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Detection of neurological conditions is becoming more critical in the face of rapidly ageing populations worldwide. Imaging of the retina and optic nerve head presents a unique approach to identify brain diseases, but the specialised expertise required may impede its utilisation by non-ophthalmic healthcare providers.

The latest review highlights artificial intelligence technologies such as deep learning, which can be applied for the automated interpretation of retinal images to uncover structural brain lesions. Further studies will provide better understanding of their potential application in clinical practice.

Illustration by Xinyu Li

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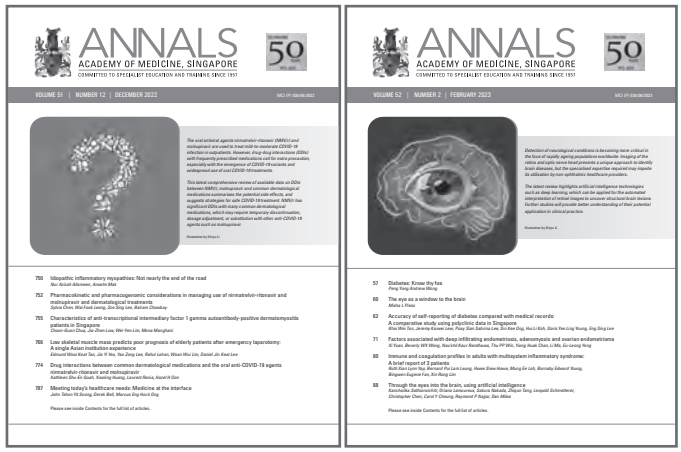

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EDITORIALS

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EDITORIAL

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Diabetes: Know thy foe

Peng Yong Andrew Wong [1]*FCFP(S)*

During the COVID-19 pandemic in 2022, Singapore's Minister for Health Ong Ye Kung mentioned, "After the COVID-19 pandemic has passed, we need to tackle a far more challenging pandemic—which is longer-term chronic illness, and diabetes is a major one."[1]

Truly, in the past decade, there has been an invisible global epidemic of non-communicable diseases and the predominant types are cardiovascular diseases (including ischaemic heart disease and cerebrovascular accidents) and diabetes.[2] In Singapore, diabetes mellitus was among the top 10 common causes of hospitalisation in 2021, accounting for 1.9% of admissions to restructured or public hospitals.[3] There are multiple subtypes of diabetes mellitus with the predominant one being type 2 diabetes mellitus (T2DM), which is largely adult in onset and characterised by insulin resistance. A closely associated disease entity is metabolic syndrome (MetS), comprising central obesity, raised blood pressure, various degrees of hyperglycaemia mediated by insulin resistance (impaired glucose tolerance [IGT] and impaired fasting glycaemia [IFG]), reduced serum high density lipoprotein and hypertriglyceridaemia. MetS is associated with an increased risk of developing T2DM and subsequent atherosclerotic diseases; however, its long latent period poses an opportunity for timely lifestyle intervention.

The War on Diabetes was launched in Singapore in 2016 on multiple fronts, involving numerous ministries and agencies.[4] The Health Promotion Board (HPB), Ministry of Education (MOE), Early Childhood Development Agency and preschool operators have come together to serve healthier food under the Healthy Meals in Schools Programme. A total of 1,230 preschools and all MOE mainstream school canteens have come on board this programme as of 2019.[4] HPB also collaborates with Sport Singapore, a government subsidiary promoting physical activity, tolead community physical activity programmes (such as Zumba) in the parks, named Sundays @ The Park. Under this programme, there were at least 90 weekly sessions over 84 sites in 2019. The Ministry of Health (MOH) had worked with HPB to roll out the Screen for Life scheme to provide subsidised, convenient and accessible cardiovascular health screening for local residents. About 65,000 Singaporeans had signed up as of 2019. The War on Diabetes resulted in the maintenance of age-standardised diabetes prevalence at 8% between 2017 and 2019.[5] Will we lose the momentum in keeping this disease and its complications at bay after the pandemic? A key starting point for success is the individual's awareness of his/her risk and diagnosis of T2DM.

Sun Tzu, a famous military strategist in China, once said, "If you know the enemy and know yourself, your victory will not stand in doubt."[6]

In this issue of the *Annals*, Tan et al.[7] reported on the prevalence of Singapore patients correctly knowing their diagnosis of diabetes and pre-diabetes. The cross-sectional study performed at a Singapore polyclinic showed a substantial concordance between self-reported and medical records of diabetes (κ=0.76, 95% confidence interval [CI] 0.67–0.85, P<0.001) and poor concordance for pre-diabetes (κ=0.36, 95% CI 0.24–0.48, P<0.001). Factors such as Chinese ethnicity and the presence of 3 or more chronic diseases are associated with a reduced concordance of the diagnosis for diabetes.

Although the reference standard (i.e. diagnosis codes) in this study is subject to human error, the study actually shows that self-reported diagnosis of diabetes can potentially be a ready and reliable source of data in both clinical practice and research. Clinically, this reflects the successful communication of the diagnosis of diabetes from the previous healthcare team, independent of educational status as shown in the study. This is particularly helpful in transitioning care across providers in the absence of detailed memorandums and shared electronic databases. It is easily performed, prevents unnecessary diagnostic retesting and frees up consultation time for healthcare providers to discuss further lifestyle plans for the patient. In research, patients' active contribution of their diagnoses to a medical database could result in quicker cardiovascular risk stratification and epidemiological studies,

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especially in geospatial prevalence studies. This would allow policymakers to design accessible lifestyle interventions closer to the homes of patients with T2DM. As such, this could also be extended to other common cardiovascular risk conditions such as hypertension and hyperlipidaemia.

On the other hand, one area of clinical concern is that the concordance of pre-diabetes between patient and medical records is low. Possible factors to explore in future research include unclear communication of the diagnosis of pre-diabetes; patients' denial or downplaying of the diagnosis since hyperglycaemia in pre-diabetes (IFG/IGT) is not perceived as severe as frank T2DM; patients' false impression of the absence of pre-diabetes or benign nature since it is not pharmacologically treated; and the lack of public awareness of the prevalence of pre-diabetes. Deliberate diagnostic labelling is a double-edged sword and may invoke fear, denial and anxiety in some patients; however, this may also serve to activate those affected to be more involved in seeking better health.[8,9] There are opportunities to explore various ways of improving communication of chronic conditions with long latency, and aid ministerial efforts in increasing public health literacy on the existence and reversibility of such conditions.

Besides Chinese ethnicity and multimorbidity, there are also other associations linked to T2DM awareness. A study by Jeong et al.[10] revealed that these associations include older age, lower educational level, normal weight, the presence of hypertension, hyperlipidaemia and the presence of a positive family history of T2DM. Although associations of pre-diabetes awareness are not explored in this current study, other studies indicated that pre-diabetes awareness may be similarly linked to lower education level and a positive family history of pre-diabetes, but this may be higher in those who are overweight and obese.[11] It may also be higher in individuals visiting their usual sources of care (such as general practitioners), possessing health insurance and having 2 or more visits a year to the doctor.[11] This may suggest that regular touchpoints for health screening and assessment at the same medical home may contribute to pre-diabetes awareness, although the methodology of these studies is not meant to infer causality.

Currently, the presence of pre-diabetes awareness has not been consistently linked to subsequent patient activation in lifestyle management. As such, it may not be the silver bullet to curb the progression to T2DM. However, a retrospective study by Sherman et al.[12] suggests that the elements of person-centred care and encouraging behavioural change in health coaching during primary care may be the answer, with a statistically significant mean reduction in HBa1c of 0.2% and weight of 10 pounds over 24 months. In Singapore's context, this health coaching role can potentially be fulfilled by many touchpoints inside and outside of our healthcare system. The former includes care coordinators in the primary care networks of general practitioners, community nurses in transitional care, nurse educators in hospitals and polyclinics, allied health colleagues (dieticians) in hospitals, and even wellbeing coordinators in social prescribing programmes. The latter includes health ambassadors from government agencies such as HPB, Sport Singapore and People's Association. Truly it takes a village to subsequently tackle both T2DM and pre-diabetes. Whether this role can also be effectively extended to digital applications or videoconferencing platforms remains an exciting area for future research efforts.

Currently, Singapore is in the midst of a major healthcare transformation under Healthier SG.[13] Aside from empanelment to a dedicated family physician who delivers value-driven healthcare, one key component is the formulation of a shared health plan between the patient and provider. Improving understanding and acceptance of chronic conditions such as T2DM and pre-diabetes will certainly pave the way to the successful implementation of the health plans in this programme, with delivery and evaluation via enhanced manpower and IT infrastructure. Health protocols under MOH's Healthier SG for common conditions such as T2DM, hypertension and hyperlipidaemia are under way, ready to serve patients upon diagnoses of these conditions by both physician and patient.

The best fight against the foe is yet to be.

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EDITORIAL

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The eye as a window to the brain

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Over the last 20 years, it has become evident that the age-old expression, "the eye is the window into the soul", might in fact hold more truth than previously thought. We are currently able to distinguish a variety of systemic diseases by funduscopic inspection. Following the dawn of high-resolution optical coherence tomography (OCT), we are now capable of supporting the diagnoses of demyelinating diseases by retinal nerve fibre layer and ganglion cell layer analysis—one of the many capabilities of this technique. This begs the question: what are the limits of our ability to peer into the eye to inform us of diseases elsewhere in the central nervous system? This question has more relevance today than ever, lending appreciation to the efforts of Sathianvichitr et al. and the thrust of the team's work[1] published in this issue of the *Annals*.

Our ability to forestall neurodegenerative diseases depends greatly on techniques to detect them in the presymptomatic stage. With the development of new, potentially effective therapies to prevent progression of the inexorable cognitive decline that characterises Alzheimer's disease (AD),[2] tests to diagnose the disease as early as possible are urgently needed. Early diagnosis of AD is a tall order. Thus far, to diagnose AD, we have principally relied on historical information provided by patients and their relatives, as well as a clinical cognitive examination. Newer neuroimaging techniques[3] and gene analysis[4] add to the neurologist's diagnostic acumen as important tools in early diagnosis.

The desperate need to devise non-invasive and sensitive tests for the diagnosis of AD was best illustrated by a salvo of interest in the pupil response to light as a means to enhance the diagnostic acumen of the neurologist. This effort reached a feverish pitch in the 1990s. In 1994, Scinto et al. at Harvard University, Cambridge, US published a study that reported the pupil response to eye drops in AD-affected individuals compared to normal individuals.[5] They stated that hypersensitivity of pupil dilation to topical instillation of the cholinergic antagonist tropicamide was a marker of disease in AD, adding that this could be used clinically in its diagnosis. The hypothesis stated that the pupil response to light in AD patients was heightened. Unfortunately, the study never led to concrete or useful diagnostic findings, although the pupil as a biomarker in AD continues to be a source of keen interest.

Many other valiant efforts to diagnose AD in the early stage have come and gone, though not without having imparted important lessons. Those which pertain to the visual pathways are briefly mentioned here. The individuals with the so-called posterior variant of AD—also known as posterior cortical atrophy—will often exhibit clinical features, which herald the better-known language and memory disorders that more saliently characterise AD. A post-chiasmal visual field defect accompanied by simultanagnosia and alexia could be the earliest manifestations of AD.[6] Following many publications that have underscored this less common AD variant, colleagues in the field of neuro-ophthalmology are positioned to provide assistance to those in the field of neuro-cognition to recognise early AD. However, there is indeed a small percentage of patients with early AD—that is, those with the posterior cortical atrophy variant of AD.

As part of continuing efforts[7] to find new and useful application of funduscopic examination to diagnose central nervous system diseases, Sathianvichitr et al.[1] have reviewed techniques of artificial intelligence (AI) and its application in the tricky world of early diagnosis of AD. Their study delves into the complex world of AD—a world already filled with hundreds of promising hypotheses and brilliant ideas, though without clear immediate application in early diagnosis so far. This lack of established pathways to obvious applications is one difficulty in advancing early detection of neurodegenerative diseases, despite great efforts in studying AD overall. In the review of AI and deep learning (DL), the team, comprising well-established investigators in the domain of AI and DL, attempted to recognise diseases which have manifestations in the ocular fundus. The researchers zero in on a topic with considerable history—that is, the detection of neurodegenerative diseases by retinal examination. They reviewed studies which have identified patients

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with AD whose features can be discriminated from cognitively normal individuals, using AI applied to retinal images.

The methods used to feed data into a DL database are well understood. The algorithms by which the DL "machine" learns and solves a problem are less so. We do know that DL uses AI methods; retrospectively, these methods have been said to be able to identify sex, age, presence of glaucoma, papilloedema and hypertension, to mention a few recognisable characteristics. How DL identifies sex is less clear, but this is of great interest. Furthermore, age determination based on fundus photography examination remains an unknown. A fundamental mystery is how a database that is entered into an AI context goes the step further to recognise features not identifiable to an experienced ophthalmologist, which when solved will yield remarkable new findings with far-reaching consequences. Much better understood are ways in which DL might solve queries for glaucoma or papilloedema.

How to transit from methods which allow DL to recognise the optic nerve pathology, to methods which allow DL to recognise features of AD patients on OCT is an exceedingly important question. Thinning of the retinal nerve fibre layer or vascular changes might provide an answer. The presence of patterns of atrophy not noted by funduscopy or the trained eye may be an additional possibility. The recognition of patterns of thinning or thickening of deep retinal or choroid vessels might also be considered. Atrophy or segmental atrophy of various retinal layers might eventually turn out to be the answer; after all, patients with advanced AD have brain atrophy. Thus, why not the retinal nerve fibre layer?

The review by Sathianvichitr et al. is a tour de force of all the efforts currently underway in using DL methods to diagnose and discriminate AD from normal age-matched individuals. The critical question is whether the race for the diagnosis of AD will be propelled by funduscopic analysis (of any type) or the discovery of a spinal fluid marker. With the view that patients in later stages of AD lose their memory and even their personality—that is, arguably their soul—peering into the eyes in search of solutions to the problem of ageing with dementia has never acquired greater relevance.

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ORIGINAL ARTICLE

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Concordance of self-reporting of diabetes compared with medical records: A comparative study using polyclinic data in Singapore

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ABSTRACT

Introduction: Studies of concordance between patients' self-report of diseases and a criterion standard (e.g. chart review) are usually conducted in epidemiological studies to evaluate the agreement of self-reported data for use in public health research. To our knowledge, there are no published studies on concordance for highly prevalent chronic diseases such as diabetes and pre-diabetes. The aims of this study were to evaluate the concordance between patients' self-report and their medical records of diabetes and pre-diabetes diagnoses, and to identify factors associated with diabetes concordance.

Method: A cross-sectional, interviewer-administered survey was conducted on patients with chronic diseases after obtaining written consent to assess their medical notes. Interviewers were blinded to the participants' profiles. Concordance was evaluated using Cohen's kappa (κ). A multivariable logistic regression model was used to identify factors associated with diabetes concordance.

Results: There was substantial agreement between self-reported and medical records of diabetes diagnoses (κ=0.76) and fair agreement for pre-diabetes diagnoses (κ=0.36). The logistic regression model suggested that non-Chinese patients had higher odds of diabetes concordance than Chinese patients (odds ratio [OR]=4.10, 95% confidence interval [CI] 1.19–14.13, *P*=0.03). Patients with 3 or more chronic diseases (i.e. multimorbidity) had lower odds of diabetes concordance than patients without multimorbidity (OR=0.21, 95% CI 0.09–0.48, *P*<0.001).

Conclusion: Diabetes concordance was substantial, supporting the use of self-report of diabetes by patients with chronic diseases in the primary care setting for future research. Pre-diabetes concordance was fair and may have important clinical implications. Further studies to explore and improve health literacy and patient-physician communication are needed.

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Keywords: Concordance, diabetes, multimorbidity, primary care, self-reported data

INTRODUCTION

Approximately 422 million people worldwide have diabetes and 1.6 million deaths are attributed to diabetes each year,[1] contributing to high economic costs worldwide. Diabetes education and awareness of the disease contribute significantly to minimising complications and reducing morbidity and mortality.[2] In addition, there is also a strong impetus to enhance the accessibility to programmes on the prevention of diabetes, pre-diabetes and associated risk factors.[3]

In Singapore, the Ministry of Health reported that more than 400,000 Singaporeans have type 2 diabetes and the condition is costing the healthcare system more than SGD1 billion a year.[4] According to the Singapore National Health Survey (SNHS) 2010 on residents, 1 in 3 patients with diabetes was not aware of having the disease.[5] There are approximately 430,000 (14%) Singaporeans aged 18–69 years diagnosed with pre-diabetes[6] and there have been no published studies on the awareness level of pre-diabetes in the country.

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CLINICAL IMPACT

What is New

- Concordance between self-reported and medical records of disease diagnoses was substantial for diabetes but not pre-diabetes.
- Diabetes concordance is less likely among Chinese patients, and patients with 3 or more chronic conditions (i.e. multimorbidity).

Clinical Implications

- Patients' self-reports of diabetes diagnoses are a reliable source of data for primary care research.
- Poorer pre-diabetes concordance could be indicative of factors such as the lack of health literacy and patient-physician communication.

Self-reported health is commonly used as a data source for epidemiological studies and national health surveys, as it generally involves lower costs than clinical assessments.[7,8] However, the agreement of such self-reported data has been mixed, and concordance with clinical records can vary based on the patients and disease factors.[9-12] Additionally, concordance could be indicative of the patients' health literacy and quality of patient-physician communication.[13] In Western countries, the concordance for diabetes ranged from 0.75 (substantial agreement) to 0.92 (almost perfect agreement).[9,14-20] In Asia, the trend was similar, although studies were limited and there were no local studies on the concordance of diabetes.

There were also limited studies showing how patient factors affected concordance. Hansen et al. reported that multimorbidity (higher disease count) was associated with better concordance for diabetes.[21] Muggah et al. reported an inverse relationship between morbidity burden and concordance.[20] Chun et al. reported that those aged 60–69 years paradoxically had better concordance for diabetes compared to those aged 50–59 years.[22] Clinically, poor concordance led to poor doctor-patient relationships, which affected the quality of care.[13]

For pre-diabetes, there were many studies comparing objective laboratory data and their concordance with pre-diabetes. To our knowledge, there are no studies that looked at the concordance of self-reported data.

This study aimed to determine the concordance between patients' self-reports of diabetes and their medical records of diabetes diagnoses, among patients visiting a primary care centre for chronic conditions management. It also explored the associations of various patient factors with concordance for diabetes. The secondary objective was to determine the concordance of pre-diabetes between patients' self-reports of pre-diabetes and their medical records of pre-diabetes diagnoses, among patients without diabetes diagnoses.

METHOD

Study setting

The public primary healthcare services in Singapore are provided through an island-wide network of outpatient polyclinics, which offer subsidised care. For this study, the recruitment of participants was based at Toa Payoh Polyclinic, which is located in central Singapore. Toa Payoh Polyclinic has an estimated base pool of more than 40,000 multiethnic patients who come for regular follow-up of their chronic disease management, of whom approximately 12% have diabetes.

Study design and data collection

Self-reported data

We conducted a cross-sectional, interviewer-administered survey on patients who come for regular follow-up of their chronic disease management at Toa Payoh Polyclinic. Patient recruitment commenced between December 2019 and January 2020, then halted due to COVID-19 safety measures, but subsequently resumed and completed from March to April 2021. Study approval was obtained from the National Healthcare Group (NHG) Domain Specific Review Board (Reference no: 2019/00719) with written informed consent from all patients who participated in the study.

Based on the inclusion criteria, the Information Management and Analytics (IMA) department of NHG Polyclinics assisted in generating a list of patients who were eligible for participation on a weekly basis. The recruiting team then approached these patients when they were at the polyclinic waiting for their consultation. They were screened for eligibility before being invited to participate in the study. The inclusion criteria were patients who were aged 21 years and above, and had made 2 or more visits to Toa Payoh Polyclinic for chronic condition management in the past one year. The exclusion criteria were patients without mental capacity or for whom communication and decisions were made via a proxy.

The questions from the survey were adapted from the SNHS 2010.[5] The following baseline characteristics

were collected: age, sex, ethnicity, marital status, education level, housing type, employment status and multimorbidity status (having 3 or more chronic conditions) (Table S1 in online Supplementary Materials). Patient responses and participant identification would be entered into the NHG Research Electronic Data apture (REDCap) system, without any patient identifiers.

As a feedback loop, IMA took into account the recruited number of patients with and without diabetes (in medical records), and attempted to keep the proportion of recruited patients with diabetes to 50%, to minimise the effect of prevalence. The recruiting team members were aware of this recruitment proportion but were blinded as to which participants had diabetes or no diabetes recorded in their medical records (Fig. 1).

Data from medical records

Data on patients' disease diagnoses were extracted by IMA from existing medical records and reconciled with the patients' survey responses collected in REDCap. The combined data spreadsheet was then de-identified before returning to the study team for analysis.

Statistical analysis

Concordance for diabetes was quantified using Cohen's kappa.[23,24] The kappa (κ) coefficient is frequently used to determine the strength of agreement between 2 raters (self-reported data and medical records). A κ value of <0.40 is considered as indicating poor to a fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement.[25] As kappa is affected by prevalence and bias,[23,26,27] we also present the prevalence-adjusted bias-adjusted kappa (PABAK).

In determining our study sample size, we assumed a kappa of 0.70 as the expected agreement, based on comparisons with similar studies in Asia.[11,22,28] Under our null hypothesis, kappa was set at 0.60 (high moderate agreement) as we believe that a poorer concordance (κ<0.60) is clinically unacceptable for an impactful disease such as diabetes. We further targeted to recruit equal proportions of patients with and without diabetes to mitigate any predisposed prevalence effect that lowers kappa.[23,26,27] In a test for agreement between 2 raters using the kappa statistic, a sample size of 472 subjects achieves 80% power at the 0.05 significance level to detect a true kappa value of 0.70, in a test where kappa was set at 0.60 under the null hypothesis with an assumed 50% proportion of positive ratings[23,29] (given that we target to recruit an equal number of patients with and without diabetes). Accounting for a 30% non-response rate, we aimed to approach 472 patients.

A multivariable logistic regression model was used to determine patient factors associated with diabetes concordance while controlling for other variables (Table S2 of online Supplementary Materials). Concordance is dichotomised into "yes" or "no", with "yes" being that the patients' self-reported diabetes matches their medical records and "no" otherwise. The multicollinearity test was performed to check for high correlations among independent variables. The variance inflation factors of all independent variables are less than 5 (i.e. not highly correlated).[30] Statistical analyses were conducted using R software version 3.6.3.[31] A P value of <0.05 was considered statistically significant.

RESULTS

A total of 751 patients were approached. Of these, 26 were excluded as they were unable to give consent due to a lack of mental capacity or whose decisions were communicated via a proxy caregiver, and 247 patients declined participation. The final number of patients recruited was 478, giving a response rate of 65.9%.

Among the 478 patients, there were 239 patients with medical records of diabetes and 239 with no medical records of diabetes. From the self-reported data, 187 (78.2%) and 234 (97.9%) were concordant for having diabetes and not having diabetes, respectively. These numbers are presented in Fig. 2.

Participant characteristics

Table 1 shows the baseline characteristics of the patients who were recruited. There were 80.6% of patients aged 60 years and above (mean age 67.9±11.0 years). There were more male patients (52.5%). The majority of the patients were Chinese (86.6%), married (70.1%), had secondary school or lower education (68.6%), and lived in public housing[32] (87.5%). Less than half of them were actively employed (42.3%) and more than half had multi-morbidity (59.4%).

Concordance between self-reported and medical records for diabetes and pre-diabetes

There was substantial agreement between patients' self-reports of diabetes and medical records of diabetes diagnoses (κ=0.76, 95% CI 0.67–0.85, P<0.001; PABAK=0.76). The results are shown in Table 2. The value of kappa (0.76) for diabetes concordance was very close to PABAK (0.76). This

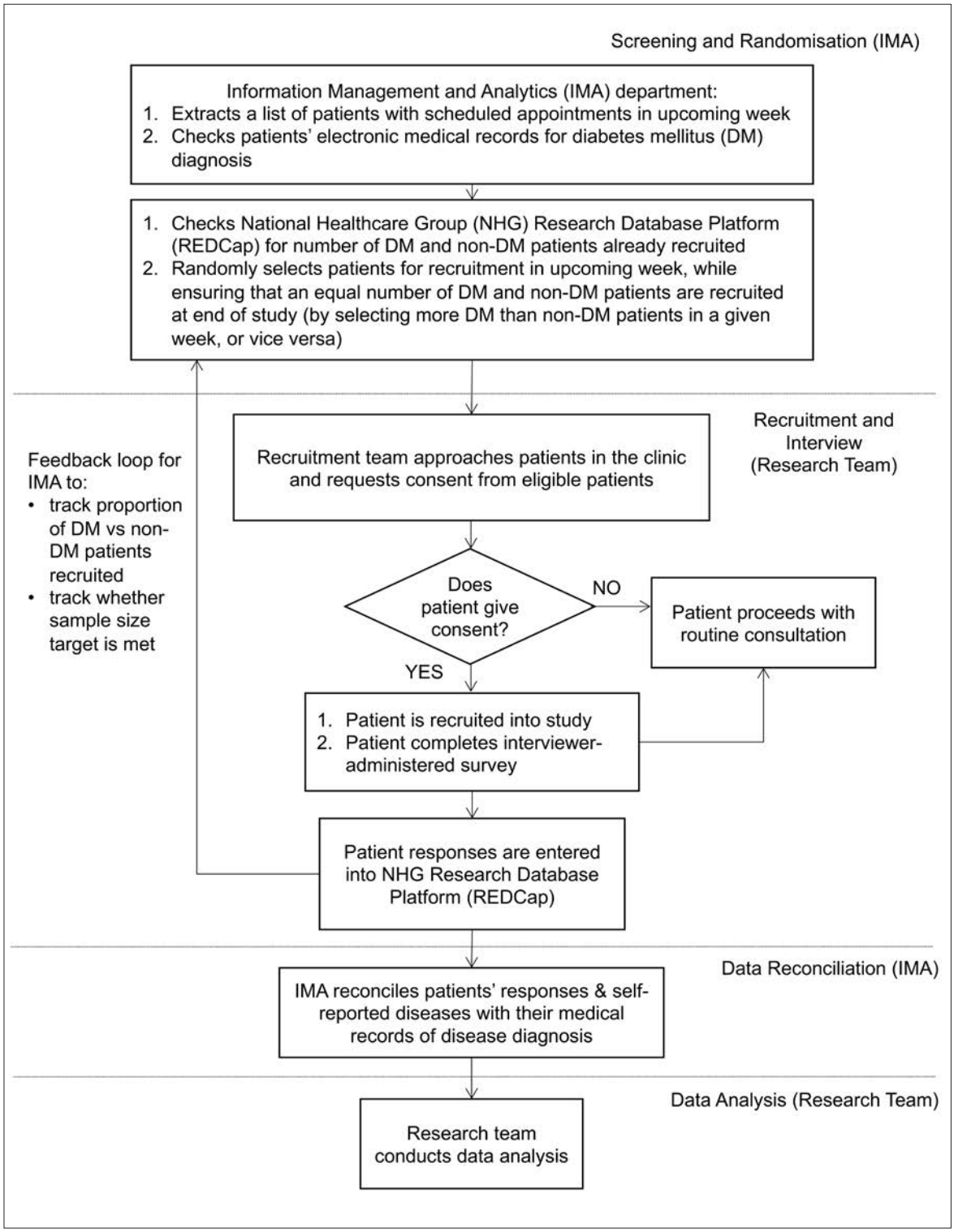

Fig. 1. Flow diagram of patient recruitment from screening to data analysis.

was expected as our proportions of patients with and without diabetes was 1:1, which minimised the effect of prevalence (PI=0.10) on the value of kappa.[26,33]

Among patients without diabetes, there was a fair agreement between patients' self-reports of pre-diabetes and medical records of pre-diabetes diagnoses (κ=0.36, 95% CI 0.24–0.48, P<0.001; PABAK=0.60). However, after adjustment for prevalence and bias using PABAK, the concordance was found to be moderate. The results are shown in Table 3.

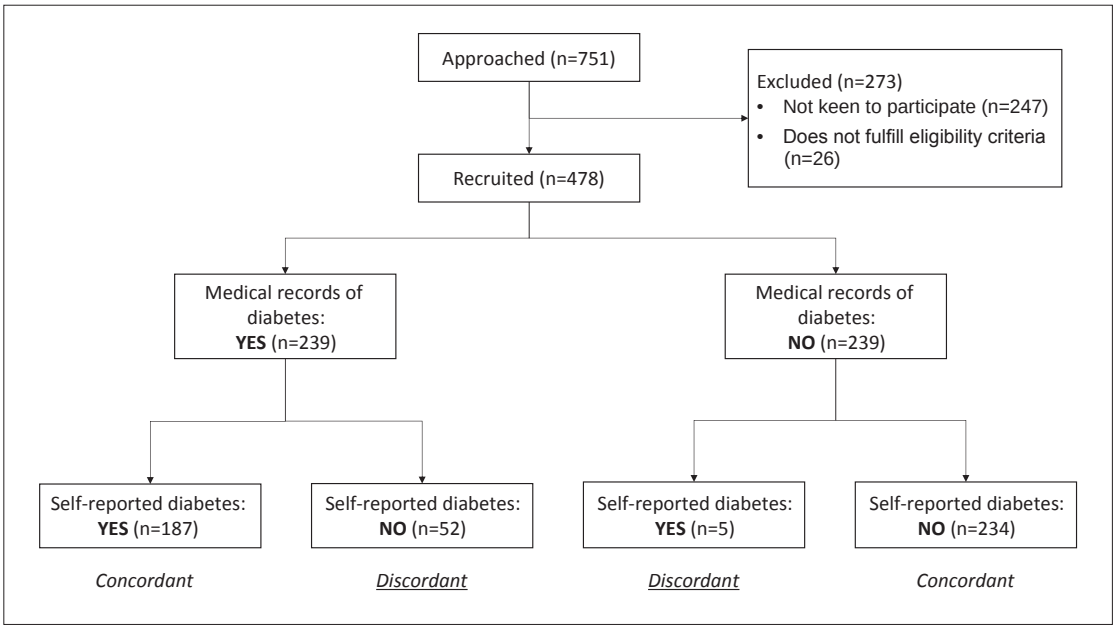

Fig. 2. Breakdown of recruited patients according to concordant and discordant status.

Logistic regression of patient factors associated with diabetes concordance

Table 4 presents the results of the logistic regression model that included all the variables listed in Table 1. All independent variables showed no statistically significant association with diabetes concordance, except for ethnicity and multimorbidity.

Chinese patients were associated with poorer diabetes concordance. The odds of diabetes concordance for Chinese patients was 0.24 times that of non-Chinese patients (P=0.03). Having multimorbidity was associated with poorer diabetes concordance (P<0.001). The odds of diabetes concordance for patients with multimorbidity (≥3 chronic diseases) was 0.21 times that of patients without multimorbidity (<3 chronic diseases).

DISCUSSION

Our study sought to quantify the concordance among patients with diabetes and to determine the patient-related factors associated with poorer concordance. Our results showed substantial agreement (κ=0.76, PABAK=0.76) between self-reported diabetes and medical records of diabetes diagnoses. This kappa value for diabetes concordance (κ=0.76) in our study was similar to other studies in Asia, namely South Korea (κ=0.82)[22] and Taiwan (κ=0.76).[28] This suggests that self-reported data for diabetes can potentially be a cost-efficient method of studying diabetes prevalence and trends in the population.

Other studies have postulated that: good concordance is observed when the disease is well defined;[10] has clear diagnostic criteria; is non-episodic;[10,20,28] requires frequent monitoring[34] or repeated engagement with the healthcare system;[10] affects daily function;[34] and when the disease is not confused with another (e.g. stroke and transient ischaemic attack).[20] Clinically, the aim is to achieve as close to the perfect agreement (κ=1.00) as possible, though perfect agreement is seldom achieved especially in healthcare research.[35] We find that the above factors are consistent with our experience with diabetes management in the primary care context, and this could explain the substantial diabetes concordance observed in our study.

In the US, the estimated awareness of pre-diabetes was lower than 14% across all population subgroups.[36] In China, a study on the Suzhou community found that only 38.5% knew they had pre-diabetes.[37] In our study, 22 out of 57 patients (38.6%) knew that they had pre-diabetes (Table 3). This proportion was very similar to the findings in China.

The concordance for patients with pre-diabetes (κ=0.36, PABAK=0.60) was lower than for diabetes. Here, kappa and PABAK values differed more, compared to the concordance results for the diabetes aforementioned. This was expected and the key contributory reason was that the prevalence of pre-diabetes in this sample was significantly lower than 50%. This does not mean that the actual kappa for pre-diabetes is 0.60. PABAK should be interpreted

Table 1. Characteristics of study participants

Characteristic	N=478 No.	%
Age (as at recruitment)		
<60 years	93	19.5
60–69 years	170	35.6
70–79 years	149	31.2
≥80 years	66	13.8
Sex		
Male	251	52.5
Female	227	47.5
Ethnicity		
Chinese	414	86.6
Non-Chinese	64	13.4
Marital status		
Married	335	70.1
Single/divorced/widowed	143	29.9
Education level		
No formal education	39	8.2
Primary	113	23.6
Secondary	176	36.8
Post-secondary	150	31.4
Housing type		
HDB 1-room/2-room flat	54	11.3
HDB 3-room flat	136	28.5
HDB 4-room flat	122	25.5
HDB 5-room/HUDC flat	106	22.2
Condominium/landed property	60	12.6
Employment status		
Employed	202	42.3
Homemaker/retired/unemployed	276	57.7
Multimorbidity status		
Non-multimorbid (<3 chronic diseases)	194	40.6
Multimorbid (≥3 chronic diseases)	284	59.4

HDB flat: Housing and Development Board flat (housing by public housing authority in Singapore); HUDC flat: Housing and Urban Development Company flat (public housing, now privatised, for middle-income households in Singapore)

alongside kappa, and it helps to contextualise the effect of prevalence on the sample. What our data highlight, however, is that the concordance of pre-diabetes is poorer than diabetes.

A contributory factor to poor pre-diabetes concordance could be the incomplete capture of pre-diabetes in the medical records as pre-diabetes is not as strictly coded for, unlike diabetes. These patients may also have a lack of understanding about pre-diabetes, which requires the doctor's effort to form an equal partnership with the patient to explain the condition and the necessary treatment plans to prevent progression to diabetes.[38] Moreover, patients with pre-diabetes may not be as actively engaged as patients with diabetes within the healthcare system. However, individuals with pre-diabetes are at high risk for developing type 2 diabetes, which accounts for 90–95% of all cases of diabetes per year.[39] Each year, 11% of individuals with pre-diabetes who do not lose weight and do not engage in moderate physical activity will progress to type 2 diabetes during an average follow-up of 3 years.[40] Managing this group of patients well can potentially reduce the incidence rate of diabetes significantly.

Our logistic regression results showed that being of Chinese ethnicity was statistically significantly associated with poorer diabetes concordance (odds ratio [OR]=0.24, i.e. lower odds of concordance compared to non-Chinese). This finding is supported by a cross-sectional survey of 2,895 participants in the Singapore general population, where the Chinese ethnicity had significantly higher odds of inadequate health literacy on diabetes compared to non-Chinese.[41] A plausible explanation is that the patients who visit Toa Payoh Polyclinic may also be seeking traditional Chinese medicine (TCM) treatment elsewhere, and the way diabetes is categorised under the TCM framework could be different from the Western medicine practice in primary care. For example, patients could consider themselves to have high blood sugar instead of diabetes under the TCM framework. A similar instance was reported by Goldman et al.[11] in the case of hypertension; however, our conjecture can only be confirmed in future studies.

Our logistic regression results also showed that having multimorbidity (defined as having 3 or more chronic diseases) was significantly associated statistically with poorer diabetes concordance (OR=0.21, i.e. lower odds of concordance compared to patients without multimorbidity). This association was similarly reported among the Canadian population[42] and Minnesota residents in the US,[10] although their definition of multimorbidity (i.e. list of diseases considered) differs from our study. Okura et al.[10] suggested that the association of having

Table 2. Concordance analysis for diabetes for study participants

Diabetes	Status from clinical diagnoses recorded data						κ	*P* value of κ	BI	PI	PABAK
	N (%)	No		Yes		Total					
		n	%	n	%	n	%	0.76	<0.001	0.10	0.10	0.76
Self-reported status	No	234	48.95	52	10.88	286	59.83					
	Yes	5	1.05	187	39.12	192	40.17					
	Total	239	50.00	239	50.00	478	100					

Table 3. Concordance analysis for pre-diabetes for study participants without diabetes

Pre-diabetes	Status from clinical diagnoses recorded data						κ	*P* value of κ	BI	PI	PABAK
	N (%)	No		Yes		Total					
		n	%	n	%	n	%	0.36	<0.001	0.09	0.62	0.60
Self-reported status	No	169	70.71	35	14.64	204	85.36					
	Yes	13	5.44	22	9.21	35	14.64					
	Total	182	76.15	57	23.85	239	100					

κ: kappa; BI: Bias Index; PI: Prevalence Index; PABAK: prevalence-adjusted bias-adjusted kappa
$PABAK = \kappa + (1 - \kappa)\ PI^2 + (\kappa - 1)\ BI^2$
Refer to online Supplementary Material S3 for more details

multimorbidity with poorer concordance could be due to the increased awareness of diseases as a result of more frequent engagements with the healthcare system. This results in over-reporting and poorer concordance. However, our data showed otherwise with patients with multimorbidity under-reporting (i.e. patients who indicated that they have not been told by a doctor to have diabetes even though the medical records showed otherwise). Further studies are needed to explore our patients' understanding and acceptance of diabetes, especially for patients with multimorbidity and diabetes.

Limitations and strengths

Our main limitation was that in comparing self-reported diabetes with medical records of diabetes, we regarded medical records as the source of truth. While this is a widely accepted standard, we acknowledge that there are instances when clinicians code diagnoses incorrectly in the system, or even misdiagnose diseases, leading to inaccuracies in the medical records.[43,44] On the other hand, the accuracy of self-reported data collected from surveys is limited by recall bias, social desirability effect,[28,45,46] the way the questions are phrased and asked,[8,47] and the comprehension ability of the participant,[47] including factors that may impair judgement such as mild cognitive impairment.

The differences in the profile of patients between our centre (elderly with multimorbidity) and the general population also limit the generalisability of our results to the rest of the population.

Lastly, we only studied non-modifiable patient factors. Chun et al. explored the impact of health-related behaviours such as smoking, drinking and exercise on concordance, although they did not find statistical significance.[22]

Despite the limitations, this is one of the first studies in Singapore to explore diabetes concordance among patients with chronic conditions in the primary care setting. In contrast, such concordance had been studied in Western countries[9,14-20] and some countries in Asia.[22,28] We took into account the limitations of kappa as a statistical tool, such as prevalence and bias, and tried to keep equal proportions of participants with and without diabetes as much as possible.[26,33] This study was also an initial attempt to understand the pre-diabetes concordance among our primary care patients.

Modifiable patient factors such as health behaviours of smoking, drinking or exercise, which could affect concordance indirectly, could be explored. The population base for the study could also be extended to cover the wider community, or recruitment could focus on a nationally representative sample for greater

Table 4. Multivariable logistic regression of independent variables with diabetes concordance

Independent variables	Adjusted odds ratio[a]	95% confidence interval[b]	*P* value[c]
Age (as at recruitment)			
60–69 years	REF		
<60 years	1.45	0.51–4.12	0.48
70–79 years	1.37	0.66–2.81	0.40
≥80 years	1.52	0.60–3.88	0.38
Sex			
Male	REF		
Female	0.82	0.43–1.54	0.53
Ethnicity			
Chinese	REF		
Non-Chinese	4.10	1.19–14.13	**0.03**
Marital status			
Married	REF		
Single/divorced/widowed	1.04	0.54–2.01	0.91
Education level			
Secondary	REF		
No formal education	0.59	0.22–1.57	0.29
Primary	1.18	0.54–2.57	0.69
Post-secondary	1.13	0.49–2.62	0.78
Housing type			
HDB 3-room flat	REF		
HDB 1-room/2-room flat	0.79	0.33–1.92	0.61
HDB 4-room flat	2.08	0.91–4.76	0.08
HDB 5-room/HUDC flat	1.83	0.76–4.38	0.18
Condominium/landed property	3.34	0.89–12.50	0.07
Employment status			
Employed	REF		
Homemaker/retired/unemployed	0.88	0.44–1.78	0.73
Multimorbidity status			
Non-multimorbid (<3 chronic diseases)	REF		
Multimorbid (≥3 chronic diseases)	0.21	0.09–0.48	**<0.001**

HDB flat: Housing and Development Board flat (housing by public housing authority in Singapore); HUDC flat: Housing and Urban Development Company flat (public housing, now privatised, for middle-income households in Singapore)

[a] The odds ratios are all adjusted in the same multivariable logistic regression model

[b] Confidence interval

[c] $P<0.05$ is considered statistically significant

generalisability. Qualitative research could also be conducted among patients with diabetes discordance, to explore perceptions and aspects of diabetes they have difficulty understanding.

CONCLUSION

The findings from this study suggested substantial concordance between self-reported and medical records for diabetes in our study population. This lends support that self-reported diabetes is a valid source of data in public health research. Further research is required to understand the association of poorer diabetes concordance among patients who have multimorbidity and are of Chinese ethnicity. Fair concordance was found between self-reported and medical records for pre-diabetes. This has important medical implications as a significant proportion of patients with pre-diabetes progress to diabetes. Further studies to explore and improve the health literacy and patient-physician communication may be important in managing patients with pre-diabetes and diabetes.

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ORIGINAL ARTICLE

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Factors associated with deep infiltrating endometriosis, adenomyosis and ovarian endometrioma

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ABSTRACT

Introduction: To compare epidemiological features and clinical presentations of deep infiltrating endometriosis with endometrioma and adenomyosis, as well as to identify risk factors for the respective histologically confirmed conditions.

Method: Patients undergoing index surgery at the National University Hospital, Singapore for endometriosis or adenomyosis over a 7-year period—from 2015 to 2021—were identified from hospital databases using the Table of Surgical Procedures coding. Social and epidemiological features of cases with histologically confirmed diagnoses of endometrioma only, adenomyosis only, and deep infiltrating endometriosis were compared. Significant variables from univariate analysis were entered into 3 binary multivariate logistic regression models to obtain independent risk factors for: deep infiltrating endometriosis versus endometrioma only, deep infiltrating endometriosis versus adenomyosis only, and adenomyosis only versus endometrioma only.

Results: A total of 258 patients were included with 59 ovarian endometrioma only, 47 adenomyosis only, and 152 deep infiltrating endometrioses. Compared to endometrioma only, deep infiltrating endometriosis was associated with higher rates of severe dysmenorrhoea (odds ratio [OR] 2.80, 95% confidence interval [CI] 1.02–7.70) and out-of-pocket private surgical care (OR 4.72, 95% CI 1.85–12.04). Compared to adenomyosis only, deep infiltrating endometriosis was associated with a higher fertility desire (OR 13.47, 95% CI 1.01–180.59) and a lower body mass index (OR 0.89, 95% CI 0.79–0.99). In contrast, heavy menstrual bleeding was the hallmark of adenomyosis, being less common in patients with endometriosis.

Conclusion: Deep infiltrating endometriosis is associated with severe dysmenorrhoea, pain related to urinary and gastrointestinal tracts, higher fertility desire and infertility rate. Patients with pain symptomatology and subfertility should be referred early to a tertiary centre with the capability to diagnose and manage deep infiltrating endometriosis.

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Keywords: Adenomyosis, deep infiltrating endometriosis, obstetrics and gynaecology, ovarian endometrioma, public health

INTRODUCTION

Endometriosis is a chronic inflammatory gynaecologic disease marked by the presence of endometrial-like tissue outside the uterus.[1] Debilitating chronic pelvic pain, dysmenorrhoea, and subfertility in women of reproductive age are commonly associated with endometriosis. The disease is estimated to affect about 1 in every 10 women of reproductive age, and half of infertile women.[2-4] The condition imposes a substantial economic burden on society, and the annual healthcare costs for endometriosis in selected European countries is estimated to be €3,113 per affected woman, which is similar to the costs for other chronic conditions such as type 2 diabetes, Crohn's disease and rheumatoid

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CLINICAL IMPACT

What is New

- This is the first and largest study in Singapore on histologically proven deep infiltrating endometriosis.
- Compared to endometrioma, deep infiltrating endometriosis was associated with higher rates of severe dysmenorrhoea and out-of-pocket private surgical care.
- Compared to adenomyosis, deep infiltrating endometriosis was associated with a higher childbearing desire and a lower body mass index.
- Heavy menstrual bleeding was the hallmark of adenomyosis.

Clinical Implications

- Patients with pain symptomatology and subfertility should be referred early to a tertiary centre with the capability to diagnose and manage deep infiltrating endometriosis.

arthritis.[5] The costs of care to manage symptoms, including chronic pelvic pain, dysmenorrhoea, deep dyspareunia, dysuria, dyschezia, tenesmus, fatigue, and infertility, are much greater. These symptoms affect physical, mental, sexual, and social well-being, resulting in the need for prolonged medical therapy, repeated surgical treatments, and the indirect costs associated with a reduced quality of life and work productivity.[4,6]

Endometriosis is diagnosed conclusively through surgical visualisation and biopsy specimens indicating the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium. Broadly, 2 major endometriotic phenotypes are encountered clinically, namely ovarian endometrioma and deep infiltrating endometriosis.[7,8] Endometriomas are ovarian cysts containing endometrium-like tissue and dark blood-stained fluid, the colour and consistency of which give rise to the name "chocolate cysts". Deep infiltrating endometriosis where endometriotic deposits exist below the peritoneum has been increasingly recognised to be responsible for disabling pain, poor quality of life and sexual dysfunction in many women.[9,10] It is also considered to be the most aggressive form of endometriosis.[11,12] There is no robust evidence of whether ovarian endometriomas and deep infiltrating endometriosis share similar risk factors.[4] Many studies consider endometriosis to be a single disease without differentiating between ovarian endometriomas and deep infiltrating endometriosis.[13] Some studies indicate that these 2 phenotypes have similar risk factors,[14,15] while others suggest that deep infiltrating endometriosis should be considered a specific disease with mechanisms of disease progression distinct from endometriomas.[9,16] Despite huge advances in our understanding of endometriosis, knowledge of the epidemiology and symptomatology of endometrioma compared to deep infiltrating endometriosis is considered rudimentary, leading to controversy about the epidemiology and development of these phenotypes.[9] Epidemiological studies underpinned by histopathologically verified cases would contribute to a better understanding of these 2 endometriotic phenotypes.

Another condition commonly associated with intense pelvic pain and subfertility is adenomyosis. It is diagnosed by the presence of endometrial glands and stroma within the myometrium. In severe adenomyosis, the pathological diagnosis is straightforward, with disease evident at both gross and microscopic examinations. However, the diagnosis may be difficult in those with more limited disease, leading to extreme variations in the prevalence of adenomyosis, which ranges from 10–88%.[17] Although adenomyosis was previously considered a disease of older multiparous women, the advent of transvaginal ultrasound as another diagnostic tool for adenomyosis has added a layer of uncertainty to the epidemiology and symptomatology of the condition.[18,19] The heterogeneity of diagnostic criteria for endometriosis and adenomyosis has led to some confusion on the presenting symptomatology and epidemiology of endometriomas, deep infiltrating endometriosis and adenomyosis.[20] There is a need to clarify the epidemiology, symptomatology and risk profiles of ovarian endometrioma, adenomyosis and deep infiltrating endometriosis, using the gold standard histopathological diagnostic criteria.

The objective of our study is to further clarify the epidemiology of deep infiltrating endometriosis, compared to patients who have only ovarian endometrioma or only adenomyosis, using cases that were confirmed by histological examination. The surgical logs for a tertiary referral centre for deep infiltrating endometriosis were examined and consecutive cases with either deep infiltrating endometriosis, ovarian endometrioma only, or adenomyosis only were identified, and their presentations and epidemiological features compared.

METHOD

Patients

The case logs of patients undergoing the index surgery for endometriosis or adenomyosis from 1 January 2015 to 30 September 2021 in the Department of Obstetrics and Gynaecology, National University Hospital, Singapore were identified and examined (Fig. 1). The study was reviewed by the Domain Specific Review Board of the National Healthcare Group, Singapore (Reference number: 2021/00498), and exemption from individual consent was granted.

Index operations were searched, and consecutive cases identified using the inpatient Table of Surgical Procedures (TOSP) codes for endometriosis or adenomyosis surgery from the Ministry of Health, Singapore:[21] SI702P, SI715U, SI726U, SI802O, SI803O, SI805O, SI806O and SI812U (online Supplementary Table S1). Electronic case records of cases identified by the TOSP search were examined and cases with confirmed histological diagnosis of endometriosis or adenomyosis during the period of 2015–2021 were selected (Fig. 1). These patients were then classified into 3 groups based on diagnostic confirmation by histopathological examination: ovarian endometrioma only, adenomyosis only, and deep infiltrating endometriosis. Cases in which both endometrioma and adenomyosis were present were not included in this analysis.

Diagnosis of endometrioma, adenomyosis and deep infiltrating endometriosis

Adenomyosis was defined as the presence of endometrial glands and stroma in the myometrium of cases with myometrium specimens. Ovarian endometrioma was confirmed by histology. Deep infiltrating endometriosis was defined as endometriosis infiltrating the peritoneum by >5mm and confirmed by intraoperative histology, located at or involving one of the following sites: recto-vaginal septum and related subperitoneal spaces; retroperitoneal spaces in the pouch of Douglas; subperitoneal involvement of fibromuscular pelvic structures such as the uterosacral and utero-ovarian ligaments; urinary tract including ureters, bladder, urethra; or digestive tract, especially colorectal sites. The presence of endometriosis at other sites did not affect the definition of deep infiltrating endometriosis.

Data collection

Sociodemographic characteristics, reproductive status, menstrual patterns, pain symptomatology, previous medical and surgical treatments prior to the index surgery, and the class of ward were retrieved from the patients' medical records and stored in a secured database on our hospital intranet. Reproductive data recorded included sexual activity, fertility desire, previous diagnosis of infertility, obstetric history and the serum level of anti-Müllerian hormone (AMH) prior to the index operation. Menstrual regularity was classified as frequent (≤23 days), regular (24–35 days), oligomenorrhoea (>35 days) or amenorrhoea (>1 year). Abnormal menstrual bleeding patterns such as heavy bleeding or intermenstrual bleeding were also recorded. Patterns of chronic pain recorded included dysmenorrhoea, dyspareunia, dyschezia, tenesmus, constipation or diarrhoea, dysuria, or urinary frequency.

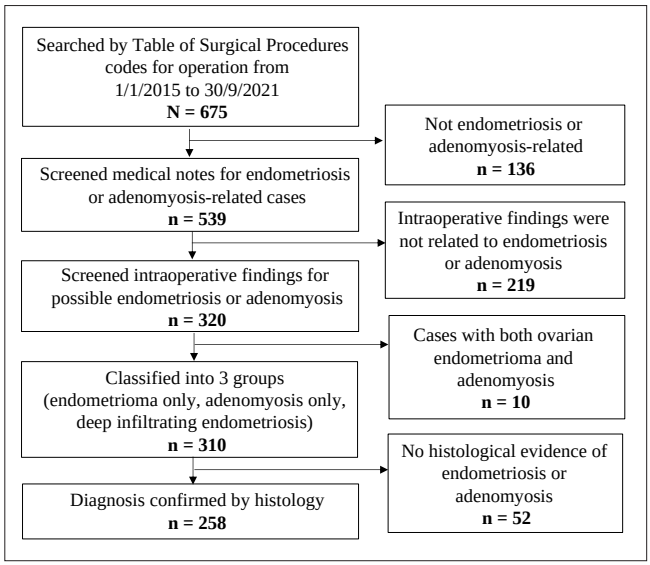

Fig. 1. Search strategy to identify cases of ovarian endometrioma only, adenomyosis only, or deep infiltrating endometriosis, confirmed by histopathological examination.

Statistical analysis

Anonymised data were analysed with the SPSS Statistics software version 28.0 (IBM Corp, Armonk, US). Univariate analysis for continuous variables across the 3 groups (endometrioma only, adenomyosis only, and deep infiltrating endometriosis) were compared using a one-way analysis of variance and Pearson's chi-square test for categorical variables. Significant variables from the univariate analysis were entered into 3 binary multivariate logistic regression models (deep infiltrating endometriosis versus endometrioma only, deep infiltrating endometriosis versus adenomyosis only, and adenomyosis only versus endometrioma only). The following were not entered into the regression models: pain score before the index operation due to collinearity

with pain symptomatology; weight being collinear with body mass index (BMI); and duration between age at first endometriosis diagnosis and age at index operation. Odds ratios (OR) with its corresponding 95% confidential interval (CI) were presented. $P<0.05$ was considered statistically significant.

RESULTS

Initial screening using TOSP codes identified 675 index operations. Cases unrelated to endometriosis or adenomyosis, cases with both conditions, and those without histological confirmation were excluded. Only 258 index cases with histologically confirmed endometriosis or adenomyosis were used in the present analysis (Fig. 1). Table 1 shows their epidemiological features. About half were of Chinese ethnicity, a fifth were Malay and 10% were Indian. Almost 70% were married, 60% were nulliparous, 40% expressed a desire for children, and a quarter of all patients having been diagnosed with infertility. Some 40% reported heavy menstrual bleeding and severe dysmenorrhoea. Their mean age at the time of index operation was 38.1±8.2 years, the mean BMI was 24.4±5.3, and the mean duration between diagnosis of the condition and index surgery was 2.7±4.0 years.

Unadjusted differences between endometrioma, adenomyosis and deep infiltrating endometriosis

Our analytical cohort consisted of ovarian endometrioma only (n=59), adenomyosis only (n=47), and deep infiltrating endometriosis (n=152) (Table 1). Subjects with deep infiltrating endometriosis were the youngest at the time of index operation (35.7±7.2 years), followed by endometrioma only (37.9±8.1 years) and adenomyosis only (45.9±6.7 years). Subjects with endometrioma only had the shortest duration between diagnosis and the index operation (1.6±2.8 years) whereas adenomyosis only had the longest (3.6±5.3 years). Consequently, cases with adenomyosis only were the oldest (42.6±9.7 years) at the time of first diagnosis. Cases with deep infiltrating endometriosis were most likely to be private patients compared to those with adenomyosis and endometrioma only (52.6% versus 44.7% vs 30.5%).

Cases with deep infiltrating endometriosis were most likely to be nulliparous (65.8% vs 29.8% vs 64.0%), expressed the highest desire for fertility (55.3% vs 4.3% vs 35.6%) and received a diagnosis of subfertility (32.2% vs 14.9% vs 18.6%) compared to cases of adenomyosis and endometrioma only.

Cases of adenomyosis were most likely to present with heavy menstrual bleeding compared to cases with endometrioma only and deep infiltrating endometriosis (78.7% vs 25.4% vs 37.5%).

Among patients reporting severe dysmenorrhoea, deep infiltrating endometriosis had the highest pain symptomatology with a 55.9% rate compared to 31.1% for adenomyosis and 20.3% for endometrioma only. Cases with deep infiltrating endometriosis also reported increased rates of dyspareunia, dyschezia and tenesmus of 17.8–24.3% compared to about 10% in patients with adenomyoma, and 5% in patients with endometrioma only. Preoperative pain scores were also highest at 5.3±4.2 compared to 3.2±4.4 and 2.8±3.8 for cases of adenomyosis and endometrioma only. Cases of deep infiltrating endometriosis were also most likely to have undergone previous surgery for endometriosis compared to adenomyosis and endometrioma only (27.0% vs 17.0% vs 11.9%).

The BMI of patients with deep infiltrating endometriosis was the lowest (23.2±4.5) and those with adenomyosis only was the highest (27.5±6.3). When comparing the 3 different groups based on diagnosis, no statistically significant differences were observed in ethnicity, marital status, sexual activity status, history of ectopic pregnancy, menstrual regularity, constipation, urinary symptoms and preoperative AMH levels.

Adjusted risk factors for deep infiltrating endometriosis

Significant univariate factors from Table 1 were entered into 3 binary multivariate logistic regression models that compared deep infiltrating endometriosis versus endometrioma only, deep infiltrating endometriosis versus adenomyosis only, and adenomyosis only versus endometrioma only (Table 2). Compared to ovarian endometrioma only, patients with deep infiltrating endometriosis suffered significantly more severe dysmenorrhoea (OR 2.80, 95% CI 1.02–7.70) and also opted for private surgical care (OR 4.72, 95% CI 1.85–12.04). Compared to adenomyosis only, patients with deep infiltrating endometriosis had 13.47 times (95% CI 1.01–180.59) higher fertility desire, a lower BMI (OR 0.89, 95% CI 0.79–0.99), and reported fewer complaints of heavy menstrual bleeding (OR 0.22, 95% CI 0.05–0.91). Overall, patients with adenomyosis had a higher risk of heavy menstrual bleeding compared to endometriosis, whether endometrioma only or deep infiltrating endometriosis.

DISCUSSION

Our study, based on histologically confirmed cases, indicates significant differences in the epidemiology

Table 1. Characteristics of patients with endometrioma only, adenomyosis only, and deep infiltrating endometriosis

Variables	All patients (n=258)	Endometrioma only (n=59, 22.9%)	Adenomyosis only (n=47, 18.2%)	Deep infiltrating endometriosis (n=152, 58.9%)	*P* value
Ethnicity, no. (%)					
Chinese	136 (52.7)	36 (61.0)	18 (38.3)	82 (53.9)	0.148
Malay	48 (18.6)	12 (20.3)	13 (27.7)	23 (15.1)	
Indian	26 (10.0)	4 (6.8)	7 (14.9)	15 (9.9)	
Others	48 (18.4)	7 (11.9)	9 (19.1)	32 (21.1)	
Reproductive factors, no. (%)					
Marital status					0.131
Single	69 (26.7)	22 (37.3)	8 (17.0)	39 (25.7)	
Married	177 (68.6)	33 (55.9)	37 (78.7)	107 (70.4)	
Divorced	12 (4.7)	4 (6.8)	2 (4.3)	6 (3.9)	
Virgo intacta (VI) status					0.452
Non-VI	213 (82.6)	46 (78.0)	41 (87.2)	126 (82.9)	
VI	45 (17.4)	13 (22.0)	6 (12.8)	26 (17.1)	
Parity					<0.001
Nulliparous	152 (58.9)	38 (64.0)	14 (29.8)	100 (65.8)	
Parous	106 (41.1)	21 (35.6)	33 (70.2)	52 (34.2)	
Previous vaginal delivery	70 (27.1)	12 (20.3)	27 (57.4)	31 (20.4)	<0.001
Previous caesarean section	40 (15.5)	9 (15.3)	9 (19.1)	22 (14.5)	0.740
Fertility desire[a]	107 (41.5)	21 (35.6)	2 (4.3)	84 (55.3)	<0.001
Previous diagnosis of infertility[b]	67 (26.0)	11 (18.6)	7 (14.9)	49 (32.2)	0.021
Menstrual pattern, no. (%)					
Menstrual regularity					0.374
Regular (24–35 days)	225 (87.2)	51 (86.4)	38 (80.9)	135 (88.8)	
Frequent (≤ 23 days)	4 (1.6)	1 (1.7)	2 (4.3)	1 (0.7)	
Oligomenorrhea (> 35 days)	17 (6.6)	3 (5.1)	4 (8.5)	10 (6.6)	
Amenorrhea (> 1 year)	9 (3.5)	2 (3.4)	3 (6.4)	4 (2.6)	
Heavy menstrual bleeding	109 (42.2)	15 (25.4)	37 (78.7)	57 (37.5)	<0.001
Intermenstrual bleeding	36 (14.0)	5 (8.5)	11 (23.4)	20 (13.2)	0.081
Pain symptomatology, no. (%)					
Pain score before index operation, mean ± SD	4.3 ± 4.3	2.8 ± 3.8	3.2 ± 4.4	5.3 ± 4.2	0.005
Dysmenorrhoea					<0.001
Mild	53 (20.5)	19 (32.2)	9 (18.0)	25 (16.4)	
Moderate	17 (6.6)	4 (6.8)	1 (2.0)	12 (7.9)	
Severe	111 (43.0)	12 (20.3)	14 (31.1)	85 (55.9)	
Dyspareunia	30 (1 1.6)	3 (5.1)	0	27 (17.8)	0.002

Table 1. Characteristics of patients with endometrioma only, adenomyosis only, and deep infiltrating endometriosis (Cont'd)

Variables	All patients (n=258)	Endometrioma only (n=59, 22.9%)	Adenomyosis only (n=47, 18.2%)	Deep infiltrating endometriosis (n=152, 58.9%)	*P* value
Pain symptomatology, no. (%)					
Dyschezia	36 (14.0)	1 (1.7)	3 (6.4)	32 (21.1)	<0.001
Tenesmus	45 (17.4)	3 (5.1)	5 (10.6)	37 (24.3)	0.002
Diarrhoea	29 (11.2)	1 (1.7)	3 (6.4)	25 (16.4)	0.005
Constipation	26 (10.1)	3 (5.1)	7 (14.9)	16 (10.5)	0.251
Dysuria or urinary frequency/ urgency	20 (7.8)	2 (3.4)	3 (6.4)	15 (9.9)	0.277
Endometriosis/adenomyosis, no. (%)					
Age at first diagnosis of endometriosis, mean ± SD, years	35.5 ± 8.7	36.3 ± 8.6	42.6 ± 9.7	33.0 ± 7.2	<0.001
Previous endometriosis operation	56 (21.7)	7 (11.9)	8 (17.0)	41 (27.0)	0.040
Previous hormonal treatment	105 (40.7)	16 (27.1)	23 (48.9)	66 (43.4)	0.043
Analgesia required before index operation (i.e. NSAIDs)	52 (20.2)	5 (8.5)	11 (23.4)	36 (23.7)	0.039
Previous abdominal/pelvic operation (non-endometriosis related)	70 (27.1)	15 (25.4)	16 (34.0)	39 (25.7)	0.499
Index operation, mean ± SD					
Age at index operation, years	38.1 ± 8.2	37.9 ± 8.1	45.9 ± 6.7	35.7 ± 7.2	<0.001
Height, m	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	0.322
Weight before index operation, kg	61.7 ± 13.4	63.4 ± 13.9	68.5 ± 15.3	58.9 ± 11.7	<0.001
BMI before index operation, kg/m^2	24.4 ± 5.3	24.9 ± 5.5	27.5 ± 6.3	23.2 ± 4.5	<0.001
Duration between age at first endometriosis diagnosis and age at index operation, mean ± SD, years	2.7 ± 4.0	1.6 ± 2.8	3.6 ± 5.2	2.8 ± 3.9	0.041
AMH level before index operation, mean ± SD, pmol/L	19.8 ± 20.8	17.8 ± 11.6	No data[c]	20.4 ± 22.5	0.729
Admission class, no. (%)					0.015
Subsidised	139 (53.9)	41 (69.5)	26 (55.3)	72 (47.4)	
Private	119 (46.1)	18 (30.5)	21 (44.7)	80 (52.6)	

AMH: anti-Müllerian hormone; BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; SD: standard deviation
All results were analysed using Pearson's chi-square test or one-way analysis of variance.
Missing data were present for the following variables: AMH level before index operation (n=161), pain score before index operation (n=118), dyspareunia (n=42), dysmenorrhoea (n=4), height and BMI before index operation (n=2), heavy menstrual bleeding, dyschezia, tenesmus, diarrhoea, constipation, dysuria, age at first diagnosis of endometriosis, weight before index operation, and duration between age at first endometriosis diagnosis and age at index operation (n=1).
[a] Fertility desire refers to whether the patient is considering future pregnancies.
[b] Previous diagnosis of infertility is defined as not being able to conceive after 12 months (or longer) of unprotected sex.
[c] No data as n=1 in this group.

and clinical presentations of deep infiltrating endometriosis, endometriomas and adenomyosis. Severe dysmenorrhoea was highest in patients with deep infiltrating endometriosis and was associated with higher rates of out-of-pocket private surgical care. Compared to adenomyosis only, deep infiltrating endometriosis was associated with a higher fertility desire and a lower BMI. In contrast, heavy menstrual bleeding was the hallmark of adenomyosis, being less common in patients with endometriosis.

The most prominent hallmark of deep infiltrating endometriosis was pain. Compared to endometrioma only or adenomyosis only, cases of deep infiltrating endometriosis suffered more severe dysmenorrhoea, dyspareunia, dyschezia, tenesmus and diarrhoea. Their mean pain score before the index operation was also the

Table 2. Independent risk factors of deep infiltrating endometriosis (compared to endometrioma and adenomyosis) and of adenomyosis (compared to endometrioma)

Variables	Deep infiltrating endometriosis (versus endometrioma only)	Deep infiltrating endometriosis (vs adenomyosis only)	Adenomyosis (vs endometrioma only)
	OR (95% CI)		
Reproductive factors			
Parity			
Parous	1.35 (0.37, 4.93)	1.76 (0.25, 12.24)	0.40 (0.04, 4.58)
Previous vaginal delivery	2.34 (0.60, 9.10)	0.52 (0.09, 3.16)	5.64 (0.69, 46.14)
Fertility desire	1.59 (0.41, 6.17)	13.47 (1.01, 180.59)	0.05 (0.00, 4.77)
Previous diagnosis of infertility	1.70 (0.55, 5.25)	0.10 (0.01, 0.81)	6.40 (0.32, 128.25)
Menstrual pattern			
Heavy menstrual bleeding	1.61 (0.65, 3.98)	0.22 (0.05, 0.91)	12.29 (2.41, 62.69)
Pain symptomatology			
Dysmenorrhoea			
Severe	2.80 (1.02, 7.70)	2.24 (0.45, 11.13)	16.59 (0.65, 421.72)
Dyspareunia	2.78 (0.53, 14.51)	ND	ND
Dyschezia	5.31 (0.60, 47.17)	ND	ND
Tenesmus	1.17 (0.24, 5.65)	1.79 (0.17, 18.56)	1.56 (0.02, 135.63)
Endometriosis/adenomyosis			
Age at first diagnosis of endometriosis (years)	1.03 (0.87, 1.23)	0.96 (0.77, 1.19)	0.90 (0.59, 1.38)
Previous endometriosis operation	3.58 (0.67, 19.13)	0.38 (0.03, 5.07)	0.21 (0.00, 18.62)
Previous hormonal treatment	2.28 (0.78, 6.61)	0.81 (0.15, 4.24)	5.71 (0.70, 46.27)
Analgesia required before index operation (i.e. NSAIDs)	3.17 (0.66, 15.25)	0.50 (0.07, 3.38)	0.56 (0.01, 23.47)
Index operation			
Age at index operation	0.94 (0.78, 1.13)	0.88 (0.70, 1.10)	1.33 (0.87, 2.03)
BMI before index operation	0.91 (0.82, 1.01)	0.89 (0.79, 0.99)	0.98 (0.88, 1.09)
Admission class			
Private	4.72 (1.85, 12.04)	1.13 (0.32, 3.93)	1.33 (0.32, 5.58)

BMI: body mass index; CI: confidence interval; ND: no data (numbers were too few for analysis); NSAIDs: nonsteroidal anti-inflammatory drugs; OR: odds ratio
Results were analysed using binary logistic regression. Significant univariate factors were entered into the model except pain score before index operation, diarrhoea, weight, and duration between age at first endometriosis diagnosis and age at index operation.

highest. Our findings differ from a study in a Chinese population where multivariate logistic regression analysis indicated that gastrointestinal symptoms during menstruation, rather than dysmenorrhoea, were more likely to be present in deep infiltrating endometriosis compared to ovarian endometriomas,[22] This was possibly due to a comparatively larger number of deep infiltrating endometriosis subjects in our study. However, our results were consistent with previous studies,[10,23] which indicated that in addition to gastrointestinal symptoms, complaints of severe dysmenorrhoea, dyspareunia and lower urinary tract symptoms were also significantly associated with deep infiltrating endometriosis.

Compared to endometrioma only, cases of deep infiltrating endometriosis had almost double the duration between diagnosis and surgery. They were also more likely to opt for the private class of surgery despite this

method being more expensive in Singapore, with an out-of-pocket funded healthcare system. The diagnostic delay in endometriosis is not new. The awareness of long delays in the diagnosis of endometriosis and unsatisfactory treatments were first raised in the 1980s by researchers in the US, and subsequent studies on more than 7,000 endometriosis patients showed the average time to diagnosis was 9 years.[24] European researchers showed similar data with an average delay of 6.7 to 11.7 years from the onset of symptoms to diagnosis of endometriosis.[25,26] Efforts to help patients identify their symptoms and seek medical attention earlier have been made in public education and primary care consultation.[27-30] The longer duration between the diagnosis of deep infiltrating endometriosis and the index operation in our study further demonstrated the delay in receiving treatments and indicated the underlying challenges in providing care for this most debilitating form of endometriosis. Patients with severe pain symptomatology should be referred to a tertiary centre with the ability to diagnose and manage deep infiltrating endometriosis as this may frequently require complicated excisions of endometriotic deposits affecting the urinary or gastrointestinal tracts.

Unlike the consensus of pain being the main symptom among patients with deep infiltrating endometriosis, their fertility desires are controversial. Previous studies reported lower fertility desire in deep infiltrating endometriosis compared to those of patients with adenomyosis or superficial endometriosis, thought to be related to the presence of pelvic pain or dyspareunia, and subsequent reduction in sexual function.[31] In our study, fertility desire was associated with deep infiltrating endometriosis and a quarter of our patients had a previous diagnosis of infertility. A recent study on deep infiltrating endometriosis demonstrated similar data with 64.1% patients with bowel endometriosis expressing the desire to conceive.[32] However, it is challenging to determine the independent impact on infertility by deep infiltrating endometriosis as deep lesions are rarely isolated and other coexisting forms of endometriosis may be the causes for subfertility. Nevertheless, early treatment for deep infiltrating endometriosis is indicated so that these patients achieve their desired family size.

Our findings need to be interpreted with the following caveats. Our series represents the most severe cases that had undergone surgery. Milder forms of endometriosis or adenomyosis that do not require surgery would not be included in our analysis. Correct identification of all cases involving endometriosis and adenomyosis depends on the accurate entry of TOSP surgical codes. Being a retrospective study, most data fields have missing datapoints. Cases with both ovarian endometrioma and adenomyosis were excluded, which may skew the symptomatology and risk factors. We have opted to include only cases confirmed with histopathological examination, thereby excluding cases that may be diagnosed based on ultrasound and other imaging methods. However, histopathology is the most rigorous diagnostic modality, and we believe this adds to the reliability of the data. One key strength of the present analysis is the relatively large number of cases of histologically proven deep infiltrating endometriosis. We also compared deep infiltrating endometriosis with cases where only ovarian endometrioma or only adenomyosis were encountered, thereby allowing clear phenotypes to be evident. Finally, the potential generalisability of the findings to other population needs to be interpreted with caution as our data represent only a surgical case series from a single centre.

CONCLUSION

In summary, our study has identified severe dysmenorrhoea, and pain related to urinary and gastrointestinal tracts, to be associated with deep infiltrating endometriosis. The highest fertility desire and infertility rate were reported in patients with deep infiltrating endometriosis. Adenomyosis was associated with heavy menstrual bleeding. Cases with pain symptomatology and subfertility should be referred to a tertiary centre with the capability to diagnose and manage deep infiltrating endometriosis.

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ORIGINAL ARTICLE

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Immune and coagulation profiles in 3 adults with multisystem inflammatory syndrome

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ABSTRACT

Introduction: There is a paucity of information on the cytokine, complement, endothelial activation, and coagulation profiles of multisystem inflammatory syndrome in adults (MIS-A), a rare but serious complication following recovery from SARS-CoV-2 infection. We aim to examine the immune biomarker and coagulation profiles in association with the clinical presentation and course of MIS-A.

Method: The clinical features of MIS-A patients admitted to our tertiary hospital were documented. Their levels of interleukin (IL)-1β, IL-6, IL-10, IL-17, IL-18, interferon-α (IFN-α), IFN-γ, interferon gamma-induced protein 10 (IP-10), tumour necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, complement activation product (complement 5a [C5a]), and endothelial biomarker intercellular adhesion molecule-1 (ICAM-1) levels were assayed. The haemostatic profile was assessed with standard coagulation testing and thromboelastography.

Results: Three male patients were diagnosed with MIS-A at our centre from January to June 2022 with a median age of 55 years. All had tested positive for SARS-CoV-2 12–62 days prior to MIS-A presentation, with gastrointestinal and cardiovascular systems as the most commonly involved. Levels of IL-6, IL-10, IL-18, IP-10 and MCP-1 were raised whereas IL-1β, IFN-α, IFN-γ, IL-17 and TNF-α remained normal. Markedly elevated levels of C-reactive protein (CRP), ferritin and ICAM-1 were present in all. C5a was elevated in 2 patients. A hypercoagulable state was demonstrated by raised levels of D-dimer, factor VIII, von Willebrand factor antigen, and ristocetin cofactor with corresponding raised parameters in thromboelastography in the 2 patients who had their coagulation profile assessed.

Conclusion: MIS-A patients demonstrate activation of pro-inflammatory cytokines, endotheliopathy, complement hyperactivation and hypercoagulability.

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Keywords: COVID-19, cytokines, hypercoagulability, hyperinflammatory syndrome

INTRODUCTION

A spectrum of immune dysregulation has been described following SARS-CoV-2 infections—from the cytokine storm in the acute phase, to hyperinflammatory syndromes that occur after the resolution of the initial infection.[1] Multisystem inflammatory syndrome (MIS) was first reported in children in April 2020 as a hyperinflammatory syndrome with features similar to Kawasaki disease and toxic shock syndrome,[2] and is increasingly being recognised in adult patients. MIS is defined as a potentially life-threatening hyperinflammatory state with multiorgan dysfunction that develops after SARS-CoV-2 infection. Following the recognition of multisystem inflammatory syndrome in children (MIS-C), similar presentations in adults were described by the US Centers for Disease Control and Prevention (CDC), which considers patients aged 21 years and above to have MIS in adults (MIS-A).[3] In contrast to MIS-C, MIS-A appears to have a lower incidence of coronary artery aneurysm development but higher

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CLINICAL IMPACT

What is New

- This study evaluates the immune biomarkers and coagulation profiles of adults with multisystem inflammatory syndrome (MIS), data on which are currently lacking.
- In contrast to MIS in children, interleukin (IL)-1β, IL-17, interferon (IFN)-γ and IFN-α remain unaffected in MIS in adults.

Clinical Implications

- The difference in cytokine profiles could have potential implications on the choice of biologic agents for adult MIS patients, as infliximab and anakinra are currently recommended for the treatment of refractory MIS in children.
- Elevated intercellular adhesion molecule-1 and complement 5a may present new insight into the pathogenesis of MIS in adults.

mortality.[4] It is postulated that MIS results from a dysregulated immune response to the virus, although the exact mechanisms by which this response is triggered remain unknown. Formation of autoantibodies, antibody recognition of persistent viral antigens on infected cells, and hyperinflammatory response due to the viral super antigens have been put forth as possible pathophysiological mechanisms. Higher levels of pro-inflammatory cytokines including interleukin (IL)-1β, IL-10, IL-17, IL-18, interferon gamma (IFN-γ), interferon gamma-induced protein 10 (IP-10), and tumour necrosis factor (TNF)-α have been demonstrated in patients with MIS-C compared to those with SARS-CoV-2.[5-7] While the clinical characteristics, presentation and treatment of this novel syndrome have been reported,[3,8,9] there is a paucity of data on the cytokine profile, complement levels, and coagulation profile in MIS-A. Here we describe 3 cases of MIS-A diagnosed and treated at our centre from January to June 2022 where we examined their underlying inflammatory milieu and haemostatic profiles associated with their clinical features.

METHOD

The diagnosis of MIS-A was based on the described clinical presentation in temporal relation to the SARS-CoV-2 infection, with other causes excluded. Blood samples were drawn 12, 29 and 11 days from the onset of MIS in patients 1, 2 and 3, respectively. These samples were drawn on the day or 1 day after our department (Rheumatology, Allergy and Immunology) was consulted. Follow-up testing was done 10–12 weeks after the onset of the illness. Serum cytokine and inflammatory biomarkers including levels of IL-1β, IL-6, IL-10, IL-17, IL-18, IP-10, IFN-γ, IFN-α, TNF-α, monocyte chemoattractant protein (MCP)-1, complement 5a (C5a), and intercellular adhesion molecule-1 (ICAM-1) were assayed by enzyme-linked immunosorbent assay (ELISA BD Biosciences, San Diego, US; R&D Systems, Abingdon, UK; and Bender Med Systems GmbH, Vienna, Austria) according to the manufacturers' recommendations. The lower limit of detection for IL-1β (0.46pg/mL), IL-6 (0.08pg/mL), IL-10 (0.2pg/mL), IL-17 (<0.9pg/mL), IL-18 (0.5pg/mL), IP-10 (<5pg/mL), IFN- γ and MCP-1 (<2pg/mL) IFN-α (<0.5pg/mL), TNF-α (<0.2pg/mL), C5a (<0.015ng/mL) and ICAM-1 (<0.063ng/mL). These cytokines were chosen based on the pro-inflammatory nature described in either MIS-A or SARS-CoV-2 infection, with IL-10 the exception as an immuno-regulatory cytokine.[1,6,7,10]

Two of the 3 patients had thrombotic risk assessed with standard haemostatic tests, namely prothrombin time, activated thromboplastin time, fibrinogen, D-dimer, anti-thrombin, protein C and S levels, factor V, factor VIII and von Willebrand factor antigen (vWF:Ag) (Diagnostica Stago SAS, Asnières sur Seine Cedex, France) and thromboelastography (TEG) (TEG 6s, Haemonetics Corp, Boston, US). Patient 2 had haemostatic profiling 1 day after intravenous immunoglobulin (IVIG) initiation and 4 days after steroid therapy was started, while patient 3 had haemostatic profiling before IVIG therapy and 3 days after steroid therapy was started. The study was approved by the institutional review board (National Healthcare Group, Domain Specific Review Board reference number: 2012/00917), and written informed consent was obtained from participants.

RESULTS

Patient 1, a previously well 44-year-old Chinese male, was admitted after a syncopal episode 4 weeks after a SARS-CoV-2 upper respiratory tract infection (URTI). Fever, right-sided throat discomfort, vomiting, and diarrhoea were also present on admission. Of interest, this patient had prominent swelling at the right submandibular area. Computed tomography (CT) of the neck showed thickening of the right fossa of the Rosenmüller and lateral oropharyngeal wall. There was fat stranding in the right parapharyngeal space, extending along the right side of the neck down to the supraclavicular fossa. Mild bilateral lower lobe consolidation with small pleural effusions was

demonstrated on the CT scan. He subsequently developed hypotension and myocarditis (depressed ejection fraction [EF] of 45%, raised troponin levels up to 1,863ng/L, and cardiac magnetic resonance imaging [MRI] features of myocarditis), leading to the diagnosis of MIS-A. His fever lysed after the initiation of ibuprofen. The patient was not treated with glucocorticoids as his fever had lysed with non-steroidal anti-inflammatory drugs alone and blood pressure had improved by the time the diagnosis was made. IVIG 2g/kg was administered in view of cardiac dysfunction. Repeat cardiac imaging showed improvement in his EF to 69%.

Patient 2, a 55-year-old Indian male with pre-existing ischaemic heart disease (IHD), mixed cardiomyopathy with a baseline EF of 30%, and dialysis-dependent end-stage kidney disease (ESKD) presented with fever and abdominal pain 8 weeks after a SARS-CoV-2 URTI. He developed recurrent ventricular arrhythmias with cardiovascular collapse not accounted for by coronary angiography findings of a widely patent right coronary artery (RCA) stent with minor coronary artery disease. His EF was stable at 30% on transthoracic echocardiography. A cardiac MRI could not be performed in view of his ESKD. He was treated with IVIG 2g/kg and intravenous (IV) hydrocortisone with good response. An implantable cardioverter defibrillator was inserted prior to discharge. Although the onset of symptoms was 62 days after his SARS-CoV-2 infection, his clinical syndrome was in keeping with MIS-A, having excluded differentials such as infection and malignancy. He had no features of other autoimmune or autoinflammatory diseases. He responded rapidly to IV hydrocortisone and IVIG. He remained well at follow-up 6 months after his illness and 4 months being off glucocorticoids. Singapore MIS-C cases presented 2–8 weeks after the initial COVID-19 infection.[11,12] Rare cases of MIS-C presenting 16 weeks after the initial COVID-19 illness have been described.[13]

Patient 3 is a 58-year-old Chinese male with virologically suppressed human immunodeficiency virus (HIV) and poorly controlled diabetes mellitus (DM). His CD4 prior to admission was 256 cells/μL and CD8 1,075 cells/μL. He presented with 3 days of generalised abdominal pain and vomiting. On day 2 of admission, he developed fever and erythematous blanchable patches over the face and chest, petechial macules over the abdomen, arms, and lower back, with changes of desquamation over the upper back. Subsequently, new-onset atrial fibrillation (AF), hypotension requiring inotropic support, acute renal failure with oliguria, and metabolic acidosis developed. He demonstrated rapid clinical improvement upon initiation of IV hydrocortisone and IVIG. A repeat TEG 5 days after IVIG showed improvement in markers for hypercoagulability (online Supplementary Materials).

Demographics, clinical presentation, laboratory findings, treatment, and outcomes are summarised in Table 1. Increased serum pro-inflammatory cytokines IL-6, IL-10, IL-18, and IP-10, together with C-reactive protein (CRP), ferritin, and ICAM-1 were observed in all 3 patients, while levels of IL-1β, TNF-α, IFN-γ, IFN- α, and IL-17 were normal. LDH, C5a and MCP-1 levels were elevated in 2 patients. Raised levels of D-dimer, factor VIII, vWF:Ag, and ristocetin cofactor were found in the 2 patients who had their coagulation profile assessed. Hypercoagulability was demonstrated in these 2 patients. Prothrombin time and activated thromboplastin values were normal. Platelet counts were elevated in 2 of the 3 patients. It is of interest that in Patient 1 and Patient 2, ferritin, IL-18 and IP-10 levels decreased but remained elevated after 10–12 weeks in the subsequent follow-up study, suggesting these inflammatory cytokines may still be active. These levels returned to the normal range for Patient 3.

DISCUSSION

MIS-A is a rare complication following recovery from a SARS-CoV-2 infection. A systemic review of 221 patients reported that 57% of patients required intensive care unit (ICU) admission, with a mortality rate of 7%.[8] Given the severity of this illness and the availability of therapeutic options, early recognition is important to guide the management.

The most common findings in MIS-A are fever, and haematologic, cardiovascular and gastrointestinal involvement;[8] however, atypical manifestations are being increasingly recognised. Our patient 1 had parapharyngeal oedema which had been described previously only in MIS-C.[14]

Cytokines play an important role in understanding pathogenesis and may help guide the treatment with biologic agents. Similar to the profiles found in paediatric patients, our patients demonstrated elevated levels of IL-6, IL-10, IP-10, IL-18 and MCP-1. Interestingly, while patients with MIS-C have been reported to have elevated IL-1β, IL-17, IFN-α, IFN-γ and TNF-α levels,[15,16] all of our patients demonstrated normal levels of these cytokines. While infliximab and anakinra are currently recommended for the treatment of refractory MIS-C,[17,18] our finding of normal TNF-α

Table 1. Demographics, clinical presentation, laboratory findings, treatment and outcomes of multisystem inflammatory syndrome in adult (MIS-A) patients

		Patient 1	Patient 2	Patient 3
Demographics				
Age, years, male sex		44	55	58
Ethnicity		Chinese	Indian	Chinese
Medical history		None	ESKD, IHD, mixed cardiomyopathy	HIV (on RAL + 3TC + ATV), poorly controlled DM (receiving metformin 850mg BD and linagliptin 5mg OM)
Clinical presentation				
Onset after SARS-CoV-2 infection, days		29	62	12
Duration of symptom onset to admission, days		4	2	2
Initial symptoms		Fever, right-sided throat pain, syncope, vomiting, diarrhoea	Fever, abdominal pain	Abdominal pain, vomiting
Maximal temperature, °C		40.8	39	39
Clinical features		Fever, cardiomyopathy, hypotension, gastrointestinal (vomiting)	Fever, recurrent VT/VF collapse, hypotension, gastrointestinal (nausea, abdominal pain)	Fever, hypotension, AF, rash, gastrointestinal (vomiting, abdominal pain), acute kidney injury
Investigations				
Laboratory tests	(Healthy reference)			
SARS-CoV-2 infection confirmed by		ART and RT-PCR (cycle threshold 16.23)	ART	ART
Range of leucocyte count during hospitalisation, $x10^9$/L	4.0–9.6	7.0–23.4	7.5–17.0	10.3–18.3
Leucocyte count corresponding to follow-up immunological profile, $x10^9$/L[a]		4.8	7.8	11.2
Range of lymphocyte count during hospitalisation, $x10^9$/L	1.10–6.60	0.44–2.02	0.36–3.84	0.45–4.65
Range of platelet count during hospitalisation, $x10^9$/L	150–360	172–1177	145–397	191–289
Platelet count corresponding to follow-up immunological profile, $x10^9$/L[a]		306	311	245
Peak CRP, mg/L	<5	>380	131.1	229.5
CRP corresponding to follow-up immunological profile, mg/L[a]		2.8	21.9	5.4
Peak ferritin, µg/L	12–307	5367	4175	669
Ferritin corresponding to follow-up immunological profile, µg/L[a]		704	613	22
LDH, U/L	270–550	448	1092	813

Table 1. Demographics, clinical presentation, laboratory findings, treatment and outcomes of multisystem inflammatory syndrome in adult (MIS-A) patients (Cont'd)

		Patient 1	Patient 2	Patient 3
Immunological profile				
Timing of initial test from onset of illness		12 days	29 days	11 days
IL-6, pg/mL	<2	74.1	177.8	109.6
IL-6 follow-up,[a] pg/mL		1.1	2.3	0.3
IL-10, pg/mL	<2	27.6	47.5	2.9
IL-10 follow-up,[a] pg/mL		1.9	1	1.2
IP-10, pg/mL	31.9 (23.2–42.6)[b]	3848.7	225	1989.9
IP-10 follow-up,[a] pg/mL		102.6	124.3	77.6
IL-18, pg/mL	138 (107–169)[b]	2601.9	1922.4	1360.1
IL-18 follow-up,[a] pg/mL		204.3	417.1	95.4
C5a, ng/mL	47.4 (32.1–53.4)[b]	79.91	111.4	28.5
C5a follow-up,[a] ng/mL		32.6	42	29.5
ICAM-1, ng/mL	<95	187.8	355.9	231.1
ICAM-1 follow-up,[a] ng/mL		52.9	76.4	42.7
MCP-1, pg/mL	168.2 (134.2–196.6)[b]	380.7	1748.7	135.8
MCP-1 follow-up,[a] pg/mL		163.3	123.9	125.7
Coagulation studies				
Prothrombin time, seconds	11.7–14.0	16.1	17.8	12.5
Activated partial thromboplastin clotting time, seconds	27.0–27.0	49.2	33.1	34.2
Thrombin clotting time, seconds	15.0–18.0	N/A	15.9	17.4
D-dimer, μg/mL	<0.50	N/A	>4	>4
Fibrinogen, g/L	1.8–4.5	N/A	2.8	6.2
Anti-thrombin (%)	80–130	N/A	65	81
Protein S activity (%)	65–130	N/A	70	81
Protein C activity (%)	70–150	N/A	63	76
Factor V (%)	70–120	N/A	43	116
Factor VIII (%)	60–150	N/A	325	304
vWF:Ag (%)	56–160	N/A	>400	280
Ristocetin cofactor	47–148	N/A	>240	240
Cardiac investigations				
Transthoracic echocardiogram		EF 45%, mild global hypokinesia	EF 30%, regional wall motion abnormality consistent with multivessel disease	EF 60%, no RWMA or significant valvular dysfunction[c]
Others		CMR features met criteria for acute myocarditis	Coronary angiogram: patent RCA stent, minor coronary artery disease	N/A

Table 1. Demographics, clinical presentation, laboratory findings, treatment and outcomes of multisystem inflammatory syndrome in adult (MIS-A) patients (Cont'd)

	Patient 1	Patient 2	Patient 3
Treatment			
High dependency or intensive care unit care	Yes	Yes	Yes
Inotrope or vasopressor use	Yes	Yes	Yes
Steroid use	No	Yes	Yes
Steroid regime	N/A	IV hydrocortisone 50mg Q6H (6 days) → IV hydrocortisone 50mg Q8H (4 days) → prednisolone 30mg OM (1 week) → prednisolone 20mg OM (2 weeks) → then tapered by 5mg each week.	IV hydrocortisone 50mg Q6H (1 week) → prednisolone 50mg (1mg/kg, 4 days) → 40mg (12 days) → 30mg (2 weeks) → then tapered by 5mg every 2 weeks.
IVIG	Yes	Yes	Yes
Anticoagulation	No	No	Yes
Others	Ibuprofen		
Outcome			
Length of hospital stay, days	17	33	16
Outcome	Discharged	Discharged	Discharged

3TC: lamivudine; AF: atrial fibrillation; ART: antigen rapid test; ATV: atazanavir; BD: twice daily; CMR: cardiac magnetic resonance imaging; CRP: C-reactive protein; C5a: complement 5a; DM: diabetes mellitus; EF: ejection fraction; ESKD: end-stage kidney disease; HIV: human immunodeficiency virus; ICAM-1: intracellular adhesion molecule-1; IFN: interferon; IHD: ischaemic heart disease; IL: interleukin; IP-10: interferon gamma-induced protein; IV: intravenous; IVIG: intravenous immunoglobulin; LDH: lactate dehydrogenase; MCP: monocyte chemoattractant protein; N/A: not applicable; OM: every morning; RAL: raltegravir; RCA: right coronary artery; RT-PCR: reverse transcription polymerase chain reaction; RWMA: regional wall motion abnormality; TNF: tumour necrosis factor; VF: ventricular fibrillation; VT: ventricular tachycardia; vWF Ag: von Willebrand factor antigen

[a] C-reactive protein, ferritin, leucocyte and platelet counts and cytokine analysis 10–12 weeks post MIS-A diagnosis

[b] Mean (95% range)

[c] Imaging was performed 2 weeks after admission

and IL-1β levels could have potential implications on the choice of biologic agents for adult MIS patients. Further studies are required to determine if this is a common feature of MIS-A.

Robust type 1 IFN gene signalling pathways and TNF-α/IL-1 have been implicated in the cytokine storm and hyperinflammation of severe SARS-CoV-2 infections.[19] The lack of IFN-α, TNF-α and IL-1β in our MIS-A patients point to a potentially different immune-dysregulation from the SARS-CoV-2 infection.

IP-10 has been suggested as a potential biomarker to predict left ventricular dysfunction in MIS-C patients.[20] Our MIS-A patients, all with cardiovascular manifestations, demonstrated elevated IP-10 levels. Patient 3's echocardiogram was performed 2 weeks after admission and administration of corticosteroids and IVIG, and it is possible that his cardiac function had improved by the time his cardiac imaging was performed.

C5a has been implicated in severe pneumonia, acute respiratory distress syndrome, and SARS-CoV-2-related manifestations, including heart, kidney and endothelial dysfunction. As the complement system is the link between innate immunity and coagulation, its overactivation could promote thrombotic events in patients with severe SARS-CoV-2 infection.[21] Our first 2 patients demonstrated elevated levels of C5a while the normal level in patient 3 could be the result of the test being drawn after 3 days of IV hydrocortisone.

ICAM-1 is a cell surface glycoprotein and an adhesion receptor regulating leukocyte recruitment from the circulation to sites of inflammation,[22] and its endothelial expression is increased in patients with severe SARS-CoV-2 infection. This increased expression of ICAM-1

may lead to a sustained pro-inflammatory state, resulting in systemic endothelial dysfunction.[23] To our knowledge, this is the first study assessing ICAM-1 in MIS-A patients.

Increased risks of thromboembolic events have been reported in patients with MIS-C;[24] risk factors include central venous catheterisation, age ≥12 years, malignancy, ICU admission, and elevated D-dimer levels >5 times the upper limit of normal.[24] The American College of Rheumatology recommends that anticoagulation should be considered on an individual basis, with stronger recommendations for paediatric patients with coronary artery aneurysms (z-score ≥10.0), EF <35%, and those with documented thrombosis.[17] At present, information on the thrombotic and bleeding risks in the adult population remains unclear. Haemostatic profiling of Patient 2 was performed on Day 5 of IV hydrocortisone and Day 2 of IVIG. While he did demonstrate features of hypercoagulability (shown by raised levels of factor VIII, vWF:Ag, ristocetin cofactor and D-dimer, and depressed levels of anti-thrombin III and protein C), the TEG did not show features of hypercoagulability. This is most likely due to the effect of immunosuppression. As Patient 2 was at increased risk of bleeding from ESRD and also because of the rapid clinical improvement with IVIG and IV hydrocortisone, thromboprophylaxis was not administered. Assessment of the haemostatic profile in Patient 3 was performed on Day 4 of IV hydrocortisone, and before IVIG was initiated. He had elevated D-dimer, hyperfibrinogenaemia, factor VIII, and vWF: Ag levels—a profile similar to the hypercoagulability seen in patients with acute SARS-CoV-2 infection. This was supported by hypercoagulable parameters present in the TEG, where there was increased maximal amplitude and raised angle, likely contributed by a hyperfibrinogenaemic state and raised factor VIII levels. Given the hypercoagulable state and a high Padua venous thromboembolism (VTE) score, he was started on thromboprophylaxis with subcutaneous heparin and later anticoagulation with dabigatran, as he had concomitant AF. Repeat TEG performed 8 days post-IV hydrocortisone and 5 days after IVIG showed marked improvement in the hypercoagulability. Mechanisms for hypercoagulability in SARS-CoV-2 survivors have been largely focused on endothelial dysfunction and hyperinflammation as the primary mechanism,[25] where the prior cytotoxic effects of SARS-CoV-2 virus results in an overwhelming immune response causing damaged endothelium, exposed tissue factor and procoagulant cytokines, culminating in secondary hypercoagulability. While none of our patients developed thromboembolic events during their hospitalisation, a hypercoagulable state was observed in the 2 patients profiled. Thus a combination of haemostatic profiling and the use of thrombotic risk assessment models—such as IMPROVE-DD VTE or Padua VTE risk scoring—while yet to be clinically validated in critically ill patients with MIS-A, should be considered to guide decisions on thromboprophylaxis.

Treatment of MIS-A is drawn from experience in the management of MIS-C. First-line treatment usually includes the immunomodulator IVIG and glucocorticoids. The mechanism of action of IVIG includes inhibition of complement deposition, enhancement of regulatory T cells, and accelerated clearance of autoantibodies.[26] Proposed immunologic mechanisms of MIS include: superantigen-like activation of the immune system; and autoantibody production resulting in activation of Fcγ receptors on neutrophils and macrophages, causing secretion of pro-inflammatory cytokines.[27] IVIG-mediated neutralisation and clearance of autoantibodies may explain IVIG efficacy in MIS. In patients with refractory disease, pulse methylprednisolone, and/or biologics such as anakinra and infliximab may be considered. While Patients 2 and 3 had good treatment responses with IVIG and IV hydrocortisone, Patient 1 responded to IVIG alone. The dramatic improvement in his clinical, laboratory markers, and recovery of his EF within a week without the use of corticosteroid is noteworthy. Further studies on the immunopathogenesis and biomarkers related to MIS-A is required, as our preliminary findings demonstrate a cytokine profile different from that of MIS-C.

CONCLUSION

MIS-A patients demonstrate activation of pro-inflammatory cytokines, endotheliopathy, complement hyperactivation and hypercoagulability. In contrast to MIS-C, IL-1β, IL-17, IFN-γ and IFN-α remain unaffected. This could have potential implications on the choice of biologic agents for adult MIS patients as infliximab and anakinra are currently recommended for the treatment of refractory MIS-C.

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REVIEW ARTICLE

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Through the eyes into the brain, using artificial intelligence

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ABSTRACT

Introduction: Detection of neurological conditions is of high importance in the current context of increasingly ageing populations. Imaging of the retina and the optic nerve head represents a unique opportunity to detect brain diseases, but requires specific human expertise. We review the current outcomes of artificial intelligence (AI) methods applied to retinal imaging for the detection of neurological and neuro-ophthalmic conditions.

Method: Current and emerging concepts related to the detection of neurological conditions, using AI-based investigations of the retina in patients with brain disease were examined and summarised.

Results: Papilloedema due to intracranial hypertension can be accurately identified with deep learning on standard retinal imaging at a human expert level. Emerging studies suggest that patients with Alzheimer's disease can be discriminated from cognitively normal individuals, using AI applied to retinal images.

Conclusion: Recent AI-based systems dedicated to scalable retinal imaging have opened new perspectives for the detection of brain conditions directly or indirectly affecting retinal structures. However, further validation and implementation studies are required to better understand their potential value in clinical practice.

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Keywords: Alzheimer's disease, deep learning, dementia, optic neuropathy, papilloedema

INTRODUCTION

Neurological dysfunction is a leading cause of disability, affecting more than 276 million people worldwide.[1] Over the last decades, the prevalence of neurological dysfunction has increased, particularly in the ageing population which is commonly affected by dementia, stroke and brain tumours.[1,2] The increasing number of patients suffering from neurological disorders raises concerns about the efficiency of screening programmes and early clinical interventions. Cognitive impairment and dementia are major causes of chronic neurological impairment in Singapore—they are also significant individual determinants of emergency department utilisation.[3] Early detection of treatable diseases in

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CLINICAL IMPACT

What is New

- Retinal imaging with standard cameras complements clinical ophthalmoscopy for the detection of associated neurological conditions affecting the optic nerves. However, these modalities require high human expertise for interpretation.
- Deep learning (DL) methods have recently enabled automated and accurate interpretation of such retinal images for the diagnosis of papilloedema due to neurological conditions that cause increased intracranial pressure.

Clinical Implications

- Recent studies suggest that DL applied to retinal images could also identify patients with Alzheimer's disease, but more prospective data are needed to assess clinical applications in real-life situations.

predisposed patients is a key strategy for improving global healthcare; it is applicable for many conditions such as colon cancer, breast cancer, diabetic retinopathy, etc. Unfortunately, few screening strategies have been developed for the detection of neurological diseases due to many factors, including phenotypic variability and disease complexity.[4]

In overcoming these issues, the eye is an excellent candidate to facilitate the detection of neurological disorders, which often also affect the retina or the optic nerve as they both contain neural tissue.[5] Standard imaging of the retina and the optic nerve (e.g. retinal fundus photography and optical coherence tomography [OCT]) are non-invasive and real-time methods to investigate the integrity of the visual system. They also provide an indirect reflection of cerebral health in various neurological conditions, such as multiple sclerosis and intracranial hypertension.[6] However, direct fundoscopy and interpretation of retinal images require high human expertise, which is a barrier for their utilisation by non-ophthalmic healthcare providers.[7] Recently, artificial intelligence (AI) methods such as deep learning (DL) have been applied for automated interpretation of medical data, including retinal images. In brief, by "learning" from a large sample of retinal images with robust reference diagnosis, specific DL algorithms have the potential to automatically identify structural lesions on retinal photographs, leading to the detection of underlying neurological conditions. The aim of this review is to summarise the current and emerging concepts related to the detection of various neurological conditions via a DL-based analysis of retinal images.

Retinal imaging modalities

The main retinal imaging modalities used in clinical practice include retinal fundus photography with adapted cameras, OCT and more recently, OCT angiography (OCTA). Colour fundus photography is the most common and affordable method for imaging the retina and optic nerve head (ONH) structures. It can be performed by desktop cameras or by recently developed handheld cameras. Traditionally, retinal fundus photography is performed by mydriatic cameras after pharmacological pupillary dilation to allow optimal visualisation of the periphery of the back of the eye. This method is associated with some inconvenience (e.g. photophobia, loss of accommodation, risk of allergy, etc.). However, non-mydriatic fundus cameras can also achieve excellent imaging performance, which may accelerate a possible transition of their use to non-ophthalmic settings, such as in the emergency departments and diabetes and endocrinology clinics.[7] New, non-mydriatic handheld fundus cameras or smartphones have also been successfully used for the detection of diabetic retinopathy (DR),[8,9] but their use is yet to be evaluated for neuro-ophthalmic purposes.

OCT is a retinal imaging technique that has transformed ophthalmology. Initially used for the evaluation of retinal diseases (e.g. diabetic macular oedema and age-related macular degeneration [AMD]) and glaucoma, OCT has been progressively used to also assess the structure of ONHs in various optic neuropathies. Based on an interferometric technique, OCT generates cross-sectional images of the retina, allowing micron-level spatial resolution. The latest generations of OCT provide greater resolution images, and increased field of view and depth of the study area within a short amount of time.

METHOD

The authors examined and summarised current and emerging concepts related to the detection of neurological conditions that uses AI-based investigations of the retina in patients with brain disease.

RESULTS

Applications of AI to retinal imaging

Retinal image analysis by humans remains a partially subjective operation, with high intra- and intergrader

variability that exposes patients to interpretation bias. Recent technological developments offered by AI—particularly machine learning (ML) and DL methods—have opened new horizons for improved, automated diagnosis on retinal images. To date, DL has been successfully developed and deployed across many different fields in medicine, such as in radiology, dermatology, pathology and ophthalmology.[10,11] In ophthalmology, there are currently 2 algorithms approved by the US Food and Drug Administration for the detection of DR, namely IDx-DR (Digital Diagnostics, Coralville, US) and EyeArt (Eyenuk Inc, Woodland Hills, US).[12] Numerous other DL systems (DLSs) have shown promise for detecting AMD, retinopathy of prematurity, and other retinal pathologies.[13]

The performance of a DLS is evaluated by comparing its predicted results with a reference standard (ground truth), which is typically provided by ophthalmologists and formulated according to expert judgment. Sensitivity, specificity, precision and accuracy are the most used indices to quantify the diagnostic effectiveness of a DLS. The area under the receiver-operator-characteristic curve (AUROC) is also a commonly used performance parameter. The performance of a model is conventionally assessed through 2 operational steps: firstly, through internal validation (cross-validation), followed by testing on an independent external dataset. Notably, the independent datasets should ideally include ethnically and demographically diverse patients, with data collected from different clinical settings to secure the generalisability of DLS.[14]

Detection of papilloedema and other optic neuropathies

The diagnosis of optic neuropathies in everyday practice is based on the identification of structural or functional abnormalities of the optic nerves. Diagnosing an optic neuropathy is based on a constellation of clinical signs and ancillary investigations (including evaluation of colour vision, visual fields, measurement of the optic nerve morphometric parameters with OCT, and sometimes electrophysiology). Ophthalmoscopically, an optic neuropathy can be associated with a normal appearance (if the lesion is very posterior within the orbit), or can cause swelling of the optic disc (if the anterior part of the nerve is affected). With time, swelling of the optic disc can either regress if appropriately treated, or can evolve into optic atrophy. Papilloedema is defined as ONH swelling due to raised intracranial pressure. It can be either idiopathic or secondary (the latter due to brain tumours, haematomas, venous sinus thrombosis, etc.). Papilloedema is not necessarily associated with visual dysfunction, which explains why patients may not complain of visual loss, especially in the early stages. Patients may present with headache or other systemic signs of raised intracranial pressure. However, detection of papilloedema at the back of the eye—whether visually symptomatic or not—is of critical importance, as delayed recognition may result in permanent visual loss, neurological deficits and even death. Papilloedema is traditionally identified by direct ophthalmoscopy, and it requires skill to differentiate the condition from other causes of optic disc swelling (e.g. ischaemic optic neuropathy and optic neuritis). More rarely, other optic disc anomalies (known as pseudo-papilloedema) such as optic disc drusen and myelinated intraocular nerve fibres can mimic papilloedema. Their appropriate detection is essential in clinical practice to avoid unnecessary, expensive and potentially harmful investigations. On the other hand, patients with intracranial hypertension usually present with headache, tinnitus and variable visual loss. They require evaluation of the optic discs, which is difficult in everyday practice without the direct assistance of ophthalmologists or neuro-ophthalmologists. As an alternative, it has been suggested that imaging of the retina and the ONH may improve the detection of various ONH abnormalities by non-ophthalmic healthcare providers.[7]

Computer-aided diagnostic systems could help improve the detection of papilloedema and other ONH abnormalities.[15] In an early study, Akbar et al.[16] developed a classification model aimed at automatically differentiating between papilloedema and normal ONHs on retinal images, based on structural features of the ONH (disc margin obscuration, disc colour and continuity of disc vessels) using support vector machine (SVM) for classification purposes. In the limited sample, the authors achieved good performance for differentiating papilloedema from normal ONH with an accuracy, sensitivity and specificity of 92.9%, 90.0%, and 96.4%, respectively.

To address the more complex reality of everyday clinical practice, a recent DLS has been developed for the detection of papilloedema and other ONH abnormalities on conventional retinal photographs. Milea and an international neuro-ophthalmology consortium called Brain and Optic Nerve Study with Artificial Intelligence (BONSAI) have developed, trained and tested a DLS[17] in a large, retrospective and multiethnic dataset. The team used multiple fundus digital cameras from 24 neuro-ophthalmology sites in 15 countries, aimed to discriminate papilloedema from normal ONHs and other ONH anomalies. The model was trained and validated on 14,341 photographs of normal and

abnormal ONHs, and the external testing dataset consisted of 1,505 photographs from 5 different countries. Papilloedema detection in the external testing dataset was achieved with high AUROC (0.96) and sensitivity (96.4%) indices, and good specificity (84.7%). Altogether, although obtained in a retrospective study, these results suggest that a DLS could accurately identify papilloedema and other abnormal optic discs on standard retinal images.

Despite the excellent classification performance of the BONSAI DLS, this retrospective study did not ascertain the model's performance in comparison with expert neuro-ophthalmologists. An additional study subsequently compared the performance of 2 expert neuro-ophthalmologists against the BONSAI DLS, using 800 fundus photographs (400 normal ONH, 201 papilloedema and 199 other ONH abnormalities photographs).[18] The performance of the BONSAI DLS for detecting papilloedema (AUROC 0.96, accuracy 91.5%, sensitivity 83.1% and specificity 94.3%) and overall correct classification (84.7%) was comparable with the performance of neuro-ophthalmology experts, but significantly better than the performance of non-expert first-line clinicians (neurologists, internists, emergency room doctors, ophthalmologists and optometrists).[19]

Determining papilloedema severity in clinical practice is important for treatment decisions and disease prognosis. Papilloedema severity is typically assessed using the 5-grade modified Frisen classification system, which is difficult to apply, not very practical, and thus results a in low interobserver agreement that can be as low as 36%.[20] For this reason, BONSAI has adopted a new, simplified classification: mild to moderate papilloedema (including Frisen grades 1 to 3); and severe papilloedema (including Frisen grades 4 and 5).[21] In order to automatically determine papilloedema severity, a specific DLS was trained on 2,103 fundus photographs of confirmed papilloedema from multiple centres. Two expert neuro-ophthalmologists then graded the papilloedema severity according to the above-mentioned simplified binary grading scale, for algorithm training. The DLS performance on the external testing dataset achieved a high diagnostic performance (AUROC 0.93), being also comparable to the majority agreement among 3 neuro-ophthalmologists (agreement score between DLS and neuro-ophthalmologists of 0.62), which was interestingly higher compared to the agreement score of 0.54 among the 3 neuro-ophthalmologists themselves.

In addition to the structural identification of papilloedema at the back of the eye, it is also essential to evaluate its functional visual consequences. Visual field (VF) testing is a critical method of measuring the optic nerve function, and it poses multiple technical and interpretation challenges in assessing the consequences of papilloedema. Recently, ML methods were applied to VF testing in patients with papilloedema due to idiopathic intracranial hypertension (IIH). For this purpose, archetypal analysis (AA) was developed based on data collected in the IIH Treatment Trial (IIHTT)—the first large randomised study that analysed baseline and laboratory characteristics of untreated patients with IIH—as an additional tool to conventional VF indices (i.e. mean deviation and pattern standard deviation). AA is an unsupervised ML technique that identifies representative patterns (archetypes) within a dataset of VFs, thereby analysing a given VF as the weighted sum of its archetypes.[22,23] As a start, Doshi et al.[22,23] identified 14 archetype patterns in the IIHTT dataset, which were comparable to expert categorisations. A subsequent follow-up study showed that archetypal weight changes were identifiable over a 6-month period and were dependent on IIH treatments. Although it is too early to generalise these initial results to various IIH severities, they are promising for the clinical management of IIH, because they provide a more standardised evaluation of IIH than the current practice, wherein individual clinical interpretation is inevitably qualitative and variable with current conventional VF indices.

Papilloedema can regress under treatment. However, if not adequately treated, it can cause optic atrophy that represents the late, non-specific stage of any optic neuropathy, irrespective of its cause (e.g. compression, ischaemia, inflammation, trauma, hereditary, etc.).[24] Identification of optic atrophy, which can be subtle, is important in clinical practice, because it can be caused by treatable causes (e.g. compression by a meningioma). However, optic atrophy may be difficult to discriminate from the similar-looking glaucomatous optic neuropathy (GON). Yet, is critical to clearly differentiate both conditions as each requires a different work-up and specific management. In a recent study, Yang et al.[25] developed a DLS aimed to discriminate non-glaucomatous optic neuropathies (NGON) from GON, based on the evaluation of standard colour fundus photographs. A total of 3,815 fundus photographs (486 GON, 446 NGON and 2,883 normal) were retrospectively collected and used for training and testing. The training dataset included a wide range of causes of NGON (including compression, hereditary diseases, ischaemia, inflammation, trauma and toxic causes). On an internal testing set of 2,675 photographs (106 GON, 66 NGON and 2,503 normal ONH), the DLS (based on the ResNet-50 classification model)

yielded an area under the precision-recall curve of 0.874, sensitivity of 93.4% and specificity of 81.8%.

More recently, modern DL methods have been applied to more sophisticated OCT retinal imaging for neurological patients, to discriminate true papilloedema (requiring prompt intervention) from pseudo-papilloedema. Clinically, it is sometimes very difficult to distinguish papilloedema (due to life-threatening conditions) from benign pseudo-papilloedema (e.g. caused by optic disc drusen), given that they may have similar visual appearance. Modern DL methods have been used to distinguish papilloedema from benign pseudo-papilloedema, in order to avoid expensive, invasive and often unnecessary investigations. In a first pilot study, DL applied to OCT raster scans of the ONH could accurately identify various ONH structures, leading to high performance for the detection of optic disc drusen (AUROC 0.99±0.001), papilloedema (AUROC 0.99±0.005) or normal discs (AUROC 0.98±0.01).[26]

In summary, recent advances of new DLSs may transform the way we detect ONH abnormalities on retinal images acquired in neurological patients. Based on a survey among general practitioners in Singapore, the application of teleophthalmology (with specialist consultation or using AI-integrated systems) will increase the performance of interpreting fundus findings.[27] However, even in this context, AI cannot replace a physician's experience or rational judgment, and it remains a complementary and assistive tool.[28] There is a high need to validate these initial results in future prospective or real-life studies. It is possible that the performance of these systems will be further improved with the incorporation of additional clinical data (visual performance, presence of headache, nausea, tinnitus, etc.).

Alzheimer's disease and dementia

Based on the population estimates in 2021, 6.2 million Americans aged 65 years or older are living with Alzheimer's disease (AD) dementia,[29] and this number is expected to increase to 131.5 million by 2050.[30] AD dementia is the most common form of dementia, but its pathophysiology is still poorly understood. The definition and diagnosis of both AD dementia and mild cognitive impairment (MCI) have evolved over recent years, moving from purely clinical evaluations to assessment of various biomarkers, with the hope of early detection. Brain amyloid-β (Aβ) deposition, identified with dedicated positron emission tomography (PET) brain scans, low Aβ42 in the cerebrospinal fluid (CSF) or elevated CSF tau protein can been detected years before the symptomatic development of AD dementia.[31,32] However, these investigations are invasive, costly, not easily accessible and difficult to perform in large-scale screening interventions. There is therefore a need to develop simple, accessible and reliable screening tools for the detection of AD dementia and other neurodegenerative diseases.[33]

For a long time, the retina has been considered a potential candidate for detecting neurodegenerative conditions, due to its high similarity and connections to the brain.[34,35] Similar to the brain, the retina is affected by ageing and neurodegenerative processes. However, a crucial question would be whether the pathological ageing of the retina reflects the nature and amount of associated brain lesions, especially in patients with dementia. Thus, a few studies have suggested that patients with AMD have a higher risk of developing AD dementia.[36] Similarly, Aβ protein deposits are present in both AMD and AD dementia, even at early AD dementia stages.

The ageing retina is characterised by neuronal loss resulting in retinal thinning, which can be easily quantified by OCT devices.[37,38] Interestingly, age-related brain atrophy is also associated with retinal thinning on OCT; ageing also affects the retinal nerve fibre layer (RNFL), retinal ganglion cell complex layer and outer nuclear layer,[39] most likely due to axonal and neuronal death.[42-44] Additional longitudinal studies are required to better delineate the dynamics of these findings.[43-47] Several studies have reported the association between the deposits of Aβ and phosphorylated tau proteins, with alterations in cerebral microvessels, including vascular dysfunction, changes in collagen content and increased cellular apoptosis.[40-42] It has been hypothesised that similar vascular changes could be detected in the retina using OCTA. Several such studies have suggested retinal capillary dropout, enlargement of the foveal avascular zone and decrease in density of the capillary plexus in pre-clinical and symptomatic AD.[43-45] Although OCTA may represent an indirect valuable biomarker showing vascular changes in AD,[46] the variability of its parameters is large and its disease specificity is not yet known, thus prompting additional prospective and methodologically robust studies.

Retinal fundus photography might represent even an interest in this context, because it can be easily implemented in non-ophthalmic clinics, including in neurology clinics. Zhang et al.[47] studied whether ML could discriminate patients with dementia and MCI, from normal individuals on standard retinal fundus photographs. This small study, which included 15 patients with dementia, 17 patients with MCI and 26 individuals

with normal cognitive function, used both SVM and extreme learning machine to classify these populations. The best model achieved an AUROC of 0.86, sensitivity of 92.8% and specificity of 69.6% in classifying patients with dementia and normal individuals. In addition, the model was able to discriminate patients with MCI from normal individuals with an AUROC of 0.87, sensitivity of 69.0% and specificity of 98.4%.

Tian et al.[48] also attempted to develop a classification model based on retinal photographs, focusing particularly on the architecture of retinal vessels. For this purpose, they used convolutional neural networks (CNN) to generate segmented retinal vascular images from fundus photographs, followed by the use of SVM for classification purposes. A total of 122 images of AD dementia patients and 122 images of age-matched normal controls from the UK Biobank database were enrolled for training of the model using 5-fold cross-validation. In the testing dataset, the model could discriminate AD dementia patients from normal controls with an accuracy of 82.4%, sensitivity of 79.2% and specificity of 84.8%. Among the various limitations of this study, the clinical diagnostic criteria for AD dementia and cognitive impairment were not well defined.

Wisely et al.[49] investigated a mix of multimodal retinal images and patient data to create a CNN to identify symptomatic AD. Colour maps of ganglion cell-inner plexiform layer (GC-IPL) thickness, OCT and OCTA images of the superficial capillary plexus, and ultra-widefield colour and fundus autofluorescence scanning laser ophthalmoscopy images were taken in patients with confirmed AD dementia and in healthy controls. Altogether, the study included 284 eyes from 159 patients, 36 of whom were clinically diagnosed with AD dementia by expert neurologists. All medical records were reviewed by 1 of 2 expert neurologists to confirm a clinical diagnosis of AD dementia using the National Institute of Aging and Alzheimer's Association standards. On the validation set, the best-performing model—which included GC-IPL maps, quantitative data and patient data—reached an AUROC of 0.861 (95% confidence interval [CI] 0.73–0.995); on the testing set, an AUROC of 0.84 (95% CI 0.74–0.94) was reached. However, this study had a few limitations, including a small sample size.[50]

In the UK, several studies have aimed to link routinely collected multimodal retinal images with systemic and neurodegenerative disease data from hospital admissions, including the ongoing AlzEye study.[51] This study, which includes more than 6 million retinal images collected from hundreds of thousands of patients, is currently aiming to identify novel retinal signatures in patients with AD dementia and cardiovascular diseases.

These initial studies share common limitations, such as small numbers of included patients, same ethnicity and lack of testing the system's performance on external and independent datasets. More generally, the results of these studies do not yet have a strong explainability, i.e. identification of well-identified features to distinguish between retinas in AD dementia versus cognitively healthy individuals. It is possible for DL algorithms to take into account several retinal features associated with AD dementia, such as: (1) visible retina drusen (or other retinal changes due to AMD or glaucoma, which are statistically associated with AD dementia); (2) retinal axonal and neuronal changes; and (3) retinal vascular changes.

A recent, largest-to-date study aiming to test a retinal photograph-based DL algorithm for AD dementia identification, has tried to address a few of these questions in retrospectively collected data from multiethnic and multinational datasets, including a total of 12,949 retinal photographs from 648 AD dementia patients and 3,240 controls with no dementia.[52] Using advanced techniques of unsupervised domain adaptation and feature fusion, the classification performance of the DLS in 5 independent external cohorts achieved accuracies ranging from 79.6% to 92.1%, and AUROCs ranging from 0.73 to 0.91. Interestingly, the DLS performed well even in the presence of concomitant eye diseases, suggesting that AD dementia might be associated with specific retinal features. In the cohorts with PET scan data, the model could discriminate Aβ-positive from Aβ-negative patients with accuracies ranging from 80.6% to 89.3%, and AUROCs ranging from 0.68 to 0.86, supporting the concept that a retinal photograph-based DL algorithm might have considerable potential for screening AD dementia at community levels.

Altogether, these recent preliminary studies suggest that DL methods applied to retinal imaging may contribute to identify AD, although not as the only or the primary AD dementia diagnostic criteria. There is a need for further validation with higher accuracy and specificity in prospective studies. If validated, implemented and adopted, AI-based retinal imaging may represent an interesting objective modality to screen elderly patients, at best in combination with other validated modalities (i.e. exploring cognition). This could be particularly useful at community levels, and especially if novel therapies are introduced for treating AD dementia. Early AD dementia diagnosis improves

the life quality of affected patients, and it is an opportune time to strive towards this goal as large resources are currently being allocated for AD dementia prevention and pharmacological treatment.[33]

CONCLUSION

The application of AI to retinal imaging in neurology is at its beginnings, with focus mainly on detecting ONH abnormalities associated with life-threatening and debilitating neurological disorders, as well as on identifying neurodegenerative conditions including AD dementia. The currently growing interest of this approach is due to the fact that retinal imaging technologies, being non-invasive, are becoming more widely accessible, often affordable and simple to use. Novel handheld, easy-to-use retinal cameras have recently become largely available, providing high-resolution images that can be acquired without pupillary dilation (non-mydriatic cameras). These encouraging initial achievements may soon translate to new forms of practice in neurology, particularly when ophthalmologists are not readily available. However, more robust replication studies are required to validate this new technology for use in clinical practice. These new concepts suggest AI-assisted interpretation of retinal imaging might become a useful, complementary tool for screening or even identification of neurological diseases in the future.

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COMMENTARY

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Approach to bradyarrhythmias: A proposed algorithm

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ABSTRACT

Bradyarrhythmias are commonly encountered in clinical practice. While there are several electrocardiographic criteria and algorithms for tachyarrhythmias, there is no algorithm for bradyarrhythmias to the best of our knowledge. In this article, we propose a diagnostic algorithm that uses simple concepts: (1) the presence or absence of P waves, (2) the relationship between the number of P waves and QRS complexes, and (3) the regularity of time intervals (PP, PR and RR intervals). We believe this straightforward, stepwise method provides a structured and thorough approach to the wide differential diagnosis of bradyarrhythmias, and in doing so, reduces misdiagnosis and mismanagement.

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Keywords: Arrhythmia, bradyarrhythmia, bradycardia, cardiology, electrocardiography

Bradyarrhythmias are common and occur in both physiological and pathological states. Bradycardia is defined as a heart rate of fewer than 60 beats per minute, and bradyarrhythmias can be caused by sinus node dysfunction or atrioventricular (AV) conduction blocks.[1,2] Atrial fibrillation (AF) with a slow ventricular response may also cause bradycardia. Numerous electrocardiographic (ECG) criteria and algorithms, such as the Brugada criteria, have been proposed for diagnosing tachyarrhythmias.[3-5] However, there is no algorithm for bradyarrhythmias to the best of our knowledge. In this article, we propose an algorithm (Fig. 1) that uses simple concepts: (1) the presence or absence of P waves; (2) the relationship between the number of P waves and QRS complexes (i.e. whether there are more P waves compared to QRS complexes); and (3) regularity of time intervals (PP, PR and RR), to aid accurate ECG diagnosis of bradyarrhythmias.

Presence or absence of P waves

The first step of the algorithm requires the reader to check for discernible P waves. If there is no P wave, possible diagnoses include sinus arrest with junctional (narrow QRS complex, heart rate usually between 40 and 60 beats per minute) or ventricular escape (wide QRS complex, heart rate usually less than 40 beats per minute), AF with complete AV block, or AF with a slow ventricular response. An irregular RR interval identifies AF with a slow ventricular response. If the RR interval is regular, the reader should determine if fibrillatory waves are present to differentiate AF with complete AV block (Fig. 2A) from sinus arrest (Fig. 2B). Occasionally, very fine AF may be difficult to discern from sinus arrest. Increasing the voltage gain setting on the ECG machine and considering the clinical context may be helpful.

Number of P waves more than the number of QRS complexes

If P waves are present, the next step is to determine the relationship between the number of P waves and QRS complexes. If there are more P waves than QRS complexes and the PP interval is regular, the diagnosis is either second-degree AV block or complete AV block. If the non-conducted P wave is premature (i.e. shorter PP interval), the diagnosis is non-conducted atrial ectopic beats (Fig. 2C). To differentiate between various AV blocks, the reader should next check for the regularity of the PR and RR intervals. If the

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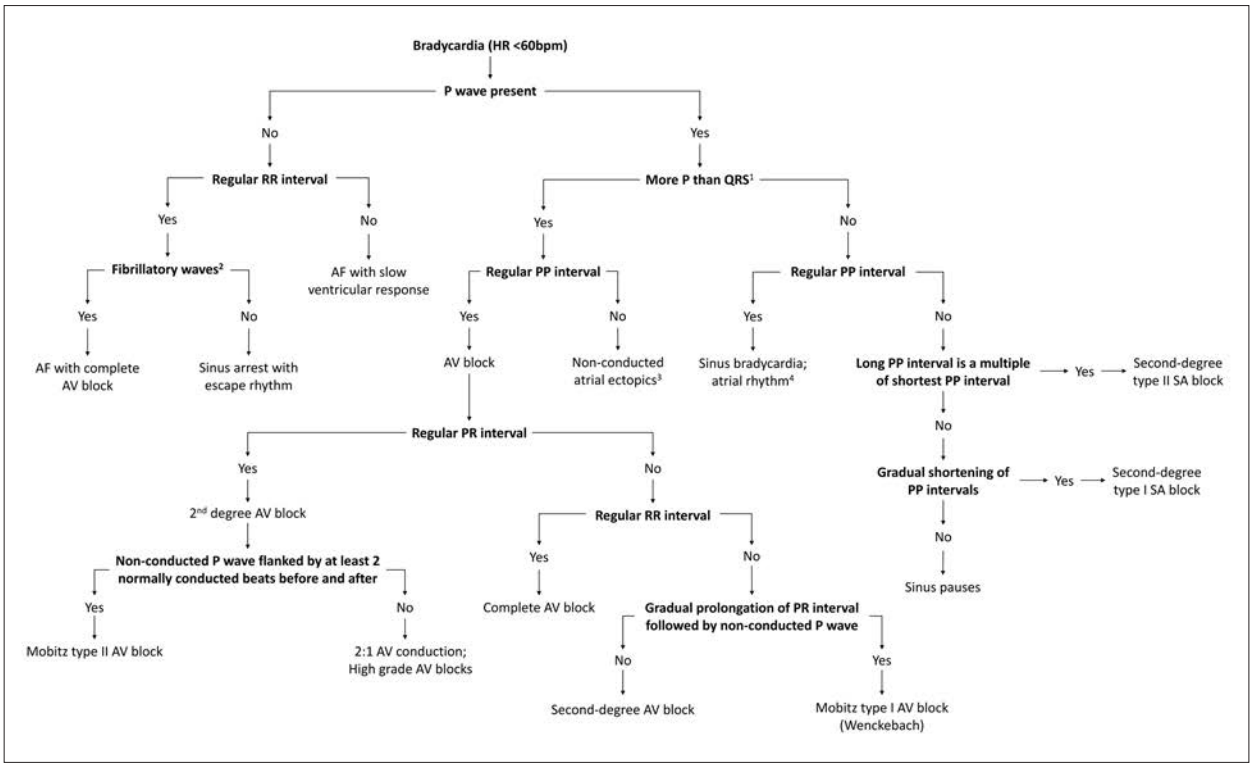

Fig. 1. An algorithmic approach to bradycardia.

AF: atrial fibrillation; AV: atrioventricular; bpm: beats per minute; HR: heart rate; SA: sinoatrial

[1] P waves best identified in inferior leads or lead V1

[2] Fibrillatory waves may not be apparent in fine AF

[3] P waves may be buried within the preceding T wave

[4] Suspect ectopic P wave if P wave axis is abnormal (e.g. inverted P waves in II, III, aVF)

Aids to distinguish supra- versus infra-Hsian site of atrioventricular block

- Markedly prolonged PR interval favours AV nodal site of block
- Broad QRS favours infra-Hisian site of block
- Autonomic manipulation
  - Supra-Hisian blocks improve with exercise/atropine, and worsen with vagal manoeuvres
  - Infra-Hisian blocks improve with vagal manoeuvres, and worsen with exercise/atropine

PR interval is regular, the diagnosis is second-degree AV block i.e. Mobitz type II AV block (Fig. 2D), 2:1 AV block (Fig. 2E), or high-grade AV block (Fig. 2F). Mobitz type II AV block is defined as intermittent non-conducted P waves with constant PR intervals before and after the blocked impulse.[2] A non-conducted P wave flanked by at least 2 normally conducted beats before and after distinguishes Mobitz type II AV block from the others. A 2:1 AV block involves alternately conducted P waves, while high grade AV blocks include 3:1, 4:1 AV conduction et cetera. QRS complexes may be narrow (supra-Hisian block) or broad (infra-Hisian block).

If the PR interval is irregular, the regularity of the RR interval is considered next. If the RR interval is regular, the diagnosis is complete AV block. Complete AV block is defined by independent atrial and ventricular activity, which manifests as AV dissociation on the ECG. This is reflected in our algorithm as a combination of regular PP and RR intervals but irregular PR intervals. The QRS width of the escape rhythm may suggest the site of the block (supra-Hisian if QRS complexes are narrow, and infra-Hisian if QRS complexes are broad) (Figs. 2G and 2H). If the RR interval is irregular, the diagnosis is either Mobitz type I AV block (Fig. 2J) or other types of second-degree AV block. Mobitz type I AV block, also known as the Wenckebach phenomenon, is characterised by gradual prolongation of the PR interval followed by a non-conducted P wave. As the increment in PR prolongation decreases with subsequent cycles, there is a progressive shortening of RR intervals prior to the non-conducted P wave. Classically, this manifests as "group beating".

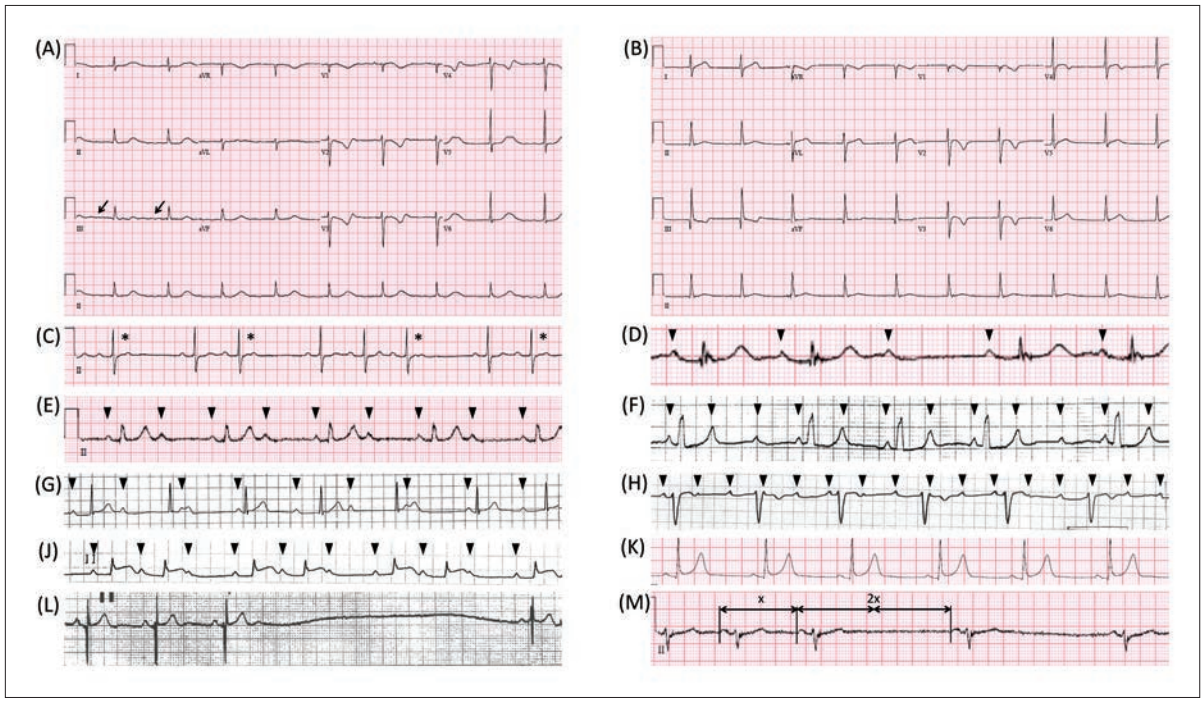

Fig. 2. Application of our algorithm on various electrocardiograms.
(A) Atrial fibrillation (AF) with complete atrioventricular (AV) block (fibrillatory waves in lead III indicated by arrows). (B) Sinus arrest with supraventricular escape rhythm. (C) Sinus rhythm with non-conducted atrial ectopics (indicated by asterisks). (D) Mobitz type II AV block. (E) 2:1 AV block. (F) High-grade AV block. (G and H) Complete AV block. (J) Mobitz type I AV block (P waves indicated by arrowheads). (K) Sinus bradycardia. (L) Sinus pause. (M) Second-degree type II sinoatrial block. The long cycle is twice as long as a short cycle.

Number of P waves not more than the number of QRS complexes

If the number of P waves does not exceed the number of QRS complexes and the PP interval is regular, the diagnosis is often sinus bradycardia (Fig. 2K) or, more rarely, an escape atrial rhythm. Escape atrial rhythms may be identified by an abnormal P wave axis (e.g. a superior axis with negative P waves in leads II, III and aVF), although they may mimic sinus bradycardia if the rhythm originates from atrial tissues close to the sinoatrial (SA) node. If the PP interval is irregular, the diagnosis is either sinus pause (Fig. 2L) or SA block (Fig. 2M). Like AV blocks, SA exit blocks may be classified as first-, second- or third-degree. First-degree SA block occurs when there is a delay between depolarisation of the SA node and the rest of the atrial tissue. Third-degree SA block occurs when no SA nodal impulses are conducted out of the SA node.[1] We did not include first- and third-degree SA blocks in our algorithm as they are not recognisable on the surface ECG. Similar to Mobitz type I AV block, second-degree type I SA block demonstrates the Wenckebach phenomenon, with progressive lengthening of intervals between the SA impulse and atrial depolarisation. This manifests on the surface ECG as the progressive shortening of the PP interval followed by a sinus pause, and the duration of the sinus pause is less than twice the last PP interval before the pause. Second-degree type II SA block involves intermittent non-conducted SA nodal impulses with constant PP intervals prior to the non-conducted impulse. This condition may be identified by the presence of a mathematical relationship between longer sinus cycles and the shortest sinus cycle (i.e. long cycle duration is a multiple of the shortest cycle duration).

Clinical utility and limitations

ECG reading remains daunting to many, especially medical students and junior doctors, with resultant misinterpretation and inappropriate management decisions.[6] To the best of our knowledge, our bradycardia algorithm is the first of its kind and may provide both novices and experienced ECG readers with a structured approach to the wide differential diagnosis of bradyarrhythmias. However, as with all decision tools, the correct diagnosis is dependent on careful application of the algorithm, and the reader must be proficient in identifying different components of the ECG—particularly hidden P waves—as well as in assessing the regularity of different time intervals

(PP, PR and RR intervals). Repeated, intentional exposure to ECGs in clinical practice remains essential for honing these pattern recognition skills. Intracardiac electrophysiological recordings may sometimes be required to accurately classify supra- and infra-Hisian blocks. Such detailed site localisation is beyond the scope of our proposed algorithm. To aid the reader, however, we have included footnotes summarising ECG features and simple autonomic manipulation, which may help differentiate supra- and infra-Hisian sites of the block (Fig. 1).

Bradyarrhythmias are common, but there is no structured approach towards their ECG diagnosis. Our novel algorithm may simplify this diagnostic challenge and reduce resultant misdiagnosis and mismanagement.

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LETTER TO THE EDITOR

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Safety and effectiveness of nitrous oxide procedural sedation in a paediatric emergency department

Dear Editor,

Nitrous oxide (N_2O) produces dissociative euphoria, amnesia and analgesia, and is a common sedative for procedural sedation in paediatric emergency departments (EDs) due to its non-parenteral administration and good safety profile.[1-3] Suitable procedures include fracture reduction, toilet and suturing, incision and drainage, and application of burn dressings. The concentration of N_2O administered ranges from 30–70%, with maximum effect at 5 minutes, and rapid recovery upon discontinuation.[1,4] Co-administered medications include intranasal fentanyl (1.5μg/kg, maximum 100μg/dose) administered 30–60 minutes prior to enhance analgesia,[3] oral analgesics, topical anaesthesia or parenteral morphine.

Although N_2O is commonly used globally, there is no published report on its effectiveness and safety in paediatric patients in Singapore. We seek to identify the effectiveness of N_2O as a form of procedural sedation and analgesia for children requiring painful procedures in a tertiary paediatric emergency department (ED), study the incidence of adverse events, and evaluate the safety of co-administered opioids.

A retrospective analysis was performed on all patients less than 18 years who underwent procedural sedation with N_2O as a primary agent from 1 April 2013 to 31 September 2021, at the ED of KK Women's and Children's Hospital, Singapore. A prospective electronic database of all procedural sedations performed at the ED was set up in April 2013. All sedation-related adverse events and interventions were prospectively documented in the sedation forms in the medical records and extracted into the database. Data on demographics, diagnosis, procedures, types of sedatives, other co-administered medications, adverse events, and interventions were electronically extracted from the database. N_2O concentration, flow rate, start and end times, and sedation depth (Children's Hospital of Wisconsin Sedation Scale)[5] were extracted manually from electronic medical records. The Children's Hospital of Wisconsin Sedation Scale has a scale of 0–6, with 6 being agitated. Data were anonymised in password-protected Excel (Microsoft Corp, Redmond, US) file.

Statistical analyses were performed using SPSS Statistics version 28.0 (IBM Corp, Armonk, US). Categorical variables were analysed using Fisher's Exact test and continuous variables using independent t-test. Univariate regression analyses were performed to identify predictors of adverse events. Variables with *P* value ≤0.1 in the univariate analysis were included in a multivariate logistic model to identify independent predictors.

In the study period from April 2013 to September 2021, 918 children underwent N_2O sedation (Table 1). The median age was 11.91 (interquartile range [IQR] 9.26–13.90) years. Majority were male (75.4%). The most common diagnosis was fracture/dislocation requiring manipulation and reduction (98.3%). The mean duration of sedation was 15±9 minutes, and the mean duration of recovery was 3±4 minutes (n=511). A total of 93.1% received 50–70% N_2O, while 177 (19.3%) received pre-planned local/topical analgesia.

Nine hundred patients (98%) had their procedures successfully completed using N_2O sedation, with or without pre-planned oral, intranasal or topical analgesia. Most (97.2%) achieved a sedation scale of 3–5 (minimal to moderate sedation), with a mean decrease in sedation scale of 0.25±0.62 (n=386). Five (1.3%) had sedation scale ≤2. Of the remaining 18 patients, six (0.7%) received Bier's block (2 for inadequate sedation, 2 given prior to N_2O sedation and 2 given concurrently). Twelve (1.3%) patients required intramuscular (IM) ketamine subsequently. None received intravenous (IV) ketamine.

Sixteen (1.7%) patients had sedation-related adverse events, of whom 2 received IM ketamine subsequently, and 14 (1.5%) received N_2O only (Table 1). Most events were minor: emesis (n=14, 1.5%), desaturation (n=1, 0.1%), and agitation (n=1, 0.1%). Twelve required no intervention, 2 required supplemental oxygen (one given prophylactically for agitation), and 2 required oral ondansetron. None required assisted ventilation or cardiopulmonary resuscitation. None were admitted for sedation-related events. Patients with adverse events (median age 9.90, IQR 6.88–12.05) were significantly younger than those without (median age 11.95, IQR 9.51–13.91, *P*=0.009). There was no significance between N_2O concentration and adverse events (*P*=1.000).

In the univariate analysis (Table 1), intranasal fentanyl (odds ratio [OR] 2.692, 95% CI 0.587–12.346, *P*=0.202) or morphine (OR 1.519, 95% CI 0.194–11.879,

Table 1. Baseline characteristics, procedural details and adverse events for patients who underwent sedation with nitrous oxide

Variable	Number (%)			
	No adverse events (n=902)	Adverse events (n=16)	Total (n=918)	*P* value
Age, median (IQR), years	11.95 (9.31–13.93)	9.90 (6.88–12.05)	11.91 (9.26–13.90)	0.009[a]
Sex				0.773
Female	222 (24.6)	3 (18.8)	225 (24.5)	
Male	678 (75.4)	13 (81.3)	693 (75.5)	
Ethnicity				0.663
Chinese	473 (52.4)	11 (68.8)	484 (52.7)	
Malay	159 (17.6)	2 (12.5)	161 (17.5)	
Indian	150 (16.6)	1 (6.3)	151 (16.5)	
Others	120 (13.3)	2 (12.5)	122 (13.3)	
Diagnosis				0.030
Fracture, dislocation	888 (98.5)	14 (87.5)	902 (98.3)	
Laceration, open wound	3 (0.3)	1 (6.3)	4 (0.4)	
Abscess, chalazion, stye	4 (0.4)	0	4 (0.4)	
Foreign body	3 (0.3)	0	3 (0.3)	
Nailbed injury	0	0	0	
Others[b]	4 (0.4)	1 (6.3)	5 (0.5)	
Site of procedure				0.141
Head, face	2 (0.2)	0	2 (0.2)	
Upper limb	780 (86.5)	13 (81.3)	793 (86.4)	
Lower limb	115 (12.8)	2 (12.5)	117 (12.8)	
Others	5 (0.6)	1 (6.3)	6 (0.7)	
Type of procedure				0.051
Manipulation and reduction	888 (98.5)	14 (87.5)	902 (98.3)	
Toilet and suturing	1 (0.1)	1 (6.3)	2 (0.2)	
Incision and drainage	4 (0.4)	0	4 (0.4)	
Removal of foreign body	3 (0.3)	0	3 (0.3)	
Debridement/dressing	2 (0.2)	0	2 (0.2)	
Others	4 (0.4)	1 (6.3)	5 (0.5)	
Co-administered medications/ analgesia[c]	191 (21.2)	8 (50.0)	199 (21.7)	0.011
Paracetamol or NSAIDs (ibuprofen/diclofenac)	86 (9.5)	1 (6.3)	87 (9.5)	1.000
Intranasal fentanyl	54 (6.0)	2 (12.5)	56 (6.1)	0.255
Morphine	43 (4.8)	3 (18.8)	46 (5.0)	0.042
Local anaesthesia (digital block/ subcutaneous lignocaine/LET gel)	10 (1.1)	2 (12.5)	12 (1.3)	0.021
None required	711 (78.8)	8 (50.0)	719 (78.3)	

Table 1. Baseline characteristics, procedural details and adverse events for patients who underwent sedation with nitrous oxide (Cont'd)

Variable	Number (%)			
	No adverse events (n=902)	Adverse events (n=16)	Total (n=918)	*P* value
Successful completion of procedure				
Yes	886 (98.2)	14 (87.5)	900 (98.0)	
Further modalities of pain management required				
Regional block (Bier's block)	6 (0.7)	0	6 (0.7)	1.000
Due to unsuccessful sedation	2 (0.2)	0	2 (0.2)	
Parenteral sedation (IM Ketamine)	10 (1.1)	2 (12.5)	12 (1.3)	0.017
Due to unsuccessful sedation	2 (0.2)	0	2 (0.2)	
Due to unsuccessful procedure or other reasons	8 (0.9)	2 (12.5)	10 (1.0)	
Nitrous oxide concentration, % (n=349)[d]				1.000
30	15 (4.4)	0	15 (4.3)	
50	56 (16.3)	1 (20)	57 (16.3)	
60	9 (2.6)	0	9 (2.6)	
70	264 (76.2)	4 (80)	268 (76.8)	
Sedation score (Children's Hospital of Wisconsin Sedation Scale) (n=386)[d,e]				0.043
1	1 (0.3)	1 (16.7)	2 (0.5)	
2	3 (0.8)	0	3 (0.8)	
3	10 (2.6)	0	10 (2.6)	
4	63 (16.6)	2 (33.3)	65 (16.5)	
5	297 (78.2)	3 (50.0)	300 (77.7)	
6	6 (1.6)	0	6 (1.6)	

Adverse events	**Number (%)**
All patients (n=918)	16 (1.7)
Emesis	14 (1.5)
Oxygen desaturation	1 (0.1)
Agitation	1 (0.1)
N_2O alone (n=807)	11 (1.4)
Emesis	10 (1.2)
Oxygen desaturation	0
Agitation	1 (0.01)
N_2O with intranasal fentanyl (n=54)	2 (3.7)
Emesis	2 (3.7)
N_2O with morphine (n=44)	1 (2.3)
Emesis	1 (2.3)
N_2O with morphine and intranasal fentanyl (n=1)	0

Table 1. Baseline characteristics, procedural details and adverse events for patients who underwent sedation with nitrous oxide (Cont'd)

Adverse events	**Number (%)**			
Patients with subsequent IM Ketamine sedation (n=16)				
N_2O without opioids (n=12)	0			
N_2O with intranasal fentanyl (n=2)	0			
N_2O with morphine (n=2)	2 (100)			
Emesis	1 (50)			
Oxygen desaturation	1 (50)			
Predictors of adverse events associated with nitrous oxide sedation				
Variable (n=918)	**Univariate analysis**		**Multivariate analysis[g]**	
	Odds ratio (95% CI)	***P* value**	**Odds ratio (95% CI)**	***P* value**
Age, years (n=906)[f]	0.754 (0.631–0.903)	0.002		
Additional analgesia (n=906)[f]				
Morphine: Yes	1.519 (0.194–11.879)	0.690		
Morphine: No	Ref			
Use of intranasal fentanyl (n=906)[f]				
Fentanyl: Yes	2.692 (0.587–12.346)	0.202		
Fentanyl: No	Ref			
Use of other sedative				
IM ketamine	12.743 (2.554–63.581)	0.002	11.553 (2.227–59.943)	0.004
None	Ref		Ref	

CI: confidence interval; IM: intramuscular; IQR: interquartile range; LET: topical lidocaine/epinephrine/tetracaine; N_2O: nitrous oxide; NSAIDs: non-steroidal anti-inflammatory drugs

[a] $P<0.05$ is considered statistically significant

[b] Other procedures included 4 paraphimosis, 1 removal of K-wires

[c] Some patients received more than one modality of analgesia

[d] Data available after June 2016

[e] Lowest sedation score documented for each patient:
0=Unresponsive to painful stimulus, 1=Arouses, but not to consciousness, with painful stimulus, 2=Arouses slowly to consciousness with sustained painful stimulus, 3=Arouses to consciousness with moderate tactile or loud verbal stimulus, 4=Drowsy, eyes open or closed, but easily arouses to consciousness with verbal stimulus, 5=Spontaneously awake without stimulus, 6=Anxious, agitated or in pain

[f] Patients who required further management with IM ketamine were excluded from this analysis

[g] Adjusted for age as a confounder

P=0.690) was not associated with increased adverse events. For patients receiving intranasal fentanyl and N_2O, 2/56 (3.6%) required ketamine due to unsuccessful procedures. Neither had adverse events. In contrast, for patients receiving morphine and N_2O, 2/46 (4.3%) required ketamine, and both had adverse events (one desaturation to 91% and one emesis) (OR 4.61, 95% CI 1.266–16.784, *P*=0.020).

Among patients who received subsequent IM ketamine, 2/12 (16.7%) had adverse events (OR 12.743, 95% CI 2.554–63.581, *P*=0.002). This was still significant (adjusted OR 11.553, 95% CI 2.227–59.943, *P*=0.004) after adjusting for age as a covariate in multivariate analysis. Older children have been observed to have increased emesis risk with IM ketamine.[6]

The risk of emesis for co-administered intranasal fentanyl with N_2O was reported to be 10–27.5%, with increased rates at 70% N_2O.[3,7] In our study, the emesis rate was 1.4% with N_2O alone, and 3.7% (2/54) for intranasal fentanyl with N_2O. This is also lower than the emesis rates (8.4%) with IM ketamine sedation reported.[6] The risk of oxygen desaturation during N_2O sedation in our study was 0.1%, compared

to 1.9% with IM ketamine sedation.[8] N_2O sedation is a safe and effective alternative with a short recovery time if only mild to moderate depth of sedation is required.

In our study, the risk of adverse events was higher when subsequent IM ketamine was given after N_2O sedation with co-administered parenteral morphine, compared with co-administered intranasal fentanyl. When additional analgesia with opioids is indicated with N_2O sedation, intranasal fentanyl is a preferred option compared to parenteral morphine.

A limitation of our study was that delayed events were not included as most patients were discharged after 30 minutes. However, the incidence is likely rare, as N_2O-related emesis is related to the duration of exposure, insignificant up to 1 hour.[9]

In summary, N_2O is safe for paediatric sedation, with or without adjunct opioids. However, caution should be taken when a third sedative is added. We experienced a low incidence of adverse events, likely also contributed by close supervision and adherence to department protocols.

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LETTER TO THE EDITOR

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Reducing non-clinical working hours of junior doctors could benefit patient outcomes

Dear Editor,

An 80-hour duty limit for residents was first introduced by the Accreditation Council for Graduate Medical Education (ACGME) in 2003, with the further addition of a 16-hour continuous duty period limit for first-year residents in 2011. Prior studies[1] have demonstrated an association between longer working hours and increased risk of mental illness,[2] attentional failures,[3] and medical errors.[4] However, because of a lack of granularity in the definition of duty hours and subsequent studies evaluating these regulations, the role of non-clinical working hours as a predictor of patient and physician outcomes has yet to be defined. We aimed to evaluate the nature of the relationship between working hours and patient safety, with particular attention to the effect of non-clinical working hours.

The entire junior doctor population of Singapore, defined as physicians employed by public healthcare institutions currently in training or yet to enter formal postgraduate training, was invited to participate in this study via direct email to their official email addresses. Participation in the survey was fully anonymous. Ethical approval was obtained from the National University of Singapore Institutional Review Board, and the requirement for informed consent was waived. In addition, these doctors were invited via direct email to participate in an in-depth interview that aimed to explore the lived experiences of junior doctors in Singapore through a semi-structured interview guide. Participation was voluntary, and informed consent was obtained through Zoom, a password-protected video-teleconferencing platform.

The following items were collected via electronic survey: (1) demographic attributes; (2) employment details; (3) working hours and conditions, non-clinical duties (defined as administrative, educational and mandated research), and call duties; (4) outcome metrics, such as the number of medical errors with the classification of error severity based on the widely used Clavien-Dindo approach; (5) whether respondents logged working hours accurately, and reasons for doing so/not doing so; (6) the Pittsburgh Sleep Quality Index (PSQI); (7) the Patient Health Questionnaire-2 (PHQ-2); (8) the Satisfaction of Employees in Health Care (SEHC) tool; and (9) opinions regarding factors which most affected their job satisfaction and perceptions of adequate compensation, via an open-ended question.

SPSS Statistics version 26.0 (IBM Corp, Armonk, US) was used for the statistical analysis of quantitative data. Analyses comparing means between groups—where errors per year were the dependent variable—were performed with non-parametric tests. Negative binomial regression models were specified to ascertain the effects of clinical hours and non-clinical hours on the incidence rate ratio (IRR) of medical errors. Models were adjusted for sex, age, marital status, discipline, designation, type of rostering, type of call system, number of days off per month, and whether the respondent had >4 calls per month.

A total of 1,117 unique responses were received and used in the final analysis, representing a response rate of 26.0%. More than half of the respondents were female (576, 51.6%), single (802, 71.8%), had 1–5 years of working experience (878, 78.6%), and had outstanding mandatory service obligations (801, 71.7%). On average, junior doctors reported working 71.79 clinical hours (median=72, standard deviation [SD]=16.29) and 8.44 non-clinical hours (median=5, SD=10.06) per week. Junior doctors who were rostered to a night float system worked fewer hours than those rostered to a traditional 24-hour call system (72.4 versus 74.9 clinical hours). The average number of self-reported medical errors per year was 3.09 (median=1, SD=12.90, interquartile range 0.33–2.50).

Two negative binomial regression models were specified to explore the relationship between working hours and self-reported medical errors. The negative binomial model with only clinical and non-clinical hours as covariates was statistically significant, $\chi^2(2)=50$, $P<0.001$. Akaike's Information Criterion was 6591, an improvement over a previously specified Poisson regression model with the same covariates. For every additional clinical hour worked per week, 1.008 times more medical errors were reported (95% confidence interval [CI] 1.007–1.009, $P<0.001$). For every additional non-clinical hour worked per week, 1.018 times more medical errors were reported (95% CI 1.017–1.019, $P<0.001$).

The adjusted binomial regression model was also statistically significant, $\chi^2(20)=155$, $P<0.001$. Akaike's Information Criterion was 6521, an improvement over the prior model. In addition to clinical and non-clinical hours, designation and marital status were significant predictors of medical error. Parameter estimates are shown in the online Supplementary Table S1.

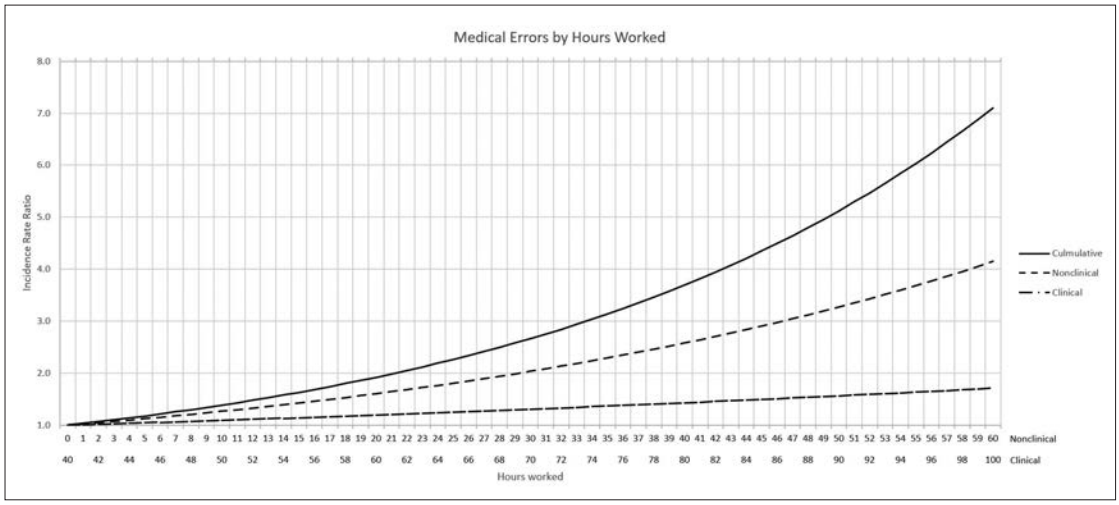

Fig. 1. Graphical presentation of the extrapolated results of the negative binomial regression.

On logistic regression, longer non-clinical hours were also associated with a decreased likelihood of good sleep quality as measured by PSQI (95% CI 0.966–0.991, *P*=0.001) and an increased likelihood of high risk for depression as measured by the PHQ-2 (95% CI 1.013–1.040, *P*<0.001).

Results from this nationwide study provide the first evidence that increased non-clinical working hours also contribute to poorer patient outcomes. Fig. 1 illustrates these new findings, with a greater increase in IRR of medical errors for each additional non-clinical (as compared to clinical) hour worked. An exponential increase in medical error was demonstrated when both clinical and non-clinical hours increased. Longer non-clinical hours were shown to increase the likelihood for poor sleep and risk of depression, which could be mediators of this relationship.

While the mean clinical hours worked was less than 80 hours a week, most respondents would have exceeded this once non-clinical hours were added. Previous studies have reported widespread working hour violations[5] and under-reporting[6] of duties, further compounding the difficulties in assessing the impact of these additional working hours. We expanded the definition of non-clinical hours beyond just on-site educational hours defined by ACGME, also including administrative and mandated academic work.

Although the response rate was 26%, this is comparable to that of nationwide surveys in other populations,[7,8] and our study represents the largest on the topic in Singapore. The qualitative interviews also provide context and rationale regarding possible reasons for non-response to the electronic survey. During these semi-structured interviews, junior doctors reported their concerns in providing feedback on working conditions, for fear of "putting a target on their back" and compromising their opportunities for entering a residency training programme or for "fear of reprisal" that could threaten livelihoods, as most junior doctors are bonded to public healthcare system. Furthermore, some respondents felt that their feedback was neglected, citing that "they (public healthcare institutions) don't seem to want to take into account what my feedback is". It is important to recognise the barriers (fears, concerns and apathy) that would need to be addressed. While further efforts should be made to confirm this study's findings, a non-anonymised methodology would be subject to the Hawthorne effect and results may prove unreliable.

It is evident from this new data that non-clinical working hours are an overlooked predictor of patient and physician outcomes, and residency programmes should be cognisant of the effect of these additional duties on junior doctor's performance and patient safety.

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LETTER TO THE EDITOR

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The role of PIVKA-II in hepatocellular carcinoma surveillance in an Asian population

Dear Editor,

Alpha-fetoprotein (AFP) is the most established biomarker for surveillance of hepatocellular carcinoma (HCC) in at-risk individuals. However, its sensitivity and specificity are not very satisfactory.[1] Protein induced by vitamin K absence or antagonist-II (PIVKA-II) is a newer biomarker for HCC but without a widely established cut-off.[2,3] Recent data suggested that the cut-off may be different for HCC due to chronic hepatitis C (CHC) and chronic hepatitis B (CHB) infection.[4] Two different reference intervals (RIs), Japan and European Union (EU), are provided in the assay kit (Architect PIVKA-II, Abbott Laboratories, Chicago, US).[5] In Singapore, CHB is the most prevalent association with HCC.[6]

Hence, we studied the distribution of PIVKA-II to determine which RI was more applicable to our Singapore patients. We also examined for significant associations between HCC and PIVKA-II alone, AFP alone, and the combination of both PIVKA-II and AFP.

Study subjects had blood drawn on the day of their 6-monthly HCC surveillance ultrasound for up to a maximum of 3 visits. PIVKA-II, AFP (Abbott Laboratories, Chicago, US) and AFP (Roche Elecsys; Roche Diagnostics, Basel, Switzerland) were assayed at the same time. Ultrasound and blood results were reviewed by a clinician. Suspicious lesions were investigated and HCC was diagnosed in accordance with international guidelines. Patient consent was obtained. SingHealth Centralised Institutional Review Board approved the study (reference CIRB 2017/2577).

Six hundred and ten patients in our HCC surveillance programme, who were without HCC for the prior 12 months, were enrolled. Majority were males (60.7%). Median age was 62 years (interquartile range [IQR] 55–69). Most had CHB (89.5%), of which 59.6% were on antiviral treatment with good control of the disease in 98.8%. Baseline median levels of alanine transaminase and aspartate transaminase of the cohort were 22U/L (IQR 17.0–32.0) and 25U/L (IQR 22.0–32.0), respectively. Median follow-up was 12.2 months, with 632 patient-years. About half (54.4%) had the second and 19.2% the third visit blood specimens taken.

Five patients developed HCC during the study period at a median age of 60 years (IQR 51.5–70.0). All had PIVKA-II levels measured at the time of diagnosis of HCC. Median PIVKA-II level was 28.5mAU/mL (IQR 19.7–42.3). Median AFP levels were 4.7µg/L (IQR 2.4–43.3) and 3.9µg/L (IQR 2.3–36.8) for Roche and Abbott assays, respectively.

Biomarker distribution. Distributions of PIVKA-II, AFP (Abbott), and AFP (Roche) in 605 study subjects without HCC are shown in Table 1A. The current cut-off, according to the manufacturer, is 40mAU/mL. The 97.5th percentile value of 48.0mAU/mL in our study cohort was closer to EU PIVKA-II of 50.9mAU/mL than Japan's 32.0mAU/mL provided by the manufacturer. The distribution of our AFP aligned more with the recommended cut-off value of AFP (Abbott) than AFP (Roche).

Diagnostic performance of PIVKA-II with/without AFP. Specificity and sensitivity were studied for PIVKA-II alone with the various cut-offs: 40mAU/mL (current), 32.0mAU/mL (Japan), 50.9mAU/mL (EU) and our study's 48.0mAU/mL. The combination of AFP (Roche) and AFP (Abbott) was also tested. (Table 1B).

All the tests had good specificity (≥82%). However, sensitivity was less ideal. Both Roche and Abbott AFP alone were statistically significant for the detection of HCC (Fisher's test, P=0.01 and P=0.03, respectively). When combining PIVKA-II and AFP, only the combination of PIVKA-II using our study's or EU's cut-offs with AFP (Abbott) was significant (Table 1B). However, the sensitivity of using combined biomarkers was the same as AFP alone.

Discussion and conclusion. We have established for the first time the distribution of PIVKA-II in the Singapore population. The distribution of PIVKA-II values in our non-HCC patients was more similar to the healthy individuals in the EU than in Japan. This could be due to the large proportion of CHB patients in our cohort, which is more akin to the EU cohort, as the Japanese cohort was largely CHC patients. Unfortunately, we could not compare between CHB and CHC due to our small number of CHC patients.

Table 1A. Distribution of tumour biomarkers in non-HCC patients

Biomarker	Percentile	Overall cohort	Chronic hepatitis B	Reference interval (manufacturer)	
PIVKA-II, mAU/mL	2.5th	14.2	14.4	11.1 (JP)	17.4 (EU)
	97.5th	48.0	45.1	**32.0** (JP)	**50.9 (EU)**
AFP (Abbott), µg/L	0	1.15	1.13	-	-
	97.5th	9.44	8.54	**8.78**	**8.78**
AFP (Roche), µg/L	0	1.30	1.30	-	-
	95th	9.80	9.07	**7.00**	**7.00**

AFP: alpha-fetoprotein; EU: European Union; HCC: hepatocellular carcinoma; JP: Japan; PIVKA-II: protein induced by vitamin K absence or antagonist-II
Bold values denote the cut-off values for determining positive levels

Table 1B. Specificity and sensitivity of PIVKA-II diagnostic performance

Biomarker	Sensitivity	Specificity	*P* value
AFP (Roche) 7.00µg/L	0.40	0. 94	**0.01**
AFP (Abbott) 8.78µg/L	0.40	0. 96	**0.03**
Singular: PIVKA-II			
PIVKA-II (current) 40mAU/mL	0.20	0.93	0.29
PIVKA-II (JP) 32.0mAU/mL	0.40	0.82	0.22
PIVKA-II (EU) 50.9mAU/mL	0.20	0.97	0.14
PIVKA-II (study) 48.0mAU/mL	0.20	0.97	0.16
Combination: PIVKA-II + AFP			
PIVKA-II (current) + AFP (Roche)	0.40	0.89	0.10
PIVKA-II (current) + AFP (Abbott)	0.40	0.90	0.08
PIVKA-II (JP) + AFP (Roche)	0.60	0.78	0.07
PIVKA-II (JP) + AFP (Abbott)	0.60	0.80	0.07
PIVKA-II (EU) + AFP (Roche)	0.40	0.92	0.06
PIVKA-II (EU) + AFP (Abbott)	0.40	0.93	**0.04**
PIVKA-II (study) + AFP (Roche)	0.40	0.91	0.06
PIVKA-II (study) + AFP (Abbott)	0.40	0.96	**0.04**

AFP: alpha-fetoprotein; EU: European Union; HCC: hepatocellular carcinoma; JP: Japan; PIVKA-II: protein induced by vitamin K absence or antagonist-II
Bold *P* values are statistically significant
Diagnostic cut-offs to relate HCC associations used in 2x2 contingency analysis
HCC: 5, non-HCC: 605

There were 5 cases of incident HCC during the study period of 632 patient-years of follow-up. This is in concordance with our institution's previously reported HCC rate of 0.8% per year.[7]

Our study also showed that PIVKA-II alone was specific but not significant for HCC diagnosis. On the other hand, AFP alone was significant for HCC diagnosis. Combining PIVKA-II and AFP was significant in diagnosing HCC in our population but the sensitivity was the same as using AFP alone.

A systematic review of des-γ-carboxyprothrombin (DCP), another name for PIVKA-II, has shown a moderate diagnostic utility for HCC.[8] DCP/PIVKA-II level has also been reported to be related to HCC size.[9] This may explain the low diagnostic utility of PIVKA-II in our HCC surveillance study cohort, where incident HCCs are early HCCs.

Previous studies have shown that adding PIVKA-II to AFP is useful for HCC screening.[10] In our cohort, this was significant only when our study's PIVKA-II cut-off was used with AFP. However, the sensitivity was the same as AFP alone. During surveillance, ruling in possible HCC cases is more important than ruling out, and hence, the sensitivity of screening biomarkers is more pertinent than specificity. Thus, combining PIVKA-II and AFP was not superior to AFP alone for HCC surveillance in our population.

Our study had limitations. There were too few incident HCC cases to allow a more robust analysis of PIVKA-II alone, compared to a combination with AFP for early diagnosis of HCC. As the HCC incidence is very low even in at-risk populations, a very large study population is necessary to yield sufficient HCC cases. There were also too few CHC patients in our cohort to allow for comparison between CHB and CHC cases. The manufacturer's different RIs of PIVKA-II in the EU and Japan may be due to different

preponderances of CHB and CHC in both these places. Our study supported the notion that diagnostic cut-off is likely population specific. We are cognisant that, unlike the manufacturer's RIs that were based on normal individuals, ours was based on an at-risk population. PIVKA-II is not a screening test for the general population. So in the real world, it would only be used in at-risk populations, which makes our basis of derivation of RIs in at-risk populations most relevant.

In conclusion, we have derived our own PIVKA-II RIs. The combination of PIVKA-II and AFP did not appear to be better than using AFP alone for HCC surveillance in our Singapore population.

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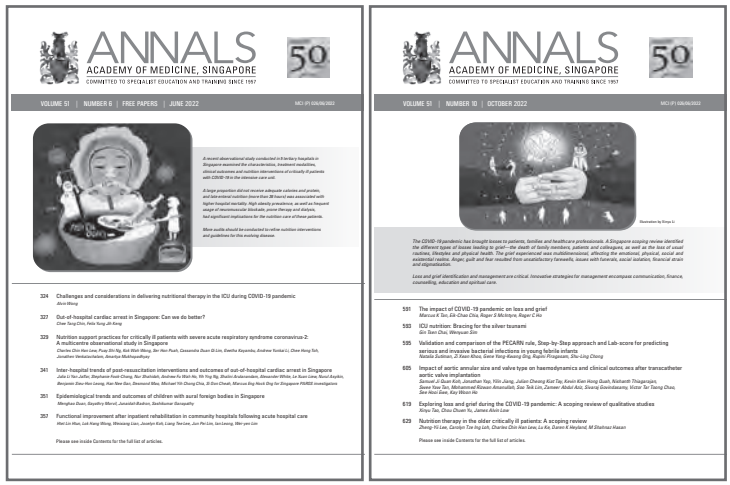

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