ANNALS

OFFICIAL JOURNAL OF THE ACADEMY OF MEDICINE, SINGAPORE

VOLUME 53

NUMBER 12

DEC 2024

Perioperative emergency laparotomy pathway for patients undergoing emergency laparotomy: A propensity score matched study

An intervention team comprising specialist clinicians, hospital administrators and quality improvement staff examined the outcomes of care pathway for emergency laparotomy patients.
(See full article, p.xxx)

Illustration by Nata Blackthorn

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ISSN 2972-4066

Annals, Academy of Medicine, Singapore

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Ann Acad Med Singap 2024;53:707-709
https://doi.org/10.47102/annals-acadmedsg.2024358

EDITORIAL

Intrapleural fibrinolytic therapy: How low can we get?

Imran Bin Mohamed Noor[1] *FCCP*, Sze Khen Tan[2] *MMed (Int Med)*

Pleural infection is a common medical problem with significant mortality and morbidity.[1] Despite advances in antibiotic therapy, the incidence of pleural infection is increasing in the Western world. The management of complicated pleural infections usually involves drainage of pleural effusion from the infected pleural cavity, typically with a pleural drain. When drainage fails, surgery is often required, but is contraindicated in patients who have significant medical comorbidities.

The Second Multicentre Intrapleural Sepsis Trial (MIST2) by Rahman et al. showed that intrapleural fibrinolytic therapy (IPFT) can improve drainage of pleural infection, resulting in the improvement of chest X-ray (CXR) opacification, shorter hospital length of stay and avoidance of surgery.[2] Patients in MIST2 were randomised into 4 groups, with the best clinical outcome seen in the group treated with the combination of alteplase and dornase (DNase). In this group, patients were administered 10 mg of alteplase and 5 mg of DNase to break down pleural septations and reduce fluid viscosity. Doses of alteplase and DNase were selected empirically by the investigators and did not undergo escalation studies. Fifty-two patients were randomised to the alteplase/DNAse group, of which 48 completed the study. Despite the modest number of patients recruited, the results attracted strong interest and many respiratory units in the world adopted this treatment. Subsequently, Piccolo et al. performed a multicentre cohort study to validate the pragmatic, real-life application of IPFT for pleural infection.[3] A total of 107 patients were included, and 92.3% of them did not require surgery. The study revealed survival rates of 97.8% and 91.2% at days 30 and 90, respectively. Significant changes in CXR opacity were also reported. Piccolo et al. concluded that IPFT with alteplase/DNAse was an effective and safe option in the management of pleural infection.

Despite the MIST2 trail protocol being practised in units around the world, studies have been performed to improve the administration of IPFT. In this issue of the *Annals*, Yong et al.'s retrospective study of patients who received IPFT for pleural infection in Tan Tock Seng Hospital is one such study.[4] This study is among the first to look at treatment success with different starting doses of alteplase, while previous works were cohort studies investigating treatment with fixed de-escalated doses.[5,6]

Studies investigating lower starting doses of alteplase were performed, as many physicians were concerned of the bleeding risks associated with alteplase. Prior to Yong et al.'s study, 2 cohort studies had been performed, looking at the effects of IPFT with lower starting doses of alteplase at 5 mg and 2.5 mg.[5,6] The Alteplase Dose Assessment for Pleural Infection Therapy (ADAPT) study by Popowicz et al. was a multicentre study evaluating 61 patients who were prescribed a starting alteplase dose of 5 mg.[5] Treatment was successful in 93.4%, with improved CXR opacity and avoiding the need for surgery. Popowicz et al. followed up with the ADAPT-2 study performed with 69 patients who were prescribed a starting alteplase dose of 2.5 mg.[6] Treatment success was seen in 88.4% of patients. The ADAPT studies showed that with lower starting doses of alteplase, successful treatment was still achievable. The difference in the success rates may be due to patient's comorbidities in both studies, rather than the difference in starting alteplase dose. Two patients died in ADAPT; while 6 died in ADAPT-2, 4 of which had metastatic cancers. Apart from the ADAPT studies, a case report by Hart et al. described a patient who was successfully treated with a starting alteplase dose of 1 mg.[7]

Yong et al.'s work is unique, as patients receiving IPFT had different starting doses of alteplase.[4] Out of 131 cases, only 9.5% received the starting alteplase dose of 10 mg. There were patients who received starting doses lower than that of ADAPT-2; 1.6%, 11.1% and 0.8% received starting doses of 0.5 mg, 1 mg and 1.25 mg, respectively. Majority of patients received starting doses similar to the ADAPT studies with 28.6% and 48.4% receiving starting doses of 2.5 mg and 5 mg, respectively. Yong et al. showed that the starting dose of alteplase did not suggest significant

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Accepted: 16 December 2024

difference in the improvement of CXR, with a treatment success of 85.5%. However, the study also showed that those who received a starting dose less than 2.5 mg had significantly longer length of stay compared to those receiving 5 mg and 10 mg. Two statistically significant findings, which were not reported in any of the previous studies, were also noted. First, Yong et al. showed that a 1 unit increase in time of drain insertion to the first dose of IPFT decreases the odds of 3-month survival by 5%. Second, an increase in age by 1 year decreases the odds of 3-month survival by 6%. While these results are interesting, more studies should be performed to validate them.

Although the ADAPT studies and Yong et al.'s work revealed that lower starting doses of alteplase resulted in the successful treatment of pleural infections, there are patients in these studies who were administered with escalated doses of alteplase for their IPFT.[4,5,6] The decision to escalate alteplase was performed at the discretion of the attending physician in accordance with the treatment response from CXR. In ADAPT, 11.5% of 61 patients received dose escalation while in ADAPT-2, 24.6% of 69 patients did. In Yong et al.'s study, 28.2% of 131 cases received dose escalation. Whether dose escalation in these patients affected the overall treatment success cannot be concluded. Among the 3 studies, only ADAPT reported evaluating treatment success after excluding those who received dose escalation, with a treatment success rate of 89%.[5]

With regard to bleeding risks, pleural bleed from IPFT in various studies ranged from 1.8 to 6.7%.[2-6,8-10] Patients in these studies were noted to have either an underlying comorbidity that increased bleeding risk or had prior anticoagulant therapy. A retrospective multicentre study by Akulian et al. reported pleural bleeding in 4.1% of 1833 patients, with those on anticoagulation and increasing RAPID scores having a statistically significant higher incident.[8] The study also reported that there was no difference in bleeding between those who received alteplase at 5 mg and 10 mg. In Yong et al.'s study, the 6.1% of pleural bleed was comparable to previous works. Although it did not report if the dose of alteplase was an independent risk factor for pleural bleeding, patients who received lower starting doses in this study tended to have more comorbidities, especially anaemia, chronic kidney disease and end-stage renal failure. This suggests that a targeted dose regime for alteplase with regard to the patient's comorbidities, rather than the starting dose of alteplase, determines risk of pleural bleed. Further studies would be necessary to validate this observation.

Other than the starting doses of alteplase, another interesting area of investigation not addressed by Yong et al. was the method of administration of IPFT—concurrent versus sequential administration of alteplase and DNAse.[9,10] In Yong et al.'s study, alteplase in MIST2 was first administered via the pleural drain and the drain was clamped for 40–60 minutes before DNase administration. While the study by Piccolo et al. adopted a similar protocol to MIST2, it was documented that 28% of the patients received concurrent administration of alteplase and DNase, i.e. DNase was administered immediately after alteplase without clamping the tube.[3] Subsequently, Majid et al. looked at the effects of the concurrent instillation of alteplase and DNase.[9] The study revealed that those who received concurrent instillation did not require the full 6 doses and treatment was successful in 90.4% of the patients. A retrospective cohort study by Goh et al. comparing sequential and concurrent administration of alteplase and DNase showed similar success rates for sequential and concurrent administration, with no significant difference in the reduction of CXR opacity and pleural bleeding.[10]

Finally, Yong et al. raised some interesting points on future research directions. Prior studies did not consider comparing the differences in CXR clearance with starting doses of alteplase and if this could be used as one of the predictors for treatment success. Yong et al. also suggested other factors that may affect survival that warrants further research, such as the timing of administration of the first dose of IPFT and patient demographics such as age.

IPFT undoubtedly plays an important role in the treatment of pleural infections. IPFT recommendation has been included in guidelines, such as the British Thoracic Society Guideline.[1] However, the optimal IPFT regime remains to be determined. While we wait for further studies on these treatment parameters, we will have to rely on current evidence for the starting dose of alteplase.

Declaration

All authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *alteplase, DNase, fibrinolytic, infection, intrapleural, pleural*

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Ann Acad Med Singap 2024;53:710-12
https://doi.org/10.47102/annals-acadmedsg.2024367

EDITORIAL

The promise and challenges of pharmacogenomics in psychiatry

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Pharmacogenomics (PGx) is an expanding field within precision medicine that is poised to play a crucial role in optimising patient outcomes, particularly in the realm of psychiatry. The remission rate for the initial antidepressant prescribed in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was only approximately 30%, underscoring the need for more personalised approaches to prescribing.[1] For psychiatric patients who may show resistance towards pharmacotherapy, PGx offers promise in reducing adverse effects and enhancing therapeutic efficacy. Personalised pharmacotherapy provides reassurance and potentially mitigates the nocebo effects and somatic symptom exacerbation that are prevalent among these patients.

Based on a comprehensive review of the current literature, a consensus workgroup of local psychiatrists developed practice recommendations for using PGx in psychiatry, focusing on the Asian perspective.[2]

The majority of evidence supporting the use of PGx in psychiatry pertain to antidepressants. While more than half of high-quality randomised controlled trials recruited patients and failed to show a statistically significant change in clinical endpoints, recent meta-analyses indicate that PGx-guided antidepressant prescribing is linked to improved patient outcomes through pooling results, mainly in patients with moderate-to-severe major depressive disorder.[3-5] Arnone et al. demonstrated that PGx testing in the treatment of depression was more effective than standard treatment in terms of improvement (odds ratio [OR] 1.63, 95% confidence interval [CI] 1.19–2.24); response (OR 1.46; 95% CI 1.16–1.85); and remission (OR 1.85; 95% CI 1.23–2.76).[4] Similarly, Brown et al. found that patients receiving PGx-guided antidepressant therapy were 1.41 times more likely to achieve remission (95% CI 1.15–1.74, *P*=0.001) compared to those who were unguided.[3] Wang et al. observed that the benefit of PGx testing was significant at week 8 and week 12, but not at week 4 (when antidepressants have not reached their full benefit) and week 24 (when clinicians would have adjusted therapy according to clinical response).[5] The International Society of Psychiatric Genetics (ISPG), Dutch Pharmacogenetics Working Group (DPWG) and the French National Network of Pharmacogenetics (RNPGx) support the use of PGx testing and personalised dosing of antidepressants metabolised by Cytochrome P450 *(CYP) 2C19* and *CYP2D6*. Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC)[6] provide recommendations for dosing adjustment or alternative antidepressants, such as serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) for *CYP2C19*, *CYP2D6* and *CYP2B6*. Similarly, the U.S. Food and Drug Administration (FDA) makes recommendations for psychotropics metabolised by *CYP2C19* and *CYP2D6* on the drug label and table of pharmacogenetic association.[7]

While literature supporting the clinical utility of PGx in other disease states, such as psychosis, remains sparse, studies such as Jukic et al.[8] and Cui et al.[9] provide robust evidence for the utility of *CYP2D6*-guided prescription for risperidone and aripiprazole. A meta-analysis by Saadullah et al. suggested that PGx-guided antipsychotic prescribing may improve symptom response and reduce side effects, emphasising the need for future randomized controlled trials with larger sample sizes for more definitive guidance.[10] It is critical to note that in Singapore, testing for HLA-B*15:02 before initiating carbamazepine (a common treatment for bipolar disorder), is considered standard of care.

Goh et al. emphasised that while PGx testing is not yet recommended as routine clinical practice, it may be considered when there are concerns about drug concentrations or potential severe adverse drug reactions.[2] The group also recommended limiting PGx testing to antidepressants and *CYP2C19/CYP2D6*, and incorporating pre-existing PGx results into clinical decision-making —

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Accepted: 20 December 2024

aligning with recommendations from international organisations e.g. FDA, CPIC, etc.

The evidence supporting PGx is primarily based on studies conducted in populations of European ancestry, with a significant gap in data from Asian populations. However, variants of pharmacokinetic genes like *CYP2C19* and *CYP2D6* are often coding and functional. In other words, regardless of Caucasian or Asian descent, a patient carrying a loss-of-function variant of a pharmacogene will typically have reduced activity of the encoded enzyme or transporter. While the prevalence of such variants may differ across genetic ancestries, their functional impact remains consistent.

The pharmacogenomic landscape in Asia reveals a higher prevalence of certain PGx variants that affect drug metabolism. For example, the allele frequency of *CYP2C19* loss-of-function variant is about 49–59% in Asians, compared to 22.8–28.6% in Caucasians. Similarly, the *CYP2D6*10* variant, associated with reduced enzyme activity, is found in 42.8% of East Asians, compared to 1.57% in Europeans.[6] These genomic variations may lead to higher plasma levels of specific psychotropics in Asians, increasing the risk of adverse effects and necessitating dosage adjustments.

Direct-to-consumer PGx panels often aggregate and analyse genetic information, using proprietary algorithms to provide treatment recommendations. We agree with Goh et al. that the variability in gene selection and lack of transparency in algorithms present significant challenges to their widespread adoption.[2] The extensive list of genes offered on commercial direct-to-consumer panels may not be consistently associated with established clinical outcomes, adding cost and confusion to the interpretation of results. The lack of adequate regulatory oversight for direct-to-consumer PGx panels is also a concern.

Other than genomics, it is essential to consider other clinical factors that affect drug response. PGx test results should be integrated as part of a comprehensive clinical assessment, which includes evaluating the patient's overall health, treatment compliance, comorbid conditions and concomitant medications. For instance, hepatic impairment may affect drug metabolism and should be factored into the interpretation of PGx results. Furthermore, the patient's preference, cost of medications and perceptions towards medications also influence treatment outcomes. A holistic approach to patient care is crucial for achieving desired outcomes.

In Singapore, particularly at the National University Health System, a proactive strategy, known as pre-emptive PGx, is being adopted. This initiative involves testing patients for a PGx panel curated based on local variants before clinical indications arise. As such, it eliminates the dilemma of "whether to test or not" and shifts the focus to "how to utilise the PGx information when it is available. " This approach is consistent with Singapore's broader trend towards embracing precision medicine. In future, as whole genome sequencing becomes more prevalent for other medical indications, PGx data could be extracted to optimise pharmacotherapy with minimal additional effort, further reducing the consideration for cost and logistics.

Pre-emptive PGx testing provides clinicians with genetic information upfront, enabling more informed decisions regarding medication selection and dosing. This may improve treatment outcomes, reduce trial-and-error prescribing and enhance patient safety.

Despite the potential benefits of pre-emptive testing, safeguards — such as robust data privacy measures, informed consent protocols, and clear policies for handling incidental findings — are required for its responsible implementation. To this end, pathways need to be developed to overcome logistical challenges such as data storage and appropriate handling of clinically relevant test findings.

To optimise the potential of PGx, medical students and clinicians should be educated about PGx to reduce inertia in using PGx to inform their practice. Conducting large-scale studies focusing on Asian populations to address gaps in ethnicity-specific data will instil confidence in the clinical applicability of PGx to the local population in our clinicians. Policy-level changes, such as introducing subsidies for PGx testing, are necessary to improve accessibility and equity in in resource-constrained settings. Finally, practical steps for integrating PGx into clinical practice include the development of decision-making algorithms, clinician training programmes, cost-effective PGx panels tailored to local genetic and clinical contexts, and resources for interpreting test results. The effort from Goh et al. marks the first step in this journey.[2]

PGx represents a promising frontier in psychiatric care, offering the potential for more personalised treatment strategies. Clinical benefits have been demonstrated for antidepressants and *CYP2C19/CYP2D6*. When available, this information should be incorporated into therapeutic decisions, aligning with practice recommendations from local psychiatrists[2] and international guidelines. Pre-emptive PGx, as part of the broader precision medicine framework, may potentially transform psychiatric practice.

Although the field is still evolving and fraught with challenges, ongoing research and clinical implementation will pave the way for more tailored interventions, improving the lives of patients with psychiatric disorders.

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *genetics, mental health, pharmacogenomics, pharmacology, psychiatry*

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Ann Acad Med Singap 2024;53:713-23
https://doi.org/10.47102/annals-acadmedsg.2024311

ORIGINAL ARTICLE

Perioperative emergency laparotomy pathway for patients undergoing emergency laparotomy: A propensity score matched study

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ABSTRACT

Introduction: Emergency laparotomy (EL) is associated with high morbidity and mortality, often exceeding 10%. This study evaluated the impact of the EMergency Laparotomy Audit (EMLA) interdisciplinary perioperative pathway on patient outcomes, hospital costs and length of stay (LOS) within a single centre.

Method: A prospective cohort study was conducted from August 2020 to July 2023. The intervention team included specialist clinicians, hospital administrators and an in-hospital quality improvement team. Patients who underwent EL were divided into a pre-intervention control group (n=136) and a post-intervention group (n=293), and an 8-item bundle was implemented. Propensity scoring with a 1:1 matching method was utilised to reduce confounding and selection bias. The primary outcomes examined were LOS, hospitalisation costs and surgical morbidity, while secondary outcomes included 30-day mortality and adherence to the intervention protocol.

Results: The utilisation of the EMLA perioperative care bundle led to a significant reduction in surgical complications (34.8% to 20.6%, $P<0.01$), a decrease in LOS by 3.3 days (15.4 to 12.1 days, $P=0.03$) and lower hospitalisation costs (SGD 40,160 to 30,948, $P=0.04$). Compliance with key interventions also showed improvement. However, there was no difference in 30-day mortality.

Conclusion: This study offers insights on how surgical units can implement systemic perioperative changes to improve outcomes for patients undergoing emergency laparotomy.

Ann Acad Med Singap 2024;53:713-23

Keywords: emergency medicine, general surgery, laparotomy, perioperative care, short-term outcomes

CLINICAL IMPACT

What is New

- This single-centre study successfully implemented a perioperative care pathway for emergency laparotomy (EL) patients, leading to sustained improvements including decreased length of stay, surgical complications and hospitalisation costs.
- This study supports the incorporation of a standardised perioperative EL pathway to achieve improved patient outcomes.

Clinical Implications

- This study can help shape future healthcare policy especially for patients undergoing EL.
- A systematic approach to the implementation of the pathway, driven by systematic Plan-Do-Study-Act cycles, continuous data monitoring and quarterly feedback is key in achieving sustained improvements.

INTRODUCTION

Patients requiring emergency laparotomy (EL) are a vulnerable subset within general surgery, with reported 30-day mortality rates ranging from 9% to 18%, which is 3 times higher than similar elective operations.[1-3] Unlike elective surgeries, the care for EL patients is time-sensitive as they move from the emergency department, radiology suite, operating theatres, and intensive care units (ICUs) or general wards. These patients are at risk of rapid deterioration without timely interventions. Furthermore, EL patients represent a diverse group with various surgical needs, and their care entails a disproportionately high healthcare cost burden.[4] A multidisciplinary approach to the implementation of a specific perioperative pathway that limits variability while allowing tailored treatment for each patient is postulated to improve patient's outcome.[1,5-7]

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Accepted: 3 December 2024

In recent years, observational studies have shown improvement in clinical outcomes with the implementation of an EL care bundle. The Emergency Laparotomy Pathway Quality Improvement Care bundle, introduced in 2015, reported a reduction in mortality from 15.6% to 9.6%.[8] The Emergency Laparotomy Collaborative demonstrated a decrease in mortality from 9.8% to 8.3% as well as a decrease in length of stay from 20.1 to 18.9 days across 28 National Health Service hospitals in the UK.[3] The National Emergency Laparotomy Audit (NELA), through the provision of high-quality comparative data and the tracking of key process measures, showed a sustained reduction in mortality rates for patients undergoing EL from 11.8% to 9.2% over the past 8 years.[1] The benefits of the EL care bundle have also been published in Swedish, Danish and Australian cohort studies.[6,9,10] In a Singapore context, Ong et al. studied the effectiveness of an EL pathway in their hospital that has an acute care surgery team and a low 30-day mortality rate of 5.3% pre-intervention.[11] In their study, the EL pathway did not show a significant reduction in mortality.

In our study, we implemented our EL pathway by addressing barriers and facilitators in implementing change, in the Singapore context.[12] This included obtaining endorsement from the hospital senior management, getting familiar with quality improvement (QI) practices and building interpersonal relationships among clinicians. This approach aligns with the "hard clinical core" supported by "soft QI periphery" as suggested by Stephens et al.[13] Our main outcome measures were the length of hospitalisation, postoperative surgical complications,, inpatient hospitalisation cost and 30-day mortality. Additionally, we evaluated the 2-year compliance with the EMergency Laparotomy Audit (EMLA) bundle to gauge the sustainability of its implementation.

METHOD

Study design

A prospective single-institution intervention study was carried out at a 700-bed general hospital in Singapore. The study included all patients aged 18 years and above who underwent EL between 1 August 2020 and 31 July 2023. After receiving approval from hospital senior management, the hospital QI team framed the effort within standard QI methodology. Stakeholder QI leads from emergency medicine, intensive care, anaesthesia and general surgery departments were identified, and basic QI training based on the Institute for Healthcare Improvement Model for Improvement was provided. An 8-step intervention bundle (Table 1) based on the Enhanced Peri-Operative Care for High-risk patients (EPOCH) 37-component care-pathway recommended processes of care was agreed upon after obtaining consensus, which became the standard of care for EL patients within the surgical department.[5]

In our study, the emergency physicians lead was responsible for improving antibiotics administration within 60 minutes; the general surgery lead was responsible for preoperative NELA scoring and ensuring timely arrival in the operating theatre; and the anaesthesia lead was tasked with goal-directed fluid therapy and maintaining normothermia. Lastly, the intensivist lead oversaw postoperative care in the high dependency/intensive care (HD/ICU)

Table 1. Pre-set clinical interventions.

No.	Phase	Clinical interventions
1	Emergency department	Administration of intravenous antibiotics within 60 mins from diagnosis of intra-abdominal sepsis
2	Preoperative	Performing NELA scoring at consent for risk stratification
3		Decision on emergency laparotomy is made by consultant surgeon
4		Moving patients to the operating theatre in a time-appropriate fashion based on their priority (P) status (i.e. ≤1 hour for P1 cases, ≤6 hours for P2 cases)
5	Intraoperative	Presence of consultant anaesthesiologist and surgeon in the operating theatre
6		Monitoring of cardiac output and ensuring goal-directed fluid therapy
7		Monitoring of intraoperative body temperature and ensuring normothermia
8	Postoperative	Transferring of patients to high dependency or intensive care unit if calculated mortality is >5% and to general ward when calculated mortality is ≤5%

NELA: National Emergency Laparotomy Audit

unit setting. Each speciality planned its own QI initiatives to enhance compliance with these clinical quality indicators (Table 1).

The pre-intervention phase was from 1 August 2020 to 30 June 2021, with all consecutive patients who underwent EL identified as the control group. The formal introduction of the EMLA perioperative care bundle occurred in July 2021. The inclusion and exclusion criteria for patients undergoing EL followed the NELA protocol.[14] Briefly, patients undergoing EL involving the stomach, small intestine, large intestine or rectum were included. The indications included perforation, ischaemia, intra-abdominal sepsis, bleeding or postoperative complications. EL procedures related to trauma; vascular pathology; laparotomies where primary pathology is appendicitis or cholecystitis; laparotomy for repair of incarcerated hernia without division of adhesions or bowel resection/repair and emergency stoma via trephine incision or via laparoscopic procedure were excluded.

The diagnosis of intra-abdominal sepsis was made based on clinical examination findings of peritonitis or pneumoperitoneum observed on imaging. The NELA preoperative risk score was computed using the online NELA risk calculator.[15] The outcomes measured were the length of hospitalisation, defined as the duration from surgery until discharge; surgical complications categorised according to the Clavien-Dindo classification system; hospitalisation costs; and 30-day mortality.

For patients undergoing EL, normothermia was maintained through pre-warming with forced-air systems for 20 to 30 minutes before surgery, maintaining the operating room temperature ≥22°C, and utilising active intraoperative warming strategies. These included surgical access warming blankets (3M Bair Hugger Warming Blanket 57000; 3M, Saint Paul, MN, US), warmed intravenous fluids, underbody warming mattresses and continuous core temperature monitoring. For high-risk patients (NELA >5%), goal-directed fluid therapy involved arterial line placement for continuous monitoring of blood pressure and pulse pressure variation. Fluid challenges with crystalloid solutions or 5% albumin were administered to maintain pulse pressure variation <15%, and vasopressors were used to sustain a mean arterial pressure ≥65 mmHg.

Process and outcome measures were defined in the electronic medical records and collected by the surgical clinical reviewer (SCR) as part of ongoing participation in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP). Diagnostic criteria for perioperative morbidity used definitions from NSQIP's Operations Manual.[16] Data veracity was ensured by weekly meetings between SCR and department surgical leads.

We collaborated with our in-house quality QI and data analytics team to ensure accurate data tracking. Feedback on compliance was provided to each speciality team during quarterly EMLA meetings, where Plan-Do-Study-Act (PDSA) cycles were employed to deepen process insight and improve performance of process outliers. The QI and data analytics team helped to track compliance for each of the clinical interventions, with monthly data evaluations to assess improvement following each PDSA cycle. If sustained improvement was observed for 3 consecutive months, the PDSA cycle was deemed successful. Conversely, if no improvement in compliance was noted within 3 months, the PDSA cycle was re-evaluated and modified accordingly.

A specialised database was set up in August 2020 after approval from the National Healthcare Group Domain Specific Review Board (NTFGH-JHS 2020-00052). Data integration was achieved through 3 primary sources: (1) EMLA Redcap Database, which contains detailed patient data entered by SCRs; (2) Epic Electronic Medical (Epic Systems Corporation, Wisconsin, US), which provides demographic information, clinical histories and outcomes; and (3) Health System Administrative Databases, which offer detailed cost metrics. Cost data for each EL encounter (up to 30 days post-discharge) were provided by the hospital finance department and adjusted for inflation. These costs comprise all relevant costs related to the encounter, including consultation, surgeon and anaesthetist costs, occupational therapy costs, room charges as well as costs of investigative equipment, medications and supplies.

Statistical analysis

To mitigate temporal and selection biases in comparing control and treatment groups, we utilised propensity score matching.[17] This method aligns groups by their intrinsic risk profiles, adjusting for systemic differences, such as demographics and other non-controllable confounders that arise across different periods. The matching criteria were age, American Society of Anaesthesiologists (ASA) score, NELA score, Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity score, operative indications and counts of pre-1-year hospital admissions.

Our study's observational design naturally dictated its sample size, capturing all EL cases

within the specified period. We conducted propensity score matching using a 1:1 nearest neighbour without replacement approach, utilising the MatchIt package version 4.5.5 (Ho, Imai, King, & Stuart et al., 2011) in R software version 4.3.2 (R Core Team, 2023). The propensity scores were estimated through a probit regression model, selected over logistic regression for its effectiveness in achieving a better covariate balance in our dataset. Post-matching balance was assessed to ensure comparability between groups to minimise selection bias.

Categorical variables were presented as frequency counts with percentages and analysed using Pearson's χ^2 test or Fisher's Exact test—selected for their appropriateness in assessing the association between categorical variables. Continuous variables were expressed as mean with ± standard deviation and differences were assessed using Student's t-test, chosen for comparing means between 2 groups under the assumption of normal distribution. All reported *P*-values were two-sided, and *P*-values <0.05 were considered statistically significant. All analyses were undertaken using RStudio Version 1.3.1093 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) due to its comprehensive statistical tools and reproducibility of results. The preparation of this paper adhered to the STROBE guidelines.[18]

RESULTS

Between August 2020 and July 2023, 429 patients underwent EL and were included in the study. Of these, 136 underwent EL before the implementation of the EMLA bundle (EL pre-intervention/control group) and 293 underwent EL following its implementation (EL post-intervention group). We matched 136 patients from the control group with an equivalent number from the intervention group, resulting in an overall cohort size of 272.

The mean age of patients was 61 years, with a slightly higher proportion of males than females. Nearly half of all patients were classified as ASA III and above, and close to 40% were identified as high risk (NELA ≥5%) (Table 2). Intestinal obstruction was the most common indication for EL in both the control group and intervention group (53.7% versus [vs] 54.4%). Sepsis was also prevalent (44.1% vs 43.4%). Other indications include ischaemia (10.3% vs 8.1%) and haemorrhage (7.4% vs 8.8%). No significant difference was noted in surgical indications.

The perioperative efficiency outcomes, presented in Table 3, were adjusted for outliers identified using the interquartile range (IQR) method, which was meticulously applied to time difference calculations—a crucial metric in assessing perioperative efficiency. Notably, there was a significant increase in the time from decision to surgery in the post-intervention group (from 136 minutes to 166 minutes, *P*=0.02). However, this increase in time was not statistically significant for patients requiring P1 (i.e. to be performed within 2 hours) or P2 (i.e. to be performed within 6 hours) operations.

Length of stay and postoperative complications

We observed a significant reduction in the average length of hospitalisation, with the EMLA intervention group having a shorter hospitalisation post-surgery as compared to the pre-intervention group (12.1 days vs 15.4 days, *P*=0.03) (Table 4). In addition, we observed a decrease in surgical complications from 34.8% to 20.6%, *P*<0.01). This extended across all grades of surgical complications as classified by the Clavien-Dindo system, with the percentage of patients experiencing major complications (Clavien-Dindo ≥3) decreasing from 19.9% to 11.8% (Table 4).

Hospitalisation costs

From the hospital's perspective, the improvements in clinical outcomes led to substantial cost savings. The average same-admission in-hospital bill size saw a notable decrease of 22.9%, from SGD 40,160 to 30,948 (approx. USD 29,998 to 23,117) (*P*=0.04). Furthermore, these cost reductions were sustained up to 30 days post-discharge, declining from SGD 44,023 to 33,380 (approx. USD 32,883 to 25,669, *P*=0.05).

Thirty-day mortality

In the assessment of 30-day mortality rates, our study revealed no difference between the pre- and post-intervention groups. In both cohorts, the mortality rate stood at 5.1%, with 7 deaths recorded within 30 days of discharge in each group. There were 4 in-hospital deaths in the post-intervention group compared to 6 deaths in the pre-intervention group.

Compliance with EMLA bundle

The introduction of the EMLA bundle within a formal QI framework significantly enhanced compliance rates in perioperative care practices. Following the intervention, there were statistically significant improvements observed in the preoperative assessment of patient mortality as determined by the NELA score (24.3% to 82.4%, *P*<0.01), as well as in the involvement of consultant surgeon and anaesthetists during surgery (74.3% to 86.8%, *P*<0.01). While not statistically significant, the percentage of antibiotics administered within 60 minutes of intra-abdominal sepsis diagnosis

Table 2. Patient demographics.

	Pre-intervention	Post-intervention	*P* value
	Mean ± SD / no. (%)		
Total cases, no.	136	136	NA
Mean age, years	61 ± 17	61 ± 17	0.88
Patients ≥65 years old	64 (47.1%)	71 (52.2%)	
Gender			0.21
Male	78 (57.4%)	88 (64.7%)	
Female	58 (42.6%)	48 (35.3%)	
Race			0.80
Chinese	97 (71.3%)	90 (66.2%)	
Malay	15 (11.0%)	18 (13.2%)	
Indian	9 (6.6%)	12 (8.8%)	
Others	15 (11.0%)	16 (11.8%)	
ASA			0.92
I	15 (11.0%)	12 (8.8%)	
II	52 (38.2%)	52 (38.2%)	
III	42 (30.9%)	47 (34.6%)	
IV	25 (18.4%)	24 (17.6%)	
V	2 (1.5%)	1 (0.7%)	
NELA			0.83
Absolute NELA score, %	10 ± 15	9 ± 15	
Low (<5%)	82 (60.3%)	84 (61.8%)	
High (≥5%)	54 (39.7%)	52 (38.2%)	
Indication for surgery[a]			NA
Obstruction	73 (53.7%)	74 (54.4%)	
Ischaemia	14 (10.3%)	11 (8.1%)	
Sepsis	63 (46.3%)	60 (44.1%)	
Haemorrhage	10 (7.4%)	12 (8.8%)	
Others	9 (6.6%)	17 (12.5%)	
Procedure approach			0.53
Laparoscopic	17 (12.5%)	22 (16.2%)	
Laparoscopic assisted	2 (1.5%)	5 (3.7%)	
Laparoscopic converted to open	23 (16.9%)	22 (16.2%)	
Open	94 (69.1%)	87 (64.0%)	

ASA: American Society of Anaesthesiologists; NA: not applicable; NELA: National Emergency Laparotomy Audit; SD: standard deviation
[a] Some patients have more than 1 indication for surgery.

Table 3. Perioperative efficiency outcomes.

	Pre-Intervention	Post-intervention	
	Mean ± SD / no. (%)		*P* value
Preoperative (post-adjustment for outliers)			
Time from decision for surgery to start of surgery, min	136 ± 93	166 ± 106	**0.02**
P1 operations (to be performed within 2 h), min	65 ± 33	76 ± 29	0.15
P2 operations (to be performed within 6 h), min	153 ± 88	183 ± 101	0.06
Arrival in theatre within timescale appropriate to urgency	123 (96.1%)	111 (92.5%)	0.28
CT scan reported before surgery	121 (89.0%)	128 (94.1%)	0.24
Risk of death documented preoperatively	33 (24.3%)	112 (82.4%)	**<0.01**
Intraoperative			
Consultant surgeon present in operating theatre	128 (94.1%)	121 (89.0%)	0.19
Consultant anesthetist present in operating theatre	107 (78.7%)	133 (97.8%)	**<0.01**
Postoperative			
NELA ≥5% patients admitted to critical care (high dependency/ intensive care unit)	39/49 (79.6%)	32/38 (84.2%)	0.58

CT: computed tomography; NELA: National Emergency Laparotomy Audit; P: priority; SD: standard deviation
P values in bold are statistically significant.

Table 4. Comparison of clinical outcomes measures for matched patient cohort.

		Pre-intervention	Post-intervention	*P* value
Length of stay, days	Mean (SD)	15.4 (14.9)	12.1 (10.8)	**0.03**
	Median (IQR)	10 (6.0–19.3)	8 (5.0–12.25)	
Inpatient cost, SGD	Mean (SD)	40,160 (42,196)	30,948 (31,008)	**0.04**
	Median (IQR)	25,028 (16,667–43,822)	20,374 (13,725–33,782)	
Inpatient cost up till 30 days post-discharge, SGD	Mean (SD)	44,023 (52,337)	33,380 (33,978)	**0.05**
	Median (IQR)	25,123 (17,321–44,763)	20,805 (14,093–37,684)	
30-day mortality rate (all deaths), no. (%)		7 (5.1%)	7 (5.1%)	1.00
30-day mortality rate (in-hospital deaths only), no. (%)		6 (4.4%)	4 (2.9%)	0.75
Presence of surgical complications, no. (%)		47 (37.8%)	28 (20.6%)	**<0.01**
Clavien-Dindo classification (only for surgical complications), no. (%)				0.94
Grade 1 or 2		20 (42.6%)	12 (42.9%)	
Grade 3		23 (48.9%)	13 (46.4%)	
Grade 4		2 (4.3%)	2 (7.1%)	
Grade 5		2 (4.3%)	1 (3.6%)	

IQR: interquartile range; SGD: Singapore dollars; SD: standard deviation
P values in bold are statistically significant.

improved (55.6% to 68.3%, *P*=0.27). Unexpectedly, we observed a decrease in compliance with surgery performed within an appropriate time (96.3% to 83.1%, *P*<0.01). However, the clinical significance is limited as arrival to theatre for P1 and P2 operations remained similar (Table 3). The other perioperative care practices remained similar (Table 5).

DISCUSSION

Our study evaluated the clinical impact of introducing and sustaining an EMLA perioperative pathway within a formal QI framework for a heterogeneous cohort of patients undergoing EL. The results of the study showed a decrease in surgical complications, length of hospital stay and hospitalisation costs. However, no difference was observed in 30-day mortality. Our institution has been operating with an established emergency surgery unit (ESU), akin to an acute care surgery unit since 2016. The American College of Surgeons reported a potential reduction in mortality of up to 31% for patients requiring emergency surgery under this model of care.[19] In our department, the ESU is led by subspeciality surgical consultants on a rotational basis. The ESU team is responsible for promptly evaluating all acute admissions and in-hospital referrals. Under this system, patients slated for admission to the general surgery department were reviewed by the ESU team within a 4-hour window. For most patients requiring EL, surgical consultation commenced in the emergency department. Additionally, expedited access to computed tomography (CT) imaging was readily available, with reporting conducted by an in-house radiology team. Our surgical team has a dedicated emergency operating theatre that can be utilised 24 hours a day, 7 days a week. EL procedures were mainly performed by consultant surgeons on the ESU roster, except for cases requiring subspecialty surgical expertise.

From our control group, we noted that our pre-intervention baseline mortality for patients undergoing EL was lower than international norms of 6.5% to 16.5%.[1,3,6,10] Our reported 30-day mortality of 5.1% was similar to other Singapore hospital reported rates of 3.1 to 5.6%.[11,20] This is often attributed to Singapore's healthcare where patients have easy and prompt access to healthcare facilities equipped with CT imaging and operating theatres. Our baseline length of hospitalisation of 15.4 days was also similar to international norms of 10 to 16.7 days.[1,6,9,21]

The EMLA pathway was introduced to provide standardised evidence-based care for patients undergoing EL. Through this process, we were able to capture data that allowed us to optimise underperforming key process measures. For example, a rapid intravenous broad-spectrum antibiotic is standard practice upon diagnosing sepsis,[22] however, there was no formal audit on the timing of antibiotic administration. Before implementation, antibiotics administration within 60 mins was only achieved in slightly more than half of our patients (55.6%). Likewise, there was no routine assessment of patients' surgical risk profiles, with only 24.3% of patients having a risk assessment score at consent.

Table 5. Care bundle compliance.

	Pre-intervention	Post-intervention	
	No. (%)		*P* value
Antibiotics within 60 mins of sepsis diagnosis	35/63 (55.6%)	41/60 (68.3%)	0.27
NELA scoring documented at consent	33 (24.3%)	112 (82.4%)	**<0.01**
Surgery decision by consultant surgeon	118 (86.8%)	113 (83.1%)	0.40
Surgery performed within appropriate time	131 (96.3%)	113 (83.1%)	**<0.01**
Senior surgeon and anaesthetist present during surgery	101 (74.3%)	118 (86.8%)	**<0.01**
Normal body temperature taken intraoperatively	109/124[a] (87.9%)	111/129[a] (86.0%)	0.66
Goal-directed haemodynamic therapy for high-risk cases	49/54 (90.7%)	43/52 (82.7%)	0.22
Transfer to high dependency/intensive care unit for high-risk cases	39/53[b] (73.6%)	32/52 (61.5%)	0.19

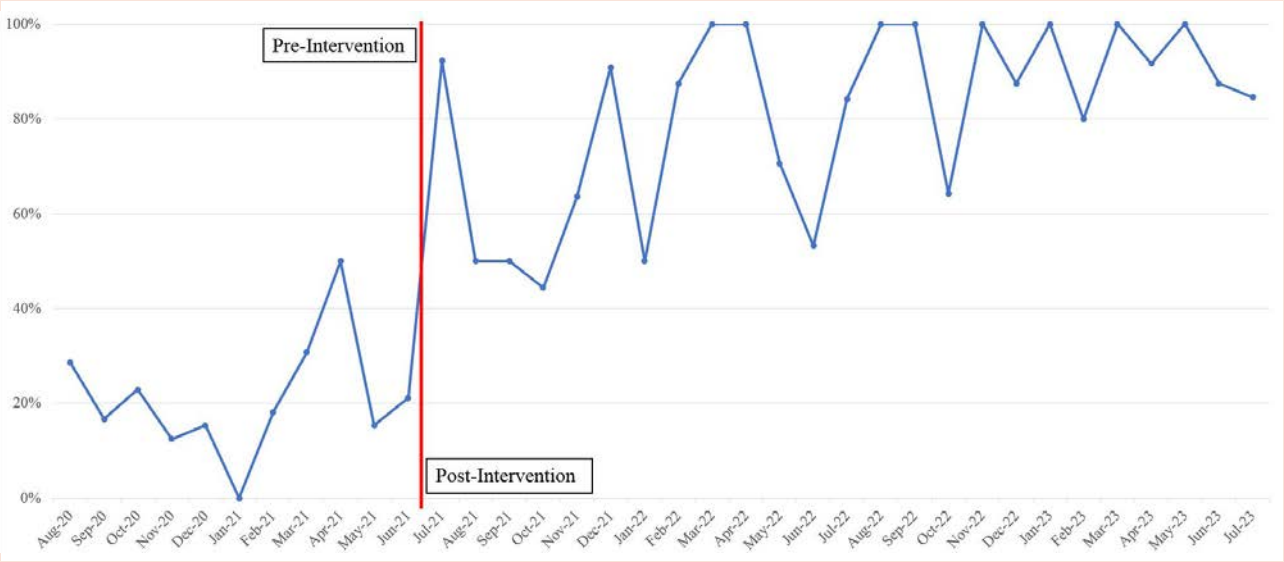
NELA: National Emergency Laparotomy Audit
[a] Excluding missing cases.
[b] Excluding 1 case of intraoperative death.
P values in bold are statistically significant.

Improvement of process performance was carried out with the use of PDSA cycles within a standard QI framework, although this was not always achieved at the first attempt. For example, in the case of preoperative risk stratification with NELA scoring, the first PDSA cycle involved the introduction of a NELA smart phrase shortcut on the Epic computer system, which automated NELA scoring on entering relevant preoperative variables. Despite the convenience, compliance fluctuated between 50–100% with variations owing to the frequent rotation of junior doctors (Fig. 1). Subsequently, as a second cycle of PDSA, cases with missing NELA scores were highlighted during the weekly department morbidity and mortality meetings. With frequent communication, we were able to facilitate behavioural change where NELA scoring became part of our department consent process for EL patients. We observed an improvement in compliance, from 24.3% to 82.4%, during our study period which continues to be sustained without the need for weekly enforcement.

In our study, a risk assessment scoring at consent and having both consultant surgeon and anaesthetist involvement for EL cases showed a statistically significant improvement. There was also a trend for improved antibiotics administration within 60 minutes, but this was not statistically significant (Table 5). These improvements were postulated to be the factors that led to a reduction in surgical complications. For patients requiring EL, early administration of antibiotics, prompt resuscitation and timely source control are crucial aspects of the surviving sepsis guidelines.[22,23] Patients undergoing EL would require collaborative involvement of clinicians from various subspecialty. The use of a documented risk assessment at the time of consent allowed for high-risk patients (NELA >5%) to be identified early and for implementation of downstream interventions. In our study, all high-risk patients were allocated a HD/ICU bed at the time of consent. The department heads mandated a senior surgeon and anaesthetist to be involved in EL cases, which was crucial in improving compliance. Notably, surgical complications were reduced from 34.8% to 20.6% (P<0.01). The reduction in surgical complications served as a pivotal factor, contributing to our study cohort achieving a decreased mean length of stay of 3.3 days (15.4 to 12.1 days, P=0.03) and a 23% reduction in inpatient cost (P=0.04) (Table 4).

The reduction in inpatient cost was noteworthy as this is not uniformly reported in the literature. Studies have raised concerns regarding the potential for increased costs associated with the use of perioperative care bundles. The use of a perioperative care bundle involving routine use of a goal-directed therapy and postoperative ICU monitoring may excessively inflate inpatient costs.[24] In the EPOCH study, the implementation of a perioperative bundle was deemed not cost-effective.[25] In our study, by risk-stratifying patients, we were able to provide appropriate levels of care. The patients at high risk of mortality were usually older (age >65 years), had higher ASA scores and were hemodynamically unstable at presentation.[10,26,27] For these patients, the implementation of goal-directed therapy and

Fig. 1. Run chart depicting compliance to preoperative NELA score risk assessment pre-intervention and post-intervention.



NELA: National Emergency Laparotomy Audit

postoperative admission to the HD/ICU were routine. This approach ensured that higher-cost interventions were reserved for high-risk patients, which helped to mitigate costs.

In our study, we found no difference in 30-day mortality at 5.1%. We postulate that the lack of improvement may be attributed to a weakness in having only preoperative NELA scoring done. This may have underestimated the severity of illness by not incorporating intraoperative data including the severity of intra-abdominal contamination, need for intraoperative vasopressor support or missed diagnoses. Numerous other factors influence 30-day mortality, which cannot be addressed solely by the perioperative care bundle. Intraoperative surgical decisions, such as choosing between open versus laparoscopic surgery, handsewn versus stapled bowel anastomosis, or the creation of a stoma versus upfront bowel anastomosis, can significantly impact clinical outcomes. These decisions are often individualised based on the patient's risk profile and intraoperative haemodynamics. In our study, 17 patients (12.5%) underwent laparoscopic surgery in the pre-intervention group while 22 patients (16.2%) underwent laparoscopic surgery in the intervention group (P=0.53). Each consultant surgeon was able to individualise surgical decisions at their discretion.

Furthermore, the preoperative NELA scoring is limited as it does not take frailty into account. Frailty is associated with doubling of mortality rates, increased morbidity rates and worsened functional outcomes after EL.[1,28,29] A routine clinical frailty scale (CFS) assessment should be advocated to aid patient's decision-making and surgery strategy. When CFS is used in conjunction with preoperative risk assessment scores, mortality prediction can be improved for older patients.[30] In our institution, we have embarked on routine CFS assessment for patients aged more than 65 years and incorporated a geriatrics speciality consultant into our clinical core group.

Our study is limited by our single-centre experience whereby generalisability to other institutions may be limited. Nonetheless, the detailed implementation process and outcomes provide a framework that could inform similar interventions elsewhere. We support the call for early engagement of a QI framework in the design phase, where change can be driven by a "hard" clinical core supported by a "soft" QI periphery.[5] The use of data tracking on process measures and patient outcomes can serve as a tool to drive behavioural changes—crucial for the effective implementation of clinical interventions.

Another limitation is that our control and intervention groups were not randomised. We employed propensity score matching and conducted a sensitivity analysis, which helped to partially control for unobserved patient-level confounders. However, we acknowledge that this approach adjusts only for observed confounders, leaving room for unmeasured variables (i.e. social determinants of health) to impact outcomes. Although formal multiplicity adjustments were not applied, our key findings showed statistical significance remained robust even with conservative corrections. Moreover, the consistent direction of effect across multiple outcomes strengthened our conclusions. Ideally, patients should be randomised to usual care versus "bundled" care (i.e. compliance to pre-determined interventions). However, our study population involves patients subjected to time-sensitive EL, making recruitment, randomisation and consent-taking logistically challenging.

Moving forward, we aim to extend the EMLA perioperative framework to a national scale, addressing the challenge of widespread implementation. Expanding a care bundle to a national level presents significant challenges. The complexity of such endeavours was illustrated by the EPOCH trial group's experience across 93 National Health Service hospitals in the UK, involving 15,873 patients.[31] In their study, there were 10 pre-defined process measures to be implemented for patients aged greater than 40 years undergoing EL. Their study methodology involved a stepped-wedge cluster randomised trial with QI intervention varying from 5 to 80 weeks. Despite their efforts, Peden et al. reported no significant differences in 90-day mortality, length of hospital stay, or hospital readmission within 180 days.[31] Their struggles to achieve consistent intervention fidelity due to time and resource constraints underscore the formidable obstacles in scaling such initiatives.

To facilitate this process, we plan to integrate a behavioural implementation science and intervention team—providing a robust framework for supporting the rollout and evaluating its effectiveness. Also, the team will need to develop adaptable, scalable interventions tailored to the diverse environments of various institutions. It is crucial to secure an endorsement from all specialities involved in the care of EL patients and customise care bundles to align with each institution's unique operational context. By incorporating behavioural strategies into the implementation process, we aim to enhance healthcare professionals' adherence to

the care bundle and optimise patient outcomes. This comprehensive approach aims to ensure that the benefits observed at our centre can be replicated and adapted across different settings, ultimately leading to improvements in patient clinical care on a national scale.

CONCLUSION

Our single-centre study successfully implemented a perioperative care pathway for EL patients, leading to sustained improvements over 2 years. The index length of stay was reduced by 3.3 days, surgical complications decreased by 14.2% and hospitalisation costs fell by 22.9%. The success of the EMLA bundle that is driven by systematic PDSA cycles, continuous data monitoring and quarterly feedback underscores the long-term potential of structured perioperative care models to enhance healthcare delivery. Our future work will involve expanding this initiative nationwide and standardise care pathways for EL patients across diverse healthcare settings.

Funding

This study was conducted by the Department of Surgery in JurongHealth Campus and supported by JurongHealth Fund.

Ethics statement

This study was approved by the National Healthcare Group Domain Specific Review Board (NTFGH-JHS 2020-00052).

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Acknowledgements

We thank all the consultant surgeons in our department who have contributed their expertise in the care of the patients in this study. They include members of the Emergency Laparotomy Group: Hang Liang Christopher Keh, Jia Jing Edwin Yang, Aung Lwin, Sian Ying Heidi Chang, Chern Yuen Cheong, Hon Ian Chong, Shulin Jesse Hu, Kang Ee Gregory Heng, Liling Kwek, Joel Wen Liang Lau, Ishara Maduka, Han Boon Oh, Choon Sheong Seow, Yuen Soon, Chuan Chien Tan, Man Hon Tang, Wee Ming Tay, Jun Liang Teh and Yongxian Thng. We thank Mr Francis Phng who helped with data validation, and Ms Sheryl Yong and Ms Valerie Seah who helped with data collection.

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Ann Acad Med Singap 2024;53:724-33
https://doi.org/10.47102/annals-acadmedsg.2024276

ORIGINAL ARTICLE

Intrapleural fibrinolytic therapy for pleural infections: Outcomes from a cohort study

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ABSTRACT

Introduction: Pleural infections are a significant cause of mortality. Intrapleural fibrinolytic therapy (IPFT) utilising alteplase and dornase is a treatment option for patients unsuitable for surgery. The optimal dose of alteplase is unknown, and factors affecting treatment success in an Asian population are unclear. We sought to determine the factors affecting treatment success in Tan Tock Seng Hospital, Singapore and evaluate the efficacy of lower doses of IPFT.

Method: A retrospective analysis of patients with pleural infections treated with IPFT between July 2016 and November 2023 was performed. Treatment success was defined as survival without surgery at 3 months. Data, including patient demographics; comorbidities; RAPID (renal, age, purulence, infection source and dietary factor) scores; and radiological characteristics, were extracted from medical records and analysed. Linear mixed effects model and logistic regression were performed to determine factors affecting treatment success.

Results: A total of 131 cases were analysed. Of these, 51 (38.9%) reported positive pleural fluid culture, and the most common organism was *Streptoccocus anginosus*. Mean age was 65 years (standard deviation [SD] 15.5). Mean time from chest tube insertion to first dose of IPFT was 10.2 days (SD 11.5). Median starting dose of alteplase was 5 mg. Treatment success was reported in 112 cases (85.5%). There were no significant differences between the alteplase dose and radiological clearance. Patient age (odds ratio [OR] 0.94, confidence interval [CI] 0.89–0.98) and interval between chest tube insertion to first dose (OR 0.95, CI 0.91–0.99) were statistically significant variables for the treatment success.

Conclusion: Lower starting doses of alteplase remain effective in the treatment of pleural infection. Early IPFT may result in better outcomes.

Ann Acad Med Singap 2024;53:724-33

Keywords: biostatistics, infectious diseases, pneumonia, pulmonary, respiratory medicine

CLINICAL IMPACT

What is New

- This study examined the use of intrapleural fibrinolytic therapy (IPFT) in an Asian cohort with a mean age that is older than that investigated in prior studies.
- IPFT remains effective for pleural infections even with lower alteplase doses.

Clinical Implications

- Early initiation of IPFT is associated with better outcomes, and efforts should be taken to minimise any delay.
- Lower doses of alteplase may be preferred for patients with higher bleeding risk.

INTRODUCTION

Pleural infection, defined as bacterial infection and replication in the pleural space,[1] remains a significant cause of mortality.[2] Over 80,000 cases of pleural infection are diagnosed each year in the US and the UK.[3,4] Data from East Asia suggest that the annual incidence of pleural infections is 8.4 to 9.6 per 100,000.[5]

Intrapleural fibrinolytic therapy (IPFT) is one of the treatment options for patients in whom surgery is contraindicated. The combination of alteplase (tPA) and dornase (DNase) was first studied in the Multicenter Intrapleural Sepsis Trial (MIST2), showing good treatment success in terms of clearance of pleural opacity on chest X-ray (CXR) and an overall reduction in hospital stay (10 mg tPA/5 mg DNase, twice a day).[6] Subsequent open-label series of intrapleural tPA/DNase demonstrated

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Accepted: 15 November 2024

treatment success rates of 84–93%, with the Alteplase Dose Assessment for Pleural Infection Therapy (ADAPT) project (5 mg tPA/5 mg DNase, BD) and ADAPT-2 (2.5 mg tPA/5 mg DNase, BD) trials demonstrating noninferiority in terms of treatment success with lower doses of alteplase.[7-9]

However, the MIST2 is the only dosing regimen evaluated in a comparative randomised controlled trial, with drug doses selected empirically rather than through traditional dose-escalation studies. Information is limited on the pharmacokinetics when delivered into the pleural space and hence, the optimum dosing remains unknown. This has resulted in variations in dosing and regimes in real-world clinical practice. Furthermore, emerging evidence in anti-thrombotic therapies suggests that East Asians have a higher risk of bleeding compared with Caucasian counterparts. While the underlying mechanisms of this "East Asian paradox" are postulated to be complex and multifactorial, this has called for ethnicity-tailored strategies.[10]

In Tan Tock Seng Hospital (TTSH), Singapore, IPFT has been used with lower starting doses since the publication of both ADAPT and ADAPT-2 trials. These studies mostly involved a Caucasian population, with very little Asian representation. As such, we sought to perform a retrospective analysis of IPFT performed in TTSH to compare our cohort of patients to those from prior studies and determine if applying a similar dosing regimen in an Asian population yielded similar treatment outcomes. We also aimed to identify any potential factors affecting treatment success in our cohort of patients.

METHOD

We performed a retrospective analysis of all patients with pleural infections who underwent IPFT in TTSH between July 2016 and November 2023. Pleural infection was diagnosed based on clinical presentation, with supportive features on pleural fluid sampling—either one of (1) purulence macroscopically, (2) presence of bacteria by Gram staining or microbial culture or (3) pleural fluid pH ≤7.20 and/or glucose ≤3.0 mmol/L. Based on our institution protocol, IPFT may be considered if patients have no clinical improvement despite 12–24 hours of pleural drainage.

All patients were managed with tube thoracostomy and systemic antibiotics in accordance with guidelines and local practice. Referrals for surgical intervention were left to the discretion of the treating physician. The decision to administer, timing to initiate IPFT and initial dose of alteplase, was left to the treating physician. Dose escalation of alteplase was permitted at any time at the discretion of the attending physician.

The IPFT protocol of TTSH involves the sequential intrapleural administration of variable doses of alteplase (diluted in 30 mL normal saline) and 5 mg dornase alpha (diluted in 30 mL sterile water), twice a day over 72 hours (6 doses in total). Following the instillation of alteplase, the chest tube is flushed with normal saline and kept clamped for 45 minutes, before being left on free drainage for 45 minutes before instillation of the second drug. Blood tests, including full blood count and inflammatory markers as well as CXR, are monitored throughout the treatment duration.

Treatment success was defined as survival without the need for surgical intervention at the 3-month mark. Data extracted retrospectively from the medical records included patient demographics; comorbidities; Charlson comorbidity index (CCI); renal, age, purulence, infection source and dietary factors (RAPID) score; and pleural fluid studies and radiological characteristics. Two experienced respiratory physicians (GY and JW), measured radiographic variables including the presence of loculation on CXR, computed tomography (CT), pleural thickening >2 mm (measured in axial cut of the thickest pleural lining) and CXR scores as described in previous publications.[6] Data on treatment details and outcomes as well as adverse events, including pleural bleeding and death during admission, were also recorded.

Statistical analysis was performed using STATA version 16 or higher (StataCorp, College Station, TX, US). For continuous or discrete variables, summary statistics (i.e. arithmetic mean, standard deviation [SD], median, minimum and maximum values) were presented, with counts and percentages presented for categorical variables.

The chi-square test was performed to determine the association between categorical variables. Fisher's Exact test was applied in the case of small cell counts. Analysis of variance (ANOVA) was used to compare the continuous variables among alteplase dose groups.

For CXR scoring, we used an ANCOVA model to investigate the effect of alteplase dose on the change from baseline in CXR scoring at day 3, or day 6 or 7, and a linear mixed effects model to investigate the effect of alteplase dose on the change from baseline in CXR over time. This model included age, baseline CXR score as covariates, with alteplase dose group and day of CXR as factors. An unstructured covariance structure was used to model the covariance structure among visits.

For the primary outcome of treatment success and 3-month survival without requiring surgery, logistic regression was fitted with age and time to the insertion of chest tube to first dose of IPFT as

covariates, with the starting dose of alteplase as a factor. Odds ratio and the corresponding 95% confidence interval were presented. All the tests were based on a 2-sided 5% significance level.

The study was approved by the Domain Specific Review Board of the National Healthcare Group (2023/00830) and was conducted in accordance with the amended Declaration of Helsinki.

RESULTS

There were a total of 129 subjects, with 131 records due to 2 subjects having 2 admissions. Baseline characteristics, stratified across 4 groups according to first dose of alteplase, are provided in Table 1. The mean age was 65 years (SD 15.5), with 99 (76.7%) subjects being male. The median CCI was 2 (3 for males, 2 for females). Top comorbidities included hypertension (75/129, 58%), hyperlipidaemia (51/129, 39.7%) and diabetes mellitus (DM) (47/129, 36.6%).

Pleural infection characteristics

Pus was present in 16 cases (12.2%), while pleural fluid culture was positive in 51 cases (38.9%). The most common organism was *Streptococcus anginosus*. Among those that had CT (129 cases), 89 (69%) had loculations, while only 39 of 131 cases (29.8%) demonstrated loculations on CXR. Pleural thickening >2 mm on CT was present in 96 cases (75.0%).

Management of pleural infections

The mean time from chest tube insertion to first dose of IPFT was 10.2 days (11.5 days). Table 2A summarises the pleural infection characteristics among our cases and management prior to IPFT.

The median starting dose of alteplase was 5 mg (0.5–10). Sixty-two cases (48.4%) received a starting dose of 5 mg, while 37 cases (28.6%) started with 2.5 mg and only 12 cases (9.5%) started with 10 mg. Doses less than 2.5 mg were initiated in 17 cases (13.5%). Dose escalation occurred in 23 cases (17.6%). The 6-dose regime was terminated in 37 cases (28.2%). Common reasons for this included chest tube dislodgement, concerns of broncho/alveolopleural fistula or bleeding and physician decision. Patients who had received higher starting doses of alteplase tended to have lower CCI

Table 1A. Baseline characteristics.

Variables	Alteplase dose (mg)[a]				*P* value[b]	Total[c] n=129
	<2.5 n=17	2.5 n=36	5 n=61	10 n=12		
Age					0.29	
Mean (SD)	69.5 (13.4)	67.1 (17.3)	62.8 (14.9)	62.6 (16.1)		65.1 (15.5)
Median (minimum, maximum)	69 (47, 95)	66.5 (19, 97)	62 (22, 89)	66 (30, 80)		66 (19, 97)
Sex, no. (%)					0.35	
Female	3 (17.7)	12 (33.3)	13 (21.3)	1 (8.3)		30 (23.3)
Male	14 (82.3)	24 (66.7)	48 (78.7)	11 (91.7)		99 (76.7)
BMI					0.18	
No.	17	32	51	9		112
Mean (SD)	23.2 (4.8)	20.3 (4.7)	22.2 (4.7)	20.6 (3.6)		21.6 (4.7)
Median (minimum, maximum)	22.6 (17.6, 36.2)	20.3 (13.2, 35.7)	21.4 (13.8, 36.2)	20.7 (16.1, 27.9)		21.1 (13.2, 36.2)
RAPID score					0.1	
Mean (SD)	4.2 (1.3)	3.5 (1.1)	3.4 (1.1)	3.5 (0.7)		3.5 (1.1)
Median (minimum, maximum)	4 (2, 6)	3 (2, 6)	3 (2, 6)	3 (3, 5)		3 (2, 6)

BMI: body mass index; RAPID score: renal, age, purulence, infection source and dietary factor; SD: standard deviation
[a] Three subjects had no record of alteplase dose.
[b] *P* value was obtained using one-way analysis of variance or Fisher's Exact test (sex).
[c] All 129 subjects were included.

Table 1B. Comorbidities.

Variables	Alteplase dose (mg)[a]				*P* value	Total[b]
	<2.5	2.5	5	10		
Hypertension, no. (%)					0.07	
Yes	14 (82.3)	22 (61.1)	30 (49.2)	6 (50)		75 (58.1)
No	3 (17.6)	14 (38.9)	31 (50.8)	6 (50)		54 (41.9)
Hyperlipidaemia, no. (%)					0.002	
Yes	14 (82.3)	13 (36.1)	20 (32.8	4 (33.3)		51 (39.5)
No	3 (17.6)	23 (63.9)	41 (67.2)	8 (66.6)		78 (60.5)
DM, no. (%)					0.03	
Yes	12 (70.6)	10 (27.8)	21 (34.4)	4 (33.3)		47 (36.4)
No	5 (29.4)	26 (72.2)	40 (65.6)	8 (66.7)		82 (63.6)
CKD, no. (%)					0.003	
Yes	7 (41.2)	5 (13.9)	4 (6.6)	3 (25)		19 (14.7)
No	10 (58.8)	31 (86.1)	57 (93.4)	9 (75)		110 (85.3)
ESRF; patients on dialysis, no. (%)					0.03	
Yes	3 (17.6)	4 (11.1)	1 (1.6)	0		8 (6.2)
No	14 (82.4)	32 (88.9)	61 (98.4)	12		121 (93.8)
Anaemia, no. (%)					0.02	
Yes	8 (47.1)	9 (25.0)	8 (13.1)	3 (25.0)		29 (22.5)
No	9 (52.9)	27 (75.0)	53 (86.9)	9 (75.0)		100 (77.5)
CCI score, no. (%)					0.0001	
Mean (SD)	6.4 (3.7)	3.3 (3.2)	2.6 (2.4)	3 (3.1)		3.3 (3.1)
Median (minimum, maximum)	7 (0, 13)	2.5 (0, 12)	2 (0, 8)	1.5 (0, 10)		2 (0, 13)

CCI: Charlson comorbidity index; CKD: chronic kidney disease; DM: diabetes mellitus; ESRF: end-stage renal failure; SD: standard deviation
[a] Three subjects had no record of alteplase dose.
[b] All 129 subjects were included.

(*P*=0.0001). Using Fisher's Exact test, patients with comorbidities of anaemia (*P*=0.02), chronic kidney disease (CKD) (*P*=0.003), end-stage renal failure (ESRF) (*P*=0.03), hyperlipidaemia (*P*=0.002) and DM (*P*=0.03) tended to receive lower doses of alteplase. Table 2B summarises the use of IPFT in our cohort of patients, and Fig. 1 depicts the distribution of alteplase starting doses.

Outcomes

Treatment success was achieved in 112 cases (85.5%). The CXR score at baseline, day 3 and day 6 or 7, stratified according to alteplase dose, is presented in Fig. 2. The median area of hemithorax occupied by pleural opacity reduced from 27% (2–100%) to 10% (0.2–100%). A linear mixed effects model did not suggest any significant differences between the alteplase dose and change in CXR score (Fig. 2).

One subject had a length of stay (LoS) of 438 days and was excluded from analysis. The remaining cases are represented in Fig. 3. A one-way ANOVA model was used to compare LoS based on different alteplase doses. There was a statistically significant difference among alteplase dose levels in LoS (*P*=0.003). LoS in the group with alteplase dose less than 2.5 mg (mean 58.7 days, SD 35.8) was significantly longer than in the 5 mg (mean

Table 2A. Pleural infection characteristics and management prior to IPFT.

Variables	Alteplase dose (mg)				Total
	<2.5 n=17	2.5 n=37	5 n=62	10 n=12	
Baseline CXR loculation, no. (%)					
Yes	4 (23.5)	14 (37.8)	16 (25.8)	4 (33.3)	39 (29.8)
No	13 (76.5)	23 (62.2)	46 (74.2)	8 (66.7)	92 (70.2)
Loculations on CT, no. (%)					
Yes	9 (52.9)	23 (65.7)	48 (77.4)	7 (58.3)	89 (69)
No	8 (47.1)	12 (34.3)	14 (22.6)	5 (41.7)	40 (31)
Pleural thickening >2 mm, no. (%)					
Yes	13 (76.5)	24 (68.6)	46 (75.4)	12 (100)	96 (75)
No	4 (23.5)	11 (31.4)	15 (24.6)	0	32 (25)
Time from chest tube insertion to first dose (days)					
Mean (SD)	13 (8.3)	12.6 (13.8)	8.5 (11.5)	8.3 (7.4)	10.2 (11.5)
Median (minimum, maximum)	10.5 (2, 27)	7 (1, 60)	5 (1, 67)	6 (1, 21)	6.5 (1, 67)

CXR: chest X-ray; CT: computed tomography; SD: standard deviation

Table 2B. Description of IPFT use.

Variables	Alteplase dose (mg)				Total
	<2.5	2.5	5	10	
No. of doses					
Mean (SD)	5.5 (2.0)	5.6 (1.4)	5.4 (1.9)	4.8 (1.9)	5.4 (1.8)
Median (minimum, maximum)	6 (1, 9)	6 (1, 8)	6 (1, 13)	6 (1, 6)	6 (1, 13)
Dose escalation, no. (%)					
Yes	7 (41.2)	6 (16.2)	10 (16.1)	0	23 (17.6)
No	10 (58.8)	31 (83.8)	52 (83.9)	12 (100)	108 (82.4)
Cessation of regime, no. (%)					
Yes	7 (41.2)	6 (16.2)	19 (30.6)	5 (41.7)	37 (28.2)
No	10 (58.8)	31 (83.8)	43 (69.4)	7 (58.3)	94 (71.8)

IPFT: intrapleural fibrinolytic therapy;
SD: standard deviation

29.9 days, SD 25.4) or 10 mg group (mean 26.6 days, SD 1.5).

Logistic regression showed that age and interval between chest tube insertion to first dose were statistically significant variables for the primary outcome of treatment success. With 1 unit increase in time of insertion to first dose, the odds of 3-month survival decrease by 5% (P=0.014). With 1 year increase in age, the odds of 3-month survival decrease by 6% (P=0.01). Alteplase dosing was not significant in predicting treatment success in this model (Table 3).

With regard to adverse events, there was a low incidence of pleural bleeding (8/131, 6.1%). Incidence of pain post-IPFT was not accurately recorded and hence not reported. There were no allergic reactions

Fig. 1. Distribution of alteplase starting doses.

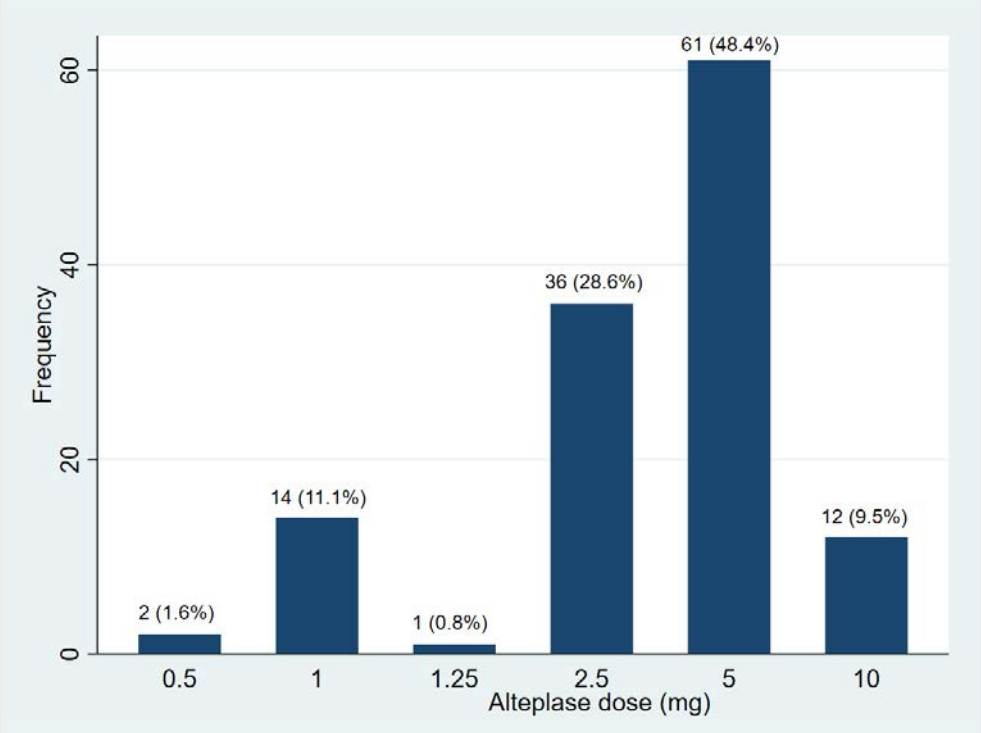
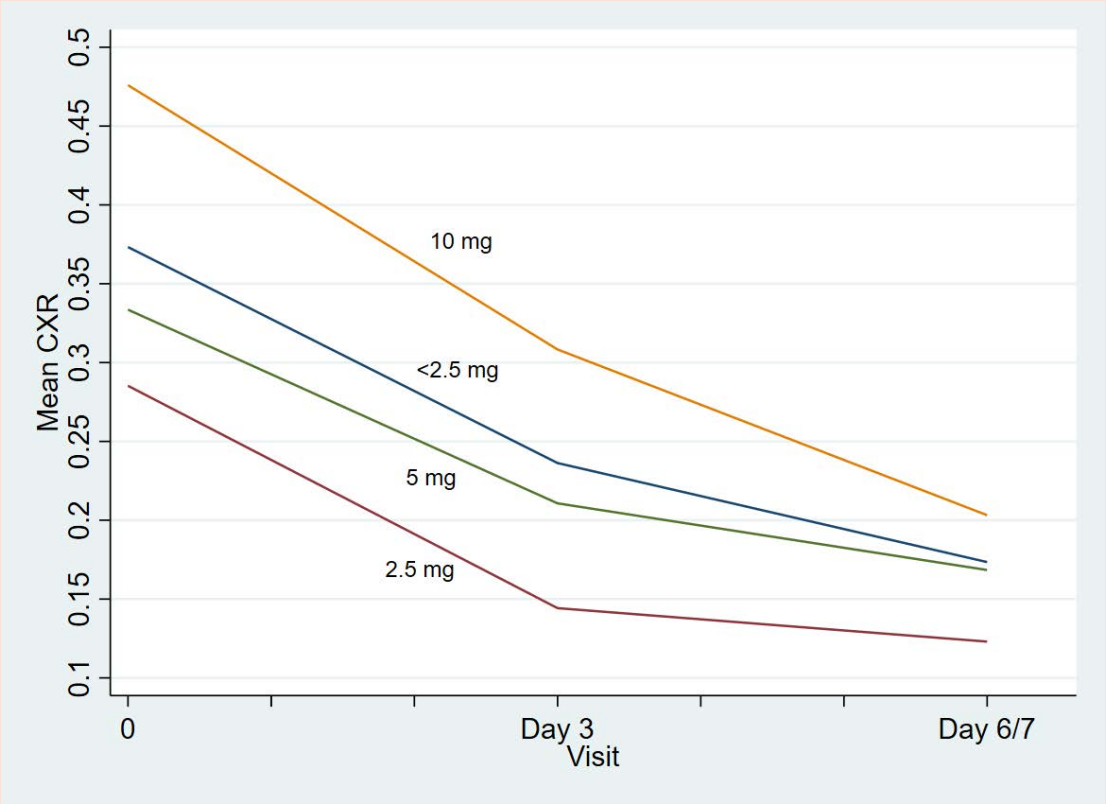


Fig. 2. Improvement in chest X-ray score across alteplase doses.



CXR: chest X-ray

Fig. 3. Hospital length of stay across alteplase doses.

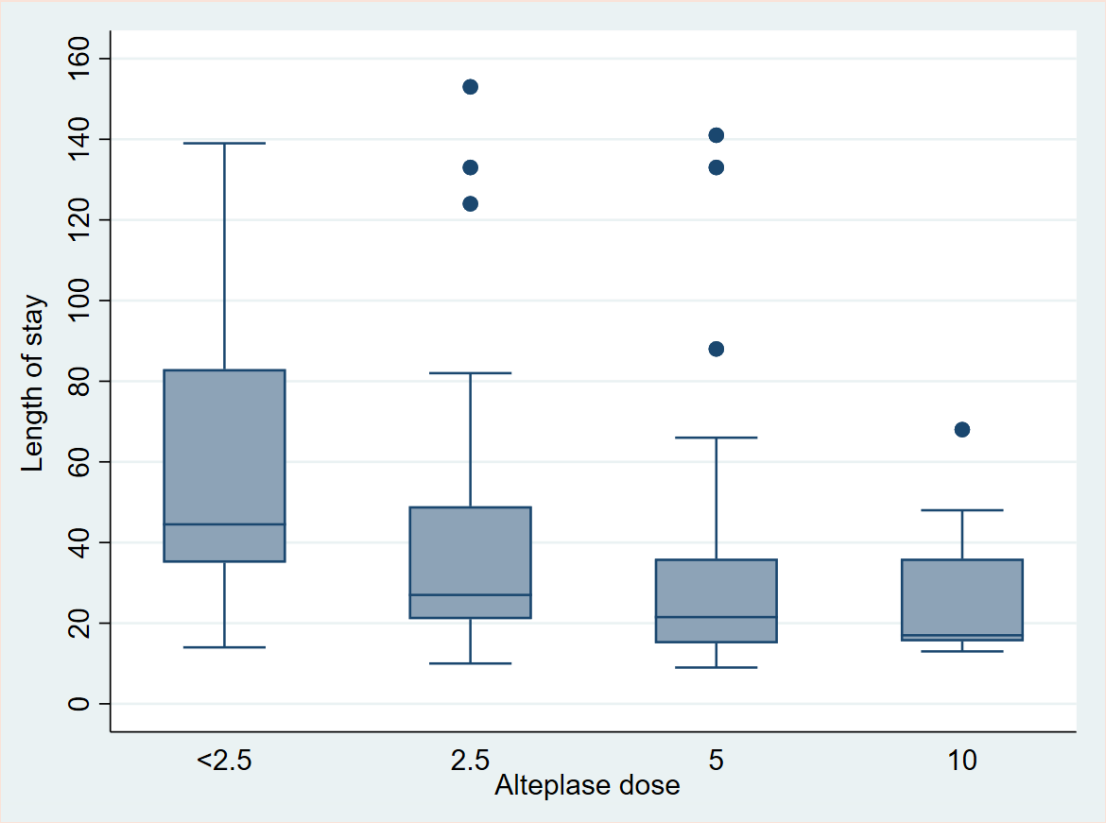


Table 3. Logistic regression.

Parameter	OR	95% CI	*P* value
Age	0.94	(0.89, 0.98)	0.01
Time of chest tube insertion to first IPFT dose	0.95	(0.91, 0.99)	0.014
Alteplase dose (mg)			
2.5 vs <2.5	4.44	(0.79, 24.91)	0.09
5 vs <2.5	1.53	(0.37, 6.30)	0.56
10 vs <2.5	2.94	(0.26, 32.93)	0.38

CI: confidence interval; IPFT: intrapleural fibrinolytic therapy; OR: odds ratio

to IPFT. Mortality rate during admission was 12.2%, with 3-month and 6-month mortality rates being 13.0% and 16.8%, respectively.

DISCUSSION

IPFT has gained acceptance as an alternative treatment to surgery for pleural infection, following the seminal MIST2 trial.[6] While there have been multiple subsequent studies demonstrating similar efficacy with lower doses of alteplase, the current dosing regimen suggested in guidelines (10 mg tPA/5 mg DNase) are weak recommendations or good practice points based on the MIST2 trial.[11] This retrospective study evaluated the real-life application of IPFT in patients with pleural infections in an Asian cohort, with selection of alteplase doses adjusted according to the patient's profile. Our treatment success rate of 85.5% remains comparable to prior studies published despite a trend towards lower doses of alteplase. This continues to add to the body of evidence that IPFT remains effective in the treatment of pleural infection, and

that treatment success can be achieved with lower doses than originally used in the MIST2 trial.

The median starting dose of alteplase was 5 mg in our cohort, and majority (48.8%) of our patients had received this starting dose. Patients who had received lower doses tended to have more comorbidities, such as anaemia, CKD and ESRF. This could reflect the conscious effort by clinicians to balance the perceived increased bleeding risks against efficacy. Interestingly, Akulian et al. found that a dose-reduction strategy (10 mg vs 5 mg alteplase) was not associated with a significant reduction in bleeding risks. However, serum urea level was found to be a significant independent predictor of bleeding, and patients with ESRF who had received a full dose regime tended to have an increased incidence of bleeding.[12]

When assessing the degree of CXR clearance, our study demonstrated similar rates of improvement in CXR opacity from baseline to the end of IPFT regardless of starting doses. While significant radiological improvements have been consistently demonstrated with IPFT use, prior studies have not compared the differences in CXR clearance stratified to alteplase doses. In addition, studies have consistently used a similar composite endpoint to define treatment success, which has not included the degree of radiological improvement on CXR. Studies have also demonstrated continued improvement in CXR clearance at day 30 from IPFT initiation.[7] Whether there is correlation between radiological improvement following IPFT and treatment outcomes or extent of CXR clearance to predict treatment success is unclear. It is possible that the degree of CXR clearance in isolation during the IPFT regimen itself has limited sensitivity in determining treatment success. Managing physicians should exercise caution not to administer IPFT for the purpose of achieving radiological resolution in isolation.

Notably, our study showed a lack of association between the starting dose of alteplase and treatment outcomes. Being a retrospective study, definitive conclusions cannot be drawn in the absence of head-to-head comparisons across the various doses while controlling for confounding variables. Nonetheless, the consistent signal of high treatment success rates across the MIST2 trial, subsequent dose de-escalation series (ADAPT, ADAPT-2) and as reflected in our current study strengthens the evidence of its use in pleural infections, though it also reinforces the need for further studies to evaluate the optimal dosing of alteplase.

The LoS for patients with lower starting doses of alteplase was longer compared to higher starting doses. Despite this, our results showed that there was no difference in treatment success across various alteplase starting doses. We postulate that the longer LoS may have been confounded by other factors, such as patient comorbidities (higher CCI, P=0.0001) (Table 1B).

Age remains a key factor when discussing pleural infections. Although our cohort was generally older compared to that investigated in prior studies, with a mean age of 65.1 years (MIST2 59 years,[6] Piccolo et al. 55.7 years,[9] Mehta et al. 54.6 years,[13] ADAPT 57 years,[8] ADAPT2 61 years[7]), treatment success was similar. However, an increasing age was also shown to reduce the odds of survival in our cohort of patients. Scoring systems, such as the RAPID score,[14] reflect the significance of age.

Our study also showed that there were fewer patients with positive pleural cultures (38.9%). This was similar to another Singapore study, which showed a 40% positive pleural culture rate in patients with complicated pleural infections.[15] The lower culture positivity in our study compared to other international cohorts deserves further investigation.

Significantly, our study revealed that our cohort of patients had a relatively long interval between chest tube insertion and first dose of IPFT. This delay may have been contributed by physician preference, waiting times for CT imaging, delays while awaiting surgical assessments and in certain cases, interventions to adjust chest drain positions or obtain additional drains. These may have been further confounded by disease complexity. The 2023 British Thoracic Society Guideline for pleural disease recommends a review of patients' clinical progress at 48 hours before considering IPFT for those with poor clinical progress. Delays in obtaining source control and evacuating the pleural space may worsen the underlying pleural sepsis, and lead to progression to a more organised stage, portending worse outcomes. With logistic regression demon-strating reduced odds of survival with every delay in initiating IPFT, our mean time of 10.2 days between chest tube insertion and first dose of IPFT, earlier recogni-tion of inadequate pleural drainage following tube thoracostomy alone should alert the clinician to expedite the administra-tion of IPFT when treating pleural infections.

The bleeding risk of 6.1% in our study is low and comparable to larger international studies (e.g. Akulian et al. 4.1%). Another retrospective study conducted in Singapore by Goh et al. also reported a similar 6.7% incidence of pleural bleeding.[14] The suggestion that lower dosages may lead to fewer adverse events seems plausible, but it is noteworthy that a dose-response relationship between alteplase dose and bleeding risk has not been demonstrated

in large multicentre retrospective studies.[11] On the contrary, our findings suggest that dose selection is influenced by patient comorbidities, and further work to refine this approach could provide more insights into dosing alteplase.

This study has its limitations. First, it is a retrospective study, with no direct head-to-head comparison between doses of alteplase. The confines of an observational study, including the lack of randomisation, blinding or inability to control for confounding variables in clinical practice or adherence to protocol, may have inadvertently affected clinical outcomes. Significantly, the publication of dose de-escalation studies may have inadvertently influenced physicians' decisions on the starting dose of alteplase. It is noteworthy that the tPA–DNase arm in the MIST2 trial had a compliance rate of 66.7%, while 36% of patients in the ADAPT study had early treatment discontinuation due to clinical improvement, and the median number of doses in the ADAPT-2 trial was 5. Additionally, 11.5% and 24.6% of patients in the ADAPT and ADAPT-2 studies respectively received dose escalations during the entire course of their treatment. These underscore the challenges and complexities of managing pleural infections, which may be even more unpredictable in a real-world setting such as in this study. A more nuanced management strategy over a protocolised treatment regimen may be preferred when managing pleural infections.

Second, in this real-world application of IPFT, patient outcomes may have been affected by factors separate to the IPFT regime received. These include the factors demonstrated to be significant predictors for treatment success such as age, time interval to receiving IPFT, as well as other potential confounders due to heterogeneity in the management of pleural infections, such as comorbidities, severity of illness and decisions involving end-of-life discussions (especially relevant given the older population compared to other studies). The cause of death was not recorded, limiting any interpretation of the mortality data. Therefore, it may be challenging to ascribe any success or failure of treatment to the IPFT regime itself.

CONCLUSION

IPFT regimes utilising lower starting doses of alteplase remain effective in the treatment of pleural infection. Early initiation of IPFT should be considered for all suitable patients, as this affects survival. The usage of IPFT remains relevant in an ageing population where surgical management may be contraindicated. In patients with comorbidities that increase bleeding risks, starting with lower doses of alteplase should be considered, with the option of increasing doses subsequently. While the optimal dose has not been determined in prospective studies, there appears to be increasing evidence for lower starting doses of alteplase and a trend towards personalised dosing. Considering the mechanism of action of IPFT within the infected pleural space, additional studies on the physiological effects of IPFT on lung function post-recovery may further validate its potential as an alternative to surgical intervention.

Ethics statement

This study was approved by the Domain Specific Review Board of the National Healthcare Group (2023/00830) and was conducted in accordance with the amended Declaration of Helsinki.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. No generative artificial intelligence (AI) or AI- assisted technologies were used.

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Ann Acad Med Singap 2024;53:734-41
https://doi.org/10.47102/annals-acadmedsg.2024217

REVIEW ARTICLE

Pharmacogenomics in psychiatry: Practice recommendations from an Asian perspective (2024)

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ABSTRACT

Introduction: Pharmacogenomic testing in psychiatry is an emerging area with potential clinical application of guiding medication choice and dosing. Interest has been fanned by commercial pharmacogenomic providers who have commonly marketed combinatorial panels that are direct-to-consumer. However, this has not been adopted widely due to a combination of barriers that include a varying evidence base, clinician and patient familiarity and acceptance, uncertainty about cost-effectiveness, and regulatory requirements. This review aims to examine recent updates in this field and provide a contextualised summary and recommendations for Asian populations in order to guide healthcare professionals in psychiatric practice.

Method: A review of recent literature about current evidence and guidelines surrounding pharmacogenomics in psychiatric practice was carried out with particular attention paid to literature evaluating Asian populations. The Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework was applied. Consensus meetings comprising workgroup psychiatrists from the public and private sectors were held prior to arriving at the key recommendations.

Results: Pharmacogenomic testing should be mainly limited to drug-gene pairs with established clinical evidence, such as antidepressants and *CYP2C19/CYP2D6*. Direct-to-consumer pharmacogenomic panels that assay multiple genes and analyse them via proprietary algorithms, are not presently recommended in Singapore's psychiatric setting due to inconclusive evidence on clinical outcomes.

Conclusion: Pharmacogenomic testing in psychiatry is not recommended as standard clinical practice. Exceptions may include concerns about drug concentrations or potential severe adverse drug reactions. Studies investigating newly identified drug-gene associations, and clinical effectiveness and cost-effectiveness of utilising pharmacogenomic testing in psychiatry is encouraged.

Ann Acad Med Singap 2024;53:734-41

Keywords: genetics, mental health, pharmacogenomics, pharmacology, psychiatry

CLINICAL IMPACT

What is New

- This article provides an update on the developments in pharmacogenomic testing in psychiatry and its current position in Singapore's landscape.
- Pharmacogenomic testing should be mainly limited to drug-gene pairs with established clinical evidence, such as antidepressants and *CYP2C19/CYP2D6*.
- Direct-to-consumer pharmacogenomic panels that assay multiple genes and analyse them via proprietary algorithms, are not presently recommended in Singapore's psychiatric setting due to inconclusive evidence on clinical outcomes.

Clinical Implications

- The practice recommendations can guide healthcare professionals on the utilisation of pharmacogenomic testing in psychiatric practice, particularly as an augmenting tool to guide medication selection and dosing, and limited to the known drug-gene pairs with established clinical evidence.

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Accepted: 27 November 2024

INTRODUCTION

Pharmacogenomic testing in psychiatry is an emerging area with the potential clinical application of guiding medication choice and dosing. Interest in this area has been fanned by commercial pharmacogenomic providers, who have commonly marketed multiple-gene or combinatorial panels that are direct-to-consumer tests. However, this has not been adopted widely due to a combination of barriers that include a varying evidence base, clinician and patient familiarity and acceptance, uncertainty about cost-effectiveness, and regulatory requirements. This was highlighted in a survey of clinicians engaged in the practice of psychiatry in Singapore and pharmacists from Singapore's Institute of Mental Health conducted by Chan et al.[1] Only 46.4% of respondents felt they were competent to order pharmacogenomic tests in psychiatry, with cost-effectiveness and the lack of clear guidelines raised as possible barriers to clinical implementation.

This review aimed to examine recent updates in pharmacogenomic testing in psychiatry, and provide a contextualised summary and recommendations for Singapore and the wider Asian audience. The recommendations serve to guide healthcare professionals on the utility of pharmacogenomic testing in psychiatric practice.

Singapore updates and practices

The first Standards for the Provision of Clinical Genetic/Genomic Testing Services and Clinical Laboratory Genetic/Genomic Testing Services were issued as a Code of Practice (COP) by Singapore's Ministry of Health (MOH) on 1 July 2018. In a further circular dated 16 December 2020,[2] MOH shared an updated COP following feedback from stakeholders and consultation with the Genetic Testing Advisory Committee.

The pertinent change for the field of psychiatry was that tests for certain genes/variants were approved for classification as Level 1 genetic tests by the Director of Medical Service (Annex B).[2] In particular, tests for *CYP2C19*, *CYP2D6* and "Actionable Pharmacogenomic Genotyping Panel" have been classified as Level 1 genetic tests. The effect of this change is that these tests can now be ordered by most registered medical practitioners, as compared to previously when they were deemed as Level 2 genetic tests, which required the registered medical practitioner to meet additional requirements, such as having relevant qualification or training in clinical genetics with at least 2 years of relevant working experience.

MOH had also published a guidance document[3] for the provision of non-clinical genetic testing in May 2021. It provides a definition of what constitutes clinical genetic testing, wherein any test that predicts a person's drug response has been included in the scope. The document also emphasised that any genetic testing that performs the same function as clinical genetic testing would be considered clinical, regardless of any disclaimers used. Together with the COP, it is stipulated that clinical genetic testing services can only be provided to consumers by healthcare institutions licensed under the Private Hospitals and Medical Clinics Act. In other words, clinical genetic tests cannot be offered as direct-to-consumer tests in Singapore. However, it is also crucial to note that MOH's regulatory framework does not apply to overseas providers, hence the need for practitioners to stay abreast of current evidence and the range of available services.

In the current Singapore psychiatric practice, as shared by members of our workgroup, pharmacogenomic testing has usually been employed to address either of the 2 following clinical issues: for aiding medication selection and dosing, and for avoiding severe adverse reactions with psychotropics. For the former, the patient commonly presents with a history of treatment resistance and failing multiple previous medication trials. With the aid of pharmacogenomic gene testing, the metaboliser status (or how quickly the body processes the drug) can be established, which helps in guiding future medication choice and dose-finding. As for the latter, psychiatrists would test for immunologic genes such as *HLA-B*1502* before prescribing carbamazepine to reduce the risk of potentially rare but severe adverse effects that may arise. This practice is standard of care and genotyping for the *HLA-B*1502* allele is subsidised by MOH.

The financial cost of pharmacogenomic tests is not insignificant and should be taken into consideration when utilised, with single gene testing costing around SGD100–200[4] and combinatorial panels costing upwards of SGD400[5] as of time of publishing.

METHOD

The consensus workgroup comprised psychiatrists from both the public and private sector. The workgroup evaluated the available literature up till June 2023 through a search of PubMed, Embase and CENTRAL databases. Keywords searched included "pharmacogenetic", "pharmacogenomic", "psychiatry" and "psychiatric disorders". The literature assessed included guidelines, meta-analyses, systematic reviews and randomised controlled trials (RCTs) in the English language. For RCTs, the search was limited from 2019 to

evaluate recent evidence reflecting the advancements in pharmacogenomic testing. The workgroup used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision framework[6] to evaluate the available evidence and arrive at the recommendations. Regular meetings were held, with workgroup members discussing each recommendation and arriving at a consensus when all members agreed. The workgroup adopted the Reporting Items for Practice Guidelines in Healthcare (RIGHT) checklist[7] in setting out the guideline.

RESULTS

Available evidence and guidelines

The majority of pharmacogenomics evidence in psychiatry revolves around antidepressants. Most studies have evaluated the pharmacogenomic variants, in particular the cytochrome *P450 (CYP450)* enzymes *CYP2C19* and *CYP2D6*. However, there exists discordance between pharmacogenomic resources such as the US Food and Drug Authority (FDA) drug labels and guidelines issued by the Clinical Pharmacogenetic Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) stemming from differences in approaches and access to information.[8,9] These resources are subject to reviews and updates and should be checked periodically in view of anticipated advancements in the field. In 2018, the FDA had initially released a safety communication[10] warning that despite the potential of pharmacogenomic testing, pending further scientific study, pharmacogenomic testing should not be used to provide information on a person's ability to respond to any specific medication to treat conditions such as depression, heart conditions, acid reflux and others. The FDA provided a further update to this in 2020, announcing a collaborative review of scientific evidence to support associations between genetic information and specific medications. The updated stance was accompanied by the publication of a Table of Pharmacogenetic Associations[11] which the FDA had deemed that while there was sufficient scientific evidence to suggest that subgroups of patients with certain genetic variants may experience differential therapeutic effects or risks of adverse events, most of the listed associations had not been evaluated in terms of clinical outcomes—such as improved therapeutic effectiveness or increased risk of specific adverse events—and that the FDA was not necessarily advocating use of a pharmacogenetic test before prescribing the corresponding medication.

Table 1. Antidepressants with actionable pharmacogenomic guidelines (CPIC and DPWG).

Antidepressant	CPIC	DPWG
Sertraline	*CYP2C19, CYP2B6*	*CYP2C19*
Citalopram	*CYP2C19*	*CYP2C19*
Escitalopram	*CYP2C19*	*CYP2C19*
Amitriptyline	*CYP2C19, CYP2D6*	*CYP2D6*
Clomipramine	*CYP2C19, CYP2D6*	*CYP2D6*
Doxepin	*CYP2C19, CYP2D6*	*CYP2D6*
Trimipramine	*CYP2C19, CYP2D6*	-
Imipramine	*CYP2C19, CYP2D6*	*CYP2C19, CYP2D6*
Paroxetine	*CYP2D6*	*CYP2D6*
Fluvoxamine	*CYP2D6*	-
Venlafaxine	*CYP2D6*	*CYP2D6*
Vortioxetine	*CYP2D6*	-
Nortriptyline	*CYP2D6*	*CYP2D6*
Desipramine	*CYP2D6*	-

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group

The CPIC[12,13] and DPWG[14] guidelines both carry recommendations for dose adjustments for certain antidepressants based on *CYP2C19* and *CYP2D6* phenotypes (Table 1). Additionally, the CPIC guideline carries a recommendation for initial dose adjustment in poor metabolisers of *CYP2B6*[12] and sertraline. Some of the notable antidepressants in the local context that currently do not have actionable pharmacogenomic guidelines include agomelatine, bupropion, fluoxetine, mirtazapine and trazodone.

As for antipsychotics, most studies to date have focused primarily on *CYP2D6*, with aripiprazole and risperidone most researched. Only the DPWG carries actionable guidelines[15] for 6 antipsychotics metabolised by *CYP2D6*, namely, aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and for *CYP3A4* poor metabolisers and quetiapine. No therapy adjustments are recommended for drug-gene pairs of *CYP2D6* and clozapine, flupentixol, olanzapine or quetiapine, and also not for *CYP1A2* and clozapine or olanzapine.

Regarding attention-deficit/hyperactivity disorder (ADHD) medications, current available evidence supports the optimisation of atomoxetine dosing based on variation in CYP2D6.[16,17] Poor metabolisers of atomoxetine are more likely to achieve the necessary blood concentrations for clinical effectiveness. DPWG recommends starting with the normal initial dose for poor metabolisers and being vigilant for side effects with a view to reducing the dose of atomoxetine in this group.[17] Likewise, CPIC recommends initiating with a standard starting dose and adjusting based on clinical response and metaboliser phenotype.[16]

There is limited or inconsistent evidence linking pharmacokinetic variants and treatment outcomes for most other common, notable psychotropic classes, such as mood stabilisers and anxiolytics. For the commonly employed mood stabilisers and anticonvulsants, valproate has no actionable guidelines for pharmacokinetic gene variants, while lithium and pregabalin are not hepatically metabolised and are excreted unchanged renally. As for the anxiolytics, the FDA Table of Pharmacogenetic Associations lists 2 benzodiazepines currently, namely, clobazam with *CYP2C19* (where data supports therapeutic management recommendations) and diazepam with *CYP2C19* (with potential impact on pharmacokinetic properties only).

Particular attention has to be paid to the immunologic genes *HLA-A* and *HLA-B* due to the potential for rare but severe side effects, such as Stevens-Johnson syndrome and toxic epidermal necrolysis following exposure to certain mood stabilisers such as carbamazepine. This is especially relevant in Singapore's context as the *HLA-B*1502* allele is more prevalent in Asian ethnicities with an estimated population frequency of 14.87%.[18] It remains that *HLA-B*1502* genotyping before prescribing carbamazepine is the only mandated pharmacogenomic test for psychiatry in Singapore.

The International Society of Psychiatric Genetics conducted a review and summarised the available evidence and treatment guidelines relating to pharmacogenomic testing in psychiatry.[19] They concluded that pharmacogenomic testing should be viewed as a decision-support tool for enhancing, rather than an alternative to standard treatment protocols. At the time of the published review, the available evidence and prescribing guidelines supported the use of pharmacogenomic testing to guide medication selection and dosing in several clinical contexts, particularly for antidepressants (*CYP2C19* and *CYP2D6*), antipsychotics (*CYP2D6*), anticonvulsants (*CYP2C19*, *HLA-A* and *HLA-B*) and the ADHD medication atomoxetine (*CYP2D6*), whereas current evidence did not support the testing of pharmacodynamic genes (e.g. *SLC6A4*, *COMT*, *MTHFR*) to inform prescribing of psychiatric medication. Additionally, a recommendation was included to screen for variants in *POLG* in patients suspected of having a mitochondrial disorder, and for *OTC* and *CPS1* in those suspected of having a urea cycle disorder prior to initiation of valproate, as the use of valproate in those with such disorders and particular gene variants may risk inducing liver toxicity, hyperammonaemia and encephalopathy.[20]

The Dutch Clinical Psychiatric Association also published their first guideline[21] on the use of pharmacogenetics in clinical psychiatric practice in 2021. Their general recommendations include considering genotyping when there is an indication (e.g. side effects or inefficacy), utilising genotype information if already available at the time of prescription, and involving patients in shared decision-making. At the time of publication, pre-emptive genotyping was not yet recommended for psychotropic drugs.

Combinatorial panels

Pharmacogenomic tests may either evaluate a single gene or multiple genes, with the latter termed "combinatorial" panels or approaches. Some combinatorial panels are produced by commercial providers, adopting a direct-to-consumer model, i.e. without healthcare professional input. Providers of these commercial panels often aggregate and analyse information from several genes using proprietary algorithms to provide recommenda-

tions for treatment choices. Pre-emptive panels that genotype for multiple genes with actionable variants (upon which clinicians can consider in their prescribing decisions) are also under development and investigation for clinical utility.[22,23]

A review of recent combinatorial pharmacogenomics testing studies revealed inconclusive or negative findings. The GAPP-MDD randomised-controlled trial (RCT) in Canada by Tiwari et al.,[24] which evaluated the GeneSight® Psychotropic combinatorial pharmacogenomic testing, found that there was no statistically significant difference between the guided-care group and the treatment-as-usual (TAU) group in response and remission rates after 8 weeks. The GUIDED trial[25] which also employed the GeneSight® Psychotropic test, found in their per-protocol analysis that at week 8, there was no significant difference in symptom improvement between the guided-care and TAU groups. However, there were statistically significant improvements in response and remission at week 8 for the guided-care group.

The PRIME Care open-label, randomised trial,[26] which likewise employed the GeneSight® panel, found that while the prescription of medications with predicted drug-gene interactions was significantly reduced in the intervention group compared to the TAU group, there was no significant difference in the remission and response rates at week 24 between groups in the treatment of depression. The PRIME Care group also noted that many of the subjects had no or only moderate predicted drug-gene interactions, which would have provided no relevant clinical information in medication choice and no effect on depression outcomes. Perlis et al.[27] conducted a double-blinded RCT using the Genecept Assay and found that there was no significant difference between the guided-care and TAU groups at week 8. Shan et al.[28] employed a proprietary assay (Conlight Medical Institute) in their 8-week, single-centre, rater-blinded study of 71 subjects of Han Chinese ethnicity. At the end of 8 weeks, there were no significant differences found in response and remission rates between the guided-care and TAU groups.

Aside from the inconclusive findings of the combinatorial approaches thus far, one of the main challenges to their adoption includes the variability across tests and the lack of regulatory standards. Selection of genes for inclusion in the assays varies by provider; and often, genes with insufficient evidence to guide prescribing are included. Even within the same selected genes, variations in the selected polymorphisms appear across the different tests, adding a layer of complexity in comparing and aggregating studies. The proprietary algorithms developed by each test provider to weigh the influence of each individual genotype in guiding medication selection lacks transparency, lends to the difficulty in generalising or aggregating results and can carry the risk that an individual alters their medication dosage so that their condition worsens. Most of the above studies also highlighted, as a limitation to generalisability of their studies, the majority Caucasian make-up of their cohorts and this is pertinent to practices that mainly interact with Asian populations.

Asian perspective

The majority of available literature on pharmacogenomics in psychiatry have chiefly examined populations of European ancestry and there is a gap in existing literature evaluating Asian populations. Ethnic variations in genetic polymorphisms are established and may result in different metaboliser phenotypes.[29,30] For the most studied group of *CYP450* enzymes, the activity of *CYP2C19* and *CYP2D6* have been found to be lower in Asians compared to Caucasians.[29,31] An implication of this can be seen in the relationship between *CYP2C19* and treatment response to escitalopram in panic disorder. He et al.[32] reported that in Chinese patients who were poor metabolisers, there was a higher treatment response compared to the extensive metabolisers. Few studies have evaluated clinical outcomes of pharmacogenomic testing in Asian populations and this is an area that should be encouraged. Apart from the aforementioned Shan et al.[28] study, Han et al. (corrigendum published in 2020)[33] evaluated the Neuropharmgen® assay in 100 Korean patients with depression. Both the guided and TAU arms had substantial improvements in terms of total Hamilton Depression Rating Scale (Ham-D) scores at the end of 8 weeks, with the guided arm having a significantly greater reduction in Ham-D, increased response rate but no significantly different remission rate compared to the TAU arm.

As for the immunologic genes *HLA-A* and *HLA-B*, a meta-analysis conducted by Deng et al.[34] found *HLA-B*1502* to be a risk allele for lamotrigine-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in Chinese populations, while *HLA-A*2402* was found to be a risk allele for both lamotrigine-induced SJS/TEN and maculopapular eruption in Chinese and Korean populations.

Singapore's population has a diverse, multi-ethnic make-up comprising representations of East Asian, Southeast Asian and South Asian ancestry. A recent study by Chan et al.[35] performed a deep interrogation of clinically significant genetic variants from 9051 Singaporean whole genomes. Of particular relevance were the findings that

51.0–77.2% of individuals across ancestries harboured alleles with actionable phenotypes in *CYP2C19*, and 31.1–47.2% of individuals carried actionable phenotypes in *CYP2D6*—both of which, as aforementioned, being involved in the metabolism of psychotropics including antidepressants and antipsychotics. Since 2013, genotyping for the *HLA-B*1502* allele prior to the initiation of carbamazepine therapy in patients of Asian ancestry has been considered standard of care with available subsidies for the genotyping test.[36]

In addition to genetic polymorphisms, lifestyle or environmental factors, such as diet and exposure to traditional or alternative medicines, may also substantially modify the activity of drug metabolising enzymes.[37]

Key recommendations

Strong recommendation that pharmacogenomic testing should not be routinely ordered in routine clinical psychiatric practice. Exceptions may include concerns about drug concentrations (due to metaboliser status) or potential severe adverse drug reactions. Pharmacogenomic testing should be mainly limited to the drug-gene pairs with established clinical evidence such as the anti-depressants and *CYP2C19* and *CYP2D6*. If pre-existing pharmacogenomic testing exists for known drug-gene pairs, this information should be taken into consideration and discussed with patients during the selection of psychotropic medications.

Direct-to-consumer pharmacogenomic panels that assay multiple genes and analyse them via proprietary algorithms, are not presently recommended in our local psychiatric setting, due to limited and inconclusive available evidence on clinical outcomes. Pharmacogenomics is a rapidly advancing field and improved panels with fewer drawbacks may be developed in the future, which would warrant further evaluation of clinical utility. Studies investigating clinical effectiveness and cost-effectiveness of utilising pharmacogenomic testing in psychiatry is encouraged.

CONCLUSION

Recommendations

In line with the available body of evidence, we recommend that pharmacogenomic testing should be employed as an augmenting tool to guide medication selection and dosing in certain clinical situations, and not as part of standard or routine clinical practice. Clinical situations could include concerns about blood concentrations of a drug (due to metaboliser status) or significant adverse drug reactions. Examples of these include patients who have failed multiple trials of medications or experienced significant adverse side effects even with low doses of medication. In the former case, patients may be ultra-rapid metabolisers, which necessitate higher doses of the affected drug or a switch to a drug not metabolised by the identified *CYP450* enzyme. For the latter, patients may be poor metabolisers and consequently have higher blood concentrations of the drug even at usual starting doses.

Pharmacogenomic testing should also be mainly limited to the drug-gene pairs with established clinical evidence such as the anti-depressants and *CYP2C19* and *CYP2D6*, which can be found within the CPIC[38] or the DPWG[39] guidelines. Clinicians should also be aware that many of the drug-gene associations have not been evaluated for clinical outcomes. Examples of available resources include the FDA Table of Pharmacogenetic Associations[11] and Pharmacogenomics Knowledgebase (PharmGKB),[40] a curated repository of clinically actionable drug-gene associations and genotype-phenotype relationships.

Existing challenges to the adoption of direct-to-consumer pharmacogenomic panels include the variability of included genes across providers, lack of transparency in the proprietary algorithms and the lack of available studies evaluating populations of Asian ancestry.

The field of pharmacogenomics and its application to psychiatry is a promising one. Larger studies, such as the PSY-PGx Project[41] and Ubiquitous Pharmacogenomics Project,[42] and collaborations to study Asian populations will most certainly be welcome additions.

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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Ann Acad Med Singap 2024;53:742-53
https://doi.org/10.47102/annals-acadmedsg.2024163

REVIEW ARTICLE

Optimising dementia screening in community-dwelling older adults: A rapid review of brief diagnostic tools in Singapore

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ABSTRACT

Introduction: Timely detection of dementia enables early access to dementia-specific care services and interventions. Various stakeholders brought together to refine Singapore's dementia care strategy identified a lack of a standardised cognitive screening tool and the absence of a comparative review of existing tools. We hence conducted a rapid review to evaluate the diagnostic performance of brief cognitive screening tools in identifying possible dementia among community-dwelling older adults in Singapore.

Method: Brief cognitive screening tools were defined as interviews or tests administered in ≤5 minutes. Studies performed in Singapore on older adults ≥60 years, which used locally-validated comparators and reported outcomes of clinician-diagnosed dementia were included. Rapid review methodology was used in study screening and selection. Quality Assessment of Diagnostic Accuracy Studies version 2 tool was used for risk-of-bias assessment. A negative likelihood ratio (LR-) of ≤0.2 was defined a priori as having a moderate effect in shifting post-test probability.

Results: Fourteen studies were included in qualitative synthesis: 3 studies evaluated self-/informant-based tools only, 4 evaluated performance-based measures only and 7 evaluated combination approaches. Eight-item Informant Interview to Differentiate Aging and Dementia (AD8) was the most studied self-/informant-based tool. One study found informant AD8 (iAD8) superior to self-rated AD8. Another study found iAD8 superior to Mini-Mental State Examination. Among performance-based measures, Abbreviated Mental Test, Visual Cognitive Assessment Test-Short form version 1 (VCAT-S1), VCAT-S2 and Mini-Cog had LR- <0.2. Minimal improvement of combination approaches compared to iAD8 alone was demonstrated.

Conclusion: Our review suggests the limited utility of dementia screening in communities with low dementia prevalence and supports a case-finding approach instead. With a reliable informant, iAD8 alone has sufficient discriminant ability. Further research is needed to specifically assess the diagnostic ability of performance-based tools in community settings.

Ann Acad Med Singap 2024;53:742-53

Keywords: cognitive screening tools, dementia, diagnostic performance, geriatrics, older adults, Singapore

CLINICAL IMPACT

What is New

- Subjective tools (e.g. self-reported or informant-rated) are recommended over performance-based tools; among these iAD8 demonstrated superior diagnostic ability compared to sAD8.
- In the presence of a reliable informant, iAD8 alone had sufficient discriminant ability, with limited additional benefit when used in conjunction with other performance-based tools.

Clinical Implication

- Based on this review, a case-finding approach to identify possible dementia in at-risk populations is recommended, rather than a community-wide or non-targeted population screening; this is also aligned with international screening guidelines.

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Accepted: 3 December 2024

INTRODUCTION

Persons living with dementia experience chronic and progressive cognitive decline in 1 or more cognitive domains, affecting their everyday activities.[1] Globally, the number of persons living with dementia is expected to rise from 55 million in 2019 to 139 million in 2050, with an estimated two-thirds in lower- and middle-income countries.[2] In Singapore, based on a 2015 nationwide study, dementia prevalence was found to be around 10%, which translates to approximately 86,000 adults aged 60 years and above.[3] The number of individuals affected is projected to increase to 130,000 by 2030. Dementia is associated with significant societal costs, resulting from a combination of greater healthcare utilisation and an increased need for both formal and informal caregivers. In 2013, the total cost of dementia care in Singapore was estimated to be SGD 532 million, with an annual cost per person of SGD 10,245.[4]

The 2017 Lancet Commission for dementia prevention highlighted the importance of timely detection of dementia among older adults with cognitive concerns, enabling early access to dementia-specific care services and interventions.[5] Multidisciplinary interventions, such as dementia counselling and education, cognitive engagement strategies, and medications, can help reduce patient and caregiver anxiety, progression of cognitive and neuropsychiatric symptoms, as well as facilitate long-term care planning, thereby reducing the occurrence of dementia-related crises. A study looking at excess dementia-related healthcare costs in Sweden found 13–25% higher healthcare costs, as early as a decade before diagnosis, peaking at the year of diagnosis. The healthcare costs subsequently reduced and became comparable to the population without dementia—supporting observations of preventable inpatient and post-acute services utilisation in the pre-dementia diagnosis period.[6]

The World Health Organization's Global Action Plan on the Public Health Response to Dementia highlighted dementia diagnosis, awareness, treatment and support as key action areas.[7] In line with this, Singapore announced the 2023 Action Plan for Successful Ageing, which highlighted managing dementia as a priority area in providing good care for older adults through (1) prevention and awareness; (2) early identification and diagnosis; (3) empowering persons living with dementia to age well in the community; and by (4) supporting dementia caregivers.[8] An integral component of this plan is the early identification of community-dwelling older adults at risk of dementia, so that appropriate assessments and interventions may be provided to these individuals.

As part of national efforts to enhance dementia management, various healthcare and community stakeholders collaborated to refine Singapore's dementia care strategy. Two key issues were identified: first, the absence of a standardised cognitive screening tool used in Singapore to identify older adults at risk of dementia; and second, the lack of a comparative review of the performance of existing tools across different settings (such as community versus primary care). Prior to this, only 1 systematic review of cognitive screening tools performed in Asia was published in 2016. This study included 2 studies carried out in Singapore based on the Mini-Mental State Examination (MMSE).[9] However, to date, there has not been an in-depth review of the various cognitive tools used to identify possible dementia in the Singapore population. This rapid review was hence conducted with the aim of evaluating the diagnostic performance of brief cognitive screening tools used to identify possible dementia among community-dwelling older adults in Singapore, with additional analysis of their performance in different settings.

METHOD

We used a rapid review methodology defined by Cochrane Rapid review guidelines.[10] Rapid reviews adopt systematic review methods and processes in a streamlined manner, allowing for accelerated yet rigorous knowledge synthesis of available literature.[10] Rapid reviews are suitable methodologies of literature review for requests for timely evidence for decision-making purposes to address urgent and emergent health issues and questions deemed of high priority. Given the need to provide relevant evidence to the dementia strategy workgroup in a timely manner, the rapid review was an appropriate methodology to address the clinical question posed by the workgroup.

Search strategy

We adapted the Joanna Briggs Institute (JBI) 3-step search strategy,[11] with an initial limited search conducted in MEDLINE by 2 reviewers (authors JPL and SL). A list of relevant articles was identified, and an analysis of the text word and Medical Subject Headings terms was performed to identify relevant search terms. The search strategy was further refined to identify studies conducted in community-based settings (such as adult day care centres and primary health clinics) with guidance from the librarian. Table 1 shows a summary of the search terms.

In the second step of the search, our full search strategy was applied across the databases: MEDLINE, Cochrane Collaborative Library, PsycInfo and Embase for published articles up till 12 March 2023

(Supplementary Tables S1A-D). The cut-off date of 12 March 2023 was set to meet the deadline provided by our stakeholders. Additional filters were applied to limit the studies to those conducted on the Singapore population and published in the English language. In the final step, reference lists of the included studies were also searched, as recommended by the JBI strategy, but yielded no additional results. We excluded unpublished studies, conference abstracts, non-English publications and grey literature. In preparation for the current manuscript, we performed an updated search for newly published studies from 13 March 2023 to 15 April 2024 using the same strategy.

Eligibility criteria

We defined cognitive screening tools as interviews conducted with patients or their caregivers, questionnaires or performance-based tests used to identify individuals at risk of cognitive impairment. A brief cognitive screening tool is one that can be administered in 5 minutes or less, reflecting its feasibility to be used by community providers. We included studies that (1) were performed on older adults aged 60 years and above; (2) used locally-validated comparators such as the MMSE or Montreal Cognitive Assessment (MoCA); (3) evaluated outcomes of clinician-diagnosed dementia; (4) were conducted in the Singapore community, primary care or outpatient clinic settings; and (5) were quantitative studies. Studies conducted in inpatient and long-term care settings were excluded. We also did not include studies that exclusively recruited patients attending tertiary memory clinics without recruiting controls from the community.

Study screening and selection

Title and abstract screening were independently completed by 2 reviewers (JPL and SL). In line with the rapid review framework, the first 20% of articles were screened by both reviewers. Conflicts were resolved through consensus discussion, with adjudication by a third reviewer (WSL) if needed. The remaining titles and abstracts were screened by the first reviewer, with all excluded articles cross-checked by the second reviewer and conflicts resolved through consensus discussion, shown in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram (Fig. 1). A similar approach was adopted for the full-text screening phase, with the first 20% of articles being dually-screened by both reviewers and conflicts were resolved before the remaining articles were singly-screened. All excluded articles were cross-checked by the second reviewer, with involvement of a third reviewer (WSL) if needed. This 2-stage screening process was managed in Covidence (Veritas Health Innovation, Melbourne, Australia) an online systematic review software.[12]

Risk-of-bias assessment

We performed a risk-of-bias and applicability assessment for all included full-text articles using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool. This is a validated tool for assessing quality of primary diagnostic accuracy studies. The domains of "patient selection", "index test", "reference standard" and "flow and timing" were rated for risk of bias and applicability to our research question. The ratings were guided by signalling questions of the QUADAS-2 tool. Quality assessment was performed independently by 2 reviewers (JPL and SL) for all included articles and discrepancies were resolved through discussion.

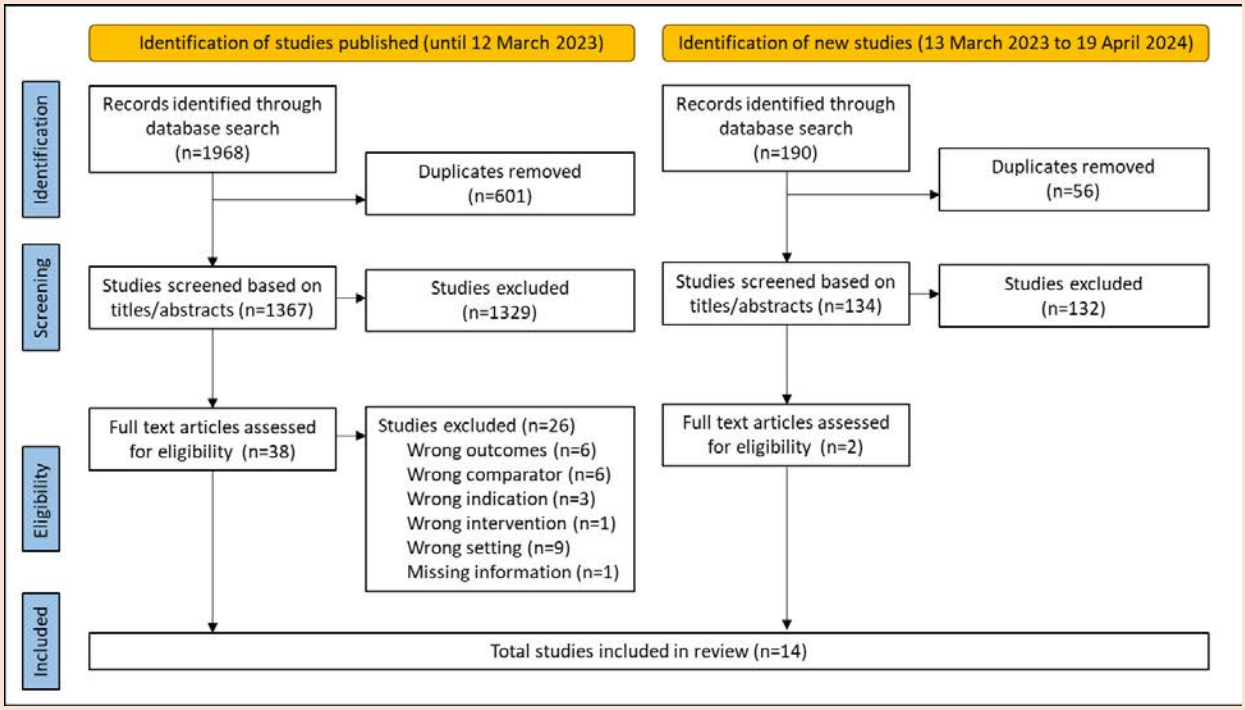
Data extraction

We created a standardised data extraction form comprising study characteristics and indicators of diagnostic accuracy. The following variables on study characteristics were extracted: sample size, gender representation, study setting, study design, index test, comparator instruments, reference standard used and dementia prevalence in the study population. Variables of diagnostic accuracy

Table 1. Summary of search terms.

	Keywords
Population	Older adult(s), older people, senior(s)
Intervention	Cognitive screen, cognitive testing, geriatric assessment/methods, mental status and dementia tests, neuropsychological tests/standards, rapid cognitive screen
Outcome	Alzheimer disease/diagnosis, cognition disorders/diagnosis, cognitive impairment, dementia, early diagnosis, executive function, mild cognitive impairment
Setting	Adult day care centers, ambulatory care, clinic visit, community health nursing, community mental health services, health services for the aged, home care services, outpatient care, primary healthcare, senior centers

Fig. 1. PRISMA flow diagram.



PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

of the cognitive screening tools included accuracy (area under the curve [AUC]); cut-offs; sensitivity (Sn) and specificity (Sp) at various cut-off points; negative and positive likelihood ratios; as well as negative and positive predictive values. Data extraction was performed by the first reviewer and cross-checked by the second reviewer.

Data synthesis

Data from all the included studies were extracted and presented in the form of frequencies and percentages. The index tests were grouped in accordance to the type of assessment (i.e. self/informant report versus performance-based tests, or a combination of these modalities). Given the varying prevalence of dementia across different settings, the data were further stratified by study setting. Diagnostic accuracy information was presented as percentages with 95% confidence interval (CI). When specific values were not explicitly stated, we calculated likelihood ratios and predictive values using the data provided in the studies. In view of marked heterogeneity in the study setting, index tests and reference standards, pooled analysis was not possible.

RESULTS

In the initial phase, we identified 1968 studies using keyword search, of which 601 were duplicates and an additional 1329 studies were excluded at the title and abstract screening stage. Thirty-eight full-text articles were assessed for eligibility, and 12 studies were included in the qualitative synthesis. In the updated search, we identified another 190 studies, of which 56 were duplicates. Out of the remaining 134 studies, 132 were excluded after screening of their titles and abstracts. Two remaining studies were assessed for eligibility at the full-text assessment stage and included. Thus, a total of 14 studies were included in the final qualitative synthesis, outlined in the PRISMA diagram (Fig. 1).

Quality assessment

Most studies (8 of 14 studies) were rated as having unclear/high risk of bias in terms of patient selection, largely due to a case-control study design (Table 2, Supplementary Table S2). Only 7 studies had a low risk of bias in the flow and timing of index test and reference standard test. Most studies (12 of 14) had low risk of bias in terms of the reference standard used in the study. In terms of applicability, concerns arose primarily from patient selection in the studies—a result of the unclear/high risk of bias status in these studies.

Study characteristics

Of the 14 studies, 5 were case-control studies.[13-17] Cases were patients with dementia recruited from memory clinics, and controls were participants

Table 2. Quality of assessment (QUADAS-2).

Author, year	Risk of bias				Concerns regarding applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Chan et al. 2016[18]	Unclear	Low	Low	High	Low	Low	Low
Chan et al. 2016[19]	Unclear	Low	Low	High	Low	Low	Low
Chong et al. 2006[24]	Low	Low	Low	Low	Low	Low	Low
Dong et al. 2013[13]	High	Low	Low	Low	High	Low	Low
Kan et al. 2019[23]	Unclear	Low	Low	Low	Low	Low	Low
Koh et al. 2020[16]	High	High	Low	Unclear	High	Low	Low
Li et al. 2006[21]	Low	Low	Low	High	Low	Low	Low
Pang et al. 2022[22]	Low	Low	Unclear	Low	Low	Low	Low
Pang et al. 2023[26]	Low	Low	Low	High	Low	Low	Low
Shaik et al. 2016[20]	Low	Low	Low	Low	Low	Low	Low
Sahadevan et al. 2000[14]	High	Low	Low	High	High	Low	Low
Tew et al. 2015[17]	High	Low	Low	High	High	Low	Low
Venketasubramanian. 2024[25]	Low	Low	Low	Low	Low	Low	Low
Yap et al. 2007[15]	High	High	Low	High	Low	High	Low

Superscript numbers: refer to REFERENCES
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies version 2

recruited from community settings. Four were studies of combined cohorts from primary care settings[18-20] and combined cohorts of patients in outpatient neuroscience clinics and community settings.[21] The remaining 5 studies were community-based studies (Supplementary Table S3).[22-26] Pooled analysis of the results was not possible due to the heterogeneity of the included studies in terms of study setting, study design and population characteristics, even with grouping according to the brief cognitive tool evaluated.

Self-reported/informant-based measures only

Three studies solely evaluated self-reported or informant-based tools (Table 3).[13,19,22] The most studied tool used was the Eight-item Informant Interview to Differentiate Aging and Dementia (AD8).[27] A study in primary care settings found that informant AD8 (iAD8) was superior to the MMSE in accuracy: AUC 0.97 (95% CI 0.95–0.99) versus AUC 0.92 (95% CI 0.88–0.97, *P*=0.047) and equivalent to MoCA: AUC 0.94 (95% CI 0.92–0.97, *P*=0.13).[19] iAD8 was also demonstrated to have superior diagnostic accuracy compared to self-rated AD8 (sAD8) in a study performed in outpatient clinic settings. At a cut-off point of 2 and above, iAD8 had a sensitivity of 93.0%, specificity of 87.0% and positive likelihood ratio (LR+) of 6.85 (95% CI 3.03–15.49), compared with sensitivity of 59.0%, specificity of 65.0% and LR+ 1.69 (95% CI 1.08–2.65) for sAD8.[13]

Another study compared single-item questions of subjective complaints from questionnaires of the 10th item on the self-rated Geriatric Depression Scale (GDS-10), 8th item of sAD8 (sAD8-8) and 8th item of iAD8 (iAD8-8).[22] Of these, iAD8-8 had the best diagnostic performance (Sn 69.2%, Sp 83.2%, LR+ 4.12) compared to sAD8-8 (Sn 41.7, Sp 76.5, LR+1.77) and GDS-10 (Sn 40.9%, Sp 82.9%, LR+ 2.4).

Performance-based measures only

There were 4 studies evaluating performance-based measures only; 3 used a case-control methodology whereby cases were recruited from specialist outpatient memory clinics, and controls were recruited from community settings such as community clubs and door-to-door surveys.[14-16] Not surprisingly, the dementia prevalence in these studies was high, ranging between 38.6–53.0%. The Abbreviated Mental Test (AMT) had good diagnostic accuracy at age and education-stratified cut-offs with sensitivities ranging 80–97% and specificities 83–100% (Table 3).

Table 3. Studies of self-rated/informant-based measures only and performance-based measures only.

Author, year	Study design; study setting	Dementia prevalence (%)	Tool (language); cut-off point	Sensitivity (%)	Specificity (%)	Accuracy (%)	Negative likelihood ratio	Positive likelihood ratio
Self-rated/informant-based measures only								
Chan et al. 2015[19]	Cross-sectional; primary care	14.2	Informant AD8 (E/C/M); 3/4	91.0	91.0	91.0	0.10	10.11
Dong et al. 2013[13]	Case-control; memory clinic (cases), community (control)	53.0	Informant AD8 (E/C/M); ≥2	93.0	87.0	91.8	0.09	6.85
			Self-rated AD8 (E/C/M); ≥2	59.0	65.0	60.0	0.63	1.69
Pang et al. 2022[22]	Cohort; community	4.8	GDS-10; yes/no	40.9	82.9	80.0	0.71	2.40
			Informant AD8-8; yes/no	69.2	83.2	82.5	0.37	4.12
			Self-rated AD8-8; yes/no	41.7	76.5	75.0	0.60	1.77
Performance-based measures only								
Koh et al. 2020[16]	Case-control; memory clinic (cases), community (control)	53.0	VCAT-S1 (LN); <12	86.0	83.0	92.0	0.17	5.06
			VCAT-S2 (LN); <10	76.0	90.0	92.0	0.27	7.60
Sahadevan et al. 2000[14]	Case-control; memory clinic (cases), community (control)	38.6	AMT (E/C); 60–74 years old: 0–6 yrs of education: 7/8	97.0	83.0	-	0.036	5.71
			60–74 years old: ≥7 years of education: 8/9	80.0	91.0	-	0.22	8.88
			≥75 years old: 0–6 years of education: 5/6	91.0	100	-	0.1	-
			≥75 years old: ≥7 years of education: 8/9	85.0	100	-	0.15	-
Yap et al. 2007[15]	Case-control; memory clinic (cases), community (control)	49.3	CLOX1 (LN); 0–6 years of education: 10	78.6	64.0	78.0	0.33	2.18
			>6 years of education: 11	88.2	68.4	88.0	0.17	2.79
			Overall: 10	75.3	76.0	84.0	0.33	3.14
			CLOX2 (LN); 0–6 years of education: 12	76.8	64.9	81.0	0.36	2.19
			>6 years of education: 13	87.5	81.6	91.0	0.15	4.76
			Overall: 12	75.0	80.0	85.0	0.31	3.75
Venketasubramanian 2024[25]	Cohort (2-phase study); community	22.8	ECAQ (E/C/M/T); ≤5	78.0	95.5	95.0	0.23	17.3

AD8: Eight-Item Informant Interview to Differentiate Aging and Dementia; AD8-8: 8th question of AD8; AMT: Abbreviated Mental Test; CLOX; clock drawing task; E/C/M/T: English/Chinese/Malay/Tamil; ECAQ: Elderly Cognitive Assessment Questionnaire; GDS-10: 10th item on the Geriatric Depression Scale; LN: language neutral; VCAT-S: Visual Cognitive Assessment Test-short form
Superscript numbers: refer to REFERENCES

Another study evaluated the diagnostic performance of the clock drawing task (CLOX), using 2 methods of performing the test (CLOX1 and CLOX2).[15] The diagnostic accuracy of CLOX1 and CLOX2 were comparable, albeit at different cut-off points of 10 and 12, respectively (CLOX1: Sn 75.3%, Sp 76.0%, LR+3.1; CLOX2: Sn 75.0%, Sp 80.0%, LR+ 3.8).

The third study evaluated the Visual Cognitive Assessment Test short-form (VCAT-S) which consisted of 5 items from the original VCAT developed in Singapore.[16] Two scoring systems VCAT-S1 and VCAT-S2 were studied. VCAT-S1 and VCAT-S2 demonstrated high diagnostic accuracy of 92%, Sn 86–90%, Sp 80–81%, and LR+ 4.53, albeit against a high prevalence of dementia at 53% in the study population.

Only 1 study evaluated the Elderly Cognitive Assessment Questionnaire (ECAQ).[25] This community study used a 2-phase approach whereby participants were first screened with a modified World Health Organization screening tool for neurological disorders. All who screened positive and a subset who screened negative were included in the second phase. This strategy, akin to a case-finding approach, resulted in a slightly high dementia prevalence of 22.8% for a community study. The ECAQ demonstrated a high diagnostic accuracy of 95%, specificity of 95.5%, sensitivity of 78.0% and high LR+17.3.

Combination approaches

Six studies looked at combination approaches where combinations of tools were used for identification of dementia (Table 4). Three studies assessed iAD8 in conjunction with performance-based tools,[17,18,23] and 1 study evaluated a risk score used together with iAD8.[20] A community-based study examined performance-based tools of either 5-min MoCA or Mini-Cog in conjunction with iAD8.[23] The study evaluated 2 combination approaches: a conjunctive approach that required both iAD8 and the additional test results to be positive versus a compensatory approach that only required 1 positive test result. The results demonstrated minimal improvement with combination approaches (whether conjunctive or compensatory) compared to iAD8 on its own (accuracy: iAD8 0.89; iAD8+5-min MoCA 0.82; iAD8/5-min MoCA 0.87; iAD8+Mini-Cog 0.84; iAD8/Mini-Cog 0.79).

Similarly, there was limited additional benefit of combination approaches of iAD8 with selected elements of the MMSE (recall question, recall and copy question)[17] and combination of National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) 5-minute protocol[18] seen in 2 other studies in the outpatient memory clinic and primary care setting, respectively. The diagnostic accuracy for iAD8 only (AUC 0.93) was comparable to iAD8+recall (AUC 0.94) and iAD8+recall+copy (0.95).[17] Compared with iAD8 alone (accuracy 93.0%), conjunctive and compensatory approach for iAD8 with NINDS-CSN 5 min had lower diagnostic accuracy of 89.4% and 82.0%, respectively.[18]

Two studies evaluated combination approaches of progressive forgetfulness (PF) as the self-rated tool and AMT as the performance-based tool.[24,26] In both studies, PF and AMT were performed for all participants in the first phase, and those who scored positive for either were included in the second phase for assessment of dementia via clinical and neuropsychological evaluations. In Chong et al.'s study, the conjunctive approach for positive PF and AMT (PF+ and AMT+) had the highest LR+ (5.31);[24] other diagnostic indices in this study were not reported. Similarly, the highest LR+ (13.37) and diagnostic accuracy (88.4%) were found for PF+ and AMT+ combination in Pang et al.'s study.[26]

DISCUSSION

This rapid review provides a comprehensive overview of the cognitive tools used to identify possible dementia among community-dwelling older adults in Singapore. Among the 12 included studies, only 3 studies were fully community-based with case prevalence corresponding to population studies.[22-24] Studies evaluating cognitive tools performed in community cohorts reported accuracy ranging 75–92%, negative predictive value (NPV) of 96.8 – 99% and low positive predictive value (PPV) of 7.2–57%. In primary care settings, studies reported higher accuracy between 81–97%, NPV 91–98% and much higher PPV of 63–92%.

Our review suggests that dementia screening has limited utility in communities with low dementia prevalence, given the low PPV of the current tools in such settings. Instead, a case-finding approach is recommended, whereby at-risk populations such as patients with chronic diseases or subjective memory complaints attending primary care services, are screened intentionally for dementia. This is consistent with screening guidelines in the UK and US.[28] Australia's clinical guidelines for dementia do not recommend population screening, and instead highlight vigilance for symptoms of cognitive impairment in older adults for referral to specialists of dementia for further detailed evaluation.[30] A recent systematic review commissioned by the US Preventive Services Task Force found no empirical evidence that screening the general population

Table 4. Studies of self-rated/informant-based measures and performance-based measures in combination.

Author, year	Study design; Study setting	Dementia prevalence (%)	Tool (language); cut-off point	Sensitivity (%)	Specificity (%)	Accuracy (%)	Negative likelihood ratio	Positive likelihood ratio
Chan et al. 2016[18]	Cross-sectional study; primary care	21.4	iAD8; ≥2	85.0	86.8	86.2	0.17	6.44
			NINDS-CSN 5-min: 6/7	81.7	86.8	85.2	0.21	6.19
			Compensatory iAD8+NINDS-CSN 5-min; 2/3 and/or 6/7	93.3	76.7	82.0	0.09	4.00
			Conjunctive iAD8+NINDS-CSN 5-min; 2/3 and 6/7	73.3	96.9	89.4	0.28	23.6
Chong et al. 2006[24]	Cohort study (2 phase); community	14.0	PF; yes/no	95.7	45.1	-	0.10	1.74
			AMT (overall); Young-old (60–74 yrs): AMT 7/8 (0–6 years education) AMT 8/9 (>6 years education) Old-old (≥75 years): AMT 5/6 (0–6 years education) AMT 8/9(>6 years education)	86.9 75.0 93.3	71.4 80.4 34.6	- - -	0.20 0.19 0.19	3.04 5.10 1.43
			PF+ and AMT+	-	-	-	-	5.31
			PF- and AMT +	-	-	-	-	0.31
			PF+ and AMT -	-	-	-	-	0.35
Kan et al. 2019[23]	Cohort study; community	5.5	iAD8; ≥3	76.0	94.0	89.0	0.26	12.67
			5-min MoCA; ≤5	81.0	90.0	92.0	0.21	8.10
			Mini-Cog; ≤2	93.0	67.0	89.0	0.10	2.82
			Compensatory iAD8+5-min MoCA; ≥3/≤5	91.0	83.0	87.0	0.11	5.35
			Conjunctive iAD8+5-min MoCA; ≥3, ≤5	67.0	97.0	82.0	0.34	22.33
			Compensatory iAD8+Mini-Cog; ≥3/≤2	95.0	63.0	79.0	0.08	2.57
			Conjunctive iAD8+Mini-Cog; ≥3, ≤2	74.0	95.0	84.0	0.27	14.80

Table 4. Studies of self-rated/informant-based measures and performance-based measures in combination. (Cont'd)

Author, year	Study design; Study setting	Dementia prevalence (%)	Tool (language); cut-off point	Sensitivity (%)	Specificity (%)	Accuracy (%)	Negative likelihood ratio	Positive likelihood ratio
Li et al. 2006[21]	Combined cohorts; neuroscience clinic patients, community cohort	13.2	IRMP (E/C); yes/no	85.7	80.7	83.2	0.18	4.44
			4IADL (E/C); ≤8	78.6	67	84.7	0.32	2.38
			IRMP+4IADL(E/C); ≤ 7	85.7	85.7	91.6	0.17	5.79
Pang et al. 2023[26]	Cohort study (2 phase); community	4.9	PF+AMT; PT: yes/no, AMT 6/7 (0–6 years education) AMT 8/9 (>6 years education) PF+ and AMT+	82.9	93.8	88.4	0.18	13.37
			PF- and AMT+	71.0	66.7	71.4	0.47	2.33
Shaik et al. 2016[20]	Cohort study (2 phase); primary care	54.8	TRS; ≥4	70.0	77.0	81.0	-0.39	3.05
			TRS+AD8 (E/C/M)	-	-	-	-	-
Tew et al. 2015[17]	Case-control; memory clinic (cases), community (age-matched control)	64.9	iAD8 (E/C); 5/6	90.7	84.3	92.0	0.11	5.78
			iAD8+Recall (E/C); 7/8	88.4	84.9	94.0	0.14	5.85
			iAD8+Recall+Copy (E/C); 8/9	87.2	88.1	95.0	0.15	7.33

4IADL: brief Instrumental Activities of Daily Living scale; 5-min MoCA: 5-minute Montreal Cognitive Assessment; AD8: Eight-Item Informant Interview to Differentiate Aging and Dementia; AMT: Abbreviated Mental Test; E/C/M/T; English/Chinese/Malay/Tamil; iAD8: informant AD8; IRMP: Informant Report of a single question on Memory Decline; NINDS-CSN 5-min: National Institute of Neurological Disorders and Stroke-Canadian Stroke Network 5-minute protocol; PF: progressive forgetfulness; TRS: total risk score
Superscript numbers: refer to REFERENCES

with neither memory concerns nor risk factors for dementia improves decision-making for patients with the earlier detection of cognitive impairment.[29] Another paper evaluating national dementia policies across 7 countries around the globe with active national dementia plans (China, Germany, Japan, South Korea, Sweden, UK and US) found that only South Korea had policies to support population screening for brain health.[31] Studies on a screening programme's cost-effectiveness were inconclusive—a South Korean study reported a cost per quality-adjusted life-year gained ranging from USD 24,150 to 35,661.[32]

Of the tools included, the AD8 was the most studied brief cognitive screening instrument. We recommend iAD8 over sAD8 in view of superior diagnostic performance. The iAD8 also retained good discriminatory ability when administered as a single test with no discernible benefit using combination approaches. The additional time needed to perform both the iAD8 and a performance-based test did not justify the marginal improvement of negative likelihood ratio in most of the combination approaches (Table 4). This finding was corroborated by studies performed in Taiwan[33] and US.[34] The use of AD8 was promoted in Taiwan with validated Chinese versions of AD8 for both sAD8 and iAD8. The accuracy for sAD8 was 59.0% while that of iAD8 was 77%.[33] Similarly, a study performed in US found that iAD8 was inversely related to the patient's MoCA scores while sAD8 had no relation with MoCA scores, suggesting that iAD8 was a more useful indicator of the patients' cognitive ability.[34] However, the generalisability of these results to the general population would need to be considered. Of note, outpatient clinics (particularly the specialist memory clinics) may represent a unique context whereby the accompanying informant would likely be more concerned about the patient's cognition and thus provide a more reliable corroborative input to complete the iAD8 compared to informants encountered in community settings.

Thus, despite the good discriminant ability of iAD8, there remains a role for performance-based tools especially in situations where there is either no next-of-kin or reliable informant available. In our review, many of the performance-based studies recruited cases from the memory clinic settings. Diagnostic performance of tools employed in specialised care settings were likely to be inflated due to spectrum bias, high case prevalence, and weaker study design (i.e. case-control). In addition, the high dementia prevalence in these studies would have affected the PPVs and NPVs. To minimise the impact of the wide range of dementia prevalence, we compared the LR- between the tools. An LR- expresses how many times less likely a normal test result is to be expected in patients with the condition as compared to those without.[35] Hence, to evaluate how informative the test is in ruling out dementia, a smaller LR- would indicate a more informative test. An LR- of 0.2 and below was determined by the study team a priori as having a moderate effect in shifting the post-test probability. The performance-based tools fulfilling this threshold were the AMT, VCAT-S1, VCAT-S2 and Mini-Cog (Tables 3 and 4). The 5-min MOCA (LR- 0.21) and NINDS-CSN 5-min (LR- 0.21) had an LR- trending close to 0.2.

Among the performance-based tools, only AMT had more than 1 study done in either the community or outpatient clinic settings. Sahadevan et al. (2000) included cases from an outpatient memory clinic and evaluated the diagnostic performance of AMT against age and education-specific cut-offs.[14] For the 60–74 years age group, the cut-offs were 7 for those with 0–6 years of education, and 8 for those with more than 6 years of education. For older adults 75 years and above, the cut-offs were 5 and 8, respectively. In contrast, Chong et al. (2006)[24] involved a community-based study which evaluated use of AMT in a sequential approach, where the AMT would only be administered if participants reported progressive forgetfulness. Both studies reported similar AMT cut-offs with comparable sensitivity for the 75 years and older age group (Sahadevan et al. 85–91%, Chong et al. 93.3%), but lower sensitivity in those aged 60–74 years (Sahadevan et al. 80–97%, Chong et al. 75.0%). The findings from Singapore studies on AMT's diagnostic performance were comparable to results from a systematic review performed for the US Preventive Services Task Force on cognitive diagnostic tools (AMT: Sn 42–100%; Sp 83–95.4%).[36]

At present, AMT is one of the most widely used tools in community settings to screen older adults for cognitive impairment in Singapore. Although the AMT is well-validated in the Singapore population, there are concerns of ceiling effects of AMT among participants of higher education levels. In recent years, there has been increasing interest to employ other performance-based tools, whether in conjunction with or in lieu of the AMT. Our review highlights the need for more community-based studies on other performance-based cognitive screening tools to evaluate the effect of age and education on cut-off scores and diagnostic performance. Other factors that would influence implementation of a new cognitive screening tool would include considerations pertaining to resources (e.g. extent of training and time required

for administration of the tool), context (e.g. validation of different language versions) and clinical applicability (e.g. ease of interpretation of the results).

Our rapid review is unique in including studies of informant-based cognitive tools in the analysis, reflecting the contextual considerations pertinent to practices in community and primary care in Singapore. Published systematic reviews of brief cognitive tools used in Latin America,[29] Chinese-speaking regions[30] and globally,[28] mainly evaluated performed-based tools or single domains of neuropsychological batteries. The time cut-offs for defining a brief cognitive assessment tool were higher as well, ranging 15–20 minutes.[37-39] In a systematic review of brief cognitive tools used in Latin America, MoCA was found to be the most widely used tool.[38] However, the authors noted a significant impact of education level on the diagnostic accuracy of MoCA. Another systematic review and meta-analysis of brief cognitive stools performed in Chinese-speaking populations found acceptable validity of MoCA and MMSE (Sn and Sp >75%).[39] However, the meta-analysis results found the best-validated tool to be Addenbrooke's Cognitive Examination (Sn 93.5% and Sp 85.6%).

The limitations of our rapid review included the relatively low number of local studies identified, especially in the community and primary care settings, and the paucity of direct comparison studies for performance-based tools. In addition, we only included local studies published in the English language—this may have potentially missed out validation studies of cognitive diagnostic tools published in the non-English language, although this is extremely unlikely in the Singapore context where English is the lingua franca. In addition, many of the included studies had conducted the cognitive assessments in the major languages spoken in Singapore, allowing for validation of these tools for the non-English speaking local population. We also acknowledge the risk of publication bias of our results as we had limited our search strategy to only published literature in indexed databases and excluded grey literature and unpublished studies.

CONCLUSION

This study is, to our knowledge, the first in-depth and comprehensive review that evaluates the diagnostic performance of brief cognitive screening tools used to identify possible dementia among community-dwelling older adults in Singapore. This review is especially timely considering the rising dementia prevalence consistent with worldwide trends, and the push towards preventive health and early identification of chronic diseases. The results from this rapid review will help to shape policy decisions on the dementia strategy in Singapore, reflecting the country's commitment to dementia as a public health priority. Timely and accurate diagnosis of dementia is important in recognising the disease burden within the nation and facilitates decisions on funding allocation.

Based on the review, we recommend a case-finding approach to identify possible dementia in at-risk populations, rather than community-wide or non-targeted population screening. This approach aligns with current screening guidelines both in Singapore and internationally. Subjective (e.g. self-reported or informant-rated) tools are recommended over performance-based tools. Among these, the iAD8 demonstrated superior diagnostic ability compared to sAD8. In the presence of a reliable informant, iAD8 alone had sufficient discriminant ability, with limited additional benefit when used in conjunction with other performance-based tools. Nonetheless, performance-based tools may still need to be considered if no reliable informant is present. Currently, in Singapore studies, AMT is the most studied performance-based tool with locally validated age and education-specific cut-offs. Further research is needed to specifically assess the diagnostic ability of brief cognitive screening tools—especially performance-based ones—in community settings, and to provide validation of cut-offs accounting for education and age in the Singapore population.

Declaration

All authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Acknowledgments

Our team would like to express our sincere thanks to Ms Yasmin Lynda Munro at the Nanyang Technological University, Lee Kong Chian School of Medicine (LKCMedicine) Medical Library, for her advice on the search strategy and for executing the database searches.

Supplementary materials

Supplementary Table S1A-D. Search strategies for PubMed, Embase, PsycInfo and Cochrane.

Supplementary Table S2. Risk-of-bias assessment on QUADAS-2 tool.

Supplementary Table S3. Extracted study characteristics of included studies.

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Ann Acad Med Singap 2024;53:754-7
https://doi.org/10.47102/annals-acadmedsg.2024242

COMMENTARY

Transforming medical education in the AI era: Balancing technological expertise with humanistic care in tomorrow's doctors

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ABSTRACT

The rapid integration of artificial intelligence (AI) into clinical practice prompts a critical re-examination of the roles of physicians and how we educate them. While AI promises unparalleled gains in accuracy and speed, and better management decisions and health outcomes, doctors must be skilled in harnessing these new AI tools effectively and wisely to improve patient outcomes. We seek to layer further upon this with a call for medical education to go further than simply improving AI literacy of doctors, but to include a comprehensive reform of medical education. This reform would aim to expand physician capabilities from the traditional cognitive knowledge of medicine to integrating AI competencies seamlessly, with a renewed focus on the humanistic aspects of medicine. We propose the Humanistic Medicine - AI-Enabled Education (HuMe-AiNE) framework, which includes the key components: (1) standardisation and individualisation of AI competencies; (2) integration of AI tools through the curriculum; (3) fostering critical thinking skills in integrating technological solutions with a humanistic approach to patient care; and (4) developing a professional identity that encompasses both technology-related and humanistic capabilities. The AI revolution provides an opportunity for developments to medical education—to train doctors to be both tech-enabled physicians and true humanists.

Ann Acad Med Singap 2024;53:754-7

Keywords: AI, artificial intelligence, humanistic skills, medical education, roles of doctor, technology skills

INTRODUCTION

Standing at the precipice of a new era in healthcare, the integration of artificial intelligence (AI) into clinical practice is progressing at an unprecedented pace. From AI algorithms detecting tumours with remarkable accuracy to predictive models forecasting patient outcomes, these technological marvels are not only changing how we practice medicine; they're redefining it. A landmark study by McKinney et al. demonstrated that AI can outperform human radiologists in breast cancer screening, reducing false positives by 5.7% and false negatives by 9.4%.[1] This transformation echoes the seismic shifts that led to the Flexner Report and the Lancet Commission, once again forcing us to re-examine the role of physicians and how we educate them.

The impact of AI on healthcare is multifaceted. At the individual level, AI promises to improve the speed and accuracy of diagnosis, recommend optimal treatment courses and prognosticate outcomes. Rajkomar et al. showed that deep learning models can predict in-hospital mortality, 30-day unplanned readmission, prolonged length of stay and final discharge diagnoses with high accuracy.[2] On a broader scale, it has the potential to enhance the efficiency and accessibility of healthcare services, and even influence population health by modifying behaviours. For instance, AI-powered chatbots have shown promise in delivering cognitive behavioural therapy for mental health conditions, potentially expanding access to care.[3]

These advancements compel a reflection on how to truly utilise them in medicine. Many voices in the medical community have called for a focus on AI literacy, that is, the ability to use these new tools effectively and understand their limitations. This community envisions the doctor of tomorrow as a "tech-enabled physician" who is skilled in harnessing the power of AI to improve patient care. A scoping review of undergraduate medical education[4] found that most AI curriculum objectives are centred around conceptual foundations needed to work and manage AI systems, knowing the ethical and legal implications of AI-dependent systems, and the critical appraisal of AI systems. However, the study also found no clear consensus on how to deliver such an AI curriculum. At the postgraduate level, a separate review found that availability of AI-specific educational material was predominant only in certain fields such as radiology, ophthalmology and cardiology.[4] While there has already been a burgeoning

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Accepted: 11 November 2024

increase in use cases of AI in medical education in recent years, calls advocating for frameworks that incorporate technical and ethical aspects of AI into medical education have also become more fervent.[5] The time is ripe, then, to re-examine how to best address the following current gaps in medical education: lack of clarity and consistency about the types AI skills and knowledge needed both at undergraduate and postgraduate levels; the current siloed approach of AI competencies being taught separately from clinical skills and knowledge; and a lack of understanding about the relationship between AI and human elements in patient care. All these gaps are undoubtedly important to address, even if they are still only part of the picture.

Verghese et al. remind us that medicine is more than just diagnosing ailments and prescribing treatments. It is about understanding the human experience of illness and connecting with patients on a deeply personal level. In this seminal paper "What This Computer Needs Is a Physician: Humanism and Artificial Intelligence," Verghese et al. argued that the rise of AI necessitates a renewed focus on the human aspects of care.[6] Topol suggests that instead of dehumanising medicine, AI can actually free physicians to focus on these crucial humanistic aspects of care.[7] In his book "Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again", Topol envisions a future where AI handles time-consuming data analysis, allowing doctors to devote more energy to empathetic communication and building meaningful relationships with their patients.[7]

A recent review on supportive and palliative care in oncology patients found that machine learning models were able to help oncologists predict clinical outcomes such as mortality and complications more effectively. This enables prioritisation of patients requiring complex decision-making, serious illness communication and advance care planning, which are tasks that require both clinical knowledge and relational skills such as empathy, trust and compassion.[8] In psychiatry, documentation of medical records, synthesisation of information for better diagnosis, treatment personalisation and prediction of treatment response have been suggested as tasks where AI can play a role, to enable psychiatrists to focus on building therapeutic relationships with their patients.[9]

Empathy, compassion and trust are foundational values for a patient-centred model of care, and broadly recognised as fundamental to good healthcare practice. However, these are not simply feel-good ideas—relational models of care have been shown to improve patient outcomes and boost the well-being of healthcare practitioners themselves. A meta-analysis by Kelley et al. found that empathic and patient-centred communication is associated with better adherence to treatment, improved patient satisfaction and better clinical outcomes.[10]

A review that outlined recommendations for the UK's National Health Service in the use of technology for patient care noted the limitations of AI in areas such as building trust and delivering care with empathy and compassion.[11] However, it notes that the introduction of such technologies bestows the clinician with "the gift of time…[which] will bring a new emphasis on the nurturing of the precious inter-human bond based on trust, clinical presence, empathy and communication." In the examples above, the clinician is not just a tech-enabled physician—employing AI for more efficient and effective diagnosis and treatment prediction—but also a true humanist, in delivering care that acknowledges and respects the patient's values and choices.

So, how do we get there? Just as the Flexner Report and Lancet Commissions charted new courses for medical education in their time, we now need a reimagining of how we train the doctors of tomorrow. This calls for a comprehensive reform of medical education—one that expands physicians' capabilities and cognitive knowledge, and integrates AI competencies seamlessly with a renewed focus on the humanistic aspects of medicine.

We propose a framework, which we term HuMe-AiNE (Humanistic Medicine - AI-Enabled Education). This approach aims to create a new paradigm of medical education that prepares future physicians and upskills current physicians to harness the full potential of AI while maintaining the core humanistic values that define our profession.

Key components of this framework include: (1) standardisation and individualisation of AI-related competencies. We need to establish a core set of AI competencies that all medical graduates should possess, while also allowing for specialisation based on individual interests and career paths. For everyone, the competencies could include base levels of understanding of areas such as machine learning algorithms, data science, concepts underlying AI and critical appraisal of AI-generated outputs. For some select few, application, analysis and synthesis of these domains may be needed. Given the fast moving nature of AI advancements, frequent reviews of AI-related competencies will be required. (2) Integration of AI tools throughout the curriculum: AI is already influencing diagnosis

and treatment decisions in healthcare, and learners need to be informed on how to use AI tools effectively. Rather than treating AI as a separate subject, it should be woven into all aspects of medical education, starting from undergraduate medical education and through to residency years where appropriate. For example, when teaching about diagnostic imaging, learners should become familiar with both traditional interpretation methods and AI-assisted diagnosis tools. Gordon et al. outlined specific suggestions for the use of AI tools in medical education, comprising AI-assisted tutoring systems and learner assessments, robot-assisted surgery simulations, chatbots to assist with clinical management, patient communications, and enhanced anatomy education.[5] (3) Fostering habits of critical inquiry together with the humanistic ability to deal with uncertainty: complexity and ambiguity are hallmarks of medicine, and while AI may provide some level of assistance, doctors will need critical thinking skills in applying technological solutions in empathic and ethical ways, integrating these with socially-constructed knowledge of the patient's illness experience in the gestalt of medical expertise. Development of critical thinking skills, perspective taking, judgement and reasoning, together with the ability to cope with uncertainty may be fostered through the use of case-based scenarios, observations in clinical settings coupled with reflective practice, as well as discussions in a multidisciplinary setting. These skills will become even more critical in preparing future and current physicians to grapple with ethical challenges associated with AI in clinical decision-making. (4) Reformulating professional identity formation in the AI era: as the role of physicians evolves, so must their professional identity. We need to help learners develop a sense of professional self that embraces technology while maintaining a strong commitment to delivering patient-centred and empathetic care, often in multidisciplinary teams. Physicians who are already in practice will need to renegotiate their own professional identity as AI makes ever-increasing inroads into their professional spaces. The medical community will thus need role models and exemplars of physicians who successfully adapt their sense of professional self in line with the evolving technological landscape.

Implementing this framework poses significant challenges. We will need to rethink everything from admission criteria to medical school, to assessment methods used in residency training and continuing professional development. Wartman and Combs suggest that medical school admissions should consider not only academic achievement but also emotional intelligence and adaptability to change.[12] We will have to upskill existing faculty, as many would not have been trained with these new paradigms. A multidisciplinary faculty, with experts in medicine, computer science, ethics and education will be needed to design curricula that are both technically rigorous and humanistically grounded. Clinician competencies need to be expanded to address critical issues such as trust, explainability and interpretability of AI systems in clinical practice.

Moreover, we must ensure that the integration of AI into healthcare does not exacerbate the existing disparities in access to technology and healthcare. This is especially pertinent in regions such as Southeast Asia, where access to technology is limited. While Singapore can lead the way in making AI-assisted healthcare technologies available and accessible to lower-income countries in the region, physicians must also be aware of algorithmic biases inherent in AI. Obermeyer et al. found that a widely used algorithm for guiding health decisions exhibited significant racial bias, demonstrating the potential for AI to perpetuate or even amplify existing inequalities.[13] Several papers have contributed important insights into the ethical challenges that must be addressed when incorporating AI into healthcare and medical education.[5,14,15] These include the need for data privacy and security regulation, automation bias and skill preservation, transparency and informed consent. They also acknowledge the difficulty of equipping learners to grapple with these issues at a time when society has neither fully understood the ethical implications of AI nor resolved how it will respond to the ethical challenges. At least 1 paper has called for institutions to respond proactively by setting up Education Ethics Boards, similar in authority to Research Ethics Boards, to focus on how AI is used in medical education.[14] This would also enable institutions to ensure that AI-integrated medical education is carried out in accordance with legal frameworks such as Singapore's Personal Data Protection Act and those of regional bodies of governance. Given the far-reaching and transformative role of AI, our curriculum must emphasise the societal implications of AI in healthcare, and equip future physicians to use these tools judiciously and ethically.

Programme evaluation is critical to document and identify the impact of integrating AI into medical education—the desired and undesired effects, as well as the unexpected ones. This remains a challenging area due to the fast-moving nature of AI-related initiatives, the intersection of AI with ethical challenges, the implications of AI on society and on healthcare relationships and practices. While literature is abundant in terms of AI-related educational initiatives, evaluation of educational

outcomes of these programmes has so far remained limited.[4] Most have either described positive immediate outcomes where participants were overall satisfied with the AI content learned, or shortterm outcomes in which learners demonstrated the acquisition of a variety of AI-related competencies and skills. Using the Kirkpatrick model of training evaluation, these would be categorised as Levels 1 and 2 (reaction: learner satisfaction and learning: skills acquisition, respectively) outcomes.[16] There is a critical need to invest in comprehensive evaluations of the long-term impacts of AI—on both the overall medical education landscape and specific learning outcomes. Such evaluations would focus on outcomes categorised as Level 3 (behaviour: degree to which learners apply what they have learned when back at work) and Level 4 (results: degree to which organisational practices and/or patient outcomes are changed) using the Kirkpatrick model.

The way forward is not without obstacles, but the potential rewards are immense. By embracing AI as a tool for enhancing rather than replacing human connection, we can create a healthcare system that is both technologically advanced and deeply compassionate. Lin et al. found that AI-assisted diagnosis, when combined with physician expertise, led to better outcomes than either AI or physicians alone,[17] thus highlighting the synergistic potential of human-AI collaboration.

As we navigate this AI revolution, let's not lose sight of Peabody's timeless wisdom: "the secret of the care of the patient is in caring for the patient."[18] Our challenge—and our opportunity—is to use AI not as a replacement for human care but as a tool to enhance it. The future of medicine lies not in choosing between technology and humanity, but in skilfully blending both. It is time for medical education to lead the way in nurturing a new generation of physicians who are as adept with algorithms as they are with empathy.

CONCLUSION

The AI revolution in healthcare presents both unprecedented challenges and extraordinary opportunities for medical education. By reimagining our approach to training and upskilling physicians, we can ensure that the doctors of today and tomorrow are equipped not only with cutting-edge technical skills but also with the timeless human qualities that lie at the heart of good medicine. As we embark on this journey of educational transformation, let us be guided by a vision of healthcare that harnesses the power of technology to amplify, rather than diminish, our humanity.

Declaration

The author declares no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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Ann Acad Med Singap 2024;53:758-61
https://doi.org/10.47102/annals-acadmedsg.2024268

LETTER TO THE EDITOR

Enhancing care in nursing homes: Qualitative insights from the ENHANCE programme

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Dear Editor,

Empower Nursing Homes And improve staNdards of CarE (ENHANCE) was a pilot programme introduced by Sengkang General Hospital to address the challenges faced by Singapore's ageing population. With nearly 1 in 4 Singaporeans projected to be aged 65 years and above by 2030, the demand for effective long-term care solutions is increasingly urgent.[1] The ageing population is a global phenomenon that results in increased healthcare expenditure.[2] ENHANCE seeks to improve nursing home care and reduce preventable hospital admissions through collaboration with an acute an hospital.[3] The initiative aligns with the World Health Organization's Integrated Care for Older People guidelines, focusing on preventive care and tailored interventions to improve elderly care in community settings.[4]

The ENHANCE programme incorporates several key interventions, including the National Early Warning Signs (NEWS) tool, teleconsultations with hospital physicians and the establishment of clinical care pathways. These components empower nursing home staff to manage residents' acute health issues more effectively, thereby reducing emergency department visits and hospital admissions.

Qualitative in-depth interviews were conducted with 26 staff members from 2 nursing homes in the northeast of Singapore that piloted the ENHANCE programme. Using semi-structured interviews (Supplementary material), we sought to understand the practical implementation, challenges faced and perceived benefits among nursing home staff. Interviews were transcribed and thematically analysed with NVivo 14.0 (Lumivero, CO, US).

The study revealed several important insights into the programme's impact and factors influencing its success. Table 1 summarises the themes and subthemes which emerged from the study. Nursing staff generally demonstrated a good understanding of the collaboration's purpose and workflow. The ability to consult hospital physicians via teleconsultation provided a valuable support system. This real-time access to expert advice was particularly appreciated, enabling staff to manage complex cases effectively within the nursing home setting. The reassurance and confidence gained from this support empowered staff to make informed decisions, thus allowing them to continue managing patients without the immediate need for hospital transfers. This not only bolstered the competence of the staff but also helped prevent overburdening of the nursing home system by identifying patients who truly required hospital intervention.[5] Despite this positive feedback, there were varying perceptions about the optimal use of the collaboration. Some staff members expressed uncertainty regarding when and how to fully utilise the available resources. Clearer guidelines and more comprehensive training are needed to ensure that all staff members can confidently leverage the collaboration most effectively.

One of the major strengths of the ENHANCE initiative was its focus on improving staff skills and knowledge. Training sessions provided nursing home staff with practical experience in using the NEWS tool, an established and validated method for assessing patient acuity and guiding escalation of care. This training was complemented by simulated scenarios allowing staff to practice and refine their skills. The user-friendly nature of the interventions, including teleconsultation and the NEWS assessment, was highlighted as a significant advantage. The collaboration also improved efficiency; by streamlining processes and providing direct access to hospital physicians, the programme helped save time and resources,

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Accepted: 28 October 2024

Table 1. Themes and subthemes that emerged from the interviews.

Categories	Themes	Selected quotes
Knowledge and understanding of the collaboration	Assurance of availability of help	"The aim is to help the staff on duty to not send out the residents to A&E (Accident & Emergency), we can call the doctors online, audio and video call to help us manage the residents here before sending out." – A9 "Actually, I think the objective of the project is so that we can communicate with the other doctors from SKH and we can follow up with them through video call, no need to bring the patient there if it's not for emergency like that. We can follow up also, through calls." – B12
Service satisfaction	Enhanced skills and knowledge	"That's why the NEWS score is useful for new staff so that they can have basis. Especially for new nurses and inexperienced ones since the data is collected quantitatively and can justify that the patient needs immediate care." – B1 "It's important to consult the doctor. We will have more confidence to carry out the intervention. Additionally, we will gain experience to handle similar situations in the future." – A6
	Applicability to nursing home residents	"The learning (teaching) is quite good as they provided one scenario for us, with a patient having complaints, so we get to do the assessment. Sufficient and informative. Content is very aligned(ed) with the homecare, it's relevant for us." – A1
	User-friendly interventions	"NEWS scoring, it's very useful. This is very easy to fill up, the hospital transfer form, the NEWS scoring is easy to fill up, it's very easy." – A14
	Improved efficiency	"I think the benefits of lesser hospital transfers is that you can save staff from following the patient when going to send the patient to the hospital"– A13
Challenges in implementation	Lack of resource and workforce	"Because we did the laboratory tests outside, everything is external, we don't have our own pharmacies also, so it's expensive." – B9 "But only one SN (staff nurse) is there, so they will only focus on their routine what, so what the staff do, the staff will call 995 for ambulance. Y eah, but the staffing is the problem, otherwise can. Our staff mostly we never call, because of the lack of staffing, otherwise this will be very useful for the staff." – B4
	Nursing staff barriers	"Although we are trained nurses, we still need supervision from the doctor." – B3 "We cannot also put intravenous cannula here, only blood extraction for the lab test and that's all… we cannot give the (cough) syrup without the doctor's order." – B7
	Other limitations	"If they (family) don't want to be sent out, we of course respect them, especially if they are comfort care residents. If they are in comfort care, we don't really send them out, we care for them in the nursing home. If the relatives really insist on sending out, then we will send out the residents." – A14 "Sometimes, no. not really, (NEWS) not accurate. Because we had one patient last time, the vital signs are okay, but the patient is not well, but vital signs are okay. But he looks unwell." - B10
Project enablers	Internal support	"We have Mr Y, just in case we are confused with the care paths, we can ask him. He will try to explain to us. If he cannot explain as well, he will email Dr J. He's like our leader." – A2
	Nursing staff competencies	"Because we already know the patient, so when we see unusual behaviour from the patient or if the patient looks weak, so that's the time we will use the NEWS scoring on the patient." – B5
	Motivation to improve patient care	"I think some conditions can be managed by the staff as well, don't have to send every patient with condition to the hospital." – B2 "If there are situations whereby, we need to refer but most of the times, we will refer to our doctor. Our focus is usually the patient." – B5

NEWS: National Early Warning Signs; SKH: Sengkang General Hospital

allowing nursing home staff to manage acute situations more effectively. This efficiency is crucial in a setting where staff often juggle multiple responsibilities and face high workloads.

However, the study identified several challenges impacting the implementation of the ENHANCE initiative. Resource limitations within nursing homes were significant issues, with many facilities facing constraints related to access to diagnostic tools, medications and other essential resources. These limitations hindered the staff's ability to manage residents effectively and contributed to higher rates of hospital transfers.[6] Additionally, a lack of staff also exacerbated these issues, limiting nursing homes' ability to fully utilise the tools and interventions provided by the programme.

Institutional policies and protocols sometimes restricted staff capabilities, leading to underutilisation of new skills and resources. Decisions regarding transferring residents to hospitals were sometimes influenced by next-of-kin preferences, complicating care pathway implementation and undermining the programme's objectives.[7] This highlights the importance of clear family involvement protocols and decision-making frameworks that foster trust between families and nursing staff, to facilitate discussions with family members.[8] This is particularly important in Asia, where family-centred care is emphasised, ensuring that family preferences and values are integrated into the care process.

Concerns were also raised about the ability of the NEWS tool to capture all relevant aspects of a resident's condition. While NEWS is a valuable tool, some staff felt it did not fully address the complexities of managing residents with multiple health issues. The additional paperwork required by the programme also added to the existing workload and could detract from direct patient care.

Despite these challenges, several factors contributed to the success of the ENHANCE initiative. Internal support, including having a designated contact point within the nursing homes, was crucial for overseeing the project and providing necessary assistance. Competent nursing staff, who are familiar with residents' baseline conditions, were better equipped to assess clinical status and decide on appropriate escalation of care. The intrinsic motivation of nursing staff to improve care quality was also a driving factor, aligning with the programme's goals and contributing to its success.[9]

To enhance the effectiveness of the ENHANCE programme, key recommendations include ongoing training and specialised geriatric education for nursing staff to keep them updated on best practices and improve their ability to manage acutely ill residents.[2,10] Expanding the nursing workforce is also essential to balance workloads and maximise the use of ENHANCE interventions. On a policy level, improving resource allocation for nursing homes, providing government support for telemedicine and integrating geriatric care into community health settings are crucial steps. These measures aim to improve care quality, facilitate access to specialists, reduce preventable hospital transfers and promote ageing in place.

The ENHANCE initiative highlights the benefits of integrating acute care services with nursing home care, offering a model potentially replicable in other regional countries facing rapidly ageing population. Addressing resource limitations and refining workflows are essential for further success. By expanding emergency care beyond traditional hospital settings, ENHANCE aims to improve care delivery as Singapore's elderly population continues to grow.

Supplementary material

Qualitative evaluation of project ENHANCE

Ethics statement

This study was approved by the SingHealth Centralised Institutional Ethics Board (201709-00124).

Declaration

The authors declare no conflict of interest.

Keywords: *emergency medicine, frailty, geriatric medicine, nursing homes, public health*

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Ann Acad Med Singap 2024;53:762-4
https://doi.org/10.47102/annals-acadmedsg.2024200

LETTER TO THE EDITOR

COVID-19 residual symptoms and adverse drug reactions after oral antiviral therapy in the Singapore primary care setting

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Dear Editor,

The COVID-19 pandemic remains a significant public health threat with over 7 million deaths worldwide (as of 14 January 2024).[1] In Singapore, oral antivirals (OAVs) nirmatrelvir/ritonavir and molnupiravir were approved in 2022 for treating mild-to-moderate COVID-19 in adults at risk of progression to severe disease.[2,3] Clinical trials in Western populations showed nirmatrelvir/ritonavir having higher efficacy in reducing hospitalisations and mortality by 88% compared to 30% for molnupiravir.[2-4] A Singapore study showed nirmatrelvir/ritonavir's effectiveness in reducing hospitalisation and severe COVID-19.[5] However, further research is needed on potential adverse drug reactions (ADRs) and control of COVID-19 symptoms in Asian populations. This study focused on the short-term safety and efficacy of nirmatrelvir/ritonavir and molnupiravir, examining associations between OAV type and dose on the incidence of ADRs and COVID-19 residual symptoms 7 days post-treatment.

A retrospective review was performed on COVID-19 patients from primary care polyclinics treated with OAVs within 5 days of symptom onset, from July 2022 to October 2022. Patients were prescribed 1 of the following for 5 days: (1) nirmatrelvir 300 mg/ritonavir 100 mg twice daily (full dose), (2) nirmatrelvir 150 mg/ritonavir 100 mg twice daily (renally adjusted dose) if impaired renal function or (3) molnupiravir 800 mg twice daily if contraindicated to nirmatrelvir/ritonavir.[2,3] OAV eligibility, type, dose and potential drug interactions were reviewed by physicians and pharmacists following guidelines from National Centre for Infectious Diseases.[6] Renal function was assessed using estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration) if <75 years or creatinine clearance (Cockcroft-Gault) if ≥75 years, considering eGFR may overestimate kidney function in the elderly.

Follow-up occurred 7 days post-treatment over phone interviews by pharmacists. Patients who were uncontactable or did not start OAVs were excluded. The following outcomes on day 7 were compared across the 3 OAV cohorts: (1) ADRs reflecting short-term safety, categorised into allergic reactions or side effects, and (2) COVID-19 residual symptoms reflecting short-term efficacy on COVID-19 symptom control. Hypothesis testing and multivariable logistic regression were used to evaluate associations between OAV type, dose, adherence and demographics on the outcomes. Statistical analyses were performed using R statistical software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), with $P<0.05$ deemed significant.

The study population comprised 902 patients, 66.6% on nirmatrelvir/ritonavir full dose, 21.1% on nirmatrelvir/ritonavir renal dose and 12.3% on molnupiravir. Nirmatrelvir/ritonavir renal dose patients were the oldest, followed by molnupiravir then nirmatrelvir/ritonavir full dose (mean age 77 versus [vs] 72 vs 64 years, $P<0.001$). The 3 cohorts were similar for sex, ethnicity and OAV adherence. Overall, patients were adherent to completing the 5-day course (nirmatrelvir/ritonavir full dose 90.2% vs nirmatrelvir/ritonavir renal dose 88.4% vs molnupiravir 85.6%, $P=0.33$).

The incidence of allergic reactions was low (molnupiravir 7.2% vs nirmatrelvir/ritonavir full dose 5.5% vs nirmatrelvir/ritonavir renal dose 2.1%, $P=0.07$). However, gastrointestinal side effects were most common. Nirmatrelvir/ritonavir full dose had the highest incidence of diarrhoea, followed by nirmatrelvir/ritonavir renal dose, then molnupiravir (28.8% vs 20.0% vs 9.9%, $P<0.001$). Dysgeusia was also more common with nirmatrelvir/ritonavir full dose than renal dose, but none for molnupiravir (18.8% vs 9.5% vs 0%, $P<0.001$).

After adjusting for baseline age, sex, ethnicity and OAV adherence, molnupiravir was associated with significantly less gastrointestinal side effects compared to nirmatrelvir/ritonavir full dose, with an

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Accepted: 28 October 2024

adjusted odds ratio (OR) of 0.42 (95% confidence interval [CI] 0.24–0.75, Table 1). OAV type and dose were otherwise not significantly associated with allergic reactions.

Although molnupiravir was associated with more COVID-19 residual symptoms, it was not statistically significant with an adjusted OR of 1.32 (95% CI 0.86–2.04, Table 1). OAV type and dose were thus not significantly associated with COVID-19 residual symptoms, with similar incidence (40%) across the 3 cohorts (*P*=0.65).

In this retrospective review, molnupiravir was associated with significantly less gastrointestinal and dysgeusia ADRs than nirmatrelvir/ritonavir full dose. Both OAVs were well tolerated with low incidence of allergic reaction and consistent with clinical trials.[2-4] However, observed incidence of diarrhoea (9.9–28.8%) and dysgeusia (9.5–18.8%) were higher compared to Western populations (diarrhoea 2–4%, dysgeusia 6%).[2,3] A Korean study found similar high incidence of dysgeusia (23.8%) for nirmatrelvir/ritonavir,[7] thus suggesting poorer tolerance in Asians. They reported lower incidence of diarrhoea (1.7–3.3%) contrary to our results, which could be due to ethnic differences or confounded by diarrhoea also being early symptoms of COVID-19.[8]

Table 1. Regression analysis of adverse drug reactions and COVID-19 residual symptom on day 7.

	Safety outcomes: allergic reactions[a]		**Safety outcomes: gastrointestinal side effects[b]**		**Efficacy outcomes: COVID-19 residual symptoms[c]**	
	Adjusted OR (95% CI)	***P* value**	**Adjusted OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Age	0.98 (0.95–1.00)	0.06	0.98 (0.96–0.99)	0.002	0.98 (0.96–0.99)	<0.001
Sex						
Female	Reference					
Male	0.76 (0.40–1.42)	0.39	0.81 (0.59–1.09)	0.17	0.73 (0.55–0.96)	0.02
Ethnicity						
Chinese	Reference					
Malay	0.12 (0.02–0.88)	0.04	0.51 (0.30–0.86)	0.01	1.02 (0.67–1.56)	0.92
Indian	0.38 (0.09–1.67)	0.20	0.73 (0.40–1.31)	0.29	0.42 (0.24–0.76)	0.004
Others[d]	0.00 (0 to infinity)	0.98	0.73 (0.18–2.90)	0.66	0.89 (0.26–3.05)	0.86
Completed OAV course						
No[e]	Reference					
Yes	0.16 (0.08–0.31)	<0.001	0.69 (0.44–1.11)	0.13	0.84 (0.54–1.30)	0.42
OAV prescribed						
Nirmatrelvir/ritonavir full dose	Reference					
Nirmatrelvir/ritonavir renal dose	0.43 (0.14–1.31)	0.14	0.78 (0.51–1.20)	0.26	1.22 (0.83–1.79)	0.31
Molnupiravir	1.41 (0.60–3.34)	0.43	0.42 (0.24–0.75)	0.003	1.32 (0.86–2.04)	0.21

CI: confidence interval; OAV: oral antiviral; OR: odds ratio
[a] Allergic reactions included rash, itch, eye swelling or unspecified reactions.
[b] Gastrointestinal side effects included diarrhoea, nausea or vomiting.
[c] COVID-19 residual symptoms included cough, sore throat, flu-like symptoms, blocked nose or phlegm.
[d] Others refer to 5 European and 6 unspecified.
[e] Patients reporting "No" discontinued the OAV from days 2 to 4. Reasons for OAV discontinuation were adverse drug reaction, improvement of condition, subsequent negative antigen rapid test results or hospital admission.

For short-term efficacy, no significant differences in COVID-19 residual symptoms were observed between both OAVs. Despite nirmatrelvir/ritonavir's higher efficacy in reducing hospitalisations and mortality,[2-4] our study demonstrated that both OAVs appeared similarly effective in reducing COVID-19 residual symptoms by day 7. Another study also found similar rates of persistence of COVID-19-related symptoms at 30 days between nirmatrelvir/ritonavir (15.9%) and molnupiravir (11.2%).[9] However, a confounder not assessed in our study was OAV administration timing. Early OAV administration may result in improved efficacy by targeting the initial rapid viral replication phase.[4] Patients should thus be counselled on possible symptom persistence regardless of the OAV prescribed.

Comparing nirmatrelvir/ritonavir full and renal dose showed no significant difference in ADRs or COVID-19 residual symptoms. This may be due to similar resultant drug exposure between both cohorts after accounting for impaired renal clearance by dose reduction. Literature suggests OAVs have heterogeneous outcomes in different populations,[4] thus future studies could guide nirmatrelvir/ritonavir dose optimisation in various comorbidities.

Both OAVs also showed similar high adherence rates, reflecting patients' tolerability and acceptance. The cost of OAVs and ancillary investigations (e.g. COVID-19 testing) were fully subsidised to ensure treatment access. OAV adherence would thus ensure cost-effective use of healthcare resources, as OAVs are increasingly prescribed in primary care.

The study limitations include absence of a control group of COVID-19 positive patients without OAV therapy, due to the retrospective design and small sample of such patients in primary care. There were unmeasured confounders, such as comorbidities or vaccination status, although OAV adherence and baseline demographics were adjusted for. To our knowledge, this study is the first in Singapore's primary care to provide real-world data on the short-term safety and efficacy outcomes of OAVs, potentially encouraging OAV uptake for timely treatment to mitigate the disease burden of COVID-19. Future studies could explore long-term outcomes of OAVs such as COVID-19 rebound in multiethnic Asian populations.

Acknowledgements

The authors express gratitude to Mr Jeremy Lew for providing statistical analysis and technical support; Ms Yap Hui Rei for proofreading; Ms Lim Li Ching for providing administrative and financial support; and Dr Christopher Chong and Dr Valerie Teo for providing clinical guidance.

Ethics statement

The study was approved by the National Healthcare Group Domain Specific Review Board (2023/00464) and granted a waiver of informed consent owing to the de-identified data and retrospective nature.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: *adverse drug reaction, COVID-19, molnupiravir, nirmatrelvir-ritonavir, paxlovid, SARS-CoV-2*

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Ann Acad Med Singap 2024;53:765-7
https://doi.org/10.47102/annals-acadmedsg.2024271

LETTER TO THE EDITOR

Prevalence and causes of rifampicin-resistance genotypic/phenotypic discrepancy detected on Xpert MTB/RIF in Singapore

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Dear Editor,

The Xpert *Mycobacterium tuberculosis*/rifampicin (MTB/RIF) (Cepheid, Sunnyvale, CA, US) has been pivotal in tuberculosis (TB) diagnostics, enabling the rapid detection of both TB and RIF resistance. Xpert, a nucleic acid amplification test (NAAT), is recommended by both the World Health Organization (WHO)[1] and Singapore's clinical management guidelines[2] as a frontline diagnostic tool for TB and RIF resistance. With a high specificity rate (98%) in detecting RIF resistance, Xpert has a positive predictive value (PPV) exceeding 90% in settings where the prevalence of RIF resistance is above 15%.[3] However, in Singapore, a country with medium incidence of TB and low prevalence of RIF resistance (<1% among individuals born in Singapore),[4] the PPV of detecting RIF resistance via Xpert is substantially lower.[3] Phenotypic-genotypic discrepant RIF resistance has been reported to result from technical errors, false-positive results in paucibacillary samples,[5] silent mutations[6] or disputed mutations where minimal inhibitory concentrations (MICs) fall below critical concentrations in phenotypic drug susceptibility testing (pDST) systems.[7] We conducted a quality assessment of sputum samples which tested positive for TB and RIF resistance using point-of-care Xpert at the Singapore National Tuberculosis Care Centre (NTBCC) to determine the prevalence and causes of false-positive RIF resistance.

There were 15,427 sputum specimens subjected to Xpert point-of-care testing at NTBCC between December 2018 and June 2022. Of these, 1786 (11.6%) tested positive for MTB with 36/1786 (2%) showing RIF resistance. These 36 samples belonged to 31 unique cases, 29 of which had both pDST and whole genome sequencing (WGS) results available. Two cases failed to isolate MTB on culture and were excluded. Among the 29 cases, 12 (41.4%) had Xpert RIF-resistant/phenotypic-susceptible results, while 17 (58.6%) were confirmed RIF-resistant by both pDST and WGS (Table 1).

We identified 3 main reasons for genotypic-phenotypic discrepancies in RIF resistance detected by Xpert. The first and most common reason for discrepancy was false-positive RIF resistance due to very low bacterial load. This aligns with the understanding that in paucibacillary samples, extended polymerase chain reaction cycles may exaggerate probe signal variability, leading to false-positive results. A significant proportion of discrepancies in our cohort at 9/12 (75%), involved cases with a very low load (cycle threshold [Ct] >28) and no *rpoB* mutation detected on WGS. Five of these cases had separate samples that did not show RIF resistance and were started on first-line treatment. Three cases were initially treated with second-line treatment but were switched to first-line treatment once pDST and WGS confirmed RIF-susceptibility with no *rpoB* mutation. One left the country before treatment initiation. Seven of the 9 cases involved individuals born in Singapore or Malaysia—both low-incidence regions for RIF resistance. For patients presenting with a very low bacterial load and low clinical suspicion of RIF resistance, repeat testing on a separate sputum specimen may be warranted to avoid unnecessary treatment with second-line anti-TB drugs. It is anticipated that the Xpert Ultra (Cepheid, Sunnyvale, CA, US) assay will reduce the likelihood of false-positive RIF resistance results in very low-load samples.[3,8] However, its utility in similar low-incidence settings remains to be thoroughly evaluated.

The second reason for genotypic-phenotypic discrepancies was silent mutations, detected in 2/12 (16.7%) cases. One case had the *rpoB* T444T mutation (absent probe C on Xpert), diagnosed during contact tracing around an index case with this silent mutation. This case was treated with first-line TB treatment. The second case had mutation *rpoB* c.1278C>T (absent probe A on Xpert; the GenoType MTBDRplus test, also known as the Hain test [Hain Lifescience, Nehren, Germany] showed

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Accepted: 30 October 2024

Table 1. Characteristics of rifampicin (RIF)-resistant cases detected by Xpert.

	True RIF resistance	Genotypic-phenotypic discrepant RIF resistance		
		False-positive RIF resistance	Silent mutation	Disputed mutation
Total, n=29	17 (58.6%)	9 (31%)	2 (6.9%)	1 (3.4%)
Load category[a]				
High (Ct value <16)	1 (5.9%)	0	0	0
Medium (Ct value 16–22)	3 (17.6%)	0	1 (50%)	1 (100%)
Low (Ct value 22–28)	6 (35.3%)	0	1 (50%)	0
Very low (Ct value >28)	7 (41.2%)	9 (100%)	0	0
Country of birth: Singapore/Malaysia	7 (41.2%)	7 (77.8%)	2 (100%)	1 (100%)
History of prior tuberculosis treatment	1 (5.9%)	1 (11.1%)	0	0
rpoB mutation on whole genome sequencing, (no.)	S450L (10) H445Y (4) H445D (2) N438- (1)	No mutations (9)	T444T (1) c.1278C>T (1)	L452P (1)

Ct: cycle threshold
Values are expressed as no. (%) unless otherwise indicated.
[a] Load category based on Xpert (*Mycobacterium tuberculosis*/rifampicin) semi-quantitative measure.

faint wild type band 1 but absent mutant band). This case was initiated on second-line TB treatment but switched to first-line treatment after confirmation of the silent mutation on WGS. Silent mutations, which do not alter the amino acid sequence of the encoded protein, can result in a false-positive signal on Xpert despite the absence of phenotypic resistance, which can lead to possible overtreatment with second-line drugs.

The final reason was a disputed mutation (in this case the *rpoB* L452P mutation) which was identified in 1/12 (8.3%) case. Disputed mutations confer low-level RIF resistance, with MICs that fall below the critical concentration used in pDST systems. WHO has reported 7 disputed *rpoB* mutations, which account for 12% of RIF resistance based on surveillance data.[9] Cases with disputed mutations are at high risk of treatment failure and relapse, if treated with first-line TB drugs,[10] highlighting the limitations of pDST in accurately reflecting the clinical implications of certain mutations. In such cases, WGS plays a crucial role in the precise characterisation of *rpoB* mutations to guide treatment decisions.

The findings of this study have significant implications for TB control in settings like Singapore, where the prevalence of RIF-resistant TB among the local population is low. Given the public health risks of RIF-resistant TB, it is recommended that all cases with RIF resistance detected on rapid genotypic testing be referred to NTBCC for further evaluation and initiation of second-line treatment while awaiting confirmatory tests, such as pDST and WGS, which have long turnaround times. The high rate of false-positive RIF resistance detected by Xpert in very low bacterial load specimens suggests that relying on a single diagnostic test may lead to unnecessary second-line treatment. One practical approach is to repeat the test on a new sample, though the same issue may persist if the bacterial load remains very low. Newer NAATs like Xpert Ultra and BD MAX MDR-TB (Becton, Dickinson and Company, NJ, US), which have improved sensitivity, may help mitigate this problem. The Hain test, which performed well on smear-positive samples and provided results more rapidly than the pDST, can be helpful. By detecting specific *rpoB* mutations, the Hain test can confirm or refute Xpert results, helping to guide early treatment decisions. While Hain tests are not as widely available or rapid as Xpert, their utility lies in providing additional layers of confirmation.

In conclusion, our study highlights the causes of genotypic-phenotypic discrepancies in RIF

resistance in Singapore. A substantial proportion was due to false-positive results in very low-load samples among patients born in Singapore or Malaysia, suggesting a need for cautious interpretation of Xpert RIF-resistant results in very low-load samples. Complementary diagnostic techniques, such as pDST and genotypic tests (Hain and WGS), are essential for confirming resistance and guiding appropriate treatment decisions.

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Ethics statement

This study was done as part of an internal audit and quality assessment and was granted exemption for review from National Healthcare Group Domain Specific Review Board (NHG DSRB Ref: 2023/00061).

Keywords: *drug resistance, infectious diseases, molecular diagnostics, respiratory medicine, tuberculosis*

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Ann Acad Med Singap 2024;53:768-71
https://doi.org/10.47102/annals-acadmedsg.2024234

LETTER TO THE EDITOR

Knowledge, attitudes and readiness of final-year medical students towards clinical goals-of-care discussion

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Dear Editor,

In a rapidly ageing global population,[1] there is increasing recognition of the importance of clinical goals-of-care (GOC) discussions aimed at understanding patients' goals, wishes and care preferences in the event of serious illness or end-of-life situations,[2] in order to affirm patient-centred decision-making, improve quality of life and facilitate their eventual transition towards end-of-life care.[3,4] Examples of GOC discussions include informal advance care planning (ACP), legally-binding advance medical directives (AMD), inpatient code status discussions,[2] and most recently, longitudinal serious illness conversations that improve patient prognostic awareness and psychological coping with advanced disease and end-of-life matters.[4]

Moreover, cultural differences exist in GOC and end-of-life discussions. While Western societies accord importance to individual autonomy, Asian and more collectivistic populations tend to place more value on shared decision-making, familial harmony and filial piety obligations (where children often make health-related decisions on behalf of their elderly parents).[5] For instance, a survey in the US found that Asian (Korean)-Americans were less likely than their European-American and African-American counterparts to deem it necessary to disclose terminal diagnoses to patients, and more likely to prefer familial decision-making in life-sustaining interventions.[6]

Nonetheless, studies in both Western and Asian societies have found that clinical GOC discussions remain highly suboptimal. A US study found that many seriously ill patients did not have inpatient code status discussions; when such discussions were held, they were often brief and contained inaccuracies or inadequate details on prognostic information, resuscitation interventions and patient-centric recommendations.[7] A 2014 Singapore study found that, with appropriate educational interventions, physicians were highly amenable and willing to engage in end-of-life conversations. Nevertheless, most still deferred GOC discussions and decision-making to patients' families, highlighting the prevailing cultural differences.[8] Aside from cultural context, there are also common practical challenges of holding GOC discussions in routine clinical practice—such as lack of time, knowledge, communication skills and confidence in tackling end-of-life issues, as well as conflicting opinions on disease prognosis and futility of medical treatments or interventions.[9]

We performed a cross-sectional study on a Singapore cohort of graduating final-year medical students, on their knowledge, attitudes and readiness to hold GOC discussion in clinical practice, where we sought to review the study implications on educational pedagogies.

We developed a survey questionnaire (see Appendix) based on literature review of relevant surveys and studies on GOC, end-of-life or code status discussions performed on medical students and practitioners.[2,10-12] The surveys were distributed physically to 303 final-year medical students from National University of Singapore's Yong Loo Lin School of Medicine. Participation was voluntary and anonymous.

Statistical analyses were performed using IBM SPSS Statistics version 29 (IBM Corp, Armonk, NY, US). Descriptive data were summarised, and univariable analyses of relationship between studied variables were analysed through chi-square/Fisher's Exact test for categorical variables and Pearson's correlation

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Accepted: 29 October 2024

for continuous variables. To rule out confounding bias, 10 covariates that pertained to participant profile/demographics, subjective/objective GOC knowledge and clinical experiences were selected for multivariable analyses (i.e. age, gender, ethnicity, presence of GOC learning in medical school, self-perceived familiarity with GOC concepts, objective GOC knowledge scores, personal observations of GOC discussions by others, personal experience participating in GOC discussions, awareness of where to find ACP information on EMR, and awareness of how to seek help for GOC discussions). A binary logistic regression was performed on the included variables, with sequential exclusion of statistically non-significant variables (initial cut-off of $P<0.1$, followed by cut-off of $P<0.05$) to generate the final multivariable model. Statistical significance was set at $P<0.05$, with effect estimate provided by prevalence odds ratio (POR) and 95% confidence interval (CI).

Our response rate for this study was 84.5% (256 out of 303 students). The mean age of participants was 24 years, with 52% males and 93% Chinese. The majority (93.4%) had learnt GOC discussion in medical school, mainly through didactic lectures/tutorials (79.9%), simulation practices (56.5%) or clinical clerkship rotations (55.6%). From subjective self-assessment of GOC knowledge in 6 different domains, median score was 5/6 (83.3%). However, on objective assessment on GOC knowledge with 17 questions, the median score was only 9/17 (52.9%). In terms of attitudes, most (94.1%) agreed that GOC/code status discussions promoted person-centred care and helped to avoid inappropriate life-sustaining therapies. While the majority (79.2%) felt that code status must always be discussed with patients/families, only 33.6% considered their approval as absolutely necessary for implementation. More than half (68.5%) believed patient preference was most important in code status decision-making. Self-identified barriers to GOC discussions included personal lack of knowledge (83.8%) or confidence (80.6%) or patient/family's lack of readiness to discuss end-of-life matters (81%). In terms of readiness, only 1 in 4 students felt confident to hold GOC discussions with patients or families. Moreover, 60.1% reported having observed GOC discussions in clinical clerkship rotations (mostly once or twice), while only 19.4% actually tried engaging in GOC discussions themselves. Only 25% knew where to find ACP documentations on electronic medical records (EMRs).

On multivariable analyses, self-perceived familiarity with GOC concepts, awareness of where to find ACP information on EMR, and personal experience with GOC discussions during clerkship rotations were associated with confidence in holding clinical GOC discussions with patients, while self-perceived familiarity with GOC concepts, awareness of where to find ACP information on EMR, personal experience with GOC discussions during clerkship, and awareness of how to seek help in GOC discussions were linked to students' confidence in holding GOC discussions with patients' families (Table 1).

There are several practice implications of this study from a medical educational standpoint.

First, the study found that there is fairly poor objective knowledge of important GOC concepts, which naturally hinders the students' ability in holding accurate and effective GOC discussions when they enter actual practice. Moreover, poor understanding of GOC concepts can have professional and ethical repercussions, where junior medical practitioners could fail to uphold important principles of beneficence and non-maleficence by acquiescing to inappropriate/harmful/futile medical interventions requested by patients/families, or neglect patient autonomy and shared decision-making by colluding with families or prioritising their wishes over the patients. Therefore, to improve GOC knowledge among medical trainees, comprehensive GOC educational courses can be conducted for medical trainees that incorporate didactic teaching on chronic disease trajectory, prognostication and end-of-life care, with simulation practice with standardised patients and supervised GOC discussions in real-life clinical encounters using mini-clinical evaluation exercise (mini-CEX) formats.[13] Communication adjuncts, such as the serious illness conversation guide,[14] can also be made readily available in the wards for use by medical trainees and practitioners. Importantly, the cultural nuances and ethical considerations behind GOC discussions should also be highlighted during the course of training, where empathic communications and understanding of how to seek hospital support/ethical consultations would be valuable to navigate these challenges. For example, in Asian contexts, strict adherence to an autonomous model of GOC decision-making, such as framing life-sustaining interventions as purely a medical decision or holding GOC conversations only with the patient, may not be culturally acceptable and can lead to complaints or even medicolegal disputes.

Second, there is a clear discrepancy between subjective and objective assessments of GOC knowledge, which we attribute to the trainees' lack of insight into own performance[15] or confounding effect of social desirability bias that skews self-

Table 1. Multivariable (binary logistic regression) model of independent covariates associated with students' confidence in holding goal-of-care discussions with patients and families.

(A) Factors independently associated with student confidence in holding goal-of-care discussions with patients.

Covariate	POR	95% CI	*P* value
Self-perceived familiarity with GOC concepts (≥5 out of 6 categories)	4.45	2.13–9.31	<0.001
Awareness of where to find ACP information on EMR	3.44	1.71–6.93	<0.001
Personal experience with engaging in GOC discussion with patients/ families during clerkship rotations	3.69	1.74–7.83	<0.001

(B) Factors independently associated with student confidence in holding goal-of-care discussions with patients' families.

Covariate	POR	95% CI	*P* value
Self-perceived familiarity with GOC concepts (≥5 out of 6 categories)	4.20	1.98–8.94	<0.001
Awareness of where to find ACP information on EMR	5.21	2.52–10.78	<0.001
Personal experience with engaging in GOC discussion with patients/ families during clerkship rotations	2.77	1.28–6.04	0.01
Awareness of how to seek help in GOC discussions	2.98	1.17–7.59	0.022

ACP: advance care planning; CI: confidence interval; EMR: electronic medical record; GOC: goals-of-care; POR: prevalence odds ratio

reported scores. From a learning theory perspective, the tendency for inaccurate trainee self-assessments may be emblematic of the Dunning-Kruger effect of illusory superiority where poorer-achieving students are not able to recognise their limitations, as well as imposter phenomenon, where high-achievers tended to be excessively critical of their own performance.[15] To illustrate this, a previous cohort study done on third-year medical students revealed that low-achievers tended to overestimate their own and their peers' performance, whereas high-achieving individuals were harsh towards themselves but accurate in scoring their peers.[16] To address this problem, metacognitive training, self-assessment practices (e.g. post-test dictions), and feedback literacy are evidence-based modalities to enhance trainee insight in medical education.[15]

Third, it is reassuring that many of the surveyed respondents held positive attitudes towards clinical GOC discussions and valued the importance of patient autonomy. For instance, the majority of the students felt that patients/families should be involved in all code status discussions and patient preference is an important consideration. However, given that approximately one-third of students believed that decisions related to life-sustaining therapies/interventions must always be approved by patients/families, there is a need for our healthcare and education systems to provide clarity on navigating between upholding patient autonomy in health-related decision-making and knowing when to withhold futile or inappropriate interventions in the end-of-life settings, even when it might conflict with the patients/families' wishes.

Finally, only a small percentage of students expressed confidence in holding clinical GOC discussions with patients/families, which could be related to the lack of experiential learning in this area during clinical clerkship rotations. From multivariable analyses, it is evident that self-perceived familiarity, direct clinical experience and awareness of how to find ACP documentations were significantly associated with greater confidence in holding GOC discussions with patients/families. To enhance task familiarity and promote hands-on clinical experience, GOC communication skills could be taught through both simulation training with standardised patients and real-life, embedded and supervised learning during clerkship rotations.

Limitations of the study include its cross-sectional nature, which prevents temporal associations from being drawn between studied variables. There is also the risk of bias that affects the study validity, particularly non-response bias where participants and non-participants may have different characteristics; as well as social desirability bias in self-reported data for knowledge and confidence. To improve accuracy of these studied variables, simulated objective structured clinical examinations can be conducted as part of the research study with observer appraisals of trainee performance in holding GOC discussions based on standardised

assessment metrics. Finally, there could be a lack of generalisability of study findings to medical students in other societies and health systems, given the significant cultural differences on the emphasis of GOC discussions and the understanding of its constructs, thereby necessitating similar studies to be replicated in other settings for comparisons.

Our findings suggest the need for more comprehensive curricular teaching and assessment of foundational GOC concepts, as well as hands-on experiential/simulated learning to improve trainee confidence in handling real-world clinical scenarios requiring GOC discussions.

Acknowledgements

The authors would like to express their gratitude to the final-year medical students from NUS Yong Loo Lin School of Medicine AY 2023/2024 for their invaluable contributions to this study and wish them the best in their upcoming journey as junior doctors.

Ethics statement

Institutional review board (IRB) approval (NUS-IRB-2023-1059) was obtained for this study.

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *end-of-life, medical education, medical students, palliative, resuscitation status, terminal care*

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