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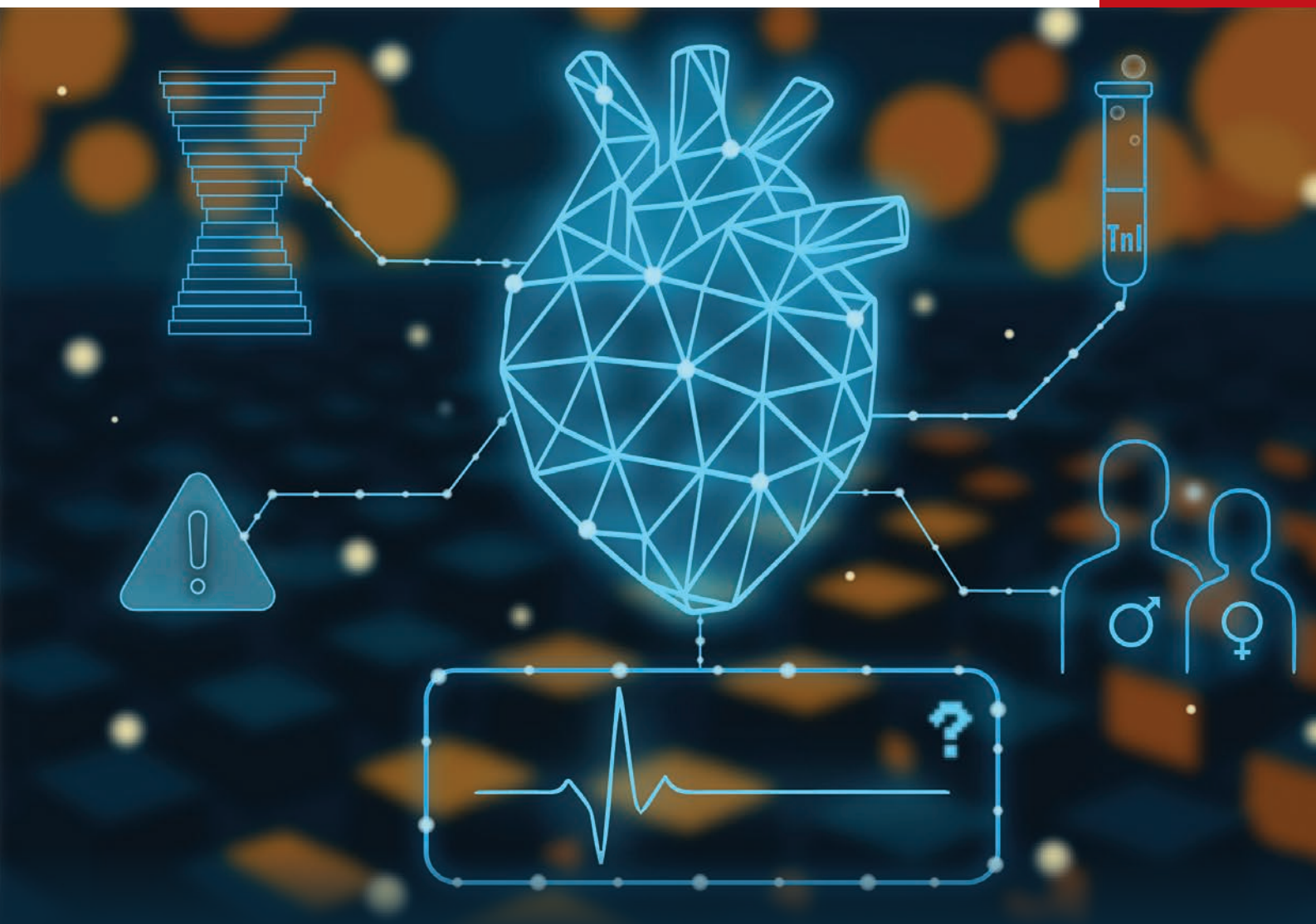

Machine learning to risk stratify chest pain patients with non-diagnostic electrocardiogram in an Asian emergency department

Myocardial infarction-ischaemic-injury index algorithm demonstrates accuracy in risk stratifying emergency patients presenting with chest pain. The algorithm is developed using gradient boosting that considers age, sex and troponin I results for the risk stratification. (See full article, p.219)

Illustration by Maria De-Castro

Also in this issue

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Annals, Academy of Medicine, Singapore
Volume 54 | Number 4 | APRIL 2025

EDITORIAL

ORIGINAL ARTICLES

REVIEW ARTICLE

COMMENTARIES

LETTERS TO THE EDITOR

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EDITORIAL

Striving for our most vulnerable children: Buffering against the impact of child maltreatment

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One of the fundamental pillars of our society is the presence of strong and stable families. In 2024, the inaugural edition of the Domestic Violence Trends Report[1] by the Ministry of Social and Family Development, which provides an overview of key domestic violence trends in Singapore, was published. From 2021 to 2023, the number of new Tier 2 cases (those with high safety and risk concerns for the vulnerable person, which may warrant more intrusive statutory intervention to keep the individual safe) decreased. However, the number of new Tier 1 cases (those with low-to-moderate safety and risk concerns for the vulnerable person) increased, suggesting greater awareness and willingness by survivors and the public to report abuse and seek help early.

This greater awareness and willingness to report abuse is reflective of Singapore's persistent efforts at tackling child maltreatment across multiple domains and agencies. These include addressing upstream factors that are linked to prevention of abuse to tackling the myriad of downstream effects on these children. Such efforts have been multidisciplinary, across-agencies and requiring community involvement and participation as well. One of the aspects of such work, especially pertinent to the medical community, is specifically looking after the developmental and behavioural needs of these children.

Negative developmental implications for victims of child maltreatment have been widely researched. It is well established that child maltreatment has an immediate[2] and long-term[3,4] negative impact on children's physical, mental, academic and emotional health. In addition, the detrimental effects of Adverse Childhood Experiences (ACEs) including child maltreatment have been found to be transgenerational. This could be mediated by social circumstances, emotional regulation difficulties or mental health issues, and physiological mechanisms.[5,6] Addressing these effects requires targeted rehabilitation efforts catered to the needs of this vulnerable group of children. In this context, it is important to note that keeping victims of abuse safe is distinct from providing rehabilitation for them.

In this issue of the *Annals*, Chan SH et al. report on a new home visitation programme,[7] Anchor, that was specifically set up to support preschool children who have been exposed to maltreatment. The aim of the programme was to assess and address the potential impact of the ACEs that these children were exposed to in a holistic cross-disciplinary manner. The focus was on working with these families to address and improve the child's health, development and behaviour, early relational health, caregiver mental health and lastly, building community partnership to ensure ongoing support for the families. The programme centred around home visits, done by community health visitors who conducted visits based on a tiered risk-based model (up to 2 times a month for higher-risk families and once every 2 months for lower-risk families). The health visitors were supported by a team of social workers, psychologists and paediatricians who conducted regular assessments and addressed medical/developmental concerns appropriately. This is a first in Singapore and the Anchor team has done the important job of setting up and studying the impact of the programme in supporting the unique developmental needs of these children as well as their families.

The key findings as outlined by Chan SH et al. include that among the study cohort of 125 children, a substantial 73.6% of them were at risk of developmental delay upon entry into the programme, with scores on developmental screeners within the at-risk range. These delays were predominantly in the personal-social and communication domains, with almost half the cohort having at-risk scores in each of these domains. Further, nearly one-third of the cohort (31.7%) had behavioural concerns such as significant tantrums and aggressive behaviour. These findings are comparable to other studies[8,9] that show a higher prevalence of developmental

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and behavioural concerns in this group as compared to the population. This highlights the importance and need to systematically screen for developmental and behavioural issues in this population locally. Encouragingly, many children in the Anchor study cohort showed improvements in their development, through the course of the programme; specifically in the gross motor and fine motor domains. This is a testimony of the resilience of these young children when specifically nurtured and given targeted support. Although the improvements were not demonstrated across all developmental domains or behavioural concerns, this shows the potential for tailored programmes like this to support development holistically in these children.

Singapore has a robust jurisdictional system to penalise offenders.[10] The Singapore Children and Young Persons Act (CYPA) protects our persons under 18 years old. Over the past decade, the CYPA has been amended to increase penalties for child abuse, with new laws against domestic violence being introduced. These laws, which are constantly reviewed and act as deterrence for future offenders, are a critical component of reducing rates of child maltreatment. Despite these, maltreatment does occur and in such instances, when a child has been harmed, there is a need for time-sensitive, prompt action, with the priority being the safety of the child. After this has been accomplished, it is then important to provide trauma-informed care and rehabilitation as justice for the affected child beyond ensuring safety. Safety is a prerequisite for rehabilitation but must be differentiated from rehabilitation in itself. Every step of this process is important to the child's recovery. In addition, although children are the primary target, it is important to realise that a child is always part of a system consisting of the family, peer group, school, neighbourhood and the community.

Hence, together with other programmes offered by the family service centres and the child protection specialist services, we need trauma-informed rehabilitation programmes to deepen our expertise and widen our reach in society. The Anchor programme is one such programme. While promising in potentially being able to ameliorate some of the developmental sequelae of child maltreatment, this current programme and many other such programmes tend to be resource-intensive due to the nature of this type of work. Implementation of a programme like Anchor, on a wide-scale will require significant resources and commitment from the relevant government agencies. Yet, such investments in this arena are warranted, especially for a high-income country like Singapore, where human capital is our primary natural resource and children are the future of our society. In parallel, we must also explore other models of rehabilitative care to cater specifically to this group of children within the educational, medical and social settings.

Ultimately, preventing and effectively dealing with child maltreatment when it does occur, is everyone's responsibility as a collective society. These children are among our most vulnerable and should not be failed by society, especially when they have already been let down once for allowing the maltreatment to occur in the first place.

Ethics statement

Not applicable

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: *adverse childhood experiences, child maltreatment, home visit, paediatrics, well-being*

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ORIGINAL ARTICLE

The impact of Anchor, a home visitation programme for maltreated children, on child developmental and behavioural outcomes

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ABSTRACT

Introduction: Adverse childhood experiences (ACEs) are associated with significant long-term impacts, yet few interventions specifically target ACE exposure, especially in Asian populations. Anchor, Singapore's first home visitation programme, addresses maltreatment among preschool children. This study evaluated Anchor's impact on children's developmental and behavioural outcomes.

Method: We conducted a prospective evaluation of children under 4 years assessed for maltreatment from November 2019 to July 2023. Developmental and behavioural progress was measured every 6 months using the Ages and Stages Questionnaires (ASQ-3) and ASQ:Social-Emotional (ASQ:SE-2), and annually using the Child Behaviour Checklist (CBCL).

Results: The results of 125 children (mean age 20.0 months, 48% female) were analysed. The mean length of stay in programme was 21.2 (7.3) months. At baseline, 92 (73.6%) children were at risk of developmental delay and 25 (31.7%) children aged ≥18 months had behavioural concerns. The programme was associated with significant improvements in gross motor (P=0.002) and fine motor (P=0.001) domains of the ASQ-3 and internalising problem scale (P=0.001) of the CBCL.

Conclusion: Anchor effectively enhances developmental and behavioural outcomes for children exposed to maltreatment. Targeted early intervention through such programmes can mitigate adverse impacts, optimising developmental trajectories and potentially reducing the long-term clinical and economic burdens associated with ACEs.

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Keywords: ACEs, adverse childhood experiences, behavioural difficulties, caregiver mental health, child development, child maltreatment, community health visitor, developmental delay, externalising behaviour, home visit, home visitation programme, internalising behaviour, paediatrics

CLINICAL IMPACT

What is New

- Anchor is the first home visitation programme in Singapore designed to support preschool children who were exposed to maltreatment, and their families.
- Findings underscore the need for intervention in early childhood for these children to mitigate the long-term effects of adverse childhood experiences (ACEs).

Clinical Implications

- The study supports the need for a holistic programme to support maltreated young children and families.
- This finding can potentially influence policymaking and guide efforts to minimise the long-term clinical and economic burden caused by ACEs.

INTRODUCTION

Adverse childhood experiences (ACEs) can occur in the form of abuse (physical, emotional, sexual), neglect (physical, emotional) and household dysfunction. The first ACEs study published in

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1998 demonstrated the association between ACEs and multiple risk factors of mortality in adulthood.[1] The greater the number of ACEs exposure, the higher the odds of having negative psychosocial or behavioural outcomes in adulthood, such as tobacco use, alcohol problem, risky sexual behaviour and mental health problems.[2,3] Early adverse experiences have been shown to cause changes to the developing brain, thereby adversely impacting long-term outcomes, such as cognitive development, academic performance, and physical and mental health in adulthood.[4-6] Early relationships, particularly with primary caregivers, also play a crucial role in the emotional and social development of the child. Insecure attachment or disrupted relationships in early childhood can contribute to difficulties in emotion regulation and social interactions, which are linked to higher likelihood of mental health problems in adolescence and adulthood.[7]

The burden of ACEs has been widely studied over past decades. National surveys have reported prevalence of ≥1 ACE for adults to be 63.9% in the US,[8] 46.4% in the UK[9] and 80.9% in China,[10] bearing in mind the difference in minimum age of recruited participants. The economic burden of ACEs was analysed across 28 European countries, which revealed the total ACE-attributable costs to range from USD0.1 billion (Montenegro) to USD129.4 billion (Germany) and these were equivalent to between 1.1% (Sweden and Turkey) and 6.0% (Ukraine) of nations' gross domestic products.[11] In Singapore, the reported lifetime prevalence of at least 1 ACE for adults was 63.9%.[12] Liu et al. described that individuals exposed to ≥3 ACEs utilised more direct medical care and experienced greater productivity losses than those without ACEs, resulting in substantial clinical and economic burden.[13] The adjusted incremental costs of ACEs, compared to no ACE, were estimated to be SGD1.18 billion (≥1 ACE) and SGD680 million (≥3 ACEs) per year.[13]

At KK Women's and Children's Hospital (KKH), approximately 100 to 120 children under 4 years old are assessed for suspected maltreatment every year. While an assessment of the families was in place to determine the case disposition, there was a lack of structured developmental, behavioural and trauma assessments of the child and caregiver mental health assessment. Referrals for interventions were made if there were obvious developmental delays, but there was minimal opportunity to ensure that the referrals were being followed through and interventions were carried out in the home setting. Furthermore, there is a paucity of evidence in the literature on targeted interventions to address ACEs, particularly in the Asian population.

Anchor, a home visitation programme, was established in KKH in 2019 with funding from Temasek Foundation, a philanthropic organisation. This programme was designed to serve maltreated young children (and their caregivers) to address exposure to ACEs. The aims of the programme were to optimise caregiver-child relationships, child development and caregiver mental wellness; break the cycles of abuse and harsh parenting; and improve the capability of the child protection community in child development and trauma management. Home visitation was the delivery model of choice for the programme because it provided trained home visitors with the opportunity to build trusting relationships with caregivers and to directly observe and understand the family dynamics, interactions and routines.[14] This not only provided valuable insights, but also enabled intervention to be more relevant and helpful to the targeted family.

The primary objective of this study was to evaluate the impact of Anchor programme on the developmental and behavioural outcomes of children. The secondary objective was to identify factors associated with the lack of improvement in developmental outcomes in the children who were at significant risk of developmental delay at recruitment into the programme.

METHOD

This was a prospective single-arm interventional study of children exposed to maltreatment who were recruited into the programme between November 2019 and July 2023. The study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2019/2683) and consent was obtained from primary caregivers. Only caregivers who consented to the study were included in the evaluation.

The Anchor programme recruited children under 4 years old, who were evaluated at KKH for suspected non-accidental injury or neglect. Siblings who were under 4 years old and living in the same household were also recruited due to their potential exposure to ACEs. Children who required foster care were recruited into Anchor programme after the foster parents took over as primary caregivers. Upon entry into the programme, these children and their caregivers received a holistic evaluation of their needs through various screening tools; comprehensive information about the family was also collected. The child's development and

behaviour were assessed using the Ages & Stages Questionnaires, Third Edition (ASQ-3),[15] the Ages & Stages Questionnaires Social-Emotional, Second Edition (ASQ:SE-2)[16] and the Child Behaviour Checklist for ages 1.5-5 (CBCL).[17] The caregiver's mental health was screened using Generalised Anxiety Disorder scale (GAD-7),[18] Patient Health Questionnaire (PHQ-9)[19] and Parental Stress Scale (PSS).[20] Details regarding caregiver's mental health will be reported in a separate paper.

Following the evaluation, the children and their families were stratified based on an inhouse tiering system adapted from The Child and Adolescent Needs and Strengths.[21] The tiering system involved assessment of the child (development, emotional-behaviour and health), primary caregiver (mental health and physical health) and social/family circumstances (Supplementary Table S1). Frequency of home visits was determined as follows: once every 2 months for Tier 1 (low risk), once a month for Tier 2 (moderate risk) and twice a month for Tier 3 (high risk). Tiering assessment was repeated annually and at the point of graduation from the programme. Home visits were helmed by Community Health Visitors (CHVs) and supported by other members of a multidisciplinary team consisting of psychologists, medical social workers and paediatricians. Children would graduate from the programme at 3 years old or after receiving interventions for at least 1 year (whichever occurred later). Families might be transited to a community agency, the preschool and/or hospital services depending on their needs for continued management.

Home visitation model in Anchor programme

The evidence-based interventions in Anchor programme focused on 4 main areas: early relational health; child's health, development and behaviour including managing trauma symptoms; caregiver mental health; and building community partnership to ensure ongoing support for the families. Interventions were both preventative as well as therapeutic to address any developmental or behavioural concerns. Caregivers of children with developmental delays were provided with targeted interventions during home visits while children with significant developmental delays were referred for additional therapy (hospital-based therapy or Early Intervention Programme for Infants and Children) in accordance with usual clinical practice. Children presenting with behaviours suggestive of trauma symptoms were supported by providing trauma informed care and supporting the relation and interactions between the caregiver and child. This included principles from Circle of Security Parenting and reflective parenting approaches to promote safety and security needed to co-regulate and support behavioural change.[22]

Training and supervision of the Anchor CHVs

The CHVs underwent an initial intensive training period of 4 weeks that included didactic lectures, direct teaching, observations, attachments to various departments such as child development department, and online training modules. The training covered topics related to childhood trauma and early adversities, relational health and attachment, caregiver mental health, child development and family engagement. They were also trained in Circle of Security Parenting, Infant Mental Health and received inhouse training on Abecedarian Approach.[23,24]

A robust supervision framework was put in place to support the CHVs. This included weekly individual supervision with the psychologist, team level supervision through weekly Anchor multi-disciplinary team meetings, and case consultations with speech therapists and occupational therapists. The psychologists were assigned as case supervisors and held weekly and ad hoc meetings with the CHVs to go through the progress of the children under their care. Furthermore, fidelity of the intervention was maintained through joint supervision visit by the CHV and a psychologist (who was not the case supervisor) every 6-monthly.

Outcome measures

Child development

Developmental assessment of each child was conducted by the CHVs using ASQ-3 and ASQ:SE-2 at 6-monthly interval. The ASQ-3 is a validated developmental screening tool for children which measures development in 5 domains: communication, gross motor, fine motor, problem-solving and personal-social. The results of ASQ-3 were recorded as categorical variables: black zone (>2 standard deviations [SD] below the mean), grey zone (1–2 SD below the mean) and white zone (equal to or above the mean).[15] A child who scored in the grey or black zone was deemed to be at risk for developmental delay.

The ASQ:SE-2 is a validated developmental screening tool, which evaluates the socio-emotional capabilities in children with questions covering behavioural aspects such as self-regulation, compliance, social-communication and interaction with people. The results of ASQ:SE-2 were similarly recorded as categorical variables: black zone (>2 SD above the mean), grey zone (1–2 SD above the mean) and white zone (social-emotional development appears to be on schedule).[16]

Child behaviour

The behaviour of each child was assessed using a parent-reported screening tool, the CBCL, which was administered to children ≥18 months old at baseline and repeated at 12-monthly interval. The CBCL categorises behaviours into 7 syndrome scales and the score of each syndrome scale was calculated as summary scores for internalising or externalising problems. The internalising and externalising problem summary scores were then analysed as categorical variables using recommended cut-offs for normal (percentile score <95th percentile), borderline (percentile score between 95th and 98th percentile) and clinical (percentile score >98th percentile) ranges.[17]

Comparison of outcome measures

The developmental and behavioural outcome measures of each child were compared across 2 timepoints—at baseline and latest timepoint (at graduation or the latest evaluation) to demonstrate the trajectory. The trajectories were then categorised into 2 distinct groups (Table 1). A positive programme impact was reflected by an improvement or remaining within the normal range in developmental or behavioural domain at latest timepoint. In contrast, children who showed deterioration or continued to have developmental or behavioural concern at latest timepoint were categorised under limited impact. Given the complex social background and ACEs exposure, it was important to note that children with age-appropriate developmental and behavioural milestones would still require significant interventions to help them maintain normal developmental trajectory and remain within age-appropriate range for emotions, behaviour and social functioning.

A subgroup analysis was performed on children with significant risk of developmental delay[25] at baseline, defined as >2 SD below the mean (black zone), in the communication, gross motor or fine motor domains of the ASQ-3. These children required referrals for additional therapy during Anchor programme as they met the clinical threshold for intervention. The purpose of this subgroup analysis was to identify modifiable or non-modifiable factors that could have contributed to the lack of improvement while being in the programme. Children in this subgroup were considered to have improved if they had fewer developmental domains in the black zone at the latest timepoint compared to baseline.

Statistical analysis

All categorical and continuous variables were expressed as mean (SD) and frequency (percentages), respectively. The primary outcome, defined as changes in paired categorical data

Table 1. Categories of possible trajectories of developmental/behavioural outcomes.

Group category	Screening tools	Trajectory of developmental/behavioural outcomes	
		Baseline	Latest timepoint
Positive impact	ASQ-3, ASQ:SE-2	White zone	White zone
		Grey zone	White zone
		Black zone	Grey/white zones
	CBCL	Normal	Normal
		Borderline	Normal
		Clinical	Borderline/normal
Limited impact	ASQ-3, ASQ:SE-2	Black zone	Black zone
		Grey zone	Grey/black zones
		White zone	Grey/black zones
	CBCL	Clinical	Clinical
		Borderline	Borderline/clinical
		Normal	Borderline/clinical

ASQ-3: Ages & Stages Questionnaires, Third Edition; ASQ:SE-2: Ages & Stages Questionnaires Social-Emotional, Second Edition; CBCL: Child Behaviour Checklist

in ASQ-3, ASQ:SE-2 and CBCL domains, was assessed using McNemar's test. The odds ratio (OR) with 95% confidence interval (CI) derived from McNemar's test was calculated from the number of children who showed improvement compared to the number of children who showed deterioration in the developmental or behavioural domain at latest timepoint. In addition, clinical significance of primary outcome was assessed by means of the effect size, calculated using Cohen's g.[26] An effect size of 0.1 to <0.3, 0.3 to <0.5 and ≥0.5 indicates small, medium and large effect size, respectively.[26] The secondary outcome, defined as the lack of improvement among children with developmental delay, was treated as binary data with categories "worsened/remained same" or "improved". Univariate logistic regression model was fitted to identify factors associated with lack of improvement among children with developmental delay at baseline. Quantitative association from logistic regression was reported as OR with 95% CI. All tests were 2-sided, and *P* value below 0.05 was considered as statistically significant. All analyses were performed using Stata software version 14.2 (StataCorp, College Station, TX, US).

RESULTS

A total of 157 children (and their caregivers) were recruited into the Anchor programme, where 19 families subsequently withdrew consent. Children without a second set of assessment (n=13) were excluded from the analysis as they were recruited <6 months at the time of reporting. There was no loss to follow-up. The baseline characteristics of the remaining 125 children (and their biological parents) are shown in Table 2. The mean age of the children at recruitment was 20.0 (13.4) months and there was equal distribution of both sex (60 [48.0%] female versus [vs] 65 [52.0%] male). There were 61 (48.8%) children who were Malays, 47 (37.6%) Chinese and 14 (11.2%) Indians. Fourteen (11.2%) children had a significant medical diagnosis that would have impacted their developmental progress. There were 63 (50.4%) children who had siblings enrolled into Anchor programme.

The mean age of biological mothers and fathers was 32.4 (6.4) and 37.0 (8.5) years, respectively. There were 42 (54.6%) mothers and 38 (54.3%) fathers who completed at least a post-secondary education. Fifty-six (64.4%) children were cared for in a 2-parent family, and 32 (38.6%) families were from low socioeconomic status with family per capita income ≤SGD650.[27]

The average length of stay in Anchor programme was 21.2 (7.3) months. Most (71.2%) children were cared for primarily by their biological parents. Most of the primary caregivers remained unchanged throughout the programme. At enrolment into the programme, 45 (36.0%) children were under Tier 1, 70 (56.0%) under Tier 2 and 10 (8.0%) under Tier 3. The overall rate of compliance to home visits stipulated by the tiering was approximately 80%.

Primary outcome

At baseline, 92 (73.6%) children were at risk of developmental delay, with scores ≥1 SD below the mean score in at least 1 domain of the ASQ-3 screen (Table 2). Personal-social (55 [44.0%] children) and communication (53 [42.4%] children) were the most impacted domains. There were 30 (24.2%) children with social-emotional concerns on the ASQ:SE-2 screen. Twenty-five (31.7%) children had behavioural concerns at baseline; 18 (22.8%) children had internalising behavioural problems and 24 (30.4%) children had externalising behavioural problems.

Table 3 depicts the developmental and behavioural trajectory of children in each domain of the screening tools. In the gross motor domain of the ASQ-3 screen, the proportion of children who had age-appropriate gross motor skills at latest timepoint was significantly larger than the proportion of children who had age-appropriate gross motor skills at baseline (85.6% vs 72.0%). The odds of seeing an improvement in gross motor skills is 3.8 times (95% CI 1.5–11.5) the odds of seeing a deterioration (*P*=0.002; Cohen's g=0.59).

In the fine motor domain of ASQ-3 screen, the proportion of children who had age-appropriate fine motor skills at latest timepoint was significantly larger than the proportion at baseline (85.6% vs 71.2%). The odds of seeing an improvement in fine motor skills is 4.6 times (95% CI 1.7–15.5) the odds of seeing a deterioration (*P*=0.001; Cohen's g=0.64). The changes in developmental outcomes were not statistically significant for the communication, problem-solving and personal-social domains of ASQ-3 and social-emotional domain of ASQ:SE-2.

A total of 79 children had complete CBCL assessments over 2 timepoints. In the internalising problem scale on the CBCL, the proportion of children who had no internalising behavioural concern at latest timepoint was significantly larger than the proportion of children who had no internalising behavioural concern at baseline (92.4% vs 77.2%), and this change was statistically significant (*P*=0.001). In the externalising problem scale on the CBCL, the proportion of children who had no externalising behavioural concern at latest

Table 2. Baseline children, biological parents and programme characteristics.

CHARACTERISTICS	
Children	
Age at recruitment (months)	n=125
Mean (SD)	20.0 (13.4)
Sex, no. (%)	n=125
Female	60 (48.00)
Male	65 (52.00)
Race, no. (%)	n=125
Chinese	47 (37.60)
Indian	14 (11.20)
Malay	61 (48.80)
Others	3 (2.40)
Known medical condition, no. (%)	n=125
Autism spectrum disorder	7 (5.60)
Genetic syndrome	2 (1.60)
Abusive head trauma	4 (3.20)
Post-Group B Streptococcal, or GBS, meningitis/sepsis	1 (0.80)
Nil	111 (88.80)
Has a sibling in Anchor, no. (%)	n=125
Yes	63 (50.40)
No	62 (49.60)
At risk of developmental delay at baseline, no. (%)[a]	n=125
Nil	33 (26.40)
At least 1 domain (on ASQ-3)	92 (73.60)
2 or more domains (on ASQ-3)	59 (47.20)
Had behavioural concern at baseline, no. (%)[b]	n=79
Yes	25 (31.65)
No	54 (68.35)
Biological parent	
Biological mother's age at enrolment (years)	n=79
Mean (SD)	32.4 (6.4)
Biological mother's highest education, no. (%)	n=77
Primary	6 (7.79)
Secondary	28 (36.36)
Post-secondary and above	42 (54.55)
Others, e.g. special education school	1 (1.30)

Table 2. Baseline children, biological parents and programme characteristics. (Cont'd)

CHARACTERISTICS	
Biological parent	
Biological father's age at enrolment (years)	n=76
Mean (SD)	37.0 (8.5)
Biological father's highest education, no. (%)	n=70
Primary	6 (8.57)
Secondary	25 (35.71)
Post-secondary and above	38 (54.29)
Others, e.g. special education school	1 (1.43)
Family	
Family structure, no. (%)	n=87
Extended family living in same household	19 (21.84)
Single-parent family	12 (13.79)
2-parent family	56 (64.37)
Family per capita income, no. (%)[c]	n=83
≤SGD650	32 (38.55)
>SGD650	51 (61.45)
Anchor programme	
Length of stay in Anchor (months)	n=125
Mean (SD)	21.2 (7.3)
Primary caregiver during Anchor, no. (%)	n=125
Biological parent	89 (71.20)
Kinship carer	13 (10.40)
Foster parent	23 (18.40)
Tiering at enrolment, no. (%)[d]	n=125
Tier 1 (low risk)	45 (36.00)
Tier 2 (moderate risk)	70 (56.00)
Tier 3 (high risk)	10 (8.00)
Child referred for external therapy, no. (%)	n=42
Attended at least 1 external therapy session	23 (54.76)
Did not attend any external therapy session	19 (45.24)

CBCL: Child Behaviour Checklist; SD: standard deviation
[a] Risk of developmental delay defined as ≥1 SD below the mean on ASQ-3
[b] Behavioural concern defined as borderline or clinical range on the CBCL
[c] Family per capital income of ≤SGD650 per month defined as low socioeconomic status based on the national benchmark (up till July 2023) when considering financial assistance and relief eligibility[27]
[d] Inhouse tiering system adapted from The Child and Adolescent Needs and Strengths[21]

Table 3. Developmental and behavioural trajectory of individual children by domains of ASQ-3, ASQ:SE-2 and CBCL screening tools.

Domains	Total, no.	Baseline	Latest timepoint, n (% of total)		Odds ratio (95% CI)	Effect size[b]	*P* value[c]
			At risk[a]	Normal			
ASQ-3							
Communication	125	At risk[a]	32 (25.60%)	21 (16.80%)	1.05 (0.54–2.04)	0.02	0.88
		Normal	20 (16.00%)	52 (41.60%)			
Gross motor	125	At risk[a]	12 (9.60%)	23 (18.40%)	3.83 (1.52–11.51)	0.59	0.002
		Normal	6 (4.80%)	84 (67.20%)			
Fine motor	125	At risk[a]	13 (10.40%)	23 (18.40%)	4.60 (1.71–15.49)	0.64	0.001
		Normal	5 (4.00%)	84 (67.20%)			
Problem-solving	125	At risk[a]	20 (16.00%)	31 (24.80%)	1.72 (0.93–3.27)	0.27	0.06
		Normal	18 (14.40%)	56 (44.80%)			
Personal-social	125	At risk[a]	29 (23.20%)	26 (20.80%)	1.18 (0.64–2.19)	0.08	0.56
		Normal	22 (17.60%)	48 (38.40%)			
ASQ:SE-2							
Social-emotional	124	At risk[a]	14 (11.29%)	16 (12.90%)	1.33 (0.59–3.09)	0.14	0.45
		Normal	12 (9.68%)	82 (66.13%)			
CBCL							
Domains	**Total, no.**	**Baseline**	**Latest timepoint, n (% of total)**		**Odds ratio (95% CI)**	**Effect size[b]**	***P* value[c]**
			Borderline/ clinical	Normal			
Internalising problem	79	Borderline/ clinical	6 (7.59%)	12 (15.19%)	NA	NA	0.001
		Normal	0 (0.00%)	61 (77.22%)			
Externalising problem	79	Borderline/ clinical	8 (10.13%)	16 (20.25%)	2.29 (0.89–6.57)	0.39	0.06
		Normal	7 (8.86%)	48 (60.76%)			

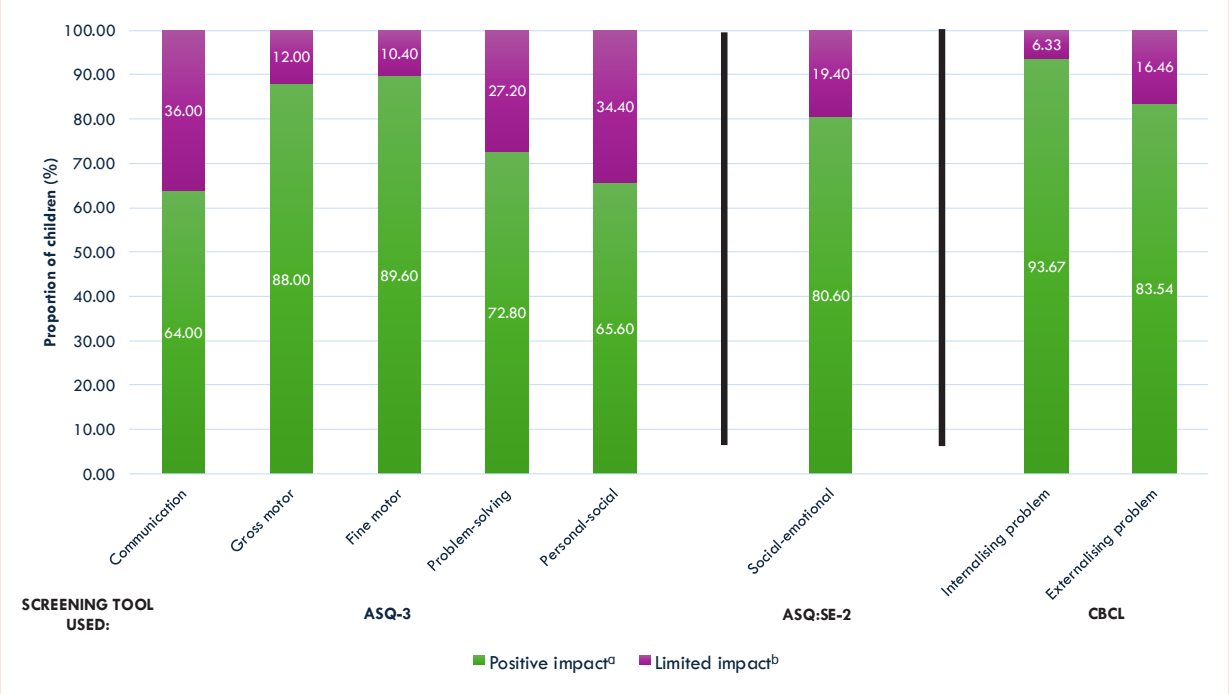
ASQ-3: Ages & Stages Questionnaires, Third Edition; ASQ:SE-2: Ages & Stages Questionnaires Social-Emotional, Second Edition; CBCL: Child Behaviour Checklist; CI: confidence interval
[a] At risk of developmental delay defined as ≥1 SD below the mean on ASQ-3 and ≥1 SD above the mean on ASQ:SE-2 (i.e. grey and black zones)
[b] Effect size derived from Cohen's g
[c] *P* value derived from McNemar's test

timepoint was larger than the proportion at baseline (81.0% vs 69.6%), but this did not reach statistical significance.

The primary outcome analysis was repeated to exclude 14 (11.2%) children with known medical conditions (Supplementary Table S2). The results were largely similar with statistically significant changes seen in gross and fine motor domains of the ASQ-3 screen and internalising and externalising problem scales on the CBCL.

Overall, most children (64.0%–93.7%) showed improvement or continued to meet age-appropriate milestones across all domains of the 3 screening tools at graduation or at latest evaluation (Fig. 1). Tiering assessment was repeated for 112 (89.6%) children. Among those children who were at Tier 2 or 3 at enrolment, 55 (73.3%) of them showed improvement in tiering at latest timepoint. A total of 92 (82.1%) children showed improvement in tiering or remained in Tier 1 at latest timepoint.

Fig. 1. Impact of Anchor programme on developmental and behavioural outcomes of children.



ASQ-3: Ages & Stages Questionnaires, Third Edition; ASQ:SE-2: Ages & Stages Questionnaires Social-Emotional, Second Edition; CBCL: Child Behaviour Checklist

[a] Positive impact is defined as the group with children who had age-appropriate developmental outcomes or normal behavioural outcomes at latest timepoint and those who showed improvement at latest timepoint.

[b] Limited impact is defined as the group with children who had developmental or behavioural concerns (i.e. grey or black zone on the ASQ-3 or ASQ:SE-2, or borderline or clinical range on the CBCL) at latest timepoint.

Secondary outcomes

Forty-two (33.6%) children in the study cohort were identified to be at significant risk of developmental delays at baseline. Sixteen (38.1%) children did not show improvement at latest timepoint. None of the child-related or parent/family-related factor was significantly associated with the lack of improvement in these children (Table 4). All 42 children were referred for additional external therapy, but only 23 (54.8%) attended at least 1 session. Among those who did not take up the external therapy referrals, 15 (78.9%) children still showed improvement in the developmental outcomes at the latest timepoint.

Discussion

Home visitation programmes such as Nurse-Family Partnership (United States), Child First (United States) and Early Start (New Zealand) are designed to serve at-risk populations such as low-income families and families with parental mental illness, substance abuse, incarceration, or domestic violence, with the intention of reducing the risk of adverse outcomes including child maltreatment.[28] In contrast, the evidence supporting the use of home visitation programme as a secondary/tertiary prevention strategy to support children under the child welfare system is not as robust. Furthermore, to the authors' knowledge, there has not been any home visitation programme, targeted at serving children exposed to maltreatment, which reported child developmental and behavioural outcomes.

The Anchor programme is the first home visitation programme in Singapore designed to support young children (and caregivers) exposed to maltreatment. Almost three-quarters of children in this study cohort were at risk of developmental delay and one-third of cohort presented with behavioural difficulties. The children in Anchor programme came from families with complex backgrounds and challenges and were exposed to early childhood adversities. This can impact normal developmental trajectory,[4] and trauma symptoms may manifest as problematic behaviours in these children.[29] Despite this, many of them showed improvement or continued to meet age-appropriate milestones across all domains of the 3 screening tools at graduation or at latest evaluation in Anchor programme. Majority of families improved from

Table 4. Univariate analysis on factors associated with the lack of improvement in children screened to have significant developmental delay at baseline.

Variables	Odds ratio (95% CI)	*P* value
Child-related factors		
Age at recruitment (months)	1.02 (0.97–1.07)	0.490
Stay in Anchor programme	0.99 (0.91–1.08)	0.851
Sex (male vs female)	1.04 (0.29–3.76)	0.950
Race (non-majority vs majority)[a]	0.68 (0.19–2.44)	0.555
Known medical condition (presence vs absence)	2.11 (0.57–7.86)	0.265
Parent/family-related factors		
Biological mother's age at enrolment (years)	0.89 (0.73–1.09)	0.264
Biological mother's highest education level (Post-secondary vs Others/Primary/Secondary)	0.75 (0.12–4.66)	0.758
Biological father's age at enrolment (years)	0.99 (0.87–1.13)	0.893
Biological father's highest education level (Post-secondary vs Others/Primary/Secondary)	0.23 (0.02–2.46)	0.223
Family per capita income (≤S$650 vs >S$650)	2.70 (0.64–11.47)	0.178

[a] Majority race refers to Chinese. Non-majority races include Malay, Indian and others.

moderate-high risk group (Tier 2-3) to low-risk group (Tier 1) at latest timepoint.

There were statistically significant improvements with large effect sizes observed in gross motor and fine motor skills and internalising behaviours among children in this study cohort. The development of fundamental gross and fine motor skills during early childhood are essential for subsequent development of adaptive and cognitive skills.[30,31] Internalising behaviours in childhood have been associated with early substance use, disruptive behaviour and mental health disorders such as anxiety and depression in adulthood,[32,33] contributing to poor long-term economic and social outcomes such as lower annual income, higher incidence of welfare receipt and lower incidence of intimate partnership.[34] Therefore, it is imperative to implement evidence-based interventions that optimise developmental skills and address problem behaviours in early childhood to mitigate the long-term consequences.

Notably, the improvement in communication and personal-social domains of ASQ-3 screen was limited during the programme. This was comparable to another study on children from low-income families in Singapore, which showed poorer Bayley cognitive and language scores in children from moderate and high-risk families.[35] Language development is influenced by multiple factors such as genetics, sex differences and family environment including socioeconomic status, parental education, and the level of engagement of parents with children.[36] Given the challenges faced by the families in this cohort, the impact on communication domain was understandably more apparent and might require longer period of observation to show improvement, as compared to the current programme duration (mean of 21 months).

The child's relationship with primary caregivers plays an essential role in the social and emotional development of the child and this could be impacted by caregivers' mental health issues. In our study, children with caregivers experiencing mental health issues were more likely to have heightened emotional and behavioural concerns.[37] Therefore, the programme also focused on the caregiver-child dyad relationship, by supporting responsive and sensitive caregiving practices, to help build secure attachments and increase moments of delight and positive childhood experiences. Interventions to address caregivers' mental health issues were also provided and the data collected will be analysed and reported in a separate study.

Among children with significant risk of developmental delay at baseline, no child-related or parent/family-related factor was significantly associated with lack of improvement in developmental

outcomes. This could be due to the small sample size. It was noteworthy that all 14 children with significant medical diagnosis such as autism spectrum disorder, genetic syndrome, abusive head trauma or post-GBS meningitis/sepsis were identified to have significant risk of developmental delays at baseline and these association were also reported in literature.[38-42] In addition, these children were referred for external therapy but only half attended at least 1 session. Many families in this cohort struggled to take up the referrals or attend external therapy sessions consistently due to other competing family needs and priorities.

It was encouraging to observe that most children who did not take up the referrals still demonstrated improvement in their developmental outcomes at the latest timepoint. This progress could be attributed to the CHVs' strategy of pacing with the family where they tailored interventions based on the child's needs and caregiver's capacity to implement them at home. This might involve frequently breaking interventions down into manageable steps, demonstrating them to the caregivers and embedding activities into daily routines.

There are limitations to this study. The nature of the study design, being a single-arm interventional study, limits the ability to conclude the definite impact of programme due to the absence of a control group. Furthermore, a diverse range of assessment tools for developmental and behavioural concerns was used across home visitation programmes that serve at-risk populations internationally, which limited the ability for direct comparison with other studies. While the small sample size could be a reason for the lack of statistical significance in the primary and secondary outcomes, statistically significant improvement was still demonstrated in 3 of the developmental and behavioural domains. Lastly, the duration in Anchor programme might be too short to demonstrate significant changes in all the developmental and behavioural outcomes in children, necessitating a longer-term study to observe the developmental and behavioural outcomes post-Anchor as well as to evaluate the cost-effectiveness of the programme.

CONCLUSION

Given the long-term deleterious consequences of ACEs, it is crucial that evidence-based interventions are put in place to optimise developmental skills and address problem behaviours in the childhood period. The study findings highlight the programme's potential to enhance the developmental and behavioural outcomes for children exposed to maltreatment. Through targeted early interventions, the programme addressed the immediate impact of ACEs and helped to mitigate their detrimental effects. By doing so, it not only reduced the burden of adversities but also paved the way for an improved developmental trajectory, thereby ensuring these vulnerable children a better foundation for lifelong success. This programme can potentially be the standard of care for preschool children exposed to maltreatment and this may reduce the clinical and economic burden of ACEs in the long run.

Supplementary Materials

Table S1. Tiering system used in Anchor programme. Table S2. Developmental and behavioural trajectory of individual children by domains of ASQ®-3, ASQ®:SE-2 and CBCL screening tools, excluding 14 children with significant medical conditions.

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Ethics statement

Not applicable

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.

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ORIGINAL ARTICLE

Machine learning to risk stratify chest pain patients with non-diagnostic electrocardiogram in an Asian emergency department

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ABSTRACT

Introduction: Elevated troponin, while essential for diagnosing myocardial infarction, can also be present in non-myocardial infarction conditions. The myocardial-ischaemic-injury-index (MI^3) algorithm is a machine learning algorithm that considers age, sex and cardiac troponin I (TnI) results to risk-stratify patients for type 1 myocardial infarction.

Method: Patients aged ≥25 years who presented to the emergency department (ED) of Singapore General Hospital with symptoms suggestive of acute coronary syndrome with no diagnostic 12-lead electrocardiogram (ECG) changes were included. Participants had serial ECGs and high-sensitivity troponin assays performed at 0, 2 and 7 hours. The primary outcome was the adjudicated diagnosis of type 1 myocardial infarction at 30 days. We compared the performance of MI^3 in predicting the primary outcome with the European Society of Cardiology (ESC) 0/2-hour algorithm as well as the 99th percentile upper reference limit (URL) for TnI.

Results: There were 1351 patients included (66.7% male, mean age 56 years), 902 (66.8%) of whom had only 0-hour troponin results and 449 (33.2%) with serial (both 0 and 2-hour) troponin results available. MI^3 ruled out type 1 myocardial infarction with a higher sensitivity (98.9, 95% confidence interval [CI] 93.4–99.9%) and similar negative predictive value (NPV) 99.8% (95% CI 98.6–100%) as compared to the ESC strategy. The 99th percentile cut-off strategy had the lowest sensitivity, specificity, positive predictive value and NPV.

Conclusion: The MI^3 algorithm was accurate in risk stratifying ED patients for myocardial infarction. The 99th percentile URL cut-off was the least accurate in ruling in and out myocardial infarction compared to the other strategies.

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Keywords: cardiology, emergency medicine, machine learning, myocardial infarction, troponin behaviour

CLINICAL IMPACT

What is New

- This study evaluates the performance of the myocardial-ischaemic-injury-index (MI^3) algorithm, a machine learning algorithm, in risk stratifying chest pain patients in the emergency department for 30-day myocardial infarction, as compared to established risk stratification strategies.

Clinical Implications

- This study shows that MI^3 is accurate in ruling in and out 30-day myocardial infarction as compared to existing strategies.
- Using the 99th percentile upper reference limit cut-off for troponin I for risk stratification is less accurate compared to other strategies.

INTRODUCTION

Risk stratification of patients presenting with chest pain poses a frequent, often difficult, challenge to the emergency physician. Cardiac biomarkers such as troponin are an important part of the evaluation of the patient suspected of having acute coronary syndrome (ACS). Serial readings are traditionally needed for troponin, given that the rise in troponin levels in older assays may not be apparent until

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hours after a cardiac event has commenced.[1] However, diagnostic protocols incorporating late generation, highly sensitive assays for cardiac troponin have decreased the time between serial troponin to a mere 1–2 hours.[2] A faster turnaround time of such patients without compromising patient safety and outcomes is welcomed, especially given the perennial problem of access block and overcrowding in the emergency department (ED). The European Society of Cardiology (ESC) currently recommends clinical pathways incorporating 0–2 or even 0–1 hour troponin results using high-sensitivity assays.[3] The American Heart Association (AHA) also recommends the use of high-sensitivity troponin as the preferred biomarker for evaluating patients with chest pain, as well as the use of chest pain protocols incorporating troponin to guide disposition.[4]

Elevated circulating troponin, while a key part of the criteria for the diagnosis of myocardial infarction, is not specific for ACS and can also be seen in non-coronary cardiac injury and in circumstances such as renal disease. Hence, troponin results must be interpreted in clinical context. Clinical scores have been developed, to risk stratify patients for adverse events such as myocardial infarction or mortality, which incorporate age, cardiovascular risk factors and presentation history together with cardiac biomarker results. The accuracy of such risk scores may differ between populations. As myocardial infarction is a high-stakes diagnosis, a very high sensitivity and negative predictive value (NPV) are required for a risk score to be considered useful, as the consequences of misdiagnosis include increased patient morbidity and mortality. Pathways, which make use of troponin to rapidly diagnose myocardial infarction, should ideally have a positive predictive value (PPV) of more than 70%.[5-7] The PPV of high-sensitivity troponin T in ruling in 30-day and 1-year major adverse cardiac events has been noted to plateau at about 70–80% with increasing troponin T cut-off values,[8] similar to a plateau of more than 70% with increasing high-sensitivity troponin I (TnI) cut-offs for the diagnosis of myocardial infarction.[9]

In recent years, machine learning has been gaining recognition as a potential tool in healthcare to increase diagnostic accuracy. Organisations such as the ESC and AHA recognise the potential utility of machine learning and artificial intelligence in the evaluation of patients presenting with chest pain,[10] which may allow an individualised approach to be taken in risk-stratifying patients for myocardial infarction.[11] The myocardial-ischaemic-injury-index (MI^3) algorithm is a machine learning algorithm developed using gradient boosting that integrates age, sex and cardiac TnI results (and the rate of change where serial results are available) to risk stratify patients for the outcome of type 1 myocardial infarction.[12] This algorithm has been shown to identify patients at low risk for index myocardial infarction, and has high sensitivity (97.8%) and NPV (99.7%)[12] with independent validation in European settings.[13-15] The MI^3 algorithm was chosen in our study as it has already been externally validated in other cohorts, and for its ease of use from a clinical standpoint as it only requires 3 objective variables which can be easily collected. Our study aims to evaluate the diagnostic accuracy of the MI^3 algorithm for myocardial infarction within 30 days in an Asian population, and to compare its accuracy to existing standards of care such as the ESC 0/2-hour pathway[3] and the 99th percentile upper reference limit (URL) for TnI.[16]

METHOD

Participants were recruited from March 2010 to April 2013 as part of a prospective observational study, which included patients aged 25 years and above who presented to the ED of Singapore General Hospital, a tertiary hospital in Singapore, with symptoms suggestive of ACS. The inclusion criteria included provision of informed written consent, and presenting symptoms consistent with suspected ACS. Patients who had an ED diagnosis of ST-elevation myocardial infarction (STEMI), a history of end-stage renal failure, those without cardiac troponin results and those lost to follow-up were excluded.

At the time of study, as part of standard care, patients with chest pain or symptoms suggestive of ACS but with no diagnostic ECG changes underwent continuous cardiac monitoring and a standard 8-hour observation protocol in the emergency cardiac care unit of our ED. Serial 12-lead ECGs and serum cardiac troponin were obtained at 0, 2 and 7 hours. At the time of study, a high-sensitive serum troponin T assay (Elecsys Troponin T high sensitive, Roche Diagnostics, Basel, Switzerland) was used at the study institution as part of clinical care. Additional serum drawn for the study and frozen at -80 °C, was used in a high-sensitivity TnI assay (ARCHITECT STAT high-sensitivity TnI, Abbott Diagnostics, Chicago, IL, US) to generate results used in the MI^3 analysis. Only the results from the samples obtained at 0 and 2 hours were used in the MI^3 analysis. The 99th percentile for serum TnI for the ARCHITECT STAT assay was 17 ng/L for females and 35 ng/L for males.[17]

A standardised dataset on each participant was acquired. This included demographic variables, such as age and past medical history, current medications, presenting signs and symptoms, test results, all interventions and outcomes. Patients were followed up for a year via telephone and/or through assessing medical records.

The primary outcome for this analysis was myocardial infarction as defined by the third universal definition of myocardial infarction[18] at 30 days. Outcomes were independently adjudicated by an emergency medicine attending physician and an attending cardiologist based on the case records, which included investigation results and data on troponin collected during the index visit and up to 1 year of follow-up. The TnI results used in the MI^3 analysis were not available to adjudicators as it was not done as part of the patient's clinical visit. Where inter-reviewer differences with respect to adjudicated outcomes occurred, discussion was held between the 2 reviewers to reach consensus.

We compared the use of MI^3 with (1) the ESC 0/2-hour algorithm and (2) using 99th percentile of TnI to see how they fared in predicting a diagnosis of myocardial infarction within 30 days.

The MI^3 algorithm was evaluated both in patients with baseline samples only and in those with serial samples available. For serial samples, the algorithm developed originally by Than et al. was applied. Thresholds for serial scores were set to <1.6 ng/L for low risk, 1.6 to <49.7 ng/L for intermediate risk, and ≥49.7 ng/L for high risk, in line with prior reports on the use of MI^3.[12,13] As described in Than et al., 1.6 ng/L was the derived threshold for rule-out corresponding to sensitivity ≥99%, and 49.7 ng/L was the derived threshold for rule-in corresponding to PPV ≥75% in the development cohort. In the present analysis, the algorithm was further adapted to allow for prediction based on a single troponin value. For patients with baseline samples only, no data indicative of rate of change (delta) in circulating troponin were available. Thresholds for rule-in and rule-out were derived for the baseline score using a similar approach as that of the serial MI^3 index score, with a threshold of <0.91 ng/L corresponding to low risk and ≥30.1 ng/L corres-ponding to high risk. Thus, a more conserva-tive threshold for rule-out was used when only a single sample was available.

For the ESC 0/2-hour pathway, the cut-off for the low-risk group was defined as a baseline troponin result of <4, or baseline result of <6 with a delta change of <2.[3] The high-risk group was defined as a baseline result of ≥64 or delta change of ≥15. When only a baseline sample was available, the delta change could not be evaluated, so only the baseline result criteria were applied (baseline troponin <4 for rule-out and baseline result ≥64 for rule-in).

Statistical analysis

For MI^3, which gives a quantitative score for risk of myocardial infarction, model performance was assessed by evaluating the area under the receiver-operating-characteristic curve (AUC). Confidence intervals (CIs) for AUC were calculated using the Delong method. For both MI^3 and ESC which provide risk categories, sensitivity and NPV were calculated for the low-risk group while specificity and PPV were calculated for the high-risk group. Predictive values were calculated using study prevalence. CIs for sensitivity, specificity and predictive values were calculated using the Wilson method. All statistical analyses were carried out using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were described as proportions and continuous variables as mean with standard deviation (SD) or median with interquartile range as appropriate.

RESULTS

Our analysis included data from 1351 patients, 901 (66.7%) of whom were male, with a mean age of 55.8 years (SD 12.3). There were 902 patients (66.8%) with only baseline (0 hour) troponin available and 449 (33.2%) with serial (both 0 and 2 hour) troponin results available. In the full cohort, 7.0% (n=94) had the primary outcome of 30-day myocardial infarction. Among those with serial troponin results available, 4.5% (n=20) had 30-day myocardial infarction. Table 1 describes the characteristics of our study cohort. Table 2 compares the 3 risk stratification strategies (MI^3, ESC 0/2-hour pathway and TnI 99th percentile as cut-offs). When serial troponin results were present, MI^3 was able to identify a higher proportion of low-risk patients with comparable sensitivity and NPV to the ESC pathways. The 99th percentile strategy had the lowest sensitivity, specificity, NPV and PPV.

MI^3 in predicting the likelihood of myocardial infarction

Overall, the MI^3 algorithm had an AUC of 0.936 (95% CI 0.906–0.966). MI^3 was able to rule out myocardial infarction in the low-risk group with a sensitivity of 98.9% (95% CI 93.4–99.9%) and NPV of 99.8% (95% CI 98.6–100%), with only 1 of 448 (0.2%) participants in the low-risk group diagnosed with myocardial infarction. MI^3 also performed well in ruling in myocardial infarction in the high-risk group (48 of 64, 75%) with a specificity of 98.7% (95% CI 97.9–99.2%) and a PPV of 75.0% (95% CI 62.3–84.6%).

Table 1. Baseline characteristics.

	Baseline only (n=902)	Serial sampling available (n=449)	Overall (n=1351)
Sex, no. (%)			
Female	295 (32.7)	155 (34.5)	450 (33.3)
Male	607 (67.3)	294 (65.5)	901 (66.7)
Race, no. (%)			
Chinese	570 (63.2)	273 (60.8)	843 (62.4)
Indian	166 (18.4)	96 (21.4)	262 (19.4)
Malay	120 (13.3)	60 (13.4)	180 (13.3)
Others	46 (5.1)	20 (4.5)	66 (4.9)
Hypertension, no. (%)	473 (52.4)	239 (53.2)	712 (52.7)
Diabetes, no. (%)	276 (30.6)	124 (27.6)	400 (29.6)
Ever smoker, no. (%)	258 (28.6)	120 (26.7)	378 (28.0)
History of myocardial infarction, no. (%)	106 (11.8)	43 (9.6)	149 (11.0)
Previous coronary artery bypass graft surgery, no. (%)	79 (8.8)	22 (4.9)	101 (7.5)
Previous coronary angioplasty, no. (%)	143 (15.9)	64 (14.3)	207 (15.3)
History of stroke or transient ischaemic attack, no. (%)	35 (3.9)	11 (2.4)	46 (3.4)

When considering only baseline troponin (n=1351), the MI^3 algorithm had an AUC of 0.933 (95% CI 0.902–0.964). In this population, MI^3 was able to rule out myocardial infarction with a sensitivity of 100% (95% CI 95.1–100%) and NPV of 100% (95% CI 96.0–100%). The baseline-only algorithm uses lower cut-offs for rule-out, resulting in a trade-off of a lower proportion being identified as low risk as compared to the overall cohort (115 of 1351 [8.5%] as compared to 448 of 1351 [33.2%] in the overall cohort). MI^3 identified 57 patients (4.2%) as high risk in this cohort, with a specificity of 98.9% (95% CI 98.1–99.4%) and PPV of 75.4% (95% CI 62.0–85.5%).

For those with serial troponin (n=449), the MI^3 algorithm had an AUC of 0.943 (95% CI 0.858–1.000). In this population, MI^3 was able to identify a larger proportion of low-risk patients (n=367, 81.7%) with a sensitivity of 95.0% (95% CI 73.1–99.9%) and NPV of 99.7% (95% CI 98.2–100%). The proportion of identified high-risk patients (3.8%) was similar to the baseline troponin and overall cohort, with a specificity of 99.1% (95% CI 97.5–99.7%) and PPV of 76.5% (95% CI 49.8–92.2%).

Comparison with ESC 0/2-hour pathway

With the full cohort, the ESC 0/2-hour pathway identified 61.7% (n=833) as low-risk with a sensitivity of 94.7% (95% CI 87.5–98.0%) and NPV of 99.4% (95% CI 98.5–99.8%), and 8.3% (n=112) as high-risk with a specificity of 96.3% (95% CI 95.1–97.3%) and PPV of 58.9% (95% CI 49.2–68.0%). Comparatively, for those with serial troponin results (n=449), the pathway identified a higher proportion of those in the low-risk group (n=334, 74.4%) with a similar sensitivity (95.0%, 95% CI 73.1–99.7%) and NPV (99.7%, 95% CI 98.1–100.0%) as compared to the full cohort. The pathway identified 6.2% (n=28) as high risk in this cohort with serial troponin results with a specificity of 87.4% (95% CI 95.3–98.6%) and PPV of 60.7% (95% CI 40.7–77.9%).

When considering only baseline results with the ESC pathway (n=1351), 58.1% (n=785) were identified as low risk with a sensitivity of 95.7% (95% CI 88.8–98.6%) and NPV of 99.5% (98.6–99.8%). Thus, while the sensitivity and NPV of the ESC pathway with only baseline troponin was similar to that of those with serial troponin results,

Table 2. Accuracy of risk stratification strategies for 30-day acute myocardial infarction.

Risk stratification strategy	Area under the curve	Proportion stratified to low risk	Proportion stratified to intermediate risk	Proportion stratified to high risk	Sensitivity (95% CI)	Negative predictive value (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)
ESC 0/2-hour algorithm for full cohort (n=1351)	0.955 (0.913–0.977)	61.7%	30.1%	8.3%	94.7% (87.5–98.0%)	99.4% (98.5–99.8%)	96.3% (95.1–97.3%)	58.9% (49.2–68.0%)
ESC 0/2-hour algorithm for baseline troponin (n=1351)	0.962 (0.921–0.981)	58.1%	34.3%	7.6%	95.7% (88.8–98.6%)	99.5% (98.6–99.8%)	96.6% (95.4–97.5%)	58.3% (48.1–67.8%)
ESC 0/2-hour algorithm for serial troponin (n=449)	0.962 (842–0.992)	74.4%	19.4%	6.2%	95.0% (73.1–99.7%)	99.7% (98.1–100%)	97.4% (95.3–98.6%)	60.7% (40.7–77.9%)
MI^3 for full cohort (n=1351)	0.936 (0.906–0.966)	33.2%	62.1%	4.7%	98.9 (93.4–99.9%)	99.8% (98.6–100%)	98.7% (97.9–99.2%)	75.0% (62.0–84.6%)
MI^3 for baseline troponin (n=1351)	0.933 (0.902–0.964)	8.5%	87.3%	4.2%	100% (95.1–100%)	100% (96.0–100%)	98.9% (98.1–99.4%)	75.4% (62.0–85.5%)
MI^3 for serial troponin (n=449)	0.943 (0.858–1.00)	81.7%	14.5%	3.8%	95.0% (73.1–99.7%)	99.7% (98.2–100%)	99.1% (97.5–99.7%)	76.5% (49.8–92.2%)
Abbott ARCHITECT STAT troponin I 99th percentile cut-off (n=1351)	0.845 (0.786–0.892)	88.6%	Not applicable	11.4%	75.5% (65.4–83.6%)	98.1% (97.1–98.7%)	93.4% (91.8–94.7%)	46.1% (38.1–54.3%)

CI: confidence interval; ESC: European Society of Cardiology; MI^3: myocardial-ischaemic-injury-index

the proportion of identified low-risk patients was less in those with only baseline troponin. A total of 103 patients (7.6%) were identified as high risk with a specificity of 96.6% (95.4–97.5%) and PPV of 58.3% (95% CI 48.1–67.8%).

Comparison with 99th percentile for serum troponin

Using the sex-specific 99th percentile for baseline troponin as a cut-off, 1197 (88.6%) were identified as low risk with a sensitivity of 75.5% (95% CI 65.4–83.6%) and NPV of 98.1% (95% CI 97.1–98.7%). Using the cut-off as a rule-in, 154 (11.4%) were identified as high risk with a specificity of 93.4% (95% CI 91.8–94.7%) and PPV of 46.1% (38.1–54.3%).

DISCUSSION

Machine learning has gained traction in recent years and has been studied in medicine as a potential tool in clinical medicine for the diagnosis of critical conditions such as myocardial infarction[19,20] and in predicting myocardial infarction-related mortality.[21] MI^3 could accurately risk stratify patients for myocardial infarction[12,22] and has been validated in other populations.[13,14] Our study further demonstrates MI^3's accuracy in predicting the risk of myocardial infarction in an Asian cohort, showing its consistent performance in different populations. While several risk scores for chest pain have been validated and used in clinical practice, some scores use components that are subjective. For example, the history component in the HEART score[23] requires clinicians to score the patient's history as either slightly, moderately or highly suspicious, which introduces subjectivity as different clinicians may have varying thresholds in interpreting the patients' presenting history. Other scores may also have numerous components, which may make it difficult to use in day-to-day practice. MI^3 only uses age, sex and troponin results, making it an objective and practical strategy as it only requires 3 variables and does not require any subjective interpretation. Moreover, rather than classifying patients into discrete risk categories, MI^3 provides an objective assessment of the patient's probability of myocardial infarction on a scale of 0 to 100, which allows flexibility for different cut-offs to be established according to the setting for which it is being adapted.

In comparison to established risk stratification strategies, such as the ESC 0/2-hour pathway, MI^3 was able to identify a larger proportion of patients at low risk for type 1 myocardial infarction within 30 days with higher sensitivity and similar NPV, making it an accurate tool in identifying which patients can be discharged from the ED. Chest pain is a common presentation in the ED and constitutes about 5% of all ED visits.[24] The MI^3 algorithm allows for patients to be assessed expediently, stratifying their risk within 1–2 hours of presentation, potentially increasing ED throughput and decreasing ED overcrowding. ED overcrowding is associated with negative effects such as increased risk of adverse outcomes, rate of medical errors and hospital-acquired infections.[25] Ruling out a larger proportion of low-risk individuals among those who present with chest pain may also potentially reduce healthcare costs, as these patients can be discharged directly from the ED, avoiding unnecessary admissions. In Singapore, the personnel cost for admissions for chest pain unrelated to a coronary event was estimated to be SGD416 per case of chest pain,[26] while the median hospital bill for the diagnosis code of chest pain ranged from SGD484 to SGD4677 in public hospitals and SGD5673 to SGD10,496 in private hospitals.[27] Reducing the number of admissions for chest pain for those at low risk may lead to cost savings for both the patient and the healthcare system. Future economic evaluations can be done to determine the extent of cost savings.

In the original study, MI^3 was able to rule out 69.4% of the cohort as low risk of 30-day myocardial infarction with a sensitivity of 96.6% (95% CI 95.3–97.8%) and an NPV of 99.5% (95% CI 99.3–99.7%).[12] In our cohort, the sensitivity of MI^3 for those with serial troponin results for 30-day myocardial infarction was slightly lower at 95.0% (95% CI 73.1–99.7%). This may be due to differences in prevalences of comorbidities in our population, for example, the higher prevalence of diabetes mellitus in our cohort (29.6%) compared to the original study's cohort (14.6% in training set, 18.7% in testing set).[12] Our cohort also had a lower proportion of those with previous myocardial infarction (11.0%) compared to the original study (21.1% in training set, 20.0% in testing set).[12] Moreover, while MI^3 was derived from an international cohort, the training and testing cohorts were noted to be from Europe, New Zealand, Australia and the US.[12] It is likely that Asians may still be underrepresented as compared to our predominantly Asian cohort, and it remains unclear to which extent ethnicity may affect baseline troponin results.[28,29]

The original MI^3 requires 2 troponin readings—a baseline reading and one at 2 hours after the first sample is taken. However, in clinical practice, there may be instances where only a single troponin is used, such as when the patient presents long after the onset of symptoms. In our study cohort, MI^3 was shown to have high sensitivity (100%, 95% CI 95.1–100%) and NPV (100%, 95% CI 96.0–100%) when considering only baseline troponin, but the proportion of those considered low risk was much smaller than when serial troponins were available

(8.5% versus 81.7%). Further studies may be required to see how MI[3] can be modified to increase its utility with single troponin readings.

Before the advent of high-sensitivity troponin, the 99th percentile URL was commonly used as the cut-off for conventional troponin. However, with high-sensitivity assays, the interpretation of troponin has changed, and international guidelines now recommend the interpretation of high-sensitivity troponin according to the time of draw (whether baseline or serial readings taken 1–2 hours later) and consider the delta change.[3] The 99th percentile URL has been used as a cut-off in clinical practice,[16,30] but our findings reinforce the concept that this is less accurate for risk stratification of myocardial infarction regardless of whether it is used as a rule-in or rule-out strategy. Institutions should thus reconsider the use of the 99th percentile URL as a cut-off for risk stratifying patients with chest pain in clinical practice.

Limitations

The use of a machine learning algorithm may enhance clinical decision-making. It should not be used indiscriminately and requires interpretation of the algorithm-generated risk stratification in the full clinical context. In that sense, machine learning is not a panacea for all diagnostic dilemmas. Physicians will still need to rule out other dangerous causes of chest pain, such as pulmonary embolism and aortic dissection, before applying the MI[3] algorithm to patients to risk stratify those with possible cardiac chest pain.

MI[3] has also only been validated for use with high-sensitivity TnI. Not all centres use high-sensitivity TnI, some may use troponin T and others may not have access to high-sensitivity assays, which will limit the utility of MI[3]. In facilities which do not have access to laboratory testing with fast turnaround times, such as in primary care settings, MI[3] may not be as beneficial. With the emergence of point-of-care troponin testing,[31] this may eventually be overcome if MI[3] is validated for these tests.

The MI[3] algorithm also requires a baseline and serial reading. Clinicians may not always deem serial troponin readings to be necessary if the patient presents much later than symptom onset. As MI[3] currently requires 2 sets of troponin results, it may not be useful in this group of patients.

CONCLUSION

The MI[3] algorithm has shown to be accurate in risk stratifying ED patients for myocardial infarction when compared to current standard of care algorithms, such as the ESC 0/2-hour algorithm. The 99th percentile reference range was shown to be less accurate in ruling in and out myocardial infarction as compared to MI[3] and the ESC 0/2-hour algorithm.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2017/2130).

Declaration

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ORIGINAL ARTICLE

Clinical and echocardiographic differences between rheumatic and degenerative mitral stenosis

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ABSTRACT

Introduction: Degenerative mitral stenosis (DMS) is frequently cited as increasing in prevalence in the developed world, although comparatively little is known about DMS in comparison to rheumatic mitral stenosis (RMS).

Method: A retrospective observational study was conducted on 745 cases of native-valve mitral stenosis (MS) with median follow-up time of 7.25 years. Clinical and echocardiographic parameters were compared. Univariate and multivariate Cox regression analyses were performed for a composite of all-cause mortality and heart failure hospitalisation.

Results: Patients with DMS compared to RMS were older (age, mean ± standard deviation: 69.6 ± 12.3 versus [vs] 51.6 ± 14.3 years, respectively; *P*<0.001) and a greater proportion had medical comorbidities such as diabetes mellitus (78 [41.9%] vs 112 [20.0%], *P*<0.001). The proportion of cases of degenerative aetiology increased from 1.1% in 1991–1995 to 41.0% in 2016–2017. In multivariate analysis for the composite outcome, age (hazard ratio [HR] 95% confidence interval [CI] of 1.032 [1.020–1.044]; *P*<0.001), diabetes mellitus (HR 1.443, 95% CI 1.068–1.948; *P*=0.017), chronic kidney disease (HR 2.043, 95% CI 1.470–2.841; *P*<0.001) and pulmonary artery systolic pressure (HR 1.019, 95% CI 1.010–1.027; *P*<0.001) demonstrated significant independent associations. The aetiology of MS was not independently associated with the composite outcome.

Conclusions: DMS is becoming an increasingly common cause of native-valve MS. Despite numerous clinical differences between RMS and DMS, the aetiology of MS did not independently influence a composite of mortality or heart failure hospitalisation.

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Keywords: calcific mitral stenosis, degenerative mitral stenosis, mitral stenosis, rheumatic heart disease, valvular heart disease

CLINICAL IMPACT

What is New

- This is the first study to our knowledge, to demonstrate a longitudinal change in the epidemiology of mitral stenosis (MS) from rheumatic to degenerative aetiologies in a developed country.
- The aetiology of MS was not independently associated with adverse clinical outcomes in this study.

Clinical Implications

- There is an increasing need to develop effective treatment options for the growing group of patients with degenerative MS, which is not well understood at present.

INTRODUCTION

Mitral stenosis (MS) commonly arises from either rheumatic heart disease or a degenerative calcification of the mitral valve (MV) apparatus.[1] Rheumatic heart disease is overall the leading cause of valvular heart disease in the developing world, and rheumatic MS (RMS), with its association with rheumatic fever, remains prevalent in developing countries.[1-3] In contrast, incidence of rheumatic heart disease is declining in developed countries.[4,5] However, degenerative causes of MS have become increasingly prevalent in developed countries, in concert with increased life expectancy and related comorbidities.[5]

The pathophysiology as well as echocardiographic features and clinical sequelae of RMS are well known, in which valve thickening and commissural fusion together with involvement of

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the subvalvular apparatus develop as a sequel to rheumatic fever.[6] In contrast, degenerative MS (DMS) arises from a different disease process involving extensive mitral annular calcification (MAC), which is a non-inflammatory, chronic and degenerative process involving the fibrous base of the MV.[7] MAC gives rise to MS when it causes progressive restriction in valve mobility and limitation of physiological mitral annular diastolic dilatation.[5,8] MAC is known to be associated with cardiovascular comorbidities, coronary calcification as well as chronic kidney disease, and has been identified as a risk factor for mortality.[9-13] On the whole, patients with DMS are therefore typically elderly with a high burden of comorbidities.[14] Contemporary guidelines recognise the significant pathophysiological and clinical differences between RMS and DMS, and recommend a predominantly medical strategy over intervention for patients with DMS due to high procedural and surgical risks.[15] Overall, the natural history, comparative differences and treatment strategies for DMS versus RMS remain an area of active investigation. We sought to investigate the differences in clinical and echocardiographic parameters for DMS and RMS, clarify changing patterns in the incidence of DMS and RMS, and identify risk factors for clinically relevant outcomes in patients with MS.

METHOD

A retrospective observational study was conducted on a cohort of 745 unique cases of native-valve MS from a multi-ethnic Asian population. The cases were identified from a database of patients who underwent transthoracic echocardiography at the National University Heart Centre, Singapore between a time period of 1991 to 2017. The research protocol was approved by the National Healthcare Group Domain Specific Review Board (2021/00603). The study conforms to the ethical principles laid out in the 1975 Declaration of Helsinki.

The aetiology of MS was determined by the reporting echocardiographer at the time of study. In ambiguous cases, a blinded investigator (CHS) adjudicated the aetiology; rheumatic aetiology was determined based on the presence of changes, such as restricted leaflet mobility, doming of the MV leaflets and commissural fusion. A degenerative aetiology was determined by the absence of the above changes with the presence of MAC and evidence of MV stenosis. The first echocardiogram within the study period, which disclosed the presence of MS, was labelled as the index echocardiogram. Baseline clinical data as well as echocardiographic parameters were collected from the electronic medical record. Outcome data pertaining to all-cause mortality and heart failure hospitalisation were recorded from follow-up encounters and hospitalisations where relevant, and a composite of the 2 outcomes was constructed. The last identified follow-up encounter was determined as the endpoint to calculate the duration of follow-up. During collection of clinical and outcomes data, investigators were blinded as to the aetiology of MS. Data collection was performed up to 31 October 2020.

To identify associations with the composite outcomes, univariate Cox regression analyses were systematically performed using clinical and echocardiographic variables for the groups with RMS and DMS separately. Thereafter, we constructed multivariate Cox regression models incorporating all parameters found to be statistically significant in univariate analysis together with age and sex as biologically important variables.

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as frequency and percentages. Continuous variables were analysed with the independent-samples t-test and categorical variables by the chi-square test. Univariate and multivariate survival analyses was performed using multivariate Cox models for the composite outcome. *P* value less than 0.05 were interpreted as statistically significant; 95% confidence intervals (CIs) are presented where relevant. Statistical analysis was performed with IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY, US).

RESULTS

Our study presents data for 745 unique patients with native-valve MS, of whom 559 patients (75.0%) had RMS and 186 patients (25.0%) had DMS. The median time of follow-up duration was 7.25 years (interquartile range: 3.84–14.1 years).

Patients with DMS, compared to those with RMS, were older (mean ± SD: 69.6 ± 12.3) versus [vs] 51.6 ± 14.3 Sears, respectively; $P<0.001$), with higher body mass index (24.9 ± 4.9 vs 24.0 ± 4.9 kg/m^2, respectively; $P=0.023$) and systolic blood pressure (142.8 ± 26.0 vs 126.8 ± 22.3 mmHg, respectively; $P<0.001$). There were no significant differences in proportion of sexes between the 2 groups of patients ($P=0.190$).

In our study, patients with DMS were more likely to have comorbidities including hypertension (147 [79.0%] vs 194 [34.7%]; $P<0.001$), hyperlipidaemia (122 [65.6%] vs 170 [30.4%]; $P<0.001$), diabetes mellitus (78 [41.9%] vs 112 [20.0%]; $P<0.001$). A greater proportion of those with

Table 1. Baseline demographic and clinical parameters for patients with rheumatic mitral stenosis compared to degenerative mitral stenosis.

Variables	Overall (n=745)	RMS (n=559)	DMS (n=186)	*P* value
Age, mean ± SD, years	56.1 ± 15.9	51.6 ± 14.3	69.6 ± 12.3	**<0.001**
Female sex, no. (%)	512 (68.7)	377 (67.4)	135 (72.6)	0.190
Ethnicity, no. (%)				**0.007**
Chinese	459 (61.6)	341 (61.0)	118 (63.4)	
Malay	158 (21.2)	120 (21.5)	38 (20.4)	
Indian	65 (8.7)	41 (7.3)	24 (12.9)	
Caucasian	3 (0.4)	2 (0.4)	1 (0.5)	
Non-local ethnicity	60 (8.1)	55 (9.8)	5 (2.7)	
Height, mean ± SD, cm	157 ± 9	158 ± 9	154 ± 9	**<0.001**
Body mass index, mean ± SD, kg/m^2	24.2 ± 4.9	24.0 ± 4.9	24.9 ± 4.9	**0.023**
Body surface area, mean ± SD, m^2	1.61 ± 0.20	1.62 ± 0.20	1.59 ± 0.20	**0.119**
Systolic blood pressure, mean ± SD, mmHg	131.5 ± 24.6	126.8 ± 22.3	142.8 ± 26.0	**<0.001**
Hypertension, no. (%)	341 (45.8)	194 (34.7)	147 (79.0)	**<0.001**
Hyperlipidaemia, no. (%)	292 (39.2)	170 (30.4)	122 (65.6)	**<0.001**
Diabetes mellitus, no. (%)	190 (25.5)	112 (20.0)	78 (41.9)	**<0.001**
Ischaemic heart disease, no. (%)	159 (21.3)	81 (14.5)	78 (41.9)	**<0.001**
Stroke or transient ischaemic attack, no. (%)	106 (14.2)	71 (12.7)	35 (18.8)	**0.039**
Heart failure, no. (%)	162 (21.7)	122 (21.8)	40 (21.5)	0.927
Atrial fibrillation, no. (%)	337 (45.2)	293 (52.4)	44 (23.7)	**<0.001**
Chronic kidney disease, no. (%)	110 (14.8)	45 (8.1)	65 (34.9)	**<0.001**
Peripheral vascular disease, no. (%)	28 (3.8)	11 (2.0)	17 (9.1)	**<0.001**
Asthma or COPD, no. (%)	66 (8.9)	43 (7.7)	23 (12.4)	0.52
Antiplatelet usage, no. (%)	228 (30.6)	123 (22.0)	105 (56.5)	**<0.001**
Anticoagulation usage, no. (%)	298 (40.0)	266 (47.6)	32 (17.2)	**<0.001**
Beta-blocker usage, no. (%)	321 (43.1)	228 (40.8)	93 (50.0)	**0.028**
ACEI or ARB usage, no. (%)	213 (28.6)	128 (22.9)	85 (45.7)	**<0.001**
Calcium channel blocker usage, no. (%)	132 (17.7)	57 (10.2)	75 (40.3)	**<0.001**
Diuretic usage, no. (%)	231 (31.0)	175 (31.3)	56 (30.1)	0.760
Statin usage, no. (%)	294 (39.5)	175 (31.3)	119 (64.0)	**<0.001**
MRA usage, no. (%)	24 (3.2)	16 (2.9)	8 (4.3)	0.336
Digoxin usage, no. (%)	211 (28.3)	199 (35.6)	12 (6.5)	**<0.001**
Antiarrhythmic usage, no. (%)	22 (3.0)	17 (3.0)	5 (2.7)	0.805

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor; COPD: chronic obstructive pulmonary disease; DMS: degenerative mitral stenosis; MRA: mineralocorticoid receptor antagonist; RMS: rheumatic mitral stenosis; SD: standard deviation

P values in bold are statistically significant.

DMS had ischaemic heart disease (78 [41.9%] vs 81 [14.5%]; *P*<0.001), stroke or transient ischaemic attack (35 [18.8%] vs 71 [12.7%]; *P*=0.039), chronic kidney disease (65 [34.9%] vs 45 [8.1%]; *P*<0.001). Conversely, patients with RMS were more likely to have co-existing atrial fibrillation compared to those with DMS (293 [52.4%] vs 44 [23.7%]; *P*<0.001). The baseline demographic and clinical parameters for the 2 groups of patients are presented in Table 1.

Table 2 presents echocardiographic data for the 2 groups. Patients with DMS had a higher left ventricular ejection fraction (mean ± SD: 60.9 ± 12.1 vs 56.9 ± 11.1%; *P*<0.001), with a smaller left atrial volume index (46.6 ± 21.2 vs 65.4 ± 33.2 mL/m^2; *P*<0.001) and lower pulmonary artery systolic pressure (PASP) (42.2 ± 13.5 vs 46.5 ± 16.7 mmHg; *P*=0.002). The MV area by planimetry was also larger (1.69 ± 0.44 vs 1.44 ± 0.49 cm^2; *P*<0.001) with a lower MV mean pressure gradient (4.87 ± 2.06 vs 7.41 ± 3.89; *P*<0.001). While the left-ventricular outflow tract time-velocity integral was greater in patients with DMS compared to RMS (22.9 ± 6.3 vs 18.9 ± 6.0 cm; *P*<0.001), ultimately there were no significant differences in stroke volume (60.5 ± 20.6 vs 64.3 ± 22.9 mL; *P*<0.001).

Regarding concomitant valve disease, patients with DMS were more likely to have moderate-or-greater aortic stenosis (42 [22.6%] vs 72 [12.9%]; *P*=0.001). Conversely more patients with RMS compared to DMS had moderate-or-greater mitral regurgitation (129 [23.1%] vs 19 [10.2%]; *P*<0.001) and aortic regurgitation (67 [12.0%] vs 6 [3.2%]; *P*<0.001). Between the 2 aetiologies, the prevalence of tricuspid regurgitation was not significantly different (RMS: 23.1% vs DMS: 17.2%; *P*=0.092).

Fig. 1 pictorially represents the longitudinal changes in the relative incidence of RMS and DMS, expressed in intervals of 5 years each (except for 2016 to 2017). From 1991 to 2000, nearly all cases of native-valve MS were rheumatic in aetiology. Thereafter, degenerative cases of MS steadily increased as a proportion of the total number of newly diagnosed cases of MS within each subsequent time period, with 41.0% of all cases of MS from 2016 to 2017 being degenerative in aetiology.

In total, 366 (49.1%) events for the composite outcome were recorded during follow-up. Of these, 288 (38.7%) were deaths while 151 (20.3%) represented heart failure hospitalisation. The results of univariate and multivariate Cox regression analysis are presented in Table 3. While the aetiology of MS was significant on univariate analysis for the composite outcome, it was not independently associated with outcomes (*P*=0.100). Instead, the factors that were independently associated with outcomes in multivariate analysis were age (*P*<0.001; hazard ratio [HR] 1.032, 95% CI 1.020–1.044), diabetes mellitus (*P*=0.017; HR 1.443, 95% CI 1.068–1.948), chronic kidney disease (*P*<0.001; HR 2.043, 95% CI 1.470–2.841), and PASP (*P*<0.001; HR 1.019, 95% CI 1.010–1.027).

DISCUSSION

In summary, our results show that patients with DMS tended to be older with a higher burden of medical comorbidities compared to those with RMS. In the period from 1991 to 2017, the proportion of newly diagnosed cases of MS due to degenerative aetiologies increased while those of RMS decreased, and the aetiology of MS was not independently associated with our composite outcome of all-cause mortality or hospitalisation for heart failure.

The associations of DMS with metabolic conditions and atherosclerotic cardiovascular disease are similar to those previously reported in the literature.[9-12] Our findings are most directly comparable to 2 relevant studies: a 2009 single-centre cohort study of 70 patients in the UK by Akram et al. and a 2020 cohort study by Pressman et al. comparing 115 American DMS patients with 510 Korean RMS patients.[16,17] Akram et al. found that DMS patients were more likely to have hypertension and hyperlipidaemia but found no significant differences in age, diabetes mellitus or renal function; other clinical information was not presented.[16] Pressman et al. found a similar association between DMS and older age, presence of hypertension, diabetes mellitus as well as chronic kidney disease.[17] Our finding that RMS is associated with atrial fibrillation was also observed in the study by Pressman et al.[17] Data comparing the prescription or use of medications for DMS and RMS patients were not previously available in the literature to our knowledge.

Pressman et al. also demonstrated a smaller MV area, greater MV mean pressure gradient and larger left atrial volume index in patients with RMS, though conversely it found a lower PASP in such patients despite these relationships.[17] In our cohort, patients with RMS tended to have more severe MS with smaller MV area by planimetry and pressure half-time. An important caveat is that MV area measurements in patients with DMS should be interpreted with caution as traditional echocardiographic measurements for MV area are extrapolated from RMS and not validated in the DMS population.[18] It is often challenging to planimeter the narrowest flow limiting orifice in DMS, which typically occurs at the base of the

Table 2. Comparison of echocardiographic parameters for patients with rheumatic mitral stenosis versus degenerative mitral stenosis.

Variable	Overall (n=745)	RMS (n=559)	DMS (n=186)	*P* value
Left atrial volume index, mean ± SD, mL/m^2	59.1 ± 31.1	65.4 ± 33.2	46.6 ± 21.2	**<0.001**
LV end-diastolic diameter, mean ± SD, mm	46.9 ± 7.1	47.3 ± 7.2	45.5 ± 6.8	**0.002**
LV end-systolic diameter, mean ± SD, mm	31.2 ± 7.1	31.8 ± 6.7	29.5 ± 7.7	**<0.001**
LV end diastolic volume, mean ± SD, mL	105.1 ± 38.3	107.5 ± 39.3	98.0 ± 34.3	**0.004**
LV end systolic volume, mean ± SD, mL	41.8 ± 25.0	43.3 ± 24.8	37.4 ± 25.2	**0.006**
LV ejection fraction, %	58.1 ± 11.3	56.9 ± 10.7	60.9 ± 12.1	**<0.001**
LV mass index, mean ± SD, g/m^2	102.2 ± 37.5	96.4 ± 35.8	115.0 ± 38.0	**<0.001**
LVOT diameter, mean ± SD, mm	19.9 ± 1.9	20.0 ± 2.0	19.7 ± 1.75	0.51
LVOT time-velocity integral, mean ± SD, cm	20.1 ± 6.4	18.9 ± 6.0	22.9 ± 6.3	**<0.001**
LVOT stroke volume, mean ± SD, mL	62.6 ± 21.8	60.0 ± 22.6	68.7 ± 18.4	**<0.001**
Cardiac output, mean ± SD, L/min	4.55 ± 1.40	4.43 ± 1.41	4.85 ± 1.32	**<0.001**
Cardiac index, mean ± SD, L/min/m^2	2.85 ± 0.90	2.75 ± 0.88	3.09 ± 0.91	**<0.001**
MVA by planimetry, mean ± SD, cm^2	1.48 ± 0.49	1.44 ± 0.49	1.69 ± 0.44	**<0.001**
MVA by PHT, mean ± SD, cm^2	1.68 ± 0.68	1.55 ± 0.58	2.00 ± 0.81	**<0.001**
PHT, mean ± SD, ms	155.3 ± 96.3	163.6 ± 92.7	136.1 ± 102.0	**0.003**
Transmitral mean pressure gradient, mean ± SD, mmHg	6.65 ± 3.6	7.41 ± 3.89	4.87 ± 2.06	**<0.001**
Pulmonary artery systolic pressure, mean ± SD, mmHg	45.2 ± 16.0	46.5 ± 16.7	42.2 ± 13.5	**0.002**

DMS: degenerative mitral stenosis; LV: left ventricle; LVOT: left ventricular outflow tract; MS: mitral stenosis; MVA: mitral valve area; PHT: pressure half-time; RMS: rheumatic mitral stenosis
P values in bold are statistically significant.

Fig. 1. Incident cases of rheumatic and degenerative mitral stenosis, expressed as a percentage of total numbers of newly diagnosed cases per 5-year timeframe.

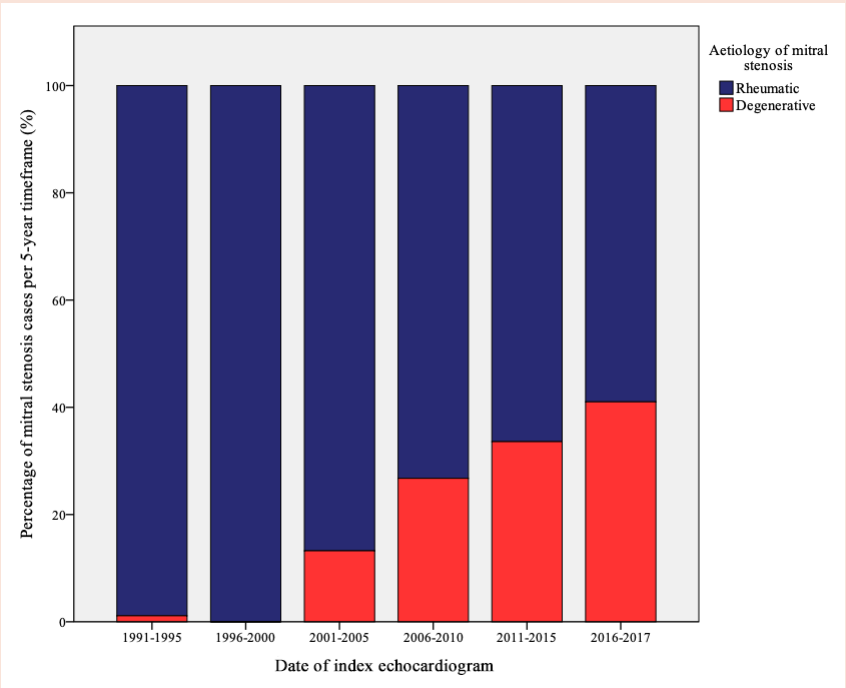

Table 3. Cox regression analysis for the combined outcome of all-cause mortality and hospitalisation for heart failure.

Univariate Cox regression analysis		Multivariate Cox regression analysis	
Variables	***P* value** **HR (95% CI)**	Variables	***P* value** **HR (95% CI)**
Age, years	***P*<0.001** **1.047 (1.039–1.055)**	Age (years)	***P*<0.001** **1.032 (1.020–1.044)**
Female sex	*P*=0.599 1.061 (0.850–1.324)	Female sex	*P*=0.362 0.879 (0.665–1.160)
Degenerative aetiology of MS	***P*<0.001** **2.768 (2.186–3.505)**	Degenerative aetiology of MS	*P*=0.100 1.297 (0.951–1.767)
Hypertension	***P*<0.001** **2.431 (1.957–3.020)**	Hypertension	*P*=0.316 0.844 (0.606–1.176)
Hyperlipidaemia	***P*<0.001** **1.807 (1.463–2.231)**	Hyperlipidaemia	*P*=0.952 1.009 (0.750–1.359)
Diabetes mellitus	***P*<0.001** **2.539 (2.025–3.184)**	Diabetes mellitus	***P*=0.017** **1.443 (1.068–1.948)**
Ischaemic heart disease	***P*<0.001** **2.110 (1.658–2.685)**	Ischaemic heart disease	*P*=0.963 0.993 (0.727–1.356)
Stroke or transient ischaemic attack	***P*=0.002** **1.546 (1.172–2.038)**	Stroke or transient ischaemic attack	*P*=0.341 1.174 (.844–1.632)
Pre-existing atrial fibrillation	*P*=0.930 1.009 (0.821–1.240)	NA	
History of heart failure	***P*=0.007** **1.383 (1.094–1.749)**	History of heart failure	*P*=0.685 1.066 (0.782–1.455)
Chronic kidney disease	***P*<0.001** **3.131 (2.424–4.044)**	Chronic kidney disease	***P*<0.001** **2.043 (1.470–2.841)**
Left atrial volume index, mL/m^2	*P*=0.641 0.999 (0.995–1.003)	NA	
Left ventricle ejection fraction, %	*P*=0.062 0.990 (0.979–1.001)	NA	
Left ventricle mass index, g/m^2	***P*<0.001** **1.008 (1.006–1.010)**	Left ventricle mass index, g/m^2	*P*=0.125 1.002 (0.999–1.006)
MVA by planimetry, cm^2	*P*=0.955 0.991 (0.732–1.343)	NA	
Transmitral MPG, mmHg	***P*=0.032** **0.962 (0.929–0.997)**	Transmitral MPG, mmHg	*P*=0.594 0.988 (0.944–1.034)
PASP, mmHg	***P*<0.001** **1.013 (1.005–1.020)**	PASP, mmHg	***P*<0.001** **1.019 (1.010–1.027)**

CI: confidence interval; HR: hazard ratio; MPG: mean pressure gradient; MS: mitral strenosis; MVA: mitral valve area; NA: not applicable; PASP: pulmonary artery systolic pressure
P values in bold are statistically significant.

MV leaflets as opposed to leaflet tips in RMS. Furthermore, heavy MAC tends to create acoustic shadowing artifacts, which obscure the MV annular interface and makes planimetry even more technically difficult.[18,19] Pressure half-time measurements rely on atrioventricular compliance, which can be confounded by reduced ventricular compliance as found in diastolic dysfunction.[20] Diastolic dysfunction commonly coexists in elderly or hypertensive patients and is associated with MAC, therefore suggesting a source of inaccuracy for pressure half-time-derived MV area in DMS. Notwithstanding these limitations for the assessment of MV area in DMS, we also found

that RMS was associated with a higher transmitral mean gradient and higher PASP compared to DMS, which supports the finding that patients with RMS had relatively more severe MS.

To our knowledge, a comparison of co-existing valve lesions in DMS versus RMS patients has not been previously described in the literature. In our study, a greater proportion of patients with RMS compared to DMS had concomitant mitral and aortic regurgitation; the former is notable given that MAC is itself a known cause of mitral regurgitation.[21,22] A retrospective cohort study by Pasca et al. of patients with DMS alone reported comparable figures for the prevalence of grade 3 or 4+ mitral regurgitation and tricuspid regurgitation of 13% and 8%, respectively, and a lower prevalence of moderate or severe aortic stenosis of 9%.[23] Conversely, the group with DMS had a higher proportion of patients with aortic stenosis, which may support a common pathophysiological process of degenerative calcification giving rise to both valve lesions.

Epidemiologically, the increasing prevalence of DMS and concomitant decline in RMS in developed countries has been frequently referenced, but contemporary longitudinal data directly comparing RMS and DMS are, to our knowledge, not available.[5,16] Several studies have produced estimates of the prevalence of DMS in varying populations, such as the EuroHeart study in 2003 that reported a prevalence of 12.5% of DMS in patients with native valve disease[24] while other studies yielded a prevalence of 6–8% of DMS in patients with pre-existing MAC.[25,26] To our knowledge this is the first study to demonstrate a clear increase in incident cases of DMS with a concomitant decline in the incident cases of RMS in a developed-country setting. The socioeconomic context of rapid industrialisation, economic growth, improved healthcare and increased lifespan in Singapore over the period of our study provides additional support to the hypothesis that the increase in cases of DMS is linked to these socioeconomic factors, while the decline in RMS is similar to other parts of the developed world.[4,5]

Our results suggest that the aetiology of MS, whether rheumatic or degenerative, was not independently associated with the studied composite outcome of all-cause mortality or hospitalisation for heart failure. Instead, age, diabetes mellitus, chronic kidney disease and PASP were identified as independently associated with these outcomes in the overall cohort. An elevated PASP is well-established as prognostically significant in the context of MS, and represents an established indication to consider MV intervention in existing guidelines that largely pertain to RMS; it has also been associated with increased mortality in DMS.[14,15] The presence of diabetes mellitus has also been shown to be linked to an accelerated rate of progression of DMS.[23] Notably, our results did not demonstrate an association between MV area by planimetry and the composite outcome, despite the central role of MV area in assessing severity of the valve lesion, particularly in RMS.[15] As previously discussed, in DMS, the quantification of MV area is challenging and the validity of methods such as planimetry have yet to be established. In previous work in isolated DMS, Kato et al. suggested that the continuity equation might be better suited for the assessment of MV area in DMS; even so, MV area by continuity was not found to be associated with mortality.[14] In our real-world cohort, the continuity equation was not applicable due to the substantial numbers of patients with concomitant mitral or aortic regurgitation.

Limitations

The chief limitation of the study relates to the retrospective nature of the study design allowing us to infer correlation but not causation from the data. We did not have transesophageal echocardiogram-derived three-dimensional MV that could have permitted accurate assessment of MV area in both groups with RMS and DMS. Our echocardiographic data pertaining to MV area and mitral pressure gradients were not verified against invasive haemodynamic studies, although invasive cardiac catheterisation is now rarely performed for the assessment of MS. In addition, we did not have serial echocardiographic studies that would have allowed us to identify differences in rates of progression between patients with RMS and DMS. We did not study outcomes pertaining to new onset atrial fibrillation or stroke in this cohort; this was related to the high baseline prevalence of atrial fibrillation with nearly half of the cohort having pre-existing atrial fibrillation. With multiple analyses to examine for differences in clinical and echocardiographic characteristics between the study groups, there is a risk of multiplicity and type I error. However, the associations we have identified, such as the increased prevalence of metabolic comorbidities in patients with DMS have been well-identified in similar studies. Lastly, our epidemiological findings pertaining to an increasing incidence of DMS may not be generalisable to other populations outside of Singapore given its unique socioeconomic and healthcare system characteristics. Further studies in other countries across the spectrum of socioeconomic development should be considered to identify temporal trends in the changing nature of aetiologies of MS.

CONCLUSION

Our data demonstrate an increase in the incidence of DMS as a proportion of cases of native-valve mitral stenosis at our centre, which we hypothesise may be related to rapid socioeconomic development and healthcare delivery in our Asian, developed-country patient cohort. The aetiology of MS, whether rheumatic or degenerative was not associated with increased all-cause mortality.

Ethics statement

The research was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was granted by the National Healthcare Group Domain-Specific Review Board (2021/00603).

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. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Use of Artificial Intelligence (AI)

Generative AI or other forms of AI-assisted technologies were not used in the study or preparation of the manuscript.

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REVIEW ARTICLE

Pregnancy-associated breast cancer: Management of the mother, fetus and tumour

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ABSTRACT

Introduction: Pregnancy-associated breast cancer (PABC) is described as breast cancer diagnosed within pregnancy or within 1 year postpartum. PABC is becoming more common due to delayed childbearing, with older maternal age increasing the likelihood of tumorigenesis coinciding with pregnancy. Our review aims to outline the important principles of managing PABC, and discusses future fertility implications, genetic testing and postnatal considerations that are not often considered in other existing reviews.

Method: A literature search was conducted using PubMed, Cochrane and Google Scholar databases.

Results: A persistent breast mass in pregnant women should be evaluated with a breast ultrasound. Total mastectomy is the standard treatment in the first trimester. Chemotherapy is contraindicated in the first trimesters, but can be given in the second and third trimester, and stopped before 35 weeks. Radiotherapy should be delayed until delivery, and hormone receptor therapy is contraindicated in pregnancy. A multidisciplinary team involving an obstetrician, medical oncologist and other allied health professionals is crucial. Delivery should be planned as close to 37 weeks as possible, and at least 3 weeks after the last chemotherapy cycle. Vaginal delivery is preferred, and breastfeeding can resume 14 days after the last chemotherapy regime.

Conclusion: A breast mass in a pregnant woman should not be dismissed. PABC must be managed by multidisciplinary teams at tertiary medical centres with access to surgery and chemoradiation therapies. Management strategies must include safe management and delivery of the fetus, contraception and future fertility planning.

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Keywords: antenatal, breast surgery, cancer, general surgery, neonatology, obstetrics and gynaecology, oncology, pathology

CLINICAL IMPACT

What is New

- Delayed childbearing and older maternal age, which increases the likelihood of tumorigenesis coinciding with pregnancy, leads to increased incidence of pregnancy-associated breast cancer (PABC).
- PABC is associated with higher recurrence and poorer survival rate compared to breast cancer outside of pregnancy, and is often diagnosed late.

Clinical Implications

- Our review summarises the current literature on diagnosis, staging prognosis and management.
- Future fertility implications, genetic testing and postnatal considerations in PABC should be considered.

INTRODUCTION

Breast cancer (BC) is the most common cancer affecting females worldwide, accounting for more than 50% of cancers in young females.[1] It occurs in 1 in 3000–10,000 pregnancies, with reported incidence rising with delayed childbearing.[2] The age standardised incidence rate in Singapore increased by 24.2% from 1993 to 2002.[3] The rising incidence in Asian countries has also been attributed to obesity and the adaptation of less traditional lifestyles that include reduced parity and breastfeeding.[3] Pregnancy-associated breast cancer (PABC) is described as BC diagnosed during pregnancy or within the first postpartum year.[4] Median maternal age at diagnosis is 33–34 years while the median gestation at diagnosis ranges from 17–25 weeks.[5]

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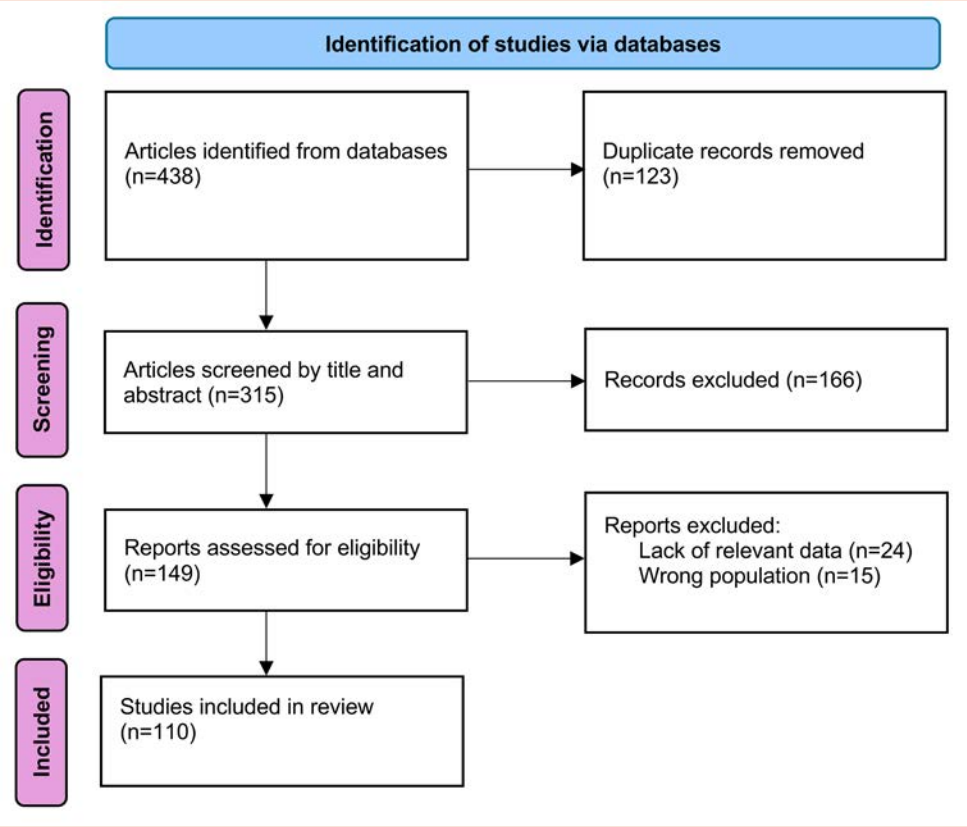
PABC is associated with worse prognosis compared to non-pregnancy associated BC. Prognostic factors include stage of cancer at diagnosis, histologically aggressive tumours, over-expression of the human epidermal growth factor receptor 2 (HER2), and negative status of progesterone (PR) and estrogen receptors (ER).[6] PABC causes higher mortality and recurrence compared to non-pregnancy-related cancers, is associated with poorer survival if diagnosed postpartum,[2,7] and late diagnosis comes at a more advanced stage of the disease where tumours are more aggressive.[8] Physiological changes in pregnancy may delay diagnosis by masking symptoms, and imaging and invasive diagnostic procedures are often delayed due to concerns of fetal harm.

METHOD

A systematic search was conducted in PubMed, Cochrane Library and Google Scholar using the terms "pregnancy associated breast cancer" or "pregnancy-related breast cancer", "breast cancer in pregnancy", "breast cancer during pregnancy" and "management of breast cancer in pregnancy". English-language narrative reviews, practice guidelines, clinical studies, systemic reviews, meta-analyses, cohort and case control studies, observational studies focusing on women diagnosed with BC during pregnancy or within 1 year postpartum, and published within the last 5 years were included. Non-pregnant populations, editorials and conference abstracts were excluded. Of 438 initial articles, 315 articles remained after removing duplicates. A total of 110 articles were selected for final review after screening abstracts and reviewing full texts (Fig. 1). A qualitative analysis was performed to summarise data and a narrative review was performed. Due to study heterogeneity, meta-analysis was not performed. Key themes included diagnosis and staging, treatment strategies, prognosis and prevention, fertility preservation, breastfeeding and contraception, and management challenges. Comparisons were made between treatment strategies for surgery, chemotherapy, radiotherapy, and hormonal and endocrine therapy—highlighting the consensus and discrepancies.

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram showing the study selection process.



Adapted from PRISMA 2020 flow diagram. Source: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

Genetic mutations and screening

Approximately 23% of BC in women are linked to pathogenic germline mutations in cancer predisposition genes *BRCA1/2, CHEK2, ATM* and *PALB2*; approx. 35% carry *BRCA1* and *CHEK2* mutations with 15% harbouring variants of uncertain significance (VUS) in *CHEK2, BRCA2* and *BRIP1*.[9,10] *BRCA1* germline mutation carries a higher risk of PABC than *BRCA2* mutations.

Genetic testing in PABC is indicated in women with diagnosis at <40 years old with a strong family history of breast, ovarian and related cancers, *BRCA1/2,* and triple-negative BC.[10-13] Identifying cancer predisposition syndromes such as Hereditary Breast and Ovarian Cancer (HBOC) is important for appropriate management. *BRCA1/2* repair deoxyribonucleic acid (DNA) double-strand breaks, and mutations can lead to genomic instability and increased oncogenesis. Germline pathogenic variants (PV) in *BRCA1/2,* inherited in an autosomal dominant pattern, increase the lifetime risk of breast and ovarian cancer via HBOC. Other genes are involved in aberrant homologous recombination of DNA that increases the lifetime BC risk.[9] The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) recommend genetic testing focused on *BRCA1/2* mutations, especially in patients with a strong family history for breast cancer and early-onset disease.[10,11] Additional multigene panel testing can be used to screen a broader range of cancer predisposition genes.[10] All patients should undergo genetic counselling before and after testing, to help women understand the implications of their results. In PABC, genetic counselling is crucial to address concerns regarding the impact of inherited mutations on current and future children.

Genetic risk evaluation in women with PABC can influence oncological management and surveillance, while facilitating family screening.[14] PV of high penetrance genes such as *BRCA1/2* and *PALB2* can guide surgical decisions to reduce contralateral BC risk and enable use of targeted therapeutics such as poly(ADP-ribose) polymerase inhibitors (olaparib).[15,16]

Genetic testing can identify low to moderate penetrance genes, like *RAD51C,* aiding risk assessment and counselling. However, VUS results, which are typically not actionable, may not explain early-onset PABC. Nonetheless, such patients, particularly those with a strong family history of cancer, should remain under cancer surveillance, as 6% of VUS may be reclassified into potentially actionable PVs .[9,17,18]

Pathology

Invasive ductal carcinoma is the most prevalent histological subtype among PABCs, often presenting with a more aggressive immune-histological profile, with higher rates of ER or PR negativity and HER2 positivity.[19,20] These tumours are larger, more aggressive, diagnosed at more advanced stages with lymphovascular invasion, and more resistant to hormonal treatment.[20-22]

Breast cancer during pregnancy

Diagnosis

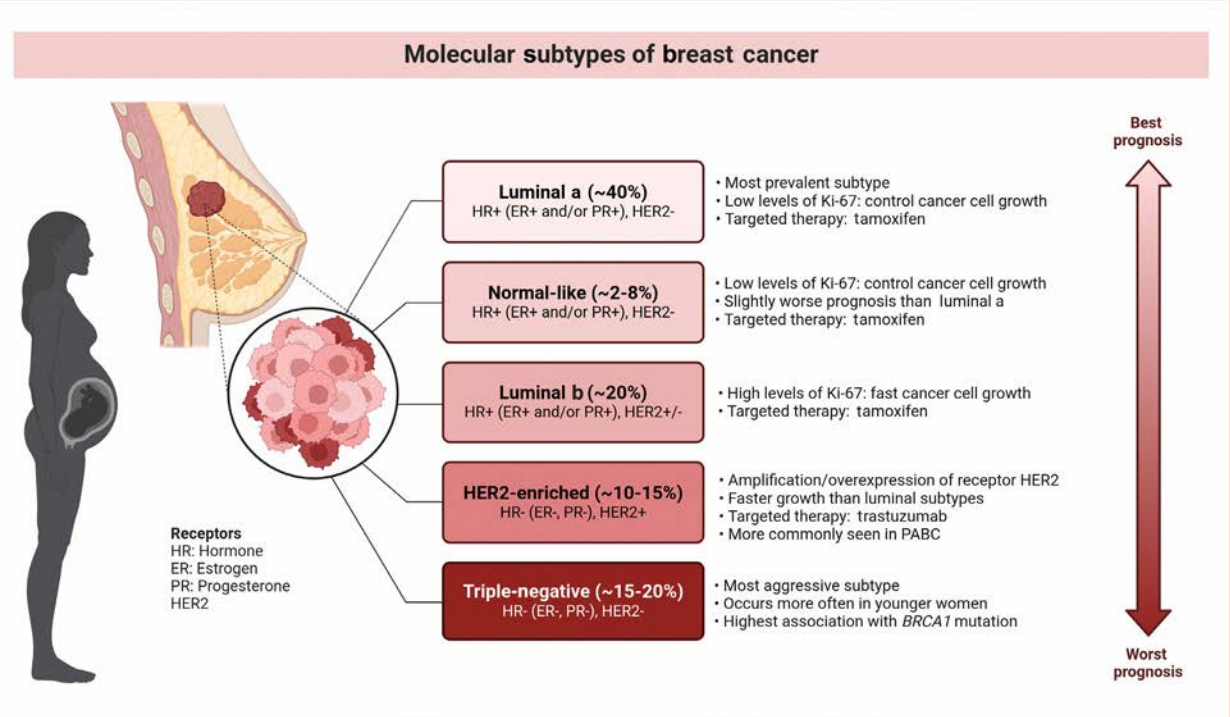
Triple assessment of breast lesions includes physical examination, imaging and histology.[16] Most women present with a painless palpable mass and rarely, with blood-stained nipple discharge.

Breast ultrasound is the firstline imaging modality for pregnant women due to the absence of ionising radiation, with a near 100% negative predictive value and good sensitivity for malignancy detection despite increased breast nodularity during pregnancy.[23] Further diagnostic imaging may be needed to characterise suspicious lesions. Although long-term cancer predisposition and genetic damage on the fetus are uncertain, radiation dose should be minimised.[24] No teratogenic effects have been documented at radiation exposures <50 mGy,[23] but risk of fetal organ malformation and mental retardation is approx. 1% with exposure >100 mGy.[25] Mammography produces radiation <3 mGy, which is generally safe during pregnancy and lactation, and should be implemented if there is high BC likelihood.[16] This is further reduced with abdominal lead apron shielding. With its detection rate of 78%, it is useful in assessing micro-calcifications, multifocality, multicentricity and contralateral lesions.[16]

Iodinated X-ray contrast may affect the neonatal thyroid gland, necessitating thyroid function monitoring in the first week after birth.[26] Magnetic resonance imaging (MRI) of the breast without contrast is safe but of limited use. Gadolinium crosses the placenta, enters the fetal circulation and amniotic fluid, and is associated with nephrogenic systemic fibrosis and renal impairment, making it relatively contraindicated in pregnancy.[26-28] Breast mass biopsy, required for histopathological diagnosis, is safe in pregnancy.[16] The sensitivity of core needle biopsy is approx. 90% and is the technique of choice.[29] It is important to inform the pathologist about the patient's pregnancy to avoid misdiagnosis due to gestational hyperproliferative changes.[24]

BC diagnosis in pregnant women is challenging and often delayed due to physiological changes

Fig. 2. Molecular subtypes of pregnancy-associated breast cancer.



ER: estrogen; HER2: human epidermal growth factor receptor 2; HR: hormone; PABC: pregnancy-associated breast cancer; PR: progesterone

Table 1. Radiation exposure dose and risk of detrimental effects on the fetus.

Absorbed radiation dose	**Effects on fetus**
1 mGy	Background
<50 mGy	Threshold of acceptable fetal exposure
60–200 mGy	Threshold of congenital fetal loss, congenital anomalies, intellectual effects
100 mGy at conception or >500 mGy after 25 weeks	Embryological/fetal death
50–500 mGy at 8-15 weeks	Growth restriction, intellectual effects
50–100 mGy (after first trimester)	0.3–1% childhood cancers
50–500 mGy (after first trimester)	1–6% childhood cancers
Absorbed radiation dose	**Imaging modality**
0.0005–0.001 mGy	Chest X-ray
0.001–0.001 mGy	Mammogram 2 views
0.1 mGy	Pelvis/Abdomen X-ray
0.01–1 mGy	Chest CT or pulmonary angiography
4–5 mGy	Bone scan Tc-99m
1.3–3.5 mGy	Abdominal CT
10–50 mGy	Pelvic CT
10–50 mGy	PET-CT whole body
Nil	MRI

CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; Tc-99m: technetium-99m

and atypical symptoms.[30] Patients are more likely to present at advanced stages with the average presentation-to-diagnosis interval being 1–2 months.[28] This delay has been reported to increase the risk of nodal involvement by 0.9%.[31] Hence, breast masses persisting for >2–4 weeks should be carefully evaluated. Atypical symptoms like bloody nipple discharge should be evaluated with ultrasound or mammography. Cytology, ductogram and ductoscopy have poor sensitivity and specificity, and should not be used. It is common to misdiagnose a new breast mass as an infected or blocked milk duct in pregnancy or puerperium. If the mass or inflammatory skin changes persist after antibiotic treatment, a biopsy is recommended.

Staging

Further staging imaging should be performed to guide therapy decisions. Multidisciplinary discussions involving radiologists and oncologists are important to ensure careful planning to minimise cumulative toxicity exposure.[24] The most common metastatic sites are the lungs, liver and bone. For T1–2 tumours (≤50 mm) with no lymph node involvement and low metastatic risk, staging can be delayed until after delivery.[16] Chest X-ray, full blood count, and liver and renal function tests are sufficient.[16] For T3 tumours (>50 mm) or with lymph node involvement, staging should include chest X-ray, hepatic ultrasonography and MRI of spine as these carry minimal radiation and contrast exposure.[16]

Management

Timely intervention is important given the variable treatment effects at different stages of pregnancy. Treatment should be carefully planned and coordinated by a multidisciplinary team including maternal-fetal medicine specialists and oncologists. The NCCN recommends following the treatment protocols for non-pregnant BC as closely as possible,[16] and not to delay therapy unless delivery has been planned within the next 2–4 weeks.[32] However, treatment of PABC diagnosed in the first trimester is particularly challenging as chemotherapy, endocrine therapy, anti-HER2 therapy and radiotherapy are contraindicated.

Chemotherapy

Almost all chemotherapeutic agents cross the placenta, and first trimester exposure is associated with the greatest risks of fetal loss, growth restriction and congenital abnormalities, such as cardiac septal defects, neural tube defects, limb deformities and cleft palate.[16,33] Its use should be avoided in the first trimester as recommended by NCCN.[33] In the second trimester, chemotherapy with taxanes, anthracyclines and cyclophosphamides may be considered with 3 weekly fetal weight and amniotic fluid monitoring.[24,34] Chemotherapy in the second and third trimesters carries a 1.3% risk of fetal malformation, similar to the baseline risk without exposure.[16] Chemotherapy should also be stopped after 35 gestational weeks or within 3 weeks of planned delivery to minimise risks of maternal myelosuppression in the peripartum period.[16,35,36] It takes at least 3 weeks for the placenta to metabolise and excrete the chemotherapy agents, and spontaneous labour is more likely to occur after 37 weeks.[37]

ESMO and NCCN recommend that chemotherapy regimens used in PABC should follow those for non-pregnant BC.[10,16,34] Anthracycline and alkylating agents are most widely used in pregnancy, but there is limited safety data on taxanes,[16,38] which are associated with fetal growth restriction and increased neonatal intensive care unit admissions, and should be avoided.[38] The safety profile is summarised in Fig. 4.

Several studies have addressed the safety of anthracycline-based regimens in PABC.[38] Hahn et al. reported congenital abnormalities including talipes equinovarus, bilateral ureteric reflux and trisomy 21 in 3 infants among 57 pregnant women treated with 5-fluorouracil, doxorubicin and cyclophosphamide.[39] Peccatori et al. reported no congenital anomalies among 20 patients treated with single agent epirubicin weekly (median 14 weeks) with a mean total dose of 420 mg/m^2.[40] Chemotherapy drugs cross the placenta via passive diffusion, with the degree and rate of transfer dependent on the concentration gradient between maternal, fetal and placental blood. In pregnancy, increased blood volume and cardiac output enhances drug delivery to tissues. An increased glomerular filtration rate, enhanced liver metabolic enzyme activity and altered hepatic function influence therapeutic levels at different gestational stages.[41] As there are no robust studies examining optimal doses in pregnancy, non-pregnant dosing regimens are used.[24]

Mastectomy, breast conservation and breast reconstruction

NCCN and ESMO recommend total mastectomy as the standard local treatment for first trimester PABC.[7,12,16] Breast conservation surgery (BCS) requires concomitant radiotherapy and is possible if radiotherapy can be safely delayed until postpartum.[16] Survival rate after mastectomy is similar to BCS, but comparative studies are

Fig. 3. Effects of chemotherapy on the fetus in the first trimester.

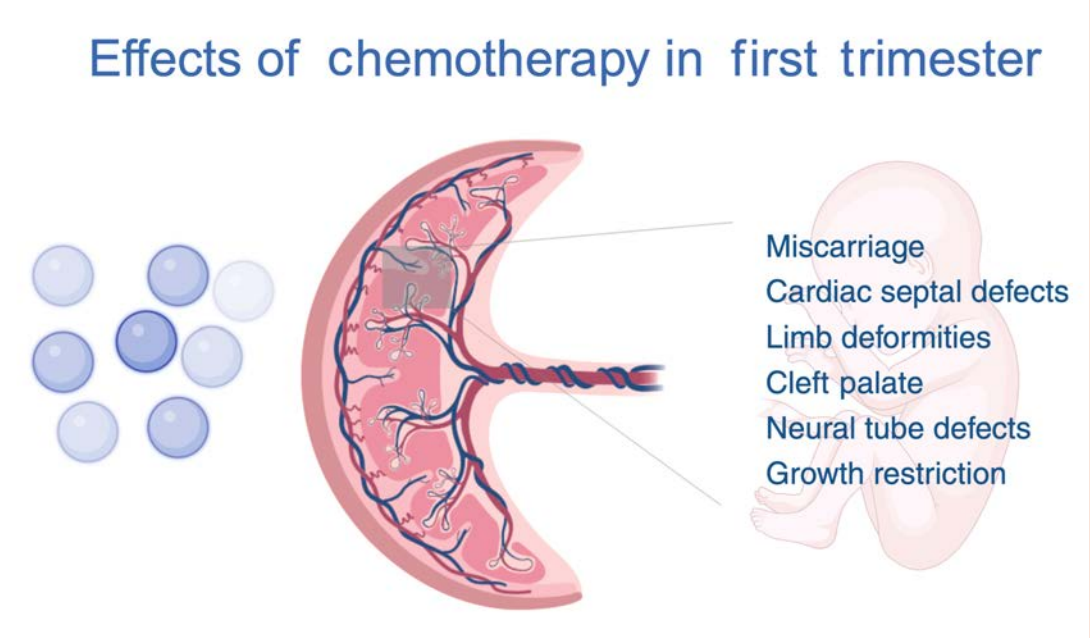


Fig. 4. Chemotherapy agents and their adverse effects in pregnancy.

	Anthracyclines	Alkylating agents	Platinum-based compounds	Antimetabolites	Vinca alkaloids
Examples	Daunorubicin Bleomycin Doxorubicin	Cyclophosphamide Chlorambucil Melphalan Busulfan	Cisplatin Carboplatin	Methotrexate 5-fluorouracil	Vincristine Vinblastine
Mode of action	Inhibits DNA synthesis and function by poisoning topoisomerase, a critical enzyme for unwinding of the DNA for replication and synthesis, thereby causing growth arrest and programmed cell death	Inhibits tumour growth by introducing alkyl groups into DNA, leading to cross-linking of DNA strands that prevents DNA separation, which is essential for replication and transcription	Covalently binds to DNA to form DNA cross-links, thereby inhibiting DNA replication and transcription	Inhibits DNA, RNA, thymidylate and purine synthesis which hampers cell division and function	Disrupts microtubule formation and inhibits microtubule polymerisation to cause mitotic arrest during metaphase and apoptosis
Maternal effects	Cardiotoxicity	Myelosuppression	Nephrotoxicity Neurotoxicity Myelosuppression	Myelosuppression Acute renal failure	Neurotoxicity
Fetal effects	Congenital malformations Miscarriage Prematurity Intrauterine demise (40, 41)	Congenital malformations growth restriction Neonatal pancytopenia (39, 41)	Limited information (41)	Fetal teratogenicity (41)	Fetal teratogenicity (41)

DNA: deoxyribonucleic acid; RNA: ribonucleic acid
Numbers in brackets: refer to REFERENCES

small.[16,42,43] Women with PABC in China were more likely to undergo mastectomy than BCS due to smaller breast sizes.[44] Multidisciplinary input from maternal-fetal medicine specialists, breast surgeons and obstetric anaesthetists is important to optimise maternal and fetal benefit-to-risk ratio. If surgery occurs between 24–30 gestational weeks, the risk of intraoperative fetal compromise and preterm delivery must be discussed, with obstetric and neonatal specialists on standby.[16] Common anaesthetic agents are not teratogenic when used at standard concentrations and for <3 hours. However, caution is required when administering the inhalational agents propofol and midazolam. Intraoperative changes like maternal hypoxaemia, hypercapnia and hypotension can cause uteroplacental hypoperfusion from uterine artery vasoconstriction, and reduced placental perfusion, fetal asphyxia and acidosis, and eventual intrauterine demise.[45] Interpretation of fetal heart rate patterns should include consideration of anaesthetic effects on fetal heart rate and variability.[46] Post-operative thromboprophylaxis is recommended due to immobility and pregnancy-related hypercoagulability.[47]

Although some studies suggest that sentinel lymph node biopsy (SLNB) can be performed safely in pregnancy, the data is limited.[16,40,48] Gentilini et al. estimated that the standard SLNB procedure exposes the fetus to <50 mGy radiation and does not significantly elevate the risk of fetal malformation, intellectual impairment or death.[49] Technicium-99m-labelled colloid is a method used for SLNB that is 99% effective at identifying positive lymph nodes. During surgery, it is injected into the peri-tumour subdermis and a gamma probe is used to identify radiotracer activity.[48] Its short half-life of 6 hours and ability to remain at the injection site minimises fetal radiation exposure.[50] Methylene blue and isosulfan blue dye should be avoided due to potential teratogenic effects and maternal anaphylaxis. The ESMO, NCCN and European Society of Mastology recommend that the decision to perform SLNB should be individualised, and avoided <30 weeks gestation as the specificity and sensitivity is not established in PABC.[16,51]

The postoperative appearance of the affected breast can leave a long-lasting emotional impact, affecting sexuality and body confidence.[52] Immediate reconstruction following mastectomy proffers superior cosmetic results, but increases operating time, blood loss and anaesthesia exposure. Moreover, lactogenesis, glandular hypertrophy and breast tissue expansion may hinder wound healing, making it more challenging to achieve aesthetic results. After breast involution, the changing shape and contour may result in permanent deformation.[24,37] Hence, the European Consensus advises against immediate reconstruction during pregnancy.

Radiotherapy

Radiotherapy should be postponed until after delivery due to potential fetal malformations, mental retardation, growth restriction and fetal loss arising from exposure during pregnancy,[2,16,37] the severity of which depends on gestational age, radiation field and total dose.[53] Radiation exposure during fetal organogenesis (weeks 2–8) may lead to structural malformations when doses exceed 0.1–0.2 Gy.[53] Lower intelligence quotient results from exposure >0.1 Gy (week 8–25), and severe mental retardation may result from exposure >1 Gy.[53] Any fetal radiation exposure may increase the likelihood of childhood cancers.[25] Mazonakis et al. studied total fetal radiation dose after breast irradiation at various trimesters and estimated dose thresholds to be between 2.1–7.6 cGy (first trimester), 2.2–24.6 cGy (second trimester) and 2.2–58.6 cGy (third trimester), depending on the field of exposure. Internal scatter and leakage radiation contribute to these doses, with the degree of scatter affected by the source, treatment field size and proximity to the fetus.[25] With the addition of abdominal lead shielding that reduces radiation exposure by 50–70%, radiotherapy is considered sufficiently safe in the first and second trimesters (2010 international consensus meeting).[24]

The first consideration in treatment planning is whether radiotherapy can be delayed. The risk of local recurrence is approx. 1% for every month of delayed radiotherapy, and a delay of <3 months is considered acceptable. Delaying radiotherapy until after delivery may promote local recurrence, unless the diagnosis is made in the late second or third trimesters, in which case radiotherapy may be postponed without significantly increasing maternal risk. If antepartum radiotherapy is necessary, the dose to the fetus should be calculated prior to the treatment and include modifications to field size, radiation energy, usage of photon energies <25 MV and the use of a lead shield with 4–5 half-value layers.[54]

Endocrine therapy

Tamoxifen selectively inhibits the hormones responsible for promoting tumour growth. Hormone-sensitive BC are stimulated by estrogen and progesterone, and inhibition of these hormones by tamoxifen (a selective estrogen receptor modulator) slows tumorigenesis. Its use

is restricted in pregnancy due to associations with ambiguous genitalia, Pierre Robin sequence and oculo-auriculo-vertebral dysplasia (Goldenhar syndrome) in the fetus.[2,55] Initiation of hormone-receptor modulators should only be used after childbirth and following completion of chemotherapy.[16,50]

Biological agents

The HER2 pathway promotes cell growth and division, but with overexpression, cell growth is accelerated beyond normal limits resulting in tumour formation. Trastuzumab is a monoclonal antibody that targets the HER2 receptors, inhibiting overexpression and limiting tumour growth. HER2 receptors are strongly expressed in fetal renal epithelium, and trastuzumab use reduces fetal urine output resulting in oligohydramnios, which predisposes to fetal limb malformations and pulmonary hypoplasia.[2] The NCCN and ESMO guidelines advise against using biological agents like trastuzumab in all trimesters.[12,16]

Considerations for the fetus

Systemic medications used in pregnancy can be sequestered in amniotic fluid due to maternal water retention, increased plasma volume and hepato-renal perfusion, cytochrome P450 activity and serum albumin levels.[2] To reduce miscarriage, congenital malformation and fetal cardiotoxicity risks in the first trimester, chemotherapy should be commenced after 14 gestational weeks.[2,24] Other gestation-dependent risks include fetal myelosuppression, growth restriction and sepsis. Dose-dense chemotherapy, where standard doses are given with shorter intervals between treatment cycles, may be considered (e.g. every 2 instead of the conventional 3 weeks), although this is supported by limited evidence.[36,56-58]

The care of both fetal and maternal health requires multidisciplinary coordination, involving the obstetrician, medical oncologist and other allied health specialists. Fetal morphology, growth and well-being should be evaluated by ultrasound screening prior to every chemotherapy cycle as per NCCN guidelines.[16,24] Most studies recommend intraoperative fetal monitoring after 22–24 gestational weeks when viability is attained.[59] Maternal haemodynamic stability, oxygenation and temperature control must be optimised to support fetal perfusion. Fetal cardiotocography is advised after each chemotherapy cycle to monitor for preterm contractions.[45] Serial fetal growth surveillance is required following chemotherapy.[50]

Delivery should be planned as close to 37 weeks as possible.[12,16] Fetal maturation and urgency of maternal therapy are both important considerations, as prematurity remains a major risk factor for impaired cognitive development. Vaginal delivery is preferred especially if treatment is incomplete as recovery is faster and there is less delay to recommencing therapy.[60] Caesarean delivery is reserved for obstetric indications. Delivery should ideally be planned at least 3 weeks after the last anthracycline-based chemotherapy for bone marrow recovery and to reduce likelihood of maternal and fetal neutropenia.[36,50,61,62] After 35 gestational weeks, chemotherapy should be avoided as labour may occur spontaneously; neonatal review for intrauterine chemotherapy exposure and placental histopathology (to exclude rare metastases) should be arranged following delivery.[12,24] It is safe to resume chemotherapy 1 week after an uncomplicated vaginal or caesarean delivery.

Breastfeeding reduces BC risk in the general population by 4–5% for every year of lactation.[63] There is a lack of data surrounding women with PABC whose challenges include reduced lactogenesis, breast and nipple scarring, fibrosis and atrophy following breast-conserving surgery, ipsilateral mastectomy or radiotherapy.[64,65] Breastfeeding is not contraindicated after breast conservation therapy, but milk quality and quantity are likely to be affected.[16] Chemotherapeutic toxins are excreted in breastmilk, causing neutropaenia in breastfed neonates.[66] The Academy of Breastfeeding Medicine recommends waiting 7–10 days after doxorubicin and paclitaxel, and 1–3 days for cyclophosphamides before breastfeeding.[41] The Royal College of Obstetrics and Gynaecology recommends waiting 14 days from the last chemotherapy administration before commencing breastfeeding.[4] The NCCN advises against breastfeeding with endocrine therapy, and recommends waiting at least 6 months after completing trastuzumab.[16,66,67] Nevertheless breastfeeding support is critical. Alternative feeding strategies include breastfeeding from the contralateral breast, milk expression without feeding during systemic therapy to maintain production, utilising donor milk, and restricted breastfeeding between chemotherapy cycles.[41]

Postnatal considerations

The postnatal implications of PABC have not been widely studied. Conservative treatment strategies prioritising fetal well-being and causing deferred treatment carry poorer prognosis. An underestimated prognostic factor is the mother's desire to postpone treatment until after delivery, which is more commonly observed among Asian women.[44] Affected women have higher rates of

mental health problems like depression, anxiety, social isolation and self-blame.[68,69] Not being able to breastfeed while coping with the side effects of chemo- or radiotherapy exacerbates these disorders and may impair mother-baby bonding. A small proportion of younger women may resume ovulation after chemoradiation.[70,71] Effective contraception is a critical component of management. Non-hormonal contraceptives like the copper intrauterine device, barriers and tubal ligation are recommended by the NCCN and ESMO.[68] Oral hormonal contraceptive use in women with current or treated BC is contraindicated and is deemed a UK Medical Eligibility Criteria category 4—an unacceptable health risk.[72] Some studies showed that the levonorgestrel-releasing intrauterine system does not increase recurrence risk and may offer endometrial protection in tamoxifen users. However, due to limited definitive data, the NCCN advises against its use.[15,16,73] The Faculty of Sexual and Reproductive Healthcare guidelines state that progesterone-only contraception (POC) can be considered on a case-by-case basis if the woman understands potential recurrence, and in consultation with a specialist, if non-hormonal alternatives are unacceptable or if the non-contraceptive benefits are desired.[74] POC has no adverse effects on lactation for patients who wish to breastfeed.[74,75]

Conception and fertility preservation

The average age of women with PABC is 28–32 years, hence fertility preservation is an important consideration.[76] Amenorrhea occurs in approx. 18–60% of women on cyclophosphamide or anthracycline regimes.[77] Chemotherapy-induced infertility is age-dependent and reflects ovarian reserve and the specific agent used.[78] Older women are at higher risk of infertility and secondary ovarian failure due to diminished ovarian reserve. Chemotherapy further accelerates this by inhibiting DNA synthesis, accelerating primordial follicular apoptosis, decreasing primordial follicle quantity, while indirectly damaging ovarian stroma tissue via vascular spasm, reduced ovarian circulation, and (particularly with doxorubicin) microvascular damage and acute ischaemia.[19] Anti-metabolites and vinca alkaloids do not cause DNA damage and present a lower risk of follicular depletion.[6]

Prior to chemotherapy, women desiring future childbearing should be referred to fertility specialists to discuss ovarian tissue cryopreservation, or oocyte or embryo freezing.[79] Unlike embryo freezing, oocyte or ovarian tissue freezing does not require fertilisation or a sperm-donor at the point of time of the procedure, making it suitable for patients without partners.[79] Ovarian tissue collection and transplantation are laparoscopic procedures with low surgical complications rates of 0.2–1.4%,[79] and is preferred for women ≤36 years or requiring urgent treatment with insufficient time for ovarian stimulation.[79] There is little data regarding appropriate intervals between treatment, cryopreservation and reproductive outcomes.[79] Oocyte preservation involves approx. 2 weeks of ovarian stimulation and reproductive outcomes are dependent on ovarian reserve.[79] Risks include ovarian hyperstimulation syndrome and an increased risk of bleeding and infection.[79] Oocyte preservation using estrogen-ovarian stimulation was conventionally expected to accelerate growth of ER positive tumours.[80,81] Recent studies however demonstrate equivalence in survival and recurrence rates between PABC women with and without ovulation induction.[82] Alternative stimulation protocols employ tamoxifen or aromatase inhibitors like letrozole.[80] Women also have the option of natural ovulation cycles for oocyte preservation. In vitro maturation of immature oocytes is a quicker alternative and may benefit women who are unable to undergo ovarian stimulation.[83] It eliminates risks associated with ovarian stimulation but results in poorer embryo quality and reproductive success rates.[83]

Prognosis and outcomes

As most recurrences occur within 2 years of diagnosis, pregnancy avoidance is recommended until >2 years from remission.[84] The effects of a future pregnancy on the risk of PABC relapse is uncertain, as <10% of women continue to have subsequent pregnancies.[2] A meta-analysis of 30 studies and 3628 women with PABC reported poorer prognosis and higher recurrence risks than non-pregnant and non-puerperal BC patients,[40] attributed to delayed diagnosis and longer duration for tumour growth and metastasis.[24,67] A study of 1174 women demonstrated higher survival rates with increasing intervals between pregnancy and cancer diagnosis, at 38%, 51% and 60% for the intervals of ≤12, 12–48 and >48 months postpartum, respectively. A comparison with age-matched controls found that the survival rate of non-PABC women was 65%.[85]

It is uncertain if pregnancy itself influences BC biology. During the remodelling phase of breast involution, the pro-inflammatory wound healing microenvironment together with rapid collagen deposition and extracellular matrix remodelling is believed to drive tumour growth.[86] Pregnancy appears to result in short-term increases in BC risk within 5 to 10 years postpartum.[87] A Swedish nationwide cohort study of 12,666 patients with BC and 61,121 age-matched controls reported

higher odds of developing BC in parous women 15 years after childbirth than in nulliparous women.[87]

Future research

There is a lack of consensus on optimal chemotherapy regimens in PABC due to tertiary centres using varying protocols and a dearth long-term longitudinal studies. More research is needed to fully characterise the psychological impact of PABC on the mother. Existing data mainly comes from high-income countries, and research involving women in minority populations and low-to-middle-income countries is urgently required.

CONCLUSION

Due to increasing maternal age and other socio-biological determinants, PABC is increasingly diagnosed, often at advanced stages as pregnancy-related physiological changes delay diagnostic processes. As a result, PABC carries an overall poorer prognosis compared to non-pregnant BC. Imaging modalities for diagnosis and staging are generally safe in pregnancy and minimal delay in instituting therapy should be the goal. PABC must be managed by multidisciplinary teams at tertiary medical centres with access to surgery and chemoradiation therapies. Protocols must include safe management and delivery of the fetus, contraception and future fertility planning, and consider the psychosocial ramifications of this diagnosis.

Ethics statement

Not applicable.

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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COMMENTARY

Re-evaluating adjuvant systemic therapy in cancer treatment: Scientific rigour to guide policy and practice

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ABSTRACT

The landscape of adjuvant treatment in cancer care is rapidly changing. Recent randomised trials have led to regulatory approvals for neoadjuvant and adjuvant hormonal agents, targeted therapies and immune checkpoint inhibitors. This has brought about increasing complexity in this space, challenging previously established paradigms of adjuvant treatment. As these treatments are increasingly implemented, healthcare systems around the world face the challenge of critically appraising these studies and determining whether the treatments proposed provide clinically meaningful benefit. This article considers the validity of these data in the context of fundamental principles of adjuvant therapy, as well as the scientific rigour of the relevant registration trials. We propose a greater role for practising oncologists in the regulatory and reimbursement process, using the Singaporean context as an example.

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Keywords: adjuvant therapy, cancer, drug approvals, oncology, quality of life

INTRODUCTION

In the 1980s, perioperative chemotherapy succeeded in improving survival for children with osteosarcoma and validated a fundamental premise: eradication of micrometastatic disease reduces distant relapse and improves survival for a proportion of patients with solid tumours undergoing curative surgery.[1] This data was built upon preclinical insights suggesting that cytotoxic chemotherapy is more effective against the extremely low burden of disease in early solid tumours compared with macroscopic high burden metastatic disease.[2] Since then, the efficacy of adjuvant chemotherapy has been replicated across tumour types though the absolute magnitudes of benefit were generally modest. Today, adjuvant chemotherapy is enshrined as a curative standard of care in the treatment of many solid organ malignancies.

The advent of other modalities of systemic therapy effective in advanced disease—endocrine therapy, tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs)—provided impetus to evaluate these in the adjuvant setting. The expanding options necessitate critical reappraisal of therapeutic value in concordance with fundamental aims of adjuvant therapy and appropriate standards of scientific validity.

Adjuvant endocrine therapy

The development of adjuvant endocrine systemic therapy in breast cancer followed on from longstanding knowledge about the therapeutic value of oophorectomy in the treatment of advanced disease. Initial trials of adjuvant endocrine therapy employed ovarian radiation[3] with the subsequent development of tamoxifen in the 1960s laying the foundation for the demonstration of reductions in breast cancer mortality with adjuvant tamoxifen[4] and subsequently aromatase inhibitors.[5] Given its lower acute and cumulative toxicities relative to cytotoxic chemotherapy, various extended durations of tamoxifen were evaluated starting in the 1970s. The demonstration of improved long-term efficacy with longer durations of therapy[4,6] is probably contributed by the proven preventive benefit of endocrine therapy in a hormonally driven cancer;[7] eradication of micrometastatic disease is necessarily an early process unlikely to be enhanced by protracted treatment.

Adjuvant TKI therapy

The first TKI to show overall survival (OS) benefit as adjuvant treatment for a solid tumour was imatinib for high-risk gastrointestinal stromal tumours (GIST). In the SSGXVIII/AIO study, 3 years versus (vs) 1 year of adjuvant imatinib improved 10-year relapse-free survival (RFS) (52.5% vs 41.8%) and OS (79% vs 65.3%).[8] In this case, delaying recurrence with longer adjuvant treatment translated into OS benefit due to identical post-progression survival in both arms, which is comparable to that achieved in first-line treatment

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of advanced disease. The majority of initial GIST recurrences following imatinib discontinuation remain sensitive to salvage imatinib,[9] likely arising from residual primary microscopic disease rather than pharmacologically-selected resistance. Additionally, the range of salvage therapies available following imatinib progression are limited. These factors also contribute to relatively uniform treatment following relapse.

The evidence in support of adjuvant TKIs in common cancers recently receiving regulatory approval is arguably more controversial. In ADAURA, 3 years of adjuvant osimertinib was compared against placebo in resected stage IB-IIIA epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). In a preplanned analysis of OS as a secondary endpoint, 5-year OS was 88% (95% confidence interval [CI] 83–91) in the osimertinib group and 78% (95% CI 73–82) in the placebo group).[10] However, only 38.5% of patients in the control arm received osimertinib upon relapse, with 56% receiving earlier-generation anti-EGFR TKIs as salvage therapy.[11] Osimertinib has superior efficacy compared with earlier-generation anti-EGFR TKIs and is established as the preferred standard of care in metastatic disease.[12] In the absence of mandatory crossover to provide all patients in the control arm access to osimertinib at progression, the validity of the OS benefit remains questionable since most patients in the control arm were not optimally salvaged at relapse.

In the monarchE study, evaluating women with hormone receptor-positive, human EGFR 2–negative, node-positive, high-risk early breast cancer (HR+ HER2- EBC), 4-year disease-free survival (DFS) with 2 years of adjuvant abemaciclib combined with endocrine therapy was 85.8% (95% CI 84.2–87.3) compared with 79.4% (95% CI 77.5–81.1) with endocrine therapy alone.[13] This trial was however plagued by methodological concerns summarised by Meirson et al., including unspecified post-progression therapy in controls, inappropriate clinical endpoints and informative censoring.[14] For example, imbalance in the number of early dropouts between the 2 arms without clearly specified reasons for this unequal attrition raises the possibility of dropout being related to treatment allocation and their outcomes differing. In such a scenario, sensitivity analyses reveal the already modest absolute benefit in DFS to be further diminished.[14] Similar to ADAURA, the rationale for protracted therapy is also unclear, given the absence of a mechanistic basis or empirical evidence for inferior outcomes with shorter durations of treatment, as distinct from the situation in adjuvant endocrine therapy in breast cancer and adjuvant imatinib in GIST as discussed earlier.

The well-deserved legitimacy of randomised controlled trials as the preeminent form of scientific evidence in biomedicine is predicated upon the proper interpretation of trial results, considerations for which extend beyond the completion of study accrual and achievement of a statistically positive finding. Suboptimal post-relapse therapy in controls and informative censoring can undermine the original randomisation to introduce differences between the experimental and control groups that account for observed differences in outcome. While limited techniques exist to mitigate such post-randomisation confounding (e.g. sensitivity analyses based on differing assumptions about the cause of drop-out imbalances to interrogate the possibility of informative censoring), the most crucial element may be a careful interpretation of trial results to account for the inevitable limitations of any scientific study, especially when critical decisions regarding access to treatments need to be made.

These issues of scientific validity stand above and apart from concerns regarding the toxicities and costs of protracted pharmacologic therapy. The cost-effectiveness of these adjuvant treatments have been questioned in published analyses.[15,16] With regard to health-related quality of life, while no measurable impairment has been demonstrated with these TKIs,[17,18] it is inescapable that non-physical forms of toxicity (e.g. time toxicity and indirect costs) will be increased in patients subjected to treatment for several years compared to those who are not. In patients with relatively more common cancers like resectable EGFR-mutated NSCLC and HR+ HER2- EBC, the cumulative costs to individuals and society will be considerable.

These concerns are brought into sharper focus by the recent LAURA study, which demonstrated a progression-free survival benefit with indefinite "adjuvant" osimertinib for unresectable stage III EGFR-mutated NSCLC following concurrent chemoradiotherapy.[19] While we await OS results, an important issue to address is how this study strains, if not outright ruptures, the fundamental concept of adjuvant therapy. The aim of adjuvant treatment is to achieve a cure through disease eradication; the inescapable corollary is that it must be time-limited, because treatment should not be given for a disease that no longer exists. Indefinite treatment conforms to a suppressive therapeutic posture more consistent with early palliative therapy rather than disease eradication. If survival is eventually improved, does distinguishing adjuvant from

palliative really matter, or is it merely semantic hair-splitting? We argue the former because of the prognostic, policy and reimbursement implications of labelling a therapy curative. Evidence from chronic myeloid leukaemia (CML), the prototypical molecularly defined disease amenable to rational targeted therapy, provides a useful reference. In CML, indefinite treatment has resulted in patients achieving survival comparable to the general population.[20] Despite these successes, molecular and clinical cure in CML is discussed only in the context of achieving a treatment free remission.[21] Indefinite systemic therapy is mechanistically and procedurally incompatible with a curative treatment approach.

Adjuvant ICI therapy

The transformative impact of ICI in the treatment of many malignancies has fueled multiple studies and approvals for adjuvant ICI, though many questions remain. While adjuvant ICI has demonstrated DFS benefit in stage III and high-risk stage II melanoma, OS benefit remains to be demonstrated.[22,23] Given the long-term remissions indistinguishable from cure achieved with ICI for a fraction of patients with metastatic disease,[24] demonstration of OS benefit with adjuvant ICI is arguably especially critical. Mechanistically, ICIs may work best when there are sufficient tumour cells to facilitate T cell clonal expansion.[25] This should privilege the evaluation of neoadjuvant ICI, possibly reducing toxicity, inconvenience, cost and allowing for earlier recognition of futile therapy. To this end, the recently reported NADINA trial represents an important advance, demonstrating that 2 cycles of neoadjuvant ICI (in whom only patients with suboptimal response received further adjuvant treatment) is superior to 1 year of adjuvant ICI for macroscopic stage III melanoma.[26] Such evaluations should be extended to earlier melanoma stages where DFS benefit has been shown with 1 year of adjuvant ICI.

Disentangling the incremental benefit of adjuvant over neoadjuvant ICI therapy is especially challenging in the setting of resectable NSCLC. Multiple completed and ongoing trials use a variety of designs, none of which definitively establishes the most parsimonious approach to effective perioperative curative therapy with ICI. This has led to FDA approvals for neoadjuvant, adjuvant and perioperative ICI in NSCLC.[27] Approval was mainly based on pathological complete response rates, event-free survival or DFS, raising the recurring question around the validity of such surrogates for OS. KEYNOTE-671 is currently the only study demonstrating OS benefit with perioperative ICI in resectable NSCLC.[28] In this study, neoadjuvant pembrolizumab combined with chemotherapy followed by adjuvant pembrolizumab achieved a 3-year OS of 71% (95% CI 66–76) compared with 64% (95% CI 58–69) with neoadjuvant chemotherapy alone in resectable stage II to IIIB NSCLC.[28] It is unfortunate that KEYNOTE-671 did not have a third arm with neoadjuvant ICI alone, to clearly define the additional value of adjuvant ICI. Clarifying this should be an urgent academic and regulatory priority, to ensure patients receive the optimal duration of perioperative ICI. Additionally, concerns about suboptimal salvage therapy in the control arm are also relevant to this study, with subsequent ICI therapy used in only 50% of the control group at time of relapse; again, this raises questions about the validity of the OS benefit reported. Indeed, a recent study confirms the likely widespread prevalence of this form of post-randomisation confounding, with only 12% of oncology studies reporting OS accounting for post-progression therapies.[29]

In the case of another immunogenic cancer, renal cell carcinoma (RCC), 1 year of adjuvant pembrolizumab following surgery for intermediate to high-risk RCC achieved 4-year OS of 91.2% (95% CI 88.3 to 93.4) compared against 86.0% (95% CI 82.6 to 88.8) with placebo.[30] Once again, however, concerns of informative censoring and suboptimal exposure to ICI at salvage in the control arm have been highlighted.[31] Furthermore, other studies evaluating adjuvant ICI in RCC patients with similar risk profiles did not demonstrate improvement in DFS or OS.[32] Situating the positive results of a flawed trial within the context of multiple negative trials, the OS benefit demonstrated in KEYNOTE-564 is considerably less compelling.

The Singaporean context: Cancer drug list

In spite of these concerns around scientific and clinical validity, these adjuvant treatments have received broad regulatory approval and are included in the treatment guidelines of the leading international professional oncologic societies like American Society of Clinical Oncology and European Society of Medical Oncology. How, then, should clinicians navigate this apparent incongruity? In Singapore, the nascent health technology assessment (HTA) landscape provides a potential avenue for cancer healthcare professionals to be more involved in optimising access to high value cancer therapies. In 2022, the Ministry of Health (MOH) in Singapore introduced the cancer drug list (CDL), a curated list of cancer drugs that are approved for reimbursement through insurance

or governmental subsidies according to strictly specified indications and lines of therapy. The assessment is usually initiated by pharmaceutical companies through a company-led submission, setting in motion a comprehensive evaluation that informs the ultimate funding decisions by the MOH Drug Advisory Committee.[33] One component of this process involves engaging subspecialty cancer experts as members of a Cancer Drug Subcommittee to determine clinical appropriateness of specific therapies based on scientific and clinical evidence, independent of cost-effectiveness. Instead of relying only on subspecialty expert clinicians, we suggest that cancer physicians from a broad range of subspecialties as well as non-cancer physicians and scientists from related specialties (epidemiologists, statisticians, family physicians), be directly involved in providing the clinical expert opinion component of the HTA. This will help ensure legitimacy of evaluations in adherence to fundamental principles of biomedical evidence and cancer therapeutic principles, consistency of decisions across multiple cancer subtypes, as well as independence and sophistication of appraisals beyond statistically positive trial results. Relying only on subspecialty experts can potentially lead to scientific scrutiny of insufficient breadth and rigour, as well as possible biases accruing from vested interests in expanding subspecialty-specific therapeutic options. Increasing the breadth and depth of academic and clinician engagement in these deliberations would lend an added safeguard to the scientific legitimacy of cancer treatment access tailored to Singapore's care needs. Considering the universal value of upholding scientific rigour in assessment of medical evidence, it is plausible that such measures would also reap benefits in other healthcare systems with different HTA mechanisms at varying levels of maturity.

CONCLUSION

The modest absolute improvements in outcome accruing from most adjuvant systemic treatment confirms that the majority of patients will have their outcome (relapse or cure) unimpacted by such therapy—adjuvant treatment necessarily subjects all patients to the toxicity and inconvenience of treatment so that only a fraction will derive benefit. Novel adjuvant therapies purporting to provide meaningful therapeutic value should thus meet the very highest standards of scientific and clinical validity, especially since such treatments are accorded a high degree of legitimacy and priority as part of a curative treatment approach. If and when they fall short, such shortcomings should be acknowledged and access to such therapies appropriately constrained. To this end, the emerging mechanism of HTA in Singapore provides oncologists and other cancer physicians a chance to play a more substantive role in ensuring that access to adjuvant systemic therapy is optimised for the benefit of patients and society.

Ultimately, what is our role as oncologists? Are we advocates and guides for individual patients or guardians of finite public goods that need to be rationed? We venture the answer to be both, though the undoubted occasional tension between these 2 roles needs to be navigated judiciously. Perhaps we can assert what our role should not be—uncritical dispensers of pharmacologic agents at the whim of regulators, industry and individuals. The fear is that we are caught in the vortex of a positive feedback loop, with low levels of trust between patients and physicians diminishing the legitimacy of clinical interactions in favour of guidelines and regulatory approvals, leading to more automatic and less nuanced guideline abidance at the bedside, diminishing trust even further. It is time for cancer physicians as a community to short-circuit this self-defeating loop through active participation in local regulatory and reimbursement processes as part of our effort to ensure cancer patients receive the highest quality of treatment available.

Ethics

Not applicable.

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.

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COMMENTARY

A person-centred approach to decision-making and care for persons living with dementia

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ABSTRACT

Global population ageing will increase the prevalence of cognitive impairment and dementia. Persons living with dementia (PLWDs) often face complex care and medical needs that entail carefully considered decisions. The current framework for decision-making prioritises mental capacity, personal autonomy and best interests. PLWDs are assessed on whether they possess the mental capacity to make informed decisions and if not, healthcare professionals (HCPs) will act in their best interests. However, as decision-making capability exists in a continuum and varies depending on the complexity of the health issue, there may be subjectivity among physicians in categorising PLWDs into those with or without mental capacity, especially in borderline cases. Furthermore, such a binary and reductive approach may not secure the best outcomes if conducted in a legalistic manner. PLWDs deemed to possess mental capacity are allowed to make decisions that may be detrimental to themselves while those assessed to lack mental capacity have unwelcome decisions imposed upon them. This paper proposes a person-centred framework that promotes relational autonomy so as to enable PLWDs to express their values and preferences in a manner that serves them best. The framework is a convenient guide in helping HCPs enable PLWDs to have a better hold on to their personhood and agency, and balance the demands of upholding autonomy with best interests.

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Keywords: autonomy, best interests, dementia, decision-making capacity, medical ethics, mental capacity, person-centred

INTRODUCTION

Assessing mental capacity in persons living with dementia (PLWDs) in high-stakes decision-making is becoming more frequent amid an ageing population with a rising prevalence of cognitive impairment and dementia. A study estimated that the population of PLWDs globally will almost triple by 2050.[1]

Among the 4 ethical principles—autonomy, beneficence, non-maleficence and justice—the primacy of autonomy[2] draws from John Stuart Mill's perspective that individual rights should only be infringed to prevent harm to others and is underpinned by the presumption of agency—that individuals make decisions based on their free will.[3]

However, agency presupposes mental capacity. It is noteworthy that the 4-step mental capacity test (understanding, recalling, weighing and communicating) is liable to examiner bias and inter-observer subjectivity in borderline cases.[4] Furthermore, autonomy may conflict with the other ethical principles, for instance, non-maleficence, which seeks to do no harm, and beneficence, which is to do good. Examples include a patient who refuses a beneficial treatment plan, or wants a potentially harmful discharge against medical advice. The following scenario below depicts the tension in balancing PLWD's agency with beneficence.

Case scenario

Mr. Edward, who has mild dementia, diabetes mellitus, knee osteoarthritis with gait instability and end-stage renal failure on dialysis, was admitted for a head injury post-fall and pneumonia. Prior to admission, he lived alone but could navigate his neighbourhood and handle simple finances. His sister, who visited him monthly, helped to coordinate his medical appointments but was busy with a full-time job. During his hospital stay, he displayed bouts of emotional outbursts, refusing medications and on occasions, rejected dialysis. Although he appreciated the risks of staying alone given his recurrent falls and declining health, he stated he "values his freedom over everything else". He was unable to elaborate how he would cope at home and mitigate the risks. When confronted with a life-threatening event alone at home, he became teary, and said he "entrusted all to God" and believed he would be "protected from harm".

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Challenges in the case scenario

Determining what is best for Mr. Edward entails finding the balance between upholding his agency and preferences, and safeguarding beneficence and non-maleficence. His desire to live alone poses hazards to his well-being, but overriding his wishes should he be deemed to lack of mental capacity risks consigning him to institutional care against his will.

Furthermore, there is ambiguity regarding Mr. Edwards' capacity. Although he demonstrates some ability to appreciate the consequences of the choices at hand and weigh the situation, he resorts to leaps of logic, becomes emotional and espouses magical thinking. Such thinking may also be influenced by personal, cultural and spiritual beliefs, which may be challenging for external parties to fully appreciate.

As Appelbaum and Grisso acknowledge, "the evaluation of competence does not…lead to unambiguous ratings of 'no ability' or 'full ability' on all dimensions. On the spectrum of functional impairment, most patients fall somewhere in the middle".[3] Unfortunately, the current medical-legal framework adopted in the UK and many Commonwealth countries conflates these complex assessments into capacity/incapacity binaries, leaving physicians with limited room to manoeuvre within these ambiguities.[5]

A proposed person-centred framework

Our approach is based on person-centred care (PCC) (Fig. 1) to better operationalise the principles of patient autonomy and beneficence in decision-making for PLWDs. PCC, per the American Geriatric Society, involves eliciting "'individuals' values and preferences…supporting their realistic health and life goals…informing decision-making to the extent that the individual desires."[6] This involves a departure from hyper-cognitivism and hence mental competence to recognising the intrinsic value of and common equality among persons. It also draws on a more expansive understanding of personhood based on enhancing relational autonomy.

Even as PLWDs lack advanced cognitive capabilities, they still possess inalienable interests, including the capacity for sadness, suffering and a "sensitivity to the behaviour" of those around them,[7] and therefore deserve the right to be respected, taken seriously and be themselves.[8] Autonomy should be broadened to social and relational roles, to better encapsulate individual nuances and support the exercise of agency in PLWDs.

The proposed approach involves appreciating the PLWD's prior preferences, values and beliefs, as well as the severity of cognitive impairment. Thereafter, ways to facilitate agency can be explored. It would entail managing ambivalence, promoting relational autonomy to support the preferences of PLWDs and enabling dyadic communication.

(1) Managing ambivalence

Mr. Edward demonstrates ambivalence in his care options: he wishes to return home and continue independent living yet refuses to stay in the hospital to receive the necessary treatment and rehabilitation to achieve it.

Navigating ambivalence requires identifying the underlying mental state, namely, whether patient is avoiding conflict, indecisive, displaying mood fluctuations, apathetic or whether he is truly ambivalent.[9] For Mr. Edward, he has conflicting preferences: refusing to be hospitalised longer even though he appreciates his need for treatment. Prolonged hospitalisation has also increased his frustration and fuelled his low mood and agitation, heightening his impulse to go home without regard of the consequences.

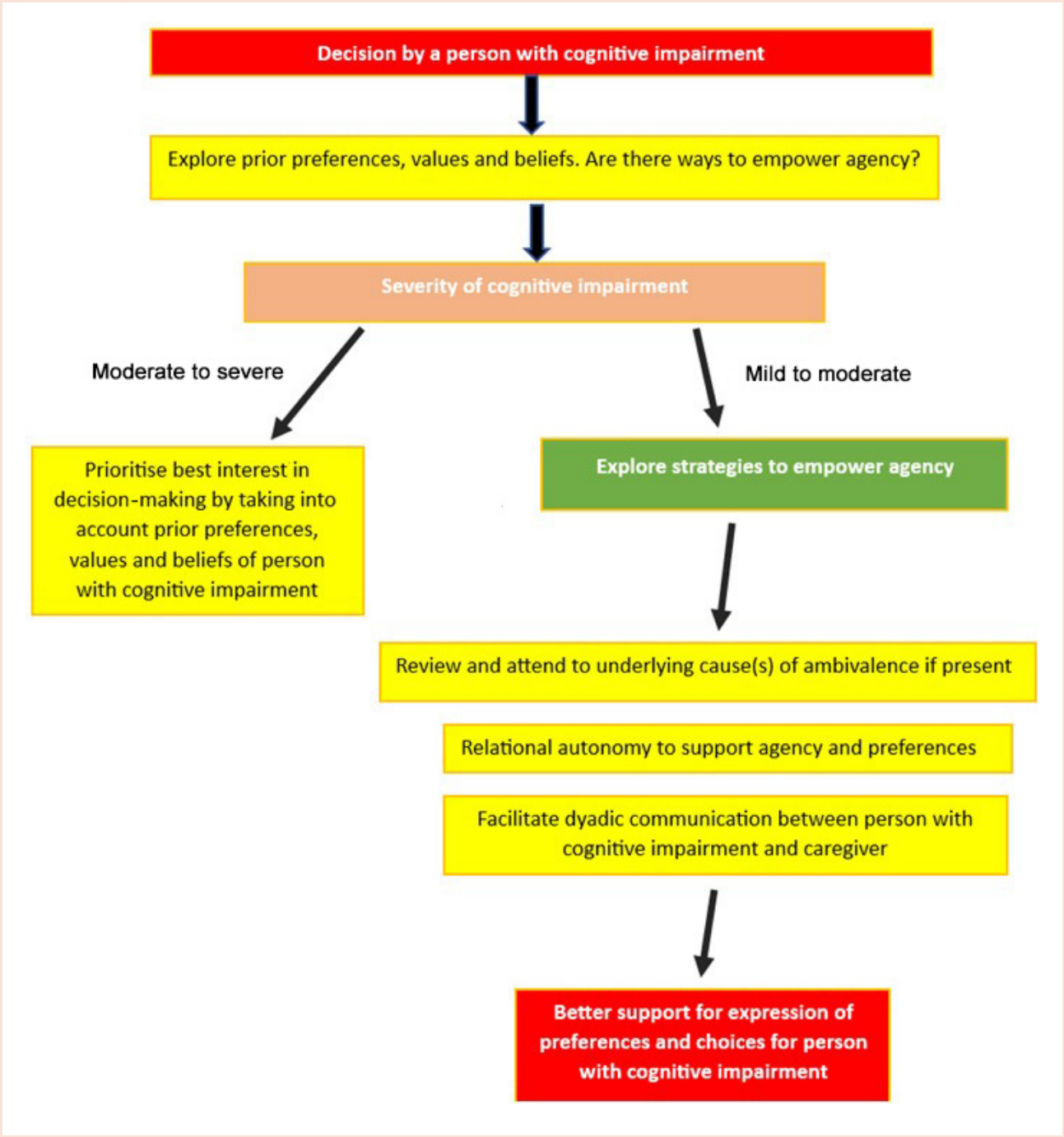
Managing ambivalence involves reviewing whether the label of "ambivalence" is secondary to any miscommunication or misunderstanding.[10] If there is genuine ambivalence, strategies include discussing the consequences of the decisions, allowing space and time to come to an optimal decision, avoiding undue pressure to make a premature decision and not labelling patients as difficult.[9] It might be useful to consider a short duration of home leave to satisfy Mr. Edward's desire to go home, which could provide greater clarity on whether he can continue to live on his own with the necessary home assistance and support put in place.

(2) Relational autonomy to promote agency and preferences

HCPs and caregivers can draw on relational autonomy to enable agency in PLWDs. Relational autonomy recognises that agency may be undermined in vulnerable populations by societal structures, norms and expectations.[11] It argues that self-determination requires access to significant social goods and opportunities to make meaningful choices.[12]

For Mr. Edward, a relational autonomy model recognises that social structures can help or hinder him from expressing his preferences, such as lacking a dedicated caregiver and transportation to and from dialysis. His inability to self-govern

Fig. 1. Proposed model of person-centred decision-making for persons living with dementia.



is contributed by the lack of familial relationships and community assistance to support his choices. Conversely, PLWDs with strong familial or social support are better able to express their autonomy and live according to their preferences. Improved home-based care services can better support PLWDs to age-in-place, while policies such as transport arrangements and subsidies for home medical services can allow PLWDs to better access healthcare without institutionalisation.

Therefore, supporting PLWDs' agency entails allowing them to exercise their personal preferences in day-to-day living, empowering them through dyadic relationships with close caregivers, and tailoring the approach according to severity of the cognitive impairment. PLWDs can hold on to longstanding values, beliefs and preferences that direct their healthcare and lifestyle choices,[13] and through this, express their agency.[14] Familial caregivers familiar with the person's personality and

biography can help identify long-standing preferences and beliefs, to enable preference-based care.[15]

Preference-based care respects PLWDs' preferences as a reflection of their values, biographies and personalities, and adjusts the physical and social environment to meet these needs. Some examples to assess preferences include the Preference for Everyday Living inventory, which includes aspects such as hobbies, social interactions, personal grooming, caregiving choices and healthcare behaviour of persons with cognitive impairments.[16] However, these standardised tools may not specifically target the Asian population given the unique sociocultural context.

(3) Promoting dyadic communication

Caregivers, often familial ones, can journey with PLWDs as dyads. In the Asian context, with strong emphasis on filial piety and familial relationships, these family members form repositories of memory, cueing the person to important anniversaries, milestones and events, as well as routines and rituals to support the exercise of their agency.[17] Other forms of collaboration include developing new means of communication, for instance, through body language or code words for persons stricken with aphasia, or providing navigation for those with visuo-spatial impairments. Close kin and friends will also be familiar with and thus able to respect and support the expression of religious and spiritual beliefs of the PLWD. If there are no close kin or neighbours to assist, the PLWD can turn to befriender or volunteer services.

In this way, caregivers help PLWDs retain personhood by maintaining a coherent biography and value structure, through the "telling, retelling and checking of stories out of which identity is built".[18] For Mr. Edward, a potential dyad is his sister, with whom he shares a close relationship. She is already performing roles to help support his independence in the community by scheduling his medical appointments and can step up further as he inevitably declines to fulfil his preference of ageing-in-place at home.

However, care must be taken to prevent paternalism, where the caregiver dominates the relationship, oversteps boundaries and takes over roles that the PLWD can still perform. For example, caregivers should seek permission from the PLWD before assisting in custodial care activities such as bathing; and when that is no longer feasible, to provide a request, explanation and expression of concern in respect for personhood.[8]

Tailoring the framework to the severity of dementia

Even a limited level of agency is challenging for persons with advanced cognitive impairment, such as patients with severe dysphasia or who are very disoriented and out-of-touch with reality. HCPs, however, must be mindful to support non-verbal or alternative forms of agency such as body language and facial expression, in appreciating the PLWD's intentions and preferences, and not "conflate" "language with rationality".[19] In addition, for PLWDs with more severe cognitive impairment, caregivers can be more mindful of prior preferences, values and beliefs. In contrast, for PLWDs with milder cognitive deficits, strategies should draw more on relational autonomy and dyadic communication.

CONCLUSION

In "Holding one another in a time of dementia", Lindemann, writing a narrative about a family's interaction with a grandmother in the thralls of dementia, shows that through small acts of caring or holding, families can construct and rebuild narratives that allow PLWDs to demonstrate moral agency and what they value.[20] Such agency can have significant meaning for PLWDs and their caregivers, allowing them to express their intrinsic humanity, dignity and value.

A more expansive person-centred model based on agency and relational autonomy can help PLWDs negotiate complex care and medical decisions in a manner consistent with their personal values and preferences, by upholding their personhood and identity, while protecting their best interests. Such a model also dovetails with Asian values emphasising communitarian, collectivist and family-oriented values, which can be facilitated by relational autonomy and dyadic communication.

Ethics statement

Not applicable.

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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LETTER TO THE EDITOR

Implementing a fantasy space-themed video distraction programme to reduce sedation in paediatric MRI

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Dear Editor,

Magnetic resonance imaging (MRI) is an important diagnostic imaging modality, especially in children where radiation exposure is an important concern. As children undergoing MRI scans need to lie still for an extended period of time in an environment with loud noises, sedation is often required.[1] However, its use comes with risks of adverse cardiorespiratory events[2-3] and utilisation of hospital resources when children are admitted for monitoring post-sedation. Optimising the MRI environment, distraction techniques and the use of mock scanners minimises the need for sedation in children.[4-8] A multifaceted approach, which combines these components, has been shown to be effective in children as young as 4 years old.[9-10]

A prospective cohort study was performed from 1 April 2018 to 31 December 2020 in National University Hospital, Singapore as a pilot for children undergoing MRI scans with the combined use of video distraction and an immersive fantasy space-themed environment (FSTE). The primary outcome of interest was to determine if FSTE could help children undergoing MRI scans avoid sedation, and the secondary outcome was to determine the contributing factors to that.

Given that an MRI machine emits loud noises and has a circular body, similar to a space shuttle, a space-themed environment was chosen. Prior to this pilot, the patients who were referred to the paediatric sedation team for MRI scans would all receive sedation. As part of this study, patients aged between 4 and 11 years, who were more likely to benefit from theme-based simulations,[9-10] and had been referred to the paediatric sedation service for MRI scans were eligible for study inclusion, while patients who were critically ill were excluded. All those recruited still underwent fasting for 6 hours and intravenous cannulation to prepare for sedation in case the child could not cooperate.

Upon recruitment, a preparatory brochure (Fig. 1A) and a preparatory video (Fig. 1B) (https://www.youtube.com/watch?v=pm67chS9F-A) produced by the study team were introduced to the patient to prepare for the scan. The preparatory brochure provided parents with information on what to expect on the day of the scan, whereas the preparatory video briefed the child through an immersive experience.' On the day of the scan, the patients were brought down 30 minutes prior to their scan to begin the FTSE in the pre-lift-off room that had been refurbished to simulate a space station (Fig. 1C) where they could put on customised space suits (Fig. 1D), practice lying still in a mock tunnel that simulates the MRI machine and view the preparatory video. Football helmets were provided to simulate the head coils used in head/neck MRI scans (Fig. 1E). Specially designed floor stickers then guided children from the pre-lift-off room to the MRI scanner. In the scanner, movies were screened using an MRI-safe mirror projection system (Figs. 1F–G). All patients received a certification of completion of space mission as a reward.

Prospective patient clinical and demographic data were obtained following informed consent of patients enrolled into the programme. Recruited parents and/or caregivers also completed survey questionnaires at the end of the scan procedure. These questions pertained to the amount of time spent for preparation for the scan procedure, how comfortable and enjoyable the experience was,

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Fig. 1. Graphic description of the fantasy space-themed experience.

(A) Preparatory brochure given to parents; (B) educational video produced by the study team made publicly available on YouTube; (C) pre-lift-off room with space station-themed wall sticker and lighting decorations; (D) customised spacesuits as part of space-themed fantasy; (E) American football helmets provided to simulate head coils used in head and neck MRI scans; (F) external mirrors used to reflect the image from the wall-mounted screen so that upright images of movies can be viewed; (G) graphic description of MRI-safe mirror projection system.

rated on a scale from 1 (least comfortable/enjoyable) to 9 (most comfortable/enjoyable), and reasons why they were successful or unsuccessful. Statistical analysis was performed using STATA version 14 (College Station, TX, US) with statistical significance set at $P<0.05$.

Sixty-seven children between the ages of 4 and 11 years were enrolled into the programme. The mean age at time of enrolment was 6.8 years; male:female distribution was 1:1.16. Moreover, 74.6% avoided sedation for their MRI scans (Table S1). Notably, 21 out of 29 patients who had previously required sedation for their MRI scans, avoided sedation with FTSE, including a child who previously had 7 MRI scans performed under sedation.

Patients who completed MRI scans without sedation had significantly higher parent-reported satisfaction scores with a mean enjoyment score of 7.3 ± 1.7 compared to a mean score of 4.9 ± 2.7

(95% confidence interval [CI] 3.6–6.3, $P<0.001$) in the group that eventually required sedation. Patients who completed MRI scans without sedation also did so more comfortably with a mean comfort score of 7.0 ± 1.9 while those who required sedation reported a significantly lower score of 5.2 ± 2.8 (95% CI 3.7–6.6). Despite failing the interventions and requiring sedation, 52.9% (9/17) of these patients responded favourably that the programme had benefited the children overall. Parents of all 29 patients who had previously undergone MRI scans also responded favourably that the study scan experience was better than their previous experience, even though 27.5% (8/29) of them eventually still required sedation.

There were 26.9% (18/67) patients in the study with underlying neurodevelopmental conditions affecting cognitive function and behaviour, including 7 with epilepsy, 3 with autism and 1 with attention deficit hyperactivity disorder. Of them, 50% (9/18) successfully completed the scans without sedation.

The success of this pilot suggests that video distraction in an immersive FSTE helps to reduce the need for sedation in children undergoing MRI scans, including children with neurodevelopmental conditions. A Swedish case-control study incorporated video distraction as a strategy, where 30 out of 33 children in the intervention group underwent MRI without sedation.[10] While the study excluded patients with obvious developmental delay, our study suggests that these patients might have benefited from it.

This study is limited by selection bias as patients who were likely to succeed would be more agreeable to join. Also, the small sample size may mean that the results were not adequately representative of most paediatric patients who require MRI scans. Furthermore, the absence of a control group makes it hard to ascertain if the success was solely due to FSTE.

Future research will look into mitigating these limitations, aim to conduct larger randomised controlled trials to verify the FSTE programme's efficacy and explore its feasibility in different cultural contexts.

Supplementary material

Table S1. Baseline characteristics of surveyed population (n=67).

Ethics statement

This study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The National Healthcare Group Domain Specific Research Board Singapore approved the study [2015/00871].

Declaration

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Keywords: *children, magnetic resonance imaging, sedation, video distraction*

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LETTER TO THE EDITOR

Acute respiratory tract infections management in private primary healthcare in Singapore

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Dear Editor,

Antibiotic use is medically unnecessary for most acute respiratory infections (ARIs), which are mostly viral aetiology and self-limiting in nature. Despite this, high rates of antibiotic use in the treatment of ARI persist, particularly in primary care where most ARI cases are managed.[1] In Singapore, antimicrobial resistance (AMR) and its control is a national priority.[2] While we have a good conceptual understanding of knowledge and attitudes to antibiotic prescribing in Singapore, in both patients and doctors,[3,4] and of actual antibiotic use in public primary care clinics through retrospective surveys,[5] data are lacking on antibiotic use and its correlates in the private sector where 80% of primary care physicians practice.[6] To address this gap, we performed a multicentre, physician-led, prospective observational study based on the HAPPY AUDIT protocol.[7] Studies of prescribing practices using this audit methodology have been an integral part of antibiotic stewardship in other countries.[8]

Our study recruited 50 general practitioners (GPs) practising in private clinics, through the Primary Care Research Network (now renamed SPARK).[9] These GPs prospectively recorded ARI consultation details on standardised case report forms (without patient identifying data) that included the following fields: age, sex, ethnicity, duration of illness, point-of-care tests performed, suspected aetiology, working diagnosis and oral antibiotics prescribed. Under signs and symptoms, GPs were also asked to record the presence of any of the following: rhinorrhoea, cough, odynophagia, increased sputum production, purulent sputum, fever, purulent ear discharge, tender cervical lymph nodes or tonsillar exudate. Consultations with adult patients (aged ≥21 years) presenting with symptoms and diagnosis of ARI (maximum duration of 21 days) between March and September 2021 were included, to a maximum of 50 patients per GP.

A total of 2176 unique ARI consultations were recorded, with a median age of 36 years (range 21–94), and 54.4% female. The median number of symptoms was 2 (range 0–7), and the median duration of symptoms at time of consultation was 2 days (range 1–21).

Antibiotic use was recorded in 355 (16.3%) patient consults. Association of antibiotic use with patient characteristics is shown in Table 1. There was no significant association of antibiotic prescription with sex or patient ethnicity. However, antibiotic use did rise with age, number of symptoms and symptom duration.

We noted a similar rate of antibiotic use across age groups below the age of 60 years, and a doubling in the rate of antibiotic use above this age. Similarly, while patients presenting with fewer than 4 symptoms were treated with antibiotics at a rate comparable to the overall average rate (16.3%), those presenting with more than 4 symptoms were predominantly prescribed antibiotics. Similarly, antibiotic use increased above the study average in patients with more than 3 days duration of symptoms, reaching 60% in patients with symptoms for longer than 7 days. Multivariate analysis of the above failed to identify any additional correlation with antibiotic prescription.

Of the antibiotic classes prescribed, the most frequent (65.0%) were penicillin (51.6% amoxicillin with clavulanic acid, 13.3% amoxicillin alone), followed by macrolides (24.7%). Macrolides and penicillin together constituted 89.7% of all antibiotics prescribed. Cephalosporins (5.6%), quinolones (2.5%), tetracyclines (0.6%) and trimethoprim/sulfamethoxazole (0.3%) were rarely used.

Three doctors (6.0%) did not prescribe antibiotics to any of their patients. The remaining 47 GPs (94.0%) varied considerably in their pattern of antibiotics prescription. While 13 GPs (26.0%) prescribed a single class of antibiotic exclusively

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Table 1. Patient characteristics and antibiotic use.

Characteristics	No. of patients prescribed with antibiotics		No. of patients not given antibiotics		Total no. of patients	OR (95% CI)
Sex						
Male	187	15.8%	995	84.2%	1182	1 (0.8–1.2)
Female	167	16.9%	822	83.1%	989	1.1 (0.9–1.4)
Total	354		1817		2171	
Ethnicity						
Chinese	233	16.4%	1189	83.6%	1422	1.0 (0.8–1.2)
Indian	38	18.8%	164	81.2%	202	1.2 (0.8–1.7)
Malay	51	13.5%	327	86.5%	378	0.8 (0.6–1.1)
Others	33	19.8%	134	80.2%	167	1.2 (0.8–1.9)
Total	355		1814		2169	
Age						
21–30	85	13.5%	543	86.5%	628	1.0 (0.7–1.4)
31–40	113	15.9%	599	84.1%	712	1.2 (0.9–1.6)
41–50	58	14.6%	339	85.4%	397	1.1 (0.8–1.6)
51–60	34	17.6%	159	82.4%	193	1.3 (0.9–2.1)
61–70	38	29.5%	91	70.5%	129	2.6 (1.7–4.1)
Above 70	27	23.3%	89	76.7%	116	1.9 (1.1–3.0)
Total	355		1820		2175	
No. of symptoms at presentation						
0	3	16.7%	15	83.3%	18	1.0 (0.2–5.8)
1	94	13.0%	630	87.0%	724	0.7 (0.2–2.6)
2	118	13.7%	745	86.3%	863	0.8 (0.2–2.8)
3	72	16.3%	370	83.7%	442	1.0 (0.3–3.4)
4	49	48.0%	53	52.0%	102	4.5 (1.3–16.6)
5	15	65.2%	8	34.8%	23	9.4 (2.1–42.3)
6	7	100.0%	0	0.0%	7	NA
7	1	100.0%	0	0.0%	1	NA
Total	359		1821		2180	
Symptom duration (days)						
1	37	6.1%	571	93.9%	608	1.0 (0.6–1.6)
2	97	10.9%	791	89.1%	888	1.9 (1.3–2.8)
3	78	21.1%	291	78.9%	369	4.1 (2.7–6.3)

Table 1. Patient characteristics and antibiotic use. (Cont'd)

Characteristics	No. of patients prescribed with antibiotics		No. of patients not given antibiotics		Total no. of patients	OR (95% CI)
Symptom duration (days)						
4	41	40.6%	60	59.4%	101	10.5 (6.3–17.7)
5	32	49.2%	33	50.8%	65	15.0 (8.3–27.0)
6	4	28.6%	10	71.4%	14	6.2 (1.8–20.6)
7	33	47.8%	36	52.2%	69	14.1 (7.9–25.2)
More than 7	33	60.0%	22	40.0%	55	23.1 (12.2–43.6)
Total	355		1814		2169	

CI: confidence interval; NA: not applicable; OR: odds ratio
Note: Percentages refer to proportion of each category. Denominators may differ due to missing data in each category. ORs are calculated with reference to the first category in each table.

(22.0% only penicillin; 4.0% only macrolides), the majority (70%) of GPs prescribed a variety of antibiotic types. Of these GPs, 18 (36%) alternated between macrolides and penicillin, whereas 17 (34.0%) GPs also prescribed other antibiotic types. Dual antibiotic use in the same patient was only noted in 2 cases. An explicit request for antibiotics was documented in 26 consultations, of which antibiotics were given in all but 1 case. Penicillin allergy was documented in 36 (1.6%) patients.

To our knowledge, this is the first published study of antibiotic prescription in the private primary care environment in Singapore. Using prospective data collection enabled a rich and complete dataset, which would have been challenging retrospectively given the many different electronic health record systems used in private clinics and variations in clinical case notation.

The antibiotic prescription rate we recorded (16.5%) compares favourably with regional estimates of antibiotic use by GPs, estimated between 34% and 85% for a number of Asian countries and Australia,[10] but is 4-fold the 3.73% rate of antibiotic use for respiratory conditions noted at Singaporean public polyclinics during the same period.[5] However, any comparison with such diverse environments should be made with caution, even between public and private clinics, due to the often-considerable variations in patient/case characteristics.[6]

We based our study on an established audit protocol. Audit approaches in themselves constitute a form of antibiotic stewardship,[11] not least by allowing practitioners to consider their prescribing in relation to others. Similarly, the implementation of guidelines for antibiotic prescription has been shown to lower overall antibiotic use in primary care.[12] The lack of specific guidelines for antibiotic use in ARI in primary care likely contributed to the variation in antibiotic use reported by GPs in our study. Patterns of use of antibiotic classes are increasingly becoming a focus of antibiotic stewardship, as embodied by the World Health Organization's Access, Watch, Reserve classification.[13] We note a relatively high use of macrolides, which are classified as "watch" antibiotics, among our GPs (and comparatively at a higher rate than in the polyclinics where prescription of antibiotics are subject to institutional guidelines).[5] As noted above, these are distinct clinical environments, and further research is needed to understand what factors may underlie antibiotic prescription decisions in each setting to effectively promote evidenced-based antibiotic prescription. Well-defined guidelines codifying antibiotics use in primary care, formulated in consultation with private general practitioners, may address many of these issues. We hope that the results of our study will help to inform the development of guidelines for the treatment of ARI in primary care in Singapore and support both relevant patient and professional education on appropriate antibiotic use.

Ethics statement

The study was approved by the Nanyang Technological University Institutional Review Board (2019-10-039).

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.

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LETTER TO THE EDITOR

Optical coherence tomography and acetylcholine provocation for diagnosing coronary vasospasm in MINOCA patients

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Dear Editor,

Myocardial infarction with non-obstructive coronary artery disease (MINOCA) occurs in up to 14% of patients presenting with acute coronary syndrome (ACS).[1] Clinically, such patients present with ACS symptoms, elevation of troponin and coronary angiograms showing non-obstructive coronary arteries (<50% stenosis).[2] MINOCA has myriad aetiologies, which are classified according to coronary (i.e. coronary embolism, spasm or spontaneous dissection) and non-coronary pathologies (i.e. trauma or myocarditis).[3]

Coronary artery vasospasm is an important cause of ACS that can lead to myocardial infarction, ventricular arrhythmias and sudden death. Asians seem to have a higher propensity of vasospastic angina, but more recent studies have shown that this condition is also common among Caucasians.[4-6] Coronary angiography alone may yield inconclusive results. Current journal consensus guidelines[7] suggest considering acetylcholine provocation tests in MINOCA patients to induce coronary artery vasospasm and establish the underlying cause of ACS.[8]

Optical coherence tomography (OCT) is a high spatial resolution intracoronary imaging modality useful to detect subtle causes of ACS not identified by coronary angiography such as plaque rupture or recanalised thrombus.[9]

OCT identifies plaque rupture as a fibroatheroma with fibrous cap disruption over necrotic core,[10] with or without cavity formation, whereas it detects thrombus as an intraluminal mass attached to the luminal surface or floating within the lumen[11] while plaque erosion can be seen as a plaque with thrombus and no evidence of rupture in multiple adjacent frames. Thrombosis of calcified nodules can be identified as evidence of thrombus in conjunction with calcium protruding into the lumen, frequently forming sharp, jutting angles.[12] Ruptured plaques of patients with ST elevation myocardial infarction (STEMI) are associated with a greater extent of cap disruption and a smaller minimal lumen area compared with ruptured plaques of patients with non-STEMI.[13,14] Ruptured culprit plaques of ACS had a lower lumen area compared with non-culprit plaques in the same patients who had undergone silent rupture.[15]

We present 3 cases of MINOCA, highlighting the roles of OCT and acetylcholine provocation tests to establish coronary vasospasm as the underlying cause.

Case 1

A 59-year-old male, without prior known cardiovascular risk factors, presented to the emergency department (ED) twice due to multiple episodes of chest pain over 1 month. He was scheduled for exercise stress echocardiogram for evaluation. Before stress echocardiogram was performed, he again presented with chest pain. Electrocardiogram (ECG) in ED showed acute anterolateral and inferior wall ST elevation. Emergency coronary angiogram showed luminal irregularities, TIMI 3 flow on all 3 coronary arteries with mild myocardial bridging on mid-left anterior descending (mid-LAD) artery (Fig. 1). OCT revealed no evidence of plaque rupture/recanalised thrombus. Acetylcholine challenge with 20 mcg and 100 mcg was positive for severe focal spasm in mid-LAD artery (Fig. 1) with reproduction of ST elevation and symptoms of chest pain. The spasm was reversed with intracoronary nitroglycerin. No coronary stents were implanted, and he was treated with dual antiplatelet therapy and oral calcium channel blockers (CCB).

Case 2

A 47-year-old male presented with recurrent left-sided chest pain. ECG showed Wellens' Type B pattern suggestive of LAD ischaemia with low-grade troponin rise and managed as non-ST elevation ACS. Coronary angiogram showed mid-LAD 30–40% stenosis, the rest of the coronaries have no significant obstruction (Fig. 1). OCT of mid-LAD lesion showed fibrous plaque with a plaque burden of 43%, but no signs of plaque rupture/recanalised

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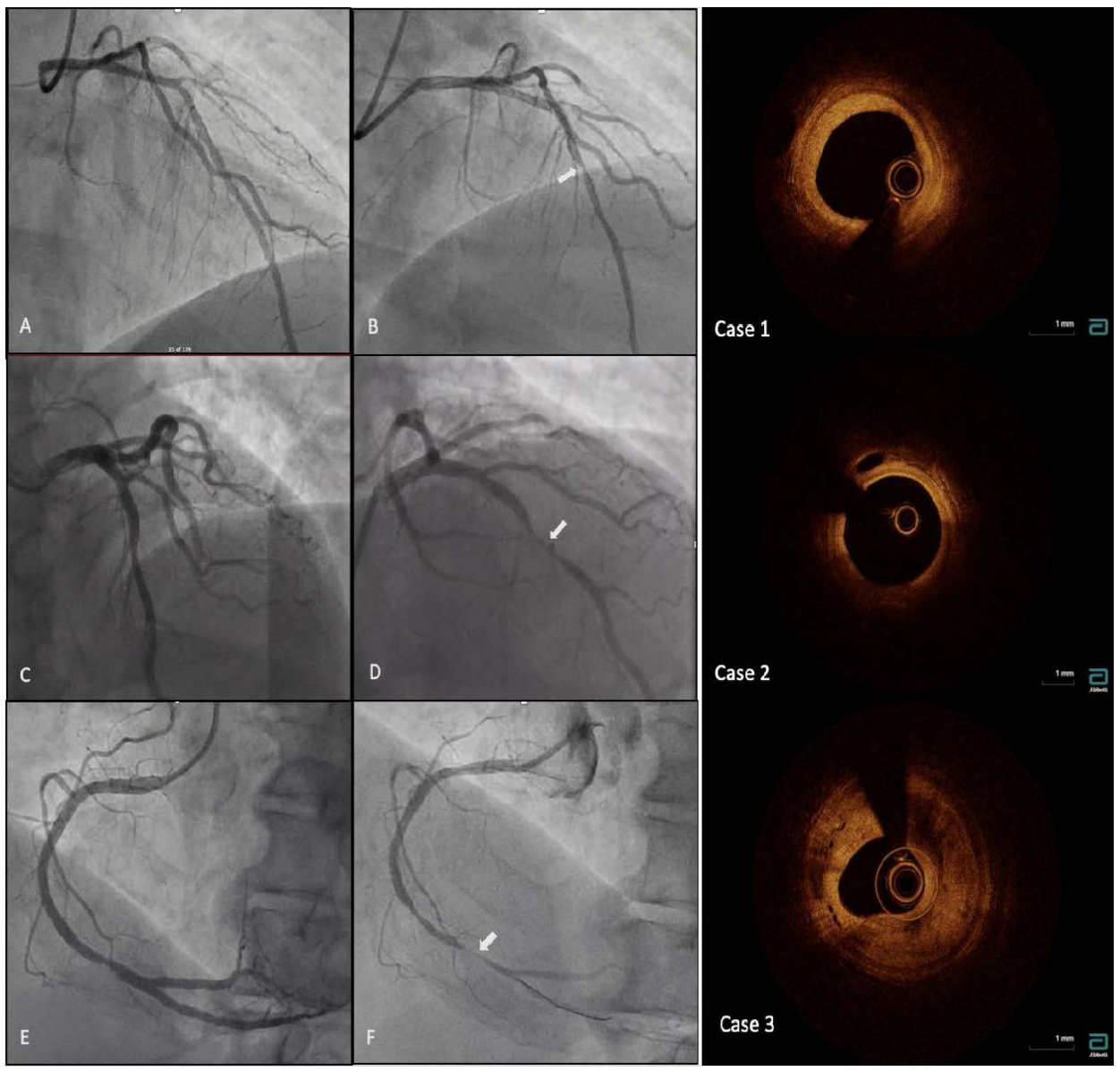
thrombus. Vasoreactivity study with intra-coronary (IC) acetylcholine 200 mcg demonstrated focal 90% coronary vasospasm of the mid-LAD (Fig. 1D) with patient developing chest pain and ECG changes. He was given CCB and nitrates as maintenance. Repeat ECG after 3 months showed resolution of deep T wave inversions.

Case 3

A 56-year-old male was admitted due to ST elevation on the inferior leads and regional wall motion in the right coronary artery during treadmill stress echocardiogram, associated with epigastric discomfort. Coronary angiogram revealed non-obstructive lesions and minor disease in distal right coronary artery (RCA) (Fig. 1E). Fractional flow reserve measured across distal RCA with intravenous adenosine infusion was not haemodynamically significant. OCT was done and was negative for plaque rupture with no signs of recanalised thrombus. Further evaluation using vasoreactivity testing with acetylcholine 200 mcg

Fig. 1. Coronary angiography of the 3 patients with acute coronary syndrome.



(A), (C), (E) Non-obstructive lesions at baseline with (B), (D), (F) interval severe focal spasm (as shown in the arrows) noted on each patient after vasoreactivity testing with acetylcholine, respectively. Rightmost figures show optical coherence tomography images at the sites of the induced spasm of the 3 patients showing predominantly fibrous plaque with intact intimal layer and no evidence of plaque rupture, plaque erosion or thrombus.

showed severe focal spasm at the distal RCA (Fig. 1F). The spasm was reversed with intracoronary nitroglycerin. No coronary stents were implanted, and he was treated with dual antiplatelet therapy and oral CCB.

In Case 3, there was evidence of neo-vascularisation within the intima, suggesting some chronicity in this plaque.

All 3 patients had typical anginal symptoms with localising ECG features either of Wellens' syndrome or ST elevation. In these patients, coronary angiogram did not identify any culprit lesions that could account for the clinical presentations. OCT was performed in all these cases and ruled out plaque rupture and/or recanalised thrombus. Finally, vasoreactivity with acetylcholine, with maximum dose of up to 100–200 mcg given via slow intracoronary bolus demonstrated coronary artery vasospasm in all 3 patients.

This case series illustrates that a comprehensive coronary evaluation using OCT with acetylcholine provocation in addition to coronary angiography is essential to establish the diagnosis of coronary vasospasm as cause of ACS. As shown above, accurate diagnosis avoids unnecessary coronary artery stenting and is indispensable for tailored therapeutic management such as the use of CCB to avoid recurrence of further symptoms and ACS occurrence. Larger, multicentre studies are still needed to validate these findings to provide more robust and generalisable results.

Ethics statement

Not applicable

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: *cardiology, coronary artery disease, coronary artery vasospasm, coronary physiology, myocardial infarction*

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