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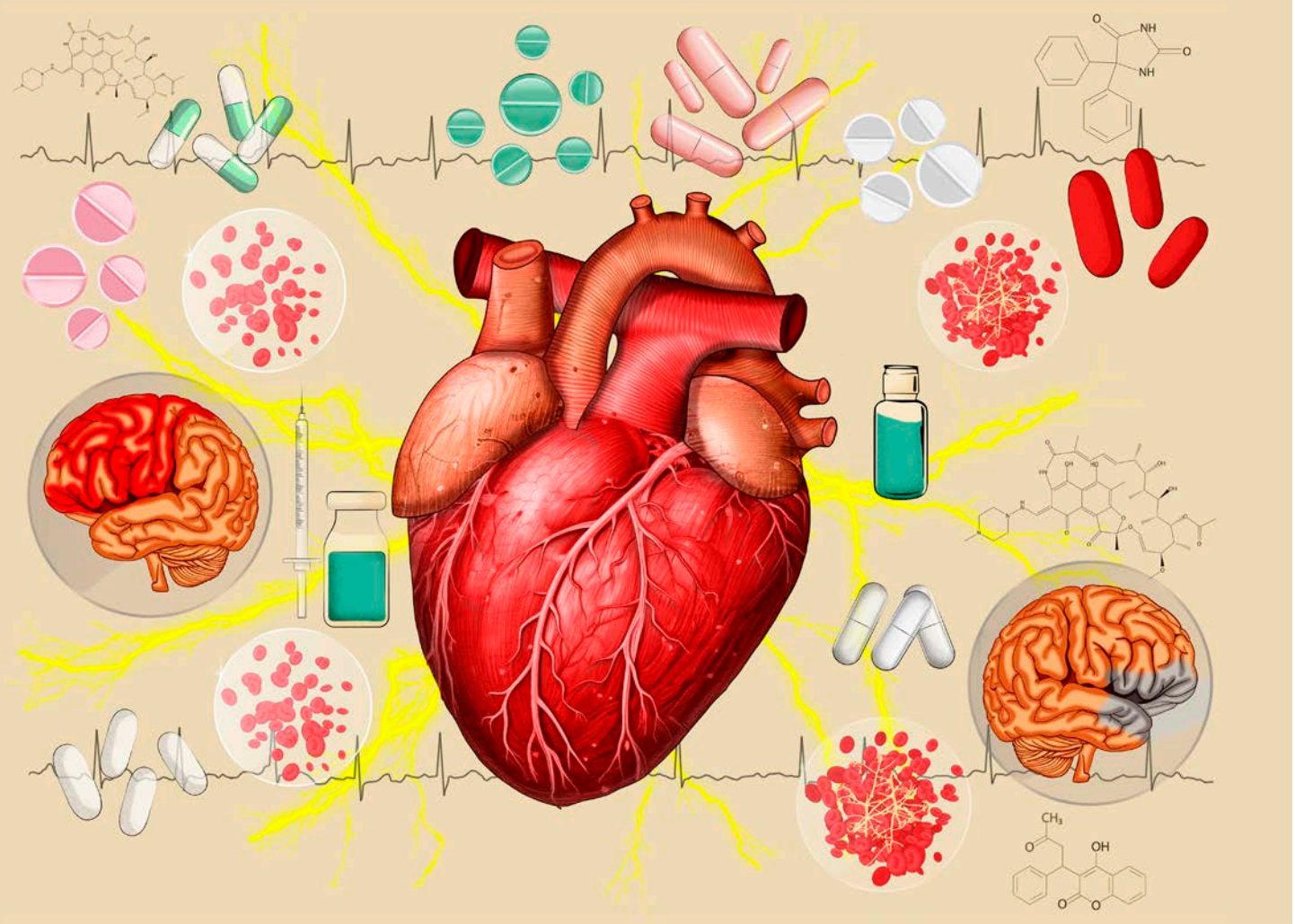

Effect of drug interactions with non-vitamin-K oral anticoagulants on thromboembolic events in patients with nonvalvular atrial fibrillation

A study group from Taiwan investigated drug-drug interactions in patients with NVAF, a type of irregular heartbeat. They concluded that the concurrent use of particular inducers increases the risk of bleeding events. (See full article, p.69)

Illustration by Nata Blackthorn

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EDITORIAL

Direct oral anticoagulant: Looking beyond convenience

Samuel Ji Quan Koh[1] *MRCP*, Jonathan Jiunn Liang Yap[1,2] *MRCP*

Since the 2010 Food and Drug Administration approval of Dabigatran as the first non-vitamin-K antagonist oral anticoagulants or direct oral anticoagulants (DOACs) as it is now more commonly referred to, there has been much development in the field with increasing availability of different DOACs and an expansion in indications of use. In the prevention of thromboembolism in nonvalvular atrial fibrillation (NVAF), DOACs have overtaken warfarin, which has been first-line therapy since the 1950s. In the most recent 2023 guidelines by the American Heart Association (AHA) for the diagnosis and management of atrial fibrillation, there is a Class 1A recommendation for patients who are candidates for anticoagulation without mechanical heart valve or history of moderate-to-severe rheumatic mitral stenosis to be prescribed DOACs over warfarin to reduce the risk of mortality, stroke, systemic embolism and intracranial haemorrhage.[1] This stance is also echoed by the European Society of Cardiology guidelines in 2020,[2] and—closer to home—in the Asia Pacific Heart Rhythm Society 2017 Consensus.[3]

The reasons for these recommendations for DOACs are several fold.[4] First, they stem from the pivotal trials comparing individual DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) with warfarin, which showed non-inferiority or in some instances superiority to warfarin for the prevention of stroke or systemic embolism in patients with NVAF. Second, there are several added benefits compared to warfarin, including reduced risk of major bleeding (especially intracranial bleeding), quick onset and offset of action that precludes the need for regular bridging therapy during interruption, and no requirement for regular international normalised ratio (INR) monitoring. Of relevance to this study, DOACs have also been known to have less food and drug–drug interactions (DDIs).

In this issue of the Annals, Chen et al.[5] aimed to explore the impact of DDIs with DOACs in patients with NVAF through a nested case-control study utilising a national administrative database. In summary, the key findings of this study were (1) the concurrent use of DOACs with CYP3A4 and/or P-glycoprotein (P-GP) inducers increased the risk of thromboembolic events; (2) interactions of DOACs with CYP3A4/P-GP inhibitors showed a marginal effect on reducing thromboembolic events; (3) distinct sex differences were noted with majority of the effects seen in males, as compared to females.

The authors should be applauded for highlighting a commonly overlooked aspect of DOACs and potential DDIs. This contrasts with warfarin whereby healthcare professionals are often more vigilant for such interactions. In the real world, this is particularly relevant for DOACs, as atrial fibrillation, which is inherently a degenerative condition, increases in incidence with age and affects a population where polypharmacy is prevalent.[6] With increasing adoption of guideline directed medical therapy,[7] the effects of DOACs and DDIs, if not addressed, would be amplified. Tellingly, Joosten et al. concluded in a recent randomised controlled trial (RCT), FRAIL-AF, that the switching of warfarin to a DOAC in frail older patients with NVAF was associated with more bleeding complications compared to continuing treatment with warfarin, without an associated reduction in thromboembolic complications.[8] This pragmatic RCT included the most vulnerable and yet increasingly relevant atrial fibrillation population, which has been largely excluded in clinical trials. While there may be several contributory factors that have led to this conclusion, the authors hypothesised that the potential benefit of DOACs may have tapered off in the elderly through a possible contributory factor of polypharmacy. This highlights the importance of addressing DOACs and its potential DDIs.

In this study, another interesting and potentially clinically relevant point raised is the sex differences noted with the effects predominantly seen in males. Of note, studies have demonstrated that women have higher levels of CYP3A4 protein tissue samples compared to men, and would metabolise drugs which are substrates of CYP3A4 more swiftly,[9,10] potentially resulting in reduced effects of such interactions on females compared to males. This will be work for further investigation.

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There are several limitations to this study. First, pertinent clinical information like renal and liver function status had been excluded from the case-control study. Given that DOACs are predominantly renally cleared but are also contraindicated in patients with moderate-to-severe liver cirrhosis, confounding interactions that could affect thromboembolic risks independent of the DDIs might not have been addressed with this study. Second, as acknowledged by the authors, the statistical power of analysis might be limited by its sample size for the various subgroup analyses. It is well known that there are differences in the metabolism of the various types of DOACs. Dabigatran is not metabolised by the CYP3A4 pathway, while rivaroxaban and apixaban are affected by strong CYP3A4 inducers and inhibitors, resulting in increased and decreased clearance, respectively. All DOACs are substrates of P-GP pathway. Despite these differences, while the overall DOAC group showed significant increase in thromboembolic events with the inducers, there were no significant differences with each of the individual types of DOAC. Third, the cohort had a significant difference in CHA_2DS_2VASc score with the case group having a higher score than the control group (5.6 ± 2.9 versus 4.3 ± 2.7, $P<0.001$). This could potentially confound any difference observed and might require further analyses in future studies. Last, while the authors reported that the use of a DOAC concurrently with CYP3A4 and/or P-GP inhibitors had a marginal effect in reducing thromboembolic events with point estimates less than 1, only 1 out of 5 models showed statistical difference.

In summary, with the current best-practice recommendations and the relative ease of use of DOACs, the uptake of DOACs in the treatment of NVAF is predicted to continue to rise. Nonetheless, despite fewer food and DDIs compared with warfarin, healthcare professionals should pay particular attention to potential drugs that may affect DOACs' efficacy or increase its adverse effect profile, as this has been shown to impact on clinical outcomes. The AHA 2023 guidelines put forth a Class 1C recommendation for managing drug interactions in patients receiving DOAC with concomitant therapy with interacting drugs, especially CYP3A4 and/or P-GP inhibitors or inducers.[1] It is, thus, prudent to take into account the pharmacological properties of individual DOACs and the possible medication interactions. On an individualised patient basis, some consideration may be afforded to the use of warfarin in such patients, especially in those with renal/hepatic impairment, given the ability to monitor and titrate INR levels.

Keywords: *cardiology, direct oral anticoagulants, epidemiology, nonvalvular atrial fibrillation, thromboembolism, vitamin-K antagonist oral anticoagulants*

Disclosure

JY received speaker's honorarium from Abbott, Biosensors, Biotronik, Boston Scientific, Edwards, GE HealthCare, J&J, Kaneka, Medtronic and Terumo.

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EDITORIAL

Breast cancer-related lymphedema (BCRL): Should we be doing more or less for the axilla?

Xue En Chuang[1] *MRCS (Ed)*, Clement Luck Khng Chia[1] *FRCS (Ed)*

Breast cancer mortality has declined steadily over the years with breast cancer screening, and improvement in diagnostic and therapeutic regimens. Despite cancer survivors living longer, breast cancer-related lymphedema (BCRL) is a significant complication after major breast surgery that can impact quality of life adversely. The incidence of BCRL reported ranges from 10.1% to 42.2%[1-5] with risk factors that include higher body mass index, larger number of dissected nodes, taxane-based regimen, total mastectomy, larger irradiation field, and conventional fractionation.[5] To mitigate the risk of BCRL, de-escalating axilla surgery and axilla radiotherapy in place of axillary dissection are increasingly recognised as the new standard of care in recent years for early breast cancer with sentinel lymph node positive.[6] Surgical innovation and advancements have also led to proponents of immediate lymphatic reconstruction to decrease the incidence of BCRL.[7] However, immediate lymphatic reconstruction is a costly additional procedure and whether it constitutes value-based care to recommend this as a routine procedure in relation to the prevalence of lymphedema in Singapore is an important decision that requires careful deliberation by the breast cancer surgical community.

The article by Hing et al.[8] is timely in providing insights to the prevalence of BCRL in Singapore via a pragmatic lymphedema surveillance programme for all breast cancer patients that underwent major breast surgery that can help formulate answers to the conundrums raised above. The authors acknowledge that the challenge lies in defining and measuring BCRL, which leads to significant variability in published studies and hence difficulty in contextualising in Singapore. As such, the proposed diagnostic algorithm by the authors—which incorporates objective arm measurement and subjective patient complaints, followed by clinical assessment by a clinician and grading for severity against a validated scale from the International Society of Lymphology—is an approach that is balanced and commendable.

Through this approach, the authors found that the cumulative prevalence rate of BCRL in their cohort was 30.9% through data captured via all 3 assessment tools in their diagnostic algorithm. However, clinically apparent BCRL was only 6.5% with the majority being subclinical and mild in severity. Several insights can be gleaned from this. First, patients may over-report symptoms of BCRL, which may account for higher incidence of BCRL in some series. Nevertheless, as the authors rightly pointed out, these patient-reported symptoms remain important to address; they can range from recurrence of disease, fluid overload, and neurological symptoms from aromatase inhibitors and chemotherapy-induced toxicity that may alter sensation and mimic "arm swelling" from the patient perspective. Second, the absence of severe lymphedema that required radical resection or lymphatic reconstruction is also reassuring that most patients with clinical-apparent BCRL can be managed with conservative measures, such as skin care advice, compressive garment and manual lymphatic drainage. Nevertheless, early detection, treatment and prevention of progression are key, and credit still goes to the authors for having a structured surveillance programme in identifying these individuals with BCRL early.

The authors also reported that the incidence of BCRL in sentinel lymph node biopsy/axillary node sampling is 1.7% compared to 9.9% in patients undergoing axillary clearance. While the lower rate of BCRL for sentinel lymph node is not surprising, it highlights that sentinel lymph node biopsy is not a completely benign procedure and risk of BCRL exists. As such, this will be useful information to consider when offering sentinel lymph node biopsy for controversial indications such as prophylactic mastectomy for BRCA mutation and also being very selective to perform sentinel lymph node biopsy in breast conserving surgery for ductal carcinoma in situ.

The authors also reported higher rates of mastectomy and axillary clearance (>50%) in their series, which are both risk factors for BCRL. With promising contemporary data from recent studies demonstrating evidence to suggest that breast-conserving surgery could confer comparable local recurrence rates and even improved survival

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compared to mastectomy,[10] coupled with the trend of de-escalating axillary surgery, intuitively the rate of BCRL could further decrease in future. Furthermore, a study in Singapore[10] also demonstrated an increasing trend in younger breast surgeons trained in oncoplastic surgery, which may also contribute to an increase in breast-conserving surgery being offered to patients. Immediate lymphatic reconstruction to decrease BCRL[7] is a notion that seems contrary to de-escalating axilla surgery and there is a need for further research to define a select group of high-risk patients that will benefit most from this complex surgical procedure. Interestingly, with the move towards de-escalating axilla surgery, assuming results from AMAROS trial[6] become the standard of care in future, one may argue that patients who still require axillary clearance may be the ones with locally advanced primary tumours, higher axillary nodal disease burden, and need for more aggressive and toxic chemotherapy regimens—all of which are risk factors for developing BCRL and may actually self-select as potential candidates for immediate lymphatic reconstruction.

Lastly, awareness and debunking myths regarding BCRL are equally important and should form part of any evidence-based BCRL advice dispensed to patients. Two myths in particular that have plagued patients, nurses and clinicians alike are measuring blood pressure and venipuncture on the arm on the side of axillary surgery. There is no contraindication to measuring blood pressure on the arm on the side of axillary surgery. Venipuncture is also safe on the arm on the side of axillary sentinel lymph node biopsy. As for patients with axillary clearance, venipuncture should be performed on the contralateral arm where possible. However, in the absence of suitable veins on the contralateral arm, it would still be preferable to consider venipuncture or siting a venous access cannula in the ipsilateral arm instead of resorting to other sites with higher infection rates, such as the foot.[11]

Overall, we believe instituting a pragmatic surveillance programme for BCRL is a move in the right direction pertaining to value-based care. While traditional measures of surgical morbidity such as 30-day unplanned readmission, unplanned return to operating theatre, need for blood transfusion and mortality is low and almost negligible in breast surgery, BCRL is an important long-term outcome that should be examined in closer detail and incorporated into the matrix of value determination. With more data accrued from different centres in Singapore regarding BCRL, we will be in a better position to make sense of the impact of de-escalating axilla surgery and make decisions on emerging surgical innovations like immediate lymphatic reconstruction in Singapore.

Keywords: *axilla, breast cancer-related lymphedema, cancer, general surgery, oncology, plastic surgery.*

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ORIGINAL ARTICLE

Effect of drug interactions with non-vitamin-K oral anticoagulants on thromboembolic events in patients with nonvalvular atrial fibrillation

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ABSTRACT

Introduction: Few real-world studies have investigated drug-drug interactions (DDIs) involving non-vitamin-K antagonist oral anticoagulants (NOACs) in patients with nonvalvular atrial fibrillation (NVAF). The interactions encompass drugs inducing or inhibiting cytochrome P450 3A4 and permeability glycoprotein. These agents potentially modulate the breakdown and elimination of NOACs. This study investigated the impact of DDIs on thromboembolism in this clinical scenario.

Method: Patients who had NVAF and were treated with NOACs were selected as the study cohort from the National Health Insurance Research Database of Taiwan. Cases were defined as patients hospitalised for a thromboembolic event and who underwent a relevant imaging study within 7 days before hospitalisation or during hospitalisation. Each case was matched with up to 4 controls by using the incidence density sampling method. The concurrent use of a cytochrome P450 3A4/permeability glycoprotein inducer or inhibitor or both with NOACs was identified. The effects of these interactions on the risk of thromboembolic events were examined with univariate and multivariate conditional logistic regressions.

Results: The study cohort comprised 60,726 eligible patients. Among them, 1288 patients with a thromboembolic event and 5144 matched control patients were selected for analysis. The concurrent use of a cytochrome P450 3A4/permeability glycoprotein inducer resulted in a higher risk of thromboembolic events (adjusted odds ratio [AOR] 1.23, 95% confidence interval [CI] 1.004–1.51).

Conclusion: For patients with NVAF receiving NOACs, the concurrent use of cytochrome P450 3A4/permeability glycoprotein inducers increases the risk of thromboembolic events.

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Keywords: drug-drug interaction, nonvalvular atrial fibrillation, non-vitamin-K antagonist oral anticoagulant, thromboembolic event

CLINICAL IMPACT

What is New

- For patients with nonvalvular atrial fibrillation (NVAF) receiving non-vitamin-K antagonist oral anticoagulants (NOACs), the concurrent use of cytochrome P450 3A4/permeability glycoprotein inducers increases the risk of thromboembolic events.

Clinical Implication

- Healthcare professionals should avoid prescribing cytochrome P450 3A4/permeability glycoprotein inducers to patients with NVAF who are taking NOACs.

INTRODUCTION

Atrial fibrillation (AF), a type of arrhythmia for which the incidence and prevalence are rising in the older population, has become a global epidemic.[1] The estimated prevalence of AF is approximately 2% to 4%,[2,3] and its prevalence is projected to increase by 2.3-fold by 2030.[3] Older

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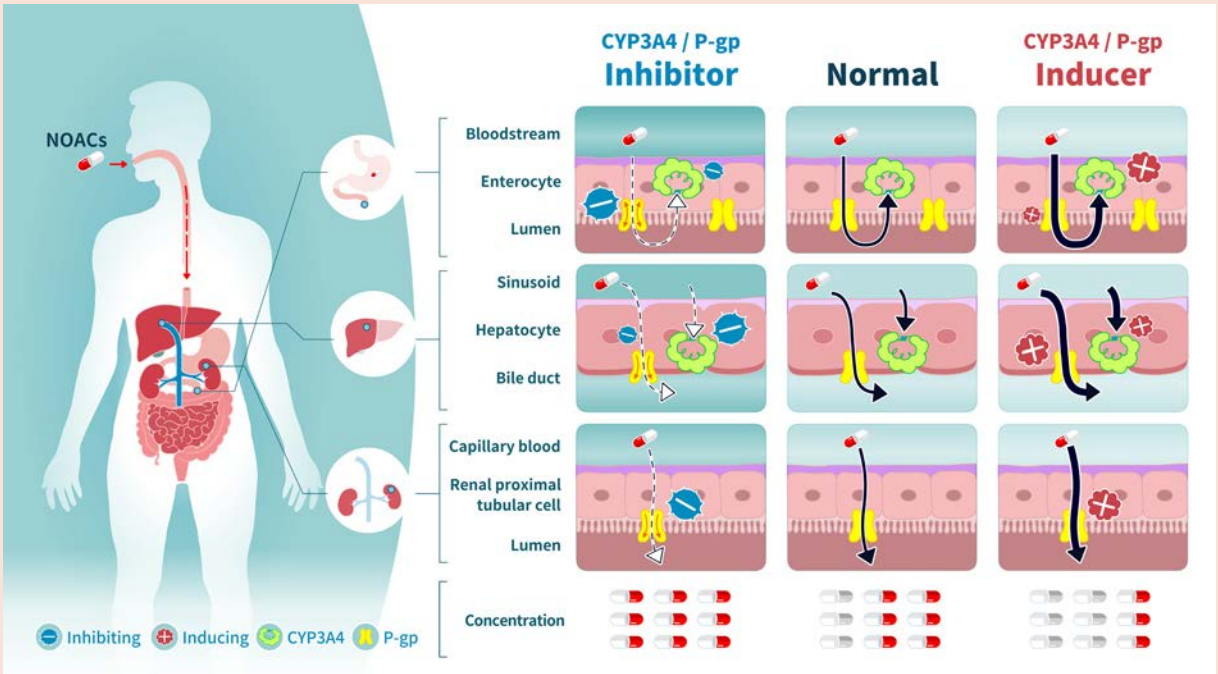
patients with AF have a substantial risk of ischaemic stroke, with this risk being 5 times that of the healthy population.[1,4] Ischaemic stroke is a leading cause of death globally. Moreover, the subsequent disabilities may adversely affect the quality of life of ischaemic stroke survivors and their families.[5-7] Hence, early diagnosis and stroke prevention therapy are the utmost priority in the management of AF.

Non-vitamin-K antagonist oral anticoagulants (NOACs) are increasingly being administered to patients with nonvalvular AF (NVAF), essentially replacing warfarin as a means of preventing ischaemic stroke and extracranial embolism because NOACs have superior efficacy and safety compared with warfarin.[8-11] Furthermore, NOAC users tend to have better adherence than warfarin users because of certain qualities of NOACs: (1) their rapid onset of action and shorter half-life, (2) no requirement of international normalised ratio monitoring, (3) fewer dietary restrictions and (4) fewer drug-drug interactions (DDIs).[2,12-14] A summary depicting the absorption, metabolism and excretion of NOACs, along with their interactions with cytochrome P450 3A4 (CYP3A4) and permeability glycoprotein (P-gp) inducers or inhibitors, is illustrated in Fig. 1. However, DDIs involving NOACs occasionally occur, especially in patients with multiple morbidities and polypharmacy.[15] The coadministration of NOACs and medications modifying CYP3A4 and P-gp activity has been reported to substantially alter patients' NOAC exposure.[16,17]

NOAC users who co-administered 9 or more drugs were determined to have a higher risk of stroke than those who received 5 or fewer drugs (adjusted hazard ratio 1.54, 95% confidence interval [CI] 1.19–1.99) in a post hoc analysis of phase 3 randomised controlled trials involving NOAC use in AF populations.[16] A recent large observational study reported that the concurrent use of NOACs with amiodarone, fluconazole, phenytoin and rifampin was associated with a significantly increased risk of major bleeding.[17] However, phenytoin and rifampin are strong P-gp and CYP3A4 inducers. They reduce the bioavailability of NOACs[18-20] and should increase the risk of thromboembolism instead of a bleeding event. As this result contradicted existing evidence, further investigation is required.

Fig. 1. Summary of absorption, metabolism and excretion of NOACs. Following the oral intake of NOACs, they are absorbed from intestinal to blood stream. P-gp and CYP3A4 are both expressed in the intestinal mucosa and attenuate drug exposure of oral drug delivery. Some NOACs would be transported back to intestine through P-gp and being metabolised by CYP3A4. Furthermore, upon reaching the liver, NOACs are subjected to metabolic transformation by CYP3A4, with P-gp playing a role in expediting their excretion into the biliary system. Finally, NOACs are also eliminated by P-gp in the kidneys. Therefore, CYP3A4/P-gp inducers increase the metabolism or excretion of NOACs, leading to a decrease in their blood concentration. Conversely, CYP3A4/P-gp inhibitors result in an increase in the blood concentration of NOACs.



CYP3A4: cytochrome P450 3A4; NOACs: non-vitamin-K antagonist oral anticoagulants; P-gp: permeability glycoprotein

Because of research ethics, older individuals and patients with multiple morbidities are usually excluded from randomised controlled trials.[21] Real-world drug interaction studies involving these vulnerable populations are thus lacking. Older adults with various comorbidities have become a major issue for those having to make decisions related to AF in clinical practice.[16] Therefore, we conducted this nested case-control study to investigate the effect of interactions between NOACs and P-gp and CYP3A4 modifiers on the risk of thromboembolic events in patients with NVAF.

METHOD

Data acquisition

This nested case-control study was conducted using Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance System comprehensively covers nearly 99% of the nationwide population in Taiwan for more than 2 decades. The NHIRD offers a broad and impartial longitudinal population for studying the potential effects of drug interactions involving NOACs on the susceptibility to thromboembolic events. Data from 1 January 2010 to 31 December 2018 were employed to evaluate the impact of DDIs on the protective efficacy of NOACs.

Study cohort

We searched the NHIRD for inpatient and outpatient records containing the diagnosis code for NVAF (International Classification of Diseases, Clinical Modification, 9th Revision code 427.31 or International Classification of Diseases, Clinical Modification, 10th Revision code I48.0, I48.2, I48.91 or I48.1). Adult (age ≥20 years) patients who had at least 2 outpatient records or 1 inpatient record of NVAF within a period of 365 days and who were prescribed an NOAC were considered eligible for inclusion. Patients with NVAF who received their first NOAC prescription between 1 January 2012 and 31 December 2017 were enrolled in the study cohort. The Anatomical Therapeutic Chemical (ATC) Classification System codes of NOACs were dabigatran (B01AE07), rivaroxaban (B01AF01 and B01AX06), apixaban (B01AF02 and B01AX08) and edoxaban (B01AF03). We excluded patients who, before the first NOAC prescription date, had mitral stenosis, a prosthetic valve, infective endocarditis or chronic kidney disease and those who had end-stage renal disease or acute renal failure and were undergoing renal replacement therapy. The definitions of the diseases for exclusion are presented in Supplementary Table S1. The flowchart for patient enrolment in this study is displayed in Fig. 2.

Cases with thromboembolic events and control patients

The healthcare records of enrolled patients were scrutinised to identify thromboembolic events. These events included ischaemic stroke, non-specified stroke, transient ischaemic attack, arterial embolism and mesenteric ischaemia. The accuracy of ischaemic stroke diagnosis in the NHIRD was reported to be 94%.[22] The positive predictive value and sensitivity of ischaemic stroke identification through diagnosis codes were reported to be 88.4% and 97.3%, respectively.[23] The cases were patients hospitalised for any thromboembolic event and undergoing computerised tomography or magnetic resonance imaging during the 7 days before their hospital admission or during hospitalisation. The index date was defined as the date of diagnosis of the incident thromboembolic event. We matched each case by age, sex and duration since NOAC commencement with up to 4 controls in the study cohort by using the incidence density sampling method. In addition, the proportion of days covered (PDC) of the NOAC during the 3 months before the index date had to be 0.8 or higher. The PDC was defined as the proportion of a given period of interest in which a specified medication was administered to a patient.[24]

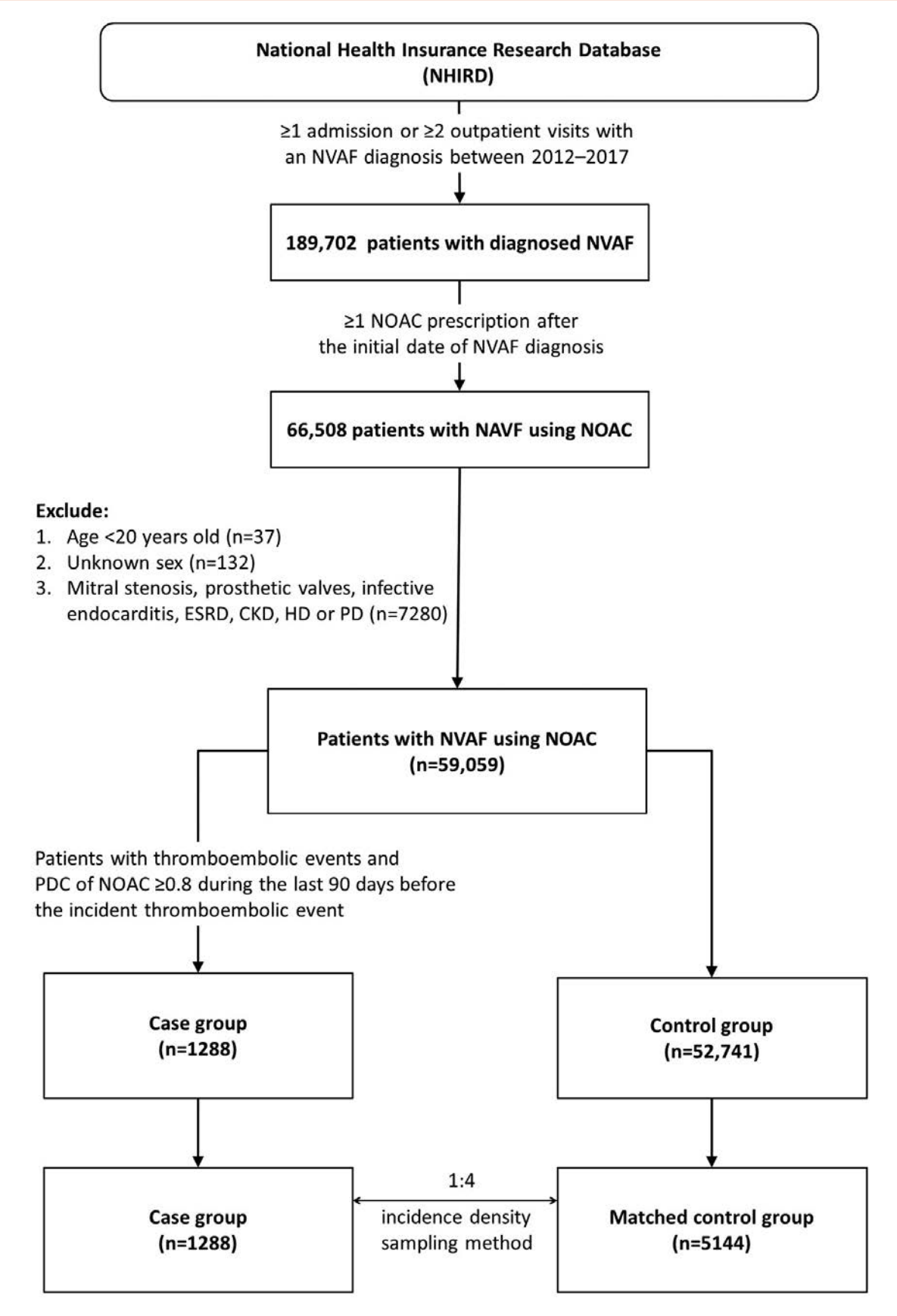
Exposure to NOAC drug interactions

The exposure of interest in this study was NOAC drug interaction, defined as the concurrent use of an NOAC and CYP3A4/P-gp inducers or inhibitors or other medications that affect a patient's effective NOAC exposure. CYP3A4/P-gp inducers, which reduce the concentrations of NOACs, include phenytoin and rifampin. CYP3A4/P-gp inhibitors, which increase the concentrations of NOACs, include fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole, erythromycin, clarithromycin, verapamil, diltiazem, amiodarone, dronedarone and cyclosporine. The ATC codes of medications are presented in Supplementary Table S2. Strong inhibitors (ketoconazole, itraconazole, voriconazole, posaconazole and clarithromycin) and inducers (phenytoin and rifampin) are drugs that increase or reduce the area under the curve of substrates of a given metabolic pathway by >5-fold and by 80%, respectively.[25] The definition of concurrent use was the prescription of any of the mentioned drugs during the 3 months before the index date.

Other confounding factors

We identified patients' baseline characteristics, comorbidities and related medications, which were considered possible confounding factors that could

Fig. 2. Flowchart of study design and case selection.



CKD: chronic kidney disease; ESRD: end-stage renal disease; HD: haemodialysis; NOAC: non-vitamin-K antagonist oral anticoagulant/ novel oral anticoagulant; NVAF: nonvalvular atrial fibrillation; PD: peritoneal dialysis; PDC: proportion of days covered

adjust the likelihood of a thromboembolic event. The baseline characteristics were patients' age, sex and income. The comorbidities were hypertension, congestive heart failure, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), malignancy, dyslipidaemia and peripheral arterial occlusive disease (PAOD). We also calculated the CHA_2DS_2VASc score, a risk stratification tool used for anticoagulation decision-making, to adjust our results for the risk of stroke.[3] The related medications were considered when more than 90 defined daily dose prescriptions were noted for antiplatelet agents, warfarin, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors and corticosteroids.

Statistical analysis

The paired-sample t-test or McNemar test was used to compare variables between the cases and controls as appropriate. Univariate and multivariate conditional logistic regressions were performed to evaluate the impact of DDIs on the risk of thromboembolic events. The covariates considered were age (≤59 versus 60–79 vs ≥80 years), sex (female vs male), monthly income (≤16,500 vs 16,501–26,400 vs ≥26,401 New Taiwan [NT] dollars) and comorbidities in Model 1; age, sex, income and higher risk of stroke (CHA_2DS_2VASc score ≥2 for men and ≥3 for women) in Model 2; age, sex, income, comorbidities and medication use (warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids) in Model 3; and age, sex, income, higher risk of stroke[26] and medication use in Model 4. In sensitivity analysis, only the concurrent use of strong CYP3A4/P-gp inhibitors or inducers was considered to cause an effective DDI. Furthermore, we performed subgroup analyses stratified by sex. Statistical significance was set at 2-sided $P<0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, US).

RESULTS

Study cohort, cases and controls

For the period from 2012 to 2017, a total of 66,508 patients with NVAF and taking NOACs were identified in the NHIRD of Taiwan. After applying the exclusion criteria, the number of patients eligible for the study was found to be 59,059. Among these patients, we identified 1288 cases of thromboembolic events where the PDC of NOACs was >0.8 during the 90 days before the index date; 5144 matched control patients were also selected (Fig. 2).

The baseline characteristics are detailed in Table 1. The mean age was 77.7 ± 9.7 years, and approximately 43% of the patients were older than 80 years. The case and control groups' age, sex and income were similar. Women comprised 51.6% of the case and control groups. Rivaroxaban and dabigatran were the most frequently used NOACs. The prevalence rates of hypertension (93.8% vs 88.7%), congestive heart failure (49.6% vs 43.5%), DM (19.4% vs 15.4%), COPD (9.2% vs 6.7%), dyslipidaemia (8.5% vs 6.7%) and PAOD (3.4% vs 1.4%) were higher in the case group than in the control group.

Exposure to DDIs was significantly different between the case and control groups ($P<0.001$). Compared with the controls, the cases were more likely to concurrently use a CYP3A4/P-gp inducer (12.4% vs 8.6%).

The CHA_2DS_2VASc score was higher in the case group than in the control group (5.6 ± 2.9 vs 4.3 ± 2.7, $P<0.001$). However, more than 90% of the patients in both groups had a high-risk score of CHA_2DS_2VASc. The patients in the case group were more likely to have concurrent exposure to the following other medications: antiplatelet agents (24.1% vs 18.8%, $P<0.001$), hypoglycaemic agents (18.3% vs 15.5%, $P<0.001$), insulin (4.4% vs 2.7%, $P<0.001$), NSAIDs (12.8% vs 11.4%, $P=0.022$) and proton pump inhibitors (9.6% vs 7.1%, $P<0.001$).

Association between thromboembolic events and interaction of NOACs with CYP3A4/P-gp modifiers in patients with NVAF

The association between DDIs with NOACs and the risk of thromboembolic events in patients with NVAF is detailed in Table 2. In the univariate analysis, a CYP3A4/P-gp inducer (OR 1.30; 95% CI 1.07–1.59) of DDI was associated with a higher risk of a thromboembolic event. After adjusting the confounding effects of demographics, comorbidities, high-risk scores of strokes, and use of other medications, we obtained consistent results for the 4 models (Table 2), indicating that the concurrent use of a CYP3A4/P-gp inducer carried a higher risk of thromboembolic events. The adjusted odds ratios (AORs) from Models 1 to 4 were 1.26 (95% CI 1.07–1.59), 1.27 (95% CI 1.04–1.56), 1.22 (95% CI 0.997–1.50) and 1.23 (95% CI 1.004–1.51), respectively. Using an NOAC concurrently with CYP3A4/P-gp inhibitors had a marginal effect in reducing the thromboembolic events that the univariate and multivariate analyses all showed point estimates of ORs less than 1. However, only 1 of the 5 models showed statistical significance. Patients using NOACs concurrently with

Table 1. Baseline characteristics of cases and controls.

	Cases with thromboembolic events (n=1288)	Controls without thromboembolic events (n=5144)	*P* value
Age, mean ± SD	77.7 ± 9.7	77.7 ± 9.6	0.206
≤59 years	64 (5.0%)	245 (4.8%)	0.383
60–79 years	670 (52.0%)	2712 (52.7%)	
≥80 years	554 (43.0%)	2187 (42.5%)	
Female sex	665 (51.6%)	2652 (51.6%)	0.962
Income (NT dollars per month), no. (%)			0.3262
≤16,500	374 (29.0%)	1571 (30.6%)	
16,501–26,400	597 (46.4%)	2290 (44.5%)	
≥26,401	317 (24.6%)	1283 (24.9%)	
Types of NOACs, no. (%)			
Rivaroxaban	656 (50.9%)	2590 (50.4%)	0.127
Dabigatran	522 (40.5%)	1978 (38.5%)	0.011
Apixaban	142 (11.0%)	633 (12.3%)	0.033
Edoxaban	36 (2.8%)	133 (2.6%)	0.394
PDC of each NOAC, mean ± SD			
Rivaroxaban	0.94 ± 0.16	0.96 ± 0.13	0.016
Dabigatran	0.95 ± 0.14	0.96 ± 0.14	0.121
Apixaban	0.88 ± 0.26	0.94 ± 0.17	0.016
Edoxaban	0.86 ± 0.28	0.88 ± 0.23	0.663
Drug-drug interaction, no. (%)			<0.001
No interaction	710 (55.1%)	2821 (54.8%)	
CYP3A4/P-gp, no. (%)			
Inhibitors	349 (27.1%)	1558 (27.4%)	
Inducers	160 (12.4%)	489 (8.6%)	
Inhibitors and inducers	69 (5.4%)	276 (5.0%)	
Comorbidity, no. (%)			
Hypertension	1209 (93.8%)	4560 (88.7%)	<0.001
Congestive heart failure	639 (49.6%)	2235 (43.5%)	<0.001
Diabetes mellitus	250 (19.4%)	794 (15.4%)	<0.001
COPD	119 (9.2%)	346 (6.7%)	<0.001
Malignancy	122 (9.5%)	525 (10.2%)	0.227
Dyslipidaemia	109 (8.5%)	342 (6.7%)	<0.001
PAOD	44 (3.4%)	70 (1.4%)	<0.001

Table 1. Baseline characteristics of cases and controls. (Cont'd)

	Cases with thromboembolic events (n=1288)	Controls without thromboembolic events (n=5144)	*P* value
CHA_2DS_2VASc score, mean ± SD	5.6 ± 2.9	4.3 ± 2.7	<0.001
High risk of stroke (≥3 in females, ≥2 in males), no. (%)	1266 (98.2%)	4667 (90.7%)	<0.001
Medication use, no. (%)			
Calcium channel blockers	368 (28.6%)	1461 (28.4%)	0.809
Antiplatelet agents	310 (24.1%)	967 (18.8%)	<0.001
Lipid-lowering agents	285 (22.1%)	731 (23.8%)	0.951
Hypoglycaemic agents	235 (18.3%)	796 (15.5%)	<0.001
NSAIDs	165 (12.8%)	585 (11.4%)	0.022
Proton pump inhibitors	124 (9.6%)	366 (7.1%)	<0.001
Antihypertensive agents	74 (5.8%)	263 (5.1%)	0.145
Corticosteroids	45 (3.5%)	106 (3.1%)	<0.270
Insulin	57 (4.4%)	137 (2.7%)	<0.001
Warfarin	12 (0.9%)	36 (0.7%)	0.185

COPD: chronic obstructive pulmonary disease; NOACs: non-vitamin-K antagonist oral anticoagulants; NSAIDs: nonsteroidal anti-inflammatory drugs; NT dollars: New Taiwan dollars; PAOD: peripheral arterial occlusive disease; PDC: proportion of days covered; SD: standard deviation

both inducers and inhibitors did not increase the risk of thromboembolic events compared to patients without DDIs.

Subgroup analyses stratified by sex and history of thromboembolic events

The results of subgroup analyses stratified by sex and history of thromboembolic events are illustrated in Fig. 3. For male patients, the concurrent use of a CYP3A4/P-gp inhibitor was associated with a reduced risk of a thromboembolic event (AOR 0.77 [95% CI 0.62–0.95]). In addition, the concurrent use of a CYP3A4/P-gp inducer was associated with an increased risk of a thromboembolic event (AOR 1.35 [95% CI 1.01–1.81]). However, for female patients, the concurrent use of CYP3A4/P-gp modifiers, either inhibitors, inducers or both, showed no significant association with the risk of thromboembolic events.

Sensitivity analysis regarding only strong CYP3A4/P-gp inhibitors and inducers

We conducted sensitivity analyses to examine the effects of strong inhibitors and inducers of CYP3A4/P-gp. The AORs of the concurrent use of strong CYP3A4/P-gp inducers for a thromboembolic event (1.96–2.06, Supplementary Table S3) were higher than that in the main scenario (1.22–1.27, Table 2). The AORs of the concurrent use of a strong CYP3A4/P-gp inhibitor for thromboembolic events were greater than 1, but the 95% CIs were much wider that the results were not significant. In addition, the AORs of a CYP3A4/P-gp inducer or inhibitor among patients using each single NOAC were not associated with the risk of thromboembolic events (Supplementary Tables S4–S7).

The dosing of NOACs, in terms of mean-defined daily doses, among patients prescribed with inhibitors or inducers is similar (Supplementary Table S8). The breakdown of the percentages of types of inhibitors/inducers is described in the supplemen-tary file (Supplementary Table S9).

DISCUSSION

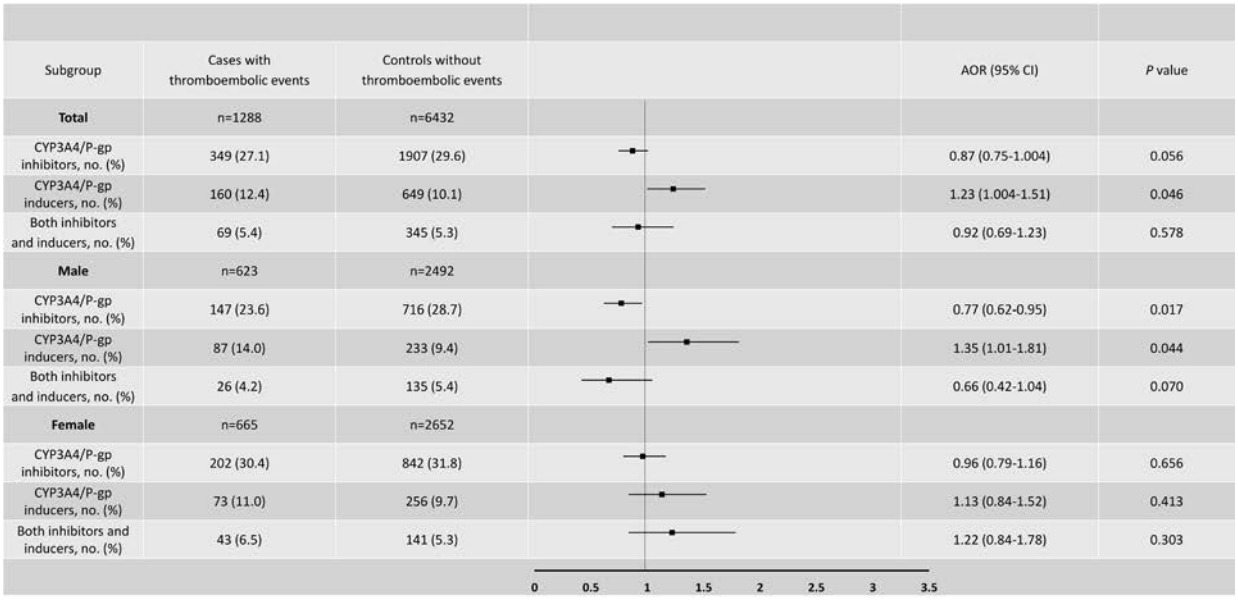
The present study showed that the concurrent use of an NOAC with CYP3A4/P-gp inducers increased the risk of thromboembolic events. The impact of strong CYP3A4/P-gp inducers on thromboembolic events was even higher. To the best of our knowledge, this is the first nested case-control study using an administrative database to investigate the association between NOAC-based DDIs and a thromboembolic event. Suboptimal drug exposure has been proposed in several studies to be the major cause of failure of NOAC-based treatments.[27,28] The relevant pharmacokinetic

Table 2. Association of the concomitant use of a CYP3A4/P-gp inhibitor or inducer with thromboembolic events.

DDI	Cases with thromboembolic events (n=1288), no. (%)	Controls without thromboembolic events (n=5144), no. (%)	Univariate OR (95% CI)	*P* value	Model 1[a] AOR (95% CI)	*P* value	Model 2[b] AOR (95% CI)	*P* value	Model 3[c] AOR (95% CI)	*P* value	Model 4[d] AOR (95% CI)	*P* value
No DDI	710 (55.1)	3531 (54.8)	1		1		1		1		1	
CYP3A4/P-gp inhibitors	349 (27.1)	1907 (29.6)	0.89 (0.77-1.03)	0.115	0.88 (0.76-1.02)	0.081	0.89 (0.77-1.03)	0.122	0.86 (0.74-0.996)	0.044	0.87 (0.75-1.004)	0.056
CYP3A4/P-gp inducers	160 (12.4)	649 (10.1)	1.30 (1.07-1.59)	0.008	1.26 (1.03-1.54)	0.024	1.27 (1.04-1.56)	0.018	1.22 (0.997-1.50)	0.053	1.23 (1.004-1.51)	0.046
Both	69 (5.4)	345 (5.3)	0.99 (0.75-1.31)	0.967	0.97 (0.73-1.29)	0.829	0.95 (0.72-1.27)	0.746	0.95 (0.71-1.26)	0.706	0.92 (0.69-1.23)	0.578

AOR: adjusted odds ratio; CI: confidence interval; DDI: drug-drug interaction; OR: odds ratio.
[a] Adjusted for age, sex, income and comorbidities (hypertension, congestive heart failure, diabetes mellitus, COPD, malignancy, dyslipidaemia and PAOD).
[b] Adjusted for age, sex, income and high risk of stroke.
[c] Adjusted for age, sex, income, comorbidities (hypertension, congestive heart failure, diabetes mellitus, COPD, malignancy, dyslipidaemia and PAOD), medication use (warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids).
[d] Adjusted for age, sex, income, high risk of stroke, medication use (warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids).

Fig. 3. Forest plot of subgroup analysis (odds ratios were adjusted for age, sex, income, high risk of stroke and medication use [warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids]).



AOR: adjusted odds ratio; CI: confidence interval

knowledge indicates that CYP3A4/P-gp inducers reduce the plasma levels of NOACs and result in NOAC users having an increased risk of a thromboembolic event. However, interactions of NOACs with CYP3A4/P-gp inhibitors showed a marginal effect in reducing the thromboembolic events while the concurrent use of both inhibitors and inducers had no effect on the risk of thromboembolic events.

Sexual pharmacokinetic differences are attributable to multiple factors, such as drug distribution, hepatic clearance and renal clearance.[29,30] Sexual dimorphisms in metabolic enzymes and transportation are critical factors affecting pharmacokinetics.[30,31] The risk of a thromboembolic event was higher in male patients when an NOAC was concurrently used with a CYP3A4/P-gp inducer. A possible mechanism is that the expression of P-gp is higher in men.[32] In the small intestine, enhanced P-gp expression increases the excretion of its substrates from epithelial cells to the bowel lumen. Such recirculation re-exposes the drugs to metabolic enzymes in the gut, thereby reducing their bioavailability.

Two retrospective cohort studies have reported interesting results regarding the NOAC DDIs contradicting the direct pharmacokinetic effects. In 2017, Chang et al. indicated that in patients with NVAF using an NOAC (dabigatran, rivaroxaban or apixaban), the concurrent use of a CYP3A4/P-gp inducer, such as rifampin (adjusted rate ratio [ARR] 1.57; 95% CI 1.02–2.41) or phenytoin (ARR 1.94; 95% CI 1.59–2.36), significantly increased the likelihood of a bleeding event (intracranial haemorrhage or gastrointestinal bleeding). In contrast, the concurrent use of a CYP3A4/P-gp inhibitor, such as erythromycin or clarithromycin (ARR 0.60; 95% CI 0.48–0.75), significantly reduced the incidence of bleeding events.[17] In 2020, Wang et al. used a similar research method to analyse the relationship of the use of NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) and antiepileptic drugs with bleeding events; their results also indicated that the concomitant use of phenytoin (ARR 2.50; 95% CI 2.13–2.93) significantly increased the occurrence of bleeding events.[33] We propose 2 reasons for such contradicting observations. First, these 2 studies did not exclude patients with impaired renal function. NOACs are excreted by the kidneys in different degrees (dabigatran: 80%; rivaroxaban: 35%; apixaban: 27%; and edoxaban: 50%).[34] Renal function impairment may negatively affect NOAC elimination, meaning that NOACs have a stronger effect and resulting in an increased incidence of bleeding events. Second, these 2 studies did not explicitly define the duration of overlap between NOAC and interacting drug use. The duration of overlap may not have been sufficiently long to produce a major DDI. In the present nested case-control study, we matched the time at risk

and ensured an overlap of at least 7 days; any interactions were thus substantial, and the findings reflected the association between NOACs and CYP3A4/P-gp modifiers in terms of the incidence of thromboembolic events. Moreover, this study covered all NOACs and considered all 3 possible combinations (NOAC plus CYP3A4/P-gp inhibitor or inducer alone or an inhibitor and inducer simultaneously). To ensure that NOACs were used continuously, meaning that achieving the maximal clinical benefit of the drug was reasonably likely and the coverage of exposed drugs before the index date was appropriate, we calculated the PDC by NOACs. In addition, because NOACs should be used with caution in patients with poor renal function, patients with AF and chronic kidney disease or end-stage renal disease were excluded from this study.

Dabigatran is a substrate of the efflux transporter P-gp but is not metabolised by CYP3A4.[35] Consequently, the influence of CYP3A4/P-gp inhibitors or inducers may vary between patients using dabigatran and those using other NOACs. Sensitivity analyses were conducted for each individual NOAC, but no statistical significance was observed among patients taking CYP3A4/P-gp inhibitors or inducers. It is worth noting that these subpopulation analyses may be inadequately powered due to the limited sample sizes.

This study has several limitations. First, this is a nested case-control study. The major disadvantage of nested case-control studies is that not all pertinent risk factors are likely to have been recorded. Second, some clinical and physical information of the participants, such as the results of liver and kidney function tests, is not included in the NHIRD claims data. Third, the statistical power of the analysis regarding the strong CYP3A4/P-gp inhibitors and inducers was limited by the sample size. Additional studies are warranted to determine the effect of strong enzyme modifiers on NOACs. In addition, the cohort consisted of primarily Asian people, and direct extrapolation to other ethnic groups may thus be inappropriate.

CONCLUSION

For patients with NVAF taking NOACs, the concurrent use of a CYP3A4/P-gp inducer increases the risk of a thromboembolic event.

Acknowledgment

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Data availability statement

Data cannot be shared for ethical/privacy reasons.

Competing interest

All authors declare that no competing interests exist.

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ORIGINAL ARTICLE

Defining breast cancer-related lymphedema (BCRL) prevalence and risk factors: A pragmatic approach to lymphedema surveillance

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ABSTRACT

Introduction: We presented the key findings from Singapore's Changi General Hospital Breast Centre's lymphedema surveillance strategy that used patients' reported symptoms, standard arm circumference measurements and clinical assessment in the diagnosis of breast cancer-related lymphedema (BCRL). Our secondary aim was to highlight and discuss important elements of a surveillance strategy that can be implemented to track this outcome measure of breast cancer treatment for future research.

Method: We conducted a cross-sectional study of 511 breast cancer patients to assess the prevalence of BCRL and its associated risk factors. We defined BCRL prevalence rates based on patients' self-reporting, objective arm circumference measurements and clinical diagnosis based on International Society of Lymphology (ISL) staging.

Results: The median follow-up of patients was 88.8 months. The cumulative prevalence rate in the cohort was 30.9%. The cohort of BCRL patients were older (58.4 versus [vs] 54.9 years), had higher mean Body Mass Index (27.7 vs 25.2), higher proportion of mastectomy (77% vs 64.3%), axillary clearance, less likely breast reconstruction, higher-grade tumour, more lymph nodes excised, more advanced nodal disease, and had undergone adjuvant chemotherapy. However, clinically apparent BCRL was only 6.5% (33 out of 511 patients). The proportion of clinically significant BCRL in patients undergoing sentinel lymph node biopsy (SLNB) or axillary sampling was 1.7% compared to 9.9% in patients who had undergone axillary clearance. Majority of the BCRL were subclinical or mild in severity.

Conclusion: Our study showed that our rates of BCRL were comparable to international rates and highlighted similar patient profiles who were at risk of developing the disease. Having a comprehensive lymphedema surveillance strategy is paramount in paving the way for future studies.

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Keywords: cancer, cancer survivorship, general surgery, lymphedema, prevalence, surveillance

CLINICAL IMPACT

What is New

- This study is the first to highlight prevalence and risk factors of developing breast cancer-related lymphedema in Singapore.
- Findings underscore the importance of a comprehensive lymphedema surveillance strategy in any breast unit.

Clinical Implications

- The study highlights the effectiveness of simple assessment tools such as patient questionnaires, regular arm circumference measurement before and after treatment, clinical assessment matrix for diagnosis of BCRL and timely intervention.
- This data can potentially inform guidelines for lymphedema surveillance strategy in Singapore.

INTRODUCTION

Breast cancer-related lymphedema (BCRL) is a chronic progressive pathological condition of the lymphatic system that can lead to significant impact on the quality of life after breast cancer treatment.[1] It is characterised by swelling and accumulation of

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protein-rich fluid in body tissues, leading to pain, tightness, skin changes such as fibrosis/thickening or recurrent infections, impaired mobility, and function of the affected arms. BCRL has an insidious onset and can occur even without precipitating events, years after treatment. Systematic reviews have shown that interventions tend to be more effective in the initial stages of lymphedema, before permanent changes such as fibrosis set in.[2,3] However, due to a lack of standardised diagnostic criteria, BCRL is still notoriously difficult to detect in its early stages.[4] Hence, it is important to have a lymphedema surveillance strategy that starts as early as from the time of cancer diagnosis and persists beyond treatment.

The incidence of BCRL has been reported to range from 0% to 94% of the breast cancer survivors.[3-12] This wide variation in incidence is largely owing to a difference in study designs, diagnostic methods, a lack in consistency of objective measures of BCRL, and varying timing of measurements. The lack of local data on the prevalence of BCRL in Singapore makes it difficult to quantify the extent of the morbidity or to study the effectiveness of interventions aimed at curtailing them.

In this paper, we present the key features of Singapore's Changi General Hospital Breast Centre's approach to lymphedema surveillance that has been using standard arm circumference measurements as an adjunct objective reading to aid in the diagnosis of BCRL. Finally, we conducted a cross-sectional study of our centre's breast cancer survivors to examine the performance of a set of predefined subjective and objective assessment tools, to assess for the prevalence of BCRL along with its associated risk factors. Our aim is to highlight and discuss the importance of a surveillance strategy that is evidence-based and can be implemented readily to track the magnitude and severity of BCRL as an outcome measure of breast cancer treatment.

METHOD

Lymphedema surveillance programme

A comprehensive lymphedema surveillance programme, started in 2019 at Changi General Hospital Breast Centre, included patient education on the condition, advice on arm care, and range-of-motion exercises (Fig. 1). These were taught to the patients prior to the initiation of any treatment and reinforced at each touch point by their respective treating clinicians and nurses. Baseline arm circumference measurements were also obtained by both trained nurses and clinicians.

Criteria for BCRL diagnosis

- Arm circumference was taken at 10 cm below and above the olecranon and a difference ≥2 cm from the contralateral arm or from baseline was taken to be indicative of BCRL.
- Patients' self-reported diagnosis of BCRL and/or subjective complaints of persistent arm swelling for more than 1 month were considered to be indicative of BCRL.
- All clinicians assessed for the presence of BCRL based on patient symptoms and arm circumference measurements. If present, clinicians graded the severity of lymphedema according to International Society of Lymphology (ISL) (Fig. 2).

Patients who were assessed to have risk factors and fulfilled any of the diagnostic criteria of BCRL or presence of triggers were offered referrals to our specialised lymphedema therapist for further evaluation and appropriate interventions.

A total of 511 patients who were treated and on follow-up for breast cancer surveillance in Changi General Hospital Breast Centre were recruited by convenient sampling between March and September 2021 for the cross-sectional study. The prevalence of lymphedema using patients' subjective complaints or self-reporting method, objective arm circumference measurements and clinicians' independent assessments were analysed for agreement. Patients who had metastatic breast cancer, bilateral breast cancer, disease recurrence or declined curative surgery were excluded. Based on the cumulative diagnosis of BCRL, we analysed the clinical risk factors associated.

This study was approved by SingHealth Centralised Institutional Review Board 2021/2068 to be conducted in Changi General Hospital.

Statistical analysis

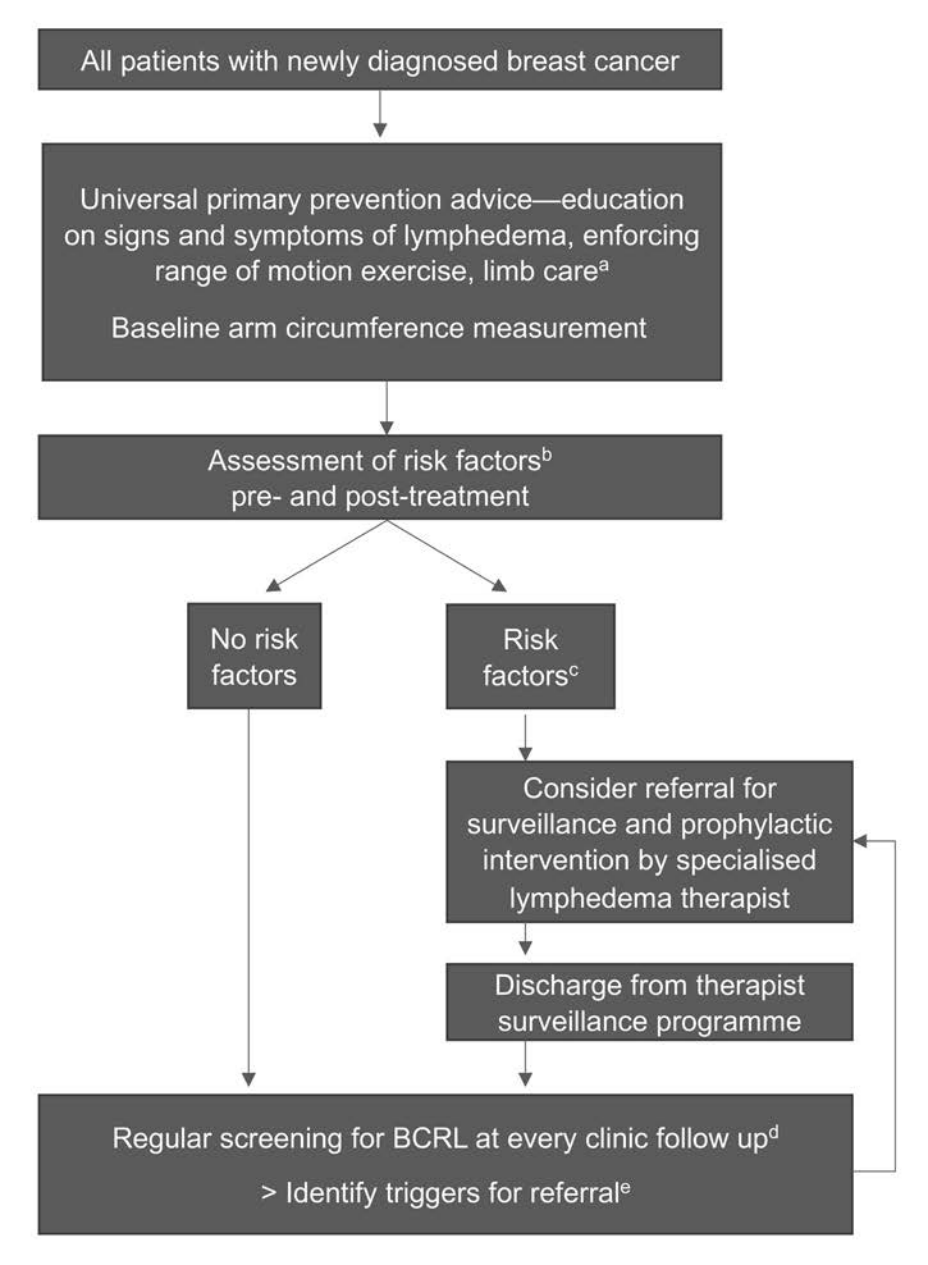
Percent agreement and Cohen's kappa coefficient were used to analyse inter-rater variability between the assessment tools. Categorical variables were analysed using the chi-square or Fisher's Exact test, and continuous variables were analysed using the Student's t-test. A P value of <0.05 was considered statistically significant. Statistical analysis was performed in March 2022 using Stata SE version 17 (StataCorp, College Station, TX, US).

RESULTS

Patients' clinical demographic and risk factors associated with BCRL

The median follow-up of patients was 88.8 months (Table 1). The cumulative prevalence rate in the

Fig. 1. Our surveillance strategy for breast cancer related lymphedema (BCRL).



[a] Universal primary prevention advice:
1) Maintain a healthy weight
2) Avoid trauma/injury to at-risk limb if possible. However, isolated blood pressure measurement, venipuncture and peripheral intravenous line placement in the ipsilateral arm not affected by lymphedema has not been shown to affect the occurrence of lymphedema
3) Regular surveillance of signs and symptoms of BCRL

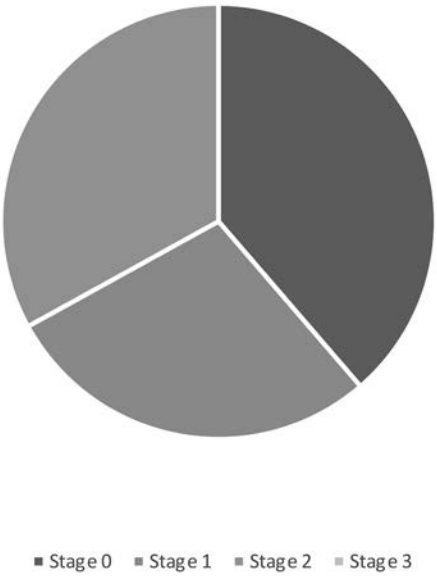
[b] Risk factors:
1) Elevated body mass index (BMI ≥25)
2) Higher pathological stage (≥T3 or ≥N1)
3) History of axillary clearance
4) Chemotherapy

[c] Screening for lymphedema signs and symptoms (PESTS):
1) Pain
2) Elevate the arm (check for fatigue, weakness, restricted range of motion)
3) Swelling
4) Tightness and altered sensation (including heaviness, numbness)
5) Skin changes (including thickening, signs of infection)

[d] Screening for confounding conditions:
1) Musculoskeletal conditions (e.g. frozen shoulder/osteoarthritis/fracture/carpal tunnel syndrome/others)
2) Neurological conditions (e.g. stroke/dystonia/cervical spondylosis/others)
3) Fluid retention/third spacing from organ failure
4) Vascular causes (e.g. deep vein thrombosis/central vein stenosis/arteriovenous fistula)
5) Other treatment associated morbidities
   a) Chemotherapy-induced peripheral neuropathy (CIPN)
   b) Aromatase inhibitor-induced musculoskeletal syndrome (AIMS)
   c) Radiation fibrosis
   d) Axillary web syndrome/cording/post mastectomy pain syndrome

[e] Triggers for referrals to lymphedema therapist:
1) Symptomatic without other attributable medical causes
2) Number of limb infections ≥1 per year
3) Arm circumferential measurement difference ≥2 cm

Fig. 2. Severity of BCRL diagnosed according to International Society of Lymphology (ISL).



ISL stage	0 (subclinical)	1 (mild)	2 (moderate)	3 (severe)
Number	20	6	7	0

cohort was 30.9% when using any of the diagnostic criteria. This cohort of BCRL patients had a higher mean age (58.4 vs 54.9 years), higher mean BMI (27.7 vs 25.2), higher proportion of whom have undergone mastectomy (77% vs 64.3%), axillary clearance, less likely breast reconstruction, higher-grade tumour, more lymph nodes excised, more advanced nodal disease, and had undergone adjuvant chemotherapy.

Prevalence by various assessment tools and inter-rater reliability

Based on our study, the prevalence of BCRL diagnosed by arm circumference measurements was the highest at 18.9% (89 out of 511), whereas clinicians' assessment was the lowest at 6.5% (33 out of 511). When using any of the diagnostic criteria, the cumulative prevalence was 30.1% (154) (Table 2). Although there was a high percent agreement rate of >80% between self-reported symptoms/arm circumference and clinical diagnosis of BCRL, the Cohen's kappa agreement for inter-rater reliability was only fair (0.19–0.31, $P<0.001$).

Clinically significant BCRL determined by attending clinician

The overall clinical BCRL diagnosed by clinician was only 6.5% (33 out of 511). Of note, the observed proportion of clinical BCRL in patients undergoing SLNB/axillary sampling was 1.7% compared to 9.9% in patients who undergone axillary clearance (Table 3). Majority of the BCRL severity were subclinical or mild (ISL stages 0–1), while only 7 out of 33 were considered moderate (ISL stage 2). None were severe (ISL stage 3) nor required radical resection with or without lymphatic reconstruction (Fig. 2). Only 33% (11 out of 33) of patients with BCRL had active therapist review. These patients were given reinforcement on skin care advice and offered compression sleeve prescription (ISL stages 0–1), or received manual lymphatic drainage, and compression bandage (ISL stage 2). Although suitable cases were discussed for lymphatic restoring procedures, there was little uptake. The rest either defaulted due to poor compliance or were discharged to self-therapy.

Table 1. Demographic of all patients cumulatively diagnosed with BCRL by self-reported symptoms, arm circumference measurements, or clinician assessment.

	All (n=511)	BCRL (n=154)	No BCRL (n=346)	*P* value
Age, median (years)	56.0 ± 12.6	58.4 ± 12.5	54.9 ± 12.5	0.003
BMI	26.0 ± 7.7	27.7 ± 9.0	25.2 ± 6.8	0.002
Breast surgery				0.01
BCS	135 (27.9%)	28 (17.7%)	107 (30.3%)	
Mastectomy	349 (72.1%)	122 (77.2%)	227 (64.3%)	
Axillary surgery				
SLNB/Axillary sampling	210 (45.4%	60 (41.4%)	150 (47.2%)	0.09
Axillary clearance	253 (54.6%)	85 (58.6%)	168 (52.8%)	
Reconstruction	48	11 (8.6%)	37 (14.5%)	0.10
Time interval from operation, months	88.8	80.1	92.6	0.09
Histology				
DCIS	87 (17.0%)	23 (14.6%)	64 (18.1%)	0.19
Ductal	318 (62.2%)	97 (61.4%)	221 (62.6%)	
Lobular	23 (4.5%)	5 (3.2%)	18 (5.1%)	
Others	83 (16.2%)	33 (20.9%)	50 (14.1%)	
Grade				
1	72 (14.9%)	14 (9.3%)	58 (17.4%)	0.047
2	226 (46.6%)	71 (47.0%)	155 (46.4%)	
3	187 (38.6%)	66 (43.7%)	121 (36.2%)	
Tumour stage				
0	109 (21.3%)	32 (20.3%)	77 (21.8%)	0.05
1	175 (34.3%)	42 (26.6%)	133 (37.7%)	
2	177 (34.6%)	65 (41.4%)	112 (31.7%)	
3	36 (7.1%)	12 (7.6%)	24 (6.8%)	
4	14 (2.7%)	7 (4.4%)	7 (2.0%)	
Nodal stage				
0	366 (71.6%)	103 (65.2%)	263 (74.5%)	0.01
1	93 (18.2%)	32 (20.3%)	61 (17.3%)	
2	31 (6.1%)	10 (6.3%)	21 (6.0%)	
3	21 (4.1)	13 (8.2%)	8 (2.3%)	
No. of lymph node positive, mean	1.4 ± 4.0	2.5 ± 6.1	0.9 ± 2.5	0.0001
No. of lymph node excised, mean	11.7 ± 8.5	13.1 ± 9.2	11.1 ± 8.1	0.02
NPI				
Good	151 (34.6%)	38 (28.4%)	113 (37.3%)	0.02
Moderate	214 (49.0%)	65 (48.5%)	149 (49.2%)	
Poor	72 (16.5%)	31 (23.1%)	41 (13.5%)	
Receptor profile				
ER+	382 (78.3%)	111 (74.5%)	271 (80.0%)	0.18
TNBC	39 (7.6%)	16 (10.1%)	23 (6.5%)	0.15
Her2+	117 (26.5%)	33 (24.4%)	84 (27.5%)	0.51
Adjuvant chemotherapy	256 (50.1%)	91 (57.6%)	165 (46.7%)	0.02
Adjuvant endocrine therapy	352 (68.9%)	107 (67.7%)	245 (69.4%)	0.70
Adjuvant radiotherapy	247 (48.3%)	76 (48.1%)	171 (48.4%)	0.94

BCS: breast-conserving surgery; BMI: body mass index (kg/m^2); DCIS: ductal carcinoma-in-situ; ER: estrogen receptor positive; Her2+: human epidermal growth factor receptor 2 positive; NPI: Nottingham Prognostic Index; SLNB: sentinel lymph node biopsy; TNBC: triple negative breast cancer

Table 2. Prevalence by assessment tools and inter-rater reliability.

Prevalence			
Clinical diagnosis	**Self-reported symptoms**	**Arm circumference**	**Cumulative**
n=33 (6.5%)	**n=83 (16.2%)**	**n=92 (18.0%)**	**154 (30.1%)**
Clinical diagnosis of BCRL			
Self-reported symptoms	Yes	No	Percent agreement 407/479 (85.0%); Kappa 0.3188; *P*<0.001
Yes	24	59	Sensitivity 24/33 (72.7%)
No	9	383	Specificity 383/446 (88.5%)
Clinical diagnosis of BCRL			
Arm circumference >2 cm	Yes	No	Percent agreement 388/478 (81.1%); Kappa 0.192; *P*<0.001
Yes	19	73	Sensitivity 19/33 (57.6%)
No	14	369	Specificity 369/445 (82.9%)

BCRL: breast cancer-related lymphedema

DISCUSSION

Local prevalence rates are comparable to internationally observed data despite higher rates of mastectomy and axillary dissection

This study highlighted the prevalence rates of BCRL in a single tertiary breast unit with an established lymphedema surveillance strategy. Comparable to other studies in our literature review, the prevalence of BCRL was estimated to be less than a third of the cohort (6.5–30.8%).[3-12] This was lower than expected despite the cohort having a higher rate of mastectomy and axillary clearance performed (>50%). These risk factors were hypothesised to contribute to the rates of BCRL due to their extent of surgical disruption of the draining lymphatics.[10,12] The proportion of breast surgery performed was at least reflective of the practice in Singapore and other Southeast Asian countries in the last decade, whereby rates of mastectomy with or without axillary dissection may be higher due to reasons such as breast cancer being diagnosed at a more advanced stage, and psychosocial reasons such as fear of cancer relapse, perception that health is more important than breast retention, possibility of involved margins.[13-17]

However, breast surgery has seen a trend of de-escalating axillary treatment aimed at producing equivalent survival outcomes and omitting previously routine surgical therapies such as axillary lymph node dissection or radiation in select group.[18-22] This is expected to further improve arm morbidities outcome assessment such as BCRL and shoulder dysfunctions. The rates of BCRL will continue to form an important part of performance indicators of any contemporary breast unit. This study is therefore important to set a benchmark for prevalence rates not only as a cumulative rate, but identify the relative risk of BCRL associated with various treatment and risk factors.

Differentiating clinical BCRL from other causes

The result demonstrated variation in the estimation of prevalence of BCRL depending on the type of assessment tools used. Patient-reported BCRL was higher compared to clinician-diagnosed BCRL. However, the latter also represented the most clinically significant BCRL requiring interventions that were not due to other medical causes. Clinical surveillance post-cancer treatment was aimed at excluding disease recurrences, and other breast cancer treatment-related morbidities that could also impair functional outcomes and quality of life. This required clinicians to take into account patients' underlying risk factors and potential competing diagnosis. Patient-subjective complaints of shoulder dysfunction or altered limb sensation may be caused by common conditions such as frozen shoulder or adhesive capsulitis, carpal tunnel syndrome, tenosynovitis.[23,24] Other contributing conditions such as chemotherapy-induced peripheral neuropathy (CIPN), aromatase inhibitor-induced musculoskeletal syndrome (AIMS), radiation-induced fibrosis, axillary cording syndrome may often co-exist (Fig. 1).[25-30] Similarly, arm swelling could be due to other causes such as fluid overload, venous disorders or disease recurrence. These should be excluded with the relevant tests. Rates of BCRL by patients' reporting may therefore be an overestimation due to any of these confounding factors.[30,31]

Table 3. Demographic of patients with clinical BCRL diagnosed by physician.

	BCRL (n=33)	No BCRL (n=478)	*P* value
Age, median (years)	61.1 ± 12.9	55.6 ± 12.5	0.02
BMI	27.2 ± 8.3	25.9 ± 7.6	0.38
Breast surgery			
BCS	2 (6.5%)	133 (29.4%)	0.02
Mastectomy	29 (93.5%)	320 (70.6%)	
Axillary surgery			
SLNB/Axillary sampling	5 (16.7%)	205 (47.3%)	0.008
Axillary clearance	25 (83.3%)	228 (52.7%)	
Reconstruction	0	48	0.02
Time interval from operation, months	84.6 ± 15.5	89.0 ± 3.5	0.75
Histology			
DCIS	3 (9.1%)	84 (17.6%)	0.29
Ductal	23 (69.7%)	294 (61.7%)	
Lobular	0	23 (4.8%)	
Others	7 (21.2%)	76 (15.9%)	
Grade			
1	0	72 (15.8%)	0.05
2	15 (50.0%)	211 (46.4%)	
3	15 (50.0%)	172 (37.8%)	
Tumour stage			
0	6 (18.2%)	103 (21.6%)	0.005
1	4 (12.1%)	171 (35.8%)	
2	15 (45.6%)	162 (33.9%)	
3	5 (15.5%)	31 (6.5%)	
4	3 (9.1%)	11 (2.3%)	
Nodal stage			
0	16 (48.5%)	350 (73.2%)	<0.001
1	6 (18.2%)	87 (18.2%)	
2	6 (18.2%)	25 (5.2%)	
3	5 (15.2%)	16 (3.4%)	
No. of lymph node positive, mean	5 ± 8	1.2 ± 3.5	<0.001
No. of lymph node excised, mean	16.9 ± 8.9	11.4 ± 8.4	<0.001
NPI			0.001
Good	4 (12.9%)	147 (31.6%)	
Moderate	12 (38.7%)	202 (43.4%)	
Poor	12 (38.7%)	60 (12.9%)	
Receptor profile			
ER+	21 (72.4%)	361 (78.7%)	0.43
TNBC	4 (12.2%)	35 (7.3%)	
Her2+	7 (24.1%)	110 (25.3%)	
Adjuvant chemotherapy	24 (72.7%)	232 (48.6%)	0.007
Adjuvant endocrine therapy	21 (63.6%)	331 (69.3%)	0.51
Adjuvant radiotherapy	20 (60.6%)	227 (47.5%)	0.15

BCS: breast-conserving surgery; BMI: body mass index (kg/m^2); DCIS: ductal carcinoma-in-situ; ER: estrogen receptor positive; Her2+: human epidermal growth factor receptor 2 positive; NPI: Nottingham Prognostic Index; SLNB: sentinel lymph node biopsy; TNBC: triple negative breast cancer

These factors ultimately explained the relatively low Cohen's kappa coefficient because the patients' signs and symptoms can be wrongly alluded to BCRL. This highlighted a significant difference and lack in objectivity across the assessment tools. However, given the limitations of the available measurement tools, the authors proposed to include all of the findings collectively from directed questioning of patient symptoms, objective measurement of arm circumference and finally, an assessment matrix to consider various confounding diagnosis in the lymphedema surveillance strategy.[31]

Focus on evidence-based recommendations

The clinical risk factors associated with BCRL identified in our current study corroborated with those in literature review.[30] These risk factors included elevated BMI, higher tumour and nodal pathological stage, presence of axillary clearance and chemotherapy. This at-risk group may benefit from a more intensive lymphedema surveillance strategy and recommendation. Risk factors directly related to disease and treatment factors may be unavoidable, but certain modifiable targets such as obesity or weight gain after treatment, and minimising infections or injury to the at-risk limb can be emphasised during patient education.[30-32] Our institutional practice was to address clinical risk factors in accordance with established lymphedema clinical guidelines and avoid precautionary advice or primary prevention strategies that may engender unnecessary fear, restrictions or confusion from the inconsistency messaging. For example, avoiding of air travel, avoiding extreme of temperatures, vigorous exercise or the restrictions of use of the at-risk limb for blood pressure taking, venipuncture and/or peripheral intravascular line placement—to date, these have largely not been shown to be conclusively associated with development of lymphedema and their level of supporting evidence remained debatable.[32-38]

Strengths and limitations

The strength of the findings was derived from a comprehensive lymphedema surveillance strategy that was practised consistently by all participating clinicians after reviewing the latest available literature.[30] The merits of this surveillance strategy included its ease of implementation as it did not rely on sophisticated tools for an objective measurement, and showcased a practical use of classical patient reported symptoms, regular arm circumference measurements to guide independent clinician assessment and grading per ISL staging. Patient education largely focused on typical signs and symptoms, risk factors that were supported by the latest evidence and avoided unnecessary precautionary advice.[31,32,39] Specialised lymphedema therapy may also be a scarce resource and we defined specific referral criteria for right-siting patients to avoid taking up unnecessary resources. This improved the sustainability of the lymphedema surveillance strategy and allowed wider implementation.

A limitation of the study was the nature of the convenience sampling method and the relatively low frequency of moderate-to-severe BCRL observed. These could be due to sampling bias and retrospective nature of the study. To address this issue, the study used the cumulative prevalence diagnosed by either of the 3 assessment tools to include a larger sample of patients with possible BCRL. We accounted for the overestimation of BCRL by patient-reported symptoms and arm measurements compared to clinical BCRL that was likely due to the presence of other distracting conditions that warranted different management. This study did not claim to have a diagnostic gold standard for BCRL but highlighted the important aids to make an accurate clinical diagnosis.[3] Although arm circumference measurement was relatively inexpensive, it required rigorous training of our staff to standardise the method of recording to improve accuracy and reduce inter-assessor variability. Educating on BCRL, addressing its risk factors, implementing regular surveillance, and timely referral for appropriate management remain cornerstone to any comprehensive lymphedema service.[30] Based on our results, we could still generate important hypothesis on the risk factors relevant to our population, better understand the limitations of the current diagnostic process and plan for future research based on this set of standardised outcome assessment.

Future implications

We aim to safely reduce the morbidity of BCRL by providing the optimal breast cancer treatment necessary without compromising on oncological outcomes. This includes reviewing our patient selection criteria for various axilla therapies including axillary lymph node dissection or radiotherapy and to avoid practices deemed to be of low value.[18]

Fortunately, the observed severity of BCRL in our cohort was largely limited to subclinical and mild. These may be contributed by timely detection and referral for specialised therapy, although we would require a larger sample size and direct studies to confirm the effectiveness of our lymphedema surveillance strategy. Lastly, there is an emerging role for lymphatic preserving

or restoring procedures that have shown promising results at reducing the severity of BCRL for those whose disease and treatment factors cannot be modified otherwise.[40] However, it would require validation of other assessment tools to diagnose, assess the severity of lymphoedema, and progress following conservative or surgical treatment.[39]

CONCLUSION

In conclusion, our study showed that our rates of BRCL were comparable to international standards and highlighted similar patient profiles who were at risk of developing BCRL. Although the severity of BCRL were largely subclinical or mild, having a comprehensive lymphedema surveillance strategy is paramount to address and further reduce the impact of this debilitating condition.

Conflict of interest

None to declare.

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ORIGINAL ARTICLE

Frailty-aware surgical care: Validation of Hospital Frailty Risk Score (HFRS) in older surgical patients

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ABSTRACT

Introduction: Frailty has an important impact on the health outcomes of older patients, and frailty screening is recommended as part of perioperative evaluation. The Hospital Frailty Risk Score (HFRS) is a validated tool that highlights frailty risk using 109 International Classification of Diseases, 10th revision (ICD-10) codes. In this study, we aim to compare HFRS to the Charlson Comorbidity Index (CCI) and validate HFRS as a predictor of adverse outcomes in Asian patients admitted to surgical services.

Method: A retrospective study of electronic health records (EHR) was undertaken in patients aged 65 years and above who were discharged from surgical services between 1 April 2022 to 31 July 2022. Patients were stratified into low (HFRS <5), intermediate (HFRS 5–15) and high (HFRS >15) risk of frailty.

Results: Those at high risk of frailty were older and more likely to be men. They were also likely to have more comorbidities and a higher CCI than those at low risk of frailty. High HFRS scores were associated with an increased risk of adverse outcomes, such as mortality, hospital length of stay (LOS) and 30-day readmission. When used in combination with CCI, there was better prediction of mortality at 90 and 270 days, and 30-day readmission.

Conclusion: To our knowledge, this is the first validation of HFRS in Singapore in surgical patients and confirms that high-risk HFRS predicts long LOS (≥7days), increased unplanned hospital readmissions (both 30-day and 270-day) and increased mortality (inpatient, 10-day, 30-day, 90-day, 270-day) compared with those at low risk of frailty.

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Keywords: frailty, general surgery, geriatrics, surgery

CLINICAL IMPACT

What is New

- Hospital Frailty Risk Score (HFRS) can identify frail older surgical patients, and has greater accuracy if combined with Charlson Comorbidity Index for 90-day and 270-day mortality and 30-day readmission.

Clinical Implications

- HFRS does not require a clinical assessment, and can predict those at risk of longer length of stay, unplanned hospital readmissions and mortality.
- HFRS is currently being adapted into an easy and low-cost tool to screen and identify patients at higher risk of adverse outcomes in an older surgical population in Singapore.

INTRODUCTION

Frailty is a clinically recognisable state of vulnerability in older people, resulting from age-associated decline in physiological reserves and function across multiple organ systems, such that the ability to cope with acute stressors is compromised.[1] Frailty is prevalent among older people[2] and is associated with higher rates of utilisation of various healthcare services,[3] increased emergency admissions[4] and a higher predictive risk for adverse health outcomes.[5] With the increasing proportion of residents aged 60 and above in Singapore,[6] the number of frail individuals attending hospital is expected to increase, and

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this highlights the need for suitable tools to stratify patients[8] and identify those at highest risk for frailty.

Studies on older surgical patients have consistently shown an association between frailty and adverse outcomes, such as postoperative complications,[9] increased length of stay (LOS)[10] and higher readmissions.[11] Identifying high-risk frailty patients preoperatively allows for identification of those who may benefit from early intervention and rehabilitation.[12] The presence of frailty may alter treatment plans as well as contribute to the informed discussion of operative risk with older patients.[13]

Currently, frailty can be identified through 3 main approaches: the Rockwood and Mitniski deficit accumulation model, Fried physical phenotype model, and mixed physical and psychosocial model.[14] These screening tools require manpower and training for face-to-face assessment and may also be associated with inaccuracies or paucity of documentation. A study performed in an emergency department setting showed significant missing Clinical Frailty Scale scores in manual data collection with up to 50% of patients being missed, highlighting the need for a systematised tool that is accurate and easy to implement.[15]

The Hospital Frailty Risk Score (HFRS) is a low-cost screening tool[16] that uses routinely collected electronic health records and removes the need for clinical assessment. It has been shown to identify a distinct patient group with higher non-elective hospitalisations, increased 30-day mortality, LOS and 30-day readmissions.[16,17] It highlights at-risk frailty patients and triggers in-depth assessment of the patient, such as a Comprehensive Geriatric Assessment (CGA). HFRS is non-operator dependent[18] and has also been validated against the 2 widely used clinical frailty screening tools, the Fried phenotype and Rockwood Frailty Index. HFRS has also been validated in multiple cohorts of patients in several countries across the world.[18-20] While there have been studies in Singapore that have evaluated the association of HFRS with delirium in patients admitted to the Division of Geriatric Medicine,[21] there has yet to be any validation or implementation of HFRS for surgical patients in Singapore.

In this study, we sought to validate HFRS in a cohort of older surgical patients in Singapore and assess the score as an independent risk factor for adverse outcomes after surgery. We postulate that patients with higher HFRS scores will have poorer health outcomes and higher healthcare utilisation, thus supporting the utility of early frailty identification in surgical patients to reduce adverse outcomes.

METHOD

Study design

The study involves a retrospective review of electronic medical records of patients 65 years old and above who were discharged from surgical service in Changi General Hospital (CGH), in Singapore between 1 April 2022 and 31 July 2022. This is a single-site study that included data from the patients' acute hospitalisation episode. Data extraction was performed by the Data Management and Information team, anonymised and analysed by the Health Systems Intelligence team at CGH. Data were analysed using Python version 3.6.4 (Python Software Foundation) and R statistical software version 3.6.1 (R Core Team 2019, Vienna, Austria). Python was used for data pre-processing, while R was used for statistical analysis.

Data collected included demographic data for age, sex and race. HFRS was calculated using an algorithm based on the methodology outlined in literature.[16] Body mass index (BMI) was included if available within the 12 months prior to admission. For cases with no BMI recorded within this time, imputation was performed to replace missing values (14%) with the median BMI of each age group (65–74, 75–84, 85–94, ≥95 years) to avoid skewing data due to outliers.[40] Sensitivity analysis showed that this method of imputation yielded the same conclusions compared to imputation using sample mean in multivariate regression. Comorbidity was assessed using the Charlson Comorbidity Index (CCI) and was calculated based on the coding of the index admission. Hospitalisation data included LOS, 30-day emergency hospital readmissions and mortality at 10 days, 30 days, 90 days and 270 days from the date of hospital admission. In the analysis of 30-day readmissions, patients who died inpatient were excluded but deaths within 30 days of discharge were included. Table of Surgical Procedure (TOSP), number of TOSP procedures and American Society of Anesthesiologists (ASA) scoring were used to determine complexity of surgical cases. TOSP is an exhaustive list of procedures ranked from 1A to 7C. Generally, higher category and/or higher number of TOSP procedures is presumed to suggest increased complexity. TOSP table number was only available for patients who underwent a surgical procedure and those who did not undergo surgery were scored with a TOSP table number of 0. ASA scoring is a subjective assessment of a patient's overall health that is based on 5 classes. Class I comprises healthy patients, class II patients have mild systemic disease, class III patients have severe systemic disease that is not incapacitating, class IV patients have incapacitating disease that

is a constant threat to life, and class V patients are moribund and not expected to live 24 hours without surgery. Patients were categorised into high risk (>15), intermediate risk (5–15) and low risk (<5) of frailty based on HFRS.[16] The 109 ICD-10 codes used to calculate the HFRS for each patient can be found in Supplementary Appendix S1. The analysis excludes day surgery and 23-hour ward admissions, and discharges from the Short Stay Unit or Emergency Department Treatment Unit or equivalent. Elective admissions that were discharged within 24 hours were also excluded. The cohort is representative of patients undergoing acute surgical admissions to a tertiary hospital in Singapore.

Informed consent was not required as the study team had no direct contact with patients and no access to patient-identifiable data, as all data collected were anonymised. SingHealth Centralised Institutional Review Board provided ethics approval (IRB number 2022/2645). All methods included in this study are in accordance with the Declaration of Helsinki.

The primary aim of this study is to compare HFRS with CCI and validate HFRS as a predictor of adverse outcomes, such as hospitalisation utilisation and mortality in older surgical patients. The secondary aim is to determine whether HFRS is associated with severity and complexity of surgery in older patients, and any other contributory factors that predict adverse outcomes.

Statistical analysis

Continuous variables are presented as means and standard deviations (SD), while categorical variables are presented as counts and percentages. HFRS was analysed as a categorical variable (high, intermediate and low risk). To compare the association of HFRS categories with various variables and outcomes, we conducted the Pearson chi-square test, Fisher's Exact test, analysis of variance, and Kruskal-Wallis test as appropriate. For our analysis of 30-day readmissions, inpatients who died were excluded from analysis. The number of TOSP procedures was presented and analysed as a categorical variable in hypothesis testing, where those with ≥5 TOSP procedures were grouped into 1 category to fulfil the assumptions of the Pearson chi-square test.

Univariate and multivariate logistic regressions were fitted to evaluate the association between HFRS (as a continuous variable) and the relevant outcomes. The multivariate model was adjusted for age, sex, race, BMI, CCI, maximum TOSP table number and number of TOSP procedures. Maximum TOSP table number and number of TOSP procedures were analysed as a continuous variable in logistic regression. Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs) . An unadjusted model was used to compare HFRS, CCI and HFRS in combination with CCI as predictors of outcomes. The area under the receiver operator characteristic curve (AUROC) was used to assess model discrimination. All statistical analyses were performed using a two-tailed test with a significance level of $P<0.05$.

RESULTS

Baseline characteristics

A total of 1829 patients were discharged from surgical service in CGH between 1 April 2022 and 31 July 2022. Mean age was 76 years (SD 7.91), with a range of 65 to 103 years (Table 1). Those at high risk of frailty were significantly older compared to those at low risk of frailty (mean: 81.1 versus 73.4, $P<0.001$) (Table 1). There was a higher prevalence of men in the study population (53.9% vs 46.1%), although the proportion of men and women were similar among those at high risk of frailty (49.3% vs 50.7%, respectively) (Table 1). There were no significant differences in race across the frailty risk groups.

Hospitalisation usage

Hospital LOS was significantly longer in those at higher risk of frailty compared with those at lower risk (60.5% vs 15.6%, $P<0.001$) (Table 2). In both univariate and multivariate analyses, women were more likely to have longer LOS (adjusted OR [aOR] 1.676, CI 1.318–2.134, $P<0.001$) (Table 3A). HFRS was associated with long LOS, in both univariate (OR 1.106, CI 1.092–1.122, $P<0.001$) and multivariate analyses (aOR 1.106, CI 1.088–1.125, $P<0.001$) (Table 3A). CCI was also associated with long LOS in both univariate (OR 1.338, CI 1.271–1.411, $P<0.001$) and multivariate analyses (aOR 1.231, CI 1.157–1.310, $P<0.001$) (Table 3A). Complexity of surgical procedures defined as higher TOSP (aOR 1.248, CI 1.170–1.333, $P<0.001$) and higher number of surgical procedures (aOR 1.680, CI 1.441–1.970, $P<0.001$) were associated with longer LOS (Table 3A).

Hospital readmission (excluding inpatients who died but including patients who died within 30 days of discharge) within 30 days was significantly higher in those at higher risk of frailty (20.3% vs 7.2%, $P<0.001$) and this remained significant for readmission within 270 days (46.1% vs 19.5%) (Table 2). Age, high risk of frailty (aOR 1.047 CI 1.030–1.065, $P<0.001$) and CCI (aOR 1.124, CI 1.042–1.211, $P<0.01$) were associated with

Table 1. Baseline characteristics.

	Low risk (n=923)	Intermediate risk (n=600)	High risk (n=306)	Overall (N=1829)	*P* value
Age, mean (SD), years	73.4 (6.74)	77.2 (7.68)	81.1 (8.51)	76.0 (7.91)	<0.001
Men, no. (%)	532 (57.6)	302 (50.3)	151 (49.3)	985 (53.9)	<0.001
BMI, mean (SD)	24.9 (4.43)	24.3 (5.00)	23.3 (4.82)	24.4 (4.72)	<0.001
Race, no. (%)					
Chinese	704 (76.3)	425 (70.8)	239 (78.1)	1368 (74.8)	0.23
Indian	47 (5.1)	35 (5.8)	14 (4.6)	96 (5.2)	
Malay	117 (12.7)	94 (15.7)	37 (12.1)	248 (13.6)	
Other races	55 (6.0)	46 (7.7)	16 (5.2)	117 (6.4)	
CCI, mean (SD)	1.09 (1.71)	1.75 (1.88)	2.66 (2.26)	1.57 (1.95)	<0.001
CCI category, no. (%)					
0	560 (60.7)	255 (42.5)	60 (19.6)	875 (47.8)	<0.001
1	47 (5.1)	39 (6.5)	51 (16.7)	137 (7.5)	
2	187 (20.3)	130 (21.7)	54 (17.6)	371 (20.3)	
≥3	129 (14.0)	176 (29.3)	141 (46.1)	446 (24.4)	

BMI: body mass index; CCI: Charlson Comorbidity Index

Table 2. Hospital outcomes.

	Low risk (n=923)	Intermediate risk (n=600)	High risk (n=306)	Overall (N=1829)	*P* value
LOS ≥7 days, no. (%)	144 (15.6)	257 (42.8)	185 (60.5)	586 (32.0)	<0.001
Inpatient mortality, no. (%)	4 (0.4)	22 (3.7)	12 (3.9)	38 (2.1)	<0.001
10-day mortality, no. (%)	6 (0.7)	15 (2.5)	8 (2.6)	29 (1.6)	<0.01
30-day mortality, no. (%)	13 (1.4)	26 (4.3)	14 (4.6)	53 (2.9)	<0.001
90-day mortality, no. (%)	24 (2.6)	41 (6.8)	39 (12.7)	104 (5.7)	<0.001
270-day mortality, no. (%)	50 (5.4)	78 (13.0)	70 (22.9)	198 (10.8)	<0.001
30-day readmission (emergency), no. (%)[a]	66 (7.2)	71 (11.8)	62 (20.3)	199 (10.9)	<0.001
270-day readmission (emergency), no. (%)[a]	180 (19.5)	211 (35.2)	141 (46.1)	532 (29.1)	<0.001

[a] Excludes cases who died inpatient but not patients who died within 30 days of hospital discharge.

30-day emergency readmissions (Table 2 and Table 3F). Women had lower likelihood of 30-day emergency hospital readmission (aOR 0.704, CI 0.511–0.965, *P*<0.05) (Table 3F).

TOSP and ASA scores

The most common admitting surgical specialty was general surgery (50.7%) followed by orthopaedic surgery (33.8%) (Table 4). Surgical procedures (TOSP) were performed in 64.3% of patients and among them, majority underwent 1 procedure (70.5%). There were more patients of high risk versus low risk (23.2% vs 17.4%) for frailty who underwent 2 or more TOSP procedures. The number of surgical procedures was associated with higher risk of frailty (*P*<0.001) as was the complexity of surgical procedure (*P*<0.001) (Table 1). Higher TOSP table number was taken

Table 3A. Multivariable logistic regression analyses results: long length of stay.

	Univariate		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.038 (1.025–1.051)	<0.001	1.015 (0.998–1.032)	0.07
Women	1.668 (1.369–2.033)	<0.001	1.676 (1.318–2.134)	<0.001
HFRS	1.106 (1.092–1.122)	<0.001	1.106 (1.088–1.125)	<0.001
Race				
Indian	1.264 (0.815–1.935)	0.29	1.287 (0.758–2.150)	0.34
Malay	1.191 (0.893–1.579)	0.23	1.182 (0.831–1.672)	0.35
Other	1.019 (0.672–1.519)	0.93	1.204 (0.732–1.945)	0.46
CCI	1.338 (1.271–1.411)	<0.001	1.231 (1.157–1.310)	<0.001
BMI	0.994 (0.973–1.015)	0.57	1.004 (0.979–1.030)	0.74
Maximum TOSP table no.	1.298 (1.240–1.359)	<0.001	1.248 (1.170–1.333)	<0.001
No. of TOSP procedures	1.965 (1.755–2.210)	<0.001	1.680 (1.441–1.970)	<0.001

Table 3B. Multivariable logistic regression analyses results: 10-day mortality.

	Univariate		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.090 (1.045–1.137)	<0.001	1.071 (1.019–1.125)	<0.01
Women	1.255 (0.599–2.644)	0.54	1.133 (0.522–2.469)	0.75
HFRS	1.046 (1.010–1.079)	<0.01	1.009 (0.967–1.049)	0.67
Race				
Indian	0.000 (NA)	0.98	0.000 (NA)	0.99
Malay	0.749 (0.176–2.183)	0.64	0.871 (0.201–2.631)	0.83
Other	2.166 (0.625–5.777)	0.16	2.363 (0.662–6.637)	0.13
CCI	1.212 (1.034–1.401)	<0.05	1.230 (1.032–1.447)	<0.05
BMI	0.921 (0.839–1.004)	0.08	0.957 (0.869–1.043)	0.35
Maximum TOSP table no.	0.701 (0.546–0.862)	<0.01	0.652 (0.470–0.862)	<0.01
No. of TOSP procedures	0.727 (0.438–1.088)	0.18	1.249 (0.793–1.623)	0.18

BMI: body mass index; CCI: Charlson Comorbidity Index; CI: confidence interval; HFRS: Hospitality Frailty Risk Score; NA: not available; OR: odds ratio; TOSP: Table of Surgical Procedure

as a proxy for surgical complexity. ASA scores were only available for 48.6% of the cohort and hence was not used as a variable in logistic regression. However, higher risk of frailty correlated with a higher ASA score (*P*<0.001) (Table 1).

Charlson Comorbidity Index (CCI)

CCI is shown in Table 1 where more than half (52.2%) of the cohort had 1 or more comorbidity, 20.3% had CCI of 2, and 24.4% had CCI of 3 or higher. Mean CCI was higher in those at high risk compared to those at low risk of frailty (2.66 vs 1.09, *P*<0.001). There was a statistically significant association between HFRS and CCI (*P*<0.001)—a higher proportion of patients with CCI 3 or more were those at high risk of frailty compared with those at low risk of frailty (Table 1). There was low collinearity between HFRS and CCI (correlation coefficient=0.32, *P*<0.05).

Table 3C. Multivariable logistic regression analyses results: 30-day mortality.

	Univariate		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.075 (1.042–1.110)	<0.001	1.055 (1.017–1.095)	<0.01
Women	1.425 (0.824–2.486)	0.21	1.352 (0.761–2.421)	0.3
HFRS	1.043 (1.017–1.069)	<0.001	1.010 (0.979–1.041)	0.5
Race				
Indian	0.368 (0.021–1.727)	0.33	0.421 (0.023–2.038)	0.4
Malay	1.017 (0.412–2.166)	0.97	1.146 (0.454–2.520)	0.75
Other	2.227 (0.894–4.811)	0.06	2.320 (0.904–5.226)	0.06
CCI	1.223 (1.088–1.365)	<0.001	1.234 (1.083–1.396)	<0.01
BMI	0.927 (0.865–0.989)	<0.05	0.951 (0.887–1.014)	0.14
Maximum TOSP table no.	0.737 (0.624–0.855)	<0.001	0.701 (0.564–0.856)	<0.001
No. of TOSP procedures	0.734 (0.509–1.002)	0.08	1.176 (0.832–1.473)	0.25

Table 3D. Multivariable logistic regression analyses results: 90-day mortality.

	Univariate		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.074 (1.049–1.099)	<0.001	1.045 (1.016–1.074)	<0.01
Women	1.086 (0.729–1.614)	0.68	1.034 (0.673–1.585)	0.88
HFRS	1.065 (1.046–1.084)	<0.001	1.033 (1.012–1.055)	<0.01
Race				
Indian	0.357 (0.058–1.157)	0.15	0.420 (0.068–1.405)	0.24
Malay	0.927 (0.485–1.640)	0.81	1.042 (0.529–1.912)	0.9
Other	1.916 (0.965–3.508)	<0.05	2.122 (1.031–4.066)	<0.05
CCI	1.305 (1.201–1.416)	<0.001	1.295 (1.179–1.419)	<0.001
BMI	0.900 (0.854–0.945)	<0.001	0.926 (0.878–0.974)	<0.01
Maximum TOSP table no.	0.799 (0.718–0.883)	<0.001	0.791 (0.685–0.909)	<0.01
No. of TOSP procedures	0.778 (0.606–0.969)	<0.05	1.024 (0.780–1.255)	0.84

BMI: body mass index; CCI: Charlson Comorbidity Index; CI: confidence interval; HFRS: Hospitality Frailty Risk Score; OR: odds ratio; TOSP: Table of Surgical Procedure

Mortality

Older age was associated with mortality in both univariate and multivariate analyses at 10 days (aOR 1.071, CI 1.019–1.125, *P*<0.01), 30 days (aOR 1.055, CI 1.017–1.095, *P*<0.01), 90 days (aOR 1.045, CI 1.016–1.074, *P*<0.01) and 270 days (aOR 1.058, CI 1.035–1.081, *P*<0.001) (Tables 3B to 3E). Women had lower mortality at 270 days only (aOR 0.653, CI 0.465–0.911, *P*=0.01).

Mortality was higher in those at high risk of frailty at 10 days (2.6% vs 0.7%, *P*<0.01), 30 days (4.6% vs 1.4%, *P*<0.001), 90 days (12.7% vs 2.6%, *P*<0.001), and 270 days (22.9% vs 5.4%, *P*<0.001). Inpatient mortality was higher in frail patients (3.9% vs 0.4%, *P*<0.001) (Table 2). However, in adjusted multivariate analyses, HFRS was only associated with mortality at 90-day (aOR 1.033, CI 1.012–1.055, *P*<0.01) and 270-day (aOR

Table 3E. Multivariable logistic regression analyses results: 270-day mortality.

	Univariate		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.077 (1.059–1.097)	<0.001	1.058 (1.035–1.081)	<0.001
Women	0.752 (0.555–1.013)	0.06	0.653 (0.465–0.911)	<0.05
HFRS	1.068 (1.053–1.083)	<0.001	1.032 (1.015–1.050)	<0.001
Race				
Indian	0.453 (0.158–1.025)	0.09	0.527 (0.179–1.236)	0.18
Malay	0.883 (0.549–1.366)	0.59	0.975 (0.583–1.577)	0.92
Other	1.803 (1.066–2.925)	<0.05	2.038 (1.156–3.470)	<0.05
CCI	1.340 (1.256–1.431)	<0.001	1.339 (1.243–1.444)	<0.001
BMI	0.903 (0.869–0.937)	<0.001	0.932 (0.895–0.969)	<0.001
Maximum TOSP table no.	0.819 (0.760–0.881)	<0.001	0.807 (0.727–0.892)	<0.001
No. of TOSP procedures	0.865 (0.733–1.003)	0.07	1.052 (0.881–1.221)	0.54

Table 3F. Multivariable logistic regression analyses results: 30-day readmission.

	Univariate		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.023 (1.004–1.041)	<0.05	1.009 (0.987–1.031)	0.42
Women	0.766 (0.566–1.032)	0.08	0.704 (0.511–0.965)	<0.05
HFRS	1.055 (1.040–1.071)	<0.001	1.047 (1.030–1.065)	<0.001
Race				
Indian	1.449 (0.770–2.545)	0.22	1.332 (0.693–2.397)	0.36
Malay	1.131 (0.727–1.706)	0.57	1.018 (0.639–1.574)	0.94
Other	1.124 (0.588–1.987)	0.71	1.077 (0.554–1.940)	0.82
CCI	1.205 (1.127–1.288)	<0.001	1.124 (1.042–1.211)	<0.01
BMI	1.017 (0.986–1.047)	0.28	1.029 (0.997–1.062)	0.07
Maximum TOSP table no.	0.959 (0.897–1.025)	0.22	0.962 (0.885–1.045)	0.36
No. of TOSP procedures	1.031 (0.904–1.155)	0.63	1.003 (0.861–1.145)	0.96

BMI: body mass index; CCI: Charlson Comorbidity Index; CI: confidence interval; HFRS: Hospital Frailty Risk Score; OR: odds ratio; TOSP: Table of Surgical Procedure

1.032, CI 1.015–1.050, *P*<0.001) mortality but not 10-day (*P*=0.67) or 30-day (*P*=0.50) mortality (Tables 3B to 3E). CCI was associated with mortality at all time points whereas surgical complexity, defined as higher TOSP, was less likely to result in mortality at all time points (Tables 3B to 3E).

Comparing HFRS with CCI, we observed that HFRS is a better predictor of long LOS (AUROC 0.757 vs 0.631), 90-day mortality (AUROC 0.663 vs 0.611) and 270-day mortality (AUROC 0.686 vs 0.684). When used in combination, HFRS and CCI were better predictors of 90-day mortality (AUROC 0.670), 270-day mortality (AUROC 0.724) and 30-day readmission (AUROC 0.679 vs 0.646 for HFRS) (Table 5).

Table 4. Surgical characteristics.

	Low risk (n=923)	Intermediate risk (n=600)	High risk (n=306)	Overall (N=1829)	*P* value
Admitting specialty, no. (%)					
Ear Nose & Throat	29 (3.1)	7 (1.2)	4 (1.3)	40 (2.2)	<0.001
Ophthalmology	6 (0.7)	5 (0.8)	2 (0.7)	13 (0.7)	
Neurosurgical	19 (2.1)	36 (6.0)	20 (6.5%)	75 (4.1)	
Oro-maxillary surgery	1 (0.1)	0	1 (0.3)	2 (0.1)	
Orthopaedic surgery	287 (31.1)	234 (39.0)	98 (32.0)	619 (33.8)	
General surgery	493 (53.4)	278 (46.3)	156 (51.0)	927 (50.7)	
Urology	88 (9.5)	40 (6.7)	25 (8.2)	153 (8.4)	
TOSP procedure performed, no. (%)	610 (66.1)	378 (63.0)	188 (61.4)	1176 (64.3)	0.24
TOSP table (maximum), no. (%)					
1	98 (10.6)	55 (9.2)	34 (11.1)	187 (10.2)	<0.001
2	71 (7.7)	46 (7.7)	22 (7.2)	139 (7.6)	
3	113 (12.2)	55 (9.2)	16 (5.2)	184 (10.1)	
4	124 (13.4)	57 (9.5)	43 (14.1)	224 (12.2)	
5	86 (9.3)	128 (21.3)	59 (19.3)	273 (14.9)	
6	94 (10.2)	27 (4.5)	8 (2.6)	129 (7.1)	
7	24 (2.6)	10 (1.7)	6 (2.0)	40 (2.2)	
No procedure	313 (33.9)	222 (37.0)	118 (38.6)	653 (35.7)	
No. of TOSP procedures, (%)					
0[a]	313 (33.9)	222 (37.0)	118 (38.6)	653 (35.7)	<0.001
1	449 (48.6)	263 (43.8)	117 (38.2)	829 (45.3)	
2	109 (11.8)	79 (13.2)	41 (13.4)	229 (12.5)	
3	40 (4.3)	16 (2.7)	14 (4.6)	70 (3.8)	
4	10 (1.1)	10 (1.7)	8 (2.6)	28 (1.5)	
≥5	2 (0.2)	10 (1.7)	8 (2.6)	20 (1.1)	
ASA status (maximum), no. (%)					
1	7 (0.8)	2 (0.3)	1 (0.3)	10 (0.5)	<0.001
2	217 (23.5)	59 (9.8)	11 (3.6)	287 (15.7)	
3	233 (25.2)	204 (34.0)	100 (32.7)	537 (29.4)	
4	14 (1.5)	20 (3.3)	18 (5.9)	52 (2.8)	
5	0	2 (0.3)	0	2 (0.1)	
No ASA	452 (49.0)	313 (52.2)	176 (57.5)	941 (51.4)	

ASA: American Society of Anaesthesiologists; TOSP: Table of Surgical Procedure
[a] TOSP of 0 indicates no surgical procedure was undertaken.

Table 5. Comparing Hospital Frailty Risk Score (HFRS) and Charlson Comorbidity Index (CCI) as a predictor of outcomes.

	AUROC		
	HFRS	CCI	HFRS and CCI
Long LOS	0.757	0.631	0.755
10-day mortality	0.512	0.492	0.508
30-day mortality	0.450	0.481	0.450
90-day mortality	0.663	0.611	0.670
270-day mortality	0.686	0.684	0.724
30-day readmission	0.646	0.646	0.679

AUROC: area under the receiver operator characteristic curve; CCI: Charlson Comorbidity Index; HFRS: Hospitality Frailty Risk Score; LOS: length of stay

DISCUSSION

Frailty is associated with poorer health outcomes, increased healthcare utilisation and cost.[5,9-11] The HFRS is promising and has been shown to predict negative outcomes and increased healthcare utilisation and costs.[19] High HFRS scores have been associated with major adverse cardiovascular events,[22] postoperative sepsis,[23] LOS,[24,25] postoperative complications,[24] time to surgery[24] and mortality.[25-27]

This retrospective analysis of 1829 patients aged 65 years old and above has shown that high HFRS scores were associated with longer hospital LOS, increased 30-day hospital readmissions, and higher risk of short and longer-term mortality. Frail patients undergoing surgery are not only at risk of adverse outcomes in the immediate perioperative period, but also have an increased risk of mortality at 90 days and at 270 days, which is consistent with other studies in surgical cohorts showing increased risk of mortality up to 2 years.[25,26] This has implications in prognostication which may influence decision making for surgery.

Early and timely assessment can guide interventions in frail patients who require in-depth assessment and/or prehabilitation to reduce the risk of adverse outcomes.[34] This maximises the benefit while minimising the harm of surgical interventions as well as healthcare cost.[35] HFRS and its association with adverse outcomes has been shown in multiple inpatient and procedural settings.[18,20,36,37] In a cohort of 487,197 patients over the age of 50 undergoing surgery, higher HFRS was associated with prolonged LOS, readmission and 30-day mortality. Notably, the addition of HFRS to CCI did not significantly improve model performance possibly due to lack of CCI and HFRS data, which was calculated in only 17% and 32% of the patients, respectively.[38] Importantly, in our cohort, the use of both HFRS and CCI increased the prediction of mortality and readmissions, and shows that HFRS may be useful when combined with other conventional morbidity assessments. The low collinearity between the HFRS and CCI (correlation coefficient=0.32, $P<0.05$) in our cohort suggests that the HFRS and CCI are not strongly correlated and might be capturing different and unique information. This is consistent with the intent and computation method of both scores. Overall, CCI was developed as a predictor of mortality, while HFRS is meant to identify more broad "adverse outcomes", which includes outcomes like LOS and readmissions. Although both scores do overlap in the conditions they utilise for scoring (e.g. renal disease, dementia and cerebrovascular diseases), the weights assigned within these models are different. To illustrate this point, dementia from Alzheimer's disease is the highest weighted code for HFRS (7.1, where weights range from 0.1 to 7.1), but is the lowest weighted in the CCI (1, where weights range from 1 to 6). Additionally, HFRS includes conditions like falls, cellulitis and electrolyte imbalance, which are not featured in CCI, while CCI includes cancers and diabetes, which are not featured in HFRS.

The largest study assessing the effects of frailty on perioperative outcomes utilised the Johns Hopkins Adjusted Clinical groups frailty-defining diagnoses indicator, which is not easily available nor utilised by clinicians on a day-to-day basis for large populations.[39] This further highlights the role of HFRS as a practical tool to trigger in-depth frailty assessment and interventions in those who will most benefit.

There are some limitations of our study. The HFRS is based on available administrative data, which were not primarily intended for research purposes, and relies on accurate coding and documentation of information to define frailty and other conditions. Coding inaccuracies may create

bias. Furthermore, ICD coding typically takes 6 to 8 weeks from the index admission, which means that the HFRS can only be used retrospectively and does not allow access to frailty risk during the patient's index admission. Using ICD-10 codes may miss important aspects of frailty that may not be covered by coding, such as polypharmacy, fatigue, severity of comorbidities and functional abilities. Finally, while the AUROC of our predictive models suggest that HFRS or a combination of HFRS and CCI might be a better predictor of selected outcomes, the AUROC indicates only moderate to good model discrimination, which might limit its use as a bedside risk prediction tool. An unexpected finding is the lower mortality in those with higher TOSP, which may be skewed by the small numbers of patients at high frailty risk or impacted by selection of patients needing complex surgery. Hence, no inference can be assumed about direct or inverse associations between frailty risk and complexity of surgery. Despite these limitations, we propose that HFRS may still be useful as a simple, low-cost screening tool to identify frailty in older surgical patients.

CONCLUSION

To our knowledge, this is the first validated study in Singapore looking at HFRS in older surgical patients in Singapore. This study has shown that HFRS predicts long LOS, higher unplanned hospital readmissions and increased mortality when compared to those at low risk of frailty and is currently being adapted to provide an easy, rapid, low-cost tool for screening and identifying patients at higher risk of adverse outcomes in an older surgical population in Singapore.

Data availability

The anonymised datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors declare no conflict of interest and have no relationships and activities to disclose.

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REVIEW ARTICLE

Consensus statements and guideline for the diagnosis and management of plantar fasciitis in Singapore

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Introduction: Plantar fasciitis (PF) is a common cause of heel pain among the general population. The lack of standard practice guideline in Singapore presents challenges in education and clinical practice for this painful condition. These consensus statements and guideline were developed to streamline and improve the management of PF, covering key aspects such as diagnosis, investigations, risk factors, treatment modalities, monitoring and return to work/play.

Method: A multidisciplinary expert panel consisting of 6 sports physicians, 2 orthopaedic surgeons, 2 podiatrists and 1 physiotherapist from SingHealth Duke-NUS Sport & Exercise Medicine Centre (SDSC) was convened based on their clinical and academic experience with PF. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to evaluate the quality of the evidence and subsequently prepare a set of clinical recommen-dations pertaining to the management of PF. A modified Delphi process was used to reach consensus.

Results: Eighteen consensus statements were developed to cover key components of PF management, from initial diagnosis to treatment modalities and finally, clinical progression. They were subsequently consolidated under a proposed treatment pathway guideline for PF.

Conclusion: The SDSC consensus statements and guideline provide concise recommendations for the management of PF in Singapore.

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Keywords: extracorporeal shockwave, plantar fasciitis, plantar pain, stretching, ultrasonography

CLINICAL IMPACT

What is New

- This guideline provides recommendations on the management of plantar fasciitis (PF) in Singapore.

Clinical Implications

- PF can be diagnosed through history and physical examinations and bedside ultrasonography (US).
- Differentiating other causes of plantar heel pain should prompt further investigation with imaging.
- Standard treatment includes patient and footwear education, activity modification and stretching.
- Extracorporeal shockwave or platelet-rich plasma therapy may be considered for recalcitrant PF before corticosteroid injection or surgery.
- Return to work/play can be guided clinically and through interval US assessment if available.

INTRODUCTION

Plantar fasciitis (PF) is a degenerative disorder of the plantar aponeurosis at the insertion of the plantar fascia into the calcaneus, most commonly at the medial tubercle of the calcaneus.[1,2] Plantar fascia, or plantar aponeurosis, supports the medial longitudinal arch of the weight-bearing foot. With excessive mechanical loading of the plantar fascia, PF develops due to cumulative microtrauma at the calcaneal-fascial interface.[2] Patients classically present with plantar heel pain, worse on the first steps in the morning or after a prolonged period of inactivity. PF is typically unilateral but as many as 30% of patients present bilaterally.[3]

The term "fasciitis" describes acute inflammation in and around the plantar fascia. However, histologic findings revealed a non-inflammatory degenerative pathologic process, better defined by the term "fasciosis".[4] Fasciopathy has been used to encompass both fasciitis (short-term inflammation) and fasciosis (long-term degradation),

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but for the purpose of simplifying the terminology in this paper, the term "fasciitis" will be used.[5]

Approximately 10% of the general population is expected to develop PF over a lifetime.[6] This amounted to a million annual patient visits in the United States during 1995–2000, of which 60% were treated by primary care physicians.[1] PF is common among runners and increasingly prevalent among sedentary individuals.[7,8] In Singapore, there are ongoing efforts to elucidate the local prevalence of PF.

PF is a self-limited condition, but it can take months to years to resolve. This poses a challenge to healthcare providers including primary care physicians and allied health professionals. The role of a clinician in the management of PF is to make an accurate diagnosis and support the treatment pathway as the condition runs its course. Early recognition and treatment of PF is expected to shorten the disease course and increase the likelihood of success with conservative therapies.

Clinical practice guidelines have been widely used to improve the quality of healthcare through evidence-based best practice.[9] Local guidelines for PF management are sparse and hence, it is timely to review current evidence and provide revised recommendations. This study aims to provide evidence-based clinical practice guidelines and develop a clinical pathway algorithm to support clinical decision-making for outpatient PF management in Singapore. The consensus was developed around 5 clinical domains: diagnosis and investigation; risk factors, treatment modalities, monitoring and return to work/play.

METHOD

Panel selection

The formation of the consensus workgroup was initiated by the SingHealth Duke-NUS Sport and Exercise Medicine Centre. Clinicians and allied health professionals from the local public hospitals were recruited for their experience in managing PF. Eleven out of the 14 invited experts agreed to participate. The 11-member panel comprised 6 sports physicians, 2 orthopaedic surgeons, 2 podiatrists and 1 physiotherapist.

Literature review

A core group of 2 experts from the panel considered key clinical questions for PF management (Table 1) and drafted 18 statements based on local practice recommendations, American practice guidelines and topic reviews.[5, 10-13] Further literature review was conducted in PubMed/MEDLINE and ScienceDirect databases up to December 2020 and the statements were revised accordingly. Examples of search terms used were "plantar fasciitis", "plantar fasciosis", "plantar fasciopathy" and "plantar heel pain". The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was used to evaluate the quality of the evidence and assess the strength of the 18 recommendations.[14]

Table 1. Clinical questions.

A) Diagnosis and investigations
• How is PF diagnosed?
• What differential diagnoses of plantar heel pain should be considered?
• What is the utility of radiographic imaging, US and magnetic resonance imaging for the diagnosis of PF?
B) Risk factors
• What are the risk factors for PF?
• How are these risk factors classified?
C) Treatment modalities
• How should PF be managed appropriately?
○ Role of counselling and activity modification
○ Role of stretching and strengthening
○ Role of adequate footwear
○ Role of antipronation taping
○ Role of orthosis
○ Role of night splint
○ Role of oral analgesia
• When should bedside procedures, such as injectables and shockwave therapy, be offered?
• When should surgery be offered?
D) Monitoring of condition
• What are the parameters to assess at follow-up visits?
• What are the considerations if a patient had undergone bedside procedures as treatment?
• Is there a utility for US to monitor response to treatment?
E) Return to work/play
• When can a patient return to lower limb impact activities or sports?
• What are the considerations if a patient uses an orthosis or had undergone bedside procedures?

PF: plantar fasciitis; US: ultrasonography

Consensus process

The consensus process was conducted via a modified Delphi method across 2 online meetings held between February 2021 and March 2021 (COVID-19 pandemic lockdown period). This method describes an iterative process that employs

a systematic progression of repeated rounds of voting to achieve expert group consensus in a given subject with poor empirical evidence and divergence among healthcare professionals.[15-17] In the statements, the use of the word "should" suggested an essential requirement, whereas "can" suggested a desirable requirement. Members of the expert panel were asked to provide agreement (agree, disagree or abstain) to each statement. All responses were kept anonymous. Consensus for each statement was predefined as ≥80% agreement. Any statement that failed the consensus criteria during the first meeting was revised and re-polled at the next meeting. Statements that were not discussed at the first meeting due to time constraints were also revisited at the second meeting.

RESULTS

Out of 18 draft statements proposed, 15 statements were polled in the first meeting with 14 statements achieving consensus. The remaining 3 statements and a revised statement from the first meeting reached consensus in a second meeting held a month later. None of the panel participants abstained from voting. The final 18 statements are summarised in Table 2, each accompanied by its quality of the evidence, strength of recommendation and proportion of the voting agreement. Majority of the 18 consensus statements achieved unanimous acceptance, with statements 4, 7, 12 and 14 achieving 91% agreement.

Consensus statements

The 18 consensus statements pertain to the diagnosis and management of PF, including investigations, assessment of risk factors, treatment modalities, monitoring and return to work/play. These statements are consolidated in a proposed PF treatment pathway algorithm (Fig. 1).

Diagnosis of plantar fasciitis

Statement 1: Plantar fasciitis is diagnosed via history and physical examinations.

Quality of evidence: Grade A

Strength of recommendation: Strong

PF is diagnosed based on clinical assessment.[10,11] Patients usually present with plantar heel pain, particularly worse with the first steps in the morning or after extended periods of inactivity.[3] Symptomatic relief may be achieved with some degree of mobilisation or by off-loading affected foot. However, walking can still be painful as symptoms are aggravated by prolonged weight bearing and expectantly worse towards the end of the day.[10]

Table 2. Summary of consensus statements.

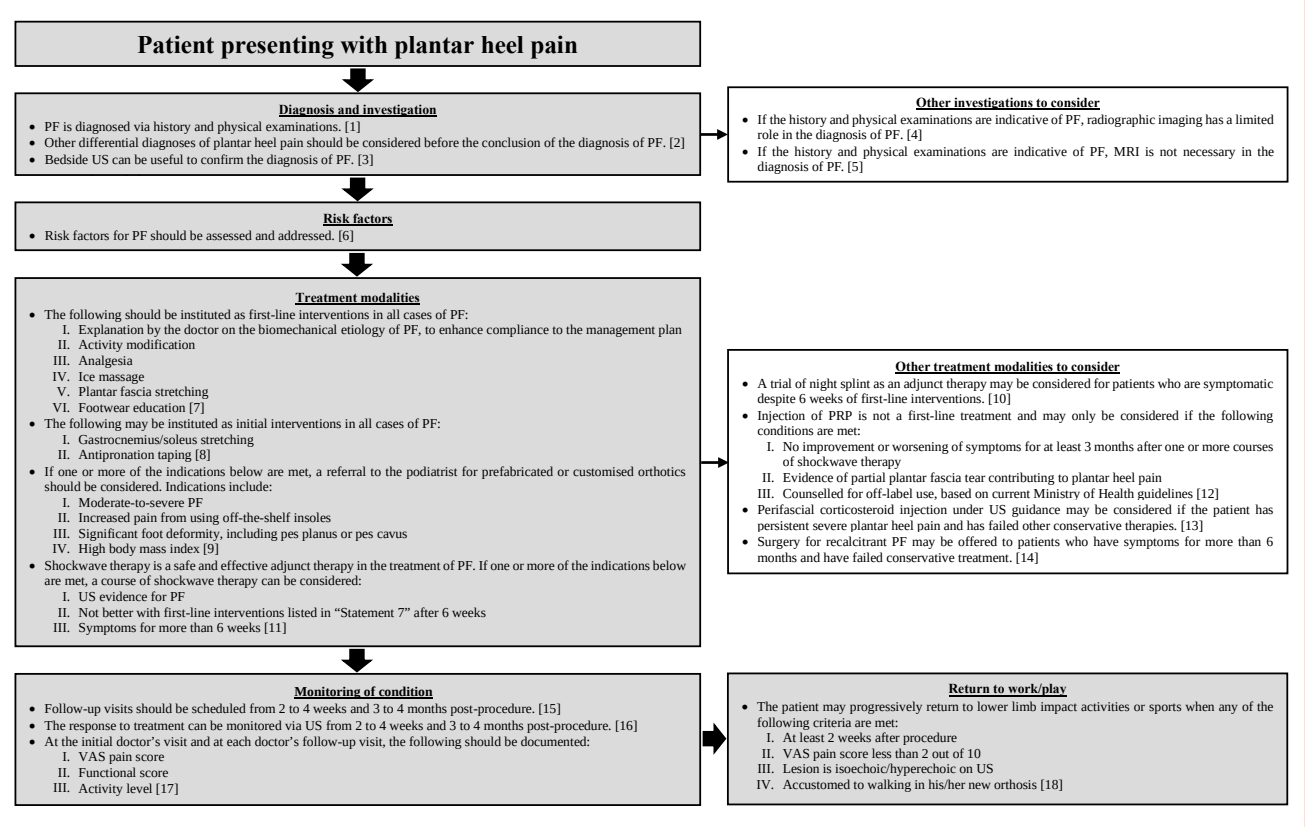
Consensus statements	GRADE	Strength of recommendation	Consensus
A) Diagnosis and investigations			
1. PF is diagnosed via history and physical examinations.	A	Strong	100%
2. Other differential diagnoses of plantar heel pain should be considered before the conclusion of the diagnosis of PF.	A	Strong	100%
3. Bedside US can be useful to confirm the diagnosis of PF.	A	Strong	100%
4. If the history and physical examinations are indicative of PF, radiographic imaging has a limited role in the diagnosis of PF.	B	Strong	91%
5. If the history and physical examinations are indicative of PF, MRI is not necessary in the diagnosis of PF.	B	Strong	100%
B) Risk factors			
6. Risk factors for PF should be assessed and addressed.	A	Strong	100%
C) Treatment modalities			
7. The following should be instituted as first-line interventions in all cases of PF: I. Explanation by the doctor on the biomechanical etiology of PF, to enhance compliance to the management plan II. Activity modification III. Analgesia IV. Ice massage V. Plantar fascia stretching VI. Footwear education	A	Strong	91%

Table 2. Summary of consensus statements. (Cont'd)

Consensus statements	GRADE	Strength of recommendation	Consensus
C) Treatment modalities			
8. The following may be instituted as initial interventions in all cases of PF: I. Gastrocnemius/soleus stretching II. antipronation taping	A	Strong	100%
9. If one or more of the indications below are met, a referral to the podiatrist for prefabricated or customised orthotics should be considered. Indications include: I. Moderate to severe PF II. Increased pain from using off-the-shelf insoles III. Significant foot deformity, including pes planus or pes cavus IV. High body mass index	A	Strong	100%
10. A trial of night splint as an adjunct therapy may be considered for patients who are symptomatic despite 6 weeks of first-line interventions.	B	Weak	100%
11. Shockwave therapy is a safe and effective adjunct therapy in the treatment of PF. If one or more of the indications below are met, a course of shockwave therapy can be considered: I. US evidence for PF II. Not better with first-line interventions listed in "Statement 7" after 6 weeks III. Symptoms for more than 6 weeks	A	Strong	100%
12. Injection of PRP is not a first-line treatment and may only be considered if the following conditions are met: I. No improvement or worsening of symptoms for at least 3 months after one or more courses of shockwave therapy II. Evidence of partial plantar fascia tear contributing to plantar heel pain III. Counselled for off-label use, based on current Ministry of Health guidelines	B	Strong	91%
13. Perifascial corticosteroid injection under US guidance may be considered if the patient has persistent severe plantar heel pain and has failed other conservative therapies.	B	Weak	100%
14. Surgery for recalcitrant PF may be offered to patients who have symptoms for more than 6 months and have failed conservative treatment.	C	Weak	91%
D) Monitoring of condition			
15. Follow-up visits should be scheduled from 2 to 4 weeks and 3 to 4 months post-procedure.	D	NA	100%
16. The response to treatment can be monitored via US from 2 to 4 weeks and 3 to 4 months post-procedure.	D	NA	100%
17. At the initial doctor's visit and at each doctor's follow-up visit, the following should be documented: I. VAS pain score II. Functional score III. Activity level	B	Weak	100%
E) Return to work/play			
18. The patient may progressively return to lower limb impact activities or sports when any of the following criteria are met: I. At least 2 weeks after procedure II. VAS pain score less than 2 out of 10 III. Lesion is isoechoic/hyperechoic on US IV. Accustomed to walking in his/her new orthosis	D	NA	100%

GRADE: Grading of Recommendations, Assessment, Development and Evaluations; MRI: magnetic resonance imaging; PF: plantar fasciitis; PRP: platelet-rich plasma; US: ultrasonography; VAS: visual analogue scale.

Fig. 1. Proposed plantar fasciitis treatment pathway.



MRI: magnetic resonance imaging; PF: plantar fasciitis; PRP: platelet-rich plasma; US: ultrasonography; VAS: visual analogue scale
Numbers enclosed within square brackets indicate the consensus statement number.

Tenderness over the medial calcaneal tubercle and discomfort with passive or active dorsiflexion of the hallux are characteristic physical findings.[13] Patients also tend to have either tight Achilles tendon or gastrocnemius, which limits ankle dorsiflexion and reduces the medial longitudinal arch angle. Associated deformities such as pes planus, pes cavus, foot overpronation, leg-length discrepancy, excessive lateral tibial torsion and excessive femoral anteversion may be present.

Statement 2: Other differential diagnoses of plantar heel pain should be considered before the conclusion of the diagnosis of plantar fasciitis.

Quality of evidence: Grade A

Strength of recommendation: Strong

There are multiple causes for plantar heel pain.[18] If the clinical assessment is atypical for PF, differential diagnoses for heel pain ought to be considered. These conditions may include soft tissue, bone, neurological and inflammatory disorders. For instance, localised tenderness over the posterior calcaneus and a positive calcaneal squeeze test would suggest a calcaneal bone stress injury. A positive Tinel's test over the tarsal tunnel accompanied by paraesthesia would suggest a neurological entrapment or compression etiology such as tarsal tunnel syndrome, medial calcaneal neuropathy or Baxter's neuropathy. Radicular pain and numbness from the lower back to the heel should prompt consideration of S1 radiculopathy related to lumbar spine disorders. Finally, systemic involvement would suggest inflammatory disorders such as reactive arthritis and spondyloarthritis.

Statement 3: Bedside ultrasonography can be useful to confirm the diagnosis of plantar fasciitis.

Quality of evidence: Grade A

Strength of recommendation: Strong

Although bedside ultrasonography US is not required for initial PF diagnosis and management, it can assist clinicians with visualising the foot anatomy in real time and confirming the diagnosis of PF. For the initial US evaluation, both quantitative (thickness) and qualitative (calcifications, echogenicity, tears and vascularity) characteristics of the plantar fascia should be documented. Side-to-side comparison with the asymptomatic heel is also recommended to account for individuals with a thicker baseline plantar fascia.

A normal plantar fascia has a uniform fibrillar echogenic structure that does not exceed 4 mm in thickness at the site of calcaneal insertion.[19] This is corroborated by unpublished local data reporting mean plantar fascia thickness of 3.2 mm among asymptomatic Asian population. Diagnosis of PF is supported by the sonographic findings of fascia thickening >4 mm, reduced echogenicity and/or perifascial effusion.[19-21] The meta-analysis of 11 randomised controlled trials (RCTs) involving 813 individuals revealed that abnormal plantar fascia thickness in PF was on average 2.16 mm thicker than controls (95% confidence interval 1.60–2.71 mm).[22] Hypervascularity of the plantar fascia and adjacent soft tissue can be further demonstrated with power Doppler in acute PF.[23]

Assessment of PF via US is comparable to magnetic resonance imaging (MRI) with regard to accuracy and reliability,[21] demonstrating 81% sensitivity and 86% specificity in a cohort study of 154 patients.[19] Although MRI is a gold standard for diagnosing PF, US is arguably superior since it is cheaper, portable, readily accessible and easy to administer with few contraindications. Combined with its ability to capture real-time snapshots and the dynamic relations of the plantar fascia, US remains a cost-effective tool to diagnose and monitor PF.[21]

Statement 4: If the history and physical examinations are indicative of plantar fasciitis, radiographic imaging has a limited role in the diagnosis of plantar fasciitis.

Quality of evidence: Grade B

Strength of recommendation: Strong

Plain film radiographic imaging is helpful in ruling out other causes of heel pain and should be performed if there is any indication of trauma, pain out of proportion or recalcitrant heel pain not responding to standard treatment. The role of radiography is however limited if the history and physical examinations are indicative of PF.[10,12] A retrospective study found that out of the 81% of a cohort of 215 heels diagnosed with PF, only 2% was found to have radiographic abnormalities which prompted further evaluation but did not change the clinical course.[24]

Common radiographic findings associated with PF include plantar calcaneal spurs, plantar calcifications, cortical irregularities at the plantar fascia origin, abnormal fat pad and plantar fascia thickening >4 mm within 5 mm of its calcaneal attachment.[25] Calcaneal spur formation has a controversial causal association with PF since it can be found in affected and unaffected individuals.[25,26] It is postulated that calcaneal spur development is an adaptive response to repetitive vertical heel compression rather than that of longitudinal traction at the calcaneal-fascial interface.[27] The key radiographic features differentiating PF from controls were changes in soft tissues instead. In an RCT involving 30 heels (24 individuals), the non-weight bearing lateral ankle radiographic findings of abnormal fat pad and thickened plantar fascia achieved 85% sensitivity and 95% specificity for PF.[25] If confirmation of PF is necessary under doubtful clinical assessment, a non-weight bearing lateral ankle radiograph may be considered as the initial radiographic evaluation.[11,25]

Statement 5: If the history and physical examinations are indicative of plantar fasciitis, magnetic resonance imaging is not necessary in the diagnosis of plantar fasciitis.

Quality of evidence: Grade B

Strength of recommendation: Strong

MRI is an important noninvasive diagnostic imaging modality with multiplanar imaging capability and contrast resolution for evaluating a wide range of foot disorders. It can be considered for patients with protracted heel pain not responding to standard treatment or when the clinical assessment is suggestive of another etiology. MRI is useful for demonstrating key pathological changes of the plantar fascia in PF, in addition to those that can already be detected with US or radiographs. However, certain associated structural changes may not always be consistent with symptoms and are not required for the diagnosis of PF. Findings such as calcaneal spurs, soft-tissue edema superficial to the plantar fascia and increased T1-weighted signal changes of the plantar fascia have been observed in asymptomatic individuals, likely reflecting physiologic changes or asymptomatic degeneration.[2] Such information conferred by MRI incurs additional cost without value-adding to the management of patients whose symptoms and signs are already suggestive of PF. Although MRI is capable of delineating structural alterations of the plantar fascia, clinical correlation remains crucial to avoid unnecessary investigation.[10]

Assessment of risk factors

Statement 6: Risk factors for plantar fasciitis should be assessed and addressed.

Quality of evidence: Grade A

Strength of recommendation: Strong

Development of PF is usually multifactorial, and it is not unusual to have more than one risk factor in the same patient. These risk factors can be broadly categorised as intrinsic or extrinsic (Table 3). They contribute to biomechanical abnormalities during gait phases, which in turn

cause mechanical overload and excessive tensile strain within the plantar fascia.

Table 3. Risk factors for PF.

Categories	Factors
A) Intrinsic	
Anatomical	• Excessive femoral anteversion
	• Leg-length discrepancy
	• Obesity
	• Pes cavus (high-arched feet)
	• Pes planus (flat feet)
Biomechanical	• Achilles tendon tightness
	• Hamstring tightness
	• Limited ankle dorsiflexion
	• Overpronation
	• Triceps surae tightness
B) Extrinsic	
Footwear	• Poor arch or heel support
	• Worn out footwear
Occupation	• Carrying heavy loads
	• Prolonged standing
Training	• Changes in running form
	• Inappropriate training load

Intrinsic risk factors are related to the individual characteristics of the person and can be divided into anatomical and biomechanical factors.[29] Anatomic risk factors include obesity, pes planus, pes cavus, excessive femoral anteversion and leg-length discrepancy. Pes planus subjects the plantar fascia to excessive stress during foot strike while pes cavus causes excessive strain on the heel because the foot fails to evert or absorb shock effectively.[30,31] Biomechanical risk factors include overpronation, limited ankle dorsiflexion and tightness of the hamstrings, triceps surae and Achilles tendon.[32,33]

Extrinsic risk factors refer to factors related to the footwear, occupation and training.[29] For example, worn out shoes with poor arch or heel support and training errors, such as inappropriate running form or volume can contribute to PF development. Occupations requiring prolonged standing or heavy lifting can also lead to mechanical overloading of the plantar fascia.[32]

Management of PF

Treatment for PF is varied, and most patients respond well to nonsurgical interventions. The following recommendations provide guidance for clinicians to tailor treatment according to the chronicity and severity of symptoms, and requirements of the patient's lifestyle.

Statement 7: The following should be instituted as first-line interventions in all cases of plantar fasciitis:

I. Explanation by the doctor on the biomechanical etiology of plantar fasciitis, to enhance compliance to the management plan
II. Activity modification
III. Analgesia
IV. Ice massage
V. Plantar fascia stretching
VI. Footwear education

Quality of evidence: Grade A

Strength of recommendation: Strong

Patient education is arguably the most important factor in a patient-centric management plan. Effective communication conveying the etiology of PF and its relations to the patient's biomechanical risk factors helps increase treatment compliance and adherence.[34] The volume and intensity of patient's physical activity should be explored and modified to minimise loading stress on the plantar fascia. For runners, it can be worthwhile to evaluate their running biomechanics as certain foot strike pattern modification may predispose them to increased risk of PF.[35] Analgesia, including paracetamol and non-steroidal anti-inflammatory drugs, can be offered for short-term pain relief.[11] Ice massage is also useful for pain and inflammation reduction in PF (Fig. 2).[11]

Plantar fascia stretching, as a form of manual therapy intervention, is an effective treatment for PF (Fig. 2). A randomised parallel study involving 102 participants with acute PF showed that improvement in pain and function with plantar fascia stretching as the initial treatment was superior to extracorporeal shockwave therapy (ESWT) after 2 and 4 months.[36] A similar study of 63 patients found that isolated manual therapy including plantar fascia stretching was more effective for pain control and function over 3 months than orthoses or combined therapy.[37] Overall, a systematic study of 7 RCTs demonstrated that manual therapy improves pain and function more effectively than comparative interventions.[38]

Appropriate footwear with good arch support and cushioned heels prevents exacerbation of

Fig. 2. (A) Calf stretch with knee extended. (B) Calf stretch with knee flexed. (C) Standing plantar fascia stretch. (D) Sitting plantar fascia stretch with assessment of plantar fascia tautness. (E) Cold massage with a frozen can.

PF by ensuring adequate support of the medial longitudinal arch.[10,39] However, plantar symptoms may still recur as the soles of shoes degrade over time. Hence, shoe fitting and construction should be routinely examined by clinicians for its foot support.[39]

Statement 8: The following may be instituted as initial interventions in all cases of plantar fasciitis:

I. Gastrocnemius/soleus and Achilles tendon stretching

II. Antipronation taping

Quality of evidence: Grade A

Strength of recommendation: Strong

Besides plantar fascia stretching, calf or Achilles tendon stretching may play an important role in PF treatment (Fig. 2).[40,41] Significant pain reduction was demonstrated in a 50-patient RCT after just 4 weeks with Achilles tendon stretches or simultaneous Achilles and plantar fascia stretches.[41] Furthermore, inclusion of myofascial trigger point massage with these stretches resulted in greater short-term pain relief in a 60-patient RCT.[40] Hence, we advocate for clinicians to educate patients on the proper stretching of the plantar fascia, Achilles tendon and calf muscles, with the consideration for a referral to outpatient supervised training.

Antipronation taping helps support the medial longitudinal arch and reduce mechanical stress on the plantar fascia. When compared against no taping or sham taping in a systematic review of 7 RCTs, taping showed significant pain reduction with improvement of weight distribution and plantar fascial thickness.[42] Another systematic review involving 4 RCTs and 1 controlled trial supported short-term pain relief with taping as early as the first week, regardless of its implementation with or without stretching.[43]

Statement 9: If one or more of the indications below are met, a referral to the podiatrist for prefabricated or customised orthoses should be considered. Indications include:

I. Moderate to severe plantar fasciitis

II. Increased pain from using off-the-shelf insoles

III. Significant foot deformity, including pes planus or pes cavus

IV. High body mass index

Quality of evidence: Grade A

Strength of recommendation: Strong

Foot orthoses are removable in-shoe devices designed to correct biomechanical foot issues and deformities. Heel inserts and insoles are commonly prescribed by podiatrists for PF, and both prefabricated and customised options are safe and effective for pain relief.[44,45] The mechanism for pain relief is attributed to adequate medial arch support and plantar pressure redistribution during prolonged weight bearing.[44] Meta-analysis of 7 RCTs of 693 patients found moderate-quality evidence supporting medium-term pain relief with orthoses for 7–12 weeks,

with no difference between prefabricated and customised orthoses.[45] Foot deformities such as pes planus and pes cavus, which subject individuals to increased plantar fascia strain, can be corrected with orthoses. Obese individuals will also expectantly benefit since they experience excessive and repetitive compressive forces under their heel when weight bearing.[46] Nonetheless, it is crucial to tailor the eventual choice of orthoses according to the patient's preference and associated musculoskeletal issues.

Statement 10: A trial of night splint as an adjunct therapy may be considered for patients who are symptomatic despite 6 weeks of first-line interventions.

Quality of evidence: Grade B

Strength of recommendation: Weak

Night splint addresses early morning heel pain by reducing nocturnal contracture of the gastrocnemius-soleus complex or damaged plantar fascia.[47] Effectiveness of night splint for PF remains controversial. Nevertheless, several studies have shown positive outcomes for night splint when included with standard conservative treatment.[42,47,48] In a controlled trial of 28 patients, application of night splints with foot orthoses was more effective than the latter alone,[48] indicating a complementary relationship in reducing nocturnal and diurnal plantar fascia stress. Furthermore, a randomised crossover study of 37 patients with recalcitrant PF demonstrated long-term pain improvement over 6 months with just a 4-week splinting protocol.[49] It is worth noting that compliance may pose a challenge as night splint can be uncomfortable.[49] Nonetheless, a trial of night splint is an acceptable adjunct if prior standard treatment has failed.

Statement 11: Shockwave therapy is a safe and effective adjunct therapy in the treatment of plantar fasciitis. If one or more of the indications below are met, a course of shockwave therapy can be considered:

I. Ultrasonography evidence for plantar fasciitis

II. Not better with first-line interventions listed in "Statement 7" after 6 weeks

III. Symptoms for more than 6 weeks

Quality of evidence: Grade A

Strength of recommendation: Strong

ESWT is an effective and safe treatment for chronic PF.[50,51] It is typically applied to the most tender point over the medial calcaneal tubercle. Its therapeutic mechanism is multimodal, providing analgesic effect via neural desensitisation and physiological healing via neovascularisation and collagen synthesis.[50] Meta-analysis of 9 RCTs found that ESWT improved visual analogue scale (VAS) pain score in recalcitrant PF by 60%, with little to no functional limitation for 3 months.[51] In acute PF, a course of 3 weekly sessions of ESWT in a randomised parallel study of 102 participants was however found to be inferior to an 8-week course of plantar fascia stretching as first-line treatment.[36] Although there are no serious adverse side effects, ESWT can be associated with higher healthcare cost and increased pain or swelling during and after intervention.[50] Therefore, all patients ought to have undergone a trial of standard treatment before considering ESWT.

Statement 12: Injection of platelet-rich plasma is not a first-line treatment, and it may only be considered if the following conditions are met:

I. No improvement or worsening of symptoms for at least 3 months after one or more courses of shockwave therapy

II. Evidence of partial plantar fascia tear contributing to plantar heel pain

III. Counselled for off-label use, based on current Ministry of Health guidelines

Quality of evidence: Grade B

Strength of recommendation: Strong

Platelet-rich plasma (PRP) is an autologous product known for its healing properties. It promotes tissue regeneration at the target connective tissue site (tendon, ligament or muscle) via release of autologous growth factors from α-granules found within platelets.[52] Evidence for PRP as first-line treatment for PF is limited. A local randomised parallel study of 54 patients with chronic PF showed that PRP, as an adjunct to standard treatment, provided better pain reduction and function for PF than standard treatment alone.[53] This outcome was echoed for patients managed by ESWT as an adjunct to standard treatment, but there was ultimately no difference between the PRP and ESWT treatment groups.[53] When compared against corticosteroid injection therapy, PRP demonstrated superior long-term pain reduction from 3 to 12 months in a meta-analysis involving 15 studies.[54] Taking heed of current national body recommendations, PRP should be considered cautiously and offered only after unsuccessful trials of ESWT or when a partial plantar fascia tear is evident.

Statement 13: Perifascial corticosteroid injection under ultrasonography guidance may be considered if the patient has persistent severe plantar heel pain and has failed other conservative therapies.

Quality of evidence: Grade B

Strength of recommendation: Weak

Perifascial corticosteroid injection to the plantar fascia under ultrasound guidance mediates symptom relief through its anti-inflammatory effects. It can provide short-term pain relief up to only 4 weeks.[55,56] Although relatively cheap and safe to administer, there is limited evidence supporting the effectiveness of corticosteroid injection against first-line interventions.[55,57] When compared to ESWT in a 49-patient RCT, corticosteroid injection was inferior at improving long-term pain and function beyond 4 weeks.[58] Should corticosteroid injection be offered, potential adverse effects such as plantar fascia rupture and fat pad atrophy ought to be counselled. If performed, corticosteroid injection is recommended to be limited to a single course and to individuals not engaged in any explosive, weight-bearing lower limb activities.

Statement 14: Surgery for recalcitrant plantar fasciitis may be offered to patients who have symptoms for more than 6 months and have failed conservative treatment.

Quality of evidence: Grade C

Strength of recommendation: Weak

Chronic PF with persistent severe symptoms despite appropriate standard treatment for at least 6 months may be considered for surgical intervention.[10,12] Plantar fasciotomy and gastrocnemius release are two commonly performed procedures aimed at reducing plantar fascial tension in PF.[12] The latter is favoured over fasciotomy as it is associated with lower morbidity and better patient satisfaction in a retrospective cohort study.[59] Newer surgical techniques such as cryosurgery and ultrasonic debridement have been introduced, but their effectiveness remains to be seen.[12]

Monitoring of PF

Statement 15: Follow-up visits should be scheduled between 2 to 4 weeks and 3 to 4 months post-procedure.

Quality of evidence: Grade D

Strength of recommendation: Not applicable

Statement 16: The response to treatment can be monitored via ultrasonography between 2 to 4 weeks and 3 to 4 months post-procedure.

Quality of evidence: Grade D

Strength of recommendation: Not applicable

Statement 17: At the initial doctor's visit and at each doctor's follow-up visit, the following should be documented:

I. VAS pain score

II. Functional score

III. Activity level

Quality of evidence: Grade B

Strength of recommendation: Weak

Guidelines for monitoring PF progression post-procedure are poorly elucidated in literature. Patient-reported outcome measures (PROMs) such as the VAS pain score, Roles and Maudsley scale and American Orthopaedic Foot and Ankle Society ankle-hind foot scale are useful tools to track improvements in pain and function throughout the treatment period. Objective interval US assessment of the plantar fascia thickness is a quick and cost-effective adjunct to PROMs since clinical progression has been shown to correlate with plantar fascia thickness.[60] Indeed, a prospective longitudinal study of 22 patients with recalcitrant PF demonstrated significant gradual reduction of VAS pain score and plantar fascia thickness over 12 months after undergoing ESWT.[61] The expert panel recommends for at least 2 interval reviews at 2 to 4 weeks and 3 to 4 months post-procedure. However, interval US changes are likely more discernible after several months versus short weeks post-procedure. This is also influenced by the experience and skills of the sonographer.

Return to lower limb impact activities or sports

Statement 18: The patient may progressively return to lower limb impact activities or sports when any of the following criteria are met:

I. At least 2 weeks after procedure

II. VAS pain score less than 2 out of 10

III. Lesion is isoechoic/hyperechoic on ultrasonography

IV. Patient is accustomed to walking in his/her new orthosis

Quality of evidence: Grade D

Strength of recommendation: Not applicable

Guidelines on the return to work/play for patients with PF are scant. Patients with prescribed orthoses

are expected to resume lower limb activities once they are accustomed to their in-shoe devices. A progressive return to lower limb activities at least 2 weeks post-procedure is recommended by the expert panel. Interval US assessment post-procedure can expectantly show a recovered plantar fascia evident by an isoechoic or hyperechoic appearance. It is worth noting that the US changes associated with PF may still be present in asymptomatic runners or athletes; as such, clinical history should primarily guide return to work/play. In general, patients experiencing an overall VAS pain score less than 2 out of 10 may attempt a graduated return to work/play.

CONCLUSION

This guide summarised the current evidence and presented recommendations on the outpatient management of patients with PF for healthcare professionals practicing in Singapore. It is acknowledged that management can vary according to the needs of the individual, resource availability and limitations of the institution of practice. Evidence gaps in certain areas of management and monitoring of PF remains, and it is crucial for clinical practice to be continuously refined as new evidence emerges. Although these guidelines do not define a standard of care, they are intended to improve the practice standards for PF management.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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COMMENTARY

The potential of RNA therapeutics in dermatology

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ABSTRACT

Ribonucleic acid (RNA) therapeutics hold great potential for the advancement of dermatological treatments due to, among other reasons, the possibility of treating previously undruggable targets, high specificity with minimal side effects, and ability to include multiple RNA targets in a single product. Although there have been research relating to RNA therapeutics for decades, there have not been many products translated for clinical use until recently. This may be because of challenges to the application of RNA therapeutics, including the dearth of effective modes of delivery to the target, and rapid degradation of RNA in the human body and environment. This article aims to provide insight on (1) the wide-ranging possibilities of RNA therapeutics in the field of dermatology as well as (2) how key challenges can be addressed, so as to encourage the development of novel dermatological treatments. We also share our experience on how RNA therapeutics have been applied in the management of hypertrophic and keloid scars.

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Keywords: antisense oligonucleotides, dermatology, hypertrophic scar, keloid, microneedles, microRNA, RNA interference, skin, small interfering RNA

The potential of RNA therapeutics

Ribonucleic acid (RNA) therapeutics involving, among others, microRNAs (miRNAs), small interfering RNAs (siRNAs) and/or antisense oligonucleotides (ASOs) hold great potential for the advancement of medical treatments in dermatology.

First, there are now novel ways to treat several dermatological conditions where existing treatments have been largely unsatisfactory. Critically, only around 1.5% of the human genome is translated into proteins;[1,2] of 20,300 protein-coding genes, only approximately slightly less than 4500 genes are considered druggable,[3] as not all proteins contain active sites for small molecule binding.[1,4] RNA therapeutics are thus able to provide sequence-specific gene therapy to many previously undruggable targets.[5] ASOs, siRNAs and miRNAs can overcome the major limitation of traditional drug molecules that can only target certain protein classes—these 3 do so by downregulating the expression of mRNA transcripts, which is useful because many diseases result from the expression of undesired or mutated genes, or from overexpression of certain normal genes.[6] Separately, RNA therapeutics can also include messenger RNA delivery to induce expression of proteins of interest. For example, the treatment of metastatic melanoma, a life-threatening form of skin cancer purported to be resistant to radiotherapy and chemotherapy, has demonstrated encouraging results,[7] with both translational repressing and mRNA-inducing forms of RNA therapeutics.[8]

Second, the high specificity of RNA therapeutics can potentially reduce the likelihood of side effects commonly associated with small molecules. This is due to, among other reasons, the ability to design an RNA sequence that is effective and specific to the target sequence to minimise any off-target effect.[6] Furthermore, application of local siRNA therapy can be limited to the area of affected skin, thereby minimalizing systemic toxicity.[9]

Third, the ability of certain RNA therapeutics to include multiple targets in a single product is another advantage. As miRNAs can inhibit numerous target genes,[10] miRNA therapeutics can be applied in the treatment of complex multigenic diseases, such as cancers and neurodegenerative disorders. [6] While siRNAs appear to be limited as they target only 1 specific gene (unlike miRNAs that can impact multiple genes), this can be overcome by employing multiple siRNA sequences in a single formulation.[6]

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Other positive attributes of RNA therapeutics include the relative cost-effectiveness,[1,7] ease in development,[1,7] as well as ability to upscale manufacturing efficiently in comparison to small molecules and biologics,[1] which result in a corresponding further reduction in cost.

Key challenges and potential solutions

Challenges to application of RNA therapeutics

Despite the existence of research relating to RNA therapeutics since decades ago,[9] as well as its potential, there have not been many products translated for clinical application until recently. This may be because of challenges to the application of RNA therapeutics. Some major hurdles are:

(1) delivery: the dearth of effective modes of delivery to the target tissue and cell type;[1,5,6,10]

(2) RNA instability: RNA degrades rapidly in the human body and environment due to the ubiquitous presence of nucleases; hence naked RNA structures that are not offered any protection (e.g. by delivery vehicles) are unstable;[1,5,6,10]

(3) side effects: undesirable consequences such as off-target effects;[6,10] and

(4) possible immunogenicity: tolerability concerns due to the immune-stimulatory potential of synthetic RNA therapeutics.[10]

Overcoming hurdles to delivery and RNA instability

The skin is an easily accessible organ for therapeutic delivery. Large molecule-size RNAs can be delivered through intact skin via transdermal delivery methods such as dissolvable hyaluronic acid (HA) microneedles. For skin diseases with compromised skin barrier, such as eczema and wounds, RNA can be delivered more easily into the dermis, without additional need for transdermal delivery modalities.

Delivering RNA therapeutics past the skin barrier is an important step to achieving therapeutic efficacy. A number of delivery modalities explored in the context of dermatology include (1) physical methods, such as: microneedles, intradermal injection, tape-stripping, ballistic methods/gene gun, cavitational ultrasound/sonophoresis, electroporation, jet injection, and iontophoresis; and (2) chemical means such as chemical enhancers and lipid based systems.[9] To provide a brief overview, some delivery techniques that have been studied for certain dermatological conditions are outlined in Supplementary Table S1. Further research may be required to identify the most suitable technology for different applications,[9] and the illustrations are non-exhaustive.

Simultaneously, RNA instability can be addressed using chemical modifications to improve RNA stability, while encapsulation of RNAs using nanoparticles can also reduce exposure to environmental nucleases.

Mitigation of off-target effects

Off-target effects occur when partial mismatch of siRNA and off-target genes result in binding and subsequent translational repression. Strategies to reduce off-target effects depend on the underlying RNA therapeutic. These include (1) applying the lowest possible RNA therapeutic dosing, as the impact of side effects are largely dependent on concentration levels;[6,10] (2) utilising chemical modifications;[6,10] and (3) carefully designing an RNA sequence based on its unique profile, so as to maximise the specificity and minimise any off-target effect.[6] As some RNAs are similarly expressed in multiple cell types, uptake of RNA therapeutic by non-target cells can contribute to undesired non-specificity. This can be addressed by conjugating ligands that bind to target cell-specific receptors to improve uptake. In respect of dermatological treatments for conditions that affect parts of the skin, side effects can be further mitigated by localising RNA therapy to the area(s) of affected skin, thus minimalizing potential side effects.[9]

Minimise the likelihood of possible immunogenicity

The body's immune system recognises foreign RNA structures by pathogen-associated molecular pattern receptors such as toll-like receptors (TLRs). Although there is a possibility for tolerability issues to arise, leading to adverse immune effects,[10] there are ways to prevent such negative outcomes. A main method would be to carefully design the RNA sequence,[6] and conduct screening to select RNA therapeutics with the smallest potential immunogenicity.[10] Other approaches include (1) chemical modifica-tions, (2) using shorter RNA sequences (as it is purported that efficient activation of TLRs requires a length of at least 21 nucleotides for single-stranded RNA) and/or (3) adjusting the treatment regimen to reduce the dose (e.g. by using combination therapies like RNA interference with additional therapeutic regimes).[10]

Our experience in applying RNA therapeutics in the management of pathological scars

We believe that RNA therapeutics can be efficacious as dermatological treatments, and we have

applied them in the management of hypertrophic and keloid scars at the National Skin Centre, Singapore.

Wound fibrosis is a multifactorial process, and one of the main mechanisms driving hypertrophic scar formation is excessive collagen deposition, which is linked to expression of the matricellular collagen-binding protein secreted protein acidic and cysteine-rich (SPARC).[5] Dissolvable and biocompatible HA microneedle patches loaded with siRNA for SPARC (siSPARC) to silence the SPARC protein were used.[5] To improve siRNA stability and cellular uptake, tyramine-modified gelatin (Gtn-Tyr) nanoplexes were used to form a siSPARC/Gtn-Tyr nanoplex, which effectively reduces collagen production, thereby potentially preventing excessive scar formation.[5]

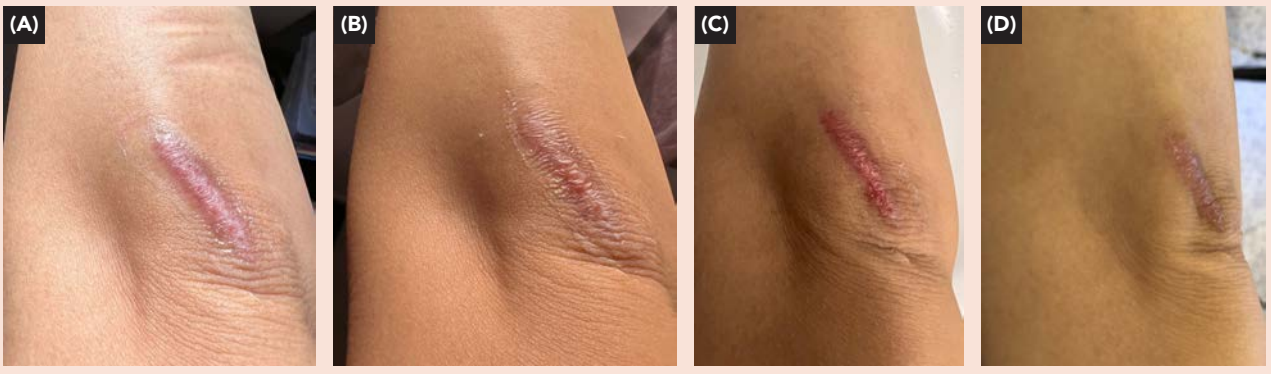
One illustration is an individual who traumatised her right elbow 6 weeks earlier and developed a hypertrophic scar with symptoms of pain and allodynia shown in Fig. 1 (pain score of 8/10). After 2 days of daily application of the siSPARC/Gtn-Tyr nanoplex-loaded HA microneedle patch, the patient reported resolution of pain, with significant improvement in allodynia, scar erythema and thickness. Five days post daily application, allodynia had fully subsided, and the scar became flatter and more pliable. After 22 days of daily application, the scar had visibly flattened with sustained improvement in hypersensitivity and erythema. When the patient self-discontinued the application for 2 days, the allodynia recurred (pain score 2/10). However, this abated with re-application of the microneedle patch. When the patient ceased application of the microneedle patch, the hypertrophic scar gradually increased in size, but did not reach the baseline scar volume. The siSPARC/Gtn-Tyr nanoplex-loaded HA microneedle patch is a promising transdermal RNA therapeutic for topical delivery of siRNA across the skin barrier to treat and prevent hypertrophic scars.[5]

This treatment modality is particularly suitable for (1) patients who prefer non-steroidal treatment due to concerns of adverse effects of steroids, including skin atrophy and telangiectasia; (2) patients who suffer from steroid atrophy; (3) patients with sensitive scars or who are otherwise unable to tolerate intralesional steroid injections, e.g. children; and (4) prevention of scar recurrence after improvement with intralesional steroid injections.

For keloid scars, we primarily use the siRNA microneedle patches to prevent the recurrence of keloids after treatment, which is a major issue in the treatment of keloids. Intralesional injection of triamcinolone is the most commonly used treatment worldwide and recurrence rates range from 33–50%.[11] We typically offer the siRNA microneedle patches to patients who experience recurrence after treatment, starting once the primary treatment flattens the keloids. Intralesional steroid injection is not suitable for such a preventive measure, as long-term steroid usage often lead to cutaneous side effects and patients have to regularly visit the dermatology clinic on a long-term basis to receive the injections.

Dermatology is a field with good potential for the implementation of RNA therapeutics. The positive observations thus far are proof of concept of the utility and potential of RNA therapeutics. They portend clinically-effective treatments for various dermatological conditions to be developed in the near future.

Fig. 1. Application in a case of hypertrophic scar. (A) At baseline, there was pain and allodynia with a pain score 8/10. (B) Day 2 of daily application of siRNA-embedded HA dissolvable microneedle patch: complete resolution of pain, with significant improvement in allodynia, scar erythema and thickness. (C) Day 5: the scar was flatter and softer, with a total resolution of allodynia. (D) Day 22: there was a sustained improvement of allodynia and significant improvement of the scar erythema and thickness compared to baseline. Subsequently, when application of the patches ceased for 2 days, the allodynia recurred, with a pain score 2/10. (All photographs are used with permission and consent is required for reproduction).



Disclosure

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LETTER TO THE EDITOR

Oral antiviral utilisation among older adults with COVID-19 in primary care: A population-wide study during successive Omicron waves in Singapore

Dear Editor,

Studies have repeatedly demonstrated the real-world effectiveness of oral antivirals (OAVs) in preventing hospitalisation and death in patients with mild-to-moderate COVID-19 at high risk for progression to severe COVID-19 when initiated within 5 days of symptom onset, even during waves of Omicron transmission.[1] However, there is a need to determine if OAVs are reaching recommended groups, particularly among older adults and socioeconomically disadvantaged groups at higher risk of severe COVID-19. Disparities in access to OAVs based on area-level socioeconomic status (SES) have been documented in the US, UK and Australia,[2-4] with substantially lower dispensing rates reported from more deprived areas. However, to the best of our knowledge, no studies have evaluated disparities in OAV access among urbanised Asian populations, including Singapore.

We therefore aimed to evaluate disparities in OAV access, including SES, among older Singaporean adults aged ≥60 years with COVID-19 presenting to primary care during successive Omicron waves over a 5-month period from 1 July 2022 to 31 December 2022, using a retrospective cross-sectional study design. We hypothesised that despite free SARS-CoV-2 testing (polymerase-chain-reaction [PCR]/rapid-antigen-test [RAT]) at all healthcare providers and full coverage of OAVs' cost,[5] primary care characteristics and SES, such as housing type, may still influence OAV uptake. In Singapore, housing type is a key indicator of SES. [6] The majority of Singaporeans (≥90%) stay in owner-occupied public housing under a tiered subsidy scheme; there are also heavily subsidised rental flats for those who cannot afford home ownership.[7] Over the study period, testing for SARS-CoV-2 was compulsory for all individuals who presented with acute respiratory illness to any healthcare provider; all COVID-19 cases were recorded in the Ministry of Health's national registry.[5] Omicron BA.4/5 predominated community transmission (≥90% of sequenced isolates on national genomic surveillance) in July 2022; subsequently, Omicron XBB emerged as the dominant strain from September 2022 onwards.[8] OAVs received interim authorisation in February 2022 and were made available at selected polyclinics and Public Health Preparedness Clinics (PHPCs)—the latter comprising a network of over 1000 private general practitioner (GP) clinics providing subsidised testing during public health emergencies.[1] Age ≥60 years was considered a risk factor for progression to severe COVID-19 and a criterion for early treatment with OAVs in the national COVID-19 treatment guidelines. Receipt of OAVs was defined as any prescription for either nirmatrelvir/ritonavir or molnupiravir, within 5 days of a positive SARS-CoV-2 result (PCR/RAT).

Anonymised data, including demographic variables, such as age, sex, ethnic group (Chinese, Malay, Indian or others), comorbidities (Charlson Comorbidity Index), immunocompromised status and indicators of SES (housing type) were extracted from official Ministry of Health databases. This study was done as part of national public health research under the Infectious Diseases Act and hence, a separate Institutional Review Board approval was not required. Given the absence of information on individual-level employment/education in the electronic-health-record data, average housing value based on individuals' place of residence (postal codes) was additionally included. Prediction of average housing value for all residential properties in Singapore listed by postal code was performed using a machine-learning algorithm and results were classified by quintiles, as per previously published methodology.[9] Multivariable logistic regression was utilised to identify clinical and sociodemographic variables independently associated with receipt of OAVs. The cluster option was used to control for potential correlation within residential districts (as defined by group representation constituencies, a type of electoral division in Singapore). Analysis was performed using STATA version 17.0 (StataCorp, College Station, TX, US).

During the study period, a total of 112,215 older adults were diagnosed with COVID-19 at primary care. After excluding those with missing sociodemographic information (n=474), a total of 111,741 older adults were included (median age 68 years, interquartile range 63–74). There were 4.71% (5,266/111,741) who received OAVs; the majority (≥95%) were prescribed nirmatrelvir-ritonavir. On multivariable analysis, after adjusting for other sociodemographic and clinical factors (sex, age, ethnicity, comorbidities, immunocompromised status and pandemic phase), primary care characteristics and indicators of SES were independently associated with receipt of OAVs at primary care (Table 1). Odds of receivin OAVs were lower among

patients diagnosed at private GP clinics, including PHPCs (adjusted odds ratio [aOR] 0.18, 95% CI 0.09–0.37) and those not part of the PHPC network (aOR 0.20, 95% CI 0.01–0.06), compared with public primary care clinics (polyclinics). This is likely reflective of more limited access to OAVs among private GPs. Odds of receiving OAVs were higher (aOR 2.32, 95% CI 1.26–4.35) among patients diagnosed at clinics offering telemedicine services for COVID-19. SES indicators, including staying in private housing (aOR 1.76, 95% CI 1.43–2.17) and living in an area with higher average housing value (aOR 1.38, 95% CI 1.93–1.86) were independently associated with higher odds of receiving OAVs (Table 1).

Table 1. Sociodemographic and clinical factors associated on multivariable analysis with receipt of oral antivirals for COVID-19 among Singaporean adults aged≥60 years who presented to primary care.

Sociodemographic and clinical factors	Received oral antivirals, no. (%)	Multivariable logistic regression of factors associated with receipt of oral antivirals (n=111,741)	
		Adjusted odds ratio [95% CI][a]	*P* value
Demographic factors			
Sex			
Female	2,714/61,270 (4.4)	1.00 (ref)	
Male	2,552/50,471 (5.1)	1.09 [1.03–1.16]	0.004
Age, years			
60–70	2,313/63,955 (3.6)	1.00 (ref)	
71–80	1,937/33,401 (5.8)	1.58 [1.45–1.72]	<0.001
≥81	1,016/14,385 (7.1)	1.92 [1.73–2.13]	<0.001
Ethnicity			
Chinese	4,359/92,262 (4.7)	1.00 (ref)	
Malay	417/10,840 (3.9)	1.00 [0.86–1.17]	0.979
Indian	392/7038 (5.6)	1.26 [1.09–1.47]	0.002
Others[b]	98/1601 (6.1)	1.49 [1.24–1.77]	<0.001
Socioeconomic factors			
Housing type			
5-room/executive condominium-type public housing	1.088/28,235 (3.9)	1.00 (ref)	
1–2 room public housing	237/5245 (4.5)	0.95 [0.74–1.23]	0.693
3–4 room public housing	2,376/58,811 (4.0)	1.00 [0.90–1.11]	0.992
Private housing	1,565/19,450 (8.1)	1.76 [1.43–2.17]	<0.001
Area-level housing value (quintiles)			
First quintile (lowest value)	826/22,086 (3.74)	1.00 (ref)	
Second quintile	806/22,527 (3.58)	0.93 [0.73–1.18)	0.559
Third quintile	876/22,395 (3.91)	0.99 [0.69–1.41}	0.940
Fourth quintile	1,112/22,682 (4.90)	1.13 [0.81–1.56]	0.472
Fifth quintile (highest value)	1,645/22,041 (7.46)	1.38 [1.93–1.86]	0.030

Table 1. Sociodemographic and clinical factors associated on multivariable analysis with receipt of oral antivirals for COVID-19 among Singaporean adults aged≥60 years who presented to primary care. (Cont'd)

Sociodemographic and clinical factors	Received oral antivirals, no. (%)	Multivariable logistic regression of factors associated with receipt of oral antivirals (n=111,741)	
		Adjusted odds ratio [95% CI][a]	*P* value
Primary care characteristics			
Primary care provider			
Public polyclinic	1,872/19,998 (9.4)	1.00 (ref)	
Private general practitioner clinic part of the PHPC network[c]	3,376/88,392 (3.8)	0.18 [0.09–0.37]	<0.001
Private general practitioner clinic not part of the PHPC network[c]	18/3351 (0.5)	0.20 [0.01–0.06]	<0.001
Clinic offers telemedicine services for COVID-19[d]			
No	3,286/85,266 (3.9)	1.00 (ref)	
Yes	1,980/26,475 (7.5)	2.32 [1.26–4.35]	0.007
Phase of pandemic			
Omicron BA.4/5 phase, earlier phase	1,936/60,647 (3.2)	1.00 (ref)	
Omicron XBB phase, later phase	3,330/51,094 (6.5)	2.04 [1.81–2.29]	<0.001
Clinical factors			
Patient is immunocompromised			
No	4,580/100,424 (4.6)	1.00 (ref)	
Yes	686/11,317 (6.1)	1.20 [1.09–1.32]	<0.001
Comorbidity burden (Charlson Comorbidity Index, CCI)			
No comorbidities, CCI 0	2,807/65,493 (4.3)	1.00 (ref)	
Mild comorbidities, CCI 1–3	1,628/30,955 (5.3)	1.09 [1.03–1.16]	0.002
Moderate comorbidity burden, CCI 3–4	559/10,276 (5.4)	1.05 [0.96–1.15]	0.285
Severe comorbidity burden, CCI ≥5	272/5017 (5.4)	1.00 [0.87–1.15]	0.986

[a] Adjusted for sex, age, ethnicity, housing type, area-level housing value, primary care provider and characteristics, comorbidity burden, immunocompromised status in multivariable logistic regression model, controlling for clustering within residential districts (as defined by Singapore's group representation constituencies).
[b] Includes individuals of other ethnicities or mixed ethnicities.
[c] Among those diagnosed at private general practitioner (GP) clinics, differences in proportions of patients receiving oral antivirals (OAVs) between those diagnosed at single-operator GP clinics versus those diagnosed at GP clinics belonging to a chain were compared using chi-square test. Those diagnosed at single-operator clinics had higher odds of receiving OAVs—single-operator: 4.2% (1971/47404), chain: 3.3% (1415/43449), odds ratio 1.28, 95% CI 1.19–1.37, *P*<0.001). Numbers do not add up to the total number of COVID-19 cases originally diagnosed at all GPs (N=91,743) because sufficient information to distinguish single-operator versus chains was not available in all cases.
[d] Information on telemedicine services provided was obtained by cross-checking the list of GPs/clinics providing telemedicine services for either the Home Recovery Programme for COVID-19 patients, or GPs/clinics providing teleconsultation for acute respiratory illness, including tele-antigen rapid testing services.

Oral COVID-19 antivirals represent a key component of public health strategies as COVID-19 moves towards endemicity. As such, ensuring equitable access is crucial. Both individual-level and area-level SES disparities were independently associated with OAV uptake, despite widespread availability and free provision. Reduced uptake of OAVs among lower SES strata—even with subsidised treatment and testing—is of concern. Although free SARS-CoV-2 treatment and testing was available at

healthcare providers, disparities in OAV uptake may persist due to individuals' past experiences with the healthcare system influencing their present care-seeking behaviour. Pre-pandemic, only a minority of lower-income Singaporean residents expressed a preference, when ill, to approach a primary care practitioner as their first choice for consultation, largely due to cost concerns.[7] Targeted efforts are needed to overcome potential barriers in a contextually sensitive manner in order to improve OAV uptake among lower SES strata.

Characteristics of primary care, specifically, being diagnosed at a public primary care clinic and being diagnosed at a clinic offering telemedicine services for COVID-19, were positively associated with higher odds of receiving OAVs. However, a potential limitation was that information on whether specific patients were diagnosed via face-to-face consultation or teleconsultation was unavailable. Telemedicine has been increasingly deployed in lieu of face-to-face consultations during the COVID-19 pandemic. By leveraging telemedicine, Singapore's healthcare system navigated successive COVID-19 waves without impacting severity/mortality rates and hospital capacity.[10] Going forward, primary care physicians have a significant role in facilitating OAV uptake in at-risk population groups during COVID-19 endemicity. Indications for OAVs can be disseminated more widely among primary care doctors, including private GPs. Telemedicine can potentially be leveraged upon to augment this capability.

Disclosure

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Data sharing

The databases with individual-level information used for this study are not publicly available due to personal data protection. Deidentified data can be made available for research, subject to approval by the Ministry of Health of Singapore. All inquiries should be sent to the corresponding author.

Keywords: *COVID-19, nirmatrelvir, oral antiviral treatment uptake, primary care, SARS-CoV-2, socioeconomic status*

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LETTER TO THE EDITOR

Hantavirus haemorrhagic fever and renal syndrome, caused by the Hantaan virus in Singapore: A case report

Dear Editor,

We outline a case of a 59-year-old Malaysian man of Indian origin with no known past medical history apart from diabetes mellitus and hypertension, who presented with a 7-day history of unrelenting fever, myalgia, confusion and unsteady gait. He worked as a shipyard engineer and travelled between Singapore and Ipoh, Malaysia. In Ipoh, he lived in a village with domesticated cows and would frequently drink cow urine as part of his religious and cultural practice. His last travel to Ipoh had been approximately 2 weeks prior to presentation. At presentation, he was febrile (39 °C), with a blood pressure of 100/82 mmHg, and narrowed pulse pressure. He had an unsteady gait, but did not have any other physical signs of cerebellar dysfunction or neurological deficits.

At presentation, his total white cell count was elevated (18.10 x 10^9/L, N: 4.30–10.40 x 10^9/L), with elevated haematocrit (50.2%, N: 40.3–50.0%) and thrombocytopenia (40 x 10^9/L, N: 150–410 x 10^9/L). There was oliguric acute kidney injury, with raised serum creatinine (153 µmol/L, N: 60–110 µmol/L) and hyponatraemia (127 mmol/L, N: 135–145 mmol/L). His liver enzymes were elevated, with raised aspartate transaminase (AST, 192 U/L, N: 6–35 U/L) and alanine transaminase (ALT, 86 U/L, N: 6–40 U/L). The alkaline phosphatase (ALP, 68 U/L, N: 30–110 U/L) and total bilirubin (6 µmol/L, N: 1–20 µmol/L) were not raised.

The magnetic resonance imaging of the brain did not show any leptomeningeal enhancement. Cerebrospinal fluid evaluation was bland, with no positive microbiological studies. He was managed supportively. Over a week, his platelet counts and haematocrit returned to normal limits. There was concurrent improvement in his transaminases and serum creatinine (from 318 µmol/L to 196 µmol/L). He was initially oliguric (<100 mL/day of urine) and subsequently became polyuric (>3 L/day of urine) (Supplementary Table S1).

Serological tests sent 7 days into illness for leptospirosis, rickettsiosis, Chikungunya and Dengue virus were negative. Blood smears for malaria and Brucella antibody test were also negative. The patient's serum was sent to our reference laboratory at the Mayo Clinic for hantavirus serology. This was an enzyme immunoassay (EIA) test performed at Quest Diagnostics using a mixture of recombinant antigens from Old World and New World hantaviruses.[1] Both Immunoglobulin G (IgG) and Immunoglobulin M (IgM) were reactive. The reactive serum was further tested with serial dilutions by indirect immunofluorescence (IIFT) for IgM and IgG against hantaviruses (Hantavirus Mosaic 1, EUROIMMUN, Germany)[2] in which Hantaan (HTNV), Sin Nombre, Puumala, Dobrava, Seoul (SEOV) and Saaremaa viruses were included. Both IgG and IgM were reactive (Supplementary Table S2 and Fig. 1), and the highest positive titrations of IgM and IgG were obtained for anti-Hantaan reactions with IgM at 1:1000 and IgG at 1:10,000. The IIFT results suggested that the patient was most likely infected with HTNV. The patient was discharged well with good functional recovery.

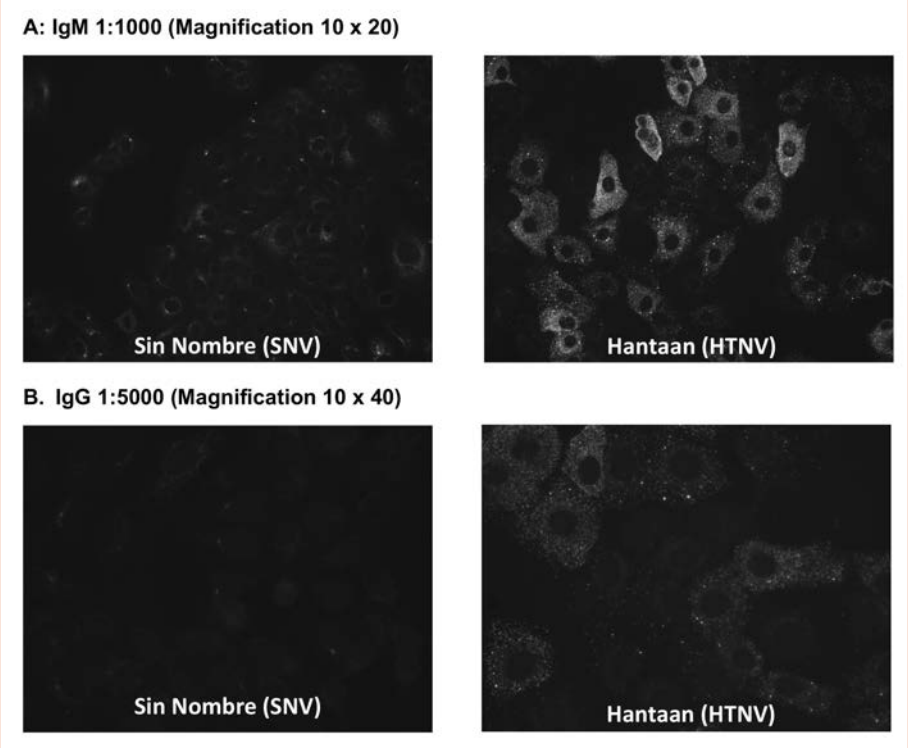
Discussion

Hantavirus infections can present with hantavirus cardiopulmonary syndrome and hantavirus haemorrhagic fever and renal syndrome (HFRS).[3] In Asia, HFRS is more commonly observed.[3] Although our patient had no history of direct rodent exposure, he reported consuming cow urine during his frequent travels to a rural area in Malaysia. This practice of cow urine and dung consumption has been associated with other zoonotic infections, such as Q-fever and leptospirosis, but not hantavirus infection.[4] In our case, the cow urine consumed was possibly contaminated with rodent excreta carrying the virus.

The typical presenting features of HFRS include fever, hypotension with narrowed pulse pressure and acute kidney injury. There is initial oliguria followed by polyuria. Thrombocytopenia, elevated haematocrit and elevated liver enzymes are also commonly seen in HFRS.[3] In patients with HFRS, central nervous system involvement in the form of posterior reversible encephalopathy syndrome has been reported.[5] In our patient, the neurologic symptoms were likely due to encephalopathy, rather than direct central nervous system involvement.

Hantavirus infections are rarely reported in Singapore and Malaysia (Supplementary Table S3).[6] Two prior cases had been reported in 2013, both in young males that had frequently travelled back to Malaysia.[7] However, these 2 cases were detected on hantavirus serological testing by EIA only and confirmatory testing via specific antibody testing, such as immunofluorescence assay, was not performed. The only confirmed case by IIFT in Singapore prior to our case was reported in 1996.[8]

Fig. 1. Indirect immunofluorescence assay result.



Representative images of negative and positive results were taken under microscope.

Although rarely reported, it is possible that hantavirus infection is underdiagnosed in Singapore. A seroprevalence study conducted from 1985 to 1986 of 142 rodents showed that 25.5% were seropositive for hantavirus.[9] A more recent, larger, seroprevalence study of 1143 rodents sampled from 2006 to 2008 in Singapore demonstrated that 35.5% of sera were reactive with SEOV (tested by ELISA serological assay), which was one of the agents of HFRS.[10] Furthermore, there was significant seroprevalence of hantavirus among patients studied who presented with a suspected diagnosis of dengue haemorrhagic fever (8.3% seropositive), hepatitis (8.1%), leptospirosis (2.66%) or acute nephritis (1.96%).[9] In a similar seroprevalence study from Malaysia, hantavirus antibody was found to be positive in 2.5% of serum samples with chronic renal failure.[6]

Underdiagnosis may be because testing for hantavirus infection remains challenging, as the gold standard of plaque reduction neutralisation testing for confirmation is often inaccessible outside of research settings. IgM positivity from EIA alone may represent a false positive result, unless subsequently confirmed with the presence of IgG in a convalescent titre. Therefore, suspected cases should first be screened with EIA for hantavirus IgG and IgM. Thereafter, if positive, it should be followed up with specific hantavirus serological testing with IIFT for confirmation and simultaneous detection of specific IgM and IgG against clinically important hantaviruses, as done in our case and in an earlier case report.[8] The mainstay of HFRS treatment is supportive. Reassuringly, despite the lack of an effective agent for targeted therapy against HFRS, reported mortality for severe HFRS has decreased in recent years.[3]

In conclusion, we report a confirmed case of HFRS in Singapore. This case was caused by HTNV, and the diagnosis was established based on both serology by EIA and specific antibody testing with indirect immunofluorescence. Given the seroprevalence of hantavirus in rodents and patients in Singapore and Malaysia, heightened alert for this condition is warranted in the appropriate clinical context and rodent exposure, which should prompt appropriate testing.

Competing interests

None reported. The authors declare no conflict of interest.

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None reported.

Ethics approval and consent to participate

Written informed consent was obtained from the patient prior for this report.

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Data availability statement

Data may be made available on reasonable request from the corresponding author.

Keywords: *haemorrhagic fever and renal syndrome, hantavirus, infectious diseases, microbiology, Singapore*

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LETTER TO THE EDITOR

Challenges to smoking cessation in patients with substance use disorders

Dear Editor,

Despite significant progress in tobacco control measures and stringent smoking policies, cigarette smoking remains one of the largest preventable causes of death and disability worldwide. The World Health Organization estimates that over 8 million global deaths are attributed to smoking yearly, and in Singapore, more than 2,000 Singaporeans die prematurely due to smoking related diseases each year.[1,2]

Smoking prevalence rates are exceptionally high among at-risk populations with comorbid substance addictions (i.e. alcohol or drugs), approximately 2 to 4 times higher than the general population.[3] Relatedly, users of alcohol and illicit drugs also smoked more heavily and had lower success rates in quitting smoking compared to non-users.[4]

Less is known however about the perceived barriers to stopping smoking among individuals seeking substance addiction treatment in Singapore. Addressing these challenges is crucial in treating substance use disorders as quitting smoking improves long-term abstinence and enhances substance addiction recovery.[5]

This cross-sectional study spanned from March 2020 to October 2021 using convenience sampling to recruit 100 outpatients seeking treatment for substance use addictions at the National Addictions Management Service (NAMS), a tertiary addiction treatment centre located within Singapore's only psychiatry hospital, Institute of Mental Health.

Information on demographics, smoking history and substance use profile was collected. This included onset age of substance use (including smoking), duration of use, quit smoking attempts, longest quit duration, current intention to quit, and reasons for not seeking NAMS smoking cessation services. The Challenges to Stopping Smoking scale (CSS-21) was administered to assess intrinsic and extrinsic challenges impacting participants' quit attempts.[6]

A consistent theme emerged: participants perceived that they lacked the desire or willpower for smoking cessation, while others felt they had the ability to exercise self-control and quit on their own. For some participants, focusing on their primary addiction to alcohol or drugs took precedence over quitting smoking. Smoking was also used as a stress relief aid, while majority struggled with multiple quit attempts and had short periods of abstinence.

Additional themes included indifference towards smoking as a concern and the influence of families and friends who smoked. Notably, participants' reluctance to seek smoking cessation treatment was influenced by factors such as cost and accessibility. Additionally, the unavailability of cessation services during non-work hours was a significant deterrent.

On analysing the CSS-21 responses, major challenges on the intrinsic subscale were easy cigarette availability; withdrawal symptoms when trying to stop smoking; being addicted to smoking; and reminders of smoking. Extrinsic challenges included difficulty finding support; cost of stop-smoking medicines; fear of failure; and belief in one's ability to stop smoking in the future if necessary (Table 1).

This study highlighted the challenges to smoking cessation among patients seeking help for substance use disorder. Participants faced difficulties in quitting smoking, which could undermine substance abuse recovery. Substance users also faced difficulties maintaining abstinence during smoking cessation, especially when using smoking as a stress reliever or substitute for alcohol and drugs.

Participants considered smoking a secondary issue, focusing on their primary addiction problems. Earlier studies reported that illicit drug use negatively affected smoking cessation success, possibly due to continued drug use hindering their ability to quit smoking. As such, smokers with substance addiction issues may have stronger motivations to continue smoking.[7]

Nearly half of our sample population experienced difficulty quitting smoking due to withdrawal symptoms accompanying smoking cessation. Similarly, studies have found recurring themes among patients with substance use disorders expressing fears and anxieties about withdrawal symptoms when quitting cigarettes, in addition to the continued use of smoking as a coping mechanism. Notably, McHugh et al. found that among substance-using inpatients, over 80% perceived anxiety towards smoking cessation with at least 60% lacking the confidence in quitting and maintaining sobriety.[8]

Focusing on quitting barriers among individuals with alcohol problems, Asher et al. found that irritability and restlessness emerged as prominent withdrawal-related barriers that hindered smoking cessation. Concerns about intolerable urges to

Table 1. Intrinsic and extrinsic factors of Challenges to Stopping Smoking scale (n=100).

Factors	Not a challenge %	Minor challenge %	Moderate challenge %	Major challenge %
Intrinsic				
Easy availability of cigarettes	26	10	14	50
Withdrawal symptoms (e.g. depression, anxiety, restlessness, irritability, sleeplessness, cravings)	18	12	26	44
Being addicted to cigarettes[a]	16	17	25	41
Seeing things or people which reminded me of smoking	18	20	24	38
Getting bored when I was trying to stop smoking	22	16	32	30
Thinking about never being able to smoke again after we stop smoking	37	15	20	28
Something stressful happened when I was trying to stop smoking	26	20	26	28
Feeling lost without cigarettes	22	21	30	27
Having strong emotions or feelings such as anger, or feeling upset when I tried stopping smoking	29	23	26	22
Extrinsic				
Difficulty in finding someone to help me to stop smoking	31	20	15	34
The cost of stop-smoking medicines such as nicotine replacement therapy	32	18	16	34
Fear of failing to stop smoking	35	21	11	33
Belief that I can stop smoking in the future if I need to	29	16	23	32
Lack of encouragement or help from family or friends to stop smoking	39	22	12	27
Use of other substances like cannabis, alcohol, etc.	49	9	16	26
Belief that medicines to stop smoking do not work	34	26	15	25
Lack of support or encouragement from health professionals to stop smoking	42	19	15	24
Fear of side effects from stop-smoking medications	41	16	21	22
Fear that stopping smoking may interrupt social relationships	52	20	12	16
Family members or friends encouraging me to smoke	59	15	11	15
Fear of weight gain if I stopped smoking	60	13	14	13

[a] Missing data = 1.

resume smoking post-smoking cessation and its effects on maintaining alcohol sobriety were also prevalent in their sample.[9]

Results from our study highlighted extrinsic barriers to treatment; particularly, costs and accessibility to treatment featured prominently as impediments to smoking cessation. Smoking cessation costs in Singapore are high, estimated at SGD200 to SGD300 (approx. USD150–220 in 2024) per month for nicotine replacement therapy or medications excluding consultation charges. Advocating for policies aimed at reducing cost of smoking cessation treatments could benefit our treatment-seeking population.

Additionally, the study emphasised the importance of structured smoking cessation programmes across the island, offering both counselling and pharmacological options to improve treatment accessibility. Better access to community-based pharmacies and clinics can further bolster the accessibility and affordability of cessation services. Improving after-hours access by extending operating hours for smoking cessation services can accommodate diverse schedules and increased engagement in smoking cessation interventions.

Providing smoking cessation interventions alongside addiction treatment positively affects substance use outcomes. Educating substance users who smoke about the importance of quitting smoking as a critical component of their recovery journey is important in motivating them to actively participate in smoking cessation programmes. Offering smoking cessation as an integrated treatment approach that concurrently addresses cravings for both substance use and smoking equips patients with the skills to effectively manage dual triggers simultaneously. Treating in tandem can prevent patients from substituting smoking for substance use or vice versa.

Clinicians treating substance-using smokers should consider providing corrective feedback regarding withdrawal symptoms and structure intervention plans to mitigate concerns about smoking cessation. Clinicians should also address concerns about the effects of smoking cessation on alcohol and drug abstinence. Interventions and treatment services should address realistic fears, such as withdrawals and fear of weight gain to enhance smoking cessation services and increase patients' confidence in quitting smoking.

Lastly, group therapy leveraging peer support and shared experiences provides insights to counter easy access to cigarettes and social support limitations in resisting smoking. These recommendations are geared towards improving smoking cessation interventions during substance addiction treatment to foster engagement in cessation efforts, enhance success rates, and to curb smoking-related chronic diseases and mortality within this vulnerable group.

Disclosure

The authors declare no conflict of interest.

Ethics approval

Ethical approval was obtained from the Domain Specific Review Board of the National Health Group and Institutional Review Board (DSRB No. 2019/01024).

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