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"Never measure the height of a mountain until you reach the top. Then you will see how low it was."

Dag Hammarskjold (1905 – 1961)
Swedish diplomat

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Free Papers

Editorial

Declining Stroke Mortality in Singapore and The Challenges Ahead

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Stroke mortality has declined considerably in Singapore. The age-adjusted mortality rate of stroke had reduced from 20.8 to 14.1 per 100,000 patients from 2011 to 2017 (Fig. 1A).[1,2] Although stroke contributed to 9.0% of all deaths as recently as 2011, mortality rates have steadily reduced to an all-time low in 2017, contributing to 6.3% of total deaths in 2017 (Fig. 1B).[3] Data from the Ministry of Health, Singapore, have indicated that stroke is now the fourth leading cause of death after cancer, ischaemic heart disease and pneumonia.[2,3]

Importantly, stroke is also the disease with the highest improvement in survival.[2,3] The decline in stroke mortality is an important milestone in our healthcare history since this took place in the face of a rising incidence of stroke in our ageing population. The crude incidence rate of stroke has increased from 187.9 to 229.6 per 100,000 population from 2008 to 2017 (Fig. 2). The incidence of stroke is also highest in those aged ≥60 years old.[2]

A stroke occurs when blood supply to a part of the brain is interrupted or reduced, depriving brain tissues of oxygen and nutrients from either blockage of blood vessels (ischaemic stroke) or rupture of brain vessels and aneurysms (cerebral haemorrhage). Ischaemic stroke is responsible for close to 80% of strokes in Singapore and from around the world.[1,2]

World Stroke Day, which falls on 29 October every year, invites a reflection on the significant progress that has been made in combating this debilitating disease in Singapore and an opportunity to define the future challenges that lie ahead.

In Singapore, stroke patients are mostly treated in organised stroke units where access to a specialised multidisciplinary team (comprising physicians, nurses, physiotherapists, occupational therapists, speech and swallowing therapists and coordinators) allows for treatment, prompt recognition of complications and early rehabilitation aimed at addressing stroke-specific impairments.[4,5] The provision of centralised stroke care in a dedicated area translates into efficient coordination of care by a multidisciplinary team whose goal is to maximise return of function and reduce fatal complications.[6]

A careful interrogation of the cardiac rhythm and cardio-cerebral vasculature undertaken within days or weeks after a stroke is important for the elucidation of stroke

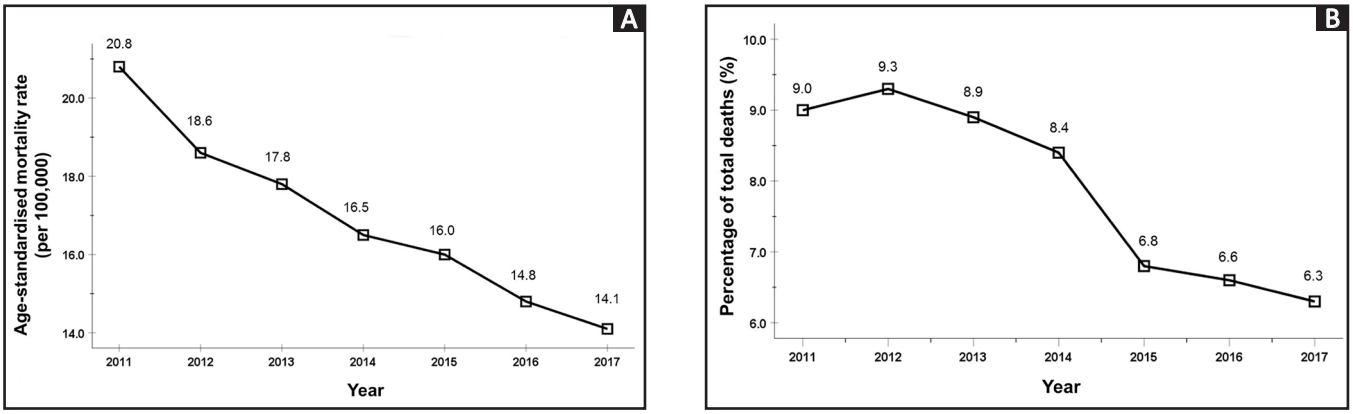

Fig. 1. Decline in stroke mortality in Singapore. A: Age-standardised mortality rate (per 100,000 population) has steadily declined from 20.8 to 14.1 per 100,000 patients from 2011 to 2017. B: The contribution of stroke as a leading cause of death has fallen from 9.0% in 2011 to 6.3% in 2017.

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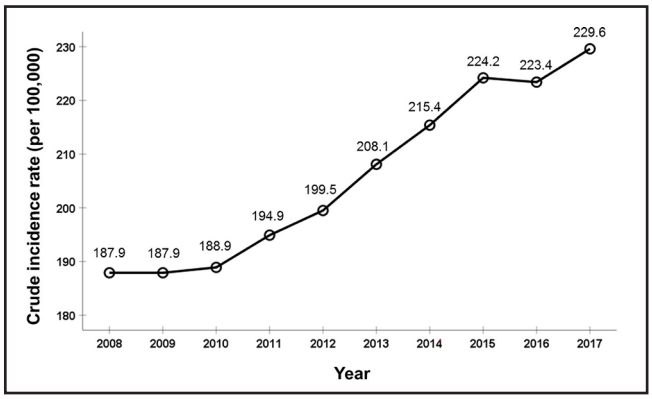

Fig. 2. Increase in stroke incidence in Singapore. The crude incidence rate of stroke has increased from 187.9 to 229.6 per 100,000 population from 2008 to 2017.

aetiology since this can have implications on the choice of antithrombotic treatment in stroke prevention. For example, patients with cardioembolism would benefit from anticoagulation while those with large artery disease and lacunar aetiology would derive more value from antiplatelet treatment.[7,8] Conversely, incomplete investigations could result in suboptimal data that could hinder accurate diagnosis of stroke aetiology. This observation has been cited as a reason why the cause of stroke was undetermined in close to a fifth of stroke patients.[7,9]

In stroke units, patients are monitored closely to assess their risk for early stroke complications and they are screened for occult risk factors such as paroxysmal atrial fibrillation.[10] Patients are counselled on stroke and its long-term consequences, urgency to tackle cerebrovascular risk factors and importance of medication compliance. When there is a need, patients are referred to agencies such as Stroke Support Station and the Singapore National Stroke Association for financial assistance and community-based support services.

Although stroke units are credited with lowering stroke mortality,[4,5] reperfusion treatment (intravenous thrombolysis and/or endovascular thrombectomy) remains the only treatment that can improve and reverse neurological deficits after an ischaemic stroke. Following arterial occlusion, brain tissues are deprived of blood supply and when this supply is not restored, a cascade of ischaemic events is triggered, ultimately leading to irreversible cell death and cerebral infarction.[11] Despite compelling trial data that supported its efficacy, utilisation of thrombolytic treatment for ischaemic stroke remained low in Singapore in the 2000s (between 0.5% and 2.9% from 2005 and 2010). This was due partly to late presentation of patients beyond the treatment window.[12,13] Subsequently, efforts to encourage reperfusion treatment had led to the reorganisation of prehospital and hospital services that facilitated expeditious screening and selection of patients who were deemed suitable for this treatment. Currently, computed tomography angiograms are routinely performed to evaluate patients for large vessel occlusion. Also, selective cerebral perfusion studies are carried out to identify patients with salvageable brain tissues (cerebral penumbra).

With the aid of social media and the mass media, educational initiatives were rolled out to inform the public on how to recognise stroke symptoms through the use of "F.A.S.T." (Face droop on one side, Arm weakness, Speech difficulty and Time to call for immediate emergency assistance) and an emphasis on the need to seek prompt medical attention in order to arrest and reverse early stroke deficits.[14] Paramedics were also trained to recognise stroke symptoms with the use of appropriate stroke screening tools and were authorised to activate hospital-based stroke response teams through the use of a prehospital notification system that facilitates fast-track stroke evaluation. Furthermore, hospital processes were reorganised to remove barriers in work flow and time-based quality parameters were implemented to improve door-to-needle time and patient outcomes.[15]

Currently, there are increasing data to support the use of endovascular thrombectomy as an adjunctive stroke treatment to improve recanalisation rates in excess of 80%.[16–20] With a more developed and organised stroke management system in place, endovascular thrombectomy was adopted with greater ease in Singapore. There is a roster of interventional stroke radiologists who provide endovascular expertise around the clock and they also hold regular discussions on complex clinical cases. By 2015, the reperfusion rate in the city-state had increased substantially to 6.5%.[21–3] Compared to cities such as London and Helsinki which have a reperfusion rate of 10.3%[23] and 13.0%,[22] respectively, the rate in Singapore is considerably lower. By tapping on requisite resources that support fast-track evaluation and treatment of stroke patients, endovascular thrombectomy should be further encouraged to harness the benefits conferred by early reperfusion treatment.

The decline in stroke mortality has translated into a growing community of stroke survivors whose long-term care poses an increasing challenge. Epidemiology data indicate that stroke occurs at a relatively young age in Singapore (mean, 68 years) compared to other developed countries.[1] Since the mean life expectancy of stroke patients had increased to 78 years,[1] it was conceivable that the population of Singapore has one of the highest prevalence of stroke in Asia.[24] Data from the Department of Statistics, Singapore, also indicated that stroke is a leading contributor to the burden of disease in Singapore.[25]

Stroke survivors are prone to suffer from permanent physical impairment (such as immobility, incontinence

and spasticity), emotional disturbances (like anxiety and depression) and cognitive issues (that range from mild cognitive impairment to severe dementia). To tackle the multifaceted needs of stroke survivors and their caregivers, a holistic approach is needed to reintegrate stroke survivors back into the community.[26] Stroke rehabilitation involves a multidisciplinary team of experts that comprise occupational therapists, physiotherapists, psychologists, rehabilitative physicians and speech therapists.[27] The demand for rehabilitative services is projected to grow and can be met through innovative solutions that minimise repeated visits to medical facilities and leverage on smart technologies and telemedicine that encourage rehabilitation to take place in one's home or in nearby facilities.[28]

After overcoming their financial, physical and psychological setbacks, stroke survivors are then confronted with the prospect of developing a cardiovascular recurrence. Findings have shown that 1 in 2 stroke survivors have a risk of developing another stroke episode.[29] Patients ought to be empowered and incentivised to adopt positive lifestyle behaviours (such as alcohol avoidance, balanced diet, physical activity and smoking cessation), medication compliance and active surveillance of risk factors (such as atrial fibrillation, diabetes mellitus and hypertension) to lower their risk of developing another stroke or myocardial infarction. With the recent availability of safer and more efficacious anticoagulants (such as apixaban, dabigatran and rivaroxaban), anticoagulation use should also be encouraged in select patients.[30,31]

Instead of using data extrapolated from overseas studies, it is vital to emphasise local stroke research since the findings from a racially diverse population such as Singapore could inform heterogeneity in stroke biology and have important treatment implications that resonate beyond her shores. The successful reduction in stroke mortality in Singapore is evidence of how we can steer the natural course of chronic diseases, even in one that is as multifactorial as stroke. It is important that a concerted effort is mounted to help stroke survivors cope with their disabilities and to guard them from having another stroke episode so they can be successfully reintegrated back into their own home and community.

REFERENCES

1. Ministry of Health, Singapore. Trends in Stroke in Singapore 2005–2010. Singapore: National Registry of Diseases Office, 2012.
2. Health Promotion Board, Singapore. Stroke Registry Annual Report 2017. Singapore: National Registry of Diseases Office, 2019.
3. Department of Statistics, Singapore. Deaths By Broad Groups of Causes, Annual. Available at: https://www.tablebuilder.singstat.gov.sg/publicfacing/createDataTable.action?refId=13247. Accessed on 20 October 2019.
4. Ministry of Health, Singapore. Clinical Guidance: Use of Intravenous Recombinant Tissue Plasminogen Activator (rtPA) in Ischaemic Stroke Patients. Singapore: Ministry of Health, 2013.
5. Ng YS, Tan KH, Chen C, Senolos GC, Chew E, Koh GC. Predictors of acute, rehabilitation and total length of stay in acute stroke: a prospective cohort study. Ann Acad Med Singapore 2016;45:394–403.
6. Venketasubramanian N, Chang HM, Chan BP. Update in the management of stroke. Ann Acad Med Singapore 2002;31:717–20.
7. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160–236.
8. Ministry of Health, Singapore. Clinical Practice Guidelines: Stroke and Transient Ischaemic Attacks—Assessment, Investigation, Immediate Management and Secondary Prevention. Singapore: Ministry of Health, 2008.
9. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
10. Seet RC, Friedman PA, Rabinstein AA. Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. Circulation 2011;124:477–86.
11. Ng GJL, Quek AML, Cheung C, Arumugam TV, Seet RCS. Stroke biomarkers in clinical practice: a critical appraisal. Neurochem Int 2017;107:11–22.
12. De Silva DA, Yassin N, Toh AJ, Lim DJ, Wong WX, Woon FP, et al. Timing of arrival to a tertiary hospital after acute ischaemic stroke—a follow-up survey 5 years later. Ann Acad Med Singapore 2010;39:513–5.
13. Tan MS, Ang ES, Ho SS, Ng SC, Talabucon L, Woon FP, et al. Wake-up stroke and onset-to-door duration delays: potential future indications for reperfusion therapy. Ann Acad Med Singapore 2014;43:11–4.
14. Lim W, Chuang DF, Chue KM, Lee DZ, Leong NJ, Ng ZG, et al. Stroke literacy in Singapore: data from a survey of public housing estate residents. Ann Acad Med Singapore 2014;43:454–63.
15. Tan BYQ, Ngiam NJH, Sunny S, Kong WY, Tam H, Sim TB, et al. Improvement in door-to-needle time in patients with acute ischemic stroke via a simple stroke activation protocol. J Stroke Cerebrovasc Dis 2018;27:1539–45.
16. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019–30.
17. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009–18.
18. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11–20.
19. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296–306.
20. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs t-PA alone in stroke. N Engl J Med 2015;372:2285–95.
21. Health Promotion Board, Singapore. Stroke Registry Annual Report 2015. Singapore: National Registry of Diseases Office, 2018.
22. Hubert GJ, Meretoja A, Audebert HJ, Tatlisumak T, Zeman F, Boy S, et al. Stroke thrombolysis in a centralized and a decentralized system

(Helsinki and Telemedical Project for Integrative Stroke Care Network). Stroke 2016;47:2999–3004.

23. Bray BD, Campbell J, Cloud GC, Hoffman A, Tyrrell PJ, Wolfe CD, et al. Bigger, faster? Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. Stroke 2013;44:3129–35.
24. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: a review. J Stroke 2017;19:286–94.
25. Ministry of Health, Singapore. Singapore Burden of Disease Study 2010. Singapore: Epidemiology & Disease Control Division, 2014.
26. Tay SS, Wee TC, Mohamed Noor S, Hassan N. View towards rehabilitation in the home–a survey of patient's mindset towards a home rehabilitation programme. Ann Acad Med Singapore 2016;45:560–2.
27. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47:e98–169.
28. Koh GC, Yen SC, Tay A, Cheong A, Ng YS, De Silva DA, et al. Singapore Tele-technology Aided Rehabilitation in Stroke (STARS) trial: protocol of a randomized clinical trial on tele-rehabilitation for stroke patients. BMC Neurol 2015;15:161.
29. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke 2011;42:1489–94.
30. Aribou ZM, Mondry A. Anticoagulation needs in Asians with atrial fibrillation: a mythbuster. Ann Acad Med Singapore 2014;43:275–8.
31. Fabiaña N, Ramaswami AP, Ang ES, De Silva DA. Underutilisation of guideline-based therapy primary prevention among patients presenting with AF-related ischaemic stroke. Ann Acad Med Singapore 2015;44:266–8.

Original Article

Confirmatory Factor Analysis and Measurement Invariance of the Multidimensional Scale of Perceived Social Support in Young Psychiatric and Non-Psychiatric Asians

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Abstract

Introduction: Studies of the 3-factor (family, friends and significant others) Multidimensional Scale of Perceived Social Support (MSPSS) have shown mixed results in non-Western and/or psychiatric populations due to factorial inconsistencies in its structure. Our study aimed to replicate and expand previous findings of MSPSS through confirmatory factor analysis (CFA) and measurement invariance analysis in a young Asian population of psychiatric and non-psychiatric subjects. Materials and Methods: Data on 209 subjects were examined. The majority were Chinese (66.5%) followed by Malays (17.2%), Indians (14.4%) and other ethnicities (1.9%). Subjects in the non-psychiatric group (n = 100) did not report any psychiatric illnesses. Subjects in the psychiatric group (n = 109) were outpatients of a tertiary hospital in Singapore who had been diagnosed with depressive disorders. Results: The 3-factor models of MSPSS showed better fit indices than the 2-factor models (friends/significant others and family, or family/significant others and friends) which indicated that the 3-factor structure of MSPSS was valid. Multigroup CFA demonstrated metric invariance, indicating MSPSS scores can be compared across groups. In the psychiatric group, descriptive and weighted univariate analyses revealed significantly lower levels of perceived social support in every domain of MSPSS. Conclusion: The 3-factor model of MSPSS can be used to compare psychiatric and non-psychiatric subjects locally. Since psychiatric patients reported lower MSPSS scores, future research could examine the causative factors that contribute to lower perceived social support in young adults seeking psychiatric intervention.

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Key words: Factorial validity, Multiethnic, Southeast Asia

Introduction

Social support is defined as a social resource that is associated with multiple health outcomes and mortality.[1-7] Poor social support has been shown to correlate with unfavourable social and psychological outcomes such as low life satisfaction and self-esteem and psychological distress such as anxiety and depression.[8–10]

In the last few decades, several qualitative and quantitative scales were developed to measure social support. One of these, the Multidimensional Scale of Perceived Social Support (MSPSS), was a questionnaire developed by Zimet et al[11] to provide quantitative measurement of perceptions of social support from one's family, friends and significant others. Since it comprises only 12 items, the questionnaire is popular among researchers as it is easy and quick to administer and—unlike other similar tools—it also measures perceptions of support in multiple domains.[11]

MSPSS has been validated in adolescent, adult, non-psychiatric and psychiatric populations and in different languages such as Chinese, Malay and Tamil.[11–17] Unfortunately, it is plagued by inconsistencies in factorial validity in psychiatric and/or non-Western populations.[12,18–20]

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For instance, Stanley et al[12] used a 2-factor model of MSPSS—instead of the original 3-factor model introduced by Zimet et al[11]—in their study of older adults who had been diagnosed with general anxiety disorder. In their study, Stanley et al[12] conflated the family and significant others into a single domain. The same methodology was also deployed in a study of non-psychiatric South Asians who lived in Hong Kong.[20] Likewise, Chou[18] employed a 2-factor model of MSPSS in his study of Chinese adolescents. Unlike Stanley et al,[12] however, his findings revealed that his subjects had conflated friends and significant others into 1 domain.[18] A study of Pakistani women had also shown that social support was viewed as a single construct regardless of its source.[19]

On the other hand, findings from the study by Clara et al[21] did not support the 2-factor model of MSPSS. Instead, they reported on the factorial validity of the 3-factor version of MSPSS. The psychiatric subjects in their study also performed worse in all domains of perceived social support. Their results were corroborated by Vaingankar et al[22] who validated the 3-factor MSPSS in a group of adults with schizophrenia from Singapore.

The lack of factorial validity in MSPSS is a major issue. It makes it difficult to compare data on social support—such as between Western and non-Western populations or between psychiatric and non-psychiatric subjects—and to generalise results across different groups. Due to inconsistencies in its factorial validity in non-Western populations, it is not known if MSPSS can be validated in different types of mental illness. There is also a lack of research that compares perceived social support between psychiatric and non-psychiatric residents in Singapore. To the best of our knowledge, previous studies have only examined either healthy non-psychiatric or psychiatric subjects, but not both.[22,23]

Based on results from a study of patients with schizophrenia in Singapore,[22] we hypothesised that the 3-factor models of MSPSS will produce the best fit for data. Our study also investigated whether the factorial structure of MSPSS meets scalar invariance. Finally, we hypothesised that psychiatric subjects would report a lower level of perceived social support from family, friends and significant others than their non-psychiatric counterparts.[8,9,21]

Materials and Methods

A total of 209 subjects were recruited for this study and their sociodemographic details—such as age, education, ethnicity, gender and household income—were collected through their self-report. In the non-psychiatric group, 100 (47.8%) subjects were recruited from the general public using the snowball sampling method. They also reported that they did not suffer from an existing psychiatric condition or illness.

In the psychiatric group (n = 109, 52.2%), only patients who were diagnosed with depressive disorders were included since confirmatory factor analysis (CFA) demands a homogeneous study population. They were also outpatients from the Institute of Mental Health, Singapore. Although a waiver of parental consent was granted for this study, caregivers who accompanied subjects <21 years old were nevertheless informed of the details of the study.

After subjects had provided their written consent to be included in the study, they proceeded to complete the 12-item MSPSS questionnaire. For psychiatric subjects, members of the research team were present to ensure that they did so without any influence from their caregivers. Subjects with intellectual disabilities were excluded from the study. This study was approved by the Domain Specific Review Board of the National Healthcare Group, Singapore.

When grading their response to each item in the MSPSS questionnaire, subjects used a Likert scale that ranged from 1 (very strongly disagree) to 7 (very strongly agree). The mean score of each domain—family, friends and significant others—was tabulated after the total score was divided by 4. Additionally, global perceived social support was derived from the division of the total score by 12.

In this study, we examined 4 models of MSPSS: the original 3-factor model by Zimet et al,[11] the 2-factor models by Stanley et al[12] and Chou,[18] respectively, and the higher-order 3-factor model by Clara et al.[21] Chi-square test, root mean square error of approximation (RMSEA), comparative fit index (CFI) and Tucker-Lewis index (TLI) were used to evaluate the overall fit of each model. Since sample size can affect the outcome of chi-square test, we refrained from using its result to evaluate each model. Instead, we used the cut-offs of ≥0.95 for CFI and TLI and ≤0.06 for RMSEA proposed by Hu and Bentler as the criteria for best fit.[24] In multigroup CFA, a change of CFI <0.01 is indicative of a restrictive model.[25] The results were analysed in 3 parts.

First, CFA was performed on both groups using Mplus version 2.1.2.[26] The ordinal response categories were treated as continuous since they were sufficiently large in numbers (≥7).[27] Due to poor multivariate normality and the small number of subjects in our study, the results were analysed with maximum likelihood estimator.[28,29] Since the study of the 3-factor model in psychiatric subjects by Clara et al[21] had shown a negative result for significant others, we introduced a constraint in CFA to control for this variable.

Second, after the model with the best fit for the data was identified, we conducted multigroup CFA to determine measurement invariance by evaluating the consistency of the parameters—factor loadings, intercepts and error residuals—in both groups. Three measurement invariance models—each one with an increasing level of restrictiveness—were tested: configural invariance (to

determine whether factor structure fitted each group in the same manner), metric invariance (to gauge whether factor loadings were similar in both groups) and scalar invariance (to assess whether factor loadings and intercepts were similar in both groups).[28] When metric invariance is present, scores can be compared in both groups. However, the scores in each group can only be compared at a latent level when scalar invariance is present.[25,30]

Third, we used inverse probability weighting to control for confounding factors that arise from the assignment of subjects to both groups. Logistic regression analysis was used to determine the probability (propensity scores) of being in the psychiatric group as a function of the sociodemographic factors of age, education, ethnicity, gender and household income. Weights were calculated based on subjects' inverse probability (propensity score) of being in the psychiatric group. Descriptive analysis and weighted univariate analysis of variance were used to ascertain differences in MSPSS scores in both groups.

Results

There were 87 male and 122 female subjects in our study. The majority were Chinese (66.5%) followed by the Malays (17.2%), Indians (14.4%) and other ethnicities (1.9%). In both groups, the mean age of the participants was 23 years old. The baseline characteristics of both groups are shown in Table 1.

Our results showed that the internal consistency of MSPSS in both groups was excellent. In the non-psychiatric group, Cronbach's alphas for family, friends and significant others were 0.89, 0.90 and 0.94, respectively. In the psychiatric group, they were 0.90, 0.94 and 0.96, respectively.

Table 1. Baseline Characteristics of Subjects

Variable	Non-Psychiatric Group (n = 100)	Psychiatric Group (n = 109)
Age (mean ± SD, years)	23.5 ± 5.9	22.3 ± 6
Gender (%)		
Male	45 (21.5)	42 (20.1)
Female	55 (26.3)	67 (32.1)
Ethnicity (%)		
Chinese	60 (28.7)	79 (37.8)
Indian	22 (10.5)	8 (3.8)
Malay	15 (7.2)	21 (10.0)
Others	3 (1.4)	1 (0.5)
Education (%)		
Primary and below	11 (5.3)	12 (5.7)
Secondary	24 (11.5)	44 (21.1)
Post-Secondary	13 (6.2)	15 (7.2)
Diploma	12 (5.7)	26 (12.4)
Degree and above	40 (19.1)	12 (5.7)
Monthly household income (%)		
<S$2000	6 (2.9)	23 (11)
S$2000 – 3999	13 (6.2)	15 (7.2)
S$4000 – 5999	21 (10.0)	5 (2.4)
S$6000 – 9999	24 (11.5)	11 (5.3)
>S$10,000	7 (3.3)	5 (2.4)
Not applicable	4 (1.9)	8 (3.8)
Do not know	25 (12.0)	39 (18.7)
Declined to reveal	0 (0)	3 (1.4)

SD: Standard deviation

Using the criteria by Hu and Bentler,[24] the original 3-factor model by Zimet et al[11] and higher-order 3-factor model by Clara et al[21] were shown to have a good fit for the data. The comparative and global fit values were within the range (CFI and TFI, ≥0.95; RMSEA, ≤0.06) recommended by Hu and Bentler. On the other hand, the 2-factor models demonstrated a poor fit. The results of the fit indices, factor loadings and correlations are shown in Tables 2 and 3.

Multigroup CFA was also performed on the 3-factor model of Zimet et al[11] instead of the higher-order 3-factor model of Clara et al[21] after the latter showed a negative correlation for the variable, significant others, in their psychiatric subjects that may indicate errors in the parameters of their model. The results of multigroup CFA, RMSEA and CFI indicated an excellent fit for the configural and metric models. Additionally, a CFI difference of 0.001 supported a more restrictive model at the metric level. At the scalar level, RMSEA and CFI indicated fair to good fit of the data. However, a CFI difference of 0.04 meant that the intercepts between both groups were not the same and scalar invariance was not achieved. The fit indices are shown in Table 4.

Based on results of descriptive analyses, mean MSPSS scores were lowest for family and highest for significant others in both groups. Univariate analysis of variance showed significant differences between both groups for family ($F = 38.98$, $P < 0.001$), friends ($F = 58.74$, $P < 0.001$), significant others ($F = 14.95$, $P < 0.001$) and global perceived social support ($F = 52.71$, $P < 0.001$). Since the Cohen's d effect size ranged from 0.62 (medium) to 0.76 (large), the difference between both groups was substantial. The results of the descriptive and weighted univariate analyses are shown in Tables 1 and 5, respectively.

Discussion

The findings of previous studies on the factor structure of MSPSS were mixed. Our study aimed to validate the factor structure of MSPSS and to investigate the differences in perceived social support between young psychiatric and non-psychiatric subjects in a multi-cultural society in Asia.

The results of our study supported the factorial validity of the original 3-factor model of MSPSS by Zimet et al[11] and the higher-order 3-factor model by Clara et al.[21] The latter showed that the overarching measure—global perceived social support—was a meaningful measure of overall perceived social support. CFA suggests that both groups viewed the 3 domains of perceived social support—family, friends and significant others—as distinct from one another. Our findings did not support

Table 2. Results of Fit Indices for 2-Factor and 3-Factor MSPSS Models in Psychiatric and Non-Psychiatric Subjects

Subject	χ^2	df	χ^2/df	CFI	TLI	RMSEA	90% CI
Psychiatric group							
2-factor model							
Stanley et al*	253	53	4.78	0.823	0.779	0.186	0.163 – 0.209
Chou†	338	53	6.38	0.747	0.685	0.222	0.200 – 0.245
3-factor model							
Zimet et al‡	64.3	51	1.26	0.988	0.985	0.049	0.000 – 0.083
Clara et al§	64.1	52	1.23	0.989	0.986	0.046	0.000 – 0.080
Non-psychiatric group							
2-factor model							
Stanley et al*	207.21	53	3.91	0.780	0.26	0.171	0.146 – 0.195
Chou†	225.91	53	4.26	0.753	0.693	0.181	0.157 – 0.205
3-factor model							
Zimet et al‡	70.8	51	1.39	0.972	0.964	0.062	0.017 – 0.095
Clara et al§	70.8	51	1.39	0.972	0.964	0.062	0.017 – 0.095

CFI: Comparative fit index; CI: Confidence interval; df: Degrees of freedom; MSPSS: Multidimensional Scale of Perceived Social Support; RMSEA: Root mean square error of approximation; TLI: Tucker-Lewis index; χ^2: Chi-square test, χ^2/df: Ratio of chi-square to degrees of freedom
Note: All values were rounded to 3 significant figures.
*Stanley MA, Beck JG, Zebb BJ. Psychometric properties of the MSPSS in older adults. Aging Ment Health 1998;2:186–93.
†Chou KL. Assessing Chinese adolescents' social support: the Multidimensional Scale of Perceived Social Support. Pers Individ Dif 2000;28:299–307.
‡Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. J Pers Assess 1988;52:30–41.
§Clara IP, Cox BJ, Enns MW, Murray LT, Torgrudc LJ. Confirmatory factor analysis of the Multidimensional Scale of Perceived Social Support in clinically distressed and student samples. J Pers Assess 2003;81:265–70.

Table 3. Standardised Factor Loadings and Correlations of 12-Item MSPSS Between Non-Psychiatric and Psychiatric Subjects

Variable	Factor Loading					
	Non-Psychiatric Group			Psychiatric Group		
	SO	FA	FR	SO	FA	FR
MSPSS						
1. There is a special person who is around when I am in need.	0.893			0.874		
2. There is a special person with whom I can share joys and sorrows.	0.924			0.986		
3. I have a special person who is a real source of comfort to me.	0.856			0.940		
4. There is a special person in my life who cares about my feelings.	0.905			0.914		
5. My family really tries to help me.		0.903			0.865	
6. I get the emotional help and support I need from my family.		0.959			0.949	
7. I can talk about my problems with my family.		0.792			0.776	
8. My family is willing to help me make decisions.		0.642			0.76	
9. My friends really try to help me.			0.851			0.900
10. I can count on my friends when things go wrong.			0.859			0.889
11. I have friends with whom I can share my joys and sorrows.			0.859			0.900
12. I can talk about my problems with my friends.			0.751			0.905
Factor correlations						
SO	-			-		
FA	0.616	-		0.462	-	
FR	0.432	0.375	-	0.492	0.217	-

FA: Family; FR: Friends; MSPSS: Multidimensional Scale of Perceived Social Support; SO: Significant others
Note: The results pertained to the 3-factor model by Zimet et al. All factor loadings are statistically significant at P <0.01.

Table 4. Results of Multigroup CFA on Goodness-of-Fit Indices for Invariance Models

Model	χ^2	df	χ^2 Difference	DF Difference	*P* Value	RMSEA	TLI	CFI	CFI Difference
Configural	135.32	102	-	-	0.0152	0.056	0.976	0.981	-
Metric	142.69	111	7.367	9	0.023	0.052	0.979	0.982	0.001
Scalar	226.17	123	83.481	12	<0.001	0.09	0.938	0.942	0.04

CFA: Confirmatory factor analysis; CFI: Comparative fit index; df: Degrees of freedom; RMSEA: Root mean square error of approximation; TLI: Tucker-Lewis index; χ^2: Chi-square test

Table 5. Results of Univariate Analysis of Variance for MSPSS in Non-Psychiatric and Psychiatric Subjects

MSPSS Domain	Non-Psychiatric Group (Mean ± SD)	Psychiatric Group (Mean ± SD)	Univariate Analysis of Variance			
			F Value	df	*P* Value	Cohen's *d*
Friends	5.72 ± 1.36	4.22 ± 2.43	58.74	1	<0.001	0.76
Family	5.52 ± 1.61	4.17 ± 2.62	38.98	1	<0.001	0.62
Significant others	5.81 ± 1.81	4.90 ± 2.84	14.95	1	<0.001	0.71
Global perceived social support	5.68 ± 1.32	4.43 ± 2.08	52.71	0	<0.001	0.72

df: Degrees of freedom; MSPSS: Multidimensional Scale of Perceived Social Support; SD: Standard deviation
Note: All values were rounded to the nearest 2 decimal places.

the 2-factor models by Stanley et al[12] and Chou.[18] The results of multigroup CFA also showed that MSPSS scores could be interpreted similarly between non-psychiatric and psychiatric subjects, but not at the latent level since scalar invariance was lacking.

Although MSPSS is widely used, there is, however, a lack of research and understanding of its factorial properties. The results of our CFA are significant in two ways. First, they supported the use of the original 3-factor model of MSPSS by Zimet et al[11] in a multicultural Asian setting since it had allowed meaningful comparisons to be made between non-psychiatric and psychiatric populations. Second, the results validated the use of the 3-factor model in a young population. Prior to our study, there was only one study on the subject in Singapore but it involved an adult population with schizophrenia.[21]

In our study, the psychiatric group reported significantly lower level of perceived social support than the non-psychiatric group. This result was expected since previous research findings had found a correlation between poor mental health and low perceived social support.[8,9,31] Depending on the level of suicide ideation, the MSPSS scores of the psychiatric subjects in our study—ranging from 3.85 to 4.89—corroborated those reported by patients with major depressive disorder in 6 Asian countries.[32]

Although our study did not specifically compare the 3 domains of social support, results of the descriptive analyses showed that subjects in both groups perceived lower support from their families than from friends and significant others, a finding which echoed that of another study.[21] This result is crucial since they could address how interventions can be targeted to help young indviduals.[8] The home is one of the first places in which mental health issues often surface. Likewise, it can be an important starting point to launch successful interventions that aid and benefit young individuals.[8,33] More research is needed on the role that the family plays to support younger individuals in Singapore and the factors that contribute to the low level of support perceived by them.

To the best of our knowledge, this is the first study that investigated perceived social support in young non-psychiatric and psychiatric subjects in Singapore. Previous studies had investigated this subject in either non-psychiatric or psychiatric participants, but not both. Since social support is linked to multiple psychosocial outcomes and mortality, the results of this study provide a preliminary comparison and understanding of perceived social support in young healthy and psychiatric individuals in Singapore.

A limitation of this study was its reliance on self-reported data. Although perceptions are best measured through self-report, confounding factors such as social desirability bias may unintentionally influence results in ways that over- or underestimate the MSPSS scores. Additionally, the subjects in our study were able to read and write English and the results may not be representative of those who are not proficient in that language.

Conclusion

Our study supported the use of the original 3-factor model of MSPSS by Zimet et al[11] in a young Asian population of non-psychiatric and psychiatric subjects. The scores of both groups revealed that the psychiatric group reported lower perceived social support in all domains of MSPSS than the non-psychiatric group. Additionally, both groups perceived support from family to be lower than that from friends and significant others. These results suggest that interventions that target the home may be helpful to enhance the support of family for young individuals with psychiatric conditions. Future research could expand on the findings of this study to examine the factors that contribute to perceived low familial support in psychiatric individuals in Singapore.

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REFERENCES

1. House JS, Landis KR, Umberson D. Social relationships and health. Science 1988;241:540–5.
2. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. J Behav Med 2006;29:377–87.
3. Thoits PA. Social support and psychological well-being: theoretical possibilities. In: Sarason IG, Sarason BR, editors. Social Support: Theory, Research and Applications. Dordrecht: Springer; 1985. p. 51–72.
4. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med 2010;7:e1000316.
5. Thoits PA. Mechanisms linking social ties and support to physical and mental health. J Health Soc Behav 2011;52:145–61.
6. Malhotra R, Ang SJ. Social support for older adults–a bane or a boon for their health? Ann Acad Med Singapore 2016;45:172–3.
7. Ng CW, Tan WS, Gunapal PP, Wong LY, Heng BH. Association of socioeconomic status (SES) and social support with depressive symptoms among the elderly in Singapore. Ann Acad Med Singapore 2014;43:576–87.
8. Uchino BN, Bowen K, Kent R. Social support and mental health. In: Friedman H, Fingerman K, editors. Encyclopedia of Mental Health. 2nd ed. Oxford: Elsevier; 2016. p. 189–95.

9. Lakey B, Cronin A. Low social support and major depression: research, theory and methodological issues. In: Dobson KS, Dozois JA, editors. Risk Factors in Depression. San Diego, CA: Elsevier Academic Press; 2008. p. 385–408.
10. Casale M, Wild L, Cluver L, Kuo C. The relationship between social support and anxiety among caregivers of children in HIV-endemic South Africa. Psychol Health Med 2014;19:490–503.
11. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. J Pers Assess 1988;52:30–41.
12. Stanley MA, Beck JG, Zebb BJ. Psychometric properties of the MSPSS in older adults. Aging Ment Health 1998;2:186–93.
13. Canty-Mitchell J, Zimet GD. Psychometric properties of the Multidimensional Scale of Perceived Social Support in urban adolescents. Am J Community Psychol 2000;28:391–400.
14. Eker D, Arkar H. Perceived social support: psychometric properties of the MSPSS in normal and pathological groups in a developing country. Soc Psychiatry Psychiatr Epidemiol 1995;30:121–6.
15. Guan NC, Seng LH, Hway Ann AY, Hui KO. Factorial validity and reliability of the Malaysian simplified Chinese version of Multidimensional Scale of Perceived Social Support (MSPSS-SCV) among a group of university students. Asia Pac J Public Health 2015;27:225–31.
16. Guan NC, Sulaiman AR, Seng LH, Ann AY, Wahab S, Pillai SK. Factorial validity and reliability of the Tamil version of Multidimensional Scale of Perceived Social Support among a group of participants in University Malaya Medical Centre, Malaysia. Indian J Psychol Med 2013;35:385–8.
17. Ng CG, Amer Siddiq AN, Aida SA, Zainal NZ, Koh OH. Validation of the Malay version of the Multidimensional Scale of Perceived Social Support (MSPSS-M) among a group of medical students in Faculty of Medicine, University Malaya. Asian J Psychiatr 2010;3:3–6.
18. Chou KL. Assessing Chinese adolescents' social support: the Multidimensional Scale of Perceived Social Support. Pers Individ Dif 2000;28:299–307.
19. Akhtar A, Rahman A, Husain M, Chaudhry IB, Duddu V, Husain N. Multidimensional Scale of Perceived Social Support: psychometric properties in a South Asian population. J Obstet Gynaecol Res 2010;36:845–51.
20. Tonsing K, Zimet GD, Tse S. Assessing social support among South Asians: the Multidimensional Scale of Perceived Social Support. Asian J Psychiatr 2012;5:164–8.
21. Clara IP, Cox BJ, Enns MW, Murray LT, Torgrudc LJ. Confirmatory factor analysis of the Multidimensional Scale of Perceived Social Support in clinically distressed and student samples. J Pers Assess 2003;81:265–70.
22. Vaingankar JA, Abdin E, Chong SA. Exploratory and confirmatory factor analyses of the Multidimensional Scale of Perceived Social Support in patients with schizophrenia. Compr Psychiatry 2012;53:286–91.
23. Tong EM, Bishop GD, Diong SM, Enkelmann HC, Why YP, Ang J, et al. Social support and personality among male police officers in Singapore. Pers Individ Dif 2004;36:109–23.
24. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model 1999;6:1–55.
25. Milfont TL, Fischer R. Testing measurement invariance across groups: applications in cross-cultural research. Int J Psychol Res 2010;3:111–30.
26. Muthén LK, Muthén BO. Mplus User's Guide. 6th ed. Los Angeles, CA: Muthén & Muthén; 2007.
27. Dolan CV. Factor analysis of variables with 2, 3, 5 and 7 response categories: a comparison of categorical variable estimators using simulated data. Brit J Math Stat Psy 1994;47:309–26.
28. Cheng ST, Chan AC. The Multidimensional Scale of Perceived Social Support: dimensionality and age and gender differences in adolescents. Pers Individ Dif 2004;37:1359–69.
29. Li CH. Confirmatory factor analysis with ordinal data: comparing robust maximum likelihood and diagonally weighted least squares. Behav Res Methods 2016;48:936–49.
30. Van de Schoot R, Lugtig P, Hox J. A checklist for testing measurement invariance. Eur J Dev Psychol 2012;9:486–92.
31. Lakey B, Orehek E. Relational regulation theory: a new approach to explain the link between perceived social support and mental health. Psychol Rev 2011;118:482-95.
32. Lim AY, Lee AR, Hatim A, Tian-Mei S, Liu CY, Jeon HJ, et al. Clinical and sociodemographic correlates of suicidality in patients with major depressive disorder from six Asian countries. BMC Psychiatry 2014;14:37.
33. Repetti RL, Taylor SE, Seeman TE. Risky families: family social environments and the mental and physical health of offspring. Psychol Bull 2002;128:330–66.

Original Article

Clinical Findings of Ankylosing Spondylitis With and Without Human Leukocyte Antigen (HLA)-B27 and HLA-B51

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Abstract

Introduction: Ankylosing spondylitis (AS) and Behçet's disease are known to be associated with the human leukocyte antigen (HLA)-B27 and HLA-B51 genes, respectively. However, many of their clinical findings—including articular and extra-articular symptoms—are similar, making diagnosis a challenge in the early stage of the disease. The aim of this study was to investigate the differences in clinical findings of AS patients with and without the HLA-B27 gene. Materials and Methods: We performed a retrospective chart review of 151 AS patients. The following clinical findings were evaluated: oral ulcer, genital ulcer, skin manifestation, uveitis, peripheral arthritis; and gastrointestinal, cardiac and pulmonary involvement. Patients were divided into 4 groups based on absence or presence of the HLA-B27 and HLA-B51 genes. The number of patients with each clinical finding was subsequently examined in each group. Results: The incidence of uveitis was significantly higher in the HLA-B27-positive group (P = 0.004); however, other clinical findings did not differ significantly according to the absence or presence of the HLA-B27 gene. There were no significant differences in the clinical findings of patients with positive and negative HLA-B51. Conclusion: HLA-B27 was associated with the development of uveitis but not with other clinical findings or disease activity in AS patients. HLA-B51 was not associated with the clinical findings or disease activity of AS.

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Key words: Axial spondyloarthritis, Behçet's disease, Uveitis

Introduction

Ankylosing spondylitis (AS) is a type of spondyloarthropathy, a chronic rheumatic disease that is characterised by sacroiliitis.[1] Other than sacroiliitis, AS has various spondyloarthropathy features and is closely related to human leukocyte antigen (HLA)-B27.[2,3] Behçet's disease (BD) is a systemic inflammatory disease of unknown aetiology. It is classified as a type of vasculitis and is known to be associated with HLA-B51.[4] The main symptom in AS is inflammatory low back pain and the disease mainly occurs in young adults.[1,5] On the other hand, the major symptom in BD is oral ulcer (>80% of cases). Cases occur regardless of age and arthritic symptoms vary from 5–90%.[6] After the 1984 New York criteria, a new set of criteria for classifying and diagnosing spondyloarthritis called the Assessment of SpondyloArthritis International Society was developed.[7] However, sacroiliitis is often not clear in radiologic studies of axial spondyloarthritis, while inflammatory low back pain occurs in approximately 12% of BD patients.[6,8] In some cases of low back pain in BD—which is an inflammatory vasculitis—abdominal aortic aneurysm may be the cause and will need to be evaluated.[9] Although AS is classified as

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a spondyloarthritis and BD as a vasculitis, they share many similar symptoms. AS and BD may both cause peripheral arthritis and show extra-skeletal involvement such as uveitis, inflammatory bowel disease (IBD) and cardiovascular diseases.[1] In most cases, it is easy to differentiate between AS and BD; however, there are some cases in which the typical clinical findings are not apparent, making it difficult to do so.[10]

HLA genes have a strong association with autoimmune diseases. AS patients with positive HLA-B27 are more likely to develop AS at a younger age, respond better to treatment with tumour necrosis factor-alpha (TNF-α) inhibitors, have a higher frequency of uveitis and a lower prevalence of psoriasis or IBD.[11] Although the association of AS with HLA-B27 and BD with HLA-B51 are well known, AS and BD can cause arthritis through a similar inflammatory pathway and are also responsive to TNF-α inhibitor treatment.[12] Case reports have shown that reactive arthritis of the spondyloarthropathy category is associated with HLA-B51.[13,14] In addition, AS is strongly associated with the carriage of certain amino acids at position 97 in HLA-B, and position 97 is also associated with the cell surface expression of HLA-B51.[15] Both HLA-B27 and HLA-B51 may play roles in a common inflammatory process and affect each other. In BD—when both HLA-B27 and HLA-B51 are positive—the prognosis of uveitis is better than other subgroups.[16] Therefore, both HLA-B27 and HLA-B51 may affect the manifestation or development of AS and BD. Investigating the clinical findings of AS patients based on the absence or presence of HLA-B27 and HLA-B51 may be useful for predicting and managing the disease. However, to date, there has been no study on the relationship between clinical findings of AS and HLA-B27 or HLA-B51. This study sought to do so.

Materials and Methods

Patients

A retrospective chart review was conducted of patients diagnosed with AS who visited Korea University Guro Hospital between 2007 and 2017 and who were tested for HLA-B27 and HLA-B51. The classification criteria for AS were based on the modified New York criteria proposed in 1984.[17] A total of 153 AS patients (120 males and 33 females) were included.

Main Outcome Variables

The following clinical findings were examined: oral ulcer, genital ulcer, skin manifestation, uveitis, peripheral arthritis; and gastrointestinal, cardiac and pulmonary involvement. Skin manifestations included erythema nodosum/multiform, acneiform lesion, furuncle, folliculitis and psoriasis. Gastrointestinal involvement included ulcerative colitis and Crohn's disease. Cardiac involvement included angina and myocardial infarction while pulmonary involvement included interstitial lung disease and pneumothorax. To determine patients' therapeutic responses, use and replacement frequency of non-steroidal anti-inflammatory drugs (NSAIDs) and use of sulfasalazine (SSZ), methotrexate (MTX) and TNF-α inhibitors were examined.

Study Factors

Patients were divided into 4 groups according to HLA-B gene types: 1) Group 1: HLA-B27-positive and HLA-B51-negative; 2) Group 2: HLA-B27-positive and HLA-B51-positive; 3) Group 3: HLA-B27-negative and HLA-B51-positive; and 4) Group 4: HLA-B27-negative and HLA-B51-negative.

Other Variables

Demographic features of age, diagnosis age, disease duration, sex, diabetes mellitus (DM), hypertension (HTN), dyslipidaemia, alcohol consumption and smoking status were also examined. Age, diagnosis age and disease duration were presented as mean ± standard deviation (SD) in years, while sex was classified into male and female. DM was defined as fasting plasma glucose level ≥126 mg/dL, with the diagnosis of DM by a clinician or prescription of an oral hypoglycaemic agent or insulin. HTN was defined as average systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg with the diagnosis of HTN by clinicians or prescription of antihypertensive drugs. Dyslipidaemia was defined based on the following: total cholesterol ≥200 mg/dL, triglyceride ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women or current use of any antidyslipidaemic drug for the purpose of controlling blood lipid concentrations. Alcohol drinker was defined by the consumption of an average of ≥5 units per week. Smoking status was defined as either current smoker or one who has never smoked or was a past smoker. Past smoker was defined as one who did not smoke for >1 year from the time of the medical examination.

Statistical Analysis

Descriptive statistics were used to analyse the frequency, mean and SD of the variables according to the patients' characteristics in each group. The differences in clinical findings were compared based on the absence or presence of HLA-B27 (groups 1 and 2 vs 3 and 4) and HLA-B51 (groups 2 and 3 vs 1 and 4). In the HLA-B27-positive and HLA-B27-negative groups, subgroup analyses were made according to HLA-B51 positive or negative status. For continuous variables, Mann-Whitney U test was used to compare both groups and Kruskal-Wallis H test was used to compare ≥3 groups. Categorical variables were subjected

to Fisher's exact test. All *P* values were two-tailed and *P* <0.05 was considered statistically significant. Data was analysed using IBM SPSS Statistics Version 23 software.

Results

Of the 153 patients, 106 were in Group 1, 16 were in Group 2, 8 were in Group 3 and 23 were in Group 4. The mean age of patients was 37.75 years (SD, 12.93) and the mean disease duration was 4.76 years (SD, 5.30). There were no significant differences in the demographic features and clinical findings among the groups except for uveitis (Table 1). There was a significant difference in the prevalence of uveitis between the HLA-B27-positive and HLA-B27-negative groups (Table 2). Uveitis occurred only in HLA-B27-positive patients. However, there was no significant difference in clinical findings according to the presence of HLA-B51 (Table 3). In addition, there were no significant differences in the clinical findings of patients with positive and negative HLA-B51 in both HLA-B27-positive and HLA-B27-negative groups (data not shown).

Discussion

HLA-B27 is a major histocompatibility complex molecule and is thought to cause inflammation by presenting intracellular peptides to CD8+ T lymphocytes.[18] AS is a representative disease that is closely related to HLA-B27.[19] The Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis lists HLA-B27 as a crucial criterion.[20] However, not all AS patients have HLA-B27, and not all the mechanisms by which HLA-B27 is involved in the pathogenesis of AS are fully understood. Thus, other factors may be associated with AS. HLA-B51 associated with BD with similar clinical manifestations may be associated with the clinical findings of AS. This study showed that in AS, the absence or presence of HLA-B27—but not HLA-B51—was associated with certain clinical findings.

Uveitis was more common with HLA-B27 positivity, irrespective of whether or not HLA-B51 was positive. HLA-B27 is mainly associated with acute anterior uveitis, and uveitis occurs in about half of AS patients with positive HLA-B27.[21] The role of HLA-B27 in the development of uveitis is not yet clear, but its molecule is thought to be activated by presentation of self-peptides to HLA-B27-restricted CD8+ T cells to induce inflammation in the eyes and joints.[22] Besides HLA-B27, other genes, including the interleukin(IL)-23 receptor gene, have been associated with uveitis.[21] HLA-B51 is significantly associated with uveitis in BD patients, but not with idiopathic uveitis.[23] This study also showed that HLA-B51 was not associated with uveitis in patients with AS. In this study, uveitis was diagnosed by ophthalmologists; when patients tested negative for HLA-B27, there was no uveitis. Thus, this study showed that HLA-B27 is strongly associated with uveitis in AS patients.

Although not statistically significant, as in a previous study, the diagnosis age was younger in AS patients with positive HLA-B27;[24] however, peripheral arthritis was more common with HLA-B27 negativity, which contradicted previous reports.[25] Cardiac involvement was found only in the HLA-B27-positive group, suggesting a higher prevalence of DM, HTN, dyslipidaemia and smokers among HLA-B27-positive patients compared to HLA-B27-negative patients. The mechanism by which smoking affects AS is unclear, but previous studies have shown that smoking increased disease activity and radiological progression of AS, especially on HLA-B27 positivity.[26,27] In this study, current smoking rates were significantly higher in the HLA-B27-positive group than the HLA-B27-negative group, suggesting that smoking is more closely related to the development of AS when the patient is HLA-B27-positive. Smoking raises C-reactive protein levels, which is associated with the development of inflammation, and aberrantly activates the Wnt pathway associated with new bone formation. However, the causal relationship between smoking and AS disease activity is ambiguous and a previous study did not show a causal effect of smoking on disease activity.[26] In addition, there is controversy on whether smoking reduces treatment response. In this study, drug usage was identified as an indicator of treatment response, and there was no difference whether HLA-B27 was absent or present.

Although the clinical findings of AS and BD were similar, HLA-B51 was not related to the clinical findings of AS. In addition, there were no differences in the use and frequency of replacement of NSAIDs or the use of SSZ, MTX or TNF-α inhibitors as indicators of the disease activity according to HLA-B type. Despite differences in smoking status among the groups, no significant difference on drug usage was found. In fact, there were some differences in the clinical manifestations of the same organs between AS and BD, which is a differentiating point. Uveitis occurs in 20–30% of cases of AS, mainly in the form of acute anterior uveitis—and oral ulcers are uncommon. In AS, skin manifestations primarily include psoriasis and pulmonary manifestations include interstitial lung diseases, emphysema, bronchiectasis and apical fibrosis.[28] On the other hand, in BD, uveitis often occurs in the form of panuveitis and oral ulcers occurs in >90% of cases. Typical skin manifestations are pseudofolliculitis, erythema nodosum, aphthosis and pathergy phenomenon while pulmonary manifestations include pulmonary infection, vasculitis, fibrosis and embolism.[6] The difference in these clinical findings is thought to occur because AS belongs to the

Table 1. Demographic Features and Clinical Findings of Ankylosing Spondylitis Patients With or Without HLA-B27 and HLA-B51 (n = 153)

Variable	Group 1 (n = 106) HLA-B27-Positive HLA-B51-Negative	Group 2 (n = 16) HLA-B27-Positive HLA-B51-Positive	Group 3 (n = 8) HLA-B27-Negative HLA-B51-Positive	Group 4 (n = 23) HLA-B27-Negative HLA-B51-Negative	*P* Value
Age, years (mean ± SD)	38.72 ± 12.87	39.50 ± 11.57	42.75 ± 8.43	37.00 ± 15.57	0.575
Diagnosis age, years (mean ± SD)	33.63 ± 12.48	34.44 ± 11.18	39.25 ± 8.86	33.57 ± 15.76	0.502
Disease duration, years (mean ± SD)	5.09 ± 5.99	5.06 ± 3.80	3.50 ± 2.72	3.43 ± 2.73	0.685
Sex (%)					0.548
Female	20 (18.9)	5 (31.2)	2 (25.0)	6 (26.1)	
Male	86 (81.1)	11 (68.8)	6 (75.0)	17 (73.9)	
Diabetes mellitus (%)					1.000
No	102 (96.2)	16 (100.0)	8 (100.0)	23 (100.0)	
Yes	4 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypertension (%)					0.900
No	88 (83.0)	14 (87.5)	7 (87.5)	21 (91.3)	
Yes	18 (17.0)	2 (12.5)	1 (12.5)	2 (8.7)	
Dyslipidaemia (%)					0.393
No	90 (84.9)	14 (87.5)	6 (75.0)	22 (95.7)	
Yes	16 (15.1)	2 (12.5)	2 (25.0)	1 (4.3)	
Alcohol consumption (%)					0.191
No	66 (62.3)	9 (56.3)	3 (37.5)	18 (78.3)	
Yes	40 (37.7)	7 (43.7)	5 (62.5)	5 (21.7)	
Smoking status (%)					0.001
None or past	68 (64.1)	9 (56.3)	6 (75.0)	23 (100.0)	
Current	38 (55.9)	7 (43.7)	2 (25.0)	0 (0.0)	
Oral ulcer (%)					0.905
No	71 (67.0)	10 (62.5)	5 (62.5)	14 (60.9)	
Yes	35 (33.0)	6 (37.5)	3 (37.5)	9 (39.1)	
Genital ulcer (%)					0.670
No	104 (98.1)	16 (100.0)	8 (100.0)	22 (95.7)	
Yes	2 (1.9)	0 (0.0)	0 (0.0)	1 (4.3)	
Skin manifestation (%)					0.499
No	76 (71.7)	12 (75.0)	6 (75.0)	13 (56.5)	
Yes	30 (28.3)	4 (25.0)	2 (25.0)	10 (43.5)	
Uveitis (%)					0.036
No	84 (79.2)	14 (87.5)	8 (100.0)	23 (100.0)	
Yes	22 (20.8)	2 (12.5)	0 (0.0)	0 (0.0)	
Peripheral arthritis (%)					0.695
No	47 (44.3)	6 (37.5)	2 (25.0)	11 (47.8)	
Yes	59 (55.7)	10 (62.5)	6 (75.0)	12 (52.2)	
Gastrointestinal involvement (%)					0.203
No	104 (98.1)	16 (100.0)	7 (87.5)	22 (95.7)	
Yes	2 (1.9)	0 (0.0)	1 (12.5)	1 (4.3)	
Cardiac involvement (%)					0.618
No	99 (93.4)	16 (100.0)	8 (100.0)	23 (100.0)	
Yes	7 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 1. Demographic Features and Clinical Findings of Ankylosing Spondylitis Patients With or Without HLA-B27 and HLA-B51 (n = 153) (Cont'd)

Variable	Group 1 (n = 106) HLA-B27-Positive HLA-B51-Negative	Group 2 (n = 16) HLA-B27-Positive HLA-B51-Positive	Group 3 (n = 8) HLA-B27-Negative HLA-B51-Positive	Group 4 (n = 23) HLA-B27-Negative HLA-B51-Negative	*P* Value
Pulmonary involvement (%)					0.111
No	105 (99.1)	16 (100.0)	7 (87.5)	22 (95.7)	
Yes	1 (0.9)	0 (0.0)	1 (12.5)	1 (4.3)	
NSAID use (%)					0.741
None	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	
1 type	80 (75.5)	10 (62.5)	6 (75.0)	19 (82.6)	
≥2 types	24 (22.6)	6 (37.5)	2 (25.0)	4 (17.4)	
Sulfasalazine use (%)					0.595
No	17 (16.0)	3 (18.8)	0 (0.0)	5 (21.7)	
Yes	89 (84.0)	13 (81.2)	8 (100.0)	18 (78.3)	
Methotrexate use (%)					0.786
No	82 (77.4)	13 (81.2)	7 (87.5)	20 (87.0)	
Yes	24 (22.6)	3 (18.8)	1 (12.5)	3 (13.0)	
TNF-α inhibitor use (%)					0.497
No	93 (87.7)	13 (81.2)	7 (87.5)	22 (95.7)	
Yes	13 (12.3)	3 (18.8)	1 (12.5)	1 (4.3)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 2. Comparison of Clinical Findings Between HLA-B27-Positive and HLA-B27-Negative Groups

Variable	Groups 1 and 2 (n = 122) HLA-B27-Positive	Groups 3 and 4 (n = 31) HLA-B27-Negative	*P* Value
Age, years (mean ± SD)	38.83 ± 12.66	38.48 ± 14.17	0.761
Diagnosis age, years (mean ± SD)	33.74 ± 12.28	35.03 ± 14.38	0.831
Disease duration, years (mean ± SD)	5.09 ± 5.74	3.45 ± 2.68	0.343
Sex (%)			0.625
Female	25 (20.5)	8 (25.8)	
Male	97 (79.5)	23 (74.2)	
Diabetes mellitus (%)			0.583
No	118 (96.2)	31 (100.0)	
Yes	4 (3.8)	0 (0.0)	
Hypertension (%)			0.573
No	102 (83.0)	28 (90.3)	
Yes	20 (17.0)	3 (9.7)	
Dyslipidaemia (%)			0.571
No	104 (84.9)	28 (90.3)	
Yes	18 (15.1)	3 (9.7)	
Alcohol consumption (%)			0.678
No	75 (62.3)	21 (67.7)	
Yes	47 (37.7)	10 (32.3)	
Smoking status (%)			0.001
None or past	77 (64.1)	29 (93.5)	
Current	45 (55.9)	2 (6.5)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 2. Comparison of Clinical Findings Between the HLA-B27-Positive and HLA-B27-Negative Groups (Cont'd)

Variable	Groups 1 and 2 (n = 122) HLA-B27-Positive	Groups 3 and 4 (n = 31) HLA-B27-Negative	*P* Value
Oral ulcer (%)			0.674
No	81 (67.0)	19 (61.3)	
Yes	41 (33.0)	12 (38.7)	
Genital ulcer (%)			0.496
No	120 (98.1)	30 (96.8)	
Yes	2 (1.9)	1 (3.2)	
Skin manifestation (%)			0.275
No	88 (71.7)	19 (61.3)	
Yes	34 (28.3)	12 (38.7)	
Uveitis (%)			0.004
No	98 (79.2)	31 (100.0)	
Yes	24 (20.8)	0 (0.0)	
Peripheral arthritis (%)			1.000
No	53 (44.3)	13 (41.9)	
Yes	69 (55.7)	18 (58.1)	
Gastrointestinal involvement (%)			0.183
No	120 (98.1)	29 (93.5)	
Yes	2 (1.9)	2 (6.5)	
Cardiac involvement (%)			0.346
No	115 (93.4)	31 (100.0)	
Yes	7 (6.6)	0 (0.0)	
Pulmonary involvement (%)			0.105
No	121 (99.1)	29 (93.5)	
Yes	1 (0.9)	2 (6.5)	
NSAID use (%)			0.771
None	2 (1.9)	0 (0.0)	
1 type	90 (75.5)	25 (80.6)	
≥2 types	30 (22.6)	6 (19.4)	
Sulfasalazine use (%)			1.000
No	20 (16.0)	5 (18.8)	
Yes	102 (84.0)	26 (81.2)	
Methotrexate use (%)			0.323
No	95 (77.4)	27 (87.1)	
Yes	27 (22.6)	4 (12.9)	
TNF-α inhibitor use (%)			0.531
No	106 (87.7)	29 (93.5)	
Yes	16 (12.3)	2 (6.5)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 3. Comparison of Clinical Findings Between the HLA-B51-Positive and HLA-B51-Negative Groups

Variable	Groups 2 and 3 (n = 24) HLA-B51-Positive	Groups 1 and 4 (n = 129) HLA-B51-Negative	*P* Value
Age, years (mean ± SD)	40.58 ± 10.55	38.41 ± 13.34	0.294
Diagnosis age, years (mean ± SD)	36.04 ± 10.53	33.62 ± 13.06	0.192
Disease duration, years (mean ± SD)	4.54 ± 3.50	4.80 ± 5.58	0.650
Sex (%)			0.416
Female	7 (29.2)	26 (20.2)	
Male	17 (70.8)	103 (79.8)	
Diabetes mellitus (%)			1.000
No	24 (100.0)	125 (96.9)	
Yes	0 (0.0)	4 (3.1)	
Hypertension (%)			1.000
No	21 (87.5)	109 (84.5)	
Yes	3 (12.5)	20 (15.5)	
Dyslipidaemia (%)			0.746
No	20 (83.3)	112 (86.8)	
Yes	4 (16.7)	17 (12.5)	
Alcohol consumption (%)			0.174
No	12 (50.0)	84 (65.1)	
Yes	12 (50.0)	45 (34.9)	
Smoking status (%)			0.473
None or past	15 (62.5)	91 (70.5)	
Current	9 (37.5)	38 (29.5)	
Oral ulcer (%)			0.816
No	15 (62.5)	85 (65.9)	
Yes	9 (37.5)	44 (34.1)	
Genital ulcer (%)			1.000
No	24 (100.0)	126 (97.7)	
Yes	0 (0.0)	3 (2.3)	
Skin manifestation (%)			0.635
No	18 (75.0)	89 (69.0)	
Yes	6 (25.0)	40 (31.0)	
Uveitis (%)			0.371
No	22 (91.7)	107 (82.9)	
Yes	2 (8.3)	22 (17.1)	
Peripheral arthritis (%)			0.371
No	8 (33.3)	58 (45.0)	
Yes	16 (66.7)	71 (55.0)	
Gastrointestinal involvement (%)			0.498
No	23 (98.4)	126 (97.7)	
Yes	1 (1.6)	3 (2.3)	
Cardiac involvement (%)			0.597
No	24 (100.0)	122 (94.6)	
Yes	0 (0.0)	7 (5.4)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 3. Comparison of Clinical Findings Between the HLA-B51-Positive and HLA-B51-Negative Groups (Cont'd)

Variable	Groups 2 and 3 (n = 24) HLA-B51-Positive	Groups 1 and 4 (n = 129) HLA-B51-Negative	*P* Value
Pulmonary involvement (%)			0.403
No	23 (98.4)	127 (98.4)	
Yes	1 (1.6)	2 (1.6)	
NSAID use (%)			0.500
None	0 (0.0)	2 (1.6)	
1 type	16 (66.7)	99 (76.7)	
≥2 types	8 (33.3)	28 (21.7)	
Sulfasalazine use (%)			0.767
No	3 (12.5)	22 (17.1)	
Yes	21 (87.5)	107 (82.9)	
Methotrexate use (%)			0.786
No	20 (83.3)	102 (79.1)	
Yes	4 (16.7)	27 (20.9)	
TNF-α inhibitor use (%)			0.488
No	20 (83.3)	115 (89.1)	
Yes	4 (16.7)	14 (10.9)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

spondyloarthritis category and BD belongs to the vasculitis category—but it remains unclear whether HLA-B27 and HLA-B51 influence each other in this process. Although the pathogenesis of AS is not clearly established, IL-17 and IL-23 are thought to cause AS.[29] HLA-B27 is associated with the IL-23/IL-17 pathway and is thought to affect the production and activation of IL-23 and IL-17,[30] whereas the role of HLA-B51 in AS is not likely to be significant. In this study, panuveitis did not occur regardless of the type of HLA-B, and the only pulmonary abnormality was pneumothorax. Therefore, the presence of the HLA-B51 gene in patients with AS does not appear to be effective in predicting the disease course. In patients with arthralgia and atypical extra-articular symptoms, determining HLA-B27 status may be useful to differentiate between AS and BD.

This is the first study to investigate clinical findings based on the absence or presence of HLA-B27 and HLA-B51 genes in AS patients. Clinical findings that were investigated included articular involvement and extra-articular manifestations of AS and BD that may be related to HLA-B27 and HLA-B51. In addition, demographic features and drug usage were also examined to reflect on patients' status and condition.

However, this study has some limitations. First, the number of patients included in the study, the number of patients between the groups and prevalence of clinical findings were small, making it difficult to clarify statistical significance. The small number of cases can cause type 2 errors. Type 2 errors are usually set at the acceptable level of 0.20.[31] No type 2 error was detected in the clinical findings of groups with or without HLA-B27. In groups classified by the absence or presence of HLA-B51, there was a possibility of type 2 error in the clinical findings of diagnosis age and alcohol consumption (Table 3). Second, the frequency or severity of clinical findings such as oral ulcers and uveitis were not considered, nor were the dose of drugs administered or the type of TNF-α inhibitor. Finally, as different subtypes of HLA-B27 affect the development or clinical manifestations of AS, analysis of the HLA-B27 subtype should have been performed.[19,32]

Conclusion

HLA-B27—rather than HLA-B51—was associated with the clinical manifestations of AS. Among the clinical findings, uveitis occurred when HLA-B27 was present; however, other clinical findings were not associated with HLA-B27. In addition, neither HLA-B27 nor HLA-B51 was associated with AS disease activity. The HLA-B51 gene test is not recommended because it does not diagnose or predict the progress or prognosis of AS. Instead, smoking status and extra-articular symptoms (including uveitis) may be helpful in the diagnosis and treatment of AS. Finally, the scale of this study was small and a larger scale investigation is warranted.

REFERENCES

1. Elyan M, Khan MA. Diagnosing ankylosing spondylitis. J Rheumatol Suppl 2006;78:12–23.
2. Akassou A, Bakri Y. Does HLA-B27 status influence ankylosing spondylitis phenotype? Clin Med Insights Arthritis Musculoskelet Disord 2018;11:1179544117751627.
3. Howe HS, Zhao L, Song YW, Springer L, Edmonds J, Gu J, et al. Seronegative spondyloarthropathy – studies from the Asia Pacific region. Ann Acad Med Singapore 2007;36:135–41.
4. Meador R, Ehrlich G, Von Feldt JM. Behçet's disease: immunopathologic and therapeutic aspects. Curr Rheumatol Rep 2002;4:47–54.
5. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002;61 Suppl 3:iii8–18.
6. Davatchi F, Chams-Davatchi C, Shams H, Shahram F, Nadji A, Akhlaghi M, et al. Behçet's disease: epidemiology, clinical manifestations, and diagnosis. Expert Rev Clin Immunol 2017;13:57–65.
7. Deodhar A. Axial spondyloarthritis criteria and modified NY criteria: issues and controversies. Clin Rheumatol 2014;33:741–7.
8. Erol K, Gok K, Cengiz G, Kilic G, Kilic E, Ozgocmen S. Extra-articular manifestations and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis. Acta Reumatol Port 2018;43:32–9.
9. Orucu M, Keles D, Peker E, Cakici M, Shimbori N, Erden I, et al. Abdominal aortic aneurysm causing lumbar vertebral erosion in Behçet's disease presenting by low back pain. Rheumatol Int 2015;35:367–70.
10. Ambrose NL, Haskard DO. Differential diagnosis and management of Behçet syndrome. Nat Rev Rheumatol 2013;9:79–89.
11. Akkoc N, Yarkan H, Kenar G, Khan MA. Ankylosing spondylitis: HLA-B*27-positive versus HLA-B*27-negative disease. Curr Rheumatol Rep 2017;19:26.
12. Aktas Cetin E, Cosan F, Kucuksezer UC, Bilgic S, Cagatay Y, Gul A, et al. Behçet's disease: immunological relevance with arthritis of ankylosing spondylitis. Rheumatol Int 2013;33:733–41.
13. Shimamoto Y, Sugiyama H, Hirohata S. Reiter's syndrome associated with HLA-B51. Intern Med 2000;39:182–4.
14. Taniguchi Y, Yorioka N, Kyuden Y, Asakimori Y. Reiter's syndrome associated with HLA-B51: a case report. J Int Med Res 2003;31:55–7.
15. Chen L, Shi H, Yuan J, Bowness P. Position 97 of HLA-B, a residue implicated in pathogenesis of ankylosing spondylitis plays a key role in cell surface free heavy chain expression. Ann Rheum Dis 2017;76:593–601.
16. Ahn JK, Park YG. Human leukocyte antigen B27 and B51 double-positive Behçet uveitis. Arch Ophthalmol 2007;125:1375–80.
17. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
18. Bodis G, Toth V, Schwarting A. Role of human leukocyte antigens (HLA) in autoimmune diseases. Methods Mol Biol 2018;1802:11–29.
19. Fong KY. The genetics of spondyloarthropathies. Ann Acad Med Singapore 2000;29:370–5.
20. Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770–6.
21. Rosenbaum JT. New developments in uveitis associated with HLA B27. Curr Opin Rheumatol 2017;29:298–303.
22. Wakefield D, Yates W, Amjadi S, McCluskey P. HLA-B27 anterior uveitis: immunology and immunopathology. Ocul Immunol Inflamm 2016;24:450–9.
23. Shenavandeh S, Jahanshahi KA, Aflaki E, Tavassoli A. Frequency of HLA-B5, HLA-B51 and HLA-B27 in patients with idiopathic uveitis and Behçet's disease: a case-control study. Reumatologia 2018;56:67–72.
24. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs positive patients with ankylosing spondylitis. Rheumatol Int 2003;23:61–6.
25. Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with recent onset axial spondyloarthritis. Ann Rheum Dis 2011;70:1930–6.
26. Ciurea A, Finckh A. Smoking and spondyloarthritis. Joint Bone Spine 2013;80:234–5.
27. Villaverde-Garcia V, Cobo-Ibanez T, Candelas-Rodriguez G, Seoane-Mato D, Campo-Fontecha PDD, Guerra M, et al. The effect of smoking on clinical and structural damage in patients with axial spondyloarthritis: a systematic literature review. Semin Arthritis Rheum 2017;46:569–83.
28. El Maghraoui A. Extra-articular manifestations of ankylosing spondylitis: prevalence, characteristics and therapeutic implications. Eur J Intern Med 2011;22:554–60.
29. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med 2016;375:1303.
30. Vanaki N, Aslani S, Jamshidi A, Mahmoudi M. Role of innate immune system in the pathogenesis of ankylosing spondylitis. Biomed Pharmacother 2018;105:130–43.
31. Akobeng AK. Understanding type I and type II errors, statistical power and sample size. Acta Paediatr 2016;105:605–9.
32. Koh WH, Boey ML. Ankylosing spondylitis in Singapore: a study of 150 patients and a local update. Ann Acad Med Singapore 1998;27:3–6.

Commentary

The Need for Scholarly Evaluation of Programmes Targeting Mental Health Stigma in Singapore

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Abstract

Stigma towards people with mental illness is widely prevalent in Singapore despite nearly 2 decades of anti-stigma efforts. The latest and most ambitious initiative to tackle stigma, "Beyond the Label", was launched in 2018. We believe that it is timely to highlight the missing gap in Singapore's anti-stigma efforts—the lack of evaluative research on anti-stigma programmes. It is crucial that organisations involved in the battle against stigma publish peer-reviewed papers detailing the construction and effectiveness of their programmes vis-à-vis established frameworks or guidelines. We also provide suggestions on useful resources for organisations that are engaged in anti-stigma work.

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Key words: Asia, Discrimination, Help-seeking, People with mental illnesses

Introduction

Stigma encompasses the various negative attitudes, cognitions and behaviours people hold/portray towards others who are experiencing mental illnesses. This results in people with mental illnesses (PMI) to experience lower quality of life,[1] self-esteem and employability which, in turn, lead to increased isolation, discrimination and other negative outcomes.[2] In Singapore, stigma and its adverse effects were first discussed in 2001.[3] However, it was only 17 years later that the country's first nationwide campaign to tackle stigma, led by the National Council of Social Services (NCSS), was launched.[4] It is timely to provide a commentary on Singapore's anti-stigma efforts and highlight an important feature which is currently missing—evaluative studies of the nation's anti-stigma programmes.

A Brief History of the Organisations Involved in Anti-Stigma Efforts in Singapore

Since the early 1990s, the Institute of Mental Health (IMH) and the Singapore Association for Mental Health have advocated for greater awareness of mental illnesses and for the reduction of stigma. Other organisations such as the Community Health Assessment Team, Club Hope, Empowerment, Acceptance and Love, Silver Ribbon Singapore, Clarity Singapore and Samaritans of Singapore had joined in these efforts in the 2000s and early 2010s. In the mid-2010s, the entry of NCSS, TOUCH Community Services, Agency for Integrated Care and greater involvement from the Health Promotion Board have created a vibrant and dynamic network of community and government agencies that work towards a common goal. (Note: These organisations

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possess overt and clear commitment towards eradicating stigma and play major roles in the national initiative. Other smaller organisations that also partake in these efforts are generally inactive or are more focused on other aspects of mental health care.)

Lack of Evaluative Studies on Anti-Stigma Programmes

We conducted a search of the following databases: PsycINFO, PubMed, CINAHL, Scopus, EMBASE, Web of Science and the Cochrane Library. We limited our search to peer-reviewed articles derived from the key words "stigma" and "Singapore" that had been published between 2000 and 2019. A total of 332 papers were found after accounting for duplicate articles. Less than 50 of the studies pertained to stigma and mental illnesses in Singapore and none of the papers had evaluated the implementation of anti-stigma programmes. Research on stigma in the past 18 years was predominantly published by IMH, which examined the phenomenon in a variety of settings[5,6] and demographics.[7-9] However, these studies focused on providing data on the various stigmatising attitudes and behaviours that people held towards PMI[5,7-9] or how stigma negatively impacted the lives of PMI.[1,6] To the best of our knowledge, neither community nor government organisations that are involved in anti-stigma work have published any peer-reviewed articles on their programmes. This raises an important question that has a multitude of implications for ground-, middle- and policy-level decision-makers: How do we know that the anti-stigma programmes that have been implemented are working?

Highlighting the Need for Peer-Reviewed Evalutive Studies

Despite anti-stigma work of close to 2 decades, mental health literacy[10] and stigma[7-9,11] studies have revealed a worrying trend among Singapore residents—their lack of an adequate understanding of mental health issues. The persistent pervasiveness of stigma within our society indicates that past programmes may not have been as effective as envisioned. Given the multifaceted nature of stigma, it is difficult to pinpoint its exact causes. This becomes even more challenging due to the lack of rigorous and quality peer-reviewed evaluative studies of anti-stigma programmes. Given the current tools and knowledge, simply using the number of participants attending anti-stigma programmes/events (which most organisations tend to do) as a measure of effectiveness is not sufficient. This does not provide any useful information on whether the participants subsequently held fewer stigmatising beliefs or behaviours. Even simple feedback forms or questionnaires—which do not seek to understand the efficacy of the programme or event—are not appropriate as they do not allow for proper evaluations.

Contrary to popular belief, improving people's knowledge of mental illnesses via educational anti-stigma programmes is not very effective. Other approaches such as large-scale campaigns can be convoluted when they try to incorporate multiple messages simultaneously (e.g., promoting help-seeking as normal behaviour rather than ending discrimination altogether). If implemented incorrectly, such programmes can lead to greater misconceptions such as the view that compared to "normal" people, PMI are unable to change or recover due to the different biological make-up of their brains.[12] Although this seems to reduce the blame on PMI, it does little to reduce the prejudice and discrimination they face in real life. Additionally, such anti-stigma programmes that rely solely on biological explanations may evoke feelings of pity towards PMI, thus mitigating the normalising impact expected of such campaigns. What has been shown to be effective are contact-type anti-stigma programmes which involve members of the public interacting with PMI[12] (although these should only be conducted if PMI are willing to disclose their conditions).

Despite this finding, most organisations prefer to use an education-based approach due to its relative low cost and ease of implementation. However, as there is a lack of evaluation of these programmes, little evidence may exist to prove their effectiveness in reducing stigma and to support their continued use. Not correctly understanding the impact that these programmes have diminishes the anti-stigma efforts in Singapore for the long-term as the potential for information to be misused and misconceived grows exponentially. Additionally, this can be potentially detrimental as more effective approaches could have been rejected due to the higher costs involved in planning and executing them.

Adopting a scientific method is vital in the creation and implementation of effective anti-stigma programmes. Peer-review and publication are critical components of this process as they instil greater confidence in the effectiveness of the anti-stigma programmes that have been implemented. They also provide an opportunity for improvement during the process when other experts in the same field evaluate and provide feedback on the quality of the study. Doing so enhances the quality of the programme through the professional feedback garnered and provides valuable information (e.g., challenges faced, benefits, etc.) to others who are preparing to embark on similar projects. Furthermore, adequate evaluation allows funding agencies to gain greater confidence in their work and provides direction for future programmes based on the previous findings. Overseas large-scale campaigns have shown this benefit by identifying populations and avenues in which anti-stigma approaches need to be adapted in order to be effective.[13] Despite the advantages, most organisations

in Singapore's mental health sector are not well placed to undertake such scientific efforts. Specifically, in the community sector (where most anti-stigma programmes are developed), a lack of adequate manpower, resources and awareness on the importance of such measures and the technical know-how may be barriers to engaging in such work.

Suggestions for Implementing Evaluative Studies

Although many organisations involved in anti-stigma efforts may not be able to produce peer-reviewed publications due to the reasons mentioned in this article, they should still endeavour to engage academic institutions such as local universities (e.g., the National University of Singapore) or organisations with established research divisions, such as IMH, to conduct evaluative studies. Additionally, because stigma is a complex, multilayered and culturally influenced construct, it is challenging to measure it adequately, and by extension, determine whether the anti-stigma programmes that have been created are useful. This can be mitigated by applying established frameworks, toolkits or guidelines such as those constructed by Corrigan[14] or Corrigan and Shapiro[15] which allow organisations to follow systematic and scientifically robust approaches to measure the effectiveness of their anti-stigma programmes. The National Consortium on Stigma and Empowerment[16] also has a useful set of tools and an extensive collection of stigma-relevant papers which could aid organisations that wish to join anti-stigma efforts in Singapore. A point to note when using these guidelines/frameworks is that they should be culturally relevant, which may require custom modifications to fit Singapore's context. We should also consider involving PMI as this would give us a deeper understanding of what stigma entails based on their own first-hand experiences.

Conclusion

Stigma is detrimental to PMI in many ways—from preventing them from seeking help promptly to causing overt discrimination.[17] Tackling stigma is challenging as it is a complex construct and requires careful consideration of the most effective ways to do so.[18] Organisations engaged in anti-stigma work need to evaluate their programmes in a scientific manner which includes having their work undergo peer-review and publication. Only then can we begin to understand how to effectively combat stigma facing PMI in Singapore.

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REFERENCES

1. Choo CC, Chew PKH, Ho CS, Ho RC. Quality of life in patients with a major mental disorder in Singapore. Front Psychiatry 2018;9:727.
2. Corrigan PW, Watson AC. Understanding the impact of stigma on people with mental illness. World Psychiatry 2002;1:16–20.
3. Lai YM, Hong CP, Chee CY. Stigma of mental illness. Singapore Med J 2001;42:111–4.
4. National Council of Social Service, Singapore. NCSS Launches First Nation-Wide Campaign to Fight Mental Health Stigma. Available at: https://www.ncss.gov.sg/Press-Room/National-Council-of-Social-Service/Press-Releases/Detail-Page?id=NCSS-Launches-First-Nation-Wide-Campaign-to-Fight. Accessed on 15 February 2019.
5. Chee CY, Ng TP, Kue EH. Comparing the stigma of mental illness in a general hospital with a state mental hospital: a Singapore study. Soc Psychiatry Psychiatr Epidemiol 2005;40:648–53.
6. Picco L, Pang S, Lau YW, Jeyagurunathan A, Satghare P, Abdin E, et al. Internalised stigma among psychiatric outpatients: associations with quality of life, functioning, hope and self-esteem. Psychiatry Res 2016;246:500–6.
7. Chang S, Ong HL, Seow E, Chua BY, Abdin E, Samari E, et al. Stigma towards mental illness among medical and nursing students in Singapore: a cross-sectional study. BMJ Open 2017;7:e018099.
8. Pang S, Liu J, Mahesh M, Chua BY, Shahwan S, Lee SP, et al. Stigma among Singaporean youth: a cross-sectional study on adolescent attitudes towards serious mental illness and social tolerance in a multiethnic population. BMJ Open 2017;7:e016432.
9. Subramaniam M, Abdin E, Picco L, Pang S, Shafie S, Vaingankar JA, et al. Stigma towards people with mental disorders and its components – a perspective from multi-ethnic Singapore. Epidemiol Psychiatr Sci 2017;26:371–82.
10. Tonsing KN. A review of mental health literacy in Singapore. Soc Work Health Care 2018;57:27–47.
11. Yuan Q, Picco L, Chang S, Abdin E, Chua BY, Ong S, et al. Attitudes to mental illness among mental health professionals in Singapore and comparisons with the general population. PLoS One 2017;12:e0187593.
12. Corrigan PW. Lessons learned from unintended consequences about erasing the stigma of mental illness. World Psychiatry 2016;15:67–73.
13. Henderson C, Stuart H, Hansson L. Lessons from the results of three national antistigma programmes. Acta Psychiatr Scand 2016;134:3–5.
14. Corrigan PW. A Toolkit for Evaluating Programs Meant to Erase the Stigma of Mental Illness. Available at: http://www.stigmaandempowerment.org/images/corrigan_outcome_measures_toolkit_10.17.2018_FINAL.pdf. Accessed on 15 February 2019.
15. Corrigan PW, Shapiro JR. Measuring the impact of programs that challenge the public stigma of mental illness. Clin Psychol Rev 2010;30:907–22.
16. National Consortium on Stigma and Empowerment. Resources. Available at: https://www.stigmaandempowerment.org/resources. Accessed on 15 February 2019.
17. Poremski D, Chong SA, Subramaniam M. Helping people with mental illness return to employment: challenging existing beliefs. Ann Acad Med Singapore 2015;44:314–6.
18. Mahendran R, Lim HA, Verma SK, Kua E. Attitudes to psychiatry can change but what about stigma? Ann Acad Med Singapore 2014;43:473–4.

Letter to the Editor

From Hospital to Home: Impact of Transitional Care on Cost, Hospitalisation and Mortality

Dear Editor,

The ageing population in Singapore poses a growing challenge and need to realign current health services and care management pathways to treat older adults with complex medical conditions.[1,2] This group of patients typically have multiple comorbidities and disabilities and are at risk of poor outcomes after they are discharged home from hospitals. Consequently, they require frequent admissions to hospitals. To address the issue of frequent readmissions of older adults with complex care needs, transitional care (TC) is offered as a care management model that can help to ameliorate this situation.[1–3]

Studies on TC have primarily targeted frail older patients and focused on health education, self-management and care coordination of social and community services that are nurse-led.[4–8] Since only care coordination is involved, frail patients with exacerbations or unresolved medical conditions had to be referred back to primary care or hospital-based physicians while patients with functional needs were referred to home- or community-based rehabilitative services.[4]

A TC model that appears to hold much promise is one that employs a multidisciplinary team comprising a medical social worker (MSW), nurse, physician and therapist to deliver comprehensive home-based care to older adults.[5,9] In the literature, the findings on the impact of TC on acute hospital utilisation, costs and mortality are mixed and inconclusive.[8,10] A local study of an integrated model of home TC had shown a reduction in readmissions to hospitals, inpatient stay and visits to the hospital emergency department (ED). However, its findings were limited by a lack of economic evaluation.[5]

Our study aimed to examine the impact of a TC programme on cost, hospitalisation and mortality in frail patients with complex functional, medical and social needs who were discharged home from a hospital located in the northern region of Singapore.

Materials and Methods

The intervention was a 3-month posthospitalisation, nurse-led home visit programme. Using an inter-disciplinary team approach, the care management team comprised a MSW, nurse, occupational therapist, physician, physiotherapist and speech therapist. The nurse was designated care manager and served as the primary point of contact for the patient, and was also responsible for the coordination of care that includes nursing procedures, monitoring chronic diseases and educating patients (and their caregivers) on chronic disease management. Additionally, the team physician was a geriatrician. Patients were selected for the programme by the geriatrician based on their clinical, functional and social profile. The workflow of the TC programme is shown in Figure 1.

For our retrospective study, we included 695 patients who were eligible for TC between April 2012 and March 2014. They were sourced from the hospital's administrative records and TC nurses' assessment forms. Data on hospital utilisation and mortality were obtained from the Ministry of Health (MOH), Singapore. Patients who were readmitted or died within 7 days postdischarge were excluded from the study. Patients were visited at a mean of 7.8 days after discharge from the hospital.

The baseline period under study was defined as 180 days prior to hospitalisation and the follow-up period was defined as 180 days after discharge from hospital. The number of hospital admissions, ED visits and duration of inpatient stay were compared between patients who had accepted (TC group, n = 533) or declined (non-TC group, n = 162) TC at follow-up 180 days later.

Other outcome measures included cost and mortality. Differences in total cost of hospitalisation between the TC and non-TC groups at 180-day follow-up were compared. Mean cost savings for the patient, government and healthcare sector were also estimated. The cost analysis included TC and inpatient charges. All cost estimates were based on normative figures published by MOH in 2012/13.[11] The costs were determined based on the requirements outlined for each care service.[11] Inpatient cost savings were derived from duration of inpatient stay (in days) multiplied by mean daily inpatient cost. The total estimated cost savings were then calculated by deducting total TC costs from inpatient cost savings.

The independent variables were intervention and time. The covariates were activities of daily living (ADLs), age, Charlson Comorbidity Index (CCI), cognitive status, ethnicity, gender, duration of inpatient stay (in days), level of care, number of admissions during the baseline

period and ward class. Data were analysed using STATA version 12.0 (College Station, TX, USA). Student's t-test and chi-square test were used for continuous and binary variables, respectively. For count or continuous outcomes, the difference-in-difference (DID) approach was used to compare outcomes between the TC and non-TC groups. For binary outcomes, we used logistic regression analysis that included independent variables and covariates. A value of P <0.05 was considered statistically significant.

The study was approved by the Domain Specific Review Board of the National Healthcare Group, Singapore.

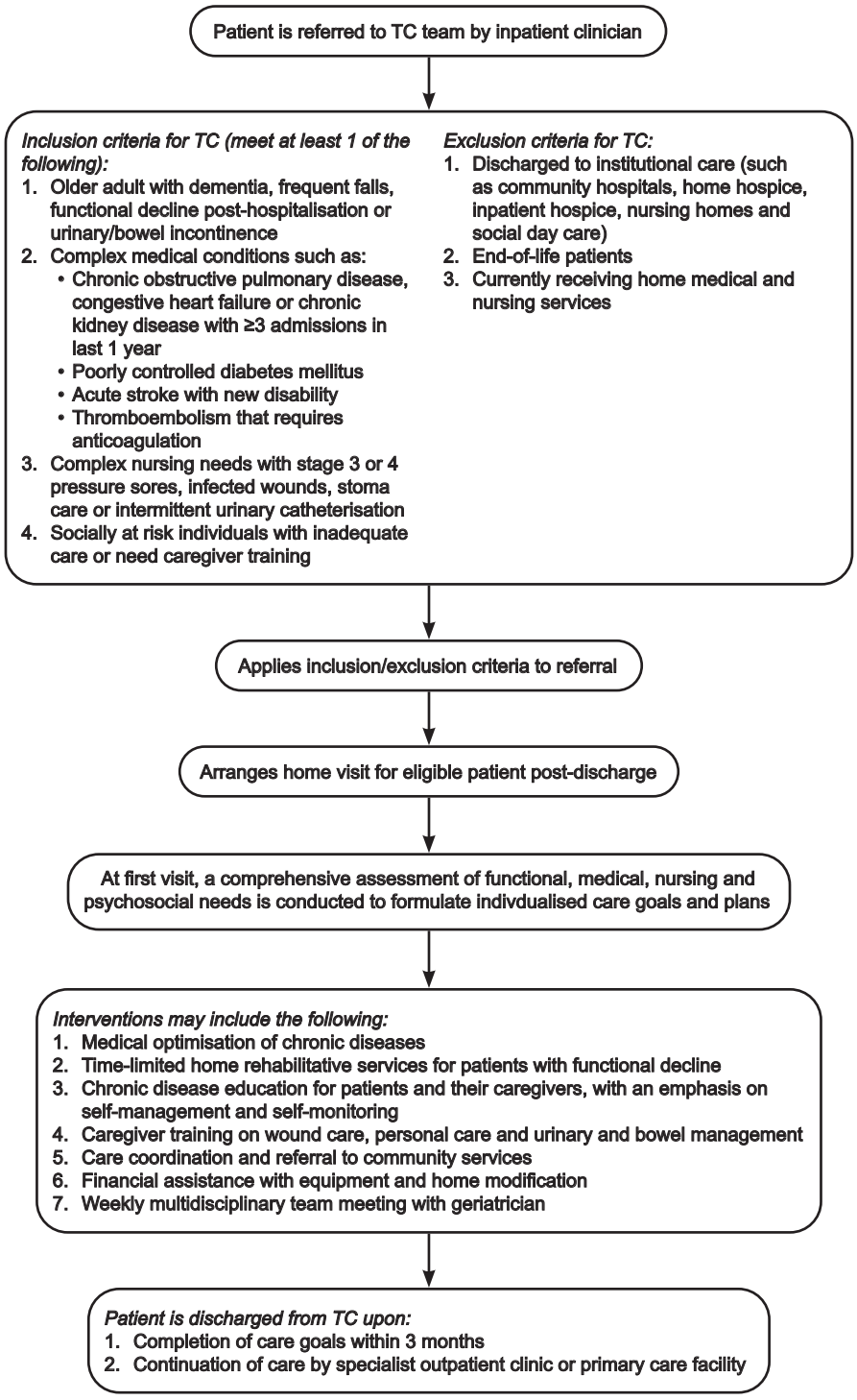

Fig. 1. Flow chart of TC programme. TC: Transitional care

Results

Patients in the TC group were older, required more assistance in their ADLs, received higher Medifund (a state endowment fund that helps needy patients to defray any outstanding healthcare charges after disbursement of subsidies and insurance payments) coverage and needed more intensive care (Table 1). At 180-day follow-up, they had 4.2 fewer days of inpatient stay (95% confidence interval [CI], −8.25– −0.14; P <0.05) than the non-TC group (Table 2). Though not statistically significant, the non-TC group had lower readmission rates (adjusted odds ratio [AOR], 0.82; 95% CI, 0.44–1.54) and mortality (AOR, 0.69; 95% CI, 0.45–1.07).

Table 1. Baseline Characteristics of Patients

Characteristic	TC Group (n = 533)	Non-TC Group (n = 162)	*P* Value
Age (mean ± SD, years)	81.9 ± 10.0	80.1 ± 12.0	0.046*
Gender (%)			0.579
Male	187 (35.1)	53 (32.7)	
Female	346 (64.9)	109 (67.3)	
Ethnicity (%)			0.882
Chinese	369 (69.2)	109 (67.3)	
Indian	43 (8.1)	16 (9.9)	
Malay	95 (17.8)	30 (18.5)	
Others	26 (4.9)	7 (4.3)	
CCI score (mean ± SD)	6.2 ± 2.2	6.0 ± 2.5	0.353
Ward class (%)‡			0.069
A	2.4	4.9	
B1	2.1	4.3	
C	53.5	58	
Non-resident	2.1	2.5	
Assisted ADLs (mean ± SD)§	2.4 ± 1.7	1.7 ± 1.7	<0.001†
Medifund (%)‖	12.4	0.6	<0.001†
Level of care (%)¶			0.04*
1	24 (4.5)	9 (5.6)	
2	258 (48.5)	94 (58.8)	
3	250 (47)	57 (35.6)	
Hospital utilisation (mean ± SD)			
Number of admissions	2.0 ± 1.4	2.3 ± 1.7	0.127
Number of ED visits	2.0 ± 1.5	2.0 ± 1.6	0.528
Inpatient stay (days)	16.0 ± 16.0	13.9 ± 11.9	0.122
Total inpatient stay (days)	24.7 ± 21.1	23.1 ± 18.8	0.383

ADLs: Activities of daily living; CCI: Charlson Comorbidity Index; ED: Emergency department; SD: Standard deviation; TC: Transitional care

*P <0.05.

†P <0.01.

‡Singaporeans are awarded subsidies depending on the class of ward they choose when they are hospitalised. For Class A ward, there is no subsidy. For Class B1 and Class C wards, the subsidies are pegged at 20% and 65–80%, respectively.

§ADLs include eating, mobility, shower/hygiene and toileting.

‖Medifund is a state endowment fund that was set up to defray any outstanding medical charges that are still incurred by needy patients after subsidies and insurance payments have been disbursed.

¶Patients were classified into 3 tiers of care based on their care needs: Level 1 patients were medically stable; Level 2 patients faced more complex medical and nursing issues; and Level 3 patients had chronic diseases and were prone to frequent exacerbations or had high functional needs.

Table 2. Hospital Admissions, ED Visits and Inpatient Stay at 180-Day Follow-Up

Variable	TC Group (n = 533)	Non-TC Group (n = 162)	Difference-in-Difference (95% Confidence Interval)		
			Unadjusted	Adjusted*	Sensitivity Analysis†
Number of hospital admissions (mean ± SD)	1.0 ± 1.4	1.2 ± 1.5	0.04 (−0.3 – 0.4)	0.03 (−0.3 – 0.4)	−0.01 (−0.34 – 0.33)
Number of ED visits (mean ± SD)	1.0 ± 1.3	1.0 ± 1.4	0.1 (−0.3 – 0.5)	0.1 (−0.2 – 0.5)	0.14 (−0.20 – 0.48)
Total inpatient stay (mean ± SD, days)	8.5 ± 14.9	11.0 ± 16.6	−4.1 (−8.6 – 0.5)	−4.2 (−8.3 – 0.1)‡	−3.41 (−6.40 – −0.42)‡

ED: Emergency department; SD: Standard deviation; TC: Transitional care

*Adjusted coefficients in the difference-in-difference analysis were used to account for intervention in TC patients. Generalised linear models with ordinary least squares regression analysis were used to adjust for age, Charlson Comorbidity Index, dementia, ethnicity, functional status, gender, inpatient stay at baseline, level of care and ward class.

†Sensitivity analysis was performed to exclude patients whose inpatient stay exceeded 60 days.

‡P <0.05.

At 180-day follow-up, the adjusted DID inpatient stay of 4.2 days translated into mean cost savings of S$2765 for every patient. The mean number of TC home visits was 4.5 for each patient, which included 1.8 (S$183/visit), 1.7 (S$344/visit) and 1 (S$252/visit) visit by the nurse, physician and therapist, respectively. However, the mean cost savings were offset by an increase in the take-up rate of the services offered by the TC programme which resulted in a mean cost of S$1166 for each patient. Nevertheless, it still resulted in mean cost savings of S$1599 for every participant.

Discussion

Our study has shown that a TC programme could reduce inpatient stay by 4.2 days at 180-day follow-up. Although most TC programmes were nurse-led, they adopted a collaborative model that involved a primary care physician.[8] In this programme, direct access by phone to the TC nurse for medical exacerbations and the presence of a geriatrician in the team had facilitated direct management of medical issues in the patients' own homes. The TC nurse also coordinated the delivery and provision of community services to participants for better continuity of care at home.[12] As such, the reduction in the number of hospital readmissions could be attributed to better access to these services and continuity of care. They also increase the likelihood of keeping older adults at home for longer periods.[13]

Although our study had demonstrated the efficacy of TC in reducing inpatient stay, it is possible that other factors may have contributed to this outcome such as earlier identification and management of the functional, medical and social problems faced by patients in their own homes and in the community. We also did not find a significant difference in the number of hospitalisations and readmissions despite a reduction in inpatient stay. Intermittent hospitalisations cannot be avoided in patients in the TC group since they had high morbidity with a CCI score of 6.2 and were at high risk for disease and symptom progression.

Various features were incorporated into the TC programme to meet the complex needs of older adults with multiple comorbidities. They included chronic disease counselling, medication management, caregiver training, nursing care and medical consultation with disease management.

Since the TC programme adopted a multidisciplinary approach, its delivery required the deployment of different resources and we therefore examined its impact on cost. Studies have shown that variability in the level and service of home medical and nursing care provided can have implications on the economic evaluation of the effectiveness of these resources.[14] Although the findings of most studies on the impact of TC on healthcare cost were inconclusive,[8,10] our study had estimated annual cost savings of S$1,119,300 (S$637,700 for patients and S$481,600 for the state) for 700 patients that accrued from a shorter inpatient stay.

Our study has a few limitations. The participants were not randomly assigned to either the TC or non-TC groups. Both groups also differed in their financial and functional status which could introduce bias. Nevertheless, the results were adjusted to account for the differences in their baseline characteristics and to exclude confounding factors. In our cost analysis, we were not able to include the costs of ED, specialist care, primary care and community support services as well as other indirect costs.

Since our TC programme had targeted a heterogeneous group of patients with complex medical issues and they were selected based on their clinical, functional and social profile by a geriatrician, this limits the generalisability of the findings in this study to other patient cohorts. It is possible that a simple tool could be developed to identify a homogeneous group of patients in terms of their care needs.[15] Future studies of the TC programme could be directed at a systematic segmentation of the study population to have a better understanding of their characteristics and needs, allocation of resources and delivery of services that can help to improve patient outcomes.

Conclusion

Our study showed that a multidisciplinary, nurse-led TC programme which targets patients with complex care needs could reduce inpatient stay and lead to cost savings. It also evaluated the real-world effectiveness of a TC programme in a heterogeneous group of patients who were stratified based on their care needs. However, more detailed studies that include better stratification of patient needs are needed to examine the impact of TC on cost, acute hospital utilisation and patient outcomes.

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REFERENCES

1. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med 2003;138:161–7.
2. Wong WC, Sahadevan S, Ding YY, Tan HN, Chan SP. Resource consumption in hospitalised, frail older patients. Ann Acad Med Singapore 2010;39:830–6.
3. Cua YM, Kripalani S. Medication use in the transition from hospital to home. Ann Acad Med Singapore 2008;37:136–41.
4. Wee SL, Loke CK, Liang C, Ganesan G, Wong LM, Cheah J. Effectiveness of a national transitional care program in reducing acute care use. J Am Geriatr Soc 2014;62:747–53.
5. Low LL, Vasanwala FF, Ng LB, Chen C, Lee KH, Tan SY. Effectiveness of a transitional home care program in reducing acute hospital utilization: a quasi-experimental study. BMC Health Serv Res 2015;15:100.
6. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc 2004;52:675–84.
7. Coleman EA, Boult C; American Geriatrics Society Health Care Systems Committee. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc 2003;51:556–7.
8. Bryant-Lukosius D, Carter N, Reid K, Donald F, Martin-Misener R, Kilpatrick K, et al. The clinical effectiveness and cost-effectiveness of clinical nurse specialist-led hospital to home transitional care: a systematic review. J Eval Clin Pract 2015;21:763–81.
9. Low LL, Tay WY, Tan SY, Chia EHS, Towle RM, Lee KH. Transitional Home Care Program Utilizing the Integrated Practice Unit Concept (THC-IPU): effectiveness in improving acute hospital utilization. Int J Integr Care 2017;17:5.
10. Le Berre M, Maimon G, Sourial N, Guériton M, Vedel I. Impact of transitional care services for chronically ill older patients: a systematic evidence review. J Am Geriatr Soc 2017;65:1597–608.
11. Ministry of Health, Singapore. Calculation of norm costs for long-term care expenditure. Available at: https://www.moh.gov.sg/news-highlights/details/calculation-of-norm-costs-for-long-term-care-expenditure. Accessed on 6 September 2019.
12. Lim SC, Doshi V, Castasus B, Lim JK, Mamun K. Factors causing delay in discharge of elderly patients in an acute care hospital. Ann Acad Med Singapore 2006;35:27–32.
13. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 2009;360:1418–28.
14. Ramos ML, Ferraz MB, Sesso R. Critical appraisal of published economic evaluations of home care for the elderly. Arch Gerontol Geriatr 2004;39:255–67.
15. Chong JL, Matchar DB. Benefits of population segmentation analysis for developing health policy to promote patient-centred care. Ann Acad Med Singapore 2017;46:287–9.

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Proximal Tibial Stress Fractures: A Diagnostic Challenge

Dear Editor,

Stress fractures are caused by repeated micro trauma to the bone over a period of time. It can happen in normal bone exposed to abnormal repetitive stress or in abnormal bone receiving normal stress. In healthy individuals, tibia stress fractures occur most frequently amongst athletes who participate in activities that involve prolonged walking, running or jumping.[1] The tibia shaft is most commonly affected, whereas the proximal tibia is less common.[2] Risk factors include excessive training, alteration in normal gait biomechanics such as tightness of calf muscles, unequal leg length, osteoporotic bone and vitamin D deficiency.[3,4] This type of fracture can be easily misdiagnosed due to its clinical presentation and location near the knee,[5,6] which can mimic medial-sided osteoarthritis, meniscal injuries and pes anserinus bursitis. We describe an atypical presentation of atraumatic proximal tibia stress fracture in a young healthy male with no known risk factors.

Case Report

The patient, a 40-year-old customer service officer, had presented to the Sports Medicine and Surgery Clinic with acute onset of left knee pain after running at work to assist a customer. He had, otherwise, been well with no known past medical history and had a body mass index of 23. There had been no trauma, fall or injury and no history of a sudden increase in physical activity. He also did not have a history of vitamin D deficiency and did not drink alcohol.

The pain, which was mostly at the medial joint line, became worse with activity. On clinical examination, the patient was able to ambulate independently and had left knee range of movement of 0–125. There was no knee effusion. He complained of medial-sided joint line tenderness on palpation. There was no ligamentous laxity.

Initial radiographs (Fig. 1) revealed no obvious fractures or radiolucent lines. The initial impression was an exacerbation of mild left knee osteoarthritis. He was prescribed a course of analgesia and physiotherapy.

He was seen 1 week later and continued to complain of left knee pain that affected ambulation. It was noted then that he had an antalgic gait with persistent medial joint line tenderness. In view of the persistent pain, magnetic resonance imaging (MRI) of the left knee was ordered to look for possible intra-articular pathology. MRI revealed a stress fracture of the medial proximal tibia (Fig. 2). There was no other concomitant intra-articular injury. The patient was subsequently kept non-weight-bearing (with crutches) and was referred to an orthopaedic surgeon. He was treated non-surgically with gradual escalation to weight-bearing status with follow-up radiographs. Repeat radiographs 3 months postinjury did not show further varus collapse (Fig. 3A). He did not experience any subsequent pain and returned to work successfully.

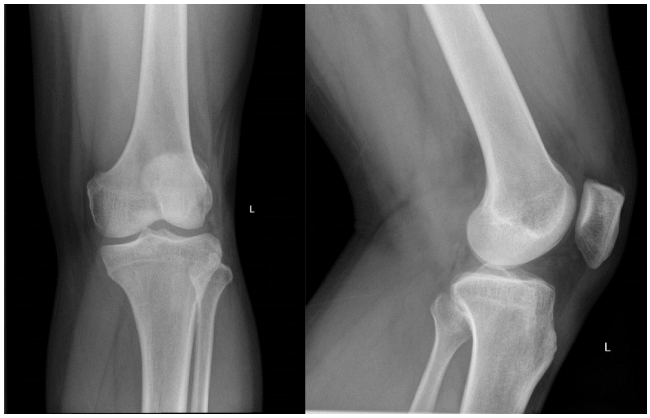

Fig. 1. Plain radiographs of the patient's left knee on initial presentation do not show any remarkable findings.

Discussion

Stress fractures of the tibia are one of the most common lower extremity stress fractures. The mid-tibial region is the most frequently involved area.[2] Proximal tibia stress fractures are less common and are usually associated with patients with significant coronal deformities.[7,8] However, this was an unlikely contributory factor in our patient as he had minimal arthritis and coronal malalignment as seen on the long leg film (Fig. 3B).

The clinical presentation of proximal tibial stress fractures can mimic other conditions in physical examination. There are few studies addressing this in the current literature, and there is a lack of proven clinical tests for the diagnosis of tibial stress fractures. While tests such as the tuning fork test (eliciting pain while placing an oscillating tuning fork over the fracture site), fulcrum test (eliciting pain while

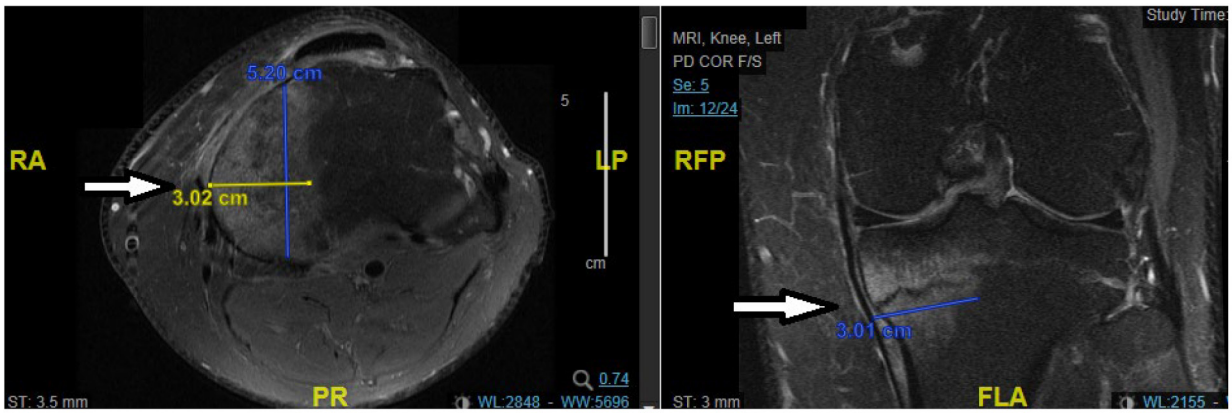

Fig. 2. T2-weighted sequence magnetic resonance images reveal stress fractures of the medial proximal tibia.

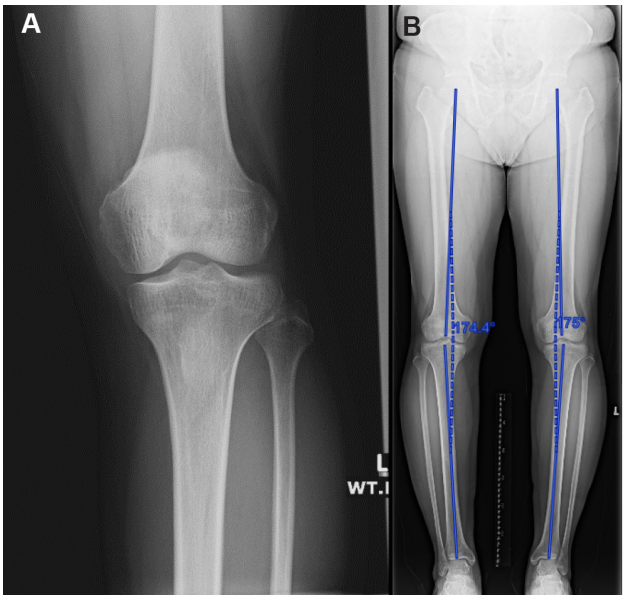

Fig. 3. Radiograph images. A: Anterior-posterior weight-bearing view of the left knee shows no further Varus collapse of the medial tibia plateau. B: Long leg film demonstrates alignment of the left lower limb.

applying a downward pressure over the fracture site using the examiner's arm as a fulcrum) and therapeutic ultrasound tests (eliciting pain while therapeutic ultrasound is applied over the fracture site) have been described, they lack adequate sensitivity or specificity to be relied upon for diagnosis.[9] It is generally recommended that clinicians have a high index of suspicion for the condition through a thorough history and examination, especially in patients that have persistent pain despite initial conservative treatment.

Early diagnosis of stress fractures is important for appropriate treatment and prevention of complications. Plain radiographs are often negative at the onset of symptoms and have a high rate of false-negatives. Compared to radiographs, MRI is a more sensitive and specific mode of evaluation of suspected stress fractures.[10] Bone scans are also highly sensitive for stress fractures. However, they are non-specific and can be mimicked by other conditions such as malignancy or infection.[11] Some studies have proposed guidelines to aid the clinician's assessment of suspected stress fractures.[10,12] However, these guidelines are dependent on the clinician having a clinical suspicion of stress fracture in the first place. This may not be helpful in the clinical setting as proximal tibial stress fractures may present in a similar manner as the more common conditions. Patients with an atypical presentation and who lack conventional risk factors for stress features can be potentially misdiagnosed. In our patient, MRI was ordered in view of persistent activity-related pain despite initial conservative treatment. Persistence or progression of activity-related pain is well documented in the literature as being suggestive of lower limb stress fracture.[13]

Classification systems for stress fractures such as Kaeding-Miller—which has high inter- and intra-observer reliability—can be used to guide treatment.[14] Treatment options for proximal tibia stress fractures can be surgical or non-surgical. Non-surgical management includes a period of offloading with gradual escalation to weight-bearing status. This may include the use of a cast or brace for immobilisation of the fracture site. Follow-up radiographs are recommended to look for complications including non-union, malunion or varus collapse of the tibial plateau that may require surgical intervention. While rare, late complications such as post-traumatic formation of osteoid osteoma have also been described in the literature.[15,16] Most patients treated conservatively can return to full activities at about 12 weeks.[17]

Conclusion

Proximal tibial stress fractures are relatively rare. Its clinical presentation may mimic other conditions leading to a delay in diagnosis. In the absence of obvious risk factors in the clinical evaluation, a stress fracture should be suspected in patients who have persistent or progressive activity-related lower limb pain despite initial conservative treatment. This can be used to guide decisions for further

imaging studies. In the absence of complications on follow-up, gradual escalation to weight-bearing status and activity modification are usually successful.

REFERENCES

1. Feldman JJ, Bowman EN, Phillips BB, Weinlein JC. Tibial stress fractures in athletes. Orthop Clin North Am 2016;47:733–41.
2. Behrens SB, Deren ME, Matson A, Fadale PD, Monchik KO. Stress fractures of the pelvis and legs in athletes: a review. Sports Health 2013;5:165–74.
3. Becker J, Nakajima M, Wu WFW. Factors contributing to medial tibial stress syndrome in runners: a prospective study. Med Sci Sports Exerc 2018;50:2092–100.
4. Kahanov L, Eberman L, Games K, Wasik M. Diagnosis, treatment and rehabilitation of stress fractures in the lower extremity in runners. Open Access J Sports Med 2015;6:87–95.
5. Yukata K, Yamanaka I, Ueda Y, Nakai S, Ogasa H, Oishi Y, et al. Medial tibial plateau morphology and stress fracture location: a magnetic resonance imaging study. World J Orthop 2017;8:484–90.
6. Vossinakis IC, Tasker TP. Stress fracture of the medial tibial condyle. Knee 2000;7:187–90.
7. Soundarrajan D, Rajkumar N, Dhanasekararaja P, Rajasekaran S. Proximal tibia stress fracture with osteoarthritis of knee – radiological and functional analysis of one stage TKA with long stem. SICOT J 2018;4:13.
8. Kahanov L, Eberman LE, Games KE, Wasik M. Diagnosis, treatment and rehabilitation of stress fractures in the lower extremity in runners. Open Access J Sports Med 2015;6:87–95.
9. Schneiders AG, Sullivan SJ, Hendrick PA, Hones BD, McMaster AR, Sugden BA, et al. The ability of clinical tests to diagnose stress fractures: a systematic review and meta-analysis. J Orthop Sports Phys Ther 2012;42:760–71.
10. Wright AA, Hegedus EJ, Lenchik L, Kuhn KJ, Santiago L, Smoliga JM. Diagnostic accuracy of various imaging modalities for suspected lower extremity stress fractures: a systematic review with evidence-based recommendations for clinical practice. Am J Sports Med 2016;44:255–63.
11. Moran DS, Evans RK, Hadad E. Imaging of lower extremity stress fracture injuries. Sports Med 2008;38:345–56.
12. Nye NS, Covey CJ, Sheldon L, Webber B, Pawlak M, Boden B, et al. Improving diagnostic accuracy and efficiency of suspected bone stress injuries. Sports Health 2016;8:278–83.
13. Shindle MK, Endo Y, Warren RF, Lane JM, Helfet DL, Schwartz EN, et al. Stress fractures about the tibia, foot and ankle. J Am Acad Orthop Surg 2012;20:167–76.
14. Kaeding CC, Miller TL. The comprehensive description of stress fractures: a new classification system. J Bone Joint Surg Am 2013;95:1214–20.
15. Soon M, Low CK, Chew J. Osteoid osteoma after a stress fracture of the tibia: a case report. Ann Acad Med Singapore 1999;28:877–8.
16. Riley ND, Camilleri D, McNally MA. Osteoid osteoma following fracture of the distal tibia: a case report and literature review. Injury Extra 2014;45:69–72.
17. Robertson GA, Wood AM. Return to sports after stress fractures of the tibial diaphysis: a systematic review. Br Med Bull 2015;114:95–111.

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Primary Angiosarcoma Masquerading as Scalp Haematoma After Head Injury

Dear Editor,

Angiosarcomas are extremely uncommon, making up <1% of all sarcomas.[1] Specifically, the scalp accounts for approximately 50% of all angiosarcoma cases, yet this comprises a mere 0.1% of all head and neck malignancies.[2] Delayed diagnosis often occurs due to difficulty in recognising this rare tumour.[3] Presumably, due to the location preference of this neoplasm, it has been previously shown that minor head trauma may sometimes alert the patient to the presence of a lesion.[4] We report a case of an elderly male who presented with what was presumed to be a scalp haematoma after a minor head injury. Given the rarity of this condition, the case is discussed in corroboration with current literature and management strategies.

Case Report

A previously well 76-year-old male presented to the neurosurgery outpatient clinic with a painless right parietal scalp lump. The patient described a history of persistent scalp swelling after minor trauma to his head approximately a month earlier. He had knocked his head against the edge of an overhead cupboard while at work. There had been some bleeding at the time of accident but this had resolved spontaneously. At the beginning, he visited his local polyclinic a few times. The patient was informed that he had an infected scalp haematoma. A trial of oral antibiotics and local dressings were prescribed but the swelling did not resolve. A decision was then made by his primary care physician to refer him to a specialist.

Clinical examination demonstrated a single, well circumscribed 3 cm raised scalp lesion that was mildly tender and centrally fluctuant. The nodular lesion had shiny and indurated edges. The edges also showed an underlying bluish tinge under close examination. Hair was observed on the dark-coloured surface of the lesion. There was no active discharge or bleeding from the lesion. There were no constitutional symptoms and the rest of the patient's system review was otherwise unremarkable. A postcontrast computed tomography (CT) scan of the head reported a non-enhancing, soft tissue mass at the high right parietal scalp region measuring about 2.8 × 2.1 cm. There was no significant surrounding fat stranding. The deep aspect of the lesion was noted to abut the underlying parietal bone but there was no radiological evidence of bony erosion or remodelling. The Hounsfield unit of the scalp lesion was 44 on both pre- and postcontrast CT images. This confirmed that the lesion had no or minimal contrast uptake (Fig. 1).

Decision was made for an incision biopsy of the lesion (Fig. 2). Histopathology showed a tumour consisting of pleomorphic spindle and epithelioid cells with mitotic activity. Immunohistochemical stain was positive for CD31, FLI-1 and ERG; and negative for AE1/3, p40, S100 and HMB45. The final report was that of angiosarcoma. As a result of the diagnosis, the patient underwent extensive staging investigations. The investigations demonstrated no radiological evidence of metastases.

The patient underwent en-bloc resection of the lesion with a generous 4 cm margin and an outer table craniectomy underlying the lesion. Intraoperative frozen section biopsies taken around the resection margins showed these to be tumour-free. An omental free flap was harvested laparoscopically and was used to cover the resultant 25 × 14 cm scalp defect. This flap was successfully anastomosed with the superficial temporal artery and vein. A split-thickness skin graft was

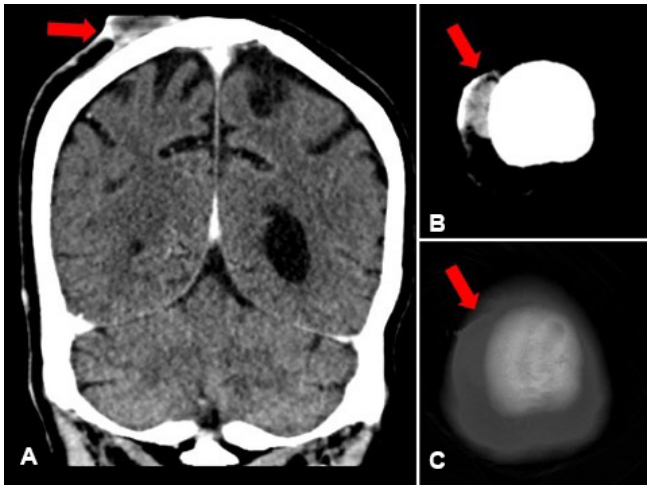

Fig. 1. Computed tomography (CT) images of the brain. A and B: Postcontrast images of the extracranial, soft-tissue mass in right high parietal scalp region in coronal (A) and axial (B) views, respectively. C: Axial bone window view that corresponds to B shows no radiological evidence of bony involvement under the extracranial, soft-tissue scalp mass.

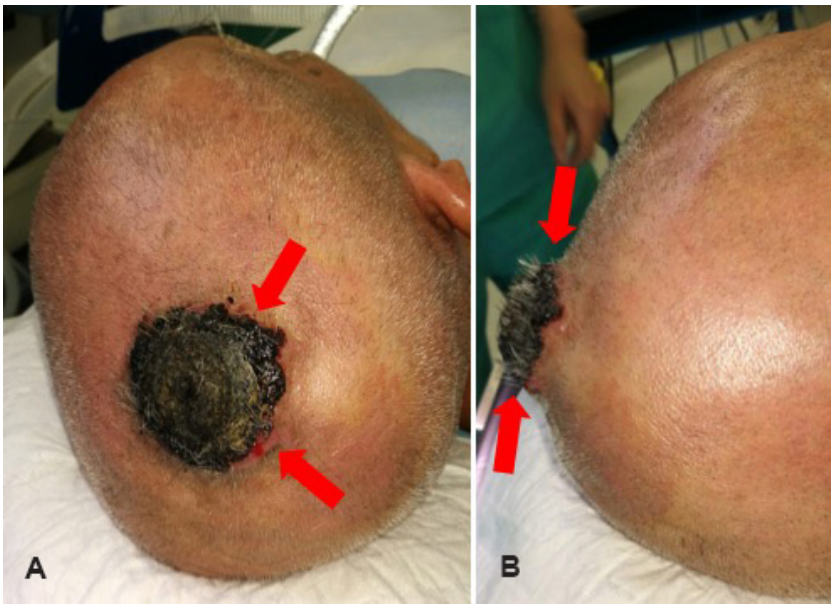

Fig. 2. Intraoperative photographs of the right parietal scalp mass showing the top (A) and side (B) views. The patient's scalp had been shaved. A broad-based and raised soft-tissue lesion with hair on its surface can be seen. There is evidence of induration at the scalp-lesion interface. No active bleeding was noted from the lesion.

harvested from the thigh and subsequently grafted onto the omental flap. Final histopathology concurred with the previous diagnosis of angiosarcoma (Fig. 3). In addition, the surgical margins were reported to be tumour-free.

Postoperatively, the patient's recovery was uneventful. Approximately 2 months after his surgery, he commenced radiation therapy. However, 1 month into his treatment, the patient developed type 1 respiratory failure. An urgent CT thorax reported multiple lung nodules within the parenchyma of both lungs. Some of the nodules were cavitating in nature. There was also bilateral hydropneumothoraces associated with pleural nodularity. Putting it all together, the working diagnosis was lung metastases. Attempts were made at draining the associated malignant pleural effusions but the fluid kept re-accumulating. Decision was made for commencement of chemotherapy once the patient was clinically more stable. However, the patient continued to deteriorate rapidly and eventually succumbed about 18 weeks following his en-bloc excision surgery.

Discussion

Angiosarcoma is an infrequent but aggressive disease that portends a poor prognosis. The aggressive lesions arise from vascular endothelial cells and tend to grow along pre-existing vascular channels, sinusoidal or cavernous spaces; often forming poorly organised vessels, solid masses or nodules.[5]

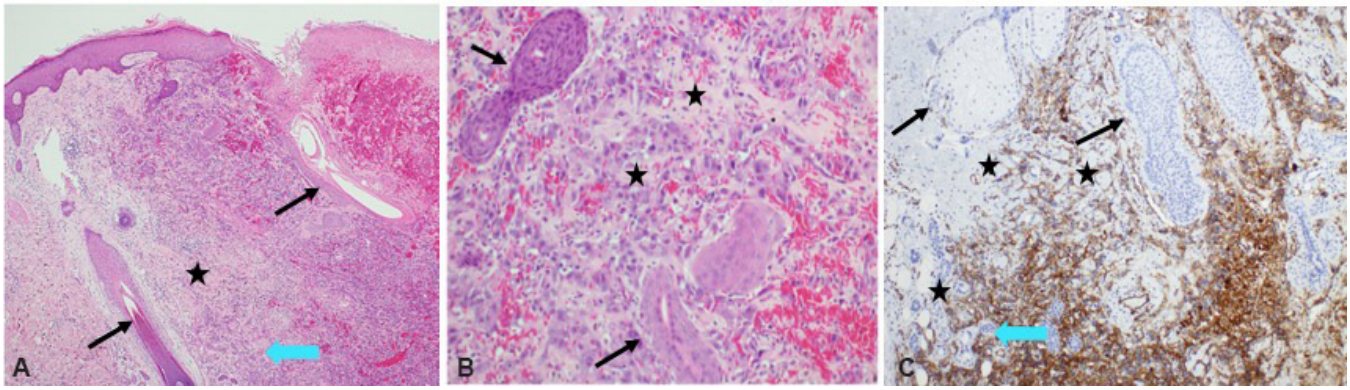

Fig. 3. A: Low-power view of the skin of the scalp reveals a cellular tumour associated with ulceration and haemorrhage. The tumour infiltrated around the skin adnexal structures, which were hair follicles (black arrows) and sweat glands (blue arrows) (haematoxylin and eosin [H & E] stain, × 40). B: The tumour consisted of pleomorphic spindle and epithelioid cells forming vascular structures and dissecting between dermal collagen bundles. Asterisks denote representative dermal collagen fibres where the tumour was dissecting between them (H & E stain, × 200). C: Immunohistochemical stain of the vascular marker CD31 showed tumour cells infiltrating around skin adnexal structures and dissecting between dermal collagen bundles (H & E stain, × 100).

Men have a higher risk of this disease than women (ratio, 1.7:1).[6] Established risk factors for this tumour include previous exposure to chemical toxins (such as vinyl chloride and arsenic), chronic lymphoedema,[7] radiation exposure and certain rare genetic syndromes.[1] Common differential mimics—which may lead to delayed diagnosis—include skin ecchymoses, capillary haemangioma, rosacea, eczema, cellulitis and angioedema.[2,3,6] The condition has also been reported to be only noticed after what was thought to be a minor skin injury of the scalp.[2,4] Patients may present with skin lesions such as a bruise, discoloured nodule or persistent ulceration.[2] Another reason for the initial difficulty in early diagnosis is that primary cancers of the scalp are extremely rare.[8] They can present as ecchymosis-like plaques, associated with haemorrhage, oedema and ulceration.[9] Amongst the imaging modalities for malignant skin neoplasms, CT is the most readily available and least costly.[10] It is able to delineate tumour extent and staging. On contrast-enhanced CT, soft tissue angiosarcoma may manifest as an irregular, enhancing soft tissue mass. In more advanced cases, underlying bone or adjacent solid organ invasion may be present.[2,11] However, this was not the case for our patient; hence, getting the correct initial diagnosis was challenging.

An estimated 20–30% of affected patients present with metastatic disease, and about 50% of patients with primary tumours will develop early interval metastases.[6] The usual sites for metastases—in decreasing order of incidence—include the lungs, bone and liver.[6,12] As a rule of thumb, radical surgery aims to reduce tumour burden. Nonetheless, surgery is unable to target "subclinical" micro-metastases, which could have occurred by the time of diagnosis.[13] These lesions may be too small to be picked up by conventional imaging techniques. Generally, angiosarcoma has a poor overall survival range of between 6–16 months.[1,2] Despite best efforts, the majority of patients succumb to disease recurrence or metastases. For our patient, it was unusual that he developed metastases close to the completion of his radiotherapy. However, given the aggressive nature of his primary tumour, it is not unexpected that such an event is likely to occur.

In addition, histopathological factors associated with worsening prognosis that include the presence of epitheloid morphology and necrosis[6,14,15] were unfortunately observed in our patient. These factors have been demonstrated in clinical studies focusing on stratification markers in cutaneous angiosarcoma.[14,16] However, there is currently no effective targeted therapy for these tumours.

The current standard of care for patients with localised angiosarcoma is wide surgical resection with histopathologically clear margins, followed by adjuvant radiotherapy.[6,17,18] This may be technically challenging as the tumour tends to be widely infiltrative beneath the skin leading to difficulty in obtaining negative margins.[1] Although there are no clear guidelines on the specific width of the surgical margins in localised angiosarcoma, widths of ≥3 cm have been recommended for both radial and deep margins.[6] Generally speaking, if the tumour is localised and operative margins are free of malignant cells, the disease can be considered curative. Conversely, if the patient has recurrent and/or metastatic disease, treatment is difficult as there remains a lack of effective chemotherapeutic and/or targeted therapy. At present, we are aware that primary angiosarcomas are genetically complex. They are reputed to have gene mutations such as *TP53*, *KRAS PTPRB* and *PLCG1* involving various oncogenic pathways.[19] To complicate matters in this rare tumour, studies have shown that primary and secondary angiosarcomas possess different molecular profiles.[6] In comparison to other cancers, the delineation of biological subtypes for angiosarcomas is still unclear at this stage. Owing to current limited adjuvant options, there is thus a global need for urgent preclinical research to elucidate the pathogenesis of this deadly tumour. Radical excision of the tumour with clear margins remains as the mainstay of curative treatment.

Conclusion

We have, in this article, looked into a case of a primary scalp angiosarcoma in a 76-year-old male who presented with what was presumed to be a scalp haematoma secondary to minor head trauma. This case strongly emphasises the need for clinicians to consider angiosarcoma as a differential diagnosis when encountering scalp lesions in the elderly, especially in the primary care setting. Early intervention is a key priority in managing this malignant disease. In addition, we advocate for more in-depth molecular studies. For patients, we recommend that they attain a better understanding and insight of the disease.

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REFERENCES

1. Florou V, Wilky BA. Current and future directions for angiosarcoma therapy. Curr Treat Options Oncol 2018;19:14.
2. Gaballah AH, Jensen CT, Palmquist S, Pickhardt PJ, Duran A, Broering G, et al. Angiosarcoma: clinical and imaging features from head to toe. Br J Radiol 2017;90:20170039.
3. Patel SH, Hayden RE, Hinni ML, Wong WW, Foote RL, Milani S, et al. Angiosarcoma of the scalp and face: the Mayo Clinic experience. JAMA Otolaryngol Head Neck Surg 2015;141:335–40.
4. Gupta MD, Chakrabarti N, Agrawal P, Narurkar S. Angiosarcoma of the scalp. Indian J Plast Surg 2009;42:118–21.
5. Lahat G, Dhuka AR, Hallevi H, Xiao L, Zou C, Smith KD, et al. Angiosarcoma: clinical and molecular insights. Ann Surg 2010;251:1098–106.
6. Shustef E, Kazlouskaya V, Prieto VG, Ivan D, Aung PP. Cutaneous angiosarcoma: a current update. J Clin Pathol 2017;70:917–25.
7. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema; a report of six cases in elephantiasis chirurgica. Cancer 1948;1:64–81.
8. Fong PH, Lee ST, Lim Tan SK. Primary scalp cancer in Singapore. Ann Acad Med Singapore 1986;15:67–70.
9. Tan SM, Tay YK, Liu TT, Mancer K. Cutaneous angiosarcoma associated with the Kasabach-Merritt syndrome. Ann Acad Med Singapore 2010;39:941–2.
10. Juan YH, Saboo SS, Tirumani SH, Khandelwal A, Shinagare AB, Ramaiya N, et al. Malignant skin and subcutaneous neoplasms in adults: multimodality imaging with CT, MRI and 18F-FDG PET/CT. AJR Am J Roentgenol 2014;202:W422–38.
11. Razek AA, Huang BY. Soft tissue tumors of the head and neck: imaging-based review of the WHO classification. Radiographics 2011;31:1923–54.
12. Ong BH, Lee ST. A case of angiosarcoma of the scalp. Ann Acad Med Singapore 1980;9:385–9.
13. Fujisawa Y, Yoshino K, Fujimura T, Nakamura Y, Okiyama N, Ishitsuka Y, et al. Cutaneous angiosarcoma: the possibility of new treatment options especially for patients with large primary tumor. Front Oncol 2018;8:46.
14. Buehler D, Rice SR, Moody JS, Rush P, Hafez GR, Attia S, et al. Angiosarcoma outcomes and prognostic factors: a 25-year single institution experience. Am J Clin Oncol 2014;37:473–9.
15. Fayette J, Martin E, Piperno-Neumann S, Le Cesne A, Robert C, Bonvalot S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol 2007;18:2030–6.
16. Deyrup AT, McKenney JK, Tighiouart M, Folpe AL, Weiss SW. Sporadic cutaneous angiosarcomas: a proposal for risk stratification based on 69 cases. Am J Surg Pathol 2008;32:72–7.
17. Pawlik TM, Paulino AF, McGinn CJ, Baker LH, Cohen DS, Morris JS, et al. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer 2003;98:1716–26.
18. Mark RJ, Poen JC, Tran LM, Fu YS, Juillard GF. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer 1996;77:2400–6.
19. Murali R, Chandramohan R, Moller I, Scholz SL, Berger M, Huberman K, et al. Targeted massively parallel sequencing of angiosarcomas reveals frequent activation of the mitogen activated protein kinase pathway. Oncotarget 2015;6:36041-52.

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