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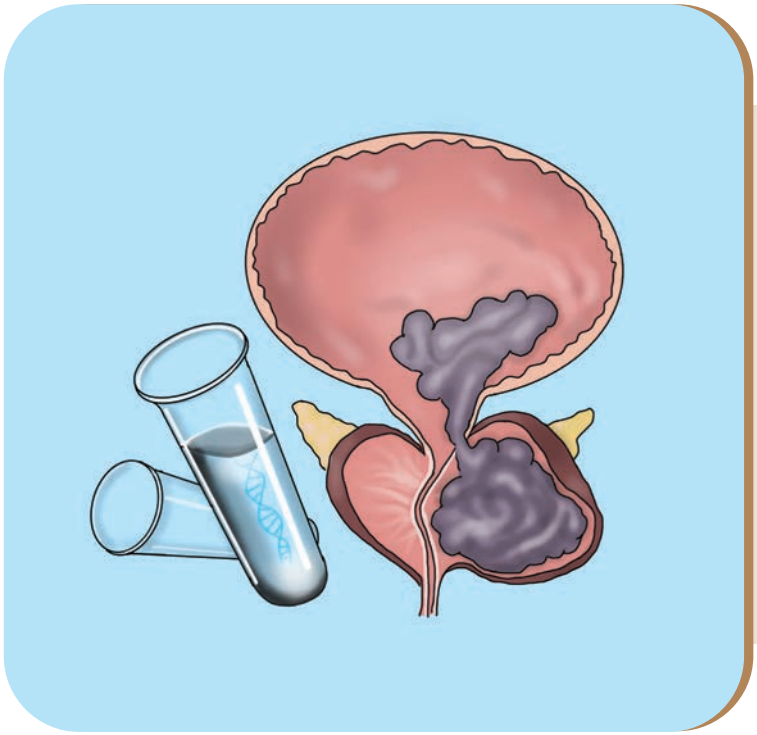

Genetic testing in patients with metastatic castration-resistant prostate cancer primarily aims to identify targetable mutations. However, the results of genetic testing may uncover unanticipated hereditary mutations and genetic predisposition.

The latest review proposes a model to incorporate genetic testing in routine clinical practice. A brief pre-test counselling by managing clinicians followed by somatic testing can reduce current bottlenecks at genetic counselling stage, for early commencement of therapy. Early detection strategies for patients harbouring genetic mutations are critical to increase overall survival and quality of life.

Illustration by Xinyu Li

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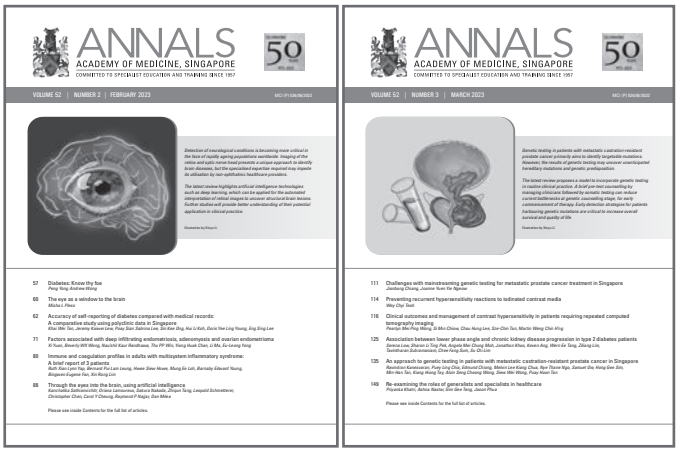

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EDITORIAL

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Challenges with mainstreaming genetic testing for metastatic prostate cancer treatment in Singapore

Jianbang Chiang [1,2]*FAMS*, Joanne Yuen Yie Ngeow [1,2,3]*FAMS*

Compared with other solid tumours, patients with metastatic prostate cancer typically have better survival in the range of years.[1] The long survival translates to a high prevalence, and thus, a large number of men living with prostate cancer. Singapore has one of the highest age-standardised incidence rates of prostate cancer in Asia, at 35 per 100,000 population.[2] Yet, after androgen deprivation therapy, existing data suggest that 4 in 5 men with prostate cancer will develop castrate-resistant prostate cancer,[3] with median survival of 20 months in the chemotherapy-naive group.[4] In recent years, the agents available to men with metastatic castration-resistant prostate cancer (mCRPC) has expanded beyond traditional chemotherapy agents (e.g. docetaxel and cabazitaxel) to include novel hormonal therapies (e.g. abiraterone and enzalutamide), and other targeted therapies.

One of the newest classes of agents is the polyadenosine diphosphate-ribose polymerase (PARP) inhibitors. Based on the results of the PROFOUND trial, mCRPC patients with *BRCA1*, *BRCA2* and ataxia-telangiectasia mutated (*ATM*) pathogenic variants have an improved overall survival of 18.5 months with olaparib (PARP inhibitor), compared to an alternative hormonal agent.[5]

Treatment-indicated germline genetic testing in breast cancer, ovarian cancer and pancreatic cancer has boosted demand for genetic counselling services, resulting in prolonged wait times in most cancer genetics clinics.[6] This is due to the importance of pre-test counselling for genetic testing. A pre-test genetics consult entails explanation of possible germline genetic results and its implication on both patient and his/her family, as well as possible ethical, legal and social ramifications of genetic testing.[7] Care must be taken to differentiate somatic from germline pathogenic variants—the former may be important in selecting targeted therapies, but only the latter has hereditary implications.

Published in this issue of the *Annals*, Kanesvaran et al.[8] proposed for pre-test counselling to be provided by the managing clinician, prior to testing all mCRPC patients for somatic variants in the homologous recombination repair (HRR) pathway. The authors suggest a "mainstreaming" approach where the managing clinician (i.e. treating urologist or medical oncologist) taking care of the patient first broach the subject of somatic testing with the patient, and if agreeable, to proceed with tumour testing that is able to detect somatic and possibly germline pathogenic variants. If tumour testing identifies somatic pathogenic variants, patients are then to be referred for a post-test discussion with a dedicated genetics counsellor, prior to germline evaluation. This clinical model serves to incorporate somatic genetic testing into routine clinical practice for the management of patients with mCRPC, and taps on existing personnel and infrastructure available in tertiary cancer centres in Singapore.

Similar mainstreaming has been trialled in other countries,[9,10] typically in cancers such as epithelial ovarian cancer, where approximately one quarter of patients have an underlying hereditary cancer syndrome.[11] A Malaysian study showed no significant differences between mainstreaming and formal genetics consultation in terms of satisfaction and psychosocial impact, with 80% of clinicians keen to integrate genetic testing into their practice.[9] Adopting such an approach requires education and training of clinicians on genetics knowledge and counselling skills, as well as development of new guidelines and improving current clinical resources. This proposed hybrid approach involving both specialists and genetic counsellors (GCs) is a popular idea in the research setting. However, it has been shown to be difficult to implement as most specialists are unwilling to perform the required pre-test counselling.[12] Mainstreaming relies on busy clinicians who are more costly on a unit-time basis compared to a genetics clinic run by GCs.[13] GC-led pre-test counselling, either through telegenetics and/or in person, remains the most cost-effective mode of delivery; also, there are increasing numbers of genetic counselling training programmes and GCs in Asia to

[1] Cancer Genetics Service, Division of Medical Oncology, National Cancer Centre Singapore, Singapore
[2] Duke-NUS Medical School, Singapore
[3] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
Correspondence: Prof Joanne Yuen Yie Ngeow, Lee Kong Chian School of Medicine, Nanyang Technological University, 11 Mandalay Road, Singapore 308232.
Email: joanne.ngeow@ntu.edu.sg

address current clinical gaps.[14] Extensive efforts have been made to train more GCs and geneticists to meet current and future demand. Mainstreaming will further help to reduce pressure on genetics services, and allow dedicated genetics-trained clinicians to focus their efforts on patients and families with hereditary cancer syndromes, rather than screen the general cancer population. Despite the increasing supply of GCs, it remains challenging for genetic services to justify headcount increase and adequate remuneration for GCs as frontline clinicians to hospitals and health systems in Asia, where a doctor-led system is common.

As Singapore moves towards Healthier SG (an initiative by the Singapore government to help the population take steps to better health) and as we aim to move from specialist-led care to care in the community, we will need to increasingly expand the roles GCs to serve in routine clinical care. A key component of clinical genetic testing is cascade testing—the down-stream flow of genetic information to the family members of an individual with a pathogenic variant.[15] This allows at-risk individuals to be identified early for gene-directed surveillance and cancer risk-reducing surgery. For family members not at risk, a negative test can help to avoid further unnecessary screening and tests. It remains unclear if mainstreaming will affect the uptake of cascade testing and would warrant monitoring.

In addition, negative somatic testing cannot rule out germline pathogenic variants. Clinicians should be cognisant of false negative results—where patients with significant personal medical history or strong family history of cancer, and negative somatic testing should still be evaluated for an underlying hereditary cancer syndrome. This is because patients with a strong family history of cancer can have a sixfold increased risk of carrying a germline pathogenic variant.[16] These patients may benefit from early direct referral to the cancer genetics clinic rather than detour to perform somatic testing first, to minimise delays and unnecessary cost of the more expensive somatic test.

With the rising indications for genetic testing, many questions remain for all health systems, especially in Asia. Mainstreaming as proposed by Kanesvaran et al.[8] for metastatic prostate cancer is a well-considered one given that only 17.2% of prostate cancer patients with 43.8% of HRR will require germline testing.[17]

Presently, industry sponsors mainstreaming approaches to help identify patients for gene-directed treatments. While this addresses the short-term concerns for access to genetic testing for patients with metastatic prostate cancer, collectively, the community will need to address reimbursement and affordability of genetic testing. Addressing these issues on a broad scale can ensure that access to testing is equitable across the health system and not limited only to those who can afford testing and/or only for patients eligible for therapy. Current industry-influenced clinical pathways preclude access to subsidised genetic testing for a 40-year-old patient with non-metastatic prostate cancer and with a family history of hereditary breast and ovarian cancer syndrome, as an example. It is important to remember that at the health system level, it is the early cancer detection of at-risk family members that drives cost-effectiveness.

We should ensure that all (and not only metastatic) prostate cancer patients who meet clinical criteria for clinical genetic testing receives support for testing and are receptive to the mainstreaming of genetic testing by GC-led consults in the near future.

Disclosure

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EDITORIAL

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Preventing recurrent hypersensitivity reactions to iodinated contrast media

Wey Chyi Teoh [1,2] *FRCR (UK)*

Iodinated contrast media (ICM) is one of the most commonly used drugs in the practice of modern medicine. ICM, as the name implies, is a contrast media that contains iodine. It is frequently used in computed tomography (CT) and angiographic procedures, to highlight important anatomical structures and for the detection of pathologies. While most ICMs are administered by radiology practices, other specialties such as cardiology and gastroenterology also use them to guide angiography and some endoscopic procedures.

They are currently many different ICMs in the market. Those which are used as intravenous or intrathecal agents are low osmolality contrast media or iso-osmolality contrast media agents. Common examples include iohexol (Omnipaque, GE HealthCare, Chicago, IL, US), iopromide (Ultravist, Bayer, Berlin, Germany) and iodixanol (Visipaque, GE HealthCare, Chicago, IL, US). High osmolality contrast media such as diatrizoate sodium/meglumine (Gastrografin, Bracco Diagnostics, Milan, Italy) are older generation agents, which are associated with a higher rate of adverse events. They are now generally used for only gastrointestinal and cystourethral administrations.

While ICM is generally safe to use, it is estimated that 0.6% of patients who received ICM will suffer an "allergic-like" or hypersensitivity reaction. A frequently used classification system for hypersensitivity reactions is by the American College of Radiology, which categorises the reactions as mild (limited urticaria, pruritis, nasal congestion), moderate (generalised urticaria/oedema, voice hoarseness without dyspnea, wheezing without hypoxia) and severe (severe oedema, respiratory distress, circulatory collapse).

Severe hypersensitivity reactions are rare, occurring in 4 in 10,000 patients. Patients who develop a hypersensitivity reaction to ICM are deemed to be at significant risk for a recurrent reaction.[1] For patients who had a previous non-severe reaction and require a repeat administration of ICM, it is currently common practice to pre-medicate them with corticosteroids as a prophylactic measure.

The article by Wong et al.[2] is timely as the study brings to our attention how ICM hypersensitivity reactions can be misunderstood by medical practitioners. It also highlights the emerging trends in prevention strategy.

Common misconceptions and the importance for appropriate documentation. It is commonly thought that a patient who developed a hypersensitivity reaction to ICM must have an allergy to iodine. While patients can be allergic to povidone iodine (a surface antiseptic), allergy to elemental iodine does not exist. After all, iodine is an essential nutrient required for the synthesis of the thyroid hormones. It is also commonly present in an everyday ingested condiment, the table salt. Another common misconception is that seafood allergy is associated with significant ICM hypersensitivity. Again, this is not true as the major allergens, parvalbumins in fish and tropomyosins in shellfish are unrelated to iodine.[3] Patients with allergies to povidone iodine and seafood allergies are actually not at greater risk from ICM than patients with other types of allergies.[1]

Wong et al. highlighted in their study, a high portion of non-specific, incomplete or misleading information in their patients' ICM hypersensitivity records. Their experience mirrors commonly encountered situations in many radiology practices in Singapore. For example, it is not uncommon to come across patients who were simply documented as having an allergy to "computed tomography (CT) contrast". This is akin to labelling a patient who had a hypersensitivity reaction to penicillin as having an "antibiotic allergy"—an important but ultimately limited piece of information. It is also not uncommon that the severity of the reactions is not described in detail. Perhaps, such practices may have been consequential from the misconceptions that have been described earlier. As Wong et al. have demonstrated, switching to a different ICM is now a viable strategy for patients with prior non-severe hypersensitivity reactions to ICM. It is therefore pertinent to re-iterate the need for accurate documentation when one encounters a patient who develops a reaction.

Firstly, it is highly recommended that the documentation and drug alert labelling of a witnessed reaction in the electronic medical records (EMR) be made by a firsthand witness rather than a secondhand account. A

[1] Department of Radiology, Changi General Hospital, Singapore
[2] Duke-NUS Medical School, Singapore
Correspondence: Dr Wey Chyi Teoh, Department of Radiology, Changi General Hospital, 2 Simei Street 3, Singapore 529889.
Email: tweiqi@yahoo.com.sg

firsthand account will likely be the most accurate and least ambiguous. In most scenarios when the reaction is acute, the firsthand account should originate from the supervising radiologist or the proceduralist who administered the ICM, rather than the physician or clinical team who manages the patient. Secondly, it is important to recognise and differentiate the severity of the witnessed episode. Description of patient's signs and symptoms should be as accurate as possible. While assessment can admittedly be subjective or challenging to differentiate between a hypersensitivity reaction and a chemotoxic physiological effect, the use of a standard classification such as that by ACR is helpful to reduce variability. Thirdly, it is important to name the specific ICM that had caused the hypersensitivity reaction. These details, when available will allow us to accurately risk stratify the patient and prescribe the appropriate preventive measures.

Emerging trends in prevention strategies. In North America and Singapore, it remains common to offer corticosteroids, with or without antihistamines to patients who are at risk of developing a hypersensitivity reaction to contrast media. However, this is not without controversy. While there is good evidence that corticosteroid prophylaxis prevents aggregate and mild hypersensitivity reaction to low osmolality contrast media in average-risk patients, there is no best data or level 1 evidence confirming that they are equally effective in preventing reactions in higher-risk patients (i.e. patients who had previous ICM hypersensitivity).[4] In addition, breakthrough contrast hypersensitivity reactions can occur in pre-medicated patients. The reported breakthrough rate is 2.1%; in most cases of about 81%, breakthrough reaction is similar in severity to the index reaction.[1] The use of corticosteroids does not come with negligible risks. They may result in transient hyperglycaemia and leucocytosis. However, more often than not, it is non-compliance, which is a greater issue. Patients who do not take their pre-medication may end up not receiving their scheduled CT scan on time, potentially leading to a delay in critical diagnosis.

Changing to a different ICM is a strategy that has been gaining traction. There is emerging evidence that doing so may be more effective than pre-medication. A recent large scale Korean prospective study with 196,081 recruited patients demonstrated that a change of ICM can reduce the risk of recurrent hypersensitivity reaction.[5] In fact, the European Society of Urogenital Radiology (ESUR) has went as far as recommending a change of ICM in lieu of corticosteroid pre-medication in their guidelines.[6]

Given these emerging trends, it is not inconceivable that the use of pre-medication prophylaxis may not be necessary in the foreseeable future or that a combination of changing ICM and use of pre-medication will become a standard. It is important that users of ICM look into how this may affect their departmental workflow. For example, there will be a need to ensure sufficient supplies and stocks on a variety of ICMs. It may also be necessary to look into cost-efficient methods to ensure that a patient's ICM hypersensitivity records can be easily documented in standard formats, retrieved and reviewed from the EMR. Wong et al. has given us examples of workflow adjustments to accommodate these new strategies in their department.

Lastly, direct referral services to an allergist are no doubt a helpful initiative. ESUR recommends that patients who had a previous ICM hypersensitivity reaction preferably consult an allergist, before using a different contrast agent. While it may not be feasible for some practices to refer all ICM hypersensitivity cases, the allergist can serve an important role, particularly in managing patients with ambiguous ICM records. It will be helpful for departments to work with their allergy services on the appropriate referral guidelines.

Prevention strategies for recurrent ICM hypersensitivities are evolving, with emerging evidence that a change of ICM may be preferred when compared to just the use of pre-medication prophylaxis. Accurate documentation of patients' ICM hypersensitivity reactions is an important tenet. Users of ICM should keep abreast with the latest recommended practice guidelines and redesign departmental workflows where necessary.

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ORIGINAL ARTICLE

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Clinical outcomes and management of contrast hypersensitivity in patients requiring repeated computed tomography imaging

Pearlyn Mei Ping Wong [1]*FRCR*, Si Min Chiow [1]*FRCR*, Chau Hung Lee [1]*FRCR*, Sze-Chin Tan [2]*MRCP*, Martin Weng Chin H'ng [1]*FRCR*

ABSTRACT

Introduction: In collaboration with the Department of Rheumatology, Allergy and Immunology, our study aims to review the outcomes of and propose an improved workflow for the management of patients with prior hypersensitivity reactions to iodinated contrast media (ICM).

Method: Outpatients coming for contrast-enhanced computed tomography (CECT) were stratified into 3 categories (definite, unconfirmed and inaccurate) based on likelihood of their contrast hypersensitivity label. Patients could be offered a different ICM, receive the same ICM, or be referred to an allergist for further evaluation. There were 4 outcomes: (1) alternative ICM tolerated; (2) same ICM tolerated again; (3) patient developed a hypersensitivity reaction to either alternative or original ICM; and (4) CECT was deferred until assessment by an allergist. Comparison was made pre- and post-intervention to see if patient outcomes were improved.

Results: There were 132 patients who made a total of 154 visits (90.3% had documented contrast hypersensitivity). Post-intervention, the number of visits postponed for premedication decreased (81.0% to 34.7%). There was a reduction in hypersensitivity reactions (from 42.9% to 14.3%). Of the 12 patients assessed by the allergist, 6 could continue using the same or alternative ICM, 4 were advised to abstain from further contrast administration and 2 were pending testing with a third agent.

Conclusion: Active intervention by the radiologist can decrease the number of postponed, converted or cancelled CECT studies as well as reduce the number of adverse allergic-like events. Direct collaboration between radiologist and allergist for specific cases may be helpful in patients who will likely need future/repeated CECTs.

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Keywords: Corticosteroid, hypersensitivity, ICM, iodinated contrast media, premedication, skin testing

INTRODUCTION

Allergic and non-allergic hypersensitivity reactions to iodinated contrast media (ICM) are increasingly recognised, particularly the latter where there is greater clarity on pathomechanisms.[1] There is limited evidence for the use of corticosteroids as premedication to prevent the occurrence of contrast-related reactions. At our institution, a dose of 30mg oral prednisolone daily for 3 days prior to a contrast-enhanced computed tomography (CECT) is recommended for patients assessed to have reactions to contrast, or whose reactions were reported to be non-severe. When this regimen was incomplete or omitted, subsequent management was left to the discretion of the attending radiologist, with variable clinical decisions. These included postponing for prednisolone premedication, switching to an alternative low osmolar ICM, opting for an unenhanced CT or different modality of imaging, or even cancelling the scan altogether.[1,2] Furthermore, even with premedication, the decision to proceed with contrast and choice of ICM were variable depending on the perceived severity of adverse reaction by the radiologist on duty that day. These variations in management led to different patient outcomes and

[1] Department of Diagnostic Imaging, Tan Tock Seng Hospital, Singapore
[2] Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore
Correspondence: Dr Pearlyn Mei Ping Wong, Department of Diagnostic Imaging, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: pearlyn.wong@mohh.com.sg

CLINICAL IMPACT

What is New

- This pilot study in the Singapore setting highlights how direct collaboration between the radiologist and allergist can ultimately improve patient outcome and quality of care by accurate allergy reporting.

Clinical Implications

- Corticosteroid premedication to prevent hypersensitivity reaction to iodinated contrast media (ICM) is controversial.
- Direct collaboration between the radiologist and allergist is useful for prompt patient management and accurate allergy reporting.
- Careful analysis of patient records and timely usage of alternative ICM can prevent unnecessary postponements, or change of imaging technique or modality, ultimately improving patient outcome and quality of care.

inconsistent quality of care. Contributing to this would be the accuracy, or even lack thereof, in allergy information pertaining to the index contrast reaction contained in the patients' Critical Medical Information Store (CMIS), which is a nationwide integrated medical information repository that allows the sharing of drug allergies and other significant medical alerts with institutions' electronic medical records.

Beginning December 2019, we emphasised a more streamlined practice by proactively reviewing CMIS allergy records on the day of scan to determine if an alternative ICM could be administered. We also started collaboration with our institution's Department of Rheumatology, Allergy and Immunology (RAI) for direct referral of patients with contrast reactions to confirm or refute, and expediently update the patient's drug allergy status in CMIS.

Our study aims to review if these 2 interventions are superior to other alternatives—including postponing for premedication, converting to an unenhanced CT, and employing different mode(s) of imaging—which are listed as equivalent management pathways for such patients. We believe that by inculcating this in the department's clinical practice, there would be resultant time and cost savings to our patients without compromising on their safety.

METHOD

We reviewed all outpatients, who presented to the Department of Radiology at Tan Tock Seng Hospital, Singapore for a CECT from 1 January 2018 to 31 December 2020, with a record of contrast hypersensitivity regardless of whether they had completed a prescribed course of prednisolone premedication. Inclusion criteria were patients (1) with a reported contrast hypersensitivity in CMIS; (2) with documented contrast hypersensitivity in the clinical records but not in CMIS; and (3) who self-reported a reaction to contrast. Exclusion criteria were patients without known contrast hypersensitivity, and who developed a de novo reaction following their current CECT.

Before intervention, management has been varied and included postponing for premedication before re-attending (only to be given the same rather than an alternative contrast), administering a single dose of intravenous hydrocortisone on site before scanning (which occurred on one occasion), opting for an unenhanced CT or different modality of imaging, or even cancelling the scan altogether (Table 1). Few underwent their CECT on the same day. Two specific interventions were introduced on 1 December 2019 to improve the management of these patients.

Firstly, we encouraged the radiologist to stratify patients according to the risk of developing a contrast hypersensitivity reaction by studying each patient's contrast reaction history. This includes evaluating credibility of the CMIS record (such as when it was made in relation to contrast administration and whether it was a retrospective entry by a secondary observer), attempt to grade the severity of the index reaction, as well as to check if the patient had received the ICM he/she was reported to be allergic to without complications in the interim. Severity was graded according to the American College of Radiology (ACR) into mild (e.g. self-limiting urticaria and sneezing), moderate (e.g. diffuse urticaria, facial swelling, and wheezing that may progress and usually requires medical management) and severe (e.g. frank anaphylactic shock that usually requires urgent critical care).[3]

Patients were stratified into 3 categories. Category 1 comprised patients with a definite contrast hypersensitivity, where there were objective signs and symptoms of a hypersensitivity reaction following administration of an ICM at least once. Category 2 comprised patients who received the same ICM recurrently throughout time with inconsistent symptoms at each exposure (thus, the probability of a hypersensitivity reaction was unconfirmed). Category 3 consisted of patients

Table 1. Options available within Tan Tock Seng Hospital for managing patients with contrast hypersensitivity requiring contrast-enhanced computed tomography pre-intervention and rationale for change in practice post-intervention

Pre-intervention	Post-intervention
30mg oral prednisolone daily for 3 days before receiving iodinated contrast media	Discourage, as evidence is not strong, and there are potential risks in patients with diabetes, tuberculosis or chronic hepatitis[5,8]
Postponing for prednisolone before re-attending	Discourage, as it causes a time delay
Administer a single dose of intravenous hydrocortisone before imaging at 4 hours later	This is feasible for CECT required urgently, but not recommended for elective outpatients[5,8]
Perform unenhanced computed tomography	Discourage, as it may be sub-optimal
Utilise a different modality of imaging	Discourage, as it may be sub-optimal, can be expensive and also adds to time delay
Cancelling the scan altogether	Discourage, as it does not solve the clinical query
Perform CECT using the same or alternative ICM	The usage of alternative ICM has not been emphasised sufficiently in our institution and can be better guided by correct interpretation of the patient's contrast history Develop direct referral route from radiologists to allergist to perform objective testing for contrast hypersensitivity (new initiative)

CECT: contrast-enhanced computed tomography; ICM: iodinated contrast media
Superscript numbers: Refer to REFERENCES

who had a reaction to ICM but tolerated the same ICM again (CMIS record inaccurate, or delabelling was not performed). Category 1 patients may attempt using an alternative ICM, and if this was tolerated, the patient's CMIS record was supplemented with the caveat that the patient was able to tolerate the alternative contrast (Outcome 1) and could circumvent premedication for future attendances. Categories 2 and 3 patients could proceed with CECT using an alternative ICM (if previous index reaction was graded as moderate), or even the same ICM (mild index reaction), which if tolerated may suggest that the CMIS record could be wrong and be delabelled (Outcome 2). Any of these patients could still develop a hypersensitivity reaction to the given ICM (Outcome 3). However, if contrast administration was considered high risk (severe index reaction) and/or the patient was not keen on proceeding, ICM was avoided altogether by way of an unenhanced CT, a different imaging modality (e.g. ultrasound, MRI or PET-CT), or all radiological evaluation was withheld until assessment by the allergist (Outcome 4). Fig. 1 illustrates this workflow.

Stratification serves 2 purposes: to guide the choice of ICM in premedicated patients; and to allow some who were not/partially premedicated to proceed on the same day, usually with a change of ICM, rather than take premedication and return at a later date. The latter group usually comprised patients who had been warned by their referring clinicians on the importance of completing the premedication. Patients who proceeded on the same day were counselled for the risk of contrast allergy and were assured that they would be observed for 1 hour to ensure that no untoward reaction occurred.[4] If the trial of the same or alternate contrast was tolerated, and the CMIS amended/delabelled, they could avoid premedication for subsequent presentations.

Secondly, we offered all patients, particularly those with severe reactions whom we deemed too risky to administer ICM, direct referral to an allergist (which was a new initiative) to objectively determine their contrast hypersensitivity status.

Clinical data were collected from the patient's hospital records and department file of problematic contrast allergy patients (containing positive reaction, postponed, cancelled and referred cases) during CECT. These included variables such as demographics, the ICM which was used, description of reaction (e.g. urticaria and maculopapular exanthem), and the final diagnosis from the allergists after their outpatient review. Data in the post-intervention period were compared to that of pre-intervention in the preceding year. All data were anonymised and tabulated in a password-protected Microsoft Excel 2018 (Microsoft Corp, Redmond, US) file. Associations between continuous data were assessed using t-tests while categorical variables were tested using Pearson's chi-square test. Statistical significance was declared if the *P* value was less than 0.05. All statistical analyses were done using SPSS Statistics version 26.0 (IBM Corp, Armonk, US). This retrospective study was approved by our Institutional Review Board (DRSB reference: 2021/00054).

RESULTS

Demographics

There were 132 patients who made a total of 154 visits to the Department of Radiology (Table 2). Each visit was for a new CT imaging request and did not include

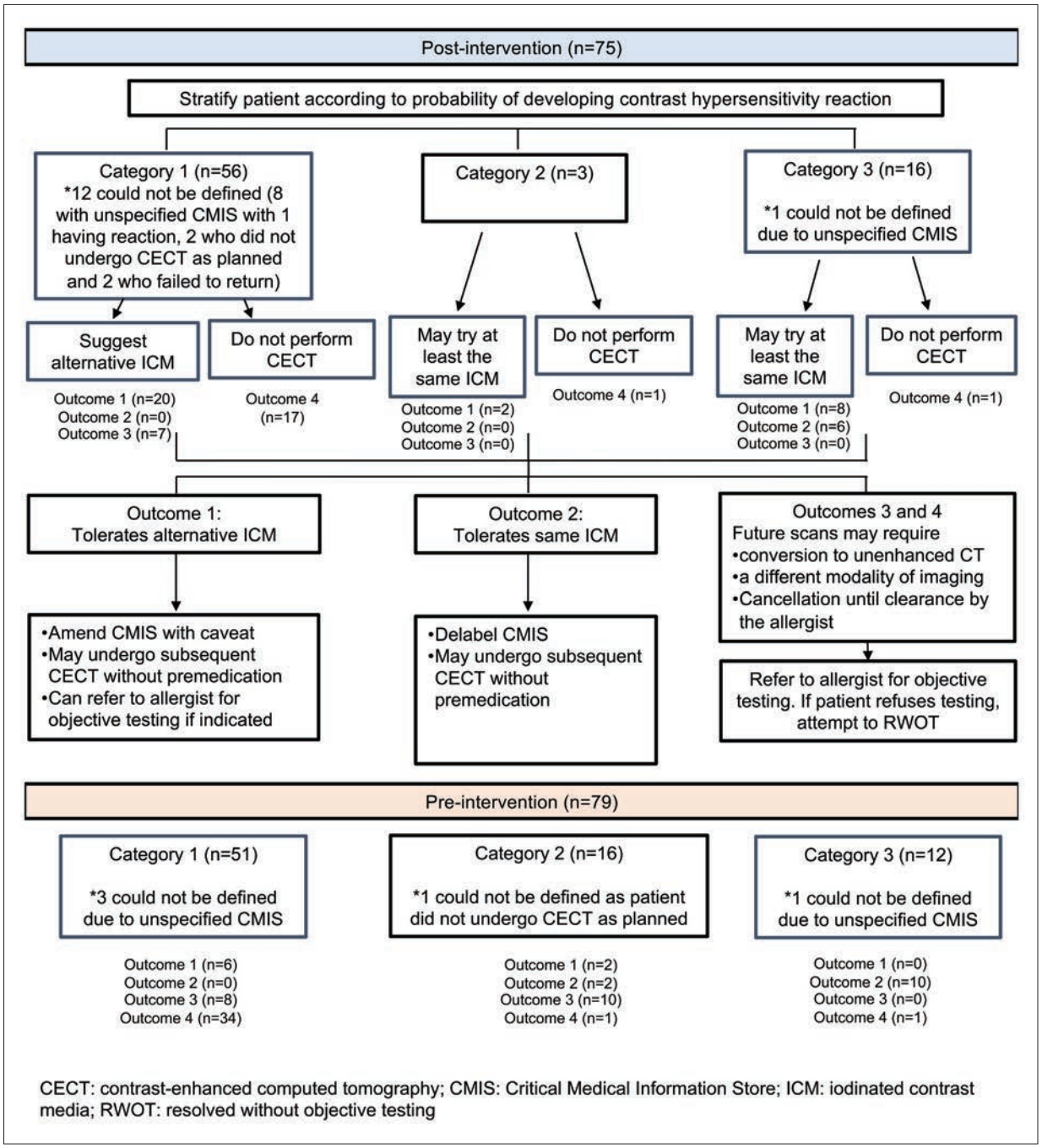

Fig. 1. Post-intervention workflow depicting categories and number of patients based on probability of hypersensitivity, decision on proceeding with contrast-enhanced computed tomography, choice of iodinated contrast media (ICM), and management depending on presence/absence of a reaction. The approximate pre-intervention categories and numbers are shown below for comparison, given that stratification of patients and use of alternative ICM had not yet been widely implemented.

the repeat attendance for patients postponed for prednisolone premedication. In the post-intervention period, there were 64 new patients, in addition to 8 regulars who had also attended pre-intervention. Throughout our study duration, 6 visited thrice, 10 visited twice and 116 presented once.

CMIS documentation

The CMIS reported 139 visits (90.3%) that showed contrast hypersensitivity. Of these, the proportions allergic to iohexol was (n=102, 73.4%), iodixanol (n=3, 2.2%), iopromide (n=2, 1.4%), iodine (n=1, 0.7%), iodamide (n=1, 0.7%), 2 contrast agents (n=4, 2.9%) and

Table 2. Patient demographics

	Pre-intervention (n=68)	Post-intervention (n=72)
Age, median (SD), years	60.7 (10.7)	66.3 (11.7)
Sex, no. (%)		
Male	28 (41.2)	28 (38.9)
Female	40 (58.8)	44 (61.1)
Ethnicity, no. (%)		
Chinese	56 (82.4)	61 (84.7)
Malay	4 (5.9)	4 (5.6)
Indian	5 (7.4)	4 (5.6)
Others	3 (4.4)	3 (4.2)
Total no. of visits	79	75

SD: standard deviation

not specified (n=26, 18.7%). The remaining 15 visits (9.7%) did not have a formal CMIS record, but indicated hypersensitivity to contrast documented in the clinical notes or were reported by patient to the radiologist, of which only 1 could be attributed to iohexol.

Management of patients pre- and post-intervention

Fig. 1 reveals 2 findings. First is found in Category 1, where a large proportion had Outcome 4 pre-intervention (i.e. CECT was not performed) when compared to Outcome 1 post-intervention (i.e. successful completion of CECT using an alternative ICM). Second is a reduction in patients with Outcome 3 (i.e. a hypersensitivity reaction to the ICM used), which showed 18 before intervention and 7 after intervention.

Table 3 presents the comparative management before and after intervention. Pre-intervention, there was a relatively higher (about 4-fold) proportion of visits postponed for premedication (n=34, 81.0%) compared to those that continued with CECT (n=8, 19.0%). When the CECT was eventually done, the same ICM patient documented as being allergic to was used in 18/42 (42.9%) of visits. Allergic reaction was observed in 11/34 (32.4%) of postponed visits and 7/8 (87.5%) of visits where patients continued with CECT. Post-intervention, the proportion of visits postponed for premedication decreased (n=26, 34.7%), with an increase in those who continued with CECT (n=30, 40.0%). Also, fewer used the same ICM 8/56 (14.3%). Hypersensitivity reactions were observed in 4/26 (15.4%) of postponed visits and 4/30 (13.3%) of continued cases.

Postponing a patient for premedication or changing the scanning modality entailed a time delay. There were 48 visits pre-intervention that were postponed (including one that had to be aborted again despite being postponed for a different scanning modality) and 26 visits post-intervention that were postponed (due to 2 patients failing to return). Median time of delay was 4 days and 5 days, respectively. Although there was no significant difference with regards to the time delay pre- and post-intervention, there was a significant decrease in proportion of cases being delayed (P=0.038).There was a decrease in adverse drug

Table 3. Comparative management before and after intervention. Visits requiring contrast were stratified by whether they used the same or different type of iodinated contrast media (ICM), with presence of hypersensitivity reaction shown within parentheses

	Pre-intervention (n=79 visits)				Post-intervention (n=75 visits)			
	Total	Same ICM	Different ICM	Others[a]	Total	Same ICM	Different ICM	Others[a]
Postponed with pre-medications	34	14 (5)	10 (5)	10[b] (1)	26	3 (0)	16 (3)	7[c] (1)
Continued with CECT	8	4 (4)	3 (2)	1 (1)	30	5 (2)	16 (2)	9 (0)
Converted to NCCT	18	-	-	-	15	-	-	-
Changed modality	15	-	-	-	2	-	-	-
Cancelled	4	-	-	-	2	-	-	-

CECT: contrast-enhanced computed tomography; CMIS: Critical Medical Information Store; ICM: iodinated contrast media; NCCT: non-contrast-enhanced computed tomography

[a] Others include patients without a formal CMIS or CMIS with unspecified contrast agent, in whom administration of ICM could neither be defined as being the same nor different.

[b] Includes 1 with failure to cannulate resulting in NCCT being performed.

[c] Includes 2 patients who ended up having NCCT (one from deteriorating renal function and another who declined after further consideration) and 2 who failed to return.

events from 18/42 cases pre-intervention to 8/56 post-intervention (P=0.005). Of the 26 encountered events during our study, 23 were managed conservatively or had antihistamine administered orally, and discharged well. Three (1 pre- and 2 post-intervention) had to be referred to the Emergency Department. No admissions were necessary, and no deaths occurred.

Evaluation by the Department of RAI

Table 4 presents cases referred to allergist and proportion of those who refused, waited for or completed testing, as well as those resolved by radiologist. Table 5 summarises the allergy testing of the 12 patients seen by allergist and recommendations for subsequent management.

If the patient could tolerate the alternative or same ICM, and henceforth was able to continue with subsequent CECT scans, the clinical issue of contrast administration was considered "resolved" (Outcomes 1 and 2). Despite the practical usefulness of this assumption, objective testing for confirmation may be justified in the case of regular patients who may benefit from reverting to iohexol, which is the department's default and cheaper ICM. Outcomes 3 and 4 were regarded as "unresolved" because the drug allergy label remained, which would lead to further time delay or increased healthcare costs with multiple attendances.

Table 4. Cases referred to allergist and proportion of those who refused, waited for or completed testing, as well as those resolved by radiologist

Refused referral to allergist, did not attend clinic appointment and declined to undergo testing	**22**
Overlooked	**15**
Awaiting clinic appointment	**13**
Seen by allergist and resolved without objective testing	**7**
Category 1 Outcome 1[a]	4
Category 1 Outcome 3	1
Category 3 Outcome 2	2
Seen by allergist requiring/completed testing	**12**
Category 1 Outcome 1[a]	1
Category 1 Outcome 3[a]	5
Category 1 Outcome 4	4
Category 1 Outcome undefined	1
Category 3 Outcome 1	1
Seen by radiologist and resolved without objective testing	**6**
Category 1 Outcome 1[a]	4
Category 3 Outcome 1	1
Category 3 Outcome 2	1
Total	**75**

[a] Best attempt was made to define an Outcome in patients with unspecified contrast agent in the Critical Medical Information Store by incorporating information from patient's recollection and available documentation.

To date, 12 patients have been assessed by the allergist. Eleven belonged to Category 1 (91.7%), and with Outcomes 3 or 4 (75.0%). Definitive assessment allowed 4 to revert to using iohexol, 2 to continue with iodixanol as alternative, and 4 to abstain from further ICM use. Another 2 had testing with iopromide deferred as they had no upcoming CECT scheduled. Despite offering objective testing to all patients, slightly more than a third refused referral, did not attend their clinic appointment, or declined to undergo testing. Judgement based only on contrast history allowed 13 patients to be resolved without objective testing by the allergist and radiologist.

DISCUSSION

The prevalence of hypersensitivity reactions to monomeric ionic contrast media is estimated to vary from 3.8% to 12.7%.[5] These reactions are classified into immediate and non-immediate. Immediate reactions are further categorised into immunoglobulin E (IgE)-mediated and non-IgE-mediated, the latter due to effect of the contrast media on mast cell membranes leading to mediator release, or by direct complement activation. Among the guidelines, the European Society of Urogenital Radiology (ESUR) has come out strongest by stating that this prophylaxis is generally not recommended due to lack of evidence, and many recommend a change in contrast media instead.[3,6-11] Studies have shown that switching contrast media has a greater effect than only administering premedication alone, but combining premedication with a change in agent appears to have the greatest effect.[12,13] Referral for allergy testing has been suggested among other recommendations but not emphasised strongly enough.[3,10] ESUR advocates it for moderate to severe reactions while the Royal Australian and New Zealand College of Radiologists proposes it for cases of anaphylaxis.[9,11] At our institution, patients with prior reaction to ICM are still premedicated with prednisolone prior to contrast-enhanced CT scan. However occasionally, such patients miss premedication or are incompletely premedicated, for various reasons.

Streamlining the department workflow and its benefits

In the pre-intervention period, management of outpatients who arrived for CECT in the Department of Radiology was not consistent. Many cases were postponed for prednisolone premedication. Even when contrast was administered, a high proportion received the same ICM that they had reported reactions to. This is despite literature stating that a prior reaction to the same class of contrast medium is deemed to be the greatest risk factor for predicting future adverse events, with a 5- to 10-fold

Table 5. Summary of allergy testing on the 12 patients seen by the allergist and recommendations for subsequent management

Patient	SPT and IDT to iohexol	DPT to iohexol	SPT and IDT to iodixanol	DPT to iodixanol	SPT and IDT to iopromide	DPT to iopromide	Test outcome
1	Negative	Not done	Negative	No immediate or delayed reaction	Not done	Not done	CMIS allergy to iohexol (Category 1 Outcome 4). DPT performed for iodixanol confirming that it was safe to use.
2	Negative	Not done	Negative	Delayed reaction	Not done	Not done	CMIS allergy to iohexol (Category 1 Outcome 4). Positive DPT to iodixanol confirming that it was unsafe. Patient not planned for further CECT hence iopromide testing was deferred.
3	Negative	No immediate or delayed reaction	Negative	Not done	Not done	Not done	CMIS allergy to iohexol (Category 1 Outcome 4). DPT performed for iohexol confirming that it was safe to use.
4	Negative	No immediate or delayed reaction	Negative	Not done	Not done	Not done	CMIS allergy to unspecified ICM (Category 1 Outcome 4). DPT performed for iohexol confirming that it was safe to use.
5	Negative	Not done	Negative	Delayed reaction	Not done	Not done	Allergy to iohexol (Category 1 Outcome 3[a]). Positive DPT to iodixanol confirming that it was unsafe. Patient not planned for further CECT hence iopromide testing was deferred.
6	Not done	Not done	Not done	Not done	Negative SPT Positive IDT	Not done	CMIS allergy to iohexol (Category 1 Outcome 3). Strong clinical history suggestive of reactions to both iohexol and iodixanol. Positive IDT to iopromide; allergist recommendation to avoid as well.
7	Positive IDT	Not done	Positive IDT	Not done	Negative SPT Positive IDT	Not done	CMIS allergy to iohexol and iodixanol (Category 1 Outcome 3). Positive IDT to iopromide; allergist recommendation to avoid as well.
8	Negative	Not done	Negative	Not done	Not done	Not done	CMIS allergy to iohexol (Category 3 Outcome 1). Assessment by allergist; recommended using iodixanol for future scans.
9	Negative	Not done	Negative	Immediate reaction	Negative SPT Positive IDT	Not done	Allergy to iohexol (Category 1 Outcome 3[a]). Positive DPT to iodixanol and positive IDT to iopromide confirming that both were unsafe.
10	Negative SPT Positive IDT	Not done	Not done	Not done	Negative SPT Positive IDT	Not done	CMIS allergy to iohexol (Category 1 Outcome 3). Strong clinical history of reactions to both iohexol and iodixanol. Positive IDT to iopromide; allergist recommendation to avoid as well.
11	Negative	No immediate or delayed reaction	Negative	Not done	Not done	Not done	Allergy to iohexol (Category 1 Outcome 1[a]). DPT performed for iohexol confirming that it was safe to use.
12	Not done	No immediate or delayed reaction	Not done	Not done	Not done	Not done	CMIS allergy to unspecified ICM (Category 1 Outcome undefined). DPT performed for iohexol confirming that it was safe to use.

CMIS: Critical Medical Information Store; DPT: drug provocation test; IDT: intra-dermal test; ICM: iodinated contrast media; SPT: skin-prick test

[a] Best attempt was made to define an Outcome in patients with unspecified contrast agent in CMIS by incorporating information from patient's recollection and available documentation.

increased risk.[3,9] In our study, the number of patients who continued with CECT increased from 8 pre-intervention to 30 in the post-intervention phase. A higher proportion received a different type of ICM while exhibiting a significant reduction in reaction rates. Radiologists have a proactive role in elucidating the contrast allergy history of patients and advocating a change of ICM, especially when the initial CMIS record appears increasingly doubtful. In so doing, more patients were able to have their CT done on the same day with a concomitant reduction in number of adverse drug events. Nevertheless, we still counselled these patients and monitored them for up to an hour post-scan. Although a few developed contrast reactions, these were mild, and the majority were discharged well. None required a hospital admission, and no deaths were encountered.

Pre-intervention, there were also patients with a CMIS record who underwent an unenhanced CT or a different imaging modality. It may be sub-optimal (in the case of an unenhanced CT) or a delay awaiting another appointment while incurring a higher expense (should more sophisticated modes of imaging be necessary). The latter 2 factors would be compounded, especially for patients requiring regular imaging. Our intervention approximately halved the numbers of patients facing this predicament and freed up time slots that could be better utilised for other patients. Even if the time delay was not significant, any rescheduling necessitates patients and their caregivers taking another day off to return for that appointment and runs the risk of them forgetting to re-attend, possibly contributing to delay in treatment.

Collaboration with the Department of RAI

Radiology guidelines have not strongly advocated allergy testing. ACR guidelines state that pretesting with intradermal skin testing with contrast media is not useful in minimising reaction risk while ESUR recommends referral for skin testing 1 to 6 months after occurrence of a contrast media adverse reaction.[3,11] Current literature recommends the use of skin testing for ICM immediate hypersensitivity reactions to prevent recurrence of adverse reactions; allow patients to benefit from ICM reuse that are sometimes essential; and identify safe alternatives for future radiologic investigations.[5,14] Complete evaluation includes skin-prick test and intra-dermal testing to check for IgE-mediated reactions followed by drug provocation testing when skin testing is negative.[5] Our allergists adopted this approach in assessing patients with ICM reactions, where either the initial reaction was disproved, or an alternative ICM was identified via negative skin testing and drug provocation test. Given that there is high cross-reactivity (up to 17.6%) between iohexol and iodixanol, iopromide—which has lower cross-reactivity to both—was introduced as a third option in our institution in mid-2020.[15] Studies estimate the negative predictive value of skin testing in ICM reactions to be 93.1–94.8% for immediate hypersensitivity reactions and 68.4–86.1% for non-immediate hypersensitivity reactions.[15,16]

A direct referral process from radiologist to an allergist, as well as a structured approach to allergy testing to ICM, is a new initiative in Singapore practice. We believe it is useful for 2 reasons: the radiologist is the best witness of the extent and severity of de novo contrast reactions; and this averts an overlooked referral by the time a patient sees the primary doctor in the clinic, where discussions are likely to focus on the disease at hand rather than the adverse drug event. Through this direct referral process, more patients with contrast hypersensitivity reactions are expected to be evaluated, making decision for subsequent administration of contrast clearer.

Maintaining accurate drug allergy documentation

A study by Deng et al. analysing the records of 2.7 million patients showed that most contrast allergy records were ambiguous (69.1%), rather than imaging modality-specific contrast (19.4%) or specific contrast agents (11.5%).[17] In our study, our patients had higher rates of their contrast reactions reported in CMIS (this may be due to the ease of reporting via an electronic platform, as well as lower threshold of reporting by cautious clinicians); our experience also mirrors that of Deng et al., where the same percentage had their contrast agent unspecified in CMIS. We found that non-specific, misleading or incomplete information of these entries were often unhelpful and contributed to unnecessary avoidance of CECT or use of premedication. Once objective testing had taken place, the patient's allergy records were promptly updated, where the contrast was delabelled if tolerated again, or a caveat inserted into the records clarifying that the patient could tolerate an alternative ICM. This will make subsequent decisions regarding contrast administration easier and safer.

This workflow has become the standard of care in our institution, with soft copies uploaded in the electronic Department Handbook and hard copies placed in the CT scan room. Regular reminders, audit and feedback are required to ensure sustenance of this workflow and maintenance of accuracy in the CMIS reporting. The initial future challenge would be to educate other clinicians of this practice and negating the illusion that steroid or hydrocortisone are sufficient to protect against

contrast allergy. Another would be to convince patients in this quandary to accept allergy testing, as the current sentiment is that apart from those with malignancy requiring regular scans, the others tended to decline testing. The final one would be to make this service more available, hence shortening the waiting time.

Limitations

As this was a retrospective study, the pre-intervention categories had to be approximated to allow comparison with post-intervention outcomes. Prospective studies would be required to confirm the true impact of these interventions. Given that this was a new initiative, the number of patients seen in the allergy clinic was small. Our study also involved only outpatients, which is a relative limitation. These patients may have a healthier premorbid condition and thus, more able to furnish a history of contrast reactions. On the other hand, they are the ones where postponement leads to inconvenience of a repeat visit, in contrast to inpatients who are already warded and may receive hydrocortisone while waiting.

CONCLUSION

In patients who have previous possible or confirmed contrast allergies, active intervention by the radiologist can decrease the number of postponed, converted or cancelled CECT studies. This approach will reduce the number of adverse allergic-like events should decision be made to proceed with CECT. Direct collaboration between the Departments of Radiology and RAI for specific cases may be especially helpful in patients who will likely need future/repeated CECTs. Hence, we propose our post-intervention workflow as depicted in Fig. 1.

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ORIGINAL ARTICLE

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Association between lower phase angle and chronic kidney disease progression in type 2 diabetes patients

Serena Low [1,2,3]*MSc (Public Health)*, Sharon Li Ting Pek [1]*PhD*, Angela Mei Chung Moh [1]*PhD*, Jonathon Khoo [1]*MPH*, Keven Ang [1]*PhD*, Wern Ee Tang [4]*FCFP*, Ziliang Lim [4]*FCFP*, Tavintharan Subramaniam [2]*MRCP*, Chee Fang Sum [2]*MRCP*, Su Chi Lim [1,2,3,5]*PhD*

ABSTRACT

Introduction: Phase angle (PhA), derived from bioelectrical impedance analysis (BIA), is the angle of vector determined by the body's resistance and reactance. It indicates cellular integrity and hydration status. Though extracellular volume excess was associated with chronic kidney disease (CKD) progression, the association between PhA and CKD progression is unknown. Matrix metalloproteinase-2 (MMP-2) is a member of zinc-dependent endopeptidase family and promotes renal interstitial fibrosis. We investigated association between PhA and CKD progression, and whether the association was through MMP-2 in patients with type 2 diabetes mellitus (T2DM).

Method: We conducted a prospective study on 1,078 patients with T2DM (mean age 58.9±9.1 years). PhA was measured using BIA. CKD progression was defined as ≥25% decrease in estimated glomerular filtration rate (eGFR) from baseline with deterioration across eGFR categories. Multiplex immunoassay was used to quantitate MMP-2. We examined association between PhA and CKD progression using Cox proportional hazards model, adjusting for demographics, clinical parameters and medications.

Results: Over 8.6 years of follow-up, 43.7% of participants had CKD progression. Compared to tertile 3 PhA (higher level), tertiles 1 and 2 PhA were associated with higher hazards of CKD progression, with corresponding unadjusted hazard ratios (HRs) of 2.27 (95% confidence interval [CI] 1.80–2.87, $P<0.001$) and 1.57 (95% CI 1.24–2.01, $P<0.001$). The positive association between tertiles 1 and 2 PhA with CKD progression persisted in the fully adjusted model with corresponding HRs of 1.71 (95% CI 1.30–2.26, $P<0.001$) and 1.46 (95% CI 1.13–1.88, $P=0.004$). MMP-2 accounted for 14.7% of association between tertile 1 PhA and CKD progression.

Conclusion: Our findings revealed a previously unobserved association between BIA-derived lower PhA and CKD progression through MMP-2 in patients with T2DM.

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Keywords: Bio-impedance analysis, chronic kidney disease, diabetes, matrix metalloproteinase, phase angle

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem with an estimated prevalence of 13.4%.[1] One of the key drivers of the global increase in CKD is the rising prevalence of diabetes mellitus (DM).[1] CKD affects about 25–40% of patients with type 2 diabetes mellitus (T2DM).[2] A few studies also reported that the prevalence of CKD among patients with T2DM was about 53% in Singapore.[3,4] The rising prevalence of DM in Singapore[5] will likely produce a ripple effect on the growing healthcare and economic burden of CKD among patients with T2DM.[6]

Despite optimal regulation of blood pressure with renin-angiotensin system (RAS) blockage (e.g. angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers,) and the emergence of new anti-diabetic medications (e.g. sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists)

[1] Khoo Teck Puat Hospital, Singapore
[2] Diabetes Centre, Admiralty Medical Centre, Singapore
[3] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[4] National Healthcare Group Polyclinics, Singapore
[5] Saw Swee Hock School of Public Health, National University of Singapore, Singapore
Correspondence: Assoc Prof Su Chi Lim, Diabetes Centre, Admiralty Medical Centre, 676 Woodlands Drive 71, #03-01 Kampung Admiralty, Singapore 730676.
Email: lim.su.chi@ktph.com.sg

CLINICAL IMPACT

What is New

- To our knowledge, this is the first study to show a longitudinal association between low phase angle (PhA) and chronic kidney disease (CKD) progression in type 2 diabetes mellitus (T2DM).
- Matrix metalloproteinase-2 mediated the association between low PhA and CKD progression in T2DM.

Clinical Implications

- Low PhA may serve as a risk marker of CKD progression in T2DM.
- There is potential for therapeutic interventions to target the underlying pathophysiological mechanisms leading to lowered PhA.

to prevent or slow down diabetic complications, a residual risk of renal outcome remains.[7] Hence, it is necessary to understand the pathophysiological mechanisms and risk factors of CKD development and progression. A diabetic milieu can result in structural alterations in the kidney, which include renal hypertrophy, glomerular sclerosis, inflammation and fibrosis of the tubule-interstitial tissue.[8] Traditional metabolic risk markers such as DM duration, sub-optimal glycaemic control, hyperlipidaemia and hypertension are well-established risk factors of CKD in T2DM.[9] Some of these risk factors have been incorporated in predictive models developed to predict the risk of CKD progression.[10] However, there is an increasing need to move beyond these conventional risk factors to explore markers that may also shed light on the pathophysiological mechanism of CKD in T2DM.

Of note, there is accumulating interest in the phase angle (PhA) of bioelectrical impedance analysis (BIA), which is the angle of vector determined by resistance and reactance in the body.[11] BIA determines impedance of the electric current in the body. The impedance comprises resistance (which describes the opposition to alternating electric current of body fluids and reflects hydration of tissue), and reactance (which describes the opposition to alternating electric current of cell membrane and is produced by capacitance of the cell membrane).[12-14] Reactance leads to a lag of the current behind the voltage, thus resulting in a phase shift expressed geometrically as PhA.[14] PhA is the angular transformation of the reactance to resistance ratio, and reflects cellular health with higher levels indicative of healthier cell membrane.[11,13,14] Numerous studies have shown that PhA may act as a prognostic indicator of nutritional status for DM, kidney disease, liver cirrhosis and malignancy.[13] PhA was also found to be associated with fasting blood glucose and haemoglobin A1c (HbA1c) in patients with T2DM.[13] This suggested that PhA may be a useful indicator of clinical outcomes and severity of T2DM.[13]

Extracellular volume excess may explain the possible deleterious effects of low PhA on renal function in T2DM. In T2DM, hyperglycaemia may exert an osmotic force that shifts water from the intracellular compartment to extracellular compartment, thereby leading to higher resistance value.[14,15] As PhA is derived from the ratio of reactance of cell membranes to resistance of body water, it is possible that low PhA is attributed to changes in body water distribution.[14] On the other hand, disruption in cellular integrity, which characterises low PhA,[13] results in accumulation of extracellular water and leads to overhydration.[16] Hence, PhA also reflects tissue hydration and is inversely associated with extracellular water.[13] Studies have shown that an increase in extracellular to total body water (ECW/TBW) ratio, which indicates extracellular volume excess, is associated with renal function decline.[17,18] Extracellular volume excess leads to increase in efferent arterial pressure and decrease in renal blood flow, thereby resulting in renal function decline.[19] Furthermore, extracellular volume excess may lead to translocation of bacterial and endotoxins via the congested intestinal walls into the systemic circulation, thereby resulting in inflammation, which is a risk factor for CKD progression.[20,21] Hitherto, the association between PhA and CKD progression remains unknown.

Interestingly, PhA is also a marker of oxidative stress which is increased in T2DM.[22,23] Oxidative stress can in turn activate matrix metalloproteinase-2 (MMP-2),[24] which is a member of the zinc-dependent endopeptidase family. MMP-2 has been implicated in CKD progression as it plays a pivotal role in the pathogenesis of renal interstitial fibrosis.[25] The interplay of MMP-2, PhA and CKD progression has not been studied.

We aimed to examine the association between PhA and CKD progression in T2DM. We hypothesised that lower PhA was associated with CKD progression. A secondary objective was to investigate whether MMP-2 accounted for the association between PhA and CKD progression.

METHOD

Population

This was a prospective cohort study on patients with T2DM. The patients were on follow-up for routine management of T2DM at Diabetes Centre in Admiralty Medical Centre, and primary care polyclinics, in Singapore. They were first recruited between January 2011 and March 2014, and were followed up for their renal function until March 2020. The following exclusion criteria were applied: active malignancy, active inflammation, oral intake of steroids with dose of more than 7.5mg per day, and/or intake of non-steroidal anti-inflammatory medications on the day of research assessment. For the purpose of this analysis, patients were further excluded if they had fewer than 2 estimated glomerular filtration rate (eGFR) readings, eGFR less than 15mL/min/1.75m^2 at baseline, and shorter than 1 year of follow-up. A total of 1,078 out of 1,732 participants were eligible for the analysis. Fig. 1 shows the flowchart of patients. All the participants provided written informed consent, and the study was granted ethics approval.

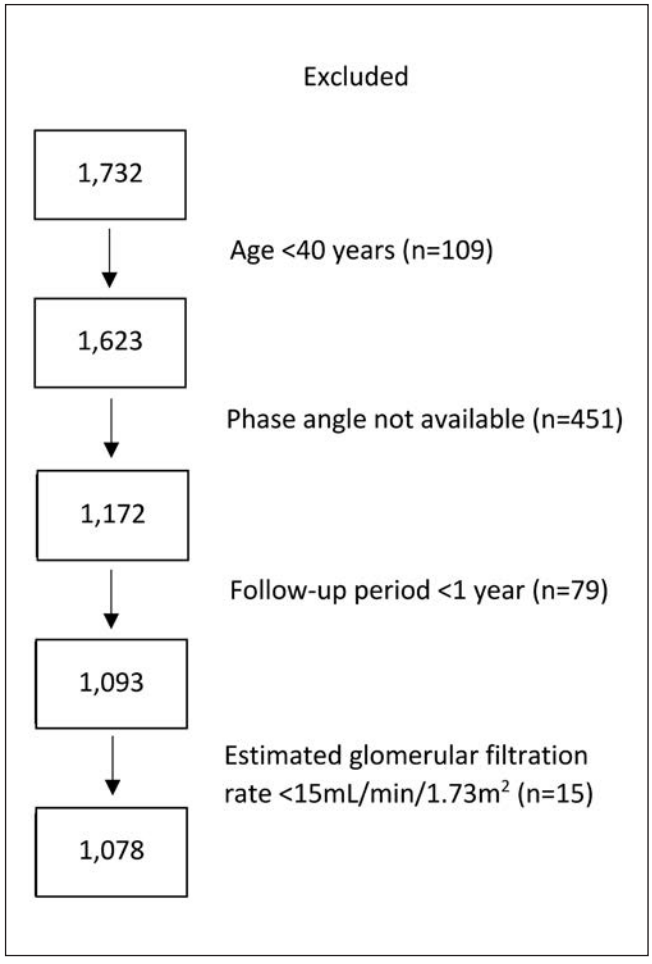

Fig. 1. Flowchart of recruited patients.

Data collection

Our trained research nurses collected data on demographics, medical history and medications using a standard questionnaire administered to the patients. Body mass index (BMI) was calculated based on weight and height, which were measured using a standard weighing scale and stadiometer, respectively. The research nurses also took blood pressure measurement using a standard automated blood pressure monitor (HEM-C7011-C1, Omron Corp, Kyoto, Japan) following a rest period of 10 to 15 minutes in a seated position.

A tetra-polar multifrequency BIA method (InBody-S10, InBody Co Ltd, South Korea) was used to measure PhA at study baseline. In BIA, electric currents flow through the body, allowing calculation of impedance and reactance of the currents. Measurements were taken at various frequencies ranging from 5–1000kHz. The PhA is the angle of the time lag between voltage waveform at 50kHz and current waveform.[11] It can be calculated as arc tangent (reactance/resistance) $\times$ 180°/π.[13]

Fasting blood and urine samples were collected at baseline and measured at the hospital diagnostic laboratory accredited by the College of American Pathologists for the following parameters: HbA1c using Tina-quant HA1c Gen.3 (Roche, Mannheim, Germany); low-density lipoprotein cholesterol (LDL-C) and triglycerides using enzymatic colorimetric test; and urinary albumin using immunoturbidimetric assay (cobas c 501 analyser, Roche, Mannheim, Germany). Serum creatinine was measured using enzymatic colorimetric test (cobas c 501 analyser, Roche, Mannheim, Germany). Serial serum creatinine readings were collected during follow-ups and used to calculate eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[26] We measured plasma MMP-2 with multiplex immunoassay on Luminex 200 platform (Thermo Fisher Scientific, Santa Clara, US).

The outcome was CKD progression—defined as at least 25% drop in eGFR—coupled with deterioration across eGFR categories as follows: stage 1 (≥90mL/min/1.73m^2), stage 2 (60–89mL/min/1.73m^2), stage 3a (45–59mL/min/1.73m^2), stage 3b (30–44mL/min/1.73m^2) and stage 4 (15–29mL/min/1.73m^2) according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease.[27]

Statistical analysis

We presented baseline characteristics as mean ± standard deviation (SD) or median with interquartile range (IQR)

for continuous variables, and number with percentages for categorical variables. As there is no current cut-off point for PhA,[28] we analysed PhA as a continuous variable and in tertiles. One-way analysis of variance or Kruskal-Wallis test was used to compare continuous variables across PhA in tertiles depending on the distribution of variables. Student's t-test or Wilcoxon rank-sum test was used to compare continuous variables by CKD progression depending on the distribution of variables. Chi-square test was used to compare categorical variables across PhA in tertiles, and between CKD progression and non-CKD progression.

We examined the association between PhA and CKD progression with Cox proportional hazards model. Model 1 was adjusted for age, sex and ethnicity. Model 2 was additionally adjusted for DM duration, BMI, systolic blood pressure (SBP), LDL-C, triglycerides, eGFR, urinary albumin-to-creatinine ratio (uACR), use of insulin and use of RAS antagonist. These adjusting covariates were chosen as the *P* value of the association with CKD progression if univariate analysis was less than 0.1 or they were known risk factors of renal decline or CKD progression.[29,30] There was no violation of the assumption of proportional hazard in the Cox regression model according to the Schoenfeld residual test. We repeated the analysis stratified by sex.

Binary mediation analysis, based on the Baron and Kenny Framework,[31] was performed to examine the mediating role of MMP-2 (mediator) in the relationship between low PhA (tertile 1 PhA) (independent variable) and CKD progression (dependent variable). The following criteria for mediation were required: (1) association between low PhA and MMP-2 in pathway a; (2) association between MMP-2 and CKD progression in pathway b; (3) association between low PhA and CKD progression in pathway c; and (4) weakening of the association between low PhA and CKD progression when MMP-2 was included in the model in pathway c'.

Statistical analysis was conducted with STATA version 14.0 (STATA Corp, College Station, US). A *P* value less than 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the 1,078 patients are presented in Table 1. The mean age was 58.9±9.1 years, with a slight male predominance (51.0%). The distribution of participants by ethnicity was 53.0% Chinese, 19.5% Malays and 24.9% Indians. The mean DM duration was 12.1±9.4 years. The mean PhA was 5.5±0.9°. The median rate of eGFR change was -1.3 mL/min/1.73m^2/year (IQR -3.6 to 0.0). When stratified by PhA in tertiles, the age, DM duration, SBP and uACR of patients decreased while the proportion of males and BMI increased with increasing PhA tertiles. The patients with tertiles 2 and 3 PhA also had higher eGFR and lower proportions of insulin and RAS antagonist use compared to those with tertile 1 PhA. The proportions of lower baseline eGFR category (Stage 3a to 4) were higher in patients with tertile 1 PhA compared to those with tertiles 2 and 3 PhA (*P*=0.005). Females had lower PhA than males (5.2±0.8° versus 5.8±0.9°; *P*<0.001).

Over a follow-up period of up to 8.6 (median 5.0, IQR 3.2–6.9) years, there were 471 patients (43.7%) who experienced CKD progression. The proportions of lower last follow-up eGFR category (Stage 3b to 5) decreased with increasing PhA tertiles (*P*<0.001). Fig. 2 shows the Kaplan-Meier survival curve for CKD progression by PhA in tertiles. The tertile 1 PhA group had the shortest time to CKD progression, followed by tertile 2 PhA group and tertile 3 PhA group (log-rank test 50.3, *P*<0.001).

Table 2 shows that patients with CKD progression tended to be older and of Malay ethnicity. They also had longer DM duration, higher proportions of insulin and RAS antagonist use, and poorer metabolic profile in terms of BMI, SBP, HbA1c, eGFR and uACR compared to those without CKD progression. The PhA was also lower in patients with CKD progression.

In Table 3, every SD increase in baseline PhA was associated with lower hazards of CKD progression in unadjusted analysis, and Models 1 and 2 with corresponding hazard ratios (HRs) 0.70 (95% CI 0.63–0.78, *P*<0.001), 0.73 (95% CI 0.65–0.82, *P*<0.001) and 0.84 (95% CI 0.75–0.95, *P*=0.004).

Tertiles 1 and 2 PhA were associated with higher hazards of CKD progression, compared to tertile 3 PhA with corresponding unadjusted HRs 2.27 (95% CI 1.80–2.87, *P*<0.001) and 1.57 (95% CI 1.24–2.01, *P*<0.001). The positive association between tertiles 1 and 2 PhA with CKD progression persisted in Models 1 and 2. In the fully adjusted Model 2, tertiles 1 and 2 PhA were associated with 71% and 46% respective increases in hazards of CKD progression, with corresponding HRs 1.71 (95% CI 1.30–2.26, *P*<0.001) and 1.46 (95% CI 1.13–1.88, *P*=0.004).

There was a statistically significant interaction in terms of sex and PhA tertile groups (*P*=0.041). Table 3 shows the association between PhA and CKD progression stratified by sex. Among females, every SD increase in baseline PhA was associated with lower hazards of CKD progression, with HRs 0.55 (95% CI 0.46–0.66,

Table 1. Baseline characteristics of patients stratified by phase angle in tertiles.

	All	T1	T2	T3	*P* value
No. of patients	1,078	360	359	359	
Age, mean ± SD, years	58.9 ± 9.1	63.0 ± 9.3	58.5 ± 7.8	55.1 ± 8.5	<0.001
Male, no. (%)	550 (51.0)	109 (30.3)	178 (49.6)	263 (73.3)	<0.001
Ethnicity, no. (%)					0.646
Chinese	571 (53.0)	193 (53.6)	197 (54.9)	181 (50.4)	
Malay	199 (18.5)	70 (19.4)	64 (17.8)	65 (18.1)	
Indian	268 (24.9)	85 (23.6)	88 (24.5)	95 (26.5)	
Others	40 (3.7)	12 (3.3)	10 (2.8)	18 (5.0)	
DM duration, mean ± SD, years	12.1 ± 9.4	14.6 ± 10.6	12.1 ± 9.1	9.5 ± 7.7	<0.001
BMI, mean ± SD, kg/m^2	27.5 ± 4.9	27.0 ± 5.1	27.4 ± 4.7	28.1 ± 4.9	0.015
SBP, mean ± SD, mmHg	139.1 ± 17.7	144.4 ± 19.1	137.6 ± 16.9	135.2 ± 15.5	<0.001
HbA1c, mean ± SD, %	7.8 ± 1.3	7.8 ± 1.3	7.9 ± 1.2	7.7 ± 1.2	0.096
LDL-C, mean ± SD, mmol/L	2.7 ± 0.8	2.7 ± 0.9	2.7 ± 0.7	2.8 ± 0.8	0.374
TG, median (IQR), mmol/L	1.4 (1.0–1.9)	1.3 (1.0–1.9)	1.4 (1.0–1.9)	1.4 (1.1–2.0)	0.568
eGFR, mean ± SD, mL/min/1.73m^2	85.1 ± 24.7	80.9 ± 26.6	87.3 ± 24.1	87.1 ± 22.6	<0.001
Rate of eGFR change, median (IQR), mL/min/1.73m^2/year	-1.3 (-3.6 to 0.0)	-1.5 (-4.0 to -0.1)	-1.3 (-3.4 to 0.0)	-1.0 (-3.2 to 0.1)	0.051
Baseline eGFR category, no. (%)					0.005
G1, ≥90mL/min/1.73m^2	568 (52.7)	163 (45.3)	206 (57.4)	199 (55.4)	
G2, 60–89mL/min/1.73m^2	320 (29.7)	110 (30.6)	97 (27.0)	113 (31.5)	
G3a, 45–59mL/min/1.73m^2	90 (8.4)	39 (10.8)	29 (8.1)	22 (6.1)	
G3b, 30–44mL/min/1.73m^2	62 (5.8)	29 (8.1)	18 (5.0)	15 (4.2)	
G4, 15–29mL/min/1.73m^2	38 (3.5)	19 (5.3)	9 (2.5)	10 (2.8)	
Last follow-up eGFR category, no. (%)					<0.001
G1, ≥90mL/min/1.73m^2	358 (33.2)	85 (23.6)	128 (35.7)	145 (40.4)	
G2, 60–89mL/min/1.73m^2	339 (31.5)	109 (30.3)	106 (29.5)	124 (34.5)	
G3a, 45–59mL/min/1.73m^2	140 (13.0)	48 (13.3)	52 (14.5)	40 (11.1)	
G3b, 30–44mL/min/1.73m^2	92 (8.5)	42 (11.7)	33 (9.2)	17 (4.7)	
G4, 15–29mL/min/1.73m^2	77 (7.1)	40 (11.1)	21 (5.9)	16 (4.5)	
G5, <15mL/min/1.73m^2	72 (6.7)	36 (10.0)	19 (5.3)	17 (4.7)	
uACR, median (IQR), mg/g	21.7 (7.3–84.5)	35.0 (10.0–156.4)	20.0 (7.0–88.3)	17.3 (5.3–53.0)	<0.001
Use of insulin, no. (%)	312 (29.0)	111 (30.8)	119 (33.4)	82 (22.8)	0.005
Use of RAS antagonist, no. (%)	673 (62.5)	248 (68.9)	214 (59.8)	211 (58.8)	0.009
Phase angle, mean ± SD, °	5.5 ± 0.9	4.5 ± 0.4	5.4 ± 0.2	6.5 ± 0.7	<0.001

BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; RAS: renin-angiotensin system; SBP: systolic blood pressure; SD: standard deviation; TG: triglycerides; uACR: urinary albumin-to-creatinine ratio

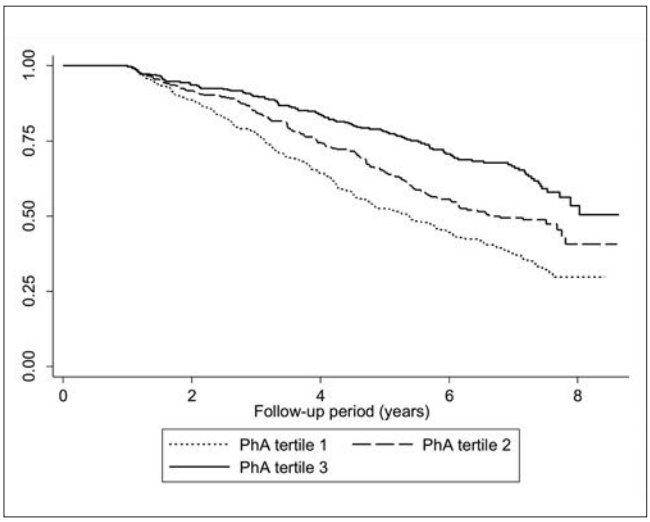

Fig. 2. Kaplan-Meier survival curve for chronic kidney disease progression by phase angle in tertiles.

P<0.001) and 0.67 (95% CI 0.55–0.81, *P*<0.001) in unadjusted analysis and Model 2, respectively. Although there was an association between per SD increase in baseline PhA and CKD progression in unadjusted analysis and Model 1 among males, the association lost statistical significance in Model 2 (*P*=0.956). Similar findings were noted when PhA was analysed in tertiles.

The mediation analysis in Fig. 3 showed that: (1) low PhA was positively associated with MMP-2 with β for pathway a=5.51, *P*<0.001; (2) MMP-2 was positively associated with CKD progression with β for pathway b=0.01, *P*=0.021; (3) low PhA was positively associated with CKD progression with β for pathway c=0.40, *P*=0.022; and (4) the association between low PhA and CKD progression was weakened upon inclusion of MMP-2 in the model with β for pathway c'=0.35, *P*=0.048. MMP-2 accounted for 14.7% of the association between low PhA and CKD progression (*P*=0.037).

DISCUSSION

Our study showed that lower PhA was associated with higher hazards of CKD progression in patients with T2DM. The association was independent of traditional cardio-metabolic risk factors. Hence, low PhA may play a potential role in the pathogenesis of CKD progression in T2DM. The association between low PhA and CKD progression was observed in females but not in males in the fully adjusted analyses. Furthermore, MMP-2 accounted for the association between lower PhA and CKD progression.

The study by Han et al. showed that PhA was higher in patients on peritoneal dialysis than those with non-dialysis CKD Stage 5.[32] PhA was also associated with protein-energy wasting that was prevalent in patients with end-stage renal disease.[32] Hence, PhA appeared as a manifestation of advanced CKD rather than a risk factor of CKD progression. Although an earlier study revealed an association between low PhA and diabetic CKD Stage 5, the study design was cross-sectional and did not establish a causal relationship between PhA and CKD.[11] To the best of our knowledge, there was no study that reported the relationship between PhA and CKD progression. Our study revealed a previously unobserved longitudinal association between low PhA and CKD progression in T2DM, and provided a fresh perspective on the contribution of PhA to renal decline.

The association between low PhA and CKD progression was observed in females but not in males in our study. In our cohort, females had lower baseline PhA than males. It was noted that reduction in oestrogen level during menopausal transition in females could result in accelerated loss of muscle mass.[33,34] As there is a correlation between low muscle mass and high resistance,[13] it is plausible that low PhA, which is influenced by high resistance, is associated with low muscle mass in females.

Our current study demonstrated that lower PhA was characterised by older age, longer DM duration, higher SBP and uACR, and lower eGFR. Our results corroborate the findings from another study that showed an inverse relationship between PhA and DM duration in patients with T2DM.[14] The same study also demonstrated that patients with T2DM had lower PhA than control subjects without DM.[14] These findings suggested that the cardio-metabolic burden may be high in patients with low PhA. Low PhA indicates reduced body cell mass. Body cell mass comprises mainly the cellular components of viscera and muscles. As DM affects these tissues, it is plausible that low PhA indicates catabolism in DM.[14]

A novel finding of this study was that lower PhA was associated with CKD progression through MMP-2 in patients with T2DM. A mediator is considered to be the mechanism via which the independent variable is able to influence the dependent variable.[31] In this case, low PhA (an independent variable) is associated with CKD progression (a dependent variable) through MMP-2 (a mediator). In T2DM, there is increased oxidative stress whereby reactive oxygen species (ROS) are produced in excess.[23] The ROS promote cellular damage and trigger inflammatory signaling.[35] Oxidative stress and inflammation can damage cellular structure and cause apoptosis.[22] PhA reflects cellular integrity, with higher levels indicating more intact cell membranes

Table 2. Baseline characteristics of patients stratified by chronic kidney disease progression.

	CKD progression		
	No	**Yes**	***P* value**
No. of patients	607	471	
Age, mean ± SD, years	57.5 ± 8.9	60.6 ± 9.2	<0.001
Male, no. (%)	305 (50.3)	245 (52.0)	0.564
Ethnicity, no. (%)			<0.001
Chinese	331 (54.5)	240 (51.0)	
Malay	73 (12.0)	126 (26.8)	
Indian	182 (30.0)	86 (18.3)	
Others	21 (3.5)	19 (4.0)	
DM duration, mean ± SD, years	10.5 ± 8.7	14.1 ± 10.0	<0.001
BMI, mean ± SD, kg/m^2	27.1 ± 4.9	27.9 ± 5.0	0.006
SBP, mean ± SD, mmHg	134.9 ± 15.5	144.4 ± 18.9	<0.001
HbA1c, mean ± SD, %	7.6 ± 1.2	8.0 ± 1.3	<0.001
LDL-C, mean ± SD, mmol/L	2.7 ± 0.8	2.7 ± 0.8	0.774
TG, SD, mmol/L	1.3 (1.0–1.8)	1.5 (1.1–2.0)	<0.001
eGFR, mean ± SD, mL/min/1.73m^2	91.8 ± 20.9	76.4 ± 26.4	<0.001
Rate of eGFR change, median (IQR), mL/min/1.73m^2/year	-0.8 (-2.0 to 0.3)	-2.7 (-5.3 to -0.6)	<0.001
Baseline eGFR category, no. (%)			<0.001
G1, ≥90mL/min/1.73m^2	388 (63.9)	180 (38.2)	
G2, 60–89mL/min/1.73m^2	160 (26.4)	160 (34.0)	
G3a, 45–59mL/min/1.73m^2	30 (4.9)	60 (12.7)	
G3b, 30–44mL/min/1.73m^2	20 (3.3)	42 (8.9)	
G4, 15–29mL/min/1.73m^2	9 (1.5)	29 (6.2)	
Last follow-up eGFR category, no. (%)			<0.001
G1, ≥90mL/min/1.73m^2	321 (52.9)	37 (7.9)	
G2, 60–89mL/min/1.73m^2	214 (35.3)	125 (26.5)	
G3a, 45–59mL/min/1.73m^2	42 (6.9)	98 (20.8)	
G3b, 30–44mL/min/1.73m^2	23 (3.8)	69 (14.7)	
G4, 15–29mL/min/1.73m^2	4 (0.7)	73 (15.5)	
G5, <15mL/min/1.73m^2	3 (0.5)	69 (14.7)	
uACR, median (IQR), mg/g	14.0 (5.3–36.5)	59.0 (16.0–279.0)	<0.001
Use of insulin, no. (%)	140 (23.1)	172 (36.7)	<0.001
Use of RAS antagonist, no. (%)	325 (53.6)	348 (73.9)	<0.001
Phase angle, mean ± SD, °	5.6 ± 0.9	5.3 ± 1.0	<0.001
Phase angle, no. (%), °			<0.001
T1	160 (26.4)	200 (42.5)	
T2	199 (32.8)	160 (34.0)	
T3	248 (40.9)	111 (23.6)	

BMI: body mass index; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; RAS: renin-angiotensin system; SBP: systolic blood pressure; SD: standard deviation; TG: triglycerides; uACR: urinary albumin-to-creatinine ratio

Table 3. Association between phase angle and chronic kidney disease progression.

	Hazard ratio (95% confidence interval) *P* value		
	Unadjusted	**Model 1[a]**	**Model 2[b]**
Phase angle (per SD increase)	0.70 (0.63–0.78) *P*<0.001	0.73 (0.65–0.82) *P*<0.001	0.84 (0.75–0.95) *P*=0.004
Phase angle in tertiles			
T1	2.27 (1.80–2.87) *P*<0.001	2.19 (1.68–2.85) *P*<0.001	1.71 (1.30–2.26) *P*<0.001
T2	1.57 (1.24–2.01) *P*<0.001	1.60 (1.24–2.05) *P*<0.001	1.46 (1.13–1.88) *P*=0.004
T3	Reference	Reference	Reference
Female			
Phase angle (per SD increase)	0.55 (0.46–0.66) *P*<0.001	0.60 (0.49–0.72) *P*<0.001	0.67 (0.55–0.81) *P*<0.001
Phase angle in tertiles			
T1	2.93 (1.88–4.55) *P*<0.001	2.70 (1.71–4.26) *P*<0.001	2.56 (1.59–4.14) *P*<0.001
T2	1.55 (0.96–2.50) *P*=0.071	1.64 (1.01–2.64) *P*=0.044	1.87 (1.13–3.09) *P*=0.014
T3	Reference	Reference	Reference
Male			
Phase angle (per SD increase)	0.75 (0.65–0.86) *P*<0.001	0.83 (0.71–0.96) *P*=0.016	1.00 (0.85–1.16) *P*=0.956
Phase angle in tertiles			
T1	2.18 (1.57–3.03) *P*<0.001	1.83 (1.27–2.62) *P*=0.001	1.34 (0.90–1.98) *P*=0.146
T2	1.85 (1.39–2.48) *P*<0.001	1.70 (1.25–2.31) *P*=0.001	1.36 (0.99–1.86) *P*=0.055
T3	Reference	Reference	Reference

SD: standard deviation
[a] Model 1: Age, sex and ethnicity (age is not included in sex-stratified analysis).
[b] Model 2: Model 1 + diabetes duration, body mass index, haemoglobin A1c, systolic blood pressure, low-density lipoprotein cholesterol, log-transformed triglyceride, estimated glomerular filtration rate, log-transformed urinary albumin-to-creatinine ratio, use of insulin and use of renin-angiotensin system antagonist (age is not included in sex-stratified analysis).

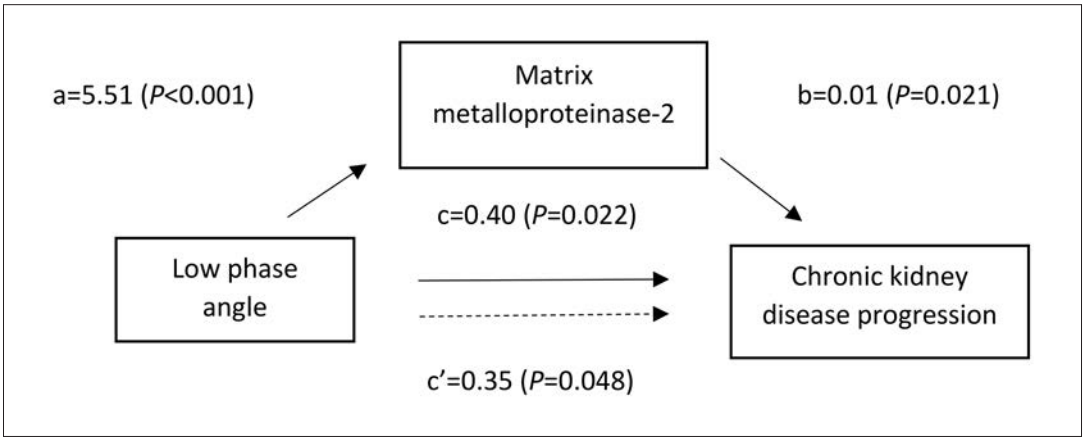

Fig. 3. Mediation of the association between phase angle and chronic kidney disease progression. The binary mediation model decomposes the total effect quantified by path c (solid arrow) of phase angle on the chronic kidney disease progression into indirect effect quantified by the product of a and b, and direct effect with the effect of matrix metalloproteinase-2 removed and quantified by path c' (dotted arrow).

Adjusted for age, sex, ethnicity, diabetes duration, body mass index, haemoglobin A1c, systolic blood pressure, low-density lipoprotein cholesterol, log-transformed triglyceride, estimated glomerular filtration rate categories, log-transformed urinary albumin-to-creatinine ratio, use of insulin and use of renin-angiotensin system antagonist.

and lower levels indicating reduced cellular integrity or cellular dysfunction.[11,13] It is plausible that oxidative stress, as reflected by low PhA,[22] activates MMP-2, which in turn initiates a cascade of events resulting in infiltration of macrophages, deposition of extracellular matrix, blockade of renal interstitial vasculature and promotion of renal hypoxia.[25] These changes lead to renal interstitial fibrosis that characterises CKD.[25] As MMP-2 was only measured at baseline, further prospective studies measuring MMP-2 at baseline and follow-ups are needed to confirm the role of MMP-2 accounting for the association between low PhA and CKD progression.

Several clinical implications emerged in our current study. Firstly, low PhA may serve as a risk marker of CKD progression in T2DM. Hence, healthcare providers may consider proactively monitoring renal function in patients with T2DM and low PhA. Secondly, it is possible to monitor PhA in routine DM management since BIA is a convenient, non-invasive, inexpensive and reliable method to measure body composition.[36] Thirdly, PhA may be considered a useful indicator for monitoring therapies targeted at slowing down CKD progression in patients with T2DM. It has been reported that high-dose vitamin D supplementation and nutritional counselling, combined with whey proteins isolate supplementation, improve PhA in patients with cancer.[37,38] Nevertheless, data on therapeutic interventions targeting the underlying pathophysiological mechanisms leading to lowered PhA remain sparse.

Our study results have provided new insights into the increased susceptibility of T2DM patients with low PhA to CKD progression. The novel interplay involving low PhA, MMP-2 and CKD progression suggests a causal pathway underlying the association between low PhA and CKD progression, although future studies are needed to confirm the finding. The other strengths of our study include a relatively large sample size, long duration of follow-up, and adjustment for a wide range of demographic and clinical variables.

We also acknowledge some limitations in our study. Firstly, we did not collect data on nutrition, which may affect the level of PhA.[39] Secondly, we were unable to generalise the results to the general population as our study population comprised only patients with T2DM.

CONCLUSION

Low PhA, mediated by MMP-2, was independently associated with CKD progression in patients with T2DM. PhA may be potentially considered as a safe, inexpensive and simple marker to predict CKD progression, especially in female patients with T2DM.

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REVIEW ARTICLE

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An approach to genetic testing in patients with metastatic castration-resistant prostate cancer in Singapore

Ravindran Kanesvaran [1]*FAMS (Med Onco)*, Puey Ling Chia [2]*PhD*, Edmund Chiong [3,4] *FAMS (Urology)*, Melvin Lee Kiang Chua [5]*FAMS*, Nye Thane Ngo [6]*FRCPath (UK)*, Samuel Ow [7]*MPH*, Hong Gee Sim [8]*FAMS (Urology)*, Min-Han Tan [9]*PhD*, Kiang Hiong Tay [10]*FAMS*, Alvin Seng Cheong Wong [7]*MRCP (UK)*, Siew Wei Wong [11]*FRACP*, Puay Hoon Tan [12]*FRCPA*

ABSTRACT

Introduction: There has been a rapid evolution in the treatment strategies for metastatic castration-resistant prostate cancer (mCRPC) following the identification of targetable mutations, making genetic testing essential for patient selection. Although several international guidelines recommend genetic testing for patients with mCRPC, there is a lack of locally endorsed clinical practice guidelines in Singapore.

Method: A multidisciplinary specialist panel with representation from medical and radiation oncology, urology, pathology, interventional radiology, and medical genetics discussed the challenges associated with patient selection, genetic counselling and sample processing in mCRPC.

Results: A clinical model for incorporating genetic testing into routine clinical practice in Singapore was formulated. Tumour testing with an assay that is able to detect both somatic and germline mutations should be utilised. The panel also recommended the "mainstreaming" approach for genetic counselling in which pre-test counselling is conducted by the managing clinician and post-test discussion with a genetic counsellor, to alleviate the bottlenecks at genetic counselling stage in Singapore. The need for training of clinicians to provide pre-test genetic counselling and educating the laboratory personnel for appropriate sample processing that facilitates downstream genetic testing was recognised. Molecular tumour boards and multidisciplinary discussions are recommended to guide therapeutic decisions in mCRPC. The panel also highlighted the issue of reimbursement for genetic testing to reduce patient-borne costs and increase the reach of genetic testing among this patient population.

Conclusion: This article aims to provide strategic and implementable recommendations to overcome the challenges in genetic testing for patients with mCRPC in Singapore.

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Keywords: Clinical model, genetic counselling, genetic testing, homologous recombination repair genes, metastatic castration-resistant prostate cancer

[1] Division of Medical Oncology, National Cancer Centre Singapore, Singapore
[2] Department of Medical Oncology, Tan Tock Seng Hospital, Singapore
[3] Department of Urology, National University Hospital, Singapore
[4] Department of Surgery, National University of Singapore, Singapore
[5] Division of Radiation Oncology, National Cancer Centre Singapore, Singapore
[6] Division of Pathology, Singapore General Hospital, Singapore
[7] Department of Haematology-Oncology, National University Cancer Institute, Singapore
[8] Ravenna Urology Clinic, Gleneagles Medical Centre, Singapore
[9] Lucence Diagnostics, Singapore
[10] Department of Vascular and Interventional Radiation, Singapore General Hospital, Singapore
[11] The Cancer Centre, Singapore
[12] Division of Pathology, Singapore General Hospital, Singapore
Correspondence: Assoc Prof Ravindran Kanesvaran, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Crescent, Singapore 169610.
Email: ravindran.kanesvaran@singhealth.com.sg
Prof Puay Hoon Tan, Division of Pathology, Singapore General Hospital, 20 College Road, Singapore 169856.
Email: tan.puay.hoon@singhealth.com.sg

CLINICAL IMPACT

What is New

- Genetic testing should be incorporated into routine practice for prostate cancer, given its prognostic and predictive values.
- A clinical model providing real-time guidance to clinicians who treat prostate cancer patients is proposed.

Clinical Implications

- Pre-test counselling by clinicians and post-test discussion by genetic counsellors (hybrid approach) are recommended.
- Clinicians managing prostate cancer should be trained to provide pre-test genetic counselling for implementing the hybrid approach.
- Pathologists play a crucial role in the testing journey and should be included in the multidisciplinary team and molecular tumour board meetings for managing mCRPC.

INTRODUCTION

Prostate cancer is the fifth most common cancer in Asian men, and with its rising incidence, is emerging as a health priority in Asia.[1] Across Asian countries, age-standardised incidence rates (ASIRs) of prostate cancer range from 0.9 to 56.1 per 100,000 population, with the second highest ASIR reported in Singapore (30.7 per 100,000 population) in 2020.[2] More than 80% of patients with an indolent, low-grade castration-sensitive prostate cancer eventually progress and develop high-grade metastatic castration-resistant prostate cancer (mCRPC) despite optimal disease control with androgen deprivation therapy.[3,4]

Several studies have extensively investigated the heritable component of prostate cancer.[5-7] In a genome-wide association study of patients with prostate cancer, 269 risk variants (86 new and 183 previously reported loci)—which represented 33.6% of the estimated familial relative risks in men of East Asian ancestry—were identified.[6] Mutations in homologous recombination repair (HRR) genes, specifically the breast cancer genes 1 (*BRCA1*) and 2 (*BRCA2*), are implicated in the development of prostate cancer and are associated with aggressive disease and poor prognosis, with a higher likelihood of nodal involvement and distant metastasis.[8,9] A genomic sequencing study in 150 patients with advanced prostate cancer identified HRR mutations in 22.7% of cases, the most frequent being *BRCA2* mutations (in 12.7% of cases).[10] The frequency of somatic and germline HRR mutations in patients with mCRPC were found to be between 28% and 33%.[11,12] In studies where only germline mutations were analysed, approximately 11.8–17.2% of patients were reported to possess HRR mutations.[13-15] Although the rate of HRR mutations in patients with prostate cancer has not been extensively studied in patients of Asian descent, limited published data suggest rates similar to those reported in Western populations (9.8–11.8%).[16,17]

Olaparib, the first polyadenosine diphosphate-ribose polymerase (PARP) inhibitor, was approved in Singapore by the regulatory agency in March 2021 for the treatment of mCRPC in patients harbouring *BRCA1*, *BRCA2* and/or ataxia-telangiectasia mutated (*ATM*) mutations (germline, somatic or both) who have progressed following a prior new hormonal agent.[18] Given that PARP inhibitors have shown clinically meaningful efficacy in patients with mCRPC,[12,19] genetic testing for HRR mutations has become paramount. Although genetic testing for patients with mCRPC is recommended by international guidelines, challenges associated with patient selection, genetic counselling processes, and sample storage and processing hinder its routine implementation in real-world clinical practice. In the Asia-Pacific region, including Singapore, clinical practice guidelines for genetic testing in patients with mCRPC are currently yet to be routinely adopted.[20] Hence, a multidisciplinary panel of medical oncologists, radiation oncologists, urologists, interventional radiologists, pathologists and cancer geneticists involved in the management of prostate cancer from both public and private institutions across Singapore was formed to address this issue. A meeting was held to formulate a reasonable approach to incorporate genetic testing into the management of patients with mCRPC in Singapore.

METHOD

In pursuance of developing recommendations for genetic testing in patients with mCRPC in Singapore, a 4-step survey-based process was implemented (online Supplementary Fig. S1). A pre-meeting survey was distributed to and completed by 12 specialists (online Supplementary Appendix). In the meeting that followed, key aspects of genetic testing, counselling and the sample journey were discussed. The specialists provided insights based on their clinical experience regarding common practices and challenges in genetic testing in Singapore and provided strategic and implementable recommendations to overcome the challenges. An

evidence-based literature search, including a review of relevant international and regional guidelines, was conducted to support the recommendations from the panel. A clinical model was formulated for incorporating genetic testing and counselling into routine practice. The recommendations and clinical algorithm were reviewed and approved by all authors. This position paper provides an overview of the burden of prostate cancer in Singapore and elucidates the challenges and recommendations for genetic testing in patients with mCRPC.

Burden of prostate cancer in Singapore

The ASIR of prostate cancer is comparatively higher in Singapore than in other Asian countries like China (34.3 versus 10.2) and India (34.3 vs 5.5).[2] According to the Singapore Cancer Registry Annual Report 2019, prostate cancer was the second most frequent cancer in males, with an incidence of 15.4%, and was the fourth leading cause of cancer-related mortality in males, with 989 deaths during 2015–2019 in Singapore.[21] During the period, the number of cases of prostate cancer reported was highest in elderly individuals (22.0% of cases in individuals aged 70–79 years and 18.3% in those aged 60–69 years).[21] Comprehensive data on the incidence of mCRPC in Singapore are lacking. According to the United in Fight against prOstate cancer (UFO) study, 73.2% of patients with metastatic prostate cancer in Singapore present with de novo metastases.[22] Despite the increased ASIR of prostate cancer from 4.0 per 100,000 population in 1968–1972 to 34.6 per 100,000 population in 2015–2019, the age-standardised relative survival almost doubled from approximately 47.3% to 87.8% in Singapore.[21] The increased incidence and survival of prostate cancer could be due to the extensive use of prostate-specific antigen testing in Singapore.[23] With targeted therapies available for patients harbouring genetic mutations, it is critical to test patients for genetic mutations with the aim to increase overall survival and quality of life.

Genetic testing in mCRPC

Patient selection and time for testing

Selecting eligible patients and determining the optimal time for genetic testing are critical in the management of mCRPC. HRR mutations, especially in *BRCA1* and *BRCA2,* have been established as negative prognostic factors and are associated with early-onset disease, high Gleason score, nodal involvement, metastatic disease at diagnosis, shorter metastatic-free survival and shorter overall survival in patients with mCRPC.[8] However, HRR mutations act as positive predictive markers with respect to treatment outcomes, as several HRR-mutated tumours have shown response to PARP inhibitors as well as platinum chemotherapy.[11,24] Several international guidelines, such as those from the National Comprehensive Cancer Network, American Urological Association, American Society for Radiation Oncology, Society of Urologic Oncology, European Society for Medical Oncology and Philadelphia Prostate Cancer Consensus, have recommended testing for HRR mutations in all patients with mCRPC (Table 1).[25-28]

It is now known that the risk of prostate cancer doubles in individuals with first-degree relatives with prostate cancer.[15,29] Although germline testing is important in identifying familial risk, solely performing germline testing may miss approximately 59% of patients with prostate cancer who have somatic mutations. Pritchard et al. reported germline HRR mutations in 11.8% of patients with metastatic prostate cancer.[13] In the PROREPAIR-B study of unselected patients with mCRPC, 16.2% of patients had germline mutations.[14] In a cross-sectional study of 3,607 men with a history of prostate cancer who underwent germline genetic testing between 2013 and 2018, 17.2% had germline mutations, 30.7% of which were *BRCA1/2* mutations.[15] Of note, genetic (somatic plus germline) mutations were reported in 33% of patients in the TOPARP-A study.[11] In the PROfound study, HRR mutations were reported in 27.9% of patients.[12] Therefore, somatic testing should be considered in patients with mCRPC since it has the ability to detect patients with HRR mutations. As recommended in international guidelines (Table 1), all patients with mCRPC should undergo testing for HRR mutations. Interestingly, studies have shown that approximately 30–40% of HRR mutation carriers may not report a family history of cancer.[13-15] Thus, family history should not be the sole factor for determining the need for testing. Table 2 describes the recommendations of international guidelines on patient selection and optimal time for genetic testing.

Genetic counselling of patients with mCRPC

Although the main aim of genetic testing in patients with mCRPC is to identify targetable mutations, the results of genetic testing may uncover unanticipated hereditary mutations.[30] A suspicion of genetic predisposition mandates extensive genetic counselling prior to and after germline testing to help patients understand the familial implications.[31] Genetic counselling has been shown to improve patient outcomes with positive downstream effects as patients are more equipped with sharing the results of genetic tests with extended families.[32] Genetic counselling has now become a critical aspect of disease

Table 1. Recommendations from international guidelines for genetic testing in patients with castration-resistant prostate cancer (mCRPC).

Guidelines	Germline testing	Tumour testing
NCCN (v1.2023)[25]	In patients with metastatic, regional (node-positive), very high- or high-risk localised prostate cancer. Any patient with prostate cancer who has Ashkenazi Jewish ancestry, strong family history of cancer[a] or breast cancer. Intraductal/cribriform histology.	In patients with metastatic prostate cancer for HRR mutations such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, *CDK12*. In patients with mCRPC that is MSI-H or dMMR.
ESMO (2020)[26]	Testing for *BRCA2* and other DDR genes associated with cancer predisposition syndromes is recommended in patients with a family history of cancer and should be considered in all patients with metastatic prostate cancer.	Testing for homologous recombination genes and dMMR (or MSI) in patients with mCRPC.
AUA/ ASTRO/ SUO (2020)[28]	In patients with mHSPC, regardless of age and family history, clinicians should offer genetic counselling and germline testing. In patients with mCRPC, clinicians should offer germline genetic testing to identify DNA repair deficiency mutations and MSI status that may inform prognosis and counselling regarding family risk as well as potential targeted therapies.	In patients with mCRPC, clinicians should offer somatic tumour genetic testing to identify DNA repair deficiency mutations and MSI status that may inform prognosis and counselling regarding family risk as well as potential targeted therapies.
Philadelphia Prostate Cancer Consensus Conference (2019)[27]	In patients with metastatic prostate cancer (either castration-resistant or castration-sensitive). Men with 1 brother or father or 2 or more male relatives diagnosed with prostate cancer at age <60 years, died of prostate cancer or had metastatic prostate cancer. Patients should undergo genetic testing for the following genes: • Comprehensive (large) panel testing for therapy/clinical trial eligibility • Priority germline testing (metastatic prostate cancer): ◦ *BRCA2*/*BRCA1* ◦ DNA MMR genes ◦ Test additional genes on the basis of personal or family history	Next-generation sequencing for all men with metastatic prostate cancer, followed by confirmatory germline testing.

ASTRO: American Society for Radiation Oncology; AUA: American Urological Association; DDR: DNA damage response and repair; dMMR: deficient mismatch repair; DNA: deoxyribonucleic acid; ESMO: European Society for Medical Oncology; HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; MMR: mismatch repair; MSI: microsatellite instability; MSI-H: microsatellite instability - high; NCCN: National Comprehensive Cancer Network; SUO: Society of Urologic Oncology

[a] Family history and/or ancestry with ≥1 first-, second- or third-degree relative with breast, colorectal or endometrial cancer at age ≤50 years, male breast cancer or ovarian cancer or exocrine pancreatic cancer or metastatic, regional, very high-risk or high-risk prostate cancer at any age; ≥1 first-degree relative with prostate cancer at age ≤60 years; ≥2 first-, second- or third-degree relatives with breast cancer or prostate cancer at any age; ≥3 first- or second-degree relatives with Lynch syndrome-related cancers, especially if diagnosed at age <50 years; a known family history of familial cancer risk mutations, especially in *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6, PMS2*, *EPCAM*.

management particularly in diverse multiethnic countries like Singapore, where the likelihood of encountering variants of unknown significance (VUS) presents challenges for clinicians and patients.[33,34] Although genetic counselling services for patients with ovarian and breast cancer are well established, such services are underutilised in patients with prostate cancer, with less than 3% of patients undergoing genetic testing from 2014 to 2019, according to the cancer genetics service of a major institution in Singapore.[32,35]

In the traditional model, patients are referred to a genetic counsellor once a decision for germline testing is made.[36] Genetic counselling is conducted in 2 phases: pre-test and post-test counselling. An in-depth genetic counselling session involves taking a detailed 3-generation family and disease history, including that of both maternal and paternal relatives, prior to genetic testing.[37,38] The components of the pre-test and post-test sessions are described in Table 3.[27,36-42] Genetic counsellors advise on the need for testing after considering patients' understanding and concerns, in addition to the ethical, legal and social implications of germline testing.[43] In post-genetic testing, patients will be counselled on the implications of the test results before they are referred to their primary oncologist for further management of mCRPC.

This conventional route, although ideal, is marked by several challenges. Particularly in Singapore, there is an acute shortage of genetic counsellors, with only approximately 10 genetic counsellors for a population

of 5.7 million being reported in 2019.[44-46] Patients are currently referred to 1 of the 3 major centres for genetic counselling: National University Cancer Institute, Singapore; National Cancer Centre Singapore (NCCS); and Tan Tock Seng Hospital. More than 9,000 new patients with cancer visit NCCS each year for cancer treatment, approximately 5% (450 patients) of which might harbour germline mutations.[32] The waiting time for genetic counselling at this institution was reported to be between 2 and 3 months, resulting in patients being lost to follow-up.[32] Thus, genetic counselling prior to germline testing has created a bottleneck because of the overwhelming demand for cancer genetics services. Other key barriers to germline testing include l ittle or no reimbursement for genetic testing and counselling, lack of definitive guidelines, and clinical time and space constraints.[47-49]

Henceforth, we recommend a hybrid method involving a brief pre-test counselling conducted by the managing clinician prior to somatic testing and a post-test discussion by a genetic counsellor (post-somatic testing, but prior to germline testing, for patients with mutations) be adopted in Singapore (Fig. 1).[27,50] A brief pre-test counselling followed by somatic molecular testing can reduce the delays and bottlenecks (Fig. 1). This method is known as the "mainstreaming" of genetic counselling and has been established for ovarian and breast cancer in several countries, with a positive impact on disease management.[51-53] In Malaysia, the mainstreaming approach led to increased patient satisfaction and a reduction in the decisional conflict in patients with ovarian cancer.[54] An Australian prospective study pioneered this mainstreaming approach in men with metastatic prostate cancer and demonstrated that it was feasible and highly accepted, as well as ensured timely and equitable access to genetic testing.[53] In this article, the specialist panel formulated a model for incorporating genetic counselling into the mainstream management of mCRPC in Singapore. The recommendations for genetic testing and counselling are summarised in Table 2 and the model is outlined in Fig. 1. Although mainstreaming of genetic counselling may increase the consultation

Table 2. Recommendations for medical/radiation oncologists and urologists for genetic testing and counselling of patients with prostate cancer.

Recommendations

- Genetic testing considerations should be part of routine practice as it can inform on personal and familial risk, and provides predictive and prognostic value
- Family history and informed consent should form part of routine clinical practice
- During patient selection for somatic/germline testing, the following factors should be considered:
  - Somatic testing
    - Patients with metastatic prostate cancer[a]
  - Germline testing
    - Age <55 years
    - Strong positive family history[b]
    - High-risk or very high-risk localised prostate cancer or metastatic prostate cancer regardless of family history
    - Intraductal histology
    - Patients who test positive on somatic testing for homologous recombination repair mutations
    - Ashkenazi Jewish ancestry
  - Germline testing should be undertaken in patients with somatic mutations to evaluate whether the mutation is of germline origin and subsequent familial risk for patients and relatives
  - In the context of available targeted therapies, somatic testing should be conducted at disease progression to metastatic castration-resistant prostate cancer, followed by germline testing to evaluate familial risk if mutations are detected
  - Genetic counselling should be performed with an overall perspective on optimal disease management and potential downstream effects
  - A hybrid method involving pre-test counselling prior to somatic testing conducted by the treating urologist or medical oncologist and post-test counselling (after somatic testing but prior to germline testing in indicated patients) by the genetic counsellor should be adopted in Singapore
  - Urologists and medical oncologists should be appropriately trained in genetic counselling
  - The distress of unexpected results should be taken into account during the counselling session

Educational points

- Genetic testing and counselling should be discussed with the patients early in the course of the disease as patients with genetic aberrations are likely to have aggressive disease leading to an early metastatic stage that needs extensive management
- Somatic testing in particular tissue testing is considered the gold standard as it is well-established and can identify more patients with HRR mutations
- An algorithm that combines testing modalities (e.g. Fig. 1) should ensure that all meaningful pathogenic variants are identified
- Relying solely on family history of prostate cancer for conducting genetic tests may lead to missing the detection of patients, as it has been shown that 30–40% of HRR mutation carriers may not report a family history of cancer

[a] In patients with low- and favourable intermediate-risk localised prostate cancer and life expectancy of ≥10 years, somatic testing should be considered on a case-to-case basis according to the discretion of the healthcare professionals and patient decision.

[b] Family history includes high-risk germline mutations (e.g. *BRCA1/2*); brother or father or multiple family members diagnosed with prostate cancer (but not clinically localised grade group 1) at <60 years or who died from prostate cancer; ≥3 cancers on the same side of the family, especially diagnosed at age ≤50 years, bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localised, grade group 1), small bowel or urothelial cancer

time for physicians, it should be encouraged with the consideration of availability of resources and funds.[55] In order to incorporate the mainstreaming approach in Singapore, every effort should be made to establish effective clinical workflows for genetic testing, enhance genetic counselling training programmes for clinicians, and provide sufficient educational materials to support them in the pre-test counselling sessions. In addition, the cost-effectiveness of genetic testing is related to cascade testing in relatives of patients identified with germline mutations. However, several studies in patients with ovarian and breast cancer indicate that only a third of at-risk relatives undergo cascade testing. Moreover, male relatives show higher reluctance towards cascade testing than their female counterparts.[56-59] This lack of cascade testing is a concern in view of the missing opportunity to detect and prevent hereditary cancers. Easier access to genetic testing and counselling and increased awareness of disclosing genetic test results to relatives are vital to improve cascade testing.

Sample journey in mCRPC

Selecting an appropriate tissue sample is essential for the success of genetic testing. Of the available testing options (e.g. tissue, blood, circulating tumour DNA [ctDNA]), tissue testing remains the gold standard as it is well established and can identify both germline and somatic mutations; however, it cannot differentiate between germline and somatic mutations based on the tumour test result alone. A confirmatory blood test is required to determine the germline status of the mutation.[12,60] An algorithm that combines testing modalities (e.g. Fig. 1) is important to ensure that all meaningful pathogenic variants are identified. In the PROfound study, most samples (83%) were obtained from tumour tissue and only 16.6% from the metastatic site. The success rate of tumour tissue testing was higher with metastatic tumours than with primary tumours (63.9% vs 56.2%).[61] Metastatic sites are associated with aggressive cancers and are rich in mutated tumour cells, thus having higher DNA yield, and are biopsied relatively later than are archived primary tumour samples (online Supplementary Fig. S2).[10,12,61] Despite higher test success rates with metastatic sites, repeat biopsy is challenging in mCRPC, with metastatic sites being bone-predominant with potential low yields and sample processing interference (e.g. decalcification).[62] Obtaining samples from metastatic sites is an invasive process that is associated with high costs, morbidity and patient reluctance.[63,64] In addition, challenges with tumour tissue heterogeneity limit sampling, which may only partially reflect tumour biology.[62]

Circulating cell-free DNA testing is an emerging, minimally invasive technique for obtaining genetic material.[59] Circulating cell-free DNA is shed into the bloodstream by cancerous and non-cancerous cells. ctDNA is obtained from the cell fragments of the tumour including the metastatic tissue. One of the

Table 3. Components of genetic counselling.

Elements	Description
Purpose of testing	Precision therapy, early detection strategies and/or to identify hereditary cancer syndrome/ risk
Possibility of uncovering hereditary cancer syndrome	Depending on the test, it might uncover a hereditary cancer syndrome, such as HBOC and Lynch syndrome
Types of test results	Mutation (pathogenic/ likely pathogenic variants), variants of uncertain (unknown) significance and negative
Potential to uncover additional cancer risks	Multiple gene-specific risks may be identified beyond prostate cancer risk that affects men and their families
Potential out-of-pocket cost	Not all insurance plans cover genetic testing; some mandate referral to a genetic counsellor
GINA and other laws that address genetic discrimination	Protects patients from genetic discrimination from health insurance companies and employers, with specific limitations on the type of employer and size of the company
Cascade testing/ additional familial testing	Testing blood relatives for pathogenic variants or additional genetic testing by family history; worry and anxiety that may result from hereditary cancer testing; effect on family relationships
Data-sharing/ data-selling policies of genetic laboratories	Each genetic testing laboratory may have unique data-sharing and data-selling policies that patients must be aware of
Privacy of genetic tests	Protection of genetic data from a data breach or access by third party

GINA: Genetic Information Non-discrimination Act; HBOC: hereditary breast and ovarian cancer

main limitations is dependence on the quality and quantity of the shredded DNA as the ctDNA fraction in the blood varies with tumour size, location, clinical disease state, tumour vascularity and metastatic location.[65] A low concentration of ctDNA is present during the early stage of the disease, making ctDNA-based testing in patients difficult.[66] In the later stages, patients with progressive mCRPC have demonstrated higher ctDNA fraction than those with metastatic hormone-sensitive prostate cancer receiving androgen deprivation therapy. Recent studies described below demonstrate the utility of ctDNA assays in identifying patients who may benefit from targeted therapies.[64,67]

In the TRITON2/3 trial, ctDNA was used for assessing genetic mutations in 3,334 patients with 75% concordance between ctDNA and tissue testing. When the authors assessed samples containing more than 20% of ctDNA, the concordance with tissue testing increased to more than 85%.[19] In the PROfound study, the high concordance between ctDNA-based testing and tissue testing was observed in patients with *BRCA1*, *BRCA2* or *ATM* mutations, with a positive percentage agreement of 81% and a negative percentage agreement of 92%, making ctDNA-based testing a viable option for patients with mCRPC.[68]

The multidisciplinary panel recommends ctDNA testing as an option for the diagnostic pathway, with sample collection preferably done at biochemical or radiological progression to mCRPC to optimise yield (Fig. 1).

A comparative chart of ctDNA-based testing with tumour and blood testing is provided in the online Supplementary Table S1.

Optimising sample processing

The role of pathologists has evolved immensely in the rapidly advancing field of oncology, with many treatment decisions guided by tumour biomarker analyses. Pathologists play a critical role in the sample journey as they are involved in every step of tissue testing, from obtaining an adequate amount of diagnostic material to appropriate storage of the remaining samples for further testing, including genetic analysis.[69] In the PROfound study, test failure occurred in 31% out of 4,047 samples. The reasons for test failure are described in the online Supplementary Fig. S3.[12,70] The journey of tumour samples from the clinic to the laboratory has 3 milestones regarding genetic testing: the pre-analytical phase that includes biopsy, sample collection, fixation, storage during transit and pre-processing; the analytical phase of procuring adequate genetic material from the sample for testing; and the post-analytical phase of presentation and interpretation of results, including preparation of the report for dissemination of information to the treating clinician.

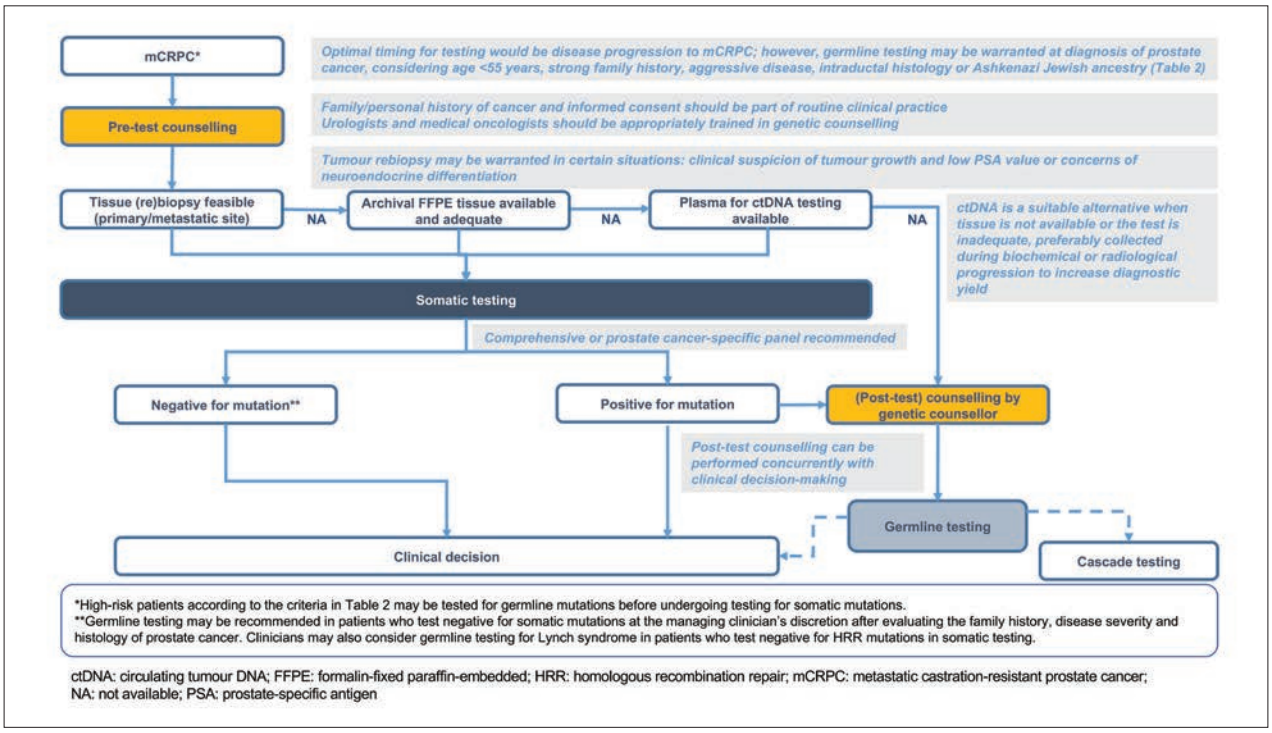

Fig. 1. Clinical model: Genetic testing for patients with metastatic castration-resistant prostate cancer (mCRPC)

Pre-analytical and analytical phases

During the pre-analytical and analytical phases, multiple challenges such as an insufficient tumour or biopsy sample, unsatisfactory DNA yield or quality and consequently the need for repeat tests are often faced. These challenges are frequently related to tissue sampling and processing issues, difficulties with bone biopsy, archived tissue age (more than 5 years), improper storage, and low tumour yield, quality or both.[71-76] The sample yield and quality may be affected by the route and technique of the biopsy. Polito et al. reported high sensitivity (98.2%) and specificity (98.1%) with transrectal fine-needle aspiration with a low false-negative rate (6.6%).[77] However, a prospective study showed that core biopsy was more accurate than fine-needle aspiration biopsy in biopsy sampling to determine cancer diagnosis (45.6% vs 33.3%).[78] In the PROfound study, core needle biopsy was the most common collection method (65.8%), followed by radical prostatectomy (12.4%), excisional biopsy (8.2%) and transurethral resection of the prostate (7.6%) of the specimens used. Among these, testing success rates were highest with radical prostatectomy (74%), which may be attributed to the availability of larger tumour quantum in radical prostatectomy.[12] When needle biopsy is used for obtaining tissue, tumour heterogeneity should be factored in and at least 12 core samples should be collected.[79,80] The accuracy of core needle biopsies can be improved by using imaging technology for guiding the needle.[81]

In the PROfound study, a higher testing success rate was observed for biopsy from metastatic sites than from the prostate tissue (63.7% vs 56.3%). The highest success rate was observed for lymph nodes (74.7%) and the lowest for bone (42.6%). Procuring a metastatic tissue sample from the bone is difficult because of low accessibility and amenability.[73] Computed tomography-guided bone biopsy is commonly used for sample collection in case of metastases to the bone.[72] The yield of bone samples and success rates can be improved by standardising the process for DNA isolation. The use of ethylenediaminetetraacetic acid for decalcification of bone instead of formic acid results in better yield as formic acidic decalcification tends to degrade DNA.[73] The separation of softer portions of the submitted specimen from hard bony parts—which require decalcification for routine processing and subsequent genetic analysis has also resulted in increased yield and higher DNA quality for testing.[82]

Although fresh paraffinised samples are preferred for genetic analysis, their utilisation is limited by the feasibility of rebiopsy and patient reluctance. Formalin-fixed paraffin-embedded (FFPE) samples are most commonly used for molecular testing as they can be stored for several years without hampering the cellular and molecular integrity and can be retrieved retrospectively for this purpose.[63,74,75] In the case of inadequate tumour content, it is advisable to obtain micro-dissected target tissue to enrich the tumour content.[83] Tissue fixation should be performed with 10% neutral buffered formalin, with a fixation time of 1 day (3 to 6 hours for core biopsies), and the heat treatment of tissue lysates at 95°C for 30 minutes may be done to ensure good-quality FFPE samples.[76,84] An individual section should be 5-10μm thick, containing a minimum of more than 5,000 total nucleated cells with more than 10–20% neoplastic content.[84] The panel recommends pre-analytical quality control of DNA samples as an imperative step to ensure that the sample reaches the minimum threshold for testing.

The sample age is often a challenge when using stored FFPE samples. In the PROfound study, the highest success rate (68.1%) was obtained in samples that were less than 1 year old (n=923), but most samples were 5–10 years old (n=1,275; success rate 50.4%).[61] This result may be attributed to the deterioration of samples over time and the different storage environments.[63] FFPE samples are usually collected at the initial prostate cancer diagnosis; hence, the time lapse from prostate cancer diagnosis to genetic testing may be more than 5 years.[85,86] A potential hurdle could be laboratory accreditation policies for sample storage. The storage period for tissues is usually 8–10 years in several legislations;[87-90] thus, patients with late disease progression may need to undergo rebiopsy, with challenges already addressed in this article. These challenges can be resolved with minimally invasive ctDNA-based "liquid biopsy". The collected plasma should be stored in Streck tubes for further processing within 1 week of collection.

Post-analytical phase

The post-analytical phase includes all the processes after the completion of laboratory analysis until the receipt of results by the treating physician. The steps involved examination and validation of results, and reporting. Commonly reported errors in this phase include erroneous data validation, delayed reporting or misreporting, and manual errors, and account for 12.5–20% of total testing errors.[91]

The interpretation of test results in accordance with the geneticist's professional judgement should also be encouraged, enabling oncologists to make an informed decision.[41] Also, the variants should be classified as

"pathogenic", "likely pathogenic", "VUS", "likely benign" and "benign", with VUS preferably reported separately, to direct disease management.[92-94] Since the reports of genetic tests are integrated into patient medical records, they should be concise and easy to interpret.[92] Other recommendations for decreasing manual errors during the post-analytical phase include effective quality control processes and training of laboratory staff personnel to mitigate manual errors. The recommendations for the sample journey are mentioned in Fig. 2.

Recommended genetic testing clinical model for mCRPC in Singapore

In clinical practice, the treating physician is often challenged with coming up with a suitable action plan regarding testing for genetic mutations. This plan includes the choice of an appropriate sample, a suitable time for testing, genetic counselling and commencement of the appropriate therapy. A model (Fig. 1) was generated by the specialists to overcome these challenges and provide real-time guidance to the multidisciplinary teams (MDTs) and, in particular, the treating oncologists and urologists in Singapore.

Tumour testing is preferred, considering the prognostic and predictive value of identifying mutations in patients with mCRPC. Somatic testing is advocated to be performed at disease progression owing to the limitation of resources and time lag between the development of mCRPC from the castration-sensitive prostate cancer stage. However, in high-risk patients (according to the criteria defined in Table 2), germline testing may be considered before somatic testing. For somatic testing, primary biopsy material or rebiopsy of metastatic tissue is preferred. However, if the rebiopsy sample is not available, testing of archived tissue followed by a plasma sample for ctDNA testing is favoured. For archived samples, FFPE samples are used, while for rebiopsy samples, freshly paraffinised tissue samples are also suitable in Singapore.

The mainstreaming approach for genetic counselling can be adopted in Singapore to reduce the bottlenecks often observed at cancer genetics services. Although not mandated by local regulations, informed consent and pre-test counselling should be conducted at the time of somatic testing. Pre-test counselling includes providing information about the genetic tests, the type of testing and significance of genetic testing on disease management, and will enable urologists or medical oncologists to obtain the necessary family history and informed consent for somatic testing. From a diagnostic perspective, somatic molecular testing does not require extensive genetic counselling; hence, a brief pre-test counselling can suffice. In the event that the somatic testing result is positive, it is important to evaluate the hereditary nature of the disease for which germline testing is recommended. Post-somatic and pre-germline test counselling can then be conducted by genetic counsellors

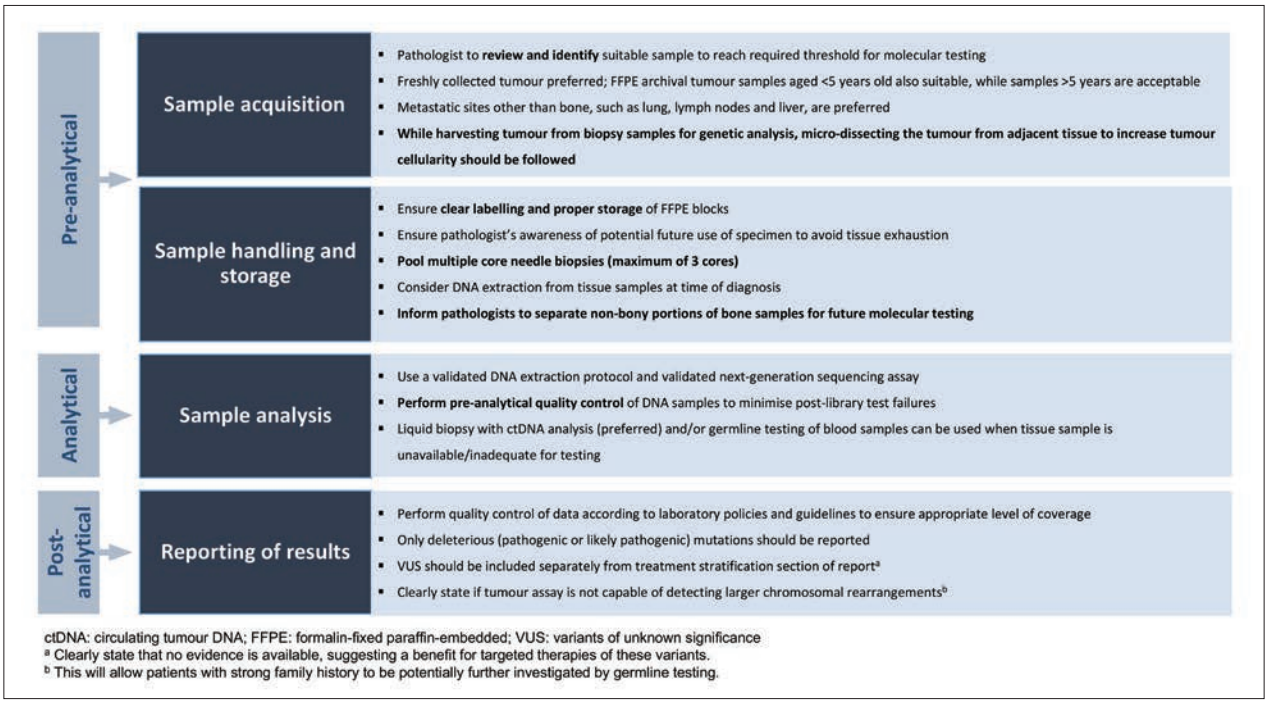

Fig. 2. Key challenges and recommendations for sample journey in patients with metastatic castration-resistant prostate cancer in Singapore.

who may also discuss the implications for cascade testing. This mainstreaming of genetic testing will lead to a decrease in the time lag between disease progression and somatic testing for patients with mCRPC and relieve overall congestion of the cancer genetics service.

Nevertheless, increased consultation time for clinicians and the lack of funds and resources should be considered prior to implementation of the mainstreaming model in clinical practice. In addition, strategies for increasing cascade testing should be implemented to increase screening and detection, and provide risk-reduction strategies for at-risk individuals.

Role of MDT and molecular tumour boards in mCRPC

With the arrival of precision medicine, MDT meetings have become crucial in managing patients with advanced prostate cancer. In the Asia-Pacific region, there has been a rise in molecular tumour boards (MTBs) that are specifically designed to assist clinicians in understanding the molecular biology of tumours and direct patients with these tumours to the appropriate targeted treatment where possible.[95,96] Typically, MDTs and MTBs for prostate cancer include medical oncologists, radiation oncologists, surgical oncologists, urologists, pathologists, genetic counsellors, nurses and other related specialists for a discussion on the treatment course. Given that patients with mCRPC are likely to harbour genetic mutations, molecular pathologists play a significant role in MDT discussions. Molecular pathologists can provide expertise in assessing the tissue sample, the need for rebiopsy in case of sample failure, and deciphering the results, especially in the case of VUS identification. These meetings aim to have a holistic discussion after taking into account the patient's overall status, disease characteristics and treatment history before formulating an action plan.[96]

In a prospective analysis, significant management decision changes were made for more than 40% of patients with prostate cancer, with most patients having a Gleason score of 7.[97] mCRPC cases managed by the MDT had a longer survival than those not managed by the team (39.7 vs 27.0 months, hazard ratio 0.549, P=0.001).[98] MDT meetings were also associated with increased patient satisfaction and adherence to treatment guidelines.[99-101] Although international guidelines recommend MDT meetings for shared decision-making,[26,102] a limited number of cases with prostate cancer are discussed in MDT meetings. In a retrospective review of 7,500 patients from a single tertiary care centre in Australia, 100% of cases with lung cancer and upper gastrointestinal cancer were discussed at MDT meetings, while almost 28% of cases with prostate cancer were discussed.[103]

Despite the increased awareness and occurrence of regular MDT meetings, adherence to the MDT recommendations has not been uniformly recorded or followed.[104] Irregularities in MDT record keeping or lack of follow-up may be some reasons for the low adherence. Introducing standardised recording of the MDT recommendations in the patients' medical records might increase adherence to the treatment plan.[104] However, the time lag between case presentation to the specialists and its discussion in MDT meetings can delay treatment initiation. Logistic challenges and costs may further exacerbate this delay. This issue may be resolved to some extent by the provision of virtual meetings to increase the frequency of MDT meetings.[105] For countries planning to implement such meetings, recommendations include emphasising the value of partnerships and interventions to reduce infrastructure costs while accelerating genetic-guided treatment.[96,104]

CONCLUSION

The arena of genetic testing for patients with mCRPC has undergone a radical change in the last 5 years. With the approval of PARP inhibitors, somatic testing in patients for identifying actionable HRR mutations is of prime importance. The incorporation of somatic testing in routine clinical practice will ensure that most patients with mCRPC are tested and, when appropriate, prescribed PARP inhibitors, which have shown improved survival outcomes. Along with the challenges discussed above, another hindrance to incorporating genetic testing in clinical practice is the associated costs. In Singapore, genetic testing and counselling costs have to be borne by the patients as they are currently not reimbursed or subsidised by the government. The reimbursement of testing, treatment and out-of-pocket costs as well as subsidies for patients may increase the reach of genetic testing to a larger population. The formation of a registry for patients with prostate cancer and the generation of real-world data on genetic testing and related treatment options such as PARP inhibitors in Singapore may help provide the impetus to convince the government to extend more financial assistance for this purpose.

This article discusses an approach for incorporating genetic testing in routine clinical practice in Singapore. We have proposed a hybrid model for genetic counselling in which pre-test counselling prior to somatic testing can be conducted by managing clinicians, while patients with HRR mutations can then be referred to genetic

counsellors for post-test counselling prior to germline testing to reduce the burden at the counselling stage. However, it is important to train managing clinicians about the fundamentals of genetic counselling. Challenges in the sample journey can be overcome with the recommended steps for sample processing and storage. Laboratory personnel engagement for appropriate handling and processing of samples is imperative for the success of genetic tests. Finally, an MDT approach with the involvement of the MTB is recommended for the effective and optimal management of patients with mCRPC in Singapore.

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COMMENTARY

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Re-examining the roles of generalists and specialists in healthcare

Priyanka Khatri [1,2]*MRCP*, Ashna Nastar [3]*MRCP*, Gim Gee Teng [4]*MD*, Jason Phua [5]*FRCP (Edin)*

ABSTRACT

Increasing workload and case complexity of a multimorbid ageing population have catalysed primary care transformation for general practitioners to meet these challenges. There is also a need to re-examine the role of hospital specialists as overly disease-centric, hospital-based specialist care is no longer sustainable. A new specialist-generalist model can maximise the potential of generalists and specialists to provide person-centred care, increase cost-effectiveness, improve appropriateness of referrals, decrease length of hospital stay and lower mortality.

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Keywords: Generalist, healthcare models, healthcare costs, integrated care, specialists

Singapore is one of many Asian countries facing the challenge of an ageing population. Its population grew from 1.65 million to 5.45 million from 1960 to 2021. By 2030, 25% will be aged 65 or older.[1] Meanwhile, the proportion of older adults with three or more chronic diseases nearly doubled from 2009 to 2017.[2] While increasing workload and case complexity have challenged general practitioners (GPs) and catalysed primary care transformation, there is also a need to re-examine the role of hospital specialists.

Specialisation has advanced medical science since the 19th century.[3] Grouping populations with similar diseases and organ involvement has allowed doctors to promote research and efficiently master domains. In its first 3 decades post-independence, Singapore's health policy and funding catered to the growth of specialist-led hospitals and national centres.[4] Correspondingly, public attitudes increasingly swung towards specialist as opposed to generalist care.

However, overly disease-centric, hospital-based specialist care is no longer sufficient or sustainable.[5] Patients with more than 1 comorbidity, who are increasingly the norm, are now referred from one specialist to another specialist, with several consequences including lack of clear clinical accountability, long referral wait time, care fragmentation and polypharmacy. Greater inconvenience and higher bills are incurred by patients from more visits to specialist outpatient clinics. For the healthcare system, manpower and financial sustainability is challenged by the need for more specialists, and the associated supporting staff and clinical spaces.

Will generalists be able to fill the gap? Generalists are typically defined as physicians who provide care to patients as a whole unit irrespective of age, sex and illness; they include GPs, paediatricians and internists who largely practise in the community.[6] This article describes hospital-based specialist-generalists who are arbitrarily divided into 2 broad groups: (1) advanced internal medicine (AIM) physicians, geriatricians and family medicine physicians, who receive broad-based training; and (2) all other specialists with an internal medicine (IM) background, e.g. nephrologists, endocrinologists, etc. (Fig. 1). Both groups are better able than other non-IM physicians to handle medical conditions beyond their own specialties because of their background training. All IM specialists in Singapore today are required to complete 3 years of IM junior residency before entering 2–3.5-year senior residency programmes. These senior residency programmes then mandate an additional 6 months of general medicine

[1] Division of Nephrology, Chronic and Fast Programmes, Alexandra Hospital, Singapore
[2] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] Division of Endocrinology, Chronic and Fast Programmes, Alexandra Hospital, Singapore
[4] Division of Rheumatology, Chronic and Fast Programmes, Alexandra Hospital, Singapore
[5] Division of Respiratory and Critical Care Medicine, Chronic and Fast Programmes, Alexandra Hospital, Singapore
Correspondence: Dr Gim Gee Teng, Division of Rheumatology, Alexandra Hospital, 378 Alexandra Road, Singapore 159964.
Email: gim_gee_teng@nuhs.edu.sg

(GM) and geriatrics rotations. Meanwhile, the 2-year AIM senior residency programme specifically provides further honing of IM competencies. While the specialist-generalist care concept may in the future apply to non-IM disciplines like surgery, this commentary is limited to IM and family medicine physicians in hospitals, for whom such a concept is more readily achievable.

At present, various care models exist in Singapore. Tertiary hospitals' inpatient and outpatient activities are primarily specialist rather than generalist-driven. Non-tertiary regional hospitals tend to admit more patients under GM, an umbrella term used for the care of patients not assigned to specific specialties. While GM is ideally covered by AIM, only 138 of Singapore's 15,430 medical practitioners were IM-accredited in 2020.[7] Thus, non-AIM medicine specialists also provide care in GM. Separately, outpatient care in most hospitals remains largely helmed by specialists who narrowly focus on their own expertise.

Is generalist or specialist care better? While comparison between generalists and specialists has been a subject of interest, there is a scarcity of literature on specialist-generalists, with most studies having evaluated primary care physicians as generalists. The validity of these studies is often questionable due to selection and publication biases. In a systematic review, 24 of 49 studies suggested better outcomes with specialists and only 4 studies suggested that generalist care was superior.[8] The studies were mostly observational and involved discrete diseases. It is unsurprising that specialists fare better in their domain expertise, just as they may better master procedural skills and adhere to disease-specific guidelines.

In contrast, some studies have reported generalists outperforming specialists in managing certain conditions. One demonstrated lower resource use by older adults with diabetes who were managed by a primary care physician instead of a medical specialist.[9] In a Singapore retrospective study, inpatients cared for by family physicians as generalists had shorter lengths of stay and lower costs than those cared for by specialists managing general medicine inpatients, with equivalent outcomes in hospital mortality and 30-day all-cause unscheduled readmissions.[10]

Existing research has generally failed to evaluate indicators of quality of care for the patient's whole journey, across conditions and settings. While specialists tackle fewer new complaints and focus less on

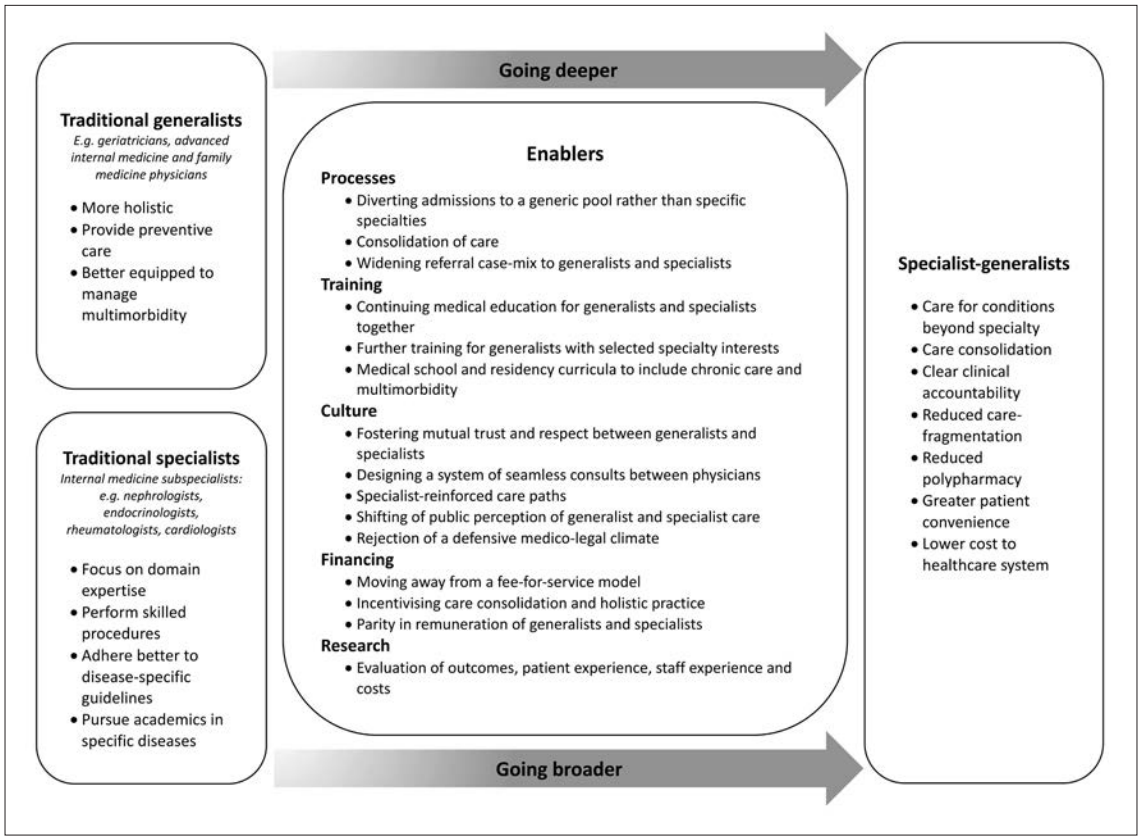

Fig. 1. Overview of traditional and generalist and specialist models.

preventive care,[11] generalists often see patients with undifferentiated problems on top of their existing conditions. Generalist physicians are trained to provide comprehensive care within the context of a patient's multimorbidity and psychosocial circumstances. Indeed, it is not always appropriate to follow guidelines upon which disease-specific quality indicators are based.

Can generalists go deeper? Generalists may take a holistic, whole-person approach, but strengthening their ability to deal with specific diseases, systems and organs may lead to multiple benefits including increased cost-effectiveness, improved appropriateness of referrals to specialists, reduced reliance on tertiary care centres,[12] and enhanced job satisfaction. Examples of interventions to strengthen generalist care include greater adoption of guidelines that address multimorbidity as identified by symptom complexes and burdens,[13] development of question lists to better manage clinical scenarios, and additional training in specific specialty areas.[14-15] In the UK, GPs with special interests lead strategic planning through the primary care lens, for areas traditionally helmed by specialties.[16] In the US, inpatient hospitalist care has become the norm. In Singapore, success in involving family medicine doctors in inpatient GM care has been achieved.[10]

Can specialists go broader? Specialists may focus on their respective domain expertise, but greater ability to deal with their patients' other comorbidities will make care substantially more holistic. A Singapore study described a model of inpatient care where physicians including those from family medicine performed generalist duties.[17] This model was associated with similar healthcare costs, shorter length of stay and lower mortality vis-à-vis a model in which specialists predominantly looked after their own specialties. However, chronic care, which involves longer-term follow-up, may be more challenging. Specialists who manage most or all their patients' health concerns as principal physicians exist but are often confined to specific populations. For example, in a survey of nephrologists, 75% led care beyond nephrology for their dialysis patients, including cancer screening, immunisation and comorbidity management.[18] Practice guidelines for chronic kidney disease encourage managing physicians to provide holistic care in the form of glycaemic control, cardiovascular risk reduction, hyperuricaemia management and lifestyle modification.[19] While specialists may provide holistic care of common chronic conditions if empowered and incentivised,[20] the tussle with diminished time left for specialty work as well as a lack of familiarity with the management of other comorbidities precludes this.

Are there systemic solutions? To maximise the potential of generalists and specialists to provide person-centred care, a specialist-generalist model facilitated by several elements is required, both in Singapore and beyond (Fig. 1).

First, hospitals should create processes that enhance such a model. In inpatient care, more systematic diversion of IM-related admissions to generic GM areas is needed. Such areas may be led not only by AIM, geriatrics and family medicine physicians, but also other committed IM specialist-generalists. In hospitals where admissions are directed to specific specialties, physicians should likewise be encouraged and empowered to practise as specialist-generalists. In outpatient care, Singapore's Alexandra Hospital's integrated general hospital model provides an example of care integration. Defragmented care by multiple specialists is consolidated to a single specialist who also manages conditions besides his/her expertise,[20] coordinates care and only refers to other specialists when necessary. To improve accessibility, referrals from primary care that are usually directed to certain specialties (especially those with long wait times), are instead channelled to generalists by condition-based triaging. Patients whose integrative care plans have been determined and who are deemed fit for discharge are appropriately right-sited to primary care.

Second, training for specialist-generalist care is required. In the hospital, regular continuing medical education sessions can be conducted, where generalists and specialists upskill each other by sharing about management of common conditions. These sessions should be bite-sized and targeted for busy physicians. Further formal training for generalists with selected interests in specialist fields should be encouraged. For IM residency and undergraduate trainees, curricula must emphasise holistic management of multimorbidity and include exposure to outpatient continuity clinics.[21]

Third, a culture that supports specialist-generalists should be built. Frequent communication and role negotiation between generalists and specialists, conducted with trust and respect and facilitated by hospital leadership are essential. A system of seamless consults between physicians should be designed, as should rapid advice provided via video, phone and text messaging when appropriate. Specialist-reinforced care paths for prevalent chronic diseases should be developed for use by specialist-generalists. Notably, patients often want access to clinicians with a deep expertise in their

illness, but simultaneously like the benefits of seeing a generalist.[22] While specialist-generalists may provide the best of both worlds, this is dependent on greater acceptance by the public. Therefore, deeper engagement with the community by political office holders, policymakers and physician leaders, particularly through traditional and social media, is necessary. Concurrently, the courts and health ministries must reject a medico-legal climate that promotes defensive medicine by censuring physicians solely because they have not referred patients to another specialist, if the clinical decision is justifiable and the generalist has provided an appropriate level of care.

Fourth, healthcare financing should move away from a fee-for-service model that incentivises hospitals and physicians to quickly see as many patients as possible. This would align with value-based healthcare initiatives—of which holistic person-centred care is an important component—that the regional healthcare systems in Singapore are embarking on.[23] Potential initiatives include reorganisation of financing models towards raising public awareness on the role of specialist-generalists and developing digital solutions for more seamless communication between specialists and community-based family medicine physicians. This will encourage a practice change among physicians practising as generalist-specialists.

Furthermore, clinics must be restructured to allow more time for each holistic patient review. Instead of reimbursing by volume, incentives should be provided for care consolidation—a practice that saves costs for the healthcare system, given the resultant reduction in care episodes. Opportunities to make this a reality is abundant in Singapore, where capitation for public healthcare will soon be implemented.[24] In tandem, gaps in remuneration due to legacy reasons which benefit procedural specialists and disadvantage non-procedural generalists should be closed.

Fifth, governments, grant agencies and academic health systems should promote more health service research on the specialist-generalist approach, with emphasis on the quadruple aim of improved outcomes, better patient experience, better staff experience and reduced costs.

Moving forward, the focus should no longer be on a generalists and specialists divide. It should instead be on creating an environment that nurtures the right skillset and mindset for all physicians to practise holistically—where with adequate support, generalists can be specialists and vice versa. William Osler once said, “The good physician treats the disease; the great physician treats the patient who has the disease”. It is time to re-imagine the roles of generalists and specialists, and elevate them from good to great.

Disclosure

There was no affiliation or financial involvement with any commercial organisation with direct financial interest in the subject or materials discussed.

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LETTER TO THE EDITOR

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Rash characteristics of paediatric patients with COVID-19 in Singapore

Dear Editor,

Children with COVID-19 infection can present with a variable spectrum of clinical manifestations, and sometimes mucocutaneous manifestations can be the only manifestation of COVID-19 infection in children.[1,2,3] We report 4 cases of paediatric patients who had COVID-19 with mucocutaneous involvement, admitted to a tertiary children's hospital in Singapore. The main objective is to describe the clinical characteristics of these patients, focusing on chilblains-like acute acral eruptions (AAE), and reactive infectious mucocutaneous eruption (RIME), with relevance to COVID-19 infection.

Case 1 was a 6-year-old Malay boy who presented acutely with painful skin lesions on his fingers with respiratory symptoms and fever. There were multiple shallow ulcers and erosions with violaceous plaques on his finger pulps (Fig. 1A). He was reviewed by the orthopaedic surgeon for initial concerns of felon progressing to septic arthritis or osteomyelitis. He was commenced on intravenous cefazolin. However, there was no clinical improvement so referral to the dermatology team was made. Blisters on his digital lesions were treated and topical cream (fusidic acid and betamethasone) was applied. Inflammatory markers were not raised. He was diagnosed to have COVID-19-related chilblains, and discharged after 4 days. There was almost full recovery of his digital lesions after another 2 weeks.

Case 2 was a previously well 10-year-old Indian boy who presented with 3 days of lower lip swelling and lip ulcers associated with mild cough and sore throat, which were complicated by poor feeding. Clinically, there were extensive erosions with crusting over the upper and lower lips, with blister formation (Fig. 1B). Coalescing ulcers were noted over the buccal mucosa, posterior pharynx and tongue. Examination by the ophthalmologist showed no keratoconjunctivitis. Results of SARS-CoV-2 polymerase chain reaction (PCR) and SARS-CoV-2 serology tests were positive. Inflammatory markers were mildly elevated (C-reactive protein 65.6mg/L, lactate dehydrogenase 326 U/L, ferritin 89.8µg/L and D-dimer 0.67mg/L). Microbiology investigations were negative for herpes simplex virus, mycoplasma and human herpesvirus 6. Antinuclear antibody was negative. He was diagnosed with RIME associated with COVID-19. He was started on intravenous fluid and analgaesia, lip treatment with mometasone cream and paraffin ointment, normal saline soaks and chlorhexidine mouthwash. He completed an empirical 5-day course of oral acyclovir, and a course of oral prednisolone (initial dose 1mg/kg/day) tapered over 12 days. He was discharged well after 1 week of inpatient hospital stay.

Case 3 was a previously well 3-year-old Chinese boy who presented acutely with fever, sore throat, hives and swelling of hands and feet. On examination, there were generalised scattered urticated papules and wheals. Both hands and feet were also slightly swollen (Fig. 1C). No other clinical features of Kawasaki disease were seen. He was diagnosed with acute urticaria related to COVID-19 infection. His symptoms improved on regular fexofenadine and he was discharged well on the second day of admission.

Case 4 was a 9-year-old Korean boy who presented with 3 days of sore throat and 5 days of itchy rash over the limbs and extremities. On examination, there were multiple urticated plaques, some with targetoid appearance, over the limbs and extremities (Fig. 1D). He was diagnosed with urticaria multiforme secondary to COVID-19 infection. He was given regular antihistamines, and topical corticosteroid twice a day with improvement.

The diagnosis of COVID-19-associated mucocutaneous manifestation in all above cases was based on morphology and distribution of the mucocutaneous lesions, temporal relationship with COVID-19 infection, clinical status of the child and laboratory confirmation by the SARS-CoV-2 PCR test. None of them had any predisposing autoimmune or vascular risk factors, drug exposure or systemic symptoms.

Compared with adults, young people demonstrate different antibody responses to SARS-CoV-2 infection and possess stronger antiviral innate and adaptive immunity (increased cytokines, interferons and T-cell response to new antigens), which likely aid in preventing serious respiratory sequelae. However, robust immune mechanisms might also contribute to alternate manifestations, including mucocutaneous eruptions.[4] Marzano et al. described 6 main clinical patterns: (1) confluent erythematous maculopapular or morbilliform rash, (2) urticarial rash, (3) papulovesicular exanthem, (4) chilblains-like acral pattern, (5) livedo reticularis and/or livedo racemosa-like pattern and (6) purpuric "vasculitic" pattern.[5] However, none of these are specific or diagnostic for the COVID-19 infection.

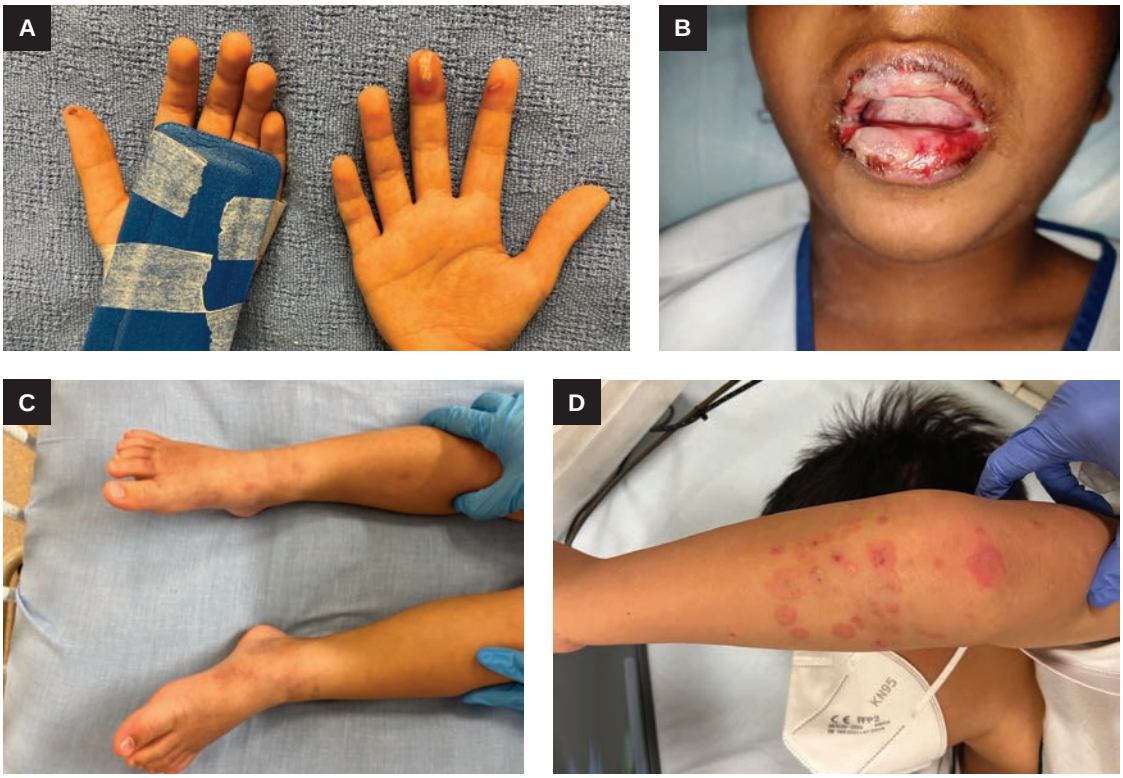

Fig. 1. (A) COVID-19-related chilblains. Multiple shallow ulcers and erosions with erythematous base and violaceous plaques were noted on finger pulps of the right second, third, fourth fingers; and left thumb. There was no lesion on his mucosal surfaces, toes or other parts of the body. (B) Reactive infectious mucocutaneous eruption in children diagnosed with COVID-19. Erosions and crusting were noted over upper and lower lips, with 1 blister over the right lower lip. There were no other rashes or eye and genital involvement. (C) Acute urticaria of hands and feet related to COVID-19 infection. He had scattered papules urticarial rashes over the extremities, thighs, trunk and back, with slightly swollen hands and feet. (D) Urticaria multiforme secondary to COVID-19 infection. He had urticated plaques, some with targetoid appearance over the elbows, hands, wrists, ankles and feet.

Traditional chilblains, also called pernio, is an inflammatory reaction of the superficial vasculature on acral surfaces (fingers, toes, nose, ears) characterised by erythrocyanotic skin lesions induced by non-freezing cold exposure. It is classified into 2 groups: idiopathic, often triggered by cool and/or damp temperatures (primary pernio); or less commonly, due to an underlying autoimmune or systemic inflammatory disease (secondary pernio).[4,7,12]

Chilblains-like AAE had gained attention during the COVID-19 pandemic. Based on observational studies across many countries,[2,3,7,12] COVID-19 chilblains (in contrast to traditional chilblains) was noted in the later course of the disease, often associated with less severe illness[1,8] in young patients having no cold exposure, pre-existing peripheral vascular disease or systemic inflammation, as observed in case 1 that occurred amid the warm and humid climate of Singapore.[2] This appearance is thought to be suggestive of acral ischaemia secondary to thrombosis in patients with severe COVID-19, which may be complicated by hypercoagulable state and often requires intensive care.[7] However, COVID-19 chilblains appear to be distinct from the ischaemic cutaneous presentations associated with severe COVID-19. It is thought that ischaemic lesions associated with severe COVID-19 may be caused by thrombotic microvascular insults induced by complement activation and a procoagulant state.[7] On the other hand, cases of multisystem inflammatory syndrome in children (MIS-C) showed greater laboratory inflammation and complications were more likely to involve the cardiac system.[4]

In COVID-19 chilblains, however, coagulation, haematological and biochemical studies; D-dimer; and autoantibodies were reportedly normal for most patients.[2,4] This is supported by findings from skin biopsies performed in a small percentage of patients with initial diagnostic dilemma involving superficial and deep lymphocytic perivascular dermal infiltration consistent with chilblains, though neither thrombosis

nor vasculitis were identified.[2,7] Thus, in the absence of symptoms and signs of secondary causes in an otherwise well child, the complete work-up of chilblains is not routinely required in suspected COVID-19 patients.[7]

Avoidance of cold, damp conditions is the cornerstone of chilblains management. Ladha et al. proposed a systematic and practical approach to COVID-19 chilblains.[7] Potent topical corticosteroids (e.g. clobetasol propionate 0.05% ointment) are often recommended, as the anti-inflammatory effect via inhibition of interferon production provides relief of the inflammatory lesions. Oral analgaesia and antihistamines also provide symptomatic relief. Gentle debridement or normal saline soaks to remove crusts can also be instituted. The second-line therapy for chilblains includes a calcium channel blocker such as oral nifedipine (0.25–0.5mg/kg/day thrice a day).[7] Additional reported treatments for chilblains include topical nitroglycerin, topical tacrolimus, oral prednisone (0.5 mg/kg once daily).[7] Our patient with chilblains-like AAE (case 1) achieved almost complete remission of his wounds within two weeks of illness. COVID-19 chilblains is mildly symptomatic, usually requiring no therapy, with excellent prognosis and full recovery.[6]

Case 2 presented with only mucosal involvement without significant cutaneous manifestation. RIME was recently proposed to replace the term, "*Mycoplasma pneumoniae* (MP)-induced rash and mucositis" to account for the fact that non-MP pathogens may also cause rash and mucositis.[9] Proposed mechanisms of pathogenesis include immune complex deposition, complement activation and molecular mimicry.[9]

To make the diagnosis of RIME, evidence of an infectious trigger is required: (1) history, clinical examination or investigations supporting a respiratory infection; (2) confirmation by ≥2 of the following criteria: non-contributory medication history, erosive mucositis affecting ≥2 sites, or vesiculobullous lesions/atypical targets affecting <10% BSA; and (3) support by prodromal symptoms and histology excluding other diagnoses.[10] Erythema multiforme has been reported in children with COVID-19, but most cases described targetoid cutaneous lesions without mucositis, similar to case 4.

Case 3 presented with acute urticaria and case 4 with urticaria multiforme, both related to COVID-19 infection. They appear morphologically different but represent the same disease spectrum, which can be caused by many other viral infections. Urticaria is commonly seen in COVID-19 infections, accounting for 10–20% of all COVID-19-related rashes. Based on previous international registry for COVID-19 dermatological manifestations, urticarial reactions typically last 4 days (interquartile range 2–10), and for a maximum of 28 days.[12] Urticarial multiforme presents with targetoid lesions, usually distributed over the thighs, knees, arms (especially around the elbows), and dorsal aspects of hands and feet. These lesions improve within 1–3 weeks with topical or oral corticosteroids, or without treatment in some cases.

In the context of COVID-19 infection with mucocutaneous involvement in children, MIS-C is a consideration and must be ruled out for the diagnosis of RIME. Screening for MIS-C based on previous case reports were unremarkable except for elevated C-reactive protein levels in some RIME cases.[11] The management of RIME is largely supportive (analgaesia, eye drops, hydration and parenteral nutrition). The role of antimicrobial agents and immunomodulatory agents including corticosteroid is unclear. In terms of prognosis, RIME is considered self-limiting with excellent prognosis.

Outcome was favorable in all our patients. No specific treatment was indicated apart from symptomatic management except for our patient with RIME (case 2) who was started on a course of oral corticosteroid in view of significant symptoms.

In conclusion, it is important for physicians to recognise self-limiting mucocutaneous involvement in children with COVID-19, and differentiate it from similar-looking severe diseases such as a thrombotic phenomenon, vasculitis or MIS-C. These lesions may become more common as the prevalence of mild infection increases with easing of safety measures and reopening of borders. Having this knowledge can prevent unnecessary investigations in otherwise well patients, and aid physicians in rendering appropriate treatment plans and counselling.

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Syen Yee Leow [1,2]*MRCPCH*, Shi Yun Chia [1,2]*MRCPCH*, Valerie Pui Yoong Ho [1,2]*MRCPCH*

[1] Department of Dermatology, KK Women's and Children's Hospital, Singapore
[2] General Paediatrics Service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore

Correspondence: Dr Syen Yee Leow, KK Women's & Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: leow.syen.yee@singhealth.com.sg

LETTER TO THE EDITOR

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Delayed treatment with nirmatrelvir/ritonavir could remain effective in patients with Omicron BA2.2 variant of COVID-19

Dear Editor,

In late February 2022, the Omicron BA.2.2 subvariant drove the outbreak of COVID-19 and rapidly spread through many parts of the world. Omicron-infected individuals aged ≥80 years who are unvaccinated are particularly at high risk of poor outcomes.

COVID-19 vaccines and antiviral therapeutics have protected individuals most at risk from the disease.[1] Paxlovid (Pfizer, New York, NY, US), composed of nirmatrelvir and ritonavir, is an orally bioavailable SARS-CoV-2 protease inhibitor.[2] Nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}) inhibitor (i.e. 3CL protease inhibitor), decreases viral replication in the early stages of the disease to prevent progression to severe COVID-19. Ritonavir is co-administered with nirmatrelvir to slow its metabolism, so that nirmatrelvir can remain active in the body at higher concentrations for a longer time, to combat the virus.

The EPIC-HR trial and real-world studies have reported that treatment with Paxlovid within the first 5 days of SARS-CoV-2 infection can effectively reduce the mortality or hospitalisation rate of patients.[3-5] This has been observed in various populations, including children aged 6–14 years, adults aged ≥60 years, and patients who are immunocompromised.[6-8] However, evidence for Paxlovid has been based on its effects in patients treated within 5 days after diagnosis. The manufacturer's instructions also recommend the drug administration to be initiated within 5 days of symptom onset.[9] However, the rapid surge of COVID-19 cases during the pandemic resulted in major difficulties for timely therapy. Our study aimed to assess the effectiveness of Paxlovid in patients with disease onset duration of ≤5 days as well as >5 days. We also observed the effectiveness of Paxlovid treatment for oldest-old patients (aged ≥85 years) and patients with malignant solid tumours who were infected with Omicron variant of COVID-19.

This was a retrospective observational study of patients hospitalised. COVID-19 was diagnosed using real-time reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR cycle threshold (Ct) values were used as an indirect method for quantifying viral replication. Viral elimination was defined as negative for both *ORF1ab* and *N* genes (Ct value ≥35) on different days. Time to viral elimination was used as an indicator of Paxlovid effectiveness.

From 10 April to 22 June 2022, 113 patients in our hospital received Paxlovid and were included in the study. Their median time from diagnosis to Paxlovid initiation was 5 days (interquartile range [IQR] 3–8). Additionally, 565 patients matched by age, sex and vaccination rate using propensity score matching (1:5 matching), who did not receive Paxlovid, were included as controls (online Supplementary Table S1). Paxlovid recipients had shorter duration of hospitalisation compared to controls (6 days [IQR 5–8] versus 8 days [IQR 5–12], $P<0.001$) (online Supplementary Table S1). They also had a shorter time from diagnosis to viral elimination (9 days [IQR 7–13] vs 13 days [IQR 10–16], $P<0.001$) (Fig. 1A).

The median times from admission to Paxlovid initiation in the early treatment group (≤5 days after diagnosis) and delayed treatment group (>5 days after diagnosis) were 2 days [IQR 1–2] and 4 days [IQR 2–6], respectively. The median time from treatment to the day of viral elimination was similar in both groups (4 days [IQR 3–6] vs 3 days [IQR 2–5], $P=0.529$) (online Supplementary Table S2). The Kaplan-Meier survival curves of the 2 groups were similar when the difference in the Paxlovid initiation time was removed ($P=0.663$) (Fig. 1B). Likewise, after Paxlovid treatment, clearance of viral load as measured by *ORF1ab* viral gene replication was very similar between the 2 groups (Fig. 1C).

There were 262 oldest-old patients hospitalised with SARS-CoV-2, including 38 (14.5%) who had received a prescription for Paxlovid. The oldest-old Paxlovid recipients had a shorter time from diagnosis to viral elimination than those who did not receive Paxlovid (10 days [IQR 7–14] vs 14 days [IQR 11–18], $P<0.001$) (online Supplementary Table S3). Among these patients, 21 (55.3%) received Paxlovid treatment >5 days after diagnosis. No significant differences were found in the median time from Paxlovid treatment to the day of viral elimination between patients treated within and beyond 5 days after diagnosis (4 days [IQR 3–5] vs 4 days [IQR 3–6], $P=0.964$)

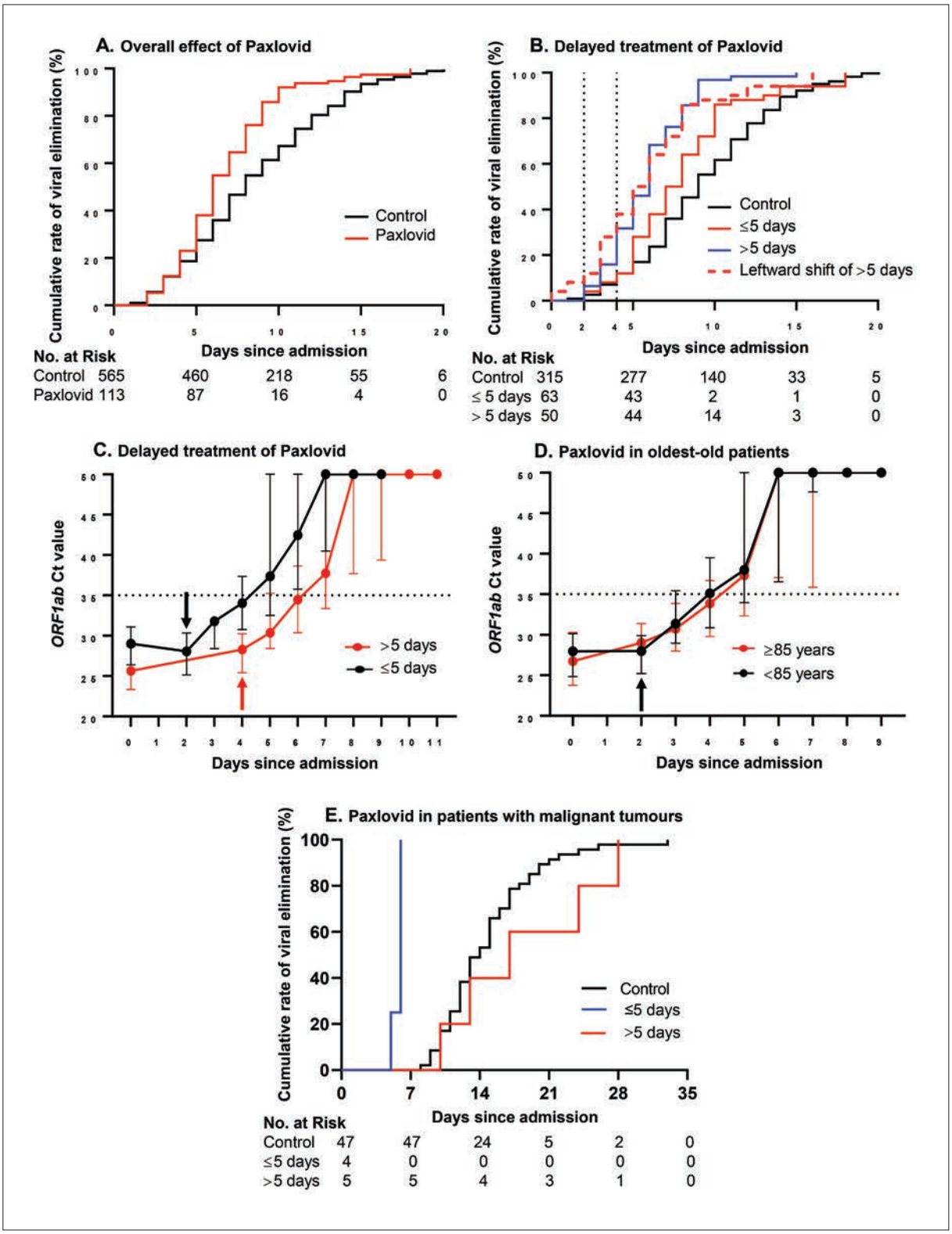

Fig. 1. Clearance of viral load and duration of viral elimination after Paxlovid treatment. (A) The comparison of cumulative rate of viral elimination in Paxlovid-treated patients versus controls who did not receive Paxlovid. (B) The cumulative rate of viral elimination in patients with Paxlovid prescriptions within 5 days vs beyond 5 days since diagnosis. (C) The changes of *ORF1ab* Ct values in patients with Paxlovid prescriptions within or beyond 5 days since diagnosis. Black and red arrows indicate the median time of Paxlovid initiation in 2 groups. (D) The changes of *ORF1ab* Ct values in patients with Paxlovid prescriptions of different age groups. Black arrow indicates the median time of Paxlovid initiation. Data in (C) and (D) are shown as medians and interquartile ranges. (E) The cumulative rate of viral elimination in patients with malignant tumours who received Paxlovid within or beyond 5 days since diagnosis.

(Supplementary Table S4). No difference was observed in the clearance of viral load after Paxlovid treatment between patients aged ≥85 years and <85 years (Fig. 1D).

There were 56 patients with malignant solid tumours in this study, including 9 (16.1%) who had received a prescription for Paxlovid. The viral elimination time of Paxlovid recipients was shorter than the patients who did not receive Paxlovid (10 days [IQR 6–20] vs 14 days [IQR 11–17], $P<0.001$) (online Supplementary Table S5). However, patients who were given Paxlovid prescription after 5 days of diagnosis had a significantly longer time of viral elimination since Paxlovid initiation (4 days [IQR 3–6] vs 2 days [IQR 1–3], $P=0.090$) (Fig. 1E and online Supplementary Table S6).

In summary, this study showed that Paxlovid treatment facilitated the eradication of SARS-CoV-2 Omicron variant, with a significantly shortened hospitalisation time. Paxlovid recipients had 4 days less time to viral elimination from diagnosis than the controls who did not receive Paxlovid. Viral load of SARS-CoV-2 decreased rapidly under Paxlovid treatment and became negative within 3 or 4 days, regardless of age and initiation time. Paxlovid effectiveness was similar in patients treated within and beyond 5 days after diagnosis. The same clinical benefit was also observed in oldest-old patients. However, for patients with malignant tumours, Paxlovid is recommended to be initiated as soon as possible after infection, since its early administration is more effective than delayed treatment.

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Wenjie Wang *[1 MD], Jing Wan *[1 MD], Wei Du [1 MD], Jing Song [1 MD], Ye Lu [1 MD], Shuiming Gu [2 MD], Yunhai Feng [3 MD], Gang Wang [4 PhD], Minfang Tao [5,6 MD], Jun Yin [1,7 MD]

[1] Department of Endocrinology and Metabolism, Shanghai Eighth People's Hospital, Shanghai, China
[2] Department of Cardiology, Shanghai Eighth People's Hospital, Shanghai, China
[3] Department of Otolaryngology, Shanghai Eighth People's Hospital, Shanghai, China
[4] Department of Pharmacy, Shanghai Eighth People's Hospital, Shanghai, China
[5] Department of Gynaecology and Obstetrics, Shanghai Eighth People's Hospital, Shanghai, China
[6] Department of Gynaecology and Obstetrics, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, Shanghai, China
[7] Department of Endocrinology and Metabolism, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, Shanghai, China

Correspondence: Dr Jun Yin, Department of Endocrinology and Metabolism, Shanghai Eighth People's Hospital, 8 Caobao Road, Shanghai 200235, China.
Email: yinjun@sjtu.edu.cn
Dr Minfang Tao, Department of Obstetrics and Gynecology, Shanghai Eighth People's Hospital, 8 Caobao Road, Shanghai 200235, China.
Email: taomf@126.com
* Joint first authors

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Robotic surgery in morbidly obese women with endometrial cancer in Singapore

Dear Editor,

The standard of care for endometrial cancer is a total hysterectomy with bilateral salpingo-oophorectomy, and pelvic lymph node dissection (THBSO-PLND). Obesity is a known risk factor for endometrial cancer, and obese patients are challenging to operate on due to their anatomy and comorbidities. A recent database search showed a limited number of studies on robotic surgeries performed in obese women for endometrial cancer, with the highest body mass index (BMI) reported in Asia as: 31.8kg/m^2 in Taiwan,[1] 30.3kg/m^2 in South Korea,[2] 35.6kg/m^2 in Thailand[3] and 33.2kg/m^2 in Singapore.[4] There is a dearth of published discussion on robotic surgery in morbidly obese women, in hand with concern about its safety and efficacy as a surgical modality. We describe our unique experience and outcomes of robotic surgery in morbidly obese women with endometrial cancer at the Obstetrics and Gynaecology Department at Singapore General Hospital, Singapore. We posit that robotic surgery technology could allow for the standard of care for endometrial cancer (i.e. THBSO-PLND) to be offered to all patients regardless of BMI.

We performed a retrospective analysis of 25 female patients with BMI >40kg/m^2, who underwent robotic THBSO-PLND surgery from January 2016 to December 2021. The average age was 53 (range 30–78) years and average BMI was 45.86kg/m^2 (range 40.0–63.0kg/m^2). There were 17 (68%) patients who were nulliparous. Twenty-two (88%) patients were assessed with the snoring history, tired during the day, observed stop of breathing while sleeping, high blood pressure, BMI >35kg/m^2, age >50 years, neck circumference >40cm and male gender (STOP-BANG) score, with an average score of 3.48 (a score of 3–4 was considered intermediate risk for sleep apnoea). The remaining 3 patients were assessed with the apnoea-hypopnoea index score, where a score of >30 was considered severe. Their scores were 33, 53 and 66. Seven (46%) patients also had ischaemic heart disease, 5 (22%) had pre-existing diabetes mellitus, 4 (18%) had sleep apnoea and 4 had chronic kidney disease. Six patients had previous abdominal or pelvic surgery.

We analysed our operative outcomes and compared our data with other studies with similar demographics. Twenty of our patients underwent THBSO-PLND while only 3 underwent THBSO without PLND. Two patients had total hysterectomy with bilateral salpingectomy (THBS)-PLND, with ovaries conserved. Eleven patients also required adhesiolysis and 2 patients had omentectomy. Only 3 patients required a mini-laparotomy for the retrieval of uterus (uterus weight of 346g, 439g and 525g). The average uterus weight across all patients was 219g. The average operative time was 240min (range 155–365min) and estimated average blood loss was 149mL. Our study was comparable to the findings of 5 other studies[5-9] that were selected after conducting a thorough literature search on PubMed and Cochrane databases, and fulfilling exclusion criteria (Table 1).

Firstly, we analysed the successful completion of intended surgery. Laparotomy has increased risks of wound infection and venous thromboembolism, in addition to greater analgaesia requirements. Laparoscopic approach circumvents these issues, but intra-abdominal insufflation of carbon dioxide and Trendelenburg positioning for visualisation of organs both contribute to inadequate ventilation in obesity. The rate of conversion has been demonstrated to positively correlate with BMI. Robotic surgery circumvents these issues by providing better visualisation of minute structures.[10] In our study, none required conversion to laparotomy.

We also analysed the postoperative recovery and complications in our patients. All patients were routinely transferred to high dependency unit (HDU) per requirements for anaesthesia and routinely stepped down to the general ward the next morning. Only 1 patient was kept in the HDU for 1 additional day for closer monitoring, but she also had an unremarkable postoperative recovery. No patient required intensive care unit admission postoperatively. There were 80% of patients ambulated on postoperative day (POD) 1, 72% opened bowels on POD 1, and the average POD 1 pain score was 2. One patient was readmitted on POD 6 for postoperative ileus and another patient was readmitted for post-site haematoma, both of whom were managed conservatively.

Three patients who were initially radiologically classified as stage 1 were revised to stage 3 postoperatively. The first patient was reported to have a 2cm tumour on the magnetic resonance imaging (MRI) scan; however, intraoperative findings and final histology showed ovarian metastasis. She subsequently received

Table 1. Summary of patient demographics in our study compared with studies where robotic surgery was performed in obese women with endometrial cancer, and their operative procedures and outcomes.

Studies	Gruhl et al.	Bernardini et al.[5]	Corrado et al.[6]	Fornalik et al.[7]	Shah et al.[8]	King et al.[9]
Country of study	Singapore	Canada	Italy	US	US	US
Total no. of patients	25	45	70	76	43	188
Patient demographics						
Mean age, years	53.0	61.0	60.7	61.0	58.2	59.9
Mean BMI, kg/m^2	45.9	40.3	43.6	47	40.5	45.5
Other comorbidities, no. (%)						
Chronic HTN	14 (56.0)	51% had ≥3 comorbidities	75% had comorbidities	46.1% had ≥4 comorbidities	Not reported	138 (73.4)
Diabetes mellitus	5 (20.0)					73 (38.8)
OSA	5 (20.0)					26 (13.8)
Previous surgeries	18 (72.0)	17 (37.8)	37 (52.9)	Not reported	29 (67.4)	117 (62.2)
Preoperative radiological classification stage, no. (%)						
1A	19 (76.0)	8 (17.8)	42 (60.0)	Not reported	Not reported	133 (70.7)
1B	4 (16.0)	16 (35.6)	12 (17.1)	Not reported	Not reported	14 (7.4)
1C	0	7 (15.6)	0	Not reported	Not reported	Not reported
2	1 (4.0)	3 (6.7)	8 (11.4)	Not reported	Not reported	13 (6.9)
≥3	1 (4.0)	10 (22)	8 (11.4)	8 (10.5)	Not reported	5 (2.7)
Surgeries performed, %						
THBSO	16.0	40.0	61.4	3.9	62.1	88.9
THBSO-PLND	84.0	60.0	38.6	96.1	37.9	11.1
Conversion to laparotomy	0	0	0	0	0	1.1
Operative outcome						
Mean operative duration, min	240	270	164.3	203	252.6	173.3
Mean estimated blood loss, mL	149	200	73.2	150	41.2	74.4
Mean uterus weight, g	219	Not reported	Not reported	Not reported	176.3	Not reported
Final postoperative histology grade						
1A, no. (%)	15 (60.0)	27 (60.0)	19 (27.1)	Not reported	Not reported	99 (52.7)
1B, no. (%)	5 (20.0)			Not reported	Not reported	
2, no. (%)	1 (4.0)	5 (11.1)	36 (51.4)	Not reported	Not reported	45 (23.9)
≥3, no. (%)	4 (16.0)	5 (11.1)	15 (21.4)	Not reported	Not reported	42 (22.3)
Postoperative complications, no. (%)	2 (8.0)	8 (17.7)	6 (8.6)	11 (14.5)	3 (7.0)	11 (5.9)
5-year survival, %	92.0	Not reported	Not reported	Not reported (90-day mortality=0)	Not reported	Not reported
Recurrence rate of disease in 3 years, %	4.0	Not reported	7.1	Not reported	Not reported	Not reported

BMI: body mass index; HTN: hypertension; OSA: obstructive sleep apnoea; PLND: pelvic lymph node dissection; THBSO: total hysterectomy with bilateral salpingo-oophorectomy

Superscript numbers: Refer to REFERENCES

3 cycles chemotherapy followed by pelvic radiotherapy, and her 5-year postoperative follow-up showed no recurrence of disease.

The second patient had an MRI of the pelvis, which showed tumour confined to the endometrium with no extension beyond the cervix. She underwent a hysteroscopy, dilatation and curettage, and was noted to have cervical involvement with histology confirming grade 3 cancer. She subsequently underwent modified radical hysterectomy. Final histology confirmed stage 3B cancer, with microscopic metastasis to the vagina. Surgical margins were clear. This patient was subsequently offered chemotherapy and pelvic radiotherapy. She was admitted for urinary tract infection 18 months later, and computed tomography (CT) scan showed lymph node recurrence with hydronephrosis. She is on palliative chemotherapy with doxorubicin at the time of writing.

The third patient was classified as radiology stage 1A, with a 3.3cm tumour confined within the endometrial cavity on her MRI scan. This was subsequently revised to stage 3C on final histology with pelvic lymph node metastasis. She completed 6 cycles of chemotherapy and radiotherapy, with no disease recurrence to date.

We had 1 patient with stage 2 cancer who underwent preoperative vault therapy. Postoperatively, no adjuvant therapy was recommended. At her 1-year follow-up, CT scan did not show any recurrence of disease.

The 30-day mortality rate is 0. One patient died 13 months after her surgery. She developed bowel obstruction requiring emergency surgery, and her postoperative recovery was complicated with sepsis and multi-organ failure. Another patient died 3 years and 3 months post operation from recurrence of endometrial cancer.

Limitations of our study include a small sample size and single institution recruitment. However, robotic surgery is a promising modality for surgical management of obese patients with endometrial cancer. With further research, robotic surgery can eventually allow for the standard of care for endometrial cancer to be possible for women with obesity. Robotic surgery is a safe and effective surgical approach for endometrial cancer in morbidly obese patients.

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Sabrina Lasini Gruhl [1]*MBBS*,
Muhammad Ashraf Yusoff [1]*MBBS*,
Hui Men Selina Chin [1]*MBBS*,
Ravichandran Nadarajah [1]*FRCOG*

[1]Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore

Correspondence: Dr Sabrina Lasini Gruhl, Department of Obstetrics and Gynaecology, Singapore General Hospital, Outram Road, Singapore 169608.
Email: sabrina.gruhl@mohh.com.sg

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Middle-aged woman with painless neck swelling

A 57-year-old woman presented with a 2-month history of an asymptomatic left neck lump. She is a non-smoker, does not drink alcohol, and has no family history of head and neck cancers. On examination, there was a 2cm left cervical level II ovoid and mobile nodule, which appeared to exhibit transmitted pulsations. Cranial nerve examination was normal nasoendoscopic and otoscopic evaluation were unremarkable.

The lesion was visualised on both computed tomography and magnetic resonance imaging (MRI) scans as a well-defined 2.8 x 2.9 x 2.8cm mass just adjacent to the major vessels in the neck (Fig. 1).

What is the diagnosis?

A. Enlarged cervical lymph node
B. Carotid body tumour
C. Vagal schwannoma
D. Sympathetic chain schwannoma
E. Branchial cleft cyst

The patient then underwent surgical excision of the lesion. Histological examination revealed a dense lesion with adjacent compressed nerve fibres containing ganglions that displayed a mixture of both cellular Antoni A and hypocellular Antoni B segments, with the latter showing vessels with surrounding hyalinisation. These findings are consistent with a schwannoma—in this case, a sympathetic chain schwannoma.

Schwannomas are nerve sheath tumours consisting of Schwann cells that confer a low risk of malignant transformation,[1] of which 25-45% are found in the head and neck region.[2] Schwannomas of cervical sympathetic chain (SCSC) are even more uncommon[3] with fewer than 80 cases reported in the literature, of which only 12 cases had preoperative Horner's syndrome.[4] The sympathetic chain is a longitudinal structure lying bilaterally adjacent to the spine, extending from the base of the skull to the coccyx with cervical, thoracic and lumbar components. It is part of the autonomic nervous system that takes part in the "fight or flight" response, which includes pupillary dilatation, perspiration and tachycardia. The cervical segment provides innervation to orbital structures (pupil dilatory muscle and Müller's muscle) and facial sweat glands, as well as contributes branches to the cardiac plexus.

Pre-excision symptom complexes are usually related to compressive effects of large tumours, for example, dysphagia, dyspnoea, and cranial nerve (CN) deficits (CN X, XII).[4] However, patients often present with an asymptomatic neck swelling for which the main differentials are vagal schwannomas (most common), carotid body tumours and schwannomas from surrounding cranial nerves (glossopharyngeal and hypoglossal).

Schwannomas typically appear heterogeneously bright on T2-weighted images due to the presence of interspersed Antoni A (hypercellular) and Antoni B (hypocellular) tissue signals.[5] Occasionally, a split-fat sign can also be appreciated (Fig. 1B arrowhead)—it describes a thin rim of peripheral fat seen

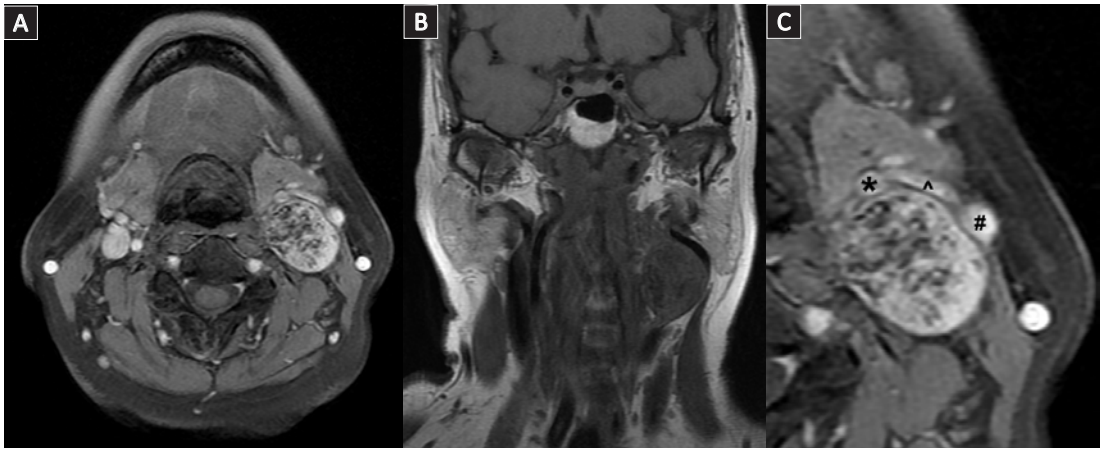

Fig. 1. (A) T1-weighted fat-suppressed axial magnetic resonance imaging (MRI) with contrast. (B) T1-weighted coronal MRI non-fat sat image. (C) Magnified T1-weighted MRI axial cuts showing relation of the lesion with major vessels.
* External carotid artery; # internal carotid artery; ^ internal jugular vein

Answer: D

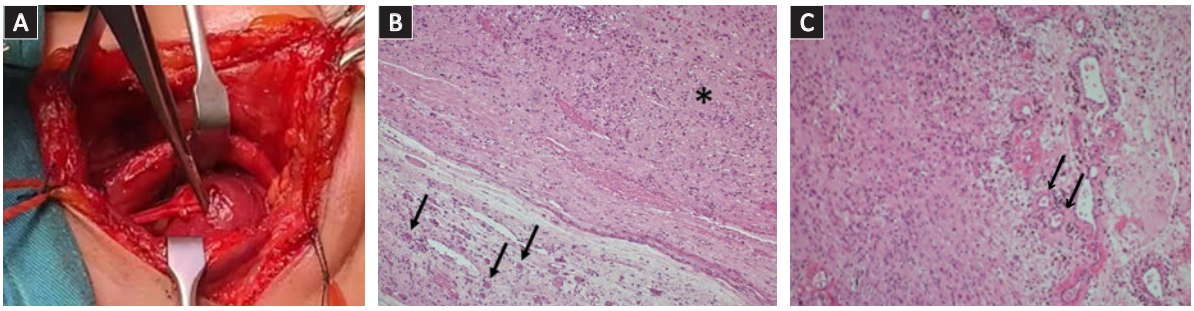

Fig. 2. (A) Intraoperative schwannoma with attached normal sympathetic chain nerve fibres inferiorly. (B) Schwannoma (*) showing a well-demarcated border from the adjacent compressed nerve tissue which contains ganglion cells (arrows) (haematoxylin and eosin [H&E] staining, 100x magnification). (C) Cellular Antoni A area (left) and hypocellular myxoid Antoni B area (right). The Antoni B area also contains vessels with surrounding hyalinisation (arrows) (H&E staining, 100x magnification).

especially on coronal cuts, suggesting a nerve sheath tumour.[6]

Due to the posteromedial location of the cervical sympathetic chain in relation to carotid sheath, it is characteristic of SCSC to:[7]

(1) displace the internal carotid artery (ICA) anterolaterally, unlike vagal schwannomas that medialise the ICA;

(2) not splay the ICA and internal jugular vein (IJV), as opposed to vagal schwannomas that characteristically do, due to their position within the carotid sheath between the carotid and IJV.

However, it must be acknowledged that the above features are not uniformly seen in all cases, and variations have been observed in literature.[8] In a study by Anil and Tan,[8] one SCSC demonstrated posterior displacement of the ICA while another had the SCSC splaying the ICA (anteriorly) and IJV (posteriorly), although this is rarely seen. It is important to differentiate between vagal and sympathetic chain schwannomas, as excising the former

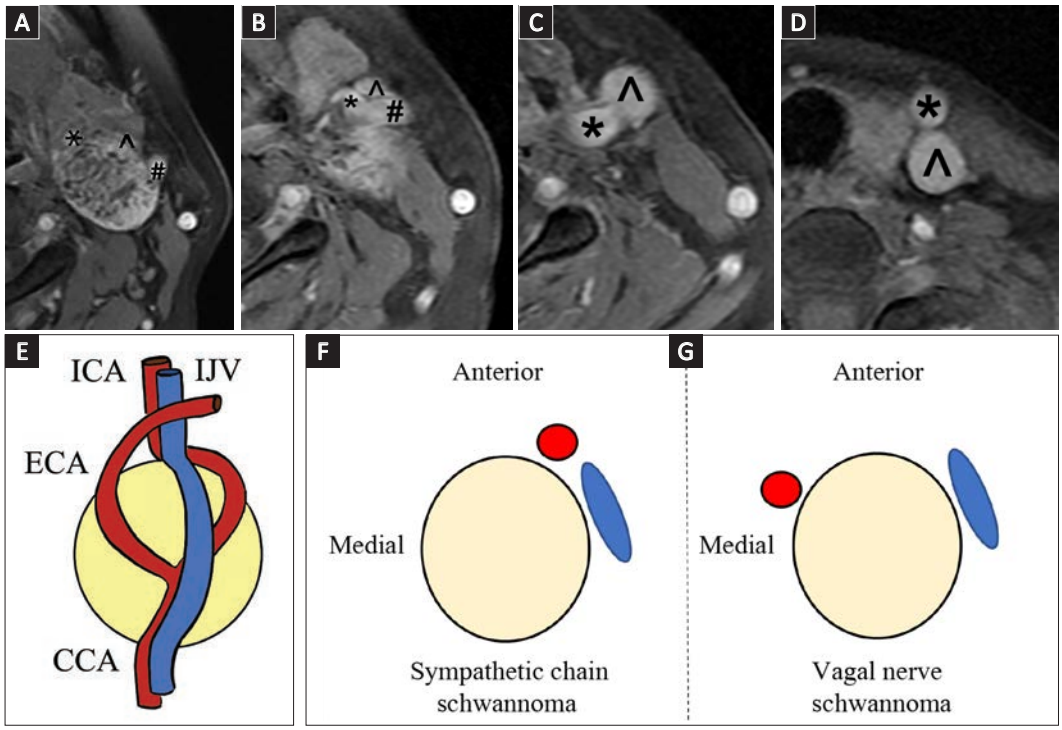

Fig. 3. Course of internal jugular vein (IJV) and carotids from superior to inferior. (A) Displacement of IJV and internal carotid artery (ICA) anterolaterally with splaying of carotids. (B and C) IJV compressed anteriorly at level of carotid bifurcation and immediately inferiorly. (D) Common carotid artery (CCA) crosses IJV and appears anterior to the vein at the level of the thyroid gland. (E) Diagram depicting altered anatomy found in this case study where the schwannoma caused displacement and intertwining of the ICA, external carotid artery (ECA) and IJV. (F and G) Schematic diagrams showing the expected relations between the structures in the cases of a sympathetic chain schwannoma, (F) or vagal nerve schwannoma.
* ECA/CCA; # ICA; ^ IJV
Large circle: lesion; small circle: ICA; flat oval: IJV

will result in more significant functional deficits such as dysphonia, dysphagia, and even dyspnoea or asphyxiation from bilateral vocal cord palsy if the patient has existing contralateral vocal cord pathology.

Paragangliomas, such as carotid body tumours, classically show a "salt-and-pepper" appearance. "Salt" represents haemorrhage presented as hyperintense foci seen on T1-weighted images, while "pepper" are vascular flow voids which are hypointense on T1/2 but should have corresponding linear vascular enhancement on post-contrast images to be true vascular flow voids. Both of these are not demonstrated in this patient's scans. Although the lesion does splay the carotid arteries superiorly, it does not demonstrate this feature exactly at the level of the carotid bifurcation (lyre sign), which is the most common location for carotid body tumours. Branchial cleft cysts will also appear markedly hyperintense on T2-weighted images due to the high fluid content.

SCSC can be managed both conservatively or surgically. The usual indications for excision of a schwannoma are: a large or fast enough growing lesion that causes problems as a result of compression of surrounding structures; or a relatively fast-growing lesion on interval scan in a younger patient, such that it is anticipated that the lesion will cause functional problems (e.g. Horner's syndrome) during the lifespan of the patient. Conservative management can be considered in an asymptomatic patient with a stable lesion, who is able to confidently identify red flag symptoms, and comply with regular surveillance scans. In this case, the patient was recommended conservative management with serial scans. However, she was very keen for excision due to derived stress from her condition and concerns regarding future potential complications and inability to tolerate surgeries with advanced age.

Patients also need to be counselled on the development of post-excision Horner's syndrome: ptosis, miosis and anhidrosis. They should also be informed of the risks of bleeding from vessel injury and adjacent cranial nerve palsies, potentially impacting swallowing, speech and articulation; and shoulder weakness.

Also, surgical exposure would likely involve significant manipulation of the ICA and thus, the carotid sinus. Carotid sinus manipulation intraoperatively has been reported to cause hypersensitivity, which may manifest as sinus bradycardia and third-degree heart blocks, more so in the elderly population.[9] As such, injection with 2mL of 1% lignocaine into the adventitia at the carotid bifurcation should be performed prior to manipulation for hydrodissection and to reduce the sensitivity of the carotid sinus body.[10]

In our patient, postoperatively, she had preserved palatal elevation, swallowing function, shoulder shrug and no tongue deviation on protrusion. Signs of Horner's syndrome were evident with left anhidrosis and miosis, but symmetrical palpebral aperture was still preserved. Two months postoperatively, the patient went on to develop left partial ptosis due to weakness of Müller's muscle and superior tarsal muscle, which completed the triad. As of her last clinic review, her ptosis has improved slightly.

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Cherie Seah Xinyi [1]*MRCS*, Yong Quan Alvin Soon [2]*FRCR*, Hai Yi Clarence Teo [3]*FRCPA*, Ming Yann Lim [1]*FAMS*

[1] Department of Otorhinolaryngology, Tan Tock Seng Hospital, Singapore
[2] Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore
[3] Department of Pathology, Tan Tock Seng Hospital, Singapore

Correspondence: Dr Cherie Xinyi Seah, Department of Otorhinolaryngology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: cherie.seah@mohh.com.sg

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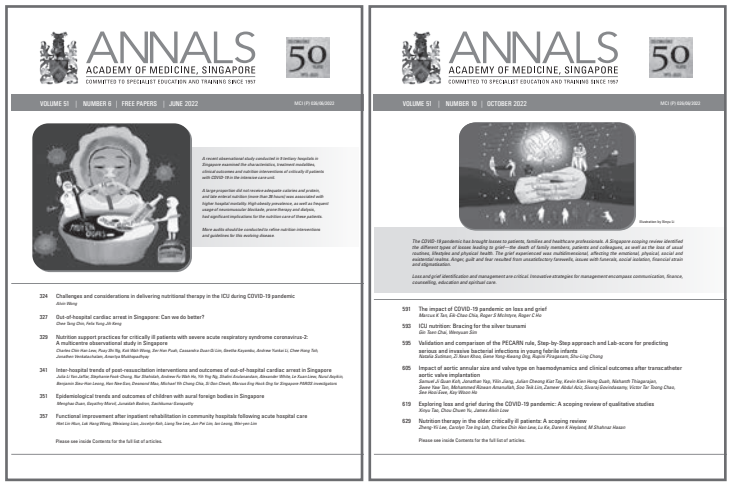

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81 Kim Keat Road, #11-00 & 12-00, NKF Centre, Singapore 328836
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