



# ANNALS

ACADEMY OF MEDICINE, SINGAPORE

COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

VOLUME 50 | NUMBER 5 | FREE PAPERS | MAY 2021

MCI (P) 078/06/2020



*Nutritional psychiatry is an emerging field of study that investigates the role of diet and nutrition in mental health. A recent study on dietary patterns of persons with mental disorders found sociodemographic factors, rather than diagnosis of mental disorders, influence dietary quality of people with depressive and psychotic disorders. Awareness of reasons behind nuanced poor dietary choices will enable clinicians to provide targeted psychoeducation to specific groups of patients. Further innovative strategies may also help alleviate adverse outcomes and burden.*

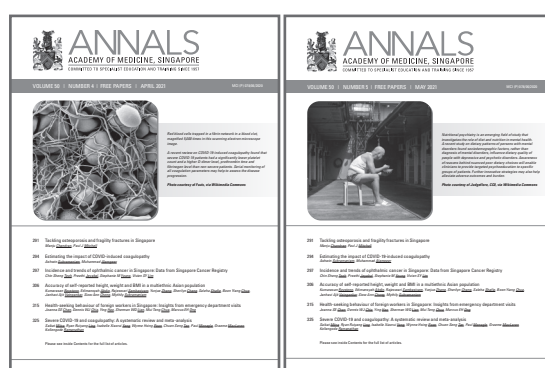
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Official Journal of the Academy of Medicine, Singapore



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Printed by Straits Printers (Pte) Ltd

ISSN 0304-4602

MCI (P) 078/06/2020

# Annals, Academy of Medicine, Singapore

Volume 50 | Number 5 | May 2021

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## Nutritional psychiatry: The next frontier in mental health treatment

Robin Goh<sup>1</sup> *MMed (Psych)*, Shang Cong Lim<sup>1</sup> *MRCPsych*

The World Health Organization has envisioned for every human being's fundamental right to be able to enjoy the highest attainable standard of health, even in the presence of disease or infirmity. Singaporeans' average life expectancy is projected to reach 85.4 years by the year 2040<sup>1</sup> and the burden of disease will inevitably rise. The second Singapore Mental Health Study conducted in 2016 revealed 1 in 7 Singaporeans (13.9%) had experienced a mental disorder in their lifetime,<sup>2</sup> and this was an increase from the 2010 study where it was reported at 1 in 8 Singaporeans (12%). Of interest, more than three-quarters of them did not seek professional help. There was also considerable treatment delay among those who sought help. Nutritional psychiatry is a developing field that explores how dietary intake patterns affect mood, behaviour and mental health. This novel approach in psychiatric management may have a role in bridging the treatment gap through the prevention of mental disorders, as part of an integrated treatment algorithm, or even as an alternative treatment modality.

Pharmacological interventions and psychotherapies have remained the main treatment modalities for psychiatric patients seeking help. However, most individuals who are suffering from mental disorders may not be aware of their conditions and the resources available.<sup>3</sup> They may also be in denial or fear stigmatisation following psychiatric consultations. There is increasing evidence that indicates a strong association between a poor diet and the exacerbation of mood disorders such as anxiety and depression. However, establishing a direct connection is difficult due to the multifactorial nature of having mental health conditions.

The Singapore Chinese Health Study,<sup>4</sup> which was one of the largest population-based cohorts in Southeast Asia, interviewed over 60,000 individuals in the 1990s about their life and food habits. During the 17 years of follow-up, researchers collected the participants' dietary information based on the Dietary Approaches to Stop Hypertension (DASH) diet and found that individuals with a diet resembling the DASH dietary

pattern were at 31–26% lower risk of death due to heart attack and stroke, even after controlling for many other coexisting characteristics of participants at baseline. This study demonstrated the close relationship between diet and diseases. The DASH diet was originally developed to prevent hypertension, but it had been extrapolated to investigate relationships with mental health disorders<sup>5</sup> on the basis that hypertension and some mental disorders do share common modifiable risk factors and underlying biological mechanisms.

Using food as an alternative for the prevention or treatment of mental disorders is not a foreign concept. *Hypericum perforatum*, commonly known as perforate St John's wort, has been used in herbalism for centuries. The plant contains hyperforin, which has been shown to inhibit the neuronal uptake of serotonin, norepinephrine and dopamine. A 2015 meta-analysis review<sup>6</sup> also concluded perforate St John's wort to be superior to placebo in treating depression and having fewer adverse effects than other antidepressants. It is approved as a dietary supplement by the Food and Drug Administration (FDA) in the US for the treatment of depression.

Nutritional psychiatry provides new insights into the treatment of mental disorders and is aligned with the principles of integrative health, which is to treat the patient as a whole person and not just the constellation of symptoms. Diets consisting of unprocessed food (lower DASH score) do contain more essential vitamins, minerals and nutrients that significantly support the body's biological and physiological processes. They are less inflammatory to the gut environment (microbiome) and support the sustainment of its probiotic population.

Probiotics in the gut have been hypothesised to exert their therapeutic effects on the central nervous system by improving the integrity of the gastrointestinal lining, reducing the ability of endotoxins to leak into the bloodstream and in turn, decreasing global inflammation.<sup>7</sup> This reduction may result in the improved regulation of the hypothalamic-pituitary-adrenal axis and neurotransmitter activity. Serotonin, which is bio-

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synthesised both in the central nervous system and the gastrointestinal tract, is increased with healthy gut microbiome and may reduce depressive symptoms.

The SMILES (Supporting the Modification of lifestyle in Lowered Emotional States) trial<sup>8</sup> investigated the efficacy of a dietary improvement programme for the treatment of major depressive episodes by comparing 33 depressive candidates on diet intervention against 34 controls. Both groups were allowed to continue their usual psychiatric treatments and followed up for 12 weeks. A modified Mediterranean diet (which resembled DASH diet) was administered to the treatment group; the participants were given higher portions of vegetables, fruits and other unprocessed food such as whole grains, beans and nuts, together with less refined carbohydrates and processed meats. Gluten was also excluded. At the end of the trial, the dietary support group demonstrated significantly greater improvement between the baseline and 12 weeks on the Montgomery-Asberg Depression Rating Scale compared with the control.

The road to recovery for mental health patients is often protracted. They have to reconstruct their life plans and reach a new balance.<sup>9</sup> The study by Lee et al. alluded to the difficulties in their journey and the often ignored dietary management.<sup>10</sup> There was a common misconception that nutritious food was bland and costly, and hence might not be easily accepted as a meal alternative. The results gave a startling realisation that females and those of an older age range of 41 to 65 years old in both depressive and psychotic disorder groups were putting more efforts in their meals. The likely postulation could be them becoming more health conscious after having severe mental disorders. The younger male demographics who did not report good dietary habits matched the profile of new onset psychotic patients. More can be done to educate them to enable a healthier relationship with their conditions.

Singapore has existing peer support<sup>11</sup> movements for mental health patients. The peer support specialists are patients who have recovered or are stable and they have demonstrated good stewardship qualities. They can be given basic dietary training by dietitians so that they are able to advise their clients. However, existing hospital dietician referrals are limited to medical nutritional conditions such as malnourishment or obesity; dietary modifications are not listed as adjunct treatments for mental health conditions.

Nutritional psychiatry is a nascent field in psychiatric treatment and will require more research and evidence before it can be considered a mainstream option. As medical practitioners, we should be open-minded about the possibility that having a healthy diet may alleviate mental health symptoms, and advocate dietary modifications. The road to mental health recovery is often long and protracted. However, Nutritional psychiatry can now be a game changer and modify the entire mental health trajectory by being a primary prevention modality, through promoting healthier diets.

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## Medical management of PAD: Expand or consolidate?

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In this issue of the Annals, a rapid review of adherence to evidence-based medical treatment<sup>1</sup> highlights an important and underappreciated aspect of the management of patients with peripheral arterial disease (PAD). It is easy, upon meeting a patient, to prescribe appropriate medication in an outpatient setting and believe that one's job is done; that the patient's risk has been optimised. It is clear from this review, and from previous work,<sup>2</sup> that this is not the case.

The authors conclude that adherence to evidence-based medical treatment is extremely variable, and that undertreatment is common. The variability in adherence is probably less surprising than how low adherence rates are in most of the studies compiled. For lipid-lowering medications, some of the larger and more recent included studies show encouraging adherence rates; however, only 10 of the 41 studies on lipid-lowering drugs report over 75% adherence. Over half (24/42) of the included studies, including the majority of the larger studies, showed between 50 and 75% adherence, while over 1 in 6 studies (7/41) reported adherence below 50%. The adherence to antiplatelet medication is more encouraging. While the majority of larger reports again fall between 50 and 75%, a much greater proportion (17/31) report adherence above 75%, and far fewer (3/31) below 50%.

There are often legitimate reasons for non-adherence with or non-prescribing of all of these medications, such as muscle cramps or liver function derangement with statins, or bleeding complications and gastrointestinal (GI) upset with antiplatelets. The use of "any antiplatelet" is more appropriate than singling out aspirin, as this reflects current guidelines and some patients may take clopidogrel given its more favourable side-effect profile regarding GI bleeding.<sup>3</sup> The lowest adherence rate in the entire review was in a study recording only aspirin use, which is perhaps instructive. This study is an outlier, and had other antiplatelets been included, the result may have been markedly different or at least more in line with the other studies.

Interpretation is more difficult in the case of antidiabetic and antihypertensive medication. The authors are of course limited in the inferences that can be drawn from each study, given the heterogeneity in reporting of both hypertensive patients and hypertensive medication use in individual publications. It is clear however that there is extreme variability in adherence to medication. It is encouraging to see that adherence rates have generally improved over time but it is clear as the authors suggest that improved adherence strategies are needed along with implementation studies to gauge the effect of this. The impact of nurse-led clinics to maximise adherence reported by Sillesen et al.<sup>4</sup> suggests a way forward in this regard. Anecdotally, in our practice, it is common to find patients have stopped, or their primary care doctor has stopped, a medication outright when dose alteration or a change to another medication in a similar class may have been more appropriate—such as using a different statin or changing antiplatelet.

Numerous recent studies have shown that a variety of medications can help either with symptom control or in reducing adverse cardiovascular events in patients with PAD. When viewed in the context of this ever-expanding repertoire of medications, this latest review forces a separate question to be confronted: in the attempt to medically manage PAD, should the focus be to introduce new and improved treatments into practice? Or should we first aim to maximise adherence to existing guidelines?

Large multicentre randomised trials have shown a modest but significant benefit in patients with PAD, both primarily and after revascularisation, to taking a combination of aspirin and low-dose rivaroxaban.<sup>5,6</sup> Pentoxifylline and cilostazol are sometimes prescribed to help in the management of PAD symptoms. A Cochrane review showed uncertain benefit with pentoxifylline due to poor-quality heterogeneous evidence;<sup>7</sup> in another review, cilostazol was considered beneficial in improving walking distance, but with an increase in adverse side effects that were generally mild and treatable.<sup>8</sup> Neither of these medications are

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recommended in the European guidelines, although cilostazol is recommended by the American College of Cardiology/American Heart Association (ACC/AHA).<sup>9</sup> Both are frequently prescribed.

These medications all show promise in the management of PAD. One must wonder however what negative effects their addition may have. A previously well claudicant could in a single outpatient visit be commenced on aspirin and a statin, cilostazol and low-dose rivaroxaban. This patient could go from no daily medications to 4, with more than once daily dosing. A similar patient with diabetes or hypertension, or both, could soon be on 6 or more separate medications with complex dosing schedules. That is to say nothing of the comorbid patient who may already be on multiple medications.

This presents 3 significant challenges. First, more than once daily dosing is a significant risk factor for non-adherence.<sup>10,11</sup> In both the COMPASS and VOYAGER PAD trials, non-adherence to trial medications was high, with a 16.5% overall non-adherence<sup>6</sup> and annualised discontinuation rate of 14% per year,<sup>5</sup> respectively. It is reasonable to expect that, outside the more controlled conditions of a randomised trial, real-world adherence rates could be lower still. A large part of this may have been due to the association between multiple daily dosing and non-adherence.

Second, as the authors of this review have correctly identified, polypharmacy is one of a number of patient and physician factors that can contribute to non-adherence. Multiple medications can be a necessary evil in the appropriate management of many conditions, and in younger patients many medications may be manageable. However, in older adults who often have multiple comorbidities, more medications and altered physiology, polypharmacy increases the risk of adverse drug events.<sup>12</sup> These patients may be prone to prescribing cascades where additional medications are prescribed for new symptoms or ailments without first considering that existing medications may be the cause of those symptoms. This can lead to increasingly complex medication regimens, with each additional medication increasing the risk of side effects,<sup>13</sup> rates of medication errors<sup>13</sup> and non-adherence.<sup>11</sup>

Finally, the additional medications that can be used in PAD outside those highlighted in the review, such as cilostazol and rivaroxaban, are not benign. Cilostazol poses a risk of polypharmacy in treating its multiple “easily managed” side effects. The combination of aspirin and rivaroxaban will lead to an increased bleeding risk compared to aspirin alone. While the

benefits may outweigh the risks in COMPASS<sup>6</sup> and VOYAGER PAD,<sup>5</sup> it is not certain how this plays out in the real world with concurrent use of hypoglycaemic medications and antihypertensives by frail patients who tend to be underrepresented in trials.

As newer treatments emerge and their evidence base grows, their adoption into guidelines and clinical practice must take into account the population in which PAD predominates. Our patients tend to be older, frequently have comorbidities and are all at high risk of polypharmacy. Younger and fitter patients may benefit from an aggressive, multimodal approach to medical management of their PAD. For others, that approach means increased risk of errors, non-adherence, and side effects. It is important that the treatments we prescribe for older adults in particular, align themselves with “what matters most” to that particular person. Current Emergency Cardiac Care (ECC) and ACC/AHA guidelines recommend lifelong aspirin and a statin, as well as management of hypertension and diabetes where indicated, in patients with PAD. Adherence to these medications is already lower than what we would hope, so an important step before considering addition of further medications is to focus on ensuring patients are appropriately prescribed, and compliant with core evidence-based best medical therapy.

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## Dietary intake of persons with depressive and psychotic disorders in Singapore

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### ABSTRACT

**Introduction:** Nutritional psychiatry is an emerging field of study that investigates the role of diet and nutrition in mental health. Studies conducted in the general population have linked depressive symptoms with poor dietary patterns. The aim of this study was to characterise the dietary intake and analyse the dietary pattern using the Dietary Approach to Stop Hypertension (DASH) in a sample of psychiatric patients in a multiethnic Asian nation.

**Methods:** Participants were recruited from an outpatient clinic and an inpatient unit at the Institute of Mental Health in Singapore. Self-reported dietary habits of a sample of psychiatric patients (N=380) were analysed using DASH. To examine the variables associated with DASH scores, a linear regression was conducted with the full sample and sociodemographic variables.

**Results:** Persons with depressive disorders had a mean DASH score of 21.3 ( $\pm 4.2$ ), while persons with psychotic disorders had a mean DASH score of 21.2 ( $\pm 4.9$ ). Respondents who were older ( $B=1.94$ , 95% confidence interval [CI] 0.91–2.96,  $P<0.001$ ), female ( $B=1.09$ , 95% CI 0.07–2.11,  $P=0.04$ ) and economically inactive ( $B=1.98$ , 95% CI 0.006–3.96,  $P=0.049$ ) were more likely to report a higher diet quality compared with their respective counterparts, while smokers ( $B=-1.39$ , 95% CI -2.45 to -0.34,  $P=0.009$ ) tended to report a lower diet quality compared with their non-smoking counterparts.

**Conclusion:** Dietary patterns of persons with mental disorders were characterised. A host of sociodemographic factors, and not diagnosis of mental disorders, influenced the dietary quality of people with depressive and psychotic disorders. Clinicians treating psychiatric patients need to be aware of the nuanced reasons behind poor dietary choices and provide targeted psychoeducation to specific subgroups within the patient population.

Ann Acad Med Singap 2021;50:379-89

**Keywords:** Depression, diet, nutritional psychiatry, psychosis, smoking

### INTRODUCTION

Unhealthy diet is a modifiable risk factor in many health conditions,<sup>1</sup> including mental disorders.<sup>2</sup> Nutritional psychiatry is an emerging field that examines the role of diet and nutrition in mental health.<sup>3</sup> Since its beginnings in the 2000s, a notable change in the field was a switch in focus from individual supplements and specific food intake to a more holistic assessment of one's dietary pattern.<sup>3</sup> The rationale for this progress was the realisation that one's diet had to be understood in the context of

whole nutrition intake, rather than individual components of one's diet. What one eats in excess is as important as what one does not.<sup>3</sup>

Diet has the potential to be used as a preventive and/or adjunctive treatment for mental disorders.<sup>4-6</sup> In the last decade, a growing body of evidence has associated poor dietary patterns with depressive symptoms in the general population,<sup>7</sup> women<sup>8</sup> and college students<sup>9</sup> across various parts of the world. Indeed, there are at least 3 meta-analyses that confirmed the findings that

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## CLINICAL IMPACT

### What is New

- Self-reported dietary habits of people with depressive and psychotic disorders in Singapore were characterised.

### Clinical Implications

- A host of sociodemographic factors, not diagnosis of mental disorders, influences the dietary quality of people with depressive and psychotic disorders.
- Clinicians treating psychiatric patients need to be aware of the nuanced reasons behind poor dietary choices and make targeted psychoeducation to specific subgroups within the patient population.

healthy dietary patterns reduce the risk of depression and that unhealthy dietary patterns elevate the risk of depression.<sup>10-12</sup> However, it is unclear if a poor diet quality is prevalent among persons with known depressive disorders.<sup>4,13</sup> Studies examining the association between diet quality and depression were commonly performed in the general population in whom the associations between diet and risk of depression or subclinical depressive symptoms, or both, were investigated; very few studies actually investigated the relationship between diet quality and clinically diagnosed depressive disorders.<sup>13-15</sup>

On the other hand, owing to the prevalence of cardiovascular risks, metabolic syndrome and obesity among persons with schizophrenia, much more attention has been paid to the diet and lifestyle habits of this population of patients.<sup>16-18</sup> A number of studies linking weight and metabolic issues in persons with depression and schizophrenia were published in the last decade.<sup>19-21</sup> For example, it was reported that people with schizophrenia spectrum disorder have poor diet quality, high refined carbohydrate intake and low intake of fibre.<sup>16,17,22,23</sup> This finding could be in part due to the use of atypical antipsychotic medications, which affect neural pathways involved in appetite control and satiety.<sup>22</sup> In addition, persons with schizophrenia spectrum disorder were more likely than the general population to have poorer dietary habits.<sup>16,17</sup> Moreover, studies from Singapore and beyond have reported that a high proportion of persons with schizophrenia are overweight, obese and living with metabolic

syndrome.<sup>17-20,22,24</sup> Healthy diet has been identified as a potential preventive and/or adjunctive treatment for depressive and psychotic disorders.<sup>13,14,23</sup>

Given the concerning state of the physical health condition of persons with mental disorders, the Lancet Psychiatry Commission recently published a blueprint for protecting their physical health in an effort to improve the quality of life and prolong the lifespan of this vulnerable population.<sup>25</sup> Five areas were identified, with modifiable factors in health-related behaviours (e.g. diet, smoking and physical activities) as key to protecting the physical health of persons with mental disorders. Yet, the extent to which lifestyle risk factors—such as diet—in various mental disorders differs from that in the general population is unknown.<sup>25</sup>

Most overseas studies that established the link between depressive symptoms and poor dietary patterns were conducted within the general population.<sup>4,13</sup> In the same vein, most local studies that investigated the dietary patterns were conducted within the general population.<sup>26-28</sup> To our knowledge, there is a paucity of data on the dietary patterns of patients with known mental disorders, especially those with depressive disorders. While there have been a lot of data internationally on the dietary patterns of persons with schizophrenia, there is a gap in the data in Singapore.

Given the ethnic diversity of Singapore, a culturally relevant diet screener needs to be developed and validated for use in the local population. Whitton et al.<sup>29</sup> have developed and validated a short diet screener, which has been shown to have good reliability for use among Singapore residents. In another study, the same investigators found that Dietary Approaches to Stop Hypertension (DASH) was the most sensitive diet score to test associations between diet and health-related outcomes.<sup>30</sup> Moreover, there exists prior literature that has linked adherence to DASH diet patterns to more positive mental health in various populations.<sup>31-33</sup> While DASH was originally designed to prevent hypertension, it was suggested that hypertension and some mental disorders share common modifiable risk factors and underlying biological mechanisms. Also, DASH diet approach emphasises intake of nutrients with benefits to mental health, and lower intake of those detrimental to mental health.<sup>31</sup>

Our study aimed to (1) characterise the diet of a population of persons with depressive and psychotic disorders in Singapore and score their diet intake according to the DASH score; and (2) identify sociodemographic correlates of DASH scores among persons with depressive and psychotic disorders.

## METHODS

### Participants

Singapore's population of 5.7 million people is made up of the 3 main ethnic groups of Chinese, Malay and Indian. During the period of October 2018 to February 2020, participants were recruited from the Institute of Mental Health, the only tertiary psychiatric hospital in Singapore. Participants comprising both inpatients and outpatients were included in the study if they were aged 21 to 65 years and had a clinician-reported diagnosis of either depressive disorders (e.g. major depressive disorder, dysthymia, depression with psychotic features) or psychotic disorders (e.g. brief psychotic disorder, schizophrenia and schizoaffective disorder). The study excluded participants who did not have the mental capacity to consent to the study, or did not meet the diagnostic criteria. Depending on the preference of the participants, the survey was administered in 1 of the 4 local languages: English, Chinese, Malay and Tamil. Data of this study came from a larger study on the prevalence and correlates of cigarette smoking among persons with mental disorders.<sup>34</sup> Ethics approval was obtained from the Institutional Research Review Board and National Healthcare Group Domain Specific Review Board (Ref: 2018/00772). Written consent was taken from all the participants. A quota was set to recruit similar proportions of persons based on depressive and psychotic disorders, sex and age.

### Measures

#### *Sociodemographic information, smoking habits, body mass index and diagnosis*

A modified version of Global Adult Tobacco Survey<sup>35</sup> was used to capture data that included sociodemographic information (e.g. age, sex, ethnicity, education, housing and income) and questions regarding smoking status. The classification of smoker, non-smoker and past smoker was based on the definitions from the National Health Interview Survey.<sup>36</sup> Participants who had smoked at least 100 cigarettes in their lifetime and were smoking at the time of the survey were classified as a smoker. Participants who had smoked at least 100 cigarettes but had quit smoking at the time of the survey were classified as former smokers. Those who had never smoked or had smoked less than 100 cigarettes in their lifetime were classified as non-smokers.<sup>37</sup> For the purpose of data analysis and interpretation, ex-smokers were subsumed under the category for current smokers to form a new classification “ever-smokers” because of the small sample size and the need to keep to the convention set

by the first article published for this project.<sup>34</sup> At the end of every interview, height and weight were measured at the clinic of recruitment. Data were analysed using the body mass index (BMI) scores. BMI was further categorised into 4 groups based on World Health Organization guidelines for Asian populations: underweight ( $<18.5\text{kg/m}^2$ ), normal range ( $\geq 18.5\text{kg/m}^2$  and  $<23\text{kg/m}^2$ ), overweight ( $\geq 23\text{kg/m}^2$  and  $<27.5\text{kg/m}^2$ ) and obese ( $\geq 27.5\text{kg/m}^2$ ).<sup>38</sup> The clinical diagnosis of each participant was captured as indicated in the electronic medical records, which followed the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.<sup>39</sup>

#### *Diet screener*

The diet screener utilised in the present study was developed and validated by Whitton et al.<sup>29</sup> with a Singapore population. It comprised a list of 30 food/beverage items, with a 10-point scale—ranging from “never/rarely” to “6 or more times per day”—the frequency at which respondents consumed a particular item within the last 1 year. The diet screener was interviewer-administered. Standard serving sizes were indicated for each food/beverage item to facilitate this process. Intake frequencies were standardised to a number of servings per day for each food/beverage item. DASH scores were calculated to account for the intakes of fruit, vegetables, nuts and legumes, whole grains, red and processed meat, low fat dairy, and sweetened beverages.<sup>40</sup> For each of these 7 DASH components, participants received a score from 1 to 5 corresponding to the quintile of intake they fall in, with reverse scoring for meat and sweetened beverages, and these 7 quintile scores were summed to form the overall DASH score.

#### *Statistical analyses*

All analyses were conducted using Stata software version 15.0 (StataCorp, College Station, US). Means and standard deviations are provided for continuous variables, while frequencies and percentages are presented for categorical variables. To examine the variables associated with DASH scores, a linear regression was conducted with the full sample and the following variables: age, sex, ethnicity, education, employment, personal income, BMI, smoking status and diagnosis. A linear regression was conducted separately for the depressive and psychotic disorders groups to further examine the associations between sociodemographic characteristics or smoking status and DASH. Respondents who had any missing values on any variables were removed listwise in the regression



analyses: 3 participants had missing values on the height and weight variables, and 2 participants had missing values on the DASH questionnaire. Estimates of the associations between DASH scores and variables with more than 1 comparison (i.e. ethnicity, education, employment, income and BMI) in each regression model were adjusted with Bonferroni correction for multiple comparisons. Lastly, to further examine sex and age group differences in DASH components within the full sample and among the depressive and psychotic disorders groups, bivariate Mann-Whitney U tests were conducted. Statistical significance was set at the conventional  $\alpha$  level of  $P < 0.05$  using 2-tailed tests.

## RESULTS

### Sociodemographic and clinical characteristics of sample

Sociodemographic and clinical characteristics of the sample are shown in Table 1. The sample consisted of 380 respondents; 46.6% (177) were diagnosed with depressive disorders, while 53.4% (203) had psychotic disorders. The mean age of the sample was  $39.8 \pm 12.0$  years (range 21–65 years), and approximately half of the sample (188, 49.5%) were aged 21 to 40. Of the sample, 55.3% were men and 73.4% were of Chinese ethnicity.

### DASH scores among psychiatric patients in IMH

The mean and standard deviations of each of the 7 DASH components (fruit, vegetables, nuts and legumes, whole grains, red and processed meat, low fat dairy, and sweetened beverages) and of the overall DASH scores of the sample for the depressive and psychotic disorder groups are presented in Table 2. Results of the regression analyses of the full sample as well as the depressive and psychotic disorder groups are given in Table 3.

Within the full sample, there were no significant differences in DASH scores between the depressive and psychotic disorder groups ( $I = 0.89$ ). However, compared with those aged 21 to 40, those in the age range of 41 to 65 had significantly a higher DASH scores ( $B = 1.94$ , 95% confidence interval [CI] 0.91–2.96,  $P < 0.001$ ). Women appeared to have higher DASH scores than men ( $B = 1.09$ , 95% CI 0.07–2.11,  $P = 0.04$ ). Those who were economically inactive (students, homemakers and retirees) had higher DASH scores than those unemployed ( $B = 1.98$ , 95% CI 0.006–3.96,  $P = 0.049$ ) (Table 3).

Within the depressive disorder group, age remained significantly and positively associated with DASH scores, with those in the age range of 41 to 65 having

higher scores ( $B = 2.65$ , 95% CI 1.08–4.22,  $P = 0.001$ ). Those who were economically inactive had better DASH scores than those who were unemployed ( $B = 2.59$ , 95% CI 0.04–5.13,  $P = 0.045$ ).

In the psychotic disorder group, age was similarly associated with DASH scores—those aged 41 to 65 years were associated with higher scores ( $B = 1.53$ , 95% CI 0.06–3.00,  $P = 0.04$ ). Those who ever smoked were also associated with lower scores compared with those who had never smoked ( $B = -1.93$ , 95% CI -3.70 to -0.17,  $P = 0.03$ ) (Table 3). Finally, we did not note significant associations between the BMI of the sample population with their dietary patterns (Table 3).

### Sex and age group differences in DASH component scores

Descriptive statistics and Mann-Whitney U tests were performed to examine sex and age group differences in DASH component scores among the total sample, and depressive and psychotic disorder groups. Based on Mann-Whitney U tests, it appeared that within the full sample, women had higher intake of fruits ( $P = 0.02$ ), whole grains ( $P = 0.01$ ) and higher overall DASH scores ( $P = 0.001$ ), but had lower intake of red and processed meat ( $P = 0.009$ ) and sweetened beverages ( $P = 0.38$ ) than men. Within the entire sample, adults aged 41 to 65 had lower intake of red and processed meat ( $P = 0.001$ ) and sweetened beverages ( $P = 0.009$ ) than those aged 21 to 40.

Within those with depressive disorders only, women had higher intake of fruits ( $P = 0.02$ ), lower intake of red and processed meat ( $P = 0.03$ ) and higher overall DASH scores ( $P = 0.02$ ) than men. Among those with psychotic disorders, women had higher intake of whole grains ( $P = 0.03$ ), lower intake of sweetened beverages ( $P = 0.03$ ) and higher DASH scores ( $P = 0.01$ ) than men.

## DISCUSSION

This study is among the first to examine the nutrition intake and DASH scores of a sample of psychiatric patients at the Institute of Mental Health in Singapore. Seven components of the DASH scores and the final DASH scores are presented in Table 2. Persons with depressive disorders had a mean DASH score of 21.3 ( $\pm 4.2$ ), while persons with psychotic disorders had a mean DASH score of 21.2 ( $\pm 4.9$ ). In addition, we observed that the ever-smokers group was more likely than the non-smokers group to report poor diet scores within our sample population. On the other hand, we found that older age, women and economically inactive

Table 1. Sociodemographic and clinical characteristics of the sample (N=380)

Characteristics	Total sample, no. (%) (N=380)	Depressive disorders, no. (%) (n=177)	Psychotic disorders, no. (%) (n=203)
Age group, years <sup>a</sup>			
21–40	188 (49.47)	117 (66.10)	71 (34.98)
41–65	192 (50.53)	60 (33.90)	132 (65.02)
Sex			
Male	210 (55.26)	90 (50.85)	120 (59.11)
Female	170 (44.74)	87 (49.15)	83 (40.89)
Ethnicity			
Chinese	279 (73.42)	119 (67.23)	160 (78.82)
Malay	55 (14.47)	28 (15.82)	27 (13.30)
Indian	39 (10.26)	26 (14.69)	13 (6.40)
Other	7 (1.84)	4 (2.26)	3 (1.48)
Education			
Primary school or lower	51 (13.42)	17 (9.60)	34 (16.75)
Secondary school	102 (26.84)	28 (15.82)	74 (36.45)
Pre-university/diploma	112 (29.47)	69 (38.98)	43 (21.18)
Vocational/Institute of Technical Education	53 (13.95)	36 (14.69)	27 (13.30)
Degree and above	62 (16.32)	37 (20.90)	25 (12.32)
Employment			
Employed	179 (47.11)	85 (48.02)	94 (46.31)
Unemployed	166 (43.68)	71 (40.11)	95 (46.80)
Economically inactive	35 (9.21)	21 (11.86)	14 (6.90)

<sup>a</sup> Mean age of total sample: 39.83±11.99 (range 21–65); mean age of depressive disorders group: 35.37±12.21 (range 21–65); mean age of psychotic disorders group: 43.73±10.35 (range 22–65)

Table 1. Sociodemographic and clinical characteristics of the sample (N=380) (Cont'd)

Characteristics	Total sample, no. (%) (N=380)	Depressive disorders, no. (%) (n=177)	Psychotic disorders, no. (%) (n=203)
Monthly personal income (SGD) <sup>b</sup>			
<2000	308 (81.05)	131 (74.01)	177 (87.19)
2000–3999	54 (14.21)	35 (19.77)	19 (9.36)
≥4000	18 (4.74)	11 (6.21)	7 (3.45)
BMI (Asian recommendations)			
Normal range ≥18.5 and <23	84 (22.11)	55 (31.07)	29 (14.29)
Underweight <18.5	12 (3.16)	6 (3.39)	6 (2.96)
Overweight ≥23 and <27.5	121 (31.84)	56 (31.64)	65 (32.02)
Obese ≥27.5	160 (42.11)	58 (32.77)	102 (50.25)
Missing <sup>c</sup>	3 (0.79)	2 (1.13)	1 (0.49)
Smoking status			
Never-smoker	196 (51.58)	82 (46.33)	
Ex-smoker	34 (8.95)	22 (12.43)	
Smoker	150 (39.47)	73 (41.24)	
Diagnosis			
Depressive disorders <sup>d</sup>	177 (46.58)	NA	NA
Psychotic disorders	203 (53.42)	NA	NA

BMI: body mass index; NA: not applicable

<sup>b</sup> USD 1 is approximately SGD1.40<sup>c</sup> Missing values were not included in the subsequent linear regression analyses<sup>d</sup> Depressive disorders only included unipolar depression, and bipolar disorders were excluded

Table 2. Dietary Approach to Stop Hypertension (DASH) components and overall DASH scores of depressive and psychotic disorders and smoking status

	Depressive disorders				Psychotic disorders		
	All (n=177)	Ever-smokers (n=95)	Never-smokers (n=82)	All (n=201) <sup>a</sup>	Ever-smokers (n=88)	Never-smokers (n=113)	
DASH components, mean (SD), servings/day							
Fruits	0.77 (0.82)	0.72 (0.74)	0.84 (0.90)	0.89 (1.12)	0.73 (1.06)	1.02 (1.14)	
Vegetables	1.35 (1.18)	1.24 (1.00)	1.49 (1.35)	1.25 (1.31)	1.10 (1.23)	1.37 (1.37)	
Nuts and legumes	0.53 (0.77)	0.45 (0.77)	0.62 (0.76)	0.62 (1.08)	0.48 (0.91)	0.72 (1.20)	
Low fat dairy	0.35 (0.64)	0.28 (0.63)	0.42 (0.64)	0.41 (0.64)	0.34 (0.68)	0.28 (0.65)	
Whole grains	1.40 (1.90)	1.34 (1.67)	1.48 (2.15)	1.99 (2.63)	1.30 (2.14)	2.53 (2.85)	
Red and processed meat	0.77 (1.06)	0.71 (0.88)	0.83 (1.23)	0.70 (1.26)	0.77 (1.57)	0.64 (0.95)	
Sweetened beverages	0.61 (0.75)	0.63 (0.74)	0.60 (0.77)	0.92 (1.51)	1.15 (1.83)	0.75 (1.18)	
DASH score <sup>b</sup>	21.27 (4.24)	20.64 (3.85)	22 (4.57)	21.18 (4.89)	19.61 (4.64)	22.40 (4.74)	

SD: standard deviation

<sup>a</sup> Sample size differs from the initial sample size because of missing data on variables<sup>b</sup> Calculated based on quantile scores of each component

groups were more likely to report better diet quality than their respective reference groups (Table 3). We also observed age and sex differences in the intake of various food groups in our sample population.

When comparing the individual nutrition intake of our sample population with that of the general population from the National Nutrition Survey 2010,<sup>41</sup> we found some interesting differences in the number of servings taken per day for various diet components. For instance, the wholegrain intake of our sample was much higher (1.34–2.53 servings per day) than the national average of 0.76 serving per day.<sup>41</sup> A reason for this difference could be the success of Singapore's Health Promotion Board to encourage the intake of wholegrain staple food in its health promotion campaigns. On the other hand, the fruit and vegetable intake of our sample population was much lower than the reported average daily intake of the general population in Singapore. The National Nutrition Survey reported an intake of 1.27 servings of fruits and 1.78 servings of vegetables per day for adult Singapore residents.<sup>41</sup> However, respondents of this present study reported a daily intake of fruits at 0.72–1.02 servings and vegetables at 1.10–1.49 servings. This finding is in line with the literature, in which fruit and vegetable intake was reported to be lower among persons with schizophrenia.<sup>2</sup>

Findings from our study supported the notion that older adults, women and persons who are economically inactive adhere to a healthier diet based on their DASH scores. Persons who smoked were more likely to report a poor diet quality than those who did not. These findings are similar to the literature. Koh et al. reported that older Chinese adults in Singapore who smoked had poor dietary habits.<sup>26</sup> It is well documented that persons who smoke have poor dietary habits.<sup>16,40</sup> Reasons for poor diet choices could be that smokers are more likely than non-smokers to have a craving for high-fat food and fast food fats, and that nicotine dependence could have an effect on smokers' cravings for other substances like sugar.<sup>41</sup> A study on fast food intake of Singapore residents found that younger adults tended to take more fast food than their older counterparts.<sup>28</sup> In another Singapore study involving pregnant women, older women were found to have a healthier dietary pattern than younger women. It was suggested that older women may be more knowledgeable in nutrition and hence are able to make healthier dietary choices.<sup>27</sup> In our study, we observed a similar trend that older people in the sample had higher DASH scores.

Diet is multifaceted, with the potential to be a preventive health measure or a modifiable health risk factor. From our study, we found a number of

Table 3. Results of linear regression analyses examining the correlates of Dietary Approach to Stop Hypertension (DASH) scores in the total sample and respondents with depressive disorders or psychotic disorders<sup>a</sup>

	DASH score			
	Total sample <sup>b</sup> (n=375)	Depressive disorders <sup>c</sup> (n=175)	Psychotic disorders <sup>d</sup> (n=200)	
	B (95% CI)	P	B (95% CI)	P
Age group				
21–40	[Reference]		[Reference]	
41–65	1.94 (0.91 to 2.96)	<0.001	2.65 (1.08 to 4.22)	0.001
Sex				
Male	[Reference]		[Reference]	
Female	1.09 (0.07 to 2.11)	0.04	1.08 (-0.23 to 2.40)	0.11
Ethnicity <sup>e</sup>				
Chinese	[Reference]		[Reference]	
Malay	-1.37 (-3.20 to -0.47)	0.30	-0.96 (-3.41 to 1.49)	>0.99
Indian	1.36 (-0.72 to 3.44)	0.50	0.63 (-1.88 to 3.14)	>0.99
Other	1.24 (-3.24 to 5.71)	>0.99	0.06 (-5.65 to 5.76)	>0.99
Education <sup>e</sup>				
Primary school or lower	[Reference]		[Reference]	
Secondary school	1.53 (-0.65 to 3.70)	0.48	0.04 (-3.70 to 3.78)	>0.99
Pre-university/diploma	2.21 (-0.12 to 4.55)	0.08	1.05 (-2.62 to 4.73)	>0.99
Vocational/ Institute of Technical Education	1.56 (-1.01 to 4.14)	0.87	-0.53 (-4.48 to 3.43)	>0.99
Degree and above	2.71 (-0.02 to 5.44)	0.05	2.07 (-2.15 to 6.29)	>0.99

B: unstandardised regression coefficient; BMI: body mass index; CI: confidence interval of B; NA: not applicable

<sup>a</sup> Sample sizes differ from the initial sample sizes because of missing data on variables in the analyses<sup>b</sup> Mean DASH score of the total sample: 21.22±4.59 (range 9–35)<sup>c</sup> Mean DASH score of those with depressive disorders: 21.27±4.24 (range 9–32)<sup>d</sup> Mean DASH score of those with psychotic disorders: 21.18±4.89 (range 9–35)<sup>e</sup> These estimates were adjusted using Bonferroni correction for multiple comparisons



Table 3. Results of linear regression analyses examining the correlates of Dietary Approach to Stop Hypertension (DASH) scores in the total sample and respondents with depressive disorders or psychotic disorders<sup>a</sup>(Cont'd)

	DASH score		
	Total sample <sup>b</sup> (n=375)	Depressive disorders <sup>c</sup> (n=175)	Psychotic disorders <sup>d</sup> (n=200)
Employment <sup>e</sup>			
Unemployed	[Reference]	[Reference]	[Reference]
Employed	0.91 (-0.35 to 2.18)	0.25 1.78 (-0.07 to 3.64)	0.06 0.56 (-1.25 to 2.38)
Economically inactive	1.98 (0.006 to 3.96)	0.049 2.59 (0.04 to 5.13)	0.045 1.38 (-2.52 to 4.15)
Monthly personal income (S\$) <sup>e</sup>			
<2000	[Reference]	[Reference]	[Reference]
2000–3999	-0.08 (-1.85 to 1.71)	>0.99 0.21 (-1.98 to 2.40)	>0.99 -0.81 (-3.94 to 2.33)
≥4000	0.09 (-2.72 to 2.88)	>0.99 -0.29 (-3.80 to 3.23)	>0.99 -0.22 (-4.94 to 4.50)
BMI (Asian recommendations) <sup>e</sup>			
Normal range ≥18.5 and <23	[Reference]	[Reference]	[Reference]
Underweight <18.5	-1.59 (-2.01 to 5.20)	>0.99 -1.20 (-6.02 to 3.62)	>0.99 -1.62 (-7.29 to 4.04)
Overweight ≥23 and <27.5	0.10 (-1.58 to 1.78)	>0.99 0.07 (-2.06 to 2.19)	>0.99 -0.04 (-2.88 to 2.81)
Obese ≥27.5	-0.83 (-2.46 to 0.80)	>0.99 -0.84 (-3.00 to 1.31)	>0.99 -0.89 (-3.57 to 1.78)
Smoking status			
Never-smokers	[Reference]	[Reference]	[Reference]
Ever-smokers	-1.39 (-2.45 to -0.34)	0.009 -0.91 (-2.25 to 0.44)	0.19 -1.93 (-3.70 to -0.17)
Diagnosis			
Depressive disorders	[Reference]	NA	NA
Psychotic disorders	-0.07 (-1.07 to 0.93)	0.89 NA	NA NA

B: unstandardised regression coefficient; BMI: body mass index; CI: confidence interval of B; NA: not applicable

<sup>a</sup> Sample sizes differ from the initial sample sizes because of missing data on variables in the analyses<sup>b</sup> Mean DASH score of the total sample: 21.22±4.59 (range 9–35)<sup>c</sup> Mean DASH score of those with depressive disorders: 21.27±4.24 (range 9–32)<sup>d</sup> Mean DASH score of those with psychotic disorders: 21.18±4.89 (range 9–35)<sup>e</sup> These estimates were adjusted using Bonferroni correction for multiple comparisons

sociodemographic factors associated with dietary patterns in persons with depressive and psychotic disorders. Looking at the dietary choices of a sample population may not give an accurate reflection of the state of dietary choices of the actual population. Indeed, when we focused on specific groups within our sample population, we observed that smokers were more likely than non-smokers to report poorer diet quality. Older, female and economically inactive respondents were more likely to report having better diet quality than their counterparts. Our study highlights the role lifestyle choices plays in influencing the dietary choices of our population. Thus, the vulnerability to poor diet choices may not be attributed to the diagnosis of a mental disorder alone.

In the same vein, BMI was not found to be a factor associated with dietary habits. This is surprising because it has been noted in the literature that persons with schizophrenia have higher-than-normal BMI<sup>16</sup> and people with depression have either lower- or higher-than-normal BMI.<sup>42,43</sup> In line with the literature, there also seems to be a greater proportion of people classified as obese in the psychotic disorder group than in the depressive disorder group. It is well documented that atypical antipsychotic medications can cause metabolic syndrome in persons with psychotic disorders and that use of medications is associated with weight gain.<sup>20,24</sup> Multiple reasons have been proposed for such weight gain, including the effect of antipsychotic drugs in neural pathways that regulate appetite control and energy metabolism.<sup>44</sup> Since BMI did not predict diet quality, it seems that people with obesity in this sample were eating more in quantity but not necessarily poorer in quality than those who were non-obese. The weight disparity within the psychiatric population compared with the general population may be due to the treatment regimen prescribed to patients. On this note, treating physicians need to be fully aware of the unwanted physical health side effects that atypical antipsychotic medications can cause.<sup>20</sup>

There are several limitations in this study that could confound the findings. Firstly, the study sample was recruited by convenience sampling at a tertiary psychiatric hospital and may not be representative of the entire psychiatric population in Singapore. However, a quota was set to have a fair proportion of persons recruited into the study based on depressive and psychotic disorders, sex and age. Secondly, the diet screener was based on a self-reported diet recall of intake over the past year, with no validation using blood or urinary samples. There may be recall bias in the self-report that we were unable to verify or refute by other

means. Thirdly, while we gave the average serving sizes in our questionnaire in written form, we did not use visual representations to illustrate them as recommended.<sup>45</sup> Fourthly, we did not make adjustments for total energy intake recommended for epidemiological-type studies.<sup>46</sup> Finally, owing to the cross-sectional design of this study, we were unable to uncover a causal relationship between unhealthy diet and mental illness.

Given the study limitations, future work could focus on using a more representative sampling method to investigate the dietary habits of the psychiatric population in Singapore. Moreover, supplementing the diet recall questionnaire with photographs, or blood and/or urine sample analysis may also clarify any recall bias and errors.<sup>45</sup> Furthermore, a host of sociodemographic factors such as lifestyle, sex and employment status, influences the dietary patterns of a given person. The significant comorbid condition of persons with mental disorders calls for innovative strategies to be implemented to alleviate the adverse outcomes and burden associated with the comorbidity.<sup>47</sup>

#### Acknowledgement

*The authors are grateful to the participants of this study.*

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# Impact of unemployment on mental disorders, physical health and quality of life: Findings from the Singapore Mental Health Study

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## ABSTRACT

**Introduction:** This study examines: (1) the employment rate among those with a mental disorder in the 12 months preceding the survey (referred henceforth as 12-month mental disorder); (2) the socio-demographic correlates of unemployment; and (3) the association of unemployment with 12-month mental disorders and chronic physical conditions in the adult resident population in Singapore.

**Methods:** Data are from the Singapore Mental Health Study 2016, a household survey of a nationally representative sample of 6,126 Singapore residents. The Composite International Diagnostic Interview (CIDI) was used to assess mental disorders and physical health conditions. Employment-related information was collected using a modified employment module of the CIDI.

**Results:** Of the 6,125 participants who took part in the study, 4,055 (72%) were employed, 1,716 (22.7%) were economically inactive, and 354 (5.3%) were unemployed. The unemployment rate was twice as high among those with a 12-month mental disorder (11.5%) than those without (4.8%). The proportion of unemployed individuals increased sharply with the increasing severity of mental disorders. Being married and higher household income were significantly associated with a higher likelihood of being employed than unemployed. In contrast, the presence of one 12-month mental disorder was significantly associated with a lower likelihood of being employed.

**Conclusion:** Our findings provide information on the significant association of mental disorders with unemployment. Clinicians should remain vigilant and consider the loss of employment a potential risk factor for adverse physical and mental health changes. Management of unemployed patients with a combination of pharmacotherapy and work-directed interventions can facilitate their re-entry into the workforce and improve health outcomes.

Ann Acad Med Singap 2021;50:390-401

**Keywords:** Employment, epidemiology, mental health, survey

## INTRODUCTION

Several reviews and meta-analyses have established an association between unemployment and psychological distress.<sup>1,2</sup> This relationship between unemployment and mental health is complex and likely bidirectional. On the one hand, unemployment may lead to psychological distress and mental disorders (social causation), but on the other, those with poor mental health may struggle to find a foothold in the labour market (health selection). Jahoda's latent deprivation model<sup>3</sup> has been widely used to explain the relationship

between unemployment and psychological distress. The author postulates that the latent functions of employment—such as providing structure to the day, enabling social contact, and contributing to collective purpose—satisfy individuals' important psychological needs. Unemployment deprives people of these benefits, leading to psychological distress. Fryer<sup>4</sup> alternatively emphasised the contribution of the manifest function of employment, namely, financial income to well-being; the loss of employment resulted in poverty, loss of agency, and subsequent psychological distress. The

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## CLINICAL IMPACT

### What is New

- In Singapore, the unemployment rate was twice as high among those with a 12-month mental disorder than those without.
- The proportion of unemployed individuals increased sharply with the increasing severity of mental disorders.

### Clinical Implications

- Loss of employment is a potential risk factor for adverse physical and mental health outcomes. Early treatment and vocational rehabilitation can facilitate the re-entry of unemployed people with mental health conditions into the workforce and improve health outcomes.

health selection or reverse causation theory suggests that unemployment is the consequence of mental health problems. This could be due to several factors, including the adverse impact of the mental disorder on job performance and productivity, which may increase the risk of dismissal. Stigma may affect the employer's hiring decision, resulting in poorer employability of those with mental disorders.<sup>5</sup> However, evidence supporting unemployment as the consequence of a mental disorder is surprisingly less robust. While qualitative studies have described the barriers faced by people with mental disorders to gain or maintain employment,<sup>6</sup> there is less evidence from quantitative studies. A study from Sweden found a gendered relationship between depression and unemployment; pre-existing major depression increased the risk of being laid off in women while this risk did not extend to men.<sup>7</sup>

Male gender, blue-collar jobs, longer unemployment duration, economically less developed countries, and countries with weak employment protection policies have been identified as significant moderators of the effect of unemployment on mental health.<sup>1</sup> Other studies suggest that culture may influence the perception of work relevance across societies.<sup>8</sup> Individualistic and collectivistic societies may differ in how they perceive the importance of work in providing social status, collective purpose and financial benefits. Thus, culture

may also act as a moderator of the effect of unemployment on mental health.

Singapore, a city state in Southeast Asia, has a highly developed global economy with a per capita gross domestic product higher than most developed countries and a low unemployment rate. The country's labour force participation has remained steady between 2015 and 2019, ranging from 67.7% to 68.3%. According to the Ministry of Manpower statistics, Singapore's unemployment rate from 2015 to 2020 varied between 1.9 and 2.3%.<sup>9</sup> Given the impact of mental disorders on labour force participation and workforce productivity, understanding the association between mental disorders and employment is crucial.<sup>10</sup> Specifically, awareness of this association can lead to better workplace mental health initiatives, including early recognition and treatment of mental disorders of those in the workforce, and implementation of programmes to ensure vocational support for those with mental disorders to gain or return to employment.

Few studies have examined the association between unemployment and mental disorders in Singapore. The national epidemiological Singapore Mental Health Study (SMHS) conducted in 2010 found that among the employed, 2.3% had a 12-month prevalence of at least one mental disorder, while 5.3% of the unemployed had at least one mental disorder (excludes those with mental illness and comorbid physical conditions).<sup>11</sup> The authors found significantly higher rates of major depressive disorder (MDD), dysthymia, generalised anxiety disorder (GAD), and obsessive-compulsive disorder (OCD) among those unemployed compared to the economically inactive and employed groups.

A second nationwide psychiatric epidemiological survey was initiated in 2016 (SMHS 2016). Using data from the SMHS 2016 study, the current research aims to examine (1) the employment rate in Singapore among those with and without a 12-month mental disorder, (2) the socio-demographic correlates of unemployment, and (3) the association of unemployment with 12-month mental disorders and chronic physical conditions.

## METHODS

### Sample

Singapore residents (citizens and permanent residents) aged 18 years and above were invited to participate in the study. A probability sample was randomly selected using a disproportionate stratified sampling.



The 3 main ethnic groups (Chinese, Malay and Indian) were sampled in an equivalent proportion of about 30% each. Residents who were incapable of doing an interview due to severe physical or mental health conditions, language barriers, living outside the country, institutionalisation or hospitalisation at the time of the survey, and those who were not contactable due to incomplete or incorrect address were excluded from the study. In all, 6,126 participants completed the survey, and the response rate among the eligible adults was 69.5%. The study has been described in greater detail in an earlier article.<sup>12</sup>

## Measures

### *Employment status*

Employment status was collected using structured questions. Participants were asked, “What is your current employment situation? Are you working now for pay, self-employed, looking for work, disabled, temporarily laid off, retired, a home-maker, a full-time or part-time student or, have never worked?”. Based on the replies to this and subsequent questions, participants were classified as “employed” (including those working full or part-time, self-employed, and working for an organisation), “unemployed” (including those looking for work/unemployed, temporarily laid off, and never worked), and “economically inactive” (comprising home-makers, students and retirees).

### *World Health Organization Composite International Diagnostic Interview*

Mental disorders were assessed by the Composite International Diagnostic Interview version 3.0 (CIDI 3.0),<sup>13</sup> which ascertains lifetime and 12-month prevalence of mental disorders through the measurement of symptoms and their impact on day-to-day activities. This instrument generates a diagnosis of mental disorders according to the criteria of the 10th Edition of the International Classification of Diseases (ICD-10),<sup>14</sup> and the 4th Edition of the Diagnostic and Statistical Manual (DSM-IV).<sup>15</sup> The mental disorders assessed in the SMHS 2016 were MDD, bipolar disorder, GAD, OCD, alcohol abuse and alcohol dependence. A modified version of the CIDI checklist of chronic medical disorders was used to check if participants had ever been diagnosed with any chronic physical conditions. Participants were asked to report if a doctor had ever diagnosed them with any of the 18 chronic diseases that are considered prevalent in Singapore’s population. Those who responded positively were then asked if

they had received treatment for the condition in the past year. If they had received the treatment, they were classified as having a 12-month physical condition.

### *Severity of disorder*

The Sheehan’s Disability Scale (SDS)<sup>16</sup> administered in each diagnostic section of the CIDI was used to determine the severity of the mental disorder. The scale assesses the level of interference caused by the worst period of symptoms in the past 12 months in 4 life domains, namely, home management, ability to work, ability to form and maintain close relationships with other people, and social life. Respondents received an overall assessment of “severe” if they rated at least 3 domains as severe. Those who reported at least 2 domains as mild received an overall assessment of “mild”. All others were classified as having a “moderate” disorder.<sup>17</sup>

### *SF-12*

The SF-12 is a multidimensional, self-reported instrument that assesses the impact of health on an individual’s everyday life. It is a shorter alternative to the 36-item Short-Form Health Survey (SF-36).<sup>18</sup> It covers the same eight domains of health outcomes as SF-36: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The subscales physical functioning, role physical, bodily pain and general health form the physical component summary (PCS) score, while the subscales vitality, social functioning, role emotional and mental health comprise the mental component summary (MCS) score. The PCS and MCS were calculated using a scoring algorithm provided by its developers and were used to assess the health-related quality of life (HRQOL) in this study.

### *Socio-demographic and other information*

Other socio-demographic factors such as age, gender, ethnicity, marital status, highest educational level achieved, monthly household income, body mass index (BMI) and smoking status were self-reported.

### *Ethical approval*

The study was approved by the relevant institutional ethics committee (National Healthcare Group, Domain Specific Review Board). Written informed consent was obtained from all participants and parents/guardians of participants between 18 and 20 years of age prior to the survey.

## Statistical analysis

All analyses were conducted with Stata version 15 (StataCorp LLC, College Station, US). Both frequency and survey-weighted percentages were provided for descriptive statistics. Logistic regression analyses were conducted (employed versus unemployed, and economically inactive versus unemployed) to determine significant socio-demographic correlates of employment. Finally, linear regression was conducted to examine the association of employment with the physical and mental component scores of the SF-12. All regression analyses were weighted using survey weights to account for complex survey design.

## RESULTS

### Employment rate of those with 12-month mental disorder and by disorder severity

Table 1 presents the nationally representative employment rate of working-age adults by mental health status and severity. Employment was 71.8% among people without a 12-month mental disorder versus 74.4% among people with a mental disorder. The unemployment rate was twice as high among those with a 12-month mental disorder (11.5%) than those without (4.8%). The proportion of employed individuals fell sharply, while that of unemployed increased in the more severe categories of mental disorders as assessed by SDS.

### Socio-demographic characteristics, mental disorders and chronic physical conditions by employment status

Of the 6,125 participants in the study, 4,055 (72%) were employed, 1,716 (22.7%) were economically inactive, and 354 (5.3%) were unemployed (Table 2).

Among those who were employed, 93.3% did not have a 12-month mental disorder, while 5.3% had one mental disorder, and 1.4% had 2 or more mental disorders assessed in the 12-month period. Among those who were unemployed, 85.8% did not

have any 12-month mental disorder, while 11.8% had one mental disorder assessed in the study, and 2.4% had 2 or more mental disorders. Those who were unemployed had a higher prevalence of the 3 most prevalent chronic physical conditions (15.6%, 15.3% and 10.3% of hypertension, hyperlipidaemia and diabetes, respectively) as compared to those who were employed (14.5%, 11.3% and 5.7% of hypertension, hyperlipidaemia and diabetes, respectively). The unemployed group had a higher prevalence of MDD, bipolar disorder, GAD and alcohol abuse than the employed and economically inactive group (Table 3).

### Associations of socio-demographic factors, mental disorders and chronic physical conditions with employment

Table 4 provides estimates from the logistic regression analyses that identified variables associated with employment status. Being married (versus unmarried) and a higher household income were significantly associated with a higher likelihood of being employed than unemployed, while the presence of one 12-month mental disorder was significantly associated with a lower likelihood of being employed.

### Unemployment and health-related quality of life

Being unemployed was significantly associated with lower PCS and MCS as compared to those employed and economically inactive, even after controlling for confounders such as age, gender, ethnicity, marital status, household income, education, smoking status, BMI, and presence of 12-month mental disorder and chronic physical conditions (Table 5).

## DISCUSSION

In a nationally representative sample of adults in Singapore, people with a 12-month mental disorder were more often unemployed than adults without a mental illness. Unemployment was associated with the

Table 1. Employment status of participants by presence and severity of 12-month mental disorder as assessed by the Sheehan's Disability Scale

Total participants N=6126	No mental disorder in past 12-months (%) <sup>a</sup> n= 5723 (93.5)	Any 12-month mental disorder (%) <sup>a</sup> n=403 (6.5)	Mild mental disorder (%) <sup>a</sup> n=231 (63.2)	Moderate mental disorder (%) <sup>a</sup> n=128 (34.6)	Severe mental disorder (%) <sup>a</sup> n=9 (2.2)
Employment status	n (%)				
Employed	3766 (71.8)	289 (74.4)	164 (79.1)	93 (69.3)	4 (19.5)
Unemployed	309 (4.8)	45 (11.5)	24 (7.8)	14 (11.7)	2 (71.3)
Economically inactive	1647 (23.3)	69 (14.1)	43 (13.1)	21 (19.0)	3 (9.2)

<sup>a</sup> Weighted percentage

Table 2. Socio-demographic and clinical characteristics of respondents by employment status

Socio-demographic and clinical variables	Employed (n=4055)		Economically inactive (n=1716)		Unemployed (n=354)		P value	
	n	Weighted percentage	n	Weighted percentage	n	Weighted percentage		
Age	18–34	1228	30.8%	370	28.7%	109	33.0%	<0.001
	35–49	1254	35.3%	177	12.4%	64	26.1%	
	50–64	1190	28.0%	323	22.5%	113	29.7%	
	65 and above	383	5.8%	846	36.5%	68	11.3%	
Sex	Male	2322	54.6%	557	32.9%	188	53.1%	<0.001
	Female	1733	45.4%	1159	67.1%	166	46.9%	
Ethnicity	Chinese	1226	75.9%	467	75.8%	89	72.6%	0.23
	Malay	1259	12.1%	600	12.8%	131	15.2%	
	Indian	1236	8.7%	497	8.6%	110	9.7%	
	Others	334	3.3%	152	2.8%	24	2.5%	
Marital status	Never married	1050	30.1%	349	29.3%	145	50.3%	<0.001
	Married	2647	62.3%	1061	58.4%	134	30.6%	
	Divorced/separated	256	5.7%	53	2.4%	34	9.9%	
	Widowed	102	1.8%	253	9.9%	41	9.2%	
Household income (SGD)	Below 2,000	527	10.0%	496	25.2%	124	36.2%	<0.001
	2,000–3,999	935	18.3%	314	17.4%	82	16.8%	
	4,000–5,999	851	21.1%	224	14.5%	38	14.2%	
	6,000–9,999	786	22.4%	185	13.1%	32	9.8%	
Education	10,000 and above	703	21.6%	144	10.5%	14	7.1%	
	Refused/Don't know	253	6.7%	353	19.3%	64	16.0%	
	Primary and below	514	12.0%	572	28.5%	101	22.3%	<0.001
	Secondary	978	20.1%	571	31.8%	99	25.4%	

BMI: body mass index; BP: blood pressure; ITE: Institute of Technical Education; Pre-U: pre-university; SGD: Singapore Dollars

Table 2. Socio-demographic and clinical characteristics of respondents by employment status (Cont'd)

Socio-demographic and clinical variables	Employed (n=4055)		Economically inactive (n=1716)		Unemployed (n=354)		P value
	n	Weighted percentage	n	Weighted percentage	n	Weighted percentage	
Pre-U/Junior college	166	4.7%	129	10.6%	9	4.1%	
Vocational institute/ITE	410	7.3%	68	3.0%	30	6.3%	
Diploma	811	21.0%	158	13.1%	54	16.4%	
University	1176	34.9%	218	13.0%	61	25.5%	
Smoking status							
Current smoker	942	18.6%	143	6.5%	91	22.3%	<0.001
Ex-smoker	503	10.7%	203	10.2%	44	9.0%	
Never smoked	2604	70.5%	1361	83.2%	215	67.2%	
BMI International							
Underweight <18.5	177	5.4%	105	8.5%	22	9.9%	0.01
Normal ≥18.5 and <25	1794	53.0%	739	53.5%	146	48.8%	
Overweight ≥25 and <27.5	1312	28.4%	508	25.7%	102	23.2%	
Obese ≥30	707	11.5%	309	10.0%	61	12.7%	
Missing	65	1.7%	55	2.3%	23	5.4%	
Chronic conditions in past 12 months							
None	2709	71.6%	762	54.2%	200	64.6%	<0.001
1 chronic condition	707	16.1%	334	18.2%	56	16.1%	
2 or more chronic conditions	635	12.3%	615	27.5%	95	18.3%	
Mental illness							
None	3766	93.3%	1647	96.0%	309	85.8%	<0.001
1 mental illness	225	5.3%	58	3.4%	38	11.8%	
2 or more mental illnesses	64	1.4%	11	0.6%	7	2.4%	
Physical conditions in past 12 months							
Diabetes/High blood sugar	375	5.7%	354	14.7%	63	10.3%	<0.001
High BP/hypertension	657	14.5%	613	29.9%	82	15.6%	<0.001
Back problem	129	3.1%	63	2.9%	10	3.9%	0.81
Migraine headaches	145	3.2%	29	1.7%	10	1.9%	0.05
Hyperlipidaemia or high cholesterol	537	11.3%	521	25.2%	73	15.3%	<0.001

BMI: body mass index; BP: blood pressure; ITE: Institute of Technical Education; Pre-U: pre-university; SGD: Singapore Dollars

Table 3. Prevalence of 12-month mental disorders by employment status

	Employed n (%)	Unemployed n (%)	Economically Inactive n (%)	<i>P</i> value
MDD	104 (2.3)	16 (5.7)	21 (1.6)	0.01
Dysthymia	16 (0.2)	1 (0.2)	4 (0.2)	0.92
Bipolar disorder	51 (0.9)	7 (3.8)	6 (0.2)	<0.001
GAD	38 (0.9)	8 (2.4)	7 (0.3)	0.03
OCD	120 (3.2)	13 (3.1)	36 (2.0)	0.26
Alcohol abuse	24 (0.6)	5 (2.1)	4 (0.1)	0.004
Alcohol dependence	11 (0.2)	3 (0.3)	4 (0.3)	0.76

GAD: generalised anxiety disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder

severity of the mental disorder as assessed by SDS. Our study demonstrated a negative association of unemployment with mental health and those who were unemployed, being 2.5 times more likely to have a past 12-month mental disorder than those employed. These results are similar to studies conducted elsewhere.<sup>19-21</sup> Using data from the Australian National Survey of mental health and well-being of adults, Comino et al. similarly found that unemployed adults were 2.5 times more likely to have anxiety and/or affective disorders.<sup>19</sup> Data from the Eurobarometer surveys of 2006 and 2010 found that unemployment rates were higher among people with mental health problems in both surveys.<sup>21</sup> These results suggest that employment is important and relevant to mental health across cultures. Industrialised societies are likely to gain several benefits from work, while specific benefits such as financial remuneration, social support and status may vary across cultures and needs further research.<sup>8</sup>

Comparing the data across the 2 nationwide mental health surveys in Singapore, the prevalence of unemployment increased from 4.5% in the earlier 2010 study<sup>11</sup> to 5.3% in the current study. While both studies employed the same methodology, the prevalence of 12-month mental disorders in the population increased from 4.4% to 6.5%. This is reflected in the increased prevalence of mental disorders in both the employed and unemployed groups in the present study (SMHS 2016) compared to the earlier study (SMHS 2010). In SMHS 2016, 6.7% of the employed group had at least one 12-month mental disorder, versus 4.7% (including those with comorbid medical conditions) in SMHS 2010, while among those who were unemployed, 14.2% had at least one mental disorder assessed in the current study compared to 10.4 % in SMHS 2010. However,

the increase seems to be larger in the unemployed group (3.8%) than in the employed (2.0%) in terms of absolute difference in prevalence.

Interestingly, MDD was the most prevalent 12-month mental disorder in the unemployed group, while OCD was most prevalent in the employed. Other studies have found a similar association between depression and employment. A study assessing the work outcomes of employees with depression found a higher prevalence of unemployment in people with MDD at 6 months than the control group and the group with rheumatoid arthritis.<sup>22</sup> Studies suggest that depression is associated with cognitive impairment and health problems, which in turn may adversely affect job performance, resulting in unemployment.<sup>23,24</sup> However, this being a cross-sectional study, it is difficult to draw conclusions about causality. Given that depression is the most prevalent mental disorder in Singapore, the association with unemployment is even more concerning.<sup>11,13</sup> The results provide further evidence for the need to promote workplace mental health, which encompasses screening for mental distress and initiation of early antidepressant treatment, reducing functional impairments, and supporting continual employment.<sup>25</sup> However, we are unable to explain the higher prevalence of OCD in the employed group.

The association between the severity of mental disorders and unemployment could be due to several reasons. People with more serious symptoms find that both the symptoms and the medications to treat the symptoms affect their ability to work.<sup>6</sup> Employers can perceive the impact of the severity in the form of relapse and decline in their performance and functioning.<sup>26</sup> Lastly, people with more severe mental illness may be unaware of or unable to access job-support schemes.



Table 4. Association between socio-demographic factors, mental disorders and chronic physical conditions with employment status

Sociodemographic and clinical variables	Employed vs Unemployed			Economically Inactive vs Unemployed		
	Odds Ratio <sup>a</sup>	95% CI	P value	Odds Ratio <sup>a</sup>	95% CI	P value
<b>Age</b>						
18–34	Ref			Ref		
35–49	0.80	0.45–1.43	0.45	0.06	0.02–0.17	<0.001
50–64	0.88	0.46–1.70	0.71	0.12	0.04–0.34	<0.001
65 and above	1.04	0.43–2.54	0.93	1.75	0.54–5.64	0.35
<b>Sex</b>						
Male	Ref			Ref		
Female	1.15	0.76–1.74	0.51	3.32	1.88–5.83	<0.001
<b>Ethnic group</b>						
Chinese	Ref			Ref		
Malay	0.97	0.62–1.51	0.89	1.09	0.67–1.77	0.73
Indian	0.76	0.51–1.11	0.15	0.93	0.58–1.49	0.77
Others	0.78	0.41–1.48	0.45	1.03	0.50–2.15	0.93
<b>Marital status</b>						
Never married	Ref			Ref		
Married	3.04	1.83–5.03	<0.001	9.64	3.64–25.55	<0.001
Divorced/separated	1.70	0.85–3.39	0.13	0.81	0.27–2.42	0.70
Widowed	0.52	0.24–1.16	0.11	0.56	0.19–1.71	0.31
<b>Monthly household income (SGD)</b>						
Below 2000	Ref			Ref		
2000–3999	3.58	2.09–6.11	<0.001	1.76	1.00–3.08	0.05
4000–5999	4.19	2.22–7.92	<0.001	1.25	0.61–2.55	0.54
6000–9999	7.97	3.52–18.03	<0.001	2.94	1.31–6.62	0.01
10,000 and above	9.93	4.11–24.01	<0.001	3.72	1.61–8.57	0.002
<b>Education</b>						

<sup>a</sup> Logistic regression

BMI: body mass index; CI: confidence interval; ITE: Institute of Technical Education; Pre-U: pre-university; SGD: Singapore Dollars; WHO: World Health Organization

Table 4. Association between socio-demographic factors, mental disorders and chronic physical conditions with employment status (Cont'd)

Sociodemographic and clinical variables	Employed vs Unemployed			Economically Inactive vs Unemployed		
	Odds Ratio <sup>a</sup>	95% CI	P value	Odds Ratio <sup>a</sup>	95% CI	P value
University	Ref			Ref		
Primary and below	1.25	0.51–3.04	0.62	2.02	0.89–4.58	0.09
Secondary	1.42	0.66–3.05	0.37	4.17	1.88–9.27	<0.001
Pre-U/Junior college	1.65	0.54–5.05	0.38	8.45	2.48–28.73	0.001
Vocational institute/ITE	1.80	0.78–4.15	0.17	2.85	1.10–7.38	0.03
Diploma	1.55	0.80–3.02	0.20	2.36	1.04–5.35	0.04
<b>Smoking status</b>						
Never smoked	Ref			Ref		
Current smoker	1.16	0.69–1.94	0.58	0.37	0.20–0.72	0.003
Ex-smoker	1.23	0.66–2.27	0.52	1.18	0.51–2.74	0.69
<b>BMI (WHO guidelines)</b>						
Normal Range $\geq 18.5$ and $<25$	Ref			Ref		
Underweight $<18.5$	0.61	0.29–1.29	0.20	1.50	0.62–3.61	0.37
Overweight $\geq 25$ and $<30$	1.08	0.68–1.72	0.73	1.33	0.77–2.29	0.31
Obese $\geq 30$	1.02	0.56–1.84	0.95	0.95	0.53–1.73	0.88
<b>Chronic physical conditions</b>						
No chronic conditions	Ref			Ref		
1 chronic condition	0.92	0.53–1.60	0.77	1.07	0.58–1.97	0.84
2 or more chronic conditions	0.86	0.49–1.49	0.58	1.16	0.60–2.22	0.66
<b>Mental illness</b>						
No mental illness	Ref			Ref		
1 mental illness	0.40	0.22–0.75	0.004	0.25	0.10–0.58	0.001
Two or more mental illnesses	0.68	0.18–2.52	0.56	0.16	0.04–0.67	0.01

<sup>a</sup> Logistic regression

BMI: body mass index; CI: confidence interval; ITE: Institute of Technical Education; Pre-U: pre-university; SGD: Singapore Dollars; WHO: World Health Organization

Table 5. Associations of physical and mental component scores with employment status

Variable	Physical component score			Mental component score		
	B	95% CI	<i>P</i> value <sup>a</sup>	B	95% CI	<i>P</i> value <sup>a</sup>
Employment status						
Economically inactive vs Employed	-0.35	-0.91 to 0.20	0.22	0.21	-0.40 to 0.82	0.49
Unemployed vs Employed	-1.98	-3.33 to -0.64	0.004	-1.75	-3.21 to -0.28	0.02
Unemployed vs Economically inactive	-1.63	-3.06 to -0.20	0.03	-1.96	-3.50 to -0.41	0.01

B: unstandardised regression coefficient; CI: confidence interval

<sup>a</sup> Linear regression adjusted for age, sex, ethnicity, marital status, household income, education, smoking status, body mass index, and presence of 12-month mental and physical illnesses

Unemployment in the current study was associated with marital status and household income. Those who were never married and those with a household income of less than SGD2,000 were more likely to be unemployed. Unemployment restricts the ability to set up an independent household and results in uncertainty about financial resources in the future.<sup>27</sup> Thus, unemployment thwarts or delays couple formation. However, research also suggests that unemployment and resultant stresses lead to the breakdown of marriages,<sup>28</sup> which was not observed in our study. People who become unemployed would experience a decrease in their income due to the loss of wages. Thus, the lower household income is an inevitable and expected consequence of unemployment.

Among those who were unemployed, the prevalence of hypertension, hyperlipidaemia and diabetes was higher than those employed. Analyses of data from the US Health and Retirement Survey (HRS) found that workers who had involuntarily lost their job had a more than 2-fold increase in the risk of myocardial infarction and stroke compared to those who continued to work.<sup>29</sup> Using data from the HRS, Dupre et al. similarly found that the risk of myocardial infarction was most significant in the first year after job loss.<sup>30</sup> Increased myocardial infarction risk was also associated with a cumulative number of job losses and cumulative time unemployed. Data from the Northern Finland Birth Cohort found that high exposure to unemployment (defined as more than one year of exposure to unemployment in the past 3 years) may predispose middle-aged men to type 2 diabetes.<sup>31</sup> Several factors could explain this association between unemployment and poor physical health. Financial insecurity and other stressors following a job loss may lead to adverse health behaviours like consuming excessive alcohol and smoking.<sup>32</sup> The lack of access to workplace benefits such as workplace wellness

programmes and health insurance,<sup>33,34</sup> and symptoms of depression and anxiety following job loss may affect the pursuit of healthy lifestyles and increase the risk of chronic conditions.<sup>35</sup> Despite the literature suggesting an association between job loss and physical ill health, it must be acknowledged that the causal relationship remains undetermined. The issue of selection bias, that is, whether job loss leads to ill health or whether individuals who have poor physical health are more likely to lose or retire from their jobs, cannot be determined from our study. On the other hand, the prevalence of the 3 most prevalent chronic physical conditions was lower among those unemployed than the economically inactive group. In this study, those who were aged 65 years and above comprised the majority of the economically inactive group and it is well established that the prevalence of hypertension, hyperlipidaemia and diabetes increases with age.<sup>36,37</sup>

Surprisingly few studies have examined the impact of unemployment on HRQOL. Our research found that unemployment was significantly associated with poorer physical and mental HRQOL even after adjusting for several possible confounders. A cross-sectional study in Sweden, using the EuroQol-5 Dimension (EQ-5D) questionnaire, similarly found that unemployment was strongly related to a poorer health-related quality of life.<sup>38</sup> A cross-sectional study from India using data from the Centre for Cardiometabolic Risk Reduction in South Asia also reported lower health status as determined by EQ-5D among the unemployed (vs employed) respondents.<sup>39</sup> The negative association persisted despite controlling for significant socio-demographic factors, physical and mental conditions. It is well established that work contributes to an individual's identity and social status.<sup>40</sup> It also gives an individual a sense of purpose and self-worth.<sup>6</sup> Unemployment leads to a loss of all these gains as well as

social support. Thus, unemployment would affect many of the domains of HRQOL that may not be completely accounted for by a physical condition or mental disorder.

Several limitations of the study must be taken into consideration. We did not collect any data on why participants became unemployed (e.g. voluntarily or through compulsory redundancies), and these different reasons could have different implications for mental health. The relatively low prevalence of 12-month mental disorders in our sample prevented us from examining the association of unemployment with individual disorders. The sample had few people who met the criteria for severe mental disorder as assessed by the SDS. While it is possible that the prevalence of severe impairment of functioning is low in a community sample, it is also possible that those with severe impairment were unable to participate in this study. This could have resulted in a lower prevalence of mental disorders in the population, especially among the unemployed. The study's cross-sectional nature does not permit causal interpretation of the association between mental illness and employment outcomes. Lastly, data on chronic physical conditions was based on self-report, and it may not be accurate.

The COVID-19 pandemic has resulted in economic activities plummeting across nations both due to lockdowns and changing consumer behaviour.<sup>41</sup> Economists have forecast a recession across many countries,<sup>42</sup> and the resulting unemployment can lead to significant harm to human health if not managed correctly. Clinicians should remain vigilant and consider the loss of employment a potential risk factor for adverse physical and mental health changes. A focus on holistic recovery that includes augmentation of medications with interventions like cognitive behavioural therapy, problem-solving therapy, and work-directed interventions can facilitate re-entry into the workforce<sup>43</sup> and improve health outcomes. Policymakers should be aware of the risks of job loss and consider economic reforms such as job guarantee and universal basic income schemes,<sup>44,45</sup> which can be adopted and implemented to ensure worker well-being.

#### Acknowledgement

*This study was funded by the Ministry of Health, Singapore and Temasek Foundation, Singapore. The funders had no role in the study design or analysis of the study.*

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## Prevalence of thyroid malignancy and hormonal dysfunction following radiation exposure in childhood

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### ABSTRACT

**Introduction:** Childhood radiation exposure is a known risk factor for thyroid malignancy and dysfunction. However, local data are limited and there is no consensus on the modality and frequency of screening in this high-risk group.

**Methods:** Retrospective analysis study evaluating patients with childhood radiation exposure in 2006–2016 and minimum of 1-year follow-up.

**Results:** Of the 132 childhood cancer survivors in the study, thyroid malignancy was detected in 2 cases (1.5%) and thyroid nodules in 13 (9.8%). The earliest thyroid malignancy was detected 5 years post-radiotherapy via ultrasound. Of the 84 patients who had screening thyroid function test, 26 (31.0%) were detected with abnormal test results post-radiation, majority being subclinical hypothyroidism.

**Conclusion:** Regular screening via clinical examination for thyroid nodules should be performed at least annually. Where feasible and if resources permit, consideration should be given to using ultrasound for thyroid nodule(s) and malignancy screening at 5 years post-radiation therapy. Screening for thyroid dysfunction can be considered from 6–12 months post-radiotherapy.

Ann Acad Med Singap 2021;50:402-10

**Keywords:** Childhood post-radiotherapy complications, post-radiotherapy secondary malignancies, thyroid cancer, thyroid dysfunction, thyroid nodules

### INTRODUCTION

The incidence of thyroid cancer has been steadily increasing worldwide. Childhood radiation exposure is a known risk factor for thyroid malignancy. However, data on the incidence of thyroid cancer in this high-risk cohort in Singapore are limited. Thus, we assessed data from patients treated in our institution with a history of childhood radiation exposure over a 10-year period to ascertain the prevalence of thyroid nodules and malignancy, as well as the time interval to the development of thyroid nodules/malignancy and thyroid disease.

### Background

Multiple previous studies have shown that childhood radiation exposure is a risk factor for the development of thyroid malignancy with a summary excess relative risk of 7.7 for every 100 centigray (cGy) of radiation, up to 3,000cGy.<sup>1-3,17</sup> However, there is a lack of high grade evidence to indicate if early detection of thyroid malignancy improves the quality of life or event-free survival rates in these patients. Hence, there is currently no strong recommendations in the 2015 American Thyroid Association (ATA) regarding thyroid nodule/cancer screening in this high-risk group.<sup>4</sup> The current

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## CLINICAL IMPACT

### What is New

- This retrospective study highlights the prevalence of thyroid malignancy and dysfunction in a high-risk group of childhood cancer survivors.
- The study describes the earliest time to development of post-radiation exposure thyroid malignancy or thyroid dysfunction.

### Clinical Implications

- The data in this study can assist in the development of guidelines for the screening and early detection of thyroid malignancy and dysfunction post-radiation exposure in childhood in Singapore.
- This study highlights the importance of regular screening for potential thyroid malignancy or hormonal dysfunction post-radiation exposure in childhood.
- Ultrasound is recommended over palpation to screen patients for thyroid malignancy.

suggestion is for annual clinical examination and the panel “can neither recommend for nor against routine screening ultrasound until more data become available”.<sup>4</sup> The 2016 American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE) and Associazione Medici Endocrinologi (AME) have recommended more aggressive measures of performing thyroid ultrasound in a patient with risk factors even when the results of palpation are normal.<sup>5</sup> They have listed a history of head and neck irradiation as a feature suggesting increased risk of malignant potential.<sup>5</sup> However, they have also not given a latency time post-radiotherapy to start screening this high-risk group, nor a recommendation regarding the interval frequency to perform ultrasound.

Local data on the incidence of thyroid malignancy in childhood cancer survivors with previous radiation exposure are non-existent. Thus, we assessed data from this high-risk population over a 10-year period (2006–2016) to ascertain the incidence of thyroid nodules and malignancy, the time interval to the development of thyroid nodules or malignancy, and the development of hypothyroidism after radiation exposure.

## METHODS

### Subjects

After obtaining approval from our institutional review board, our team conducted a retrospective analysis of the medical records of 212 patients who received radiotherapy below the age of 20 in 2006–2016. Clinical details such as age, sex, radiation dosages, past history of malignancy, family history of thyroid malignancy or cancer syndromes, treatment, histology findings and image reviewing were collected.

For inclusion in the study, patients had to have undergone radiation exposure for a childhood primary malignancy with a minimum follow-up duration of at least 1 year post-radiation treatment. Of the 212 patients, 132 patients were included and 80 did not meet the study requirement. Of the excluded patients, 68% were foreigners who were lost to follow-up. The remaining patients had not been followed up for 1 year yet at the time of data collection.

### Clinical follow-up

Currently, there are no clear national guidelines in Singapore for the surveillance of thyroid nodules or thyroid dysfunction in patients who have undergone radiation exposure. Patients were reviewed by their primary treating physicians for underlying malignancy, and surveillance imaging was ordered as per routine clinical guideline specific for the underlying malignancy. In our institution, clinical examination of the thyroid gland was done annually at clinical review where possible. Screening neck ultrasound was performed 2 years post-radiation exposure and follow-up neck ultrasound was conducted every 2 years or earlier if thyroid nodule(s) were detected. Screening neck ultrasound was done regardless of presence or absence of palpable nodules. If any thyroid nodules were detected, the following features were reported including size, composition, echogenicity, shape, margin, presence of echogenic foci and internal vascularity. Thyroid Imaging Reporting and Data System (TIRADs) score was not reported. Screening thyroid function tests (TFTs) were left to the discretion of the primary physician. From 2016, asymptomatic patients had screening TFT 1 year post-radiation and annually thereafter. TFTs were performed earlier in patients who exhibit symptoms or signs suggestive of thyroid dysfunction. Repeat TFT is performed during the next follow-up if an abnormal TFT is detected, depending on how abnormal the initial results were.

## Clinical outcomes

We aim to assess the adverse clinical outcome of thyroid malignancy arising from childhood radiation exposure. As some of the patients with thyroid nodules may have occult thyroid malignancy, we have included these patients in the data analysis. Records were reviewed until 31 December 2018. We reviewed available imaging modalities including ultrasound, computer tomography, X-ray, positron emission tomography and magnetic resonance imaging for thyroid nodules. Medical records were reviewed for thyroid nodule evaluation and malignancy treatment.

Fine needle aspiration was performed if the thyroid nodule(s) had the following characteristics, including size more than 1cm, irregular margins, microcalcifications, abnormal cervical lymph nodes, taller than wide, extrathyroidal extension or diffusely infiltrative enlargement of the thyroid lobe. For patients with Bethesda 3–4 cytology results, we followed the 2015 ATA recommendation of hemithyroidectomy in view of the increased probability of malignancy in children.<sup>4</sup> In patients with non-diagnostic cytology results, we would repeat fine needle aspiration in 3 months.

Treatment response for thyroid cancer was in accordance to the 2015 ATA guidelines.

All TFTs were processed at our institution laboratory using Beckman DXI 680 assay. TFTs measuring the free thyroxine levels (T4) and thyroid-stimulating hormone (TSH) done during the study period were reviewed and categorised in the following subgroups: (1) primary hypothyroidism (low free T4<8.0pmol/L, elevated TSH>4.5mIU/L), (2) central hypothyroidism (low free T4<8.0pmol/L, inappropriately normal 0.45–4.5mIU/L or low TSH<0.45mIU/L), and (3) Sub-clinical hypothyroidism (normal free T4 8.0–16.0pmol/L, high TSH>4.5mIU/L).

## Statistical methods

Continuous data were presented as median and ranges for each variable. The data were not normally distributed.

Table 1. Characteristics of study patients at baseline

Patients	N=132
Female, n (%)	47 (36)
Male, n (%)	85 (64)
Age when first received radiotherapy (years), median (range)	13.5 (1.4–19.9)
Follow-up duration (years), median (range)	4.62 (1.02–12.15)
Dose in cGy, median (range)	2250 (200–6996)
Prevalence of thyroid cancer, n (%)	2 (1.5)
Prevalence of thyroid nodules, n (%)	13 (9.8)

The chi-square test was used to compare proportions, and Mann-Whitney U Test was used to compare median. Analysis was performed using SPSS Statistics software version 18.0.1 (IBM, Armonk, US). A value of  $P \leq 0.05$  was considered statistically significant.

## RESULTS

### Baseline clinicopathological characteristics

Patients were predominantly male (64%), with a median follow-up duration of 4.62 years (range 1.02–12.15 years) (Table 1).

Most patients had total body irradiation/total nodal irradiation/craniospinal irradiation (44.0%); 31.8% had radiation to the head and neck region; 10.6% had radiation to the thorax; and 8.3% had radiation to the abdomen/pelvis (Table 2).

Of the 132 patients, 71 (53.8%) had a primary haematological malignancy; 22.0% had primary central nervous system malignancy; and 16.6% had primary musculoskeletal malignancy. None of the patients had a family history of thyroid malignancy nor familial cancer syndromes such as Li-Fraumeni syndrome or Cowden syndrome.

The 80 patients who were excluded from the study had radiotherapy with a median dose of 2,130cGy (range

Table 2. Distribution of radiation site

Radiation site	n	%
Total body irradiation/ total nodal irradiation/ craniospinal irradiation	58	44.0%
Head and neck/ central nervous system	42	31.8%
Thorax	14	10.6%
Abdomen/ pelvis	11	8.3%
Extremity	7	5.3%

200–5,940cGy), comparable to the 2,250cGy dose (range 200–6,996cGy) ( $P=0.881$ ) received by the 132 included patients. There was no significant difference in the age of the 132 patients in the study (median age 13.5 years, 1.4–19.9 years) compared to the 80 excluded patients (median age 11.2 years, 0.6–19.4 years) ( $P=0.057$ ). Of the excluded subjects, 33.8% had total body irradiation/total nodal irradiation/craniospinal irradiation, 31.2% had head/neck region radiation, 13.8% had thorax radiation, 8.7% had radiation to abdomen/pelvis and the remainder 12.5% had radiation to the extremities. We believed that the conclusions drawn from the participants included in study can be applicable to patients with radiation exposure for the treatment of childhood malignancy.

### Clinical outcome during follow-up

In the 132 childhood cancer survivors in the study, the incidence of thyroid nodules is 9.8% (13/132 cases) and incidence of thyroid malignancy is 1.5% (2/132 cases). If we only screened patients who received radiotherapy to the total body, head and neck or thorax region, the incidence of thyroid nodules and malignancy

would be higher at 11.4% (13/114 cases) and 1.75% (2/114 cases), respectively.

Table 3 provides the details of the 2 patients diagnosed with papillary thyroid cancer (PTC). Of note, both patients had acute lymphoid leukaemia and underwent bone marrow transplant with total body irradiation.

Table 4 shows a comparison of patients who developed thyroid nodules or malignancy compared to those who did not.

Fig. 1 indicates the proportion of thyroid dysfunction. Of the 132 patients included in the study, 13 patients had thyroid dysfunction prior to radiotherapy. Post-radiotherapy TFT in 6 of these patients had normalised, while 7 patients continued to have abnormalities—6 with central hypothyroidism and 1 with subclinical hypothyroidism. Five patients with central hypothyroidism had primary brain malignancy.

Of the remaining 119 patients with normal thyroid hormone status prior to radiation therapy, 84 had screening TFT. Twenty-six of these screened (31.0%) were detected with abnormal test results post-radiation, mainly subclinical hypothyroidism (24/26), whereas

Table 3. Details of patients with thyroid malignancy

	Patient 1	Patient 2
Sex	Male	Male
Primary malignancy	Acute lymphoid leukaemia	Acute lymphoid leukaemia
Site of radiation	Total body irradiation	Total body irradiation
Total dose of radiation (cGy)	1200	1200
Age when received radiotherapy (years old)	11	5
Latency period from radiotherapy to diagnosis of thyroid cancer (years)	9	5
Type of thyroid cancer	Papillary thyroid cancer	Papillary thyroid cancer
Indication for ultrasound thyroid	Tuberculosis lymphadenitis	Surveillance
Ultrasound findings	1.6x1.2x1.0cm isoechoic thyroid nodule with irregular margins and microcalcifications. Bilateral cervical lymphadenopathy	1.9x1.6x1.3cm heterogenous nodule with irregular margins
FNA cytology	Atypia Follicular Lesion of Undetermined Significance (Bethesda Class III)	Suspicious for PTC (Bethesda V)
Histology	Multifocal PTC with largest 1.5cm with extra-thyroidal extension and vascular invasion	Multifocal PTC with lymphovascular invasion and extrathyroidal extension
TNM staging	Stage 1 T1bN1bM0	Stage 1 T1N0Mx
Treatment	Right hemithyroidectomy followed by completion left thyroidectomy RAI 30mCi	Total thyroidectomy RAI 30mCi

FNA: fine needle aspiration; PTC: papillary thyroid cancer; RAI: radioiodine; TNM: tumour, nodes and metastases

Table 4. Comparison of patients with thyroid nodules or malignancy versus no thyroid nodules

	Thyroid nodules/malignancy n=13	No thyroid nodules n=119	P value
Time post-radiotherapy to detection of nodule, months (range)	14–122	–	–
Radiation dose cGy, median (range)	3000 (200–6000)	3000 (200–7996)	0.606
Euthyroid patients, n	6	52	0.09
Hypothyroid patients, n	7	19	0.09
<b>Site of radiation</b>			
TBI, n (%)	7 (12)	51 (88)	
Head/neck radiation, n (%)	4 (9.5)	38 (90.5)	
Thorax, n (%)	2 (14)	12 (86)	
Abdomen/ pelvis, n (%)	0	18 (100)	

TBI: total body irradiation

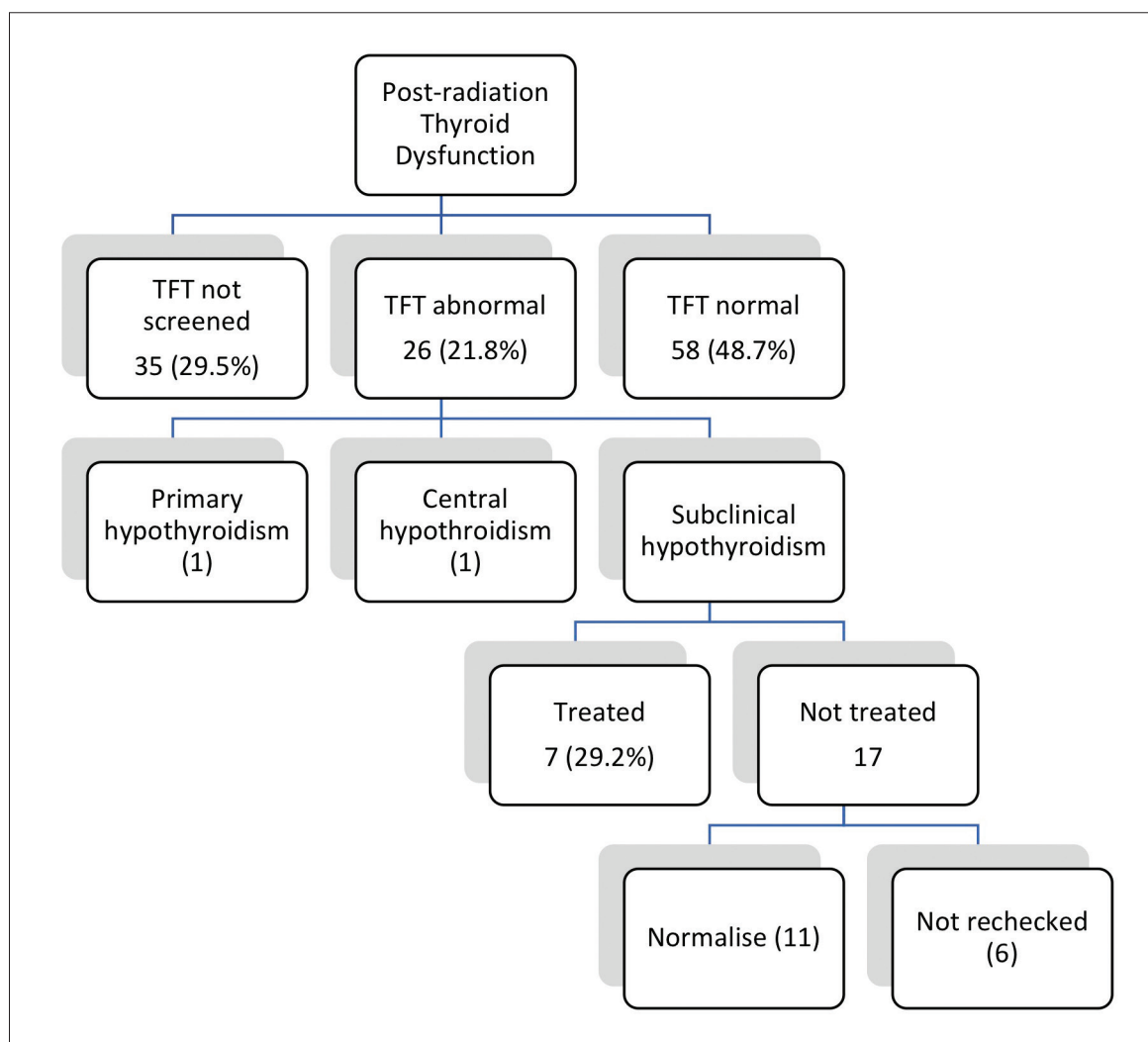


Fig. 1. Post-radiation thyroid dysfunction: Primary hypothyroidism (free T4 of <8.0pmol/L and TSH >4.5mIU/L); central hypothyroidism (free T4 <8.0pmol/L and TSH <4.5mIU/L); subclinical hypothyroidism (free T4 8–16pmol/L and TSH >4.5mIU/L). TFT: thyroid function test



1 had primary hypothyroidism, and another had central hypothyroidism. Both patients with primary hypothyroidism and central hypothyroidism received thyroxine replacement. Of the 24 patients with subclinical hypothyroidism post-radiotherapy, 7 (29.2%) were treated with thyroxine replacement and 11 patients were not treated as their TSH was only marginally elevated. In these 11 untreated patients, their TSH returned to normal spontaneously (Table 5). The remaining 6 had no further TFT done at the completion of the study. Five of the 7 patients treated with levothyroxine had TSH levels >10mIU/L. The remaining 2 were started on treatment due to persistently elevated TSH 2 years post-radiotherapy. Interestingly, the patient who had positive anti-thyroglobulin and anti-thyroid peroxidase antibody results had normal TFT on follow-up 6 months later and thereafter. This could be due to transient thyroiditis in Hashimoto's disease. The correlation between dose of radiation to hypothyroidism achieved statistical clinical significance with a *P* value of 0.014. The median dose of patients who remained euthyroid was 1,800cGy (range 200–7020cGy) compared with 5,580cGy (range 1,200–5,580cGy) in patients who developed hypothyroidism. If patients with radiation to the extremities, abdomen or pelvis was excluded from analysis, the median dose of

radiation to the group with normal TFT would be 2,600cGy with the same dose range of 200–7,020cGy. The *P* value remains statistically significant at 0.017. There was also a strong suggestion that the site of radiotherapy (head and neck radiation) is associated with primary hypothyroidism. The patients with thyroid nodules were more likely to have abnormal TFT (26.9%) compared to those without thyroid nodules (10.3%) (Table 4).

## DISCUSSION

The prevalence of childhood cancer survivors is increasing with a significant proportion having previously undergone radiation therapy.<sup>6</sup> This group is at a higher risk of developing thyroid disorders and malignancy. Secondary malignancies can occur outside the field of radiation treatment due to scatter radiation,<sup>7</sup> which includes sites far removed from the initial radiation receiving minute doses of radiotherapy.<sup>7,8</sup> Therefore, it is important to include patients with no direct thyroid radiation exposure.

In this study, thyroid malignancy was detected in 13% of survivors with thyroid nodule(s). This is in keeping with the reported incidence of thyroid malignancy of 7.1–40%.<sup>1,3,9,10</sup> In contrast, the risk of differentiated thyroid malignancy in the general population adults with thyroid nodules is only 5%.<sup>11</sup> The incidence of

Table 5. Comparison of patients with persistent versus transient subclinical hypothyroidism

	Persistent n=7	Normalised n=11	Not checked n=6
Time to development of abnormal TFT (months), median (range)	14.5 (3.4–59.6)	3.7–63.1	4.3–60.7
TSH range (mIU/L) (first TFT)	4.67–23.36	4.16–10.19	4.63–6.72
<b>Anti-TPO Abs/ Anti-Tg Abs</b>			
Negative	6	3	–
Positive	–	1	–
Not checked	1	7	–
Radiation dose, median (range)	5580 (1200–5580)	800 (200–5580)	3840 (200–6000)
<i>P</i> value	0.023		
<b>Site of radiation</b>			
TBI	4	9	4
Head/neck	2	1	2
Thorax	1	–	–
Abdomen/pelvis/ extremity	–	1	–

anti-TPO Abs: anti-thyroid peroxidase antibodies; anti-Tg Abs: anti-thyroglobulin antibodies; TBI: traumatic brain injury; TFT: thyroid function test; TSH: thyroid-stimulating hormone

differentiated thyroid malignancy in the paediatric population is even lower at 0.54 case per 100,000 children.<sup>12</sup> One of the major differences between thyroid cancer (specifically PTC) diagnosed in childhood and adulthood is the higher proportion of extrathyroidal extension, lymph node and pulmonary metastases, and higher recurrence rate.<sup>13–18</sup> This is evident in both our patients with PTC. Fortunately, the mortality rate is still low at 2% or less and there is better progression-free survival compared to adults.<sup>13,14,16,18</sup>

As the risk of malignancy is up to 20 fold higher compared to the general population,<sup>19</sup> regular surveillance is important.

In our study, both patients who were diagnosed with PTC received a total of 1,200cGy of radiation. This result is consistent with a pooled analysis done on the strength of the relationship between external radiation exposure and thyroid carcinoma.<sup>20,21</sup> The dose-relationship relative risk of thyroid radiation exposure and thyroid carcinoma development is supralinear from 200–400cGy, plateaus at 1,000–3,000cGy and declines after 3,000cGy.<sup>20</sup> The relative risk remains significantly elevated up to 5,000cGy.<sup>20</sup> This is because thyroid tissues that receive higher doses of radiotherapy are more likely to undergo cell death from lethal double-stranded DNA breaks, rather than develop malignant cell transformation into thyroid carcinoma.<sup>22</sup> We included patients who had no direct thyroid irradiation as scatter radiation is a known risk factor for secondary malignancies.<sup>6,17</sup>

The latency period from radiation exposure to the development of thyroid malignancy is approximately 5–10 years with peak incidence at 25–29 years post-exposure.<sup>2,21</sup> In our cohort, we excluded data from patients who have had radiation therapy within 1 year of analysis of the data due to the low probability of radiation being the direct cause of the thyroid malignancy. In the patients who developed thyroid malignancy, patient 1 and 2 had a time latency of 9 years and 5 years, respectively (Table 3). This is concordant with the expected time latency. As we only had data for the past 10 years, this cohort of patients will need to be followed up as we have yet to reach the peak incidence of thyroid nodules and thyroid cancer.

Previous data have indicated that ultrasound is more sensitive in the detection of thyroid nodules compared to palpation.<sup>22</sup> There is no consensus between the major guidelines of ATA, AME and AACE on screening patients using ultrasound.

The International Guideline Harmonization Group (IGHG) recommendation is to screen high-risk patients with previous radiation therapy directly or indirectly around the thyroid region.<sup>23</sup> However, IGHG has left the screening modality up to the discretion of the healthcare provider in discussion with the patient.<sup>23</sup> IGHG also suggests that screening for thyroid nodules or malignancy can start 5 years post-radiotherapy.<sup>23</sup>

A retrospective review of adult survivors of childhood cancer with previous neck radiation involving 585 patients found that only 1.2% of patients with abnormal physical examination were diagnosed with PTC.<sup>24</sup> The authors concluded that annual physical examination without routine ultrasound can be used as a screening tool.<sup>24</sup>

In our study, one of our patients with thyroid malignancy was only detected on surveillance ultrasound and not clinically. He had T1bN1bM0 papillary thyroid cancer that could have resulted in a higher morbidity with delayed detection.

Based on our cohort data, clinical assessment for thyroid malignancy using palpation should be performed annually. Subsequently, consideration should be given to performing thyroid ultrasound every 1–2 years from 5 years post-radiotherapy to improve the sensitivity of detecting thyroid nodules. Two main reasons for our suggestion are the latency period of 5 years prior to development of thyroid malignancy post-radiation exposure in our and other cohorts, and to reduce delay in the detection of potentially malignant thyroid nodules.

Thyroid hormone dysfunction is a well-documented complication post-radiation therapy.<sup>25–28</sup> Primary hypothyroidism is the most common with a prevalence of 13.8–20.8%.<sup>25–27</sup> The average time to the development of hypothyroidism have been reported to be 5–7 years (range of 0–27 years).<sup>25,28</sup> In our cohort, 9 out of 84 (10.7%) patients who had screening TFTs developed hypothyroidism (Fig. 1). The dose of radiation therapy (higher risk with higher dose) (Table 5) is associated with the development of primary hypothyroidism. Risk factors shown to correlate with the development of primary hypothyroidism include higher radiation doses, proximity to the thyroid gland, and female gender.<sup>25,28,29</sup> The actual dose-event rate is not well-established as some studies reported total radiation doses and others estimated radiation dose to the thyroid gland.<sup>25,28,29</sup> We could not determine the actual radiation dose that was delivered to the thyroid gland, thus are unable to derive the “pathogenic” radiation dose. Our sample size was too small to determine if gender is an independent

risk factor. Additionally, the median follow-up in our sample population was 4.59 years, which likely represents an underestimate of the true hypothyroidism prevalence.

The Children's Oncology Group have advocated for annual (or more frequent) TFT screening in patients at risk of central hypothyroidism or primary hypothyroidism secondary to radiotherapy starting at 2 years post-radiotherapy.<sup>30</sup>

Based on our cohort, the risk of thyroid dysfunction is high. Screening TFTs should be performed 6–12 months post-radiotherapy or earlier if the patient develops clinical symptoms or signs suggestive of thyroid dysfunction. Thus, our recommendation allows for more targeted screening and abnormal TFT from non-thyroidal illness to resolve.

Previous cohorts have shown that thyroid dysfunction can occur up to 20 years post-radiation exposure.<sup>25</sup> Therefore, these high-risk patients will require long-term follow-up to monitor for the development of thyroid dysfunction.

Another limitation of our study stems from a large percentage of patients (68%) who were excluded due to lost follow-up, resulting in exclusion bias. Additionally, median follow-up time was short at 4.62 years. It would be worthwhile to re-analyse the data of these patients after a longer period of follow-up.

## CONCLUSION

Screening for thyroid nodules, malignancy and thyroid dysfunction is an important aspect in the long-term follow-up of childhood cancer survivors post-radiotherapy. Regular screening via clinical examination for thyroid malignancies should be performed at least annually. Where feasible and if resources permit, consideration should be given to using ultrasound for thyroid nodule(s) and malignancy screening at 5 years post-radiation therapy as it is more sensitive compared to palpation at detecting smaller nodules based on data from our cohort. Screening for thyroid dysfunction in asymptomatic patients should start from 6–12 months post-radiotherapy, as data from our cohort show that it can occur at an earlier interval. Longer term follow-up is required to determine the actual incidence of thyroid malignancy and thyroid dysfunction in this high-risk cohort.

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# Evidence-based medical treatment of peripheral arterial disease: A rapid review

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## ABSTRACT

**Introduction:** Peripheral arterial disease (PAD) treatment guidelines recommend the use of statins and antiplatelets in all PAD patients to reduce adverse cardiovascular and limb-related outcomes. In addition, hypertension and diabetes should be treated to reach recommended targets. The aim of this rapid review was to evaluate the level of adherence to evidence-based medical therapy (EBMT) recommended by PAD treatment guidelines in the real-world setting.

**Methods:** We searched PubMed and Embase using keywords, MeSH and Emtree terms related to the population, exposure and outcomes from their inception to 22 September 2020. We included randomised controlled trials, non-randomised studies, and observational studies reporting adherence to at least 1 of these 4 drug classes: (1) statins, (2) antiplatelets, (3) antihypertensives and (4) antidiabetic drugs. Non-English articles, abstracts, dissertations, animal studies and case reports or series were excluded. A narrative summary of the results was performed.

**Results:** A total of 42 articles were included in the review. The adherence to lipid-lowering drugs/statins ranged from 23.5 to 92.0% and antiplatelets from 27.5 to 96.3%. Only 7 and 5 studies reported use of “any anti-hypertensive” and “any anti-diabetic” medications, respectively, and the proportion of the cohort treated were generally close to the proportion with hypertension and/or diabetes. Adherence in studies published in 2016–2020 ranged from 52.4–89.6% for lipid-lowering drugs and 66.2–96.3% for antiplatelets.

**Conclusion:** EBMT adherence in PAD patients was highly variable and a substantial proportion in many settings were undertreated. There was also a notable lack of studies in Asian populations.

Ann Acad Med Singap 2021;50:411-24

**Keywords:** Evidence-practice gap, medication adherence, pharmacoepidemiology

## INTRODUCTION

Peripheral artery disease (PAD) is characterised by debilitating atherosclerotic occlusion of arteries in the lower extremities.<sup>1</sup> Globally, it was estimated that more than 230 million individuals suffer from PAD in 2015, including about 50 million in Southeast Asia and 74 million in the Western Pacific Region.<sup>2</sup> The incidence of PAD is increasing significantly across Asia with an advancing age and increasing prevalence of diabetes, which is associated with 2- to 4-fold increase in the incidence of PAD.<sup>3</sup> Given that Asia has more than 50% of the diabetes prevalence worldwide, it is estimated that there are several million patients with PAD in Asia, many asymptomatic and undiagnosed.<sup>4</sup> The

severity of PAD ranges from atypical lower-extremity symptoms, intermittent claudication to chronic limb threatening ischaemia (CLTI), which causes rest pain, ulcers or gangrene.<sup>5</sup> A recent systematic review found that CLTI was associated with a 1-year mortality rate of 40% and 1-year amputation rates ranged from 15% to 20%.<sup>6</sup> Moreover, PAD patients are at an increased risk of cardiovascular morbidity and mortality.<sup>1</sup> Although endovascular or surgical revascularisation procedures are important facets of PAD management, medical and lifestyle interventions are also essential elements of evidence-based PAD care, both from a perspective of improving cardiovascular mortality as well as limb-related outcomes.<sup>1,5</sup> Dyslipidaemia

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## CLINICAL IMPACT

### What is New

- This review provides an update of evidence-based medical therapy (EBMT) used in peripheral arterial disease (PAD) since the last systematic review 12 years ago.

### Clinical Implications

- The review highlights existing gaps in the use of EBMT in PAD patients, given the highly variable level of adherence found for all 4 classes of EBMT.
- There was a lack of Asian studies, pointing to a need for more research on EBMT use in Asian PAD patients.

and hypertension are estimated to nearly double the risk of PAD.<sup>1</sup> Lifestyle changes and control of risk factors increase the short and long-term patency of angioplasties and surgical bypasses, resulting in a reduction of target lesion revascularisation.<sup>1</sup>

The 2016 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients with Peripheral Arterial Disease and 2017 European Society of Cardiology (ESC) Guidelines recommend that PAD patients be treated lifelong with a statin and an antiplatelet drug, aspirin alone (range 75–325mg per day) or clopidogrel alone (75mg per day), to reduce the risk of cardiovascular events and death.<sup>1,5</sup> All patients should have their serum low-density lipoprotein cholesterol (LDL-C) reduced to <1.8mmol/L (<70mg/dL) or decreased by >50% if the initial LDL-C level is between 1.8 and 3.5mmol/L (70 and 135mg/dL).<sup>7</sup> Statin therapy has been shown to reduce major extremity amputation by 18%, adverse cardiovascular events by 20%, and all-cause mortality by 19%.<sup>8</sup> Furthermore, the use of antiplatelet agents and statins at the time of intervention for PAD patients without known cardiovascular disease has also been associated with better 5-year survival compared to PAD patients receiving no treatment.<sup>9</sup> In addition, hypertension and diabetes should be treated and controlled. As per guidelines, a target blood pressure <140/90mmHg is recommended except in patients with diabetes, for whom a diastolic blood pressure ≤85 mmHg is considered a safer policy.<sup>10</sup>

Despite these guidelines, there is evidence that PAD patients are undertreated. A systematic review of implementation of recommended secondary prevention in PAD patients found that antiplatelet medication, lipid-lowering agents and antihypertensives were prescribed only in 63%, 45% and 46% of PAD patients, respectively.<sup>11</sup> There is also evidence of variation in perioperative antiplatelet and statin usage by procedure and among centres.<sup>11</sup> This rapid review aims to provide an updated evaluation of the level of adherence to evidence-based medical therapy (EBMT) recommended by PAD treatment guidelines in the real-world setting.

## METHODS

### Study selection

We searched PubMed and Embase using keywords, MeSH and Emtree terms related to the population, exposure and outcomes (Table 1), from their inception to 22 September 2020. Terms in each element were combined using the Boolean operator “OR” and then results from each element combined using “AND”. Filters were applied to restrict language to “English”. We included randomised controlled trials, non-randomised studies, and observational studies reporting adherence to at least 1 of these 4 drug classes: (1) statins (“any lipid-lowering drugs” were also included as they are likely to represent overall antilipid treatment including when statins were not suitable), (2) antiplatelets, (3) antihypertensives and (4) antidiabetic drugs. The following types of studies were excluded: (1) full text not available in English, (2) conference abstracts, (3) dissertations, (4) animal studies, or (5) case reports. We also screened reviews but included the primary studies instead of the reviews themselves. Two authors screened the studies identified through the search strategy independently, and conflicts were resolved through discussion with a third reviewer.

There were variable definitions of PAD in the studies screened, with some including diseases of the aorta, carotid and/or renal arteries. For the purposes of this review, we restricted the population to lower extremity PAD (disease affecting the aorta-iliac segments and below). Studies that included other populations but reported the results of interest in the PAD subgroup were included. Among duplicate reports of the same study population or database, we selected reports in this order of priority: (1) those that reported more exposures, (2) larger sample size, and (3) most updated results (later study period or publication date). The Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed.<sup>12</sup> This rapid review protocol was also registered in International Prospective Register of Systematic Reviews (PROSPERO) on 12 August 2020.

### Data collection

One reviewer extracted key information and results from each study: first author, publication year, country of origin, setting, study design, study period, population inclusion and exclusion criteria, sample size, exposures, outcome measurement method, outcomes, and information needed for risk of bias assessment. A random 10% sample was checked by a second reviewer and the compliance rate was 100%. Risk of bias was assessed using the National Heart, Lung and Blood Institute (NHLBI) standardized Quality Assessment Tool by one reviewer and was randomly checked by the second reviewer.<sup>13</sup>

### Data analysis

As the studies were rather diverse in the types of PAD patients included, context and definition of adherence, we performed a narrative summary of the results. For studies that measured adherence trend over several years, we took the value at the latest time period where available. However, for studies that reported adherence at different timepoints relative to a medical encounter for PAD diagnosis, intervention or management (e.g. before admission, after admission and follow-up), the data for each timepoint were retained as this provides a view on the effect of the encounter on quality of treatment. In these cases, the latest time point reported was used for showing the overall trend.

For the main results, we only showed the overall drug classes and the main drug or drug class of choice to simplify data presentation, rather than all specific drug entities or classes. For studies that reported angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARBs) separately but not ACEI/ARBs, this was imputed by adding ACEI and ARBs as these drugs were generally not used together. Results for ACEIs alone were also presented in the same category. For antidiabetic medications, only results for “any antidiabetics” and/or metformin (drug of choice) were shown. We also explored the results by continent of origin and publication year to determine if there were regional differences and if adherence has improved over time. Due to the varied

nature of the PAD populations included, it was difficult to accurately group them by severity. Comorbidities were also not consistently reported to allow for subgroup analysis by these characteristics. All analyses were conducted in R version 3.5.1.<sup>14</sup>

## RESULTS

### Search results

The search strategy yielded a total of 1,843 articles from both PubMed and Embase as of 22 September 2020; 42 articles were finally included in this review (Fig. 1). The details of the included studies are shown in Table 2. The studies were published between 2004 and 2020, with almost two-thirds in the last 5 years. Most of the studies originated from the US or Europe, with only 1 paper from Asia. The median sample size was 588 patients (range 72–175,865). The type of PAD populations in the included studies varied from those patients with mild symptoms (only intermittent claudication) to those with rest pain/tissue loss (CLTI). Thirty-four studies (81%) were rated as “good” quality while the remaining 8 were “fair”, according to the NHLBI quality assessment tool.

### Overall adherence to EBMT

Of the 42 included studies, 41 (97.6%), 31 (73.8%), 25 (59.5%) and 8 (19.0%) studies reported adherence on lipid-lowering drugs, antiplatelets, antihypertensives and antidiabetic drugs, respectively. However, among the 25 studies that reported antihypertensives, only 7 (28.0%) reported use of “any antihypertensives”,<sup>15,16,31,35,44,45,52</sup> and among the 8 studies that reported antidiabetic drugs, only 5 (62.5%) reported use of “any antidiabetics”.<sup>15,16,39,44,52</sup> The rest reported specific drugs or classes of antihypertensives/antidiabetics separately, and it was not possible to infer the proportion of the cohort who received pharmacological treatment as patients may be on multiple agents.

There was substantial variability in the level of adherence to all 4 classes of drugs (Fig. 2). The adherence to lipid-lowering drugs or statins ranged from 23.5 to 92.0% and antiplatelets from 27.5 to 96.3%. There was a strong correlation between adherence to lipid-lowering drugs and antiplatelets. Studies that had low adherence to lipid-lowering drugs also tended to have low antiplatelet adherence, and vice versa (Pearson’s  $r=0.81$ ,  $P<0.0001$ ).

The adherence to antihypertensives and antidiabetics were also highly variable (Figure 2). These values reflect the proportion of the entire PAD cohort treated

Table 1. Search terms

Element	Plain text	MeSH terms (PubMed)	Emtree terms (EMBASE)
Population	“peripheral arterial disease” OR “peripheral artery disease” OR “chronic limb ischemia” OR “chronic limb threatening ischemia” OR (limb AND ischemia) OR (limb AND atherosclerosis)	“peripheral arterial disease”	“peripheral occlusive artery disease”
Exposure	“medical therapy” OR “medical treatment” OR guideline* OR medication* OR drug* OR aspirin OR clopidogrel OR antiplatelet* OR anticoagulant* OR statin* OR antihypertensive OR antidiabetic OR antihyperglycemic OR hypoglycemic OR “antithrombotic agent”	“evidence-based practice” OR aspirin OR clopidogrel OR “platelet aggregation inhibitors” OR anticoagulants OR “hydroxymethylglutaryl-CoA reductase inhibitors” OR “antihypertensive agents” OR “hypoglycemic agents”	“drug therapy” OR “evidence-based practice” OR “acetylsalicylic acid” OR clopidogrel OR “antithrombotic agent” OR “anticoagulant agent” OR “hydroxymethylglutaryl coenzyme A reductase inhibitor” OR “antihypertensive agent” OR “antidiabetic agent”
Outcome	adherence OR compliance	“medication adherence” OR “guideline adherence” OR “treatment adherence and compliance”	“medication compliance”

\*: wildcard search symbol

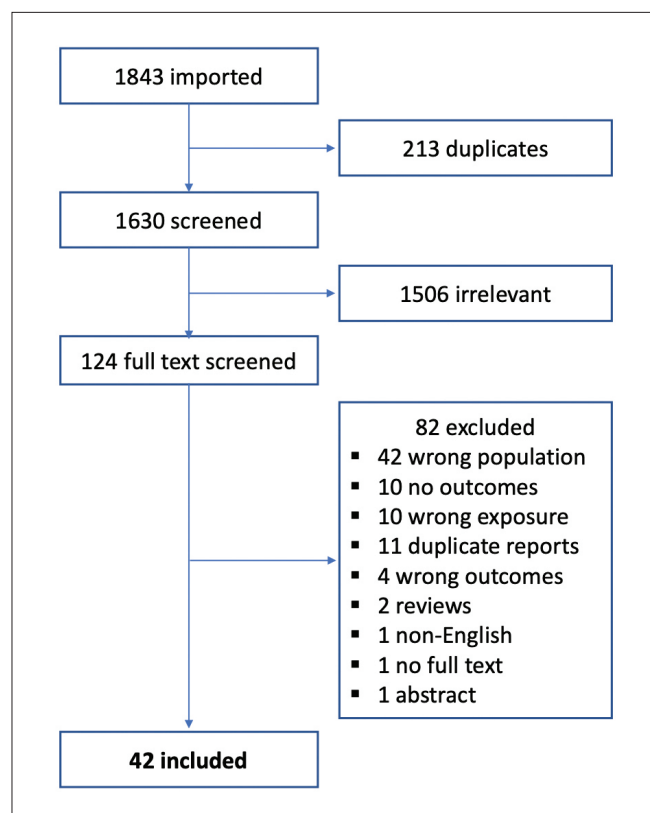


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

with these drugs, so the proportion of those with hypertension and diabetes were also indicated where available to provide more context for the results (Fig. 2, light grey squares). Several studies have very

high or 100% adherence relative to the proportion of the cohort who had the corresponding comorbidities (hypertension or diabetes).<sup>15,16,31,45,46,52,54</sup> For the other studies with seemingly suboptimal antihypertensive adherence, only ACEI/ARBs were represented and/or the proportion of the cohort with hypertension was unknown. Similarly, for antidiabetics, either only metformin was represented or the proportion of diabetics was unknown.<sup>31,39</sup>

### Adherence to EBMT by continent and publication year

European and North American studies had similarly wide distributions in adherence to both lipid-lowering drugs (31.3–92.0% and 23.5–85.3%, respectively) and antiplatelets (27.5–92.9% and 44.5–91.3%, respectively). International studies tended to have higher adherence (range 64.2–89.6% for lipid-lowering drugs and 81.7–89.6% for antiplatelets) (Fig. 3 panel A).

When grouped by publication year, there was a trend of increasing adherence with newer studies. Adherence in studies published in 2016–2020 ranged from 52.4–89.6% for lipid-lowering drugs and 66.2–96.3% for antiplatelets (Fig. 3 panel B).

### Adherence at different timepoints around a medical encounter

In general, adherence to all classes of medications improved immediately after discharge from an admission or consultation for peripheral arterial disease diagnosis, intervention or management, when compared to before the encounter (Fig. 4). However, in studies that continue to follow up further, adherence tends to drop slightly

Table 2. Characteristics of included studies

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Bhatt, <sup>15</sup> 2006	International	Outpatients (REACH registry)	Prospective cohort	Dec 2003–Jun 2004	8273	IC or hx of related interventions	Baseline	Manual extraction (definition unclear)
Bianchi, <sup>16</sup> 2007	US	Vascular surgery clinic	Retrospective cohort	Not stated; 1-year period	167	IC and CLI	At presentation to vascular clinic	Manual extraction (definition unclear)
Brown, <sup>17</sup> 2004	Canada	Population-based (Saskatchewan Health)	Retrospective cohort	1991–2000	281	DM with symptomatic PAD	Not stated	Dispensing records
Cambou, <sup>18</sup> 2010	France	Academic hospital (COPART registry)	Prospective cohort	Jun 2004–Oct 2008	903	LE-PAD	At discharge	Manual extraction (definition unclear)
Chaudhry, <sup>19</sup> 2018	US	Community primary care practice	Retrospective cohort	May–Jul 2015	73	Symptomatic PAD, previous revasc/amp, or evidence of occlusion	Within 6 months from PAD diagnosis	Manual extraction (definition unclear)
Chen, <sup>20</sup> 2017	US	Vascular centre	Retrospective cohort	Jun 2006–May 2013	879	IC or CLI	Pre-procedure and during follow-up	Prescription records
Chung, <sup>21</sup> 2013	US	Vascular surgery clinic	Prospective cohort	Aug 2010–Jan 2012	98	CLI	Baseline	Manual extraction (definition unclear)
Ciminiello, <sup>22</sup> 2017	Italy	Specialised vascular outpatient clinics (IDOMENEO study)	Prospective cohort	Jun 2011–Dec 2013	213	Symptomatic PAD excluding candidates for revasc and CLI	Not stated	Prescription records
de Grijjs, <sup>23</sup> 2018	US	Vascular surgery clinic	Retrospective cohort	Jul 2004–Jul 2014	250	Patients undergoing SFA/PA stenting	At time of procedure	Largely self-report
de Liefde, <sup>24</sup> 2008	Netherlands	Tertiary hospital	Prospective cohort	Jul 1993–Dec 2005	2022	Hx of IC, leg pain or other symptoms	Baseline	Prescription records
Dopheide, <sup>25</sup> 2018	Switzerland	University hospital	Cross-sectional	Jan 2010–Sep 2017	1109	Chronic symptomatic PAD (Fontaine II, III, IV) referred for LL revasc	At referral to vascular surgery outpatient clinic	Prescription records
Federman, <sup>26</sup> 2005	US	Hospital	Retrospective cohort	Sep 2001–Apr 2003	143	ABI<0.9 or had LEB	12–18 months after non-invasive testing	Prescription records

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus; hx: history; IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revasc: revascularisation; SFA/PA: superficial femoral artery/popliteal artery

Superscript numbers: Refer to REFERENCES

Table 2. Characteristics of included studies (Cont'd)

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Gebauer, <sup>27</sup> 2016	Germany	University hospital	Prospective cohort	Jan 2005–Jan 2010	572	Symptomatic PAD undergoing angiography/angioplasty	At discharge and 3-year follow-up	Prescription records
Hageman, <sup>28</sup> 2018	Netherlands	General practitioners in primary care	Cross-sectional	Jan–Dec 2015	123	New patients with abnormal ABI	At referral to vascular surgery outpatient clinic	Mention of drug in medication list in referral
Halle, <sup>29</sup> 2018	US	Outpatient vascular clinic	Retrospective cohort	May–Aug 2016	96	IC, rest pain or tissue loss	At follow-up at outpatient vascular clinic	Having prescription and patient knowing it and taking it with not more than 1 missed dose in preceding 7 days
Hogh, <sup>30</sup> 2013	Denmark	Population-based	Retrospective cohort	Jan 1996–Dec 2006	9866	Primary vascular reconstruction for IC, ischaemic rest pain, ulceration or gangrene	After discharge from primary vascular reconstruction	Filling at least 1 prescription within 6 months after primary vascular surgery reconstruction
Iacopi, <sup>31</sup> 2019	Italy	Tertiary hospital	Retrospective cohort	Jan 2011–Dec 2015	603	CLI	At admission	Manual extraction (definition unclear)
Khan, <sup>32</sup> 2007	UK	Vascular clinics (PREPARED-UK registry)	Prospective cohort	Jun 2002–Sep 2003	478	IC and new referral only	Baseline	Manual extraction (definition unclear)
Ko, <sup>33</sup> 2017	South Korea	Hospital (K-VIS ELLA registry)	Retrospective cohort	Jan 2006–Jul 2015	3073	LE-PAD treated with endovascular therapy	At discharge	Prescription records
Komajda, <sup>34</sup> 2016	International	Hospitals (CICD-PILOT registry)	Prospective cohort	Apr 2013–Dec 2014	201	Patients undergoing PVI	Before hospital admission/consultation and at discharge	Manual extraction (definition unclear)
Laféber, <sup>35</sup> 2013	The Netherlands	Academic medical centre (SMART study)	Prospective cohort	Jan 1996–Dec 2009	936	IC, angioplasty or amp	On diagnostic screening day	Self-reported

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus, hx: history, IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revasc: revascularisation; SFA/PA: superficial femoral artery/ popliteal artery

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Table 2. Characteristics of included studies (Cont'd)

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Maggioni, <sup>36</sup> 2017	Italy	Community (ARNO Observatory)	Retrospective cohort	Jan 2011–Dec 2014	1038	PVD with IC or rest pain	First month and first year after discharge	Prescription continuity (≥300 treated days/year)
Martin, <sup>37</sup> 2020	US	Vascular clinics	Time series (Plan-Do-Study-Act)	Feb–Apr 2018	120	LE-PAD	After clinic visit	Prescription records
Meltzer, <sup>38</sup> 2018	US	Vascular clinics (VQI database)	Retrospective cohort	2011–2013	1030	PVI or LEB for symptomatic PAD	Preoperative	Prescription records
Müller-Bühl, <sup>39</sup> 2011	Germany	Primary care (CONTENT database)	Case-control	Apr 2007–Mar 2010	479	IC	Not stated	Prescription records
Neumann, <sup>40</sup> 2009	Germany	Primary care (PACE-PAD study)	Prospective cohort	Dec 2004–Jun 2005	6129	Fontaine I-IV	Baseline	Indicator on questionnaire
O'Donnell, <sup>41</sup> 2017	US	Academic medical centre (Vascular Study Group of New England)	Retrospective cohort	Jan 2005–Dec 2014	931	Chronic limb-threatening ischaemia undergoing first-time revascularisation	Postoperative	Discharge medication list
Pâquet, <sup>42</sup> 2010	Canada	Tertiary hospital (RAMQ database)	Retrospective cohort	Jan 1997–Dec 2006	5962	LE-PAD	At discharge	Prescribed medications in pharmaceutical file
Pepió Vilaubi, <sup>43</sup> 2018	Spain	Primary care (PREseAP study)	Prospective cohort	Jan 2004–2009	72	PAD confirmed by Echo Doppler or positive ABI test	Baseline	Prescription records
Perren, <sup>44</sup> 2009	Switzerland	Tertiary hospital	Prospective cohort	Mar–May 2007	88	PAD based on symptoms or testing	At discharge	Prescription records
Poussa, <sup>45</sup> 2007	Finland	Vascular clinics	Cross-sectional	Jan 2002–Dec 2003	214	Patients admitted for diagnostic angioplasty or revascularisation	At referral and after consultation	Prescription records
Qvist, <sup>46</sup> 2019	Denmark	Population-based (VIVA substudy)	Retrospective cohort	Oct 2008–Jan 2011	2051	Diagnosed based on ABI	Initiators 120 days after screening	Prescription records

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus, hx: history; IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revascularisation: revascularisation; SFA/PA: superficial femoral artery/popliteal artery; Superscript numbers: Refer to REFERENCES

Table 2. Characteristics of included studies (Cont'd)

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Rehring, <sup>47</sup> 2006	US	Managed care system	Cluster randomised controlled trial	May 2003–Sep 2004	90	IC or hx of peripheral revascularisation	Within 4 months of baseline	Prescription records
Renard, <sup>48</sup> 2015	US	Hospitals	Prospective cohort	Jan 2008–Dec 2011	10,169	Patients undergoing LE PVI for symptomatic PAD	Prior to PVI, after procedure and at 6 months	Discharge prescription and self-report at 6 months
Reynolds, <sup>49</sup> 2020	US	Integrated healthcare delivery system	Retrospective cohort	Oct 2002–Sep 2015	11,059	Severe PAD	At diagnosis (12 months before and within 1 month after diagnosis)	Dispensing records
Saxon, <sup>50</sup> 2020	International	PAD specialty clinics (PORTrait registry)	Prospective cohort	Jun 2011–Dec 2015	1275	Patients with new or worsening PAD symptoms, excluding Rutherford II–III	After PAD workup at subspecialty clinic	Prescription records
Sillesen, <sup>51</sup> 2007	Denmark	Nurse-led rehabilitation clinic	Prospective cohort	Apr 2000–May 2004	693	Symptomatic PAD	At entry and over 12 months	Prescription records
Skórkowska-Telichowska, <sup>52</sup> 2018	Poland	Angiology outpatient unit	Prospective cohort	2011–2013	126	IC (Fontaine II)	At entry	Self-report
Slovut, <sup>53</sup> 2014	US	Hospital	Prospective cohort	Jan 2007–Dec 2010	734	Patients undergoing revascularisation for LE-PAD	At admission and discharge	Medication listing
Steenhof, <sup>54</sup> 2014	Canada	Tertiary hospital	Retrospective cohort	Jan 2010 until 150 patients	150	LE-PAD patients admitted to vascular surgery	Before and after admission	Listing of medications in discharge summary
Thiney, <sup>55</sup> 2018	France	University hospital	Retrospective cohort	Jan 2013–Jul 2017	140	Patients hospitalised for LE-PAD revascularisation	At discharge and end of follow-up (4 years)	Prescription records
Willey, <sup>56</sup> 2018	US	Population-based	Retrospective cohort	2009–2011	175,865	LE-PAD	Filling of prescription within 90 days of initial PAD diagnosis	Prescription records

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus; hx: history; IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revascularisation: revascularisation; SFA/PA: superficial femoral artery/popliteal artery; Superscript numbers: Refer to REFERENCES

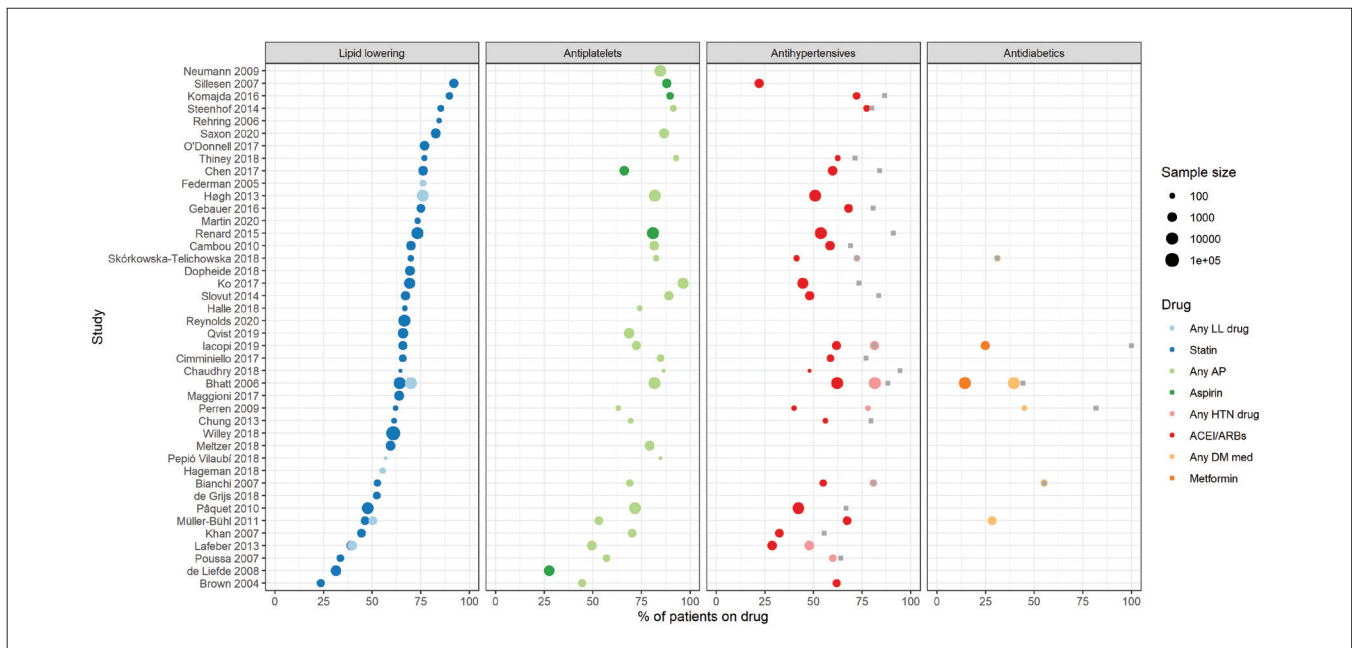


Fig. 2. Adherence to lipid-lowering drugs, antiplatelets, antihypertensives and antidiabetic medications.

For studies that reported adherence at different time points, the latest one is presented here. For antihypertensives and antidiabetic medications, the results reflect the percentage of the entire peripheral artery disease cohort taking those drugs. The light grey squares in the antihypertensives and diabetes mellitus medications panels represent the percentage of the cohort that have hypertension and diabetes, respectively.

LL: lipid lowering; AP: antiplatelets; HTN: hypertension; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; DM: diabetes mellitus

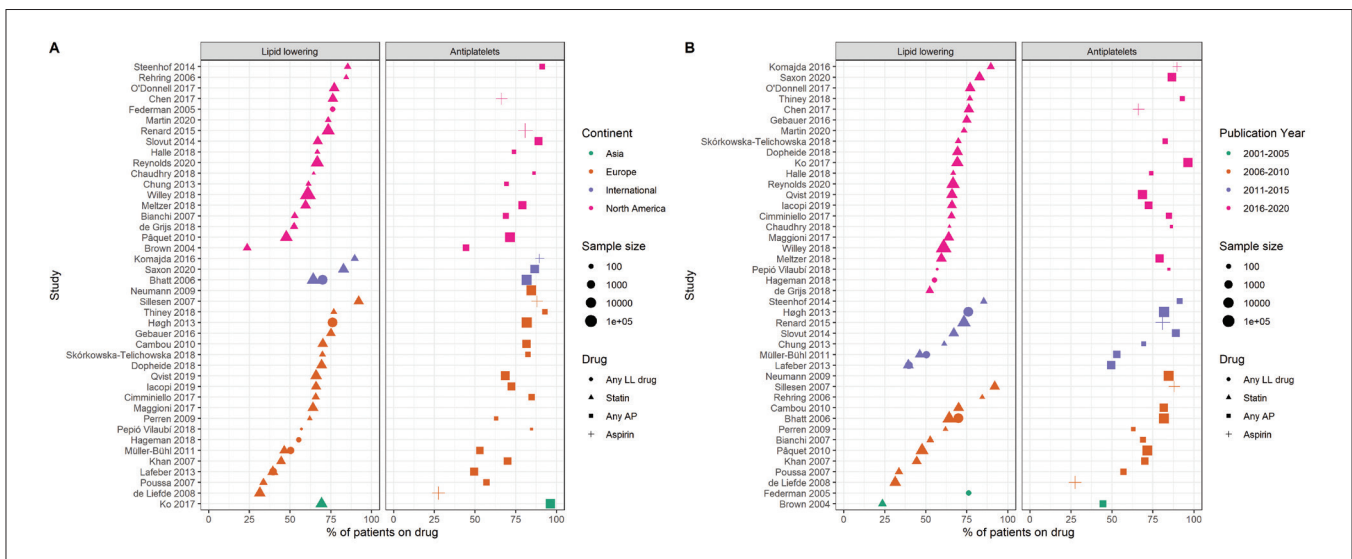


Fig. 3. Adherence to lipid-lowering drugs and antiplatelets by continent and publication year.

For studies that reported adherence at different time-points, the latest one is presented here. Panel A shows similarly wide distributions in adherence to both drug classes in Europe and North America, whereas international studies tended to have higher adherence. Panel B shows a general increasing trend in adherence to both drug classes over time.

LL: lipid lowering; AP: antiplatelets

(absolute decrease ranging from 0.4 to 11.0%),<sup>27,48,55</sup> with an exception in Maggioni et al., where an absolute increase of 26.5% might have been contributed by the high rate of readmissions within the first year. However,

over a longer follow-up of 3 years, adherence to statins (in the entire cohort including patients with acute coronary syndrome and cardiovascular disease) did drop from 59.9 to 48.4%.<sup>36</sup>

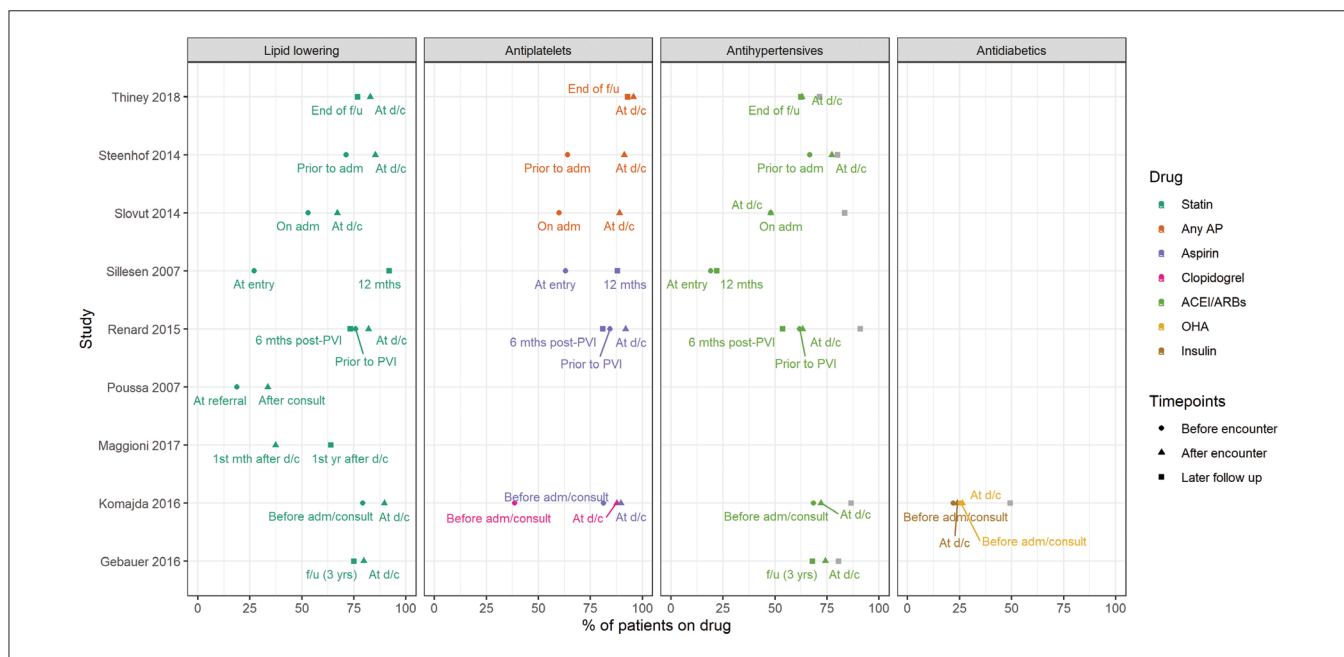


Fig. 4. Effect of healthcare encounter for peripheral artery disease (PAD) on drug adherence.

The adherence at different time-points relative to a medical encounter for PAD is shown. The medical encounter is usually a consultation or an admission for a PAD-related intervention. Generally, adherence is improved after the encounter and falls slightly upon further follow-up. For antihypertensives and antidiabetic medications, the results reflect the percentage of the entire PAD cohort taking those drugs. The light grey squares in the antihypertensives and diabetes mellitus medications panels represent the percentage of the cohort that have hypertension and diabetes, respectively.

f/u: follow-up; d/c: discharge; adm: admission; PVI: peripheral vascular intervention; AP: antiplatelets; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; OHA: oral hypoglycaemic agent

## DISCUSSION

Twelve years after the last systematic review on the use of EBMT in PAD patients, the situation remains sadly the same.<sup>11</sup> The main findings of this review showed that medical therapy adherence was highly variable, and undertreatment with EBMT in PAD patients was common. Another striking finding was the lack of Asian studies. We found only one Korean study,<sup>33</sup> highlighting a gap in the literature for Asian PAD patients in general. This was also the same as the previous systematic review, which had one study from China.<sup>11</sup> The Korean study included 3,434 patients treated for intermittent claudication or CLTI from 2006 to 2015 at 31 hospitals across Korea, and found prescription rates at discharge to be relatively high for any antiplatelet drug (96.3%) but moderate for statins (69.2%).<sup>33</sup> However, in the Chinese study from the previous systematic review, PAD patients with another cardiovascular risk factor had much lower prescription rates for antiplatelets (72.4%) and statins (41.9%).<sup>57</sup> The variation mirrors that seen in North America and Europe, suggesting that there may be local contextual factors affecting the implementation of PAD guidelines.

We used the 2016 ACC/AHA and 2017 ESC guidelines for management of PAD patients as the reference for

best medical therapy.<sup>1</sup> Both guidelines, which originated from different continents, as well as the global vascular guidelines for CLTI patients,<sup>58</sup> agree on the universal treatment of PAD patients with statins and antiplatelets, and control of hypertension and diabetes in those who have them. The ESC guidelines recommend ACEI/ARBs as first line therapy for hypertension in PAD patients, while metformin was recommended as the hypoglycaemic agent of choice in the global vascular guidelines for CLTI patients.<sup>5,58</sup> Unlike the previous systematic review by Flu et al., we did not focus on heart rate lowering medications because this was not a class of drug specifically recommended in the guidelines.<sup>1,5,11</sup> In fact, beta blockers had been thought to worsen PAD symptoms but this has been revised and beta blockers are now considered acceptable treatments in recent guidelines.<sup>1</sup> We also excluded exercise therapy and smoking cessation to focus on EBMT.

The evidence supporting these recommendations have been present for a long time and the same recommendations have been made as early as in 1999.<sup>59</sup> However, there are gaps in knowledge and action on the recommended treatment targets for vascular surgeons.<sup>60</sup> One of several potential reasons is low provider comfort levels in treating PAD patients.<sup>45</sup> The

previous systematic review by Flu et al. also summarises possible factors for suboptimal implementation of recommended secondary prevention in PAD patients. The authors grouped them into patient-related factors (understanding of disease, compliance, polypharmacy), physician-related factors (underdiagnosis of PAD, lack of knowledge of risk factor modification, lack of time and reimbursement) and healthcare-related factors (responsibility is spread out).<sup>11</sup> A systematic meta-review of the barriers and facilitators to implementation of clinical practice guidelines echoed many of these factors but included factors in the guideline, and political and social contexts.<sup>61</sup> In particular, consistent leadership, which provides clear objectives of care and rallies together care providers from different disciplines, is a key facilitator.<sup>61</sup>

The large variation we saw in the level of adherence to EBMT is likely due to varying efforts in the implementation. We observed a trend of increasing adherence with time, possibly due to the increasing recognition that focused efforts are needed for understanding the implementation factors and designing strategies to overcome the barriers to implementing clinical practice guidelines in recent years.<sup>61</sup> In particular, collaborative care between vascular surgeons, primary physicians and internists, is important and effective in bringing about better EBMT adherence and thus long-term outcomes, given that the responsibility of instituting EBMT is unclear otherwise.<sup>60</sup> Suboptimal adherence to EBMT is associated with higher risk of major amputation and death.<sup>21</sup> Statin use is associated with lower major adverse cardiovascular events and mortality.<sup>56</sup> It is therefore important that more research efforts are directed towards understanding and improving implementation of the PAD guidelines into practice.

It was difficult to ascertain the quality of hypertension and diabetes treatment due to the variability in the type of drugs or drug classes that were reported. For hypertension, ACEI/ARBs are the drugs of choice according to the ESC guidelines, but treatment with any antihypertensive would have been considered adherent.<sup>5</sup> Among the 6 studies that reported use of “any antihypertensive”, the level of use was quite close to the proportion with hypertension, suggesting that majority of hypertensive patients were being treated.<sup>15,16,31,35,44,45</sup> Comparing the level of ACEI/ARBs use with “any antihypertensive”, it appears that ACEI/ARBs were not always the drug of choice.<sup>15,31,35</sup> In one study though, ACEI/ARBs use was very close to the hypertensive proportion.<sup>54</sup> For diabetes, treatment was 100% in 2 studies<sup>16,52</sup> but less than ideal in the study by Perren et al.<sup>44</sup> For these 2 conditions, we reported the level of

use in the entire cohort and the proportion with the conditions for context, instead of assuming that antihypertensives and antidiabetic drugs are only used in patients with hypertension and diabetes, respectively, as it may not be necessarily the case.

Our protocol initially included anticoagulants as an exposure, as guidelines recommend that they should not be used for prevention of atherosclerosis.<sup>1,5,58</sup> However, in the course of the review it was difficult to establish if there were other indications for anticoagulants, so we decided to exclude this exposure. Some studies reported use of “antiplatelets and/or anticoagulants” but again it was not possible to establish if patients had good justifications to be given anticoagulants instead of antiplatelets. The recent COMPASS and VOYAGER trials showed that the combination of low-dose rivaroxaban and aspirin significantly reduced the incidence of acute or chronic limb ischaemia and its related complications (amputations and death) compared to aspirin alone, suggesting a potential role for rivaroxaban in the management of PAD patients. However, the risk of major bleeding is higher with the combination of an antiplatelet and anticoagulant, and the decision to use requires an individualised assessment of the risks and benefits.<sup>62</sup>

The 9 studies that reported adherence at multiple timepoints relative to a medical encounter for PAD diagnosis or treatment suggested that these encounters were opportunities to review and institute EBMT in patients who have not been receiving them (Fig. 4). In one setting where CLTI patients were managed in a nurse-led PAD rehabilitation clinic, the statin adherence rate increased dramatically from 27 to 92% after a year with 5 visits.<sup>51</sup> This was a successful example of active implementation of EBMT in practice, through collaborative management of the patients, regular monitoring and feedback to patients and their family and/or family practitioners on their performance on risk factor targets using printouts.<sup>51</sup> Other care settings for PAD patients will need to understand their context, barriers and facilitators to find a strategy that works for improving EBMT adherence rates.

There are several limitations in our study. Firstly, there was some variability in the outcome definitions in the studies. Most of the studies measure adherence by whether patients were prescribed the drugs, and this was ascertained by dispensing records, documentation in various sources, and even self-reporting. This therefore represents a mixture of physician's and patient's adherence. Secondly, the results may have been an underestimate of physicians' adherence to



EBMT prescription. There could be legitimate reasons for withholding certain treatments or drug substitution (e.g. other lipid-lowering agents instead of a statin), but the reasons were not captured in most studies. Also, if dispensing records were used, the non-adherence could be on the patients' part. Despite these issues, the results still provided useful indications of EBMT exposure in PAD patients. Thirdly, the reported adherence levels do not reflect actual patient adherence. Having a prescription or dispensing record does not necessarily mean drug administration. However, this is an inherent limitation of large scale pharmaco-epidemiological studies. Fourthly, by including only articles published in English, we might have missed some studies. Lastly, our review did not include most of the primary studies in the previous systematic review by Flu et al. likely due to the slightly different search terms used.<sup>11</sup> However, we found very similar results so this was unlikely to have affected our conclusions.

## CONCLUSION

In conclusion, EBMT adherence in PAD patients is highly variable and a substantial proportion in many settings are undertreated. Our results also point to research gaps in 2 areas. Firstly, more Asian studies of EBMT adherence are needed. Secondly, for settings with less-than-ideal EBMT adherence, implementation studies on strategies to improve adherence to EBMT are the logical next steps.

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## ST-segment elevation myocardial infarction in post-COVID-19 patients: A case series

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### ABSTRACT

Coronavirus disease 2019 (COVID-19) is associated with an increased risk of thromboembolic events in the acute setting. However, the abnormal thrombotic diathesis is not known to persist into the recovery phase of COVID-19 infection.

We described 3 cases of ST-segment elevation myocardial infarction in healthy male patients who recovered from COVID-19 with no prior cardiovascular risk factors. They shared features of elevated von Willebrand factor antigen, factor VIII and D-dimer level. One patient had a borderline positive lupus anticoagulant. Intravascular ultrasound of culprit vessels revealed predominantly fibrotic plaque with minimal necrotic core. Clot waveform analysis showed parameters of hypercoagulability. They were treated with dual antiplatelet therapy, angiotensin-converting-enzyme inhibitor, beta blocker and statin. These cases highlight the strong thrombogenic nature of COVID-19 that persisted among patients who recovered from infection. Several suspected mechanisms could explain the association between vascular thrombosis in the convalescent period (endothelial dysfunction, hypercoagulability, systemic inflammatory response and vasculopathy). Additional studies on “long COVID” are essential for identifying endotheliopathy and thrombotic sequelae.

Ann Acad Med Singap 2021;50:425-30

**Keywords:** Coronary artery disease, hypercoagulability, pandemic, thrombosis

Coronavirus disease 2019 (COVID-19) has been associated with thromboembolic phenomenon in the early phase of disease. Growing evidence suggests a hypercoagulable state as well as abnormal platelet activation, impaired fibrinolysis, and endothelial dysfunction in COVID-19 patients, resulting in thrombosis.<sup>1-3</sup> The lungs are thought to be the epicentre of thrombosis, where thrombosis may manifest as in situ pulmonary thrombosis, as well as systemic micro- and macrovascular thrombosis. Little is known about post-COVID-19 thrombotic complications.<sup>4</sup>

Singapore adopted a mass screening strategy for its foreign workers after COVID-19 clusters were discovered in their dormitories.<sup>5</sup> We report 3 cases of healthy male foreign workers who presented with massive acute myocardial infarction (AMI) after recovery from COVID-19. All 3 had raised immunoglobulin G levels for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that is indicative of seroconversion

(Table 1). Prior to their AMI presentation, the cases were asymptomatic and belonged to a low-risk group. They did not require hospital admission nor thromboprophylaxis and were quarantined at isolation facilities.<sup>6</sup>

**Case 1.** A 38-year-old man, with no significant cardiovascular risk factors, was admitted to the emergency department with an out-of-hospital ventricular fibrillation (VF) cardiac arrest. He presented 80 days after his positive SARS-CoV-2 antibody serology on 9 July 2020. He was successfully resuscitated, and a subsequent electrocardiogram (ECG) showed ST-segment elevation in anterior leads. He was intubated for airway protection and started on vasopressor support for cardiogenic shock. Urgent coronary angiogram showed single vessel coronary artery disease with a complete occlusion of the left anterior descending artery (LAD) (Fig. 1A). Intravascular ultrasound (IVUS) with Eagle Eye IVUS Catheter (Philips Healthcare,

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Table 1. Characteristics and investigation of 3 cases of post-COVID-19 acute myocardial infarction

	Case 1	Case 2	Case 3
Age, years	38	50	36
Sex	Male	Male	Male
Cardiovascular risk factors	None	None	None
SARS-CoV-2 RT-PCR results and dates	Negative 24 Jun, 27 Sep, 28 Sep, 3 Oct 2020	Positive 4 Jun 2020  Negative 29 Nov, 30 Nov 2020	Negative 6 Jun, 14 Jul, 30 Nov 2020
SARS-CoV-2 total antibody result and date	Positive 9 Jul 2020	Positive 8 Jun 2020	Positive 18 Jun 2020
Arterial event	27 Sep 2020	29 Nov 2020	30 Nov 2020
	VF arrest, myocardial infarction, occlusion of LAD	VF arrest, myocardial infarction, occlusion of proximal LAD	Myocardial infarction, occlusion of LAD
No. of days from positive serology to thrombosis	80	174	165
D-dimer, µg/mL (reference range <0.5µg/mL)	>4	1.02	0.43
Fibrinogen, g/L (reference range 1.8–4.5g/L)	5.2	5.7	3.6
Activated partial thromboplastin time, s (reference range 27–37s)	31.8	26.5	28.8
Prothrombin time, s (reference range 11–14s)	15.7	13.7	12.7
Lupus anticoagulant	Weakly present	Absent	Absent
VWF antigen, % (reference range 56–160%)	366	215	92
Factor VIII, % (reference range 60–150%)	273	338	162
Treatment	Aspirin, ticagrelor, drug eluting stent implantation	Dual antiplatelet therapy, drug eluting stent implantation, glycoprotein IIb/IIIa inhibitor	Dual antiplatelet therapy, drug eluting stent implantation
Follow-up and outcome	Successful treatment, undergoing rehabilitation	Successful treatment, discharge on day 12	Successful treatment, discharge on day 6

LAD: left anterior descending artery; RT-PCR: reverse transcription-polymerase chain reaction; VF: ventricular fibrillation; VWF: von Willebrand factor

Cambridge, US) revealed a minimal amount of clot, which was retrieved using a thrombectomy device. Virtual histology (via IVUS) showed a focal, heavily fibrous plaque burden of 59% with minimal necrotic core and minimal lumen diameter of 2.1mm in the ostial LAD (Fig. 1B). A drug-eluting stent (3.8x40mm) was subsequently implanted in the LAD with optimal result and an intraaortic balloon catheter was inserted for mechanical circulatory support.

The patient was initiated on our protocolised post-cardiac arrest care bundle including targeted

temperature management at 33 degrees Celsius in the cardiac intensive care unit. Chest X-ray revealed mild pulmonary congestion with no evidence of consolidation. His reverse transcription-polymerase chain reaction (RT-PCR) results for COVID-19 was negative. Transthoracic echocardiography (TTE) revealed moderate left ventricular systolic dysfunction (left ventricular ejection fraction 40%) with hypokinesia in the LAD territory. Laboratory results showed elevated von Willebrand factor (VWF) antigen of 366%, factor VIII 273%, elevated D-dimer 2.98µg/mL, and borderline



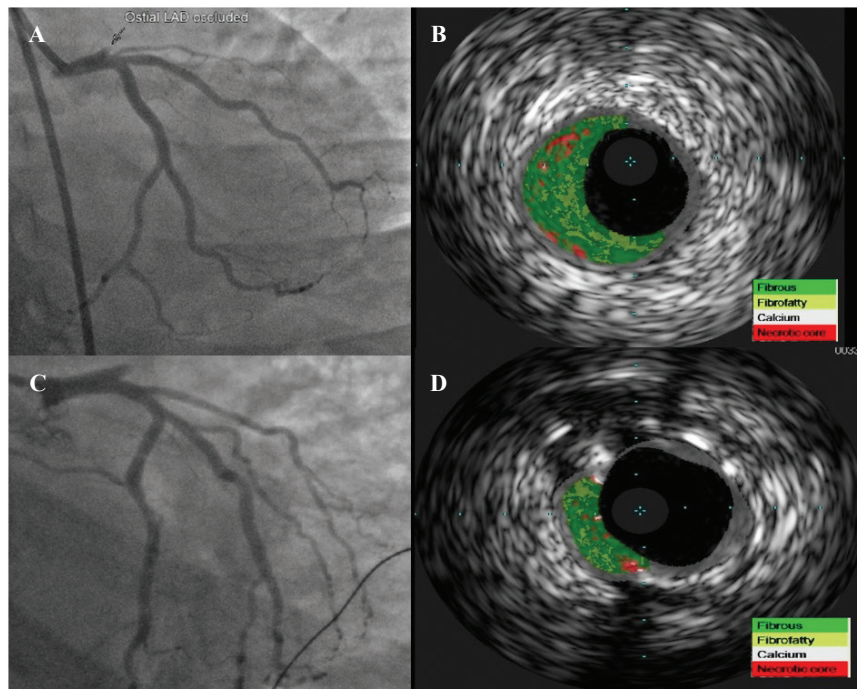


Fig. 1. (A) Coronary angiogram of Case 1 revealed acute occlusion of the ostial left anterior descending artery. (B) Virtual histology showed focal, heavily fibrous plaque burden of 59% with minimal necrotic core. (C) Coronary angiogram of Case 2 showed acute occlusion of the left anterior descending artery. (D) Subsequent virtual histology showed predominantly fibrous plaque burden of 31%.

positive lupus anticoagulant. A further workup did not reveal any evidence of hyperlipidaemia, diabetes mellitus, thyroid disorder or metabolic syndrome.

The patient's hospitalisation was complicated by lower limb compartment syndrome, which was treated with fasciotomy; acute kidney injury; and critical illness neuromyopathy. Tracheostomy was performed in view of prolonged mechanical ventilation and myopathy. He is currently undergoing intensive rehabilitation in our institution.

**Case 2.** A 50-year-old man presented to the emergency department for worsening chest pain. Initial physical examination revealed his blood pressure as 116/93mmHg; a heart rate of 120 beats per minute; and oxygen saturation 100% (on 2 litres of supplementary oxygen). Heart sounds were normal without murmurs and there were no abnormalities detected on lung auscultation. The man presented 174 days after his positive SARS-CoV-2 antibody test result on 8 June 2020. He developed a VF arrest while waiting for an ECG, where immediate resuscitation and defibrillation were carried out successfully. The ECG post-defibrillation showed ST-segment elevation in the anterior leads. The patient was subsequently intubated and transferred to the cardiac catheterisation laboratory. Coronary angiogram revealed acute thrombotic occlusion of

the ostial segment of LAD. Virtual histology (via IVUS) revealed a predominantly fibrous plaque (31% burden) that was successfully treated through thrombectomy, followed by stent implantation (Figs. 1C and 1D). Given the thrombus burden, he was treated with glycoprotein IIb/IIIa inhibitor (eptifibatide) infusion. TTE showed mild left ventricular systolic dysfunction (left ventricular ejection fraction 45%) with hypokinesia in the apex and anterior wall.

The patient had a high fibrinogen level of 5.7g/L (1.8–4.5g/L); elevated VWF level of 215% (56–160%); factor VIII level of 338%; and a raised D-dimer level of 1.02µg/mL (<0.5µg/mL). His cardiovascular risk factor screening panel and SARS-CoV-2 RT-PCR results were negative. Clot waveform analysis (CWA) through activated partial thromboplastin time using automated blood coagulation analyser CN-6000 (Sysmex Corp, Kobe, Japan) found a markedly elevated median maximum velocity (Min1) of 8.007%/s (reference range 2.86–6.78/s), elevated median maximum acceleration (Min2) of 1.341 (reference range 0.46–1.10), and a high median delta change of 68.6%/s (reference range 25.21–63.09) (Fig. 2).

The patient's clinical and haemodynamic condition improved gradually. He was extubated and discharged after 12 days of hospitalisation.

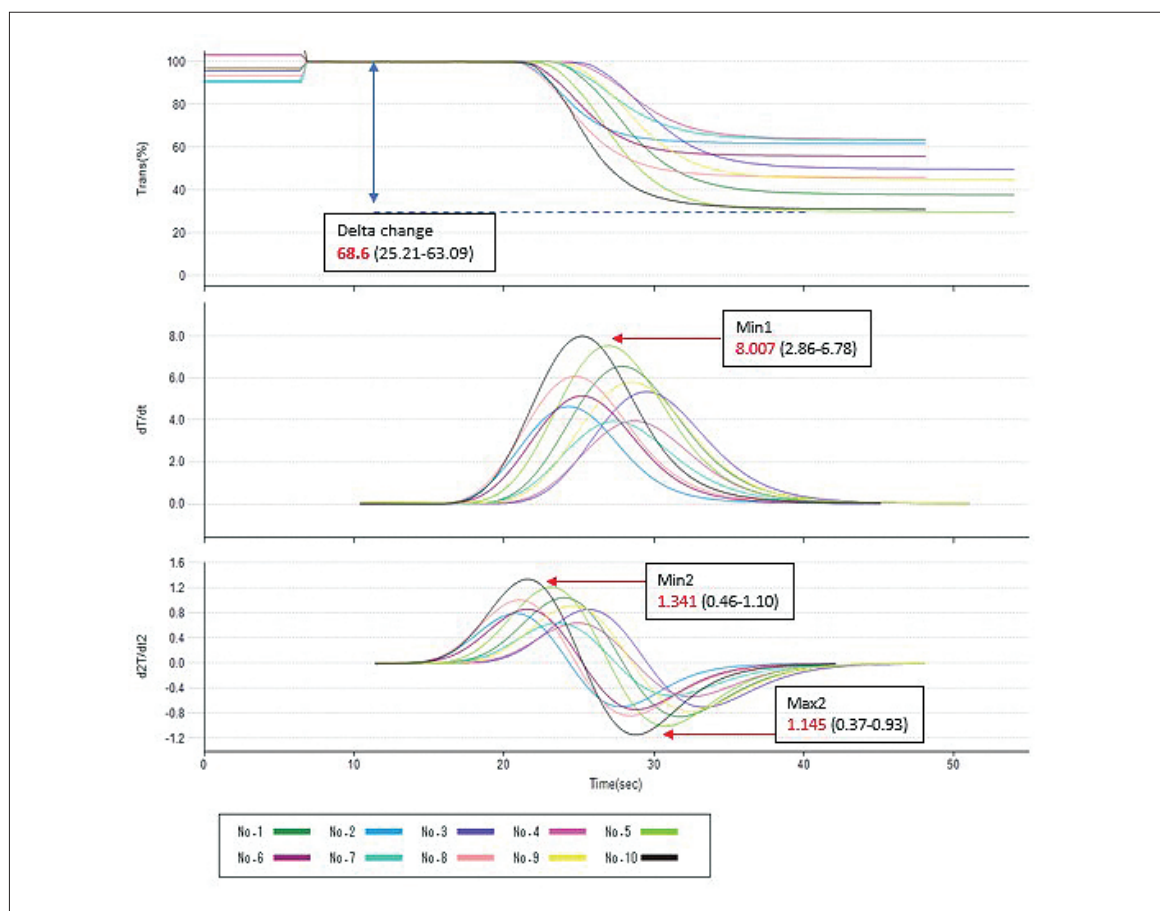


Fig. 2. Clot waveform analysis of Case 2. Patient's tracing is in black; healthy controls (for reference) in multicolour. CWA showed markedly elevated median Min1 of 8.007%/s, elevated median Min2 of 1.341 and high median delta change of 68.6%/s. Min1: maximum velocity; Min2: maximum acceleration; Max2: maximum deceleration

**Case 3.** A 36-year-old man was admitted to our hospital with a persistent chest pain of 3 hours. On admission, his blood pressure and heart rate were 120/88mmHg and 88 beats per minute, respectively. Oxygen saturation was 100% on room air with normal lung auscultation. ECG showed hyperacute T waves in the anterior leads and his RT-PCR results for COVID-19 was negative. He presented 165 days after his positive SARS-CoV-2 antibody serology on 18 June 2020. He demonstrated a raised factor VIII level of 162% and a VWF level of 92%. Coronary angiogram revealed an acute mid-LAD occlusion, for which he underwent angioplasty with successful implantation of a drug-eluting stent (Fig. 3). After percutaneous coronary intervention, the chest pain and ST-segment deviation resolved. The patient was discharged well on day 6 of his hospitalisation.

While it is known that approximately 30% of myocardial infarctions are preceded by an upper respiratory infection, in particular influenza; less is known about the thrombotic sequelae in COVID-19

during the convalescent period.<sup>7,8</sup> We described 3 cases of COVID-19 recovered patients who presented with AMI. The remarkable characteristics of these cases included their relatively young age without preexisting cardiovascular risk factors, preceding asymptomatic SARS-CoV-2 infection, and the presence of a long latency period between initial positive SARS-CoV-2 serology and their AMI.

Thrombosis has been classically associated with Virchow's triad of blood stasis, endothelial activation, and hypercoagulable state. However, in the convalescent phase after a COVID-19 infection, studies have described a waning hypercoagulable state with possible persistence of endothelial dysfunction in patients. This has been well described in children during their recovery from COVID-19.

Multisystem inflammatory syndrome in children (MIS-C) is a newly defined post-viral myocarditis and inflammatory vasculopathy of children following COVID-19 infection. MIS-C is likely due to viral tropism of myocardial and endothelial cells by the

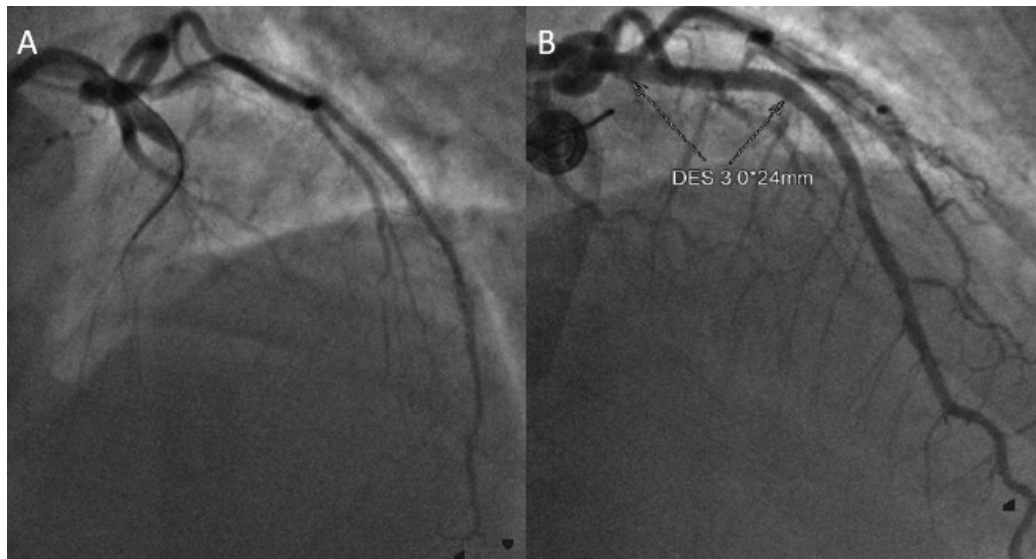


Fig. 3. (A) Coronary angiogram of Case 3 showed an occlusion of mid left anterior descending artery. (B) Re-establishment of blood flow after implantation of drug eluting stent.

coronavirus. The best evidence supporting MIS-C have been demonstrated in paediatric cases presenting with self-limited, chilblain-like acral purpuric lesion.<sup>9</sup> The children remain otherwise asymptomatic, and interestingly, often test negative for SARS-CoV-2 in nasopharyngeal samples. Some acute viral infections are associated with transiently elevated lupus anticoagulant, but they can persist and lead to thromboembolic complications by various mechanisms, including the release of microparticles and exposure of prothrombotic phospholipids.<sup>10</sup> Although the significance of these antibodies is not well established yet, COVID-19-induced lupus anticoagulant could favour the occurrence of thromboembolic events in children populations and hence should be systematically tested for.

Virtual histology via IVUS revealed heavily fibrous plaques in the coronary arteries of the cases described. This is unusual as fibrotic lesions are usually deprived of lipid and inflammatory cells, and hence less likely to rupture and generate thrombosis.<sup>11</sup> A fibrotic plaque consists mainly of fibrous tissue without a necrotic core or calcium.<sup>12,13</sup> This type of plaque is mostly indolent and stable in comparison with thin cap fibroatheroma, the main culprit in acute coronary syndrome. Interestingly, in the current cases described, delayed thrombotic arterial events occurred 80–174 days from the onset of positive SARS-CoV-2 serology. Laboratory evaluation of the haemostatic profiles with raised factor VIII, VWF and D-dimer supported an ongoing vasculopathy. The CWA, a global haemostatic test that was performed on case 2, demonstrated parameters of hypercoagulability. There were increased (1) clot Min1

“thrombin burst”; (2) peak of second derivative curve; (3) clot maximum deceleration; and (4) delta change (decreased light transmission reflective of increased clot thickness) as demonstrated by Fan et al.<sup>14</sup> In addition, autopsy series demonstrated the presence of cardiac microemboli despite the absence of viral particles in the myocardium.<sup>15</sup>

Our case series suggest that life-threatening myocardial infarction can occur unexpectedly in otherwise healthy patients with asymptomatic COVID-19 infection. Physicians should have a high index of suspicion in managing patients in the convalescent phase. Screening for and strict management of cardiovascular risk factors are of utmost importance post COVID-19. Further longitudinal studies in patients with “long COVID” should be performed to look for post-COVID-19 associated endotheliopathy and thrombotic sequelae, where there may be a role for thromboprophylaxis in high-risk groups.

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## Rhabdomyolysis following an intensive indoor cycling exercise: A series of 5 cases

### Dear Editor,

Spin cycling (spinning) is an increasingly popular indoor sport both in Singapore and worldwide. We find a growing trend in cases of spin-induced rhabdomyolysis (SIR) among beginners of this sport presenting to our Emergency Department (ED), all requiring hospitalisation for further treatment.

Spinning is an indoor cycling sport using a specialised stationary bicycle. It is often touted as an optimal aerobic sport, and a quick solution to increase one's metabolic rate and relieve stress. It is sometimes done in a group, with each session lasting 30–60 minutes. The intensity of cycling can be adjusted through cadence (i.e. the rate at which the cyclist pedals) and pedalling resistance.

Exertional rhabdomyolysis is the breakdown of muscle that occurs after excessive or unaccustomed exercise. It is characterised by muscle pain, markedly elevated levels of serum muscle enzyme (e.g. creatine kinase) and myoglobinuria.

We present a case series of 5 patients, all new to the sport, who developed exertional rhabdomyolysis after their spin session in March 2020. They presented to the ED of the Changi General Hospital, Singapore. This study was approved by the SingHealth Institutional Review Board (CIRB 2020/2475).

**Cases.** The 5 patients' presenting history, clinical features, diagnostic workup, and medical management are as described. All patients were young adults in their 20s, non-smokers, with no significant comorbidities. Three of them did not exercise regularly (once per month), while 2 did aerobic exercises 3–4 times a week. Four were attending their first spin class, while 1 was attending her second class. In all the cases, the spin sessions were done as a group and in the presence of a class instructor. The spin duration for these patients was 45 minutes.

The patients presented 2–4 days after their spin class. All had a common presenting complaint of bilateral thigh pain. Four also passed brown or dark urine, with the onset occurring 2–3 days after spinning. None of the patients had any intercurrent illnesses, or had any trauma.

All 5 patients were given intravenous fluids and hospitalised. Peak serum creatine kinase (CK) levels for 1 patient remained at >100,000U/L for 3 days, while

peak levels for the rest ranged 11,000–65,000U/L. None presented with, nor developed renal impairment or compartment syndrome. The average length of stay was 2.4 days (range 1–4 days). All patients had decreasing serum CK levels, made good recovery and were well on discharge. Their demographic and clinical data are presented in Table 1.

**Discussion.** Spinning is a high-intensity workout, with a typical session lasting 30–60 minutes. A vigorous 30-minute class can burn as much as 300–500 calories. SIR has been documented after just 15 minutes into a spinning session in an untrained person.<sup>1</sup>

A spin bicycle, compared to a stationary exercise bicycle, closely mimics the body position of a road bike as the handlebar position is lower and causes the rider to lean forward more. When spinning from a seated position, exertion is focused on the large muscle groups, namely the quadriceps and gluteal muscles.<sup>2</sup> Therefore, the commonest complaint of those suffering from overexertion and rhabdomyolysis is thigh pain.

In the literature, a large majority of cases reported were women.<sup>2–5</sup> This is in contrast to exertional rhabdomyolysis across all other sports that occur more frequently in men.<sup>6</sup> This may reflect the popularity of spinning among women or temporal trends in class enrolment, rather than any predisposition of females for SIR. Most cases of SIR presented after the first spin class, which is consistent with our study<sup>2,5,7</sup> and reflect the increased risk of overexertion in spinning for those who are not accustomed to high-intensity workouts.

The average time of presentation to the ED is 3 days after the spin class, which is concerning. Patients may have attributed symptoms of thigh pain to unaccustomed exercise and the effect of a good workout, leading to delayed attention. All but 1 patient presented to the ED only after the onset of brown or dark urine, which occurred 2–3 days after the spinning session. One patient even presented to our ED after receiving treatment for a urinary tract infection. We extrapolated that she was treated presumptively for this due to the presence of haematuria, which also occurs in rhabdomyolysis due to myoglobinuria. These delayed presentations reflect a lack of awareness among beginners on the possibility of rhabdomyolysis following spinning. Many cases may also have been missed.



Table 1. Patient characteristics and clinical details

	Patient				
	1	2	3	4	5
<b>Demographics</b>					
Age	26	25	23	23	25
Sex	F	F	F	M	M
Frequency of aerobic exercise (per week)	3	0 <sup>a</sup>	0 <sup>a</sup>	4	0 <sup>a</sup>
<b>Spin class details</b>					
Attended previous spin class?	No	Yes <sup>b</sup>	No	No	No
	1st spin class	2nd spin class	1st spin class	1st spin class	1st spin class
Class duration (min)	45	45	45	45	45
<b>Clinical details</b>					
Presentation, day (from day of spin session)	4	3	4	3	3
<b>Symptoms</b>					
	Bilateral thigh pain Brown urine	Bilateral thigh pain Back pain Dark urine	Bilateral thigh pain	Bilateral thigh pain Dark urine	Bilateral thigh pain Brown urine
<b>Serum CK (U/L)</b>					
Peak	>100,000	65,619	11,581	65,794	55,451
Before discharge	27,982	9,045	9,881	34,308	49,054
Peak ALT/AST (U/L)	(not done)	193/692	52/132	536/910	171/830
Renal impairment	No	No	No	No	No
Other complications	No	No	No	No	No
LOS (days)	4	4	1	2	1

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; LOS: length of stay

<sup>a</sup> Less than once a month<sup>b</sup> Participated in a spin class 1.5 years ago

In our literature review, most patients with SIR do well following aggressive hydration with intravenous fluids. However, there have been rare cases of renal failure requiring haemodialysis, and compartment syndrome of the thighs requiring fasciotomy.<sup>1,7,8</sup>

Compared to outdoor cycling, external factors that may decrease the intensity of exercise such as the need to turn, avoid obstacles or stop for traffic are removed in spin cycling. Spin cycling can also be done in a comfortable air-conditioned environment that is free of obstacles, where participants are kept engaged with fast tempo music. Videos may also be projected during sessions, heightening engagement or even distraction from exhaustion. Dimmed lights may also make participants feel less self-conscious and push them to exercise harder. They are also encouraged to “ride with the pack” and teamwork is often emphasised. It is possible that a combination of these conditions will push a newcomer to go beyond his or her physical limit.

**Preventive measures.** We suggest the grading of spin classes and advocate lower levels of intensity for initial sessions. More attention should be given to participants who are new to the sport, as well as those with sedentary lifestyles. Instructors should exercise extra care towards these participants, as they are more likely to push themselves beyond their limit. Participants should be educated on the risk of overexertion and its complications, and be informed of preventive measures such as adequate warm-up, hydration and nutrition.<sup>6</sup> Finally, spin class should not be advertised as merely casual exercise and a trendy fad, but instead, as a high-intensity workout.

This article was written to raise awareness on the increasing number of SIR cases among beginners. SIR can occur after just a brief period of intense spinning in an untrained person. It may be under-reported as severe complications are rare, and participants are usually young

and healthy. We advocate setting an advisory to inculcate safe practice especially for beginners, such as through recommendations for graded training, awareness of overexertion among trainers and participants, and pre-/post-exercise preventive measures.

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## Factors influencing choice of treatment modality for varicose veins in Singapore

### Dear Editor,

Chronic venous insufficiency (CVI) is common and potentially debilitating.<sup>1</sup> Following technological advances, management of CVI has shifted from traditional high tie, ligation and stripping to minimally invasive endovenous ablative techniques, resulting in faster recovery.<sup>2</sup>

While the National Institute of Health and Clinical Excellence (NICE), UK<sup>3</sup> and the Society of Vascular Surgery, US<sup>4</sup> that cater largely to Western populations<sup>5,6</sup> recommend endothermal ablation as first line treatment for CVI, there are no Singaporean guidelines for varicose vein treatment. Asian and Caucasian superficial venous anatomy and reflux patterns can differ significantly,<sup>7</sup> with Asians presenting with more severe CVI than their Caucasian counterparts. Hence the applicability of the UK and US guidelines to the Singapore context may be limited.<sup>8</sup>

This study aimed to investigate the modalities offered by vascular surgeons in Singapore for the treatment of CVI and factors influencing their choice.

**Questionnaire and analysis.** A postal questionnaire was sent to all accredited members of the Society for Vascular and Endovascular Surgeons of Singapore, accompanied by a letter explaining the aims of the study. Vascular surgeons in both restructured public and private hospitals were included.

Four key areas assessed were the type of venous practice, motivations and obstacles faced in the use of treatment, follow-up practice, and clinical scenarios where respondents had to choose their preferred treatment modality.

Numerical data were presented as mean (standard deviation) for parametric and median (interquartile range) for non-parametric data. Factors that influenced treatment choices were ranked by the respondents according to perceived importance. Consensus was defined as when >33% of the respondents responded in agreement in view of the small cohort (n=34).

**Baseline characteristics of respondents.** Between April and December 2018, 31/34 (91.2%) vascular surgeons in Singapore responded to the questionnaire; 24/31 (77.4%) surgeons worked in public restructured

hospitals, 6/31 (19.4%) worked in the private sector and 1/31 (3.2%) worked in both. The mean age of respondents was 41.7 ( $\pm 5.9$ ) years and the mean number of years practising as a vascular specialist was 8.8 ( $\pm 5.5$ ) years.

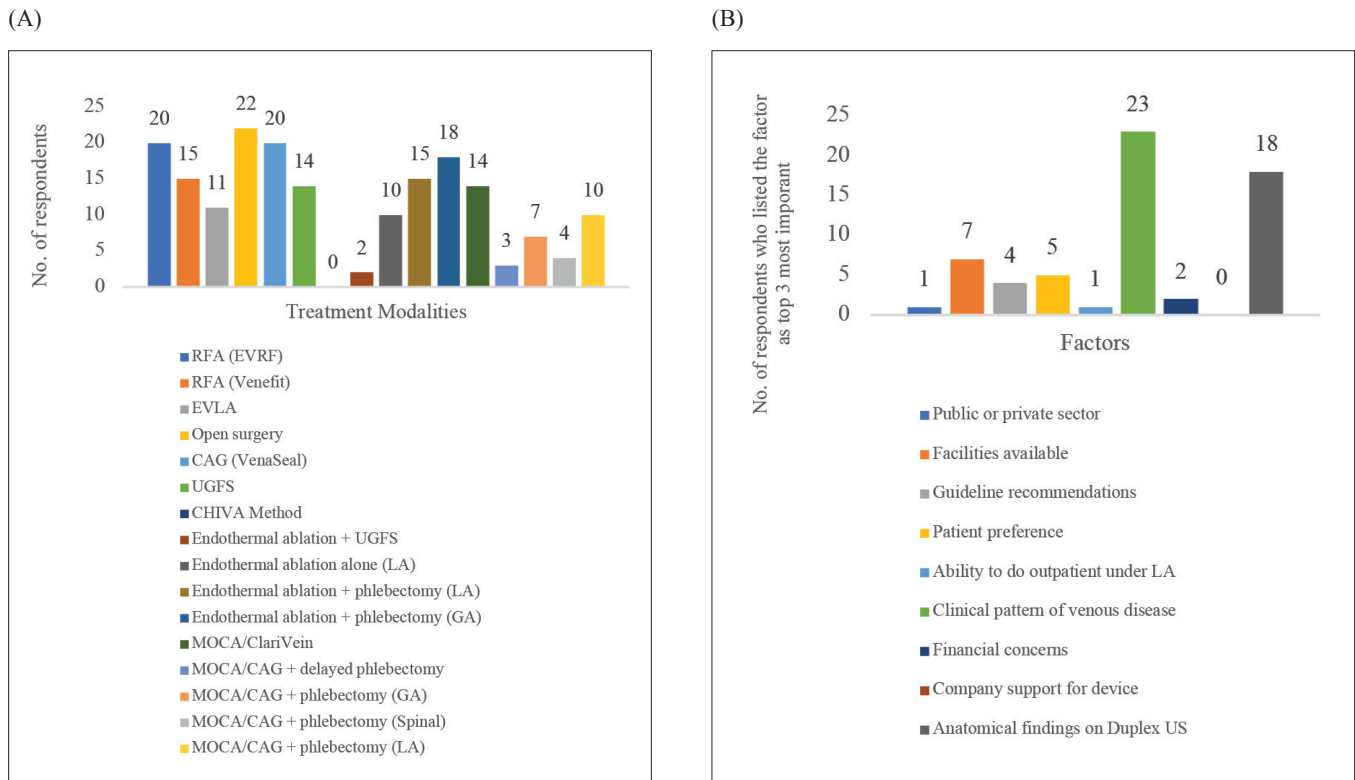
The median range of superficial venous procedures performed annually was 51–100; 19/31 (61.3%) respondents indicated that they treated CVI of Clinical, Etiological, Anatomical, Pathophysiological classification (CEAP)  $\geq 3$  with endovascular or open techniques, and CEAP  $\leq 2$  were treated conservatively with compression hosiery.

**Factors influencing choice of treatment.** Open surgery (22/31, 70.9%), cyanoacrylate glue (CAG) ablation (20/31, 64.5%) and radiofrequency ablation (20/31, 64.5%, Fig. 1) were the 3 most commonly offered treatment modalities. “Clinical pattern of venous reflux” (23/31, 74.1%) was the most important factor influencing respondents’ choices of treatment, followed by “duplex ultrasound findings of anatomy of truncal vein” (18/31, 58.0%) and “facilities available” (7/31, 22.5%). Only 4/31 (12.9%) ranked “guideline recommendations” among the top factors in influencing treatment choice.

Respondents had consensus in choosing treatment based on truncal vein anatomy (90.3%), treating from the lowest point of truncal reflux (71.0%), performing stab phlebectomies concurrent with truncal ablation (77.4%), and prescribing post-operative compression stockings (77.4%).

Endothermal ablation with phlebectomy was the preferred mainstay treatment for majority of the scenarios. There was consensus (35.5%) for the use of endothermal ablation with phlebectomy in patients with “very extensive varicose veins in one and both legs”. There was also consensus (35.5%) for conservative management in “patients above 80 years of age”. However, there were several instances where other treatment options were preferred, such as mechanochemical endovenous ablation (MOCA) for “below knee great saphenous vein (GSV) incompetence” and “total GSV incompetence”; CAG for “patients above 80 years of age” and patients with “below knee GSV incompetence”; conservative treatment for “patients above 80 years of age”, patients

Fig. 1. (A) Preferred treatment modality (N=31). (B) Ranking importance of factors influencing treatment choice. (C) Respondents' response to common treatment practices. (D) Treatment preference for various scenarios.



CAG: cyanoacrylate glue (ablation); CHIVA: Conservatrice Hémodynamique de l'Insuffisance Veineuse en Ambulatoire (ambulatory conservative haemodynamic correction of venous insufficiency); DUS: duplex ultrasound; DVT: deep vein thrombosis; EVLA: endovenous laser ablation; EVRF: endovenous radiofrequency ablation; GA: general anaesthesia; GSV: great saphenous vein; LA: local anaesthesia; MOCA: mechanochemical endovenous ablation; PAD: peripheral artery disease; RFA: radiofrequency ablation; SSV: small saphenous vein; UGFS: ultrasound-guided foam sclerotherapy; US: ultrasound; VTE: venous thromboembolism

with “concomitant severe deep venous reflux” and cosmetic reasons; and surgery for “very large incompetent truncal vein”.

**Post-operative follow-up.** There was no consensus in post-operative follow-up interval and performing post-operative duplex ultrasound. More than half of the vascular surgeons (54.8%) scheduled clinical follow-up 2 weeks post-operatively.

**Discussion.** Our study attempted to investigate the beliefs and practices of vascular surgeons in Singapore. Our response rate (91.2%) surpassed that of the UK and Canada-based studies we reviewed.<sup>5,6</sup>

Endothermal ablation, open surgery and CAG ablation were the most commonly offered treatment modalities, consistent with present NICE guidelines. When deciding treatment for CVI, clinical reasons most strongly influenced the decisions of vascular surgeons in Singapore, with pattern of disease and anatomical

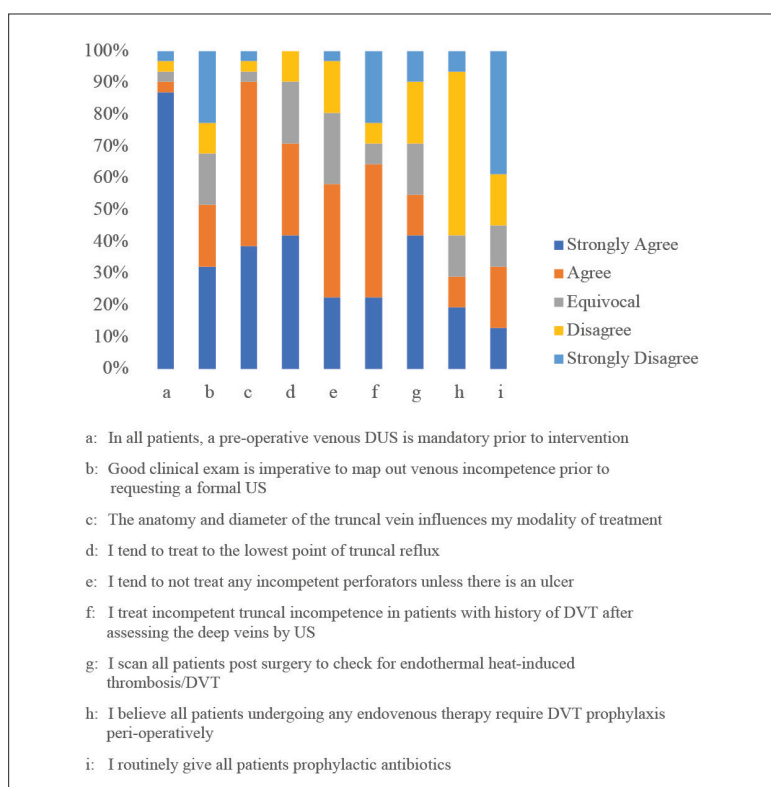
findings on duplex ultrasound being the predominant factors surgeons consider. Guideline recommendations were not commonly cited as influencing treatment choice, reflecting the preference for individualised treatment for different CVI presentations. Possible reasons for variation in practice include prior training expertise, beliefs, cost concerns and diversity of patient pool.

Endothermal ablation with phlebectomy was favoured for treating extensive unilaterally (41.9%) or bilaterally (38.7%) varicose veins, and women (35.5%). This was in contrast with 9.7%, 19.4% and 6.5% who preferred open surgery for unilateral varicose veins, bilateral extensive varicose veins and women respectively. Endothermal ablation was likely preferred due to the superior cosmetic outcome and lower risk of saphenous nerve damage.

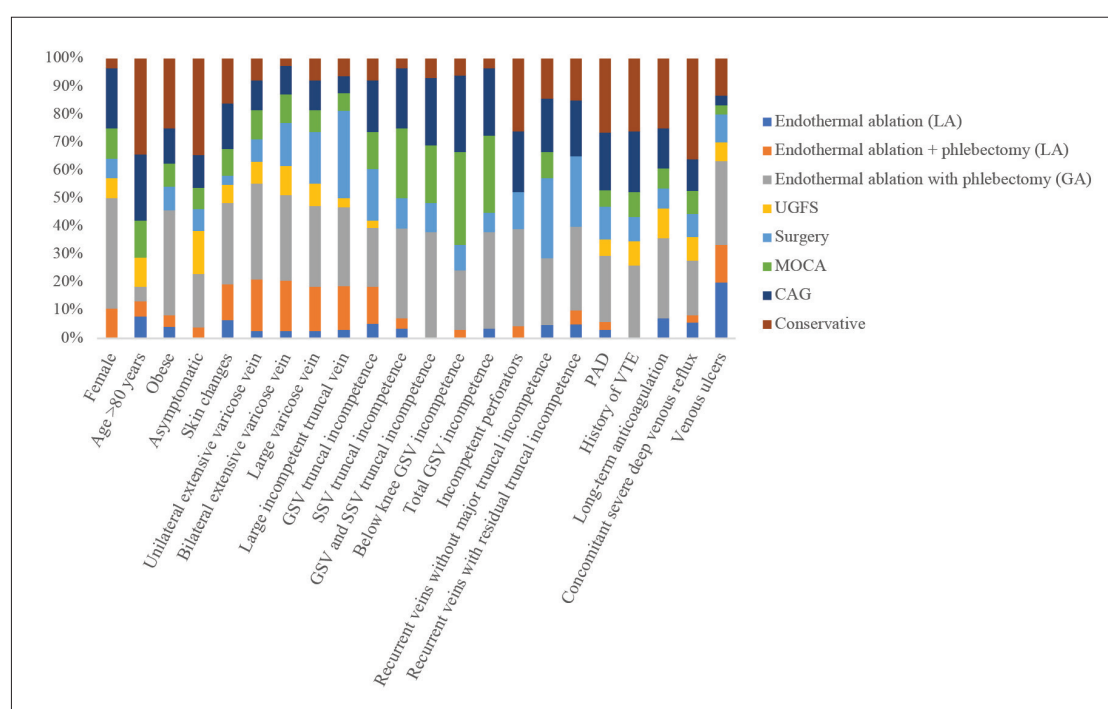
MOCA was favoured by vascular surgeons in treating below knee GSV incompetence (35.5%), compared to

Fig. 1. (A) Preferred treatment modality (N=31). (B) Ranking importance of factors influencing treatment choice. (C) Respondents' response to common treatment practices. (D) Treatment preference for various scenarios. (Cont'd)

(C)



(D)



CAG: cyanoacrylate glue (ablation); CHIVA: Conservatrice Hémodynamique de l'Insuffisance Veineuse en Ambulatoire (ambulatory conservative haemodynamic correction of venous insufficiency); DUS: duplex ultrasound; DVT: deep vein thrombosis; EVLA: endovenous laser ablation; EVRF: endovenous radiofrequency ablation; GA: general anaesthesia; GSV: great saphenous vein; LA: local anaesthesia; MOCA: mechanochemical endovenous ablation; PAD: peripheral artery disease; RFA: radiofrequency ablation; SSV: small saphenous vein; UGFS: ultrasound-guided foam sclerotherapy; US: ultrasound; VTE: venous thromboembolism



25.8% for total GSV incompetence. Below knee GSV incompetence treated with MOCA has been shown to have faster recovery and lower post-procedural pain.<sup>9</sup> The choice of conservative management with stocking and venoactive medication was influenced by patients' age (>80 years old, 41.9%), possibly because elderly patients with physical impairments were less likely to comply with treatment such as compression stockings.<sup>10</sup>

There were several limitations to our study. First, due to the wide variety of treatment options available, only the more commonly used modalities were included in our questionnaire for pragmatic purposes. Second, as this was a questionnaire administered on a self-reported basis, there might have been response bias where respondents were more receptive to newer treatment modalities. Nevertheless, the response rate of >90% was uncharacteristically high, lending strength to the findings.

Conventional treatment modalities continue to be mainstays of CVI treatment in Singapore. Vascular surgeons had consensus in certain aspects, but also had differing opinions on the preferred treatment modalities for different scenarios. Future studies comparing the efficacy of various treatment modalities would help to further examine consensus among vascular surgeons in Singapore and aid in forging guidelines for treatment of varicose veins in Singapore.

#### Acknowledgement

*This project was funded by a SingHealth Medical Student Talent Development Award (SMSTDA) (2018/2019).*

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## Concomitant fracture of the coracoid process following acromioclavicular joint dislocation

### Dear Editor,

Isolated acromioclavicular joint (ACJ) dislocations occur in 9% of shoulder injuries. However, ACJ dislocations with concomitant fracture of the coracoid process are rare. We describe a case of ACJ dislocation in detail, and review all 57 cases reported in the literature for clinical and radiographic characteristics; mechanism of injury; treatment plans; and overall outcomes in relation to such injuries.

A 53-year-old right-handed man missed the steps of a staircase and fell, sustaining a left shoulder injury. The man had a previous medical history of chronic kidney disease, hypertension, ischaemic heart disease, type 2 diabetes mellitus as well as hyperlipidaemia. He was a non-smoker and does not consume alcohol.

He presented to the emergency department 9 days after the accident, complaining of pain and limited mobility of his left shoulder. On examination, he had tenderness, swelling and a painful step deformity at the ACJ, with an active range of motion (ROM) limited to 90 degrees of abduction. There were no neurological symptoms. During subsequent orthopaedic consultation, post-trauma left shoulder radiographs showed ACJ dislocation and an Ogawa<sup>1</sup> Type I coracoid process fracture. When compared with the contralateral side, the displacement of the left coracoclavicular (CC) distance was not significant. Left shoulder magnetic resonance imaging (MRI) confirmed a mildly displaced avulsion fracture through the base of the coracoid process; torn AC ligament; and sprained but intact CC ligament (Fig. 1). A small posterosuperior glenoid labral tear was seen at the 11 o'clock position. The coracoid fracture was not demonstrated to be close to neurovascular structures on MRI.

The patient elected for conservative management, given his significant cardiovascular comorbidities and relatively low functional demands. Treatment with an arm-sling was instituted. A month later, the patient experienced reduced pain, but active ROM remained limited at 90 degrees of abduction and ACJ step deformity persisted. He underwent physiotherapy for passive ROM exercises with subsequent progression to active ROM and strengthening exercises. At 2 months follow-up, ROM improved to 140 degrees forward flexion and 100 degrees abduction. The patient's pain was minimal—3 out of 10 on the visual analogue scale for pain. The

patient was then discharged from physiotherapy for continued home exercise. Interval radiographs taken 2 months after the initial dislocation revealed a stable left ACJ dislocation with mild superior displacement of the coracoid process. At a final review 2 years post-injury, although a small palpable bump was present, the patient was free of pain, with full ROM (forward flexion and abduction 170 degrees; external rotation 60 degrees; internal rotation to the level of T10). He declined further imaging as he had been clinically well and was discharged.

The ACJ and coracoid process form an integral part of the superior shoulder suspensory complex (SSSC), which includes the distal clavicle, acromion, glenoid and CC ligaments,<sup>2</sup> that contributes to biomechanical stability. Therein lies the importance of recognising ACJ dislocations with concomitant coracoid fractures, because they represent a double disruption of the SSSC to weaken biomechanical stability significantly.

Three main mechanisms of ACJ dislocations with concomitant coracoid process fractures were described by DiPaolo et al.<sup>3</sup> The second mechanism, involving a direct blow to the ACJ, best describes our patient's injury following his fall. The traumatic force pushes the acromion caudad while the coracoid process is pulled by the CC ligament with the clavicle cephalad, avulsing it from its base.

ACJ injuries are typically classified based on the Rockwood 6-type classification system. In spite of the normal radiographic CC distance, our patient's case was likely a Rockwood Type III variant. The broken coracoid process was displaced superiorly and the ACJ was dislocated with superior displacement of the clavicle, resembling a Rockwood Type III in principle where both acromioclavicular and CC ligaments are ruptured. We also observed the concomitant Ogawa Type I coracoid fracture,<sup>1</sup> as the fracture occurred at the base of the coracoid process (Fig. 1). This association with an Ogawa type I coracoid fracture has been reported in more than 50% of ACJ injuries associated with coracoid fractures.<sup>3</sup>

We summarise our case presentation and review all 57 cases reported in the literature (Table 1). Kose et al. reported 2 cases and reviewed 46 cases in the literature in 2015.<sup>4</sup> There were 9 additional cases reported after 2015.<sup>5-12</sup>

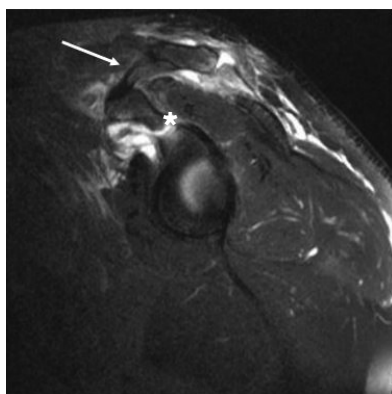


Fig. 1. Sagittal T2-weighted MRI of the left shoulder 10 days post-injury, demonstrating a mildly superiorly displaced avulsion fracture through base of the coracoid process; torn AC ligament; and sprained coracoclavicular ligament. White arrow indicates intact coracoclavicular ligament; asterisk shows site of coracoid fracture.

Half (47.3%) of the documented cases were managed completely by conservative means, reflecting the ongoing debate on conservative versus surgical approaches for such fractures. Given the rarity of case reports in the literature, and that most surgeons have treated a few cases at most with varying surgical techniques and indications, statistical analysis of the cases was not feasible. However, functional outcomes for both conservative and surgical management of the cases have largely been good and excellent.

Surgery may be indicated for a few reasons, such as: (1) young patients requiring significant upper limb strength for work or hobbies; (2) neurovascular compromise; (3) open fractures; and (4) symptomatic non-union. However, conservative treatment may be preferred due to the peri-operative anaesthetic and procedural risks,

Table 1. Outcomes of published cases<sup>a</sup> of ACJ dislocation associated with coracoid process fracture, including the current case presentation

Management of coracoid process fracture (n=55)				
Outcome	Excellent	Good	Poor	NR
Conservative treatment	18	9	1	2
<b>Surgical treatment</b>				
Open reduction and internal fixation	14	3		2
Dewar-Barrington procedure <sup>b</sup>		3		
Kirschner wire	1			
Non-specific	2			
Management of ACJ dislocation (n=57)				
Outcome	Excellent	Good	Poor	NR
Conservative treatment	14	9	1	2
<b>Surgical treatment</b>				
Coracoclavicular ligament repair			1	
Kirschner wire	7	2	1	
Tension-band wiring		1		
Screw fixation	5			1
Hook plate fixation	3	1		
Dewar-Barrington procedure <sup>b</sup>		3		
Modified Neviaser's procedure <sup>c</sup>		1		
Non-specific				1
<b>Non-specific</b>	4			

ACJ: acromioclavicular joint; NR: not recorded

<sup>a</sup> Cases in REFERENCES numbers 3–12

<sup>b</sup> Dewar-Barrington procedure: A method of transferring the conjoint tendon to the lateral clavicle for the treatment of high-grade AC dislocations to stabilise the clavicular strut and maintain anatomical apposition of the acromioclavicular and coracoclavicular ligaments for recovery

<sup>c</sup> Modified Neviaser's procedure: Reduction of a complete ACJ dislocation by surgical transfer of the coracoacromial ligament, along with a piece of bone detached from the acromial end, to the distal end of the clavicle and fixed with a cancellous screw

and we recommend that each case be considered individually before arriving at a treatment decision. Lastly, depending on the fracture morphology and injury mechanism, further imaging with computed tomography may be considered for further evaluation.

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## Asthma, drug allergies and iodinated contrast media: A retrospective evaluation and proposed CT workflow

Dear Editor,

Contrast-enhanced computed tomography scans (CECT) are frequently employed in clinical practice. However, there are adverse reactions associated with the administration of intravenous iodinated contrast media (IOCM). Apart from contrast nephropathy, patients with asthma and multiple drug allergies have an increased risk of contrast-related reactions compared to the normal population.<sup>1,2</sup>

Reactions can be divided into minor (e.g. rash and itch), intermediate (e.g. hypotension and bronchospasm) or severe (e.g. angioedema and cardiorespiratory collapse), and further classified into immediate, delayed and late reactions.<sup>3</sup> Immediate reactions occur within the first hour after contrast administration. The incidence of mild immediate reactions has been reported to be up to 3%, and severe reactions in up to 0.04%.<sup>3</sup> Delayed reactions are classified as occurring from 1 hour to 1 week post-contrast injection, while late reactions are defined as hypersensitivity reactions occurring more than 1 week post-contrast administration. Both of these are usually self-limiting, requiring only symptomatic treatment or none at all.<sup>4</sup>

At Tan Tock Seng Hospital in Singapore, the Department of Radiology's standard protocol requires patients with asthma or multiple drug allergies (excluding allergy to contrast media) scheduled for CECT to be premedicated with oral prednisolone 10mg 3 times a day for 3 days prior to the scheduled scan. Those who did not take or complete this regimen had to have their CECT postponed and rescheduled. Outpatient scans are not deemed medically urgent and intravenous hydrocortisone is discouraged.

However, in practice, we find a degree of non-compliance to the steroid premedication guidelines, particularly so for outpatient scans. There are 3 main reasons for this: (1) referring clinicians fail to prescribe the required medications; (2) patients forget to purchase or collect the medications from the pharmacy; and (3) patients overlook completing the regimen prior to their scan. In the preceding 6 months prior to implementation of our modified workflow, the number of postponements was 181 cases with a rate of 30.2 cases per month.

Similar statistics in 2017 and 2018 revealed 18.5 and 21.8 postponements per month, respectively, illustrating an increasing trend.

Recent literature is equivocal regarding the benefits of steroid prophylaxis in the prevention of adverse reaction to IOCM in these patients. While steroid premedication reduces occurrence of mild and moderate reactions, it appears to have minimal impact on severe reactions.<sup>5</sup> There is also suggestion that the use of premedication prophylaxis in patients with asthma is not necessary prior to contrast media administration, particularly when asthma is the sole indication or if it is well controlled.<sup>4,7</sup> Several major guidelines now do not mandate steroid premedication for patients with asthma or multiple drug allergies.<sup>1,3,6-8</sup> Furthermore, steroid premedication itself carries potential risks of hyperglycaemia and infection. Postponement may result in possible delay in diagnosis. Multiple sources have also shown a disproportionately large number of patients who need to be given prophylaxis, in order to prevent a reaction in a few, particularly for severe reactions.<sup>1</sup>

Based on the evidence, our institution has modified the existing protocol. Over a 6-month period from 1 August 2019 to 31 January 2020, outpatients who had inadequate steroid premedication on their day of scan were allowed to proceed with contrast administration for CECT if they had asthma (which had to be stable and well controlled) or multiple drug allergies, but not both. The Asthma Control Test (ACT) was used as screening tool, with stable well-controlled asthma defined as an ACT score of  $\geq 20$ .<sup>9</sup> This questionnaire is easy to apply in an outpatient setting and has been locally peer reviewed to show good accuracy.<sup>10</sup> Multiple drug allergies was defined as being allergic to  $\geq 4$  classes of drugs (excluding contrast media).<sup>1,5,6</sup> Patients must also have been counselled, understood risks of IOCM administration and were agreeable to a 1-hour observation period after the scan. This was more conservative compared to the recommended 30 minutes.<sup>4</sup> Follow-up for adverse reactions was done in one of 2 ways: via phone for patients who consented to be contacted; or review of the electronic medical records up to the time of the next clinic appointment.



Over the study period, there were 120 outpatients who did not receive optimal steroid premedication but proceeded with their scans. Of these, there were 2 patients with asthma having ACT scores of 16 and 17 who were inadvertently included after being counselled. This occurred in the first month of implementation due to possible lack of clarity, and it was reiterated that having a suboptimal ACT score despite patient agreeing were not mutually exclusive criteria. Details of these patients are summarised in Table I.

Follow-up of our patients revealed that 5 patients had documented adverse reactions. Three had background of asthma while two had multiple drug allergies. The adverse reactions were rash and pruritus ( $n=3$ ), wheal below the eye ( $n=1$ ) and wheeze ( $n=1$ ). Four of these patients developed symptoms during the 1-hour observation period and were managed accordingly before leaving the department. Phone review the next day revealed no recurrence of symptoms. One patient who was followed-up by phone described symptoms beginning only after leaving the department, but which had resolved at the time of review. All the adverse reactions were categorised as mild, and at worse, borderline moderate in the case of wheezing. They

were self-limiting or resolved with simple treatment. The 2 asthmatic patients with ACT scores of 16 and 17 remained asymptomatic after the scan and on follow-up. Fischer's exact test shows no significant difference between the asthma and allergy cohort developing a reaction ( $P=0.227$ ) and no difference by gender ( $P=0.647$ ).

Over this period, another 24 patients' scans were postponed either because they did not meet the criteria or were not keen to proceed with the modified protocol. They had their scans after completing the premedications. Of these, 22 had asthma and 2 had multiple drug allergies. Only 1 patient with asthma developed a rash that was self-limiting and could be discharged from the department. The delay for these 24 patients ranged from 3 to 21 days, with an average of 7.25 days per patient. The risk ratio of a patient with asthma or multiple drug allergies developing contrast reaction if they did not take their premedication was 1.00, suggesting no significant benefit of steroid premedication in this group of patients.

Under the modified workflow, this translated to a reduction in computed tomography scan postponement number averaging 20 patients per month and a salvage rate of 83.3%. This achieves our aim of reducing

Table 1. Patient demographics

	Value	Mean age (years)
<b>Age</b>	20–88 years n (%)	60.9 (SD=14.99)
<b>Sex</b>		
Male	47 (39.2)	61.0 (SD=15.40)
Female	73 (60.8)	60.9 (SD=14.82)
<b>Race</b>		
Chinese	81 (67.5)	63.3 (SD=14.63)
Malay	15 (12.5)	52.5 (SD=11.58)
Indian	16 (13.3)	63.1 (SD=15.43)
Others	8 (6.7)	48.1 (SD=13.43)
<b>Diagnosis</b>		
Asthma	98 (81.7)	60.9 (SD=15.40)
Allergy	22 (18.3)	61.1 (SD=13.30)
<b>Premedication</b>		
Not premedicated	109 (90.8)	
Not prescribed	79 (65.8)	
Forgot to collect from pharmacy	17 (14.2)	
Forgot to begin the course	13 (10.8)	
Partially completed	8 (6.7)	
Uncertain status	3 (2.5)	
<b>Mode of follow-up</b>		
Phone call	100 (83.3)	
Review of electronic medical records	20 (16.7)	

SD: standard deviation

wastage of precious scan slots, lowering cost, preventing delays in diagnosis, as well as overcoming patient and caregiver inconvenience and dissatisfaction. Nevertheless, there are limitations to our study. Firstly, the sample size is small and selective, and not generalisable. Secondly, we relied on medical record review for 20 patients. The number of delayed or late reactions may be under-reported, particularly if the outpatient visit was too long from the time of scan or deemed unimportant compared to the main clinical problem. Fortunately, these reactions are usually mild and may thus be considered clinically inconsequential.

In conclusion, although steroid premedication is still currently part of our local institution guidelines for patients with asthma or multiple drug allergies undergoing CECT, in the event that steroid premedication was inadvertently not administered, it is generally safe to allow patients with asthma (stable and well controlled) or multiple drug allergies (other than contrast allergy) to receive intravenous IOCM, after counseling for risks. This would reduce CT scan postponement rates without compromising patient safety.<sup>4</sup>

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## Quality of life in colorectal cancer patients with stoma or adjuvant therapy

### Dear Editor,

Colorectal cancer is one of the most common cancers worldwide. In Singapore, 9,324 new cases of colorectal cancer were diagnosed in 2010–2014, and it is the most common cancer among men (17.2% of cancer burden).<sup>1</sup> Compared to the period 2005–2009, there was an increase in the overall survival of all colorectal cancer patients in 2010–2014 (from 46.0% to 51.0%).<sup>1</sup> This trend may be due to earlier diagnosis of colorectal cancer and advances in multimodality treatment of the disease over the past few years.

Besides disease-free survival, quality of life (QoL) has emerged as an important outcome measure for cancer patients. Colorectal cancer patients may undergo surgery, radiotherapy, chemotherapy, or a combination of these modalities. These treatments can have long- and short-term effects and complications, resulting in a decrease in the QoL of cancer survivors; studies have reported the physical and psychological problems faced by cancer patients due to both disease and treatment.<sup>2,3</sup> In addition, rectal cancer patients are also thought to have a higher incidence of decreased QoL due to the risk of developing anal impairment.<sup>4</sup>

Nonetheless, there is a paucity of studies examining the consistency of these findings within an Asian setting. This cross-sectional exploratory study therefore aims to evaluate the QoL of colorectal cancer patients after diagnosis and treatment, focusing on the impact of chemotherapy or radiotherapy (chemo/RT) and creation of stoma.

The purposive sample of our study consisted of 100 patients who were above 21 years of age, had been diagnosed with colorectal cancer, and had undergone treatment within the National University Hospital, a tertiary hospital in Singapore. Patient eligibility was assessed using the hospital's clinical management system. The research team identified and recruited eligible patients between October 2015 and May 2016 when they presented for follow-up at the hospital's colorectal outpatient clinics. Written informed consent was obtained from participants before the administration of a pen-and-paper survey consisting of three sections: (1) participant sociodemographic characteristics, (2) type(s) of treatment undergone, and (3) the European Organisation for Research and Training of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).<sup>5</sup>

The EORTC QLQ-C30 is a 30-item patient questionnaire on general quality of life for cancer patients.<sup>6,7</sup> The EORTC QLQ-C30 has demonstrated high validity and reliability scores when adapted for use in Asian populations.<sup>8–10</sup> The present research only utilised the Global Health Status subscale, which corresponds to QoL. This was scored on a range of 0 to 100, in which 100 denotes perfect QoL.

Results were analysed using SPSS Statistics software version 21 (IBM Corp, Armonk, US) and  $P < 0.05$  was considered statistically significant. Sociodemographic variables (except age) were presented using frequencies and proportions. Age was presented using median and range. Univariate analysis was performed using independent samples t-tests or Mann-Whitney U tests for continuous variables. Fisher's Exact test was used to analyse for categorical variables.

The median age of our sample ( $N=100$ ) was 65 years (range 27–87 years). Fifty-one (51.0%) participants were men, with majority of Chinese ethnicity (82.0%). Most participants (93.0%) underwent surgical resection of the primary tumour, of which nearly half (45.7%) had a stoma created. Anterior resection (38.0%) and ultra-low anterior resection (19.0%) were the most common operations undertaken by patients in this cohort. More than half of the sample (61.2%) underwent chemotherapy or radiotherapy either as neo-adjuvant or adjuvant therapy. Table 1 reflects the baseline characteristics of our population. The mean QoL score of the sample was 68.0 (standard deviation  $=\pm 23.6$ ).

Table 2 compares the effect of stoma creation on QoL. Analysis was restricted to participants who had undergone the index operation within 2 years of the interview date. This was performed to understand the immediate physical and psychological effect of stoma creation on a person's QoL. We observed that stoma creation in the index operation had no significant effect on the QoL of participants ( $P=0.95$ ). Stoma reversal also did not have a statistically significant effect on the QoL ( $P=0.55$ ). When the QoL of patients with reversed stoma were compared to those without any stoma creation at all, there were also no significant differences ( $P=0.41$ ).

Comparing the QoL of patients who underwent chemo/RT within 2 years of the interview date against patients who never had chemo/RT at all (Table 3), no statistically significant difference was noted ( $P=0.27$ ). Among those patients who underwent surgical resection, chemo/RT within 6 months of interview did not result in a significantly different QoL compared to those without chemo/RT ( $P=0.43$ ). In a similar vein, patients who underwent chemo/RT within one month of interview had no significantly different QoL compared to those with chemo/RT more than 2 years ago ( $P=0.99$ ).

**Discussion.** Stoma creation and chemo/RT can potentially affect the QoL of patients with colorectal cancer. Our findings seem to suggest otherwise. Stoma creation or its subsequent reversal did not seem to have any statistically significant effect on patients' QoL. In addition, patients with chemo/RT did not suffer from a lower QoL.

It may seem logical that patients undergoing chemo/RT suffer from a lower QoL compared to those without. After all, there are plenty of potential side effects that may arise from chemoradiotherapy, such as nausea, vomiting, headaches, diarrhea and loss of appetite.<sup>2,3</sup> The results of this study suggest that the relative effects of adjuvant, compared to the psychological trauma of being diagnosed with cancer and undergoing surgical treatment, may not be as high as initially presumed.

Similarly, the creation of stoma is fraught with potential complications. These can range from physical effects, such as stomal stenosis or prolapse, to long-term psycho-sexual effects that may affect the well-being of the patient.<sup>11</sup> On the other hand, our findings seem to support several other studies such as that by Neuman et al. on QoL in patients with stoma by suggesting otherwise.<sup>12</sup> Surgeons and healthcare professionals may have underestimated the resilience patients have in relation to their disease.

Nonetheless as an exploratory study, the authors recognise that there are several limitations to the present research. One key issue was that the relatively small purposive sample precluded direct comparisons between colon and rectal cancer patients. The clinical

Table 1. Baseline characteristics of study population

	No. (%)
N=100	
Median age in years (range)	65 (27–87)
Gender	
Male	51 (51.0)
Female	49 (49.0)
Ethnicity	
Chinese	82 (82.0)
Malay	8 (8.0)
Indian	5 (5.0)
Others	5 (5.0)
Underwent surgical resection	93 (93.0)
Stoma created	43 (45.7)
Stoma not created	51 (54.3)
Underwent chemo/radiotherapy	61 (61.2%)
Operation	
Right colon resection	18 (18.0)
Left colon resection	8 (8.0)
Anterior resection	38 (38.0)
Ultra-low anterior resection	19 (19.0)
Abdominal perineal resection	6 (6.0)
Subtotal/total colon resection	5 (5.0)
No resection	6 (6.0)
Cancer type	
Colon	59 (59.6)
Rectum	40 (40.4)
Cancer stage	
I	15 (15.8)
II	29 (30.5)
III	39 (41.1)
IV	12 (12.6)
Mean quality of life score	68.0±23.6

Table 2. Comparison of effect of stoma creation on quality of life (QoL) within 2 years of index operation

	n	QoL score	Days from index operation	P value
Stoma created in index operation				0.947
Yes	29	65.0±24.8	248±163	
No	22	64.8±23.6	199±228	
Stoma reversed by the time of interview				0.546
Reversed	7	60.7±21.4	278±81	
Not reversed	22	66.7±26.1	173±175	
Reversed stoma compared to no initial stoma creation				0.405
Reversed	7	60.7±21.4	278±81	
No initial stoma	22	64.8±23.6	199±228	

Table 3. Comparison of effect of chemo/RT on quality of life (QoL)

	n	QoL score	P value
Effect of chemo/RT			
Chemo/RT within 2 years of interview	37	64.0±22.3	0.272
No chemo/RT at all	38	70.0±24.5	
Patients with surgery +/- chemo/RT			
Chemo/RT within 6 months of interview	22	66.7±24.7	0.433
No chemo/RT at all	35	71.7±22.3	
Effect of cessation of chemo/RT			
Chemo/RT within 1 month of interview	10	70.0±24.3	0.994
Chemo/RT more than 2 years ago	23	69.9±23.9	

Chemo/RT: chemotherapy/radiotherapy

stage of cancer could affect the overall QoL and could be a source of potential bias. In addition, the higher prevalence of individuals who undergo operations for left-sided colorectal cancer is not surprising as the majority of colorectal cancer occurs distal to the splenic flexure. However, we are aware that the high incidence of patients with stoma lends itself to considerable biases and is not reflective of the overall picture of all colorectal cancer patients undergoing surgery. This is likely purely down to chance and convenience sampling. Hence, moving ahead, as the interest in health services research and patient QoL increases, the present research has led the authors to embark on a larger scale multicentre prospective study with a more robust sampling frame.

To conclude, QoL continues to be an important aspect in the treatment of patients suffering from colorectal cancer. Stoma creation and chemo/RT may not have as large an impact on the QoL of patients as previously thought. We encourage further evaluations of the impact of colorectal cancer treatment on patients' QoL based on stage and type of cancer, sociodemographic profile, and treatment modality.

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## Meropenem and piperacillin-tazobactam levels for critical care patients during empiric therapy

### Dear Editor,

Individualised beta-lactam dosing in critically ill patients has been proposed as these patients have substantially altered pharmacokinetics (PK) of beta-lactams due to hypoalbuminaemia, aggressive fluid resuscitation, the existence of organ failure(s), as well as augmented renal clearance.<sup>1-4</sup> These physiologic changes are the basis for the significant inter-patient PK variability observed among the critically ill. In addition, intra-individual variability must also be anticipated due to rapidly changing clinical condition towards either improvement and cure, or deterioration and organ failures, after as short as 4 days of treatment.<sup>5</sup> Given that antibiotic dosing regimens are derived from healthy volunteers or non-critically ill patients and do not account for such PK variations, standard antibiotic dosing regimens may not be appropriate for the critically ill.

Pharmacodynamic effect of beta-lactams is described by the free drug concentrations above bacterial minimum inhibitory concentrations (MIC) over a desired percentage of the dosing period (%*fT*>MIC). These time-dependent antibiotics achieve more bacterial killing the longer they remain at serum levels above the MIC.<sup>6</sup> In vitro and in vivo animal studies have demonstrated that beta-lactam concentration should be maintained above the MIC between 40% and 70% of the dosing interval.<sup>7</sup> Improved clinical and microbiological outcomes have been demonstrated in patients with at least 100% *fT*>MIC for beta-lactams, especially in the critically ill.<sup>2</sup> A study also reported that clinical cure in critically ill patients required beta-lactam plasma concentration reaching 4 to 6 times the MIC to ensure adequate tissue penetration and to prevent resistance development.<sup>6</sup>

Given the lack of data on critically ill Asian patients, we aim to determine total meropenem and piperacillin component of piperacillin-tazobactam concentration in the first 24–48 hours (pre-steady state) and at day 3–4 (steady state) in our population.

A prospective observational study was carried out from July 2016 to March 2017 in the medical and surgical intensive care units (ICUs) of Tan Tock Seng Hospital, a 1,700-bed acute-care hospital in Singapore. Ethics approval and informed consent from patients or legal representatives were obtained. The inclusion

criteria were adult patients ( $\geq 21$  years), ICU admission and administration of piperacillin-tazobactam or meropenem. The exclusion criteria were expected mortality within 48 hours and pregnancy.

During pre-steady state, blood was drawn at 30 minutes, 1.5 hours and 3 hours from the start of infusion, and 30 minutes before the next dose. This was repeated at steady state. All assays were performed using liquid chromatography-tandem mass spectrometry. PK modelling and Monte Carlo simulations were performed using non-parametric adaptive grid algorithm in Pmetrics version 1.5.0 (Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, US) using a one-compartment model. Free drug concentration was estimated based on published protein binding values (2% for meropenem and 30% for piperacillin).

Among the total of 42 patients, 16 (38.1%) were prescribed piperacillin-tazobactam and 26 (61.9%) were prescribed meropenem. Patients were predominantly male (31/42, 73.8%). Median age was 70 years (interquartile range, IQR 60–74), median total body weight was 60kg (IQR 55–70) and median Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score was 23 (IQR 20–28) on day 1 of blood taking. Majority (34/42, 81.0%) required mechanical ventilation and inotropic support. Median calculated creatinine clearance using the Cockcroft-Gault formula was 29mL/min (IQR 17–55mL/min), and 9 patients (21.4%) required dialysis. The most common sources of infections were pneumonia (30/42, 71.4%), unspecified sepsis (8/42, 19.0%) and bacteremia (4/42, 9.5%). All patients received doses according to manufacturers' product information leaflet. Only 8 (19.0%) received extended infusion. Enterobacteriaceae spp. was most frequently isolated (12/18, 66.7%). Among these, the non-susceptible organisms had meropenem MIC of 4mg/L (1 isolate); piperacillin MIC of 32mg/L (1 isolate) and  $\geq 128$ mg/L (1 isolate); the remaining were susceptible (piperacillin-tazobactam, piperacillin MIC  $\leq 16$ mg/L, meropenem MIC  $\leq 0.25$ mg/L).

Attainment of PK targets for meropenem and piperacillin-tazobactam are reported in Table 1. Meropenem levels obtained were 3.5–96.9mg/L, with all patients obtaining 40% *fT*>5xMIC (free

Table 1. Attainment of PK targets for meropenem and piperacillin-tazobactam

Therapeutic target reached	50% <i>fT</i> >5×MIC (PT), 40% <i>fT</i> >5×MIC (M)	100% <i>fT</i> >MIC	100% <i>fT</i> >5×MIC
	n (%)	n (%)	n (%)
<b>Pre-steady state</b>			
Meropenem (M)	17/17 (100)	17/17 (100)	12/17 (70.6)
Piperacillin-tazobactam (PT)	4/12 (33.3)	7/12 (58.3)	3/12 (25.0)
<b>Steady state</b>			
Meropenem (M)	15/16 (93.8)	14/16 (87.5)	5/16 (31.3)
Piperacillin-tazobactam (PT)	4/10 (40.0)	7/10 (70.0)	2/10 (20.0)

%*fT*>MIC: free drug concentrations above bacterial minimum inhibitory concentrations (MIC) over a desired percentage of the dosing period;

M: meropenem; PT: piperacillin-tazobactam

Protein binding was assumed to be 2% for meropenem and 30% for piperacillin.

For patients without cultures, the most conservative MIC breakpoint of potential pathogens according to the Clinical and Laboratory Standards Institute, US were assumed (2 or 4mg/L for meropenem and 16mg/L for piperacillin).

meropenem concentrations at least 5 times the MIC for 40% of the dosing interval) within 48 hours, and 15/16 (93.8%) at steady state. In contrast, piperacillin levels were 7.3–302.5mg/L, with only 4/12 (33.3%) of patients obtaining 50% *fT*>5×MIC (free piperacillin concentrations at least 5 times the MIC for 50% of the dosing interval) within 48 hours, and 4/10 (40.0%) at steady state. Among the patients with non-susceptible organisms, the patient with piperacillin-tazobactam MIC ≥128 mg/L did not achieve any of the PK targets in Table 1. The 30-day all-cause mortality is 5/16 (31.3%) for patients on piperacillin-tazobactam and 10/26 (38.5%) for patients on meropenem.

This study observed that majority of the critically ill patients in our population achieved the PK targets chosen for meropenem. However, a multinational point prevalence study, the Defining Antibiotic Levels in Intensive care unit patients (DALI) study, described <70% of their population achieved 50%*fT*>4×MIC or 100%*fT*>MIC for meropenem.<sup>2</sup> We postulate that the difference in our findings might be related to differences in the baseline characteristics of the study populations. The smaller build of our Asian population, higher incidence of impaired renal function, lower albumin and age >60 compared with the DALI population could have contributed to more patients achieving PK targets for meropenem with standard doses.

Of significant concern, many patients prescribed with piperacillin-tazobactam were not able to achieve the PK targets with the standard doses prescribed.

Discrepant findings between meropenem and piperacillin-tazobactam could be a result of the wide variation in the PK of critically ill patients. This re-emphasises the need for strategies such as implementation of a beta-lactam therapeutic drug monitoring service, to improve chances of PK target attainment in our group of patients with extremely unpredictable beta-lactam PK.

This study has notable limitations. Firstly, this is a single-centre study with a relatively small sample size and heterogeneity of infections that may limit generalisability of the results. Secondly, creatinine clearance was calculated using the Cockcroft-Gault formula and was not directly measured. Such calculations generally provide poor estimates at extremes of creatinine clearance or unstable renal function, and may not be optimal for accurate dosing, despite being commonly used clinically.<sup>8</sup> Thirdly, more than half of our patients did not have a causative pathogen isolated. Therefore, the PK targets and associated results represented the worst-case scenario where the presence of the least susceptible pathogen was assumed. Lastly, the current analysis only provides data on PK exposure and not clinical outcomes. The impact of antibiotics PK target attainment on clinical outcome was not evaluated.

Further studies are needed to define optimal dosing regimens in our Singapore population with diverse PK profiles, and to evaluate the clinical implications and outcomes of using therapeutic drug monitoring to attain PK targets.

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## A red swollen forearm in an elderly man

A 90-year-old man with chronic kidney disease, ischaemic heart disease, hypertension and a history of recurrent falls presented with a circumferential, erythematous and indurated right forearm plaque for 2 weeks (Fig. 1). Pinprick sensation was intact over the lesion and the rest of the upper limbs. His left arm was not affected. He fell 3 months prior to this episode and sustained 2 right forearm lacerations, which had healed with scarring before he noticed the plaque. It did not improve after a week's course of oral amoxicillin-clavulanic acid given by his primary care provider. He was afebrile and physical examination was otherwise unremarkable. Laboratory investigations revealed a white cell count of  $6.9 \times 10^3/\mu\text{L}$  with no neutrophilia or eosinophilia, c-reactive protein of 1.9mg/L, and procalcitonin of 0.08 $\mu\text{g/L}$ . A Doppler venous ultrasound and right forearm X-ray were performed. These were reported as normal. A skin biopsy was performed for histologic examination (Figs. 2 and 3) as well as tissue cultures.



Fig. 1. Circumferential erythema and oedema arising from a background of linear scars and senile purpura on the right forearm.

What is the most likely diagnosis?

- A. Borderline leprosy
- B. Angiosarcoma
- C. Eosinophilic cellulitis (Wells syndrome)
- D. Extensive senile purpura
- E. Non-tuberculous mycobacterium infection

We suspected an infection with an atypical organism because of the history of recurrent skin trauma, degree of induration and non-response to amoxicillin-clavulanic acid.

Skin biopsy revealed a necrotising granulomatous inflammation in the dermis (Fig. 2) with a few acid-fast bacilli demonstrated on Fite stain (Fig. 3). A rapidly growing non-tuberculous mycobacterium was isolated

from the bacterial, fungal and mycobacterial skin tissue cultures. This was identified as *Mycobacterium fortuitum*. The isolate was sensitive to imipenem, amikacin, ciprofloxacin, moxifloxacin, trimethoprim/sulfamethoxazole and doxycycline. It was resistant to clarithromycin, likely from an inducible ribosomal RNA methylase (*erm*) gene.<sup>1</sup> The patient received empirical oral clarithromycin initially but developed bicytopenia, which was attributed clinically to clarithromycin. He was switched to oral doxycycline and ciprofloxacin, but developed non-specific symptoms, which he attributed to doxycycline. He eventually received oral ciprofloxacin 500mg daily, with a plan to complete 6 months. The redness and swelling on his right arm were almost resolved when we reviewed him 3 months after treatment.

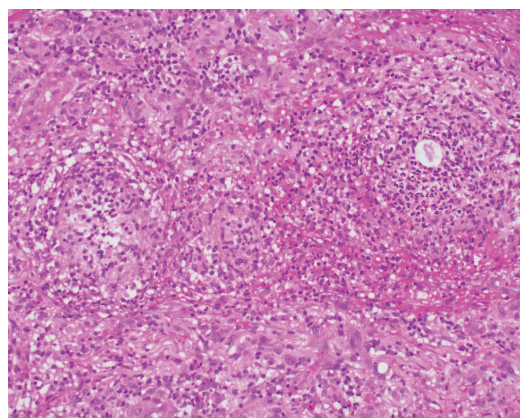


Fig. 2. Histological examination revealed a necrotising granulomatous infiltrate in the dermis (haematoxylin and eosin stain, magnification 400X).

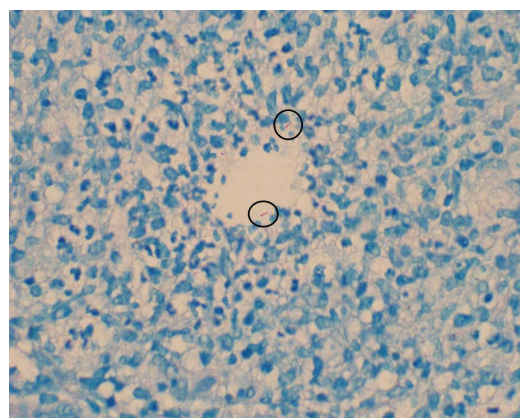


Fig. 3. A few acid-fast bacilli (circled) on Fite stain (magnification 600X).

Answer: E



*M. fortuitum* accounted for 19% of non-tuberculous mycobacterial skin infection cases reviewed in a Singapore study.<sup>2</sup> This rapid-growing mycobacterium is a saprophytic organism that causes infection following traumatic inoculation from contaminated surfaces or instruments. Cutaneous infection presents as nodules, abscesses, ulcers or cellulitis. A high index of suspicion for infection with uncommon organisms such as *M. fortuitum* is required when confronted with treatment-resistant cellulitis, especially if it was preceded by a recent skin injury. Diagnosis is confirmed with histological examination and mycobacterial culture of affected tissue, as was done for this case. The recommended treatment regime for *M. fortuitum* skin infection is at least 4 months of treatment with at least 2 antibiotics guided by the antimicrobial sensitivity analysis of the clinical isolate, in combination with surgical removal of any retained foreign bodies or drainage of abscesses.<sup>3</sup>

The clinical presentation of leprosy falls within a spectrum that is determined by the interaction between the organism and the host immune system.<sup>4</sup> Borderline leprosy can present on the skin with several asymmetrically distributed annular erythematous plaques with associated reduced sensation and hair growth. The peripheral nerves may be thickened. Histological examination often reveals a granulomatous inflammatory infiltrate surrounding the cutaneous nerves with very few acid-fast bacilli in tuberculoid leprosy, or a generalised dermal lymphohistiocytic infiltrate sparing a narrow area of the papillary dermis (grenz zone) and numerous acid-fast bacilli in clumps (globi) within histiocytes in lepromatous leprosy. The points against this diagnosis in our patient are the acuity of the presentation, lack of sensory loss and lack of multiple lesions. The histology examination was not consistent with leprosy as well.

Angiosarcoma in the elderly often presents on the face and scalp as chronic erythematous plaques that progress to tumours or ulcers over time.<sup>5</sup> Angiosarcoma involving the limbs occurs in the context of chronic lymphoedema (e.g. from prior ipsilateral mastectomy with axillary lymph node clearance) or after radiotherapy. Our patient presented acutely and did not have a history of preceding chronic lymphoedema or irradiation to the right arm. The histology examination was not consistent with angiosarcoma as well.

Wells syndrome or eosinophilic cellulitis presents with an acute itchy cellulitis-like plaque that remits and relapses.<sup>6</sup> It does not respond to antibiotics and is associated with peripheral eosinophilia. Histology of the affected skin reveals an eosinophilic dermal infiltrate with flame figures consisting of eosinophilic major

basic protein coating the dermal collagen. Although the acute nature of our patient's presentation and lack of response to antibiotics might suggest this diagnosis, the histological findings and tissue cultures led to the correct diagnosis of *M. fortuitum* infection.

Extensive purpura on areas of cutaneous trauma can be seen in elderly patients with recurrent falls, especially if there is concomitant use of anti-platelet or anti-coagulation agents, or in the context of systemic diseases causing fragile dermal blood vessels (e.g. scurvy or systemic amyloidosis), thrombocytopenia (e.g. myelodysplastic syndrome or dengue), coagulopathy (e.g. chronic liver disease) or skin atrophy (e.g. after systemic or topical steroid use). Our patient had clinical swelling and induration of the affected skin which are not typically seen in senile purpura. This observation should alert the clinician to consider an alternative cause.

Our case highlights the differential diagnoses to consider for patients with an upper limb cellulitis that does not respond to empirical antibiotic therapy. Infections with atypical organisms should be considered and confirmed with tissue histology and cultures.

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## A rare presentation of fever, sore throat and painful leg nodules

A 38-year-old Chinese man presented with a painful rash over bilateral shins for 2 days. He also had a 5-day history of fever, sore throat and myalgia. There were no other localising symptoms of infection. On systems review, he denied having joint pains, alopecia, weight or appetite loss, or any change in bowel habit. Drug history was unremarkable. He had no recent sick contacts or travel history.

Physical examination revealed tender, non-ulcerated purpuric nodules over bilateral legs extending from ankles and shins up to thighs (Fig. 1A). There were no digital ulcers or infarcts; no evidence of livedo reticularis. Notably, multiple discrete punched-out ulcers with an erythematous rim were seen over the hard palate and posterior pharyngeal wall (Fig. 1B). Similar well-demarcated ulcers were present over the base of his penis and inferior scrotal sac (Fig. 1C). There was no evidence of conjunctival injection, perianal ulcers or active synovitis. Periungual erythema and telangiectasia were absent. Abdomen was soft and non-tender on palpation. No evidence of clinical pathergy was seen. A 6mm punch biopsy was taken from an indurated purpuric shin nodule, which revealed histological features consistent with a medium vessel vasculitis.

What is the most likely diagnosis?

- A. Crohn's disease
- B. Behçet's disease
- C. Orogenital herpes
- D. Syphilis
- E. Pemphigus vulgaris

The answer is Behçet's disease (BD). Recurrent aphthous stomatitis is the most common and often first presentation of BD. The oral ulcers measure 5–10mm in diameter and are well-demarcated with a yellowish pseudomembrane, clear margins and erythematous rim. They are also often clinically indistinguishable from complex aphthosis, and present similarly to genital ulcers.<sup>1</sup> In males, they are commonly found over the scrotum, foreskin and penis shaft. In females, the most common site is the labia majora.<sup>1</sup> Common skin manifestations include erythema nodosum (EN)-like rash, pseudofolliculitis and purpuric papules.<sup>2</sup> While the EN-like rash is usually found on the anterior shin, it can be present elsewhere (e.g. thighs or buttocks).<sup>2</sup>

Arthritis occurs in more than half of BD patients<sup>3</sup> and can be mono- or poly-articular. It is typically non-erosive, and most commonly affects the knees, though it can also affect the ankles, elbows and wrist.<sup>3</sup> Other systemic manifestations include gastrointestinal tract ulceration, variable vessel vasculitis and thrombophlebitis.<sup>3</sup> Neurological manifestations occur late and portend a poor prognosis.<sup>2</sup>

Histological findings of cutaneous lesions vary and commonly include angiocentric and neutrophilic infiltrates with fibrinoid change, leukocytoclasia, and extravasation of red blood cells to a lobular or mixed septal-lobular panniculitis with a mixed inflammatory infiltrate.<sup>4</sup>

The clinical criteria of the International Study Group for Behçet's Disease are widely used to diagnose BD, given its high sensitivity and specificity.<sup>5</sup> There must be recurrent oral aphthae, and at least 2 of the following:

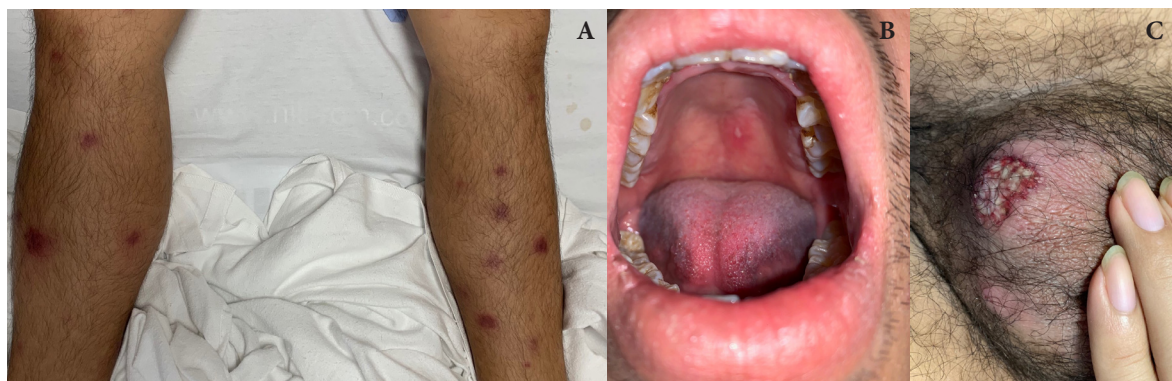


Fig. 1. (A) purpuric shin nodules, (B) oral ulcers, and (C) scrotal ulcer.

Answer: B

recurrent genital ulceration, ocular involvement (e.g. uveitis), skin lesions (e.g. EN-like lesions, pseudofolliculitis, etc.) and positive pathergy test.<sup>5</sup>

Both EN and recurrent aphthous ulcers can be seen in Crohn's disease. However, perianal ulcers and/or fistulas, rather than scrotal ulcers should be expected. The absence of altered bowel habits also makes this unlikely in our case. Ulcers resulting from grouped vesicles seen in orogenital herpes are often herpetiform with scalloped edges, and the association with EN is uncommon. Primary chancres in syphilis are painless and occur with indurated edges, unlike those shown in Fig. 1. The absence of cutaneous erosions makes pemphigus vulgaris unlikely.

In conclusion, BD is characterised by a constellation of clinical signs and symptoms. Early diagnosis improves overall morbidity.

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# Acknowledgement

The Editorial Board of the Annals, Academy of Medicine, Singapore  
gratefully acknowledges the generous support of:

**The Lee Foundation**

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Vol. 50 No. 6, June 2021 — Free Papers

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