Am Med Dir Assoc.* 2012; 13(4):319–25.
31. Montero-Odasso M, Van Der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. *Age and ageing.* 2022 Sep;51(9):afac205.
32. Wijekoon A, Jayawardana S, Milton-Cole R, Chandrathilaka M, Jones A, Cook S, et al. Effectiveness and equity in community-based rehabilitation on pain, physical function, and quality of life after unilateral lower limb amputation: a systematic review. *Arch Phys Med Rehabil.* 2023;104(9):1484–97.
33. Godlwana L, Stewart A, Musenge E. The effect of a home exercise intervention on persons with lower limb amputations: a randomized controlled trial. *Clin Rehabil.* 2020;34(1):99–110.
34. Pinzur MS, Cox W, Kaiser J, Morris T, Patwardhan A, Vrbos L. The effect of prosthetic alignment on relative limb loading in persons with trans-tibial amputation: a preliminary report. *J Rehabil Res Dev.* 1995;32(4):373–7.
35. Arifin N, Abu Osman NA, Ali S, Gholizadeh H, Wan Abas WAB. Postural stability characteristics of transtibial amputees wearing different prosthetic foot types when standing on various support surfaces. *Sci World J.* 2014;2014:856279.
36. Van Velzen J, van Bennekom CA, Polonski W, Slootman J, van der Woude LH, Houdijk H. Physical capacity and walking ability after lower limb amputation: a systematic review. *Clin Rehabil.* 2006;20(11):999–1016.
37. Wong CK, Gibbs WB. Factors associated with committed participation in a wellness-walking program for people with lower limb loss: a prospective cohort study. *Prosthet Orthot Int.* 2019;43(2):180–7.

Corrigendum to: Survival and Factors Predictive of Survival in Patients with Thymic Carcinoma

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The author would like to correct the error in the publication of the original article¹ and has informed the editor to correct as follows:

Content of Correction:

Incorrect: The COA number in the article:
COA no. Si 609/2014(EC2)

Correct:
COA no. Si 710/2014

REFERENCE

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