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Improving the effectiveness of cervical cancer screening: Managing positive high-risk human papillomavirus results

To reduce the incidence of cervical cancer in Singapore, a new study highlights the need for a structured recall system in cancer screening and to address surveillance hesitancy. (See full article, p.342)

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Assessing the impact of frailty in elderly patients undergoing emergency laparotomies in Singapore

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EDITORIAL

Evaluating the effectiveness of cervical cancer screening and prevention in Singapore

Felicia Hui Xian Chin[1] *MMed(O&G)*

Cervical cancer is the fourth most common cancer in women globally, with approximately 660,000 new cases and 350,000 deaths reported in 2022.[1] In Singapore, it ranks as the 11th most common cancer among women and the 5th most frequent cancer among young women aged 15–44 years, with 309 new cases and 172 deaths reported in 2023.[2] Worldwide, the highest incidence and mortality rates are observed in low- and middle-income countries, such as those in Africa, Melanesia and Southeast Asia, while the lowest rates are found in Western Asia, Australia-New Zealand and North America.[1]

The development of cervical cancer is closely linked to the human papillomavirus (HPV), a double-stranded DNA virus. To date, more than 200 genotypes have been identified, 40 of which infect the anogenital region. HPV is primarily transmitted through close contact such as sexual intercourse. Twelve high-risk HPV (hrHPV) subtypes have been identified—HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58 and HPV-59. hrHPV plays a crucial role in the pathogenesis of cervical dysplasia and carcinoma,[3] with 99% of all cervical cancers are attributable to hrHPV, with HPV-16 and HPV-18 alone accounting for 70% of all cervical cancers.[4]

While 85% of women will contact HPV during their lifetime, up to 90% will clear the infection through their innate immunity. Approximately 67% of women manage to clear the infection without intervention within 12 months, and more than 90% of women do so within 24 months.[5] Persistent hrHPV infection, however, can lead to high-grade cervical dysplasia and eventually cervical cancer, a process that takes decades in immunocompetent women. This extended precancerous phase of cervical intraepithelial neoplasia (CIN) makes cervical cancer highly preventable through close surveillance and treatment of precancerous lesions.

The approach to eliminating cervical cancer is three-pronged—cervical cancer screening, prompt treatment of high-grade CIN, and vaccination against HPV. Access to screening, treatment of preinvasive and invasive cervical disease, and HPV vaccination are the main determinants of cervical cancer incidence and mortality rates.

In 2020, the World Health Assembly adopted a global strategy to eliminate cervical cancer, defined as fewer than 4 cases per 100,000 women per year. To achieve this by the end of the 21st century, the World Health Organization set the 90–70–90 targets for 2030: 90% of girls fully vaccinated with the HPV vaccine by age 15, 70% of women screened with a high-performance test by ages 35 and 45, and 90% of women identified with cervical disease receiving treatment.

As of 2022, only approximately 10 countries—all in the eastern Mediterranean region—have estimated incidence rates below the threshold.[1] Australia and the Nordic countries such as Norway and Sweden, are leading the effort to eliminate cervical cancer, with nationwide registries for cervical cancer screening and call-and-recall systems to monitor attendance. To improve access and inclusivity, these countries have integrated HPV self-sampling, which has proven to be as sensitive in detecting high-grade CIN as physician-collected samples.[6,7]

In Singapore, cervical cancer screening with cytology, more commonly known as the Papanicolaou (PAP) test, was first introduced in the 1960s. Government-led initiatives and public health campaigns, such as CervicalScreen Singapore, helped to promote cervical cancer screening uptake among women. HPV DNA testing was incorporated into screening protocols in the 2000s due to its improved sensitivity in detecting high-grade CIN[8] and greater protection against invasive cervical carcinomas compared to cytology.[9] In 2019, HPV testing replaced cytology as the primary screening method for women aged 30 and older.

HPV testing via clinician-collected samples is the mainstay of screening in Singapore. While HPV self-sampling is not yet widely performed, a study of 300 women in Singapore showed that most participants found self-sampling easy and believed that it would increase their likelihood of participating in screening.[10] The Society for Colposcopy and Cervical Pathology of Singapore recently supported the adoption of HPV self-testing based on current evidence.[11]

HPV and PAP tests are available at various healthcare institutions and clinics in Singapore,

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with subsidies through MediSave and Community Health Assist Scheme programme, making screening affordable and accessible. Initiatives like the "Healthier SG" and "Screen for Life" offer fully subsidised cervical cancer screening for enrolled Singaporeans at selected clinics.

Despite these efforts, the National Population Health Survey 2022 revealed that among Singapore female residents aged 25 to 74 years, 89.9% were aware of the PAP test and 54.6% were aware of the HPV test.[12] However, only 43.1% of female residents in this age group participated in cervical cancer screening, a significant decline from 57.9% in 2007. This downward trend was statistically significant ($P<0.05$). The most commonly cited reason for not participating in screening was a belief that it was unnecessary if they were healthy.

Tay's study found that even with an abnormal HPV test result, only 28.2% of patients returned for follow-up after 12 months.[13] The overall follow-up attendance rate was 42.8% over 5 years. The reluctance to return for surveillance significantly increases the risk of detecting high-grade CIN in persistent HPV infection.[13] Understanding the reasons behind non-attendance—whether due to cost, lack of a national registry, or the absence of a call-recall system—is crucial.

HPV vaccination was introduced in Singapore in 2006, with MediSave funding available to defray the costs for the bi- and quadrivalent vaccines. The bivalent Cervarix vaccine (GlaxoSmithKline) and the nonavalent Gardasil vaccine (Merck Sharp & Dohme) are currently available in Singapore. The quadrivalent Gardasil vaccine has been phased out.

Since 2010, HPV vaccination has been part of the National Childhood Immunisation Programme, offered free-of-charge to all female students in Secondary 1. A 2014 study found that only 13.6% of women aged 18 to 26 years were immunised.[14] However, the inclusion of HPV vaccination in the National Adult Immunisation Schedule in 2017 and the introduction of a school-based programme significantly increased vaccination rates to over 90%.[15] While it may take decades to see the full impact of HPV vaccination, the promising school-based vaccination rates indicate positive progress.

Cervical cancer has long been considered the most preventable gynaecological cancer. However, with a cervical cancer incidence rate of 6.8 per 100,000 women in Singapore,[12] suboptimal screening uptake, and a relatively new HPV vaccination programme, more concerted efforts are needed from all stakeholders to eliminate cervical cancer. Recognising that a death from cervical cancer is death from neglect is imperative as we work towards a future where no woman is left behind.

Declaration

No conflict of interest is declared by the author.

Keywords: *cancer prevention, cervical cancer, HPV vaccination, human papilloma virus, public health, screening*

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EDITORIAL

The value of frailty assessments in older surgical patients undergoing emergency laparotomies in Singapore

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Mortality in emergency laparotomy (EL) far exceeds that of elective bowel surgery, and standards for the National Emergency Laparotomy Audit (NELA) in the UK were introduced due to the high mortality within 1 month of EL.[1] In Singapore, 30-day mortality varies between 5.4% and 14.7% after EL.[2,3] However, 30-day mortality in older patients has been reported to be as high as 31.5%.[3]

Frailty is defined as a dynamic state of health that involves the gradual loss of physiological in-built reserves, leading to losses in 1 or more domains of human function (physical, cognitive, psychological and/or social), and increases the vulnerability of older adults to adverse health-related outcomes.[4] There is burgeoning evidence that frailty is a better predictor of postoperative morbidity and mortality than chronological age alone.[5] Although the benefit of frailty assessment has been established in other countries, a recent study has established the importance of frailty assessment in older patients (age ≥65 years) and identified frailty as a pivotal factor in the postoperative trajectory of patients undergoing EL in Singapore. The study reported 1 in 4 (26%) older patients as frail,[6] which is considerably higher than the NELA cohort where only 1 in 5 patients were frail.

Among the multiple tools developed to assess the multidimensional construct of frailty, the Clinical Frailty Scale (CFS) has been recommended in many international guidelines[5,7] as a clinically feasible and validated tool for screening frailty. Specifically, large multicentre trials, such as the UK emergency laparotomy frailty (ELF) study[8] which utilises the CFS as the primary measure of frailty, has demonstrated its strong association with 30-day and 90-day mortality, postoperative complications, length of intensive care unit (ICU) and overall hospital stay. Both the ELF study and Goh et al. defined those CFS 5 and above as frail. Although this cut-off does exclude patients who are very mildly frail, both studies have been able to identify those at highest risk of adverse outcomes. In fact, a frailty score of CFS 5 and above was an independent predictor of 90-day mortality, with frail patients experiencing a 3-fold higher 90-day mortality.[5]

Undertaking frailty assessments in older surgical patients can be challenging, as measures such as gait speed or grip strength may not be feasible, whereas the CFS is relatively easy to score. Introducing a standardised methodology across Singapore would improve benchmarking of surgical outcomes for frail older patients and reduce confusion among healthcare professionals regarding when to screen for frailty. Benchmarking can also be achieved with retrospective frailty screening tools such as the Hospital Frailty Risk Score (HFRS), which is derived from routinely collected electronic healthcare data.

While frailty addresses risk from the vantage point of an individual's characteristics, overall risk also needs to consider the specifics of the surgery and current physiological parameters. The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) had been recommended as a tool to predict mortality and morbidity in the initial 30 postoperative days.[9] However, studies have shown that POSSUM can overestimate mortality particularly in low-risk patients, leading to the development of the Portsmouth-POSSUM (P-POSSUM) score.[10] In the study by Goh et al., a high proportion of frail patients had P-POSSUM mortality risk ≥10% (65.6%), and the combination of frailty and high P-POSSUM mortality >10% was more predictive of 90-day mortality. This was reflected in the mortality rate of 1 in 5 (21.3%) for frail patients, compared to 1 in 20 (6.4%) for non-frail patients.[6]

The American Society of Anesthesiologist (ASA) Physical Status Classification System also helps to categorise a patient's physiological status and predict operative risk. However, frailty assessment has not been routinely incorporated into operative risk scores. It is unsurprising that frail patients had poorer preoperative physical status, with 91.8% classified as ASA grades 3–5.[6] Frailty increases with age, and both advanced age and higher ASA scores were independent predictors of ICU or high dependency unit (HDU) utilisation, with frail patients typically having longer ICU/HDU stays (2 days compared to 1 day for non-frail patients).

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Advanced age is an independent predictor for prolonged length of stay (LOS) of more than 14 days, and Goh et al. highlighted the lack of consistency in definitions of long LOS.[6] This inconsistency complicates the comparison of surgical cohorts. Although LOS is typically reported for the acute hospital stay, overall LOS, including time spent in acute sub-acute or rehabilitation settings, may be helpful. Advanced age was also an independent predictor of 30-day readmission,[6] and a recent multinational systematic review also supports the association of frailty with increased risk of 30-day readmission.[11]

The time and effort invested in frailty screening can provide better risk stratification preoperatively, improving predictive accuracy when frailty assessment is combined with P-POSSUM scoring risk.[6] The decision for EL presents an ethical dilemma particularly in frail older patients, who are 3-fold higher risk of postoperative complications compared to non-frail patients.[6] Identifying patients at increased risks allows clinicians to provide targeted interventions and individualised care plans to optimise their surgical outcomes.

Comprehensive geriatric assessment is well established as beneficial in hip fracture care pathways and more recently in vascular surgical cohorts.[12] Older patients present with more cognitive impairment, sarcopenia and age-related physiological impairment,[2] making an integrated approach to their care imperative. One common challenge in cognitively impaired patients is their higher likelihood to suffer from delirium, and early planning of acute postoperative care can include the use of delirium care bundles or initiatives such as the Hospital Elder Life Programme (HELP).[12] The study by Goh et al. suggested that the lack of geriatric assessment was an independent predictor of ICU/HDU utilisation, likely reflecting unrecognised frailty syndromes requiring intensivist interventions.

Postoperative geriatric assessments are low overall in those undergoing EL, although higher in frail patients. Achieving postoperative geriatric assessment has clear benefits, but the greater challenge lies in initiating this preoperatively. Early frailty screening would allow interventions at the point of admission, given the limited time for preoperative assessment in EL. Frailty screening could be triggered during emergency department admission, anaesthetic review or initial geriatric assessment. Incorporating frailty into perioperative care should extend beyond a medicalised model to include the multidisciplinary team, with EL care bundles initiating standardised frailty interventions beyond the current delivery of intermittent comprehensive geriatric assessment and medical stabilisation.

With an ageing population, surgical interventions in older and more frail patients present significant challenges. Evidence supports the value of frailty screening, and integrating it into surgical services alongside geriatric and rehabilitation services to improve outcomes for older complex surgical patients. Future work is needed to determine whether frailty interventions during the perioperative period can further impact recovery, and which components are most beneficial.

Declaration

The authors declare no conflicts of interest.

Keywords: *emergency laparotomy, frailty, general surgery, geriatric medicine, rehabilitative medicine, surgery*

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ORIGINAL ARTICLE

Improving the effectiveness of cervical cancer screening: Managing positive high-risk human papillomavirus results

Sun Kuie Tay[1] *MD*

ABSTRACT

Introduction: Good compliance of the management of abnormal results is important for effective cervical screening. This study investigated the rate of surveillance and follow-up outcomes for human papillomavirus (HPV)-positive women in cervical screening.

Method: Women on surveillance by repeat HPV testing were identified in a prospectively managed database. Data retrieved included women's age, country residence status, history of colposcopy, HPV-DNA status on the first and repeat tests, dates of follow-up during the 5 years since the initial screening, and histological diagnosis of cervical lesions. The main outcome measures were compliance rate for repeat HPV testing, regression and persistence rates of HPV subtypes, and detection rate of high-grade lesions (CIN2+).

Results: This analysis included 680 residents in the community, mean age 44.8 (95% confidence interval 20.1–69.5) years. The compliance rate of repeat testing was 28.2% at 12 months and, cumulatively, 42.8% for the entire 5-year follow-up period. The rates were unaffected by age (P=0.5829) nor prior colposcopy (P=0.1607). There were 5 (1.7%) cases of CIN2+ detected. Of 391 women on longitudinal follow-up, 194 (60.8%) cleared their HPV infection. Some women with multiple HPV infection cleared 1 but not the other subtype(s). Thus, the regression rate was 90.3% for HPV-16, 87.0% for HPV-18 and 65.2% for HPV-12-others (P=0.001). The annualised HPV regression rates were similar for HPV subtypes and for each follow-up year.

Conclusion: Surveillance of HPV positivity is clinically important for detecting high-grade lesions. Despite a high regression rate of HPV, surveillance hesitancy is a serious weakness in routine cervical screening.

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Keywords: cervical screening, CIN2+, colposcopy, high-grade lesions, HPV positivity, HPV regression

CLINICAL IMPACT

What is New

- The novel findings of this study indicate the prevalence of surveillance hesitancy in cervical cancer screening in Singapore—a reluctance in the follow-up monitoring of abnormal test results.
- To our knowledge, for the first time in Singapore, data are presented to show the importance of surveillance of HPV screening positivity in terms of the detection rate of high-grade lesions of the cervix and the regression rate of cancer-causing HPV subtypes.
- Findings underscore weak points in the current strategy of cervical screening in Singapore.

Clinical Implications

- The study highlights the need to introduce structured call-recalled system in the surveillance of abnormal screening results in cervical cancer screening in Singapore.
- This data can potentially help further reduce the incidence of cervical cancer in Singapore.

INTRODUCTION

Cervical cancer is one of the most preventable public health challenges worldwide.[1-3] In 2020, a global estimate reported that 604,127 new cases of cervical cancer were diagnosed and 341,831 died from it.[4] The World Health Organization launched a Cervical Cancer Elimination Initiative in 2018, with an aim to reduce the incidence of cervical cancer to 4 of 100,000 women in every country by the year 2030. This ambitious goal called for a concerted effort to mass vaccinate against high-risk HPV for girls below 15 years old, screen 70% or more of eligible women, and adequately treat 90% or more of pre-malignant conditions of the cervix. The plethora of publications have provided undisputable evidence on the efficacy of organised cervical cancer screening; even more data are available on sensitivity and specificity of several screening tests.[5-9] Challenges in the execution of a mass screening programme include implementation of follow-up surveillance, and diagnostic and therapeutic measures, are well recognised. In

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addition, many important considerations have been raised for implementing cervical screening programme, including demographic characteristics of the screening population, and the local political and financial settings of Singapore.[10-11]

A mathematical modelling analysis reported that an increase by 2% in compliance rate in screening would reduce the lifetime risk of cervical cancer by up to 3%.[12] On the other hand, lapses in follow-up action for abnormal screening results would greatly derail the cost-effectiveness of the screening programme. However, to date, literature on studies with primary objectives focusing on the compliance of follow-up after abnormal screening was surprisingly sparse. Information to fill this knowledge gap is needed for a comprehensive appraisal of optimal strategy in cervical screening.

The objectives of the current study aimed (1) to determine the follow-up attendance rate of women placed on clinical surveillance after abnormal primary human papillomavirus-deoxyribonucleic acid (HPV-DNA) screening, and (2) to investigate the follow-up outcome of the abnormal results by examining the regression and persistence of HPV infection and detection rate of high-grade lesions of the cervix.

METHOD

This was a retrospective descriptive quantitative study of data extracted from a research database, which contained clinical data prospectively collected between January 2014 and 31 July 2021 for investigating the effectiveness of cervical screening using primary HPV-DNA test at the Singapore General Hospital.

Ethical approval

This research project was approved by the SingHealth Centralised Institutional Review Board (CIRB number 2016/2385, expiry October 2021).

Subjects

The database included 10,967 women who undertook primary HPV cervical screening. Of these, 822 women who were tested positive for 14 high-risk HPV-DNA testing between January 2014 and 31 July 2021 formed the basis of subjects for the current study. Women who undertook cervical excision procedures—either loop electro-excision procedure or conisation—and laser vaporisation of the transformation zone of the cervix after the initial round of screening were excluded.

HPV-DNA test

Physician-collected cervical smear samples were kept in 20 mL PreservCyst® Solution (ThinPrep, Hologic, US). Laboratory polymerase chain reaction test for the DNA of 14 high-risk HPV subtypes was carried out in the institutional molecular diagnostic laboratory using Cobas 4800 platform (Roche, US) according to the manufacturer's manual of protocols. The data outputs were either positive or negative for HPV-DNA in 3 HPV subtype groupings—HPV-16, HPV-18 and HPV-12-others—which included HPV subtypes: HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66 and HPV-68.

Data collection

Information extracted from the database included women's age; country residential status; dated HPV-DNA status for HPV-16, HPV-18 and HPV-12-others on primary screening and at follow-up visits; colposcopy attendance; histology diagnosis based on biopsies; and conisation or hysterectomy.

Data analysis

The analysis was performed in 2 parts: (1) compliance of follow-up and (2) the outcome of HPV positivity on follow-up. The follow-up compliance analysis included residents of Singapore only (women normally living in Singapore, excluding migrant workers who stayed in the country for a variable duration and would naturally not be available for follow-up surveillance). The analysis for the outcome of HPV positivity on follow-up included women of all residential status in Singapore and who had attended at least 1 follow-up repeat HPV-DNA testing.

Compliance of follow-up was defined as a follow-up for a repeat HPV testing within the 5 years from the initial screening test. Only the first follow-up attendance was counted towards the computation of compliance rate. The denominator for the computation of overall compliance rate was the entire cohort of women who had attended their first attendance, and the numerator was the total number of women who had attended for the first follow-up visit within the 5 years from their initial screening date. A breakdown of follow-up compliance rate for successive years following the initial date of screening was computed using the number of new first-time follow-up for the year as the numerator.

Analysis was also performed to assess the potential impact of women's age and colposcopy attendance on follow-up compliance.

Outcome of HPV positivity was analysed for HPV regression or persistence on follow-up and the detection of high-grade lesions of the cervix. HPV regression was defined by a negative HPV testing. Regression rate was computed for individual HPV subtype groupings at yearly interval after the initial positive test. Incidence of HPV regression

was defined as clearance of all HPV subtypes in an individual woman. The cumulative incidence rate of HPV regression was computed for the period of analysis. HPV persistence was defined as detection of HPV-DNA of the same subtype grouping in the consecutive repeat tests 12 months apart.

Detection of high-grade lesions included all cases of CIN2, CIN3, invasive epithelial carcinoma of the cervix, and adenocarcinoma in-situ of the cervix. The overall detection rate was computed from the cumulative number of high-grade lesions detected among the total number of women in the compliance of follow-up study who had attended at least 1 follow-up visit.

Statistical analysis

Statistical Package for Social Sciences version 21.0 (SPSS, Chicago, IL, US) was used to analysed for the significance of difference for variables that could influence the follow-up compliance rate or outcome of HPV positivity between groups. Continuous data such as women's age were analysed using 2 independent sample t-test and categorical data, and frequency distribution between categories was analysed using chi-square statistics. Statistical significance was set at $P<0.05$.

RESULTS

Outcome of follow-up study

There were 680 women in the follow-up study cohort. The mean age of the women was 44.8 years (95% confidence interval [CI] 20.1–69.5). Of these, 292 women had colposcopy evaluation for their HPV and/or reflex cytology abnormalities and were subsequently recommended for a 12-month surveillance by repeat HPV testing. Also, there were 388 patients who were HPV-12-others positive with normal cytology and were managed clinically by a recommended repeat HPV/cytology testing in 12 months.

Follow-up attendance rate

The overall follow-up attendance rate was 42.8% (291 of 680) for the entire period of analysis. It included 116 out of 292 (39.7%) women in the subgroup who were initially evaluated by colposcopy and 175 of 388 (45.1%) from the subgroup of women who were managed by recommendation for repeat screening in the following 12 months (Table 1). The difference in the overall follow-up rate between the 2 subgroups of follow-up attendees was not significant statistically (chi-square=1.9678, P=0.1607). Only 28.2% of the women attended the recommended follow-up 12 months after the initial screening (year 1). The frequency of attendance reduced sharply with increasing duration after the initial screening, as shown in Table 1. Of the total number of 291 follow-up attendees, 192 (66.0%) returned during the first year of follow-up (Fig. 1).

The frequency trend of follow-up was similar regardless of experience of prior colposcopy. Exploration of the impact of women's age on follow-up rate showed that the mean age (95% CI) was 42.6 (16.6, 68.6) years for the defaulters and 42.1 (19.7, 64.5) years for those who attended the follow-up for repeat testing. Fig. 2 shows the comparison of the frequency distribution of age-grouping between patients who attended and who defaulted follow-up. The difference was not statistically significant (P=0.5829).

Table 1. Comparison of follow-up rate between subgroups of women characterised by prior colposcopy evaluation.

	Follow-up subgroups (no. of cases)		Total cohort	
	With prior colposcopy evaluation	No prior colposcopy evaluation	no.	%
Year 0	292	388	680	100
Year 1	76	116	192	28.2
Year 2	29	28	57	8.3
Year 3	7	17	24	3.5
Year 4	2	5	7	1.0
Year ≥5	2	9	11	1.6
Total	116*	175*	291	42.8
P value	*chi-square=1.9678, *P*=0.1607			

Fig. 1. Cumulative rate of follow-up over the 5-year period after the initial screening.

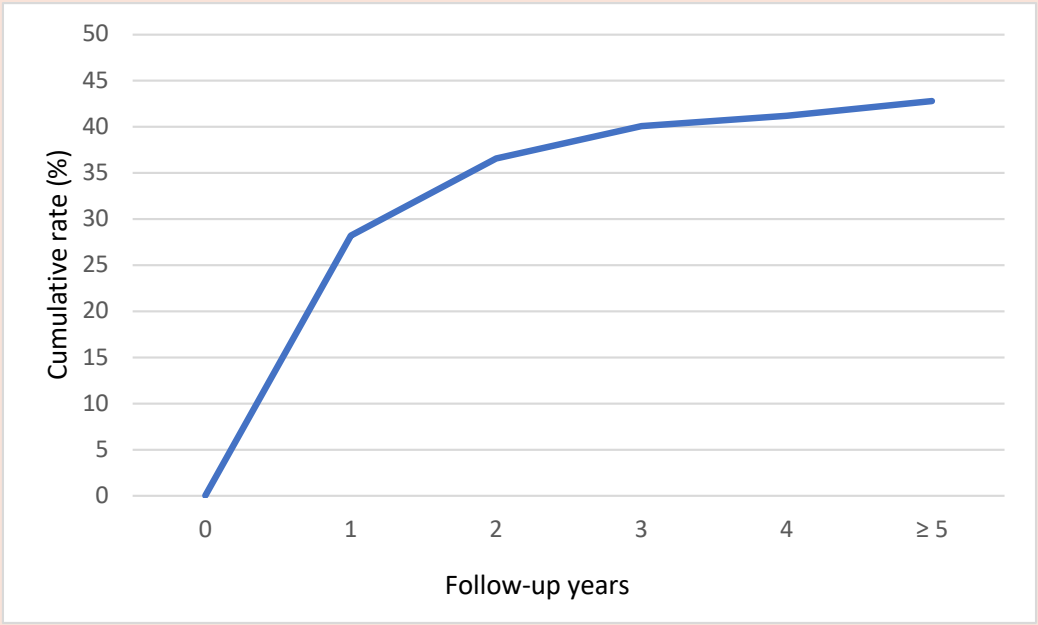
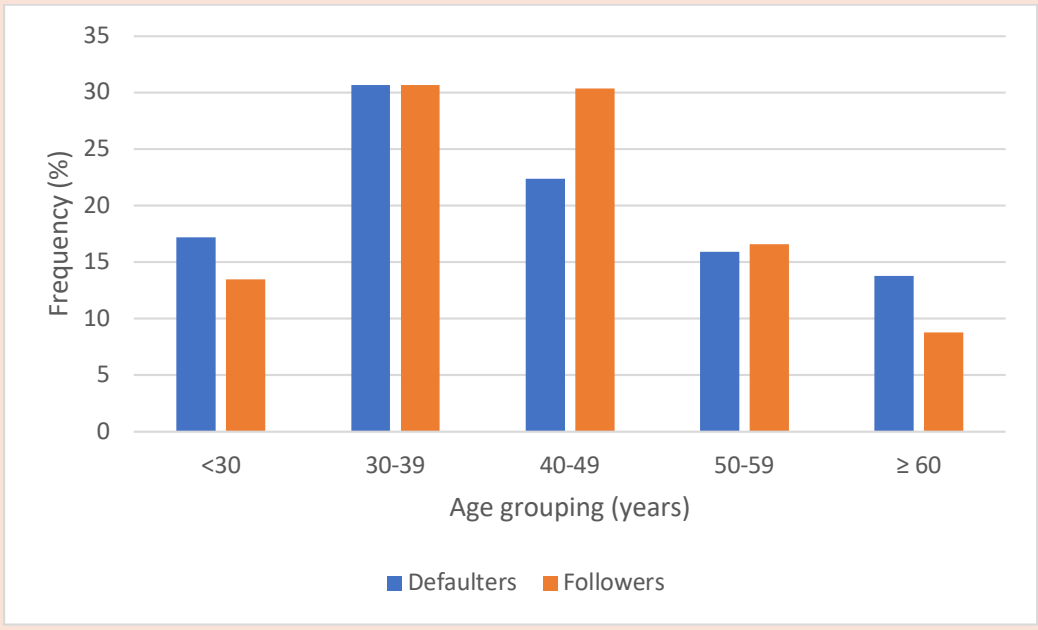


Fig. 2. Comparison of frequency distribution of age-groupings between follow-up defaulters and attendees.



Potential impact of HPV subtypes of follow-up was evaluated. The distribution of HPV subtypes among HPV-positive patients during the initial screening and for the follow-up patients is summarised in Table 2. HPV-12-others were the most prevalent HPV subtypes at both testing settings but more pronounced among the follow-up patients. However, HPV subtype distribution between the follow-up population and the initial screening population was not statistically significant (P=0.4808).

Incidence of high-grade lesions

During the study period, 4 cases of CIN2 and 1 case of CIN3 were detected. The details of these cases are summarised in Table 3. The incidence of high-grade squamous lesions (CIN2$^+$) was 1.7% (5 of 291).

Outcome of HPV clearance study

HPV clearance was separately analysed for the cohort of women for follow-up study and for

Table 2. Distribution of HPV subtypes at the initial screening and during follow-up.

	HPV-positive (subtypes)			HPV-negative	
	n	HPV-16	HPV-18	HPV-12-others	Total cohort no.
Initial screening*	680	105	46	529	0	680
	%	15.4	6.8	77.8	
Follow-up*	152	19	8	125	139	291
	%	12.5	5.3	82.2	
Statistical analysis: Initial screening versus follow-up	*chi-square=1.4646, *P*=0.4808				

HPV: human papillomavirus

Table 3. Details of high-grade lesions identified during follow-up.

Case no.	Age (year)	Follow-up year	HPV subtype	Histology
1	42	1	16	CIN2
2	28	2	16	CIN2
3	44	2	12-others	CIN3
4	53	2	16	CIN2
5	57	3	12-others	CIN2

HPV:human papillomavirus

longitudinal clearance study. In the longitudinal HPV clearance study cohort were 319 women, mean age was 42.5 years (95% CI 19.5–65.3). The follow-up duration of the entire group of women ranged from 1 to 7 years, mean number of years was 2 years (95% CI 1.87–2.13).

HPV clearance rate in the follow-up cohort (n=291)

Women in the follow-up cohort were counted once on the first follow-up attendance. HPV clearance rate was therefore referred to the first repeat testing. Overall, 47.8% of women (139 of 291) were found to be HPV-DNA negative on the follow-up. The clearance rate of HPV infection was similar for all HPV subtypes for the follow-up that took place at different time points throughout the span of 5 or more years (Table 4).

Longitudinal study cohort (n=319)

Overall, 194 (60.8%) women cleared the HPV positivity for all subtypes on repeat HPV-DNA testing over the period of follow-up of up to 7 years. For individual HPV subtypes, the overall clearance rate was 90.3% (56 of 62 cases) for HPV-16, 87.0% (20 of 23 cases) for HPV-18 and 65.2% (165 of 253 cases) for HPV-12-others (Table 5). The difference in HPV clearance between the HPV subtypes was statistically significant (*P*=0.0001). The longitudinal study showed that HPV clearance continued to occur in successive follow-up years at a similar rate across the period of study for each HPV subtype groups (Table 6).

There was no statistical difference in the mean age of women between women in each group of HPV subtypes (Table 5). Comparison analysis between HPV persistence and clearance groups showed that women in the HPV persistence

Table 4. Comparison of HPV-negative rate across follow-up period.

		HPV-positive			HPV-negative		
		n			n	%	
		HPV-16	HPV-18	HPV-12-others			Comparison of HPV-negative rate across follow-up period
Year 1	192	12	7	84	89	46.4	chi-square=1.9785, P=0.7397
Year 2	57	3	1	26	27	47.4	
Year 3	24	1	0	11	12	50	
Year 4	7	1	0	1	5	71.4	
Year ≥5	11	2	0	3	6	54.5	
Total	291	19	8	125	125	47.8	

HPV: human papillomavirus

Table 5. Details of women's age and follow-up duration and spontaneous clearance rate according to HPV subtypes.

		HPV subtypes			Group comparison (*P* value)		
		HPV-16	HPV-18	HPV-12-others	2 independent sample t-tests		
					HPV-16 vs HPV-18	HPV-16 vs HPV-12-others	HPV-18 vs HPV-12-others
	n	62	23	253	-	-	-
Age (years)	Mean	42.5	43.9	42.4	0.6608	0.9550	0.5795
	95% CI	39.2–45.8	39.0–48.8	41.0–43.8			
Follow-up period (year)	Mean	1.5	1.9	2.1	0.1267	0.0007	0.4744
	95% CI	1.24–1.7	1.42–2.38	1.15–2.25			
HPV clearance	Rate (%)	90.3*	87.0*	65.2*	HPV-16 vs HPV-18 vs HPV-12-others		
	95% CI	0.61–1.51	0.46–1.30	0.54–0.73	0.0001*		

CI: confidence interval; HPV: human papillomavirus
Note: *chi-square analysis for significance in HPV clearance rate between HPV subtypes. *P*=0.001.

group tended to be older (Fig. 3). The difference between the 2 groups, however, was not statistically significant.

DISCUSSION

Compliance of follow-up for abnormal results is one of the critically important determining factors in an effective screening programme.[13] Based on a mathematical model analysis, Burger et al. reported that a 2% increase in compliance to screening protocol could reduce a woman's lifetime cancer risk by 1–3%.[12]

This study found that the compliance for follow-up attendance at 12 months after an abnormal initial screening result was merely 28.2%. Investigation on an extended period of 5 years after initial screening showed that the latecomers for follow-up came in dribs and drabs, and in a diminishing number for each successive year (Table 1). Taking all attendance during the 5-year period together, the overall follow-up attendance rate was 42.8% (Fig. 1). Of these, 66.0% occurred during the first year. This study confirmed the significance of the follow-up of HPV-positive cases. The findings showed that almost 40% of women had persistent HPV infection for more than 12 months. More concerning, some women remained HPV-positive in the last testing 7 years later. Most importantly, the detection rate of high-grade lesions in the cervix—1.7%—was 4.6 times higher than the prevalent rate in the local screening population.

The current study performed a novel analysis comparing the follow-up rate of women who had attended colposcopy against women whose abnormal initial screening results prompted a recommendation for a repeat screening test at 12 months. The study included 292 (42.9%) women who were stratified into the subgroup at clinically significant, high probability of a high-grade lesion and who had undertaken a colposcopy evaluation (Table 1). One might have thought that these women would have taken the cue of their risk for the disease and showed a higher compliance for follow-up compared to other HPV-positive women at intermediate risk for high-grade lesions and who were managed with a recommended repeat screening at 12 months. This was proven not to be the case in this study. The frequency of attendance for follow-up was statistically similar between the 2 subgroups of women (39.7% for colposcopy subgroup vs 45.1% for repeat screening subgroup, *P*=0.1607).

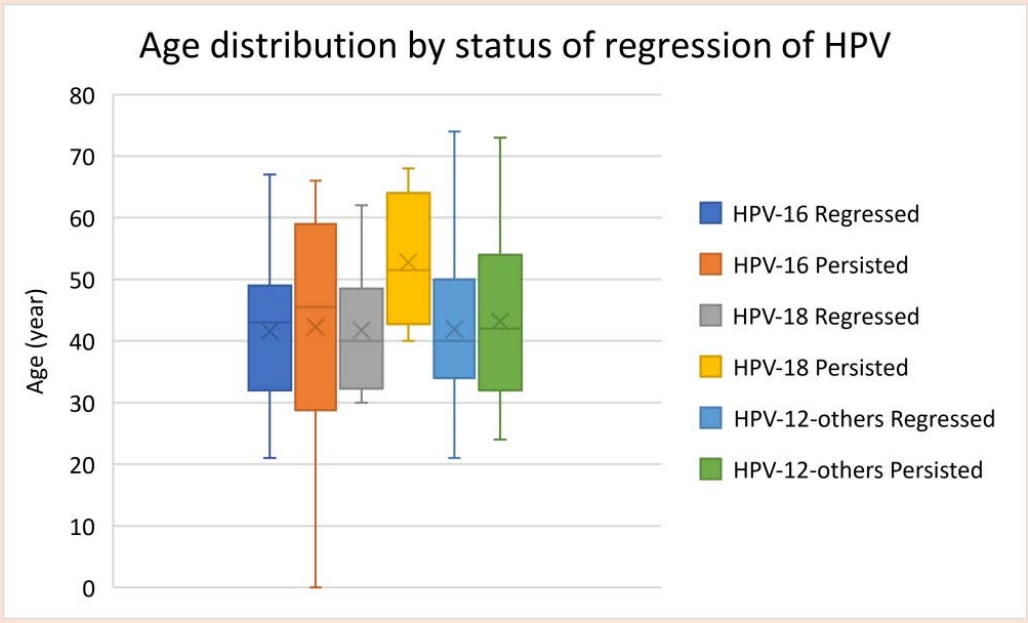
It is known that appropriate follow-up testing in cervical screening was highly variable, ranging from around 50% in Brazil and Japan to more than 80% in European countries.[14-18] Poor compliance rate of less than 50% was also reported in Nigeria and Hong Kong.[19,20] However, the overall follow-up rate of 42.8% for an extended period of 5 years found in the current study was one of the lowest rates ever reported in literature. This rate was akin to the local routine primary screening rate found in several previous reports.[21,22] The exact reasons for the low follow-up rate were unknown. Commonly reported reasons for low participation rate of cervical screening included women in older age group, poor socio-economic status, low educational levels and poor access to healthcare. These factors might not be operating for follow-up testing as the women had taken the step of initial

Table 6. Comparing HPV-negative rate between HPV subtypes for each follow-up year.

Follow-up period		Overall		HPV-16		HPV-18		HPV-12-others		Comparing HPV-negative rate between subtypes (chi-square-statistics *P* value)
Year	Positive/Negative cases	n	HPV clearance rate (%)	n	%	n	%	n	%	
0	HPV-positive	319		62		23		253*		
1	Evaluable no. of cases	247		46		16		185		
	HPV-positive			14	30.4	5	31.2	105	56.8	
	HPV-negative	123	49.8	32	69.6	11	68.8	80	43.2	0.2152
2	Evaluable no. of cases	132		21		11		100		
	HPV-positive			4	19	3	27.3	63	63	
	HPV-negative	62	47	17	81	8	72.7	37	37	0.0002
3	Evaluable no. of cases	72		7		1		64		
	HPV-positive			2	28.6	1	100	37	57.8	
	HPV-negative	32	44.4	5	71.4	0	0	27	42.2	0.2818
≥ 4	Evaluable no. of cases	44		6		3		35		
	HPV-positive			4	66.7	2	66.7	14	40	
	HPV-negative	24	54.5	2	33.3	1	33.3	21	60	0.3001
Overall	HPV-negative	194	60.8	56	90.3	20	87.0	165	65.2	0.0001

HPV: human papillomavirus
Note: * included cases that are also found to be positive for HPV-16 or HPV-18.

Fig. 3. Age comparison of women according to HPV regression and persistence status for each HPV subtype.



HPV: human papillomavirus
Note: Box marks the upper and lower quantile values; bar in the box refers to median value; ends of whisker refer to upper and lower extreme values.

screening. Indeed, the current study found that the frequency distribution of women's age groupings between the defaults and attendees was similar (Fig. 2).

It was interesting to note that a study on the follow-up of abnormal screening results for breast, colorectal and cervical cancers found a return rate of 46.6% for cervical cancer screening compared to 93.2–96.7% for breast cancer and 46.8–68.7% for colorectal cancer.[23] These findings highlight that it was not screening lethargy or cancer phobia (a phenomenon of fear of cancer) but something specific or peculiar to cervical cancer screening that results in the low return rate for screening. Unlike mammography in breast cancer screening and fecal immunochemical test in colorectal cancer screening, cervical screening is emotionally stressful and embarrassing, as it involves sensitive sexual organs and is physically invasive in vaginal examination and instrumentation. Attempts to overcome deterrence of attending a screening clinic by physical distance and time factor and anxiety of embarrassment have led to the development of women's self-sampling technique and devices. However, many women who failed to attend routine cervical screening were also poor respondents of self-sampling.[24] Sharp et al. identified that women's high level of anxiety and distress in general, experience of pain in prior screening, and lack of support as significant factors negatively influenced women's participate rate and return to follow-up of cervical screening.[25] In this respect, the heightened anxiety and psycho-sexual morbidity commonly associated with colposcopy could have further contributed to the low follow-up rate found in the current study among the colposcopy subgroup (39.7% overall or 26.0% at 12 months). Research to identify effective measures to address this concern and explanation of compliance hesitancy and reluctance is critically important to improve the completeness of cervical screening cycle to achieve the optimal efficacy of the programme.

Of practical importance, an active call-recall approach to encourage women to participate in cervical screening has been shown to increase the primary screening uptake.[26] Similar data are not available for the impact of call-recall on the compliance of surveillance of abnormal screening results. Emerging anecdotal information from several community screening clinics in Singapore suggests that designated personnel to call-recall women for follow-up increased the return rate for re-testing. The impact of call-recall system warrants a formal evaluation.

Data from this study showed that there was no difference in the distribution of HPV-16, HPV-18 and HPV-12-others between women in the initial screening and at follow-up (Table 2). The apparent numerical predominance of HPV-12-others compared to HPV-16 and HPV-18 was not statistically significant. Overall, 60.8% of women on longitudinal study became HPV-DNA negative over a mean follow-up period of 2 years (range

from 1 to 7 years). HPV clearance rate was statistically significantly higher (P=0.0001) for HPV-16 (90.3%) and HPV-18 (87.0%) compared to HPV-12-others (65.2%). The overall HPV clearance rate and the high persistence of HPV-12-others observed in this study concurred with the data reported from elsewhere.[27-29] In the current study, HPV clearance was similar for all age groups (Fig. 3). Adebamowo et al. had previously reported that HPV clearance was similar for all subtypes of high-risk HPV and for women across all ages.[30] It was interesting to note that HPV clearance occurred throughout the follow-up period at a similar annualised rate, 49.8–54.5% (Tables 3–5). Evidently, a small group of women seemed to be unable to clear the genital HPV infection (Table 5). The long duration of the persistence of HPV is etiologically related to the risk of neoplasia development in the cervix. Existing data indicated that follow-up should continue until HPV clearance is confirmed.[31]

The importance of follow-up surveillance was shown in this study by the detection of 5 cases of high-grade lesions among the 291 women or 1.7% (Table 6). This rate was 4.6-fold higher than the prevalence rate (0.37%) in the cohort analysis of the initial screening.[32] The cases were associated both with HPV-16 and HPV-12-others within 3 years of follow-up.

Strengths and limitations

The data collected prospectively in the database were reliable information and the analysis of compliance rate for the residents of Singapore ensured the best captive population for the study. The completeness of data for analysis was strengthened further by the inclusion of follow-up cases who appeared late but within the 5 years of the initial screening to accommodate women who might have difficulties with accessing the follow-up facilities.

On the analysis of HPV clearance rate, the study included a subgroup of women who attended repeated HPV testing. The subgroup population was increased by including foreign nationals who resided long-term in Singapore and attended the repeat HPV testing. The analysis was repeated for each followed up year, which showed the consistency in the clearance rate.

The main limitation of the study was the fact that the database from a single institution may miss some women who might have attended other healthcare facilities for follow-up of their abnormal results. There was no reason to believe that this had happened in any significant number if one referred to the same database that reported almost a complete compliance of calls for colposcopy on abnormal results on the initial screening.[32]

CONCLUSION

The compliance of follow-up after abnormal HPV tests in this study was unacceptably low. Although many women cleared HPV spontaneously, a group of women remained HPV-positive for a long duration. There was a significant absolute risk of high-grade lesions of the cervix among these women. Research in compliance hesitancy and reluctance, including the evaluation of the impact of a call-recall system, is needed for formulating measures to improve the effectiveness of cervical screening.

Declaration

This study was not affiliated to or financially supported by any commercial organisation.

Ethics statement

This manuscript was approved by the SingHealth Centralised Institutional Review Board (Reference number 2016/2385).

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ORIGINAL ARTICLE

Assessing the impact of frailty in elderly patients undergoing emergency laparotomies in Singapore

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ABSTRACT

Introduction: The global rise in ageing populations poses challenges for healthcare systems. By 2030, Singapore anticipates a quarter of its population to be aged 65 or older. This study addresses the dearth of research on frailty's impact on emergency laparotomy (EL) outcomes in this demographic, emphasising the growing significance of this surgical intervention.

Method: Conducted at 2 tertiary centres in Singapore from January to December 2019, a retrospective cohort study examined EL outcomes in patients aged 65 or older. Frailty assessment, using the Clinical Frailty Scale (CFS), was integrated into demographic, diagnostic and procedural analyses. Patient data from Tan Tock Seng Hospital and Khoo Teck Puat Hospital provided a comprehensive view of frailty's role in EL.

Results: Among 233 participants, 26% were frail, revealing a higher vulnerability in the geriatric population. Frail individuals exhibited elevated preoperative risk, prolonged ICU stays, and significantly higher 90-day mortality (21.3% versus 6.4%). The study illuminated a nuanced connection between frailty and adverse outcomes, underlining the critical need for robust predictive tools in this context.

Conclusion: Frailty emerged as a pivotal factor influencing the postoperative trajectory of older adults undergoing EL in Singapore. The integration of frailty assessment, particularly when combined with established metrics like P-POSSUM, showcased enhanced predictive accuracy. This finding offers valuable insights for shared decision-making and acute surgical unit practices, emphasising the imperative of considering frailty in the management of older patients undergoing emergency laparotomy.

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Keywords: emergency surgery, frailty, general surgery, geriatric medicine, surgery

CLINICAL IMPACT

What is New

- This study assesses the correlation between frailty and outcomes following emergency laparotomy in older patients in Singapore.
- Frail patients had a 3-fold higher 90-day mortality rate, longer ICU stays, and more postoperative complications.
- Mortality prediction following emergency laparotomies can be enhanced by combining P-POSSUM score with the Clinical Frailty Scale

Clinical Implications

- Integration of P-POSSUM score with Clinical Frailty Scale in acute surgical units can facilitate shared decision-making, assist in guiding preoperative optimisation, postoperative care and rehabilitation planning

INTRODUCTION

The ageing population is a growing global phenomenon. In 2019, 14.4% of the population in Singapore, equivalent to 3.9 million people, were aged 65 years or older.[1] This percentage is expected to increase to 25% by 2030, primarily due to increased life expectancy and lower fertility rates.[1] Consequently, older patients are more likely to develop age-related physical impairments, frailty, sarcopenia, functional and cognitive impairments.[2] Emergency laparotomy (EL) is a common procedure for the treatment of acute abdominal catastrophes in Singapore. A significant proportion of these procedures are performed on the geriatric population, who tend to have higher postoperative morbidity, mortality and intensive care unit (ICU) resource utilisation rates.[3] Older patients also have longer hospital and ICU stays after EL than younger patients.[3] According to the latest patient report from the UK National Emergency Laparotomy Audit (NELA) covering December 2019 to November 2020, 1 in 5 older people undergoing emergency laparotomy was

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frail.[4] Frailty is associated with greater risks of postoperative mortality and morbidity independent of age. Frailty has also been shown to predict adverse outcomes after emergency general surgery.[5-7] The Asian population has been shown to have increased prevalence of frailty compared to the Western population.[8] Additionally, the physique of Asian patients also differs, with lower muscle mass, higher body fat with central distribution and weaker handgrip strength; hence, it is possible that postoperative outcomes may differ. Thus, the objective of this study is to examine the impact of frailty on morbidity, mortality, length of hospital stay after EL, and to evaluate the performance of the Clinical Frailty Scale (CFS) as a predictor of mortality in a Singaporean population.

METHOD

Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (Ref: 2018/01227). A retrospective cohort study was conducted to investigate EL outcomes at 2 tertiary centres in Singapore, namely, Tan Tock Seng Hospital and Khoo Teck Puat Hospital, in the period of January 2019 to December 2019. Inclusion criteria were patients 65 years or older who underwent EL. Exclusion criteria were similar to the NELA guidelines and excluded laparotomies for trauma, vascular, gynaecological emergencies, relook laparotomy, appendectomy, cholecystectomy and non-gastrointestinal surgeries.[4] The 11 key elements of the NELA guidelines—preoperative assessment, timely surgery, intraoperative excellence, postoperative monitoring, ICU and high dependency unit (HDU) care, recovery and ward care, nutrition and hydration, delirium management, physiotherapy and mobility, rehabilitation, and discharge planning—were adopted by both hospitals prior to the study. Postoperative geriatric assessments were recommended for patients aged ≥65 years in the hospital workflows.

Patient demographics, diagnoses and preoperative risk assessment using the Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM) scores were collected. The physical state of patients before EL was assessed using the American Society of Anesthesiologists (ASA) Physical Status Classification System. The efficiency outcomes were also assessed, which include time from decision of surgery to time in operating theatre, presence of consultant surgeon and anaesthetist, number of geriatric assessment and patients admitted into HD/ICU. The priority (P) accorded to each EL was also recorded. In our institution, P1 refers to procedures that were performed within 1 hour; P2 for procedures undertaken within 4 hours; and P3 denotes those that took place within 24 hours. The CFS was used to classify patients into either frail (CFS 5–9) or non-frail (CFS 1–4) categories and was calculated by the attending physicians upon admission, as it was found to be a valid and reproducible score that is simple to understand and apply. For the purpose of clarity and comprehension, it is important to note that in this context, the CFS is designated as 5 and above, as opposed to the recently revised classification by Rockwood, which includes CFS 4 for mildly frail individuals. This distinction ensures a clearer understanding of the frailty categorisation in the context of the study. Postoperative complications were defined as incidence of any medical and/or surgical complications postoperatively deviating from the normal postoperative course, and were graded according to the Clavien-Dindo classification system. Postoperative geriatric assessment rates were also compared. Data on length of stay (LOS), 90-day mortality, 30-day readmission and ICU/HDU utilisation were evaluated. Prolonged LOS was defined as >14 days; while there is no standard definition for "prolonged" in existing literature, we used an arbitrary cut-off of 14 days based on the Seventh Patient Report of the NELA,[4] which showed median LOS of 14 days for patients aged ≥65 years and with CFS ≥5, as well as the first United Kingdom report on patient outcomes following EL, with median LOS of 16 days.[9] Percentages were used for categorical data and means with standard deviations (SD) for continuous data unless otherwise specified. Comparisons between groups for categorical data were made using chi-squared test or Fisher's Exact test, whereas comparisons between groups for continuous data were made using Student's t-test for parametric distribution, and Mann-Whitney U test for non-parametric distribution. All P values <0.05 were considered statistically significant, and all P values were 2-tailed.

We analysed the outcomes of older adults who underwent EL using univariate and multivariate logistic regression, to compare between the frail and non-frail groups. Age ≥75 years, P-POSSUM mortality >10%, and lack of geriatrician assessment were used as covariates for multivariate logistic regression. The accuracy of P-POSSUM and CFS in predicting 90-day mortality rates were evaluated using Receiver Operating Characteristic (ROC) curve. P<0.05 was considered statistically significant. We performed all statistical analyses using SPSS version 25 (SPSS, SPSS Inc, Chicago, IL, US).

RESULTS

The analysis included a total of 233 participants, 61 (26%) of whom were frail and 172 (74%) were non-frail (Table 1). Within the frail group, 28 (45.9%) of the 61 patients were male with a mean age of 79 years (SD ±7). Moreover, the frail group tended to have poorer pre-operative physical status, with 56 (91.8%) having a high ASA grade of 3–5, and the majority of the population being at ASA 3 with 41 patients (67.2%). A total of 40 (65.6%) patients had P-POSSUM mortality risk ≥10%, and the mean P-POSSUM score was 25.2 ± 25.1. The most common indications for EL were intestinal obstruction (47.6%), gastric or bowel perforation (29.5%), and bowel ischemia (9.8%), as shown in Table 1.

Table 1. Demographics and characteristics.

Demographics and characteristics	n (%) / mean ± SD		
	CFS 1–4	CFS 5–9	*P* value
Total cases (n)	172	61	–
Mean age (years)	75 ± 7	79 ± 7	<0.01
Gender			
Male	94 (54.7%)	28 (45.9%)	0.30
Female	78 (45.3%)	33 (54.1%)	
BMI	23.2 ± 4.8	23.0 ± 5.4	0.88
ASA			
1	1 (0.6%)	1 (1.6%)	0.46
2	47 (27.3%)	4 (6.6%)	<0.01
3	95 (55.2%)	41 (67.2%)	0.14
4	29 (16.9%)	14 (23.0%)	0.39
5	0	1 (1.6%)	–
3–5	124 (72.1%)	56 (91.8%)	<0.01
P-POSSUM			
P-POSSUM mortality (%)	18.6 ± 22.9	25.2 ± 25.1	0.06
Low (<5%)	54 (31.4%)	4 (6.5%)	<0.01
Medium (5–10%)	34 (19.8%)	17 (27.9%)	0.26
High (>10%)	84 (48.8%)	40 (65.6%)	0.04
Indication for surgery			
Intestinal obstruction	90 (52.3%)	29 (47.6%)	0.62
Gastric / bowel perforation	46 (26.7%)	18 (29.5%)	0.80
Bowel ischaema	16 (9.3%)	6 (9.8%)	0.90
Adhesiolysis	8 (4.7%)	4 (6.6%)	0.52
Bleeding	7 (4.1%)	1 (1.6%)	0.68
Hernia	3 (1.7%)	2 (3.3%)	0.61
Others*	2 (1.2%)	1 (1.6%)	1.00

ASA: American Society of Anesthesiologists; BMI: body mass index; CFS: Clinical Frailty Scale; P-POSSUM: Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; SD: standard deviation
*Others include anastomotic leak and abdominal infection

When comparing frail versus non-frail groups, there was significant differences in mean age (79 ± 7 versus [vs] 75 ± 7, *P*<0.01), ASA status (6.6% ASA 2, 91.8% ASA 3–5 vs 27.3% ASA 2, 72.1% ASA 3-5, *P*<0.01), and P-POSSUM score 6.5% low (<5%) vs 31.4% low, *P*<0.01 and P-POSSUM score 65.5% high (>10%) vs 48.8% high, with frail older patients having a higher ASA status and P-POSSUM score. However, other characteristics, such as gender, BMI and indications for surgery, were not statistically significant.

In terms of efficiency outcomes (Table 2), postoperative geriatric assessments were low, the frail group having received more assessments than the non-frail group (49.2% vs 27.9%, *P*<0.01). Other pre-operative (time from decision for surgery to time in operating theatre [OT] at start of surgery), intraoperative (presence of consultant anaesthetists and surgeons in OT), and postoperative (P-POSSUM >10% patients admitted to ICU/HDU) efficiency outcomes were not statistically significant.

Concerning clinical outcomes (Table 3), frail patients had longer LOS in ICU/HDU, i.e. 2.0 days (interquartile range [IQR]=1.0–6.5) vs 1.0 day (IQR=0–4.0), *P*<0.01; and higher 90-day mortality (21.3% vs 6.4%, *P*<0.01). Other clinical outcomes, such as postoperative complications, unplanned return to OT, overall length of stay, 30-day mortality and 30-day readmission, were higher in frail patients but were not statistically significant.

Multivariate analysis (Table 4) revealed that P-POSSUM mortality >10% (OR 10.601, 95% CI 2.363–47.547, *P*<0.01) and CFS 5–9 (OR 3.238, 95% CI 1.263–8.300, *P*=0.014) were independent predictors of 90-day mortality. Age >75 years old was also found to be an independent predictor for prolonged LOS >14 days (OR 2.848, 95% CI 1.595–5.086, *P*<0.01), ICU/HDU utilisation (OR 2.502, 95% CI 1.164–5.380, *P*=0.019), and 30-day readmission (OR 2.845, 95% CI 1.266–6.391, *P*=0.011). ASA 3–5 (OR 3.708, 95% CI 1.709–8.045, *P*=0.001), P-POSSUM mortality >10% (OR 6.022, 95% CI 2.782–13.036, *P*=0.00), and lack of postoperative geriatric assessment (OR 3.366, 95% CI 1.579–7.172, *P*<0.01) were also identified as independent predictors of ICU/HDU utilisation. In addition, frail patients were found to be associated with 3 times more postoperative complications compared to non-frail patients (OR 3.038, 95% CI 1.528–6.039, *P*=0.002).

A scatter plot of CFS against incidence of 90-day mortality was plotted (Fig. 1). With increasing CFS, incidence of 90-day mortality also increased. However, based on the scatter plot, it appears that the relationship between CFS and 90-day mortality is nonlinear, with a sharp increase in 90-day mortality when CFS was 8 or 9.

The Area Under the Receiver Operating Characteristic (AUROC) and 95% CI for P-POSSUM

Table 2. Efficiency outcomes.

Efficiency outcomes	n (%) / mean ± SD		
	CFS 1–4	CFS 5–9	*P* value
Total cases (n)	172	61	
Pre-operative			
Time from decision for surgery to time in OT (min)	159 ± 177	159 ± 163	0.99
P1 operations (min) [n=26]	42.2 ± 23.2	51.2 ± 19.4	0.40
P2 operations (min) [n=181]	143.3 ± 116.8	134.7 ± 110.0	0.65
P3 operations (min) [n=26]	381.5 ± 344.5	470.0 ± 260.0	0.57
Intraoperative			
Consultant surgeon presence in OT	160 (93.0%)	58 (95.1%)	0.76
Consultant anaesthetist presence in OT	98 (57.0%)	36 (59.0%)	0.90
Postoperative			
Geriatric assessment	48 (27.9%)	30 (49.2%)	<0.01
P-POSSUM >10% patients admitted to critical care (HD/ICU)	74/84 (88.1%)	37/40 (92.5%)	0.55

CFS: Clinical Frailty Scale; HD: high dependency; ICU: intensive care unit; OT: operating theatre; P1: Priority 1 operations; P2: Priority 2 operations; P3: Priority 3 operations; P-POSSUM: Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; SD: standard deviation

Table 3. Clinical outcomes.

Clinical outcomes	n (%) / median [IQR]		
	CFS 1–4	CFS 5–9	*P* value
Total cases	172	61	
Postoperative complications			
Clavien-Dindo III	21 (12.2%)	7 (11.5%)	0.88
Clavien-Dindo IV	9 (5.2%)	4 (6.6%)	0.75
Clavien-Dindo V	10 (5.8%)	6 (9.8%)	0.44
Unplanned return to OT	9 (5.2%)	4 (6.6%)	0.75
Hospital length of stay (days)			
Overall length of stay, median [IQR]	13.0 [8.0–22.8]	16.0 [9.5–25.0]	0.147
Critical care days, median [IQR]	1.0 [0–4.0]	2.0 [1.0–6.5]	<0.01
Mortality			
30-day mortality	8 (4.7%)	8 (13.1%)	0.051
90-day mortality	11 (6.4%)	13 (21.3%)	<0.01
30-day readmission	25 (14.5%)	14 (23.0%)	0.19

CFS: Clinical Frailty Scale; IQR: interquartile range; OT: operating theatre

mortality >10% and CFS ≥5 in predicting 90-day mortality were 0.83 (0.76–0.90) and 0.68 (0.55–0.80), respectively. The AUROC and 95% CI for P-POSSUM in predicting 90-day mortality in frail and non-frail groups were 0.75 (0.61–0.89) and 0.88 (0.82–0.95), respectively (Fig. 2). This result shows that the AUROC of P-POSSUM was better in the non-frail group than in the frail group (*P*<0.01). These results suggest that P-POSSUM mortality >10% is a better discriminator of outcomes in the older population for predicting 90-day mortality. When comparing the use of P-POSSUM mortality >10% vs P-POSSUM mortality >10% + CFS ≥5 in predicting the 90-day mortality rate, P-POSSUM + CFS (AUROC=0.83) and P-POSSUM (AUROC=0.83) had comparable AUROC scores. However, P-POSSUM + CFS had a slightly better AUPRC (positive predictive value) of 0.42 against 0.38 for P-POSSUM, *P*=0.19. This indicates that P-POSSUM + CFS is more likely to predict 90-day mortality if both criteria were fulfilled (i.e. P-POSSUM mortality >10% and CFS ≥5).

DISCUSSION

Frail older patients typically present with a greater burden of symptoms, including fatigue, medical complexity, and reduced tolerance for medical and surgical interventions such as emergency laparotomy.[10] The emergency laparotomy and frailty trial in the UK has demonstrated that frailty is associated with higher postoperative mortality and morbidity, independent of age.[5] Genetic heterogeneity, socio-economic dynamics, cultural paradigms, healthcare accessibility and lifestyle choices collectively contribute to the distinctive portrayal and implications of frailty in Asian societies. These factors may exert influence over the prevalence, phenotypic expression and consequent outcomes associated with frailty. This study adds valuable input to existing literature on the impact of frailty on Asian older patients undergoing EL. Up to 26% of older patients undergoing EL in this study were frail. Frailty was an independent predictor of postoperative mortality and was associated with 3-fold higher mortality compared to the non-frail.

Both 30-day and 90-day mortality rates were higher in the frail as compared to the non-frail but the difference was more pronounced in the latter. The 90-day mortality rate was 1 in 5 (21.3%) for frail patients as compared to 6.4 % in the non-frail. Complications related to functional decline and long-term mortality risk can occur in frail patients during their hospitalisation stay, which may not be captured within the first 30 days after surgery. These complications can manifest later in the postoperative period, such as pneumonia

Table 4. Results of univariate and multivariate analyses of factors associated with outcomes in older adults undergoing emergency laparotomy.

	Univariate				Multivariate			
	OR	95% CI		*P* value	OR	95% CI		*P* value
		Lower	Upper			Lower	Upper	
90-day mortality								
Age >75 years old	1.715	0.719	4.093	0.224	0.852	0.326	2.226	0.743
P-POSSUM mortality >10%	11.539	2.646	50.323	**0.001**	10.601	2.363	47.547	**0.002**
CFS 5–9	3.964	1.669	9.417	0.002	3.238	1.263	8.300	**0.014**
Without geriatrician input	0.675	0.285	1.598	0.372	0.834	0.323	2.151	0.707
Prolonged LOS >14 days								
Age >75 years old	3.545	2.065	6.088	**0.000**	2.848	1.595	5.086	**0.000**
ASA 3–5	2.585	1.342	4.978	**0.005**	1.630	0.799	3.324	0.179
P-POSSUM mortality >10%	2.311	1.364	3.916	**0.002**	1.665	0.943	2.939	0.079
CFS 5–9	1.700	0.943	3.067	0.078	1.223	0.636	2.350	0.546
Without geriatrician input	1.182	0.685	2.041	0.549	1.385	0.761	2.521	0.287
Critical care utilisation								
Age >75 years old	4.098	2.147	7.823	**0.000**	2.502	1.164	5.380	**0.019**
ASA 3–5	5.589	2.882	10.837	**0.000**	3.708	1.709	8.045	**0.001**
P-POSSUM mortality >10%	7.622	3.767	15.424	**0.000**	6.022	2.782	13.036	**0.000**
CFS 5–9	2.951	1.312	6.638	**0.009**	1.994	0.760	5.231	0.161
Without geriatrician input	2.070	1.134	3.778	**0.018**	3.366	1.579	7.172	**0.002**
30-day readmission								
Age >75 years old	2.941	1.386	6.242	**0.005**	2.845	1.266	6.391	**0.011**
ASA 3–5	1.759	0.694	4.456	0.234	1,239	0.456	3.367	0.675
P-POSSUM mortality >10%	1.031	0.517	2.055	0.931	0.730	0.348	1.533	0.406
CFS 5–9	1.751	0.842	3.642	0.133	1.380	0.626	3.044	0.425
Without geriatrician input	0.769	0.378	1.568	0.470	0.899	0.425	1.900	0.780

Values in bold indicate where *P* is <0.05 and of statistical significance.
ASA: American Society of Anesthesiologists; BMI: body mass index; CFS: Clinical Frailty Scale; CI: confidence interval; LOS: length of stay; OR: odds ratio: P-POSSUM: Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity

or thromboembolic events due to prolonged bed rest or hospitalisation. While these complications may not be immediately fatal, they can significantly impact a patient's quality of life and contribute to long-term mortality risk. Therefore, using 90-day mortality as an outcome metric may provide a more representative assessment of a frail patient's postoperative outcome, as it allows for the identification of late complications and the impact of postoperative functional decline on mortality. Of note, incidence of 90-day mortality for CFS 8 and 9 were 50% and 100%, respectively, which is markedly higher compared to that of CFS 1–7. This is apparent from Fig. 1, which shows a nonlinear relationship between increasing CFS and incidence of 90-day mortality. Ideally, subgroup analysis should be performed for patients with CFS 5–7 and CFS 8–9 to ensure results are not falsely skewed by inclusion of more frail patients (i.e. CFS 8–9). However, these patients form only a minority of all frail patients, rendering subgroup analysis impossible due to a small sample size. Additionally,

Fig. 1. Scatter plot of CFS and 90-day mortality in older adults undergoing EL.

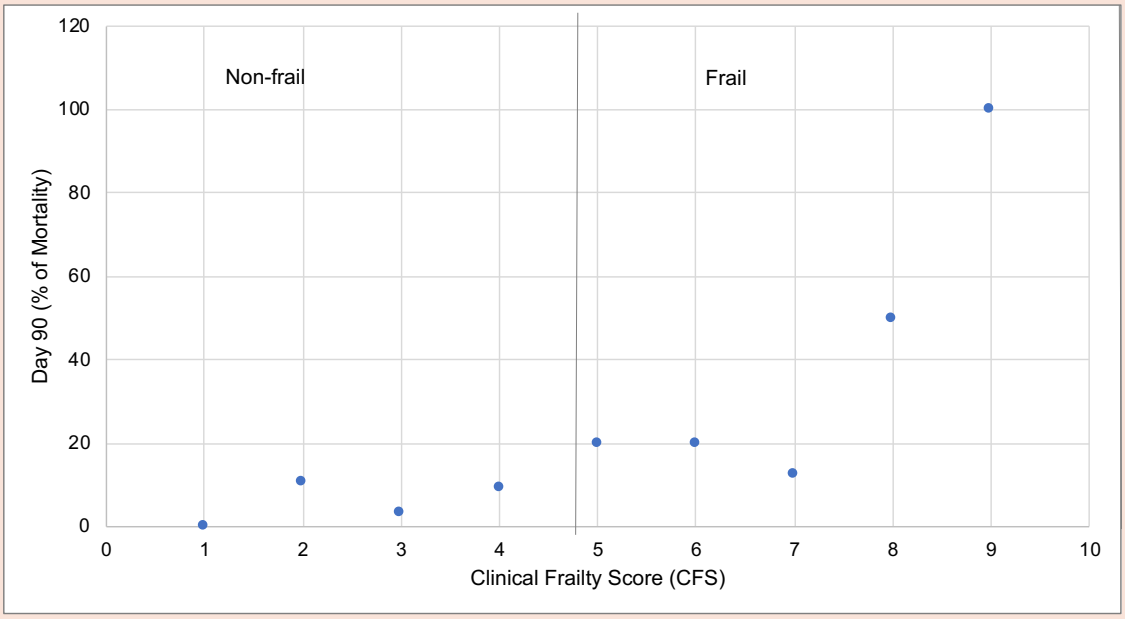
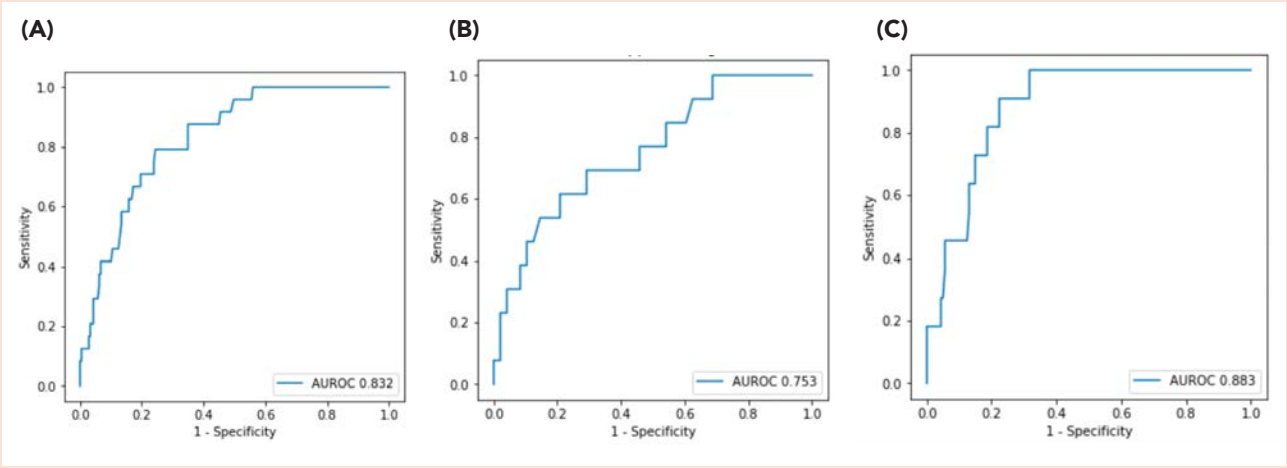


Fig. 2. AUROC of P-POSSUM (A) for all patients (B) for frail patients (C) for non-frail patients.



the use of CFS ≥5 has been investigated in existing studies for older patients undergoing EL with similar results as our study.[11] The duration of ICU stay was also longer in frail patients and this was associated with higher 90-day mortality. Aggressive treatments commonly administered in the ICU, such as mechanical ventilation and vasopressor support, have been described to be associated with increased risk of complications and mortality in frail patients.[12]

We sought to evaluate the clinical utility of combining the established P-POSSUM score with the CFS in predicting 90-day mortality. Interestingly, the discriminative power of the CFS alone for predicting 90-day mortality was modest, with an AUROC of 0.675 (0.550–0.799). Our findings suggest that a combination of predictors may be more useful, particularly given that the P-POSSUM score performed better in predicting 90-day mortality in the non-frail group. This highlights the potential contribution of frailty to mortality beyond the components of the P-POSSUM score. Our results support the clinical utility of combining P-POSSUM and CFS scores to improve mortality prediction in older patients undergoing EL. To improve the identification of high-risk patients who may benefit from preoperative optimisation and the involvement of senior clinicians, integrating frailty scoring into acute surgical units could be helpful. This can facilitate shared decision-making and discharge planning, which is crucial for improving patient outcomes and reducing hospital

readmissions. By identifying patients who are at increased risk for complications and poor outcomes, clinicians can provide targeted interventions and individualised care plans to optimise patient outcomes.

This study found that postoperative geriatrician assessment was associated with lower intensive care use, although geriatrician engagement remained low for both frail and non-frail patients (49.2% and 27.9%, respectively). The decision for ICU/HDU admission usually arises preoperatively or immediately postoperatively based on holistic assessment of a patient's co-morbidities, vital parameters, laboratory and radiological investigations. Should patients require postoperative ICU/HDU admission, these usually happens immediately postoperatively due to postoperative events, such as inability to extubate and haemodynamic instability requiring inotropes. Therefore, it is unlikely that the lack of postoperative geriatric assessment will directly predict ICU/HDU utilisation. Instead, it is more likely that postoperative geriatric assessments were carried out in patients who were more frail and had more co-morbidities that required ICU/HDU admission.[13] Use of comprehensive geriatric care models with pre-operative geriatric assessment, nutritional assessment and interventions, as well as postoperative follow-up have been shown to reduce mortality and major morbidity for older patients undergoing elective colorectal surgery.[14] Hence, the role of postoperative geriatrician assessment may similarly be useful. The American College of Surgeons and the American Geriatrics Society highlighted that older patients are at higher risk of postoperative delirium, functional decline, pulmonary complications and urinary tract infections, and recommended for the implementation of geriatric care models for multidisciplinary and holistic management of older patients.[15,16] Further studies should evaluate the incidence of specific complications as mentioned above to truly identify the clinical utility of postoperative geriatric assessment.

There were several limitations to our study that should be considered. The length of rehabilitation in community hospitals was not accounted for in our study. To assess the true duration of institutionalisation and loss of independence, the total length of stay in both acute and community hospitals should be evaluated. The meta-analysis by Kennedy et al. showed increased LOS in the frail (n=3 studies, mean difference 3.91 days, 95% CI: 0.18-7.63 days, $p<0.05$).[17] However, our study did not show any statistical significance between frail and non-frail patients (16.0 vs. 13.0 days, $p=0.147$). Kennedy et al. attributed the increased length of stay among the frail in his study to postoperative complications or discharge to a skilled care facility. Similarly, in the local setting, many frail surgical patients were transferred to community hospitals for further rehabilitation but this was not accounted for in total LOS. Additionally, the variability and heterogeneity of surgical pathology can make accurate comparisons challenging, particularly as certain pathologies are known to be associated with higher morbidity. The sample size was also considerably smaller for the cohort of frail patients, which we attempted to circumvent through inclusion of patient data from 2 institutions. In view of the small sample size, subgroup analysis for specific indications for emergency laparotomy was also not possible as this would further dilute the sample size. In addition, there was incomplete data on patients' co-morbidities such as Charlson Comorbidity Index and specific type of postoperative complications outcomes which may have influenced the prediction of postoperative mortality. Nonetheless, this study was necessary to understand the significance of frailty in patients undergoing EL in Singapore and serves as a springboard for shared decision-making on the ground and development of potential strategies to mitigate frailty.

CONCLUSION

Up to a quarter of the older population who underwent EL were frail. Frail patients were associated with a longer length of stay in the ICU and a 90-day mortality rate more than 3 times that of their non-frail counterparts. The combination of PPOSSUM with CFS was shown to improve the positive predictive value for mortality following EL. Since frailty scoring was a significant predictor of 90-day mortality, integrating it into acute surgical units to facilitate shared decision-making should be considered.

Declaration

The study was not supported by any grant or foundation. The authors declare that they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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ORIGINAL ARTICLE

Impact of family and caregiver factors on development and behaviours in maltreated young children

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ABSTRACT

Introduction: This study aimed to evaluate the prevalence of developmental and emotional/behavioural concerns in maltreated children and to examine the impact of adverse family/caregiver risk factors on these outcomes.

Method: We analysed family demographic and baseline data of 132 maltreated children and their caregivers from a family support programme in Singapore. We examined the associations of 3 main risk factors (i.e., caregiver mental health, educational attainment, and family socio-economic status [SES]) with developmental/behavioural outcomes using multivariable logistic regression, controlling for caregiver relationship to the child. Caregiver mental health was assessed using the Patient Health Questionnaire 9 (PHQ-9) and General Anxiety Disorder 7 (GAD-7) tools. Developmental/behavioural outcomes were assessed using the Ages and Stages Questionnaires (ASQ-3), ASQ-Social-Emotional (ASQ-SE), and the Child Behaviour Checklist (CBCL).

Results: The children ranged in age, from 2 months to 3 years 11 months (median age 1.7 years, interquartile range [IQR] 0.9–2.6). Among caregivers, 86 (65.2%) were biological mothers, 11 (8.3%) were biological fathers, and 35 (26.5%) were foster parents or extended family members. Low family SES was associated with communication concerns on the ASQ-3 (adjusted odds ratio [AOR] 3.04, 95% CI 1.08-8.57, *P*=0.04). Caregiver mental health concerns were associated with increased behavioural concerns on the CBCL (AOR 6.54, 95% CI 1.83–23.33, *P*=0.004) and higher scores on the ASQ-SE (AOR 7.78, 95% CI 2.38–25.38, *P*=0.001).

Conclusion: Maltreated children with caregivers experiencing mental health issues are more likely to have heightened emotional and behavioural concerns. Those from low SES families are also at increased risk of language delay, affecting their communication.

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Keywords: behaviours, caregiver mental health, child development, child maltreatment, paediatrics

CLINICAL IMPACT

What is New

- One of the first locally conducted prospective studies of family/caregiver risk factors for maltreated young children aged between 0–3 years.
- Findings from the study help justify the necessity to provide support for these high-risk children and their families.

Clinical Implications

- Having caregivers with mental health concerns was significantly associated with increased emotional/behavioural concerns in maltreated children.
- Maltreated children from low socio-economic status-families were also at increased risk of language delay, affecting their communication.

INTRODUCTION

Child maltreatment is defined as the neglect and abuse of children under 18 years old. It encompasses physical/emotional ill-treatment, sexual abuse, negligence and/or exploitation that causes harm to the child.[1] Evidence has shown that Adverse Childhood Experiences (ACEs), such as maltreatment experienced during childhood, have a significant impact on the developing brain especially in the first 1000 days of life.[2,3]

These negative experiences may result in disruption of the brain architecture with an impact on early childhood development, socio-emotional competence and behaviours resulting in problems with attention and emotional regulation.[4-6] The impact persists with far-reaching effects and difficulties into adulthood.[7,8,9] It worsens economic and social outcomes, such as school participation/

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achievement, increased welfare- dependency, addiction, risky sexual behaviours and violence.[10] From a public health perspective, child maltreatment incurs a high lifetime cost per victim and creates a significant economic burden for the society.[11]

The impact of ACEs on brain development and multiple body systems has now been documented with substantial international data. Considering that maltreated children are at an increased risk of developmental, physical, behavioural, and mental health problems, early identification of their needs is imperative to help improve both their short- and long-term outcomes.[2-6] Moreover, there is also increasing evidence that the effects of ACEs in early childhood outcomes may be buffered by early intervention and participation in psychotherapeutic home visiting.[12,13] With this background knowledge and the recognition of a gap in the local support provided for maltreated children and their families, the Division of Medicine at KK Women's and Children's Hospital (KKH) in Singapore initiated and led a home visitation programme called Anchor with the help of philanthropic funding from Temasek Foundation, to identify and support this high-risk group.[14]

The adverse effects of childhood maltreatment in middle childhood, adolescence and adulthood are well-documented by a vast number of studies as described above, but there is relatively less literature reporting the association of maltreatment with developmental outcomes in early childhood. With a paucity of data on the impact of ACEs on developmental and socio-emotional outcome in maltreated young children, the aim of the current study was to evaluate the prevalence of developmental and emotional/behavioural concerns in a cohort of maltreated children and to identify the impact of adverse family/caregiver risk factors on behavioural and developmental outcomes. This would also allow better understanding of the baseline profile/needs of the children and their families that are being enrolled into the programme.

METHOD

A prospective cohort study of children and caregivers/families enrolled into the Anchor home visitation programme from September 2020 to June 2023, at KKH, the largest women's and children's hospital in Singapore was undertaken. Children seen at KKH for suspected maltreatment below the age of 4 years old were referred to the programme.

The programme inclusion criteria targeted children under the age of 4 years for suspected maltreatment. Their siblings living in the same household (under the age of 4 years) were also eligible. The programme was not offered to children who have sustained extrafamilial maltreatment and children whose families were under any other community home visitation programmes.

Half of the caregivers for the maltreated children that were referred, agreed to be screened to enter the programme for support. The remaining caregivers declined the Anchor programme with reasons such as "feeling overwhelmed", or already receiving support from other community agencies (also an exclusion criterion for the programme). After obtaining caregiver consent, the child and family underwent comprehensive screening to assess developmental/socio-emotional profile and caregiver mental health status and for provision of further recommendations and interventions with follow-up. The interventions were delivered through home visitation by a community health visitor supported by doctors, psychologist, and medical social workers.[14] Family demographic data, baseline and follow-up assessment data were collected to track progress of the child and family. The study was approved and conducted in accordance with SingHealth Centralised Institutional Review Board (CIRB ref 2019/2683).

An interim cross-sectional study of the family demographic data and baseline assessment data was required to understand the profile and needs of the children and their families before commencing support. The Anchor programme's supporting philanthropic organisation and healthcare professional team also required the demographic data and baseline assessment data to be analysed for results to justify the necessity of the support provided by the programme.

Demographic data

From the family demographic data collected, specific data on caregiver mental health status, educational attainment and family income were used for analysis, as these are well-recognised risk factors in current literature.[8,9] This data was obtained through an initial interview conducted with the primary caregiver by the Anchor professional. Educational attainment of the primary caregiver was stratified as low if the caregiver had completed ≤12 years of formal education. This cutoff value of 12 years was selected because in Singapore, it is compulsory for all citizens to complete 6 years of primary school education and 4 years of secondary school education, which can be extended from a total of 10 to 12 years depending on an individual's academic progression. Family socio-economic status (SES) was stratified into 2 discreet family groups, PCI (per capita

income) ≤SGD650 and PCI of >SGD650 per month. Family PCI of ≤SGD650 per month was defined as low SES, as per Singapore's national benchmark when considering financial assistance and relief eligibility.[15]

Caregiver mental health status

Mental health screening of the primary caregiver was conducted using the Patient Health Questionnaire 9 (PHQ-9) and the General Anxiety Disorder 7 (GAD-7) tools to objectively assess the presence or absence of mental health concerns.[16,17] These tools encompass the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) depression/anxiety diagnostic criteria, translating the frequency of self-reported symptoms into tabulated scores. Presence of caregiver mental health concerns was defined as PHQ-9 and/or GAD-7 score of 10 and above (Table 1) for the purpose of the study, as guided by the KKH Psychiatry specialist to help streamline referrals to hospital mental health services during the Anchor programme.

Child outcome measures

ASQ-3

The Ages and Stages Questionnaires-3 (ASQ-3) is a validated developmental screening tool for children, which measures development in 5 domains: communication, gross motor, fine motor, problem solving and personal social.[18] Responses of "yes", "sometimes" and "not yet" to questions under each domain are scored as 10, 5 and 0 points, respectively. The total domain scores were tabulated by adding points from each domain item and comparing them to cut-off scores from a normative sample. When the child scored close to or below the cutoff (a score equal or more than 1 or 2 standard deviations [SD] below the mean score), they were considered to have developmental concerns and being "at risk" for developmental delays. To enhance this study, a further sub-analysis was done for the communication and problem-solving domains. This is because language and cognition are important skills to develop early as they are predictors of school readiness, especially for children from high-risk families whereby there is growing interest on ways to improve their long-term educational outcomes.[19,20]

ASQ-SE

The Ages and Stages Questionnaires-Socio-Emotional (ASQ-SE) is a validated developmental screening tool for children to help evaluate socio-emotional capabilities with item questions covering different behavioural aspects.[21] Each scoring item is rated with one of three possible responses — most of the time, sometimes and rarely/never — then added up into a total score and compared to cut-off score from a normative sample. When the child scored close to or above the cutoff, they were considered to have socioemotional concerns.

CBCL

Child Behavioral Checklist (CBCL) is another tool to help evaluate behavioural/emotional concerns. The CBCL quantifies total, internalising and externalising problems scores based on parental responses of their child's behavioural or emotional difficulties. Each item was scored on a 3-point scale (0=not true [as far as you know], 1=somewhat true, and 2=very true/often true). Internalising problems include the withdrawn/depressed and anxious syndrome scales, while externalising problems include the oppositional, aggressive behaviour and overactive syndrome scales. When the tabulated scores (T scores) suggested borderline or clinically significant internalising, externalising or both behaviours, these were considered clinically significant or concerning.

Analytical strategy

Statistical analysis and data extraction were done using Stata version 11 (StataCorp, College Station, TX, US). Frequencies (percentages) and median (interquartile range [IQR]) were reported for categorical and numerical variables, respectively. With the categorical groups as described above, multivariable logistic regression methods were used to compute adjusted odds ratio (OR) and look for any associated increased risk of behavioural or developmental concerns within our cohort of maltreated children when there were other family or caregiver factors present as they entered the programme. Caregiver relationship to the child was added to the multivariable logistics regression models to control for confounding effect of caregivers being non-biological parents. Statistical significance was set at P value <0.05 and 95% confidence intervals were calculated for all ORs. Pairwise deletion analysis was used when there were missing data from incomplete questionnaires.

RESULTS

Study participant profile

The sample for this study included a total of 132 children over a 34-month period from September 2020 to June 2023. The children were aged from 2

months to 47 months old. Among them, 74 (58%) were below 2 years of age (median age 1.7 [IQR 0.9–2.6] in years), with 69 (52%) being male.

The primary caregivers of the children at the time of enrolment into the programme consisted of biological mothers, fathers, or foster parents or extended family members of the children. The median age of primary caregivers was 32 years old (IQR 28.0–35.0), with only 121 of the 132 primary caregivers disclosing their ages. Out of the 132 primary caregivers, 86 (65.2%) were biological mothers and 11 (8.3%) were biological fathers. The remaining 35 (26.5%) caregivers were foster parents or extended family members of the children. For this subgroup of caregivers, the caregivers were either the biological parents or extended family members before the children became looked-after children due to their maltreatment episode. For caregiver mental health status, 27 (21%) of the 128 primary caregivers who responded had raised scores on the PHQ-9 and/or GAD-7. Low SES was seen in 45% of the families while 50% of the primary caregivers had completed ≤12 years of formal education. These are summarised in Table 1.

The developmental outcomes based on ASQ-3 and the behavioural concerns and socio-emotional outcomes based on the CBCL and ASQ-SE, respectively, are shown in Table 2. Overall, 99 (75%) of the 132 children screened at enrolment had scores of at least 1 SD below the mean cut-off in any domain on the ASQ-3. The domains with the highest percentage of delay were personal-social skills (60 [45%]), communication (58 [44%]), and problem-solving skills (54 [41%]). On the ASQ-SE, 37 (28%) of the 131

Table 1. Demographic profile of study cohort and mental health status of primary caregiver.

Variable	Total (n)	n (%) / median (IQR)
Child's age (years) at first assessment	128	1.7 (IQR 0.9–2.6)
Child's sex	132	
Female		63 (47.7%)
Male		69 (52.3%)
Child's ethnicity	132	
Chinese		49 (37.1%)
Malay		66 (50.0%)
Indian		14 (10.6%)
Others		3 (2.3%)
Caregiver age (years) at child's enrolment	121[a]	32.0 (IQR 28.0–35.0)
Caregiver relationship to child	132[b]	
Biological mother		86 (65.2%)
Biological father		11 (8.3%)
Non-biological parents		35 (26.5%)
Caregiver education ≤12 years of formal education	114[c]	57 (50.0%)
Social economic status PCI ≤SGD650	114[d]	51 (44.7%)
Presence of caregiver mental health concerns	128[e]	
PHQ-9 score 10 and above and/or GAD-7 score 10 and above		27 (21.1%)
PHQ-9 score 10 and above		22 (17.2%)
GAD-7 score 10 and above		20 (15.6%)

[a] n=121, 11 caregivers either declined or did not declare their age during interview.
[b] n=132, 86 caregivers were recorded as biological mothers, 11 caregivers were recorded as biological fathers whilst 35 were either extended family members or fosters carers recorded as caregivers at time of entry into programme.
[c] n=114, 18 caregivers either declined or did not declare their educational attainment during interview.
[d] n=114 because 18 caregivers either declined or did not declare their income during interview.
[e] n=128, 4 caregivers either declined or did not fill up the questionnaire completely.
GAD-7: General Anxiety Disorder 7; PCI: per capita income; PHQ-9: Patient Health Questionnaire 9; SGD: Singapore dollars

Table 2. Outcomes of developmental and socio-emotional behavioural screening using the ASQ-3, ASQ-SE and CBCL.

	Normal n (%)	With concerns (or significant) n (%)	Total numbers n (%)
ASQ-3 (overall)	33 (25%)	99 (75%)	132 (100%)
ASQ-3 (communication)	74 (56.1%)	58 (43.9%)	132 (100%)[a]
ASQ-3 (gross motor)	97 (73.5%)	35 (26.5%)	132 (100%)
ASQ-3 (fine motor)	93 (70.5%)	39 (29.5%)	132 (100%)
ASQ-3 (problem solving)	78 (59.1%)	54 (40.9%)	132 (100%)
ASQ-3 (personal social)	72 (54.5%)	60 (45.5%)	132 (100%)
ASQ-SE	94 (71.8%)	37 (28.2%)	131 (100%)[b]
CBCL	85 (72%)	33 (28.0%)	118 (100%)[c]

[a] n=132 because 1 extra patient with only ASQ-3 Communication section completed.
[b] n=131 because 1 of the original 132 ASQ-SE was not completed.
[c] n=118 because 14 of the original 132 CBCL questionnaires were not completed.
ASQ-3: Ages and Stages Questionnaires-3; ASQ-SE: Ages and Stages Questionnaires-Socio-Emotional; CBCL: Child Behavioral Checklist

children cohort had raised scores while 33 (28%) of the 118 children cohort had clinically significant raised T scores above the cut-off on the CBCL.

Risk factors or exposures

The major risk factors evaluated for an association with developmental, behavioural, socio-emotional concerns were caregiver mental health status, caregiver education attainment ≤12 years and low family SES and controlling for caregiver relationship to the child.

As seen in Table 3, overall concerns in the ASQ-3 and in the problem-solving domain were not associated with any of the 3 risk factors, while a low family SES was significantly associated with scores below the cut-off in the communication domain with an adjusted odds ratio (AOR) of 3.04 (95% CI 1.08–8.57], *P*=0.04). Caregiver mental health and caregiver education status were not significantly associated with delay in the communication domain.

Table 4 demonstrates the association of caregiver mental health concerns with raised scores on the ASQ-SE (AOR 7.78, 95% CI 2.38–25.38, *P*=0.001). Caregiver education and low family SES were not significantly associated with raised ASQ-SE scores. A significant association was seen between increased behavioural concerns on the CBCL and caregiver mental health concerns (AOR 6.54, 95% CI 1.83–23.33, *P*=0.004). Caregiver education and low family SES were not significantly associated with increased behavioural concerns on the CBCL.

DISCUSSION

Our study showed that among our cohort of maltreated children, low family SES was significantly associated with delay in the communication domain of ASQ-3. A significant interaction exists between poverty and its cofactors, such as maternal stress, malnutrition, overcrowding, lower parental educational levels with associated structural brain changes and resultant behavioural, cognitive and academic difficulties.[22] Another study by Justice et al. confirmed the Family Stress Model as a viable representation of the adverse effects of poverty and proposed that the language skills in toddlers may be affected by poverty through caregiver stress, depression and dysregulated parent-child interaction.[23] Our study also found a significant association between presence of caregiver mental health concerns, such as anxiety and depression, with both lower socio-emotional competence on the ASQ-SE and behavioural concerns on the CBCL. There is compelling evidence globally that mental health symptom of mothers has been associated with unfavourable outcomes in various domains of development in young children. Wall-Wieler et al. in their study demonstrated that early childhood exposure to maternal depression was associated most strongly with vulnerabilities related to social-competence and emotional-maturity.[24] Woolhouse et al. also found that maternal depressive symptoms were associated with significantly increased odds of child emotion or behavioural difficulties.[25] Indeed, caregiver mental depression is one of the most

Table 3. Multivariable association of caregiver/family risk factors and developmental concerns on ASQ-3.

	ASQ-3 Concerns (1 SD/ 2 SD score in any areas)			ASQ-3 Communication Concern (1 SD/2 SD score)			ASQ-3 Problem Solving Concern (1 SD/2 SD score)		
Risk factors	**Yes n (%)**	**No n (%)**	**Adjusted OR (95% CI)**	**Yes n (%)**	**No n (%)**	**Adjusted OR (95% CI)**	**Yes n (%)**	**No n (%)**	**Adjusted OR (95% CI)**
Caregiver mental health concerns									
Yes	18 (66.7%)	9 (33.3%)	0.63 (0.21–1.85)	11 (40.7%)	16 (59.3%)	0.81 (0.28–2.37)	11 (40.7%)	16 (59.3%)	2.07 (0.72–5.97)
No	76 (76.8%)	23 (23.2%)	Reference group	45 (45.5%)	54 (54.5%)	Reference group	41 (41.4%)	58 (58.6%)	Reference group
Caregiver ≤12 years of formal education									
Yes	43 (75.4%)	14 (24.6%)	0.74 (0.26–2.17)	28 (49.1%)	29 (50.9%)	0.84 (0.29–2.42)	22 (38.6%)	35 (61.4%)	0.82 (0.29–2.29)
No	39 (69.6%)	17 (30.4%)	Reference group	21 (37.5%)	35 (62.5%)	Reference group	20 (35.7%)	36 (64.3%)	Reference group
Lower SES PCI ≤SGD650									
Yes	39 (76.5%)	12 (23.5%)	1.47 (0.50–4.29)	30 (58.8%)	21 (41.2%)	3.04 (1.08–8.57)*	20 (39.2%)	31 (60.8%)	1.06 (0.38–2.91)
No	42 (67.7%)	20 (32.3%)	Reference group	19 (30.6%)	43 (69.4%)	Reference group	23 (37.1%)	39 (62.9%)	Reference group
Caregiver relationship to child									
Biological mother	59 (68.6%)	27 (31.4%)	0.54 (0.17–1.74)	38 (44.2%)	48 (55.8%)	1.42 (0.49–4.11)	32 (37.2%)	54 (62.8%)	0.56 (0.20–1.57)
Biological father	11 (100.0%)	0 (0.0%)	Not applicable	6 (54.5%)	5 (45.5%)	2.01 (0.28–14.30)	3 (27.3%)	8 (72.7%)	0.12 (0.01–1.42)
Non-biological parents	29 (82.9%)	6 (17.1%)	Reference group	14 (40.0%)	21 (60.0%)	Reference group	19 (54.3%)	16 (45.7%)	Reference group

Family/caregiver factors added to multivariable logistics regression models include caregiver mental health concerns, caregiver education attainment <12 years, low family socio-economic status and caregiver relationship to child.

* OR with $P<0.05$

ASQ-3: Ages and Stages Questionnaires-3; CI: confidence interval; OR: odds ratio; PCI: per capita income; SES: socio-economic status; SGD: Singapore dollars: SD: standard deviation

Table 4. Multivariable association of caregiver/family risk factors and significant socioemotional concerns or internalising/externalising behaviours.

	ASQ-SE (1SD/2SD score in any areas)			CBCL Concerns		
Risk factors	**Yes n (%)**	**No n (%)**	**Adjusted OR (95% CI)**	**Yes n (%)**	**No n (%)**	**Adjusted OR (95% CI)**
Caregiver mental health concerns						
Yes	14 (51.9%)	13 (48.1%)	7.78 (2.38–25.38)*	14 (56.0%)	11 (44.0%)	6.54 (1.83–23.33)*
No	22 (22.7%)	75 (77.3%)	Reference group	18 (20.7%)	69 (79.3%)	Reference group
Caregiver ≤12 years of formal education						
Yes	14 (24.6%)	43 (75.4%)	0.65 (0.19–2.17)	20 (39.2%)	31 (60.8%)	1.93 (0.52–7.18)
No	15 (26.8%)	41 (73.2%)	Reference group	10 (19.2%)	42 (80.8%)	Reference group
Lower SES PCI ≤SDG650						
Yes	13 (25.5%)	38 (74.5%)	0.87 (0.26–2.91)	18 (39.1%)	28 (60.9%)	1.80 (0.50–6.42)
No	14 (22.6%)	48 (77.4%)	Reference group	8 (14.0%)	49 (86.0%)	Reference group
Caregiver relationship to child			0.57 (0.16–2.09)			0.64 (0.17–2.44)
Biological mother	23 (27.1%)	62 (72.9%)	0.60 (0.07–5.05)	18 (24.0%)	57 (76.0%)	1.76 (0.12–26.37)
Biological father	3 (27.3%)	8 (72.7%)	Reference group	6 (60.0%)	4 (40.0%)	Reference group
Non–biological parents	11 (31.4%)	24 (68.6%)		9 (27.3%)	24 (72.7%)	

Family/caregiver factors added to multivariable logistics regression models include caregiver mental health concerns, caregiver education attainment <12 years, low family socio-economic status and caregiver relationship to child.
* OR with $P<0.05$
ASQ-SE: Ages and Stages Questionnaires-Socio-Emotional; CBCL: Child Behavioral Checklist; CI: confidence interval; OR: odds ratio; PCI: per income capita; SES; socio-economic status; SD: standard deviation; SGD: Singapore dollars

important factors contributing to toxic stress response and its potential disruption of brain-circuitry during sensitive developmental periods.[3] Shonkoff et al. have described the eco-bio-developmental framework of the development and impact of toxic stress on the developing brain.[3] A recent systematic review also found evidence that maternal depression was associated with maladaptive emotion processing in the offspring through biological and social mechanisms.[26]

Our study adds to the current literature on the prevalence of delayed development and socio-emotional competence in maltreated children in the early years and the influence of adverse family risk factors between the critical years of 0–3. More than a quarter of the cohort had concerns for socio-emotional competence or behavioural difficulties. Nearly 40% of the cohort presented with concerns in the domains of communication or problem-solving skills. Our study analysed the communication and problem-solving domains on the ASQ-3 separately because current literature suggests significant associations of delay in these domains with subsequent cognitive ability at ages 5–7 years, and the recognition that language skills was significant determinants of cognitive, education and health-related outcomes.[27,28]

Reporting on the Fragile Families and Child Well-Being study, Berger and Font suggested a strong association of early childhood maltreatment with delayed cognitive skills and behaviour problems at age 3.[29] The authors postulated that the maltreatment caused a disruption in the parent-child attachment, with resultant insecure, avoidant, or disorganised attachment orientation, creating a predominant pathway which gave rise to maladaptive behavioural and affective responses on the part of the child, particularly anxiety, depression and externalising problems.[29] Similarly, a review study by Jaffe demonstrated that children aged under 3 were at the highest risk of victimisation from abuse or neglect, and that child victims of maltreatment were at an elevated risk of psychopathology.[30] The author posited that this increased psychopathological risk was mediated through increasing threat sensitivity, decreasing responsivity to reward and deficits in emotional recognition and understanding.[30]

For local context, the prevalence of developmental delay in our study was significantly higher than the reported prevalence of delay in a low-risk birth cohort at 2 years of age in Singapore.[31] Similarly, the prevalence rate of 28% for social or behavioural difficulties seen in our study was much higher than the estimated prevalence of 12% in preschool children in a local community sample.[32] Similar to our study findings where only 25% of the cohort had typical development in all domains, a large Australian population study by Green et al. demonstrated that only 30% of the children exposed to maltreatment were on track in all developmental domains, with approximately half demonstrating delays in communication, cognitive or socio-emotional domains at age 5.[33] With both local and international studies suggesting significantly higher prevalence of both developmental and emotional or behavioural concerns in maltreated children as compared to the general population, it is imperative to support this high-risk group of children and their families.[31-35]

Our various findings contributed to the increasing literature on the convergence of multiple risk factors that result in a final pathway leading to the increased risk of developmental and behavioural concerns in maltreated children. Given the significant impairments seen in maltreated children, early identification and intervention is essential to break the cycle of toxic stress and improve outcomes across the life span. The positive effects of family-focused programmes have been well documented.[36] The authors found significant effect sizes for interventions focusing on improving parenting skills and interventions providing social and/or emotional support.[36] These included cognitive behavioural therapy, home visitation, parent training, and family-based/multisystemic interventions including that of substance abuse.[36]

Our study was one of the first locally conducted prospective studies for high-risk young children aged between 0–3 years who have been maltreated. A specific study of associated family risk factors locally helps to enhance Anchor programme's home visiting support. Data capture in this programme have been detailed, starting from the structured and systematic screening during recruitment, and right down to the evaluation and intervention process within the program itself. Providing targeted intervention in the presence of specific risk factors would assist in optimising the outcomes for the high-risk family and child. Results from this study suggest that maltreated children from lower SES families may need targeted support in language development. Also, working towards supporting caregiver's mental health well-being can potentially have a positive effect on behaviours among maltreated children.

Sample size could be one of the limitations of this study. However, with the programme recruitment still ongoing, a larger sample size can be obtained in the future and retrospective re-analysis can be done consequently to strengthen the statistical significance. Another potential limitation was the use of caregiver-answered questionnaires, which could risk introducing potential bias. Apart from caregiver-answered questionnaires/tools, multisource feedback, such as preschool feedback, could also be considered to offset any under-reporting or over-reporting of the children's developmental skills or behaviours by their caregivers. Although the children were presenting to KKH for the first time for suspected maltreatment, some might have already been implicated with previous recurrent maltreated episodes or even exposed to multiple forms of maltreatment that had neither been disclosed at the point of referral to the programme, nor documented in the hospital data system as the children/families have not had previous hospital referrals. These data that were difficult to capture may have confounding effects. As child maltreatment is only one form of ACEs, further studies might need to be considered to address the intricate interplay of other ACEs among our high-risk children and the effects that they could have if more significant family or social history transpire during the follow-up and support of the families and children during the duration of the programme. The future analysis of long-term follow-up data of the children and their families after they have commenced on support may also help to uncover any other possible confounding risk factors. After all, families involved in child maltreatment are often complex.

CONCLUSION

In summary, this study has allowed us to evaluate the impact of family and caregiver risk factors that are associated with poorer outcomes in maltreated children. Among maltreated children, having caregivers with mental health concerns was significantly associated with increased emotional/behavioural concerns. Maltreated children from low SES families were also at increased risk of language delay, affecting their communication. This contributes towards the current limited literature and understanding of risk factors that predict poorer outcomes among maltreated children. This also justifies the necessity of the family support provided by the programme to improve outcomes.

Declaration

The authors declare that there is no conflict of interest.

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REVIEW ARTICLE

Consensus recommendations for optimising the diagnosis and treatment of paroxysmal nocturnal haemoglobinuria in Singapore

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ABSTRACT

Introduction: Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematologic disease characterised by intravascular haemolysis, thrombophilia and bone marrow failure. There is a lack of established clinical guidance on the screening, diagnosis and management of PNH in Singapore. A relatively low level of awareness among healthcare professionals regarding PNH manifestations further contributes to diagnostic delays. Additionally, limited access to complement inhibitors, like eculizumab, may delay treatment and impact patient outcomes.

Method: Nine haematologists from different institutions in Singapore convened to formulate evidence-based consensus recommendations for optimising the diagnosis and management of patients with PNH and improving access to novel treatments. The experts reviewed the existing literature and international guidelines published from January 2010 to July 2023, focusing on 7 clinical questions spanning PNH screening, diagnostic criteria, investigations, treatment and monitoring of subclinical and classic disease, PNH with underlying bone marrow disorders, and PNH in pregnancy. A total of 181 papers were reviewed to formulate the statements. All experts voted on the statements via 2 rounds of Delphi and convened for an expert panel discussion to finetune the recommendations.

Results: Sixteen statements have been formulated for optimising the screening, diagnosis and management of PNH. Upon confirmation of PNH diagnosis, individuals with active haemolysis and/or thrombosis should be considered for anti-complement therapy, with eculizumab being the only approved drug in Singapore.

Conclusion: The current recommendations aim to guide the clinicians in optimising the screening, diagnosis and management of PNH in Singapore.

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Keywords: aplastic anaemia, bone marrow failure, complement inhibitors, intravascular haemolysis, practice guidelines

CLINICAL IMPACT

What is New

- Diagnosis of paroxysmal nocturnal haemoglobinuria (PNH) requires a heightened index of suspicion, and once confirmed, patients with haemolytic PNH and/or PNH with thrombosis should be considered for anti-complement therapy.
- Eculizumab is the only approved therapy for PNH in Singapore; other complement inhibitors are under various stages of investigation.

Clinical Implication

- This expert consensus will help guide healthcare professionals to optimise the screening, diagnosis and management of PNH in Singapore.

INTRODUCTION

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare clonal blood disorder caused by acquired mutations in haematopoietic stem cells.[1] Mutations in the X-linked phosphatidylinositol glycan class A (PIG-A) gene and consequent impairment in glycosylphosphatidylinositol (GPI) anchor synthesis result in the deficiency of complement-inhibiting proteins, CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis).[1,2] The deficiency of CD55 and CD59 in red blood cells (RBCs) results in an increased sensitivity of erythrocytes to complement-mediated intravascular haemolysis (IVH), lysis of RBCs and release of haemoglobin into plasma, which may lead to haemoglobinuria.[1]

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Clinically, PNH is characterised by IVH, increased susceptibility to thrombosis and bone marrow failure.[3] While IVH is the hallmark feature of PNH,[3] the deficiency of nitric oxide (NO) due to its sequestration by free plasma haemoglobin may increase the risk of thrombotic events that may affect multiple organs, including the liver, kidneys, central nervous system and/or lungs.[3,4] Other disease sequelae include renal failure and pulmonary hypertension.[5] Common PNH symptoms include dark-coloured urine (observed in 25% of patients), fatigue, anaemia and shortness of breath.[3,6] Additional non-specific signs related to NO depletion (and vasoconstriction) include abdominal pain, chest pain,[7] dysphagia and erectile dysfunction in men.[7]

Globally, PNH incidence is 1–1.5 cases per million individuals.[8] However, there is limited data on its prevalence in Singapore. PNH affects both men and women equally, but a few studies suggest a slightly high prevalence in women due to lyonisation.[8] Clinical manifestations of PNH can occur across all ages, with rare cases in children and a higher incidence between 30–40 years.[9] PNH may be associated with aplastic anaemia (AA), myelodysplastic syndromes (MDS) or acute myeloid leukaemia (AML). In most cases, PNH develops in patients previously diagnosed with AA or MDS.[2] The disease burden of PNH varies widely and is influenced by the proportion of GPI-anchor protein (AP) deficient cells or clone size.[3] Despite the most comprehensive supportive care, PNH may be associated with a 35% mortality rate at 5 years and approximately 50% at 10 years.[5]

The International PNH Interest Group classifies PNH into 3 subgroups: (1) classic PNH, characterised by clinical and laboratory findings of IVH without evidence of bone marrow deficiency; (2) PNH associated with bone marrow disorder (e.g. AA, MDS); and (3) subclinical PNH, observed in patients with a small population of PNH cells, without evidence of haemolysis or thrombosis.[5]

While international guidelines exist,[4-7,10-13] clear recommendations for PNH screening, diagnosis and management in Singapore are lacking. This, in addition to the lack of awareness among general healthcare professionals about various manifestations of PNH, may hinder timely referral, diagnosis and treatment initiation. Moreover, limited access and funding for complement inhibitors, such as eculizumab, may potentially limit treatment options, affecting outcomes in patients with PNH. Therefore, we used a modified Delphi methodology to develop evidence-based recommendations for screening, diagnosing and treating subclinical and classic PNH to optimise disease management and facilitate improved access to emerging treatments in Singapore.

METHOD

Expert panel

Nine haematologists from different academic institutions and private medical centres across Singapore were identified based on their clinical expertise in treating PNH and relevant publication experience. An expert haematologist from Taiwan, involved in developing the Taiwanese PNH guidelines, was also invited to share his clinical insights.

Literature search, review and evidence rating

Seven core categories focusing on the key aspects of PNH screening, diagnosis and management were identified, and clinical research questions were drafted for each category: (1) indications for screening of PNH; (2) diagnosis of PNH; (3) clinical, laboratory and imaging investigations after the diagnosis of PNH; (4) treatment and monitoring of patients with subclinical PNH; (5) treatment and monitoring of patients with classic PNH; (6) treatment and monitoring of patients with PNH in the setting of underlying bone marrow disorders; and (7) treatment and monitoring of patients with PNH in pregnancy.

A comprehensive literature search was performed in Medline via PubMed using search strings developed from a combination of relevant medical subject headings and free-text terms. Studies (randomised controlled trials [RCTs], observational studies, systematic reviews and meta-analyses) spanning January 2010 through July 2023, conducted in humans, with abstracts in English, were considered for inclusion. As eculizumab was approved in 2007, all articles from January 2006 to December 2009 on the use of eculizumab for the treatment of PNH were also included in the initial screening. Narrative reviews, news articles, letters to the editor and commentaries were excluded. The search results were screened by title and abstract, followed by a full-text review of shortlisted articles and data extraction for the final set. Clinical guidelines for PNH screening, diagnosis and management were also considered and reviewed while preparing the statements (Supplementary Fig. S1).

Through an iterative editing process, draft statements were developed using available evidence and real-world clinical experience from the core expert panel. The quality of evidence

supporting the PNH management recommendations was assessed using the Oxford Levels of Evidence 2011 (Oxford Centre for Evidence-Based Medicine, Supplementary Table S1).[14]

Consensus building

The consensus recommendations were developed by a modified Delphi-based approach, described by Gustafson et al.[15] The draft statements underwent the first round of Delphi voting (August 2023) using Microsoft Forms. Experts independently rated statements on a Likert scale (1: completely agree to 5: completely disagree) with an option to submit their comments for further optimisation. Consensus (the average of ratings for "completely agree" and "agree with minor changes") was set a priori at ≥70% agreement.[16] Delphi round 1 results and statements were presented and discussed in an advisory board meeting on 13 September 2023, where the expert panel discussed to further refine the statements based on real-world practices in Singapore. Revised draft statements were again shared for final agreement rating (October 2023). The strength of the consensus was defined as "strong" (>90% agreement), "moderate" (70–90% agreement) and "no consensus" (<70% agreement).

RESULTS

The systematic literature search identified 1679 records. After title and abstract screening, and deduplication, 290 articles underwent detailed full-text screening. Finally, 181 articles on PNH diagnosis (n=48) and treatment (n=133) were considered for data extraction (Supplementary Fig. S1) to draft 16 consensus statements and substatements. Additionally, 10 international and regional PNH guidelines were reviewed to optimise the statements. While the key studies are cited in the paper, additional articles that were reviewed to develop the consensus statements are included in Supplementary Table S2. Over 80% of included studies were observational, and draft statements on PNH management were primarily supported by level 2 evidence. Nevertheless, all statements achieved >90% agreement (strong recommendation) after 2 rounds of Delphi voting (Supplementary Table S3).

DISCUSSION

When to consider PNH?

Early identification of a PNH defect is crucial for optimising the treatment and improving the prognosis of the disease. Although PNH is characterised by a triad of haemolysis, thrombosis and bone marrow failure, patients can present with varying combinations of symptoms. The most common initial presenting signs and symptoms include anaemia[17] (severe fatigue,[18] dyspnoea,[18] headache[17]) and/or dark-coloured urine.[19] The NO deficiency in PNH often leads to gastrointestinal muscular dystonia, manifested by abdominal pain, and vascular muscular dystonia, resulting in dysphagia,[17] chest pain[7] and erectile dysfunction.[17] The non-specific nature of these symptoms can lead to delays in diagnosis and treatment. To facilitate more efficient screening of PNH, the experts proposed that 3 groups of patients should be considered for further evaluation for the diagnosis of PNH (Fig. 1, Statement 1).

The first group includes patients with Coombs' negative haemolytic anaemia[4,6,12] and one or more of the following features, based on observational studies: haemoglobinuria,[17] renal dysfunction,[17] elevated serum lactate dehydrogenase (LDH, ≥1.5 x upper limit of normal [ULN]),[17] elevated reticulocyte count,[19] reduced serum haptoglobin[19] or unexplained iron deficiency.[17] Chronic IVH may result in renal disease, and the presence of unexplained haemolysis with signs of renal failure may indicate the need for further PNH testing.

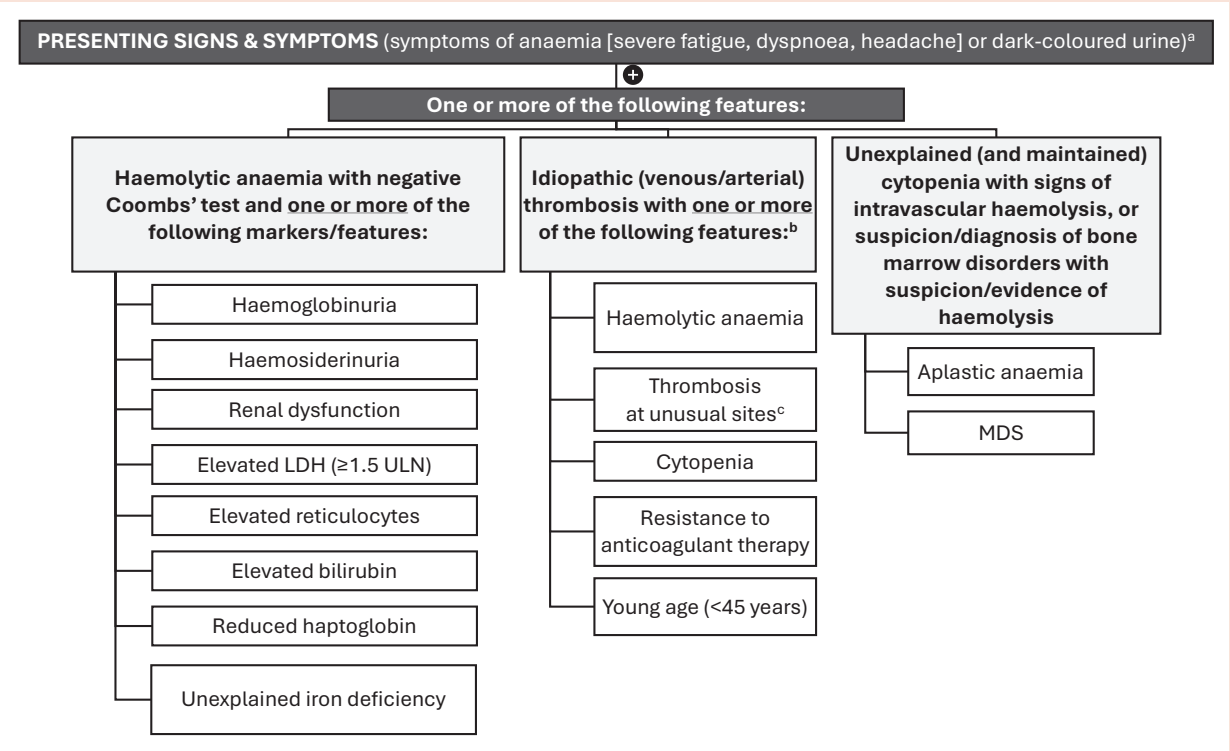
The second group includes patients with unexplained or unusual sites of thrombosis, possibly with signs of intravascular haemolysis or cytopenia. Patients experiencing thrombosis despite adequate anticoagulation therapy, especially young patients (<45 years),[17] should also be tested for PNH. About 29–44% of patients report thromboembolic events at least once in the course of the disease, with these events being the main cause of death in 40–67% of cases before the introduction of eculizumab treatment.[20] Some of the common thrombosis sites in PNH include cerebral and intra-abdominal regions (including portal[17] and hepatic veins, resulting in Budd–Chiari syndrome).

The third group includes patients with evidence of bone marrow dysfunction, including AA and MDS, coupled with suspicion or signs of haemolysis. Cytopenia, a consequence of bone marrow failure (BMF) syndrome, is often present concomitantly with subclinical PNH.[21] While IVH is the main cause of haemolytic anaemia in PNH, the underlying anaemia may be aggravated by BMF. Abnormal erythropoiesis is reported in cases of haemolysis associated with BMF.[22] Throughout the course of PNH, BMF of varying severity is detected in almost all patients.[23] In classic PNH, approximately 30–40% of patients develop AA, MDS or AML during a 10-year follow-up.[22]

Diagnosis of PNH

Flow cytometry is the gold standard for the diagnosis of PNH (Table 1, Statement 2). The

Fig. 1. Indications to consider screening of PNH (Statement 1).



LDH: lactate dehydrogenase; MDS: myelodysplastic syndrome; PNH: paroxysmal nocturnal haemoglobinuria; ULN: upper limit of normal
[a] Other clinical features may include intermittent dysphagia, abdominal pain or erectile dysfunction of unknown aetiology
[b] Arranged in an order with the subcriterion raising the highest suspicion of PNH at the top. Young age as the sole subcriterion is not sufficient to raise the suspicion for PNH in patients with idiopathic thrombosis and should be considered along with any one of the other listed subcriteria, based on clinical discretion and on a case-to-case basis.
[c] Hepatic veins (Budd–Chiari syndrome), cerebral venous sinus, cutaneous veins and other intra-abdominal veins (portal, splenic, visceral)

use of the latest International Clinical Cytometry Society/European Society for Clinical Cell Analysis recommendations not only helps detect GPI-defective cell clones in PNH but also identifies even fewer cells with the PNH phenotype in patients with BMF.[24] Tests are routinely performed on neutrophils, monocytes and erythrocytes from peripheral blood. GPI-defective cell identification is performed by labelling cells with monoclonal antibodies against GPI-AP antigens or fluorescently labelled aerolysin (FLAER), which directly binds to GPI anchors.[17]

The diagnostic criteria mandate the demonstration of deficiencies in at least 2 distinct GPI proteins within 2 separate cell lines—granulocytes, monocytes or erythrocytes—via flow cytometry.[6] The diagnosis of PNH is confirmed in individuals who meet the following criteria: (1) granulocytes: absent or decreased expression of FLAER or CD24, (2) monocytes: absent or decreased expression of FLAER or CD14, and (3) red cells: absent or decreased CD59 expression (type II and type III PNH populations).[22] The flow cytometry tests have the capability to quantify the proportion

Table 1. Recommendations for optimising the diagnosis of PNH (Statement 2).

Statement 2.1	We recommend the use of FLAER or high-sensitivity flow cytometry to detect the deficiency of GPI-anchored proteins in peripheral blood (leucocytes [both neutrophils and monocytes] and erythrocytes), to confirm the diagnosis of PNH.[a]
Statement 2.2	Annual follow-up flow cytometry may be considered when clinically indicated in patients with clone size <1% on initial flow cytometry. While 6-monthly follow-ups may be considered in patients with (1) clone size >1% on initial flow cytometry or (2) underlying bone marrow failure syndromes, especially in case of disease progression or for guiding treatment.[b]

FLAER: fluorescently labelled aerolysin; GPI: glycosylphosphatidylinositol; PNH: paroxysmal nocturnal haemoglobinuria
[a] Based on the International Clinical Cytometry Society guidelines to detect GPI-deficient cells in PNH and related disorders
[b] Subject to clinician's discretion on a case-to-case basis

of cells exhibiting the PNH abnormality. Assessing the size of the PNH clone within the neutrophil or monocyte population provides the most accurate reflection of disease progression, as the circulation of PNH erythrocytes (type II and type III) is generally low. Normal erythrocytes (type I), which are CD59-positive, have an extended lifespan of approximately 120 days. Conversely, erythrocytes with diminished CD59 expression (type II) are 3 to 5 times more sensitive to complement attack. CD59-negative red cells (type III) are markedly more vulnerable and 15 to 25 times more susceptible to complement attack than type I cells. Consequently, type III cells have a shortened circulating lifespan of 10 to 15 days as they are swiftly eliminated from circulation, especially during periods of complement system activation such as infections.[22]

Laboratory investigations after confirmation of PNH diagnosis

Comprehensive laboratory and imaging investigations should be conducted in patients diagnosed with PNH, in addition to the clinical evaluation described under screening. Full blood and reticulocyte count, as well as serum LDH, haptoglobin and bilirubin levels, should be assessed to confirm IVH.[4-7] Haemoglobin concentration and serum haptoglobin levels are low, while reticulocyte count, serum LDH and bilirubin levels are elevated in patients with PNH. The diagnosis may be further confirmed by the detection of haemosiderin in urine through microscopy and a urine dipstick test.[4-7] Other investigations include testing for D-dimer, prothrombin time, activated partial thromboplastin time and international normalised ratio.[5] Renal function should be assessed by analysing serum creatinine levels and proteinuria.[11] The absence of antibody-mediated IVH in PNH results in a negative direct antiglobulin (Coombs) test in treatment-naïve patients (Table 2, Statement 3).

Imaging investigations include computed tomography or ultrasound for thromboembolic events, echocardiogram for pulmonary hypertension, and cranial magnetic resonance imaging for intracranial thrombosis in case of headache or other neurological symptoms. A bone marrow aspirate or biopsy is recommended for patients with suspected concomitant AA/MDS.[4,6,7,11] A summary of clinical, laboratory and imaging assessments for confirmed PNH diagnosis, based on existing guidelines[4,6,7,11] and real-world practices in Singapore, is outlined in Table 2 (Statement 3).

Management of PNH

Subclinical PNH

The expert panel recommendations for optimising the management and monitoring of subclinical PNH in Singapore are shown in Table 3 (Statement 4). As subclinical PNH is asymptomatic with a low thromboembolic risk compared to classic PNH, no treatment is needed.[3,5,9] In subclinical PNH, blood cells lack GPI-AP and the PNH clone size (≤10% granulocyte clone) is typically small, often significant only in the context of immune-mediated BMFs.[9] Therefore, the primary focus of treatment should be on addressing the underlying bone marrow disease—AA (in PNH/AA) or MDS (in PNH/MDS).[5] However, close monitoring every 6–12 months or more (in stable cases) may be considered as progression to haemolytic or thrombotic PNH may occur due to PNH clone expansion or the emergence of cells with a PNH phenotype.[9,11]

Classic PNH

Classic PNH, diagnosed in approximately one-third of patients, is characterised by normocellular to hypercellular bone marrow, erythroid hyperplasia, elevated reticulocyte count and LDH levels 2–10 times ULN.[9] It usually features large PNH clones (mean granulocyte clone size of >50),[22] with thrombosis risk proportionate to clone size.[5] Other manifestations include smooth muscle dystonia, fatigue, renal impairment and pulmonary hypertension.[9]

Six recommendations were drafted by the expert panel for the management of classic PNH in Singapore and are provided in Supplementary Fig. S2 (Statements 5.1–5.8), Table 3 (Statements 5.2–5.4 and 5.6) and Table 4 (Statement 5.5). Multidisciplinary clinical management involves optimal management of haemolysis with standard-of-care complement C5 inhibitors (e.g. eculizumab) and tailored supportive treatments for symptomatic anaemia, haemoglobinuria, iron deficiency, thrombosis, smooth muscle dystonia, kidney damage and/or underlying BMF disorders such as AA and MDS (Supplementary Fig. S2, Statement 5.1).

Complement inhibitor therapy

Complement inhibitors are indicated for classic haemolytic PNH, and criteria for initiating complement C5 inhibitors are detailed in Table 3 (Statement 5.2). These indications are in line with the existing guidelines.[6,7,22] Eculizumab, the first monoclonal antibody targeting complement C5

Table 2. Clinical and laboratory/imaging investigations after the confirmation of PNH diagnosis (Statement 3).

Investigations	**Purpose/interpretation**
Clinical history	
Severe asthenia, dyspnoea	Anaemia
Dark-coloured urine, jaundice	Intravascular haemolysis
Oesophageal spasm, dysphagia, abdominal pain, erectile dysfunction (unexplained)	Smooth muscle dysfunction
Abdominal pain, chronic headache, neurological deficit	Atypical thrombosis
History of fever/infections	Granulocytopenia
Co-existing bone marrow failure syndromes (AA/MDS)	To aid in treatment planning
Medication and transfusion history	
Pregnancy history and/or plans	
Baseline investigations	
Complete blood count with haemoglobin, neutrophils, platelets	Low levels indicate anaemia or cytopenia (granulocytopenia or thrombocytopenia)
Reticulocyte count	Elevated count indicates haemolysis
Serum LDH	≥1.5 x ULN indicates haemolysis
Unconjugated or indirect bilirubin	Elevated levels indicate haemolytic anaemia
Haptoglobin	Low levels indicate intravascular haemolysis
Serum iron profile (ferritin, total iron binding capacity)	Low ferritin and high total iron binding capacity indicate iron deficiency
Serum creatinine	High levels indicate renal insufficiency
Prothrombin time (PT)	To guide anticoagulant therapy or thromboprophylaxis
Activated partial thromboplastin time (aPTT)	
Direct antiglobulin (Coombs') test	Negative test excludes autoimmune haemolytic anaemia
Urine dipstick	Clear, red/amber-coloured urine that remains pigmented (with haemoglobin) after centrifugation, with haemoglobin in urine indicates haemoglobinuria during haemolytic episodes
Urine microscopy	Presence of stainable iron indicates intravascular haemolysis and haemosiderinuria
Urinary albumin	Presence (above reference) indicates microalbuminuria and proteinuria
Glomerular filtration rate	Low levels (below reference) indicate renal dysfunction
Bone marrow aspirate (cytology and cytogenetics)	In patients with suspected or concomitant AA/MDS
Bone marrow biopsy	
Investigations (only when clinically indicated)	
Serum erythropoietin	Levels are often high in PNH and correlate with reticulocyte count
Abdominal ultrasound with Doppler	To detect thrombi
Doppler echocardiography	To evaluate pulmonary hypertension
Pulmonary CT angiography	To evaluate pulmonary hypertension
Cranial MRI/CT	Relevant in case of headache or other neurological symptoms

Table 2. Clinical and laboratory/imaging investigations after the confirmation of PNH diagnosis (Statement 3). (Cont'd)

Investigations	Purpose/Interpretation
Investigations (only when clinically indicated)	
Bone density	Relevant in patients on prior steroids
Abdominal MRI	To assess the degree of hepatic iron deposit
Investigations (optional)	
HLA typing	May be considered in young patients for future stem cell transplantation
NT-proBNP	In patients with pulmonary hypertension (higher than reference levels indicate heart failure)
Vitamin B12	To exclude other causes of anaemia
Folic acid	

AA: aplastic anaemia; CT: computed tomography; HLA: human leucocyte antigen; LDH: lactate dehydrogenase; MDS: myelodysplastic syndromes; MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PNH: paroxysmal nocturnal haemoglobinuria; ULN: upper limit of normal

protein, is approved for the treatment of PNH, with subsequent Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for ravulizumab. Both inhibitors block terminal complement C5 activation, preventing C5a and C5b-9 formation.[5] As of August 2023, only eculizumab is approved in Singapore, based on the results of 2 large phase III randomised studies, TRIUMPH (87 cases)[25] and SHEPHERD (97 cases).[26] The studies demonstrated that eculizumab prevents IVH in PNH, eventually leading to haemoglobin stabilisation; reduction or elimination of the need for RBC transfusions; and resolution of most disease-related symptoms. A follow-up study showed a substantial reduction in the rate of thromboembolic events, dropping from 7.4 to 1.1 events per 100 patient-years.[27] A systematic review of 6 studies confirmed eculizumab's efficacy in decreasing LDH levels and transfusion rates and in increasing haemoglobin levels.[28] Long-term follow-up studies (up to 5 years) have confirmed the efficacy of continuous maintenance eculizumab treatment with haematological improvement and no safety concerns.[29] Eculizumab also reduced thromboembolic risk (relative risk reduction: 85%) over 3 years, thus reducing morbidity and improving long-term survival in patients with PNH.[27]

In an open-label phase II study, AEGIS, involving 29 Japanese patients with PNH, eculizumab significantly reduced haemolysis (87%, $P<0.0001$) and transfusion frequency ($P=0.006$).[30] Fatigue and dyspnoea significantly improved within 1–2 weeks of treatment, independent of changes in haemoglobin.[30] These results were confirmed in a 2-year long-term and post-marketing surveillance study in Japanese patients, demonstrating sustained reduction in IVH ($P<0.001$) and RBC transfusions ($P=0.0016$) compared with baseline levels.[31] Two independent studies also showed >90% 5-year survival rates for patients with PNH who received continuous treatment with eculizumab.[32,33] A study by Ueda et al. showed improved quality of life (QOL) patients with PNH receiving eculizumab,[34] revealing a relationship between the QOL test components and haemoglobin and LDH concentrations.[34] The safety and efficacy of eculizumab have also been demonstrated in paediatric patients.[35]

Ravulizumab is indicated for treating PNH in adults and children (≥10 kg) with haemolysis and clinical symptom(s) indicative of high disease activity, and who are clinically stable after ≥6 months of previous eculizumab treatment.[36] Ravulizumab has a mean terminal half-life approximately 4 times longer than eculizumab, providing complete and sustained terminal C5 inhibition with an 8-week dosing interval.[36] Two studies (phase Ib and phase II) and 2 large phase III trials (n=441 for both) evaluated the efficacy and safety of ravulizumab; one phase III study was in eculizumab-treated patients (study 302) and the other in treatment-naïve PNH patients (study 301).[37-39] Results revealed that ravulizumab was non-inferior to eculizumab for haemolysis control and transfusion avoidance, with similar adverse events.[40] These results were maintained in long-term studies.[41,42] In a long-term study spanning from 27 weeks to 2 years and involving over 400 patients with PNH previously (662 patient-years), ravulizumab sustained improvement in LDH levels in both study populations (studies 301 and 302). The study reported that 81.9% of patients in study

Table 3. Recommendations for the management of subclinical PNH (Statement 4) and classic PNH (Statement 5).

Management of subclinical PNH		
Statement 4.1	Asymptomatic patients with subclinical PNH with small PNH clones and no evidence of haemolysis may be monitored every 6–12 months for (1) symptoms of haemolysis, underlying bone marrow disorder and emerging complications, and (2) expansion or evolution of subclinical PNH clones by FLAER or high-sensitivity flow cytometry.[a]	
Statement 4.2	Initiation of anti-complement therapy is not needed in patients with subclinical PNH. Appropriate treatment should be offered to treat the underlying bone marrow disease and associated complications, and thromboprophylaxis may be initiated in patients at high risk of thrombosis (e.g. during pregnancy).	
Management of classic PNH		**Level of evidence**
Statement 5.2	Complement C5 inhibitors are indicated for the treatment of patients with PNH, with increased haemolysis (LDH >1.5 ULN), granulocyte PNH clone >10%, and one or more of the following criteria: • clinical symptoms indicative of high disease activity (weakness, fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [Hb <10 g/dL], thrombosis, dysphagia and/or erectile dysfunction), regardless of transfusion history • history of thromboembolic events requiring anticoagulant therapy due to PNH • history of regular transfusions (at least 4 packs of RBC over the past 12 months) due to haemolysis • organ damage due to haemolysis (chronic renal failure or repeated episodes of acute renal failure; chest pain with New York Heart Association class III or IV; respiratory failure or an established diagnosis of pulmonary hypertension; and/or smooth muscle dystonia) • pregnancy with a high risk of thrombosis or history of gestational complications	2
Statement 5.3.1	Consider (1) increasing the dose of eculizumab, (2) decreasing the time between infusions or (3) switch-over from eculizumab to ravulizumab,[b] in case of inadequate response to eculizumab therapy (transfusion dependency due to intravascular haemolysis or failure to decrease serum LDH levels to <1.5 x ULN) or regular breakthrough haemolysis during eculizumab treatment (≥3 months).[c]	2
Statement 5.3.2	Switch-over from C5 to C3 inhibitor therapy[d] may be considered in case of any one of the following conditions: (1) breakthrough intravascular haemolysis during regular C5 inhibitor treatment (≥3 months) (2) clinically relevant C3-mediated extravascular haemolysis on C5 inhibitor treatment (≥3 months) (3) unprovoked thromboembolic event during C5 inhibitor therapy (4) unexplained severe fatigue and impaired quality of life despite C5 inhibitor therapy for ≥3 months (5) inadequate response to C5 inhibitor therapy (transfusion dependency due to intravascular haemolysis or failure to decrease serum LDH levels to <1.5 x ULN)	2
Statement 5.4	Vaccination against meningococcus with a tetravalent vaccine including serotypes A, C, Y and W135, along with vaccination against serotype B[e] is recommended at least 2 weeks before initiating treatment with C5 inhibitor therapy.	2
Statement 5.6	Complement C5 inhibitor therapy should ideally be continued for an extended duration. Discontinuation of treatment may be considered in selected cases with significant lack of clinical improvement, severe bone marrow failure, non-compliance/contraindications to treatment or due to patient's decision to stop the treatment.	2

FLAER: fluorescently labelled aerolysin; Hb: haemoglobin; LDH: lactate dehydrogenase; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell; ULN: upper limit of normal
[a] Monitoring using FLAER or flow cytometry may be considered on a case-to-case basis
[b] Subject to local approval, patient factors and resource constraints
[c] Exclude acute or pharmacodynamic causes such as infections or pregnancy
[d] Subject to local approval, patient factors and resource constraints
[e] Subject to availability

301 and 85.6% of patients in study 302 maintained transfusion avoidance. Additionally, FACIT-F scores remained stable.[42] Similar results were reported in a sub-analysis of Japanese patients (study 301: n=33; study 302: n=12), which evaluated the efficacy of ravulizumab in PNH,[43] with 83.3% (15 of 18) of patients successfully avoiding transfusion (study 301) and with adjusted prevalence of 52.1% for LDH normalisation. In study 302, the least-squares-mean percentage change from baseline in LDH was 8.34%.[43]

All individuals with large PNH clones (>50% granulocytes, >10% erythrocytes) significantly elevated LDH levels, and a high reticulocyte count may benefit from eculizumab therapy,[22] but only a fraction with high disease activity show

Table 4. Recommended follow-up assessments in patients with PNH along with their frequency (Statement 5.5).

Follow-up investigations	Frequency[a]
Clinical symptoms (fatigue, pain [abdominal pain, oesophageal spasms], episodes of increased haemolysis, haemoglobinuria, anaemia, dyspnoea, erectile dysfunction)	Monthly for 3 months after initiating therapy for PNH followed by every 3 months
CBC, reticulocyte count, LDH	
Renal function (electrolytes, estimated creatinine clearance, microalbumin, urine analysis [routine and microscopic])	
Liver function test	
Iron status (ferritin, transferrin saturation)[b]	Every 3 months
Direct Coombs' test[c]	Every 3–6 months
NT-proBNP	Every 6 months
History of transfusions	Every 6 months
FLAER or high-sensitivity flow cytometry (PNH clone analysis)	As per Statement 2.2
Meningococcal infection and history of penicillin or antibiotics for meningococcal prophylaxis[d]	Every 12 months
MRI to analyse hepatic iron deposition (in case of iron overload)[b]	
2D echocardiography[b]	

CBC: complete blood count; FLAER: fluorescently labelled aerolysin; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PNH: paroxysmal nocturnal haemoglobinuria
[a] Frequency of follow-up may be revised at the clinician's discretion based on disease activity
[b] Only when clinically indicated
[c] In patients with suspected autoimmune haemolytic anaemia
[d] Only in patients on complement C5 inhibitor therapy

significant improvement in haemoglobin levels and become transfusion-free.[44] Possible reasons for this lack of desired treatment response include (1) very rare C5 polymorphisms,[45] mainly observed in Japanese patients, hindering eculizumab (and ravulizumab) binding at desired epitopes; (2) suboptimal eculizumab dosing leading to recurrent pharmacokinetic breakthrough haemolysis (BTH);[46,47] (3) pharmacodynamic BTH associated with complement activity leading to infections or inflammation;[48] and (4) eculizumab (or C5 inhibitors) causing C3-fragment associated extravascular haemolysis (EVH).[48] BTH occurs in 11–27% of patients receiving eculizumab.[46] Once BTH is confirmed, management options include increasing eculizumab dose (e.g. 1200 mg every 14 days) or shortening infusion intervals (e.g. every 12 days) (Table 3, Statement 5.3.1). Another strategy is switching from eculizumab to ravulizumab, as ravulizumab may prevent BTH by keeping free C5 levels lower than eculizumab.[37,41,49-51] An open-label, randomised, phase III study in eculizumab-treated adult patients with PNH who switched to ravulizumab demonstrated the non-inferiority of ravulizumab to eculizumab in efficacy and safety.[52]

In a US cross-sectional study in patients with PNH on eculizumab (n=35) or ravulizumab (n=87), approximately 85% were anaemic, 80% experienced fatigue and 10–20% had thromboembolic events despite 12 months of C5-inhibitor treatment.[53] Similar results were reported in a recent US-based electronic medical record network study; after 12 months of treatment with C5 inhibitor, 50–82% remained anaemic, 8–32% required ≥1 transfusion and 13–59% had BTH.[54] This highlights an unmet need for newer treatments for PNH with better outcomes. Agents targeting complement C3 (e.g. pegcetacoplan, approved in 2021 by FDA and EMA) are underway. These agents primarily prevent EVH caused by the activation of complement C3.[22] Approval of pegcetacoplan was based on the results of a 16-week, multicentre, randomised, open-label, active comparator-controlled phase III clinical trial, PEGASUS. The results revealed that pegcetacoplan was superior to eculizumab in enhancing haemoglobin levels with an adjusted (least squares) mean difference of 3.84 g/dL (P<0.001) and non-inferior in various clinical and haematologic outcomes.[55] A systematic review of 3 studies showed that pegcetacoplan effectively improves haemoglobin level and decreases transfusion requirements in patients with PNH, including those unresponsive to eculizumab.[56] Over a 48-week treatment period,

pegcetacoplan exhibited superior long-term efficacy and safety compared to eculizumab. There was a statistically significant improvement in adjusted mean haemoglobin level (3.8 g/dL) at week 16 (P<0.001). Moreover, 85% of pegcetacoplan-treated patients were transfusion-free, whereas only 15% of eculizumab-treated patients achieved this outcome.[57] However, during the study period, 7% (3 of 41) pegcetacoplan-treated patients discontinued treatment due to BTH. In other studies, pegcetacoplan showed improved QOL after 26 weeks in complement inhibitionnaïve PNH patients.[58,59] The expert panel recommends the criteria listed in Table 3, Statement 5.3.2, for switching from C5 to C3 anti-complement therapy.

Infection is a major risk with complement inhibitors.[22] Eculizumab increases the risk of life-threatening infections with *Neisseria* spp., including *N. meningitidis*, by blocking terminal complement activation.[2,52] The estimated risk is 0.5% per year or 5% after 10 years of treatment.[2] Therefore, all patients with PNH planned for eculizumab initiation should be vaccinated against *Neisseria* with a quadrivalent vaccine against ACYW135 serotypes and serogroup B (subject to availability) at least 2 weeks before the first dose of eculizumab (Table 3, Statement 5.4).[4-6,10,60]

Appropriate monitoring is important for assessing treatment response and overall disease outcome, and for predicting plausible risks. The expert panel recommends monthly assessments of full blood and reticulocyte count, serum LDH and bilirubin for patients on eculizumab during the initial 3 months, followed by 3-monthly intervals[4,5,7,11] (Table 4, Statement 5.5). Reassessing the benefits of eculizumab every 6 months, based on the patient's clinical progress and laboratory results, is advisable. Treatment discontinuation may be considered in non-adherent patients after a comprehensive assessment and weighing the pros and cons[7] (Table 3, Statement 5.6).

Allogenic stem cell transplantation

Allogenic stem cell transplantation (SCT) still remains the only curative treatment for PNH; however, it is associated with significant morbidity and mortality. The most extensive study on SCT in PNH was conducted at French centres between 1978 and 2007. Out of the 211 patients with PNH, 62% underwent transplantation for BMF, 70% for haemolysis and 25% for thromboembolism.[61] At 5 years, 40% experienced Grades 2–4 acute graft-versus-host disease (GvHD), and 29% had chronic GvHD. Overall survival (OS) was 68%, with varying rates based on indication: highest for haemolysis (86%), followed by BMF (69%) and thromboembolism (54%).[61]

The morbidity and mortality outcomes associated with SCT have improved considerably in the post-eculizumab era. A retrospective analysis of 78 patients with PNH (27 and 51 patients with type I and type II PNH, respectively) transplanted between 2002 and 2016 in 11 centres of the Polish Adult Leukemia Group showed a 3-year OS of 87% in the total cohort and 92% in the group of patients without thrombosis.[62,63] While the survival of PNH patients with SCT has improved over time, long-term post-transplant complications such as GvHD will likely result in less favourable QOL compared to eculizumab.[64] Hence, SCT is not recommended as an initial therapy and should be limited to selected young patients with PNH/AA or PNH/MDS (Supplementary Fig. S2, Statement 5.8).[65]

Anticoagulation therapy

In patients with a large PNH clone who are not receiving complement inhibitors (eculizumab), primary prophylaxis with anticoagulant therapy should be considered to reduce the risk of thrombosis, if there is no contraindication such as thrombocytopenia or bleeding risk.[6,22] These patients remain at a high risk of thrombotic events and death, despite anticoagulation treatment,[66] underscoring the need to initiate eculizumab in this population. On the other hand, primary prophylaxis may be discontinued once complement inhibitors are initiated, as it may offer little benefit and increase the risk of bleeding complication[22] (Supplementary Fig. S2, Statement 5.7).

In PNH patients with a history of thromboembolic events who have been initiated on complement inhibitors, long-term anticoagulation (with coumarin derivatives and heparin) is recommended by several guidelines.[4,66] The decision to stop anticoagulation in these patients has to be individualised. Emerging evidence and expert opinion suggest that anticoagulation for 3–6 months is sufficient in PNH patients who are well-controlled on complement inhibitors.[67,68] Extended duration (lifetime) anticoagulation can be considered in patients with additional provoking risk factors for thrombosis and those with a history of life-threatening thrombotic events.

Supportive therapy

Supportive therapy plays an important role in treating the symptoms and complications of PNH.[1,6,7,10] Folic acid, vitamin B12 and packed RBC transfusions are provided in the presence of symptomatic anaemia and haemoglobinuria. Oral or parenteral iron supplementation is initiated to prevent and control iron deficiency from haemoglobinuria and haemosiderinuria. Short-term steroids may be considered in haemolytic episodes;

long-term treatment is not recommended. Analgesia can be considered for smooth muscle dystonia.

PNH in the setting of BMF

The expert panel recommends that patients with small PNH clones in the context of BMF syndromes may be assessed every 6–12 months (Table 5, Statement 6.1). The beneficial effects of eculizumab treatment in patients with PNH/AA or PNH/MDS without haemolysis or thrombosis have not been well established.[69] However, patients with AA or MDS and a high percentage of PNH cells may benefit from the use of C5 inhibitors. In individuals with predominant BMF, immunosuppressive therapy and/or SCT should be considered (Table 5, Statement 6.2).[6]

PNH in pregnancy

There is a high risk of thrombosis during pregnancy, thus increasing maternal-fetal morbidity and mortality. Studies have suggested that the maternal mortality rate during pregnancy and shortly after childbirth is estimated to be 12–21% in patients with PNH.[70,71] Additionally, there is a high risk of experiencing miscarriages or premature births. No RCTs have been conducted to evaluate the use of eculizumab or ravulizumab in pregnant females. Based on the findings from observational studies, the panel recommends that pregnant women with PNH may be treated with eculizumab to prevent the risk of thromboembolic complications. Eculizumab is reported to be safe in pregnancy, with no untoward effects on the mother and the child (Table 5, Statement 7.1).[70] Pregnant women should be monitored frequently, as there may be a need for higher doses of eculizumab to mitigate haemolysis and minimise the risk of thrombotic events (Table 5, Statement 7.3). An analysis of 75 pregnancies involving 61 women with PNH showed that eculizumab reduced the rate of maternal complications and improved the rate of fetal survival.[70] The recommendation in Statement 7.2 (Table 5) on prophylactic or therapeutic anticoagulation in pregnant women with PNH is in line with the existing guidelines.[4-7] As the risk of thrombosis is usually high in most cases for at least 6 weeks post-partum, anticoagulants can be extended at the clinician's discretion on a case-to-case basis.[4,70]

Novel treatment options for PNH

Several novel anti-complement agents for PNH are in various stages of clinical development, including crovalimab (phase III studies are underway), tesidolumab (LFG316), pozelimab, zilucoplan and cemdisiran.

Crovalimab, a sequential, highly soluble, monoclonal antibody recycling technology (SMART) antibody

Table 5. Management of PNH in special populations (Statements 6 and 7).

In the setting of BMF		**Level of evidence**
Statement 6.1	Patients with small PNH clones in the context of bone marrow failure syndromes may be assessed every 6–12 months with flow cytometry for expansion or evolution of PNH clones, especially when there is evidence of haemolysis.	2
Statement 6.2	The use of immunosuppressants or allogeneic haematopoietic stem cell transplantation may be considered in patients with PNH (non-pregnant) and associated bone marrow disorders such as AA or high-risk MDS, based on the risk/benefit profiles of the treatments. The underlying bone marrow failure may be treated as per the respective treatment (AA/MDS) guidelines. Additional supportive therapy may be based on the corresponding recommendations for classic PNH.	2
In pregnancy		
Statement 7.1	Eculizumab treatment may be continued in pregnant women with PNH, especially those with associated risk factors for thrombosis. The dose of eculizumab may be increased in the third trimester or in case of breakthrough haemolysis, on an individual case-to-case basis. Treatment with eculizumab may be continued for up to at least 6 weeks postpartum.[a]	2
Statement 7.2	In pregnant women with PNH with associated risk factors for thrombosis and no known contraindication to anticoagulants, prophylactic or therapeutic anticoagulation (with low molecular weight heparin) may be initiated and continued for up to at least 6 weeks postpartum.[b]	2
Statement 7.3	The frequency of monitoring may be increased in PNH patients who are pregnant after detailed assessment on a case-to-case basis, regardless of the ongoing treatment.	5

AA: aplastic anaemia; MDS: myelodysplastic syndrome; PNH: paroxysmal nocturnal haemoglobinuria
[a] Further continuation of eculizumab may be at the clinician's discretion on a case-to-case basis
[b] Duration of thromboprophylaxis postpartum may be extended at the clinician's discretion on a case-to-case basis

is administered subcutaneously every 4 weeks and can be self-administered. It may be a treatment option for patients with rare C5 mutations not benefitting from eculizumab or ravulizumab treatment.[72] Three large phase III studies in patients previously treated with eculizumab (COMMODORE 1; ClinicalTrials.gov identifier: NCT04432584) and patients naive to standard complement inhibitors (COMMODORE 2; NCT04434092 and COMMODORE 3; NCT04654468) are ongoing to confirm its efficacy and safety.[22,73] Preliminary results showed thatcrovalimab is non-inferior to eculizumab for the control of haemolysis and transfusion avoidance, with a well-tolerated safety profile.

Building on the success of pegcetacoplan, a variety of proximal inhibitors have emerged. Notably, several of these inhibitors have reached advanced stages of development for treating PNH. Recently, oral iptacopan (inhibitor of factor B) was approved as a breakthrough therapy for PNH based on the positive phase II data.[72] In phase II trials with iptacopan, 10 clinical BTH events were reported; all were mild or moderate except 1 severe event.[74] Other oral C3 inhibitors under development are danicopan, BCX9930 and vemircopan.[9] The rationale behind combining terminal and proximal inhibitors is to enhance control and effectively prevent both intravascular and extravascular haemolyses. The preliminary results of the ALPHA trial, a phase III double-blind RCT, showed that add-on danicopan versus placebo in patients receiving eculizumab or ravulizumab significantly improved haematological responses by addressing EVH while maintaining control of IVH.[75] These emerging therapies will expand the PNH therapeutic armamentarium and help improve the quality of life of patients with PNH.

Access to emerging treatments for PNH in Singapore

Currently, eculizumab is the only complement inhibitor approved by the Health Sciences Authority for the treatment of patients with PNH in Singapore. However, limited access to treatment poses a significant barrier to optimising the management of PNH. In Singapore, the Rare Disease Fund (RDF), established in 2019, utilises a multi-party funding model (with community-government donation ratio of 1:3) to support drug treatment for rare disease patients. RDF has a limited budget to meet the huge unmet need of innovative rare disease treatments. The process of inclusion of a rare disease drug into the RDF involves evaluation of proposals based on predefined criteria by the Rare Disease Expert Group and Rare Disease Fund Committee, with technical support from the Agency for Care Effectiveness (ACE).

The second option to improve accessibility of eculizumab for patients with PNH is to enlist in the cancer drug list (CDL). Until September 2022, all cancer drug treatments were fully covered by MediShield Life (MSL) up to SGD3000/month with additional support from Integrated Shield Plans (IP) and the Medication Assistance Fund (MAF). From September 1, 2022, only treatments listed on the CDL receive MSL coverage. Furthermore, IP insurers have aligned outpatient cancer coverage plans according to CDL from April 2023, with non-CDL drugs being non-claimable under IPs. In addition to these challenges, ACE/healthcare practitioner-led submission of application for enlisting drugs into the CDL usually takes 12–18 months, while company-led submission requires about 12 months.

The coverage of eculizumab treatment cost under the RDF and/or enlisting of eculizumab into the CDL will help improve its access and allow early intervention and improved treatment outcomes for patients with PNH in Singapore.

CONCLUSION

The 16 statements on the screening, diagnosis, treatment and monitoring of PNH presented in this consensus paper have been drafted based on a comprehensive review of the literature and real-world clinical practice sharing by PNH experts in Singapore. Based on the best available evidence, we have outlined the current guidance on the diagnosis and management of PNH in Singapore. Nevertheless, it may be warranted to refine the recommendations in the future as more evidence evolves.

Supplementary Materials

Fig. S1. *Literature search and article screening strategy.*

Fig. S2. *Multidisciplinary management of classic PNH (Statements 5.1–5.8).*

Table S1. *Oxford Centre for Evidence-Based Medicine 2011 levels of evidence.*

Table S2. *Bibliography for additional reading.*

Table S3. *Central themes for the consensus recommendations and summary of agreement ratings from the 2 rounds of Delphi voting.*

Conflict of interest

YTG received consultancy fees for participating in scientific advisory board meetings from AbbVie, Amgen, Antengene Corp, Astellas, AstraZeneca,

DKSH, GlaxoSmithKline, Janssen, Novartis, Pfizer, Recordati, Roche and Sanofi.

ESY, CWT, DT, YSL, LLC, ZYL and HT declare no conflict of interest.

YSML participated in scientific advisory board meetings conducted by Astellas, Amgen, AbbVie, AstraZeneca, GSK, Janssen, Kite/Gilead, MSD, Novartis, Pfizer, Sanofi and DKSH.

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LETTER TO THE EDITOR

A consensus survey of neurologists and clinical geneticists on spinal muscular atrophy treatment in Singapore

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Dear Editor,

Just a decade ago, spinal muscular atrophy (SMA) was considered a debilitating, progressive neuromuscular disease that inevitably led to chronic disability and a shortened lifespan. Now, it is treatable with nusinersen, onasemnogene abeparvovec (OAV) and risdiplam—the 3 disease-modifying drugs approved by the US Food and Drug Administration, the European Medicines Agency and most recently, the Health Science Authority in Singapore.[1] Clinical trials and real-world data have consistently shown improvement in motor milestones for all 3 drugs, especially if introduced early in the disease course.[2-4] More significantly, presymptomatic treatment has enabled age-appropriate development of motor milestones, leading to improved respiratory, orthopaedic and nutritional outcomes.[5-8]

However, there remains a multitude of challenges facing SMA patients in Singapore, in particular, the equitable access to these hyper-expensive therapies. OAV carries a hefty price tag of SGD 2.4 million (approx. USD 1.7 million), nusinersen costs approximately SGD 330,000 per year (after the initial SGD 660,000 for the first 4 loading doses) and risdiplam costs up to SGD 375,000 per year. None of these drugs are yet eligible for governmental subsidies under existing healthcare financing models, and patients have to rely on either private philanthropic donations or public crowdfunding to raise sufficient funds for treatment.

To identify a consensus for SMA treatment in Singapore, we surveyed 14 clinicians comprising 6 paediatric and 4 adult neurologists, and 4 paediatric clinical geneticists, all who directly care for SMA patients (Table 1). These are the key takeaways:

(1) The most important determinants for treating symptomatic patients were type of SMA or *SMN2* gene copy number, disease stage, ventilatory requirement, family support and compliance to multidisciplinary care.

(2) A total of 72% of respondents supported treatment over best supportive care in patients under 2 years of age with 2 or 3 *SMN2* copy numbers, with all 10 respondents preferring OAV to *SMN2* gene modifiers. Additionally, 72% also supported treatment for patients older than 2 years with 2 to 3 *SMN2* copies if they were not ventilated. Support for those with 4 or more *SMN2* copy number was more equivocal, with a slightly higher preference to treat if they were ambulant.

(3) A total of 93% of respondents supported presymptomatic treatment, with 77% choosing OAV as first choice. All supported newborn screening, with the vast majority electing to treat patients with up to 3 *SMN2* copies (>85%). Only 21% would consider treating 4 *SMN2* copy number patients.

(4) Respondents were willing to consider combination therapy if there was potential to wean off ventilatory support, ambulate independently, feed orally or delay scoliosis surgery.

The nuanced responses indicate a cognisance that systemic implementation of this new standard of care is being hindered by the lack of a strategic funding framework at present in Singapore. As such, a stricter criterion that limits use to those assessed to potentially yield the greatest benefit may be necessary to balance the competing needs of the wider collective. Yet these benchmarks may be hard to define fairly.[9]

Expert consensus currently prioritises early OAV treatment for presymptomatic and symptomatic patients with 2 to 3 *SMN2* copy number below 2 years of age as these patients are deemed to benefit the most from treatment. Support for disease-modifying treatment such as nusinersen or risdiplam in those above 2 years with 2 to 3 *SMN2* copy number only without ventilator dependence also underpins this pragmatism. Patients with milder disease (4 *SMN2* copy number) may need to be individually considered based on the magnitude

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Table 1. Consensus survey on spinal muscular atrophy (SMA) treatment in Singapore (March to April 2023).

Regarding symptomatic treatment[a]	**Agree, no. of votes (%)**
Factors influencing decision to start treatment	
Type of SMA/*SMN2* copy number	14 (100)
Requirement for ventilatory support	13 (92.9)
Stage of disease	13 (92.9)
Family support	11 (78.6)
Compliance to multidisciplinary care	11 (78.6)
Requirement for assisted feeding	8 (57.1)
Financial status	8 (57.1)
Comorbidities, e.g. scoliosis	8 (57.1)
Factors influencing decision to exclude from treatment	
Previous hypoxic-ischaemic injury/cognitive impairment	11 (78.6)
Poor family compliance	10 (71.4)
Permanent ventilation/tracheostomy dependence	8 (57.1)
Cardiomyopathy	6 (42.9)
Chronic diseases	6 (42.9)
Psychiatric illness	5 (35.7)
Liver dysfunction	3 (21.4)
Swallowing dysfunction requiring feeding tube >1 month	1 (7.1)
Scoliosis	1 (7.1)
Factors influencing decision to stop treatment	
Poor compliance	13 (92.9)
Unacceptable side effects of drugs	12 (85.7)
Progression to ventilatory support	11 (78.6)
Persistent decline in motor function scores (>10% drop across 3 visits)	8 (57.1)
Increase in ventilatory support for >3 months	6 (42.9)
Progression to NGT feeding/gastrostomy	5 (35.7)
Frequent respiratory infections requiring hospitalisations ≥3x/year	4 (28.6)
No improvements in motor function scores	4 (28.6)
Loss of patient-reported functional skills	4 (28.6)
Progressive scoliosis (Cobbs angle >40°)	2 (14.3)
Clinical worsening of swallowing function	1 (7.1)
Drop in weight across ≥2 centiles	1 (7.1)
Reasonable minimum treatment period for efficacy assessment	
6 months	2 (14.3)
9 months	1 (7.1)
12 months	10 (71.4)
2 years	1 (7.1)
Regarding presymptomatic treatment	**Agree, no. of votes (%)**
I support presymptomatic treatment over best supportive care	13 (92.9)
First-line treatment	
Nusinersen	1 (7.1)
OAV	10 (71.4)
Risdiplam	2 (14.3)
I support newborn screening	14 (100)
Opt-out	8 (57.1)
Opt-in	6 (42.9)
I support treatment for these patients:	
1 *SMN2* copies	12 (85.7)
2 *SMN2* copies	14 (100)
3 *SMN2* copies	13 (92.9)
4 *SMN2* copies	3 (21.4)
>4 *SMN2* copies	1 (7.1)
Funding should be prioritised for:	
Carrier screening	3 (21.4)
Preconception screening	1 (7.1)
Newborn screening	10 (71.4)

NGT: nasogastric tube; OAV: onasemnogene abeparvovec

[a] Case scenarios to investigate treatment threshold in separate unpublished appendix (available upon reasonable request from the corresponding author).

and urgency of the individual's clinical need. Consideration for add-on therapy to patients previously treated with OAV may warrant clear, objective improvements given the absence of adequate data justifying the additional cost.

Several studies have sought to determine the cost-effectiveness of drugs by calculating the cost of treatment relative to the benefit of supportive care, known as the incremental cost-effectiveness ratio (ICER). These benefits are mostly quantified by health-related quality-of-life (QoL) indices known as quality-adjusted life-years (QALYs). However, QALYs may neither fully capture all treatment benefits nor take into account the QoL of caregivers, especially in the areas of caregiver fatigue and mental health.[10] Some studies have demonstrated an unsustainably high ICER for all 3 drugs, but when applied to presymptomatic treatment versus later symptomatic treatment, there was significant cost savings and improved health outcomes, with particular sensitivity to treatment strategy (gene therapy over *SMN2* modifiers) and disease severity (treating those with 3 or more *SMN2* copy number).[11-13] This provides a strong argument for nationwide implementation of newborn screening to maximise cost-effectiveness, although the threshold of treatment will still need to be addressed. A total of 28.5% of the respondents also prioritised preconception/carrier screening over newborn screening, reflecting differing views on the efficacy of disease prevention and management in the population in the light of high treatment costs.

In the absence of presymptomatic testing and treatment, it is imperative to understand that while symptomatic treatment provides a means of modifying a previously debilitating condition to one that achieves an acceptable level of functional independence, it is not curative. Differences in outcomes primarily depend on disease severity and timing of therapy. Even as we acknowledge tangible benefits in treated patients, families need to be made aware of disease complications and availability of palliative options. This requires a continuing process of clear communication and value exploration between healthcare professionals and families to define their shared goals of care and manage expectations.

However, it is difficult to quantify the value of life and life experiences, with physicians, policymakers and insurance payers likely having differing perspectives from patients and their families. In a qualitative study of 123 adult SMA patients and their physicians, definitions of meaningful change were highly variable between patients, and was relative to their current functional ability rather than a simple increase in motor scores.[14] Extending the lifespan of a patient with SMA Type 1 may add many years of treasured experiences, even if patients remain on ventilatory support. Reducing hospital admissions or prolonging distal hand function in patients with SMA Type 2 enables them to continue working, which gives meaning to their lives. Preventing wheelchair-dependence in patients with SMA Type 3 prolongs functional independence. It may be difficult for society to articulate the value of some of these aspirations over others.

Ultimately, decision-making needs to be collaborative between physicians, caregivers and patients based on evidence-based knowledge of their condition, and the changing risks and benefits of treatment. In our survey, poor compliance, unacceptable adverse effects from disease-modifying drugs, progression to ventilator dependence and persistent decline in motor function were the top considerations for treatment withdrawal. Physicians will need to individualise treatment strategies considering each patient's disease type, family resources and personal beliefs.

SMA is presently one of the rare genetic diseases that has viable life-changing treatments. There is clear support among experts in Singapore for these therapies but until a structured funding framework is developed, access will likely be inequitable and limited only to those who have the resources and the wherewithal to engage in public fundraising. This consensus survey will go some way in standardising treatment decisions for the patients most in need, but there remains an urgent need for a systemic funding framework to be introduced to facilitate timely treatment in this devastating disease. Difficult ethical considerations may also require oversight from an independent core committee.

Given the ongoing advances in genetic therapies, SMA is the first of many other treatable genetic disorders, which will incur enormous financial cost to patients and society. As a disease entity, it forms the ideal model for discussion of treatment and early diagnosis as the genetics are homogeneous with predictable and measurable disease types and severity. Not all diseases and their treatments will be as clearly defined, especially if there are alternative therapies available. The differing durability of treatment effect will also be a major concern. Against this backdrop, decisions about which disease and which patient to treat will need to be considered in light of the lessons learned from treating SMA.

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Ethics approval

The National Healthcare Group Domain Specific Review Board deemed that ethics review was not required.

Conflict of interest

The authors declare that there is no conflict of interest.

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Data availability statement

Data are available upon reasonable request from the corresponding author.

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LETTER TO THE EDITOR

Predictors of complicated influenza infection in children presenting in a tertiary hospital in a tropical country: A case-control study

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Dear Editor,

Influenza causes significant healthcare burden globally[1] with highest risks in children and the elderly. In children, multiple studies have identified risk factors for severe influenza such as young age (<5 years), presence of comorbidities, abnormal vital signs (e.g. hypoxia, shock) and bacterial coinfections.[2-4] We found similar findings in our centre which included children during the influenza A (H1N1) 2009 pandemic with age <2 years and comorbidity as risk factors for complicated influenza.[5]

We conducted a retrospective case-control study of hospitalised paediatric patients (<17 years old) with laboratory-confirmed (respiratory immunofluorescence antigen testing or multiplex polymerase chain reaction [PCR] testing) influenza infection admitted to our hospital over 7 years between January 2011 and October 2017. Cases were defined as severe influenza requiring intensive care unit (ICU) or high-dependency (HD) care anytime during their hospitalisation. Three unmatched controls were selected per case; controls were admitted into the general ward with laboratory-confirmed influenza infection within 3 days of the admission of their corresponding cases.

Our primary outcome was to compare the risk factors that predispose children to severe complicated course requiring ICU/HD care. Our secondary outcome was to study the risk factors associated with mortality.

This study was approved by the SingHealth Centralised Institutional Review Board (CIRB number: 2015/2453) for a waiver of consent.

A total of 209 patients (55 cases, 154 controls) were included in this study, with a median age of 2.9 years (interquartile range [IQR] 0.9–5.8 years); there were 17 deaths reported (8.1%). Only 33 of the patients (15.8%) had 1 underlying comorbidity, and 9 patients (4.3%) had ≥2 comorbidities. Influenza A (n=161, 77.0%) was more common than Influenza B. There was no difference between Influenza A and Influenza B when comparing for HD/ICU admission or mortality risks. Concurrent viral infections occurred in 6.2 % (n=13) of patients, most commonly adenovirus (n=5, 38.5%) infection. Proven bacterial infections—either from positive mycoplasma PCR, respiratory cultures from endotracheal tube if intubated or from positive blood cultures—were found only in a minority of patients (n=20, 23.0%). There was no statistical difference for bacterial coinfection rates between cases or controls.

Mortality occurred in 8.1% (n=17) of patients. Among them, all required inotropic support; 52.9% (n=9) required intubation; 29.4% (n=5) required extra-corporeal membrane oxygenation, or ECMO support; and 11.8% (n=2) needed dialysis. A high proportion (n=7, 41.2%) had underlying comorbidities with neurological conditions being the most prevalent (n=4, 23.5%).

By univariate analysis (Table 1), risk factors for HD/ICU admission or mortality were drowsiness (odds ratio [OR] 5.81, $P<0.001$; OR 10.49, $P<0.001$, respectively), any comorbidities (OR 4.46, $P<0.001$; OR 3.14, $P=0.02$, respectively) and viral coinfections (OR 7.34, $P=0.001$; OR 6.26, $P=0.002$, respectively). Additional risk factors for HD/ICU admission were age >5 years old (OR 2.17, $P=0.02$), presence of seizure (OR 3.00, $P=0.01$) or tachypnoea (OR 6.86, $P<0.001$). By multivariate logistic regression analysis, risk factors for HD/ICU admission were tachypnoea (multivariate OR 9.27, $P<0.001$), viral coinfections (multivariate OR 10.42, $P=0.002$), seizure (multivariate OR 7.42, $P<0.001$), comorbidity (multivariate

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Table 1. Univariate comparison of cases admitted to ICU/HD versus controls admitted to general ward and univariate comparison of mortality cases versus survivors of paediatric Influenza infection.

Clinical characteristics	ICU/HD admissions/ cases (n=55) (%)	GW admissions/ controls (n=154) (%)	Univariate analysis	Univariate analysis	Mortality (n=17) (%)	Survivors (n=192) (%)	Univariate analysis	Univariate analysis
			Odds ratio	*P* value			Odds ratio	*P* value
Age, median (years)	4.5 (IQR 1.83–7.9)	2.6 (IQR 0.8–4.95)		0.02	4.3 (IQR 2.29–4.33)	2.8 (IQR 0.83–5.80)		0.2
Age category								
0–5 years	32 (58.2)	116 (75.3)			11 (64.7)	137 (71.4)		
>5 years	23 (41.8)	38 (24.7)	2.17 (1.15–4.17)	0.02	6 (35.3)	55 (28.6)		0.56
Race								
Chinese	33 (60.0)	86 (55.8)		0.6	12 (70.6)	107 (55.7)		0.54
Malay	12 (21.8)	44 (28.6)			4 (23.5)	52 (27.1)		
Indian	5 (9.1)	16 (10.4)			1 (5.9)	20 (10.4)		
Others	5 (9.1)	8 (5.2)			0 (0.0)	13 (6.8)		
Influenza type								
Influenza A	43 (78.2)	118 (76.6)		0.81	12 (70.6)	149 (77.6)		0.51
Influenza B	12 (21.8)	36 (23.4)			5 (29.4)	43 (22.4)		
Presenting symptoms								
Fever	51 (92.7)	145 (94.2)		0.71	16 (94.1)	180 (93.8)		0.95
Cough	33 (60.0)	121 (78.6)	0.41 (0.251–0.79)	0.007	12 (70.6)	142 (74.0)		0.76
Poor feeding	23 (41.8)	55 (35.7)		0.42	7 (41.1)	71 (37.3)		0.73
Rhinorrhoea	22 (40.0)	112 (72.7)	0.25 (0.13–0.48)	<0.001	8 (47.1)	126 (65.6)		0.13
Sore throat	3 (5.5)	6 (3.9)		0.63	1 (5.9)	8 (4.2)		0.91

Table 1. Univariate comparison of cases admitted to ICU/HD versus controls admitted to general ward and univariate comparison of mortality cases versus survivors of paediatric Influenza infection. (Cont'd)

Clinical characteristics	ICU/HD admissions/ cases (n=55) (%)	GW admissions/ controls (n=154) (%)	Univariate analysis	Univariate analysis	Mortality (n=17) (%)	Survivors (n=192) (%)	Univariate analysis	Univariate analysis
			Odds ratio	*P* value			Odds ratio	*P* value
Any tachypnoea	19 (34.5)	11 (7.1)	6.86 (3.0–15.7)	<0.001	5 (29.4)	25 (13)		0.07
Vomiting	16 (29.1)	45 (29.2)		0.99	7 (41.2)	66 (34.4)		0.57
Diarrhoea	9 (16.4)	21 (13.6)		0.62	3 (17.6)	27 (14.1)		0.69
Any seizure	22 (40.0)	28 (18.2)	3.00 (1.52–5.90)	0.01	7 (41.2)	43 (22.4)		0.08
Drowsiness	23 (41.8)	0 (0.0)	5.81 (4.24–7.97)	<0.001	8 (47.1)	15 (7.8)	10.49 (3.53–31.15)	<0.001
Any significant comorbidities	22 (40.0)	20 (13)	4.46 (2.18–9.17)		7 (41.2)	35 (18.2)	3.14 (1.12–8.85)	0.02
No high risk comorbidity	33 (60.0)	134 (87.0)			10 (58.8)	157 (81.8)		
1 high risk comorbidity	17 (30.9)	16 (10.4)			4 (23.5)	29 (15.1)		
≥2 high risk comorbidity	5 (9.1)	4 (2.6)			3 (17.6)	6 (0.03)		
High risk factors								
Respiratory	6 (10.9)	9 (5.8)		0.21	1 (5.9)	14 (7.3)		0.83
Neurology	10 (18.2)	6 (3.9)	5.48 (1.88–15.91)	<0.001	4 (2.4)	12 (6.3)	4.62 (1.30–16.33)	0.01
Cardiac	4 (7.3)	1 (0.6)	12.00 (1.21–109.84)	0.006	2 (11.8)	3 (1.6)	8.40 (1.30–54.22)	0.01
Immunology	3 (5.5)	1 (0.6)	8.83 (0.898–86.73)	0.03	2 (11.8)	2 (1.0)	12.67 (1.67–96.37)	0.002

Table 1. Univariate comparison of cases admitted to ICU/HD versus controls admitted to general ward and univariate comparison of mortality cases versus survivors of paediatric Influenza infection. (Cont'd)

Clinical characteristics	ICU/HD admissions/ cases (n=55) (%)	GW admissions/ controls (n=154) (%)	Univariate analysis	Univariate analysis	Mortality (n=17) (%)	Survivors (n=192) (%)	Univariate analysis	Univariate analysis
			Odds ratio	*P* value			Odds ratio	*P* value
Abnormal chest radiograph	19 (34.5)	6 (3.9)	13.02 (4.85–34.95)	<0.001	8 (47.1)	17 (8.9)	9.15 (3.12–26.80)	<0.001
Normal chest radiograph	36 (65.5)	148 (96.1)			9 (52.9)	175 (91.1)		
Median duration of stay (days)	12 (IQR 6–31)	2 (IQR 2–3)		<0.001	11 (IQR 4.5–31.0)	3 (IQR 2–5)		0.001
Use of oseltamivir								
Yes	41 (74.5)	7 (4.5)	61.5 (23.29–162.41)	<0.001	14 (82.4)	34 (17.7)	21.69 (5.91–79.64)	<0.001
No	14 (25.5)	147 (95.5)			3 (17.6)	158 (82.3)		
Concurrent viral infections								
Present	9 (16.4)	4 (2.6)	7.34 (2.16–24.93)	0.001	4 (23.5)	9 (4.7)	6.26 (1.70–23.10)	0.002
Absent	46 (83.6)	150 (97.4)			13 (76.5)	183 (95.3)		
Bacterial cultures*	49 (89.1)	38 (24.7)			17 (100.0)	70 (36.5)		
Negative	35 (71.4)	32 (84.2)		0.16	11 (64.7)	56 (80.0)		0.18
Positive	14 (28.6)	6 (15.8)			6 (35.3)	14 (20.0)		

GW: general ward; HD: HD: high dependency; ICU: intensive care unit; IQR: interquartile range
* Bacterial coinfections include *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Mycoplasma pneumoniae, Escherichia coli, Moraxella catarrhalis, Enterobacter cloacae, Klebsiella pneumoniae, Citrobacter koseri, Pseudomonas aeruginosa.*

OR 3.86, *P*=0.002) and age >5 years (multivariate OR 3.34, *P*=0.005). Multivariate logistic regression analysis for mortality showed drowsiness (multivariate OR 7.97, *P*<0.001) and abnormal chest radiograph (multivariate OR 6.88, *P*=0.001) as risk factors.

Our study showed that children >5 years had a higher risk of severe influenza complications (OR 3.34) resulting in ICU/HD admissions. This is unlike previous studies[6,7] which showed that the highest rate of complications was more common in children ≤5 years of age. A previous study conducted by our hospital's emergency department (ED) could explain this phenomenon.[8] The study showed that the patient's age was inversely proportional to the reattendance rate in ED. Interestingly, older paediatric patients were more likely to be admitted on their reattendance compared to younger patients. Extrapolating from this paper, we could infer that older patients are admitted when they have significant clinical progression or deterioration; and thus, the risk factors of severe influenza and its complications are more likely to be seen in hospitalised children who are older. In younger children, most are admitted earlier during the infection as parents tend to be more anxious regarding their symptoms, and this is reflected in our study with younger age groups having lower risk for severe influenza infection.

There may be residual confounders in our current study such as influenza vaccination status, which we would need to explore in future studies. Important risk factors for HD/ICU admission and influenza mortality were symptoms suggestive of neurological involvement, such as seizures and drowsiness. The presence of drowsiness was a significant risk factor for mortality (OR 7.97, *P*<0.001) with acute encephalitis as the commonest complication (n=9, 52.9%) among mortality cases in our study. This is consistent with previous studies showing higher mortality once the patient develops neurological complications.[2,6,9]

Interestingly, viral coinfections were seen in a small minority (6.2 %) of patients, but was the greatest risk factor for HD/ICU admission (OR 10.42, *P*=0.002) similar to previous studies.[2,10] Surprisingly, our study did not demonstrate a bacterial coinfection as a risk factor for complications or mortality. This is likely attributed to the small proportion with proven bacterial infection (n=20, 9.6%) and the empiric use of antibiotics in a large proportion of patients (n=92, 44.0%).

Similar to previous studies,[11,12] this study showed an increased risk (HD/ICU admission OR 12.00, *P*=0.006, mortality OR 8.40, *P*=0.01) in patients with cardiac conditions; immunodeficiency (HD/ICU admissions OR 8.83, *P*=0.03, mortality OR 12.67, *P*=0.002); and neurological conditions (HD/ICU admission OR 5.48, *P*=0.001, mortality OR 4.62, *P*=0.01). This highlights the need for the attending physician to be hypervigilant and preempt any possible deterioration in the clinical status of patients who have influenza infection especially when they have significant comorbidities.

Our study has several limitations including knowledge of patients' influenza vaccination status. Such additional data could help us to ascertain if prior vaccination reduces the risks of complicated influenza or mortality especially in high-risk patients. We also acknowledge that testing strategy has changed during the period of this study from respiratory immunofluorescence (IF) to multiplex PCR. The detection of concomitant viral infections is higher when using multiplex PCR preferentially. Since the attending physician determined the method of testing; we may have under-estimated the presence of viral coinfections in patients whose testing was performed using IF. Another limitation was the inability to study obesity as a risk factor as height measurements were not recorded consistently. Future studies should include obesity as recent papers have highlighted obesity as an emerging risk factor for severe influenza.[4,13]

In conclusion, influenza infection can result in severe complications that may lead to mortality especially in patients with neurological presentation of seizures and drowsiness. For clinical applicability, if there are suggestions of any neurological involvement, the attending physician should escalate care and be vigilant for the progression of symptoms and preempt the possible deterioration of the patient.

Declaration

The authors declare no conflicts of interest.

Keywords: *drowsiness, influenza, morbidity, mortality, paediatric, seizure*

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LETTER TO THE EDITOR

Seroprevalence of cytomegalovirus over the last 2 decades (2001–2020): A retrospective data analysis from a single laboratory in Singapore

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Dear Editor,

Cytomegalovirus (CMV) is ubiquitous and infects human of all ages, where it remains latent after primary infection and can reactivate upon various triggers.[1] Reactivated CMV may cause complications and end organ damages in immunocompromised hosts, leading to increased morbidity and mortality.[2] In addition, the presence of actively replicating CMV during pregnancy can result in congenital sequelae, a leading cause of nongenetic sensorineural hearing loss in children.[3] Despite the potential harm, few women of childbearing age in Singapore are aware of this risk.[4]

Worldwide CMV seroprevalence is estimated at 83%, but could vary between 44–100% in different regions depending on the socioeconomic status of the population.[5,6] With rapid advances in the economy and living standards in Singapore,[7] a decrease in CMV seroprevalence is expected, as observed in countries with high socioeconomic status. However, little is known regarding this trend over the past decades.

To fill this gap, a retrospective data analysis from a single laboratory was performed on Singapore citizens and permanent residents who had CMV Immunoglobulin G (IgG) result between 2001 and 2020 (Supplementary Material). Only the first result from individuals were included in the analysis. The associations of CMV seroprevalence with age, gender, ethnicity and year of test performed were tested by multivariate logistic regression analysis. Age and year of test were modelled as continuous variables and ordinal variables in separate regression analyses. When categorised into ordinal variables, the year of test performed was stratified into 2 time periods of 10-year interv als: Period 1 (2001–2010) and Period 2 (2011–2020), and the age at time of test was categorised into 6 age groups: 2–14, 15–24, 25–34, 34–44, 45–54, and ≥55 years. Ethnicity was grouped into Chinese, Malays, Indians and Others. Categorical variables were compared using Fisher's Exact test and multiple comparisons were corrected using the Benjamini-Hochberg false discovery rate method. All analyses were done with R version 4.2.2 (R Core Team 2023).

Results from a total of 16,985 unique individuals aged 2–101 years were included in the multivariate regression analysis (Supplementary Table S1). While CMV seropositivity increased with age (adjusted odds ratio [AOR], 1.082; 95% confidence interval [CI] 1.078–1.085), seroprevalence decreased significantly over 2 decades from a peak of 87.9% (2002) to 73.7% (2020) (Fig. 1A; AOR, 0.951; 95% CI 0.944–0.959). Women were less likely to be seropositive than men (AOR, 0.880; 95% CI 0.802–0.955); Malays (AOR, 2.646; 95% CI 2.351–2.981), Indians (AOR, 1.592; 95% CI 1.367–1.858) and other ethnic groups (AOR, 1.843; 95% CI 1.553–2.195) had higher seropositivity than Chinese.

A significant interaction in multivariate logistic regression was found between age and year of test performed ($P<0.001$), and to ease further analysis, these variables were categorised as ordinal variables into 6 age groups and 2 time periods respectively (Supplementary Table S1). When stratified by 2 time periods, the seroprevalence was observed to decrease significantly for age groups ≥25 years in Period 2 for both genders (Figs. 1B–C). However, the rates of change in seropositivity were different between sexes. Females reached higher seropositivity at an earlier age group (15–24 years) compared to males, while the largest decline observed for males was in the 25–34 age group but between 35–44 for females (Figs. 1B–1C).

Between the 2 time periods, the seropositivity for Chinese adults ≥25 years decreased significantly. The Malays also experienced a decline in seropositivity across most age groups, with a significant decrease (10%) in the 25–34 age group. Although not statistically significant, the seropositivity for Indians similarly decreased in Period 2. In contrast, other ethnic groups did not show significant changes across the 2 time periods (Supplementary Figs. 1A–D).

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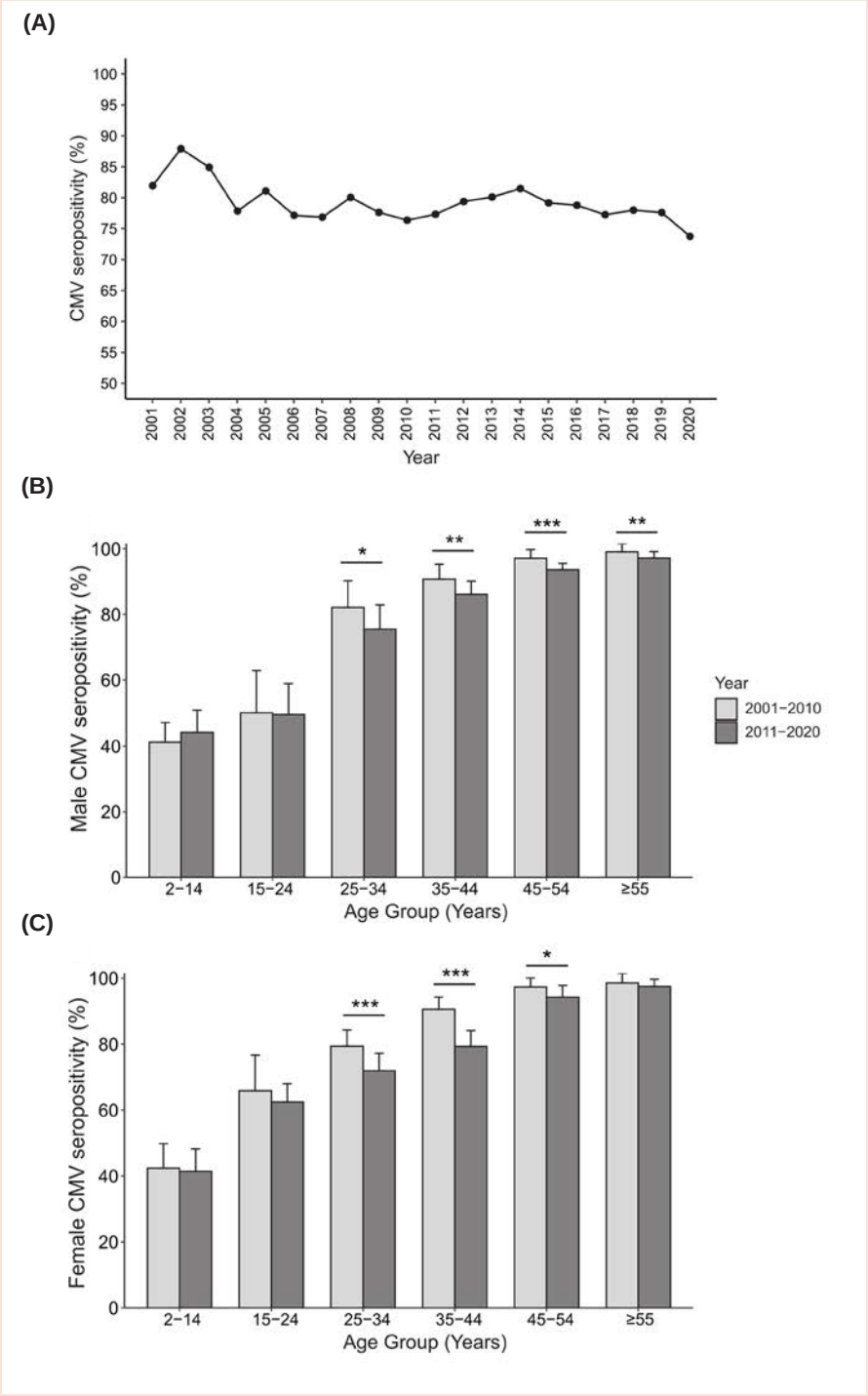
Fig. 1. Changes in cytomegalovirus (CMV) seroprevalence (A) overall trend over 20 years, (B) male and (C) female by age group over the 2 time periods.



*P<0.02, **P<0.01, ***P<0.001. Error bars represent standard deviations (SDs).

To correlate the observed change of CMV seroprevalence trend with the socioeconomic status of residents, we extracted data from the Singapore Census of Population surveys.[8-11] The household median incomes of residents doubled from SGD3638 in 2000 to SGD7744 in 2020. Education levels improved considerably, while the proportion of singles has increased every decade from 2000–2020; in fact, the Chinese had the highest proportion of singles among the ethnic groups. In addition, the average number of children born had decreased for all ethnicities over the past 2 decades. These changes in demographic characteristics and socioeconomic statistics of Singapore residents together with our seroprevalence data are consistent with studies that

demonstrated CMV seroprevalence decreases as countries becomes more developed.[5,6]

The significant decrease in CMV seropositivity in females of childbearing age observed in the recent decade in Singapore translates to an increasing proportion of women who are at risk of primary CMV infection during pregnancy. CMV screening is currently not part of routine antenatal care; coupled with the low awareness in the local context, this means that education on CMV transmission and preventive hygiene behaviours is of utmost importance for expectant mothers.[4]

The risk of CMV disease in organ transplant patients is dependent on the serostatus of the donor and recipient, with the highest risk for complications occurring in seropositive donor (D+)/seronegative recipient (R-). Imlay et al. found a significant increase in the proportion of CMV D+/R- mismatch in solid organ transplants that resulted from a disproportionate increase in R- and a smaller corresponding change in D+ over a period of 20 years.[12] More studies would be needed to determine if the decrease in CMV seropositivity locally may result in a similar increase in the number of high-risk CMV D+/R- mismatch, which may have an impact in risk management for organ transplant patients.

Admittedly, the data from this study originate from clinical samples sent by clinicians for various reasons including clinical investigation or as part of screening protocols prior to certain management, which may result in bias in our data set. Nonetheless, indications for testing have not changed, hence the information presented over the past 2 decades remain comparable.

Although still in development, CMV vaccine has been proposed as a preventive measure in the CMV-naive to prevent primary infection or offer to boost immunity for those already exposed. Our study showed that approximately 42% of the population were already infected with CMV by the age of 15 years; therefore the optimal age for vaccination should be considered at a much earlier age in life for maximum effectiveness. Until an effective vaccine is available, continuous monitoring of changes in seroprevalence is essential to predict the impact of CMV in pregnancies, organ transplant patients and in those who are severely immunosuppressed.

Acknowledgement

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Declaration

The authors declare no conflicts of interest.

Ethics approval

Institutional review board application and informed consent were not required for this study under the SingHealth Institutional rules for research using unidentifiable data.

Data availability

Aggregated data can be shared on reasonable request to the corresponding author, conditional on ethical vetting.

Keywords: *cytomegalovirus, epidemiology, infectious diseases, public health, socioeconomics, statistics*

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LETTER TO THE EDITOR

Tele-ECG collaboration between tertiary and primary care in Singapore: Outcomes and learning over a 6-year period

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Dear Editor,

An electrocardiogram (ECG) is the mainstay of cardiac evaluation available in primary care, after which assessment in relation to clinical symptoms and signs is made by family physicians to assess the patients holistically. Subsequently, based on this clinical evaluation, patients may then be referred for tertiary review at a cardiology department or managed in primary care. In Singapore, ECG abnormalities found in asymptomatic patients may require a specialist review and thus make up a substantial number of patients referred by primary care physicians from public healthcare polyclinics to cardiology outpatient clinics. Some of these patients may be clinically managed in primary care with no further evaluation necessary, yet others may require a non-urgent or expedited review.

Right-siting of care for patients and decreasing referrals would therefore free up valuable limited resources in tertiary hospitals for patients who require more urgent reviews. This would then decrease economic burden both for the patients and public healthcare system. Tan Tock Seng Hospital (TTSH) and Khoo Teck Puat Hospital (KTPH) are acute hospitals currently affiliated with 7 primary care polyclinics within the National Healthcare Group Singapore. The close collaboration between TTSH and KTPH cardiologists and the 7 polyclinics facilitated the launch of a Tele-ECG programme with the objective to provide kerbside ECG consults, to allow quick reviews and management of patients in primary care, thus reducing the number of referrals for ECG abnormalities in asymptomatic patients to tertiary specialist centres.

The project commenced in April 2016. At the initial phase, identified TTSH cardiologists and primary care doctors from 3 polyclinics (Ang Mo Kio, Hougang and Toa Payoh) were included in this collaborative effort. This subsequently expanded to include KTPH cardiology department and the other 4 polyclinics (Yishun, Woodlands, Geylang and Kallang), gradually from November 2018. The designated family physicians involved in this programme served as the link between the cardiologists and their teams in the polyclinics. They were given a list of ECG abnormalities that could be managed in primary care or guided in the need and urgency of referral. ECG findings that were not in the list were collated with patients' summaries from fellow colleagues and discussed with the cardiologists of both hospitals on the same day. The collected data included ECG diagnoses made by the primary care and the outcomes after consulting the cardiologists. There were 3 possible outcomes post kerbside consult: routine referral, expedited direct-access referral (within 2 weeks) to be reviewed by the cardiologists, or no further action needed.

Over the period of April 2016 to December 2022, there were a total of 1808 polyclinic tele-ECG referrals. The mean age of the patients was 58.4 years, where the majority of the patients were aged 60 to 79 years old (54%), male (57%) and of Chinese ethnicity (63%). Of these, a total of 1244 (69%) did not require tertiary care referral and could continue to be managed in primary care, thus saving an average of 15 referrals per month during this period. The breakdown of total referrals made, and average number of referrals saved per year during this period of 81 months is illustrated in Fig. 1A. Here, 564 (31%) patients required further evaluation in the cardiology specialist outpatient clinic. Of these patients, 127 (7%) required expedited review within 2 weeks by cardiologists and 437 (24%) were given routine referral appointments. Common ECG findings that primary care could identify and manage included premature atrial and ventricular complexes, non-specific T-wave inversions and left ventricular hypertrophy. More complex ECGs would be referred and discussed through the tele-ECG collaboration. Up till 31 December 2022, there

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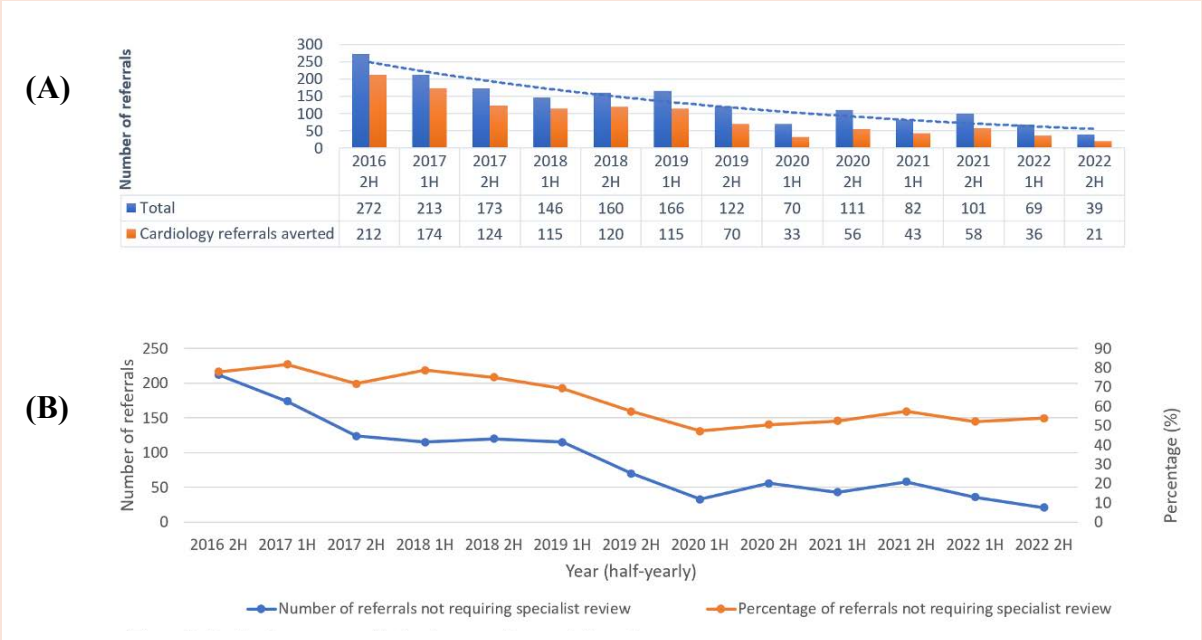
Fig. 1. Total number of referrals made and number of referrals saved (A); decline in percentage of referrals not requiring specialist review (B).



were no known major adverse cardiac events in patients whose ECGs were managed in primary care and were deemed not to require further evaluation.

Tele-ECG support for primary care physicians has, in previous studies, conclusively demonstrated the effectiveness, safety and promptness to patients receiving appropriate therapy in the setting of acute coronary syndromes.[1-3] Data for tele-ECG support in the non-urgent setting remain scarce. Challenges remain in these settings when primary care physicians must decide whether the patient whose ECG is reviewed, can be safely managed in primary care, or requires a referral to tertiary care expediently or non-urgently. In cases of ECG interpretation uncertainty or that of unclear clinical significance, the primary care physicians may choose to refer these patients to tertiary care for a cardiology opinion. This economic burden can be reduced through appropriate right-siting and prompt cardiology inputs through tele-ECG, by enabling majority of such referrals to be safely managed in the community. Therefore, we embarked on this tele-ECG initiative between the primary care physicians and the cardiologists within the National Healthcare Group in Singapore.

The results of this initiative where cardiologists provide kerbside consultations and interpretation over 81 months, showed that only approximately a third of these patients require further evaluation in specialist outpatient clinics. After accounting for the cost of implementing the tele-ECG intervention and the referrals avoided during this period, a system-level cost savings of over SGD300,000 was achieved, of which almost SGD50,000 were accrued to patients from the reduction in specialist outpatient clinic charges.

Over time, there was also a notable decline in cases requiring kerbside consult with the cardiologists as the family physicians' skills in ECG interpretation were enriched in the process as shown in Fig. 1B. There was also continuous education led by the designated family physicians to the polyclinics culminating in confidence in ECG interpretation. Only more complex ECGs were discussed via tele-ECG as the programme gradually matured. Additionally, our tele-ECG collaboration also demonstrated safety and efficacy.

Such collaborations are essential in the right-siting of patients and to ensure those who required expedited cardiologist assessment were seen in a timely manner. These efforts help to save time and cost for patients and also provide strong clinical collaborations between primary and tertiary care to ensure that resources and care are allocated appropriately.

Our tele-ECG initiative is a viable and sustainable collaboration between tertiary and primary care providers. Its successful implementation reduced referrals with more efficacious use of clinical resources in a safe and effective manner.

Acknowledgement

We would like to acknowledge Kenny Tan, Victoria Leung, Candice Lee and Charlene Lee for their contributions towards the tele-ECG project.

Declaration

The authors declare no conflicts of interest.

Keywords: *cardiology, ECG, family medicine, specialist outpatient clinics, tele-ECG*

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