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This study evaluates the criteria used to diagnose systemic lupus erythematosus, a disease often referred to as lupus (Latin for "wolf"). It examines an East Asian cohort with childhood onset, predominantly female, with a median diagnosis age of 12.9 years. (See full article, p.277)

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ORIGINAL ARTICLES

REVIEW ARTICLE

LETTERS TO THE EDITOR

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ORIGINAL ARTICLE

Diagnostic performance of classification criteria for systemic lupus erythematosus: A validation study from Singapore

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ABSTRACT

Introduction: Classification criteria for systemic lupus erythematosus (SLE) include American College of Rheumatology (ACR) 1997, Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) 2012 and European Alliance of Associations for Rheumatology (EULAR)/ACR 2019 criteria. Their performance in an Asian childhood-onset SLE (cSLE) population remains unclear as the clinical manifestations differ. We aim to evaluate the diagnostic performance in a cSLE cohort in Singapore.

Method: Cases were physician-diagnosed cSLE, while controls were children with mixed and undifferentiated connective tissue disease that posed an initial diagnostic challenge. Data were retrospectively reviewed to establish the 3 criteria fulfilled at diagnosis and over time.

Results: The study population included 120 cSLE cases and 36 controls. At diagnosis, 102 (85%) patients fulfilled all criteria. SLICC-2012 had the highest sensitivity (97.5%, 95% confidence interval [CI] 92.3–99.5), while ACR-1997 had the highest specificity (91.7%, 95% CI 77.5–98.3). All criteria had diagnostic accuracies at more than 85%. Over time, 113 (94%) fulfilled all criteria. SLICC-2012 remained the criteria with the highest sensitivity (99.2%, 95% CI 95.4–99.9), while ACR-1997 had the highest specificity (75.0%, 95% CI 57.8–87.9). Only SLICC-2012 and ACR-1997 had more than 85% diagnostic accuracy over time. Using a cutoff score of ≥13 for EULAR/ACR-2019 criteria resulted in improved diagnostic performance.

Conclusion: SLICC-2012 criteria had the highest sensitivity early in the disease course in this first study evaluating the SLE classification criteria performance in a Southeast Asian cSLE cohort, while the ACR-1997 criteria had the highest specificity. Using a cutoff score of ≥13 for EULAR/ACR-2019 improved the diagnostic performance.

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Keywords: classification criteria, paediatrics, rheumatology, systemic lupus erythematosus, validation

CLINICAL IMPACT

What is New

- To the authors' knowledge, this is the first study to evaluate systemic lupus erythematosus (SLE) classification criteria in an East Asian childhood-onset SLE (cSLE) cohort.
- The results concurred that the SLICC-2012 criteria had the highest sensitivity, and the ACR-1997 criteria had the highest specificity. We also demonstrated that a cutoff score ≥13 is more suitable for the EULAR/ACR-2019 criteria.

Clinical Implications

- Local and regional medical professionals can be informed about the better sensitivity of the SLICC-2012 classification criteria and the common clinical manifestations, leading to an earlier diagnosis of cSLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a broad spectrum of clinical presentation.[1] Clinical diagnosis by rheumatologists remains the gold standard, but the diagnosis is often challenging due to variability in disease expression mimicking other conditions.

As such, classification criteria have been developed to establish homogeneous groups of patients to include in clinical trials and epidemiological studies. In 1971, the American College of Rheumatology (ACR) developed the first set of classification criteria consisting of 11 clinical and laboratory features, which was later modified in 1997.[2-4] The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) group subsequently developed a new set of criteria, and patients must meet at least 4 of 17 criteria, including

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at least 1 clinical and 1 immunological criterion or have documented lupus nephritis (LN) with positive autoantibodies.[5] More recently, the European Alliance of Associations for Rheumatology (EULAR)/ACR-2019 criteria were developed, with a positive level for antinuclear antibody (ANA) at a serum dilution of 1:80 as a required entry criterion followed by weighted items including 7 clinical domains and 3 immunological domains.[6]

These classification criteria were initially developed and validated in adult SLE cohorts. Childhood-onset SLE (cSLE) represents 20% of the total SLE patient.[7] Compared to the adult population, there is more haematological and renal involvement with lesser arthritis and serositis in cSLE.[8] Even among the paediatric population, there is variation in clinical manifestation frequencies.[9] Several studies have thus attempted to validate the classification criteria in cSLE cohorts. A recent meta-analysis showed that SLICC-2012 had the highest sensitivity while the ACR-1997 had the highest specificity.[10] In that meta-analysis, only one predominant East Asian cohort was included.[11]

Southeast Asia comprises 11 countries with diverse histories, religions and cultures. There is a paucity of studies evaluating the performance of SLE classification criteria in cSLE cohorts in this region. The primary aim of this study is to assess and compare the performance of ACR-1997, SLICC-2012 and EULAR/ACR-2019 classification criteria in a cSLE cohort in Singapore both at diagnosis and over time.

METHOD

Patient selection

We included all patients with cSLE diagnosed in KK Women's and Children's Hospital, Singapore, from August 2002 to December 2022. All patients were younger than 16 years at onset and were diagnosed by trained paediatric rheumatologists. The control group consisted of patients with well-established diagnoses of mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD) who posed an initial diagnostic challenge. Positive antinuclear antibodies (ANA) was not a mandatory criterion in the control group, as the diagnosis of cSLE is also considered in patients with negative ANA, especially in the early stages of the disease. Patients were excluded if they were followed up for less than a year.

Data collection

Patients were recruited from our web-based prospective and ongoing registry (RECORD, or Registry for Childhood Onset Rheumatic Diseases).[12] Demographic, clinical and laboratory data were recorded. Definitions of cutaneous manifestations, oral ulcers, arthritis, serositis, cytopenia, and renal and neurological involvement were those provided by the respective criteria.[4-6] ANA was determined by indirect immunofluorescence on human cell epithelioma (HEp-2) cells substrate and defined as positive if staining reactivity at ≥1:80. Anti-double stranded DNA (dsDNA) test was determined by enzyme-linked immunosorbent assay (ELISA) and/or indirect immunofluorescence on *Crithidia lucilae* substrate. The anti-extractable nuclear antigen (anti-ENA) profile, including Ro, La, Smith, and ribonuclear proteins, were measured qualitatively using the ELISA technique and were considered positive if the values were above the laboratory reference range. Lupus anticoagulant was determined by the dilute Russell's viper venom time with confirmatory testing. Both anti-cardiolipin antibody and anti-β2-glycoprotein antibody isotypes Immunoglobulin M (IgM) and Immunoglobulin G (IgG) were determined by ELISA with a cut-off value of 20 IgM phospholipid (MPL) or IgG phospholipid (GPL) units, respectively, for ACR-1997 and SLICC-2012 criteria; and a cut-off value of 40 MPL or GPL for EULAR/ACR criteria set.

Statistical analyses

Non-parametric analyses were used to describe data and were shown as median (interquartile range [IQR]) for continuous variables and percentages for categorical variables. Sensitivity, specificity, predictive values and diagnostic accuracies were estimated for each of the classification criteria. We also calculated the diagnostic performance of EULAR/ACR-2019 criteria using a separate cutoff score of 13 to compare our results to similar studies. Chi-squared or Fisher's exact, Mann Whitney U or Kruskal Wallis tests were applied to compare differences between groups where appropriate. McNemar's test was performed to assess differences in sensitivity and specificity between the criteria. The diagnostic performances were also evaluated for patients with specific organ involvement in subgroup analyses. All analyses were performed using SPSS, version 23.0 (IBM Corp, NY, US) and GraphPad Prism V.7 (GraphPad Software, Inc, CA, US) with statistical significance set at $P<0.05$.

Ethics

This study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The SingHealth Centralised Institutional Review Board (CIRB) approved this study and waived the need for informed consent for this database study (CIRB: 2019/2961 and 2019/2192).

RESULTS

Sample demographics

The demographic characteristics of our study cohort are presented in Table 1. A total of 120 cSLE patients were included (83% females, 52% Chinese). The median age at onset was 12.1 years (10.0–14.0), and the median age at diagnosis was 12.9 years (10.6–14.4). The median duration of follow-up was 5.7 years (3.0–8.4). Controls consisted of 32 patients with UCTD and 4 with MCTD (total 36 patients, 89% females, 64% Chinese). Patients with cSLE had a younger age at disease onset (P=0.022), younger age at diagnosis (P=0.004), shorter duration of follow-up (P=0.004) and a shorter duration from disease onset to diagnosis (P=0.022).

Clinical characteristics

The clinical characteristics of our study cohort are presented in Table 2. The most common clinical manifestations at diagnosis were haematologic involvement (83%), fever (60%) and arthritis (51%). Renal involvement was present in 37% of the cSLE patients at diagnosis and 47% over time. In the control group, only haematologic involvement had a prevalence of more than 50% at diagnosis and over time.

Immunologic characteristics

ANA was positive in 98% of the cSLE cohort and 94% of the control at diagnosis. One control patient only developed positive ANA later, while all cSLE patients who were ANA positive were already noted to have positive ANA at diagnosis. Anti-dsDNA antibody was present in 88% of the cSLE patients compared to 33% in the control group. The most common anti-ENA antibody in the cSLE cohort was anti-Ro/SSA (58%), while anti-U1RNP was the most common in the control group (39%).

Performance of the criteria at diagnosis

At diagnosis, 102 patients (85%) fulfilled all 3 criteria, 1 patient only fulfilled SLICC-2012 criteria, 2 patients only fulfilled EULAR/ACR-2019 criteria, and none fulfilled only ACR-1997 criteria (Fig. 1). One patient did not fulfil any of the criteria as there was only biopsy-proven lupus nephritis without positive ANA. SLICC-2012 criteria had the highest sensitivity (97.5%, 95% CI 92.3–99.5), followed by the EULAR/ACR-2019 criteria (96.7%, 95% CI 91.7–99.1), both of which were higher than the ACR-1997 criteria (86.7%, 95% CI 79.3–92.2, P<0.001 and P=0.004, respectively; see Table 3 and Fig. 2). ACR-1997 criteria had the highest specificity (91.7%, 95% CI 77.5–98.3%) compared to SLICC-2012 (69.4%, 95% CI 51.2–83.7%, P=0.008) and EULAR/ACR-2019 (50.0%, 95% CI 32.9–67.1%, P<0.001) criteria. When a cutoff score of ≥13 was used for the EULAR/ACR-2019 criteria, the sensitivity remained similar to the original score of ≥10 (95.8%, 95% CI 90.5–98.6% P=0.999), but the specificity increased significantly (75.0%, 95% CI 57.8–87.9%, P=0.031). SLICC-2012 criteria had the highest diagnostic accuracy (91%, 95% CI 85.4–95.0%), but a cutoff score of ≥13 for EULAR/ACR-2019 criteria resulted in similar diagnostic accuracy to SLICC-2012.

Table 1. Demographic characteristics of the study cohort.

Characteristics	SLE[a] (n=120)	Controls[b] (n=36)	*P* value
Female, no. (%)	99 (83)	32 (89)	0.445
Ethnicity, no. (%)			0.270
Chinese	62 (52)	23 (64)	
Malay	33 (27)	10 (27)	
Indian	8 (7)	2 (6)	
Others	17 (14)	1 (3)	
Age at disease onset, years*	12.1 (10.0–14.0)	13.4 (11.2–15.1)	0.022
Age at diagnosis, years*	12.9 (10.6–14.4)	14.4 (11.9–16.0)	0.004
Duration from onset to diagnosis, months*	1.2 (0.5–3.1)	2.9 (1.0–20.9)	0.022
Duration for follow-up, years*	5.7 (3.0–8.4)	2.9 (1.2–5.4)	0.004
Positive ANA, no. (%)	118 (98)	34 (94)	0.228

ANA: antinuclear antibody; SLE: systemic lupus erythematosus
* Median (interquartile range)
[a] According to certified paediatric rheumatologists' diagnosis.
[b] Controls are 4 patients with mixed connective tissue disease and 32 patients with undifferentiated connective tissue disease.

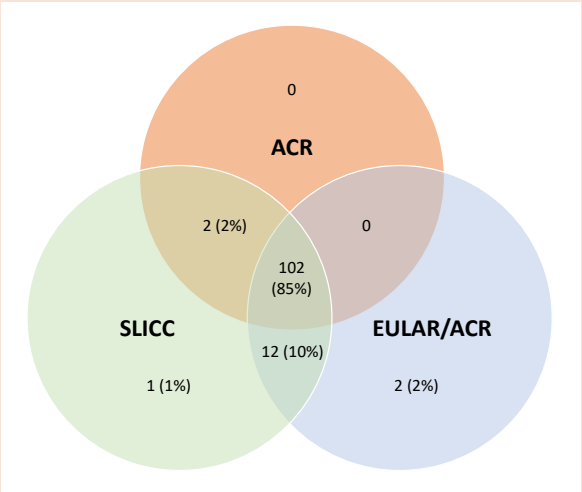
Table 2. Clinical characteristics of cases and controls at diagnosis.

Clinical characteristics	At diagnosis		Over time	
	Cases, n=120	Controls, n=36	Cases, n=120	Controls, n=36
Fever	72 (60.0)	9 (25.0)	74 (61.7)	9 (25.0)
Malar rash	53 (44.2)	1 (2.8)	58 (48.3)	1 (2.8)
Discoid rash	14 (11.7)	0 (0)	22 (18.3)	0 (0)
Photosensitivity	17 (14.2)	2 (5.6)	19 (15.8)	2 (5.6)
Oral ulcer	39 (32.5)	1 (2.8)	43 (35.8)	1 (2.8)
Alopecia	37 (30.8)	3 (8.3)	54 (45.0)	3 (8.3)
Haematologic involvement	**100 (83.3)**	**19 (52.8)**	**108 (90.0)**	**21 (58.3)**
Renal involvement	44 (36.7)	1 (2.8)	56 (46.7)	1 (2.8)
Neurological involvement	6 (5.0)	0 (0)	9 (7.5)	0 (0)
Arthritis	**61 (50.8)**	16 (44.4)	**73 (60.8)**	17 (47.2)
Serositis	11 (9.2)	1 (2.8)	16 (13.3)	1 (2.8)
Low complements	**97 (80.8)**	**13 (36.1)**	**113 (94.2)**	**18 (50.0)**
ANA	**118 (98.3)**	**34 (94.4)**	**118 (98.3)**	**35 (97.2)**
Anti-dsDNA	**105 (87.5)**	12 (33.3)	**106 (88.3)**	13 (36.1)
Anti-Smith	46 (38.3)	5 (13.9)	48 (40.0)	7 (19.4)
Anti-Ro/SSA	**66 (55.0)**	13 (36.1)	**70 (58.3)**	13 (36.1)
Anti-La/SSB	29 (24.2)	8 (22.2)	29 (24.2)	8 (22.2)
Anti-U1RNP	56 (46.7)	12 (33.3)	**60 (50.0)**	14 (38.9)
Antiphospholipid antibodies	31 (25.8)	3 (8.3)	36 (30.0)	3 (8.3)

ANA: antinuclear antibody; dsDNA: double-stranded DNA; La/SSB: Sjögren's syndrome B; Ro/SSA: Sjögren's syndrome A; U1RNP: U1-ribonucleoprotein

Data presented in median (interquartile range) and number (%). Features with more than 50% are highlighted in bold.

Fig. 1. cSLE (n=120) patients classified according to ACR 1997, SLICC-2012, EULAR/ACR 2019 classification criteria.



ACR: American College of Rheumatology 1997 criteria; EULAR/ACR: European Alliance of Associations for Rheumatology 2019 criteria; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics 2012 criteria.

Table 3. Performance measures for the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria.

	ACR 1997	SLICC	EULAR/ACR	EULAR/ACR*
At diagnosis				
Sensitivity	86.7 (79.3 – 92.2)	97.5 (92.3 – 99.5)	96.7 (91.7 – 99.1)	95.8 (90.5 – 98.6)
Specificity	91.7 (77.5 – 98.3)	69.4 (51.2 – 83.7)	50.0 (32.9 – 67.1)	75.0 (57.8 – 87.9)
PPV	97.2 (92.1 – 99.0)	91.4 (86.7 – 94.6)	86.6 (61.9 – 92.6)	92.7 (87.9 – 95.8)
NPV	67.3 (56.4 – 76.7)	89.3 (72.3 – 96.3)	81.8 (61.9 – 92.6)	84.4 (69.2 – 92.9)
Positive LR	10.4 (3.51 – 30.8)	3.19 (1.95 – 5.23)	1.93 (1.39 – 2.65)	3.83 (2.17 – 6.76)
Negative LR	0.15 (0.09 – 0.23)	0.04 (0.01 – 0.11)	0.07 (0.02 – 0.18)	0.06 (0.02 – 0.13)
Accuracy	87.8 (81.6 – 92.5)	91.0 (85.4 – 95.0)	85.9 (79.4 – 91.0)	91.0 (85.4 – 95.0)
Over time				
Sensitivity	95.0 (89.4 – 98.1)	99.2 (95.4 – 99.9)	98.3 (94.1 – 99.8)	96.7 (91.7 – 99.1)
Specificity	75.0 (57.8 – 87.9)	50.0 (32.9 – 67.1)	36.1 (20.8 – 53.8)	69.4 (51.9 – 83.7)
PPV	92.7 (87.8 – 95.7)	86.9 (82.7 – 90.2)	83.7 (80.0 – 86.8)	91.3 (86.6 – 94.5)
NPV	81.8 (66.9 – 90.9)	94.7 (71.3 – 99.2)	86.7 (60.6 – 96.5)	86.2 (70.0 – 94.4)
Positive LR	3.80 (2.15 – 6.70)	1.98 (1.43 – 2.75)	1.54 (1.20 – 1.97)	3.16 (1.93 – 5.18)
Negative LR	0.07 (0.03 – 0.15)	0.02 (0.01 – 0.12)	0.05 (0.01 – 0.20)	0.05 (0.02 – 0.13)
Accuracy	90.4 (84.6 – 94.5)	87.8 (81.6 – 92.5)	84.0 (77.3 – 89.4)	90.4 (84.6 – 94.5)

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics
*ACR/EULAR using a score ≥13 instead of ≥10.
Data presented in % or ratio (95% CI).

Performance of the criteria over time

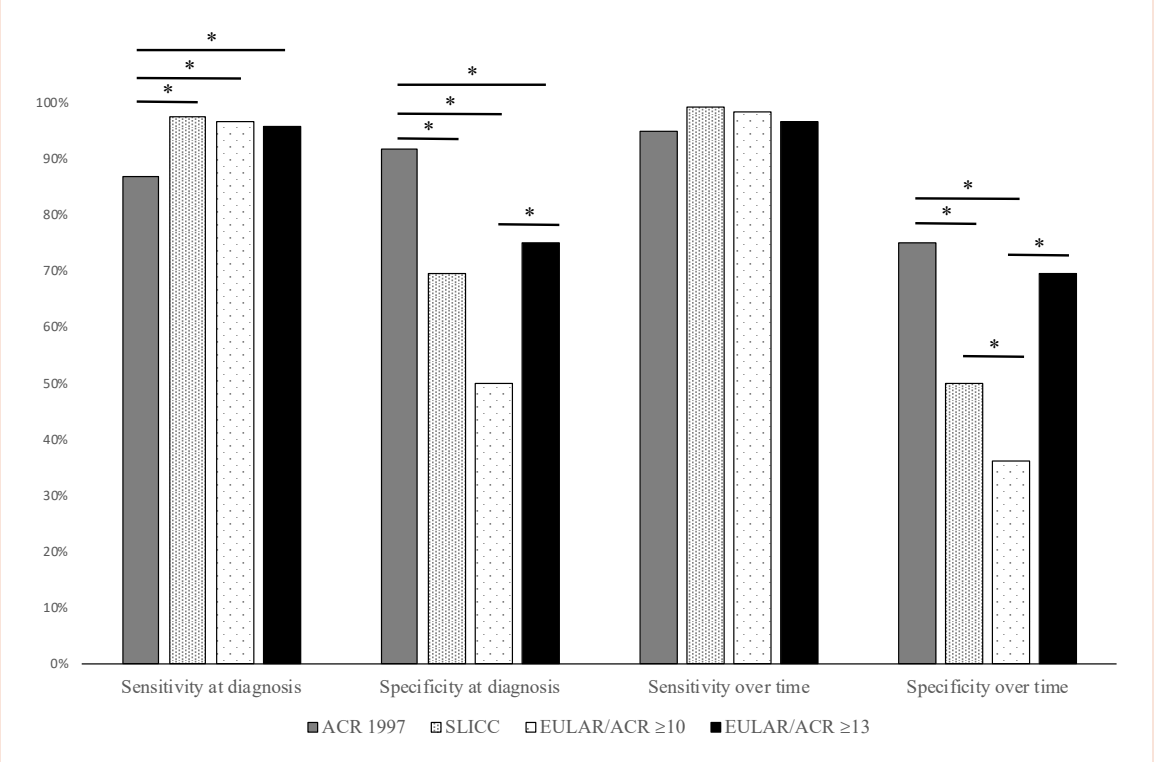
Over time, SLICC-2012 criteria had the highest sensitivity (99.2%, 95% CI 95.4–99.9), but all 3 criteria sensitivities were no longer significantly different (Table 3, Fig. 2). The specificities of all 3 criteria decreased over time. ACR-1997 criteria retained the highest specificity (75.0%, 95% CI 57.8–87.9) compared to SLICC-2012 (50.0%, 95% CI 32.9–67.1, P=0.004) and EULAR/ACR-2019 (36.1%, 95% CI 20.8–53.8, P<0.001) criteria. When a cutoff score of ≥13 was used for the EULAR/ACR-2019 criteria, the sensitivity remained similar to the original score of ≥10 (96.7%, 95% CI 91.7–99.1, P=0.500). However, the specificity increased significantly and no longer differed from the ACR-1997 criteria (69.4%, 95% CI 51.9–83.7, P=0.687). Over time, both ACR-1997 and EULAR/ACR-2019 criteria using a cutoff score of ≥13 had the highest diagnostic accuracy (90.4%, 95% CI 84.6–94.5).

Performance of the criteria at diagnosis for patients with specific organ involvement

We studied the diagnostic performance of the criteria at diagnosis according to specific organ involvement. The sensitivities of SLICC-2012 and EULAR/ACR-2019 criteria remained similar for patients with renal involvement, arthritis, haematologic involvement, hypocomplementemia and positive ANA (Fig. 3). The sensitivity of ACR-1997 criteria improved slightly for patients with renal involvement and arthritis (86.7% versus [vs] 95.5% and 98.4%, respectively).

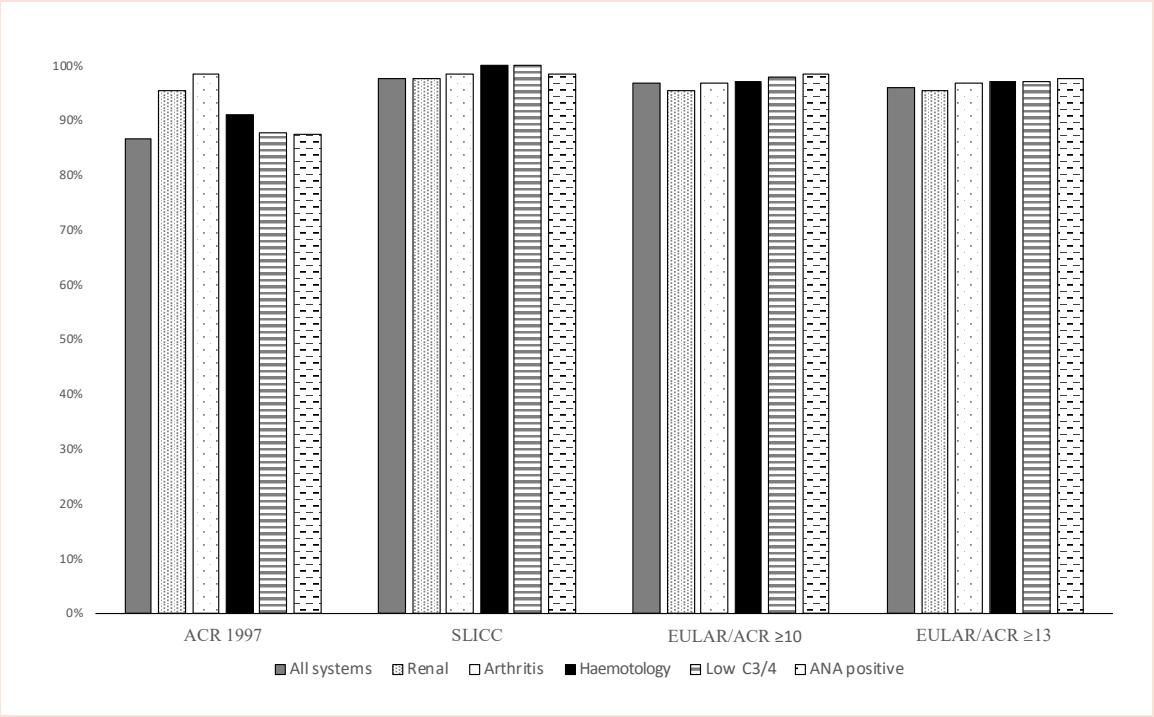
All 3 criteria had 100% specificities for patients with renal involvement at diagnosis, while specificities were the same for patients with positive ANA. All 3 criteria had decreased specificities in patients with hypocomplementemia (ACR-1997: 91.7% vs 76.9%, SLICC-2012: 69.4% vs 38.5%, EULAR/ACR-2019: 50.0% vs 23.1%). SLICC-2012 criteria specificity decreased for patients with

Fig. 2. Comparison of sensitivity and specificity of the classification criteria at diagnosis and over time (* denotes $P<0.05$).



ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics

Fig. 3. Comparison of the sensitivity of the classification criteria at diagnosis for patients with various system involvement.



ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics

haematologic involvement (69.4% vs 52.6%) but increased for patients with arthritis (69.4% vs 75.0%). EULAR/ACR-2019 criteria had decreased specificity for patients with arthritis (50.0% vs 37.5%), but the decrease in specificity is lesser when a cutoff score of ≥13 is used (75.0% vs 68.8%).

DISCUSSION

Owing to different frequencies of clinical manifestations and immunological markers in cSLE patients, studies have attempted to examine the diagnostic performance of existing SLE classification criteria. A recent meta-analysis of predominant Western cSLE studies showed that the SLICC-2012 criteria had the highest sensitivity, while the ACR-1997 criteria had the highest specificity.[10] In the present study comprising a Southeast Asian cSLE cohort, our findings concurred that the SLICC-2012 criteria had the highest sensitivity, and the ACR-1997 criteria had the highest specificity, both at diagnosis and over time.

The clinical presentation of SLE is highly diverse. cSLE patients have more renal, haematological and neurological involvement and less arthritis and cutaneous manifestations.[7,8] In addition to differences across age groups, genetics and ethnicity also influence SLE phenotypic expression resulting in clinical heterogeneity among cSLE patients. In an analysis of the Southeast Asian cSLE cohorts, renal and haematological manifestations featured prominently compared to Western and East Asian cSLE cohorts, while discoid rash was comparatively less common in this region except for the Philippines.[9] There was also a more significant proportion of patients with positive anti-dsDNA antibodies. In our cohort, haematological abnormalities were the most common manifestations at diagnosis, followed by fever and arthritis. Cutaneous manifestations were less common, and even the prevalence of malar rash was less than that of a Western cSLE cohort (48% vs 63%).[13] Regarding immunological markers, almost all our cSLE patients had a positive ANA. Our cohort had a high proportion of positive anti-dsDNA antibodies and hypocomplementemia, and more than half of the patients also had positive anti-Ro and anti-U1RNP antibodies.

Given that the diagnostic performance of SLE classification criteria in different cohorts varies according to disease phenotypic expression, this study observed several similarities and differences in our cohort. At diagnosis, all 3 classification criteria demonstrated good sensitivity. Still, the exclusion of hypocomplementemia, a common manifestation, along with the combination of haematologic abnormalities into a singular feature, resulted in an inferior sensitivity of the ACR-1997 criteria compared to that of the SLICC-2012 and EULAR/ACR-2019 criteria. This finding is concordant with the results of the meta-analysis by Chang et al., albeit the ACR-1997 criteria sensitivity in our cohort was higher than that of the meta-analysis.[10] As a more stringent criterion, all patients who fulfilled the ACR-1997 criteria also fulfilled the SLICC-2012 and EULAR/ACR-2019 criteria, but the converse was invalid. The highest sensitivity was found with the SLICC-2012 criteria, similar to the meta-analysis result. However, this differs from a later Chinese study that demonstrated the highest sensitivity with the EULAR/ACR-2019 criteria.[14] As classification criteria are often used in clinical practice to guide diagnosis, the SLICC-2012 criteria and EULAR/ACR-2019 criteria, both with high sensitivities and diagnostic accuracies, minimise the chance of physicians missing out on potential cSLE patients, especially early on in the disease. Overall, the SLICC-2012 criteria are more practical for clinical use without the need of a weighted score as well as positive ANA as an entry criterion.

At diagnosis, the ACR-1997 criteria had the highest specificity. Notably, the specificities across all 3 criteria in our study were significantly lower than that reported in the current literature. We attribute this to selecting patients with UCTD and MCTD as the control group, compared to other studies that commonly recruited patients with positive ANA or other distinct rheumatic diseases as controls. The latter groups of patients either lack multisystem involvement or display distinct clinical manifestations specific to other rheumatic diseases, making it easier for the criteria to classify patients who do not have cSLE correctly. Patients with UCTD and MCTD often present overlapping features with SLE, and it is of interest if the classification criteria can accurately distinguish cSLE patients in the face of diagnostic dilemmas at initial presentation. The specificities of SLICC-2012 and EULAR/ACR-2019 criteria were dismal, while the ACR-1997 criteria retained relatively high specificity. Ohara et al. also demonstrated more misclassification of cSLE when they analysed the subgroup of patients with MCTD using the EULAR/ACR-2019 and SLICC-2012 criteria.[15] As classification criteria require high specificity, the performance of SLICC-2012 and EULAR/ACR-2019 remains debatable in cSLE patients.

The effect of time on the diagnostic performance of the 3 classification criteria was assessed in this study, given the cumulative characteristics of these 3 classification systems. While the SLICC-2012 and EULAR/ACR-2019 criteria could classify patients

earlier than the ACR-1997 criteria, the latter's sensitivity increased and caught up over time. Fonseca et al. reported similar findings in their Brazilian cSLE cohort.[16] However, another study conducted in Oman showed that the sensitivity of ACR-1997 criteria remained inferior to the other 2 classification criteria despite increasing over time.[17] On the other hand, the specificities of all 3 classification criteria decreased substantially over time. Contrary to our results, both Fonseca et al. and Levinsky et al. reported no significant differences in the ACR-1997 and SLICC-2012 criteria specificities at first-year visits in their respective cSLE cohorts.[18,19] We attributed this difference to our selection of the control cohort and cautioned the use of SLICC-2012 and EULAR/ACR-2019 criteria in cSLE clinical trials, which may falsely include patients with MCTD and UCTD.

The EULAR/ACR-2019 criteria were developed through a collaborative effort to create a single, internationally accepted set of classification criteria for SLE.[6] In our study, the EULAR/ACR-2019 criteria did not confer additional benefits in terms of sensitivity or specificity compared to the earlier ACR-1997 and SLICC-2012 criteria, similar to the findings in the meta-analysis.[10] Furthermore, cSLE patients with a negative ANA will be missed out. Suda and colleagues suggested an ANA titre of ≥1:40 as the entry criterion to achieve better sensitivity.[20] Cheng et al. also pointed out that patients with UCTD and MCTD in a Chinese cSLE cohort were most likely to be misclassified as having SLE by the EULAR/ACR-2019 criteria due to high weightage of arthritis and mucocutaneous manifestation.[14] Despite having an entry criterion, the specificity of the EULAR/ACR-2019 criteria did not surpass that of the ACR-1997 and SLICC-2012 criteria in our study. However, a EULAR/ACR-2019 score ≥13 significantly improved the specificity without compromising the sensitivity, along with improved positive predictive value and diagnostic accuracy, making it comparative to the earlier 2 criteria. This finding echoed previous studies' results.[14,17] Over time, both sensitivity and specificity of the EULAR/ACR-2019 criteria, using a cutoff score of ≥13, were also similar to the ACR-1997 and SLICC-2012 criteria, with superior specificity compared to the SLICC-2012 criteria. This new cutoff score appears to be more appropriate in cSLE cohorts.

SLE patients with major organ involvement have a poorer prognosis, and prompt diagnosis is essential to improve patient outcomes. Cheng and colleagues demonstrated higher sensitivity of the SLICC-2012 and EULAR/ACR-2019 criteria in patients with renal involvement compared to ACR-1997 criteria.[14] This difference in sensitivities was not appreciated in our study, presumably due to a ceiling effect as all 3 criteria had high sensitivities in patients with renal involvement. On the other hand, all 3 criteria had 100% specificity for patients with renal involvement. Therefore, renal involvement is particular to cSLE patients compared to MCTD and UCTD, concurring with a high weightage assigned to biopsy-proven lupus nephritis in both the SLICC-2012 and EULAR/ACR-2019 criteria. We also analysed the diagnostic performance of these classification criteria in patients with haematologic involvement and hypocomplementemia, given the high prevalence of these features in our cSLE cohort. Unsurprisingly, there was a substantial decrease in the specificity of SLICC-2012 criteria given that haemolytic anaemia, leukopenia or lymphopenia, and thrombocytopenia all represent individual features and, therefore, a disproportionate weightage in patients with Evans syndrome. Remarkably, the specificities across all 3 criteria decreased when analysing only patients with hypocomplementemia, as our control patients with MCTD and UCTD also had relatively high rates of hypocomplementemia.

This study presents several unique findings in the diagnostic performance of existing SLE classification criteria in a Southeast Asian cSLE cohort, but it is not without limitations. First, the data for patients diagnosed before 2009, before the setup of our registry, were retrieved retrospectively from medical records. However, this number represents the minority (n=15, 10%). Second, our control cohort is small. We selected only patients with MCTD and UCTD who posed an initial diagnostic challenge to test the diagnostic performance of the 3 criteria, simulating daily clinical practice, as the inclusion of healthy controls or patients with distinct rheumatic diseases often resulted in the overly optimal diagnostic performance of the classification criteria. Third, there is an inherent lack of an objective diagnosis as the standard of reference other than the treating physician's diagnosis, which could lead to inconsistency. Yet, this allowed the evaluation of classification criteria in a real-world setting. Lastly, our cSLE cohort is a heterogeneous cohort of mixed races. As the sample size was small, we could not examine the diagnostic performance in subgroups of patients according to race. We hope that with more data from the region, the diagnostic performance of these classification criteria in cSLE can be further validated.

CONCLUSION

The SLICC-2012 criteria had the highest sensitivity in this first study evaluating the SLE classification criteria performance in a Southeast Asian cohort, especially early in the disease course, while the ACR-1997 had the highest specificity both at diagnosis and over time. The low specificities of the SLICC-2012 and EULAR/ACR-2019 criteria in our study cautioned using these classification criteria in cSLE cohorts. Although the EULAR/ACR-2019 criteria did not confer additional benefits compared to the earlier two, adopting a cutoff score ≥13 instead of 10 further improved the diagnostic performance of the EULAR/ACR-2019 criteria in cSLE, making it comparative to the earlier 2 criteria.

Authors' contributions

All authors contributed to the study's conception and design. Kai Liang Teh (KLT), Yun Xin Book (YXB), and Thaschawee Arkachaisri (TA) performed data collection and interpretation. KLT and TA did the data analysis. KLT and TA wrote the first draft of the manuscript authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration

The authors have declared no conflicts of interest.

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ORIGINAL ARTICLE

Delayed presentation is associated with serious bacterial infections among febrile infants: A prospective cohort study

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ABSTRACT

Introduction: Febrile young infants are at risk of serious bacterial infections (SBIs), which are potentially life-threatening. This study aims to investigate the association between delayed presentation and the risk of SBIs among febrile infants.

Method: We performed a prospective cohort study on febrile infants ≤90 days old presenting to a Singapore paediatric emergency department (ED) between November 2017 and July 2022. We defined delayed presentation as presentation to the ED >24 hours from fever onset. We compared the proportion of SBIs in infants who had delayed presentation compared to those without, and their clinical outcomes. We also performed a multivariable logistic regression to study if delayed presentation was independently associated with the presence of SBIs.

Results: Among 1911 febrile infants analysed, 198 infants (10%) had delayed presentation. Febrile infants with delayed presentation were more likely to have SBIs (28.8% versus [vs] 16.3%, *P*<0.001). A higher proportion of infants with delayed presentation required intravenous antibiotics (64.1% vs 51.9%, *P*=0.001). After adjusting for age, sex and severity index score, delayed presentation was independently associated with the presence of SBI (adjusted odds ratio [AOR] 1.78, 95% confidence interval 1.26–2.52, *P*<0.001).

Conclusion: Febrile infants with delayed presentation are at higher risk of SBI. Frontline clinicians should take this into account when assessing febrile infants.

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Keywords: delayed presentation, emergency medicine, febrile infants, paediatrics, serious bacterial infections

CLINICAL IMPACT

What is New

- Febrile infants who present later are more likely to suffer from serious bacterial infections (SBIs) and require intravenous antibiotics.
- Even after accounting for age, sex and severity index score, delayed presentation continues to be an independent predictor of SBIs in these infants.

Clinical Implication

- When assessing febrile infants aged 0–90 days, clinicians should consider the timing of presentation as a significant factor.

INTRODUCTION

Young infants ≤90 days old are at risk of serious bacterial infections (SBIs) due to their immature immune systems and may develop severe complications resulting in neurocognitive deficits, hearing loss and even mortality.[1,2] The diagnosis of SBIs remains challenging as fever may be the only symptom of SBIs in this age group.[3] Clinicians need to weigh the risk of a missed or delayed diagnosis against the cost and harm of overdiagnosis and overtreatment.

Researchers have sought to derive and validate early predictors of SBI. Known clinical predictors for SBIs include high temperature, raised inflammatory markers including C-reactive protein (CRP), total white blood cell (WBC) count, absolute neutrophil count (ANC) and procalcitonin.[4,5] The PECARN rule used procalcitonin, ANC and urinalysis to identify febrile infants aged 29–60 days at low risk of SBIs, with the aim of reducing risk and cost from unnecessary hospital admissions and lumbar punctures.[6] The step-by-step approach uses a sequential method to identify febrile infants ≤90 days old at risk of SBI by considering age, clinical appearance, ANC, CPR and procalcitonin and

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urinalysis.[7] External validation of these prediction rules has demonstrated variable performance in different populations ≤90 days old.[5,8]

Previous studies have explored temperature as a predictor of SBIs. High temperatures are associated with the presence of SBIs,[9] and this has been validated in Singapore.[4] A secondary analysis of a multicentre prospective study reported a lower risk of SBIs in infants who had a history of fever but were afebrile on arrival to the emergency department (ED), as compared to infants who were febrile in ED (relative risk 0.68, 95% confidence interval [CI] 0.56–0.84).[10] In a study among children 3–36 months old, it was reported that every 1-hour increase in the duration of fever resulted in an increased odds of 1.01 for occult bacteraemia (adjusted odds ratio [AOR] 1.01; 95% CI 1.00–1.03, *P*=0.01), after adjusting for CRP and ANC.[11] However, among young infants ≤90 days old, there is limited literature on the association between the delayed presentation and the presence of SBIs.[12]

We aimed to investigate if delayed presentation (defined as arrival in the ED more than 24 hours after the onset of fever) is associated with the presence of SBIs among febrile infants ≤90 days of age. We also sought to compare the clinical characteristics of febrile infants with delayed presentation, with those who did not have delayed presentation.

METHOD

Study setting and design

We performed a prospective study among infants ≤90 days in the paediatric ED of KK Women's and Children's Hospital (KKH) in Singapore between November 2017 and July 2022. KKH is 1 of 2 paediatric tertiary centres in Singapore, and the ED sees about 150,000 children a year. Institutional review board (IRB) approvals were obtained for the conduct of this study. Between November 2017 and December 2020, patients were recruited as part of an ongoing study that sought to understand heart rate variability among febrile young infants (IRB: 2022/2457). From January 2021 to July 2022, we obtained IRB approval for the consecutive recruitment of all eligible febrile infants (IRB: 2017/2680).

Patient population

We recruited infants ≤90 days old with an axillary or rectal temperature of ≥38.0 °C. We excluded infants with than 35 weeks gestation, since these preterm infants would constitute a higher-risk population. These infants have a lower threshold for investigations and interventions in view of their prematurity. In KKH, all febrile infants ≤90 days old are hospitalised. Neonates <28 days old usually undergo a full septic workup that includes blood culture, urinalysis and urine culture, as well as cerebrospinal fluid (CSF) analysis and culture. Infants between 28 and 90 days old undergo further risk stratification and may receive a more limited workup depending on physician discretion. All infants are monitored until they are afebrile for 24 hours before discharge.

Study variables

The following were obtained at ED triage: temperature, heart rate and severity index score (SIS). Nurses obtained the temperature at triage, with the infant in a single layer of wrapping. Fever is defined as an axillary or rectal temperature of ≥38.0°C measured at triage. Heart rate was obtained from pulse oximetry. Where there was interference with movement, the heart rate was obtained manually. SIS is a composite score comprising respiratory effort, colour, activity, temperature and play, with a score of 10 (not very sick), 8–9 (moderately sick) and ≤7 (very sick).[13] We defined delayed presentation as infants who presented more than 24 hours after the onset of fever, as reported by parents. Laboratory results included WBC, ANC, haemoglobin, platelets, CRP and procalcitonin. We also recorded interventions such as fluid bolus and intravenous antibiotics.

Outcome measures

SBIs are defined as bacteraemia, urinary tract infections or bacterial meningitis.[14] Invasive bacterial infection (IBI) is defined as bacteraemia and/or bacterial meningitis.[8] UTI was defined as presence of a single bacteria of >100,000 colony-forming unit (CFU)/mL in a clean midstream sample odds ratio (OR) ≥50,000 CFU/mL in a catheterised sample or 10,000–50,000 CFU/mL in a catheterised sample with an abnormal urinalysis (positive for leukocyte esterase or nitrite).[15] Bacteraemia was defined as growth of a single bacterial pathogen in blood, excluding growth of contaminants (e.g. coagulase-negative *Staphylococcus* determined as a priori).[16] Bacterial meningitis was defined as CSF leucocytes >5 cells/uL and positive bacterial culture.[8] We also documented the hospital length of stay (in days).

Statistical analysis

Categorical variables were presented with frequencies and proportions, while continuous variables were presented using mean or median, with standard deviation (SD) or interquartile range (IQR), depending on whether the data were parametric. We compared the clinical presentation,

laboratory findings, management variables between infants with delayed presentation compared to those without. Categorical variables were analysed using the chi-square test, while continuous variables were analysed using the t-test or Wilcoxon rank-sum test, depending on normality.

We also performed a multivariable logistic regression to investigate if delayed presentation was independently associated with the presence of SBI. Variables were chosen based on their univariate significance as well as known risk factors in the literature and clinical discretion. Known predictors from the literature and earlier studies that we had performed in the febrile population were age, male sex and SIS.[5,6,12] Hence, we took these into account when performing the multivariable regression. We presented the unadjusted ORs and AORs, together with their *P* values. Statistical significance was taken at $P<0.05$. We did not perform multiple imputation for missing data unless there were more than 10% missing in the analysed variables.

RESULTS

Among 1912 patients analysed, 198 infants (10.4%) had delayed presentation (Fig. 1). The baseline demographics, clinical characteristics and outcomes are described in Table 1. Febrile infants with delayed presentation were significantly older compared to those without delayed presentation (mean 50 days SD 24.6 vs 38 days, SD 27.6 $P<0.001$). The mean temperature (38.6°C SD 0.6°C vs 38.4 °C SD 0.6°C, $P<0.001$) and mean heart rate (168/min SD 19.5 vs 161/min, SD 20.4, $P<0.001$) were significantly higher for infants with delayed presentation compared to those without.

When comparing the group with delayed presentation to the group without, the median CRP (10.3 mg/L, IQR 0.6–47.7 vs 1.5 mg/L, IQR 0.5–8.1, $P<0.001$), median WBC (12.1 x 10^9/L, IQR 9.1–15.9 vs 11.1 x 10^9/L, IQR 7.5–14.5, $P=0.001$) and median procalcitonin (0.1 ug/L, IQR 0.07–0.35 vs 0.08 ug/L, IQR 0.05–0.15, $P<0.001$) were higher (Table 2). The ANC for both groups was comparable (median 4.6 x 10^9/L, IQR 2.4–7.6 vs 3.9 x 10^9/L, IQR 2.2–6.5, $P=0.33$).

Fig. 1. Classification of recruited patients and incidence of serious bacterial infections (SBIs).

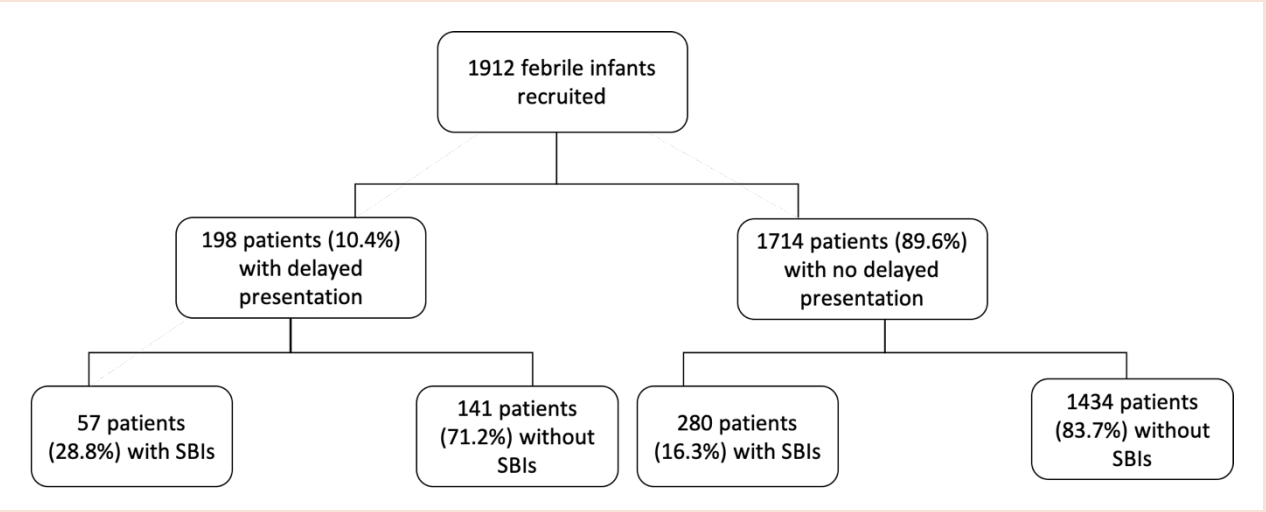

Table 1. Baseline demographics and clinical characteristics of infants with delayed presentation compared to those without delayed presentation.

Variables	Infants with delayed presentation (n=198)	Infants with no delayed presentation (n=1714)	*P* value
Age in days, mean ± SD	50 ± 24	38 ± 28	<0.001
Male sex, no. (%)	113 (57.1)	981 (57.2)	0.965
Temperature in °C, mean ± SD	38.6 ± 0.6	38.4 ± 0.6	<0.001
Heart rate/min, mean ± SD	168 ± 20	161 ± 20	<0.001
SIS, median (IQR)	9 (8–9)	9 (9–10)	<0.001

IQR: interquartile range; SD: standard deviation; SIS: severity index score

Table 2. Laboratory results of infants with delayed presentation compared to those without delayed presentation.

Variables	Infants with delayed presentation (n=198)	Infants with no delayed presentation (n=1714)	*P* value
Haemoglobin in g/dL	11.3 (10.3–12.9)	12.1 (10.8–15.8)	<0.001
Total white cell count x 10^9/L	12.1 (9.1–15.9)	11.1 (7.5–14.5)	0.001
Absolute neutrophil count x 10^9/L	4.6 (2.4–7.6)	3.9 (2.2–6.5)	0.33
Platelets x 10^9/L	419 (324–509)	396 (323–484)	0.106
C-reactive protein in mg/L	10.3 (0.6–47.7)	1.5 (0.5–8.1)	<0.001
Procalcitonin in ug/L	0.10 (0.07–0.35)	0.08 (0.05–0.15)	<0.001

All values are in median (interquartile range).

There were 337 infants with SBIs, among whom 37 (11.0%) had meningitis or bacteraemia (defined as IBIs) and 300 (89.0%) were UTIs (Table 3). Infants with delayed presentation were more likely to have SBIs in general (28.8% vs 16.3%, *P*<0.001), specifically UTIs (25.8% vs 14.5%, *P*<0.001) and require intravenous antibiotics (64.1% vs 51.9%, *P*=0.001), compared to those without delayed presentation. IBI rates (3.0% vs 1.8%, *P*=0.237) and requirement for fluid bolus (6.1% vs 3.5%, *P*=0.073) were comparable between the 2 groups. We did not find clinically important differences in the median length of hospital stay.

In the multivariable logistic regression (Table 4), after adjusting for age, sex and SIS, we found that delayed presentation was independently associated with the presence of SBIs (AOR 1.78 95% CI 1.26–2.52, *P*<0.001). Male sex and low SIS were also independently associated with the presence of SBIs (AOR 2.47 95% CI 1.89–3.23, *P*<0.001 and AOR 0.66 95% CI 0.57–0.77, *P*<0.001). After adjustment, delayed presentation was an indepen= dent predictor for UTI (AOR 1.75 95% CI 1.22–2.51, *P*=0.002) but not for IBI (AOR 1.63 95% CI 0.65–4.08, *P*=0.298) (Supplementary Tables S1 and S2).

Table 3. Clinical outcomes of infants with delayed presentation compared to those without delayed presentation.

Variables	Infants with delayed presentation (n=198)	Infants with no delayed presentation (n=1714)	*P* value
SBI, no. (%)	57 (28.8)	280 (16.3)	<0.001
Urinary tract infections, no. (%)	51 (25.8)	249 (14.5)	<0.001
Invasive bacterial infections, no. (%)	6 (3.0)	31 (1.8)	0.237
Antibiotics, no. (%)	127 (64.1)	890 (51.9)	0.001
Fluid bolus, no. (%)	12 (6.1)	60 (3.5)	0.073
Length of hospital stay in days, median (IQR)	3.00 (3–4)	3.00 (2–4)	0.009

IQR: interquartile range; SBI: serious bacterial infection
Invasive bacterial infections = bacteraemia and meningitis

Table 4. Multivariable logistic regression for delayed presentation in predicting the presence of serious bacterial infections in febrile infants.

Variables	Unadjusted odds ratio (95% CI)	Unadjusted *P* value	Adjusted odds ratio (95% CI)	Adjusted *P* value
Age in days	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	0.054
Male sex	2.45 (1.88–3.18)	<0.001	2.47 (1.89–3.23)	<0.001
Severity index score	0.63 (0.54–0.72)	<0.001	0.66 (0.57–0.77)	<0.001
Delayed presentation	2.07 (1.48–2.89)	<0.001	1.78 (1.26–2.52)	0.001

CI: confidence interval
Bold text represents the variable of interest.

We also compared the prevalence of SBI between 2 subgroups in our study population—neonates and infants between 29–90 days old. The prevalence of SBI in neonates was 13%; this was 20.6% in infants between 28–90 days old. On performing a sensitivity analysis, we found that delayed presentation was independently associated with SBI among neonates (AOR 2.50, 95% CI 1.13–5.49, *P*=0.023) and in older infants between 29–90 days old (AOR 1.64, 95% CI 1.12–2.41, *P*=0.012) (Supplementary Tables S3 and S4).

DISCUSSION

In this prospective cohort study among febrile infants ≤90 days old, we found that febrile infants with delayed presentation (>24 hours from fever onset) were more likely to have SBIs (AOR 1.78 95% CI 1.26–2.52, *P*<0.001) after adjusting for age, sex and SIS, and were more likely to require intravenous antibiotics (64.1% vs 51.9%, *P*=0.001). Further analysis showed that delayed presentation is associated with increased risk of SBI both in neonates and older infants between 29–90 days old.

Febrile infants are at risk of SBIs, with a reported prevalence of 9–25%.[8,17] Early identification enables the timely initiation of antibiotics which reduces mortality, and shortens the duration of hospitalisation.[18,19] Delayed presentation potentially leads to delayed investigations and administration of empirical antibiotics, resulting in a higher risk of sepsis and death.[19-21] Our findings highlight the importance of vigilance, especially among febrile infants who present >24 hours after fever onset. These infants require a robust assessment with consideration for early antibiotics.

Although the specific association between delayed presentation to the ED and risk of SBI has not been evaluated, several other studies have reported the relationship between duration of fever and SBIs in febrile children.[12] Some studies among patients up to 36 months old report that a longer duration of fever was associated with an increased risk of SBI.[22,23] However, in a systematic review, the duration of fever was not significantly associated with SBIs among children 1 month–18 years old presenting to ambulatory care settings in developed countries.[24] Similarly, another systematic review done among children between 2 months and 6 years old showed that fever duration was inconclusive for SBI.[25] We recognise that the patient populations in these systematic reviews included children, which differ from ours. We chose to focus on the young infant population ≤90 days old, who are at high risk of SBIs due to their immature immune system. This group warrants close monitoring and prioritisation of investigations and early management.

Additionally, it is not presently known whether the significance of this association differs depending on the different types of SBIs. Young children with fever lasting >48 hours have been reported to have a higher likelihood of UTIs.[26] We did find that infants with delayed presentations were more likely to have an underlying UTI. There were smaller numbers with IBI (i.e. both meningitis and bacteraemia) in our population. Despite not achieving statistical significance, we did find that the proportion of those with IBIs was almost double in the group with delayed presentation compared to those without delayed presentation. In a prospective cohort study conducted in 9 paediatric emergency centres, the duration of fever in young children with and without bacteraemia were comparable.[27,28] We postulate that the strength of association between delayed presentation and disease may differ between different types of SBIs due in part to the different rate of clinical progression of these conditions. Future larger prospective studies should consider investigating this association stratified by different types of SBIs.

We recognise the limitations of this study. First, while the prospective nature of this study allowed for variables determined a priori to be captured, this was a single-centre study and the findings require external validation. Second, in view of differences in clinical practices among physicians in the management of febrile infants, not all infants recruited to the study had the complete diagnostic tests performed, which makes it possible that some SBIs were missed. However, we believe that this number is small because it is our institutional practice that all infants are monitored in the hospital until afebrile for at least 24 hours. Furthermore, we did not account for any treatments received by the infant prior to the emergency visit. We did not have the necessary information to investigate socioeconomic status of these families and the association with delayed presentation, which could potentially impact health education policies. Future studies should investigate socio-economic status in SBI epidemiology and outcomes. Third, as part of routine clinical practice, ED nurses usually measure axillary temperature because it is less invasive than rectal temperature. However studies have shown that rectal temperature is more accurate in infants.[29,30] Finally, the number of infants with IBIs was small, limiting our conclusions on delayed presentation in this subpopulation.

CONCLUSION

In conclusion, febrile infants with delayed presentation >24 hours from fever onset are at higher risk of SBIs. As such, clinicians should take this into account when assessing febrile infants. In addition, future studies should evaluate the association between delayed presentation and specific types of SBIs. Such findings have potential for translation into clinical risk stratification protocols in the ED.

Supplementary materials

Table S1. Multivariable logistic regression for delayed presentation in predicting the presence of urinary tract infections among febrile infants.

Table S2. Multivariable logistic regression for delayed presentation in predicting the presence of invasive bacterial infections among febrile infants.

Table S3. Multivariable logistic regression for delayed presentation in predicting the presence of serious bacterial infections in neonates less than 28 days old.

Table S4. Multivariable logistic regression for delayed presentation in predicting the presence of serious bacterial infections in infants 29 days to 60 days old.

Author contributions

KPR, NS and S-LC made substantial contributions to the conception and design of the work, the analysis and interpretation, drafted the initial manuscript and revised it critically for important intellectual content. SS contributed in the conception and design of the work, data interpretation and drafting of the initial manuscript. SG, ZXK and GY-KO contributed in the analysis, interpretation of data for the work, revising it critically for important intellectual content. LW and RP acquired and interpreted the data, and revised the draft for important intellectual content. All authors agree for the final approval of the version to be published and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Prevalence and risk factors of depression and anxiety in primary care

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ABSTRACT

Introduction: Anxiety and depressive disorders are highly prevalent mental health conditions worldwide. However, little is known about their specific prevalence in primary care settings. This study aimed to determine the prevalence of depression and anxiety in the primary care population and identify associated patient characteristics.

Method: We conducted a cross-sectional study using stratified sampling by age with a self-administered questionnaire survey in Singapore's National Healthcare Group Polyclinics from December 2021 to April 2022. A total score of Patient Health Questionnaire-9 (PHQ-9) ≥10 represents clinical depression, and a total score of Generalised Anxiety Disorder-7 (GAD-7) ≥10 indicates clinical anxiety. Multivariable logistic regression was used to identify the factors associated with depression and anxiety.

Results: A total of 5694 patients were approached and 3505 consented to the study (response rate=61.6%). There was a higher prevalence of coexisting clinical depression and anxiety (DA) (prevalence=5.4%) compared to clinical depression only (3.3%) and clinical anxiety only (1.9%). The odds of having DA were higher among those aged 21–39 years (odds ratio [OR] 13.49; 95% confidence interval [CI] 5.41–33.64) and 40–64 years (OR 2.28; 95% CI 1.03–5.03) compared to those ≥65 years. Women had higher odds of having DA (OR 2.33; 95% CI 1.54–3.50) compared to men. Respondents with diabetes had higher odds of having DA (OR 1.78; 95% CI 1.07–2.94) compared to those without diabetes.

Conclusion: Coexisting clinical depression and anxiety are significantly present in the primary care setting, especially among younger individuals, patients with diabetes and women. Mental health screening programmes should include screening for both depression and anxiety, and target these at-risk groups.

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Keywords: comorbidity, family medicine, general practice, mental health, psychology

CLINICAL IMPACT

What is New

- To our knowledge, this study is the first to examine the prevalence of clinical depression and anxiety in the Singapore primary care setting.
- Findings highlight the burden of mental illness in primary care and its associated factors.

Clinical Implications

- The study supports the screening for coexisting depression and anxiety, rather than either one alone, especially in at-risk groups such as younger individuals, patients with diabetes and women.
- This data can potentially help policymaking and guide efforts to improve community mental wellness in Singapore.

INTRODUCTION

The global prevalence of individuals living with a mental disorder in 2019 was 970 million, with anxiety and depressive disorders being the most common.[1] The Singapore Mental Health Study 2016 showed that the lifetime prevalence of at least one mood, anxiety or alcohol use disorder was 13.9% in the adult Singaporean population. Major depressive disorder (MDD) had the highest lifetime prevalence of 6.3%, and the lifetime prevalence of generalised anxiety disorder (GAD) was 1.2%.[2] People with chronic diseases, such as diabetes, coronary heart disease and stroke, had a higher prevalence of depression and anxiety.[3]

The Singapore inter-agency COVID-19 Mental Wellness Taskforce Report found a majority

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preference to seek help from primary care providers for emotional or psychological problems related to COVID-19.[4] Findings from the Mind Matters study in 2014 similarly indicated that individuals would seek help from general practitioners for various mental health conditions.[5]

With this trend in help-seeking behaviour, coupled with a growing movement towards community prevention and management of mental illness, this study aimed to determine the prevalence of depression and anxiety in the Singapore primary care setting, and identify the associated factors of patients with depression and anxiety. This is particularly relevant given the paucity of relevant literature to guide practice and intervention.

METHOD

Study setting, design, recruitment and data collection

Primary care is provided through an islandwide network of outpatient polyclinics and clinics run by private general practitioners in Singapore. At the time of study in 2021, 23 polyclinics were organised into 3 healthcare clusters, of which the National Healthcare Group (NHG) ran 7 polyclinics located in the north and central regions (at the time of publication, there are 26 polyclinics with 9 run by NHG).[6] We conducted a cross-sectional study among patients ≥21 years old, who visited any of the 7 NHG polyclinics between December 2021 to April 2022, during the COVID-19 pandemic.

To reduce selection bias, patients were approached for recruitment via systematic sampling based on the last digit of their registration queue numbers. These polyclinic-specific queue numbers were generated daily and assigned in ascending order by a central computerised system according to the sequence of patient registration at the polyclinic. On Mondays, Wednesday and Fridays, only patients with an odd number as the last digit of their queue numbers were approached. On Tuesdays, Thursdays and Saturdays, only patients with an even number in the last digit of their queue numbers were approached.

Patients who were incapable of completing the questionnaire due to severe physical or mental conditions or language barriers were excluded. Eligible patients who agreed to participate in the study were asked to sign on the written consent forms that indicated approval for their electronic medical records to be accessed after completing a set of questionnaires. The set of self-administered questionnaires were provided in patients' preferred language (English, Chinese or Malay) for their completion while they waited to be seen by their healthcare professional at the polyclinic. Patient education materials on mental health were given to every respondent upon questionnaire completion.

Relevant diagnoses of cardiovascular disease, diabetes (including pre-diabetes) and stroke (including transient ischaemic attack) were retrieved from respondents' electronic medical records by the study team.

Study instruments

Socio-demographic questionnaire

Data on sex, age, ethnicity, marital status, highest education level attained, employment status and type of dwelling were collected.

Quality of life and social support questionnaires

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L) is a 5-level patient-reported tool that measures health-related quality of life. It consists of the 5-dimension descriptive system (EQ-5D) and the visual analogue scale (EQ-VAS). The EQ-5D evaluates 5 items related to health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. There are 5 possible responses for each item, which is scored 1 to 5 respectively: no problems, slight problems, moderate problems, severe problems and extreme problems. Scores from the 5 items are used to derive a single utility index. The utility index ranges from -1.00 (worst possible health state) to 1.00 (perfect health state). The EQ-VAS is a vertical scale that is scored from 0 (worst imaginable health state) to 100 points (best imaginable health state). A higher score indicates better health status.[7,8]

The modified Medical Outcomes Study Social Support Survey (mMOS-SS) is an 8-item self-reported measure of individual experience of social support, with 2 subscale measures of emotional support and instrumental support. Respondents rate how often they receive support for physical needs and emotional assistance using these ratings: 1 = "none of the time", 2 = "a little of the time", 3 = "some of the time", 4 = "most of the time" and 5 = "all of the time". The score for mMOS-SS is calculated as the average score of subscale items transformed to a 0 to 100 scale, with higher scores indicating more support.[9]

Mental health questionnaires

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item tool that screens for and measures the severity of self-reported depression. The response options to each item are 0 = "not at all",

1 = "several days", 2 = "more than half the days" and 3 = "nearly every day". A 2-week recall period is used. The total score ranges from 0 to 27, with a higher score indicating greater self-reported depression. A total score of ≥10 indicates clinical depression, with a sensitivity of 80% and specificity of 92%.[10-12]

The Generalised Anxiety Disorder-7 (GAD-7) is a 7-item tool that screens for and measures the severity of self-reported anxiety. The response options to each item are 0 = "not at all", 1 = "several days", 2 = "more than half the days", and 3 = "nearly every day". A 2-week recall period is used. The total score ranges from 0 to 21, with a higher score indicating greater self-reported anxiety. A total score of ≥10 indicates clinical anxiety, with a sensitivity of 89% and specificity of 82%.[12-14]

Sample size estimation

Sample size estimation was based on previously published data, which reported the prevalence of depression in Singapore's primary care of 10.8%.[15] Considering a 5% margin of error and achieving a comparable representation across 3 age groups, namely 21–39 years, 40–64 years and ≥65 years, the approximate sample size of 3299 was obtained.

Statistical analysis

Descriptive statistics were used to describe the socio-demographic profile of respondents. Mean score of EQ-5D utility index, mean score of EQ-VAS, mean score of mMOS-SS, prevalence of clinical depression (PHQ-9≥10) and clinical anxiety (GAD-7≥10) were calculated. We further described the prevalence of 3 clinical categories and considered them as outcome variables in the subsequent statistical analysis. The 3 clinical categories were: (1) respondents with clinical depression only (DO), i.e. PHQ-9≥10, GAD-7<10; (2) respondents with clinical anxiety only (AO), i.e. PHQ-9<10, GAD-7≥10; and (3) respondents with coexisting clinical depression and anxiety (DA), i.e. PHQ-9≥10, GAD-7≥10. Associations between the socio-demographic variables, EQ-5D, EQ-VAS, mMOS-SS and presence of diabetes/cardiovascular disease/stroke with the 3 clinical outcome categories above were explored using multivariable logistic regression. All statistical analyses were performed using R statistical software version 4.1.2 (R Core Team 2021, Vienna, Austria)[16] with P values <0.05 indicating statistical significance.

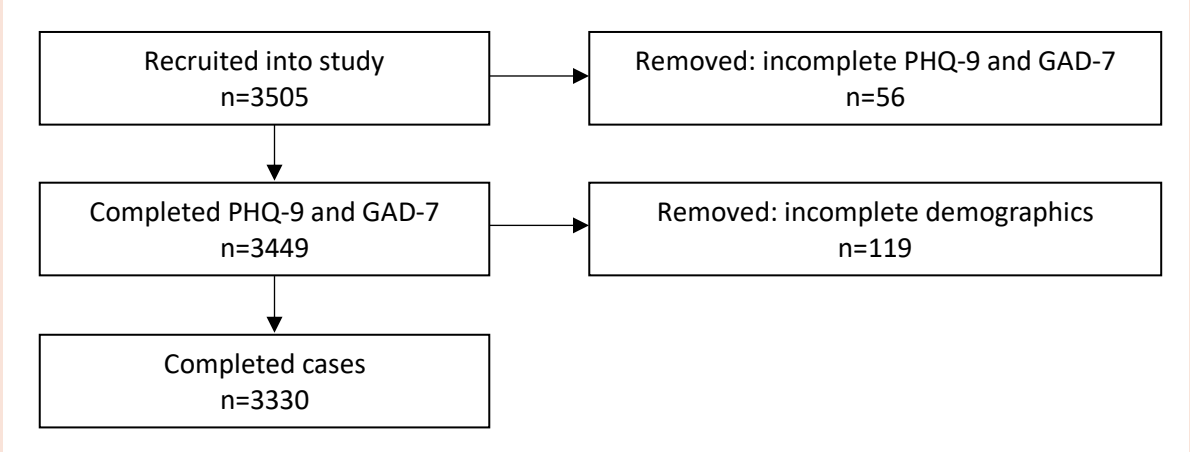
Approval from the NHG Domain Specific Review Board was obtained for the study methods (Reference number: 2021/00741).

RESULTS

A total of 5694 patients were approached across 7 NHG polyclinics and 3505 consented to the study (response rate=61.6%). Respondents with incomplete PHQ-9 and GAD-7 components of the questionnaire (n=56) and those with incomplete demographic information (n=119) were removed from the analysis. The remaining 3330 completed questionnaires were used for the study analysis (see Fig. 1).

The mean age of the respondents was 52.3 years old (SD=17.1). There were 1797 (54.0%) male respondents, 2313 (69.5%) were Chinese, 2105 (63.2%) were married, 1873 (56.2%) were working full time, 805 (24.2%) did not complete secondary education and 201 (6.0%) stayed in a 1-room or 2-room Housing and Development Board apartment (managed by the public housing authority in Singapore).

Fig. 1. Participant inclusion flowchart.



The overall prevalence of clinical depression was 8.7% (n=289) and the overall prevalence of clinical anxiety was 7.3% (n=243). Of the respondents, 3.3% (n=110) had DO, 1.9% (n=64) had AO, and 5.4% (n=179) had DA. The prevalences of DO, AO and DA were consistently the highest in respondents who were 21–39 years old, followed by respondents who were 40–64 years old.

The mean EQ-5D utility index was 0.85 (SD=0.20) and the mean EQ-VAS was 78.1 (SD=15.9). Respondents with DA had the lowest EQ-5D utility index (mean=0.53, SD=0.26) compared to respondents who had DO (mean=0.66, SD=0.25) and AO (mean=0.72, SD=0.16). This trend was also observed for the EQ-VAS score.

The mean mMOS-SS score was 60.2 (SD=30.3). Respondents with AO had the highest mMOS-SS score (mean=62.6, SD=19.1) compared to all other clinical categories, even those without any clinical depression or anxiety. Respondents with DA had the lowest mMOS-SS score (mean=49.7, SD=26.8).

Of the 3330 respondents, 38.6% (n=1,286) of them had diabetes, 9.3% (n=310) had cardiovascular disease and 4.7% (n=158) had stroke recorded in their electronic medical records.

Descriptive analysis of the respondents without missing data, stratified according to the 3 clinical categories (DO, AO and DA) are in Table 1.

Associated factors

Multinomial logistic regression was conducted to explore the factors associated with the 3 clinical categories (Table 2).

Younger age groups exhibited a stronger association with both depressive symptoms (DO) and anxiety symptoms (DA) compared with older individuals. Those aged 21–39 years (OR 13.49; 95% CI 5.41–33.64) and 40–64 years (OR 2.28; 95% CI 1.03–5.03) had higher odds of DA than those aged ≥65 years. Similarly, for DO, elevated odds were seen in the 21–39 years group (OR 6.34; 95% CI 2.50–16.09) compared to those aged ≥65 years. In terms of sex, females had greater odds of DA (OR 2.33; 95% CI 1.54–3.50) than males. Regarding employment, National Service men had significantly higher odds of DO (OR 2.52; 95% CI 1.14–5.57) compared with full-time employees, while homemakers had lower odds of DA (OR 0.23; 95% CI 0.06–0.87). Individuals with diabetes had higher odds of DA (OR 1.78; 95% CI 1.07–2.94) compared with those without diabetes. Respondents with higher EQ-5D-5L utility index scores or EQ-VAS scores were less likely to have DO, AO and DA. Similarly, higher mMOS-SS scores were associated with lower odds of DO (OR 0.99; 95% CI 0.98–1.00) and DA (OR 0.99; 95% CI 0.98–0.99). No statistically significant associations were found for ethnicity, education level, marital status, and type of dwelling with DO, AO or DA.

DISCUSSION

To our knowledge, this is the first study that examined the prevalence of depression and anxiety in the Singapore primary care setting. Anxiety and depressive disorders are known to coexist with each other. A worldwide survey reported that 45.7% of individuals with lifetime major depressive disorder had a history of one or more anxiety disorders.[17] Our study observed that respondents with DA had the lowest EQ-5D-5L utility index and lowest EQ-VAS, which indicated a poorer health state and poorer quality of life. Studies have found that patients with MDD and comorbid anxiety disorders tend to have more depressive episodes, greater functional impairment, and greater severity of episodes than individuals with MDD alone.[18,19] Early recognition of comorbid clinical depression or anxiety in anxiety disorders and depression disorders, respectively, affects management and prevents worsening of the conditions. Hence, screening for clinical depression and anxiety should be encouraged in patients presenting with symptoms suggestive of either. Mental health screening programmes should also consider screening for both depression and anxiety rather than either one alone.

There is a higher prevalence of DA in the younger population (90.5%), who also reported more severe symptoms. A study of patients with multiple chronic conditions found that patients <65 years old were more likely to report depression and worse quality of life, compared with those ≥65 years old.[20] Findings from a study in Singapore noted that young adults between 21–29 years old and adults between 40–49 years old reported declining mental and emotional health due to various family, workplace and societal factors.[21] Based on the Global Health Estimates 2020, the top 10 causes of disability-adjusted life years (DALY) in Singapore for both sexes between 20–50 years old included depressive disorder and anxiety disorders.[22] There is an urgency to reduce DALYs especially among the young, as Singapore's strategic resource is its human capital. However, resource constraints in healthcare limit the help available to them. Moreover, these patients are often not forthcoming with their mood issues. The use of digital mental health tools that provide targeted self-help resources and brief psychotherapy may be an effective intervention as the young are

Table 1. Descriptive analysis of respondents without missing data (n=3330).

	PHQ-9<10 & GAD-7<10 (n=2977)	PHQ-9≥10 & GAD-7<10 (DO) (n=110)	PHQ-9<10 & GAD-7≥10 (AO) (n=64)	PHQ-9≥10 & GAD-7≥10 (DA) (n=179)	Total (n=3330)	*P* value
Age, years						<0.001
21–39	737 (24.8%)	65 (59.1%)	37 (57.8%)	119 (66.5%)	958 (28.8%)	
40–64	1185 (39.8%)	29 (26.4%)	20 (31.2%)	43 (24.0%)	1277 (38.3%)	
≥65	1055 (35.4%)	16 (14.5%)	7 (10.9%)	17 (9.5%)	1095 (32.9%)	
Sex						0.061
Male	1629 (54.7%)	56 (50.9%)	31 (48.4%)	81 (45.3%)	1797 (54.0%)	
Female	1348 (45.3%)	54 (49.1%)	33 (51.6%)	98 (54.7%)	1533 (46.0%)	
Ethnicity						<0.001
Chinese	2113 (71.0%)	64 (58.2%)	41 (64.1%)	95 (53.1%)	2313 (69.5%)	
Malay	457 (15.4%)	25 (22.7%)	11 (17.2%)	54 (30.2%)	547 (16.4%)	
Indian	275 (9.2%)	12 (10.9%)	11 (17.2%)	24 (13.4%)	322 (9.7%)	
Others	132 (4.4%)	9 (8.2%)	1 (1.6%)	6 (3.4%)	148 (4.4%)	
Marital status						<0.001
Never married/single	691 (23.2%)	50 (45.5%)	34 (53.1%)	93 (52.0%)	868 (26.1%)	
Married	1963 (65.9%)	49 (44.5%)	26 (40.6%)	67 (37.4%)	2105 (63.2%)	
Separated/divorced/widowed/others	323 (10.8%)	11 (10.0%)	4 (6.2%)	19 (10.6%)	357 (10.7%)	
Highest level of education attained						<0.001
Below secondary	755 (25.4%)	18 (16.4%)	8 (12.5%)	24 (13.4%)	805 (24.2%)	
Secondary and pre-university	907 (30.5%)	21 (19.1%)	13 (20.3%)	43 (24.0%)	984 (29.5%)	
Diploma and professional qualification	615 (20.7%)	43 (39.1%)	19 (29.7%)	74 (41.3%)	751 (22.6%)	
Degree and above	700 (23.5%)	28 (25.5%)	24 (37.5%)	38 (21.2%)	790 (23.7%)	

Table 1. Descriptive analysis of respondents without missing data (n=3330). (Cont'd)

	PHQ-9<10 & GAD-7<10 (n=2977)	PHQ-9≥10 & GAD-7<10 (DO) (n=110)	PHQ-9<10 & GAD-7≥10 (AO) (n=64)	PHQ-9≥10 & GAD-7≥10 (DA) (n=179)	Total (n=3330)	*P* value
Main work status, over the last 12 months						<0.001
Working (full-time)	1669 (56.1%)	57 (51.8%)	44 (68.8%)	103 (57.5%)	1873 (56.2%)	
Working (part-time)	326 (11.0%)	10 (9.1%)	5 (7.8%)	18 (10.1%)	359 (10.8%)	
Student (full-time)	62 (2.1%)	3 (2.7%)	4 (6.2%)	10 (5.6%)	79 (2.4%)	
National Service[a]	66 (2.2%)	15 (13.6%)	2 (3.1%)	18 (10.1%)	101 (3.0%)	
Homemaker/housewife	257 (8.6%)	11 (10.0%)	2 (3.1%)	3 (1.7%)	273 (8.2%)	
Retired	460 (15.5%)	8 (7.3%)	1 (1.6%)	9 (5.0%)	478 (14.4%)	
Unemployed	137 (4.6%)	6 (5.5%)	6 (9.4%)	18 (10.1%)	167 (5.0%)	
Type of dwelling						0.043
HDB 1-room/2-room apartment[b]	172 (5.8%)	5 (4.5%)	4 (6.2%)	20 (11.2%)	.0%)	
Other types of housing	2805 (94.2%)	105 (95.5%)	60 (93.8%)	159 (88.8%)	3129 (94.0%)	
EQ-5D-5L utility index						<0.001
Mean (SD)	0.88 (0.17)	0.66 (0.25)	0.72 (0.16)	0.53 (0.26)	0.85 (0.20)	
Median (Q1, Q3)	0.88 (0.85, 1.00)	0.74 (0.55, 0.88)	0.75 (0.64, 0.86)	0.56 (0.36, 0.73)	0.88 (0.76, 1.00)	
Range	-0.56–1.00	-0.21–1.00	0.29–1.00	-0.26–1.00	-0.56–1.00	
EQ-VAS						<0.001
Mean (SD)	79.97 (14.78)	61.86 (15.47)	68.69 (13.86)	59.38 (15.75)	78.05 (15.89)	
Median (Q1, Q3)	80.00 (70.00, 90.00)	61.00 (50.00, 70.00)	70.00 (60.00, 80.00)	60.00 (50.00, 70.00)	80.00 (70.00, 90.00)	
Range	3.00–100.00	25.00–95.00	35.00–100.00	10.00–100.00	3.00–100.00	

Table 1. Descriptive analysis of respondents without missing data (n=3330). (Cont'd)

	PHQ-9<10 & GAD-7<10 (n=2977)	PHQ-9≥10 & GAD-7<10 (DO) (n=110)	PHQ-9<10 & GAD-7≥10 (AO) (n=64)	PHQ-9≥10 & GAD-7≥10 (DA) (n=179)	Total (n=3330)	*P* value
mMOS-SS						<0.001
Mean (SD)	61.13 (30.78)	51.48 (23.33)	62.60 (19.13)	49.72 (26.82)	60.22 (30.32)	
Median (Q1, Q3)	68.75 (37.50, 87.50)	50.00 (35.16, 65.62)	62.50 (50.00, 75.00)	50.00 (31.25, 70.31)	65.62 (37.50, 84.38)	
Range	0.00–100.00	0.00–100.00	28.12–100.00	0.00–100.00	0.00–100.00	
Diabetes (including pre-diabetes)						<0.001
No	1772 (59.5%)	86 (78.2%)	48 (75.0%)	138 (77.1%)	2044 (61.4%)	
Yes	1205 (40.5%)	24 (21.8%)	16 (25.0%)	41 (22.9%)	1286 (38.6%)	
Cardiovascular disease (angina, myocardial infarction, atrial fibrillation, poor circulation of lower limbs)						0.041
No	2685 (90.2%)	104 (94.5%)	61 (95.3%)	170 (95.0%)	3020 (90.7%)	
Yes	292 (9.8%)	6 (5.5%)	3 (4.7%)	9 (5.0%)	310 (9.3%)	
Stroke (including transient ischaemic attack)						0.955
No	2833 (95.2%)	105 (95.5%)	62 (96.9%)	172 (96.1%)	3172 (95.3%)	
Yes	144 (4.8%)	5 (4.5%)	2 (3.1%)	7 (3.9%)	158 (4.7%)	

AO: clinical anxiety only; DA: coexisting clinical depression and anxiety; DO: clinical depression only; EQ-5D-5L: EuroQol Group 5-dimension 5-level Self-Report Questionnaire; EQ-VAS: EuroQol Group visual analogue scale; GAD-7: Generalised Anxiety Disorder-7; HBD: Housing and Development Board; mMOS-SS: modified Medical Outcomes Study Social Support Survey; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation

[a] National Service: A 2-year mandatory conscription duty that every male citizen and permanent resident in Singapore must undertake upon attaining the age of 18.

[b] HDB 1-room/2-room: public housing 1-room and 2-room apartments managed by HDB, the state's public housing authority.

All values in no. (%) unless indicated otherwise.

Table 2. Multinomial logistic regression analysis of respondents without missing data (n=3330).

	PHQ-9≥10 & GAD-7<10 (DO)			PHQ-9<10 & GAD-7≥10 (AO)			PHQ-9 & GAD-7≥10 (DA)		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age, years									
≥65	Ref			Ref			Ref		
21–39	6.34	2.50–16.09	<0.001	3.15	0.98–10.10	0.05	13.49	5.41–33.64	<0.001
40–64	1.85	0.84–4.04	0.12	1.55	0.57–4.23	0.39	2.28	1.03–5.03	0.04
Sex									
Male	Ref			Ref			Ref		
Female	1.36	0.85–2.19	0.20	1.32	0.77–2.28	0.31	2.33	1.54–3.50	<0.001
Ethnicity									
Chinese	Ref			Ref			Ref		
Malay	1.28	0.74–2.18	0.38	1.02	0.50–2.11	0.95	1.49	0.94–2.36	0.09
Indian	1.16	0.58–2.29	0.68	1.92	0.93–3.92	0.08	1.31	0.73–2.34	0.36
Others	1.67	0.73–3.84	0.23	0.33	0.04–2.50	0.28	0.50	0.17–1.44	0.20
Marital status									
Married	Ref			Ref			Ref		
Never married/single	1.01	0.58–1.75	0.97	1.85	0.97–3.54	0.06	0.98	0.61–1.57	0.93
Separated/divorced/widowed/others	1.07	0.51–2.26	0.86	0.85	0.27–2.63	0.77	0.77	0.39–1.51	0.44

Table 2. Multinomial logistic regression analysis of respondents without missing data (n=3330). (Cont'd)

	PHQ-9≥10 & GAD-7<10 (DO)			PHQ-9<10 & GAD-7≥10 (AO)			PHQ-9 & GAD-7≥10 (DA)		
	Odds ratio	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Highest level of education attained									
Below secondary	Ref			Ref			Ref		
Secondary and pre-university	0.78	0.39 to–1.59	0.50	1.11	0.43–2.87	0.83	1.26	0.65–2.43	0.49
Diploma and professional qualification	1.14	0.54–2.41	0.73	1.19	0.43–3.27	0.74	1.32	0.65–2.67	0.44
Degree and above	0.95	0.44–2.05	0.90	1.38	0.51–3.74	0.53	0.86	0.41–1.82	0.70
Main work status, over the last 12 months									
Working (full-time)	Ref			Ref			Ref		
Working (part-time)	1.46	0.69–3.09	0.32	0.91	0.34–2.41	0.85	1.50	0.78–2.87	0.22
Student (full-time)	0.65	0.18–2.35	0.51	1.12	0.36–3.47	0.84	1.34	0.57–3.16	0.50
National Service[a]	2.52	1.14–5.57	0.02	0.56	0.12–2.59	0.46	1.87	0.87–4.01	0.11
Homemaker/housewife	2.30	1.00–5.29	0.05	0.50	0.11–2.32	0.38	0.23	0.06–0.87	0.03
Retired	1.62	0.61–4.31	0.33	0.20	0.02–1.69	0.14	1.05	0.38–2.90	0.93
Unemployed	1.38	0.53–3.58	0.51	1.95	0.74–5.14	0.18	1.74	0.83–3.64	0.14
Type of dwelling									
HDB 1-room/2-room apartment[b]	Ref			Ref			Ref		
Other types of housing	1.88	0.70–5.07	0.21	1.09	0.36–3.32	0.88	1.00	0.50–2.01	1.00
EQ-5D-5L utility index	0.05	0.02–0.11	<0.001	0.05	0.02–0.15	<0.001	0.01	0.00–0.01	<0.001
EQ-VAS	0.96	0.94–0.97	<0.001	0.98	0.96–0.99	<0.01	0.96	0.95–0.97	<0.001
mMOS-SS	0.99	0.98–1.00	<0.01	1.00	0.99–1.01	0.38	0.99	0.98–0.99	<0.001

Table 2. Multinomial logistic regression analysis of respondents without missing data (n=3330). (Cont'd)

	PHQ-9≥10 & GAD-7<10 (DO)			PHQ-9<10 & GAD-7≥10 (AO)			PHQ-9 & GAD-7≥10 (DA)		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Diabetes (including pre-diabetes)									
No	Ref			Ref			Ref		
Yes	0.99	0.57–1.74	0.98	1.28	0.65–2.52	0.47	1.78	1.07–2.94	0.03
Cardiovascular disease (angina, myocardial infarction, atrial fibrillation, poor circulation of lower limbs)									
No	Ref			Ref			Ref		
Yes	0.93	0.36–2.45	0.89	1.00	0.28–3.56	1.00	1.17	0.48–2.86	0.72
Stroke (including transient ischaemic attack)									
No	Ref			Ref			Ref		
Yes	1.97	0.70–5.60	0.20	1.30	0.29–5.83	0.73	1.44	0.51–4.11	0.49

AO: clinical anxiety only; CI: confidence interval; DA: coexisting clinical depression and anxiety; DO: clinical depression only; EQ-5D-5L: EuroQol Group 5-dimension 5-level Self-Report Questionnaire; EQ-VAS: EuroQol Group visual analogue scale; GAD-7: Generalised Anxiety Disorder-7; HBD: Housing and Development Board; mMOS-SS: modified Medical Outcomes Study Social Support Survey; PHQ-9: Patient Health Questionnaire-9

[a] National Service: A 2-year mandatory conscription duty that every male citizen and permanent resident in Singapore must undertake upon attaining the age of 18.

[b] HDB 1-room/2-room: public housing 1-room and 2-room apartments managed by HDB, the state's public housing authority.

P values in bold indicate statistical significance.

generally digital natives. It would also allow for reduction in manpower-intensive initiatives while ensuring accessibility of support services. Further studies are needed to understand the help-seeking behaviour of young people with mental health issues to guide the development of effective strategies and interventions to support them.

National Service (NS) in Singapore is a 2-year mandatory conscription duty that every male citizen and permanent resident must undertake at 18 years old. It is a period of many changes as they transit from civilian life into regimentation, resulting in multiple stressors and adjustments, which may present as symptoms of depression and possibly escalate to depressive disorders. Studies show that the prevalence of depression in the military community was higher than that in the general community.[23] While our respondents may not be a representative sample of the NS population, further research to study this observation would be needed to better understand the prevalence of mental illnesses among those in NS. Support for the mental wellness of NS men should be made readily available, together with psychoeducation to enable NS men to develop healthy coping strategies.

Findings from our study reflected a differing relationship between homemaking and mental health compared to the literature. Homemakers have traditionally been at greater risk of adverse mental health compared with those who worked outside of the home[24,25] via mechanism of increased codependency and negative self-perception.[26] This, taken together with findings from the Singapore 2022 Labour Force Survey,[27] could suggest that homemakers in our study exercised the choice to leave the workforce to be involved in housework or the caring for their family members, and may have the option, skills and resourcefulness to return to the workforce if they wished to. Thus, they possibly had reduced codependency, a more positive view of their role in the family, and an increased sense of purpose and satisfaction, which buffer against adverse mental health outcomes. Further studies can be done to better understand the challenges and needs of homemakers in Singapore, and to ascertain if such findings are generalisable to the population, so that adequate support may be provided to safeguard their mental wellbeing.

It is well established in literature that females have a higher risk of depression and anxiety compared with males. Our study reported similar findings. Studies during the COVID-19 pandemic also found that females experienced greater psychological impact compared to males, with a greater propensity to develop symptoms of anxiety and depression.[28,29] While the exact reasons for this difference are not fully understood, it is important to recognise this complexity in the management of mental health issues and encourage a more inclusive approach to ensure that both men and women who are struggling with depression and anxiety receive targeted support needed for their recovery.

Studies have observed that the presence of social support predicts better mental health function and can be regarded as a protective factor against the onset of mental health difficulties.[30,31] In managing depression and anxiety in the community, efforts to improve social support should be considered. Further research to understand the specific social support that has the highest influence on depression and anxiety will guide resource planning and improve the availability of this support system.

There is a complex relationship between diabetes, anxiety and depression. People with diabetes have a higher risk of developing anxiety and depression, and those with anxiety and depression are at a higher risk of developing diabetes.[32,33] In various Asian studies, individuals with diabetes exhibited an elevated likelihood of depression compared with those without diabetes, with a 5-fold higher odds found in a study conducted in Malaysia (OR 5.05; 95% CI 2.08–12.27),[34] a 1.3 times higher odds in a study conducted in Hong Kong (OR 1.35; 95% CI 1.25–1.46),[35] and a 2.22 times higher odds in a study conducted in Thailand (adjusted OR 2.22; 95% CI 1.28–3.84).[36] Studies found that treatment of depression in people with type 2 diabetes were associated with improved glycaemic control and quality of life.[37] In addition, the use of metformin in patients with diabetes is associated with a lower risk of depression, although the exact mechanism is still unclear.[38] Hence, patients with diabetes should be screened for depression and anxiety, which should be treated when identified for better health outcome.

Our study had various strengths. We had a good response rate of 61.6% and a large sample size of 3505 respondents, which meant that the results of our study are representative of the patient population visiting the NHG polyclinics. In addition, we employed systematic sampling to reduce selection bias during the recruitment and had questionnaires in 3 major local languages to reduce the chances of misinterpretation. Lastly, the study questionnaires were self-administered, which reduces social desirability bias and interviewer bias.

There are several limitations to our study. First, it was conducted during the COVID-19 pandemic, potentially inflating reported depression and anxiety levels. Second, the study was confined to NHG polyclinics, representing about 20% of the central-north population visiting primary care. Furthermore, the study's demographics featured a higher proportion of males, Malays and other ethnicities compared with the national population.[39] Hence, our study population may not be an inclusive representation of the nation. Third, the study did not investigate the association of important factors such as body mass index (BMI) on the impact on mental health. These are areas for further research.

CONCLUSION

Our study showed that there was significant presence of coexisting clinical depression and anxiety (5.4%) in the primary care setting, especially among younger individuals, patients with diabetes and females. We propose that mental health screening programmes in the community should include screening for both depression and anxiety, rather than either of these only. Mental health screening should target at-risk groups, such as younger individuals and patients with diabetes. Studies to explore the help-seeking behaviours of younger individuals will help to guide interventional strategies to support them in the community.

Disclosure

The authors have no conflict of interest to declare.

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REVIEW ARTICLE

Holistic preconception care: Providing real-time guidance via a mobile app to optimise maternal and child health

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ABSTRACT

Introduction: Preconception is a critical period to optimise gamete function and early placental development, essential for successful conception and long-term maternal-child health. However, there is a lack of preconception services and consequently, global fertility rates continue to fall and mothers embark on their pregnancy journey in poor health. There is an urgent need to implement a holistic community-level preconception care programme to optimise risk factors for poor fecundability and improve long-term maternal-child health.

Method: We reviewed current evidence on fecundability lifestyle risk factors, the efficacy of existing preconception interventions and the use of digital platforms for health optimisation, to create a new digital-based preconception intervention model that will be implemented via an app. We present the theory, content and mode of delivery of this holistic model targeting couples planning for pregnancy.

Results: We propose a new model featuring a user-friendly mobile app, which enables couples to self-assess fecundability risks through a personalised risk score that drives a tailored management plan. This tiered management provides anticipatory guidance supported by evidence-based recommendations, and promotes ongoing engagement for behavioural optimisation and specialist referrals as required. Based on the health belief model, this new model delivered with a mobile app seeks to shift couples' perceptions about their susceptibility and severity of subfertility, benefits of making a change and barriers to change.

Conclusion: Our proposed digital-based intervention model via a mobile app stands to enhance preconception care by providing personalised risk assessments, real-time feedback and tiered management to optimise preconception reproductive health of couples. This model forms a reference content framework for future preconception care intervention delivery.

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Keywords: fertility, health optimisation, mobile health, obstetrics and gynaecology, preconception care

INTRODUCTION

Global fertility rates have decreased by more than half since 1950, recorded at 2.3 births per woman in 2021.[1] By 2056, this figure is projected to decline further to 2.09, which falls below the replacement fertility rate of 2.1 children per woman.[1] In Singapore, the fertility rate has reached a historic nadir of 1.05 in 2022.[2] The repercussions of such ultra-low fertility are enormous, including a decline in human capital. In developed countries like Singapore, this trend has precipitated an ageing

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CLINICAL IMPACT

What is New

- We propose a new holistic couples-based preconception care programme that optimises lifestyle and sexual health using a mobile health app to be integrated within the framework of the Healthy Early Life Moments in Singapore (HELMS) initiative.
- The programme involves a comprehensive reproductive health self-assessment, which provides a personalised fecundability risk score to guide triaged care and intervention.

Clinical Implications

- Implementation of the programme via a digital platform allows for real-time guidance and timely intervention to improve fecundability in the short-term.
- Intervention during the critical preconception period can better safeguard maternal-child health outcomes in the long-run.

population, characterised by a diminished old-age support ratio and a reduced influx of individuals into the workforce.[3] Consequently, this portends adverse societal and economic outcomes.[4] The fertility rate is affected by a number of factors, encompassing biological, psychological, social and environmental determinants. Various risk factors, including lifestyle and sexual health have been associated with poor fecundability,[5] which refers to a reduced probability of spontaneous conception within a cycle as indicated by an extended time to pregnancy. Herein, we aim to present contemporary evidence on risk factors associated with poor fecundability and draw insights from the 2 largest birth cohorts in Singapore. We also propose an individualised preconception model to be implemented and delivered via a mobile health (mHealth) platform, to improve fertility in couples and promote better maternal-child health outcomes in the long-run.

METHOD

We reviewed the current evidence on lifestyle risk factors impacting fecundability, the efficacy of existing preconception interventions and the use of mHealth platforms for health optimisation, to create a new holistic preconception intervention model. The approach was non-systematic to obtain a broad overview of the field, and synthesise significant developments and emerging trends into a tangible interventional programme that can be used as a reference model.

The primary source of our review was PubMed, which was supplemented with information from government reports and World Health Organization guidelines. Search themes included risk factors of low fecundability, current gaps in preconception fecundability interventions and the efficacy of mHealth apps in health optimisation. Publications were selected based on their relevance to our objectives, and priority was given to articles published in the last 5 years to ensure contemporary relevance. The evidence was then synthesised to provide novel insights, presented in the Results section below.

RESULTS

Risk factors for low fecundability

Multiple factors can negatively affect fecundability.[5] A well-established factor is advanced parental age, which reduces fecundability. The emphasis on education and career progression has led to a trend of delayed maternal age at first pregnancy, impacting fertility dynamics.[6] Another notable phenomenon, particularly prevalent in developed nations, is the rise of metabolic health issues. Shifting dietary choices towards high-calorie fast foods and adopting sedentary lifestyles have exacerbated the global obesity and metabolic disorder epidemic, further worsening fecundability.[7] Additionally, the detrimental effects of smoking and excessive alcohol consumption on fecundability are well-documented.[8] In 2022, tobacco smoking rates remained at 22.3%,[9] and the global average alcohol consumption reached 6.2 litres per person per year among those aged 15 years or older.[10] Sexual dysfunction, influenced by factors including fertility challenges, gynaecological and andrological conditions, and ongoing medications has been associated with prolonged time to pregnancy.[11] Globally, 51% of adults reported insufficient sleep due to intensified work demands, contributing to the landscape of factors affecting fecundability. The escalation in mental health deterioration, both as a contributing factor and a consequence of reduced fecundability, is noteworthy. Global survey indicates that 41% of adults have experienced significant stress, while 42% reported substantial worry.[12] Finally, while the aforementioned factors offer avenues for modification through advocacy and education, current maternal-child health systems across the globe are primarily structured to prevent unintended pregnancies, manage infertility and address medical conditions during pregnancy via routine antenatal care visits.[13]

Evidence from 2 mother-offspring cohorts in Singapore

Similar findings have been reported from 2 large prospective cohorts in Singapore, namely the Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) and the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohorts.[14,15] These cohorts collectively suggest a reciprocal relationship between metabolic syndrome, suboptimal body mass index (BMI), female sexual dysfunction and mental health concerns, culminating in subsequent implications on reproductive function (Fig. 1).[14] Furthermore, these factors are now known to underpin adverse maternal and child health outcomes over the long run.[16]

The preconception period

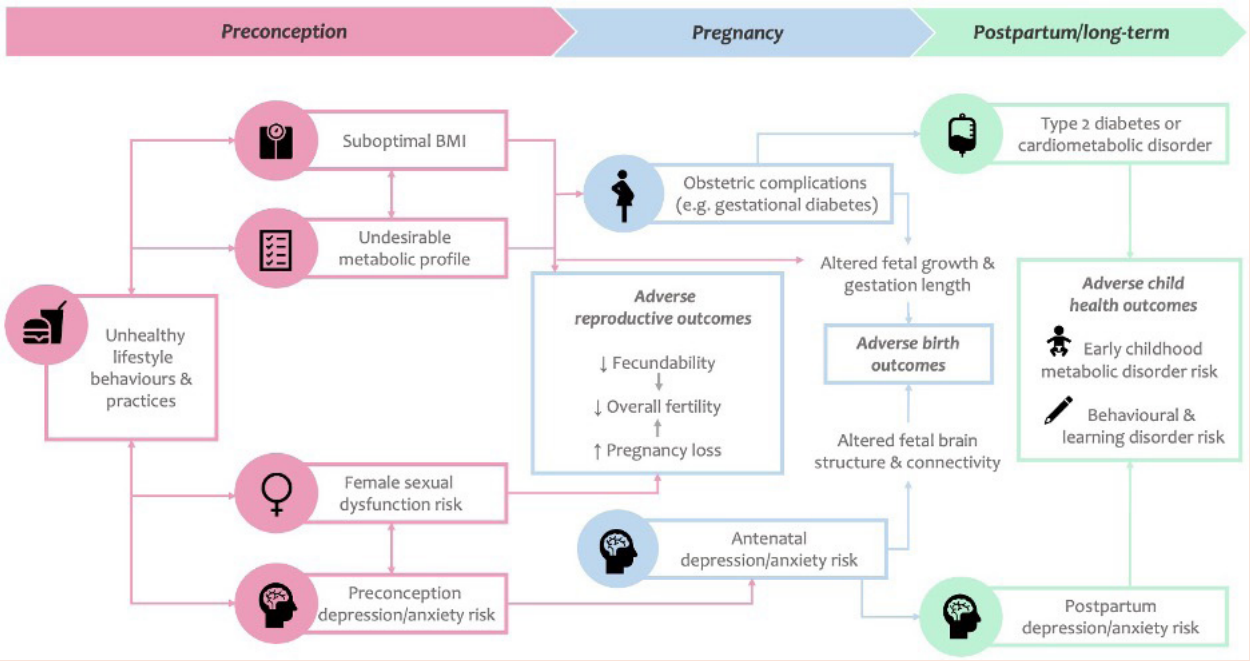
The preconception phase represents a critical period to optimise gamete function and facilitate early placental development for successful conception.[17] Achieving optimal health during the preconception window is crucial for long-term maternal-child health outcomes.[17] However, it is concerning that a substantial 44% of pregnancies globally are unplanned.[18] Moreover, the prevalence of inadequate nutrition and obesity is alarmingly widespread worldwide.[19] In Singapore, 43% of women are overweight or obese and 18% have metabolic syndrome at preconception.[20] These factors contribute to compromised preconception health, which has far-reaching implications, spanning pregnancy complications to long-term child health, as substantiated by the Developmental Origins of Health and Disease (DOHaD) paradigm.[21]

Overall, there is an urgent need to translate knowledge into action and implement a holistic preconception intervention that optimises lifestyle and sexual health factors to improve fecundability in the short-run, as well as maternal-child health in the long-run.

Gaps in current preconception interventions

Despite a pressing need for a preconception care programme, Singapore's current healthcare lacks such an initiative. Internationally, preconception care programmes can be categorised as: (1) multi-risk factor interventions; (2) technology-assisted

Fig. 1. Preconception exposures and maternal-child health outcomes. Preconception health risks (i.e. suboptimal body mass index (BMI), undesirable metabolic profile, female sexual dysfunction risk and mental health issues) and related unhealthy lifestyle behaviours as observed in Singapore women who are trying to conceive can coexist and influence each other. These have adverse implications on fecundability, obstetric and long-term mother-child health outcomes, specifically risks of metabolic and mental/neurodevelopmental disorders. Boxes in pink represent preconception risk factors. These findings are based on the S-PRESTO and GUSTO studies, with each cohort involving approximately 1000 preconception and pregnant women.[14,15]



S-PRESTO: Singapore PREconception Study of long-Term maternal and child Outcome; GUSTO: Growing Up in Singapore Towards healthy Outcomes
Superscript numbers: refer to REFERENCES

interventions; (3) targeted counselling for women with pre-existing medical conditions; (4) group-based health education; (5) community-driven social marketing initiatives; and (6) interpregnancy interventions.[22] However, these existing strategies bear notable constraints in that they often emphasise individualised over population-wide approaches and adopt short-term pathology-centric perspective over long-term holistic well-being within preconception care. To holistically optimise reproductive health, both partners should be integrated into the approach.[23] Preconception health can be viewed through a life-course lens that encompasses the cumulative impact of lifestyle behaviours and social determinants on fecundability.[24] Furthermore, a prevailing limitation lies in the conventional face-to-face delivery of existing programmes, which impedes scalability to a broader population level.

Effectiveness of mobile health (mHealth) for community health promotion

The utilisation of mHealth platforms has demonstrated effectiveness in promoting desired lifestyle behaviour changes compared to conventional health programmes. This innovative approach empowers individuals to proactively navigate their preconception journey, offering a sustainable avenue to enhance the overall preconception health of the population. Beyond this, mHealth platforms serve as an effective and convenient medium for diverse healthcare functions, including disease screening, treatment, rehabilitation, behaviour modification and chronic condition management. Specifically, for pregnancy care, mHealth apps have proven efficacious in optimising maternal health, including weight management, gestational diabetes mellitus control and improving maternal mental health.[25] Recent findings from a systematic review and meta-analysis that focused on Asian populations indicate that integrating a personalised mHealth app with multifactorial standard care resulted in more substantial weight loss than what was observed with either intervention independently.[26] mHealth represents a secure and sustainable means to deliver preconception care, facilitate discrete guidance for couples throughout their journey to conceive and enable timely health interventions. This is especially important as fecundability is often shrouded in deep-seated social stigma, which can incite shame, secrecy and delay the time to healthcare. In tandem with preserving privacy, the convenience of mobile apps extends the potential for engagement and outreach. Moreover, the concurrent engagement of various participants through mHealth generates a community effect, motivating couples to work towards their goals.

Emerging data from pilot apps indicate notable user engagement and uptake rates. Specifically, the Smartphone App to Restore Optimal Weight trial in Singapore maintained high user-app engagement with 70.8% and 60.8% of participants using at least 1 feature in the first and fourth month, respectively.[27] Furthermore, a systematic review and meta-analysis on mobile health apps' impact on health behaviours and clinical outcomes indicated that 80% of the studies observed a positive effect, with a marked increase in user satisfaction.[28] Fundamental characteristics that lead to the success of such mobile health apps include personalisation, adaptive and timely feedback, option to engage with a healthcare provider, culturally adapted practices and information, and the ability to track health behaviour.[29] All the aforementioned factors have a role to play in fostering strong adherence and user engagement, leading to the long-term sustainability of such platforms.

A holistic preconception intervention model

There is currently a lack of preconception services available for couples globally and in Singapore. Other than BMI assessment, most of the aforementioned health risks are under-evaluated in couples who are trying to conceive, despite their significant prevalence. Hence, it is imperative to develop a preconception intervention tailored to provide guidance and support for couples who possess the time and opportunity to strategically plan conception. This initiative aligns seamlessly with Singapore's revised healthcare masterplan, characterised by a shift from healthcare provision to health promotion.

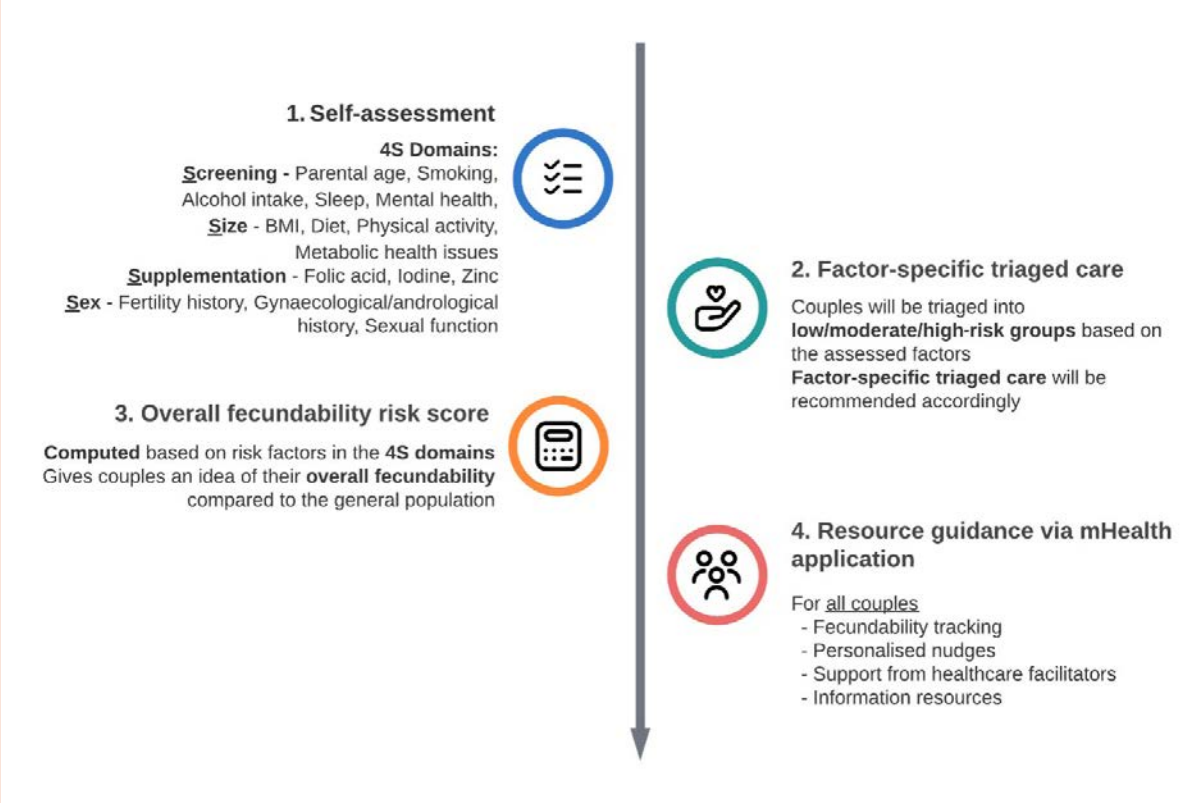
Thus, we propose a focused couples-centric preconception self-assessment and management model, integrated within the framework of the Healthy Early Life Moments in Singapore (HELMS) initiative.[30] HELMS is a new model of care that aims to optimise maternal and offspring health outcomes in the general population by optimising preconception metabolic and mental wellness. In a preliminary stage, HELMS piloted a lifestyle intervention delivered via an mHealth platform, catering to overweight/obese women. This effort aims to improve the metabolic and mental health of women from preconception until 18 months postpartum, potentially enhancing fecundability, pregnancy experiences as well as maternal-child outcomes.[30]

Adopting a personalised approach for all preconception couples, we have developed a comprehensive reproductive health evaluation programme conducted through an mHealth app. The development of this programme draws upon the health belief model, which is based on the framework of perceived susceptibility, perceived severity, health motivation, perceived benefits, perceived barriers and eventual action taken by the target group.[31] Such an intervention model seeks to reshape couples' perceptions regarding their reproductive health (perceived susceptibility) by first, engaging couples in a self-assessment component where they are screened for lifestyle and sexual health factors through self-administered questionnaires within the mHealth platform or biochemical tests conducted in the primary care setting. The responses from these evaluations are subsequently uploaded onto the mHealth platform (see section 1. Self-assessment). This aims to highlight areas of higher fecundability risk (perceived severity) to the couples. Depending on the identified factors spanning the 4S domains, the programme dispenses personalised guidance and targeted care, disseminated either through mHealth or via appropriate referrals (see section 2. Factor-specific triaged care). The culmination of this preconception health appraisal is the establishment of a fecundability risk score, which informs the couple's fecundability risk profile (see section 3. Overall fecundability risk score). The benefits of making changes, which would be in this case, increased chances of successful conception, is then emphasised to the couples (perceived benefits). The provision of targeted guidance will hopefully reduce the barriers to change (perceived barriers) for the couples and heighten motivation for them to proactively improve their fecundability.[31] Ongoing app engagement (health motivation) solidifies this process, offering resourceful guidance for action to be taken by the couples (see section 4. Resource guidance via mHealth app) (Fig. 2).

1. Self-assessment

The self-assessment process employs the comprehensive screening, size, supplementation and sex (4S) care strategy during preconception

Fig. 2. Framework and procedures of preconception care based on the Healthy Early Life Moments in Singapore (HELMS) programme. The process begins with couples undergoing self-assessment via an mHealth app, employing the 4S domains as the foundation. Subsequently, couples will be triaged and receive pertinent suggestions or necessary referrals according to their distinct factor-specific risks. The culmination of this assessment yields a composite fecundability risk score, enabling couples to benchmark their fecundability against the broader population, thereby gauging their comparative fertility level. Continuous guided intervention creates a supportive environment to steer and navigate couples through their preconception journey.



(Fig. 2). This couples-oriented approach systematically covers critical factors influencing fecundability, identifies areas necessitating improvement and offers tailored interventions to individual patients.[24,30]

Screening (lifestyle factors and mental health)

Screening for the couple's age, lifestyle, sleep and mental health allows early detection and intervention to improve preconception health and fecundability, and prevention of transgenerational effects of poor parental health on their future offspring.

Advanced parental age, a non-modifiable risk factor, is recognised for its influence on subfertility.[5] Although age remains unmodifiable, screening for age equips couples with insights into their fecundability profile. Concurrently, it serves as an educational avenue, apprising couples of the detrimental ramifications of advanced age on fecundability. Such awareness empowers couples to contemplate initiating conception sooner, thus enabling more informed family planning decisions. Apart from age, lifestyle behaviours such as smoking and alcohol consumption have detrimental effects on fecundability, underscoring the need for holistic screening encompassing type, amount and duration of these practices.[8] Additionally, sleep plays a significant role in fecundability. Screening tools such as the Pittsburgh Sleep Quality Index (PSQI) facilitates identification of individuals at elevated risk, indicated by a PSQI score ≥5.[32] Lastly, mental health is correlated with fecundability. Mental wellness can be influenced by perceived stress levels, presence of psychiatric disorders and sleep health. Perceived stress can be assessed using the Perceived Stress Scale (PSS),[33] a 10-question screening tool with a total score of 40. Scores are categorised as low (PSS score 0–13), moderate (PSS score 14–26) and high (PSS score 27–40) levels of stress. Psychiatric disorders, such as major depressive disorder, negatively impact fecundability. The severity of depressive symptoms was inversely associated with fecundability, regardless of the use of psychotropic medications, highlighting the need to diagnose and treat underlying psychiatric disorders as part of a holistic preconception programme.[34] The Edinburgh Postnatal Depression Scale (EPDS) is a 10-item tool that can be used with a 3-tier risk stratification system: probable depression (EPDS score ≥14), possible depression (EPDS score 10–13) and unlikely depression (EPDS score ≤9).[35,36]

Size (weight optimisation with diet, physical activity and metabolic risk factor management)

Body size optimisation involves weight monitoring coupled with personalised adjustments in dietary choices and physical activity regimens based on self-determined goals, and management of metabolic risk factors. Positive weight management outcomes are closely tied to adopting eating habits that incorporate a diverse range of foods in controlled portions, as recommended by My Healthy Plate, a visual guide to plan healthy meals by Singapore's Health Promotion Board.[37] This includes a diet low in fats and calories, minimising the intake of fast food and sugar-sweetened beverages,[38] while emphasising ample consumption of fresh fruits, vegetables, nuts and healthy oils for a balanced nutritional profile.[39] Beyond these guidelines, there should also be a stronger emphasis on reducing calorie-dense snacks,[40] chrono-nutrition that advocates caloric restriction at night when resting metabolic rate is low[41] and considering motivation to drive long-term sustainable behavioural change.[40]

Physical activity is a pivotal driver of metabolic health, conferring a number of health benefits including enhanced metabolic and mental well-being, and perceived quality of life.[42] The World Health Organization advocates a weekly minimum of 150 minutes of moderate intensity or 75 minutes of vigorous intensity physical activity, which is linked to positive outcomes.[43]

The synergy of nutritional interventions and augmented physical activity manifests within the validated intervention tool, which streamlines eating and activity decisions into 6 distinct factors: portion, proportion, pleasure, phase, physicality and psychology (i.e. the 6P tool) (Table 1).[40] This forms an intuitive mental model that couples can utilise to screen, understand, monitor and modify their eating and activity habits. This is largely guided by the Theory of Planned Behaviour, which emphasises the role of attitude, subjective norms and perceived behavioural control on human behavior.[44] By rationalising the components that make up healthy eating patterns, the 6P tool seeks to enable behavioural modification such that couples are empowered to set their own 6P goals and take control of and improve their current eating habits.

Metabolic screening includes biomarker assessments, specifically glucose and lipid profiles. Results are automatically integrated into individual profiles, enabling timely recognition and intervention for metabolic syndrome,[45] a precursor to potential health issues.

Supplementation (micronutrients)

Multi-micronutrient supplementation is recommended for couples during preconception. The intervention incorporates an educational platform emphasising supplementation requirements and

Table 1. Components of the portion, proportion, pleasure, phase, physicality and psychology (6P) tool (adapted from Ku et al. 2021).[40]

	6P	Description
P1	Portion	Amount of food intake
P2	Proportion	Caloric-density of food intake
P3	Pleasure	Frequency of snacks and sugar-sweetened beverages and meal regularity
P4	Phase	Time of day of food intake
P5	Physicality	Physical activity and sedentary behaviour
P6	Psychology	Readiness for change

significance to foster adherence.[46] Micronutrient supplements such as folic acid,[47] iodine,[47] zinc, and vitamin D[48] have been associated with improved fecundability and/or multiple obstetric and postnatal outcomes. Individuals log daily supplement intake on the app, with tracking facilitated through the digital tracker function, thus promoting sustained adherence.

Sex (sexual health and function)

Last, sexual health and function are important considerations in the preconception stage. Marital relationship quality and the overall reproductive health of the couple dictate sexual health optimisation. Evaluation includes (1) fertility history, (2) gynaecological or andrological history, and (3) sexual function.

Fertility history includes the period of trying to conceive, intercourse frequency and history of recurrent pregnancy loss and/or miscarriages. Couples attempting to conceive for over a year despite regular unprotected intercourse, or encountering 2 or more consecutive clinical pregnancy losses, will receive triaged care and directed to a specialist fertility assessment. Concurrently, all couples are encouraged to engage in optimal behavioural practices for conception, including regular unprotected sex every 2–3 days,[49] timed intercourse within a week of ovulation,[50] and early initiation of conception.

Gynaecological history involves screening for history of sexually transmitted diseases (STDs), pelvic or abdominal surgeries, as well as gynaecological medical conditions. STDs such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* contribute to tubal factor infertility.[51] Gynaecological conditions potentially impeding fecundability encompass ovarian dysfunction (e.g. polycystic ovarian syndrome), uterine structural abnormalities (e.g. bicornuate uterus) or pathology (e.g. fibroids), cervical abnormalities, fallopian tube dysfunction and endometriosis.[52] Past pelvic or abdominal surgery may result in pelvic adhesions, which adversely impacts fecundability. Andrological history includes identifying past genital trauma. Testicular injury may be due to mechanical trauma or a previous mumps infection,[53] both of which have been shown to increase the risk of subfertility. Medications potentially affecting fecundability are examined, considering direct toxic effects or indirectly through the alteration of the reproductive hormonal axis.[54]

Sexual health investigation involves screening for sexual dysfunction. Female sexual dysfunction can be assessed via the 6-item Female Sexual Function Index;[55] while male sexual function can be evaluated using the International Index of Erectile Function tool.[56]

In sum, the preconception self-assessment module requires approximately 30 minutes for completion and serves as an approximate baseline profile of the couple's health status.

2. Factor-specific triaged care

A dual-tier scoring system is implemented, stemming from the reproductive health assessment, i.e. the factor (F) score and an overall fecundability risk score. Guided by the 4S screening and intervention strategy, each individual's risk profile is quantified through the F score, stratifying across distinct risk levels aligned with established clinical guidelines. This represents a triage process to navigate subsequent management decisions (Table 2). Low-risk individuals are encouraged to engage with the mHealth app to track their fecundability journey. Moderate-risk individuals are offered follow-up care in the primary care setting where they will be guided to make lifestyle modifications and optimise health. High-risk individuals are referred to tertiary care, such as fertility specialists for comprehensive fertility consultations and evaluations, or relevant specialists for more intensive intervention.

3. Overall fecundability risk score

The composite score of all factors, termed the fecundability risk score, estimates the potential impact of the overall factors on fecundability and

Table 2. A multi-level scoring system will be used to triage a user using the 4S screening and intervention strategy as framework (screening, size, supplementation and sex). Each individual will receive a factor-specific score (F score) based on a relevant screening tool and receive triaged care accordingly. The amalgamation of all factor-specific scores and the fecundability risk score will serve as visual/numeric guides for couples to track and compare their progress.

Preconception model	Factor	Screening tool	Factor (F) scoring system
Screening	Parental age	Preconception screening form	• Score of 0: Maternal age <35 years • Score of 1: Maternal age ≥35 years
	Lifestyle: Smoking	Preconception screening form + continuous app engagement	• Score of 0: Non-smoker • Score of 1: Smoker
	Lifestyle: Alcohol intake	Preconception screening form + continuous app engagement	Yes/no, type of alcohol, quantity & frequency
	Lifestyle: Sleep health	Pittsburgh Sleep Quality Index (PSQI)[32]	• Score of 0: PSQI score <5 • Score of 1: PSQI score ≥5
	Mental health: (a) Stress	Perceived Stress Scale (PSS)[33]	10-question screening tool of perceived stress levels with a total score of 40: • Score of 0: Low (PSS score 0–13) • Score of 1: Moderate (PSS score 14–26) • Score of 2: High (PSS score 27–40)
	Mental health: (b) Psychiatric disorders, e.g. major depressive disorder	Edinburgh Postnatal Depression Scale (EPDS)[35]	A 10-item tool that can be used with a 3-tier risk stratification system: • Score of 0: Unlikely depression (EPDS score ≤9). • Score of 1: Possible depression (EPDS score 10–13) • Score of 2: Probable depression (EPDS score ≥14)
Size	Body mass index (BMI)	Singapore Health Promotion Board BMI Guidelines	• Score of 0: Low risk (BMI <22.9) • Score of 1: Moderate risk (BMI 23–27.5) • Score of 2: High risk (BMI >27.5)
	Diet	6P tool: Portion, proportion, pleasure, phase, physicality and psychology[40]	• Score of 0: >50% • Score of 1: <50%
	Physical activity	World Health Organization (WHO) Physical Activity Vital Sign[43]	• Score of 0: Green/highly active (≥150 minutes of moderate or ≥75 minutes of vigorous activity/week) • Score of 1: Amber/minimally active (<150 minutes of moderate or <75 minutes of vigorous activity/week)
	Metabolic health issues	WHO Metabolic Syndrome (MetS) Diagnostic Criteria[57] In-person metabolic screen of glycaemic and lipid profiles	• Score of 0: No metabolic syndrome • Score of 1: Presence of metabolic syndrome
Supplementation	Folic acid, iodine and zinc	Preconception screening form + continuous app engagement	• Score of 0: Adequate supplementation (individualised dose) • Score of 1: Inadequate supplementation (individualised dose)

Table 2. A multi-level scoring system will be used to triage a user using the 4S screening and intervention strategy as framework (screening, size, supplementation and sex). Each individual will receive a factor-specific score (F score) based on a relevant screening tool and receive triaged care accordingly. The amalgamation of all factor-specific scores and the fecundability risk score will serve as visual/numeric guides for couples to track and compare their progress. (Cont'd)

Preconception model	Factor	Screening tool	Factor (F) scoring system
Sex	Fertility history	Preconception screening form + continuous app engagement	• Score of 0: Individuals who do not fulfil the infertility criteria • Score of 1: Individuals who have been trying to conceive for >1 year despite regular unprotected sexual intercourse, or with 2 or more consecutive clinical pregnancy losses will be considered high risk.
	Gynaecological & andrological history	Preconception screening form + Continuous app engagement	• Score of 0: No concerning gynaecological or andrological history • Score of 1: Any concerning gynaecological or andrological history
	Sexual function	6-item Female Sexual Function Index (FSFI-6)[55]	• Score of 0: FSFI-6 score of >26 • Score of 1: FSFI-6 score of ≤26
		International Index of Erectile Function (IIEF)[56]	• Score of 0: IIEF score of ≥12 • Score of 1: IIEF score of 8–11 • Score of 2: IIEF score of 5–7
Total composite score (taking into account all previous sections)			
Fecundability risk score	Low risk: 0–33% Moderate risk: 34–66% High risk: 67–100%		

Superscript numbers: refer to REFERENCES

serves as a visual/numeric guide for couples to track and compare their progress. The 4S self-assessments are used to compute the fecundability risk score. Using data from the S-PRESTO study, fecundability was found to be reduced in women with higher-risk score levels.[5] However, this risk score system only considered maternal factors and neglected paternal factors. Herein, we suggest a more comprehensive fecundability risk score that considers combined maternal and paternal factors relevant to fecundability.

4. Resource guidance via mHealth app

The triage care system and corresponding information guidance are delivered via mHealth, enhancing accessibility to personalised and continuous care via the support, inform, guide and nudge (SIGN) approach.[24] Users stand to benefit from timely digitalised health support and interventions resulting from continuous health status monitoring. At the same time, users gain insights into pertinent preconception topics, such as diet, exercise, mental wellness and sleep hygiene through digestible educational bites. Individuals are empowered to attain lifestyle modification goals through habit trackers; while real-time, tailored-made performance feedback generated by the mHealth algorithm enables users to dynamically monitor their health and behaviour. Nudges, aligned with individual lifestyle goals, guide users toward favourable trajectories. This framework is applicable to both couples who are trying to conceive and couples who are considering conception soon. For couples currently not attempting conception, this preconception programme functions as an extended preparatory phase, fostering familiarity with preconception facets and facilitating health optimisation well ahead of conception intention.

DISCUSSION

Taken together, a modifiable risk factor-based self-assessment approach, with the 4S screening and intervention strategy, along with a personalised fecundability risk score for both the individual and the couple, can be utilised to triage preconception couples, and provide anticipatory guidance and support in their preconception journey. A substantial demand for improved preconception care underscores the significance of timely, relevant information and an encompassing delivery framework with sustained engagement.[58] The

HELMS programme was designed to address these pivotal factors and more. First, a user-friendly mobile app offers a unified hub for couples to access educational materials and personalised nudges, enhancing the accessibility of essential information during their preconception journey. The concurrent engagement of numerous participants on the app generates a community effect, fostering motivation among couples to pursue their individual objectives. Second, the private nature of self-assessment enhances objectivity and the uptake of the derived fecundability risk score. The secure environment mitigates apprehensions about judgment or stigma, encouraging greater participation and informed awareness of their fecundability risk profiles.[59] Third, the triaged care model ensures targeted interventions, increasing the effectiveness of this programme. Couples have the option of following the recommendations provided by mHealth or seeking relevant medical advice at their own discretion. This patient-centric approach empowers couples to actively shape their preconception journey. Last, the programme embraces a personalised approach that is accessible to the wider population. It aims to identify individuals who may be unaware of their fecundability risks and provide customised interventions, thus ultimately promoting healthier families and communities.

However, possible challenges must be acknowledged. Foremostly, the successful adoption of the HELMS preconception programme hinges on couples' proactive engagement in self-assessment and subsequent action. Barriers such as time constraints and perceived relevance could hinder adherence. To overcome these obstacles, the mobile app provides convenience and privacy, reinforced by ongoing nudges and healthcare support with primary care collaboration being essential for community education and empowerment. Beyond personal barriers, there are societal determinants as part of the socioecological model of behavioural change[24] beyond the individual's control. To this end, the app allows for participants to choose actionable goals to achieve. Furthermore, an increased healthcare system burden is plausible. The programme encourages comprehensive screening to identify potential fecundability risk factors, possibly leading previously generally well couples to seek medical advice. The triaged approach, however, directs couples to appropriate healthcare partners and promotes self-modification to lifestyle before specialist consultation, thus balancing system demands. Besides, healthcare professionals might not be equipped with the skills or may be reluctant to consider the DOHaD approach when caring for their patients. Adequate training will ensure that primary care physicians and specialists alike are more familiar with preconception care and are better equipped to manage preconception concerns.[60] Last, a lack of access to digital devices might prevent certain groups from reaping the benefits of this mHealth app. Nonetheless, this is unlikely to pose a significant challenge, as the mobile penetration rate has reached 95.4% in Singapore in 2023.[61] Furthermore, the app's design does not differentiate based on users' educational backgrounds, presenting a risk of unequal information accessibility. To address this, the design incorporates a user-friendly interface with visual cues and straightforward language to ensure clarity and ease of use for all. We also intend to pilot the app in English, with plans to diversify language options progressively. Hence, this mHealth app and preconception programme will be accessible to most of the population. Despite potential challenges, optimising health upstream through preconception care holds the promise of substantial long-term cost savings by mitigating chronic disease development and its associated costs.

CONCLUSION

Given the global decline in fertility rates and the rising burden of non-communicable diseases, a holistic preconception programme becomes imperative to address modifiable risk factors and improve couples' preconception health. This preconception programme adopts a modifiable risk factor-based self-assessment approach, along with the 4S screening and intervention strategy encompassing screening, size, supplementation and sex. Bolstering this framework is the introduction of a personalised fecundability risk score for both individuals and couples, which serves to triage and provide them with insightful foresight and support throughout their preconception journey. Successful implementation of this programme requires strong collaboration at individual, interpersonal, community, institutional and national levels. By providing couples with a strong foundation in their preconception journey and influencing each life course, it is hoped that each child will receive the best start in life as well as ultimately achieving a population with healthy life cycles.

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LETTER TO THE EDITOR

Understanding treatment burden in adults with multimorbidity in the Singapore primary care setting: An exploratory study using the Multimorbidity Treatment Burden Questionnaire

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Dear Editor,

Patients with multimorbidity often undertake several tasks to manage their health. These include learning about their conditions, taking medications correctly, implementing lifestyle changes, etc., which can be overwhelming and burdensome.[1] Their perceptions of the effort required to manage their health conditions and its impact on their general well-being are known as treatment burden.[1] Although, treatment burden is often overlooked by healthcare providers, there is growing recognition of its negative effects on medical adherence, quality of life and wasted healthcare resources.[1,2] Dobbler et al.[1] and the National Institute for Health and Care Excellence (NICE) guidelines[3] have suggested incorporating treatment burden into the clinical practice guidelines recommendations to better inform clinicians of the associated benefits and burden.

To enable prompt assessment of treatment burden, the Multimorbidity Treatment Burden Questionnaire (MTBQ) was developed[4] and validated across various countries.[5,6] These studies showed how different healthcare systems and cultural health beliefs influenced the treatment burden experienced. Singapore's unique healthcare environment, with its uneven distribution of chronic and acute care across public and private care sectors[7] and emphasis on individual healthcare co-payment,[8] may influence patients' treatment burden distinctly.

Understanding treatment burden can help policymakers and healthcare providers manage the healthcare workload by patients, and is in line with the national "Healthier SG" goals of transforming primary and community care delivery to improve population health and quality of life for the long term. We conducted an exploratory study describing the treatment burden in adults with multimorbidity in a public primary care clinic in Singapore using the MTBQ, with the aim of understanding its prevalence in our sample population, the domains of treatment burden that affected the most participants, and the factors associated with having treatment burden. Ethical approval was obtained from the National Healthcare Group Domain Specific Review Board (Reference 2021/00004) prior to commencement of the study.

Participants that had multimorbidity, i.e. self-reported having 3 or more chronic conditions,[9] completed a self-administered questionnaire about their chronic conditions, demographic information and treatment burden (MTBQ). The MTBQ consists of 13 items requiring participants to rate their difficulty in performing specific healthcare tasks over a 5-point Likert scale, from "0" (not difficult) to "4" (extremely difficult), with an additional option of "does not apply". Returned surveys with 2 or fewer conditions reported, i.e. no multimorbidity, or more than 50% missing responses for the MTBQ section, were excluded.[4] The sample size was 264, based on the estimated proportion of participants with no treatment burden (22%),[4] confidence interval of 95%, and width of 0.1. Treatment burden was assessed dichotomously as "no treatment burden", i.e. reporting "not difficult", "does not apply" or no response to 13 items of the MTBQ; versus "having treatment burden", i.e. reporting difficulty ("a little" to "extremely") to at least 1 or more of the 13 items. Data analysis was conducted using R Core Team version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

The study had a response rate of 75.4% and included 264 participants after excluding 39 for declaring less than 3 conditions (no multimorbidity) and a further 21 for answering less than half of the MTBQ. Participants were mostly male (62.5%) and Chinese (73.9%), with mean age of 62.9 ± 9.9 years. The proportion of participants with 3, 4 and 5 or more chronic conditions were 42%, 25.8% and 31.8%, respectively.

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Most (67.8%) had treatment burden and the most commonly reported burdens were "making recommended lifestyle changes" (35.6%) and "taking lots of medications" (34.5%). The majority of participants had no difficulty "collecting prescription medications" (75%), "obtaining clear and up-to-date information about [their] conditions" (71.6%), and "arranging appointments with health professionals" (70.5%). A large proportion (68.9%) reported that "getting help from community services" did not apply to them (Table 1).

We conducted binomial logistic regression, adjusting for sociodemographic factors and chronic conditions, to understand the factors associated with having treatment burden. Participants younger than 65 years and those with 5 or more chronic conditions had higher odds of having treatment burden compared to those who were older and those with 3 conditions (odds ratio [OR] 2.22, 95% confidence interval [CI] 1.17–4.17), P=0.01; and OR 3.54, 95% CI 1.77–7.10), P<0.01, respectively).

Our study is the first study to explore treatment burden in a public primary care setting in Singapore, and it showed the significant burden experienced by adults with multimorbidity. We also demonstrated that younger/middle-aged adults and those with 5 or more chronic conditions had higher odds of treatment burden, which is in keeping with other studies.[4,5] The ability to promptly screen and assess treatment burden may be key to optimising care, and the self-administered nature of our study and its good response rate demonstrated the potential utility and feasibility of using the MTBQ to measure treatment burden in research and clinical practice. However, further validation of the MTBQ in the local healthcare setting is needed. In particular, more work is required to determine the applicable domains of the MTBQ, its reliability, and its scoring system with the minimally important difference. Subsequently, the actual impact of treatment burden on health outcomes and expenditure in our local healthcare setting needs to be established, especially with regard to the higher-risk subpopulations identified in our study.

By highlighting the aspects of treatment burden that affected the most and the least participants, our study also demonstrated the potential of the MTBQ as a valuable patient reported outcome measure.[10] It can give healthcare professionals an overall view of the burden from their combined

Table 1. Results of answers to individual MTBQ questions.

Question	Difficult*		Not difficult		Does not apply		No response	
	n	(%)	n	(%)	n	(%)	n	(%)
1. Taking lots of medications	91	(34.5)	154	(58.3)	19	(7.2)	0	(0.0)
2. Remembering how and when to take medication	73	(27.7)	177	(67.0)	13	(4.9)	1	(0.4)
3. Paying for prescriptions, over the counter medications or equipment	60	(22.7)	183	(69.3)	19	(7.2)	2	(0.8)
4. Collecting prescription medication	54	(20.5)	198	(75.0)	10	(3.8)	2	(0.8)
5. Monitoring your medical conditions	74	(28.0)	172	(65.2)	16	(6.1)	2	(0.8)
6. Arranging appointments with health professionals	58	(22.0)	186	(70.5)	20	(7.6)	0	(0.0)
7. Seeing lots of different health professionals	75	(28.4)	122	(46.2)	62	(23.5)	5	(1.9)
8. Attending appointments with health professionals	72	(27.3)	140	(53.0)	50	(18.9)	2	(0.8)
9. Getting health care in the evenings and at weekends	47	(17.8)	99	(37.5)	111	(42.0)	7	(2.7)
10. Getting help from community services	22	(8.3)	49	(18.6)	182	(68.9)	11	(4.2)
11. Obtaining clear and up-to-date information about your condition	34	(12.9)	189	(71.6)	36	(13.6)	5	(1.9)
12. Making recommended lifestyle changes	94	(35.6)	135	(51.1)	33	(12.5)	2	(0.8)
13. Having to rely on help from family and friends	36	(13.6)	116	(43.9)	108	(40.9)	4	(1.5)

* Responses for "extremely", "very", "quite" and "a little difficult" were combined.

treatments on patients and guide clinical decision making and treatment choices. Additionally, the MTBQ also assesses the impact of healthcare services and delivery on patients' health-related quality of life, and can be used to inform policies and programmes.

Our exploratory study highlights the high prevalence of treatment burden, its important aspects and associated factors in a public primary care population with multimorbidity. Our findings underline the importance of detecting and minimising treatment burden, and can guide future research to understand treatment burden in a larger, more representative population to improve health outcomes and quality of care.

Ethics

Ethical approval was obtained from the National Healthcare Group Domain Specific Review Board (Reference 2021/00004) prior to commencement of the study.

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Keywords: *health-related quality of life, multimorbidity, primary care, treatment adherence, treatment burden*

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LETTER TO THE EDITOR

Physician sentiments on low-value investigations in Singapore: Part of Choosing Wisely campaign

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Dear Editor,

Low-value investigations provide marginal benefit and may result in harm to the patient or disproportionate healthcare costs.[1] The introduction of Singapore's Choosing Wisely (CW) campaign in 2012 aims to reduce such investigations.[2] CW was designed to encourage conversations between physicians and patients to weigh the risk-benefit ratio behind each clinical decision.[3] A CW campaign was launched in July 2023 at Singapore General Hospital to reduce unnecessary tests and treatments.[4]

We collected responses to a 32-question quantitative questionnaire from 1 June 2023 to 1 July 2023 across public healthcare institutions in Singapore. We included all doctors working in these institutions. A total of 5600 survey invitations were distributed through official emails and group messages. The anonymous survey was answered by 280 doctors (5.0% response rate), comprising 122 (43.6%) junior doctors (house officers, medical officers and residents with 1–2 years of experience), 83 (29.6%) registrars (residents with 3–5 years of experience), and 75 (26.8%) specialists (specialists with more than 5 years of experience). Among them, 121 physicians (43.2%) were from medical disciplines, while 159 (56.8%) were surgical.

The vast majority (85–95%) agreed that this reduction would benefit healthcare professionals, patients and the healthcare system. Similarly, 73% of respondents believed that patient investigations could be safely reduced, contingent upon adherence to international (86%) and departmental guidelines (92%), effective training (91%), and a supportive organisational culture (94%).

The majority of respondents (87%) acknowledged personal responsibility for patient investigations. Contrarily, 53% either disagreed or strongly disagreed with the notion that reducing investigations would delay treatments or procedures. Opinions were divided regarding the risk of missed diagnoses due to reduced investigations: 34% disagreed or strongly disagreed, 45% remained neutral, and 19% agreed or strongly agreed. Views on increased physician liability were also varied: 25.7% disagreed or strongly disagreed, 37.2% were neutral, and 36.9% agreed or strongly agreed.

When examining the reasons behind ordering excessive investigations, medico-legal concerns (21.9%) and clinical safety precautions (21.7%) were prominent. The influence of these factors varied among different professional levels, with more experienced physicians relying more on national and departmental guidelines. Interestingly, adherence to these guidelines and practices of senior physicians was preferred over international guidelines, particularly among junior doctors and registrars (Fig. 1). A summary of the survey results can be found in Supplementary Table S1.

Low-value investigations may persist due to perceived patient demands, juxtaposed against limited time for patient assessment and engagement.[5] While patients might overestimate the benefits and overlook the harms of low-value testing, they also tend to re-evaluate their choices when presented with simple information about the overuse of investigations that provide little benefit.[5,6] Patient education could be an area of opportunity to implement change.

Regarding awareness of the CW campaign, which aims to reduce low-value investigations, most respondents were not familiar with it (71%), though those who were showed a high degree of openness to changing current practices (91%). Awareness of the campaign was more prevalent

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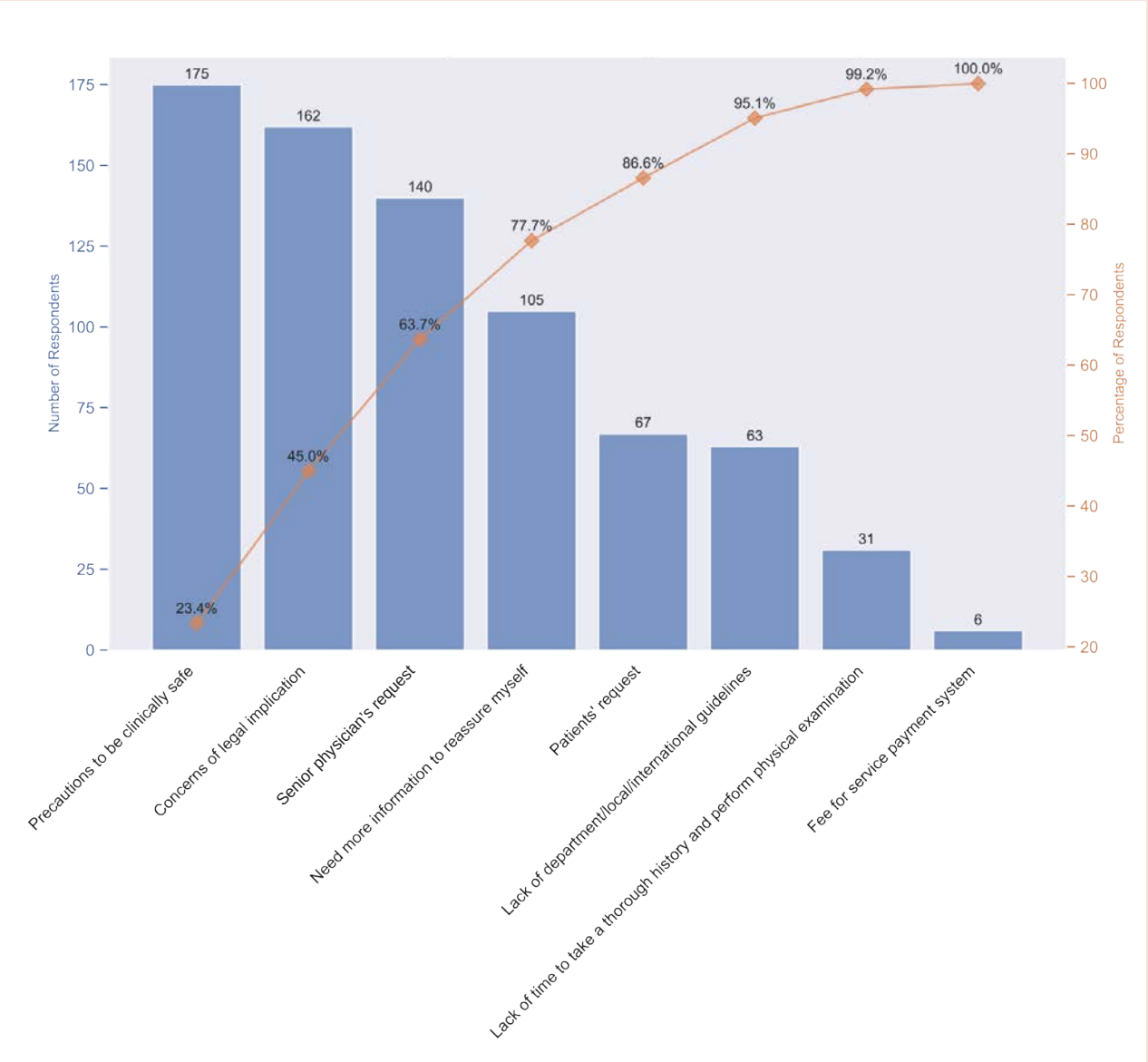
Fig. 1. Pareto chart of reasons why physicians order more investigations than necessary.



among specialists compared to junior doctors (37/75 at 49.3% versus 25/122 at 20.5%). Among those aware of the CW campaign, the majority agreed that it would influence their practice, indicating that enhancing campaign awareness is crucial (65%). One pertinent consideration would be to incorporate the principles of the CW campaign into medical education.[3]

Next, the survey highlighted that the main reasons for ordering preoperative chest x-rays were instructions from senior physicians and departmental policies, with less experienced physicians more influenced by their seniors. This is unsurprising as the senior doctor is the leader of the team and junior doctors usually defer to the seniors instead of guidelines. This trend suggests that reliance on theoretical knowledge alone may not be sufficient to reduce the frequency of unnecessary investigations and chest x-rays.[7] It is necessary to obtain buy-in from senior doctors in order to make CW a successful campaign in Singapore.

The study's limitations encompass a relatively small sample size, with a low response rate (5.0%), potentially restricting generalisability within the Singapore cohort. This could also potentially cause non-response bias. Recall and response bias might affect responses regarding reasons for excessive investigations. Specific inclusion criteria might induce selection and specialty bias. The absence of qualitative insights and a single time-point for data collection could limit understanding. Lastly, the study's construct validity and reliability might be influenced by the structured questionnaire

such as one validated by methods like Cronbach's alpha,[8] and potential biasedness of respondents to trainees and hospital-based physicians.

The findings of this island-wide survey shows promising readiness for change regarding low-value investigations in our local physicians. Effectively addressing physicians' concerns, enhancing awareness of initiatives like CW, and incorporating CW into local clinical guidelines are essential steps toward reducing unnecessary investigations and improving healthcare efficiency.

Supplementary Material

Table S1. Survey responses to the reasons for ordering more investigations than necessary.

Declaration

There is no conflict of interests.

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Ethics and consent

Written informed consent was obtained from the respondents for this report.

Keywords: *anaesthesiology, "choosing wisely", cost-effectiveness, health economics, low-value investigations*

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LETTER TO THE EDITOR

Factors affecting outcomes among older trauma patients in Singapore: A retrospective observational study

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Dear Editor,

Singapore faces a rapidly ageing population with its median age projected to be above 45 years by 2030. Our greying demographics is accompanied by a rise in chronic diseases and medication use, including polypharmacy.[1] Longer life expectancy and increased activity levels have contributed to higher incidence of geriatric trauma locally, with a three-fold rise between 2004 and 2015.[2] Older patients are at greater risk of poorer outcomes following trauma.[3] However, the impact of comorbidities and medication use on post-trauma outcomes in Singapore's ageing population remains unclear.

From the trauma registries at 2 tertiary trauma centres—Singapore General Hospital and National University Hospital—in Singapore, we identified patients aged 45 years and above who presented to the emergency departments (EDs) for injuries between 2011 and 2015. Data on demographics, injury types and severity, comorbid conditions and medication use were collected through chart reviews of electronic medical records. We evaluated these factors in relation to clinical outcomes including mortality, ED disposition, hospital length-of-stay and discharge venue. Patients were divided into the following age groups for analysis: 45–64 (middle-aged), 65–74 (young-old), 75–84 years (middle-old) and 85 years and above (old-old) (Table 1).[4]

Among 4522 patients in the study, the median age was 70 (interquartile range [IQR] 59–80) years with slight male predominance (53.8%). More males were in the "middle-aged" (70.2%) and "young-old" (55.3%) groups, whereas more females were in the "middle-old" (59.8%) and "old-old" (69.4%) groups. The prevalence of various medical conditions (e.g. cardiovascular diseases, chronic obstructive lung disease and renal disease) in the study cohort increased with rising age, except for asthma. The use of medications such as antiplatelets, antihypertensives and hypoglycaemic agents also increased across the age groups, but not for opioids, antiepileptics and benzodiazepines/hypnotics.

One in 5 patients required trauma team activation in the "middle-aged" group compared to 1.9–7.6% in the 3 other age groups. The "middle-aged" group also had the highest proportion of injuries due to road crashes. Most injuries sustained by the "young-old", "middle-old" and "old-old" groups were due to falls (71.4%, 83.2% and 89.8%, respectively) and occurred at home (44.7%, 63.9% and 74.1%, respectively). Overall, all-cause mortality at discharge was 8.4%, with significantly lower mortality in the "middle-aged" group (6.8%) compared to elderly patients aged 65 and above (10.9%) (P=0.004). Among elderly patients, overall mortality increased from the "young-old" (8.0%) to "old-old" (11.6%) subgroups, despite no significant differences in tier of injuries between age-differentiated subgroups. A higher proportion of patients in the younger age groups were admitted to the intensive care and high dependency units. These younger patients had a shorter median length of inpatient stay ("middle-aged" 7.5 [IQR 3.6–15.3] days, "young-old" 9.2 [4.2–18.2] days, "middle-old" 10.3 [4.8–18.3] days and "old-old" 9.7 [4.3–16.8] days, P<0.001). More patients in the older age groups required stepdown care to a community hospital or long-term care facility upon discharge ("middle-aged" 13.8%, "young-old" 24.6%, "middle-old" 32.1% and "old-old" 29.0%, P<0.001).

The presence of cardiac arrhythmia, congestive heart failure, coronary artery disease, moderate-to-severe renal disease, valvular heart disease, and use of antiplatelets, anticoagulation and diuretics were significantly associated with mortality in univariate analyses. After adjustment for age and Injury

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Table 1. Comorbidities, medications, injury epidemiology and outcomes.

Variables	"Middle-aged" 45–64 years (n=1772)	"Young-old" 65–74 years (n=962)	"Middle-old" 75–84 years (n=1151)	"Old-old" 85 years and above (n=637)	*P* value
Comorbidities, no. (%)					
Asthma	47 (2.7)	34 (3.5)	45 (3.9)	24 (3.8)	0.236
Congestive heart failure	43 (2.4)	32 (3.3)	72 (6.3)	54 (8.5)	<0.001
Coronary artery disease	143 (8.1)	163 (16.9)	265 (23.0)	157 (24.7)	<0.001
Cerebrovascular accident	102 (5.8)	135 (14.0)	219 (19.0)	98 (15.4)	<0.001
Chronic obstructive lung disease	8 (0.5)	13 (1.4)	34 (3.0)	18 (2.8)	<0.001
Diabetes mellitus	384 (21.7)	347 (36.1)	396 (34.4)	170 (26.7)	<0.001
Hypertension	612 (34.5)	622 (64.7)	825 (71.7)	474 (74.4)	<0.001
Moderate-to-severe renal disease[a]	77 (4.3)	59 (6.1)	80 (7.0)	46 (7.2)	0.007
Medications, no. (%)					
Antiplatelets	204 (11.5)	259 (26.9)	388 (33.7)	210 (33.0)	<0.001
Anticoagulation	29 (1.6)	43 (4.5)	66 (5.7)	27 (4.2)	<0.001
ACE-Is/ARBs	276 (15.6)	300 (31.2)	380 (33.0)	199 (31.2)	<0.001
Beta blockers	245 (13.8)	264 (27.4)	359 (31.2)	187 (29.4)	<0.001
Calcium channel blockers	258 (14.6)	298 (31.0)	406 (35.3)	242 (38.0)	<0.001
Diuretics	92 (5.2)	121 (12.6)	164 (14.2)	91 (14.3)	<0.001
Opioids	10 (0.6)	6 (0.6)	11 (1.0)	2 (0.3)	0.558^
Antiepileptics	46 (2.6)	26 (2.7)	32 (2.8)	14 (2.2)	0.751
Benzodiazepines/Hypnotics	27 (1.5)	6 (0.6)	15 (1.3)	8 (1.3)	0.241
OHGAs[b]	282 (15.9)	260 (27.0)	273 (23.7)	99 (15.5)	<0.001
Insulin	89 (5.0)	65 (6.8)	50 (4.3)	9 (1.4)	<0.001^
Injury epidemiology, no. (%)					
Mechanism of injury (Top 3 listed)					<0.001
Fall	824 (46.5)	687 (71.4)	957 (83.2)	572 (89.8)	
Road traffic crash	555 (31.3)	135 (14.0)	72 (6.3)	10 (1.6)	
Blunt	187 (10.6)	102 (10.6)	98 (8.5)	47 (7.4)	
Place of occurrence (Top 3 listed)					<0.001
Home	393 (22.2)	430 (44.7)	735 (63.9)	472 (74.1)	
Road	628 (35.4)	175 (18.2)	99 (8.6)	15 (2.4)	
Public places	329 (18.6)	243 (25.3)	211 (18.3)	103 (16.2)	

Table 1. Comorbidities, medications, injury epidemiology and outcomes. (Cont'd)

Variables	"Middle-aged" 45–64 years (n=1772)	"Young-old" 65–74 years (n=962)	"Middle-old" 75–84 years (n=1151)	"Old-old" 85 years and above (n=637)	*P* value
Tier of injury, no. (%)					0.314
T1	548 (30.9)	319 (33.2)	338 (29.4)	199 (31.2)	
T2	1224 (69.1)	643 (66.8)	813 (70.6)	437 (68.8)	
Outcomes, no. (%)					
ED disposition (excluding deaths in ED)	n=1740	n=952	n=1138	n=634	<0.001
Intensive care unit	213 (12.2)	92 (9.7)	81 (7.1)	20 (3.2)	
Intermediate care unit[c]	57 (3.3)	36 (3.8)	41 (3.6)	14 (2.2)	
High dependency	391 (22.5)	175 (18.4)	148 (13.0)	69 (10.9)	
General ward	1,079 (62.0)	647 (68.0)	867 (76.2)	531 (83.8)	
Discharged from ED[d]	0	2 (0.2)	1 (0.1)	0	
Stepdown care to community hospital or ILTC on discharge	210 (13.8)	205 (24.6)	320 (32.1)	164 (29.0)	<0.001
Overall mortality, no. (%)	121 (6.8)	77 (8.0)	108 (9.4)	74 (11.6)	0.001

ACE-Is: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; COPD: chronic obstructive pulmonary disease; ED: emergency department; ILTC: intermediate and long-term care; OHGAs: oral hypoglycaemic agents.
[a] Defined as estimated glomerular filtration rate of less than 45 ml/min/1.73 m^2.
[b] Number of OHGAs used ranged from 1 to 4.
[c] Intermediate care unit: only in 1 of the 2 centres (Singapore General Hospital).
[d] Includes discharges against medical advice.
^ Fisher's Exact test.

Severity Score in multivariate analyses, congestive heart failure (adjusted OR [AOR] 1.73, 95% confidence interval [CI] 1.04–2.88), moderate-to-severe renal disease (AOR 1.75, 95% CI 1.10–2.80) and diuretic use (AOR 1.90, 95% CI 1.30–2.78) remained statistically significant for overall mortality.

Our study highlighted that trauma among older adults in Singapore is a public health concern with significant mortality and burden on healthcare resources. We sought to better elucidate epidemiological trends by categorising our study population into age-differentiated subgroups, based on the understanding that the elderly are a heterogenous population group with varying functional status as ageing progresses.[4] We found that "middle-old" patients (75–84 years old) accounted for the highest proportion of ED trauma presentations. This subgroup required the longest inpatient length-of-stay and was least likely to be discharged home after hospitalisation. The "middle-old" age range may represent a watershed period where patients are more prone to falls due to poorer physiological reserves compared to the "young-old", but are relatively more mobile compared to the "old-old". More attention should be given to this subgroup, and future studies can focus on how to prevent injuries and improve outcomes among patients in this age range.

Additionally, we found that congestive heart failure and moderate-to-severe renal disease were independently and significantly associated with higher mortality in our study population following multivariate analysis. This was consistent with earlier studies which reported poorer outcomes in adult trauma patients with these conditions.[5,6] A unifying feature shared between both conditions is fluid overload. Current Advanced Trauma Life Support guidelines recommend initial resuscitation with a litre of crystalloids followed by early resuscitation with blood products, regardless of patient's age or premorbid status. However, elderly trauma patients with congestive heart failure or moderate-to-severe renal disease may be susceptible to develop fluid overload following

intensive volume resuscitation. This can result in higher mortality due to complications of fluid overload such as pulmonary oedema and poor wound healing.[7] A judicious fluid resuscitation strategy may be considered for elderly trauma patients with underlying diseases which can predispose them to fluid overload.

Among the medication classes we investigated, the pre-injury use of diuretics was found to be significantly associated with higher mortality in our study population. To our knowledge, there is no current literature to suggest an association between diuretic use and mortality in elderly trauma patients. However, previous systematic reviews have highlighted that diuretic use was associated with increased risk of falls among older adults.[8,9] Use of alternative antihypertensive agents among older adults has been found to be associated with lower risk of injurious falls.[9,10] These findings may be helpful in guiding prescription practices for elderly patients with hypertension.

Our study highlighted the intricate disease-drug-injury interactions, which may affect outcomes following trauma in older patients. Tailoring the management of older trauma patients while being aware of their underlying comorbid conditions and pre-injury medication use may help improve clinical outcomes.

Keywords: *emergency medicine, geriatric trauma, mortality, outcomes, Singapore*

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LETTER TO THE EDITOR

Optimising percutaneous valve-in-valve TAVI with bioprosthetic valve fracture

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Dear Editor,

Percutaneous transcatheter aortic valve implantation (TAVI) has become an established therapy for inoperable patients, for high, intermediate and low surgical-risk patients over 65 years old with severe aortic valve stenosis (AS).[1,2] Valve-in-valve (ViV) TAVI is an approved indication for patients with degenerated aortic surgical bioprostheses.

Several ViV TAVI registries have demonstrated good clinical outcomes.[3-5] One limitation is the elevated residual mean pressure gradient (MPG ≥20 mmHg) after ViV TAVI, which occurred in 27% of patients, particularly in small (≤21 mm label size) surgical valves, as the expansion of the new transcatheter heart valve (THV) is constrained by the sewing ring.[3] The high residual MPG increases the likelihood of patient-prosthesis mismatch (PPM), which results in lesser symptomatic improvement, poorer valve durability and increased mortality.[3,6] Bioprosthetic valve fracture (BVF) was developed to break the surgical valve sewing ring, increasing the internal diameter (ID) and reducing the residual MPG.[7] We report 2 cases of ViV TAVI that required BVF to improve valve haemodynamics.

A 65-year-old male presented with 4-month exertional dyspnoea (New York Heart Association [NYHA] class II). He underwent surgical aortic valve replacement (SAVR) with a 21 mm Perimount (Edwards Lifesciences, Irvine, CA, US) bioprosthesis (Fig. 1a) (true ID 19 mm) and a bypass with a vein graft to the right coronary artery 11 years ago. The MPG post-SAVR was 15 mmHg. Echocardiography showed normal left ventricular ejection fraction (LVEF) (60%), severe bioprosthetic AS (MPG 45 mmHg, aortic valve area [AVA] 0.8 cm^2) and mild aortic regurgitation (AR), consistent with a degenerated tissue valve. Due to his elevated surgical risk (redo surgery, patent bypass graft) and refusal to consider repeat surgery, we proceeded with ViV TAVI and BVF.

Under local anaesthesia and sedation, a balloon-expandable 23 mm Sapien 3 valve (Edwards Lifesciences, Irvine, CA, US) sized according to the VIV aortic app from the App store or Google Play store, was successfully implanted (Fig. 1b) with cerebral embolic protection using the Sentinel system (Boston Scientific, Marlborough, MA, US). The aortic MPG (simultaneous catheter measurement) was 14 mmHg. BVF was then performed using a noncompliant 22 mm True Dilatation balloon achieving better TAVI frame expansion (Fig. 1c). The final aortic MPG was 8 mmHg.

The patient was discharged 2 days post-procedure on dual antiplatelet therapy (DAPT—aspirin and clopidogrel). At 30-day follow-up, he was in NYHA functional class I. Echocardiography showed a stable Sapien 3 valve, an aortic MPG of 16 mmHg and trivial AR. Subsequent 6-month echocardiography showed aortic MPG 13 mmHg (Table 1), AVA 1.2 cm^2 and trivial AR.

A 76-year-old male presented with 9-month exertional dyspnoea (NYHA class III). He underwent SAVR with a 19 mm Mitroflow (Sorin Group USA Inc, Arvada, Colo, US) bioprosthesis (Fig. 1e) (true ID 15.4 mm) 9 years ago. The MPG post-SAVR was 22 mmHg. Echocardiography showed normal LVEF (60%), severe bioprosthetic AS (MPG 56 mmHg, AVA 0.7 cm^2) and severe transvalvular AR (without paravalvular leak), consistent with a failed tissue valve. Due to his elevated surgical risk (redo surgery, advanced age), we proceeded with ViV TAVI and BVF.

Under local anaesthesia and sedation, a balloon-expandable 20 mm Sapien 3 valve (smallest Sapien valve based on the manufacturer's recommendation, as the ViV app does not recommend any THV due to the concerns of underexpansion and high residual gradient in such a small surgical valve) was successfully implanted (Fig. 1f) with cerebral embolic protection using the Sentinel system. The aortic MPG (simultaneous catheter measurement) was 37 mmHg. BVF was then performed using a 20-mm True Dilatation balloon achieving a significantly better TAVI frame expansion (Fig. 1g). The final aortic MPG was 14 mmHg.

The patient was discharged 2 days post-procedure on DAPT. At 30-day follow-up, he was in NYHA functional class I. Echocardiography

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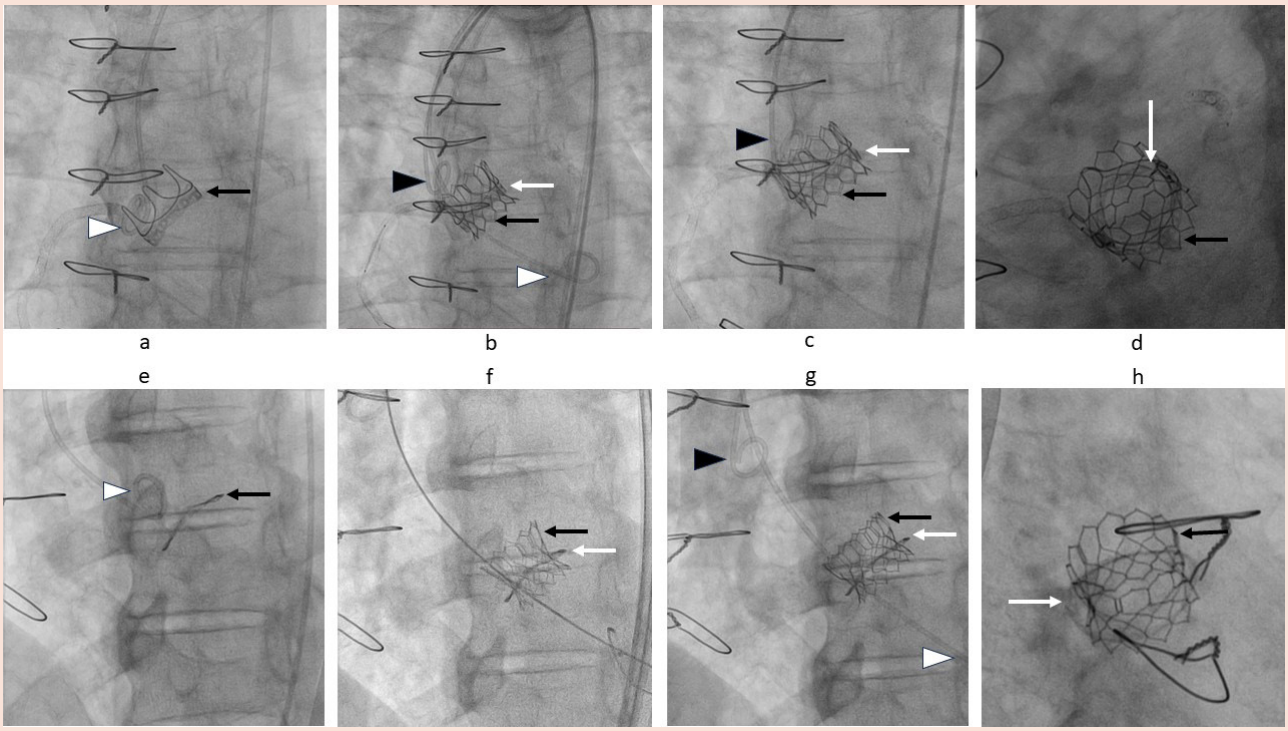
Fig. 1. Fluoroscopic images of valve-in-valve TAVI with bioprosthetic valve fracture.



(A) Fluoroscopic image of the 21 mm Perimount surgical valve (arrow) in the aortic position. The arrowhead denotes the pigtail catheter in the aortic root. (B) Fluoroscopic image of the 23 mm Sapien 3 THV (black arrow) within the 21-mm Perimount surgical valve. The white arrow denotes the "waist" where the Sapien 3 THV is constrained by the sewing ring of the Perimount surgical valve. The black and white arrowheads denote the pigtail catheters in the aortic root and LV, respectively. (C) Fluoroscopic image of the 23-mm Sapien 3 THV (black arrow) within the 21-mm Perimount surgical valve. The white arrow shows that the Sapien 3 THV is now well expanded within the Perimount surgical valve. The black arrowhead denotes the pigtail catheters in the aortic root. Successful BVF was indicated by a sudden visual release of the "waist" of the THV and a rapid drop in the balloon inflation device pressure. (D) Fluoroscopic image of the 23-mm Sapien 3 THV (black arrow) within the 21-mm Perimount surgical valve. The white arrow denotes the fracture of the sewing ring of the Perimount surgical valve. (E) Fluoroscopic image showing the sewing ring (arrow) of the Mitroflow surgical valve (the rest of the valve is not visible). The arrowhead denotes the pigtail catheter in the aortic root. (F) Fluoroscopic image of the 20 mm Sapien 3 THV (black arrow) within the 19-mm Mitroflow sewing ring. The white arrow denotes the "waist" where the Sapien 3 THV is constrained by the sewing ring of the Mitroflow surgical valve. (G) Fluoroscopic image of the 20-mm Sapien 3 THV (black arrow) within the 19 mm Mitroflow surgical valve. The white arrow shows that the Sapien 3 THV is now well expanded within the Mitroflow surgical valve. The black and white arrowheads denote the pigtail catheters in the aortic root and LV, respectively. Successful BVF was indicated by a sudden visual release of the "waist" of the THV and a rapid drop in the balloon inflation device pressure. (H) Fluoroscopic image of the 20-mm Sapien 3 THV (black arrow) within the 21-mm Perimount surgical valve. The white arrow denotes the fracture of the sewing ring of the Mitroflow surgical valve.
BVF: bioprosthetic valve fracture; LV: left ventricle; THV: transcatheter heart valve

showed a stable Sapien 3 valve, an aortic MPG of 18 mmHg and trivial paravalvular AR. Subsequent 3-month echocardiography showed aortic MPG 14 mmHg (Table 1), AVA 1.2 cm^2 and trivial AR.

ViV TAVI is increasingly performed for failed surgical bioprotheses with good results.[3,4] In one local series, there were no procedural complications, and short-term outcomes were excellent.[5]

However, there are 2 major concerns. First, there is a risk of coronary occlusion as the valve leaflets are pushed outwards, especially in externally mounted leaflets such as the Mitroflow bioprosthesis.[3] This risk can be predicted using a computerised tomography scan, which was performed in both patients. In the patient with the Mitroflow prosthesis, the left and right coronary artery heights were 11 and 17 mm, respectively; the sinus of Valsalva diameter was 29 mm; and the sinotubular junction height was 21 mm. As the right coronary artery was higher than the Mitroflow valve height of 11 mm, there was no risk of right coronary occlusion. Because the left coronary artery was just below the Mitroflow valve height, the virtual THV to coronary (VTC) distance was then measured and was 6.8 mm, indicating low risk for coronary occlusion (VTC <4 mm is deemed high risk and VTC >6 mm low risk).[8]

Second, the residual MPG after ViV TAVI may be elevated. The global aortic ViV registry showed that elevated MPGs occurred more frequently in small surgical (≤21 mm label size) bioprosthesis, and with the balloon-expandable THVs.[3] The self-

Table 1. Serial mean pressure gradient in mmHg.

	Baseline post-SAVR	Pre-TAVI	Post-TAVI	Post-BVF	1 month	3 months	6 months
Patient 1	15	45	14	8	16	-	13
Patient 2	22	56	37	14	18	14	-

BVF: bioprosthetic valve fracture; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation

expanding THVs, due to their supra-annular leaflet design, produced lower gradients, although PPM could still occur.[3] As balloon-expandable THVs facilitate easier coronary artery access (compared to supra-annular self-expanding THVs), this was selected for the first patient as he had multiple coronary angioplasties, and may require repeat percutaneous intervention. For the second patient, a balloon-expandable THV was chosen as the upper and lower edges would flare during THV deployment, making it more secure (less embolisation risk) during BVF.

BVF to lower gradients during aortic ViV was first described in 2015.[9] This technique utilises a noncompliant balloon (1 mm larger than the surgical valve label size) to fracture the sewing ring, increasing its true ID, optimising THV expansion and leaflet coaptation, and reducing the residual gradient.[7]

This technique has been shown to be effective and safe, if the BVF is performed after ViV TAVI. Performing BVF before ViV TAVI valve increased the risk in-hospital mortality and stroke, which were not observed if BVF followed ViV TAVI.[7] This is an important finding as the risk of stroke and mortality during ViV TAVI was similar to native valve TAVI.[10] Data on THV leaflet thrombosis after ViV TAVI are sparse, and optimal antithrombotic regimen is still uncertain, although single antiplatelet or short-term DAPT is recommended by the American College of Cardiology/American Heart Association guidelines.[2]

In our 2 patients, there was underexpansion of the THV that improved after BVF, with corresponding MPG reduction, good clinical outcomes and satisfactory gradients despite having small surgical bioprostheses.

In conclusion, this report demonstrates that BVF is an effective and safe method of optimising haemodynamics after ViV TAVI. This may enhance symptomatic improvement, THV durability and survival of patients with small surgical bioprostheses, although long-term data would be required before routinely offering this therapy to low surgical-risk patients.

Keywords: *aortic stenosis, bioprosthetic valve fracture, cardiology, percutaneous, transcatheter aortic valve replacement, valve-in-valve implantation*

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LETTER TO THE EDITOR

Group B Streptococcus screening with antenatal culture and intrapartum polymerase chain reaction: A prospective cohort study

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Dear Editor,

Group B Streptococcus (GBS) is a common genital and gastrointestinal tract commensal in healthy women. Vertical transmission of GBS may cause neonatal early-onset GBS disease (EoGBS), and this is prevented by intrapartum antibiotic prophylaxis (IAP). Notably, intermittent GBS colonisation,[1] coupled with long turnaround time of GBS culture, challenges the accuracy of conventional antenatal GBS screening in predicting carriage during labour, especially for those without prior antenatal GBS screening. Polymerase chain reaction (PCR) offers a rapid and accurate alternative, demonstrating 98.5% sensitivity and 99.6% specificity, surpassing the 58.3% positive predictive value of antenatal culture screening in a retrospective study,[2] resulting in the reduction of EoGBS from 1.01 to 0.21 per 1000 live-births. This study aimed to compare the sensitivity and specificity of intrapartum GBS PCR to antenatal GBS swab culture, using intrapartum GBS culture as a reference for maternal colonisation status.

This cross-sectional study from March 2021 to December 2021 in KK Women's and Children's Hospital included pregnant women aged ≥21 years, ≥37 weeks' gestation, with antenatal swab culture (COPAN M40 Amies Agar Gel Transystem, COPAN, US) for GBS broth culture collected within 5 weeks (window of validity as per American College of Obstetrics and Gynaecology)[3] prior to delivery, and intact membranes with no leaking liquor at presentation. Those with spontaneous rupture of membranes, in labour <37 weeks' gestation, and who received antibiotics after 35 weeks of gestation or after routine antenatal GBS screening were excluded. Informed consent was obtained. This study is approved by the SingHealth Centralised Institutional Research Board (CIRB 2020/2126). Medical records were accessed for demographic and clinical information related to labour and delivery.

During labour, double-vaginal swab was collected prior to antibiotics administration. One was sent for intrapartum culture (as per antenatal swab), while the other was processed as a point-of-care test, using Cepheid collection device as transport medium before being loaded into an Xpert GBS cartridge. The Xpert GBS PCR assay (Cepheid, Sunnyvale, CA, US) was performed using the Cepheid GeneXpert device, according to manufacturer's protocol. Results were reported in the Cepheid GeneXpert software. Patients with positive antenatal GBS culture were covered with IAP as per hospital guidelines regardless of intrapartum results. Patients with negative antenatal GBS culture but positive intrapartum PCR result were offered IAP.

Continuous data were presented as mean± standard deviation (SD), while categorical data were presented as frequencies (percentages). Diagnostic measures were reported using sensitivity, specificity and area under the curve (AUC) from receiver operating curve with a 95% confidence interval (CI). Gwet's AC1 agreement was reported between antenatal and intrapartum cultures, and between intrapartum culture and PCR. Sensitivity and specificity from antenatal culture and intrapartum PCR were compared using McNemar tests of paired design. All tests were two-sided, and $P<0.05$ was statistically significant. All analyses were performed in SAS version 9.4 software (SAS Institute, Cary, NC, US).

Among 170 participants, 86 (50.6%) had positive and 84 (49.4%) had negative antenatal GBS culture. Their mean age was 30.6±4.6 years, mean body

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Table 1. Detection of GBS status by antenatal culture and intrapartum PCR, compared to intrapartum culture as the reference standard.

		Intrapartum culture		
		Positive	Negative	Total
Antenatal culture	Positive	35	51	86
	Negative	3	81	84
	Total	38	132	170
Intrapartum PCR	Positive	33	25	58
	Negative	4	105	109
	Total	37	130	167

GBS: Group B Streptococcus; PCR: polymerase chain reaction

mass index was 29.7±5.7 kg/m^2, and mean gestational age at delivery was 39.1±0.9 weeks. Most were nulliparous (50.6%), without gestational diabetes (81.8%), and delivered vaginally (84.7%). None of the neonates developed EoGBS sepsis. The mean duration required for intrapartum PCR was 54±3 minutes.

The detection of GBS status by antenatal culture and intrapartum PCR was compared with intrapartum culture as the reference standard (Table 1). Antenatal culture and intrapartum PCR have sensitivities comparable to those of intrapartum culture at 92.1% (95% CI 78.6–98.3) and 89.2% (95% CI 74.6–97.0), respectively. However, intrapartum PCR has a higher specificity of 79.6% (95% CI 71.7–86.1) compared to 61.4% (95% CI 52.5–69.7) for antenatal culture. AC1 (71.7% versus 40.8%), AUC (0.85 vs 0.77) and odds ratio (OR) (30.8 vs 16.1) of intrapartum PCR were also higher. Furthermore, the false positive rates of intrapartum PCR (19.2%, 25 of 130) were lower than those of antenatal culture (38.6%, 51 of 132).

Three (1.8%) women had inconclusive PCR results, 2 of which were antenatal and intrapartum culture negative, and 1 was antenatal and intrapartum culture positive. Six participants (3.5%) had discordant results. Intrapartum PCR did not detect the positive GBS colonisation status of 3 (1.8%) women determined by intrapartum culture. Another 3 (1.8%) women had a change in GBS status (from negative antenatal culture to positive intrapartum culture), 2 of whom were correctly identified as positive with intrapartum PCR.

There is increasing evidence supporting nucleic acid amplification tests for intrapartum GBS screening,[4] due to higher sensitivity, specificity and rapid 1–2 hour turnaround time. The Cepheid Xpert GBS test used in this study is also the only in vitro diagnostic test that meets the criteria of Centers for Disease Control and Prevention for rapid intrapartum GBS testing without requiring 24-hour Lim broth enrichment[5] and has shown to have comparable results.[6] In this study, intrapartum PCR demons-trated comparable sensitivity and superior specificity compared to antenatal culture, with higher AC1, AUC and OR. With a disease prevalence of 22% (38 of 170), despite the modest sample size of 170, this study achieves over 85% power to detect change in sensitivity from 50% to 75% using a two-sided binomial test and 100% power to detect change in specificity from 50% to 80% using a two-sided binomial test at the target significance level of 5%.

In this study, 51 (59.3%, 51 of 86) participants experienced a change in GBS status from positive antenatal to negative intrapartum GBS colonisation, which resulted in unnecessary IAP use for over half the participants. This overuse impacts maternal and neonatal microbiomes, affecting infants' immune and metabolic functions,[7] and increases treatment cost, which could potentially be used to offset any additional cost of PCR testing. Notably, PCR detected 2 of 3 women with negative antenatal GBS culture but subsequently positive intrapartum GBS culture, highlighting its potential in preventing missed opportunities for IAP.

Admittedly, intrapartum PCR has limitations. Three (1.8%) participants had inconclusive PCR results, lower than similar studies reporting up to 13.6% invalid results.[8,9] This can be minimised by repeating the test, which has shown to increase success rate from 86.4% to 91.3%. Among 4 with negative intrapartum PCR but positive intrapartum culture, 3 had positive antenatal culture results, potentially missing the opportunity for IAP if they were screened with intrapartum PCR only. The presence of such discordant results is possibly due to sampling or processing errors.[2,8] In

addition, we acknowledge that recto-vaginal swabs are recommended for GBS screening, instead of vaginal swabs, which was the routine practice in this centre due to cultural reasons. This may have affected the sensitivity of GBS detection. However, vaginal swabs were consistently used for the antenatal and intrapartum swab cultures and PCR.

Intrapartum PCR has shown comparable sensitivity and superior specificity in detecting GBS colonisation. It provides an alternative strategy for the universal screening of GBS, especially in those who have missed out on antenatal screening.

Keywords: *Group B Streptococcus, Group B Streptococcus screening, intrapartum screening, obstetrics and gynaecology, polymerase chain reaction*

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LETTER TO THE EDITOR

Comparing the effectiveness, safety and cost of teleconsultation versus face-to-face model of pharmacist-led anticoagulation clinic: A single institution experience

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Dear Editor,

Teleconsultation-based (TELE) anticoagulation clinic (ACC) is an alternative modality, but its use in Singapore's clinical setting has not been well studied. In Tan Tock Seng Hospital (TTSH), the TELE ACC service was established to enrol patients who (1) perform self-testing using a loaned point-of-care (POC) international normalised ratio (INR) coagulometer or (2) visit the nearest polyclinic for INR blood test on days instructed by an ACC pharmacist; the patients will be followed up with via telephone consult or video conference on the same day. This enables patient convenience and reduces patient wait time compared with face-to-face (F2F) consultation.

A retrospective study was done to compare the effectiveness, safety and cost of TELE ACC versus F2F ACC model in TTSH. Records of ACC patients seen via TELE and F2F visits were retrieved from 2014 to 2021. Patients on warfarin for any indication seen by ACC, 21 years old and above, and those on the same model of teleconsultation (TELE/F2F) for at least 5 months were included. Exclusion criteria include patients on direct-acting oral anticoagulants, pregnant or breastfeeding patients, and patients who were switched from either of the 2 models of consultation within the study period of 5 months unless it was part of the workflow.

Data such as number of episodes of non-compliance, dietary/herbal/supplement intake changes, lifestyle changes (physical activity, smoking and alcohol), unwell periods and changes in interacting medications were collected as they are confounders to the time in therapeutic range (TTR). For patients with atrial fibrillation, CHA_2DS_2-VASc and HAS-BLED scores were collected.

Thirty patients were recruited for each of the F2F and TELE groups. Table 1 shows the baseline demographics of the patients. The TELE group comprised 19 patients (63%) who did perform self-testing, and 11 patients (37%) who visited the nearest clinic for blood taking. There was no statistically significant difference between both groups for age, sex, ethnicity, indication for warfarin, target INR range, comorbidities, as well as CHA_2DS_2-VASc and HAS-BLED scores for those with atrial fibrillation.

Clinical outcomes. The TTRs for both F2F and TELE service were not significantly different from each other at 64.4% and 58.3%, respectively (P=0.35) using the Rosendaal method, and 57.4% and 53.2%, respectively (P=0.53) using the traditional method (Table 1).

The results from our study were similar to another Singapore study with only atrial fibrillation patients where the TELE group had a mean TTR of 64.6% compared with 65.7% for the F2F group over 6 months using Rosendaal method.[1]

Safety outcomes. There is no significant difference in the safety outcomes between the TELE and F2F ACC services in terms of the warfarin-related emergency department visits and hospitalisation, and thromboembolic events (Table 1).

To compare safety outcomes across different studies, the complication rate per patient-year was calculated. For our study, the TELE ACC and F2F ACC services had complication rates (patients with warfarin-related complications/total number of patients) of 40% (n=12) and 63% (n=19). The complication rate per patient-year was 3.2% and 5% for the TELE ACC and F2F ACC services, respectively. This is comparable to reported event rates of 2.8–7.6% per patient-year in other anticoagulation centers.[2-4]

Comparison of direct patient cost for TELE ACC and F2F ACC services. The mean direct patient cost for the TELE service over a period of 5 months was \$198.70 ± \$71.80. This cost is significantly higher compared with the F2F service, which was \$130.80 ± \$46.90 (P<0.01) (Table 1).

The higher cost of TELE service was attributed to the significantly higher number of ACC consultations done per patient for the TELE service (9.8 ± 3.3) compared with the F2F service (6.7 ± 2.4) (P<0.01). In addition, the average number of test strips used was greater for the TELE service, with an average

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Table 1. Comparison of face-to-face (F2F) and teleconsultation (TELE) groups.

Variable	F2F (n=30)	TELE (n=30)	*P* value
Baseline demographics			
Age, mean (SD), years	76 (11.4)	74 (17.1)	0.65
Male, no. (%)	14 (46.7)	10 (33.3)	0.48
Ethnicity, no. (%)			
Chinese	21 (70.0)	21 (70.0)	0.47
Malay	4 (13.3)	6 (20.0)	
Indian	1 (3.3)	2 (6.7)	
Others	4 (13.3)	1 (3.3)	
Indication for warfarin,[a] no. (%)			
Atrial fibrillation	18 (60.0)	21 (70.0)	0.46
Stroke/transient ischaemic attack	8 (26.7)	11 (36.6)	0.41
Deep vein thrombosis	7 (23.3)	6 (20.0)	0.75
Pulmonary embolism	4 (13.3)	5 (16.7)	0.72
Mitral valve replacement	5 (16.6)	3 (10.0)	0.45
Left ventricular clot	0 (0)	3 (10.0)	-
Valvular heart disease	5 (16.6)	3 (10.0)	0.45
Aortic valve replacement	1 (3.3)	2 (6.7)	0.55
Antiphospholipid syndrome	0 (0.0)	1 (3.3)	-
Others	3 (10.0)	5 (16.7)	0.45
Target INR range, no. (%)			
2.0–3.0	22 (73.3)	21 (70.0)	0.19
2.0–2.5	3 (10.0)	4 (13.3)	
2.5–3.5	2 (6.7)	0 (0)	
2.5–3.0	1 (3.3)	3 (10.0)	
Others	2 (6.7)	2 (6.7)	
Consultation type, no. (%)			
Face-to-face	30 (100)	-	-
Phone	-	18 (60.0)	-
Video	-	12 (40.0)	-
Location of blood test, no. (%)			
INR coagulometer (perform self-testing)	-	19 (63.3)	-
Polyclinic/nursing home/general practitioner	-	8 (26.6)	-
Tan Tock Seng Hospital	30 (100)	3 (10.0)	<0.01
Comorbidities,[b] no. (%)			
Hypertension	22 (73.3)	20 (66.6)	0.57
Congestive cardiac failure	4 (13.3)	10 (33.3)	0.07
Diabetes	11 (36.7)	13 (43.3)	0.60

Table 1. Comparison of face-to-face (F2F) and teleconsultation (TELE) group. (Cont'd)

Variable	F2F (n=30)	TELE (n=30)	*P* value
Baseline demographics			
Vascular disease[c]	12 (40.0)	15 (50.0)	0.44
Renal disease	0 (0)	5 (13.3)	-
Liver disease	1 (3.3)	1 (3.3)	1
Stroke history	11 (36.7)	14 (46.6)	0.43
Bleeding history	10 (33.3)	13 (43.3)	0.43
Medication use predisposing to bleeding,[d] no. (%)	5 (16.7)	2 (6.6)	0.23
CHA_2DS_2-VASc score, mean (SD)[e]	4.5 (1.5)	5.6 (2.2)	0.08
HAS-BLED score, mean (SD)[e]	2.3 (1.1)	3.0 (1.3)	0.10
First visit encounters, no. (%)	8 (26.6)	0 (0)	-
Total number of days for INR monitoring, mean (SD)	177.8 (24.9)	167 (19.8)	0.09
Dietary/herbal/supplement intake changes, no. (%)	16 (53.3)	14 (46.7)	0.61
Changes in interacting medications, mean, no. (%)	4 (13.3)	3 (10.0)	0.69
Lifestyle changes, no. (%)	1 (3.3)	6 (20.0)	0.04
Non-compliance to warfarin, no. (%)	11 (36.6)	5 (16.7)	0.09
Clinical outcomes between TELE and F2F services, mean (SD)			
TTR by traditional method	57.4 (25.7)	53.2 (25.5)	0.53
TTR by Rosendaal method	64.4 (25.5)	58.3 (24.4)	0.35
Percentage of INR above TTR	6.97 (13.2)	9.8 (11.5)	0.25
Percentage of INR below TTR	28.7 (24.9)	31.9 (25.0)	0.70
Safety outcomes between TELE and F2F services, no. (%)			
Patient with INR >5.0 within 5 months	1 (3.3)	1 (3.3)	1.0
Warfarin-related emergency department visits	0	0	-
Warfarin-related hospitalisation	2 (6.6)	4 (13.3)	0.74
Thromboembolic events	0	1 (3.3)	0.31
Major bleeding	2 (6.6)	1 (3.3)	0.55
Clinically relevant non-major bleeding	1 (3.3)	1 (3.3)	1.0
Other bleeding	7 (23.3)	12 (40)	0.27
Cost comparison between TELE and F2F services,[f] mean (SD)			
Number of INR test done (PT/POCT-INR)	7 (2.4)	13 (5.5)	<0.01
Number of outpatient visits	6.7 (2.4)	1.2 (1.0)	<0.01
Number of teleconsultations	0	8.9 (3.1)	<0.01
Cost of service per patient, USD	130.8 (46.9)	198.7 (71.8)	<0.01

INR: international normalised ratio; PT/POCT: prothrombin time test/point-of-care testing; SD: standard deviation; TTR: time in therapeutic range

[a] Patients may have more than 1 indication.
[b] Patients may have more than 1 comorbidity.
[c] Prior myocardial infarction, peripheral vascular disease and ischaemic heart disease.
[d] Anti-platelets or non-steroidal anti-inflammatory agents.
[e] For patients with atrial fibrillation.
[f] Costs were reported in US dollars based on the pegged exchange rate USD 0.72/SGD 1.

of 13 INR test strips. This was due to the 3-monthly quality control check of the home POC-INR coagulometer with the hospital POC-INR coagulometer to ensure that INR readings do not deviate significantly from each other. Additionally, some TELE patients may use more than 1 INR test strips due to failed attempts at self-testing, thus incurring a higher cost compared with F2F visits where testing was performed by a professional medical technologist.

For our study, a direct patient cost from a patient's perspective was considered to evaluate cost from a patient's point of view. Even from a patient's perspective, some costing study included different cost components, such as the cost of the coagulometer that will incur higher patient cost.[5] For our study, the home POC INR coagulometer was loaned to the patient until the INR stabilises so that it was more cost-saving for patients. Other studies also considered indirect patient costs, such as transportation fees, time of registration and waiting time as well as time off work into account.[6] Most cost studies do not consider practical aspects of patient's cost from the wastage of using more than 1 POCT INR test strips due to failure of attempting INR self-testing, which our study considered.

Overall, teleconsultation modality for pharmacist-led ACC service was shown to be as effective and safe as F2F ACC service in this study. The TELE ACC service requires strict compliance to local personal data protection guidelines. This includes using secured video consultation platform and conducting them in a private setting. Recording of video consultation was not permitted.

The limitation of this study is the short follow-up period of 5 months and the small sample size. Future studies can be conducted over a longer period with larger sample size, incorporate indirect patient cost, and consider travel cost and time saved, which would be a more holistic cost study from a patient's perspective. To our knowledge, this study was also the first in Singapore to examine cost of teleconsultation service compared with usual anticoagulation management. Future cost studies can also be done from healthcare payers' and societal perspective, and consider costs such as for time taken by the healthcare provider for teleconsultation and technological infrastructure.

Disclosure

No conflict of interest.

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Keywords: *anticoagulation, cardiology, clinical pharmacy service, general medicine, neurology, stroke, teleconsultation, telepharmacy, warfarin*

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