STUDY PROTOCOL

study design

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Implementing a transmural model of early palliative care in advanced dementia: the use of a hybrid effectiveness-implementation



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Abstract

Background People with dementia receive differential access to palliative care services despite suffering from a significant burden of the disease in the advanced stage. Professional and familial caregivers may not view dementia as a terminal illness and are less likely to engage in end-of-life care discussions. Healthcare providers also face challenges coordinating palliative care in the community for dementia, demonstrating a lack of understanding of the needs of patients living with advanced dementia, and resources available to support them within the community.

Aim The aim of this study is to implement a transmural model of care in a tertiary care setting where patients living with advanced dementia (PLAD) at risk of deterioration in one year are identified early to receive tailored palliative care interventions using a predictive algorithm.

Methods/Design The updated medical research council (MRC) framework for complex interventions is used to guide the development and implementation of the transmural model which incorporates a predictive algorithm in clinical practice, with interventions tailored for at risk PLAD both within, and beyond the tertiary care setting. The *PRO*gnostic *Model* for *Advanced DE*mentia (PRO-MADE) developed to predict one-year all-cause mortality in PLAD presenting to an acute care hospital was embedded into the electronic health records of the tertiary care setting as a mathematical equation. Predictive modeling markup language in the digital records platform is used to calculate the risk score for PLAD by inputting the predictors. The clinical team is alerted of at risk PLAD through timed directive prompts, with advice on management given through tailored care bundles. The study will adopt a mixed methods approach in a Type 1 effectiveness-implementation study design to concurrently study the effectiveness of the transmural model in practice, and the barriers and facilitators to its implementation.

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Conclusion The implementation of a transmural model of early palliative care for patients with advanced dementia requires the coordination between clinicians in the tertiary care setting and community, together with health information technologists. This study protocol describes its development and implementation, and the study design to evaluate its outcomes.

Keywords Advanced dementia, Predictive algorithm, Transmural, Early palliative care, Implementation

Background

Access to palliative care for patients living with advanced dementia (PLAD) remains poor despite evidence that it alleviates suffering and rationalises healthcare utilization [1–3]. PLAD suffer significantly from complications related to severe cognitive and functional decline. Despite having the same predicted average activities of daily living score 17 months before death as individuals without dementia at least six months before death, PLAD had significantly less hospice use in the last three months of life [4]. Unsurprisingly, healthcare utilization such as hospital admissions, and emergency room visits in the last year of life is high, particularly when compared with patients living with other life limiting illnesses [5].

Barriers to integrating palliative care for PLAD include the lack of widespread acknowledgement that dementia is a terminal illness which leads to death [6]. This lack of knowledge amongst the general healthcare community also extends to the inability to identify the vulnerable population of PLAD at risk of deterioration [7, 8]. Instead of an appropriate and timely response to their unmet needs, PLAD are often subjected to burdensome interventions within tertiary care settings that do not add quantity or quality to their lives, spending their last days in the hospital [5, 9, 10]. Communication of advanced disease trajectories, goals of care discussions and shared decision making is also fragmented as PLAD transition between care settings, leading to suboptimal outcomes for patients, caregivers, and the healthcare community [8].

Early palliative care integration in PLAD can mitigate symptom suffering with early recognition, promoting care across and within healthcare sites with the appropriate resources in place. However, there is a paucity of evidence about the benefit of early palliative care in PLAD, much less its implementation within transmural palliative care models [11]. Hence, the aim of this study is to implement a transmural model of palliative care where PLAD in a tertiary care setting identified with a predictive algorithm to be at risk of deterioration in one year receive tailored palliative care interventions ("care bundles"). The hypothesis is that PLAD identified with a predictive algorithm are more likely to receive early transmural palliative care leading to improved patient, caregiver, and health utilization outcomes.

Methodology/Design

The phases illustrated within the Medical Research Council (MRC) updated Framework for Developing and Evaluating complex interventions were adopted to guide the development of the transmural early palliative care model for PLAD, test its feasibility, and evaluate the implementation outcomes. An implementation, clinical effectiveness type 1 hybrid study design is adopted [12–14]. This study is approved by the institutional ethical review board (2023/00743).

Study population

PLAD at Functional Assessment Staging Tool (FAST) stages 7 C to 7 F who are admitted into the Geriatric Medicine Department (Intervention group receiving transmural early palliative care in addition to usual care) and the General Medicine Department (Control group receiving usual care only) of a tertiary care setting between July 12th 2023 to June 30th 2026 will be recruited into the study. All patients with advanced dementia admitted to these two departments will be eligible for the study. These two departments are chosen as they care for the largest population of patients with dementia in the hospital where the study is conducted.

The *PRO*gnostic *M*odel for *A*dvanced *DE*mentia (PRO-MADE) scores will be tabulated for PLAD FAST 7 C to 7 F and patients with a probability threshold of more than or equal to 0.4 will be enrolled to received interventions recommended in the low-risk, or high-risk care bundles. PLAD with FAST Stage 4 to 7B are not eligible for the study.

Intervention - developing the transmural early palliative care model

A predictive algorithm— the *PRO*gnostic *Model* for *Advanced DE*mentia (PRO-MADE) - will be incorporated into the transmural early palliative care model to stratify PLAD in the intervention group into low and high risk of deterioration and death within one year of advanced dementia diagnosis. (Fig. 1: Transmural Early palliative care model for Patients Living with Advanced Dementia) Physicians in the intervention group (Geriatric Medicine Department) will receive prompts in the electronic medical records system regarding the one-year mortality risk estimates of their PLAD with care bundles recommending follow-up actions. Physicians in the control group (General Medicine) will not be exposed to the

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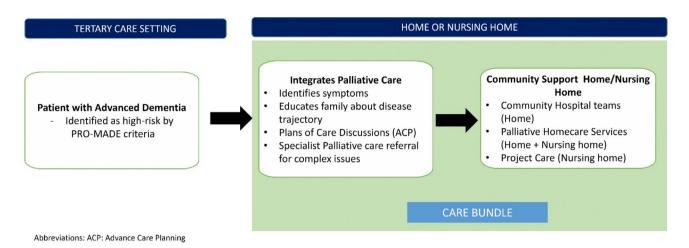


Fig. 1: Transmural Early palliative care model for Patients Living with Advanced Dementia

PRO-MADE risk score and will perform care as usual. However, clinicians in both departments will continue to receive regular teaching sessions in palliative care and advanced dementia as part of the implementation of the model, with emphasis on transmural collaboration. Usual care involves routine management of acute medical issues, with plans of care discussions and use of palliative care interventions initiated as deemed appropriate by the primary medical team.

In the transmural early palliative care model, in addition to usual care, the care bundle for low risk PLAD now includes the intentional conduct of plans of care discussions with the patient's family. For high risk PLAD, the care bundle is further expanded to integrate plans of care discussions with education about the disease trajectory to the patient's family. Palliative interventions are also introduced with the identification of symptoms such as pain using the pain assessment in advanced dementia (PAI-NAD) scale, and referral to community support services on discharge home or nursing home [15]. The components of the care bundles serve to integrate the practice of basic palliative care into the primary medical team's daily clinical practice. To enhance knowledge and confidence in the care of PLAD, each care bundle component is accompanied by a guide. These guides are embedded into the electronic health records to encourage compliance with recommendations such as the assessment and response to symptoms in PLAD who are often unable to speak for themselves, as well as carry out timely discussions with their caregivers based on an understanding of their anticipated needs outlined in the guides.

In the transmural model, the inpatient specialist palliative care team only becomes involved when the primary medical teams are unable to manage the complex physical, psycho-emotional, or spiritual issues that patients experience. Patients will continue to be supported with palliative care interventions in their homes or nursing

homes on discharge by community homecare services referred by the medical teams as part of the care bundle.

Feasibility

PRO-MADE is a predictive algorithm that was developed and validated within a tertiary care setting to predict one-year all-cause mortality in PLAD. Age>85 years, being male, having a pneumonia diagnosis, pressure ulcers, Charlson comorbidity index≥8, functional dependency in ≥4 activities of daily living, dysphagia, as well as abnormal urea and albumin levels at the time of advanced dementia (AD) diagnosis were predictive of one-year mortality. The PRO-MADE attained good model discrimination with an optimism-adjusted area under the curve (AUC) of 0.76, and an AUC of 0.70 in temporal external validation [16].

PRO-MADE is embedded into the electronic health records of the tertiary care setting as a mathematical equation (Supplementary Table), using predictive modeling markup language in the digital records platform and predictors as inputs to calculate the risk score for PLAD. Regular meetings between the clinical, research, and health information technology teams were conducted to ensure that variables within PRO-MADE could be drawn from various multidisciplinary records within the health system and were accessible within the defined timelines for computation. (Supplementary Table) The clinical team is alerted of at risk PLAD through timed directive prompts, with recommendations on management given through care bundles. The directive prompts were designed as best practice advisories to remind clinicians to assess patients' dementia severity using the Functional Assessment Staging Tool (FAST), and to integrate management using the care bundles (Fig. 2: Incorporation of PRO-MADE and Care Bundles for At Risk PLAD: Digital to Clinical Workflow) [17]. These directive prompts will be embedded into the electronic health records after

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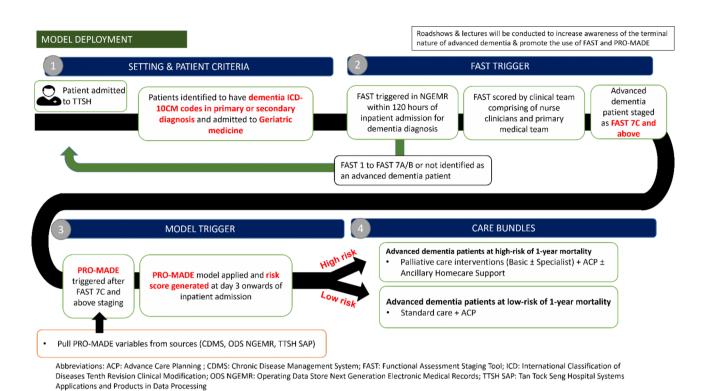


Fig. 2: Incorporation of PRO-MADE and Care Bundles for At Risk PLAD: Digital to Clinical Workflow

a pilot trial of manual prompts through the national healthcare platform which allows healthcare providers to communicate confidentially regarding care of patients. The directive prompts will be linked to practice guides for ease of assessment and documentation. Compliance with the directive prompts will be assessed every two months by the research and health information technology teams to ensure that PRO-MADE is used in the target population, digital and manual prompts are adhered to, and outcomes are measurable across the transmural model. Implementation of the transmural model for PLAD was supported by the hospital board, with education about the integration of early palliative care in dementia conducted regularly with the pilot medical teams to encourage compliance to the directive prompts. As the tertiary care setting is a teaching, university affiliated hospital with rotational changes in junior clinical staffing, unfamiliarity with the transmural model may arise, which could result in absent or inaccurate documentation. To overcome this, procedures in relation to the transmural early palliative care model for PLAD will be incorporated into medical department briefings at regular, timed intervals.

In the transmural model, a probability threshold of 0.4 for PRO-MADE will be used to stratify patients into high and low risk of death within one year of AD diagnosis as it yields a sensitivity of 51.18% and specificity of 85.59%, increasing the referral rate to the specialist palliative department and community by 16%. This was deemed

acceptable after considering the resource constraints within the palliative, medical and homecare teams in the hospital and community which form the transmural care model [16].

In the high-risk care bundle, PLAD will continue to be supported in the community, beyond the tertiary care setting by palliative homecare services. The Ministry of Health in Singapore subsidizes homecare support for one year, with provisions to extend the subsidy duration based on patient's needs. The palliative homecare teams are multidisciplinary, and can provide clinical, social, and emotional support to patients and caregivers, giving them the option to be cared for, and to spend the final days of life in their homes or nursing homes. Dedicated homecare services for PLAD were piloted in 2014, which have extended its reach to serve the whole population of Singapore in the last three years based on positive health-care utilization outcomes [3].

Implementation and evaluation

Components of the transmural model will be translated and implemented as part of clinical practice using the Implementation Research Logic Model (IRLM), a semi-structured tool used for the planning, execution, and evaluation of practice change initiatives [18]. As an amalgamation of frameworks, the IRLM is well-suited to assist with the planning and reporting of all strategies undertaken in the implementation of the transmural model and to study the outcomes resulting from the

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change. Serving as a "roadmap" for the conduct of the study, the IRLM increases understanding of the relationships between determinants, mechanisms, and outcomes in the implementation of the transmural early palliative care model for PLAD (Appendix 1).

Determinants refer to context-specific barriers and facilitators to the implementation and effectiveness of the transmural model in practice. An evidence-based determinant framework used in the IRLM is the Consolidated Framework for Implementation Research (CFIR) which reflects the factors that may influence implementation [19]. The five domains which could affect the implementation outcome of the transmural model include intervention characteristics, features of the implementing organization, the environment, characteristics of the individuals involved in the implementation, and the strategies that characterize the implementation process. Strategies to embed the transmural model into usual care include the development of implementation plans, documentation of quality indicators, academic and clinical outreach.

Mechanisms refer to the processes that the strategies act through to achieve adoption of the transmural model. With the use of PRO-MADE and guided prompts about goal planning, needs assessment and resource allocation beyond the hospital in the transmural model, time-pressured healthcare providers will be able to identify at risk PLAD and undertake a considered approach to their care.

A hybrid type 1 effectiveness-implementation study design will be used to concurrently examine the implementation feasibility, and clinical impact of the transmural early palliative care model for PLAD [14, 20]. The RE-AIM evaluation framework within the IRLM will be used to analyze the implementation outcomes of the transmural model, focusing on the steps in the design and dissemination, as well as the processes that facilitate or hinder the successful adoption of the components of the transmural model. Standing for Reach, Effectiveness (of the clinical intervention), Adoption, Implementation, and Maintenance, each metric is useful for assessing the public health impact of the transmural model. (Table 1) As the RE-AIM framework considers the interrelatedness between the implementation outcomes and the clinical effectiveness of the intervention being implemented, it is particularly well suited for effectiveness-implementation hybrid trials [21]. Outcomes to be measured to evaluate the implementation and effectiveness of the transmural model include the proportion of (1) patients assessed using FAST, (2) at risk PLAD identified with PRO-MADE, (3) at risk PLAD who complete the tailored care bundles, or receive specialist palliative care interventions, and (4) clinicians with eligible patients who adopt the recommendations, as well as (5) concordance in end-of-life care preferences, (6) healthcare utilization and cost. In addition, the PRO-MADE model will be prospectively validated to assess for potential shifts in model accuracy. Model performance will be evaluated based on overall measures of predictive accuracy (Nagelkerke's R2 and Brier's score), discrimination (AUC) and calibration (calibration slope and calibration-in-the large). If a shift in calibration properties is observed, the model weights and/or intercepts will be updated accordingly. Based on an AUC of 0.76 and a 30% mortality rate within one year, a sample size of 700 patients is required to achieve 80% power at 5% level of significance [22]. To understand the barriers and facilitators to the implementation of the transmural model, focus group discussions (FGDs) and in-depth interviews (IDIs) will be conducted 6 to 9 months, and 18 to 24 months after implementation with relevant stakeholders including healthcare professionals. Data collected will be analysed using thematic analysis [23]. Each transcript will be read and re-read for data immersion and familiarisation with initial thoughts and ideas noted. Thereafter, each transcript will be coded with the data relevant to each code organized to generate a list of preliminary codes. Subsequently, these codes will be examined and collated to inform the development of potential themes using an inductive-deductive approach. Themes focusing on barriers and facilitators will be developed inductively, grounded on participants' experiences with the implementation strategies and deductively based on the CFIR domains and its outcomes addendum, which forms the determinants framework in IRLM [19, 24]. Interpretations and refinements of themes will be conducted over iterative discussions with the medical and research teams to allow for reflexivity, with findings translated into new or revised implementation strategies to promote the uptake of the transmural model among clinicians. These implementation strategies will be evaluated using mixed methods that integrate qualitative IDI and FGD data with quantitative process indicators data. Software tools such as NVIVO (Release 14.23.2) and/ or Microsoft Excel will be leveraged to facilitate data analysis.

The process and patient outcomes across high and low risk PLAD between the Geriatric Medicine Department (Intervention) and the General Medicine Department (Control) of the tertiary care setting will be compared to assess the feasibility of the transmural model in clinical practice (Fig. 3: Feasibility Study and Evaluation of the Transmural model of Early Palliative Care in Advanced Dementia).

Discussion

PLAD are frequently hospitalized in the last year of life and are more likely to die in the hospital in spite of treatments received [2, 16]. Even when referred for palliative Hum et al. BMC Geriatrics (2025) 25:303 Page 6 of 10

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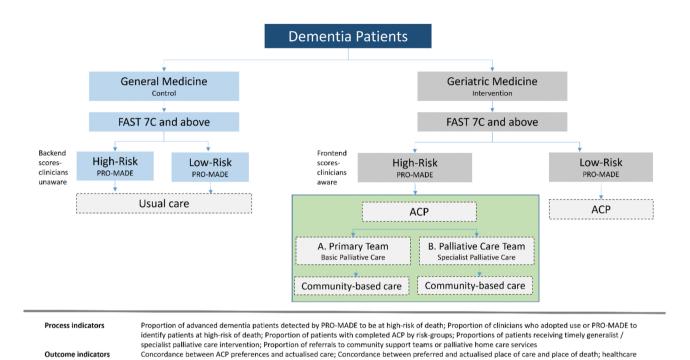
Table RE-AIIVI EVAIUATION OF THE FRANKLINIAL IVIN	IADIE I KE-AIM EVALUATION OF THE HANSMURI MODEL OF EATH FAMILYE CARE IN ADVANCED DEMENTA MODEL
REACH	Did the model reach the intended audience? • Proportion of *PLAD who identified to be at risk of deterioration within 1 year with *PRO-MADE
EFFECTIVENESS	How do we know the program was effective? • Proportion of caregivers of at risk PLAD who engage in plans of care, and advanced dementia trajectory with palliative care integration discussions • Proportion of high risk PLAD who were assessed with *PAINAD, and referred to community services • Proportion of high risk PLAD referred to palliative homecare services • Prospective validation of PRO-MADE • Healthcare utilization of PLAD in the transmural model.
ADOPTION	What was the proportion of clinicians and caregivers who adopted the intervention? • Number and proportion of clinicians of at risk PLAD who are compliant to: - Plans of care discussion - Discussions about advanced dementia trajectory and palliative care integration with caregivers - PAINAD assessment - Referral to palliative homecare services
IMPLEMENTATION	How did we ensure that the processes within the transmural model was adhered to? • Fidelity to the use of PRO-MADE and adaptations to the process and protocol by stakeholders involved in implementation • Opportunities and challenges of implementation faced by stakeholders
MAINTENANCE	Maintenance and Sustainability of the transmural model Opportunities and challenges in implementing the transmural model beyond the pilot (sustainability) and it's scaling up Cost Benefit Analysis of implementation of the transmural model

*PLAD: Patients living with Advanced Dementia

*PRO-MADE: PROgnostic Model for Advanced DEmentia

*PAINAD: Pain assessment in Advanced dementia Scale

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Abbreviations: ACP: Advance Care Planning ; FAST: Functional Assessment Staging Tool

utilisation and cost

Fig. 3: Feasibility Study and Evaluation of the Transmural model of Early Palliative care in Advanced Dementia

care support, it is in the last days to weeks of their lives; more than 50% of patients in a palliative homecare program were referred in the last month of their lives [2]. Significant reasons why patients are not referred or referred too late in their disease trajectory include the uncertainty surrounding prognostication, and lack of knowledge about palliative care and associated resources in advanced dementia [25, 26]. As a result, caregivers miss the opportunities to have honest discussions with clinicians about the declining health of their family members living with advanced dementia, and to formulate alternate plans of care that focus on the relief of suffering with end-of-life care sited where they would be most comfortable.

An integrative review of qualitative studies from the perspectives of stakeholders including frontline health-care staff, national experts, families, and people with dementia found seven factors that are key to facilitating good end-of-life care in dementia. They include timely planned discussions, recognition of end of life with provision of supportive care, co-ordination of care, effective working relationships with primary care, managing hospitalisation, continuing care after death, valuing staff, and ongoing learning. It is recommended that these factors be practiced across the spectrum of the dementia disease trajectory [26]. The transmural early palliative care model described in this study protocol for PLAD seeks to address these gaps by building on the palliative care resources already established within the community in

Singapore in the last decade but have yet to be utilized to its full potential. To overcome the barrier of prognostication inaccuracy, PRO-MADE was developed in a tertiary care setting, and validated for one-year mortality specifically to incorporate early, basic palliative care into daily clinical care for at risk PLAD. By utilizing computational advances in machine learning techniques, and the incorporation of PRO-MADE into the electronic medical records to risk stratify patients with advanced dementia in real time, patient care is empowered by artificial intelligence. Based on the stratification, the medical teams could be directed to adopt evidence-based, risk-tailored care pathways which include care planning discussions, needs assessment and co-ordinated homecare services for PLAD.

As part of machine learning predictive analytics, PRO-MADE was intentionally developed to be implemented as part of a broader system or workflow, rather than a stand-alone tool [27]. Components of the care bundles reflect basic palliative care practice and are accompanied with user friendly guides to facilitate documentation in the electronic medical records. In addition, the way the predictive algorithm is presented to the medical teams is carefully considered as it has an impact on patient outcomes. A prediction presented as a numerical probability without treatment recommendations is an assistive approach, as opposed to a directive approach where predictions are associated with decision recommendations. Whilst an assistive presentation format allows more

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room for clinical judgement to be exercised, studies have suggested that a directive format has a greater impact on patient outcomes [28].

Moreover, prompts and guides for the transmural model were developed in consideration of the potential for alert fatigue, lack of training and increased work burden on the medical team, issues most often cited as challenges in a systematic review of clinical implementation of predictive models in electronic health record systems [29]. In addition, systematic, institutional training and education of healthcare providers to help them recognize the needs of PLAD, and increase their awareness that dementia is a terminal illness which will benefit from palliative care is also instrumental to the success of integration.

Many patients would prefer to spend their last days at home, but only a minority of PLAD are able to achieve this. In a systematic review of factors important in facilitating home deaths for PLAD, the provision of general and specialist community-based palliative care services were key to supporting this endeavour [30]. Palliative homecare services in Singapore are subsidized by the Ministry of Health. Although they were mainly cancer centric in the beginning, they have since expanded to include the ever-growing population of patients living with end organ diseases, including dementia. Evidence shows that healthcare utilization is lower in PLAD enrolled into integrated geriatric palliative homecare services, with emergency room visits, hospital admissions and cumulative length of stay lower, compared with patients not enrolled [3]. The homecare team offers timely advice, empowering caregivers to use a combination of pharmacological and non-pharmacological measures to care for loved ones living with advanced dementia at home. Discussions with the homecare team about care preferences allow caregivers to come to a realistic understanding of the advanced dementia disease trajectory, resulting in less aggressive interventions, including hospitalization [31]. However, not all healthcare providers are aware of the availability of these resources within the community. The transmural model could direct clinicians to avail of these services for high risk PLAD with directive prompts.

The updated MRC framework for complex interventions with its diverse components of education, knowledge awareness, and behaviours involved in knowledge translation, and the inclusion of multiple stakeholders within, and between healthcare institutions is useful for guiding the development and evaluation of the transmural early palliative care model for PLAD [12]. Together with the RE-AIM framework, it enables the systematic evaluation of its implementation within a busy tertiary care setting and the community, with ongoing review of its processes to sustain its implementation throughout

Singapore. With the rising prevalence of dementia in Singapore and globally due to rapid population aging, there is an impetus to increase the awareness and practical application of evidence-based palliative care interventions and initiatives in all healthcare settings for PLAD [32, 33].

Strengths

Implementing transmural palliative care programs is challenging, with the failure to meet outcomes due to gaps in palliative and dementia care knowledge among healthcare providers. At risk PLAD may not be identified in a timely manner, and transitions of care could be fragmented with multiple healthcare providers involved [11]. Disagreement about goals of care between hospital and non-hospital healthcare providers, lack of support from the organizational management, and inequity in financial reimbursement for hospital and out-of-hospital care could also impede success [34]. Translating machine learning algorithms into clinical practice is also challenging, with lack of accord regarding palliative care needs of the patients or misunderstanding regarding the intent of palliative care [35].

The medical and research teams behind the transmural early palliative care model for PLAD took these shared experiences in practice into consideration in this trial in a tertiary care setting. This is a pragmatic approach given that PLAD experience an exponential increase in hospital admissions in the last year of life [5]. The model also leverages on the palliative homecare services for advanced dementia that have already been developed and subsidized by the Ministry of Health in Singapore in the last decade.

The scale of this model was designed to be manageable within the manpower, and workload constraints of the tertiary and community care settings. A PRO-MADE probability threshold of 0.4 will increase the referral rate of at risk PLAD by 16% without overstretching the resources. This can be adjusted if needed based on resource availability at the study settings.

Limitations

This is a single site study involving one tertiary care setting with palliative homecare service providers throughout Singapore. The delivery of early, tailored interventions requires accurate documentation within the electronic medical records, and timely response to the directive prompts which may be deferred amidst heavy clinical workloads. Regular reminders in department meetings, including educational teaching sessions will be used to ensure accurate and timely documentation of the variables within the electronic medical records. An understanding of clinician behaviours with the implementation of this model will further refine the

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workflow to minimise burden on the clinical team. As the clinical behaviour of the teams is being observed during the study, with regular reminders to ensure compliance to the interventions in the care bundles, there could be social desirability bias, potentially resulting in an overestimation of the intervention's impact. Moreover, regular reminders to ensure compliance may be unsustainable. This will be mitigated through the evaluation which will triangulate data derived from process indicators, qualitative interviews, and analysis to form a realistic appraisal of the effects of transmural care and its sustainability.

The conduct of the transmural model, and its funding is unique to the healthcare system in Singapore and may not be easily transferable to another country with different healthcare funding. However, components of the transmural model, including the predictive algorithm and basic tailored palliative care interventions can be adapted for use within other tertiary care settings.

Caring for PLAD is a collaborative effort involving multidisciplinary communities across different healthcare settings. To ensure seamless, timely care that addresses the unmet needs of PLAD, initiatives that intentionally assess needs and educate caregivers should be developed within the tertiary care setting, while available resources within the community could be capitalized to maintain support within patients' homes or nursing homes. The transmural model of care described in this protocol is designed to increase palliative care awareness and its early integration into advanced dementia care not only for caregivers, but for professional healthcare providers as well. Results of this endeavour which has commenced will be reported subsequently.

Abbreviations

AD Advanced dementia AUC Area under the curve

CFIR Consolidated Framework for Implementation Research

FAST Functional Assessment Staging Tool

FGDs Focus group discussions
IDIs In-depth interviews

IRLM Implementation Research Logic Model

MRC Medical Research Council

PAINAD Pain Assessment IN Advanced Dementia PLAD Patients Living with Advanced Dementia PRO-MADE PROgnostic Model for Advanced DEmentia

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05955-0.

Supplementary Material 1
Supplementary Material 2

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Author contributions

A.H., R.T., Y.H.W., M.K., W.S.T., Y.Y.D. and N.B.A have contributed to the study conceptualization. Design of study methodology by A.H, W.Y.G., H.Y.N., N.B.A, W.S.L., Y.L.J.T., W.S.T. and all other authors. Besides, A.H., Palvinder K., and all authors have involved in manuscript writing and review.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study is approved by institutional ethical review board: Domain Specific Review Board (DSRB) and the informed consent for study subject was waived. DSRB reference: 2023/00113.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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