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Sepsis is a life-threatening complication that occurs when the body responds to an infection attacking the host. A narrative review in this issue highlights that circular RNAs (circRNAs) might exert pivotal roles in regulating the immune system against pathogens and sepsis-induced organ damage.

Investigating the regulation of circRNAs in sepsis could uncover new molecular targets for diagnosis and intervention. Such an understanding will be important for the development of therapeutic drugs.

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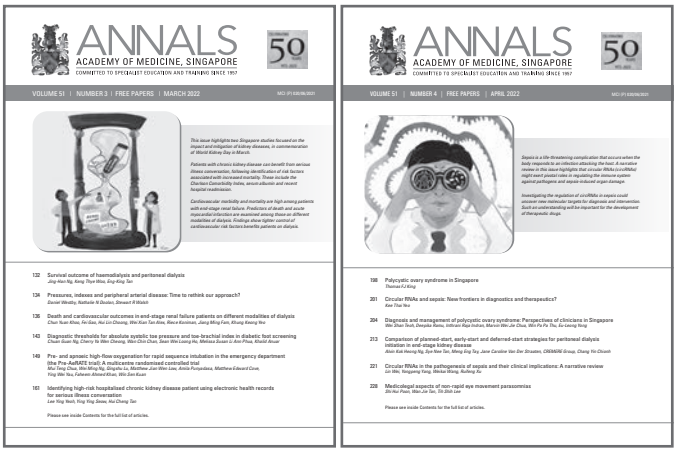

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EDITORIAL

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Polycystic ovary syndrome in Singapore

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in young women, affecting approximately 10% of women. It is a heterogeneous condition that can present with a wide spectrum of signs and symptoms, including acne, hirsutism, obesity, menstrual irregularities and infertility. It is a complex trait that is thought to arise from the interaction of genetic and environmental factors. The underlying pathophysiology is a combination of both ovarian hyperandrogenism and insulin resistance, which in itself is linked to other long-term cardiometabolic consequences.

Standardised diagnostic criteria are important to allow appropriate identification of patients for clinical management and for screening of associated complications. The diagnostic criteria have evolved over the years, and this evolution has led to some diagnostic differences and even difficulty among healthcare providers, which can translate to mixed messages and patient confusion. The first diagnostic criteria stemmed from a meeting at the US National Institutes of Health (NIH) in 1990, which recommended that the diagnosis be made on the basis of chronic anovulation (CA) and clinical or biochemical hyperandrogenism (H), but without reference to polycystic ovary morphology (PCOm) on ultrasound.[1]

In 2003, a joint meeting of the European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ESHRE/ASRM) was held in Rotterdam, the Netherlands to update the diagnostic criteria.[2] These revised criteria proposed that the presence of 2 of the 3 features, namely, CA, H and PCOm, would be sufficient for diagnosis of PCOS.

In terms of the specifics of the 3 criteria, CA is defined as less than 8 menstrual cycles per year, or more than 35 days between cycles. Hyperandrogenism is defined by clinical features (hirsutism, acne and androgenic alopecia), or an elevated serum testosterone level. Ultrasound features are classified as more than 12 antral follicles (measuring 2–9mm in diameter) or an ovarian volume of greater than 10cm^3 in either ovary. Before confirming a diagnosis of PCOS, other conditions such as thyroid dysfunction, hyperprolactinaemia, congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome should be excluded.[2]

From the diagnostic selection of 2 out of 3 of the clinical features emerge 4 distinct potential phenotypes: H-CA, H-PCOm, CA-PCOm and all 3 features in H-CA-PCOm. A phenotype-based approach can help to tailor the management to a patient's specific needs, which is particularly useful in a heterogeneous condition that is managed by many disciplines. In Singapore, PCOS is generally managed by primary care, endocrinology, gynaecology and reproductive medicine, and each discipline has its own strengths that can be tailored to the patient's phenotype and specific needs. Regardless of the managing discipline, screening for associated conditions such as endometrial hyperplasia, metabolic syndrome, type 2 diabetes, subclinical cardiovascular disease, obstructive sleep apnoea, anaemia, vitamin D deficiency, depression and anxiety should be considered.[3]

In 2006, the Androgen Excess and PCOS (AE-PCOS) Society suggested a compromise between the 2 sets of diagnostic criteria, proposing that PCOS is mainly a hyperandrogenic disorder, and hyperandrogenism is essential for the diagnosis.[4]

The 2003 Rotterdam diagnostic criteria have been the mainstay in medical education and clinical practice, and they are useful for standardisation for clinical research. However, there are some caveats with their use.

With the development of high-resolution transvaginal ultrasonography, features that fit the diagnostic criteria set out in 2003 may be seen in more than 50% of normal young ovulatory women.[5] In 2018, updated joint guidelines from ESHRE/ASRM revised the ultrasound criteria, specifically that for >8MHz transvaginal scans, a cut-off of >20 follicles per ovary should be applied.[6] They also highlight the diagnostic difficulties in adolescents, where menstrual irregularity and multifollicular ovaries are common, and that scanning may be deferred until 8 years post-menarche.

Hirsutism may be graded based on the modified Ferriman-Gallwey score, but this is still relatively

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subjective. It is also important to bear in mind normal ethnic differences in hair distribution. While a score of ≥8 is taken to be abnormal in Caucasian women, scores of 3–6 may be more appropriate cut-offs for East Asian populations, and possibly higher values for South Asian populations.[7] Furthermore, hirsutism may be less severe in adolescence and it is often self-treated before the patient presents to her doctor.

The measurement of testosterone is subject to clinical and assay variation. The majority of circulating testosterone is bound to sex hormone binding globulin (SHBG) and albumin, so conditions that affect these levels will affect the interpretation of the total testosterone result.

Biochemical assessment can be made using total testosterone, calculated free testosterone, calculated bioavailable testosterone or free androgen index. Where necessary, free testosterone may be measured by liquid chromatography-tandem mass spectrometry, but the currently available direct immunoassays for free testosterone are of limited value.[6]

In this issue of the *Annals*, Teoh et al. noted the complications in diagnosis, and the wide spectrum of clinicians treating PCOS in Singapore.[8] This is because there is a spectrum of patient profiles, and those presenting with menstrual irregularities or infertility may be seen by a gynaecologist, while those with hyperandrogenism and glucose intolerance may be seen by an endocrinologist. The authors also noted a lack of studies in Southeast Asia, and an absence of a systemic referral system specific to PCOS. Hence their aim was to study clinicians treating PCOS, primarily with regard to knowledge of clinical features and diagnostic criteria, and secondarily to assess physician knowledge of complications and management of PCOS. A web-based survey was sent to all clinicians involved in the care of PCOS patients in Singapore, throughout disciplines in the public and private sector. Respondents had to identify modalities for diagnosis that aligned with guidelines including those from NIH 1990, Rotterdam 2003, AE-PCOS 2006 and ESHRE 2018. Along with the 4 core diagnostic criteria (CA, PCOm, clinical hyperandrogenism and biochemical hyperandrogenism), peripheral criteria such as luteinising hormone to follicle-stimulating hormone ratio, anti-Müllerian hormone and SHBG were included.

Data from 160 participants were included in the analysis, around half of whom were specialists. Almost all physicians from gynaecology and endocrinology reported using diagnostic criteria, of which the 2003 Rotterdam were the most commonly used (66.3%). This is consistent with data on current physician practice in Europe and North America—71% chose at least 1 incorrect modality to diagnose PCOS, and only 39.5% could identify the correct clinical features, of whom a significant majority were gynaecologists. The majority (over 95%) recognised type 2 diabetes and infertility as complications of PCOS, but only about one third of respondents recognised other complications such as depression and anxiety. Endocrinologists were most concerned about non-alcoholic steatohepatitis, and gynaecologists were most concerned about endometrial cancer. Gynaecologists were most likely to have a standardised protocol at their workplace (62%). The majority of respondents expressed that the provision of standardised educational materials would help them care for patients.

In summary, care for patients with PCOS in Singapore could be improved in a number of areas. Investigating patient experiences and satisfaction levels would complement the findings of the current study. Singapore clinical practice guidelines could help to streamline referral pathways, harmonise diagnosis and management, improve screening for complications, and lead to overall better patient satisfaction and long-term outcomes.

Table 1. Summary of 3 diagnostic criteria for polycystic ovary syndrome

National Institutes of Health consensus criteria 1990[1] (all required)	**Rotterdam ESHRE/ASRM 2003[2] (2 out of 3 required)**	**AE-PCOS definition 2008[4] (all required)**
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism
Oligo- or anovulation	Oligo- or anovulation	Ovarian dysfunction: oligo/anovulation and/or polycystic ovary morphology on ultrasound
	Polycystic ovary morphology on ultrasound	

AE-PCOS: Androgen Excess and PCOS Society; ESHRE/ASRM: European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; PCOS: polycystic ovary syndrome

Superscript numbers: Refer to numbers in REFERENCES

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EDITORIAL

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Circular RNAs and sepsis: New frontiers in diagnostics and therapeutics?

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Circular RNAs (circRNAs) are a group of endogenous RNAs characterised by their covalently closed-loop structures. These molecules are part of a large class of non-coding RNAs that includes microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). CircRNAs were initially thought to be of low abundance and represent errors in splicing. However, recent interest in these molecules, coupled with advancements in sequencing techniques, has led to the identification of thousands of specific circRNAs among many eukaryotes. The high abundance, stability and conservation of circRNAs between species suggest that these molecules may have important roles in physiological processes and pathological conditions.[1] They are increasingly recognised as having important functions in gene regulation, and these RNAs have been implicated in the pathogenesis and progression of a variety of diseases, specifically in cancers, cardiovascular conditions, neurological disorders and infectious diseases.[2] Thus, there is great interest in investigating circRNAs as potential disease biomarkers and novel therapeutic targets.

Recent advances in high-throughput sequencing techniques and bioinformatics approaches have spurred the identification of a large number of previously unknown circRNAs in different organisms and conditions. Unlike linear RNA, the 3' and 5' ends in circRNAs are joined together, forming a covalently closed, continuous loop that prevents degradation by RNA exonucleases, conferring it stability in the cell cytoplasm.[3] Canonical pre-mRNA splicing is catalysed by the intracellular spliceosomal machinery to remove introns and to join the exons, resulting in the formation of linear RNA transcripts (Figs. 1A and 1B).[3,4] By comparison, circRNAs are typically formed by a non-canonical splicing process known as backsplicing (Fig. 1C). They are derived from canonical splice sites, utilising their canonical splicing machinery. Looping of the long intron sequences leads to flanking of the downstream splice-donor site and the upstream splice-acceptor sites. The close proximity of these sites allows for spliceosomes to engage in backsplicing. This looping can be mediated by pairing of structures such as inverted repeat elements and dimerisation of RNA-binding proteins. Three different types of circRNAs can arise depending on their composition of exons and introns: exonic, intronic and exon-intron circRNAs (Fig. 1).[5] Additionally, lariat formation during exon skipping or intronic lariats that escape debranching can also lead to the formation of exonic circRNAs and circular intronic RNAs (ciRNAs), respectively (Figs. 1A and 1B). Following production, most circRNAs, with the exception of intron-containing ones, are exported to the cytoplasm.

CircRNAs are known to regulate gene expression through several mechanisms, including regulation of transcription and splicing; miRNA sponges; mRNA traps; and translational and post-translational modification.[6] Even so, most of the mechanisms of circRNA function in physiological and pathological conditions remain to be defined—a big part of our current understanding of their functions relates to their ability as miRNA sponges. miRNAs are a family of small non-coding RNAs that have been shown to regulate a wide variety of biological processes by regulating gene expression at the post-translational level.[7] CircRNAs are thought to impair miRNA activity through sequestration, resulting in regulation of the miRNA target gene expression. Even so, only a limited number of circRNAs have since been identified and proposed as miRNA sponges to date, suggesting many other functions and capabilities of these molecules.[5] CircRNAs have been proposed to interact with many different RNA binding proteins to act as protein sponges, enhance protein function, act as scaffolds and recruit specific proteins.[3]

In this issue of the *Annals*, Wei et al. provide an update on our current understanding of circRNAs in the pathogenesis of sepsis and the resultant multiorgan dysfunction that ensues.[8] The authors summarise the accumulating evidence on the central role of these molecules in the biological pathways leading towards infection-related organ dysfunction. In this regard, circRNAs have been implicated in the pathogenesis of sepsis-related inflammation, immunosuppression and the associated multiorgan dysfunction. With their inherent

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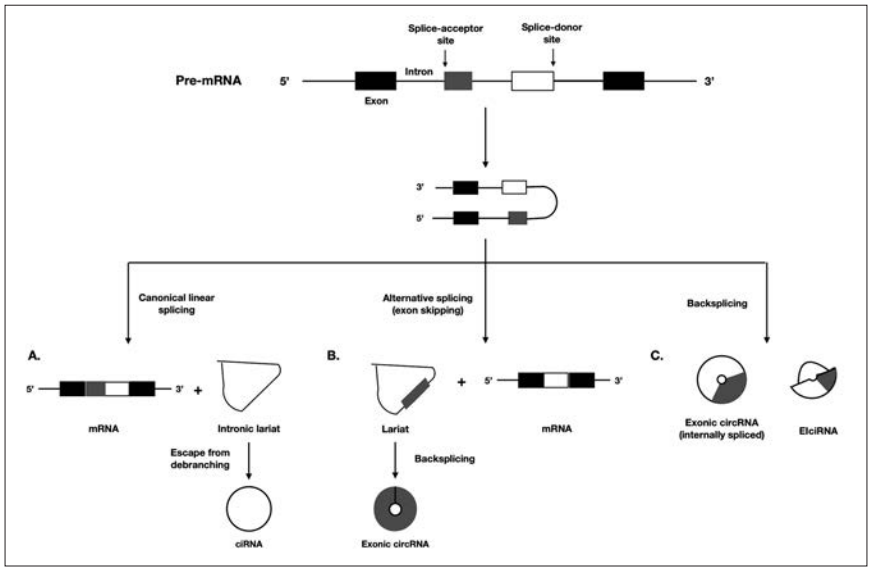

Fig. 1. Major proposed mechanisms in the biogenesis of circular RNAs. (A) Canonical linear splicing with the splicing of introns. (B) circRNAs are also formed from splicing intermediates such as lariat. (C) Long flanking introns, inverted repeat elements and RNA binding proteins favour backsplicing. These elements bring a downstream splice-donor site in close proximity to upstream splice-acceptor leading to backsplicing, resulting in formation of exonic circRNAs and exon-intron circRNAs (EIcircRNAs).

stability in blood and tissue, the authors highlight the potential of circRNAs as biomarkers for the diagnosis of sepsis, and also as potential therapeutic targets in preventing multiorgan dysfunction in view of their ability as miRNA sponges.

The prospects of clinical application of circRNAs in the field of infectious diseases have been highlighted by recent studies on viral infections. Several studies have showed differentially expressed host circRNAs associated with infection by a multitude of viruses, including hepatitis B virus (HBV), human immunodeficiency virus (HIV) and herpes simplex virus (HSV).[6] Analyses of interactions between circRNA, miRNA and mRNA have revealed different pathways that may be implicated in the progression of chronic viral infections such as HBV. These illustrate the potential role of circRNAs in regulating virus replication through modulation of antiviral immune responses.[6,9] Of interest, proof-of-concept in vitro experiments utilising synthetic, engineered circRNAs were able to demonstrate inhibition of viral protein production in a hepatitis C virus cell culture system by sequestering miRNA-122, an important miRNA for the viral life cycle.[10]

In spite of these advancements, standardised protocols and workflows for the detection of circRNAs are still developing. Advancements are still needed to experimentally elucidate and verify the many functions of circRNAs. Detection of circRNAs exploits the presence of backspliced junctions as a key feature for identification of cirRNA. Many circRNA studies utilise RNase R treatment of samples to deplete all linear RNAs before sequencing. The rare cases of RNase R-resistant linear RNAs and RNase R-sensitive circRNAs are potential limitations of this strategy.[11] Other studies are based on sequencing total, ribosomal-depleted or non-polyadenylated RNA, thus avoiding issues surrounding the usage of RNase R. However, with the presence of both linear and circRNAs, circularity confirmation of the circRNAs is required.[3] The discovery of chimeric transcripts from the abundant circular DNAs further complicates these analyses as circRNAs are not the only transcripts with chimeric junctions.[11] Further advances in sequencing technology, bioinformatics and better algorithms for circRNA detection are needed.

Recent advancement in our understanding of the biogenesis and functions of circRNA have emphasised the potential importance of these molecules in the pathophysiology of a multitude of complex human diseases such as sepsis. The specificity of circRNAs for certain diseases, their stability in human cells and their proposed regulatory functions have highlighted circRNAs' potential as diagnostic and therapeutic targets in complex conditions such as sepsis and beyond. However, further progress in our knowledge is needed—through improvements in sequencing technology and bioinformatics for detecting and verifying circRNAs' functions in human diseases—before this potential can be realised.

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ORIGINAL ARTICLE

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Diagnosis and management of polycystic ovary syndrome: Perspectives of clinicians in Singapore

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ABSTRACT

Introduction: To harmonise the diagnostic processes of polycystic ovary syndrome (PCOS) and enable clinicians to provide better patient care, it is critical to understand the knowledge gaps in PCOS diagnosis. We evaluated how clinicians in endocrinology, family medicine, general practice and gynaecology diagnose PCOS.

Methods: This cross-sectional survey involved 208 clinicians from specific subspecialties across various healthcare settings in Singapore.

Results: A total of 160 responses were included in the final analysis. Among all the diagnostic criteria, the Rotterdam 2003 criteria was most frequently used (66.3%). More than half of the gynaecologists reported having a standardised workplace protocol while the majority from other specialties reported otherwise. A large percentage of respondents (60.5%) were unable to identify the correct PCOS clinical features, which is concerning. Only 8.8% of respondents used clinical and biochemical hyperandrogenism, menstrual disturbances and pelvic ultrasound to diagnose PCOS without performing unnecessary and incorrect investigations. Most clinicians recognised insulin resistance/type 2 diabetes mellitus and fertility problems as complications while only a few recognised psychological complications. Many clinicians (37.3%) sought standardisation of PCOS diagnosis and management guidelines for improvement in PCOS care and 81.9% of respondents would appreciate standardised educational materials.

Conclusion: This is the first study to the best of our knowledge that gives an insight into the diagnostic and management processes of PCOS among various healthcare institutions in Singapore. This study calls for greater harmonisation of diagnostic processes and holistic evidence-based management of patients with PCOS through standardised workplace protocols and patient education resources.

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Keywords: Diabetes, endocrinology, family medicine, obstetrics and gynaecology, polycystic ovary syndrome, public health

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder estimated to affect 4–21% of women, depending on the diagnostic criteria used.[1] Clinical manifestations of the syndrome are varied, and multiple parameters are needed for its diagnosis.[2,3] This complicates the diagnosis of PCOS and may cause patient dissatisfaction arising from delayed diagnosis, conflicting management regimes and differing views on prognosis.[2,4,5]

The situation is aggravated by a plethora of definitions that professional societies and organisations use to diagnose PCOS.[6-11] The 1990 National Institutes of Health (NIH) criteria require hyperandrogenism, either clinical (Ferriman-Gallwey score ≥8) or biochemical hyperandrogenism (elevated total or free testosterone)

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CLINICAL IMPACT

What is New

- 62.2% of gynaecologists reported having a standardised workplace protocol to diagnose polycystic ovary syndrome (PCOS) compared to clinicians from family medicine (31.5%), endocrinology (19.2%) and general practice (11.6%).
- Only 8.8% of respondents used the correct combination of clinical and biochemical hyperandrogenism, menstrual disturbances and pelvic ultrasound to diagnose PCOS.
- 60.5% of respondents were unable to correctly identify PCOS clinical features.

Clinical Implications

- There is a need for greater harmonisation of diagnostic processes and holistic evidence-based management of PCOS.

and chronic oligoanovulation (<6–9 menses per year) to diagnose PCOS.[12] On the other hand, the commonly used Rotterdam 2003 criteria added a new parameter—polycystic ovarian morphology, which is measured by transvaginal ultrasound counting of antral follicles (follicles ≥12 in each ovary measuring 2–9mm in diameter) and/or increased ovarian volume (>10mL).[13] With the advent of highly sensitive 8MHz transvaginal ultrasound probes, the antral follicle count threshold for PCOS diagnosis was revised upwards variably to 19–25 follicles.[3] The Androgen Excess and PCOS Society (AE-PCOS) further specified that there must be hyperandrogenism with either oligoanovulation or polycystic ovarian ultrasound morphology.[14] Recently, the revised European Society of Human Reproduction and Embryology (ESHRE) 2018 guideline notably provided detailed radiological guidelines based on route and frequency bandwidths of the ultrasound scans.[15] For transvaginal scans ≥8MHz, follicle number per ovary should be >20 and/or ovarian volume ≥10mL, whereas for transabdominal or transvaginal scans ≤8MHz, ovarian volume should be ≥10mL.[15]

It is therefore not surprising that clinicians and patients alike may be confused about the syndrome. This has resulted in patient dissatisfaction after clinic visits due to delayed or inaccurate diagnosis.[2,4,5] There is a lack of studies about this issue in Southeast Asia. In Singapore, as in many other nations, this is magnified by an absence of a systemic referral system specific to PCOS, with the condition being treated by clinicians in endocrinology, family medicine, fertility, general practice and gynaecological practices.[16] Knowledge of the diagnostic criteria used, accuracy of application of these criteria, and recognition of potential complications by clinicians across these disciplines are important to reduce patient dissatisfaction and anxiety.[17]

To study clinician knowledge on PCOS, we conducted a questionnaire survey to evaluate how clinicians in the fields of endocrinology, family medicine, general practice and gynaecology diagnosed and evaluated PCOS. The primary aim was to document clinician knowledge of PCOS clinical features, and the clinical, biochemical and imaging modalities used to diagnose PCOS. The secondary outcome of the survey was to document clinician knowledge of PCOS complications and its management.

METHODS

The study was approved by the National University of Singapore Institutional Review Board. Participation was anonymous and voluntary.

Study group selection

Clinicians working in endocrinology, family medicine, general practice and gynaecology were invited to participate in the current study. The chosen subspecialties represented the clinician groups most likely to encounter patients with first presentations of PCOS. General practice consisted of clinicians without a Master of Medicine degree in Family Medicine. The recruitment period for the study was from October 2020 to June 2021. The URL link to the questionnaire was disseminated through posters and emails to hospitals, primary care units and societies affiliated with the chosen subspecialties. The surveys were sent to both the government-subsidised public sector clinics and hospitals, and non-subsidised private clinics and hospitals. We had aimed to send the questionnaire to all clinicians treating PCOS in Singapore.

Study design and tools

We used Qualtrics platform, a secure online database, to administer the questionnaire. The questionnaire was adapted from another validated questionnaire previously used to survey clinicians in North America on PCOS knowledge and practice patterns.[6] It was modified by content experts in the fields of reproductive endocrinology, benign gynaecology and family medicine to contextualise and further find out about clinicians' perspectives and challenges regarding PCOS diagnosis and treatment in Singapore. The questionnaire comprised questions pertaining to several domains: clinician demographics,

diagnostic criteria, clinical features, investigations, non-fertility and fertility management, clinician opinion on patient education and challenges faced in PCOS care. The questionnaire was first piloted in a smaller group of 30 clinicians and further refined before disseminating to our bigger target group.

Statistical methods

Statistical analysis was performed with SPSS Statistics software version 27.0 (IBM Corp, Armonk, US). The main outcomes measured were clinician knowledge of correct PCOS clinical features, and the clinical, biochemical and imaging modalities used to diagnose PCOS. The secondary outcome measures included clinician knowledge of complications and management of PCOS and their perspectives of PCOS care in Singapore. Descriptive statistics were reported as count and percentage responses, and groups were compared using chi-square tests. Binary logistic regression models were performed. Odds ratios and 95% confidence intervals were presented. All variables with $P<0.1$ in the univariate analyses were added to the models. $P<0.05$ was considered statistically significant.

Respondents were asked to identify from a mixed list of correct and incorrect modalities, and peripheral recommendations that they could use to diagnose PCOS. The correct and incorrect modalities were based on a constellation of evidence-based guidelines including the latest ESHRE 2018 guidelines.[15] The correct modalities could be broadly classified into 4 main diagnostic categories: (1) clinical hyperandrogenism; (2) biochemical hyperandrogenism; (3) menstrual disturbances; and (4) polycystic morphology on ultrasound. Acne, male pattern baldness and hirsutism were grouped under clinical hyperandrogenism. Biochemical hyperandrogenism included testosterone levels and free androgen index. Menstrual disturbances included amenorrhoea/oligomenorrhoea. Lastly, ovarian antral follicle count and ovarian volume were grouped under polycystic morphology on ultrasound. Respondents had only needed to select a minimum of 1 modality from each category to be considered to have recognised a category used in PCOS diagnosis. Incorrect modalities included body mass index, fertility problems, prolactin levels, androstenedione levels, estradiol levels and 17-hydroxyprogesterone. Peripheral recommendations included luteinising hormone (LH) to follicle-stimulating hormone (FSH) ratio (LH/FSH),[14] anti-Müllerian hormone[3,18] and sex hormone binding globulin.[19] These investigations were included as peripheral recommendations as they have not been formally included in any published guidelines, but have potential utility in diagnosing PCOS.

RESULTS

A total of 208 responses were received. Data from 160 participants who completed at least 78% of the survey, including all essential questions on the diagnostic criteria pertinent to the study were included. As the number of clinicians who received invitations to participate in the questionnaire could not be accurately determined due to the multiple channels of information dissemination used, reach and response rates could not be estimated.

Socio-demographic characteristics of respondents

Table 1 summarises the socio-demographic characteristics of the 160 respondents. Of this number of respondents, nearly two-thirds were aged 50 years and below; more than half (56.9%) were women; a majority worked in the public sector (67.5%); and 28.7% respondents reported not being involved in the care of, and have not seen, any patients with PCOS in the last 12 months. Nearly half of the respondents (45%) were specialists.

Diagnostic criteria and availability of standardised protocol at workplace

Almost all clinicians from gynaecology and endocrinology specialties reported that they followed diagnostic criteria, as compared to those from general practice and family medicine (Table 2). Among the 4 sets of diagnostic criteria, Rotterdam 2003 was the most commonly utilised (66.3%). Significantly more gynaecologists (62.2%) reported having a standardised protocol at their workplace as compared to clinicians from family medicine (31.5%), endocrinology (19.2%) and general practice (11.6%).

Recognition of PCOS clinical features

Factors influencing respondents' ability to correctly identify PCOS clinical features were investigated (Table 3). The binary logistic regression model explained 31.3% of variance in the ability to identify correct clinical features of PCOS and correctly classified 73.8% of cases. Only 39.5% of respondents could identify the correct clinical features, of whom a significant majority were gynaecologists (62.2%).

The respondents' area of work, professional grade, practice of not following any diagnostic criteria nor having a workplace protocol were significant in determining their ability to correctly identify PCOS clinical features. Years involved in the care of patients with PCOS, number of patients with PCOS seen in the

Table 1. Characteristics of clinicians responding to questionnaire

Characteristics	No. (%) N=160
Age, years	
25–30	29 (18.1)
31–40	57 (35.6)
41–50	31 (19.4)
51–60	32 (20.0)
>60	11 (6.9)
Specialty	
General practice	43 (26.9)
Family medicine	54 (33.8)
Gynaecology	37 (23.1)
Endocrinology	26 (16.3)
Location of practice	
Private sector	52 (32.5)
Private clinic	49 (30.6)
Private hospital	3 (1.9)
Public sector	108 (67.5)
Polyclinic	46 (28.8)
Public hospital	62 (38.8)
Years involved in the care of PCOS patients	
No involvement	46 (28.7)
≤5 years	35 (21.9)
6–10 years	31 (19.4)
11–20 years	24 (15.0)
>20 years	24 (15.0)
PCOS patients seen in the last 12 months	
0	46 (28.7)
1–10	59 (36.9)
11–20	19 (11.9)
21–30	8 (5.0)
>30	28 (17.5)
Professional grade	
Residents-in-training	25 (15.6)
Specialists	72 (45.0)
Others	63 (39.4)

PCOS: polycystic ovary syndrome

preceding 12 months, and self-reported clarity about PCOS diagnostic criteria, did not significantly predict the ability to correctly identify PCOS clinical features.

Diagnostic modalities

Table 4 summarises modalities used to diagnose PCOS by respondents. Fifty-five (34.3%) of the 160 respondents chose modalities from all 4 diagnostic categories to diagnose PCOS. However, of these 55 respondents, 33 (60%) respondents chose modalities from the 4 diagnostic categories along with incorrect modalities. There were 35% of the respondents who chose modalities from 3 of the 4 diagnostic categories. Of the 4 diagnostic categories, biochemical hyperandrogenism (50.6%) was the most common category that was not used by respondents for the diagnosis of PCOS. There were 48.1% of clinicians who used peripheral recommendations to aid their diagnosis of PCOS. Of the peripheral recommendations, LH/FSH ratio (43.8%) was the most frequently used. Finally, 71.3% of respondents chose at least 1 incorrect modality to diagnose PCOS, with fertility problems (58.8%) being the most selected incorrect modality.

PCOS complications

Table 5 summarises complications recognised by clinicians. Overall, insulin resistance/type 2 diabetes mellitus (95.6%) and fertility problems (96.8%) were best recognised as complications of PCOS by the clinicians. On the other hand, psychological complications of PCOS such as depression (40.5%) and anxiety (29.7%) were less appreciated. Clinicians from gynaecology and family medicine were more likely to recognise abnormal uterine bleeding and cardiovascular disease complications. Interestingly, the majority of endocrinologists reported non-alcoholic steatohepatitis as a complication. Gynaecologists were most concerned about endometrial cancer compared to other specialties.

Perspectives from clinicians

When clinicians were asked to share how they educated their newly diagnosed patients, only 18.6% of respondents indicated the use of evidence-based guidelines (12.4%) and/or institution pamphlets (6.2%). There were 14.7% of clinicians who reported that they do not counsel their patients. A majority of respondents (81.9%) expressed that provision of standardised educational materials for clinicians will benefit them in caring for patients with PCOS. The respondents were then asked to share the main challenges they faced in caring for patients with PCOS. Interestingly, ensuring

Table 2. Association of diagnostic criteria and availability of standardised protocol with different specialties

	General practice[a]	Family medicine[b]	Gynaecology	Endocrinology	Total N=160	*P* value
Follows diagnostic criteria, no. (%)						<0.0001
Yes	25 (58.1)	35 (64.8)	36 (97.3)	25 (96.2)	121 (75.6)	
No	18 (41.9)	19 (35.2)	1 (2.7)	1 (3.8)	39 (24.4)	
Diagnostic criteria, no. (%)						<0.0001
NIH 1990	3 (7.0)	1 (1.9)	3 (8.1)	0 (0)	7 (4.4)	
Rotterdam 2003	22 (51.2)	34 (63.0)	31 (83.8)	19 (73.1)	106 (66.3)	
AE-PCOS 2009	0 (0)	0 (0)	1 (2.7)	2 (7.7)	3 (1.9)	
ESHRE 2018	0 (0)	0 (0)	1 (2.7)	4 (15.4)	5 (3.1)	
Has standardised protocol at workplace, no. (%)						<0.0001
Yes	5 (11.6)	17 (31.5)	23 (62.2)	5 (19.2)	50 (31.3)	
No	30 (69.8)	25 (46.3)	12 (32.4)	19 (73.1)	86 (53.8)	
I don't know	8 (18.6)	12 (22.2)	2 (5.4)	2 (7.7)	24 (15.0)	
Follows criteria and workplace protocol	5 (11.6)	15 (27.8)	22 (59.5)	6 (23.1)	48 (30.0)	<0.0001
Either follows criteria or has protocol	22 (51.2)	25 (46.3)	15 (40.5)	19 (73.1)	81 (50.6)	
Neither follows criteria nor has protocol	16 (37.2)	14 (25.9)	0 (0)	1 (3.8)	31 (19.4)	

AE-PCOS 2009: Androgen Excess and PCOS Society 2009 criteria; ASRM: American Society for Reproductive Medicine; ESHRE 2018: revised European Society of Human Reproduction and Embryology (ESHRE) 2018 guidelines; NIH 1990: National Institutes of Health 1990 criteria; PCOS: polycystic ovary syndrome; Rotterdam 2003: Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group criteria

[a] General practice is represented by physicians without a Master of Medicine in Family Medicine degree

[b] Family medicine is represented by physicians with a Master of Medicine in Family Medicine degree

patients' compliance to lifestyle modifications (30.3%) and diagnosing PCOS using the correct criteria (24.5%) were the 2 most selected challenges.

DISCUSSION

Clinical features and diagnostic modalities

The diagnosis and management of PCOS is complex, and uncertainties can cause undue stress and anxiety for the patient. Herein, we report findings relevant to PCOS diagnosis and management that showed variations among different healthcare specialties and settings.

We found that a large percentage (60.5%) of respondents (n=98) were unable to identify the correct clinical features of PCOS, which could be a cause for concern. Of these respondents, 80% of them do not follow a diagnostic criterion and/or lack a standardised workplace protocol. This is alarming given that most respondents in similar studies were aware of the clinical features associated with PCOS.[9] Overall, only 34.3% of respondents recognised the use of all 4 diagnostic categories, including clinical and biochemical hyperandrogenism, menstrual disturbances and polycystic morphology on ultrasound for the diagnosis of PCOS. Similar to our findings, a study by Chemerinski et al. involving obstetrics and gynaecology residents identified that only 55% of the residents were able to identify at least 1 component of the 3 criteria in the Rotterdam 2003 criteria, and that over 90% of the residents were unable to identify all components of the criteria.[20] Clinicians from China were also found to have a low accurate application rate (31.3%) of their chosen diagnostic criteria.[7] These findings highlight the knowledge gap present in identifying the correct clinical features of PCOS, and discrepancies in the diagnostic criteria used.

Diagnostic criteria and standardised workplace protocol

We found that most clinicians followed the Rotterdam 2003 criteria and others the latest ESHRE 2018 guidelines to diagnose PCOS. This is in line with studies performed in Europe and North America that showed most clinicians still used the Rotterdam criteria.[6,21] On the other hand, a recent study found that the AE-PCOS criteria was most frequently used to diagnose PCOS in China.[7]

Table 3. Factors influencing ability to correctly identify PCOS clinical features of menstrual disturbances and clinical hyperandrogenism

N=160	Crude OR (95% CI)	Adjusted OR (95% CI)
Specialty		
General practice	Reference	Reference
Family medicine	4.8 (1.0–7.5)	4.8 (1.3–17.6)
Gynaecology	8.4 (3.0–24.1)	10.1 (1.5–67.6)
Endocrinology	5.1 (1.7–15.7)	7.8 (1.5–41.0)
Professional grade		
Residents-in-training	Reference	Reference
Specialists	2.2 (0.8–5.9)	3.2 (0.8–13.6)
Years involved in the care of patients with PCOS		
No involvement	Reference	Reference
≤5 years	2.8 (1.0–7.8)	2.7 (0.4–18.9)
6–10 years	6.6 (2.3–18.7)	3.7 (0.5–25.9)
11–20 years	4.0 (1.3–12.2)	1.3 (0.2–10.3)
>20 years	4.8 (1.6–14.3)	2.0 (0.3–12.4)
Number of patients with PCOS seen in the last 12 months		
0	Reference	Reference
0–10	3.3 (1.3–8.2)	1.2 (0.3–5.6)
11–20	3.5 (1.1–11.3)	0.7 (0.1–3.2)
21–30	7.9 (1.6–40.1)	1.6 (0.3–10.3)
>30	7.3 (2.5–21.5)	Not available
Follows criteria and workplace protocol		
Follows criteria and workplace protocol	Reference	Reference
Either follows criteria or has protocol	0.4 (0.2–0.9)	0.5 (0.2–1.4)
Neither follows criteria nor has protocol	0.1 (0.03–0.4)	0.2 (0.04–0.8)
Clear about PCOS diagnostic criteria		
Yes	2.4 (1.2–4.8)	0.9 (0.3–2.7)
No	Reference	Reference
Perception of PCOS diagnosis		
Correctly diagnosed	Reference	Reference
Under diagnosed	0.3 (0.1–0.8)	0.5 (0.2–1.4)
Over diagnosed	0.6 (0.2–2.0)	0.4 (0.1–1.5)
I don't know	0.2 (0.1–0.7)	0.5 (0.1–2.1)

CI: confidence interval; OR: odds ratio; PCOS: polycystic ovary syndrome

We noted that a higher proportion of clinicians from general practice and family medicine reported that they did not follow any criteria. This could be due to the limited resources to diagnose PCOS in the primary care facilities, and/or reduced access to teaching sessions on PCOS as compared to the gynaecology specialty. There were 68.8% of respondents who reported that they did not have a standardised protocol in their workplace for the

Table 4. Modalities used to diagnose PCOS by the respondents

Modality	No. (%) N=160
Diagnostic category A: clinical hyperandrogenism	142 (88.9)
Acne	100 (62.5)
Male pattern baldness	49 (30.6)
Hirsutism	141 (88.1)
Diagnostic category B: biochemical hyperandrogenism	79 (49.4)
Testosterone levels	75 (46.9)
Free androgen index	30 (18.8)
Diagnostic category C: menstrual disturbances	149 (93.1)
Diagnostic category D: ultrasound	105 (65.6)
Number of ovarian antral follicles	99 (61.2)
Ovarian volume	47 (29.4)
Peripheral recommendations	
LH/FSH ratio	70 (43.8)
Anti-Müllerian hormone levels	14 (8.8)
Sex hormone binding globulin levels	11 (6.9)
Incorrect modalities	
Fertility problems	27 (16.9)
Body mass index	20 (12.5)
Androstenedione levels	8 (5.0)
17-hydroxyprogesterone	6 (3.8)
Estradiol levels	5 (3.2)
Prolactin levels	3 (1.9)
Respondents who chose modalities from all 4 diagnostic categories	55 (34.4)
Only chose modalities from all 4 diagnostic categories	14 (8.75)
Chose modalities from all 4 diagnostic categories and peripheral recommendations	8 (5.0)
Chose modalities from all 4 diagnostic categories and incorrect modalities	33 (20.6)

LH/FSH: luteinising hormone to follicle-stimulating hormone; PCOS: polycystic ovary syndrome

management of PCOS. As a lack of standardised protocols may contribute to greater inconsistencies in diagnosing and managing PCOS patients, this could be an area for improvement.[6,10,11]

Due to its comprehensive evidence-based diagnostic and management approaches, including its recommendation of "PCOS model care", the ESHRE 2018 PCOS guidelines could be recommended as the standardised criteria for diagnosing PCOS in Singapore. The "PCOS model of care" entails a sustainable approach to multidisciplinary and holistic management of PCOS patients. Similarly, a standardised protocol can be implemented for diagnosis and holistic management of PCOS patients in Singapore, providing a clear evidence-based, multidisciplinary management framework involving clinicians from gynaecology, endocrinology, family medicine, psychiatry and dietetics. This would eliminate some of the challenges faced by clinicians in PCOS care such as inconsistencies in diagnostic and management processes, the need for further PCOS education for clinicians, and clearer referral pathways. Put together, these interventions may help to improve patient satisfaction through a systematic and holistic care provision that targets physical and psychosocial aspects of PCOS.

Perspectives from clinicians

Notably, 31.3% of respondents did not offer any counselling and only 16% used evidence-based guidelines and institution pamphlets for counselling. Easier access to educational resources regarding PCOS and its complications would promote greater understanding of the condition, which will in turn increase patient compliance to lifestyle modifications and other treatment plans.[2] This would be highly desirable given that non-compliance to lifestyle modifications was highlighted to be one of the main challenges for clinicians. Most clinicians believed that standardised educational brochures could be created and shared with patients. Studies overseas reflected similar findings in that most clinicians from North America, Europe and other regions from gynaecology and reproductive endocrinology believed that they could be best supported in caring for women with PCOS through curation of broadly available education materials.[21] We could consider sharing e-resources with our patients, such as the "Ask PCOS" phone application created by Monash University[22] that contains infographics and interactive videos by PCOS experts.

Residency committees could consider to include more training hours and clinical exposure to PCOS in endocrine, family medicine and gynaecology residency programmes. Clinicians may also be updated about PCOS guidelines through various modes such as workshops, webinars and flexible learning opportunities involving existing online PCOS courses for healthcare professionals via renowned and accredited platforms.[21,22] Creating consolidated and standardised resources for all clinicians and patients across Singapore may further harmonise workflow and protocols.

Table 5. Table of complications recognised by clinicians across specialities

N=160	General practice No. (%)[a] n=43	Family medicine No. (%)[a] n=54	Gynaecology No. (%)[a] n=37	Endocrine No. (%)[a] n=26	Total No. (% of total responses)	*P* value
Fertility problems	42 (97.7)	52 (96.3)	35 (94.6)	24 (92.3)	153 (96.8)	0.725
Insulin resistance/type 2 diabetes mellitus	38 (88.4)	53 (98.1)	35 (94.6)	25 (96.2)	151 (95.6)	0.072
Abnormal uterine bleeding	19 (44.2)	38 (70.4)	37 (100.0)	11 (42.3)	105 (66.5)	<0.001
Cardiovascular disease	15 (34.9)	33 (61.1)	23 (62.2)	10 (38.5)	81 (51.3)	0.046
Endometrial cancer	9 (20.9)	21 (38.9)	32 (86.5)	17 (65.4)	79 (50.0)	<0.001
Depression	14 (32.6)	25 (46.3)	13 (35.1)	12 (46.2)	64 (40.5)	0.455
NASH	10 (23.3)	22 (40.7)	8 (21.6)	17 (65.4)	57 (36.1)	0.002
Anxiety	8 (18.6)	19 (35.2)	10 (27.0)	10 (38.5)	47 (29.7)	0.279

NASH: non-alcoholic steatohepatitis
[a](%) in columns represent percentage of doctors in the subspecialty choosing the complication

Strengths and limitations

The sample is not representative of the whole population of family medicine, gynaecology and endocrine specialists. Selection bias might be present as clinicians who were more involved in PCOS work might be more inclined to participate in this study. Regardless of the limitations, this is the first study to the best of our knowledge that gives an insight into the diagnostic and management processes of PCOS in Singapore among various healthcare institutions. Further studies could recruit a larger and more diverse population of clinicians with a stratified sampling approach to obtain a more representative opinion. Investigating the patient's satisfaction level with regards to PCOS diagnosis and management would also provide a new perspective and can be used to supplement the findings from this study. This would help to create targeted interventions to improve the diagnostic and management processes of PCOS in Singapore.

CONCLUSION

The current study evaluated the diagnostic processes adopted by clinicians from different specialties and healthcare settings in Singapore. It is anticipated that similar conundrums are faced by patients in Singapore as the patients worldwide. This study calls for greater harmonisation of diagnostic processes and holistic evidence-based management of PCOS patients, through standardised workplace protocols and patient education resources.

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ORIGINAL ARTICLE

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Comparison of planned-start, early-start and deferred-start strategies for peritoneal dialysis initiation in end-stage kidney disease

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ABSTRACT

Introduction: In patients with end-stage kidney disease (ESKD) suitable for peritoneal dialysis (PD), PD should ideally be planned and initiated electively (planned-start PD). If patients present late, some centres initiate PD immediately with an urgent-start PD strategy. However, as urgent-start PD is resource intensive, we evaluated another strategy where patients first undergo emergent haemodialysis (HD), followed by early PD catheter insertion, and switch to PD 48–72 hours after PD catheter insertion (early-start PD). Conventionally, late-presenting patients are often started on HD, followed by deferred PD catheter insertion before switching to PD≥14 days after catheter insertion (deferred-start PD).

Methods: This is a retrospective study of new ESKD patients, comparing the planned-start, early-start and deferred-start PD strategies. Outcomes within 1 year of dialysis initiation were studied.

Results: Of 148 patients, 57 (38.5%) patients had planned-start, 23 (15.5%) early-start and 68 (45.9%) deferred-start PD. Baseline biochemical parameters were similar except for a lower serum urea with planned-start PD. No significant differences were seen in the primary outcomes of technique and patient survival across all 3 subgroups. Compared to planned-start PD, early-start PD had a shorter time to catheter migration (hazard ratio [HR] 14.13, 95% confidence interval [CI] 1.65–121.04, *P*=0.016) while deferred-start PD has a shorter time to first peritonitis (HR 2.49, 95% CI 1.03–6.01, *P*=0.043) and first hospital admission (HR 2.03, 95% CI 1.35–3.07, *P*=0.001).

Conclusion: Planned-start PD is the best PD initiation strategy. However, if this is not possible, early-start PD is a viable alternative. Catheter migration may be more frequent with early-start PD but does not appear to impact technique survival.

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Keywords: Early start, end-stage kidney disease, mortality, nephrology, peritoneal dialysis, technique survival, urgent start

INTRODUCTION

Peritoneal dialysis (PD) is a well-established long-term dialysis modality for patients with end-stage kidney disease (ESKD).[1] It is recommended that a PD catheter should be placed at least 2 weeks prior to the anticipated need of long-term PD treatment for a planned-start PD.[2] Despite wide-spread promotion of planned-start dialysis for patients with advanced chronic kidney disease, late presentation and emergent initiation of chronic dialytic therapy remains a worldwide reality, and haemodialysis (HD) by means of a central venous catheter (CVC) is the most utilised initial modality.[3] In recent years, studies on incident HD patients have identified CVC use to be directly associated with worse survival, especially in the first year of therapy.[4] The risks of initiation of HD using CVC include bacteraemia and central venous stenosis.[4,5] It also necessitates multiple procedures before definitive access is established.[6,7]

In planned-start PD, the catheter is inserted electively and typically rested for several weeks following insertion

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CLINICAL IMPACT

What is New

- We compared planned-start, early-start and deferred-start peritoneal dialysis (PD). Our early-start strategy (emergent haemodialysis with early switch to PD) can be easily adopted by many centres.

Clinical Implications

- Technique and patient survival were similar across all 3 subgroups. Planned-start PD is the best PD initiation strategy. For patients who present late, the early-start strategy is a viable option.

to minimise the risk of mechanical complications, such as catheter leak.[2] Over this period, many patients require urgent initiation of interim HD to bridge this gap. There is significant interest in the practice of urgent-start PD, defined as the initiation of PD within 48–72 hours of catheter placement,[8,9] which circumvents the need for temporary vascular access. The urgent-start strategy also facilitates uptake of PD and is cost-effective short term and long term.[10] Several observational studies support the safety, efficacy and feasibility of this approach.[10-18] Urgent-start PD patients exhibit a similar short-term patient survival and technique failure as the traditionally planned counterpart.[19,20]

The successful implementation of urgent-start PD programmes requires the availability of procedurists for immediate implantation of the PD catheter and the commitment of a multiprofessional team to the routine operation of the programme.[17,21]

To overcome the unique logistical demands for urgent-start PD, our centre adopted an early-start PD strategy. In this approach, HD is started urgently, followed by early PD catheter insertion, and PD is started within 14 days after PD catheter insertion.[9] Compared to urgent-start PD, data are limited regarding the impact of early-start PD in new patients with ESKD.[19]

More often, patients who present late in ESKD are started on interim HD. If suitable for PD, PD catheter insertion and PD initiation would be deferred to a later date, termed as deferred-start PD. It would be important to evaluate how an early start-strategy compares to this more conventional deferred-start strategy.

In this observational study, we compared the clinical outcomes and relevant complications between patients initiated on PD with planned-start, early-start and deferred start PD strategies.

METHODS

Study population

We performed a retrospective cohort study of patients with ESKD who were started on PD from 1 January 2010 to 31 October 2017. This research project was approved by the local commission of ethics in research, the SingHealth Centralised Institutional Review Board, and waiver of informed consent was obtained (CIRB Reference: 2018/2737).

Group definitions

The PD patients were divided into 3 cohorts: planned-start PD group, early-start PD group and deferred-start PD group.[9] For planned-start PD, the PD catheter was inserted electively, rested for at least 14 days before initiating long-term PD as the first dialysis modality. In the early-start PD group, HD would be initiated first via a non-tunnelled short-term dialysis catheter for emergent indications, followed by PD catheter insertion and then switched to peritoneal dialysis 48–72 hours after insertion. In the deferred-start PD group, patients would be initiated on interim HD via a tunnelled dialysis catheter, and PD catheter insertion would be performed non-urgently before switching to PD at least 14 days after PD catheter insertion.

PD preparation and regimen

All PD catheters were inserted using the open surgical technique by surgeons experienced in PD catheter placement and all patients received preoperative antibiotic prophylaxis. Prior to initiation of PD, all patients and/or their caregivers would undergo a standardised 4-day PD training.

In the planned-start and deferred-start PD group, patients were started on a full dose of PD at least 2 weeks after PD catheter insertion. For continuous ambulatory PD, the patients were started on 4 exchanges of 2L bags per day. For automated PD, 10L of PD fluids were delivered in 5 exchanges over 10 hours nightly via a cycler. PD fluids with 1.5% dextrose was invariably the initial choice, unless poor ultrafiltration volume was already seen during the initial dwells.

For the early-start group, in the first 14 days post-catheter insertion, low-volume PD was applied using a cycler, with each fill ranging from 1–1.2L for a total of 5–6L over 8–10 hours per day. After 14 days, a full dose is prescribed as described above.

Outcome measures

Clinical characteristics recorded included patient demographics, comorbidities, date of first dialysis, date of creation of dialysis access and baseline laboratory test results on dialysis initiation.

The primary outcome of interest was technique and patient survival. Technique survival was assumed in the absence of technique failure, which was defined as long-term transfer to HD for any reason. Duration of patient survival is determined from the date of first dialysis (HD or PD). For calculation of patient survival, all deaths following dialysis initiation were included. Patient survival includes the time on HD for the early-start and deferred-start PD groups. Secondary outcomes of interest were the incidence and time-to-event for peritonitis, exit-site infection, peri-catheter leakage and catheter migration within 1 year of PD initiation. The frequency of peritonitis and number of unplanned hospitalisations in the first year of PD were also studied.

Statistical analysis

Descriptive statistics were reported as median and interquartile range (IQR) for continuous data, and as number (percentage) for categorical data. A comparison of baseline characteristics between the 3 subgroups was undertaken. Categorical data were analysed by chi-square test or Fisher's Exact test as appropriate, while continuous data were compared with the Kruskal-Wallis test.

In the primary time-to-event analysis for technique failure and patient mortality, Cox regression analysis was used to compare between the 3 main subgroups of patients and derive the survival curves. For the secondary outcomes, a time-to-event analysis using Cox regression was undertaken for the first episode of peritonitis, exit-site infection, peri-catheter leakage, PD catheter migration and hospitalisation. The hazard ratio (HR) and the 95% CI was presented, with planned-start PD as the reference group.

The incidence of peritonitis, exit-site infection, peri-catheter leakage, PD catheter migration and hospitalisation within the first year of PD was analysed by Pearson chi-square test or Fisher's Exact test where appropriate. A post hoc pairwise analysis with Bonferroni correction for multiple comparisons was planned if a significant difference was found. The number of peritonitis episodes and number of hospitalisations within the first year of PD was compared between the 3 subgroups with the Kruskal-Wallis test and if significant, Dunn's multiple comparisons test was planned.

Level of significance was set at α=0.05. Data were processed using SPSS Statistics version 20 (IBM Corp, Armonk, US).

RESULTS

Patient characteristics

A total of 148 patients (mean age 62 years, 48% male, 90% Chinese) were enrolled in this study from January 2010 to October 2017. The baseline characteristics of these participants are listed and categorised according to the PD initiation strategy in Table 1. Among these patients, there were 57 (38.5%) planned-start, 23 (15.5%) early-start and 68 (45.9%) from the deferred-start group. A history of coronary heart disease or congestive heart failure were noted to be more frequent in the early-start PD patients, compared with the planned-start and deferred-start PD counterparts. There were otherwise no significant differences in the other baseline characteristics of the groups. Initial biochemical parameters were also similar between the groups except for serum urea. Median serum urea levels were lower in the planned-start PD group (28mmol/L) as compared to the early-start group (37mmol/L) and deferred-start group (32mmol/L) (P<0.001).

Primary outcomes

The survival plot for technique survival is shown in Fig. 1A. When compared to planned-start PD in the time-to-event analysis, early-start PD was similar to planned-start PD with a HR of 1.08 (95% CI 0.28–4.06, P=0.915). Deferred-start PD appeared to have a higher HR for technique failure at 1.60 (95% CI 0.66–3.86) but this observation was not statistically significant (P=0.297).

The plot for patient survival is shown in Fig. 1B. Planned-start PD patients appeared to have the best survival, while it appeared to be lower with early-start PD (HR 1.35, 95% CI 0.65–2.81, P=0.426) and with deferred-start PD (HR 1.62, 95% CI 0.99–2.66, P=0.053). However, these findings were also not statistically significant. Table 2 tabulates the results from Cox regression analysis.

Secondary outcomes

The number and proportion of patients who experienced secondary outcomes are presented in Table 3. No statistically significantly differences between the subgroups were found for incidences of peritonitis, exit site infection and peri-catheter leakage within the first year of PD. The frequency of peritonitis and number of hospitalisations between the 3 subgroups in the first year on PD were also similar.

Table 1. Baseline characteristics of study cohort, stratified by how peritoneal dialysis (PD) was initiated

	All (N=148)	Planned-start PD (n=57)	Early-start PD (n=23)	Deferred-start (n=68)	*P* value
Male, no. (%)	71 (48)	23 (40.4)	9 (39.1)	39 (57.4)	0.113
Ethnicity, no. (%)					0.401
Chinese	90 (60.8)	38 (66.7)	16 (69.6)	36 (52.9)	
Malay	35 (23.6)	10 (17.5)	6 (26.1)	19 (27.9)	
Indian	15 (10.1)	6 (10.5)	0 (0)	9 (13.2)	
Others	8 (5.4)	3 (5.3)	1 (4.3)	4 (5.9)	
Comorbidities, no. (%)					
Diabetes mellitus	112 (75.7)	42 (73.7)	17 (73.9)	53 (77.9)	0.840
Hypertension	133 (89.9)	52 (91.2)	20 (87)	61 (89.7)	0.817
Coronary artery disease	62 (41.9)	18 (31.6)	14 (60.9)	30 (44.1)	0.054
Congestive cardiac failure	39 (26.4)	12 (21.1)	12 (52.2)	15 (22.1)	0.010
Cerebrovascular disease	30 (20.3)	11 (19.3)	6 (26.1)	13 (19.1)	0.760
Malignancy	1 (0.7)	0 (0)	0 (0)	1 (1.5)	1.000
Peripheral vascular disease	21 (14.2)	8 (14)	4 (17.4)	9 (13.2)	0.901
Age at initiation of PD, median (IQR), years	62 (53–74)	63 (53–74)	64 (55–77)	60 (53–71)	0.487
eGFR at initiation, median (IQR), mL/min/1.73m^2	5 (4–7)	6 (4–9)	6 (5–7)	5 (3–7)	0.006
Serum urea at initiation of dialysis, median (IQR), mmol/L	31 (26–39)	28 (22–33)	32 (27–38)	37 (29–45)	<0.001
Days on HD, median (IQR)	26 (0–61)	0 (0)	18 (12–33)	67 (43–119)	<0.001
Duration of follow-up on PD, median (IQR), years	2.8 (0.9–4.4)	3.2 (1.3–6.2)	1.3 (0.7–3.3)	2.5 (0.7–4.2)	0.014

eGFR: estimated glomerular filtration rate; HD: haemodialysis; IQR: interquartile range; PD: peritoneal dialysis

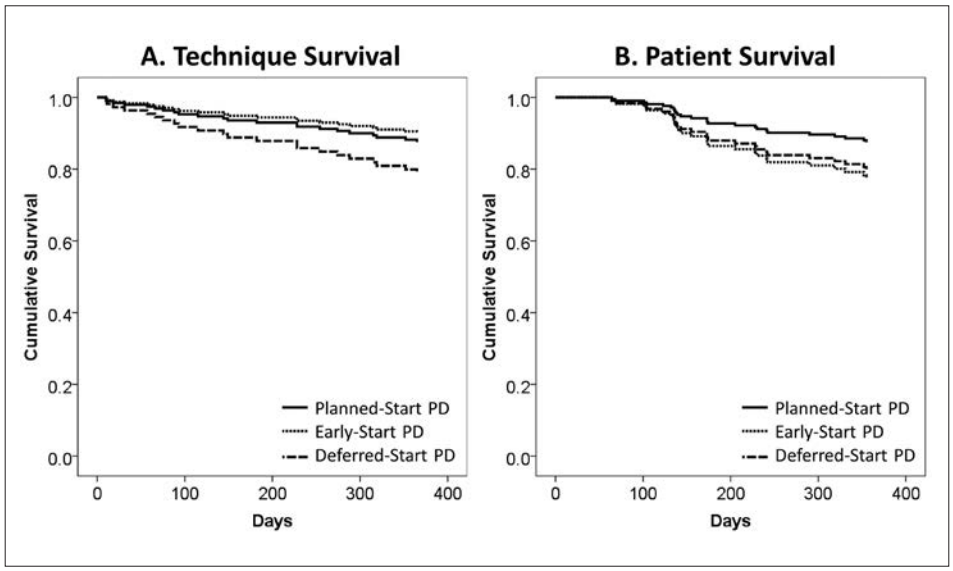

Fig. 1. Survival plot from Cox regression analysis for primary outcomes of interest in (A) Technique survival and (B) patient survival, comparing between planned-start peritoneal dialysis (PD), early-start PD and deferred-start PD.

Table 2. Results of cox regression analysis of primary and secondary outcomes

Outcome (total events)	Subgroup	Number of events No. (%)	Hazard ratio	95% CI for hazard ratio		*P* value
				Lower	Upper	
Technique failure (n=22)	Planned-start	7 / 57 (12.3)	-	-	-	-
	Early-start	2 / 23 (8.7)	1.08	0.28	4.06	0.915
	Deferred-start	13 / 68 (19.1)	1.60	0.66	3.86	0.297
Patient mortality (n=31)	Planned-start	7 / 57 (12.3)	-	-	-	-
	Early-start	7 / 23 (30.4)	1.35	0.65	2.81	0.426
	Deferred-start	17 / 68 (25)	1.62	0.99	2.66	0.053
Peritonitis (n=29)	Planned-start	7 / 57 (12.3)	-	-	-	-
	Early-start	5 / 23 (21.7)	2.10	0.67	6.64	0.205
	Deferred-start	17 / 68 (25)	2.49	1.03	6.01	0.043
Exit site Infection (n=16)	Planned-start	7 / 57 (12.3)	-	-	-	-
	Early-start	2 / 23 (8.7)	0.79	0.16	3.79	0.764
	Deferred-start	7 / 68 (10.3)	0.95	0.33	2.70	0.917
Peri-catheter leak (n=4)	Planned-start	3 / 57 (5.3)	-	-	-	-
	Early-start	0 / 23 (0)	0	0	0	0.989
	Deferred-start	1 / 68 (1.5)	0.32	0.03	3.11	0.328
PD catheter migration (n=10)	Planned-start	1 / 57 (1.8)	-	-	-	-
	Early-start	5 / 23 (21.7)	14.13	1.65	121.04	0.016
	Deferred-start	4 / 68 (5.9)	3.56	0.40	31.87	0.256
First hospitalisation (n=114)	Planned-start	39 / 57 (68.4)	-	-	-	-
	Early-start	19 / 23 (82.6)	1.44	0.83	2.50	0.193
	Deferred-start	56 / 68 (82.4)	2.03	1.35	3.07	0.001

CI: confidence interval

A significant difference between the 3 subgroups was noted in the number of patients who experienced PD catheter migration in the first year by chi-square test (*P*=0.008). Post hoc subgroup analysis found that the early-start PD group had a significantly higher incidence of PD catheter migration at 21.7%, as compared to 1.8% of patients in the planned-start PD group (Bonferroni corrected *P*=0.011).

Cox regression analysis of the secondary outcomes is presented in Table 2 and Fig. 2. The first episode of peritonitis was significantly earlier in the deferred-start PD group (HR 2.49, 95% CI 1.03–6.01, *P*=0.043) and a trend towards earlier peritonitis was also seen in the early-start PD group (HR 2.10, 95% CI 0.67–6.64, *P*=0.205), as compared to planned-start PD (Fig. 2A).

As reflected in Fig. 2B, time to catheter migration was significantly shorter for early-start PD, with a hazard ratio of 14.13 (95% CI 1.65–121.04, *P*=0.016). Time to first hospital admission was significantly shorter for patients in the deferred-start group (HR 2.03, 95% CI 1.35–3.07, *P*=0.001) while no differences were found between planned and early-start PD (Fig. 2C). There were no differences in the time to first exit site infection (Fig. 2D) and peri-catheter leak (Fig. 2E).

DISCUSSION

In this study, no differences were found between the 3 PD initiation strategies for our primary outcomes of interest—technique and patient survival. Planned-PD had the best secondary outcomes with a longer time to the

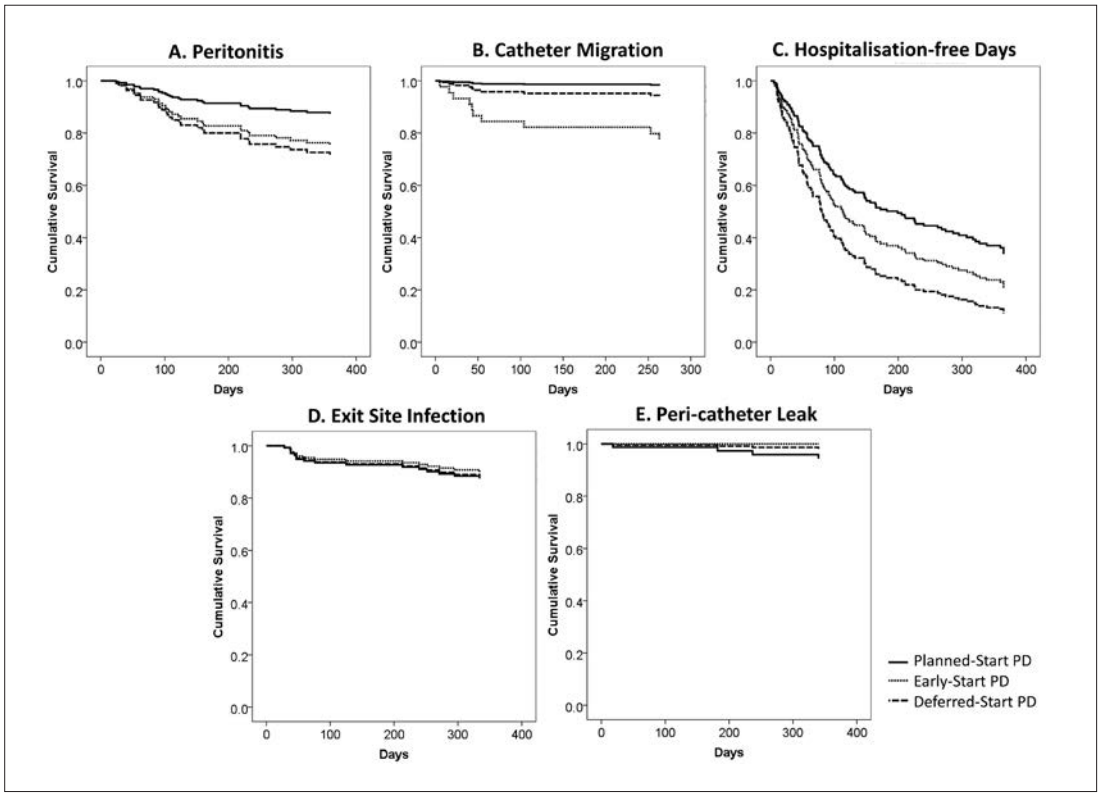

Fig. 2. Survival plot from Cox regression analysis for secondary outcomes of interest in (A) peritonitis, (B) catheter migration, (C) hospitalisation-free days, (D) exit site infection and (E) peri-catheter leak, comparing between planned-start peritoneal dialysis (PD), early-start PD and deferred-start PD.

Table 3. Complications within the first year of peritoneal dialysis (PD) initiation

	All	Planned-start PD (n=57)	Early-start PD (n=23)	Deferred-start (n=68)	*P* value
Patients with technique failure in the 1st year, no. (%)	22 (14.9)	7 (12.3)	2 (8.7)	13 (19.1)	0.424[a]
Deaths in the 1st year, no. (%)	31 (20.9)	7 (12.3)	7 (30.4)	17 (25.0)	0.103[a]
Patients with peritonitis within 1 year, no. (%)	29 (19.6)	7 (12.3)	5 (21.7)	17 (25)	0.201[a]
Patients with exit-site infection within 1 year, no. (%)	16 (10.8)	7 (12.3)	2 (8.7)	7 (10.3)	0.938[a]
Patients with peri-catheter leakage within 1 year, no. (%)	4 (2.7)	3 (5.3)	0 (0)	1 (1.5)	0.376[a]
Patients with catheter migration within 1 year, no. (%)	10 (6.8)	1 (1.8)	5 (21.7)	4 (5.9)	0.008[a]
Peritonitis episodes in the 1st year, median (IQR)	0 (0)	0 (0)	0 (0–1)	0 (0–1)	0.140[b]
Hospital admissions in the 1st year, median (IQR)	2 (1–3)	1 (0–3)	2 (1–2)	2 (1–3)	0.336[b]

IQR: interquartile range; PD: peritoneal dialysis
[a] Fisher's Exact test
[b] Kruskal-Wallis test

first episode of peritonitis. Of note, early-start PD had the highest incidence of catheter migration, but there was no increased risk for peri-catheter leak. Following initiation of dialysis, the time to first hospital admission was the shortest for patients in the deferred-start group.

Studies had consistently shown that urgent-start on PD may be associated with an increased risk of mechanical complications but with no detrimental effects on peritonitis, patient and technique survival as compared to planned-start PD.[17,19] Our study reached similar

conclusions with early-start PD. With no differences in technique and patient survival between various strategies, the physician is given the flexibility to utilise any of the strategies based on available resources, patient's clinical circumstances and preferences. Further studies should evaluate if this strategy of early-start PD can increase long-term uptake of PD.

Early infection is a primary concern with an urgent-start strategy.[10] In the present study, there was no statistically significant difference in the incidence of infectious complications within the first year of PD although the first peritonitis episode was significantly earlier in the deferred-start group while a trend towards significance was seen in the early-start group. Future studies should explore the underlying reasons for this observation and if different antibiotic prophylaxis regimens are required.

The early-start PD group had a significantly higher incidence of PD catheter migration at 21.7% compared to 1.8% of patients in the planned-start PD group, although it did not have a significant impact on technique survival. This may be a significant problem in early-start PD, as there is less time to institute conventional prescription for bowel clearance[10,20] and wait for spontaneous repositioning. It is important to be aware of this common complication and assess early for catheter malposition if there are flow issues.

Abdominal wall complications, especially peri-catheter leakage, are major concerns in urgent-start PD.[22] No peri-catheter leak occurred in our study, which could be attributed to the use of low-volume regimens, to avoid high intraperitoneal pressures in the first 14 days after catheter insertion.

PD patients previously on HD are known to have poorer survival.[5] This was attributed to a more rapid loss of residual renal function, a major determinant of survival in PD patients.[23-25] The median duration on HD for the deferred-start PD group is 67 days as compared to 18 days in early-start PD group. The deferred-start PD group did show a trend towards poor survival, though this did not reach statistical significance. Further studies would be needed to investigate if there was an impact on residual renal function and if this was a substantial factor affecting survival.

Besides ESKD, the early-start strategy can also be adopted for other applications of PD, such as in the management of acute kidney injury or chronic heart failure.[26,27] When patients transit from the acute treatment phase to long-term kidney support, the early-start PD approach may be more practicable with less logistical prerequisites.

The limitation of this study lies in the single-centre observational design. The PD strategy was based on the recommendations of individual nephrologists, taking into account patient and caregiver preferences and circumstances. While individual bias cannot be avoided, our study reflects real-life clinical decision-making and the choice of PD initiation strategy is expected to have no impact on patient and technique survival. Prospective randomised trials would provide more definitive conclusions, but randomised HD vs PD study designs in ESKD patients had not been successful.[28] While early-start PD may strike a balance between planned-start and deferred-start PD, it remains resource- and manpower-intensive and may not a suitable strategy in many centres.

The study was non-randomised and the patient numbers in each subgroup was small. In particular, there were only 23 patients in the early-start group. Furthermore, the event rates were low for some of the outcomes and these limitations may increase the possibility of biased results. Additional baseline clinical factors were not included in the Cox model as the number in each subgroup was small. Socio-economic factors were not included in the study.

For observational studies on the effect of dialysis initiation on mortality, lead time bias is another potential confounder. However, the lead time differences between early-start PD vs deferred-start PD were not expected to be different but may instead favour planned-start PD in terms of survival.

CONCLUSION

A planned start is the best strategy for initiation of dialysis. If this is not possible, our results suggest that early-start PD is a possible alternative that is less resource-intensive compared to urgent-start PD. With a wide choice of various PD initiation strategies, PD is a viable option in most patients who require urgent dialysis initiation.

Availability of data and materials

Individual de-identified participant data will be shared. Data that underlie the results reported in this article, after de-identification, will become available after 9 months and stored for at least 36 months following article publication. This will be provided to investigators who propose the use of data for meta-analysis with proof of approval by an independent review committee identified for this purpose. Proposals may be submitted through the corresponding author. Data will be provided without investigator support other than provision of deposited data.

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REVIEW ARTICLE

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Circular RNAs in the pathogenesis of sepsis and their clinical implications: A narrative review

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ABSTRACT

Introduction: Sepsis is defined as a life-threatening complication that occurs when the body responds to an infection attacking the host. Sepsis rapidly progresses and patients deteriorate and develop septic shock, with multiple organ failure, if not promptly treated. Currently no effective therapy is available for sepsis; therefore, early diagnosis is crucial to decrease the high mortality rate. Genome-wide expression analyses of patients in critical conditions have confirmed that the expression levels of the majority of genes are changed, suggesting that the molecular basis of sepsis is at the gene level. This review aims to elucidate the role of circular (circ) RNAs in the pathogenesis of sepsis and sepsis-induced organ damage. In addition, the feasibility of using circRNAs as novel diagnostic biomarkers for sepsis is also discussed, as well as circRNA-based therapy.

Method: This narrative review is based on a literature search using Medline database. Search terms used were "circular RNAs and sepsis", "circRNAs and sepsis", "non-coding RNAs and sepsis", "ncRNAs and sepsis", "circRNAs and septic pathogenesis", "circRNAs and septic model", "circRNAs and septic shock" and "circRNAs, biomarker, and sepsis".

Results: Numerous studies indicate that circRNAs might exert pivotal roles in regulating the immune system of the host against various pathogens, such as bacteria and viruses. Dysregulation of circRNA expression levels has been confirmed as an early event in sepsis and associated with the inflammatory response, immunosuppression and coagulation dysfunction. This impairment in regulation eventually leads to multiple organ dysfunctions, including of the kidneys, lungs and heart.

Conclusion: By investigating the regulation of circRNAs in sepsis, new molecular targets for the diagnosis and intervention of sepsis can be identified. Such an understanding will be important for the development of therapeutic drugs.

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Keywords: Acute kidney injury, biomarker, circRNAs, inflammation, sepsis

INTRODUCTION

Sepsis is a condition with life-threatening organ dysfunction, resulting from abnormal responses of the host to various infections.[1] The underlying pathogenic mechanisms include an imbalanced inflammatory response, immune disorder, neuroendocrine abnormality, coagulopathy, mitochondrial damage and endoplasmic reticulum stress.[2] A recent study reported that the age-standardised sepsis incidence rate fell by 37.0% and the mortality rate decreased by 52.8% from 1990 to 2017.[3] Despite the declining incidence and mortality rates, sepsis is still a global problem, with the highest health-related burden in sub-SaharanAfrica.[3]

Biomarkers can be used in clinics to evaluate the pathophysiological process of various diseases, and play important roles in assisting the diagnosis, monitoring the efficacy of treatment and influencing the prognosis. There have been >170 biomarkers identified that are associated with sepsis; however, the majority of them lack sensitivity or specificity, and only a few have been used in the clinical diagnosis of infections, including C-reactive protein, procalcitonin, high mobility group protein B-1,

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CLINICAL IMPACT

What is New

- This review provides an update on the understanding of circular RNAs (circRNAs) in the pathogenesis of sepsis and the associated organ dysfunction. It investigates their feasibility as effective and efficient diagnostic and therapeutic biomarkers for sepsis.

Clinical Implications

- The understanding of circRNA-modulated sepsis-induced organ failure is still at a very early stage. Thus, further research is urgently required to investigate the regulation of circRNAs in the progression of different diseases, and to identify specific circRNAs in certain diseases.

interleukins and soluble triggering receptor expressed on myeloid cells-1.[4] Therefore, the severity and recovery of sepsis cannot be objectively evaluated, which limits the wide application of these biomarkers in a clinical setting. Thus, identification of more effective biomarkers is an urgent need to improve diagnosis/prognosis.

Circular (circ) RNAs are newly identified endogenous non-coding RNAs formed by exon scrambling during the splicing process. They are typically covalently closed-loop molecules, which distinguish them from the other 2 linear non-coding RNAs—microRNAs (miRNA/miR) and long non-coding RNAs—which possess caps at the 5' terminal and tails at 3' terminal.[5] With rapid evolution of high-throughput sequencing techniques, circRNAs have been found to be widely distributed in various eukaryotes. They exert significant roles in gene transcription and participate in a range of cellular events such as cell differentiation, apoptosis, autophagy and proliferation, which are all associated with septic pathogenesis.[6] Here, we provide an update on the progress of our understanding of circRNAs in the pathogenesis of sepsis and the associated organ dysfunction. We also investigate their feasibility as effective and efficient diagnostic and therapeutic biomarkers for sepsis.

METHOD

This narrative review is based on a literature search of the Medline database. Search terms used were "circular RNAs and sepsis", "circRNAs and sepsis", "non-coding RNAs and sepsis", "ncRNAs and sepsis", "circRNAs and septic pathogenesis", "circRNAs and septic model", "circRNAs and septic shock" and "circRNAs, biomarker, and sepsis".

Overview of circRNAs

circRNAs have a stable structure, are highly expressed, have specific tissue distribution patterns and are highly conserved among different species.[7] They are widespread and substantial within transcriptomes, an observation confirmed using high-throughput sequencing and analysis platforms.[8] circRNAs are principally derived from exons of protein-coding genes and generally formed via the cyclisation of special mRNAs by reverse splicing, which produces covalently closed-loop structures with a length of about 100 nucleotides.[9] circRNAs are generated by multiple mechanisms, including cyclisation via lariat, intron pairing or RNA binding protein pairing. circRNAs cannot be cut by RNA exonuclease.[10] In addition, based on their origin of biogenesis, circRNAs are categorised into exon-, intron-, exon-intron-, and intergenic circRNAs.[11]

Many circRNAs have been indicated to function as "miRNA sponges" to regulate miRNAs in various body fluids and to also function as protein sponges to determine the concentration of proteins in cells.[5] circRNAs have a longer half-life than their homologues and show good stability.[12] It is well-known that circRNAs are not simply the by-products from mis-splicing; instead they are actively involved in pathological processes of diverse diseases.[13] miRNAs have been found to be differentially expressed during the development of sepsis, suggesting certain circRNAs might also be involved. For example, circ_0091702 was found to serve as a sponge for miR-545-3p to alleviate sepsis-induced acute kidney injury (AKI) by increasing the expression level of thrombospondin 2.[14] These biological characteristics and physiological functions suggest that circRNAs have the potential to be septic biomarkers.

In addition, as miRNA sponges, circRNAs also function as a "miR reservoir". For example, circ-HIAT1 was found to target miR-29a-3p and miR-29c-3p, and increase the stability of miRNAs in human atherosclerosis and cancer.[15] In solid tumours, circ-HIAT1 was found to target matrix metalloproteinases that were increased in both the serum and lung tissues in patients with severe sepsis.[16] The high serum level of miR-29a-3p secreted by immune cells has shown a prognostic value in evaluating the 28-day mortality rate in patients with sepsis, while circ-MYLK and circ-CTDP1 have shown a modulatory role in the expression levels of miR-29a-3p.[17]

circRNAs in sepsis-related inflammation

miRNAs have been confirmed to regulate the cytokine storm of sepsis. For example, miRNAs regulated the differential expression of many key cytokines that were involved in sepsis, including TNF-α, IL-6, IL-10 and IL-18.[18] circRNAs have been proposed to exert essential

roles during different stages of sepsis by regulating lipopolysaccharide (LPS)-induced inflammation and the activation of NF-κB signalling via sponging miRNAs. A recent study found that knockdown of circ_0114428 expression inhibited cereblon expression, and attenuated LPS-induced inflammation and oxidative stress in human kidney 2 (HK2) cells by sponging miR-495-3p.[19] Xiong et al. found that the knockdown of circ_0003420 expression could attenuate the effect of LPS on cell apoptosis, proliferation and inflammation by targeting NPAS4 mRNA.[20] Wei et al. showed that overexpression of hsa_circ_0068,888 could suppress the LPS-induced inflammatory response and oxidative stress, while knockdown of expression could increase these processes.[21] A further study found that hsa_circ_0068,888 inhibited the activation of NF-κB signalling by sponging miR-21-5p.[21] Furthermore, Liu et al. found that circ_0001105 protected the integrity of the intestinal barrier from intestinal inflammation and oxidative stress in septic rats, providing a new perspective to treat sepsis.[22]

circRNAs in sepsis-related immunosuppression

The majority of patients with sepsis may die during the early stage of the cytokine storm. Patients who survive this stage can exhibit immunosuppression—they fail to eliminate primary infections, develop secondary opportunistic infections, and viruses can potentially reactivate—which seriously affects their survival.[2] circMAN2B2, a circRNA abundant in glioma tissues, was found to regulate S100A8 expression levels by inhibiting miR-1205.[23] S100A8 is known to be an important modulator involved in the immunosuppression of sepsis,[24] suggesting a potential role of circMAN2B2 in sepsis-related immunosuppression. miRNAs are able to suppress ZEB1/2-mediated drug resistance and immunosuppression; therefore, circRNAs as upstream modulators of the miR/ZEB1 axis could have a possible role in sepsis-induced immunosuppression.[25]circMET was found to drive immunosuppression in hepatic carcinoma via the miR-30-5p/zinc finger protein SNAI1 (Snail) axis,[26] while Snail was markedly elevated in glomerular tissue in septic patients,[27] suggesting potential roles of circMET's in sepsis-related immunosuppression.

circRNAs in sepsis-related coagulation dysfunction

Activation of the coagulation system is affected during sepsis, which is a critical indicator during the development of sepsis. Endothelial cells (ECs) exert an essential effect on maintaining vascular homeostasis and are the primary targets of inflammatory mediators in sepsis. The persistent damage to ECs could cause organ failure.[28] A recent study showed that the overexpression of circ-C3P1 suppressed cell apoptosis and pro-inflammatory cytokines in pulmonary microvascular ECs in an LPS-induced sepsis mouse model by negatively modulating miR-21.[29] These findings indicate that the endothelial function could be damaged by the abnormal expression level of circRNAs, which finally leads to coagulation disorder and expedited septic progression.

circRNAs and sepsis-related organ dysfunction

circRNAs in sepsis-induced AKI

AKI is a frequently observed condition in the clinic with a high incidence rate, and acute inflammation and tissue injury are common indications. Sepsis is one of the most common causes of AKI, accounting for more than half of AKI cases. Among them, sepsis, triggered by LPS, is the dominant factor of AKI in patients in a critical condition, and is often used to establish in vitro sepsis-induced AKI models. Recently, a range of circRNAs have been shown to be involved in the development of AKI. For example, knockdown of circ-FANCA was found to alleviate LPS-induced HK2 cell injury by modulating the miR-93-5p/OXSR1 axis in sepsis-induced AKI.[30] circ-Ttc3 was found to reduce the inflammatory response and oxidation by targeting the miR-148a/Rcan2 axis in rats with sepsis-induced AKI, indicating that circ-Ttc3 could be a potential therapeutic target.[31] In addition, the involvement of circRNAs in regulating programmed cell death and cell cycle progression indicates that they are novel modulators for sepsis-induced AKI.[20] For example, circRar1 was found to induce the transcriptional activity of apoptosis-related factors in lead-induced neurotoxicity by regulating miR-671.[32]

circRNAs in sepsis-related acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is known as an independent risk factor for mortality in patients with sepsis. Accumulating evidence has shown that LPS can induce the activation and migration of the monocyte-macrophage system. This system further engulfs inflammatory particles invading the lungs, and secretes a mass of bioactive substances that facilitate neutrophil migration during ARDS development.[33] A recent study investigated the circ-ANKRD36-associated molecular mechanism underlying sepsis-related ARDS and confirmed that circ-ANKRD36 expression levels were markedly increased in the serum of patients with sepsis-related ARDS. In addition, knockdown of circ-ANKRD36 expression reduced cell viability and migration in LPS-treated RAW264.7 cells by sponging miR-330, suggesting a novel strategy in treating sepsis-related ARDS.[34] Another study confirmed the protective roles of the P2X7R antagonist in mice with sepsis-related

ARDS by regulating the expression levels of circ_0001679 and circ_0001212, suggesting these 2 circRNAs could be potential targets for sepsis-related ARDS treatment.[35]

circRNAs in sepsis-related myocardial dysfunction

Sepsis-related myocardial dysfunction **(**SIMD) is another significant complication following sepsis. Myocardial depressant factors, apoptosis, inflammatory cytokines, complement activation as well as nitric oxide have been found to contribute to the pathological course of SIMD.[36] The current strategies to treat SIMD include maintaining the stability of haemodynamics and supporting the normal cardiac function. Nevertheless, specific medications were limited, due to the undefined regulatory mechanism underlying the pathogenesis of SIMD. circRNAs are emerging as important modulators in a range of biophysiological processes, including myocardial dysfunction. For example, circ-HIPK2 was found to regulate proliferation and differentiation during myogenesis by targeting ribosomal protein Rpl7.[37] circACSL1 was found to modulate MAPK14 expression by sponging miR-8055 and aggravating myocardial inflammation and damage. This effect suggests that circACSL1 could be an effective biomarker used in the diagnosis and treatment of myocardial dysfunction.[38] In addition, miR-23b-induced activation of myocardial fibrosis has been confirmed as a key factor of myocardial dysfunction in advanced sepsis, while a miR-23b inhibitor was found to reduce cardiac fibrosis during the late stage of sepsis. A recent study found that the inhibition of miR-23b by circ_0005075 prevented polymicrobial sepsis-induced cardiac disorder by modulating TG-interacting factor 1 (TGIF1), phosphatase and tensin homologue deleted on chromosome 10 (PTEN), suggesting that circ_0005075 might be an effective modulator in the treatment of SIMD.[39] Recent studies on the roles of circRNAs in sepsis-induced organ failure are shown in Table 1.

circRNAs in virus-induced sepsis

Sepsis is commonly induced by bacterial infection; however, it can also be triggered by viral or fungal infection, causing weaker inflammatory responses. Until now, there is no definite diagnostic criterion for virus-induced sepsis. The discovery of circRNAs shows their advantages over other biomarkers, such as a high stability in the presence of viral infection, and may thus be used as potential diagnostic tools. A recent study found that NF90/NF110 released from host circRNP complexes could couple with viral mRNAs as part of the anti-viral immune response and against viral infection.[55] As circRNA expression is generally low, a certain group of circRNAs, not a single specific circRNA, may function together as molecular reservoirs of NF90/NF110 for rapid immune response upon viral infection.[55]

Technologies used to identify and evaluate circRNAs as biomarkers

The difficulty in distinguishing circRNAs from other non-coding RNAs has led to the late discovery of circRNAs. Currently, subject to the limited detection methods, circRNAs have to lose its circularity in order to be successfully detected. A protocol called Circle-Sequencing (Circle-Seq) has been recently proposed and used to process linear RNAs using RNase R enzyme, while keeping circRNAs intact.[56] However, this protocol shows certain limitation in determining the circularity of a RNA transcript as certain circRNAs are sensitive to RNase R, and might lead to false negative results. Other strategies, including 2-dimensional denaturing polyacrylamide gel electrophoresis, ribosomal RNA or poly(A) depletion, are also used to isolate and concentrate circRNAs in samples with unknown efficacy in clinical practice.[57] Microarray is another promising diagnostic tool, which can be used to determine the relative levels of different circRNAs due to its sensitivity and specificity. However, it is only able to evaluate those circRNAs covered in the array, and cannot be used to measure the total amount of circRNAs.[58]

Currently, reverse transcription-quantitative polymerase chain reaction is broadly utilised to recognise and quantify circRNAs. It shows great advantages over other methods as it is simple and inexpensive as a detection tool for diagnostic biomarkers.[59] In addition, RNA-sequencing (RNA-Seq) technology, combined with bioinformatics analysis, enables the comprehensive study on circRNAs, and significantly contributes to the discovery and characterisation of circRNAs.[60] Disease-related circRNAs have been identified in human peripheral blood using RNA-Seq.[45]

circRNAs have a crucial role in sepsis, thus it is essential to clarify the underlying mechanisms of different circRNAs involved in the pathogenesis of sepsis, in addition to identifying novel circRNAs that regulate the heterogeneity of sepsis.

CONCLUSION

Diagnosis of early sepsis is extremely important to maximise the survival rate in patients with sepsis. The availability of accurate biomarkers will be particularly beneficial to enable the delivery of prompt and appropriate treatment. However, none of the current biomarkers, that are clinically evaluated could offer 100% specificity for the diagnosis of sepsis.[4] circRNAs, as newly identified

Table 1. Recent studies on the roles of circRNAs in sepsis-induced organ failure

circRNAs	Downstream targets	Functions
circ-ANKRD36	miR-330	Its knockdown suppresses cell viability and migration in LPS-stimulated cells[34]
circ-BNIP3L	miR-370-3p/MYD88	Its knockdown alleviates LPS-induced renal tubular epithelial cell injury[40]
circ-C3P1	miR-21	Attenuates pro-inflammatory cytokine production and cell apoptosis in septic ALI[29]
circ-DMNT3B	miR-20b-5p	Its downregulation is conducive to intestinal mucosal permeability dysfunction[41]
circ-FADS2	miR-15a-5p	Suppresses LPS-induced lung cell apoptosis[42]
circ-FANCA	miR-93-5p/OXSR1	Its knockdown alleviates LPS-induced HK2 cell injury[30]
circ-Fryl	miR-490-3p/SIRT3	Attenuates sepsis-induced lung injury[43]
circ-HIPK3	miR-29b	Promotes homeostasis of the intestinal epithelium[44]
circ-PRKCI	miR-545	Associated with sepsis risk, disease severity and 28-day mortality[45]
	miR-545/ZEB2	Relieves LPS-induced HK2 cell injury[46]
	miR-106b-5p/GAB1	Alleviates LPS-induced HK2 cell injury[47]
circ-PTK2	miR-181c-5p/HMGB1	Regulates microglia activation and hippocampal neuronal apoptosis induced by sepsis[48]
circ-TLK1	miR-106a-5p/HMGB1	Promotes sepsis-associated AKI by regulating inflammation and oxidative stress[49]
circ-Ttc3	miR-148a/Rcan2	Regulates inflammation and oxidative stress in septic rats with AKI[31]
circ-VMA21	miR-199a-5p/NRP1	Ameliorates LPS-induced AKI[50]
	miR-9-3p/SMG1	Ameliorates sepsis-associated AKI inflammation and oxidative stress[51]
circ_0001105	YAP1	Protects intestinal barrier in septic rats by inhibiting inflammation and oxidative damage[22]
circ_0003420	NPAS4	Mediates inflammation in sepsis-induced liver damage[20]
circ_0068,888	miR-21-5p	Protects against LPS-induced HK2 cell injury[21]
circ_0091702	miR-545-3p/THBS2	Attenuates sepsis-related AKI[52]
	miR-182/PDE7A	Relieves LPS-induced cell injury[53]
circ_0114428	miR-495-3p/CRBN	Regulates sepsis-induced kidney injury[19]
circ_104484/circ_104670	-	Serves as potential novel biomarkers and therapeutic targets for sepsis[54]

AKI: acute kidney injury; ALI: acute lung injury; circ/circRNA: circular RNA; CRBN: cereblon; GAB1: growth factor receptor binding 2-associated binding protein 1; HK2: human kidney 2; HMGB1: high mobility group box 1; LPS: lipopolysaccharide; miR: microRNA; MYD88: myeloid differentiation primary response protein 88; NPAS4: neuronal PAS domain protein 4; NRP1: neuropilin-1; OXSR1: oxidative stress-responsive 1; PDE7A: phosphodiesterase 7A; Rcan2: regulator of calcineurin 2; SIRT3: sirtuin 3; SMG1: suppressor of morphogenesis in genitalia 1; THBS2: thrombospondin 2; YAP1: Yes-associated protein 1; ZEB2: zinc finger E-box binding homeobox 2

Superscript numbers: Refer to numbers in REFERENCES

non-coding RNAs, have been associated with various molecular responses such as inflammation, immune suppression and endothelial function, and are significantly altered during the progression of sepsis.

circRNAs show promising potential as biomarkers based on their strong resistance to exonucleases and high stability in blood. Their levels are increased and have an average half-life of 48 hours compared to 10 hours for other linear non-coding RNAs in the serum.[61] The putative function of circRNAs as miRNA sponges makes them particularly interesting therapeutic targets for future research. Furthermore, circRNAs have tissue-specific and developmental stage-specific features. Their expression levels have been shown to be associated with the occurrence and development of various diseases, including sepsis. However, the understanding of circRNA-modulated sepsis-induced organ failure is still at a very early stage. Further research is urgently required to investigate the regulation of circRNAs in the progression of different diseases, and to identify specific circRNAs in certain diseases. Therefore, circRNAs are attracting increasing attention in sepsis research, and may play significant roles in the diagnosis, treatment and prognosis of sepsis.

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REVIEW ARTICLE

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Medicolegal aspects of non-rapid eye movement parasomnias

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ABSTRACT

Introduction: In a subset of adults with non-rapid eye movement (NREM) parasomnias, clinical variants might be violent in nature and can potentially result in unintentional but considerable harm. As such, there is substantial interest on the forensic ramifications of these sleep behaviours.

Methods: This review examined the diagnostic criteria for parasomnias established in the context of international classification systems; medicolegal case reports; legal frameworks; and court cases in and outside of Singapore, to provide an overview of the implications of NREM parasomnias.

Results: Violent or injurious behaviours that occurred in the context of somnambulism, otherwise known as sleepwalking, have challenged traditional legal theories of criminal culpability. Yet little has changed in the application of sleep science to criminal responsibility. In Singapore, the defence of somnambulism has hitherto not been directly raised. Nonetheless, sleep medicine practitioners may increasingly be requested to render their opinions on legal issues pertaining to violent or injurious behaviours allegedly arising during sleep. Although the understanding of NREM parasomnias has improved, there is still a dearth of evidence to support both medical and legal decisions in this area.

Conclusion: NREM parasomnias come with disquieting legal and forensic implications for adjudicating criminal responsibility. There is a need to critically examine legal perspectives on behaviours occurring during sleep. More reliable empirical studies investigating the pathophysiology of NREM parasomnias can offer clearer diagnostic guidelines and address complex behaviours of NREM that often come with medicolegal implications.

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Keywords: Criminal law, forensic evaluation, sexsomnia, sleep violence, sleepwalking

INTRODUCTION

Parasomnia is a clinical sleep disorder, which involves undesirable physical or behavioural phenomena that arise predominantly during sleep.[1,2] This can occur during any stage of sleep, including the transition from wakefulness to sleep, while asleep, or during awakening.[3]

One category of parasomnias occurs primarily during sudden but incomplete awakening from slow-wave sleep, which is the deepest stage of non-rapid eye movement (NREM) sleep, known as NREM stage 3 sleep.[4,5] This category of parasomnias occurs most commonly in the first third of the night.[4,5] In the International Classification of Sleep Disorders, third edition (ICSD-3), this category of parasomnias, also known as NREM-related parasomnia, is subdivided into 4 types: confusional arousals, sleepwalking, sleep terrors and sleep-related eating disorder.[1] In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), the terminology is "NREM sleep arousal disorders", with specification of sleepwalking type, sleep-related eating disorder as a subtype of sleepwalking, and sleep terror type.[2] Notably, "sleepwalking" is not confined to simple ambulation, with subtypes outlined in the DSM-5.[2]

Another category of parasomnia outlined in the ICSD-3 is the rapid eye movement (REM) sleep behaviour disorder (RBD). The criteria for RBD require (1) repeated episodes of behaviour and/or vocalisation that are documented by polysomnography (PSG) to arise from REM, or presumed to arise from REM based on reports of dream enactment; and (2) evidence of REM sleep without atonia on PSG.[6] When REM sleep without atonia is not observed, other clinical findings that may be strongly suggestive may guide the diagnosis of RBD.[6]

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CLINICAL IMPACT

What is New

- This paper provides an overview of the legal implications of non-rapid eye movement (NREM) parasomnias, and explores the role of sleep disorder specialists and expert witnesses, with references to court cases in and outside Singapore.

Clinical Implications

- Sleep medicine practitioners will increasingly be requested to render their opinions on legal issues pertaining to violent or injurious behaviours allegedly arising from NREM parasomnias.
- There is a need for clear guidelines to support both medical and legal decisions on these complex behaviours.

NREM parasomnias can affect both children and adults, but its prevalence in the general population tends to vary with age. NREM parasomnias are much more prevalent in childhood, and often with episodic recurrence that typically decreases with age.[5,7] For example, NREM parasomnias may affect as many as 20% of children and 4% of adults.[8] Similarly, a systematic review and meta-analysis showed that the prevalence of somnambulism, otherwise known as sleepwalking, is 5% in children within the past 12 months, while the prevalence in adults is 1.5%.[9]

NREM parasomnias are characterised by several clinical features. These include unresponsiveness or altered perception to external stimuli;[10,11] time and space disorientation;[10] diminished conscious awareness accompanied by affective, autonomic and motor activation;[12,13] and full or partial post-episodic amnesia.[14] The prototypical behavioural patterns of NREM parasomnias are confusional arousal, somnambulism and night terrors, which are postulated to represent a hierarchical continuum rather than distinct entities.[10] Although 1 behavioural pattern might predominate, most individuals with NREM parasomnias also experience other variants of sleep disorders.[15]

Many disorders within the category of parasomnias are generally benign and do not invite legal scrutiny. However, a minority of these clinical variants might be violent in nature, and can potentially result in unintentional but considerable harm to self and others, or damage to the environment.[5,16] In a study by Lopez et al., almost half of the clinical patients with NREM parasomnias reported self-injurious and aggressive behaviours (47/100 sleepwalkers).[17] More commonly observed in males, these behaviours appear to involve complex behaviours that require some executive functions (e.g. moving furniture and driving).[11,14]

During an episode of NREM parasomnia, individuals may also display sleep-related sexual behaviours or sexsomnia. The first known case of sexsomnia was described in a report from Singapore in 1986, involving a married man with nocturnal episodes of masturbation during sleep despite having nightly sexual intercourse with his wife.[18] It is a subtype of confusional arousals and sleepwalking. It subsumes a wide spectrum of sexual activities occurring during sleep, ranging from explicit sexual vocalisation, violent masturbation, indecent exposure, and sexual contact with oral, genital or anal regions.[19,20]

Sexsomnia can be problematic. It can result in sleep disruption for the bed partner, and physical injury and harm to the individual or bed partner due to aggressive sexual behaviours. It can also cause psychological disturbance to the bed partner from offensive sexual sleep-talking, inappropriate time and type of sex, and non-consensual nature of the sexual behaviours.[21] Sexsomnia can also become a significant legal issue if the sexual misconduct leads to accusations of sexual assault or rape, or when a minor is involved.

METHODS

This review examined medicolegal case reports, and court cases in and outside of Singapore, to provide an overview of the implications of NREM parasomnias. It also provides a summary of legal frameworks upon which criminal liability of NREM parasomnias is determined, and summarises some of the overarching challenges presented by the case reports and court cases.

RESULTS

In a systematic review of medicolegal case reports on sexsomnia conducted by Ingravallo et al., victims in 4 out of 9 cases were aged between 4 and 10 years old, and victims in 2 other cases were adolescents.[22] Of these 9 cases, the verdict for 8 cases was in favour of the defendant (the accused), while the trial outcome for the remaining case was unknown.[22] Cases of sexsomnia, however, often go unreported as patients and/or their bed partners are hesitant to talk about it unless there is a legal issue.[21]

Some individuals with NREM parasomnia may also exhibit sleep-related violent behaviours, or violent somnambulism.[23-25] In a study by Lopez et al., 55/100

patients diagnosed with somnambulism at a sleep disorders clinic presented violent behaviours, with 31.25% directed at the patients themselves and 45.83% towards their bed partners.[15] Notably, despite the classic view of NREM parasomnias as non-dreaming states, this complex subtype has a pattern of vehement dream enactments, which occur in the absence of REM sleep without atonia on PSG.[25] When actively probed about these complex and agitated episodes of NREM parasomnia, patients often reported vague recollections of terrifying dream-like experiences and imagery that involved some form of perceived threat to themselves or to a loved one.[26,27] This elicits an intrinsic sense of emergency, and the patient's corresponding emotionally charged responses to these perceived threats were often the cause of injury.[28] Such pattern of vehement dream enactments in NREM parasomnia has to be distinguished from the dream enactment of REM parasomnias. Furthermore, available reported cases on violent somnambulism refer almost exclusively to adults.[10] This phenomenon parallels the gradual development of cognitive abilities and dream imagery in children, where children have fewer dreams than adults.[29] As a result, children likewise have less frequent reports of the mental content of NREM parasomnia episodes than adults.[10,29]

The ICSD-3 does not acknowledge sleep-related violence to be a separate pathophysiological subtype, although it mentions the possibility of nocturnal violence for disorders of arousal.[11] Similarly, the DSM-5 mentions that violence during sleepwalking as likely to occur in adults,[2,11] and not as a subtype of parasomnia.[2]

The law and NREM parasomnias

English common law may describe a legal tradition, rather than reflective of current territorial jurisprudence. For example, the influence of the English common law on the development of Singapore law may be more evident in traditional common law areas (e.g. Restitution) than in other statute-based areas (e.g. Criminal Law).[30] It should also be noted that within the UK, there are differences in Scotland and Northern Ireland, which maintain some of their own laws and precedents. Similarly, former dominions such as Canada and former colonies such as Singapore have developed their own Constitutions, Acts of Parliament, and case law. Singapore law, which was enacted since independence and includes the Penal Code, has not specifically addressed the issue of culpability in cases of sleep-wake disorders, and there are no legal precedents of such cases. In the absence of legislation and legal precedent, the Singapore courts may choose, as they often do, to use precedent cases in the UK and Commonwealth countries with similar legal frameworks but these precedents are not binding. This review does not discuss other countries with other legal systems.

There is substantial interest in the forensic ramifications of sleep-related behaviours, such as personal injury, inappropriate sexual behaviours and homicide.[13] Although these behaviours occurring during sleep are rare, they come with troubling legal and forensic implications for adjudicating criminal responsibility.[31]

In the English legal tradition, criminal liability requires the presence of 2 elements: actus reus (i.e. guilty act) and mens rea (i.e. guilty mind).[32] This is derived from the Latin maxim "actus non facit reum nisi mens sit rea", which means "the act does not make a person guilty unless the mind is also guilty".[33] Presence of both elements are required before a person can be convicted of an offence.

When violent behaviour and harm towards others occur, the law considers citizens to be responsible unless medical testimony can convincingly establish the absence of consciousness, such as during sleep or an epileptic seizure.[31] Hence, the diagnosis of NREM parasomnias has been raised as a legal defence to deny mens rea for the crimes alleged, including road traffic accidents, rape, murders and attempts to conceal forensic evidence.[8] Sleep medicine practitioners are increasingly requested to render their opinions on legal issues pertaining to violent or injurious behaviours allegedly arising from sleep.[16] In NREM parasomnia where there is no "state of mind", and the absence of the requisite mens rea, an individual cannot be convicted of a criminal offence[8] except in possible instances of negligence, which will be discussed later.

Although acts that occurred in the context of somnambulism have challenged traditional legal theories of criminal culpability, little has changed in the application of sleep science to criminal responsibility since the late 19th and early 20th centuries.[8] Society continues to struggle with the concept of violent behaviours and criminal acts during sleep, and individuals who use episodes of NREM parasomnia to establish a legal defence are often viewed as malingering and exploiting the legal system.[31] Given the lack of conscious awareness and control during these sleep behavioural episodes, deleterious consequences can ensue unpredictably, and with no forewarning in individuals with usually benign and non-violent NREM parasomnias.[10]

Automatism

During an episode of NREM parasomnia, the individual is capable of performing acts that are not the product

of any "conscious" decision or will. Thus, actions in legally unconscious states are termed "automatisms".[8,34] Automatism would not be deemed an actus reus of a crime as it is not a voluntary act. "Sane" automatisms have an external cause, such as hypoglycaemia (e.g. caused by a blow to the head).[35] "Insane" automatisms, on the other hand, are a result of internal factors—such as brain tumour or a psychological disorder—and are referred to as "diseases of the mind". Idiopathic cases of NREM parasomnia and those associated with family history would also be categorised as insane automatisms. Where sane automatisms can result in complete acquittal, insane automatisms traditionally result in compulsory confinement in a psychiatric facility.[35]

Insanity

Somnambulism has also been considered a variant of the insanity defence for criminal acts during sleep. The insanity defence undermines the mens rea requirement by establishing that at the time of the crime, the defendant lacked the mental capacity to comprehend the nature of his act or to distinguish between right and wrong in accordance with the law.[31] This requires an extensive psychological and psychiatric examination by experts to determine if a mental disorder or defect had impaired the defendant's ability to conform to the law at the time of the crime, and the experts will then have to testify at trial.[36] In England and Wales, somnambulism is classified as insane automatism because an internal factor must be involved for the behaviour complex to be evoked. When a sleepwalking episode is triggered by a sudden arousal from an external factor such as a blow, it is classified as sane automatism.[37]

The defence of insanity for crimes arising from somnambulism, however, is rarely pleaded in the UK.[38] This is because modern legal systems are abandoning the classification of somnambulism as an insanity defence, as criminally insane defendants are often admitted to a mental institution, which is an inappropriate treatment for sleepwalkers.[39] Another major problem with the current legal system is the endeavour to label automatism as sane or insane, which is stigmatising and medically untenable, and hence should be dropped.[37] Instead, Popat and Winslade proposed to consider that different factors may evoke automatisms or NREM parasomnias in individuals differently.[35] Accordingly, there should be varying levels of legal responsibility and appropriate legal consequences for cases where an offence occurred as a result of NREM parasomnia.[35] In cases where automatisms were caused by factors within one's control, the individuals should be held legally accountable for their actions. On the other hand, individuals who exhibit automatism due to factors that are out of their control should not be held responsible for their actions.[31,35] Consider, for example, an individual who has been accused of an offence during an episode of NREM parasomnia triggered by excessive alcohol consumption. In the current jurisprudence, it would be classified as sane automatism because the episode was triggered by an external factor. Hence, the individual may be acquitted as he did not have full mental capacity while he was intoxicated, despite the voluntary act of getting drunk. The new schema, in contrast, would hold the individual legally responsible for his actions as the automatisms were triggered by factors within his control.[35]

Physiological features of NREM parasomnia

A new theory known as "state dissociation theory" was developed to understand NREM parasomnias, in which brain activity lies between the sleeping and waking states.[35] According to this theory, sleep and wakefulness are neither dichotomous nor mutually exclusive, and can mix or oscillate rapidly. Typically, the body's physiological mechanisms synchronise or line up for one particular state. However, in the case of somnambulism, although the body prepares to enter the deep stages of NREM sleep, some important mechanisms do not occur and significant motor activity (an aspect of wakefulness) remains.[40] Studies conducted on NREM parasomnia using PSG found that 97% of patients with somnambulism displayed an abnormal motor behaviour or sustained muscle activity during an episode of NREM parasomnia or when there was one hypersynchronous delta wave arousal.[15]

Although this apparent conflict of activation appears to result in NREM parasomnias, it does not explain why certain NREM behaviours occur in some people but not in others. Currently, video PSG is not performed for routine evaluation of NREM sleep parasomnia as it has limitations in differentiating between patients and normal sleepers due to its low sensitivity for positive diagnosis.[41] Instead, video PSG is utilised only to rule out differential diagnoses, including REM sleep behaviour disorder, sleep-related epilepsy, and other sleep disorders such as obstructive sleep apnoea syndrome.[10] Further research is needed to elucidate the exact mechanisms that enable this state dissociation, and the causative factors or triggers that are unique to NREM parasomnias.

The first documented probable case in England arose in 1686 when Colonel Cheyney Culpeper shot and killed a guardsman and his horse. He was tried and convicted of manslaughter by reason of insanity at the Old Bailey in London. Culpeper, who was known to be a sleepwalker,

was eventually pardoned by King James II.[42] Over the centuries, there have been several cases of interest, with judgements largely based on applications of the concepts of automatisms, consciousness and sanity. The defence of somnambulism has hitherto not been raised in Singapore to date. There may come a time when Singapore courts will have to consider the plea, with the opportunity for it to be better dealt with.[43]

One of the first few cases in this region where the defence of automatism was asserted took place in 1955 (prior to the independence of Malaysia and Singapore) in an appeal case of *Sinnasamy v Public Prosecutor* [1956] 1 MLJ 36 Court of Appeal (Malaya).[44] In this case, the appellant was accused of murdering his infant daughter. An expert witness testified that the appellant was epileptic, but further stated that although automatism is associated with epilepsy in some cases, an individual acting under automatism would not have been conscious. Automatism is often perceived as amounting to a lack of consciousness rather than an inability to control one's actions. It was so regarded by the Malayan Court of Appeal in this case.[45] As the appellant was able to relate in great detail what transpired immediately before and after the alleged offence, the Court of Appeal hence concluded that the appellant was conscious at the time of the crime and was not acting in a state of automatism.

In a subsequent case of *Public Prosecutor v Kenneth Fook Mun Lee* (No. 1) [2002] 2 MLJ 563 (High Court of Malaysia), the accused was having a hypoglycaemic attack at the time of an alleged murder. This resulted in a state of automatism, which the judge referred to as "a state of defective consciousness in which a person performs unwilled acts".[46] It was further remarked that "[t]he defence of automatism can be reduced to the question whether at the material time the accused had the mental capacity to form the particular mental ingredients of the crime with which he is charged".[46] As the cause of the accused's hypoglycaemic attack was not known and was likely to recur, the Malaysian High Court thus concluded that the case was classified as insane automatism.

Rather than consciousness per se, the necessary component of automatism and actus reus is the impaired mental capacity to restrain and control one's behaviour. There is the danger of associating automatism with unconsciousness as illustrated in the cases before, and it would be too restrictive to limit automatism to cases where an individual is totally unconscious. Cases have been presented where the individual is in a dream-like state, such as during an episode of NREM parasomnia, and the capacity to consciously control one behaviour is compromised. It is crucial to understand that it is not unconsciousness per se, but incapacity that renders an act as involuntary.[43]

In Singapore, a search of the public databases and court files showed that NREM parasomnia was mentioned in only 1 case in 2018, in *Public Prosecutor v Thompson Matthew* [2018] SGMC 22 at the State Courts of Singapore.[47] An Australian veterinarian was charged with outraging the modesty of a flight attendant on a Singapore-registered aircraft. According to the first charge, he was accused of using his left hand to touch the victim "at her right hip, over her stomach until her lower breast in one motion".[47] According to the second charge, he used his left hand to touch the victim "at her right hip and over the stomach in one motion".[47]

During the trial, the victim testified that upon being first touched, she asked the defendant, "Sir, are you okay? Would you like some water?" and pushed his hand away. She "noticed the Accused looking at her blankly, and that his eyes were red and puffy. She did not notice any alcoholic smell around him. The Accused did not respond to her and continued to stare blankly at her".[47] This happened 4 hours into the flight. Within the first 2.5 hours of departure, the defendant had consumed 4 alcoholic drinks, and reportedly fell asleep.

The role of sleep disorder specialists and expert witnesses

In the above case, the defence had brought testimony from a psychologist in Australia who diagnosed the defendant with mixed anxiety and depression, and reported that the defendant had undergone a course of psychotherapy. The defence also reported that an Australian medical doctor had given venlafaxine for generalised anxiety disorder, and doxylamine succinate, an antihistamine used for mild insomnia, which the defendant had taken prior to the flight. Furthermore, he was sleep-deprived before boarding the flight. After he was charged, the defendant saw a Singapore psychiatrist, who testified that the accused's behaviour appeared to have been an involuntary exaggerated startle response directly related to his underlying generalised anxiety disorder and being awakened from sleep.

During the examination by the defence counsel, the psychiatrist opined that besides the startle response, the accused also "likely experienced a 'disorder of arousal' when he transited from deep non-Rapid Eye Movement sleep to wakefulness".[47] However, upon cross-examination, the psychiatrist stated that he "did not diagnose the Accused with disorder of arousal in his report and that it would be dangerous to make a

psychiatric assessment of such a disorder on the basis of the few facts that had been put to him in court, since there is a rigorous set of interviews and history-taking before psychiatrists can come to a psychiatric assessment and diagnosis".[47] The psychiatrist further testified that while he "considered doing a polysonography [sic] on the Accused, he had decided against it as it would have been difficult to replicate all the conditions surrounding the commission of the alleged offences including the level of his sleep deprivation and the level of blood alcohol".[47]

With regard to disorder of arousal, the District Judge found that since the psychiatrist was "not prepared to make a diagnosis of a disorder of arousal in the absence of history-taking from persons who have observed the patient and witnessed the manifestations of the disorder, or an assessment by a neurologist or sleep disorder specialist"[47] and "was not prepared to accept that the Accused had committed the offending acts in the two charges as a result of a disorder of arousal",[47] the accused was found guilty of outrage of modesty on both counts. The case was appealed to the High Court, but the issue of disorder of arousal did not arise in the appeal.

Forensic evaluation for NREM parasomnia

Forensic evaluation for NREM parasomnia includes psychiatric history (including family and personal history of sleep disorder), and complete physical and neurological examinations.[22] Even though a full night of PSG with audiovisual monitoring is warranted, complex sleep behaviour episodes may not be captured as NREM parasomnia episodes are less likely to occur in clinical settings.[48] In order to address this, sleep behaviour can be monitored at home using a portable PSG recorder.[49] Alternatively, common provocative tests, such as alcohol ingestion and sleep deprivation prior to the sleep study, may be undertaken to evoke and replicate the sleep behaviour.[50]

Despite great advances in sleep medicine, such as in the use of electroencephalography, sophisticated imaging techniques to monitor sleep, and the recognition of the comorbidity between parasomnias and psychiatric disorders, it is difficult to discern between true and fraudulent claims of NREM parasomnias. This is because circumstances can never be reliably reproduced. Thus, ascertaining whether a criminal act arose as a result of a sleep disorder, dissociative disorder, or deliberate behaviour with denial of recall is a challenge.[8,11] For example, the utility of PSG and technical scientific data from a formal sleep study would only indicate if the defendant has an NREM parasomnia disorder, with no relevance as to whether an NREM parasomnia episode was occurring at the time of the incident. PSG as a diagnostic tool is not associated with the crux of the legal focus on the defendant's mens rea in a criminal allegation. Thus, PSG is not routinely performed as part of a medicolegal evaluation.[51]

DISCUSSION

NREM parasomnias lie at the very intersection of sleep medicine, forensic neuropsychiatry and jurisprudence. Currently, the term "conscious" is used legalistically in the sense that consciousness and unconsciousness are binary and dichotomous states. However, in scientific reality, they exist on a continuum from coma to hyperarousal states like panic attacks and psychosis.[52] Similarly, in legal parlance, an act is either voluntary or involuntary, whereas the extent of voluntariness may in fact be nuanced, e.g. in the case of tics and choreas. In English common law, the legal defence of automatism is divided into 2 explicit categories: sane and insane automatisms,[31] again in a manner supposing that sanity is "all or nothing".

The medicolegal aspect of NREM parasomnia is particularly complex, with little evidence to support judgement in court, and expert evidence is largely opinion-based—built on history from patients, family and friends, and eyewitnesses. There is a need to increase scientific knowledge on the different aspects for diagnosis, pathophysiology and treatment modalities of NREM parasomnias, and to critically re-examine legal perspectives on behaviours occurring during sleep. Empirical studies investigating the pathophysiology of NREM parasomnias may offer reliable and clear diagnostic guidelines and insight into complex behaviours of NREM parasomnias that often come with medicolegal implications.[11]

CONCLUSION

An undiagnosed or incorrect diagnosis of NREM parasomnia can have significant medicolegal implications. If incorrectly diagnosed, the guilty or potentially dangerous individual may go free. Conversely, an individual with a treatable but unrecognised NREM parasomnia may be wrongly incarcerated.[8] In spite of the dearth of evidence to support both medical and legal decisions in this area, it is imperative to recognise and diagnose NREM parasomnias properly.

Formulating guideline recommendations is, however, beyond the scope of this review, but the proposal has indeed been suggested.[8,37,53] Clearer guidelines can ensure that assessment is supported by strong evidence, based on prevalence and pathogenesis of criminal behaviours

in sleep. This can help address the challenges and ambiguities of presenting legal cases related to sleep disorders in the courtroom setting. It can ultimately assist the jury in making a well-founded decision on the presence of mens rea associated with the alleged criminal act. Over 2 millennia ago, Socrates was particularly astute when he summed it up with this quote from Plato's *The Republic*, "in all of us, even in good men, there is a lawless wild-beast nature, which peers out in sleep".

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COMMENTARY

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Health economics of kidney replacement therapy in Singapore: Taking stock and looking ahead

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ABSTRACT

The prevalence of end-stage kidney disease (ESKD) in Singapore remains high and continues to rise. We continue to face major challenges in containing the rising incidence of ESKD and providing sustainable kidney replacement therapy. Our cost projections provide an insight into the present and future, urging a call to action to augment existing initiatives to address the emergent issues.

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Keywords: End-stage kidney disease, health economics, peritoneal dialysis, kidney replacement therapy, sustainable costs

Burden of ESKD in Singapore. The incidence of chronic kidney disease (CKD) stage 5 in Singapore increased by 31% from 383.9 per million population (pmp) in 2010 to 503 pmp in 2018. The prevalence of patients with end-stage kidney disease (ESKD) on dialysis increased by 58% from 1,218 pmp in 2010 to 1,925.9 pmp in 2019. This is attributed to the high prevalence of diabetes mellitus and an ageing population. Diabetes remains the leading cause of ESKD in new patients starting dialysis, accounting for 68.2% of cases in 2019.[1]

With diabetes on the rise, it is estimated that 1 in 2 Singaporeans will have type 2 diabetes by 2050,[2] which will have a ripple effect on the burden of CKD and ESKD. There are currently no available registry data capturing the number of CKD patients and its related costs. Based on a prior projection of CKD patients in Singapore, there are about 400,000 CKD patients in 2021, translating to an estimated cost of SGD1.35 billion annually.[3] Another study reported mean annual costs for patients with type 2 diabetes who had CKD to be SGD3,385 annually, which was 2.2 times higher than that for diabetic patients without CKD.[4]

Low kidney transplant rates. Kidney transplant rates have remained stagnant over the last decade, in stark contrast to the increasing rate of ESKD in Singapore. In 2019, living donors contributed to 54% of all transplants done locally, while deceased donors contributed 33%.[1] Despite a steady increase in the number of living donor kidney transplants over the years, the increase is unable to meet demand. While the introduction of the Human Organ Transplant Act legislation in 1987 and its subsequent amendment in 2004 led to initial increases in deceased donor transplants, the rate of transplantation at 24.8 pmp in 2019 remained well short of demand; in 2020 the average waiting time for a deceased donor kidney transplant was 9.3 years.[5]

Dialysis modalities in Singapore. Dialysis modalities in Singapore include haemodialysis (HD) that is typically done in-centre, and peritoneal dialysis (PD) that is home-based. There are a small number of patients on home HD in Singapore, but this is limited due to various reasons. PD is the primary established home-based dialysis in Singapore.

A recent meta-analysis suggested that PD and in-centre HD carry equivalent survival benefits, where reported differences in survival between treatments largely reflect a combination of factors unrelated to clinical efficacy.[6] PD therapy has benefits such as preservation of residual kidney function, better survival in the initial period of dialysis therapy[7] and improved quality of life.[8]

In Singapore, however, the survival of PD patients has remained inferior to HD, although progress has been made over the past 10 years. Multiple factors contribute to inferior PD outcomes, including: patient selection bias; older, frail patients; patients with contraindications for HD who are initiated on PD; lack of PD clinical outcome key performance indicators (KPIs) such as anaemia,

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bone disease and Kt/V at a programme level; absence of national registry of PD KPIs such as peritonitis and exit site infections; and insufficient manpower and clinical governance to support PD in the community.

In 2019, there were 128 dialysis centres in Singapore. In order to keep up with the growing need for HD, there needs to be an increase to 748 dialysis centres by 2035.[3] As a country with limited land resources, building more dialysis centres is not sustainable or cost-effective. In addition, guidelines from the Ministry of Health (MOH), Singapore, mandates a nurse to patient ratio of 1:5 for HD, which is a greater manpower requirement compared to 1:20 for PD.[9] The growing need for HD will create a major strain on nursing manpower. Despite target-setting by MOH previously, increase of subsidies and educational efforts by the government, PD penetration has remained under 14% from 2010 to 2019.[1]

Growing healthcare expenditures and COVID-19 pandemic—a new reality. At a recent MOH work plan seminar headed by Singapore's health minister, it was reported that Singapore's healthcare expenditure had doubled from SGD10 billion in 2010 to SGD21 billion in 2018. This will almost be tripled to SGD59 billion by 2030. The exponential rise has been made worse by the COVID-19 pandemic.

Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines indicated that the costs of dialysis and transplantation consume disproportionate amounts within healthcare budgets worldwide.[10] Dialysis costs for 2021 were estimated to be about SGD300 million. This is 2% of the MOH non-COVID-19-related annual budget (SGD14.4 billion),[11] being consumed by 1.38% (7,754 prevalent patients on dialysis in 2019) of the population. The actual financial burden of CKD is difficult to assess without a national CKD registry that captures the number of patients by CKD stage.

Currently, many measures remain in place to control the spread of COVID-19. ESKD patients are at higher risk of severe illness due to their compromised immune system and high comorbidity burden. Dialysis clinics and hospitals have adopted telehealth to continue care provision without having in-person visits.[12] Recent data have also suggested that home-based dialysis has a protective effect over centre-based haemodialysis, with an approximate 3-fold reduction in the risk of infections.[13]

With the added burden of COVID-19-related healthcare costs, it has become more pressing to find a sustainable model of kidney replacement therapy provision and financing. To examine costs associated with in-centre HD and home PD and its economic impact, we ran cost simulations using data from existing literature.

Cost simulation for in-centre HD and home PD. We ran simulations over different timelines to reach a 40% PD penetration nationally. This target was set by the government previously, to increase the proportion of patients on continuous ambulatory PD to 40% by 2010.[14] The incident number of PD initiations needed was estimated based on 10-year median changes in incidence and prevalence of definitive PD numbers, as reported by the national registry.[1] Subsequent real-time dropout rates captured in a PD registry would reflect actual PD uptake more accurately for estimation of numbers required to maintain and/or increase PD prevalence in Singapore.

We first projected a gradual 2–4% increase in incident PD numbers annually, to increase PD penetration from the current 14% to 40% by 2029. Based on the historical growth rate of 5.4% in prevalence number of definitive dialysis,[1] we projected that there would be 13,120 patients requiring dialysis in 2029. In order to reach the target of 40% PD penetration, a gradual increase to at least 7 out of 10 patients who would ever start dialysis to initiate PD therapy is required. Of note, although the numbers required were high, once the deficit is overcome, only 2–3 out of 10 patients were needed to initiate PD to maintain a 40% PD prevalence (Table 1).

We highlight that given the mere 3.5% increment in incident uptake of PD in our dialysis population over the past 10 years,[1] unless there is an urgent push to increase PD uptake dramatically, it would take more than 10 decades to increase the incident initiations by 40% to reach the desired PD prevalence.

We ran a second projection with an accelerated increase to 40% PD penetration in the next 5 years, considering the rapid rise of patients needing dialysis and its associated healthcare costs (Table 2). To reach the target by 2026, at least 7 in 10 patients who would ever start dialysis need to initiate PD over the next 4 years. Again, the target would become more manageable once the deficit is recovered. To achieve the target of 65–75% incident PD numbers in the coming years, it would require concerted efforts from the nephrology community and the government. We can also learn from the sustained success of the PD programme in Hong Kong, where its PD-first policy has >70% of their dialysis population treated with PD.[7,15]

We next looked at the cost savings if a 40% PD penetration nationally is achieved by 2026 (Table 3). Associated costs were referenced mostly from the

Table 1. Forecast of incident peritoneal dialysis initiations needed to reach target of 40% PD penetration by 2029[1]

	2021	2022	2023	2024	2025	2026	2027	2028	2029
Prevalent number of definitive dialysis[a]	8,614	9,079	9,569	10,086	10,631	11,205	11,810	12,448	13,120
Target PD penetration, %	14.0	15.9	18.3	21.2	24.5	28.0	31.8	35.8	40.0
Target number of definitive PD	1,206	1,444	1,751	2,138	2,605	3,137	3,756	4,456	5,248
Target increase in number of definitive PD	238	307	387	467	532	619	700	792	283
Incident number of definitive PD needed[b]	680	877	1,106	1,334	1,520	1,769	2,000	2,263	809
Incident number of PD initiations needed[c]	414	534	674	813	926	1,078	1,219	1,379	493
Incident number of ever-started dialysis[d]	1,472	1,538	1,608	1,680	1,755	1,834	1,917	2,003	2,093
Incident PD initiations needed, %	28.0	34.7	41.9	48.4	52.8	58.8	63.6	68.8	**23.6**

PD: peritoneal dialysis
[a] Projection based on 10-year average 5.4% annual growth rate, calculated from Singapore Renal Registry Annual Report 2019
[b] Estimation based on 10-year median of 65% annual dropout rate of prevalent definitive PD, calculated from Singapore Renal Registry Annual Report 2019
[c] Estimation based on 10-year median of 64.1% annual gain in incident definitive PD numbers from ever starting PD, calculated from Singapore Renal Registry Annual Report 2019
[d] Projection based on 10-year median of 4.5% annual growth of number of ever-started dialysis, calculated from Singapore Renal Registry Annual Report 2019
[1] National Registry of Diseases Office. Singapore Renal Registry Annual Report 2019, 30 July 2021. Available at: https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/srr-annual-report-2019.pdf?sfvrsn=8822fcf8_0. Accessed on 13 December 2021.

Table 2. Accelerated forecast of incident PD initiations needed to reach target of 40% PD penetration by 2026[1]

	2021	2022	2023	2024	2025	2026	2027
Prevalent number of definitive dialysis[a]	8,614	9,079	9,569	10,086	10,631	11,205	11,810
Target PD penetration, %	14.0 (current)	20.0	25.0	30.0	35.0	40.0	40.0
Target number of definitive PD	1,206	1,816	2,392	3,026	3,721	4,482	4,724
Target increase in number of definitive PD	610	576	634	695	761	242	Not applicable
Incident number of definitive PD needed[b]		1,646	1,811	1,986	2,174	691	
Incident number of PD initiations needed[c]		1,003	1,104	1,210	1,325	421	
Incident number of ever-started dialysis[d]		1,538	1,608	1,680	1,755	1,834	
Incident PD initiations needed, %		65.2	68.7	72.0	75.5	**23.0**	

PD: peritoneal dialysis
[a] Projection based on 10-year average of 5.4% annual growth rate, calculated from Singapore Renal Registry Annual Report 2019
[b] Estimation based on 10-year median of 65% annual dropout rate of prevalent definitive PD, calculated from Singapore Renal Registry Annual Report 2019
[c] Estimation based on 10-year median of 64.1% annual gain in incident definitive PD numbers from ever starting PD, calculated from Singapore Renal Registry Annual Report 2019
[d] Projection based on 10-year median of 4.5% annual growth of incident number of ever-started dialysis, calculated from Singapore Renal Registry Annual Report 2019
[1] National Registry of Diseases Office. Singapore Renal Registry Annual Report 2019, 30 July 2021. Available at: https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/srr-annual-report-2019.pdf?sfvrsn=8822fcf8_0. Accessed on 13 December 2021.

Table 3. Projected healthcare costs and savings if target of 40% PD penetration is achieved by 2026

	Current, 2021		Future, 2026 (Status quo)		Future, 2026 (40% PD)	
	PD	HD	PD	HD	PD	HD
Percentage prevalence, %	14	86	14	86	40	60
Number of patients	1,206	7,408	1,569	9,636	4,482	6,723
Treatment costs, SGD						
APD (74% of all PD)/ month[a]	1,600		1,600		1,600	
CAPD (26% of all PD)/month[a]	1,200		1,200		1,200	
HD/month[b]		2,500		2,500		2,500
Annual treatment cost	21,648,000	222,240,000	28,166,400	289,080,000	80,462,400	201,690,000
Other associated costs per annum, SGD[15]						
Other PD costs[c]	28,706,177		37,346,593		106,684,150	
PD home visits[d]	30,330		148,667		226,210	
PD training[d]	387,550		1,899,630		2,890,467	
Other HD costs[c]		237,207,864		308,549,538		215,273,822
Total healthcare costs per annum		510,219,921		665,190,828		607,227,048
Cost savings per annum				57,963,780		

APD: automated peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; HD: haemodialysis; PD: peritoneal dialysis
[a] Proportion of APD and CAPD patients, estimated treatment costs based on data from Baxter Heathcare (Asia)
[b] HD treatment cost estimation based on data from The National Kidney Foundation Singapore
[c] Includes other medical costs for set-up (one-time), drugs, laboratory tests, outpatient visits, hospitalisation, death (one-time), and non-medical costs such as transportation and loss of productivity
[d] Cost estimation based on data from Baxter Healthcare (Asia) from May 2020 to April 2021
[15] Li PK, Chow KM. Peritoneal dialysis-first policy made successful: perspectives and actions. Am J Kidney Dis 2013;62:993-1005.

study by Yang et al.[16] We projected that a 40% PD prevalence would bring approximately SGD58 million per annum in cost savings, compared to remaining at 14% PD prevalence.

We then simulated the nursing manpower[9] needed to reach the target of 40% PD penetration (Table 4). By achieving 40% PD prevalence nationally, nursing manpower needed to care for patients on dialysis will be reduced by about 22%.

Lastly, we looked at infrastructure savings. Based on data from The National Kidney Foundation Singapore, a HD centre with 20 stations and space to house a central water treatment system costs approximately SGD2 million to build. In contrast, a PD clinic costs under SGD20,000. If the current dialysis landscape persists, there will be an additional 2,000 patients on HD by 2026. This will require 100 more 20-station HD centres to meet the demand, costing SGD200 million in infrastructure costs alone.

The need for transformative strategies. Based on our cost simulations, the rising healthcare costs will not be sustainable in the long term. Better utilisation of healthcare budgets to provide quality and affordable care for patients with kidney disease is needed. We propose the following strategies:

(1) **Halting the CKD wave** via intensified national movements to concentrate efforts on prevention, early screening and detection of diabetes and hypertension especially in high-risk groups, empowering primary care providers with adequate resources to manage chronic diseases, and encouraging early referrals for specialist management.

(2) **Advocating cost-effective home PD** via early discussion of treatment options, expansion of patient education programmes, increasing support for a community shared-care model by multidisciplinary care teams with assisted and respite care services, revision of subsidy structure and strengthening the support for PD healthcare professionals in terms of funding, infrastructure, and manpower.

(3) **Developing strategies to increase organ donation** such as establishing quality improvement programmes where healthcare professionals are responsible for improving processes to increase rates of donor

Table 4. Nursing manpower required to manage increase of PD prevalence to 40%

	2021	2026 (Status quo)	2026 (40% PD)
Total number of dialysis patients[a]	8,614	11,205	11,205
Patients on PD, no. (%)	1,206 (14)	1,569 (14)	4,482 (40)
Patients on HD, no. (%)	7,408 (86)	9,636 (86)	6,723 (60)
Nurses needed	60	78	224
For PD (1:20 nurse to patient ratio)	1,482	1,927	1,345
For HD (1:5 nurse to patient ratio)	1,542	2,005	1,569
Total number			
Reduction in nursing manpower needs, no. (%)		436 (21.7)	

HD: haemodialysis; PD: peritoneal dialysis
[a] Projection based on 10-year average of 5.4% annual growth rate, calculated from Singapore Renal Registry Annual Report 2019

actualisation and donation after circulatory death. Strategies are needed to address socio-cultural anxieties as well as professional and societal vulnerabilities which contribute to the barriers and ethical quandaries in living kidney donation.[17]

In conclusion, the expanding burden of kidney failure is a major public health problem worldwide. It is critical that we continue to search for more cost-effective ways to provide kidney replacement therapy. While PD could be a sustainable treatment model, more health economics studies are warranted for further evaluation. Concurrently, we must look at long-term solutions for CKD prevention and reducing CKD progression to ESKD, as well as increasing kidney transplant rates.

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Retrospective analysis of neonates born after assisted reproductive technology and admitted to the neonatal intensive care unit

Dear Editor,

There are limited studies evaluating neonatal outcomes after assisted reproductive technology **(**ART) in Asia, especially Southeast Asia, hence this study aimed to fill this gap in literature. We conducted a retrospective study on a group of neonates conceived via ART performed at the National University Hospital (NUH), Singapore and admitted to its neonatal intensive care unit (NICU), over a 5-year period from January 2013 to December 2017 to evaluate the immediate neonatal outcomes after ART.

Six hundred and thirty-nine babies were conceived via ART in NUH and born in NUH during the period, of whom 102 were admitted to NICU. The characteristics are represented in Table 1. Thirty-seven (5.8%) were born at less than 35 weeks gestation, with majority of them (25/37, 67.6%) associated with multiple births. Of the 639 babies, 41 (6.4%) were of low birth weight (<2kg); and 35 of these low-weight babies were associated with multiple births. Of the whole cohort, 34 (5.3%) were small for gestational age.

Majority of the NICU-admitted neonates were products of multiples (66, or 65% versus 35% singletons). Sixty were from twins and 6 from triplets. The mean gestational age and birth weight of multiples was 34.6±2.4 weeks and 2052±506g, compared to 35.1±3.9 weeks and 2387±854g in the singletons, respectively. Gestational age was similar but weight was significantly lighter for the multiples compared to singletons (P=0.01).

Top reasons for admission to NICU were: low birth weight of less than 2kg (41), less than 35 weeks gestation (37) and respiratory distress syndrome (RDS) (25). Sixteen of these neonates were admitted for the aforementioned reasons, with 11 of them products of multiples.

Twenty-four, or 3.8% of the study cohort had major congenital anomalies, giving an incidence of 37.6 per 1,000 ART live births. The overall incidence of congenital anomalies for all births in NUH during the 5-year period was 17.3 per 1,000 live births (334/19,325). Fifteen of these neonates in the study cohort were products of multiples. One third of these neonates had 2 or more systems affected, while the rest had a single system affected.

The overall median length of stay for neonates admitted to the NICU was 10.5 (interquartile range [IQR] 5–21) days. The median length of stay in multiples was 12 (IQR 7–19.3) vs 8.5 (IQR 5–25.8) days in singletons (P=0.89). The twin with the congenital anomaly stayed significantly longer—31 days (IQR 12–58) compared with the other twin without any congenital anomaly—16 days (IQR 4–43) (P<0.01).

Neonates born with congenital anomalies were more likely to die (P<0.001) than those born without congenital anomalies. There were 3 inhospital deaths (3/639), giving an incidence of 4.69 deaths per 1,000 ART birth conceived and delivered in NUH. This is in contrast to the overall mortality rate in NUH for all births in NUH over the 5-year period, which was 1.6 deaths per 1,000 births (30/19,325) (chi-square 10.5, P<0.05). Prematurity and congenital anomalies contributed to all deaths in the ART-conceived neonates admitted to NICU.

Major neonatal morbidities after ART in our study included prematurity from multiple births, and its attendant complications of low birth weight, growth retardation and RDS requiring mechanical ventilation. There was a relatively long duration of hospitalisation of 1 month on average for pre-term multiples with congenital malformations.

Our findings concur with international studies that multiplicity from ART pregnancies correlates with a high prevalence of pre-term births and its attendant complications of prematurity.[1-3]

Singapore's national infant mortality rate is 2.1 deaths per 1,000 live births.[4] In our study cohort, we estimated this to be 3.8 to 4.7 per 1,000 live births conceived via ART. The high prevalence of prematurity and congenital malformations in our ART-conceived cohort with multiple births may have contributed to the higher infant mortality rate observed. However, it is important to recognise that in addition to ART processes, adverse neonatal outcomes may also result from underlying subfertility.[5]

Since 2011, the Ministry of Health (MOH), Singapore has mandated that the maximum number of embryo transfers be limited to 2 at any one time, with only exceptional cases allowing 3.[6] The impact of the implementation of this policy on the rates of prematurity and multiplicity has not yet been determined. We suggest single embryo transfer (SET) be mandated by legislation and policy in couples with better prognosis. Fortunately,

Table 1. Characteristics of the cohort admitted to NICU

Characteristics	n=102
Ethnicity,[a] no. (%)	
Chinese	51 (50.0)
Indian	22 (21.6)
Malay	16 (15.7)
Of other Southeast Asian descent (Vietnamese, Filipino)	4 (3.9)
Caucasian	9 (8.8)
Total of Asian descent	93 (91.2)
Maternal age,[a] mean±SD, years	
Overall	35.0±3.7
Range	28–47
Gestational age,[a] mean±SD, weeks	
Overall	34.8±3.0
Range	27–41
Multiples	34.6±2.4
Singletons	35.1±3.9
Neonates <35 weeks n=37	33.8±2.7
Neonates <28 weeks n=4	26.3±1.0
Birth weight,[a] mean±SD, g	
Overall	2170±666
Range	750–4190
Multiples	2052±506
Singletons	2387±854
Neonates <35 weeks	1985±547
Terms	2808±655
Parity,[a] no. (%)	
Multiples	66 (64.7)
Twins	60 (58.8)
Triplets	6 (9.1)
Singletons	36 (35.3)
Congenital anomalies,[b] no. (%)	**N=639**
Multiples	15 (2.3)
Singletons	9 (1.4)
Total	24 (3.8)

Table 1. Characteristics of the cohort admitted to NICU (Cont'd)

Characteristics	n=102		
Reasons for admission to NICU,[b] no. (%)			
	Total N=639	Multiples n=66	Singletons n=36
Low birth weight <2kg	41 (6.4)	31 (46.9)	10 (27.8)
Prematurity <35 weeks	37 (5.8)	25 (37.9)	12 (33.3)
Respiratory distress syndrome	25 (3.9)	18 (27.3)	7 (19.4)
Hypoglycaemia requiring intravenous drip	30 (4.7)	22 (33.3)	8 (22.2)

NICU: neonatal intensive care unit
[a] 102 babies were admitted to NICU.
[b] 639 is the study cohort, i.e. the total number of babies conceived via assisted reproductive technology at the National University Hospital and born in the hospital. Data on the babies not admitted to NICU were not available due to confidentiality issues. The numbers do not add up to 100% as each baby may have more than 1 reason for admission.

Singapore has facilities to freeze embryos, which encourage elective SET (eSET) over multiple transfers, while also reducing procedures and costs.

At our centre, we advocate eSET, which is in tandem with a review of the National ART Surveillance System data done in the US. The review concluded that substantial reduction of ART-related multiple births could be achieved by single-blastocyst transfers among favourable and average prognosis patients less than 35 years old.[7] A Singapore study by KK Women's and Children's Hospital In Vitro Fertilisation Centre similarly concluded that single-blastocyst transfers confer lower multiple pregnancy rates and should be offered as standard practice where possible.[8] Currently, only a third of our patients undergo eSET and only 1 embryo is transferred for first-time patients below 35 years old. Women above 35 years old are encouraged to transfer only 1 embryo. From 2017 to 2019, our eSET rate ranged from 21.8 to 37.1%. In 2017 to 2018, we encountered only 1 case after eSET where the embryo split after transfer, resulting in twins. Our centre's total clinical pregnancy rate (included fresh, thawed and ≥1 embryo transfer) was 32.3 to 38.4% from 2017 to 2019. The multiple pregnancy rate for 2017 to 2018 was 10.5%. Hence, we advocate eSET to avoid complications arising from multiple births.

At a national level, outcomes of ART-conceived pregnancies should be available for audit by the Agency for Care Effectiveness, MOH Singapore. Lack of national audit data of neonatal outcomes makes it

difficult to determine the true healthcare costs of these fertility treatments.

We encourage all countries to set up robust ART registries to enable better tracking of neonatal outcomes after ART. Pre- and antenatal counselling of couples considering ART,[9] and redefining obstetric practices—including rigorous patient selection, procedural techniques and limiting the number of embryo transfers—are crucial. Public healthcare budgeting and provisions of tertiary neonatal intensive care and specialised paediatric centres should also move in tandem with the observed trend of increasing ART usage.

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Haemoglobin H disease and outcomes in Singapore

Dear Editor,

Haemoglobin H (HbH) disease is a haemoglobinopathy affecting 3 of 4 α-globin genes on chromosome 16. It results from the deletion of 2 linked α-globin genes (α^0-thalassaemia) on one chromosome and either a single α-globin gene deletion (--/-α) or non-deletional gene mutation (--/$\alpha^T\alpha$) on the other chromosome. The disease is common in East Asia with increasing numbers noted in Western countries due to migration. The prevalence of HbH in Hong Kong is 6 in 10,000 while the incidence in Thailand is 7 in 1,000 live births.[1,2]

In α-thalassaemia, the deficiency of α-globin chain results in an imbalance of excess β chains to form tetramers that are unstable. Individuals with 1 or 2 α-globin genes affected are usually asymptomatic, while patients with 3 affected α-globin genes show HbH with varied clinical presentations. Severity depends on the genetic heterogeneity and the subtype of HbH, namely deletional or non-deletional.[1] Deletional mutation involves removing 2 α-globin genes on one chromosome, e.g. Southeast Asian (SEA) and Thai (THAI) deletional mutations, and a single α-globin gene on the other chromosome, e.g. $-\alpha^{-3.7}$ and $-\alpha^{-4.2}$. In the non-deletional subtype, both α-globin genes on one chromosome are deleted, but the other α-globin gene has a non-deletional mutation, e.g. Hb Constant Spring (CS) or Hb Quong Sze (QS) non-deletional mutations. Patients with non-deletional HbH usually have more severe anaemia requiring transfusions.[3]

Couples at high risk of producing offspring who might be transfusion dependent may be counselled to undergo invasive diagnostic tests such as chorionic villus sampling or amniocentesis to confirm the diagnosis and to consider termination.[4,5] This study is the first in Singapore to characterise the severity of HbH in our population and aims to provide a rational basis for prenatal counselling.

The National Thalassaemia Registry (NTR) was set up in 1992 to register all Singapore citizens and permanent residents with the thalassaemia gene. It offers counselling and subsidised screening to spouse and first-degree relatives of registrants.[6] Screening includes full blood count, Hb electrophoresis, HbH inclusion bodies tests, DNA analyses and high-performance liquid chromatography. The NTR receives notifications of thalassaemia cases from other medical institutions and is based in KK Women's and Children's Hospital (KKH), Singapore.

This is a retrospective descriptive study looking at the genotype and clinical characteristics of HbH in KKH patients only. Clinical parameters are obtained from hospital electronic records and clinical notes. Diagnosis of HbH is confirmed by the presence of HbH inclusion bodies or DNA analysis.[5] Hb level is the Hb at diagnosis or lowest Hb recorded. Hepatomegaly and splenomegaly are considered if the measurement is at least 1cm below the costal margin. The last recorded height is used for analysis, and a height percentile is obtained from the World Health Organization Child Growth Standards for 0–24 months and the US Centers for Disease Control and Prevention from 2 years onwards.[7,8] Deletional and non-deletional groups are compared and statistical evaluation is carried out with chi-square test using SPSS Statistics software (IBM Corp, Armonk, US). This study is approved by the Institutional Ethics Review Board in KKH.

Results. Of a total of 45,092 registrants in the NTR from February 1992 to December 2017, 678 HbH (1.5%) were recorded (Fig. 1). The incidence of deletional and non-deletional HbH in Singapore are 0.6% and 0.058%, respectively. Clinical data for 166 patients are analysed and 87 patients with genotype data are sub-analysed (Table 1).

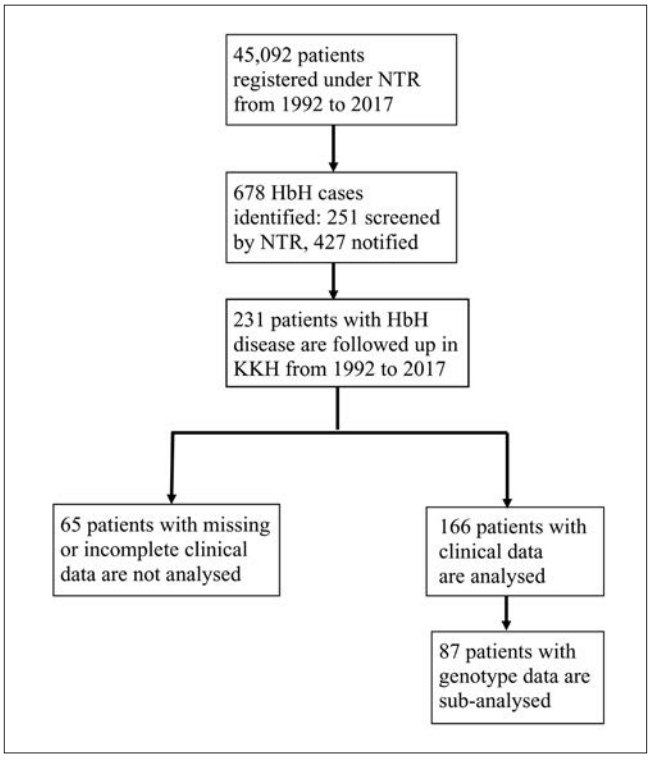

Fig. 1. Flow diagram of patients included in study.
HbH: haemoglobin H; KKH: KK Women's and Children's Hospital; NTR: National Thalassaemia Registry

Table 1. Clinical characteristics of patients with haemoglobin H (HbH) disease

Clinical characteristicss	Total number of patients, N=166 No. (%)	Number of patients with molecularly confirmed deletional HbH disease, n=77 No. (%)	Number of patients with molecularly confirmed non-deletional HbH disease, n=10 No. (%)	*P* value[a]
Sex				
Male	39 (23.5)	22 (28.6)	2 (20)	0.568
Female	127 (76.5)	55 (71.4)	8 (80)	
Ethnicity				
Chinese	141 (84.9)	66 (85.7)	9 (90)	0.620
Malay	16 (9.6)	7 (9.1)	0 (0)	
Indian	2 (1.2)	1 (1.3)	0 (0)	
Others	7 (4.2)	3 (3.9)	1 (10)	
Age at diagnosis				
<12 years old	120 (72.3)	69 (89.6)	9 (90)	0.505
12–21 years old	15 (9.0)	5 (6.5)	0 (0)	
>21 years old	31 (18.7)	3 (3.9)	1 (10)	
Genotype[b]				
Deletional HbH disease	-	**77 (46.4)**	-	-
SEA deletion/3.7kb deletion ($-^{SEA}/-\alpha^{3.7}$)		58 (34.9)		
SEA deletion/4.2kb deletion ($-^{SEA}/-\alpha^{4.2}$)		17 (10.2)		
SEA deletion/4.2kb deletion with Q mutation ($-^{SEA}/-\alpha^{4.2}$ ($Q-^{THAI}$))		1 (0.6)		
THAI deletion/4.2kb deletion ($-^{THAI}/\alpha^{4.2}$)		1 (0.6)		
Non-deletional HbH disease	-	-	**10 (6.0)**	-
SEA deletion/CS ($-^{SEA}/\alpha^{CS}\alpha$)			8 (4.8)	
SEA deletion/QS ($-^{SEA}/\alpha^{QS}\alpha$)			2 (1.2)	
Haemoglobin level, g/dL				
<8.0	21 (12.7)	6 (7.8)	3 (30)	0.003
8.0 to <10.0	128 (77.1)	60 (77.9)	7 (70)	
≥10.0	17 (10.2)	11 (14.3)	0 (0)	
No. of transfusion episodes				
0	142 (85.5)	77 (100)	2 (20)	<0.001
1	10 (6.0)	0 (0)	4 (40)	
2–3	4 (2.4)	0 (0)	1 (10)	
>4	10 (3.0)	0 (0)	3 (30)	
Complications of disease				
Hepatomegaly (>1cm)	25 (15.1)	13 (16.9)	7 (70)	<0.001
Splenomegaly (>1cm)	19 (11.5)	6 (7.8)	5 (50)	<0.001
Splenectomy	4 (2.4)	0 (0)	0 (0)	-
Cholecystectomy	0 (0)	0 (0)	0 (0)	-
Hypothyroidism	2 (0.1)	1 (1.3)	0 (0)	0.876
Hypoparathyroidism	0 (0)	0 (0)	0 (0)	-
Other marker of severity				
Height <3rd percentile[c]	20 (13.3)	7 (9.9)	1 (12.5)	0.856

[a] *P* value applies to the comparison between the deletional and non-deletional groups

[b] Genotypic data are not available for 79 patients (47.9%)

[c] Denominator taken as 150 in the full cohort, 71 in the deletional group and 8 in the non-deletional group due to missing height data

SEA: Southeast Asian; THAI: Thai

The higher percentage of female patients (76.5%) is attributed to the study being conducted in a women's and children's hospital. Median age of diagnosis is 5.7 (2–12.9) years, with most patients (72.3%) diagnosed before 12 years old. Median Hb is 8.7 (8.2–9.3) g/dL with most patients (85.5%) not requiring any transfusion. Ten patients (6.0%) have higher transfusion requirements (>4); of these, 3 had genetic studies done and all belong to the SEA deletion/Constant Spring (--^{SEA}/ $\alpha^{CS}\alpha$) non-deletional subtype.

Ten patients have hepatosplenomegaly (6.0%), 15 (9.0%) have isolated hepatomegaly and 9 (5.4%) have isolated splenomegaly. Only 4 required (2.4%) splenectomy and have higher transfusion requirements, although their genetic profiles are unknown. No cholecystectomy or hypoparathyroidism are reported. Two patients have hypothyroidism; one with a history of Turner syndrome and congenital hypothyroidism, and the other has subclinical hypothyroidism. Twenty patients (13.3%) are below the third percentile for height.

Among the 87 patients with genotyping, there is a higher percentage of deletional HbH (88.5%). Median age of diagnosis is 4.1 (1.8–7.5) compared to 3.5 (0.7–6.4) years in non-deletional group. Patients in the non-deletional group have significantly lower Hb, higher rate of hepatomegaly and splenomegaly, and higher transfusion rate (80%) compared to the deletional group.

Discussion. The percentage of non-deletional HbH in Singapore is 7% according to NTR, compared to 43.5% in Thailand, 24–30% in Hong Kong and 28.9% in Taiwan.[2,9,10] This corresponds to a lower rate of transfusion (14.5%) in our study compared to the Thai study (44.2%) involving patients of similar age distribution. There is also a lower rate of hepatomegaly (15.1% versus 54.4%), splenomegaly (11.5% vs 49%), splenectomies (2.4% vs 5%), cholecystectomies (0% vs 3.4%) and growth deficiency (13.3% vs 20%) in Singapore compared to Thailand.

The most common non-deletional variant is Hb CS followed by Hb QS in Singapore, Taiwan and Hong Kong compared to Hb CS followed by Hb-Paksé and Hb QS in Thailand. The 2-gene deletional variants (--^{SEA}, --^{THAI}) and single gene deletional variants ($\alpha^{3.7}$ and $\alpha^{4.2}$) were similar in incidence among the countries. Presence of any non-deletional mutations portends a worse outcome rather than the different molecular basis of the deletional mutations.[2,9,10]

Our data suggest that most HbH in Singapore belongs to the deletional subtype with mild phenotype. Most patients have a good outcome with low rate of transfusion and complications, hence routine prenatal diagnosis is not necessary. This is in accordance with the European Molecular Genetics Quality Network Best Practice Guideline, which recommends prenatal diagnosis only in cases where severe phenotypes are expected.[11] As this is not a population-based study, a multicentre study involving all institutions treating HbH patients would give a more comprehensive picture of HbH in Singapore.

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LETTER TO THE EDITOR

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Injection site reactions after COVID-19 mRNA vaccination

Dear Editor,

The Pfizer-BioNTech (BNT162b2 mRNA) and Moderna (mRNA-1273) COVID-19 vaccinations were approved for use in Singapore in December 2020 and February 2021, respectively. To date, over 10 million doses of mRNA vaccines have been administered for the primary series and booster doses.[1] Initial studies have shown that 0.8% of individuals who received Moderna mRNA vaccine developed delayed injection-site reactions. These reactions were characterised as tender erythematous, indurated plaques and were commonly misdiagnosed as cellulitis or allergic reactions.[2-5] Such reactions to the Moderna mRNA vaccine are thought to be generally benign and not a contraindication to further doses. On the other hand, injection-site reactions associated with the Pfizer-BioNTech mRNA vaccine are less clearly defined. In this current study, we report the characteristics of mRNA COVID-19 injection-site reactions, comparing the clinical features between Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) reactions in the Singapore adult population.

We retrospectively reviewed patients referred to the Dermatology Service/Allergy Centre at the Singapore General Hospital for reactions post COVID-19 vaccination from 10 January to 26 August 2021. Inclusion criteria were adult patients who developed a localised injection-site reaction after either Moderna or Pfizer-BioNTech mRNA COVID-19 vaccination. Patients who developed non-injection site reactions or had reactions assessed as unrelated to vaccination were excluded. Patient's demographics, clinical history, management and recurrence of subsequent reactions were collected and analysed. Data are presented as median for discrete data, and counts or percentages for categorical data. Fisher's Exact test was performed in comparison of categorical variables between groups, and Mann-Whitney U test was performed for discrete variables. *P* value of ≤0.05 was considered statistically significant. The data were analysed using SPSS Statistics version 22 (IBM Corp, Armonk, US).

During the study period, there were 322 patients referred for post-COVID-19 vaccine cutaneous reactions. Of these, 21 developed post-vaccination injection-site reactions. Eleven (52%) had received the Moderna mRNA vaccine while the remaining 10 (48%) received the Pfizer-BioNTech mRNA vaccine. The median age (range) was 55 years (24–80), with 17 (81%) being female. Twenty (95%) cases developed after the first dose of vaccine.

In the group receiving the Moderna mRNA vaccines, median duration to onset of the reaction (range) was 8 days (1–9). These patients developed pruritic, erythematous plaques with varying degrees of induration and swelling at or near the site of vaccination.

In the group receiving the Pfizer-BioNTech vaccine, median duration to onset of the reaction (range) was 1 day (1–8). These patients developed similar injection-site reactions that were pruritic, mildly erythematous and mildly oedematous.

Patients receiving the Moderna mRNA vaccine had a longer median latency period (*P*=0.001) and were more likely to have a latency duration of >5 days (*P*=0.009) as compared to patients receiving the Pfizer-BioNTech vaccine.

Two patients developed injection-site reactions with secondary dissemination. The reactions started from the injection-site and sequentially spread to the rest of the body (Table 1). One patient required admission for treatment of the symptoms. A skin biopsy performed on the lesions showed focal interface dermatitis with moderate superficial and deep chronic inflammation.

Eleven (52%) of these reactions resolved without treatment, while the remaining 10 (48%) required symptomatic treatment with topical corticosteroids, antihistamines, or a combination of both. Patients who developed an injection-site reaction post Moderna mRNA vaccine were more likely to receive symptomatic treatment (*P*=0.03).

All 21 patients went on to receive the second vaccine dose. Of these, 2 patients experienced recurrence of the reaction. These reactions developed earlier and were less intense in terms of pain, erythema and oedema. They were self-limited and did not require treatment. Table 1 summarises the characteristics of the cases.

Localised injection-site reactions are uncommon side effects that can develop after either Moderna or Pfizer-BioNTech mRNA COVID-19 vaccination.[6,7] From our series, we demonstrate phenotypic differences between the injection-site reactions following the 2 different mRNA vaccines.

In injection-site reactions following Pfizer-BioNTech vaccination, the latency between vaccination and onset of cutaneous lesions is significantly shorter. While

Table 1. Characteristics of patients and injection-site reaction

	Moderna (n=11)	Pfizer-BioNTech (n=10)	*P* value
Sex, no. (%)			
Male	3 (27)	1 (10)	0.586
Female	8 (73)	9 (90)	
Median age (range), years	56 (24–77)	51 (29–80)	0.691
Prior allergies, no. (%)			
NSAID	1 (9)	2 (20)	0.499
Penicillin	0 (0)	1 (10)	
Contrast	1 (9)	0 (0)	
Tetracycline	1 (9)	1 (10)	
Sulfonamide	1 (9)	0 (0)	
Onset of reaction			
Median (range), days	8 (1–9)	1 (1–8)	0.001
Latency >5 days, no. (%)	9 (82)	2 (20)	0.009
Disseminated lesions, no. (%)	1 (9)	1 (10)	1
Other symptoms, no. (%)			
Headache	0 (0)	1 (10)	0.476
Axillary swelling	1 (9)	0 (0)	1
Urticaria	0 (0)	1 (10)	0.476
Pre-referral diagnosis, no. (%)			
Possible allergy	7 (64)	10 (100)	0.09
Cellulitis/erysipelas	2 (18)	0 (0)	0.476
Treatment, no. (%)			
No treatment	3 (27)	8 (80)	0.03
Topical steroids	7 (64)	0 (0)	
Antihistamines	5 (45)	2 (20)	
Need for admission, no. (%)	1 (9)	0 (0)	0.524
Recurrence, no. (%)	1 (9)	1 (10)	0.738

NSAID: non-steroidal anti-inflammatory drug

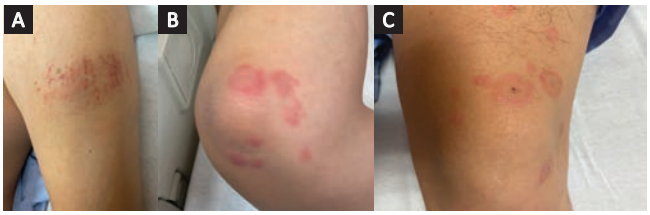

Fig. 1. (A) Injection-site reaction over the left deltoid with secondary dissemination of lesions. Sites of dissemination on (B) right elbow and (C) right knee.

swelling and redness within 7 days of Pfizer-BioNTech mRNA vaccine have been reported in up to 7% of patients, the true incidence of injection-site reactions is unknown.[8] Our study has also confirmed the benign nature of the delayed local injection-site reactions to Moderna mRNA and Pfizer-BioNTech mRNA vaccines. All the patients went on to receive the second dose despite the initial first dose reactions. None of the patients developed severe allergic reactions, even in those who had disseminated lesions. These findings are consistent with Singapore studies evaluating the safety profile of mRNA vaccines.[9]

Histologically, reactions that develop after Moderna mRNA vaccine demonstrate a superficial to mid perivascular inflammatory infiltrate composed of lymphocytes and eosinophils with vacuolar interface dermatitis.[4,7,10] These features support a drug-mediated delayed hypersensitivity reaction. Histological evaluation of Pfizer-BioNTech mRNA vaccine reactions are less well characterised, and features of epidermal hyperplasia with spongiosis and an eosinophil rich infiltrate have been reported.[7] It remains unclear if pathogenic mechanisms behind injection reactions across the 2 vaccines differs.

Although uncommonly reported with Moderna mRNA vaccine, our study has shown that dissemination of lesions can be seen in Pfizer BioNTech mRNA vaccine as well. Nonetheless, these reactions appear self-limited, with none recurring after vaccine challenge. The mechanism of dissemination of these lesions is unclear, but we postulate that these may arise as interface dermatitis

reactions where a secondary immunologic host response develops after the initial primary reaction.

Our study's limitations include its small sample size and retrospective nature. We also acknowledge the presence of a referral bias, where included patients are only those referred to our centre. Mild cases may have consequently been missed.

With the call for booster vaccinations globally, it is important to recognise that these reactions are mild, self-limited and should not deter one from subsequent vaccines. Ongoing surveillance is necessary to better characterise the behaviour of such reactions with subsequent booster vaccination.

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Previous history of hyperthyroidism in emergency department patients with atrial fibrillation does not increase the risk of thromboembolism and death

Dear Editor,

Atrial fibrillation (AF) is frequently encountered in the emergency department (ED) and is a major risk factor for thromboembolic events. The clinical decision for anticoagulation is guided by risk scoring systems that include factors such as age, sex and comorbidities.[1,2] AF can sometimes occur in patients with active hyperthyroidism, but because the condition is often transient and reversible, most risk scores and guidelines do not recommend anticoagulation for these patients.[3-7] However, few studies have evaluated if a past history of hyperthyroidism affects stroke rates in patients with AF. We review the data collected from a large international AF registry to study this relationship.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)-AF registry prospectively collected data of patients presenting to the ED (or equivalent acute care setting) of participating sites with AF as the primary or secondary diagnosis.[8,9] Information regarding demographics, past medical history and medications was collected, and a 1-year follow-up regarding outcomes of death and thromboembolic events was done with written consent from the patients. This included a history of hyperthyroidism. A total of 15,400 patients were recruited from 2008 to 2011 at 164 sites in 46 countries. The study design and protocol were developed by the principal investigators of the original trial, and the study was coordinated and data were managed by the Population Health Research Institute at McMaster University in Hamilton, Canada, with assistance from regional coordination centres.

Baseline demographic information, and anticoagulation, antiplatelet and rate control strategies were summarised for patients with and without a past history of hyperthyroidism. Data were collected through interviews with patients, review of medical records, and contacts with treating physicians.

A past history of hyperthyroidism was reported in 571 (3.7%) of all recruited patients. The prevalence of a prior history of hyperthyroidism was highest in those from Eastern Europe at 7.0%, followed by Southeast Asia at 5.4%. Patients with a history of hyperthyroidism were more likely to be female (64.4% versus 46.5%, $P<0.001$) and have a history of prior AF (72.9% vs 64.3%, $P<0.001$). They were less likely to have a history of rheumatic heart disease (6.3% vs 11.8%, $P<0.001$), significant valvular disease as defined by moderate-to-severe or severe regurgitation or stenosis on echocardiography (14.4% vs 22.0%, $P<0.001$), and history of myocardial infarction (11.4% vs 14.5, $P=0.037$) compared with patients without history of hyperthyroidism. They also did not appear to have an increased risk of stroke or transient ischaemic attack prior to involvement in the study (13.1% vs 13.8%, $P=0.633$). There was no difference in the $CHADS_2$ (congestive heart failure, hypertension, age≥75 years, diabetes mellitus, stroke) score or congestive heart failure, hypertension, age >75 years, diabetes, and stroke/transient ischaemic attack, and vascular disease, age 65–74 years (CHA_2DS_2-VASc) scores between patients with and without history of hyperthyroidism (Table 1).

Permanent AF was the predominant subtype in both groups (37.7% in those with prior history of hyperthyroidism and 40.5% in those without, $P=0.181$), followed by paroxysmal and then persistent AF. This differs from other large registries such as the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry that reports about half the patients have paroxysmal AF.[10] It is probable that the ED setting might have selected more clinically advance disease, i.e. more permanent than paroxysmal AF, compared with other registries that recruited from more diverse sources.

Patients with a previous history of hyperthyroidism were more likely to receive beta-blockers compared to those without this history (56.6% vs 48.8%, $P<0.001$). Aspirin use was lower at the 1-year follow-up in patients with a history of prior hyperthyroidism compared with those without (37.6% vs 41.8%, $P=0.047$). There was no difference between the 2 groups for oral anticoagulant use (45.7% for those with a past history vs 42.0% for those without, $P=0.079$). After multivariable adjustment, there was no difference between patients with and without a history of hyperthyroidism in terms of rates of overall death (odds ratio [OR] 0.93, confidence interval [CI] 0.65–1.34, $P=0.664$), cardiovascular death (OR 1.18, CI 0.75–1.86, $P=0.413$), and stroke/non-central nervous system (CNS) embolism (OR 0.76, CI 0.44–1.30, $P=0.267$) at the end of 1 year. There was also no difference in the rate of recurrent AF (OR 1.18, CI 0.92–1.50, $P=0.158$) after 1 year (Table 1).

Table 1. Baseline charateristics, and anticoagulation and rate control strategies at 1 year

	Prior history of hyperthyroidism	No prior history of hyperthyroidism	*P* value[a]
Baseline characteristics	**n=571**	**n=14829**	
Age, mean±SD, years	65.8±13.9	65.9±14.8	0.887
Male, no. (%)	203 (35.6)	7928 (53.5)	<0.001
Smoker, no. (%)	89 (15.6)	2522 (17.0)	0.375
History of diabetes mellitus, no. (%)	121 (21.2)	3242 (21.9)	0.703
History of hypertension, no. (%)	362 (63.4)	9189 (62.0)	0.489
History of heart failure, no. (%)	201 (35.2)	5147 (34.7)	0.808
History of CAD, no. (%)	179 (31.3)	4837 (32.6)	0.525
History of MI, no. (%)	65 (11.4)	2150 (14.5)	0.037
History of rheumatic heart disease, no. (%)	36 (6.3)	1752 (11.8)	<0.001
History of stroke or TIA, no. (%)	75 (13.1)	2052 (13.8)	0.633
Significant valvular heart disease, no. (%)	82 (14.4)	3267 (22.0)	<0.001
Prior diagnosis of AF before visit, no. (%)	416 (72.9)	9533 (64.3)	<0.001
Type of AF at ED visit			
Persistent, no. (%)	149 (26.1)	3763 (25.4)	0.699
Paroxysmal, no. (%)	207 (36.3)	5060 (34.1)	0.292
Permanent, no. (%)	215 (37.7)	5999 (40.5)	0.181
AF/flutter when patients left ED, no. (%)	433 (75.8)	11681 (78.8)	0.092
Lone AF, no. (%)	0 (0)	796 (5.4)	<0.001
$CHADS_2$ score, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.874
CHA_2DS_2-VASc score, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.170
Beta blocker prior to ED visit, no. (%)	286 (50.1)	6150 (41.5)	<0.001
Beta blocker after ED visit, no. (%)	378 (66.2)	8021 (54.1)	<0.001
Anticoagulation and rate control strategies at 1 year visit	**n= 569**	**n=14792**	
Received ASA, no. (%)	214 (37.6)	6182 (41.8)	0.047
Received OAC, no. (%)	260 (45.7)	6211 (42.0)	0.079
Received anti-arrhythmic drug, no. (%)	117 (20.6)	3255 (22.0)	0.415
Received rate control drug, no. (%)	419 (73.6)	10390 (70.2)	0.082
Calcium channel blockers, no. (%)	90 (15.8)	2242 (15.2)	0.667
Beta blockers, no. (%)	322 (56.6)	7216 (48.8)	<0.001
Digoxin, no. (%)	139 (24.4)	4017 (27.2)	0.151
Received cardioversion, no. (%)	52 (9.1)	1170 (7.9)	0.288
Received AV node ablation, no. (%)	6 (1.1)	75 (0.5)	0.126
Received AF ablation, no. (%)	13 (2.3)	349 (2.4)	0.908

AF: atrial fibrillation; ASA: acetylsalicylic acid (aspirin); AV: atrioventricular; CAD: coronary artery disease; $CHADS_2$: congestive heart failure, hypertension, age>75 years, diabetes mellitus, stroke; CHA_2DS_2-VASc: congestive heart failure, hypertension, age >75 years, diabetes, and stroke/transient ischaemic attack, and vascular disease, age 65–74 years; ED: emergency department; IQR: interquartile range; MI: myocardial infarction; OAC: oral anticoagulant; SD: standard deviation; TIA: transient ischaemic attack

[a] *P* value is from chi-square test for categorical variables, two-sample t-test for normally distributed variables, and Wilcoxon rank-sum test for non-normally distributed variables.

This large multinational registry demonstrates that a prior history of hyperthyroidism does not appear to be an independent risk factor for 1-year risk of overall death, cardiovascular death, stroke/non-CNS thromboembolism and recurrent AF in patients with AF. The strength of this study lies in the extensive, international multicentre records of the AF RE-LY registry, and the subsequent follow-up that captured outcomes and details of anticoagulation and rate control strategies.

The clinical implication of our study is that a history of prior hyperthyroidism does not appear to impact the risk of AF complications. Thus, for patients with a history of hyperthyroidism, the use of oral anticoagulation should continue to be selected according to the CHA_2DS_2-VASc score.

As this study was retrospectively performed, thyroid function test results and details of treatment of hyperthyroidism were not collected at baseline or at the follow-up visit, and neither was the information on AF onset in relation to the diagnosis of hyperthyroidism. Patients with a past history of hyperthyroidism were more likely to receive beta-blockers for their AF. It was possible that some of these patients had active hyperthyroidism at their ED visit but because no data were collected about their thyroid status, we have no way of ascertaining it. Future studies looking at AF in patients in the ED should consider including information on thyroid status during index visit and follow-up.

In summary, nearly 1 in 25 patients presenting to the ED with AF have prior history of hyperthyroidism. The latter is not an independent risk factor for thromboembolic complications and death, and should not influence therapeutic decisions for anticoagulation.

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An initial experience with laser haemorrhoidoplasty in addition to mucopexy for symptomatic haemorrhoids

Dear Editor,

Symptomatic haemorrhoids is the most common anorectal disorder, where up to 75% of people experience symptoms sometime in their lives.[1]

The current gold standard for the surgical management of haemorrhoids is the Milligan-Morgan haemorrhoidectomy,[2] with unrivalled long-term results.[3] However, the technique is associated with significant postoperative pain,[4,5] leading to delayed return to normal activities and readmissions.

Laser haemorrhoidoplasty (LHP) is an emerging procedure whereby haemorrhoidal arterial flow is ceased by laser coagulation.[6] Small comparative studies have shown that LHP is associated with less postoperative pain when compared to conventional open haemorrhoidectomy (COH).[7]

The authors would like to describe our initial experience and evaluate the short-term effectiveness of LHP in Singapore. This initial assessment was conducted during the familiarisation period that preceded a single-centre randomised controlled trial (RCT) (NCT04329364) comparing LHP to COH. All patients presenting with symptomatic haemorrhoids were evaluated for suitability. Inclusion criteria included patients aged 21–90 years with symptomatic grade II–IV haemorrhoids; those willing to attend follow-up visits; and patients who were able to complete postoperative monitoring questionnaires. Exclusion criteria included patients on anticoagulation and those with previous surgical treatment (excluding rubber band ligations). Patients would undergo endoscopic evaluation to ascertain symptoms were attributed to haemorrhoids alone.

LHP is performed as an elective day surgery under general anaesthesia by colorectal surgeons. The procedure is performed with LEONARDO Laser Dual 45 (biolitec AG, Vienna, Austria) using a 1470nm diode laser wavelength. Mucopexy is done as an adjunct prior to laser treatment, to address the external or prolapsed component of the haemorrhoids. It is performed by placing a vicryl 2/0 stitch starting above the dentate line and progressing proximally to hitch haemorrhoidal tissue proximally; no tissue excised. The laser probe is then introduced by direct puncture into the haemorrhoidal cushion under direct vision to a level higher than the dentate line, aided by the guiding beam emitted from the laser probe. The laser treatment uses the "pulsed treatment mode" with power of 10–15W and pulse durations of 3 seconds each. After each laser firing, the haemorrhoidal pedicles are compressed with finger for 3 minutes, and iced in glove for 2 minutes. The probe is then withdrawn by 5mm, resulting in a cylindrical treatment area. After treatment, a lubricated Spongostan (Johnson & Johnson, US) is inserted to tamponade the operative area. Postoperatively, patients will be prescribed oral metronidazole, analgesia, stool softeners and Daflon.

Postoperative pain was recorded using a visual analogue scale (VAS), where 0 represents no pain and 10, the worst pain imaginable. VAS scores were collected every day from postoperative day (POD) 0 to POD10.

Quality-of-life (QoL) assessment was performed using 2 validated surveys to evaluate the effectiveness of LHP, by comparing patient's preoperative and postoperative symptoms. Nyström's questionnaire[8] and Chew's questionnaire[9] focused on frequency and severity of haemorrhoid-related symptoms, respectively. They were performed on patients preoperatively, POD7 and 3 months postoperatively (POD 3 months).

A total of 13 patients aged 41–72 years were recruited for this study. Majority of the patients had grade III–IV haemorrhoids (n=11, 84.6%). The 2 most common symptoms that patients experienced were bleeding (n=8, 61.5%) and prolapse (n=7, 53.8%). The median operating time was 60 (range 44–101) minutes. The median laser therapy duration was 78 (range 28–180) seconds, not including insertion of laser probe and checking of its positioning. The median energy used was 761J (range 262–1,192.6J).

Overall, there was significant improvement of symptoms in both QoL assessments. Seven of the patients (53.8%) noted complete resolution of preoperative symptoms by POD7, and 100% of patients noted complete (n=12, 92.3%) or partial resolution (n=1, 7.7%) of symptoms by POD 3 months. Nine patients (69.2%) complained of bleeding from the haemorrhoids preoperation. By POD7, only 3 of these patients (23.1%) had residual per-rectal bleeding. At POD 3 months, none of the patients were experiencing per-rectal bleeding. Six patients (46.2%) complained of daily occurrence of prolapse preoperatively. By POD 3 months, none of the patients had prolapse.

Overall, there was a downward trend in the mean score for postoperative pain (Fig. 1). The mean score for POD0 was 2.6, and gradually decreased towards

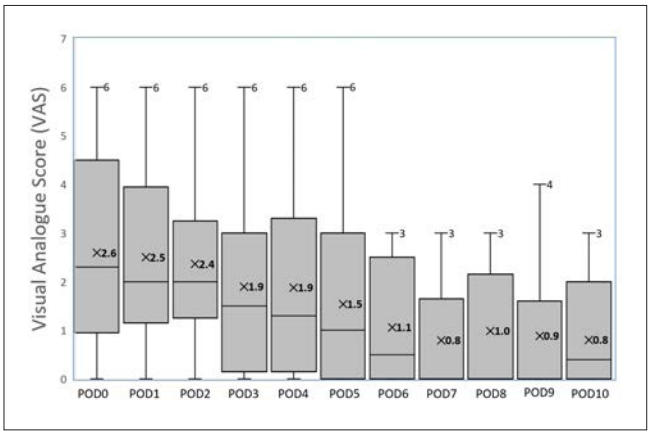

Fig. 1. Postoperative pain using visual analogue scale.

POD10, where the mean score was 0.8. The results showed that most patients had little to no pain by POD7 (mean score 0.8). From POD0–POD5, the maximum pain score of 6 can be explained by a patient who experienced pain from a thrombosed haemorrhoid post-LHP, requiring analgesic adjustment without further intervention. Subsequent review at 3-months showed resolution of the thrombosis.

There were no intraoperative adverse events. Post-operative complications that required re-admission occurred in 2 patients (15.4%). The first had acute urinary retention secondary to severe benign prostate hyperplasia and was managed by urology. The other was for thrombosis of remnant haemorrhoidal tissue requiring analgesia adjustment as mentioned before.

The results from our initial experience show that LHP is effective in addressing symptoms faced by patients with haemorrhoids. It is also a safe procedure with minimal postoperative complications. There was no return to the operating theatre and no sphincter injury noted from this pool of patients. Postoperative pain was minimal (low mean VAS score) and resolved within 1 week postoperation. While not a direct comparison, this initial experience potentially shows that LHP has less postoperative pain. In contrast, COH usually causes significant postoperative pain because of wide external perianal wounds, with pain lasting up to 2 weeks.[4,5]

Preliminary studies have shown significantly better postoperative pain scores and less bleeding risk[7,10] in LHP. However, none has addressed the QoL and longer-term outcomes of LHP in comparison to COH.

Limitations in our study include the small number of reviewed cases, hence may not be representative of the population. There is no control group thus the inability to do direct comparison to confirm the suggested benefits in terms of efficacy as well as less postoperative pain.

LHP is a relatively new technique in Singapore; thus, surgeons are still mounting the learning curve during this study. Despite that, the early outcomes of LHP are already favourable, with its promise of being a new approach towards treating haemorrhoids. The initial study shows that LHP has the potential to be as effective as COH, without the latter's inconvenience. The Colorectal Department of Sengkang General Hospital, Singapore is currently doing a RCT (NCT04329364) to compare LHP and COH, with follow-up of up to a year. We look forward to seeing favourable short- and long-term results from the trial.

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A 52-year-old woman with beading of intracranial arteries

A 52-year-old woman of Indian ethnicity with a history of well-controlled hypertension, hyperlipidaemia and recurrent transient ischaemic attacks presented with altered mentation and slurred speech. Physical examination revealed generalised weakness. Initial blood tests showed raised total white cell count, raised erythrocyte sedimentation rate at 35mm/h and fasting low-density lipoprotein of 1.7mmol/L. Magnetic resonance imaging (MRI) of the brain showed small acute infarcts scattered in bilateral deep white matter (Fig. 1A), with extensive periventricular, deep and subcortical white matter leukoariosis (Fig. 1B) indicative of advanced small vessel disease. Angiography showed stenosis along the right anterior cerebral artery and beading of the left posterior cerebral artery (Fig. 1C). Digital subtraction angiography (DSA) showed beading along the right posterior cerebral artery (Fig. 1D).

What is the most likely differential diagnosis?

A. Atherosclerotic small vessel disease
B. Central nervous system lymphoma
C. Neurosyphilis
D. Reversible cerebral vasoconstriction syndrome (RCVS)
E. Vasculitis

In view of the imaging findings of advanced small vessel disease out of proportion to underlying cardiovascular risk factors, beading and stenosis of intracranial arteries, the clinical impression was that of vasculitis. Differentials were broad, including infective, inflammatory and neoplastic causes. Thorough systemic history revealed no recent fever, weight loss, chronic cough, haemoptysis, haematuria, change in bowel habits, rash, ulcers, alopecia, arthritis or sicca syndrome symptoms, and no previous history of venous thrombosis or miscarriages. Blood investigations demonstrated raised levels of anti-cardiolipin immunoglobulin M antibody and anti-nuclear antibody but anti-double-stranded DNA antibody, lupus anticoagulant and anti-beta-2-glycoprotein antibody were negative. Further physical examination revealed no clinical manifestations of systemic lupus erythematosus and anti-phospholipid syndrome. Other autoimmune, infective and malignancy tests, including anti-neutrophil cytoplasmic antibody, syphilis immunoglobulin G and rapid plasmin reagin were normal. A cerebrospinal fluid (CSF) evaluation revealed raised nucleated cells at 75 cells/μL and protein 0.6g/L. The presence of advanced small vessel disease, elevated inflammatory markers and CSF nucleated cells and protein made RCVS less likely. In addition, atherosclerotic small vessel disease could not account for the non-lacunar infarct presentation in the presence of well-controlled cardiovascular risk factors of hypertension and hyperlipidaemia. A right parietal brain biopsy subsequently showed granulomatous vasculitis. Fungal stains (periodic acid-Schiff, periodic acid-Schiff with diastase, and Grocott methenamine silver), acid-fast bacillus stain and culture, and *Mycobacterium tuberculosis* polymerase chain reaction were negative.

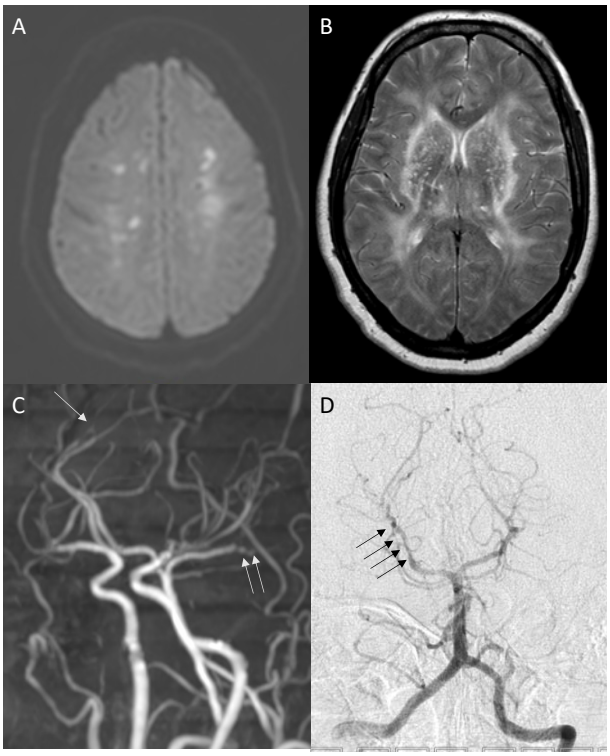

Fig. 1. (A) Magnetic resonance imaging revealed small acute infarcts scattered in bilateral deep white matter. (B) Evidence of advanced, chronic small vessel disease involving deep grey matter as well as periventricular, deep and subcortical white matter. (C) Magnetic resonance angiogram showed stenosis along the right anterior cerebral artery (single white arrow) and beading of the left posterior cerebral artery (double white arrows). (D) Digital subtraction angiography showed beading along the right posterior cerebral artery (black arrows).

The diagnosis of primary angiitis of the central nervous system (PACNS) was made and the woman received intravenous methylprednisolone followed by

Answer: E

Table 1. Key findings of 5 patients with primary angiitis of the central nervous system in our institution

Case	Age	Sex	Medical history	Presenting symptoms	Inflammatory markers[a]	Immune markers	CSF	MRI	MRA	Biopsy
1	76	Female	Hypertension, hyperlipidaemia	Ataxia	Normal	Normal	Normal	Predominantly white matter lesions in the middle cerebellar peduncles, brainstem and right anterior temporal lobe; no diffusion restriction	Normal	Lymphocytic vasculitis
2	59	Male	Hyperlipidaemia, presumptive TIA	Altered cognition, headache	Raised WCC	Normal	Normal	Right temporo-occipito-parietal gyral swelling and enhancement	Normal	Lymphocytic vasculitis
3	82	Male	None	Altered cognition, unilateral weakness	Raised WCC, CRP, ESR	Normal	Raised nucleated cells 22 cells/μL and protein 2.32g/L	Bilateral deep white matter lesions with patchy and ring enhancement	Normal	Granulomatous vasculitis
4	87	Female	Hypertension, hyperlipidaemia	Unilateral weakness, slurred speech	Normal	Normal	Normal	Small infarcts scattered in the right parietal cortices, sulcal subarachnoid haemorrhage and diffuse, thick leptomeningeal and patchy parenchymal enhancement	Normal	Vasculitis, unspecified
5[b]	52	Female	Hypertension, hyperlipidaemia, recurrent ischaemic strokes	Altered cognition, unilateral weakness, slurred speech	Raised WCC, ESR	Positive ANA and anti-cardiolipin antibody titres	Raised nucleated cells 75 cells/μL and protein 0.7g/L	Small acute infarcts scattered in bilateral deep white matter with extensive periventricular, deep and subcortical white matter leukoariosis	Multifocal stenosis and beading	Granulomatous vasculitis

ANA: anti-nuclear antibody; CRP: C-reactive peptide; CSF: cerebrospinal fluid; ESR: erythrocyte sedimentation rate; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; TIA: transient ischaemic attack; WCC: white cell count

[a] C-reactive peptide, erythrocytes sedimentation rate and white cell count

[b] Patient 5 was presented with full details in our case illustration

tapering doses of oral prednisolone and methotrexate. At a review after 6 months, the patient was neurologically stable with residual memory impairment and frontal lobe dysfunction.

PACNS is a rare form of vasculitis that is limited to the brain and spinal cord. The underlying cause and pathogenesis are unknown, but possible triggers include viral infections such as varicella-zoster virus infection. The association between cerebral amyloid angiopathy and PACNS also suggests that amyloid deposition could trigger vascular inflammation.

PACNS has neither pathognomonic features nor a typical clinical course.[1] Common presenting symptoms are stroke-like events, headache and altered cognition.[2] Typical MRI findings of PACNS include infarcts in small to medium-sized vessel territories, haemorrhage and microhaemorrhage, and multifocal stenosis and beading on magnetic resonance angiography (MRA). However, there is heterogeneity in the clinical presentation, neuroimaging, blood and CSF workup. Of note, 7% of PACNS cases have normal MRI.[3] Additionally, CSF analysis can be normal in up to 26% of cases.[3] Hence, a low threshold of suspicion is required for diagnosis and the value of investigations lies in excluding a secondary cause of vasculitis and other PACNS mimics including infection and malignancy. Table 1 demonstrates the experience of our institution and reflects the heterogeneity in clinical manifestations of PACNS.

The gold standard for diagnosis of PACNS is the demonstration of transmural vessel wall inflammation on cerebral and/or leptomeningeal biopsy.[1] Although there is a relatively high rate of false negative due to the inherent patchy nature of the disease,[3] biopsy is useful to rule out other conditions such as central nervous system intravascular lymphoma and reversible cerebral vasoconstriction syndrome.[4] One study showed that brain biopsy confirmed vasculitis and alternative diagnoses in 75% of patients.[5] It is noteworthy that brain biopsy has been shown to be relatively safe with mortality and morbidity rates of less than 1% and 3.5%, respectively.[6] Early brain biopsy should be considered in patients due to the importance of histological diagnosis.

Digital subtraction angiography, which is inherently less invasive than a craniotomy, has been considered a potential replacement for brain biopsy. However, the utility of DSA remains controversial due to the lack of concordance between DSA and histology.[1,3,5,7] While superior to MRA, DSA has a limited resolution in detecting abnormalities at the level of small arteries and arterioles. In addition, similar to computed tomography and MRA, DSA provides luminal but not vessel wall information, hence vessel wall disease that has not resulted in luminal abnormality may not be detected. In studies with pathological correlation, both sensitivity and specificity of DSA was shown to be only 25–35%.[3,5] High-resolution MRI of the vessel wall, or "black blood imaging" is an emerging and promising imaging choice that may help to differentiate PACNS from other vasculopathies such as RCVS,[2] and it can direct a brain biopsy target to allow for more diagnostic histology.[8] However, black blood imaging remains non-routine as resolution at the level of small arteries/arterioles remains a challenge,[9] with additional studies needed to demonstrate direct histological correlation.

There is no standardised treatment regime for PACNS. It is generally accepted that initial treatment consists of high-dose corticosteroids, followed by steroid-sparing agents such as azathioprine or mycophenolate mofetil.[10] In more severe cases, cyclophosphamide is added. Treatment is further escalated to tumour necrosis factor-α (TNF-α) inhibitors or rituximab for patients who do not respond.[2] Nonetheless, treatment-related complications, including life-threatening infections due to chronic immunosuppression, may arise. At our institution, of 5 patients histologically diagnosed with PACNS who achieved clinical stability with immunosuppressive therapy (Table 1), 3 patients succumbed to life-threatening pneumonia within 1 year of treatment, highlighting the risks associated with immunosuppressive agents. Consistent with recent efforts to advocate pathological diagnosis,[7] we recommend early biopsy for histological confirmation prior to aggressive immunosuppressive therapy.

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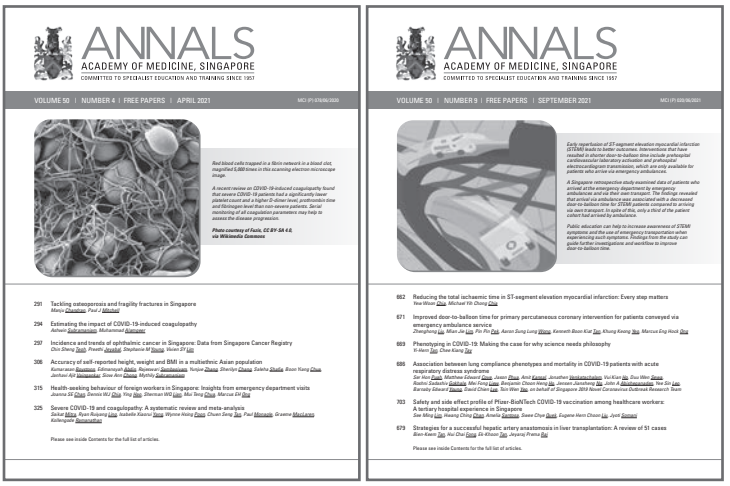

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