ANNALS
ACADEMY OF MEDICINE, SINGAPORE
COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

VOLUME 48 | NUMBER 1 | FREE PAPERS | JANUARY 2019 MCI (P) 104/07/2017

"The important thing is not to stop questioning. Curiosity has its own reason for existing."

Albert Einstein (1879-1955)
German physicist

Reproduced with permission from:
Anonymous

Please see inside Contents for the full list of articles.

Annals, Academy of Medicine, Singapore **Vol. 48 No. 1 January 2019**

Free Papers

Images in Medicine

Acknowledgements

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

The Lee Foundation

*****

Forthcoming Issues

Vol 48 No. 2, February 2019 – Free Papers
Vol 48 No. 3, March 2019 – Free Papers

* * * * *

General Information

* * * * *

For all enquiries, please contact the Annals Editorial Office at: Annals, Academy of Medicine, Singapore, 81 Kim Keat Road, #11-00 & 12-00, NKF Centre, Singapore 328836. Email: annals@ams.edu.sg; Homepage: http://www.annals.edu.sg

Online submission: http://www.annals.edu.sg/OnlineManuscript/

Editorial

Deep Learning in Medicine. Are We Ready?

Daniel SW Ting, [1,2]*MD, PhD*, Tyler H Rim,[3]*MD, MBA*, Yoon Seong Choi, [4]*MD, PhD*, Joseph R Ledsam, [5]*MBChB*

The real-world application of artificial intelligence (AI), machine learning (ML) and deep learning (DL), have generated significant interest throughout the computer science and medical communities in recent years. This interest has been accompanied by no small amount of hype. Though the term 'ML' was coined 50 years ago by Arthur Samuel, who stated that machines should have the ability to learn without being programmed,[1] the advent of the graphics processing unit (GPU) has enabled much improved processing power and enabled new possibilities with AI. DL—an approach that utilises multiple neural networks to learn representation of data using multiple levels of abstraction[2]—has revolutionised the computer vision field, and achieved substantial jumps in diagnostic performance for image recognition, speech recognition, and natural language processing.[2] In the technical world, DL has been heavily used in autonomous vehicles,[3] gaming[4,5] and numerous smart phone applications. The availability of different software (e.g. Caffe, Tensorflow), and the off-the-shelf convolutional neural networks (e.g. AlexNet, VGGNet, ResNet and GoogleNet) have removed barriers to entry for many academics and clinicians, resulting in the recent surge of interest within the medical settings. To date, this technique has shown promising diagnostic performance, across specialties including ophthalmology (e.g. detection of diabetic retinopathy [DR], glaucoma and age-related macular degeneration from fundus photographs and optical coherence tomographs),[6-11] radiology (e.g. detection of tuberculosis from chest X-rays [CXRs], intracranial haemorrhage from computed tomography of the brain),[12-15] and dermatology (e.g. detection of malignant melanoma from skin photographs).[16]

DL is a tool that can, when applied effectively, serve multiple roles in different medical settings. Examples of this include screening, triaging referral urgency, prognosticating and monitoring diseases progression. In order to increase the explainability of the outcome, many of the more recent DL systems experiment with attempts to visualise the decision process. Examples include demonstrating disease activities via heat maps,[10] and displaying pathological features with image segmentation. With such abilities, this may help to increase the DL systems' adoption rate by physicians and their acceptability by patients.

In ophthalmology, one of the most promising areas is DR screening. Globally, 600 million people will have diabetes by 2040; a third will develop DR.[17] Given the increasing prevalence of diabetes and ageing population, DR screening programmes are constantly challenged by issues related to implementation, availability of human assessors and long-term financial sustainability.[18] In order to rectify the manpower shortage, DL systems can be an alternative DR screening tool. In 2016, both Gulshan et al and Abramoff et al reported excellent diagnostic performances of the DL systems in detecting referable DR using publicly available datasets, with area under the receivers' operating curves (ROCs) (AUC) of >0.95 in both studies.[8,19] Ting and co-workers have also developed and tested a DL system for identifying DR, and related eye diseases using nearly half a million images from multiethnic community, population-based and clinical datasets.[7] Consistent with the minimum screening performance (sensitivity of at least 80%) set by the Diabetes United Kingdom,[20] the diagnostic performance of this DL system was clinically acceptable with AUC of >90%, sensitivity of >90% and specificities >85% for referable DR, vision-threatening DR, glaucoma suspect and age-related macular degeneration. More importantly, this DL system was also tested on 10 external datasets, consisting of multiple ethnicities and settings (by patients' demographics and glycaemic control, status of pupil dilation, retinal cameras and width of field for retinal images), using diverse reference standards in DR assessment by professional graders, optometrists or retinal specialists. In order to ensure generalisability, it is always important to test a DL system on previously unseen datasets. A similar

[1]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore
[2]Duke-NUS Medical School, National University of Singapore, Singapore
[3]Department of Ophthalmology, Institute of Vision Research, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Radiology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[5]DeepMind, London, United Kingdom
Address for Correspondence: Asst/Prof Daniel Ting Shu Wei, Singapore Eye Research Institute, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751.
Email: daniel.ting.s.w@singhealth.com.sg

example was demonstrated by Abramoff et al in a recent United States Food and Drug Administration (US FDA)-approved autonomous DR detection software – IDx, which was tested in prospective clinical trials in the US.[21] Thus, DL systems for DR can potentially be deployed in the countries with and without existing DR screening programmes, as semi-automated or fully-automated models, with the aim to prevent DR-related visual impairment for the global population with diabetes worldwide.

Skin cancer is another major public health concern.[22] In the US, it is estimated that approximately 9000 people are dying from melanoma each year, with $3.3 billion of skin cancer treatment costs attributable to skin melanoma.[23] Given the shortage of dermatologists, a DL system may be an alternative solution for this. Esteva et al reported a robust, dermatologist-level comparable DL system for detection of skin cancer.[16] Using a dataset of 129,450 clinical images with 2032 different diseases, this DL system was tested against 21 board-certified dermatologists on biopsy-proven clinical images (photographic and dermoscopic images) for 2 groups – keratinocyte carcinomas (the most common cancer) versus benign seborrhoeic keratosis; and malignant melanomas (the deadliest skin cancer) versus benign nevi. This DL system showed on par diagnostic performance with all tested dermatologists, with AUC of >0.90 for keratinocyte carcinoma (skin photographs) and melanoma (skin photographs and dermoscopic images). Future research is beneficial to assess the cost-effectiveness of this DL system for patients with skin lesions.

Pulmonary tuberculosis (TB) is an infectious disease that poses a significant public health problem, causing 1.5 million deaths worldwide in 2013.[24] CXRs play an important role in screening and diagnosis of pulmonary TB, but their interpretation requires radiological expertise and is resource-intensive, particularly in developing countries. As such, there has been interest in the development of effective automated DL methods for detection and diagnosis of pulmonary TB from CXRs. Both Lakhani et al and Hwang et al have reported good diagnostic performance in using DL systems for detection of TB.[12,13] Using AlexNet and GoogLeNet, Lakhani and co-worker reported an AUC of 0.99 in detection of TB in a dataset consisting of approximately 1000 CXRs.[12] The testing dataset for this study, however, may be underpowered.[25] Using a much larger sample size (approximately 60,000 CXRs), Hwang et al, recently, also reported a robust DL system to detect TB (AUC = 0.988), with the ability to localise abnormal lesions (AUC = 0.977). The reference standard consists of 15 readers—5 non-radiology physicians, 5 general radiologists and 5 thoracic radiologists. This robust performance, again, showed consistency in 6 external datasets (4 Korean datasets, 1 US dataset, and 1 Chinese dataset), with AUC of >0.97. This study is a good example to emphasise the importance of having multiple reference standards, independent datasets and the ability to localise the disease activity areas. The algorithm published in this paper can be tested via the website, https://insight.lunit.io/.

Aside from screening, the DL system has been reported to be a robust tool to triage the urgency of referrals to the tertiary healthcare settings. Earlier this year, DeepMind and Moorfields Eye Hospital delineated 15 different retinal morphologic features from retinal optical coherence tomography scans, using a 2-stage convolutional neural network (CNN) architecture consisting of separate segmentation and classification networks. This DL system has excellent ability (AUC >0.90) to make a referral triage decision from 4 categories (urgent, semi-urgent, routine, observation), and classifies the presence of 10 different retinal diseases.[26] This DL system may be a useful clinical tool to be implemented in the rapid access "virtual" clinics that are now widely used for triaging of macular disease in the United Kingdom.[27]

In this issue, a review by Liew et al describes the role of AI in radiology with a focus on the Singapore setting.[28] AI expands beyond helping or substituting human work, to extracting quantitative information for clinical decision-making and prognosis prediction; the authors provide a comprehensive commentary of the willingness of local radiologists to work together and collaborate with key stakeholders within the context of our "smart nation". This timely review and its declaration of intention to embrace the science and implementation of new tools is a laudable first step, and should perhaps also be expanded to take into account other promising techniques being added to the toolkit of diagnostic imaging to contribute to precision medicine. In radiology, an emerging technique is the so-called "radiomics", where high-dimensional numeric information is extracted from the medical image and put into ML to non-invasively predict relevant clinical information. For example, glioma (the most common primary tumour) and glioblastoma (a grade IV glioma and the most malignant glioma), have poor prognosis with median survival of only 18 months, making early correct diagnosis and prognosis prediction important. It has been reported that radiomics showed excellent performance (AUC >0.90) in preoperatively differentiating confusing cases of glioblastoma and primary central nervous system lymphoma (PCNSL) which may show similar magnetic resonance imaging (MRI) findings but have different treatment strategies.[29] Bae et al reported that radiomics can improve prognosis of glioblastoma beyond the established prognostic factors including clinical and molecular subtype information. In this study, when radiomics models were trained with MRI-based radiomic features using random

survival forest on training cohort (n = 163) and integrated into clinical and molecular information, the prognostication improved (integrated area under the time-dependent ROC curve showed improved performance on the test set [n = 54], integrated area under the time-dependent ROC curve, 0.696 vs 0.782, $P = 0.04$) for overall survival prediction.[30] Radiomics is recently evolving from extracting handcrafted features based on specific equations, to automatically extract and train the algorithm by CNN. Chang et al reported that residual network can predict isocitrate dehydrogenase in grade II to IV gliomas, a major molecular subtype for treatment response and prognosis.[31] In this study, multiplanar preoperative MR images were put into the 34-layer residual network and trained, validated and tested on a total of 496 multicentre patients, yielding excellent performance (AUC = 0.94, accuracy = 95.7%).

DL methods may be employed to predict features and pathologies beyond those conventionally used in clinical practice. Poplin et al recently reported an interesting DL system used to predict cardiovascular risk factors (e.g. age, gender, blood pressure) from fundus photographs.[32,33] Along with convolutional neural network, the recurrent neural network can be applied for natural language processing, analysing the longitudinal medical record to predict in-hospital mortality, 30-day unplanned readmission, prolonged length of stay, and all of a patient's final discharge diagnoses.[34]

Although DL systems have been reported to have robust performances in different clinical settings, many limitations still exist in the literature in terms of safe integration into practice. For example, there have been many studies investigating plain film X-ray, but most are limited to a binary classification between normal and one disease or grade in a certain disease. Where studies investigate larger numbers of disease classes, reported accuracy tends to be lower.[35] The imageability (also known as gradability) also remains as a challenging aspect in any DL system. Most studies have trained and validated with good quality photographs, yielding robust diagnostic performance (AUC >0.90). One given algorithm can yield variable performance, depending on the quality of input data. For example, MRI can vary according to the scan protocol or vendor manufacturer (e.g. 1.5T vs 3T, or Philips vs Siemens), thus affecting the performance. One also needs to be mindful about the concept of "garbage in and garbage out". In other words, even in the most robust convolutional neural network, the accuracy of the teaching datasets ground truth is perhaps the most important consideration in a study. To assure reproducibility and generalisability, larger training sample size, validation on more variable study cohort, and sharing details and even codes of preprocessing and training algorithm are mandatory.[10] As such, the radiomic quality score (RQS) system has been published to measure the quality of radiomics study, allowing the description of the details of image processing pipeline, training algorithms, the characteristics, and inclusion/exclusion criteria of the study cohort.[36]

In summary, AI using DL is a promising novel state-of-art technology for the medical world. And it is crucial that we, as a community, ensure a robust training datasets with reliable ground truths and to test the implementation of these models in clinical practice. The formation of the Radiological AI, Data Science and Imaging Informatics (RADII) under the Singapore Radiological Society is a good platform to gather all stakeholders from the clinical and ML community.[28] Although there are still many challenges that need to be solved prior to the mass AI adoption in healthcare, it is important for physicians to collaborate widely,[37] aiming to improve the work efficiency and the access to tertiary health, from Singapore, and potentially to the global setting.

Acknowledgement

Financial Disclosure: Dr Daniel Ting is the co-inventor of a deep learning system for retinal diseases, the co-founder and shareholder of EyRIS Ptd Ltd, Singapore. Dr Tyler Rim is a shareholder of Mediwhale, Korea. Dr Joseph Ledsam is a clinician scientist and employee of DeepMind, UK.

REFERENCES

1. Samuel AL. Some Studies in Machine Learning using the Game of Checkers. In: Computer Games. New York: Springer;1988. p. 335-65.
2. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature 2015;521:436-44.
3. Chen C, Seff A, Kornhauser A, Xiao J. DeepDriving: Learning Affordance for Direct Perception in Autonomous Driving. Proceedings of the IEEE International Conference on Computer Vision (ICCV) 2015. p. 2722-30.
4. Silver D, Huang A, Maddison CJ, Guez A, Sifre L, van den Driessche G, et al. Mastering the game of Go with deep neural networks and tree search. Nature 2016;529:484-9.
5. Silver D, Schrittwieser J, Simonyan K, Antonoglou I, Huang A, Guez A, et al. Mastering the game of Go without human knowledge. Nature 2017;550:354-9.
6. Ting DSW, Liu Y, Burlina P, Xu X, Bressler NM, Wong TY. AI for medical imaging goes deep. Nat Med 2018;24:539-40.
7. Ting DSW, Cheung CY, Lim G, Tan GSW, Quang ND, Gan A, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA 2017;318:2211-23.
8. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA 2016;316:2402-10.
9. Ting DSW, Wu WC, Toth C. Deep learning for retinopathy of prematurity screening. Br J Ophthalmol 2018. pii: bjophthalmol-2018-313290.

10. Ting DSW, Pasquale LR, Peng L, Campbell JP, Lee AY, Raman R, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol 2019;103:167-75.
11. De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nat Med 2018;24:1342-50.
12. Lakhani P, Sundaram B. Deep learning at chest radiography: automated classification of pulmonary tuberculosis by using convolutional neural networks. Radiology 2017;284:574-82.
13. Hwang EJ, Park S, Jin KN, Kim JI, Choi SY, Lee JH, et al. Development and validation of a deep learning-based automatic detection algorithm for active pulmonary tuberculosis on chest radiographs. Clin Infect Dis 2018.
14. Ting DSW, Tan TE, Lim CCT. Development and validation of a deep learning system for detection of active pulmonary tuberculosis on chest radiographs: clinical and technical considerations. Clin Infect Dis 2018.
15. Titano JJ, Badgeley M, Schefflein J, Pain M, Su A, Cai M, et al. Automated deep-neural-network surveillance of cranial images for acute neurologic events. Nat Med 2018;24:1337-41.
16. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017;542:115-8.
17. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-64.
18. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clin Exp Ophthalmol 2016;44:260-77.
19. Abramoff MD, Lou Y, Erginay A, Clarida W, Amelon R, Folk JC, et al. Improved automated detection of diabetic retinopathy on a publicly available dataset through integration of deep learning. Invest Ophthalmol Vis Sci 2016;57:5200-6.
20. Yang Z, Chan YS, Wong TM. Effects of kainic acid administered to the caudal ventrolateral medulla on arterial blood pressure in the spontaneously hypertensive and normotensive Wistar-Kyoto rats. Neurosci Lett 1996;202:145-8.
21. Abramoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digital Medicine 2018;39:1-8.
22. Apalla Z, Lallas A, Sotiriou E, Lazaridou E, Ioannides D. Epidemiological trends in skin cancer. Dermatol Pract Concept 2017;7:1-6.
23. Giuffre G, Lodato G, Dardanoni G. Prevalence and risk factors of diabetic retinopathy in adult and elderly subjects: the Casteldaccia eye study. Graefes Arch Clin Exp Ophthalmol 2004;242:535-40.
24. Dheda K. Getting bang for buck in the latent tuberculosis care cascade. Lancet Infect Dis 2016;16:1209-10.
25. Ting DS, Yi P, Hui F. Clinical applicability of deep learning system in detecting tuberculosis using chest radiography. Radiology 2018;286:729-31.
26. De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nat Med 2018:24:1342-50.
27. Buchan JC, Amoaku W, Barnes B, Cassels-Brown A, Chang BY, Harcourt J, et al. How to defuse a demographic time bomb: the way forward? Eye (Lond) 2017;31:1519-22.
28. Liew CJY, Krishnaswamy P, Cheng LTE, Tan CH, Poh ACC, Lim TCC. Artificial intelligence and radiology in Singapore: championing a new age of augmented imaging for unsurpassed patient care. Ann Acad Med Singapore 2019;48:15-23.
29. Suh HB, Choi YS, Bae S, Ahn SS, Chang JH, Kang SG, et al. Primary central nervous system lymphoma and atypical glioblastoma: differentiation using radiomics approach. Eur Radiol 2018;28:3832-9.
30. Bae S, Choi YS, Ahn SS, Chang JH, Kang SG, Kim EH, et al. Radiomic MRI phenotyping of glioblastoma: improving survival prediction. Radiology 2018;289:797-806.
31. Chang K, Bai HX, Zhou H, Su C, Bi WL, Agbodza E, et al. Residual convolutional neural network for the determination of IDH status in low-and high-grade gliomas from MR imaging. Clin Cancer Res 2018;24:1073-81.
32. Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nature Biomedical Engineering 2018;2:158-64.
33. Ting DS, Wong TY. Eyeing cardiovascular risk factors. Nature Biomedical Engineering 2018;2:140-1.
34. Rajkomar A, Oren E, Chen K, Dai AM, Hajaj N, Hardt M, et al. Scalable and accurate deep learning with electronic health records. NPJ Digital Medicine 2018;1:18.
35. Choi JY, Yoo TK, Seo JG, Kwak J, Um TT, Rim TH. Multi-categorical deep learning neural network to classify retinal images: a pilot study employing small database. PLoS One 2017;12:e0187336.
36. Lambin P, Leijenaar RT, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, et al. Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol 2017;14:749.
37. Yi PH, Hui F, Ting DS. Artificial intelligence and radiology: collaboration is key. J Am Coll Radiol 2018;S1546-1440:30001-2.

Original Article

Evaluation of Thalassaemia Screening Tests in the Antenatal and Non-Antenatal Populations in Singapore

Shir Ying Lee, [1]*MBBS, MRCP, FRCPath*, Eng Soo Yap, [1]*MBBS, MRCP, FRCPath*, Elaine YP Lee, [1]*BSc*, Jia Hui Goh, [1]*BSc*, Te Chih Liu, [1]*MBBS, MRCP, FRCPath*, Christina Yip, [1]*PhD*

Abstract

Introduction: Haemoglobinopathy testing is performed for carrier screening and evaluation of microcytic anaemia. We evaluated the effectiveness of thalassaemia screening tests at our institution and suggest ways of improving the testing algorithm. Materials and Methods: A total of 10,084 non-antenatal and 11,364 antenatal samples with alkaline gel electrophoresis (AGE), capillary electrophoresis (CE), haemoglobin H (HbH) inclusion test, mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV) were retrospectively reviewed. A subgroup of 187 samples with genetic testing was correlated with HbH inclusions and MCH/MCV. The effect of iron deficiency on percentage haemoglobin A2 (HbA2) was studied. Results: HbH inclusion test showed low sensitivity of 21.43% for α-thalassaemia mutations but higher sensitivity of 78.95% for $--^{SEA}$ deletion. Byreceiver operating characteristic (ROC) analysis, MCH ≤28 pg or MCV ≤80 fl for non-antenatal samples and MCH ≤27 pg or MCV ≤81 fl for antenatal samples had >98% sensitivity for HbH inclusions. Above these thresholds, the probability that HbH inclusions would be absent was >99% (negative predictive value [NPV] >99%). MCH ≤28 pg had 100% sensitivity (95% CI 95.63%-100%) for α-thalassaemia mutations and 97.68% calculated NPV in the antenatal population. Detection of haemoglobin variants by CE correlated highly with AGE (99.89% sensitivity, 100% specificity). Severe iron deficiency reduced HbA2 in haemoglobin E (*P* <0.001) and α-thalassaemia (*P* = 0.0035), but not in β-thalassaemia. Conclusion: MCH/MCV thresholds have adequate sensitivity for α-thalassaemia in the antenatal population, and genotyping plays an important role as HbH inclusion test shows low sensitivity. CE without AGE, may be used as initial screening for haemoglobin variants. Our study provides contemporary data to guide thalassaemia screening algorithms in Singapore.

Ann Acad Med Singapore 2019;48:5-15

Key words: Haemoglobinopathy, Mean corpuscular haemoglobin, Mean corpuscular volume

Introduction

Haemoglobinopathies are inherited disorders of haemoglobin (Hb) in which the genetic abnormality leads to reduced synthesis of normal globin chains (α- and β-thalassaemia) or functional changes in haemoglobin (haemoglobin structural variants).[1] The haematological parameters of patients with thalassaemia differ widely, ranging from asymptomatic carriers to severe anaemia requiring regular blood transfusion. Globin chain imbalance results in ineffective erythropoiesis, anaemia and microcytosis, the degree of imbalance translating into clinical severity. Deletion of 1 or 2 of 4 alpha-globin genes (–α/αα, – –/αα, –α/–α) causes α-thalassaemia trait; deletion of 3 alpha-globin genes –α/– – or deletions in combination with non-deletional mutation (e.g. $\alpha\alpha^{CS}$/– –) leads to haemoglobin H (HbH) disease; while deletion of all 4 alpha-globin genes (– –/– –) causes Barts hydrops fetalis, a fatal condition in-utero.[2] Alpha^0 denotes 2 gene deletions in *cis* (– –) while alpha$^+$ denotes 1 gene deletion (–α). β-thalassaemia trait arises from inheritance of 1 β-thalassaemia allele, whereas homozygous inheritance of 2 β-thalassaemia alleles leads to thalassaemia major or a moderate form termed 'thalassaemia intermedia'. In Southeast Asia and Singapore, compound heterozygosity for haemoglobin E (HbE) (*HBB*:c.79G>A, β26(B8)Glu>Lys) and β-thalassaemia is a common cause of thalassaemia intermedia.

[1]Department of Laboratory Medicine, National University Hospital, Singapore
Address for Correspondence: Dr Lee Shir Ying, Department of Laboratory Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.
Email: shir_ying_lee@nuhs.edu.sg

Thalassaemia is frequent in the multiethnic population of Singapore which comprises 74% Chinese, 13% Malays, 9% Indians and 3% of other races and where interracial marriages are common. In contrast, sickle haemoglobin (HbS) and sickling disorders are uncommon. In a genotype study of cord blood in Singapore, 6.4% of Chinese, 4.8% of Malays and 5.2% of Indians had α-thalassaemia including Hb Constant Spring (Hb-CS) (overall rate 5.5%). Alpha^{+} deletions accounted for 68% of mutations and $--^{SEA}$ deletion was the commonest type of alpha^{0} deletion.[3] β-thalassaemia including HbE was found in 2.7% of Chinese, 6.3% of Malays and 0.7% of Indians, with β-thalassaemia occurring in 1.6% and HbE in 1.7% overall.[3] Therefore, the major concerns of haemoglobinopathy screening in Singapore are Barts hydrops fetalis and HbH disease in Chinese, HbE/β-Thalassaemia in Malays and β-thalassaemia major in all groups.

Thalassaemia screening is performed either for diagnosis of anaemia and microcytosis or for carrier screening—which is important for assessing a couple's risk of having a severely affected child and at the population level for reducing the burden of thalassaemia major in the community.[4] Prenatal diagnosis and preimplantation genetic diagnosis in ethically allowable settings[5] may potentially be offered to couples at risk.

The International Committee for Standardization in Hematology (ICSH) expert panel in 1978, the World Health Organization in the 1989 Guidelines for the Control of Hemoglobin Disorders, and more recently the Thalassaemia International Federation[6] made recommendations regarding the laboratory investigation of these conditions. Screening is usually performed by a full blood count (FBC) and haemoglobin analysis with quantification of HbA2 and haemoglobin F (HbF). Major haemoglobin variants such as HbS (*HBB*:c.20A>T), haemoglobin C (HbC) (*HBB*:c.19G>A) and HbE are detected as shifted band patterns on Hb electrophoresis. If haemoglobin variant is identified by one technique, a second technique is recommended for positive identification of the variant. However, electrophoresis does not detect all variants, for example, unstable haemoglobins may not be present in sufficient amounts and require detection by heat or isopropanol stability test. Deoxyribonucleic acid (DNA)-based genetic testing is used for unusual or ambiguous results of Hb electrophoresis, cases which require genetic confirmation or can only be confidently detected by genetic testing.

Percentage haemoglobin A2 (HbA2) above 3.5% measured by a robust method such as high performance liquid chromatography (HPLC) or capillary electrophoresis (CE) is the standard for presumptive diagnosis of β-thalassaemia.[6,7] Various factors affect the level of HbA2 in β-thalassaemia, one of which is the type of mutation. For example, mutations which lead to mild reduction of β-globin synthesis may manifest only borderline increased HbA2 of 3.4% to 3.6%, and less common silent β-thalassaemias have HbA2 from 3.1% to 3.5%.[8] Iron deficiency is known to suppress HbA2 levels, and could reduce the sensitivity of the test.[9, 10]

For α-thalassaemia, genetic diagnosis is suggested as the preferred method because of the limited sensitivity of protein-based tests.[1, 6, 11] The commonly used HbH inclusion test, in which red cells are observed for precipitation of unstable β^{4} tetramers, is highly specific for α-thalassaemia and positive in HbH disease, but reported to have poor sensitivity for carrier detection especially in aged samples,[12-14] is time consuming and observer-dependent. Genetic testing is not available in most laboratories and poses cost constraints for large scale screening programmes in high prevalence areas like Singapore. To implement α-thalassaemia genotyping for antenatal screening, screening programmes apply mean corpuscular haemoglobin (MCH) and/or mean corpuscular volume (MCV) thresholds to prioritise patients for screening.[6, 7, 15-18]

Our study aimed to evaluate the effect of applying the above recommendations to thalassaemia screening in our institution. To this aim, we investigated the following: 1) sensitivity and specificity of HbH inclusions (HbH-I) for α-thalassaemia mutations, 2) optimal MCH or MCV thresholds for performing α-thalassaemia testing with HbH inclusion test or α-thalassaemia genotyping in antenatal and non-antenatal populations, 3) determine whether CE alone without alkaline gel electrophoresis (AGE) is sufficient as initial method to detect haemoglobin variants in the Singapore population, and 4) effect of iron deficiency on HbA2 levels as this may impact β-thalassaemia screening.

Materials and Methods

We conducted a retrospective study based on results of adult samples received at the hospital laboratory over a 3-year period from 1 January 2013 to 31 December 2015. The study was approved by the Domain Specific Review Board of the National Healthcare Group. Blood samples from patients submitted to the laboratory for haemoglobinopathy/thalassaemia screening had the following investigations performed concurrently: 1) Haemoglobin gel electrophoresis at alkaline pH (AGE), 2) CE, 3) HbH inclusion test, and 4) FBC with red blood cell (RBC) indices of MCH and MCV. Samples in which 1) and/or 2) detected haemoglobin variant were further subjected to haemoglobin gel electrophoresis at acid pH. Results of serum ferritin were obtained, where available. A proportion of samples additionally had genotyping for α-thalassaemia and β-thalassaemia performed. The decision to perform genotyping was made by the primary physician for reasons such as antenatal cases with unexplained microcytosis, or

haemoglobin variants and positive HbH inclusions which require genetic confirmation. Patients' ethnicity was recorded as the self-reported ethnic group or country of origin. Antenatal samples were from women attending the hospital obstetrics department who were planning for or in their first pregnancy. As per local practice, all women had thalassaemia screening performed, hence antenatal samples approximated unselected population screening.

RBC count, haemoglobin, hematocrit, MCV and MCH were measured on the Sysmex XE5000 automated FBC analyser (Sysmex Corporation, Kobe, Japan). Haemoglobin electrophoresis was performed on agarose gel using the Hydragel System (Hydragel 15 HEMOGLOBIN (E) kit; Sebia Inc., Evry Cedex, France) at alkaline pH 8.6 or acid pH 6.0. The resulting electropherograms were evaluated visually for pattern abnormality by comparing to the reference control. CE of haemoglobin was performed using the automated Capillarys 2 analyser HEMOGLOBIN (E) kit (Sebia Inc., Evry Cedex City, France). This was used to measure the percentages of HbA, HbA2 and HbF as well as any haemoglobin variants, including HbE, HbS, Hb-CS and Hb Barts.

HbH-I stain was made by mixing 1% Brilliant Cresyl Blue (BCB)-staining solution prepared by dissolving 1.0 g of BCB (Sigma-Aldrich, St Louis, Mo) in 100 mL of citrate-saline solution, with K3-ethylenediaminetetraacetic (EDTA) blood in a 1:1 ratio, then incubating in a 37°C water bath for at least an hour. Two smears were prepared, and 10,000 to 50,000 RBCs observed for inclusions. Serum ferritin concentration was measured by chemiluminescent two-site sandwich immunoassay using Beckman Coulter Unicel DXI 800 (Beckman Coulter Inc., Brea, CA, USA).

Genotyping: The alpha-globin gene cluster was examined for 7 deletional mutations ($--^{SEA}$, $-\alpha^{3.7}$, $-\alpha^{4.2}$, $--^{FIL}$, $--^{THAI}$, $-[\alpha]^{20.5}$ and $--^{MED}$) by gap-polymerase chain reaction (gap-PCR)[19] and 6-point mutations within the α2-globin (*HBA2*) gene (codon 30 or α30(B11) Glu→0, *HBA2*:c.91_93delGAG); Hb Adana or codon 59 (*HBA2*:c.179G>A [or *HBA1*]; Hb Quong Sze [Hb QS, *HBA2*:c.377T>C]; Hb-CS [Hb CS, *HBA2*:c.427T>C]; Hb Paksé [*HBA2*:c.429A>T] and the polyadenylation [polyA] signal [*HBA2*:c.*92A>G and *HBA2*:c.*94A>C]) by polymerase chain reaction (PCR) and sequencing. PCR amplification of the 3 exons of the beta-globin gene followed by direct sequencing was performed on the ABI Prism 3130XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

The following analyses were performed: 1) The sensitivity and specificity of HbH inclusion test for α-thalassaemia was determined by comparing with the gold standard of α-thalassaemia genotyping; 2) To determine the optimal sensitivity and specificity of various MCH and MCV cutoffs for HbH-I, receiver operating characteristic (ROC) analyses were performed in antenatal and non-antenatal samples. In non-antenatal samples, analysis was limited to samples without β-thalassaemia and iron deficiency, i.e. HbA2 <3.5%, HbF <1% and ferritin >30 ng/ml. To preserve better sensitivity, analysis included all samples in the antenatal population; 3) ROC analysis was performed on genotyped samples to determine the sensitivity and specificity of various MCH and MCV cutoffs for genotype-confirmed α-thalassaemia; 4) Results of CE were compared with that of AGE in a 2 x 2 contingency table; and 5) To evaluate the effect of iron deficiency on HbA2, samples were divided into 3 groups by ferritin level: Group 1: ferritin <10 ng/ml (severe iron deficiency),[20] Group 2: ferritin 10 ng/ml to 29 ng/ml (iron deficiency),[21] Group 3: ferritin 30 ng/ml to 200 ng/ml (iron deficiency unlikely). Median HbA2 of Groups 1 and 2 were compared with median HbA2 of Group 3, in the following 4 subgroups: a) samples positive for HbH-I (α-thalassaemia), b) samples negative for HbH-I, c) samples with HbE, and d) samples with HbA2 ≥4.0% (β-thalassaemia). HbA2 ≥4.0% was chosen as these were more likely to have genetic β-thalassaemia, than lower levels.[8]

Data was analysed using GraphPad PRISM Version 7 (GraphPad Software, La Jolla, CA, USA). ROC analysis was used to determine the optimal sensitivity and specificity for continuous variables. Two-by-two contingency tables were used to calculate sensitivity and specificity of categorical data. The Wilson-Brown method was used to compute confidence intervals (CIs) for sensitivity and specificity. Kruskal-Wallis test was used to compare more than 2 groups of non-parametric data. Chi-squared test was used for comparison of proportions. Modified Wald method was used to derive CI of proportions. Statistical significance at a two-tailed *P* value of <0.05 was assumed.

Results

A total of 21,448 samples were analysed, of which 10,084 were non-antenatal and 11,364 were antenatal samples. Genotyping was performed on 187 (0.87%) and ferritin was measured on 5162 samples (24.1%). Figures 1A and 1B show the distribution of all cases and genotyped cases by results. Table 1A shows the demographic distribution and frequency of thalassaemia subtypes, and Table 1B shows the haemoglobin variants detected by electrophoresis among all samples. Figure 2 shows the MCH and MCV of various thalassaemia subtypes.

Correlation of HbH-I with Genotype-Confirmed α-Thalassaemia

Eighty-four cases had at least 1 α-thalassaemia mutation. Table 1C lists the mutations and their correlation with HbH inclusion results. The sensitivity of HbH inclusion test

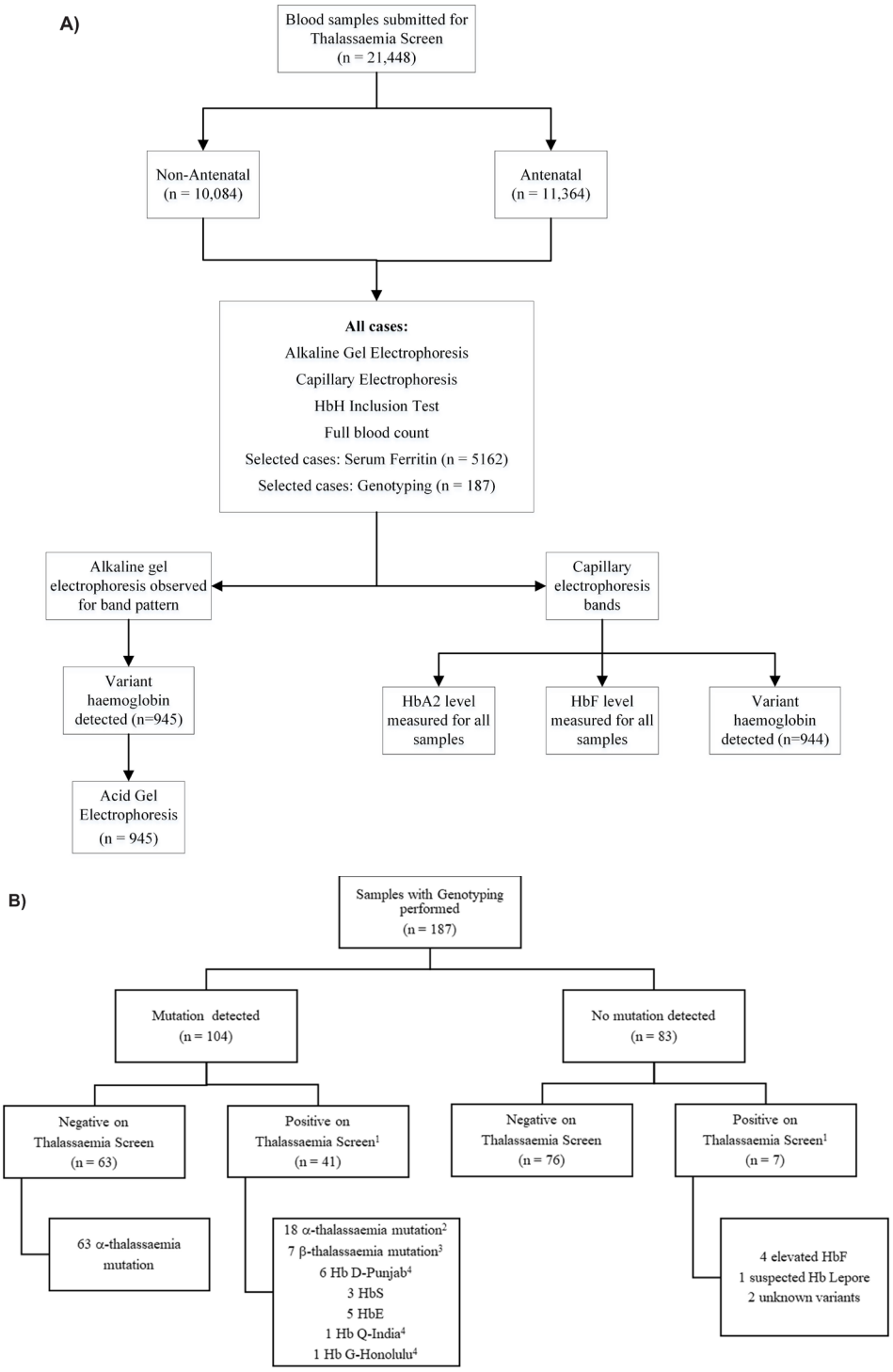


Fig. 1. A) Distribution of samples according to current thalassaemia screening algorithm. B) Distribution of cases by results of genotyping and their correlation with thalassaemia screening tests.[1]Any of the following: HbH inclusion detected, HbA2 >3.5%, variant haemoglobin band on electrophoresis, unexplained HbF elevation. [2]Hb Q-Thailand (*HBA1*:c.223G>C) and Hb Constant Spring (*HBA2*: c.427T>C) are detectable on electrophoresis, hence positive on thalassaemia screen. [3]β-thalassaemia genotypes: IVS1 nt5 (G>C), IVS1 nt2 (T>C), IVS2 nt751 (T>A), codon 41/42 (-TCTT), codon 8/9 (+G) mutation, 619bp deletion, -34TATA (G>A). [4]Hb D-Punjab (*HBB*:c.364G>C), Hb Q-India (*HBA1*:c.193G>C), Hb G-Honolulu (*HBA2*:c.91G>C).

for detecting any α-thalassaemia mutation was 21.43% and specificity was 100.00% (Table 2A). The sensitivity of HbH inclusion test for $--^{SEA}$ deletion was 78.95% and specificity was 98.21% (Table 2B).

Determining Optimal MCH/MCV Cutoffs for HbH-I Testing

By ROC analysis among non-antenatal samples without β-thalassaemia or iron deficiency (n = 2343), MCH and MCV were both highly predictive of HbH-I (area under

Table 1. A) Characteristics of Non-Antenatal and Antenatal Cases, B) Frequency of Haemoglobin Variants Detected by Haemoglobin Gel and Capillary Electrophoresis, C) Alpha Thalassaemia Genotype-Confirmed Cases Correlated with Results of HbH Inclusion Test

A) Characteristics of Non-Antenatal and Antenatal Cases	**Non-Antenatal**	**Antenatal**
Number	10,084	11,364
Age (years), median (interquartile range)	48.6 (34.6 – 63.7)	30.6 (27.5 – 34.0)
Female:male (%)	61.3%:38.7%	100%:0%
Chinese (%)	55.3%	42.2%
Malay (%)	37.1%	16.7%
Indian (%)	6.7%	27.0%
Others (%)	0.9%	14.1%
South-east asian	0.8%	12.4%
East asian	0.0%	0.5%
Middle eastern	0.0%	0.1%
Caucasian	0.1%	1.9%
HbH inclusion positive (%)	15.15%	1.59%
Beta thalassaemia (%) i.e. HbA2 >3.5% without HbE (%)	11.07%	1.21%
HbE (%)	4.76%	1.50%
Others (%)		
B) Frequency of Hb Variants Detected by Hb Gel and Capillary Electrophoresis		
Presumptive Identities of Hb Variants	**No. (Total n = 945)**	**Frequency of Detection**
Hb E trait	715	75.66%
Homozygous Hb E	29	3.07%
Hb Constant Spring	65	6.88%
Hb D-Punjab trait	19	2.01%
Hb S	16	1.69%
Hb Q-Thailand	16	1.69%
Hb Kaohsiung (New York)	13	1.38%
Hb Lepore	9	0.95%
Hb Q-India	4	0.42%
Hb C	0	0%
Hb O-Arab	0	0%
Others	59	6.24%
C) Alpha Thalassaemia Genotype-Confirmed Cases Correlated with Results of HbH Inclusion Test		
Genotype	**HbH Inclusion Detected**	**HbH Inclusion Not Detected**
$-\alpha^{3.7}$ heterozygote	1	41
$-\alpha^{4.2}$ heterozygote	1	2
$-\alpha^{3.7}$ homozygote	0	14
$--^{SEA}$ heterozygote	13	4
$-\alpha^{3.7}/--^{SEA}$ compound heterozygote	2	0
$-\alpha^{3.7}$/Hb Adana compound heterozygote	1	0
Hb Adana heterozygote	0	1
Hb Q-Thailand with $-\alpha^{4.2}$	0	2
PolyA(2) AATAAA>AATA--	0	1
Hb Constant Spring heterozygote	0	1
Total	18	66

Hb: Haemoglobin

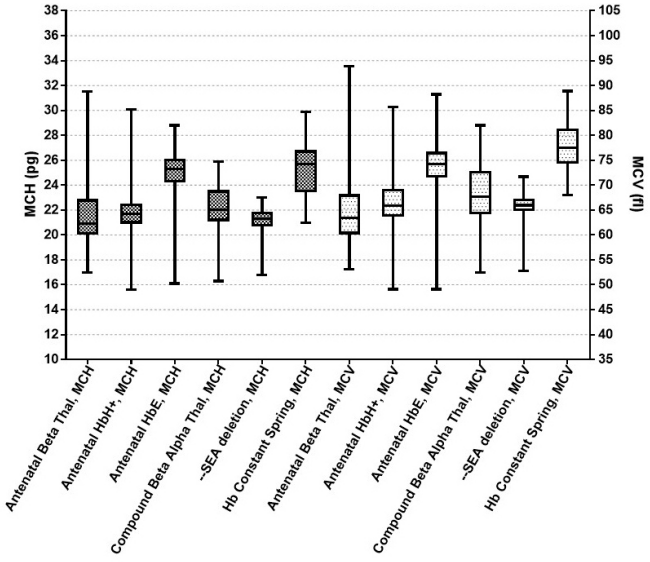


Fig. 2. MCH and MCV of various thalassaemia groups. Data represented as median, interquartile range, minimum and maximum. MCH: Mean corpuscular haemoglobin; MCV: Mean corpuscular volume; Thal: Thalassaemia.

receiver operating characteristic [AUROC] for MCH = 0.9279, P <0.0001; AUROC for MCV = 0.9424, P <0.0001) (Fig. 3). MCH ≤28 pg had a sensitivity of 99.87% (95% CI 99.25%-100%) and specificity of 50.59% (95% CI 48.11%-53.07%) for HbH-I. MCV ≤80 fl had a sensitivity of 99.87% (95% CI 99.25%-100%) and specificity of 63.02% (95% CI 60.61%-65.39%) for HbH-I.

MCH ≤28 pg and MCV ≤80 fl were then evaluated in non-antenatal samples with unknown ferritin and any HbA2 to evaluate their accuracy in unselected cases. The cutoffs showed sensitivities above 98% and negative predictive values (NPVs) above 99% for HbH-I (Table 2C). Positive predictive value (PPV) of MCH cutoff was 19.50% (95% CI 19.11%-19.89%) and PPV of MCV cutoff was 23.96% (95% CI 23.37%-24.57%). Both MCH and MCV had comparable sensitivities (P = 0.2414), but specificity of MCV was higher than that of MCH (P <0.0001).

By ROC analysis among antenatal samples, MCH and MCV were both highly predictive of HbH-I (AUROC for MCH = 0.9398, P <0.0001; AUROC for MCV = 0.9469, P <0.0001) (Fig. 3). Sensitivity, specificity and NPV of MCH <27 pg for HbH-I was 98.90% (95% CI 96.07%-99.87%), 68.65% (95% CI 67.47%-69.81%) and 99.98% (95% CI 99.91%-99.99%). Increasing the MCH cutoff to ≤28 pg did not increase sensitivity but instead reduced specificity to 58.86% (95% CI 57.62%-60.09%). Sensitivity, specificity and NPV of MCV ≤80 fl for HbH-I was 97.24% (95% CI 93.67%-99.10%), 70.28% (95% CI 69.12%-71.42%) and 99.95% (95% CI 99.87%-99.98%). Increasing the MCV cutoff to ≤81 fl increased sensitivity to 98.24% (95% CI 95.23%-99.66%), while NPV remained high at 99.97% (95% CI 99.0%-99.99%). Both MCH and MCV cutoffs had low PPV for HbH-I (5.42%, 95% CI 5.26%-5.60% and 7.26%, 95% CI 6.99%-7.54%, respectively). Hence, MCH ≤27 pg and MCV ≤81 fl were determined to be the best cutoffs for antenatal samples.

Determining Optimal MCH/MCV Cutoffs for Genotype-Confirmed α-Thalassaemia

By ROC analysis among genotyped samples, MCH and MCV were both predictive of genotype-confirmed α-thalassaemia, but with low specificity (AUROC for MCH = 0.6135, P = 0.0069; AUROC for MCV = 0.6104, P = 0.0086) (Fig. 3). MCH ≤28 pg was found to have sensitivity of 100% for genotype-confirmed α-thalassaemia (Table 2D). Using guideline-recommended threshold of MCH <27 pg, the sensitivity for genotype-confirmed α-thalassaemia was lower at 94.05% (95% CI 86.65%-98.04%), 95% CI of the difference: 0.42% to 13.19%, P = 0.024. Using guideline-recommended threshold of MCV <80 fl, the sensitivity for genotype-confirmed α-thalassaemia was 97.62% (Table 2D). The 3 cases with MCH between 27 pg to 28 pg all had MCV ≤81 fl and were single-gene deletions (2 heterozygous $–\alpha^{3.7}$, 1 heterozygous $–\alpha^{4.2}$). The 1 case with MCV >81fl had an MCH of 26 pg and was heterozygous $–\alpha^{3.7}$ plus β-thalassaemia trait.

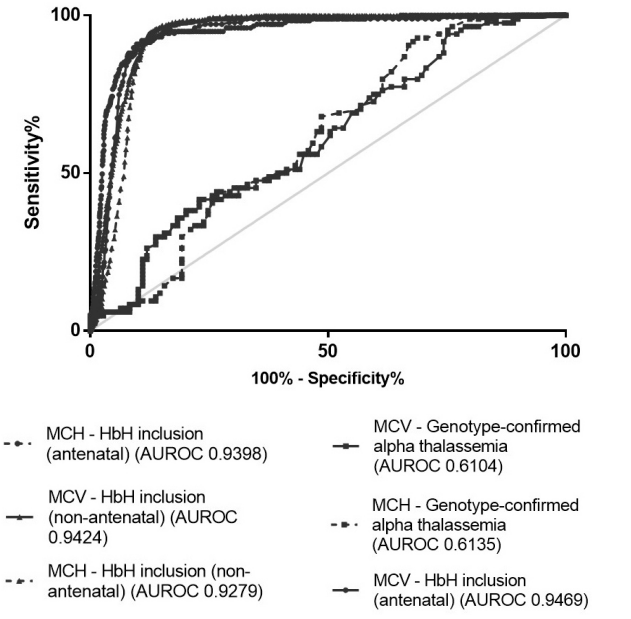


Fig. 3. ROC curves for sensitivity and specificity of MCH and MCV for HbH inclusions in A) antenatal and B) non-antenatal samples. MCH: Mean corpuscular haemoglobin; MCV: Mean corpuscular volume.

Table 2. Two-by-Two Contingency Table for Calculating Sensitivity, Specificity and NPV

Test		Condition Positive (n)	Condition Negative (n)	Test Sensitivity (95% CI)	Test Specificity (95% CI)	NPV (95% CI)
Table 2A		**Alpha Thal Genotype Positive**	**Alpha Thal Genotype Negative**			
HbH inclusion positive		18	0	21.43% (14.01% – 31.35%)	100% (96.40% –100%)	NA*
HbH inclusion negative		66	103	21.43% (14.01% – 31.35%)	100% (96.40% –100%)	NA*
Table 2B		**– –^{SEA} positive**	**– –^{SEA} negative**	78.95% (56.67% – 91.49%)	98.21% (94.88% – 99.51%)	NA*
HbH inclusion positive		15	3	78.95% (56.67% – 91.49%)	98.21% (94.88% – 99.51%)	NA*
Table 2C		**HbH Inclusion Positive**	**HbH Inclusion Negative**			
Sample type	**Test**					
Non-antenatal, unknown ferritin, any HbA2						
	MCH <28 pg	658	2717	99.40% (98.46% – 99.76%)	40.95% (39.53% – 42.38%)	99.79% (99.46% – 99.92%)
	MCH >28 pg	4	1884	99.40% (98.46% – 99.76%)	40.95% (39.53% – 42.38%)	99.79% (99.46% – 99.92%)
	MCV <80 fl	654	2075	98.79% (97.63% – 99.39%)	54.90% (53.46% – 56.33%)	99.68% (99.38% – 99.84%)
	MCV >80 fl	8	2526	98.79% (97.63% – 99.39%)	54.90% (53.46% – 56.33%)	99.68% (99.38% – 99.84%)
Table 2D		**Alpha Thal Genotype Positive**	**Alpha Thal Genotype Negative**			
Sample type	**Test**					
Samples with genotyping performed						
	MCH <28 pg	84	87	100% (95.63% – 100%)†	15.38%* (9.697% – 23.54%)†	NA‡
	MCH >28 pg	0	16	100% (95.63% – 100%)†	15.38%* (9.697% – 23.54%)†	NA‡
	MCV <80 fl	82	87	97.62% (91.73% – 99.58%)†	15.38%* (9.697% – 23.54%)†	NA‡
	MCV >80 fl	2	16	97.62% (91.73% – 99.58%)†	15.38%* (9.697% – 23.54%)†	NA‡
	MCV <81 fl	82	91	97.62% (91.73% – 99.58%)†	11.65%* (6.17% – 19.47%)†	NA‡
	MCV >81 fl	2	12	97.62% (91.73% – 99.58%)†	11.65%* (6.17% – 19.47%)†	NA‡

AGE: Alkaline gel electrophoresis; CI: Confidence interval; Hb: Haemoglobin; MCH: Mean corpuscular haemoglobin; MCV: Mean corpuscular volume; NA: Not applicable; NPV: Negative predictive value; Thal: Thalassaemia

*Specificity may be underestimated, because true negative rates could be higher as samples with MCH >28 pg may not have been genotyped. However, this is not expected to reduce the NPV.

†Lower limit of the 95% CI was used to calculate NPV for antenatal cases.

‡NPV derived from the sample prevalence is not stated as prevalence among genotyped samples is higher than actual population prevalence.

To obtain the NPV and PPV of MCH ≤28 pg and MCV ≤81 fl for genotype-confirmed α-thalassaemia, NPV and PPV in the antenatal population was calculated using the formulae:

$$NPV = \frac{specificity\ x\ (1 - prevalence)}{(1 - sensitivity)\ x\ prevalence + \ specificity\ x\ (1 - prevalence)}$$

$$PPV = \frac{sensitivity\ x\ prevalence}{sensitivity\ x\ prevalence + (1 - specificity\ )\ x\ (1 - prevalence)}$$

and using the lower limit of the 95% CI of sensitivity and specificity, and 5% as the population prevalence of α-thalassaemia. The calculated NPV of MCH ≤28 pg was 97.68% and that of MCV ≤81 fl was 95.70%. The calculated PPV of MCH ≤28 pg was 5.28% and that of MCV ≤81 fl was 4.89%.

Correlation between CE and AGE

There were 945 samples in which haemoglobin variant was detected on AGE. All AGE positive samples, except 1, also had the haemoglobin variant detected on CE. The exception had a faint band which was not further characterised migrating between HbS and HbC zones on AGE but no variant on CE. The sensitivity, specificity, NPV and PPV of CE, using AGE as gold standard, were 99.89%, 100.00%, 99.99% and 100.00%, respectively.

Hb-CS is an important haemoglobin variant to detect on thalassaemia screening. Hb-CS typically appears as a faint slow migrating band on AGE. All 65 cases of Hb-CS which were detected as a slow band on AGE were similarly detected and quantified on CE. The percentages of Hb-CS ranged from 0.2% to 3.1%. Majority of them were HbH-I negative (60 cases, 92.31%). Median (range) of the values were: Hb 12.0g/dl (7.5 g/dl-16.6 g/dl), MCV 77.3 fl (68.0 fl-88.9 fl) and MCH 25.5 pg (19.6 pg-29.9 pg).

Effect of Iron Deficiency on the Percentage of HbA2

HbA2 was significantly lower in samples with severe iron deficiency among HbE positive, HbH-I positive and HbH-I negative subgroups (Fig. 4), with median HbA2 (interquartile range) of each respective subgroup being 3.3% (3.0%-3.6%), 2.2% (2.0%-2.4%), 2.2% (1.9%-2.4%) in samples with severe iron deficiency, compared with 3.6% (3.4%-3.9%), 2.3% (2.2%-2.4%), 2.7% (2.5%-3.5%) in samples without iron deficiency. However, no significant differences in HbA2 was observed in iron deficient samples in the HbA2 ≥4% (β-thalassaemia) subgroup – HbA2 5.1% (4.7%-5.5%) in severe iron deficiency, HbA2 5.2% (4.7%-5.5%) in iron deficiency, HbA2 5.3% (5.0%-5.7%) without iron deficiency.

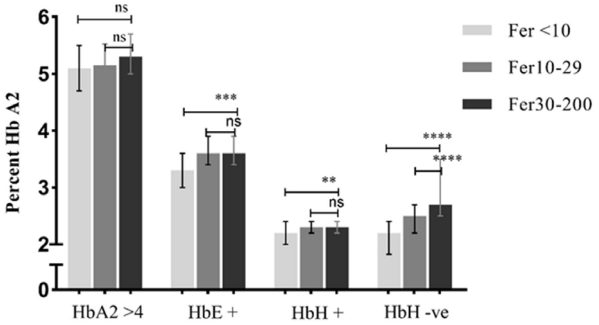


Fig. 4. Effect of iron deficiency on the percentage HbA2 among different thalassaemia subgroups. Data is presented as median with interquartile range; n = 418 in HbA2 ≥4% subgroup, n = 442 in HbE subgroup, n = 238 in HbH+ subgroup, n = 4001 in HbH -ve subgroup. Comparison between groups was performed using Kruskal-Wallis test with Dunn's multiple comparison test. Adjusted *P* value less than 0.0001, 0.001 and 0.001 are indicated as ****, *** and ** respectively. *P* values above 0.05 are denoted as ns: Non-significant. Fer: Ferritin; +: Positive; -ve: Negative.

Discussion

Our study shows that HbH inclusion testing has a low sensitivity of 21.43% for any α-thalassaemia mutation, concordant with other literature.[14, 22] The sensitivity for $--^{SEA}$ deletion is higher at 78.95% but still suboptimal considering that alpha^0 deletion is important to detect for antenatal screening. Even though our results could potentially have underestimated the true sensitivity (as HbH inclusion positive cases may not have been genotyped), it nonetheless reaffirms that genetic testing for α-thalassaemia is essential in cases of unexplained microcytosis. The rate of HbH-I positivity of only 1.59% in our antenatal population compared with 5.5% of α-thalassaemia in the cord blood genotype study[3] corroborates the low sensitivity of the test.

Screening for α-thalassaemia poses challenges because non-genetic tests are insensitive, while genetic tests are costly and unfeasible to implement in all patients. Current antenatal guidelines recommend that patients with unexplained microcytosis directly undergo genetic testing,[6, 15] while other guidelines recommend HbH inclusion test followed by genetic testing and/or partner testing.[17] As screening based on MCH/MCV should have high NPV to reduce misdiagnosis, our study evaluated the predictive values of thresholds. If guideline-recommended thresholds of MCH <27 pg[17] were applied in our antenatal samples, 2 out of 11,364 antenatal samples (0.018%; 95% CI <0.01%-0.08%) would be missed, whereas if MCV <80 fl17 was applied, 5 out of 11,364 (0.044%; 95% CI 0.02%-0.12%) would be missed. However, if MCV <81 fl was used, the number missed would be 3 out of 11,364 (0.026%; 95% CI <0.01%-0.09%). In non-antenatal samples, if MCH >28 pg or MCV >80 fl were taken as a threshold not to screen for HbH-I, 5 out of 10,084 samples (0.049%; 95% CI 0.02%-0.12%) and 10 out of 10,084 samples (0.099%; 95% CI 0.05%-0.19%), respectively would be missed.

In antenatal samples, MCH ≤27 pg and MCV ≤81 fl performed well for predicting HbH inclusions, but MCH ≤28 pg showed excellent NPV for genotype-confirmed α-thalassaemia. It should be emphasised that evaluation should take both MCH and MCV into account because unusual cases of coinheritance of α- and β-thalassaemia may have normal MCV but low MCH, and MCH is a more stable parameter during storage and is less influenced by age.[7, 23]

One study from Thailand found 3 cases of $--^{SEA}$ deletion with MCV >80 fl[24] and a study from Hong Kong illustrated that alpha^{+} deletions can occur with MCV >80 fl.[25] Knowledge of the magnitude of risk of missed diagnosis can inform the decision-making process. In non-antenatal samples, more cases of positive HbH-I occur at high MCH/MCV. We postulate that the reason for this is the higher prevalence of comorbid conditions affecting MCH/MCV, usually by increasing MCH/MCV, such as reticulocytosis, megaloblastic anemia, drugs and liver disease.[16]

Our finding that CE is equivalent to AGE for detecting haemoglobin variants is in agreement with studies comparing CE with AGE which concluded that the 2 methods correlate closely[26] and that CE identified the majority of important haemoglobin variants, i.e. HbS, C, E, D-Punjab, O-Arab, Lepore, without difficulty.[27-29] Both methods are based on separation of haemoglobins by electrophoretic charge and molecular size in alkaline buffer which, although not synonymous, could explain their concordance.

Recent studies found that iron deficiency does not reduce HbA2 to a sufficient degree to affect the diagnosis of β-thalassaemia caused by moderate or severe β-thalassaemia mutations.[10, 30] Our data provides additional reassurance that iron deficiency does not significantly affect the diagnosis of β-thalassaemia in our population. However, the effect on milder β-thalassaemia mutations is not well defined, and since we found that severe iron deficiency significantly reduced HbA2 values in HbE, a mild β-thalassaemic mutation with borderline elevated HbA2 levels,[31] we cannot exclude that other mild β-thalassaemia mutations might be similarly affected. It would therefore be prudent to repeat borderline HbA2 levels (e.g. 3.2%-3.5%) after correction of iron deficiency if time permits.[8] However, in pregnancy when time is of the essence, it may not be possible to repeat testing after treating iron deficiency and proceeding to genetic testing or partner testing may be preferable so that prenatal diagnosis can be offered.[7, 16] The proportion of antenatal patients with borderline HbA2 levels that could potentially be impacted is approximately 2%.

Co-inheritance of α- and β-thalassaemia shifts the MCV and MCH towards normal and lowers HbA2 levels.[32-34] Recent studies showed that in most cases of co-inheritance, HbA2 remains well above 3.5% such that diagnosis of β-thalassaemia is not compromised.[35] Because β-thalassaemia may mask the presence of α-thalassaemia, genotyping for α-thalassaemia is recommended if 1 partner has β-thalassaemia trait and the other is a carrier of alpha^{0} thalassaemia.[33, 36] Finally, other rare causes to consider after thalassaemia and iron deficiency have been ruled out are the δβ-thalassaemias and alpha-globin gene triplication causing microcytosis.[13, 16]

Based on the findings of our study, we propose that the thalassaemia screening algorithm may be simplified. CE and AGE need not be performed together as primary screen, since we showed that both are highly concordant. CE is preferred over AGE as it provides quantification of haemoglobin fractions. Upon detection of a variant on CE, a second alternative, separate method—for example, high performance liquid chromatography (HPLC), isoelectric focusing or electrophoresis in a different medium or pH[16]—should be employed to confirm the identity of the variant. If HPLC is used as primary screen, the same principle applies where a second alternative method should be performed to verify the variant. The choice of methods will depend on the local availability, cost, expertise, ease of use, reproducibility and sample material, whether liquid blood or dried blood spots.[7] If second-line techniques are still unable to confirm the variant or resolve between 2 clinically important variants, then further testing in reference laboratories or DNA analysis is recommended.

In non-antenatal samples, no specific threshold for HbH inclusion testing needs to be applied and all samples may have the test performed, since normocytic samples are more likely to harbour HbH-I (0.05%-0.1% chance) and diagnosis of HbH disease is clinically important in this population. As illustrated in our cohort, 2999 cases (30%) had MCH and MCV above the thresholds, out of which 12 cases harboured HbH-I, including 1 case of HbH disease (Fig. 2). On the other hand, if the clinical impact of α-thalassaemia is deemed low in certain patients, it would be equally possible to omit HbH-I testing in normocytic samples, with the knowledge that non-diagnosis rate is low.

In antenatal samples, both MCH and MCV should be assessed and presence of MCH <27 pg or MCV <81 fL may be used to prioritise samples for HbH inclusion test, since normocytic samples have a lower likelihood of harbouring HbH-I (0.02%). As 7950 samples (69%) in our cohort have MCH and MCV above those thresholds, this strategy (compared to universal HbH testing) would reduce the need for HbH inclusion testing by 60% to 70% with significant conservation of resources. Positive HbH-I should be followed by genetic testing to define the genetic lesion (alpha^{+} versus alpha^{0} deletion) to determine the risk of Barts hydrops fetalis, especially if the partner has α-thalassaemia. A negative test in the presence of confirmed or possible α-thalassaemia in the partner should also prompt genetic

testing. Conversely, partners of women with α-thalassaemia should be offered genetic testing if they have MCH or MCV below the thresholds, and cases of β-thalassaemia trait but unusually "high" MCH/MCV should be genotyped for α-thalassaemia if HbH inclusions are negative.

The question of whether all patients with microcytosis but no HbH-I or β-thalassaemia should undergo genetic testing for alpha^0 deletions remains a matter of debate in a high prevalence population like Singapore, given the significant numbers who require to be tested. In our antenatal cohort, 887 patients (7.8%) fulfill guideline criteria of MCH <25 pg for testing. Our study cannot answer this important question and prospective studies looking at outcomes (number of at risk couples detected, hydrops fetalis prevented) are needed in this regard.

Our study had several limitations. Firstly, only 0.87% of cases had genotyping performed, which limited our study of specific genotypes, for example, $--^{SEA}$. Secondly, genotyped cases were also selectively more likely to have microcytosis without HbH inclusions, which will underestimate the specificity of MCH/MCV as most samples with MCH >28 pg would not have been genotyped, but this effect would not significantly alter the sensitivity. Thirdly, our study focused on the thresholds for HbH-I testing and did not study the thresholds required for single alpha-gene deletion and double alpha-gene deletions. Of note, we considered both alpha$^+$ ($-\alpha^{3.7}$, $-\alpha^{4.2}$) and alpha^0 deletions as positive for α-thalassaemia. Traditionally, the target of genetic screening for α-thalassaemia are alpha^0 deletions rather than alpha$^+$ deletions.[6,8] The Thalassaemia International Foundation recommends that genetic diagnosis be performed if both parents have MCH <25 pg, with the aim of detecting alpha^0 deletions, to reduce anxiety and the burden of genetic testing.[6] Our limited analysis of the 19 samples with $--^{SEA}$ deletions in our cohort revealed that all had MCH <25 pg (Fig. 2). Fourthly, as this was a retrospective study, genetic confirmation was not performed in most of the discordant cases. We cannot exclude false positive HbH due to operator over-reporting, other unstable haemoglobins (e.g. Hb Gun-Hill)[37] or acquired HbH disease occurring in myelodysplastic syndrome.[38] The strength of our study is the large sample size of 21,000 which allowed for narrow CIs. Our sample of approximately 11,000 antenatal samples allowed us to determine the optimal MCH/MCV cutoffs for HbH-I testing with a NPV of more than 99%.

In summary, our study provides contemporary data from a large Singapore cohort to help inform thalassaemia screening algorithms in Singapore.

REFERENCES

1. Sabath DE. Molecular diagnosis of thalassemias and hemoglobinopathies: an ACLPS critical review. Am J Clin Pathol 2017;148:6-15.
2. Chui DH. Alpha-thalassemia: Hb H disease and Hb Barts hydrops fetalis. Ann NY Acad Sci 2005;1054:25-32.
3. Kham SK, Quah TC, Loong AM, Tan PL, Fraser A, Chong SS, et al. A molecular epidemiologic study of thalassemia using newborns' cord blood in a multiracial Asian population in Singapore: results and recommendations for a population screening program. J Pediatr Hematol Oncol 2004;26:817-9.
4. Li D, Liao C, Li J, Xie X, Huang Y, Zhong H. Detection of alpha-thalassemia in beta-thalassemia carriers and prevention of Hb Bart's hydrops fetalis through prenatal screening. Haematologica 2006;91:649-51.
5. Yap C, Tan AS, Wang W, Lim MN, Chong SS. First successful preimplantation genetic diagnosis in Singapore – avoidance of beta-thalassaemia major. Ann Acad Med Singapore 2009;38:720-3.
6. Old J, Harteveld CL, Traeger-Synodinos J, Petrou M, Angastiniotis M, Galanello R. Prevention of thalassaemias and other haemoglobin disorders. Volume 2: Laboratory protocols. Nicosia, Cyprus: Thalassaemia International Federation; 2012.
7. Ryan K, Bain BJ, Worthington D, James J, Plews D, Mason A, et al. Significant haemoglobinopathies: guidelines for screening and diagnosis. Br J Haematol 2010;149:35-49.
8. Old J. Prevention of thalassaemias and other haemoglobin disorders. Volume 1: Principles. 2nd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2013.
9. El-Agouza I, Abu Shahla A, Sirdah M. The effect of iron deficiency anaemia on the levels of haemoglobin subtypes: possible consequences for clinical diagnosis. Clin Lab Haematol 2002;24:285-9.
10. Verhovsek M, So CC, O'Shea T, Gibney GT, Ma ES, Steinberg MH, et al. Is HbA2 level a reliable diagnostic measurement for beta-thalassemia trait in people with iron deficiency? Am J Hematol 2012;87:114-6.
11. American College of Obstericians and Gynecologists Committee Opinion No. 691 Summary: Carrier Screening for Genetic Conditions. Obstet Gynecol 2017;129:597-9.
12. Higgs DR, Bowden DK. Clinical and laboratory features of the alpha-thalassemia syndromes. In: Steinberg MH, Forget BG, Higgs DR, Weatherall DJ, editors. Disorders of hemoglobin: genetics, pathophysiology, and clinical management. New York: Cambridge University Press; 2001. p. 431-69.
13. Barrett AN, Saminathan R, Choolani M. Thalassaemia screening and confirmation of carriers in parents. Best Pract Res Clin Obstet Gynaecol 2017;39:27-40.
14. Bergstrome JA, Poon A. Evaluation of a single-tube multiplex polymerase chain reaction screen for detection of common alpha-thalassemia genotypes in a clinical laboratory. Am J Clin Pathol 2002;118:18-24.
15. American College of Obstericians and Gynecologists Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol 2017;129:e41-55.
16. Bain BJ. Haemoglobinopathy diagnosis: algorithms, lessons and pitfalls. Blood Rev 2011;25:205-13.
17. Langlois S, Ford JC, Chitayat D. Carrier screening for thalassemia and hemoglobinopathies in Canada. J Obstet Gynaecol Can 2008;30:950-9.
18. Hoppe CC. Prenatal and newborn screening for hemoglobinopathies. Int J Lab Hematol 2013;35:297-305.
19. Chong SS, Boehm CD, Higgs DR, Cutting GR. Single-tube multiplex-PCR screen for common deletional determinants of alpha-thalassemia. Blood 2000;95:360-2.
20. Guyatt GH, Patterson C, Ali M, Singer J, Levine M, Turpie I, et al. Diagnosis of iron-deficiency anemia in the elderly. Am J Med 1990;88:205-9.

21. Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. Clin Chem 1998;44:45-51.
22. Chan AY, So CK, Chan LC. Comparison of the HbH inclusion test and a PCR test in routine screening for alpha thalassaemia in Hong Kong. J Clin Pathol 1996;49:411-3.
23. Velasco-Rodriguez D, Blas C, Alonso-Dominguez JM, Vega G, Soto C, Garcia-Raso A, et al. Cut-off values of hematologic parameters to predict the number of alpha genes deleted in subjects with deletional alpha thalassemia. Int J Mol Sci 2017;18:pii: E2707.
24. Sirichotiyakul S, Maneerat J, Sa-nguansermsri T, Dhananjayanonda P, Tongsong T. Sensitivity and specificity of mean corpuscular volume testing for screening for alpha-thalassemia-1 and beta-thalassemia traits. J Obstet Gynaecol Res 2005;31:198-201.
25. Chan LC, Ma SK, Chan AY, Ha SY, Waye JS, Lau YL, et al. Should we screen for globin gene mutations in blood samples with mean corpuscular volume (MCV) greater than 80 fL in areas with a high prevalence of thalassaemia? J Clin Pathol 2001;54:317-20.
26. Kim JE, Kim BR, Woo KS, Kim JM, Park JI, Han JY. Comparison of capillary electrophoresis with cellulose acetate electrophoresis for the screening of hemoglobinopathies. Korean J Lab Med 2011;31:238-43.
27. Borbely N, Phelan L, Szydlo R, Bain B. Capillary zone electrophoresis for haemoglobinopathy diagnosis. J Clin Pathol 2013;66:29-39.
28. Greene DN, Pyle AL, Chang JS, Hoke C, Lorey T. Comparison of Sebia Capillarys Flex capillary electrophoresis with the BioRad Variant II high pressure liquid chromatography in the evaluation of hemoglobinopathies. Clin Chim Acta 2012;413:1232-8.
29. Van Delft P, Lenters E, Bakker-Verweij M, de Korte M, Baylan U, Harteveld CL, et al. Evaluating five dedicated automatic devices for haemoglobinopathy diagnostics in multi-ethnic populations. Int J Lab Hematol 2009;31:484-95.
30. Passarello C, Giambona A, Cannata M, Vinciguerra M, Renda D, Maggio A. Iron deficiency does not compromise the diagnosis of high HbA(2) beta thalassemia trait. Haematologica 2012;97:472-3.
31. Mais DD, Gulbranson RD, Keren DF. The range of hemoglobin A(2) in hemoglobin E heterozygotes as determined by capillary electrophoresis. Am J Clin Pathol 2009;132:34-8.
32. Saleh-Gohari N, Khademi Bami M, Nikbakht R, Karimi-Maleh H. Effects of alpha-thalassaemia mutations on the haematological parameters of beta-thalassaemia carriers. J Clin Pathol 2015;68:562-6.
33. Viprakasit V, Limwongse C, Sukpanichnant S, Ruangvutilert P, Kanjanakorn C, Glomglao W, et al. Problems in determining thalassemia carrier status in a program for prevention and control of severe thalassemia syndromes: a lesson from Thailand. Clin Chem Lab Med 2013;51:1605-14.
34. Rosatelli C, Falchi AM, Scalas MT, Tuveri T, Furbetta M, Cao A. Hematological phenotype of the double heterozygous state for alpha and beta thalassemia. Hemoglobin 1984;8:25-35.
35. Law HY, Chee MK, Tan GP, Ng IS. The simultaneous presence of alpha- and beta-thalassaemia alleles: a pitfall of thalassaemia screening. Community Genet 2003;6:14-21.
36. American College of Obstericians and Gynecologists Practice Bulletin No. 78: Hemoglobinopathies in pregnancy. Obstet Gynecol 2007;109:229-37.
37. Rieder RF, Bradley TB, Jr. Hemoglobin Gun Hill: an unstable protein associated with chronic hemolysis. Blood 1968;32:355-69.
38. Steensma DP, Viprakasit V, Hendrick A, Goff DK, Leach J, Gibbons RJ, et al. Deletion of the alpha-globin gene cluster as a cause of acquired alpha-thalassemia in myelodysplastic syndrome. Blood 2004;103:1518-20.

Review Article

Artificial Intelligence and Radiology in Singapore: Championing a New Age of Augmented Imaging for Unsurpassed Patient Care

Charlene JY Liew, [1]*MMed (Diag Radiol), FRCR*, Pavitra Krishnaswamy, [2]*MS, PhD*, Lionel TE Cheng, [3]*MBBS (Hons), FRCR, MMed (Diag Radiol)*, Cher Heng Tan,[4]*MBBS, FRCR, FAMS,* Angeline CC Poh, [1]*MBBS, FRCR*, Tchoyoson CC Lim, [5]*MBBS, FRCR (UK), MMed (Diag Radiol)*

Abstract

Artificial intelligence (AI) has been positioned as being the most important recent advancement in radiology, if not the most potentially disruptive. Singapore radiologists have been quick to embrace this technology as part of the natural progression of the discipline toward a vision of how clinical medicine, empowered by technology, can achieve our national healthcare objectives of delivering value-based and patient-centric care. In this article, we consider 3 core questions relating to AI in radiology, and review the barriers to the widespread adoption of AI in radiology. We propose solutions and describe a "Centaur" model as a promising avenue for enabling the interfacing between AI and radiologists. Finally, we introduce The Radiological AI, Data Science and Imaging Informatics (RADII) subsection of the Singapore Radiological Society. RADII is an enabling body, which together with key technological and institutional stakeholders, will champion research, development and evaluation of AI for radiology applications.

Ann Acad Med Singapore 2019;48:16-24

Key words: Diagnostic radiology, Machine learning, Neural networks

Introduction: How Will Artificial Intelligence and Machine Learning Impact Radiology?

When a patient's diagnosis is uncertain, diagnostic radiologists study images created using X-rays, computed tomography (CT), ultrasound, and magnetic resonance (MR), to infer disease patterns and identify the most likely cause of the patient's signs and symptoms. The medical specialty of diagnostic radiology has always been greatly affected by advances in the fields of physics, medicine, biology and engineering, but is now also increasingly disrupted by innovations in computer and data sciences. Over the past few years, there have been abundant and frequent scholarly publications, news articles, and opinion pieces published on this subject. Some authors have gone so far as to predict the demise of diagnostic radiology as a specialty, if human image interpretation can be replaced by advanced machine learning (ML) techniques and big data analysis.[1]

Others see a brighter future for medical imaging experts by harnessing the power of artificial intelligence (AI) to augment human diagnostic abilities, especially in today's milieu of quantitative imaging biomarkers, precision medicine and value base radiology.[2] Radiologists are no strangers to disruptive technologies, having pioneered the translation of complex cross-sectional imaging technologies such as MR and positron emission tomography (PET) to clinical medicine, the digitisation of workflow in picture archiving and communication systems (PACS) and radiological information systems (RIS), and the incorporation of teleradiology and computer-aided detection

[1]Department of Diagnostic Radiology, Changi General Hospital, Singapore
[2]Deep Learning Department, Healthcare Department, Institute for Infocomm Research, A*STAR, Singapore
[3]Department of Diagnostic Radiology, Singapore General Hospital, Singapore
[4]Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore
[5]Department of Neuroradiology, National Neuroscience Institute, Singapore
Address for Correspondence: A/Prof Tchoyoson Lim Choie Cheio, Department of Neuroradiology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: tchoyoson.lim@singhealth.com.sg

(CAD) systems into practice.[3] So, what has changed? What does this potentially disruptive technology mean for radiology? And what lessons can we learn that can be applied to the rest of the medical community, for we all will surely be impacted by these rapid innovations?

AI can be defined as any technique that enables computers to mimic various aspects of human intelligence—including pattern recognition, data-driven learning, audiovisual perception, natural language understanding, knowledge-based reasoning, planning and control (Table 1). Although AI has a long and checkered history in medical applications stretching back to the 1970s, it is presently resurgent in the hype cycle, due to 3 factors: a) the availability of large-scale digital image databases, b) widespread availability of powerful general processing units (GPU)[4] and cloud resources, and c) the advancement of deep learning algorithms that enable computers to "learn" by mapping patterns in large amounts of data to their associated ground truth or labels.[5,6] In recent times, these artificial neural networks have achieved spectacular attention-grabbing headlines. Prominent examples include Google DeepMind's computer programme AlphaGo that beat a human expert at the board game of Go, Hanalytic's Biomind brain tumour diagnosis and test-taking robots that can pass medical examinations.[7,8] Some AI technologies such as facial recognition and customised predictive advertising, are already applied to our daily lives. For medical applications, deep learning has been successfully employed for interpretation of retinal images, skin lesion photographs and histopathological slides.[9] Notwithstanding the promise of AI for radiology, there is a need to learn from recent high profile missteps involving big data, ethics and privacy. For example, the breach of large-scale personally identifiable information by Facebook and Cambridge Analytica,[10] the development of dialogue systems that are susceptible to bias in training,[11] and the misuse of electronic surveillance[12] have caused considerable disquiet both to the general public and medical policymakers. Therefore, careful development and validation of these powerful tools for clinical medicine applications is crucial to optimise positive impact on large numbers of people, and prevent unforeseen or undetected effects. Hence, there is need for a strategic framework to guide the research, development and application of such powerful technologies in healthcare, so that big data and AI can be judiciously, safely and appropriately harnessed for the benefit of our patients.

Table 1. Common Definitions for Artificial Intelligence Terms

Nomenclature	Definition
Artificial intelligence	Techniques which enable computers to mimic various aspects of human intelligence – including pattern recognition, data-driven learning, audiovisual perception, natural language understanding, knowledge-based reasoning, planning and control.
Machine learning	A field of artificial intelligence that uses statistical techniques to allow computers to learn to make predictions from data.
Deep learning	A class of machine learning algorithms that employ a cascade of neural network layers to learn from vast amounts of data.

How Can Radiologists Use AI to Enhance Medical Diagnostics?

The value proposition of diagnostic radiologists extends far beyond mere image interpretation. Even before the first X-ray image is taken, important information about patient safety, radiation protection, pretest probability, appropriateness, study protocol and patient preparation, need to be processed using our understanding of medical physics, epidemiology and systems-based practice. These ancillary tasks entail radiologists working in teams alongside nurses, radiographers and technologists. Once the image is taken, radiologists must navigate through the image noise to distil the relevant signal, and only then, proceed to interpret the meaning of the image with reference to the patient's condition and the referring doctor's needs. Radiologists must also combine knowledge of false-positives (arising from artifacts or false signals), false-negatives (anatomic pitfalls, heuristics and cognitive biases that potentially lead to errors) with the timely communication of uncertainty, urgency, and unexpected findings. As such, radiology training and practice encompasses both crucial interpretive and non-interpretive (ancillary) tasks.[13]

Further, even the interpretive tasks in radiology extend well beyond the recognition of pathological patterns in images. Radiologists routinely employ "real" intelligence to convert accurate image interpretation into actionable, holistic patient-centric decision-making[14] in variable medical settings ranging from office-based outpatient private imaging centres, to tertiary academic research hospitals with complex casemix and comorbid patients whose care involve multidisciplinary team consultations and problem solving. Hence, the interpretive task of pattern recognition of pathological features within anatomical structures and extraction of biological meaning from low-contrast images (where contrast represents the difference between normal and abnormal structures, and the differences among many different causes of abnormalities) is only one, albeit important, part of the radiologists' workflow. Currently, it is mainly in this high-profile, thin slice of the diagnostic pathway, that AI is currently being focused. This, however, is set to change, and future interations of AI systems will conceivably combine multimodal sources of data, from imaging data to electronic medical records (EMR), as well as genomic and wearable sensor data.[15]

However, radiology can leverage AI technologies for both interpretive and ancillary tasks. The value proposition of AI is its speed and accuracy in detection, segmentation and classification of image features. Unlike humans, it does not suffer from fatigue, forgetfulness, nor social limitations of prescribed working hours. Potential use cases of narrow AI currently include tuberculosis and pneumonia detection in chest radiography[16,17] acute ischaemic stroke detection,[18] and radiographic bone age assessment;[19] the number of applications can only get larger. Outside the confines of image interpretation, AI can potentially have an even larger positive effect on the non-interpretive but resource-intensive ancillary imaging processes that take place in the background—for example, scanner and hospital workflows, decision support, and retrospective studies.

On the scanner front, as AI learns and implements ever faster and efficient methods of CT and MR image reconstruction, it is possible to realise abbreviated sequences and improved scanner productivity.[20] On the hospital workflow front, examples include smart data analytics in patient scheduling, decision support for safe and appropriate order entry, natural language processing-based querying and annotation of radiology reports, resource utilisation dashboards, and predicting healthcare economic trends. With neural networks capable of self-learning, constant and autonomous improvement and refinement of workflow can take place in the background.[21,22] A compelling case can thus be made that research and development resources for AI in radiology should focus on tasks that can yield larger net efficiencies, rather than on mere pixel-based computer-aided detection tools.

AI and Machine Learning: How is Singapore Responding?

Singapore radiologists have been adapting and innovating, building on previous experience, being early adopters of technologies such as PACS, voice recognition, teleradiology,[23] National Electronic Health Record (NEHR), and using computers in medical education and research.[24,25] Completed and ongoing projects in AI include abnormality detection in chest radiography, nasogastric tube detection on chest radiography (Fig. 1), automated fracture detection and labelling (Fig. 2) (Thian YL, personal communication), haematoma detection,[26] detection and quantification of midline shift in traumatic brain injury,[27,28] text-mining and natural language processing of radiology reports.[29]

In 2017, the Changi General Hospital Department of Radiology in partnership with SingHealth and Carestream Health, won the Ministry of Health (MOH) National Information Technolog (IT) Award in the 'Beyond Quality to Value' category for being the first hospital to implement an Artificially Intelligent module in the RIS to rightsite radiology reporting resources, ensuring higher quality

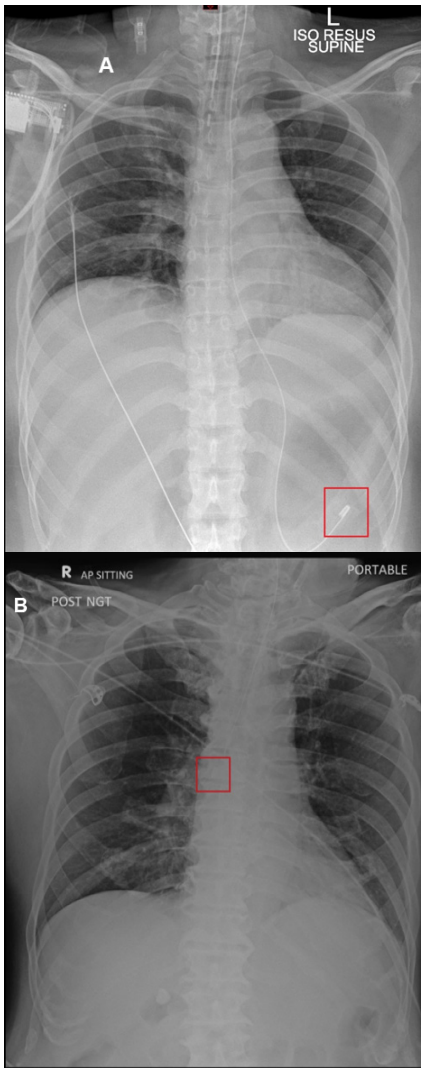


Fig. 1. Artificial intelligence (AI) for automated nasogastric tube (NG) tube detection. An AI convolutional neural network (CNN) is trained using a dataset of images enriched with radio-opaque NG tubes. It can subsequently detect and identify the position of the tip of the NG tube on a chest radiograph (red box) in these test/validation images. Images courtesy of Dr Charlene Liew, Dr May Lim, et al.

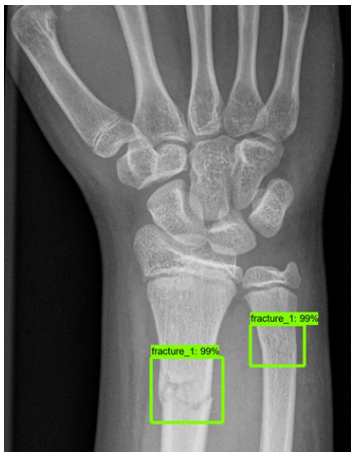


Fig 2. AI detecting distal radial and ulnar fractures in a child. Convolutional neural network trained using a dataset of fractures and normal radiographs, is able to localise both distal radius and ulna fractures with a confidence of 99%. Image courtesy of Dr Thian Yee Liang.

and faster report turnaround time for clinicians and at the same time increasing radiologist and radiographer work satisfaction[30] (Fig. 3). This system— albeit a rudimentary form of narrow, rules-based AI—nonetheless serves to highlight the potential of AI systems to automate non-imaging tasks in the radiology workflow, and future iterations may be enhanced with self-learning and self-improving AI models. The productivity gains from the system allowed radiologists, radiographers and administrators to spend more time in more pressing areas of patient care. This dovetails neatly into the 3 "Beyonds" initiative of the MOH to transform our healthcare landscape to meet the challenges of our ageing population, and illustrates the immense potential of radiologist-directed AI to streamline workflow and deliver better care to patients.[31]

Instead of a scattershot approach, the community of Singapore radiologists have formed a Singapore Radiological Society subsection for AI, Data Science and Imaging Informatics (RADII),[32] supported by the College of Radiologists, Singapore and the Academy of Medicine, Singapore to promote the research, educational and industrial aspects of AI, and to coordinate a national effort to align initiatives with national priorities. The recent Singapore Radiological Society Annual Scientific Meeting in 2018 featured dedicated sessions on Imaging Informatics and AI, bringing together local and international experts in radiology informatics, computer science research and industry to share ideas and experience. RADII teams in public healthcare institutions have also started formal and informal assessments of early FDA approved clinical AI systems and business models in the market, in order to understand the potential opportunities and challenges these nascent products offer.[33] Furthermore, a national coordinating body would be ideally placed to partner worldwide radiologist professional bodies such as the American College of Radiology, Radiological Society of North America (RSNA), Society for Imaging Informatics in Medicine (SIIM), Royal College of Radiologists (RCR)[34-37] and the wider medical community of ophthalmologists, dermatologists, cardiologists, endoscopists, and pathologists driving AI. RADII has established partnerships in particular, with the RCR to create AI imaging standards and guidelines, as well as participating in SIIM and RSNA international committees and Health Data Research UK (HDRUK) advisory workgroups.

Extensive translational research remains to be done in order to bring promising standalone performance testing results for diagnostic AI models into carefully evaluated and validated real-world clinical practice and meaningful outcomes.[38] There is an urgent need to develop means to standardise evaluation of AI algorithms, codify clinical guidelines for AI interpretation and reporting, and translate existing technology into reporting of real patient images. RADII—representing the stewards of data and resources within the AI radiological community—can consolidate and match clinical expertise with collaborators within the AI technology community in Singapore, including universities and research institutions like the National

SITE_RAD_ROSTER

LOCAL_LOOKUPTABLE_KEY	ACTIVE	CODE	VALUE	D1_SUN_AM	D1_SUN_PM	D2_MON_AM	D2_MON_PM	D3_TUE_AM	D3_TUE_PM	D4_WED_AM
103039	☑	CG0001	CG0001			LC,BN	LC,BN	KS,BN	KS,TV	KS,BN
103040	☑	CG0002	CG0002			CL		CL		AP
103041	☑	CG0003	CG0003			YR,LS	RY,AS	SS	YR	RY,SY
103042	☑	CG0004	CG0004			SS,AS	YR,AG	CK,SY	SN,AG	TY,AG
103043	☑	CG0005	CG0005							
103044	☑	CG0006	CG0006			SC,CC	AT,GH	AP,LS	CL	RM,WI
103045	☑	CG0007	CG0007				WC,CC	CT	LC,GH	
103046	☑	CG0008	CG0008			RY,MW	CT,WH	YR,CC	YY,VB	SC,LS
103047	☑	CG0009	CG0009			RT,GH				YR,HW
103048	☑	CG0010	CG0010			CT,ZH	SC	RY,TT	RM,TT	LC,TT
103049	☑	CG0011	CG0011				LR,ZH			
103050	☑	CG0012	CG0012			JN,TT	JF,LS	YY,TN	JF	YY,ZH
103051	☑	CG0013	CG0013					TJ		LR
103052	☑	CG0014	CG0014			RD	RD	RD,SO	RD,SO	CK,SO
103053	☑	CG0015	CG0015			SH		SH		
103054	☑	CG0016	CG0016							
103055	☑	CG0017	CG0017			TY	RM	WC,KN		TJ
103056	☑	CG0018	CG0018			WC,KN	YY		RY,KN	
103057	☑	CG0019	CG0019						WC	
103058	☑	CG0020	CG0020			LR,SY	TY	TY		JF,KN
103059	☑	CG0021	CG0021	NA,TV	NA,TV	RM	RT	SN	SC	SH
103060	☑	CG0022	CG0022	NA,HW	NA,HW	NA,HW	NA,MI	NA,GH	NA,LS	NA,MW
103061	☑	CG0023	CG0023			JF	CL	RM	JN	NA,PV
103062	☑	CG0024	CG0024			NA,WH		LR	NA,MI	NA,TV
103063	☑	CG0025	CG0025					NA,TV		
103064	☑	CG0026	CG0026			NA,AG	NA,MW	NA,WH	NA,CC	NA,GH
103065	☑	CG0027	CG0027							

Fig. 3. Load balancing module integrated into clinical RIS PACS system and radiologist roster. Screenshot of work distribution module showing individually tailored reading lists. The system assigns different studies to radiologists based on rules such as subspecialty, relative value unit and patient type in order to balance the workload within a radiology department.

University of Singapore (NUS), Nanyang Technological University (NTU) and Agency for Science, Technology and Research (A*STAR), to build multidisciplinary research and development teams. Already, the Singapore AI technology community, with over 1000 scientists and students, is ranked second in the world by citation impact.[39-44] Key strengths include machine learning, deep learning, computer vision, robotics and natural language processing, all of which are essential for developing a core technology toolkit for medical imaging. There is also a vibrant entrepreneurial ecosystem with over 60 AI startups across the entire stack, providing a base of business and commercialisation know-how that can be adapted to radiology use cases.

Further, the Singapore healthcare ecosystem is well known for its strong digital infrastructure, centralised electronic medical record systems, and position as a trusted custodian of sensitive data, across public and private healthcare institutions alike. As such, there are compelling and immense opportunities for focused and structured research partnerships between Singapore clinical radiologists, AI technologists, entrepreneurs and healthcare providers alike to drive research and development for overcoming the challenges in AI for medical imaging applications.

Overcoming Challenges: Judicious Application of AI in Radiology

The first key challenge is in effectively leveraging the vast and rich troves of clinical imaging data that is latent in restructured hospital PACS for AI development research and development. Current AI methodologies require large volumes of high-quality artefact-free, datasets that are intensively annotated with ground truth labels for the learning tasks at hand. This introduces the need for careful extraction; matching across metadata fields and final diagnosis; as well as resource-intensive, clinically consistent labelling and image annotation. These curation and data preparation tasks occupy 50% to 70% of the time to develop AI prediction models, but are essential to ensure that the learned models are accurate, representative and generalisable for clinical use.

Recent works have explored partial automation of data curation tasks with preprocessing pipelines as well as the use of Natural Language Processing (NLP) to automatically derive image labels from radiology reports.[45,46] However, more careful efforts along these lines are urgently needed. Yet, it should also be noted that "ground truth labels" in clinical scenarios are often not straightforward, and patients can have many concurrent medical issues which may not be apparent from written medical records or radiology reports. For example, in interstitial lung disease, even a biopsy result is not necessarily a gold standard, as there can be sampling bias and histological mimics. Hence, the final diagnosis is often the result of a multidisciplinary review of each case with inputs from the primary respiratory physician, surgeon, radiologist and pathologist, which may not be apparent in the annotation process.

Furthermore, in complex cases, independent reads by different radiologists can lead to different assessments on ground truth labels (interobserver variability). To overcome these challenges, the technology research community is advancing deep learning approaches (e.g., by employing generative adversarial networks [GANs]) to learn from images in scenarios where clearly demarcated ground truth annotations are not available.[47-49] There is a need to rigorously evaluate the performance of such approaches across a range of medical imaging use cases to assess their applicability for clinical radiology tasks.

Radiologists need to work actively with relevant stakeholders to address the above challenges. First, there is a need to develop standards and tools to facilitate and encourage collaborative data use agreements,[50,51] and address important concerns around patient privacy and data security. Standards for de-identification, encryption and network access need to be developed. Researchers and institutions, mindful of the recent controversy over recent high-profile data leaks may be reluctant to share data without an assurance that the risks of compromise of data security have been adequately addressed. Second, there is a need for data integrity standards, grounded in rigorous evaluation of the different approaches for data curation as well as the degree and types of labelling and annotation required. For these efforts, a balance must be struck between realising potential research gains on the one hand, and the ethical protection of patients' autonomy and rights to privacy, and the responsibilities of clinical institutions to protect the data they contain, on the other.

The second key challenge lies in the translational process of integrating AI into existing hospital information and radiology systems, where they can be validated clinically and systemically. Non-trivial questions around whether AI models should reside inside PACS like any other analytical tool or in between image acquisition modality and PACS—presenting numerical opinions to the radiologist in form of a mini-report such as calcium scoring, bone age, myocardial tissue native relaxation properties and likelihood ratios need to be answered. These challenges present important opportunities for research and development.

It is critical to ensure that medical ethics are front and centre in any efforts to develop and translate AI for medical use. Included in the basic tenets of medical ethics are respect for autonomy, non-maleficence, beneficence, and justice, to work for the common good and benefit of humanity. These principles—familiar to all radiologists—will need to be hard-wired in the development or implementation of AI

for clinical use. Although it ought to be self-evident that AI should not be given any autonomous power to deceive, harm, destroy, or diminish the rights of individual human beings or communities, it may not possible to programme such ethical principles directly, since the machine is equipped only with pauci-dimensional linguistic and logical-mathematical intelligence.[52,53] Thus, care should be taken to ensure the safe development and implementation of AI tools in clinical radiology. While AI is less subject to cognitive biases experienced by human operators, it is still vulnerable to non-apparent biases in the data and/or algorithm.[11] If an AI model is trained using incorrect, contaminated or biased data, it could subsequently make systematic errors. Radiologists will need to validate predictions made by AI models for false-negatives and false-positives.[54] This also poses a large but not insurmountable problem of the "black box" nature of AI systems, which requires a serious and focused effort by those engineering these systems to increase the transparency and explanability of the processes contained within diagnostic or predictive models.[55] Crucially, with life-critical investigations, AI interpretation should require mandatory supervision by a human expert "in-the-loop" in order to guarantee safety, accountability and legal liability, in this case, the radiologist.[56]

Systemic entry barriers for early innovations in digital health innovation need also to be addressed. A potential national initiative to address such barriers is through the Licensing Experimentation and Adaptation Programme (LEAP),[57] a sandbox environment that allows patients and caregivers to benefit from early access to new healthcare models, without the high costs associated with large scale implementation.[58] This can serve as a way to scale up sufficiently before widespread adoption and licensing under the Healthcare Services Act (HCSA), allowing a 'Fail Early, Fail Fast, Learn Cheaply' approach.[59]

The third key challenge lies in developing a framework for radiologists, AI technologists and stakeholders to work together to drive progress. The funding and resource allocations for AI are currently being developed, and recent initiatives by the Singapore government toward developing AI at a broad strategic level have created exciting possibilities for researchers. Launched in 2017, the AI SG initiative is backed by $150 mil funding from the National Research Foundation, and driven by partnerships across various government agencies.[60] Within the MOH, digital innovation to improve patient outcomes is being supported by the National Health Innovation Centre (NHIC), which provides translational funding and strategic guidance to accelerate healthcare innovation,[61] and the Integrated Health Information Systems (IHiS) Research and Innovation Enterprise Programme (RIEP), which launched its inaugural National HealthTech Challenge 2018 in March, attracting submissions from all healthcare clusters.[62] More recently, the first clinician-innovator award was introduced by the National Medical Research Council (NMRC) in June 2018.[63] Indeed, opportunities are available for Singapore radiologists to partner with strategic government initiatives for AI in healthcare, and work with research and commercial stakeholders (Fig. 4).

How do we balance protecting the patient's individual interests and at the same time make sure society as a whole, benefits? A sensible approach would be to assert that "if big data research of today is clinical practice tomorrow", then this research should be considered a core business of the Singapore restructured hospital system.[64] Early adopters must also be prepared to deal with any unintended consequences and failures (conspicuous or otherwise) arising from disruptive technology.[65] There is a great deal of private health information in imaging data, and we are obligated by data privacy laws and radiologists' foundational medical ethics, to be responsible stewards of the trust the public has placed in us.[66,67] Hence, a framework to address issues such as the risks of bad actors/hackers compromising AI systems is needed within the vocabulary of institutional review boards (IRBs) and as complementary amendments to the law such as the Human Biomedical Research Act (HBRA)[68] to ensure ethics, safety, and data protection.

The "Centaur" Paradigm and Augmented Radiology

One of the consequences of the made-for-mass-media events pitting human and machine, such as the famous chess match between world champion Garry Kasparov and IBM's Deep Blue, has been the creation of a new form of chess player. A "centaur" chess player (evoking the half-horse, half-human of Greek mythology) combines human creativity and the ability to understand opponents using empathy, with a computer's brute-force calculations and memory

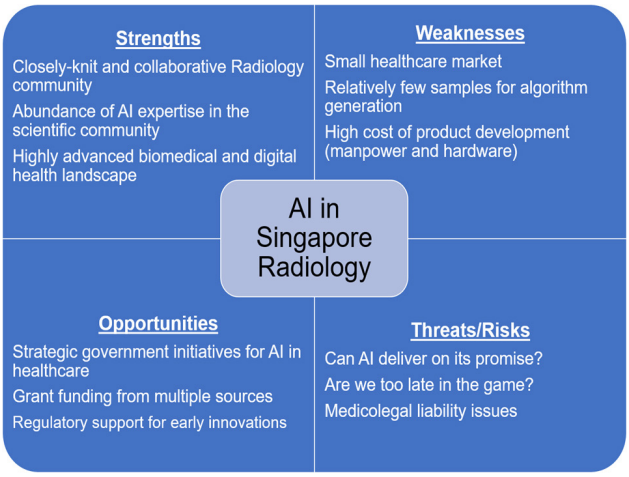


Fig 4. Strength, weakness, opportunity and threat (SWOT) analysis of AI in Singapore Radiology.

of almost all known chess moves and possible outcomes, to suggest a new paradigm of interconnectedness between humans and machines. Today, "centaur" chess players not only surpass grandmasters, but more importantly, also beat solo computers without humans. More recently, a cybersecurity system where people and machines worked together to detect cyber attacks was 3 times more accurate than the computer alone: machines outperformed humans at detecting unusual activity on the network, but humans were better at recognising which kinds of unusual activity were purely random and which were malicious.[69]

Similarly, the AI radiology systems being designed today are also human-computer "centaur" systems, and it is imperative to effectively leverage the respective strengths and roles of both.[70] The higher order metacognition, situational awareness, intuition, and creative thinking of humans can be augmented by appropriately designed smart machines to better facilitate complex pattern recognition as well as quantitative and probabilistic interpretation of clinical data to inform decision-making.[71,72] For example, a radiologist reading a complex oncology case with non-evident diagnosis or prognosis, may benefit from augmentation by semantic image retrieval and NLP tools that can automatically query the database for similar cases and display the overlaps and diagnostic/clinical outcomes for consideration. Smart tools may also have been helpful in previous disease outbreaks—clusters of individuals from different hospitals suffering magnetic resonance imaging (MRI)-detected hypoglycaemic brain damage from consumption of illicit medications could have been discovered earlier and more comprehensively if augmented by machine-learned data aggregation and pattern recognition, separating cases into typical and atypical.[73] A radiologist-in-the-loop, using smart narrow AI tools, may even be able to discern MRI lesion patterns that differentiate between 2 different types of brain infection (Nipah virus versus Japanese encephalitis), and make the mental leap to suggest pathogenesis in a novel infectious agent, even at the height of disease outbreak.[74]

Ancillary reporting tasks offer one example of a radiologist and machine augmenting one another to increase efficiency and accuracy. An AI with vision and NLP capabilities may learn from retrospective databases to present auto-complete options and fill-ins on the fly. This would augment the radiologist in writing their reports, who would then improve the AI by making corrections.

Conclusion

AI has tremendous potential to transform the practice of diagnostic radiology for the better, and play a pivotal role in Singapore's vision of patient-centric, value-added medical care that goes beyond healthcare to health. When the great diagnostician, Sir William Osler, declared that "Medicine is a science of uncertainty and an art of probability", he did so in the days when diagnosis depended mainly on clinical history and examination, not on an image. Living with uncertainty has been a fundamental patient experience of illness, and although medical images can provide an illusory visual representation of certainty, patient distress and suffering does not end when a diagnostic label is found. Today, as AI harnesses the full power of the probabilistic sciences, radiologists are poised on the cusp of a new revolution in the art of uncertainty. Building on the ethical, compassionate roots of good medical practice, AI can augment and refine the radiologist's human judgement in our constant pursuit of better care for our patients, and for humanity, because "the secret of the care of the patient, is in caring for the patient".[75,76]

Acknowledgement

The authors gratefully acknowledge Cheng Qianhui (National Neuroscience Institute Singapore) for her editorial assistance, and many colleagues for their input and advice.

REFERENCES

1. Hinton G. Machine Learning and the Market for Intelligence. In: Machine Learning and the Market for Intelligence Conference. Toronto; 2016. Available at: http://www.marketforintelligence.com. Accessed on 7 July 2018.
2. Ellenbogen PH. Imaging 3.0: What is it? J Am Coll Radiol 2013;10:229.
3. Saurabh J, Topol EJ. Adapting to artificial intelligence: radiologists and pathologists as information specialists. JAMA 2016;316:2353-4.
4. Lilly P. Nvidia CEO says Moore's Law is dead and GPUs will replace CPUs. PC Gamer. 2017. Available at: https://www.pcgamer.com/nvidia-ceo-says-moores-law-is-dead-and-gpus-will-replace-cpus/. Accessed on 3 August 2018.
5. Greenspan H, Ginneken B van, Summers RM. Guest editorial: deep learning in medical imaging: overview and future promise of an exciting new technique. IEEE Trans Med Imaging 2016;35:1153-9.
6. Kermany DS, Goldbaum M, Cai W, Valentim CCS, Liang H, Baxter SL, et al. Identifying medical diagnoses and treatable diseases by image-based deep learning. Cell 2018;172:1122-1131.e9.
7. Cheong D. Singapore firm's AI machine trumps doctors in test. The Straits Times. 2018. Available at: https://www.straitstimes.com/asia/east-asia/singapore-firms-ai-machine-trumps-doctors-in-test. Accessed on 7 July 2018.
8. Copestake J. Babylon claims its chatbot beats GPs at medical exam. BBC Click. 2018. Available at: https://www.bbc.com/news/technology-44635134. Accessed on 7 July 2018.

9. Ting DSW, Cheung CYL, Lim G, Tan GSW, Quang ND, Gan A, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA 2017;318:2211-23.
10. Cadwalladr C, Graham-Harrison E. Revealed: 50 million Facebook profiles harvested for Cambridge Analytica in major data breach. The Guardian. 2018. Available at: https://www.theguardian.com/news/2018/mar/17/cambridge-analytica-facebook-influence-us-election. Accessed on 7 July 2018.
11. Neff G, Nagy P. Automation, Algorithms, and Politics. Talking to Bots: Symbiotic Agency and the Case of Tay. Int J Commun 2016;10:4945-31.
12. Goldsmith J, Burton E. Why teaching ethics to AI practitioners is important. In: AAAI 2017: Proceedings of the Thirty-First AAAI Conference on Artificial Intelligence (AAAI-17). Available at: aaai.org/ocs/index.php/AAAI/AAAI17/paper/download/14271/13992. Accessed on 7 July 2018.
13. Tang A, Tam R, Cadrin-Chênevert A, Guest W, Chong J, Barfett J, et al. Canadian Association of Radiologists White Paper on Artificial Intelligence in Radiology. Can Assoc Radiol J 2018;69:120-35.
14. The Royal College of Radiologists. Cancer Multidisciplinary Team Meeting – Standards for Clinical Radiologists. Available at: https://www.rcr.ac.uk/sites/default/files/publication/BFCR(14)15_MDTMs.pdf. Accessed on 7 July 2018.
15. Dreyer KJ, Geis JR. When machines think: radiology's next frontier. Radiology 2017;285:713-8.
16. Rajpurkar P, Irvin J, Zhu K, Yang B, Mehta H, Duan T, et al. CheXNet: radiologist-level pneumonia detection on chest x-rays with deep learning. Available at: https://stanfordmlgroup.github.io/projects/chexnet/. Accessed on 10 November 2017.
17. Lakhani P, Sundaram B. Deep learning at chest radiography: automated classification of pulmonary tuberculosis by using convolutional neural networks. Radiology 2017;284:574-82.
18. Bluemke DA. Radiology in 2018: are you working with AI or being replaced by AI? Rsdiology 2018;287:365-6.
19. Kim JR, Shim WH, Yoon HM, Hong SH, Lee JS, Cho YA, et al. Computerized bone age estimation using deep learning based program: evaluation of the accuracy and efficiency. AJR Am J Roentgenol;2017;209:1374-80.
20. Zhu B, Liu JZ, Cauley SF, Rosen BR, Rosen MS. Image reconstruction by domain-transform manifold learning. Nature 2018;555:487-92.
21. Basha TA, Akçakaya M, Liew C, Tsao CW, Delling FN, Addae G, et al. Clinical performance of high-resolution late gadolinium enhancement imaging with compressed sensing. J Magn Reson Imaging 2017;46:1829-38.
22. Akçakaya M, Rayatzadeh H, Basha TA, Hong SN, Chan RH, Kissinger KV, et al. Accelerated late gadolinium enhancement cardiac MR imaging with isotropic spatial resolution using compressed sensing: initial experience. Radiology 2012;264:691-9.
23. Cheng LTE, Ng SES. Teleradiology in Singapore – taking stock and looking ahead. Ann Acad Med Singapore 2006;35:552-6.
24. Yang GL, Lim CCT. Singapore National Medical Image Resource Centre (SN.MIRC): a world wide web resource for radiology education. Ann Acad Med Singapore 2006;35:558-63.
25. Yang GL, Tan YF, Loh SC, Lim TCC. Neuroradiology imaging database: using picture archive and communication systems for brain tumour research. Singapore Med J 2007;48:342-6.
26. Ker J, Wang L, Rao J, Lim T. Deep learning applications in medical image analysis. IEEE Access 2018;3536:1-1.
27. Liu R, Li S, Su B, Tan CL, Leong TY, Pang BC, et al. Automatic detection and quantification of brain midline shift using anatomical marker model. Comput Med Imaging Graph 2014;38:1-14.
28. Dinh TA, Silander T, Su B, Gong T, Pang BC, Lim CCT, et al. Unsupervised medical image classification by combining case-based classifiers. Stud Health Technol Inform 2013;192:739-43.
29. Cheng LTE, Zheng J, Savova GK, Erickson BJ. Discerning tumor status from unstructured MRI reports-completeness of information in existing reports and utility of automated natural language processing. J Digit Imaging 2010;23:119-32.
30. Integrated Health Information Systems. Awards & Accolades. Available at: https://www.ihis.com.sg/Awards/Pages/awards_and_accolades.aspx?Page=2&show. Accessed on 3 August 2018.
31. Ministry of Health. Ministry of Health 2017 Budget Initiatives. Available at: https://www.moh.gov.sg/content/moh_web/home/pressRoom/Current_Issues/2017/ministry-of-health-2017-budget-initiatives.html. Accessed on 19 June 2018.
32. Singapore Radiological Society. Singapore Radiological Society. Available at: http://www.srs.org.sg/. Accessed on 3 August 2018.
33. US Food and Drug Administration. FDA permits marketing of clinical decision support software for alerting providers of a potential stroke in patients. FDA News Release 2018 Feb 13. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596575.htm. Accessed on 7 July 2018.
34. American College of Radiology. Available at: https://www.acr.org/. Accessed on 3 August 2018.
35. Radiological Society of North America. Available at: http://www.rsna.org/. Accessed on 3 August 2018.
36. Society for Imaging Informatics in Medicine. Available at: https://siim.org/. Accessed on 3 August 2018.
37. The Royal College of Radiologists. Available at: https://www.rcr.ac.uk/. Accessed on 3 August 2018.
38. Park SH, Han K. Methodologic guide for evaluating clinical performance and effect of artificial intelligence technology for medical diagnosis and prediction. Radiology 2018;286:800-9.
39. Lin J, Duan LY, Wang S, Bai Y, Lou Y, Chandrasekhar V, et al. HNIP: Compact deep invariant representations for video matching, localization, and retrieval. IEEE Trans Multimed 2017;19:1968-83.
40. Lin J, Morère O, Veillard A, Duan LY, Goh H, Chandrasekhar V. DeepHash for image instance retrieval: Getting regularization, depth and fine-tuning right. In: Proceedings of the 2017 ACM on International Conference on Multimedia Retrieval; 2017. p. 133-41.
41. Morère O, Veillard A, Lin J, Petta J, Chandrasekhar V, Poggio T. Group Invariant deep representations for image instance retrieval. CoRR 2016 Jan 9;abs/1601.0.
42. Bai Y, Lin J, Chandrasekhar V, Lou Y, Wang S, Duan LY, et al. Deep regional feature pooling for video matching. In: International Conference on Image Processing; 2018. p. 380-4.
43. Lou Y, Bai Y, Lin J, Wang S, Chen J, Chandrasekhar V, et al. Compact deep invariant descriptors for video retrieval. In: Data Compression Conference Proceedings; 2017. p. 420-9.
44. Zeng Z, Liang N, Yang X, Hoi S. Multi-target deep neural networks: theoretical analysis and implementation. Neurocomputing 2018;273:634-42.
45. Dargan R. Standardized Data is Critical to Machine Learning. RSNA News. Available at: http://www.rsna.org/News.aspx?id=24363. Accessed on 11 June 2018.
46. Hripcsak G, Austin JHM, Alderson PO, Friedman C. Use of natural language processing to translate clinical information from a database of 889,921 chest radiographic reports. Radiology 2002;224:157-63.
47. Lecouat B, Foo CS, Zenati H, Chandrasekhar VR. Semi-supervised learning with GANs: revisiting manifold regularization. CoRR 2018;abs/1805.0.
48. Zenati H, Foo CS, Lecouat B, Manek G, Chandrasekhar VR. Efficient GAN-based anomaly detection. CoRR 2018;abs/1802.0.

49. Yazici Y, Yap KH, Winkler S. Autoregressive generative adversarial networks. In: ICLR 2018. Available at: https://openreview.net/pdf?id=Hyo9zDuIz. Accessed on 7 July 2018.
50. Lomas N. Building health AIs should be UK ambition, says strategy review. Techcrunch. Available at: https://techcrunch.com/2017/08/31/building-health-ais-should-be-uk-ambition-says-strategy-review. Accessed on 11 June 2018.
51. Pennic J. Mana Health Launches Health IT Sandbox to Test Digital Health Innovation. HIT Consultant Media. Available at: https://hitconsultant.net/2016/09/27/35720/. Accessed on 11 June 2018.
52. Brooks RA. Intelligence without representation. Artif Intell 1991;47:139-59.
53. Russell SJ, Norvig P. Artificial Intelligence: A Modern Approach. Neurocomputing. New Jersey, USA: Prentice-Hall, Inc; 1995.
54. The Royal College of Radiologists. Standards for interpretation and reporting of imaging investigations. Second edition. London: The Royal College of Radiologists; 2018. Available at: https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfcr181_standards_for_interpretation_reporting.pdf. Accessed on 26 May 2018.
55. Kahn CE. From images to actions: opportunities for artificial intelligence in radiology. Radiology 2017;285:719-20.
56. Asilomar AI Principles. Future of Life Institute. Available at: https://futureoflife.org/ai-principles/. Accessed on 19 June 2018.
57. Ministry of Health. Licensing Experimentation and Adaptation Programme (LEAP) - A MOH Regulatory Sandbox. Ministry of Health Singapore. Available at: https://www.moh.gov.sg/content/moh_web/home/our_healthcare_system/RegulatorySandbox.html. Accessed on 19 June 2018.
58. Bhunia P. First healthcare regulatory sandbox launched in Singapore for telemedicine services. Available at: https://www.opengovasia.com/articles/first-healthcare-regulatory-sandbox-launched-in-singapore-for-telemedicine-services. Accessed on 19 June 2018.
59. Gelder R. The Right Way To Do Innovation: Fail Early, Fail Fast, Learn Cheaply. Available at: https://www.cebglobal.com/blogs/the-right-way-to-do-innovation-fail-early-fail-fast-learn-cheaply/. Accessed on 19 June 2018.
60. AI Singapore. National Research Foundation Singapore. Available at: https://www.nrf.gov.sg/programmes/artificial-intelligence-r-d-programme. Accessed on 19 June 2018.
61. National Health Innovation Centre. About us. National Health Innovation Centre. Available at: http://nhic.sg/web/index.php/about-us. Accessed on 19 June 2018.
62. Chew G. National HealthTech Challenge. Integrated Health Information Systems (IHiS). Available at: https://www.ihis.com.sg/nhtchallenge/SiteAssets/National HealthTech Challenge_Overview.pdf. Accessed on 19 June 2018.
63. National Medical Research Council. Clinician Innovator Award. National Medical Research Council. Available at: http://www.nmrc.gov.sg/content/nmrc_internet/home/top_nav/grants/talent-development/clinician-innovator-award.html. Accessed on 19 June 2018.
64. Health Data Research UK. Grand Challenge In Imaging AI. Health Data Research UK. Available at: https://www.hdruk.ac.uk/news/grand-challenge-in-imaging-ai/. Accessed on 22 May 2018.
65. Bostrom N. Ethical issues in advanced artificial intelligence. In: Science fiction and philosophy: from time travel to superintelligence. Schneider S, editor. Wiley-Blackwell; 2009. p. 277-84.
66. Char DS, Shah NH, Magnus D. Implementing machine learning in health care - addressing ethical challenges. N Engl J Med 2018;378:981-3.
67. Altman DG. The scandal of poor medical research. BMJ 1994;308:283.
68. Ministry of Health. Human Biomedical Research Act. Available at: https://www.moh.gov.sg/content/moh_web/home/legislation/legislation_and_guidelines/human-biomedical-research-act.html. Accessed on 3 August 2018.
69. Veeramachaneni K, Arnaldo I, Korrapati V, Bassias C, Li K. AI^2: Training a big data machine to defend. In: 2016 IEEE 2nd International Conference on Big Data Security on Cloud (BigDataSecurity), IEEE International Conference on High Performance and Smart Computing (HPSC), and IEEE International Conference on Intelligent Data and Security (IDS). IEEE; 2016. p. 49-54.
70. Liew C. The future of radiology augmented with artificial intelligence: a strategy for success. Eur J Radiol 2018;102:152-6.
71. Gichoya JW, Nuthakki S, Maity PG, Purkayastha S. Phronesis of AI in radiology: superhuman meets natural stupidity. Available at: http://arxiv.org/abs/1803.11244. Accessed on 9 July 2018.
72. Verghese A, Shah NH, Harrington RA. What this computer needs is a physician. JAMA 2018;319:19.
73. Lim CCT, Gan R, Chan CL, Tan AWK, Khoo JJC, Chia SY, et al. Severe hypoglycemia associated with an illegal sexual enhancement product adulterated with glibenclamide: MR imaging findings. Radiology 2009;250:193-201.
74. Lim CC, Sitoh YY, Hui F, Lee KE, Ang BS, Lim E, et al. Nipah viral encephalitis or Japanese encephalitis? MR findings in a new zoonotic disease. AJNR Am J Neuroradiol 2000;21:455-61.
75. Gutzeit A, Heiland R, Sudarski S, Froehlich JM, Hergan K, Meissnitzer M, et al. Direct communication between radiologists and patients following imaging examinations. Should radiologists rethink their patient care? Eur Radiol 2019;29:224-31.
76. Peabody FW. The care of the patient. JAMA 1927;88:877.

Commentary

Translating the Science of Frailty in Singapore: Results from the National Frailty Consensus Discussion

Wee Shiong Lim,[1] *MBBS, MRCP, MHPE*, Chek Hooi Wong,[2,3] *MBBS, FRCP, MPH*, Yew Yoong Ding,[1,2] *MBBS, FRCP, PhD*, Kenneth Rockwood,[4] *MD, FRCPC, FRCP*, Christopher Lien,[5] *MBBS, FRCP, MPA*

Introduction

Frailty is an age-related risk state characterised by multisystem deficits with loss of physiologic reserves, which increase the vulnerability of older adults such that even trivial stressor events can lead to a higher risk of negative health-related outcomes.[1] Against the backdrop of population ageing, the prevalence of frailty in community-dwelling older adults in the Asia-Pacific region is expected to increase exponentially from the current reported figures of 3.5% to 27%.[2] The incremental effect on ambulatory health expenditure approximates an additional 750 Euros per person per year even for people with the very mildest degree of frailty (sometimes called 'prefrailty'), and doubles to 1500 Euros per person per year for those with varying degrees of clinically apparent frailty.[3] Not surprisingly, the burgeoning number of people living with frailty has been described as an emerging public health priority.[4]

Frail patients challenge the usual approach to care due to the complexity of their needs. The encapsulation of physical, cognitive, social, and psychological dimensions within the frailty construct is attractive from the public health perspective, as it allows the complexity of care needs to be a viable indicator of the magnitude of health and social care burden, service utilisation, and ageing well.[5,6] However, uncertainty persists over existing definitions, concepts and how evidence can be translated into effective and impactful real-world models of care and interventions. Due to inherent challenges and limitations in definition and measurements, frailty is often not incorporated into practice-based settings or used to inform policy.[5,7,8] This conceptual and measurement challenge compounds contextual and methodological limitations in measuring relevant outcomes within different settings in the healthcare system.[9] Other challenges in translation to care include the exclusion of representative frail older adults from clinical trials and an evidence base underpinning frailty management that is largely derived from Europe and North America.[2,10] Meanwhile, frailty research continues to grow in size and complexity, frustrating attempts to arrive at meaningful consensus over a practical way forward.

In April 2018, the Chapter of Geriatricians, Society of Geriatric Medicine Singapore (SGMS), Geriatric Education & Research Institute (GERI), and Institute of Geriatrics & Ageing (IGA) convened the National Frailty Consensus Discussion. The 1-day discussion was held in conjunction with key stakeholders in the Ministry of Health, Agency for Integrated Care, Regional Health Systems and health practitioners; academic partners; community partners such as foundations, voluntary welfare organisations and social enterprises; and implementation partners. In light of the Asia-Pacific Clinical Practice Guidelines which were released in 2017,[2] the over-arching purpose was to discuss how the science of frailty can be translated so as to foster alignment in local policy, practice and research in contextualising the clinical practice guidelines to Singapore.

Our objectives were: 1) To describe the current state of evidence and science that can inform our action; 2) To identify gaps in local research and evaluation that can inform the future agenda; and 3) To discuss the implications for community programmes and healthcare services. During the 1-day conference, experts from the areas of practice, policy and research presented on identified key areas followed by facilitated discussion among the various stakeholders. The key findings were consolidated, summarised and agreed upon through an iterative process by the local authors (WSL, CHW, YYD and CL) of this paper, and further refined through inputs of an international expert (KR) who was an author of the Asia Pacific Clinical Practice Guidelines. We outline below the key results of the discussion.

Understanding the Science: Insights from Background Evidence

The hallmark of frailty is the decline in homeostatic reserve and resiliency that increases an individual's vulnerability to stressors, resulting in increased risk of adverse health outcomes and/or death.[1] Frailty is multidimensional

[1]Department of Geriatric Medicine, Institute of Geriatrics and Active Ageing, Tan Tock Seng Hospital, Singapore
[2]Geriatric Education and Research Institute, Singapore
[3]Department of Geriatric Medicine, Khoo Teck Puat Hospital, Singapore
[4]Department of Medicine, Dalhousie University, Canada
[5]Department of Geriatric Medicine, Changi General Hospital, Singapore
Address for Correspondence: Adj A/Prof Lim Wee Shiong, Department of Geriatric Medicine, Institute of Geriatrics and Active Ageing, Tan Tock Seng Hospital, Annex, Level 2, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: Wee_Shiong_Lim@ttsh.com.sg

and represents a complex interplay between genetic, environmental, ageing, inflammatory and neuroendocrine factors that over time results in impairment of multiple inter-related systems.[11,12] Notably, frailty is neither an inevitable consequence of ageing nor synonymous with disability or comorbidity.[13] Frailty, disability and comorbidity can affect individuals independently or coexist in any combination;[14] however, overlap is more frequent and increases with the degree of frailty.[15] Reflecting its complex dynamics,[16] frailty is also potentially reversible, with community studies reporting reversion rates of 13% to 32% to prefrail/non-frail states.[17,18]

The Comprehensive Geriatric Assessment (CGA) is the recommended "gold standard" to detect and grade frailty, although the resources required are not easily available, particularly in primary care.[2] Clinical impression through "eyeballing" per se is inadequate, and can result in false-negatives ("under-detection") and false-positives ("over-detection"). Therefore, frailty should be identified with validated tools,[2] which can be broadly conceptualised as the physical/phenotypic model[19] and the deficit accumulation model.[20] The latter derives a frailty index (FI) from a predetermined list of 30 or more variables. Whilst laborious to collect manually, it has the potential of being computed from the increasingly routine use of electronic health records to risk-stratify the frailty state.[21] Other validated tools include the FRAIL Scale,[22] Clinical Frailty Scale (CFS),[23] Tilburg Frailty Index (TFI)[24] and Edmonton Frailty Scale.[25] These frailty instruments differ in their domains and predictive abilities and thereby are not interchangeable;[26] the setting can also influence their diagnostic performance.[27] The choice of frailty instrument should be fit-for-purpose, such that it is simple to use, well validated, and provides a language to appropriately guide goal setting and care planning in the clinical setting.[2] Frailty identification should not simply result in a "label",[28] but impact management in a meaningful context-appropriate way that is used to make care rational and not to ration care.[7,29]

The Lifestyle Interventions and Independence for Elders (LIFE) study corroborates the benefits of multimodal physical activity programmes (balance and flexibility, resistance training, and aerobic components) in reducing major mobility disorder in older adults; surprisingly, the effects of multimodal training were highest among those who were frail.[30] Evidence supports the benefit of the following interventions: 1) progressive, individualised physical activity programmes that contain a resistance training component;[31,32] 2) reducing or deprescribing any inappropriate or superfluous medications;[1,2] 3) screening persons with frailty for causes of fatigue;[1,33] 4) screening for reversible causes of unintentional weight loss[2,34] and ensuring adequate protein and caloric intake;[1,35,36] and 5) vitamin D supplementation for vitamin D deficiency.[1,2] Little is known about the successful translation of evidence into real-world implementation.[7,9] Implementers have to face the challenge of an uncontrolled real-world environment with the heterogeneity of subjects, treatments and settings.[37] Beyond efficacy in controlled settings, translational research is required to better understand effectiveness in real-world settings, scalability, sustainability, and dissemination.[38]

Translating the Science: Insights from Local Evidence

The prevalence of frailty ranges from 5.7% to 6.2% among older adults in Singapore, depending on the population studied and identification tool used.[39-42] While these figures are comparable to those from other countries, it is useful to examine frailty in specific subpopulations defined by ethnicity and disease. For example, the prevalence of frailty was observed to be highest among Indians (10.1% compared with 5.6% and 6.6% among Chinese and Malays, respectively), and about twice the overall prevalence (11.6%) among people with diabetes mellitus.[39] This is an interesting finding that merits further research on mechanisms underlying these ethnic differences and their implications on a population-level approach to frailty. Of relevance, a recent scoping review of the extant scientific and grey literature from Singapore focusing on measurement of frailty suggests that its identification is influenced by the tools employed and the constructs they include.[43] In the final analysis, the choice of instrument will depend on clinical setting, purpose of assessment, and available resources.[29] In line with the Asia-Pacific guidelines,[2] for older adults identified as being frail, the recommended next steps include comprehensive geriatric assessment or at least clinical assessment of relevant aspects such as medication review;[44,45] reversible causes of fatigue and unintentional weight loss (if present); and vitamin D status. In addition, clinical guidelines that are context-specific are needed for management of individuals who have been identified as frail and prefrail.[29,46,47]

Local evidence supports the premise that frailty is reversible. In a randomised controlled trial, physical, nutritional, and cognitive interventional approaches over 6 months were found to be effective in reversing frailty among community-living older persons.[48] This positive effect persisted across 1 year and was greater when all 3 approaches were combined. Cognitive frailty—defined by the presence of both physical frailty and cognitive impairment in the absence of dementia—conferred 5- to 27-fold increased risk of adverse outcomes such as decreased quality of life, functional disability and mortality compared to robust non-cognitively impaired older adults, as opposed to corresponding risks of 1.5- to 5.5-fold in those with frailty but no cognitive impairment.[49]

Moreover, mild cognitive impairment increased the risk of physical frailty and prefrailty, most uniquely due to low lean muscle mass, slow gait speed, or gait impairment.[50] This suggests that both frailty and cognitive impairment need to be identified and managed, and further research is required to understand how best to translate these findings to practical clinical approaches. Frailty is also a significant condition encountered in acute care. Among hospitalised older adults, frailty is highly prevalent (50.0%-87.1%) and predicts in-hospital mortality, prolonged length of stay, as well as death, functional decline, and institutionalisation at 1-year.[27,51] Frailty is also an independent predictor for residual subsyndromal delirium and poorer functional recovery at 12 months postdelirium.[52] For these reasons, detection of frailty should trigger closer postdischarge monitoring. In the acute setting, frailty can be feasibly assessed using validated instruments such as FI, FRAIL, TFI and CFS, all of which afford short- and longer-term prognostication.[27,53] Further research to fill the practice gaps in using frailty to guide the management of hospitalised older adults is now needed.

The Science in Action: Applying the Insights

Singapore's response hitherto to the ongoing frailty movement has been both strategic and opportunistic, on the back of a number of parallel developments. At the national level, public healthcare has been reorganised into regional healthcare systems in recent years to achieve the triple aim of improving population health, enhancing experience of care, and reducing per capita cost[54] by forging a frailty-ready healthcare system across the spectrum, which includes the well healthy ("living well"), well unhealthy ("living with illness"), unwell unhealthy ("living with frailty"), and end-of-life ("dying well").[29] On the community front, the Healthy Living Masterplan (2013) envisages healthy living as accessible, natural and effortless for all Singaporeans through an emphasis on the physical and social environments in community settings.[55] This was followed in 2015 by the $3 billion national 'Action Plan for Successful Ageing', which included a goal to transform the city via transport and 'Active-Ageing Hubs' into an enabling "city for all ages" for seniors to live and commute independently in their own homes or communities.[56] In recent years, there has been a surge in the network of programmes, activities and campaigns to promote physical activity and mental well-being amongst community-dwelling older adults through collaborative efforts between the Health Promotion Board and government-linked agencies such as the National Trade Union Congress (NTUC) Health and Sport Singapore.[57,58]

Complementing these national initiatives are innovations in the delivery of exercise and nutrition in the community via philanthropic, academic and non-profit collaborations, such as 'Gym Tonic',[59] Happy Aging Promotion Program for You (HAPPY),[57] and the Share-a-Pot programme.[60] Preliminary results from these programmes are encouraging: 1) 'Gym Tonic', a 12-week strength training programme using customised equipment and trained therapists, improved 41% and 55% of frail seniors in nursing homes and senior care centres, respectively to the prefrail state,[59] and 2) HAPPY, adapting dual-tasking exercises from the Cognicise Programme at the National Centre for Geriatrics and Gerontology (NCGG) in Nagoya, Japan, improved components of fatigue, resistance and illnesses of the FRAIL scale.[61] There remains a gap in evidence regarding the effective translation of these programmes in the real-world setting. Programme evaluation and implementation research will need to incorporate appropriate frameworks and outcome measures for complex interventions to understand the mechanisms and interrelated components, which affect the efficacy, cost-effectiveness, scalability, and sustainability of these programmes.

Summary and Recommendations

Two trends underpin the ongoing transformation of healthcare systems and practice in Singapore, namely the changing needs of an ageing population that portend the epidemiologic transition towards non-communicable chronic diseases with increasingly complex healthcare needs, and a growing shift toward disease prevention and population health. Not surprisingly, policymakers and health service providers—locally and worldwide—have increasingly turned their attention toward the frailty concept to more significantly target the healthcare needs of the ageing population. For instance, the United Kingdom's "GP contract" policy initiative requires general practitioners (GPs) to identify and manage all older patients aged 65 years and older who are moderately to severely frail.[62] In contrast, many other countries (including Singapore) have yet to systematically incorporate frailty into practice on a wider scale.

Against this backdrop, the National Frailty Consensus Discussion was convened in conjunction with key stakeholders to leverage upon the recently released Asia-Pacific Clinical Practice Guidelines to move forward the agenda of translating the science of frailty in Singapore. In summary, the current body of evidence has established that frailty represents a clinical state that is common, serious, costly and potentially preventable. From the public health perspective, frailty provides a useful construct that can be potentially applied across the spectrum of healthcare from robust, community-dwelling older adults through to end-of-life care. The body of evidence from international and local studies supports the potential of translating frailty and related concepts into real-world models of care and intervention in

a tangible way that may benefit health outcomes for older adults. This evidence base provides the foundation with which to plan and appraise ongoing and future initiatives at the national and ground level. We also identified gaps in local research that pertain largely to frailty epidemiology, identification, and evaluation of innovations and real-world implementation. We propose that these developments be viewed through the lenses of the 4A framework of agenda, ambition, alignment and action (Table 1).[63]

To adequately respond to the multifaceted challenges posed by population ageing, a comprehensive agenda is required to address the frailty conundrum across its spectrum, ranging from the well healthy ("living well"), well unhealthy ("living with illness"), unwell unhealthy ("living with frailty") through to end-of-life ("dying well").[29] This approach transcends the ongoing debate about whether frailty is more a predisability at-risk state or a geriatric syndrome.[9,11] Instead, frailty should be the cornerstone of health and social care systems for population ageing, integrated at multiple levels and supported by a multifactorial systems-based approach to bring together multiple stakeholders in the community, healthcare system, academia and policymaking.[5,64] While the emphasis on preventative population health approaches is laudable, it is also important not to overlook the pressing needs of the established frail who are negotiating the healthcare system.[65,66] A recent study using a large English inpatient database reported that frailty accounted for one-fifth of inpatients and almost half of all hospitalisation days,[67] reiterating the urgency for close attention to this at-risk group to reduce health utilisation arising from frailty and its complications.[8] We need to better understand how incorporating frailty tools in clinical practice can help formulate and improve the care plan for shared decision-making,[68] as well as spur innovations in the areas of admission avoidance;[69] inpatient collaborative care models such as delirium units, ortho-geriatrics services, and geriatric surgical services;[70-72] postdischarge support;[29] and transition to end-of-life care.[73]

This leads to the next point about ambition. Instead of piecemeal and elaborate adhoc programmes that tend to only benefit specific segments of the at-risk population, it is important to consider integrated programmes with a potential for scalability and sustainability, either at the level of public health or integrated care models. This necessitates an alignment of frailty threshold concepts, evaluation measures, and evidence-based interventions among stakeholders, ranging from healthcare practitioners, community partners, policymakers, and academics. Specifically, in the area of frailty identification, consensus on tools for frailty identification and measurement is required, given that new instruments that demarcate frailty into physical, cognitive, psychological, and social dimensions can contribute to further confusion.[5,74] Alignment in standardisation of measurement is needed for case definition in the community, healthcare system and policy databases, akin to the National Health Service primary care strategy in frailty for older adults aged 65 years and above, which includes standardising a frailty measure (the electronic FI) and creating an ecosystem that supports the identification and guidelines-based management of frailty.[75]

What next in terms of action? A strategic approach is required to translate frailty concepts to design fit-for-purpose health and social services that would genuinely impact the health of older adults.[64] On the community front, the action has already begun in terms of translating the Asia-Pacific guidelines into evidence-based multicomponent programmes. More can be done to promote the incorporation of resistance training beyond aerobic and balance exercises in physical activity programmes.[2] Because older adults may find frailty a difficult concept to engage with,[76] more research is required on how best to frame and communicate the frailty concept for public education and in clinical practice. Recently, there are increasing calls to develop frailty research concurrently with health service research in order to incorporate frailty into meaningful clinical management protocols,[5] for instance, rapid comprehensive geriatric assessment and intervention by a designated inter-professional team in acute frailty units to optimise functional outcomes, reduce length of stay and reduce readmissions.[77] In considering uptake by the system, it will be important to distinguish between tools for frailty screening and then the assessment of frailty in those who screen positive. The

Table 1. Summary of Key Points

• Frailty represents a clinical state that is common, serious, costly and potentially preventable.
• Frailty provides a useful construct that can be applied across the continuum of care from preventative, treatment to end-of-life care.
• More local research is required to address gaps in the evidence-base in frailty epidemiology, identification, and evaluation of innovations and real-world implementation.
• Key recommendations:
1) Comprehensive agenda that addresses the frailty conundrum across its spectrum from the robust/prefrail in the community through to established frail in the healthcare system.
2) Ambition for care models and approaches to be integrated such that impact at the level of public health can be scaled and sustained.
3) Alignment of identification measures, case definitions, and evidence-based interventions for frailty.
4) Multifaceted action, including: a. Public education and engagement b. Incorporating frailty into routine clinical care plans c. Enhancing research methodologies, evaluation approaches and outcomes for complex interventions d. Broad-based interdisciplinary expertise

goal is to achieve actionable, feasible, individualised and patient-centred care plans.

Regarding programme evaluation, the exclusive application of randomised controlled trials and related experimental designs may not be the most appropriate for evaluating complex interventions.[78,79] Paralleling research developments in non-pharmacological interventions for persons with dementia,[80] understanding the complexity of frailty could benefit from the use of implementation-specific research methods such as pragmatic trials to test interventions embedded within the real-world context.[81] In addition, evaluations that adopt realist approaches to uncover "what works, for whom, under what circumstances, and how?" can help build theory that links context, mechanisms and outcomes of complex multicomponent real-world interventions.[82,83] Studies should incorporate clinically relevant and meaningful outcomes such as quality of life, cognition, physical function and psychosocial consequences,[84] and encompass plurality of methods (including the rich diversity of qualitative methods) to answer use-inspired Pasteur's quadrant research questions.[37,85] Lastly, as we embark on the next phase of population-wide preventative strategies, we advocate a broad-based interdisciplinary approach that integrates expertise from other fields. For instance, insights from the social and behavioural sciences can be explored to bridge the knowledge-practice gap in healthy living, optimise the behavioural affordance of an enabling environment, and address the low adherence to multicomponent interventions for frailty.[86-88] Leveraging upon accessible platforms, analytics, technological advances and marketing expertise of the business and technology sectors to improve population health is another relatively untapped dimension.[89]

Conclusion

In recent years, frailty has emerged as a public health priority for policymakers and practitioners worldwide. Likewise, Singapore needs to respond to the frailty conundrum in the ongoing efforts to transform healthcare to meet the needs of its rapidly ageing population. In this paper, we discussed the current international and local evidence base and the implications for translating the science of frailty in Singapore. The existing evidence for frailty appears promising and suggests that systematic and fit-for-purpose frailty identification that is linked to appropriate follow-up intervention would lead to better health outcomes of frail older adults.[1,2] Whilst the Asia-Pacific guidelines represent a positive step in recommending clinical practice management of frailty, significant gaps in the evidence base remain regarding the implementation of these guidelines and evaluating outcomes of successful implementation in a real-world environment. There is a need for more comprehensive and coordinated inclusion of frailty into clinical management protocols and models of care, along with more robust research and evaluation in well designed pragmatic trials which test effectiveness and build theory around complex interventions in the real-world context of Singapore's healthcare, social and payment systems. Ultimately, these gaps within the evidence base will need to be resolved if frailty were to be established as a "real", relevant and reachable concept that meaningfully impacts our healthcare and social systems in Singapore.[5]

Acknowledgements

The authors would like to thank the Chapter of Geriatricians; the Society of Geriatric Medicine, Singapore (SGMS); the Institute of Geriatrics and Ageing, Tan Tock Seng Hospital (TTSH) and the Geriatric Education and Research Institute (GERI) for co-hosting the National Consensus Discussion on Frailty at Changi General Hospital (CGH), Singapore. They thank the speakers and the moderators: Dr Mark Chan Peng Chew (TTSH), A/Prof Wong Wei Chin (TTSH), A/Prof Reshma Merchant (National University Hospital), Dr Rahul Malhotra (Duke-NUS Medical School), A/Prof Ng Tze Pin (GERI), Dr Laura Tay (Sengkang General Hospital), Mr Lee Poh Wah (Lien Foundation), and Dr Wong Sweet Fun (Khoo Teck Puat Hospital). They are also thankful for the exercise conversations and demonstrations throughout the meeting led by: Mr Isaiah Chng (ProAge Singapore), Ms Junisha Jamala (CGH), Mr Lutfi Zianalabidin (Sport Singapore), Ms Sharifa Norzila (Active Health, Sport SG), Ms Lee Sin Yi (Singapore Physiotherapy Association), and Mr Hedehiko Shirooka (HAPPY programme). They are also grateful to Dr Melvin Chua (Past President SGMS) and Dr Chew Aik Phon (President, SGMS) for their support in shaping this meeting, and Professor Tan Chor Chuan (Office of Transformation, Ministry of Health) for being present. Finally, they wish to thank Deputy Secretary of Health, Ms Teoh Zsin Woon for her engagement in the discussion and for her resounding support before and after the meeting, especially in the development and delivery of frailty programmes for the elderly in Singapore.

REFERENCES

1. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14:392-7.
2. Dent E, Lien C, Lim WS, Wong WC, Wong CH, Ng TP, et al. The Asia-Pacific clinical practice guidelines for the management of frailty. J Am Med Dir Assoc 2017;18:564-75.
3. Sirven N, Rapp T. The cost of frailty in France. Eur J Health Econ 2017;18:243-53.
4. Cesari M, Prince M, Thiyagarajan JA, De Carvalho IA, Bernabei R, Chan P, et al. Frailty: an emerging public health priority. J Am Med Dir Assoc 2016;17:188-92.
5. Woo J. Challenges of population ageing: putting frailty as a cornerstone of health and social care systems. Eur Geriatr Med 2018;9:273-6.
6. Woo J, Leung J, Zhang T. Successful aging and frailty: opposite sides of the same coin? J Am Med Dir Assoc 2016;17:797-801.

7. Rodriguez-Manas L, Fried LP. Frailty in the clinical scenario. Lancet 2015;385:e7-9.
8. Searle SD, Rockwood K. What proportion of older adults in hospital are frail? Lancet 2018;391:1751-2.
9. Sloane PD, Cesari M. Research on frailty: continued progress, continued challenges. J Am Med Dir Assoc 2018;19:279-81.
10. Holroyd-Leduc J, Resin J, Ashley L, Barwich D, Elliott J, Huras P, et al. Giving voice to older adults living with frailty and their family caregivers: engagement of older adults living with frailty in research, health care decision making, and in health policy. Res Involv Engagem 2016;2:23.
11. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752-62.
12. Walston JD. Frailty. In: Geriatrics for specialists. Springer; 2017. p. 3-12.
13. Wong CH, Weiss D, Sourial N, Karunananthan S, Quail JM, Wolfson C, et al. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. Aging Clin Exp Res 2010;22:54-62.
14. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255-63.
15. Theou O, Rockwood MR, Mitnitski A, Rockwood K. Disability and co-morbidity in relation to frailty: how much do they overlap? Arch Gerontol Geriatr 2012;55:e1-8.
16. Mitnitski AB, Rutenberg AD, Farrell S, Rockwood K. Aging, frailty and complex networks. Biogerontology 2017;18:443-6.
17. Chong MS, Tay L, Chan M, Lim WS, Ye R, Tan EK, et al. Prospective longitudinal study of frailty transitions in a community-dwelling cohort of older adults with cognitive impairment. BMC Geriatr 2015;15:175.
18. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Arch Intern Med 2006;166:418-23.
19. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
20. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001;1:323-36.
21. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing 2016;45:353-60.
22. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601-8.
23. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.
24. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg Frailty Indicator: psychometric properties. J Am Med Dir Assoc 2010;11:344-55.
25. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526-9.
26. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev 2016;26:53-61.
27. Chong E, Ho E, Baldevarona-Llego J, Chan M, Wu L, Tay L, et al. Frailty in hospitalized older adults: comparing different frailty measures in predicting short- and long-term patient outcomes. J Am Med Dir Assoc 2018;19:450-7e3.
28. McTighe J. Three key questions on measuring learning. Educational Leadership 2018;75:14-20.
29. Lim WS, Wong SF, Leong I, Choo P, Pang WS. Forging a frailty-ready healthcare system to meet population ageing. Int J Environ Res Public Health 2017;14:1448.
30. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE study randomized clinical trial. JAMA 2018;311:2387-96.
31. Bauman A, Merom D, Bull FC, Buchner DM, Fiatarone Singh MA. Updating the evidence for physical activity: summative reviews of the epidemiological evidence, prevalence, and interventions to promote "active aging". Gerontologist 2016;56 Suppl 2:S268-80.
32. Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C, Vandervoort AA, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. J Aging Res 2011;2011:569194.
33. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007;55:780-91.
34. Morley JE. Undernutrition in older adults. Fam Pract 2012;29 Suppl 1:i89-93.
35. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013;14:542-59.
36. Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Database Syst Rev 2009:CD003288.
37. Lim WS, Ding Y. Evidence-balanced medicine:"real" evidence-based medicine in the elderly. Ann Acad Med Singapore 2015;44:1-5.
38. Werner-Seidler A, Perry Y, Christensen H. An Australian example of translating psychological research into practice and policy: where we are and where we need to go. Front Psychol 2016;7:200.
39. Merchant RA, Chen MZ, Tan LWL, Lim MY, Ho HK, van Dam RM. Singapore Healthy Older People Everyday (HOPE) Study: prevalence of frailty and associated factors in older adults. J Am Med Dir Assoc 2017;18:734.e9-.e14.
40. Vaingankar JA, Chong SA, Abdin E, Picco L, Chua BY, Shafie S , et al. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatr Gerontol Int 2017;17:1444-54.
41. Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Frailty and malnutrition: related and distinct syndrome prevalence and association among community-dwelling older adults: Singapore Longitudinal Ageing Studies. J Am Med Dir Assoc 2017;18:1019-28.
42. Ge L, Yap CW, Heng BH. Prevalence of frailty and its association with depressive symptoms among older adults in Singapore. Aging Ment Health 2018:1-6.
43. Bautista MA, Malhotra R. Identification and Measurement of Frailty: A Scoping Review of Published Research from Singapore. Ann Acad Med Singapore 2018;47:455-91.
44. Lim WS, Low HN, Chan SP, Chen HN, Ding YY, Tan TL. Impact of a pharmacist consult clinic on a hospital-based geriatric outpatient clinic in Singapore. Ann Acad Med Singapore 2004;33:220-7.
45. Mamun K, Lien CT, Goh-Tan CY, Ang WS. Polypharmacy and inappropriate medication use in Singapore nursing homes. Ann Acad Med Singapore 2004;33:49-52.
46. Chan KM, Pang WS, Ee CH, Ding YY, Choo P. Self-perception of health among elderly community dwellers in Singapore. Ann Acad Med Singapore 1998;27:461-7.
47. Joshi VD, Malhotra R, Lim JF, Ostbye T, Wong M. Validity and reliability of the expectations regarding aging (ERA-12) instrument among middle-aged Singaporeans. Ann Acad Med Singapore 2010;39:394-8.
48. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. Am J Med 2015;128:1225-36.e1.

49. Feng L, Zin Nyunt MS, Gao Q, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: findings from the Singapore Longitudinal Ageing Studies (SLAS). J Am Med Dir Assoc 2017;18:252-8.
50. Nyunt MSZ, Soh CY, Gao Q, Gwee X, Ling ASL, Lim WS, et al. Characterisation of physical frailty and associated physical and functional impairments in mild cognitive impairment. Front Med (Lausanne) 2017;4:230.
51. Wu HY, Sahadevan S, Ding YY. Factors associated with functional decline of hospitalised older persons following discharge from an acute geriatric unit. Ann Acad Med Singapore 2006;35:17-23.
52. Chew J, Lim WS, Chong MS, Ding YY, Tay L. Impact of frailty and residual subsyndromal delirium on 1-year functional recovery: a prospective cohort study. Geriatr Gerontol Int 2017;17:2472-8.
53. Chong E, Ho E, Baldevarona-Llego J, Chan M, Wu L, Tay L. Frailty and risk of adverse outcomes in hospitalized older adults: A comparison of different frailty measures. J Am Med Dir Assoc 2017;18:638.e7-11.
54. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Aff (Millwood) 2008;27:759-69.
55. Ministry of Health, Singapore. Healthy Living Master Plan. Available at: https://www.moh.gov.sg/content/dam/moh_web/Publications/Reports/2014/HLMP/MOH_Healthy%20Living%20Master%20Plan_Inside%20Page_8d.pdf. Accessed on 30 July 2018.
56. Ministry of Health, Singapore. Action Plan for Successful Aging. 2016. Available at: https://www.moh.gov.sg/content/dam/moh_web/SuccessfulAgeing/action-plan.pdf. Accessed on 30 July 2018.
57. Health Promotion Board. New exercise campaign to encourage active living among seniors, including those with reduced mobility. 2017. Available at: https://www.hpb.gov.sg/article/new-exercise-campaign-to-encourage-active-living-among-seniors-including-those-with-reduced-mobility. Accessed on 30 July 2018.
58. Activesg. Be a Sport Volunteer. Available at: https://www.myactivesg.com/whats-on/team-nila-sport-volunteer-drive. Accessed on 30 July 2018.
59. Gym Tonic. Exercise as medicine. Available at: www.gymtonic.sg. Accessed on 30 July 2018.
60. Wong SF. Building Health Systems to Support Physical Activity & Active Ageing. 12 August 2016. Proceedings of the Asia Pacific Geriatric Conference; Singapore.
61. Straits Times. Happy hour helps seniors delay frailty and disability. 2017. Available at: https://www.straitstimes.com/singapore/health/happy-hour-helps-seniors-delay-frailty-and-disability. Accessed on 30 July 2018.
62. Chapman S, Thomas S. Falls and the rise of the GP contract: An EMIS web protocol and template to help identify frail patients. Br J Community Nurs 2017;22:554-6.
63. Teoh ZW. 9 April 2018. Proceedings of Translating the Science of Frailty in Singapore: A National Consensus Discussion; Singapore.
64. Woo J. Designing fit for purpose health and social services for ageing populations. Int J Environ Res Public Health 2017;14:457.
65. Sahadevan S, Earnest A, Koh YL, Lee KM, Soh CH, Ding YY. Improving the diagnosis related grouping model's ability to explain length of stay of elderly medical inpatients by incorporating function-linked variables. Ann Acad Med Singapore 2004;33:614-22.
66. 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.
67. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018;391:1775-82.
68. Theou O, Squires E, Mallery K, Lee JS, Fay S, Goldstein J, et al. What do we know about frailty in the acute care setting? A scoping review. BMC Geriatr 2018;18:139.
69. Foo CL, Siu VW, Ang H, Phuah MW, Ooi CK. Risk stratification and rapid geriatric screening in an emergency department - a quasi-randomised controlled trial. BMC Geriatr 2014;14:98.
70. Chong MS, Chan MP, Kang J, Han HC, Ding YY, Tan TL. A new model of delirium care in the acute geriatric setting: geriatric monitoring unit. BMC Geriatr 2011;11:41.
71. Ramason R, Chong MS, Chan W, Rajamoney GN. Innovations in hip fracture care: a comparison of geriatric fracture centers. J Am Med Dir Assoc 2014;15:232-3.
72. Chia CL, Mantoo SK, Tan KY. 'Start to finish trans-institutional transdisciplinary care': a novel approach improves colorectal surgical results in frail elderly patients. Colorectal Dis 2016;18:O43-50.
73. Hum AYM, Wu HY, Ali NB, Leong I, Chin JJ, Lee A, et al. The dignity in advanced dementia (diadem) study: developing an integrated geriatric palliative homecare program. Progress in Palliative Care 2018;26:65-72.
74. Morley JE. Cognitive frailty: A new geriatric syndrome? Eur Geriatr Med 2015;5:408-11.
75. Supporting routine frailty identification and frailty through the GP Contract 2017/2018. Available at: https://www.england.nhs.uk/publication/supporting-routine-frailty-identification-and-frailty-through-the-gp-contract-20172018/. Accessed on 30 July 2018.
76. Archibald MM, Ambagtsheer R, Beilby J, Chehade MJ, Gill TK, Visvanathan R, et al. Perspectives of frailty and frailty screening : protocol for a collaborative knowledge translation approach and qualitative study of stakeholder snderstandings and experiences. BMC Geriatr 2017;17:87.
77. Atkins A, Egbe M, Kallat A. Modernising geriatric care: establishing an acute frailty unit. Future Hospital Journal 2015;2:s25.
78. Blackwood B, O'halloran P, Porter S. On the problems of mixing RCTs with qualitative research: the case of the MRC framework for the evaluation of complex healthcare interventions. J Nurs Educ 2010;15:511-21.
79. Van Belle S, Rifkin S, Marchal B. The challenge of complexity in evaluating health policies and programs: the case of women's participatory groups to improve antenatal outcomes. BMC Health Serv Res 2017;17:268.
80. Baier RR, Mitchell SL, Jutkowitz E, Mor V. Identifying and supporting nonpharmacological dementia interventions ready for pragmatic trials: results from an expert workshop. J Am Med Dir Assoc 2018;19:560-2.
81. Gibbons M. Mode 2 society and the emergence of context-sensitive science. Science and Public Policy 2000;27:159-63.
82. Pawson R. The realist foundations of evidence-based medicine: A review essay. Evaluation 2018;24:42-50.
83. Vareilles G, Pommier J, Kane S, Pictet G, Marchal B. Understanding the motivation and performance of community health volunteers involved in the delivery of health programs in Kampala, Uganda: a realist evaluation protocol. BMJ Open 2015;5:e006752.
84. Theou O, Searle SD. Using frailty tools as prognostic markers in patients who are acutely ill. CMAJ 2018;190:E182-3.
85. Stokes DE. Pasteur's quadrant – basic science and technological innovation. Washington, DC: Brookings Institution Press; 1997.
86. Abbasi J. New strategic plan for behavioral and social sciences research. JAMA 2017;317:350.
87. Stolte E, Hopman-Rock M, Aartsen MJ, van Tilburg TG, Chorus A. The theory of planned behavior and physical activity change: outcomes of the Aging Well and Healthily Intervention Program for Older Adults. J Aging Phys Act 2017;25:438-45.
88. Yu R, Wang D, Leung J, Lau K, Kwok T, Woo J. Is neighborhood green space associated with less frailty? Evidence from the Mr. and Ms. Os (Hong Kong) study. J Am Med Dir Assoc 2018;19:528-34.
89. Stey A, Kanzaria H, Brook R. How disruptive innovation by business and technology firms could improve population health. JAMA 2018;320:973-4.

Brief Smoking Cessation Interventions on Tuberculosis Contacts Receiving Preventive Therapy

Dear Editor,

Tobacco is one of the greatest public health threats, accounting for more than 7 million deaths each year.[1] In Singapore, the prevalence of smoking was estimated as 13.3% of the population aged 18 to 69 years in 2013.[2] The positive association between tuberculosis (TB) and smoking is well established in regard to the increased risk of latent TB infection (LTBI), active TB, TB recurrence and mortality due to suppression of the immune system.[3-5] Brief smoking cessation advice by healthcare professionals is demonstrated to be effective[6-9] and recommended by the United States Preventive Services Task Force.[10]

Although previous studies have determined smoking cessation effectiveness on active TB patients, few studies have examined the impact on contacts with LTBI.[11-14] Hence, this trial was established to determine the effectiveness of brief, opportunistic regular smoking cessation advice, which can be easily incorporated into routine clinical outpatient settings in contacts with LTBI undergoing 6 months of preventive therapy (PT) at the Singapore TB Control Unit Contact Clinic.

Materials and Methods

A prospective cohort (intervention) group was compared to a historical control group. The period of the intervention group recruitment was from 28 March to 30 September 2016 and comprised current smokers with LTBI who had self-reported their status on commencement of their PT. The control group was recruited 6 months earlier (30 September 2015 to 27 March 2016) using similar criteria. For the control group, brief, uniformed smoking cessation advice was given by the clinic nurses only at the start of PT, and their smoking status was confirmed again upon completion of their 6 months of treatment.

Interventions in the cohort group consisted of a smoking cessation booklet published by the Singapore Health Promotion Board (HPB) and brief, uniformed smoking cessation advice by the same group of nurses as those advising the control group at the initial visit; similar smoking cessation advice would be repeated at 4 to 5 weekly intervals until their treatment completion. Patients were instructed to peruse the booklet, with no assistance offered. Nurses were instructed to tell patients that smoking increases their chances of developing active TB and can cause other serious illnesses such as cancer and heart disease. Smoking status was checked and recorded by the same group of nurses at each visit, with the approximate date of smoking cessation, if applicable, and number of sticks smoked, if reported by the patient.

Information pertaining to patient demographics and presence of comorbidities such as diabetes mellitus, human immunodeficiency virus (HIV) infection and end stage renal failure were captured as per routine contact clinic patient's initial interview data. Patients who ceased PT prematurely were excluded from the analysis.

Ethics approval was not sought as this intervention was a programmatic initiative implemented for detection of benefits on contacts undergoing PT at our centre.

Data were analysed using SPSS (version 13; SPSS, Inc., Chicago IL), where Pearson's χ^2 was used to compare the results for the 2 groups. The level of significance was $P < 0.05$. Variables which were compared included the age, country of birth, gender, ethnicity and comorbidities such as diabetes mellitus and end stage renal failure.

Results

There were 41 individuals in the control group and 56 cases in the cohort group for analysis. Comparison of the baseline characteristics as described in Table 1 showed no significant differences in most variables, except for a significantly higher number of smokers who were of ethnicities other than Chinese, Malay and Indians in the cohort group ($P = 0.03$).

A significantly higher proportion of individuals in the intervention group achieved successful smoking cessation at the completion of their PT compared to the control group (35.7% vs 9.8%, $P = 0.003$), or decreased their cigarette consumption (32.3% vs 19%, $P = 0.024$). Table 2 shows the analysis of baseline characteristics between those who achieved smoking cessation against those who did not in the intervention group, with no significant differences demonstrated.

Discussion

A significantly higher proportion of smokers in the intervention group quit smoking at the time of PT completion compared to a historical control group, demonstrating effectiveness of brief regular, uniform smoking cessation

Table 1. Baseline Characteristics of the Control and Cohort Groups

Characteristics		Controls (n = 41)	Cohort Group (n = 56)	Univariate Analysis		Multivariate Analysis	
				Odds Ratio	*P* Value (CI 95%)	Odds Ratio	*P* Value (CI 95%)
Age							
≥40 years		20 (48.8%)	28 (50.0%)	1		1	
<40 years		21 (51.2%)	28 (50.0%)	0.95	0.91 (0.43 – 2.13)	1.72	0.27 (0.65 – 4.54)
Ethnicity							
Chinese		23 (56.1%)	19 (33.9%)	1		1	
Malay		5 (12.2%)	11 (19.6%)	2.66	0.12 (0.79 – 9.01)	2.73	0.12 (0.77 – 9.68)
Indian		6 (14.6%)	6 (10.7%)	1.21	0.77 (0.34 – 4.37)	1.64	0.55 (0.33 – 8.20)
Others		7 (17.1%)	15 (26.8%)	3.46	0.02 (2.21 – 9.92)	5.50	0.03 (1.22 – 24.70)
Country of birth							
Singapore		24 (58.5%)	30 (53.6%)	1		1	
Others		17 (41.5%)	26 (46.4%)	1.22	0.63 (0.54 – 2.76)	1.59	0.48 (0.45 – 5.66)
Gender							
Male		34 (82.9%)	49 (87.5%)	1.44	0.54 (0.46 – 4.49)	1.80	0.36 (0.52 – 6.24)
Female		7(17.1%)	7 (12.5%)	1		1	
Comorbidities							
Diabetes mellitus	No	37 (90.2%)	55 (98.2%)	1		1	
	Yes	4 (9.8 %)	1 (1.8 %)	0.12	0.17 (0.018 – 1.57)	0.14	0.10 (0.01 – 1.49)
End stage renal failure	No	40 (97.6%)	55 (98.2%)	1		1	
	Yes	1 (2.4%)	1 (1.8%)	0.82	0.73 (0.04 – 11.98)	0.74	0.84 (0.04 – 13.28)

Table 2. Baseline Characteristics of Cohort Group Individuals Who Stopped or Continued Smoking

Characteristics		Stopped (n = 20)	Did Not Stop (n = 36)	Multivariate Analysis	
				Odds Ratio	*P* Value (CI 95%)
Age					
≥40 years		11 (55.0%)	17 (47.2%)	1	
<40 years		9 (45.0%)	19 (52.8%)	2.16	0.17 (0.72 – 6.45)
Ethnicity					
Chinese		5 (25.0%)	14 (38.9%)	1	
Malay		4 (20.0%)	7 (19.4%)	3.02	0.12 (0.74 – 12.28)
Indian		2 (10.0%)	4 (11.1%)	1.21	0.85 (0.19 – 7.78)
Others		9 (45.0%)	11 (30.6%)	2.99	0.17 (0.63 – 14.30)
Country of birth					
Singapore		8 (40.0%)	22 (61.1%)	1	
Others		12 (60.0%)	14 (38.9%)	2.06	0.31 (0.51 – 8.34)
Gender					
Male		18 (90.0%)	31 (86.1%)	2.65	0.24 (0.52 – 13.59)
Female		2 (10.0%)	5 (13.9%)	1	
Comorbidities*					
Diabetes mellitus	No	20 (100%)	35 (97.2%)		
	Yes	0 (0 %)	1 (2.8 %)		
End stage renal failure	No	20 (100%)	35 (97.2%)		
	Yes	0 (0%)	1 (2.8%)		

*Sample size was too small for any meaningful analysis to be made.

advice from healthcare providers. This outcome was achieved without specific training of our clinic nurses as to smoking cessation advice. As the cohort group was also given a HPB smoking cessation booklet at the beginning of their PT, it is not possible to tease out the effect/contribution of the smoking cessation booklet from that of repeated, brief smoking cessation advice; we therefore view and discuss these interventions as a package.

Brief smoking cessation advice to TB patients at each clinic visit has been shown to result in high quit rates in a Directly Observed Treatment Short (DOTS) course service in Indonesia,[15] and reinforced smoking cessation health messages have been found to be effective in routine TB services in rural China,[16] in addition to numerous other studies.[11-14]

Interestingly, another study by Lancaster and Stead, estimated the effect of physician's advice on patients' smoking cessation rate at 1% to 3% at 6 months.[7] The apparent increased intervention impact may be explained by the high frequency of interactions with our clinic staff as these individuals were seen every 4 weeks for 6 months, resulting in higher intervention exposure of subjects. The contacts might also relate more to the message of reduced active TB progression risk via smoking cessation.

Although a higher percentage of foreign-born individuals succeeded in smoking cessation compared to the control group, this could partly be due to the small sample size, further compounded by a significantly higher number of foreign-born subjects. Another possible explanation might be the desensitisation of Singapore-born persons to antismoking messages, having had repeated exposures from an early age.

Older individuals (≥40 years old) were also more likely to stop smoking. This could be due to perceived increased benefits of smoking cessation, with increased probability of concurrent pre-existing comorbidities. In contrast, those of younger ages (<40 years old) would likely be healthier, with less smoking cessation benefits perceived, especially where smoking might be conceived as fashionable within their social circle.

Our small sample size might have resulted in certain characteristics being both over- and under-represented. For example, the numbers of other ethnicities besides Chinese, Malay and Indian were significantly different in the cohort group, which might have accounted for the higher number who stopped smoking.

As in all studies which rely on patient self-reporting, our findings may have been influenced by biases of both social desirability and acquiescence, where participants might feel compelled to report what they think reflects better on them. However, trials such as Stange et al have shown high sensitivity (0.7) and specificity (0.96) based on patients' report in smoking cessation studies during exit surveys.[17] Still, perhaps more objective measures such as biological markers at certain time-points could be considered in future studies. We also measured outcomes only at the 6-month time-point, and the long-term impact of the interventions remains a question. Hence, further resources would be required before any definitive conclusions can be reached.

Although this intervention is suited to the chronic disease outpatient setting where regular follow-up is required, our results may not be replicable should the individuals be subjected to a once-off exposure. This, however, should not deter healthcare professionals from offering advice at every opportunity, as it is possible that repeated exposures in different consultations might still exhibit some effect. This would be similar to a real-world setting, where physicians and other healthcare professionals would be subjected to time constraints and thus would not be able to conduct a structured interview.

Conclusion

Repeated advice for smoking cessation is effective in patients undergoing TB treatment. Further studies should examine whether these benefits of smoking cessation are sustained over time.

Acknowledgements

The authors would like to thank the study participants and staff of the TBCU Contact Clinic.

REFERENCES

1. World Health Organization. Tobacco, 2018. Available at: http://www.who.int/news-room/fact-sheets/detail/tobacco. Accessed on 8 September 2018.
2. Second Reading Speech by Dr Amy Khor, Senior Minister of State for Health on the Tobacco (Control of Advertisements and Sale) (Amendment) Bill, 2016. Available at: https://www.moh.gov.sg/content/moh_web/home/pressRoom/speeches_d/2016/second-reading-speech-on-the-tobacco--control-of-advertisements-.html. Accessed on 20 June 2017.
3. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med 2007;4:e20.
4. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke. Arch Intern Med 2007;167:335-42.
5. Feng JY, Huang SF, Ting WY, Lee MC, Chen YC, Lin YY, et al. Impact of cigarette smoking on latent tuberculosis infection: does age matter? Eur Respir J 2014;43:630-2.

6. Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. JAMA 2008;299:2037-47.
7. Lancaster T, Stead LF. Self-help interventions for smoking cessation. Cochrane Database Syst Rev 2005;3:CD001118.
8. Betson C, Lam T, Chung T, Chung S. A randomized controlled trial of smoking cessation in Government out-patient clinics in Hong Kong (Abstract OS 321). Proceedings of the 10th World Conference on Tobacco or Health. Beijing; 1997. p. 113.
9. Campbell IA, Hansford M, Prescott RJ. Effect of a "stop smoking" booklet on smokers attending for chest radiography: a controlled study. Thorax 1986;41:369-71.
10. Siu AL, U.S. Preventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2015;163:622-34.
11. Kaur J, Sachdeva KS, Modi B, Jain DC, Chauhan LS, Dave P, et al. Promoting tobacco cessation by integrating ′brief advice′ in tuberculosis control programme. WHO South East Asia J Public Health 2013;2:28-33.
12. El Sony A, Slama K, Salieh M, Elhaj H, Adam K, Hassan A, et al. Feasibility of brief tobacco cessation advice for tuberculosis patients: a study from Sudan. Int J Tuberc Lung Dis 2007;11:150-5.
13. Awaisu A, Nik Mohamed M, Mohamad Noordin N, Abd Aziz N, Syed Sulaiman S, Muttalif A, et al. The SCIDOTS Project: evidence of benefits of an integrated tobacco cessation intervention in tuberculosis care on treatment outcomes. Subst Abuse Treat Prev Policy 2011;6:26.
14. Awaisu A, Haniki Nik Mohamed M, Noordin NM, Muttalif AR, Aziz NA, Syed Sulaiman SA, et al. Impact of connecting tuberculosis directly observed therapy short-course with smoking cessation on health-related quality of life. Tob Induc Dis 2012;10:2.
15. Bam TS, Aditama TY, Chiang CY, Rubaeah R, Suhaemi A. smoking cessation and smokefree environments for tuberculosis patients in Indonesia – a cohort study. BMC Public Health 2015;15:604.
16. Lin Y, Wang LX, Qiu LX, Huang Q, Shu Q, Lin HX, et al. A smoking cessation intervention among tuberculosis patients in rural China. Public Health Action 2015;5:183-7.
17. Stange KC, Zyzanski SJ, Smith TF, Kelly R, Langa DM, Flocke SA, et al. How valid are medical records and patient questionnaires for physician profiling and health services research? Med Care 1998;36:851-67.

Min Zhi Tay, [1]*MB BCh BAO, MSc(Public Health)*, Lovel Galamay, [1]*MD*, Sugunavalli Bhoopalan, [1]*BSc(Nursing)*, Kyin Win Khin Mar, [1]*MBBS, MMed(Public Health)*, Yee Tang Wang, [1]*MBBS, FRCP (Lon)*, Cynthia BE Chee, [1]*MBBS, FRCP (Edin)*

[1]Tuberculosis Control Unit, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Tay Min Zhi, Tuberculosis Control Unit, Tan Tock Seng Hospital, 142-144 Moulmein Road, Singapore 380807.
Email: Minzhi@doctors.org.uk

Specific Serum Immunoglobulin G (IgG) Levels Against Antigens Implicated in Hypersensitivity Pneumonitis in Asymptomatic Individuals

Dear Editor,

Hypersensitivity pneumonitis (HP) is a complex syndrome resulting from repeated exposure to a variety of organic particles. It was previously thought to be uncommon, with an incidence of 0.9 per 100,000 person-years,[1] but a recent retrospective case-cohort study demonstrated that in a population of patients initially diagnosed with idiopathic pulmonary fibrosis, up to 43% may be reclassified as HP.[2] This highlights the challenges in making a diagnosis of HP in patients who have presented with an undifferentiated interstitial lung disease, particularly when the clinical history of allergen exposure cannot be elicited. There is currently no universally agreed upon diagnostic criteria for HP. Vasoka et al has proposed a novel classification system and diagnostic algorithm wherein the diagnosis of HP may be made confidently if there is positive exposure history to a known allergen along with typical radiological and bronchoalveolar lavage findings. In the setting of negative or uncertain history of exposure to a known allergen, serum specific immunoglobulin G (IgG) may be used as a surrogate for said exposure history to support a diagnosis of probable or possible HP.[3]

Serum specific IgG remains the main method of demonstrating causality in HP, and therefore has a role to play in patient counselling and antigen avoidance. Worldwide, the most commonly implicated antigens are thermophilic actinomycetes species, fungi, and bird proteins.[4-7]

Identification of positive serum specific IgG facilitates performance of a specific inhalation challenge if the diagnosis of HP remains to be in doubt. Normal individuals may have elevated levels of specific IgG directed against common causes of HP without significant disease or long-term sequelae.[8] Conversely, in patients who present with unclear exposure history, the absence of elevated serum specific IgG directed against particular exposures may help to reduce the diagnostic probability of HP being due to those exposures. Diagnostic certainty and antigen identification is paramount as early diagnosis and exposure avoidance are cornerstones to disease management.

In Singapore, there was previously no laboratory that performed specific serum IgG directed against antigens commonly implicated in HP. A commercial kit, ImmunoCAP Specific IgG (Phadia Laboratory Systems, Thermo Scientific, Sweden), is available for testing of some antigens implicated in HP. Detection limits of 2.0 to 200 mgA/L are furnished in the product manual, but reference ranges specific for particular IgG directed against specific antigens are not provided.

This study aimed to test for these specific serum IgG levels in asymptomatic individuals, thereby enabling the establishment of operationally ready reference ranges for a panel of specific serum IgG antibodies directed against antigens commonly implicated in HP for use within our institutional laboratory.

Materials and Methods

Healthy volunteers who work in, and are employees of the Department of Respiratory and Critical Care Medicine in a tertiary care university-affiliated academic hospital, as well as inpatients and outpatients seen by the same department, who did not have a clinically suspected diagnosis of HP were included in the study.

Patients requiring intensive care unit or high dependency admission were excluded. The study was approved by the local Institutional Review Board (CIRB Ref 2016/2735). Vulnerable persons including intellectually impaired and incarcerated persons, as well as pregnant patients were excluded from the study.

Five millilitres of blood was prospectively drawn from each of the study participants by routine venipuncture after obtaining informed consent. The blood specimens were centrifuged at 3000 rpm for 10 minutes and sera separated into sterile serum tubes and kept at -20°C until processing. Sera were then tested for a panel of 9 specific IgG antigens implicated in HP using the commercial kit ImmunoCAP Specific IgG (Phadia Laboratory Systems, Thermo Scientific, Sweden).

ImmunoCAP assays were fluoroenzymeimmunoassays. Specific IgG antibodies from study subjects' sera bind to antigens that had been fixed on a cellulose derivative. After washing away non-specific IgG antibodies, fluorescent enzyme-labelled antibodies directed against IgG were added to form a complex. Excess enzyme anti-IgG antibodies were washed away, and the bound complex was incubated with a developing agent. At the end of the reaction, the fluorescence of the final complex was measured in order

to quantify the amount of specific IgG that were present in the sample.

Demographic information including age, gender and ethnicity were collected from each of the study participants.

The authors' approach to sample size calculation followed recommendations from EP28-A3C Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline, 3rd Edition.[9]

As there were no pre-existing local studies of serum specific IgG levels in asymptomatic individuals, mean reference values and standard deviations are not available for further power calculations. This study is hence intended as a pilot study for larger population studies to determine a range of normal values, or for future case-control studies to determine a range of possibly abnormal values. An estimated sample size of 120 was taken to achieve a 90% confidence limit.

Results

The mean age of the study participants was 42.6 years (standard deviation 15.3). Forty-two (35%) of them were male. The study participants were distributed amongst Chinese (50.8%), Malay (9.2%), Indian (25.8%) and other ethnic groups (10.0%).

Levels of IgG directed against various antigens implicated in HP are presented in Table 1 as mean with standard deviation.

Analysis for statistical significance was conducted using paired 2 tailed t-tests. The levels of IgG directed against *Aspergillus fumigatus* and *Candida albicans* were significantly higher than levels of IgG antibodies directed against other antigens (P <0.01). Levels of IgG directed against *Aspergillus fumigatus* were also significantly higher than those directed against *Candida albicans* (P <0.01).

Table 1. Mean Levels of IgG Directed Against Antigens Implicated in Hypersensitivity Pneumonitis

Antigen	Serum Level of Specific IgG (mg/L)
Penicillium chrysogenum, Cladosporium herbarum (homodendrum), Mucor racemosus, Alternaria alternata	9.59 + 7.33
Micropolyspora faeni, Thermoactinomyces vulgaris	7.31 + 5.11
Stachybotrys atra	4.80 + 5.34
Aspergillus fumigatus	30.9 + 31.7
Candida albicans	47.3 + 43.0
Aureobasidium pullulans	5.46 + 5.13
Budgerigar serum proteins, feathers and droppings	6.40 + 4.62
Parrot serum proteins, feathers and droppings	14.4 + 9.26
Pigeon serum proteins, feathers and droppings	12.3 + 9.63

Data is presented as mean + standard deviation.

Discussion

There is currently no published data on the prevalence and incidence of HP in Singapore. International data and experience suggests that HP is underdiagnosed and undertreated, especially the chronic form of the disease.[10] This has been postulated to reflect the lack of unified diagnostic criteria and variations in practice,[11] as well as challenges in the overall diagnostic process.

Serum specific IgG antibodies can provide objective evidence of sensitisation of individuals to certain allergens, but cannot be used in isolation to diagnose HP, as sensitised individuals may have elevated levels of serum specific IgG without developing clinically significant disease.

'Normal' levels of IgG against different antigens depend on the prevailing level of exposure within a population, and are likely to vary in different populations in accordance with different environmental exposures. In our study population of 120 subjects not known or suspected to have HP, levels of IgG antibodies directed against *Aspergillus fumigatus* and *Candida albicans* were significantly higher than levels of IgG antibodies directed toward other antigens commonly implicated in HP. This study was intended to sample individuals without clinical suggestion of HP in order to provide operationally ready reference ranges for use within the institutional laboratory, but has highlighted that significant variations in sensitisation and hence exposure exist even within an asymptomatic population. It is, hence, vital for individual laboratories to establish reference ranges within their own populations.

Our study has several limitations. Firstly, this was a single centre study where a large proportion of the study volunteers were employees within a single healthcare institution. This may contribute a significant source of selection bias as these individuals are likely to share a significant number of environmental exposures. Study subjects were also not age-matched, and there were no patients with HP to form a control group. We are, therefore, unable to determine the sensitivity or the specificity of our findings. Secondly, the mean age of the study population was 42.6 years old. Experience from the HP study by Lacasse et al in 2003 suggests that patients with HP present at a mean age of 46 to 50 years old. As such, our study population is younger than the at-risk population and may not be fully representative.[12] Thirdly, there were no criteria for selecting or excluding subjects with any particular hobbies that would predispose them to exposure to antigens relevant to HP such as bird keeping or agricultural work.

Nevertheless, with the completion of our study, testing for serum specific IgG directed against a panel of antigens commonly implicated in HP is now available locally. Alongside the international call to greater consideration and recognition of HP amongst patients presenting with undifferentiated diffuse interstitial lung disease, we hope this is an important step towards facilitating the diagnostic process for patients suspected of having HP in Singapore.

Conclusion

Our study demonstrated that significant variations in sensitisation and exposure exist even within an asymptomatic population and highlighted the importance for individual laboratories to establish reference ranges within their own populations. As this was a pilot study, the standard deviations for the reference values generated are large, implying that the true mean of the parametric or non-parametric distribution of normal values remains uncertain. Larger studies are therefore required to determine the 95% confidence intervals for normal values of normal ranges in the general population.

REFERENCES

1. Solaymani-Dodaran M, West J, Smith C, Hubbard R. Extrinsic allergic alveolitis: incidence and mortality in the general population. QJM 2007;100:233-7.
2. Morell F, Villar A, Montero MÁ, Muñoz X, Colby TV, Pipvath S, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. Lancet Respir Med 2013;1:685-94.
3. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. Am J Respir Crit Care Med 2017;196:680-9.
4. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. Mayo Clin Proc 2007;82:812-6.
5. Glazer CS. Chronic hypersensitivity pneumonitis: important considerations in the work-up of this fibrotic lung disease. Curr Opin Pulm Med 2015;21:171-7.
6. Selman M, Pardo A, King TE. Hypersensitivity pneumonitis. Insights in diagnosis and pathobiology. Am J Respir Crit Care Med 2012;186:314-24.
7. Selman M, Lacasse Y, Pardo A, Cormier Y. Hypersensitivity pneumonitis caused by fungi. Proc Am Thorac Soc 2010;7:229-36.
8. Cormier Y. Significance of precipitins and asymptomatic lymphocytic alveolitis; a 20 year follow-up. Eur Respir J 2004;23:523-5.
9. CLSI. Defining, establishing, and verifying reference intervals in the clinical laboratory; approved guideline – third edition. CLSI document EP28-A3C. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.
10. Molyneaux PL, Maher TM. Time for an international consensus on hypersensitivity pneumonitis. A call to arms. Am J Respir Crit Care Med 2017;196:665-6.
11. Walsh SL. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. Lancet Respir Med 2016;4:557-65.
12. Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, et al. Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med 2003;168:952-8.

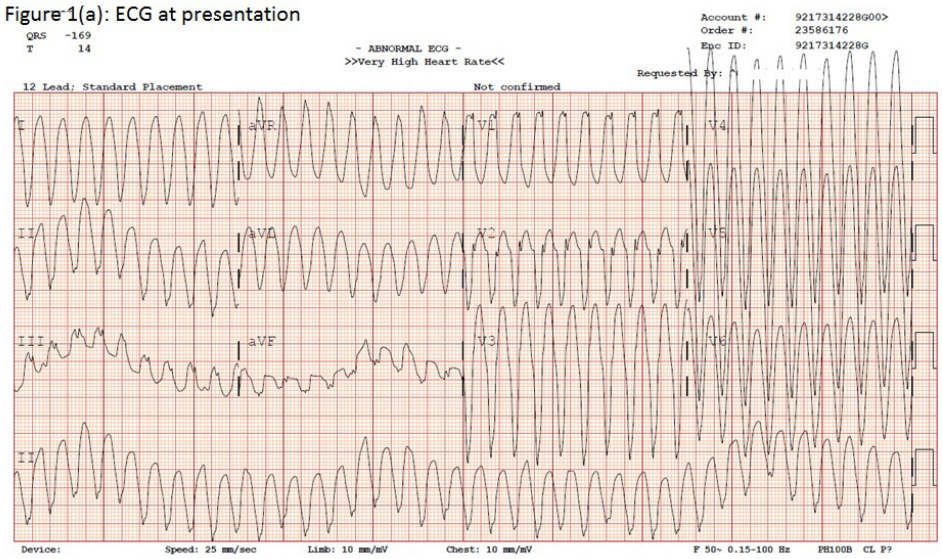
Yi Hern Tan, [1]*MBBS (Singapore), MRCP (Edinburgh)*, Cecilia CL Ngan, [2]*MBBS, MSc*, Shan Wei Huang, [2]*MBBS (China), MSc*, Chian Min Loo, [1]*MBBS, MRCP (UK)*, Su Ying Low, [1]*BMBCh (Oxon), MRCP (UK)*

[1]Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore
[2]Immunology and Serology Section, Department of Microbiology, Singapore General Hospital, Singapore

Address for Correspondence: Dr Tan Yi Hern, Department of Respiratory and Critical Care Medicine, Academia, 20 College Road, Singapore 169856. Email: yihern.tan@mohh.com.sg

Multimodality Cardiac Imaging in the Evaluation of a Patient with Near-Fatal Arrhythmia

A previously well 64-year-old man presented with 2 episodes of non-vertiginous giddiness during exercise. The patient had no history of drug use, prior history of syncope or family history of sudden cardiac death. Systolic blood pressure was 55 mmHg on presentation at the emergency department, with the presenting electrocardiography (ECG) shown (Fig. 1). Synchronised cardioversion was successfully performed and the postcardioversion ECG is as below (Fig. 1). The patient underwent a coronary angiogram which showed minor coronary artery disease, followed by transthoracic echocardiography and cardiac magnetic resonance imaging (MRI) (Figs. 2 and 3).



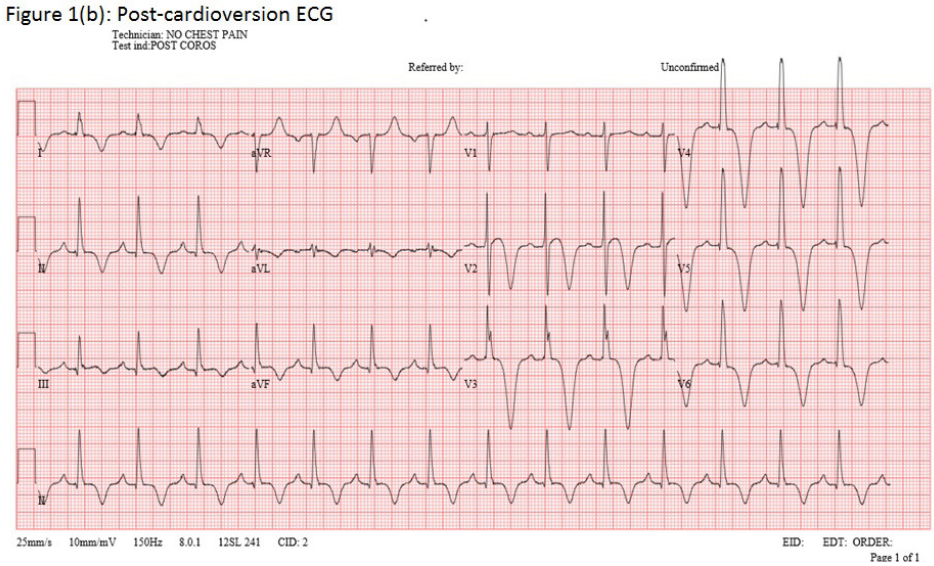


Fig. 1. ECG at initial presentation and postcardioversion ECG monomorphic ventricular tachycardia originating from the LV apex converting to sinus rhythm with deep, symmetrical T wave inversions suspicious for apical hypertrophic cardiomyopathy.

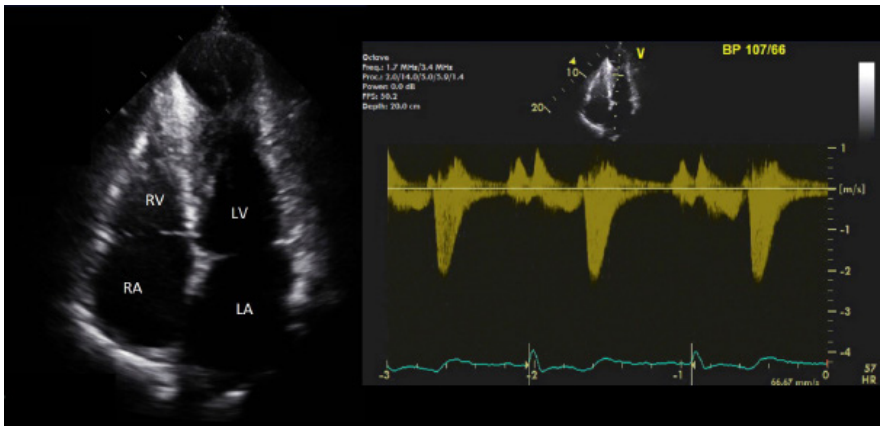


Fig. 2. Transthoracic echocardiography 4-chamber view showing left ventricular (LV) apical aneurysm with mid-ventricular and apical hypertrophy. Doppler interrogation showed increased gradient, consistent with narrowing at the entrance of the LV aneurysm.

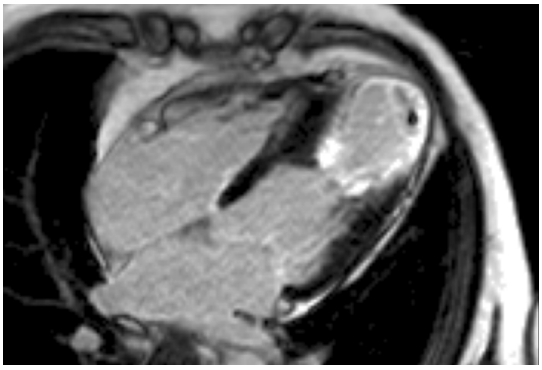


Fig. 3. Cardiac magnetic resonance imaging with late gadolinium enhancement sequence demonstrating subendocardial fibrosis within left ventricular (LV) aneurysmal wall, as well as the presence of a thrombus within the LV apex.

Given the above clinical presentation and multimodality imaging findings, what is the likely underlying diagnosis?

A. Dilated cardiomyopathy
B. Tachycardia-induced cardiomyopathy
C. Apical hypertrophic cardiomyopathy with apical aneursym
D. Cardiac amyloidosis
E. Takotsubo cardiomyopathy

The clinical presentation and imaging findings are consistent with apical hypertrophic cardiomyopathy (ApHCM) with apical aneurysm, presenting with unstable ventricular tachycardia. The postcardioversion ECG demonstrated precordial T-wave inversions associated with ApHCM. The 4-chamber view on transthoracic echocardiography (TTE) demonstrated hypertrophy that was localised to the left mid-ventricular and apical region, with aneurysm of the apical portion of the left ventricle. Figure 4 shows an example of a different patient with ApHCM without aneurysm formation for comparison. Subsequently, late gadolinium enhancement sequences of the cardiac MRI showed subendocardial fibrosis of the apical wall of the left ventricle and additionally morphologically demonstrated the apical hypertrophy and aneurysm, with an LV thrombus contained within.

The expanded and aneurysmal LV apex and hypertrophy on TTE was more consistent with ApHCM with apical aneurysm rather than Takotsubo cardiomyopathy or dilated cardiomyopathy. In Takotsubo cardiomyopathy, the ballooned LV apex is classically reversible (usually over weeks or months), so subsequent follow-up imaging should show normalisation of LV ejection fraction and LV dimensions. In dilated cardiomyopathy, the entire LV may be dilated and the walls uniformly thinned or normal in thickness. Tachycardia-induced cardiomyopathy is usually a diagnosis made after excluding other causes of cardiomyopathy, and patients may show improvement in cardiac function after treatment of the tachyarrhythmia. Furthermore, atrial tachyarrthymias are also more commonly associated with tachycardia-induced cardiomyopathy compared to ventricular tachyarrhythmias.[1] Lastly, the cardiac MRI findings are not consistent with cardiac amyloidosis. In cardiac amyloidosis, diffuse increased left ventricular (LV) wall thickness may be expected, with the late gadolinium enhancement images showing generalised gadolinium uptake representative of amyloid infiltration, which was not the case in this patient.

Discussion

ApHCM is more common in East Asians and typically has a more benign clinical course compared to non-ApHCM.[2] When associated with apical aneurysm formation, these patients may, however, experience more significant complications.[3] Although its incidence is unclear, in 1 study, 11 out of 46 patients with ApHCM had apical aneurysms, and this was associated with increased severity of cavity obliteration.[4]

We present the case of a premorbidly well middle-aged man who presented with 2 episodes of non-vertiginous giddiness during exercise. The patient had no relevant history of drug use or family history. He presented with severe hypotension at the emergency department, with

Answer: C

ECG showing monomorphic ventricular tachycardia originating from the LV apex (Fig. 1). Synchronised cardioversion was successfully performed. The postcardioversion ECG demonstrated deep T-wave inversions (Fig. 1).

Subsequently, the patient underwent emergency coronary angiogram, which showed minor coronary artery disease. TTE performed raised the suspicion of ApHCM with an apical aneurysm (Fig. 2). There was associated LV mid-cavity obstruction as well. The LV ejection fraction was mildly reduced at 45%. Cardiac MRI confirmed these findings, and further demonstrated the presence of a thrombus within the LV apical aneurysm (Fig. 3). For ease of comparison, a different patient with ApHCM without aneurysm is shown as well (Fig. 4).

The patient was started on anticoagulation, and an automatic implantable cardioverter-defibrillator (AICD) was implanted prior to discharge.

The mechanism of apical aneurysm in hypertrophic cardiomyopathy (HCM) remains unclear. Previous authors have suggested that it may be related to the presence of mid-ventricular obstruction that led to increased intracavitary pressures and wall stress, consequently resulting in ischaemia, fibrosis and aneurysmal dilatation.[5] Imaging in our subject favoured this pathophysiological process. Other potential factors may include genetic predisposition and left anterior descending artery myocardial bridging, but were not consistently reported in all cases of apical aneurysm.[5]

Although studied in conventional HCM, the incidence and prevalence of apical aneurysm in ApHCM remains unclear.[6] Though typically having a more benign course, ApHCM when coexisting with an apical aneurysm likely predisposes patients to more significant complications. These include: a) malignant arrhythmias, where the myocardial fibrosis in the aneurysm wall (as shown by the gadolinium enhancement pattern on cardiac MRI) may form an arrhythmogenic substrate, b) thrombus formation within the aneurysm, and c) poorer LV systolic function in view of the aneurysm.[6]

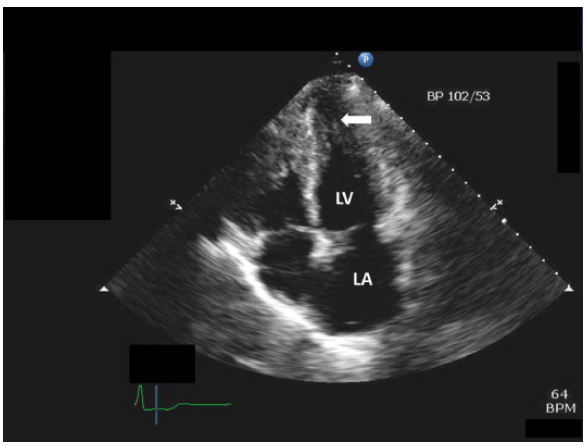


Fig. 4. Transthoracic echocardiography of a different patient at the 4-chamber window, showing hypertrophy of the left ventricular (LV) apex (arrow), consistent with apical hypertrophic cardiomyopathy (without aneurysm). LA: Left atrium.

Our case demonstrated the important role of cardiac imaging in the management of patients with ApHCM. We also demonstrated apical aneurysm to be an important comorbidity to consider in such patients. Apical aneurysm appears to be a novel risk factor to consider in ApHCM, but it remained unclear if the presence of an aneurysm in ApHCM without prior arrhythmia or thrombus warranted AICD placement for primary prevention or prophylactic anticoagulation. Of note, pharmacologic therapy does not provide protection against malignant arrhythmia but may be used for symptom control. For patients with frequent sustained ventricular arrhythmias that require AICD shocks, adjunctive anti-arrhythmic therapy may be considered.[7] Failing which, radiofrequency catheter ablation may also be successful in terminating the arrhythmia.[5]

REFERENCES

1. Shah RP, Kam Rm, Teo WS. Incessant ectopic atrial tachycardia and tachycardia-related cardiomyopathy: therapeutic options and potential for cure. Ann Acad Med Singapore 1999;28:871-4.
2. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;39:638-45.
3. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, et al. Prevalence, clinical significance, and natural history of left ventricular aneurysms in hypertrophic cardiomyopathy. Circulation 2008;118:1541-9.
4. Matsubara K, Nakamura T, Karibayashi T, Azuma A, Nakagawa M. Sustained cavity obliteration and apical aneurysm formation in apical hypertrophic cardiomyopathy. J Am Coll Cardiol 2003;42:288-95.
5. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, et al. Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. J Am Coll Cardiol 2017;69:761-73.
6. Schwalm JD, Ahmad M, Mulji A. Images in cardiology. Apical hypertrophic cardiomyopathy with apical aneurysm. Can J Cardiol 2007;23:1087.
7. Maron BJ, Maron MS. Contemporary strategies for risk stratification and prevention of sudden death with the implantable defibrillator in hypertrophic cardiomyopathy. Heart Rhythm 2016;13:1155-65.

Nicholas Ngiam, [1]*MBBS*, Nicholas Chew, [1]*MBBS*, Ping Chai, [2]*MBBS*, Kian Keong Poh, [2,3]*MBBChir, FACC*

[1]Department of Medicine, National University Health System, Singapore
[2]Department of Cardiology, National University Heart Centre Singapore, National University Health System, Singapore
[3]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for Correspondence: A/Prof Poh Kian Keong, Department of Cardiology, National University Heart Centre, National University Health System, Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 9, Singapore 119228.
Email: kian_keong_poh@nuhs.edu.sg

ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Tel: +65 6593 7800 | Fax: +65 6593 7867 | E-mail: annals@ams.edu.sg | Homepage: http://www.annals.edu.sg