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The oral antiviral agents nirmatrelvir-ritonavir (NMV/r) and molnupiravir are used to treat mild-to-moderate COVID-19 infection in outpatients. However, drug-drug interactions (DDIs) with frequently prescribed medications call for extra precaution, especially with the emergence of COVID-19 variants and widespread use of oral COVID-19 treatments.

This latest comprehensive review of available data on DDIs between NMV/r, molnupiravir and common dermatological medications summarises the potential side effects, and suggests strategies for safe COVID-19 treatment. NMV/r has significant DDIs with many common dermatological medications, which may require temporary discontinuation, dosage adjustment, or substitution with other anti-COVID-19 agents such as molnupiravir.

Illustration by Xinyu Li

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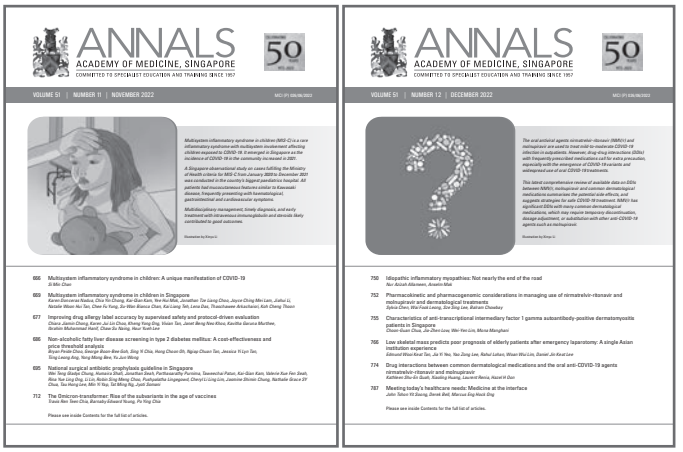

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EDITORIAL

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Idiopathic inflammatory myopathies: Not nearly the end of the road

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The clinical spectrum of idiopathic inflammatory myopathies (IIM) has broadened over the past half century from a simple disease characterised primarily by muscle and skin manifestations, to a potentially life-threatening complex condition of multiple organ involvement. In the recent decade, the discovery and addition of novel autoantibody profiles including the myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) have led to considerable advances in our understanding of the clinical and pathological heterogeneity of IIM. The knowledge and interpretation of the presence of an MSA enable the identification of distinct clinical phenotypes and facilitate early diagnosis of IIM, obviating the need for invasive tests such as muscle biopsy in some cases. Serologically defined subgroups of IIM provide valuable insights into the genetic susceptibility factors, and oncogenic as well as environmental triggers of the disease.[1] More importantly, these autoantibodies have allowed physicians to ascribe prognosis.

The conventional screen for the presence of an autoantibody, in patients with a suspected systemic autoimmune rheumatic disease, is the anti-nuclear antibody (ANA) test. ANA is an array of autoantibodies that direct against nuclear constituents such as single- or double-stranded deoxyribonucleic acid (dsDNA), centromeres, proteins complexed with ribonucleic acid (RNA), and enzymes such as topoisomerase. ANA screen is usually performed by indirect immunofluorescence (IIF) using rodent tissues or a human cell line (usually HEp-2 cells) as the substrate. While it is useful in the diagnosis of most connective tissue diseases such as systemic lupus erythematosus (SLE) and systemic sclerosis, it is not so in IIM. MSAs and MAAs yield a cytoplasmic rather than a nuclear staining pattern on IIF, often leading to a negative ANA test result. Myositis autoantibody testing must therefore be specifically requested in addition to an ANA screen when the pre-test probability of IIM is high.

Approximately 50–60% of adults and children with IIM carry an identifiable MSA.[2,3] MAAs are less specific to IIM, and may be found in other autoimmune conditions that overlap with myositis such as SLE and systemic sclerosis. Classic MSAs include antibodies to Jo-1 such as histidyl transfer RNA (tRNA) synthetase, and other aminoacyl tRNA synthetases (ARS), anti-nucleosome remodelling deacetylase complex (Mi-2), anti-signal recognition particle (SRP), anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), anti-melanoma differentiation-associated gene 5 (MDA5), anti-transcription intermediary factor 1γ (TIF1-γ), anti-nuclear matrix protein 2 (NXP2), anti-small ubiquitin-like modifier activating enzyme (SAE), and anti-cytosolic 5'-nucleotidase 1A (cN1A).

The association between MSAs and clinically important disease features—such as interstitial lung disease and malignancy—makes the autoantibody profile a useful tool to guide further investigations and appropriate monitoring. Paramount to the finding of anti-TIF1-γ or anti-NXP2 in adult-onset IIM is their strong correlation with cancers, with a 38–71% risk of malignancy occurring within 3 years prior to or following an IIM onset.[4] Children with anti-TIF1-γ or anti-NXP2 antibodies, on the contrary, are at risk for severe skin diseases including calcinosis, rather than that of cancers.[1]

In this issue of the *Annals*, Chua et al.[5] describe and compare the main clinicopathologic features and outcomes between 36 patients with dermatomyositis who were positive for anti-TIF1-γ antibody and 60 counterparts negative for the antibody at a tertiary institution in Singapore. The study revealed a higher prevalence of cancers among dermatomyositis patients with anti-TIF1-γ antibody compared with those without (63.9% versus 8.3%; odds ratio 19.1, 95% confidence interval 6.1–59.8, $P<0.001$), with nasopharyngeal carcinoma and breast cancer being the most common malignancies (26.1%) in these patients. Previous local studies[6,7] predating the advent of most MSAs established a similar link between these malignancies and dermatomyositis in adults.

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The data and recommendations by Chua et al. are timely and complement the recent evidence and consensus-based cancer screening guideline issued by the International Myositis Assessment and Clinical Studies Group (IMACS) at the American College of Rheumatology Convergence 2022.[8] Most cancers are diagnosed simultaneously with IIM, or during the first year after the diagnosis of IIM.[9,10] The absence of cancer at IIM onset does not negate the likelihood of its future occurrence; surveillance of malignancy is therefore required. The intensity of cancer surveillance can vary, depending on various clinical and epidemiological factors. All adult IIM patients should undergo basic laboratory testing and country/region-specific age and sex-appropriate cancer screening at diagnosis of IIM.[8] The IMACS further recommends stratifying cancer risk according to disease subtypes, autoantibody status and clinical features. Patients with an increased risk of developing cancer should undergo enhanced screening. This includes basic and sex-based screening, as well as computed tomography (CT) scanning of the thorax, abdomen and pelvis; cancer antigen 125 (CA 125) test; abdominal or transvaginal ultrasound for ovarian cancer evaluation; and prostate-specific antigen test. In addition to these recommendations by IMACS, Chua et al.[5] propose magnetic resonance imaging of the neck and posterior nasal space and otolaryngology assessment for all patients with dermatomyositis in accordance with the high prevalence of nasopharyngeal carcinoma in Singapore.[6,7] Patients with 2 or more of the following features including (1) dermatomyositis, (2) anti-TIF1-γ antibody positivity, (3) anti-NXP2 positivity, (4) aged more than 40 years at onset, (5) persistent high disease activity despite immunosuppressive therapy, (6) moderate to severe dysphagia, and (7) cutaneous necrosis, are encouraged to undergo cancer surveillance for up to 3 years after the onset of IIM.[8]

Glucocorticoids are the first-line therapy for IIM. In most cases, additional immunosuppressive agents are required for patients with IIM, and introducing them early in the course of the illness can attenuate glucocorticoid toxicity and facilitate rapid resolution of disease features. Combination therapy with different immunosuppressants and the use of intravenous immunoglobulin, an immunomodulatory agent, are considered in certain disease subtypes. Patients with cancer-associated myositis should be managed from the perspective of both their cancers and myositis. Physicians who manage IIM often closely collaborate with oncologists to devise individualised therapy plans, taking care to mitigate potential drug interactions.

In recent years, substantial work has been undertaken towards establishing the epidemiology, genetic associations, disease subtype classification of IIM and novel therapeutic strategies. Despite these significant advances, major unmet needs endure. The establishment of personalised medicine in IIM, while tantalising, requires better data harmonisation and international collaborations. We remain optimistic, fully cognisant of the sinuous path that accompanies this odyssey.

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EDITORIAL

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Pharmacokinetic and pharmacogenomic considerations in managing use of nirmatrelvir-ritonavir and molnupiravir and dermatological treatments

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The COVID-19 pandemic has been unprecedented in its impact on global health, economic, financial, psychosocial and political systems. The World Health Organization estimates approximately 627 million confirmed cases and 6.5 million deaths reported globally.[1] In Singapore, the swift and prompt public health response of the government during the early days of the pandemic led to a relatively low cumulative fatality count of 1,709 deaths as of mid-December 2022.[2]

The SARS-CoV-2 is a ribonucleic acid (RNA) virus belonging to the genus betacoronavirus and it is constantly evolving through random mutations. The viral spike glycoprotein binds to the angiotensin-converting enzyme 2 receptor on the plasma membrane of the host cell to facilitate host cell invasion. The spectrum of presentation due to SARS-CoV-2 infection may vary from mild upper respiratory tract infection that is usually accompanied by fever, muscle pain and fatigue, to a severe infectious state characterised by a hyperinflammatory response, vasculopathy, microangiopathy and widespread thrombosis. Mortality increases in patients of advanced age and with underlying comorbidities.

With a better understanding of the structure of the SARS-CoV-2 virus and its mechanism of replication, several therapeutic agents such as corticosteroids, antivirals, immunomodulatory agents, antimalarial agents and therapeutic antibodies have been investigated in its clinical management. The choice of drugs depends on the presenting clinical conditions of the patients and is particularly challenging, when dealing with those who have severe infections. Current therapeutic interventions are generally based on the following approaches: (1) targeting host cell entry of SARS-CoV-2, (2) inhibiting viral genome replication, (3) priming of immune system via memory T cell production and (4) inhibition of pro-inflammatory markers that manifest as viral-induced cytokine storms.[3]

Two new oral antivirals, nirmatrelvir-ritonavir (NMV/r) and molnupiravir are approved for emergency outpatient use in adult and paediatric patients who are considered to be at high risk for progression to severe COVID-19.[4,5] Nirmatrelvir is a protease inhibitor targeting the Mpro protease of SARS-CoV-2, resulting in inhibition of viral replication. Hammond et al.[4] reported that nirmatrelvir plus ritonavir, administered twice daily for 5 days at a respective oral dose of 300mg and 100mg, was effective in reducing the risk of COVID-19-associated 30-day mortality by 89% compared with placebo when treatment was started within 3 days of onset of COVID-19 symptoms.[4]

Molnupiravir was authorised for emergency use by the U.S. Food and Drug Authority (FDA) for individuals ≥18 years in the event that alternative COVID-19 treatments authorised by FDA are unavailable, among other usage parameters.[5] On 19 April 2022, the Singapore Health Sciences Authority granted interim authorisation for molnupiravir (LAGEVRIO) to treat mild-to-moderate COVID-19 for those ≥18 years and at risk of developing severe COVID-19, among other usage parameters.[6] As a prodrug of ribonucleoside β-D-N^4-hydroxycytidine (NHC) that is incorporated by viral RNA polymerase to induce viral mutations and lethal mutagenesis, molnupiravir is metabolised via the pyrimidine metabolic pathways, and renal or hepatic elimination of NHC is not meaningful or expected routes, respectively.[7]

Nirmatrelvir undergoes rapid clearance in the body due to extensive metabolism by hepatic cytochrome P-450 (CYP) 3A4. It is thus co-administered with ritonavir, a potent irreversible CYP3A4 inhibitor, which acts as a pharmacokinetic enhancer to prolong its half-life.[8] Significant drug-drug interactions (DDIs) associated with NMV/r result from the strong inhibitory effect of ritonavir on CYP450 enzyme (e.g. CYP3A4) and drug transporters (such as P-glycoprotein, and organic anion transporting polypeptides 1B1 and 1B3).

Ritonavir's inhibitory effect on CYP3A4 is rapid and maximal at a dose of 100mg.[8] It can therefore potentially result in elevated plasma concentrations

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of co-medications that are metabolised primarily by CYP3A enzymes, and/or have a narrow therapeutic index (e.g. ciclosporin and tacrolimus), and/or are substrates or P-glycoprotein (e.g. digoxin). Pharmacokinetic modelling suggests that approximately 80% of CYP3A4 inhibition is reversed by 72 hours following cessation of ritonavir in young and elderly adults. On the other hand, ritonavir can also induce other CYP450 enzymes such as CYP1A2, CYP2B6, CYP2C9, CYP2C19 and uridine diphosphate glucuronosyltransferases. However, as opposed to ritonavir's inhibitory effect on CYP3A4/5, its inductive effect on other CYP450 enzymes is unlikely to be clinically relevant with NMV/r as the maximal effect is unlikely to be reached during the short treatment course of 5 days. Due to its significant DDIs, the use of NMV/r may not be feasible in patients with severe comorbidities. To date, DDIs with molnupiravir have not been identified due to a lack of supporting studies.

In this issue of the *Annals*, the systematic review by Quah et al.[9] is timely and summarises several potential DDIs of NMV/r with commonly used dermatological medications. Immunosuppressants such as ciclosporin, are often prescribed for autoimmune diseases and severe atopic dermatitis, while tofacitinib, another immunosuppressant, is prescribed for severe alopecia areata and psoriatic arthritis. Both these drugs undergo CYP3A4/5-mediated hepatic metabolism and their concomitant use with NMV/r may exacerbate concentration-dependent toxicities by elevating nirmatrelvir concentrations, which may induce renal impairment and transaminitis. It is recommended that ciclosporin administration be stopped and resumed 3 days after the last NMV/r dose has been administered, whereas dose reduction is recommended for tofacitinib.[10] In situations where immunosuppressants such as ciclosporin cannot be temporarily withheld, such as for solid organ transplantation, it may be advisable to consider alternative treatments such as molnupiravir. Similarly, as a strong inducer of CYP3A4, rifampicin is contraindicated with nirmatrelvir-ritonavir, whereby the therapeutic concentrations of nirmatrelvir could be reduced to subtherapeutic levels that may compromise its antiviral activity. Rifampicin is also a potent inducer of P-glycoprotein, which may affect the bioavailability of ritonavir.

The potential for severe DDIs in the elderly population presenting with COVID-19 infection should not be overlooked. The practice of polypharmacy is rife in this population, and with their underlying comorbidities, they are often prescribed multiple drugs that are metabolised via the CYP3A4/5 pathway. Extreme precaution should be taken when NMV/r is prescribed in this particular patient population. Also, systemic bioavailability of topical agents that are CYP3A4 substrates may vary depending on their physicochemical and pharmacokinetic properties, which may culminate in potential DDIs when administered with NMV/r. This pharmacokinetic interaction may be important in patients with severe COVID-19 infection whereby the release of inflammatory cytokines has been shown to cause suppression of hepatic CYP450-mediated metabolic functions.[11]

A limitation of the systemic review by Quah et al.[9] is the lack of information on the pharmacogenomic impact of functional variants in the genes encoding the various CYP450 enzymes that can significantly affect a particular phenotypic outcome. Genetic polymorphisms are most prevalent in 5 CYP isozymes, namely, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4—the latter 2 being the most important of all CYP isozymes. The pharmacogenetics of some of these isozymes are complex, and contributes greatly to the wide variation in drug response and toxicity within a population, as well as between populations of different ethnic origins.[12] Although CYP3A4 metabolises approximately 60% of drugs in the human body, it shares similar substrate specificity with CYP3A5. Also, pharmacogenetic variability in CYP3A4 is less common in Asians but less so for CYP3A5. The latter is highly polymorphic in Asians and the frequency of the defective *CYP3A5*3/*3* genotype varies from 30% in Malays and Indians, to 60% in Chinese.[13] The *CYP3A5*3* allele results in a truncated protein with resultant loss of hepatic CYP3A5 expression and decreased catalytic activity. Thus, dermatologic agents that are CYP3A4 substrates may also undergo CYP3A5-mediated metabolism in the liver. An understanding of the pharmacogenetic impact of CYP3A4/5 variants on the pharmacokinetics of candidate drugs when administered concomitantly with ritonavir would be crucial to alleviate the risk of serious DDIs. Such considerations are particularly important when patients on NMV/r are also prescribed drugs with low therapeutic indices such as immunosuppressive agents.

Thus, given the complexity in the multiplicity of drug metabolising enzymes and transporters involved in the disposition of dermatologic agents when co-administered with NMV/r to COVID-19 patients, it is imperative that special precautions be taken to avoid serious DDIs.

Safe management of DDIs are possible if healthcare professionals are aware of their presence. Apart from pharmacokinetics-based interactions, the impact of pharmacogenomics factors should also be considered in the dose optimisation strategies of NMV/r when prescribing with dermatologic agents or other co-medications.

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ORIGINAL ARTICLE

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Characteristics of anti-transcriptional intermediary factor 1 gamma autoantibody-positive dermatomyositis patients in Singapore

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ABSTRACT

Introduction: This study aimed to determine the clinical profile and outcome of anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1-γ Ab)-positive dermatomyositis patients and propose cancer screening programmes based on regional cancer trends.

Method: Data on history, physical findings and investigations were collected using chart review on dermatomyositis patients seen at a tertiary hospital in Singapore from 1 January 2015 to 30 June 2021. Comparisons were made between anti-TIF1-γ Ab-positive and anti-TIF1-γ Ab-negative dermatomyositis.

Results: Ninety-six dermatomyositis patients were analysed and 36 patients were positive for anti-TIF1-γ Ab. Anti-TIF1-γ Ab-positive patients had more frequent heliotrope rashes, shawl sign, periungual erythema, holster sign, Gottron's papules, dysphagia and truncal weakness (P<0.05). They had less frequent interstitial lung disease, polyarthritis, cutaneous ulcers, palmar papules and mechanic's hands (P<0.05). After 48 months of follow-up, a higher proportion of anti-TIF1-γ Ab-positive patients developed cancer compared with Ab-negative patients (63.9% versus 8.5%; odds ratio 19.1, 95% confidence interval 6.1–59.8; P<0.001). Nasopharyngeal carcinoma (NPC) and breast cancer were the most common malignancies, followed by bowel, lung and non-Hodgkin lymphoma. Most malignancies (78.3%) occurred within 13 months prior to, or 4 months after the onset of dermatomyositis. The mortality rate for anti-TIF1-γ Ab-positive patients was significantly higher than Ab-negative patients (36.1% vs 16.7%, P=0.031), and Kaplan-Meier survival estimates at 24 months were 66% and 89%, respectively (P=0.0153).

Conclusion: These observational data support periodic screening of NPC and other malignancies in patients with anti-TIF1-γ Ab-positive dermatomyositis in Singapore.

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Keywords: Autoantibody, cancer, dermatomyositis, nasopharyngeal carcinoma, transcriptional intermediary factor 1 gamma

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired, systemic autoimmune conditions characterised by muscular and extramuscular manifestations. As a subset within the family of IIM, dermatomyositis is distinguished by cutaneous features and has twice the risk of associated malignancy than polymyositis.[1-3]

Various meta-analyses have shown that between 10% and 47% of dermatomyositis patients have an underlying malignancy, and the associated cancers vary with different geographical populations.[1-3] Ovarian, lung, pancreatic, non-Hodgkin lymphoma, stomach, colorectal and breast cancers are more frequently reported in Western studies.[1-3] In comparison, nasopharyngeal carcinoma (NPC) is more frequently reported among cancer-associated myositis (CAM) patients in studies from Taiwan, Hong Kong, Japan and South Korea, with a frequency of up to 40%.[3-9]

The discovery of myositis-specific autoantibodies (MSAs) associated with distinct clinical phenotypes is a major advancement that enables the identification of

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CLINICAL IMPACT

What is New

- Anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1-γ Ab) was the most common myositis-specific autoantibody subtype seen in our dermatomyositis patients.
- Nasopharyngeal carcinoma and breast cancers were the most common malignancies observed in our autoantibody-positive cohort.

Clinical Implications

- Periodic malignancy screening should be performed for patients with dermatomyositis, particularly those who are anti-TIF1-γ Ab-positive.
- Nasopharyngeal carcinoma screening should be included in the cancer surveillance programme for dermatomyositis patients in Singapore.

distinct patterns of disease. Among the MSAs, anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1-γ Ab) is strongly associated with malignancies in adult-onset dermatomyositis.[10-14] Human TIF1-γ belongs to the tripartite motif (TRIM) containing protein and is involved in a broad range of biological processes and diverse pathological conditions, such as developmental disorders, neurodegenerative diseases, viral infections and cancer. It is found at varying levels in skeletal muscles and skin,[15-17] and its involvement in the transforming growth factor TGF-β signalling pathway has been most extensively studied.[18-20] TIF1-γ normally inhibits tumourigenesis by inhibiting TGF-β-induced epithelial-to-mesenchymal transition via mono-ubiquitination of *SMAD4* (a tumour suppressor gene). Both suppression and overexpression of TIF1-γ have been associated with different cancers depending on the cellular context and cancer stage.[21-26] Inactivation, mutation or down-regulation of TIF1-γ by hypermethylation, histone modification, short non-coding microRNA or sumoylation can promote tumourigenesis, which has been reported in hepatocellular carcinoma, non-small-cell lung carcinoma and clear cell renal cell carcinoma.[21,22] Overexpression of TIF1-γ has been described in early-stage breast cancer, and both early and advanced stage colorectal cancer.[25,26]

In anti-TIF1-γ Ab-positive CAM, it is hypothesised that TIF1-γ functions as a tumour autoantigen and triggers dermatomyositis through activation of both adaptive and innate immune responses.[27-29] CAM has been reported to occur within 3 years prior to or following the onset of dermatomyositis, with the presence of anti-TIF1-γ Ab conferring a 9.37-fold higher risk of developing cancer with a 52% sensitivity and 92% specificity.[10-14,30] Some of the characteristics observed in anti-TIF1-γ Ab-positive CAM patients include (1) a higher risk of developing cancer among those who are ≥39 years of age at the onset of dermatomyositis;[14,31] (2) a higher prevalence of solid cancers compared to haematological cancers (19.9% versus 1.4%);[2,30] and (3) increased risk of ovarian cancer in females.[2,14,32] These observations were drawn mainly from studies on Western cohorts with a paucity of data from the Asian population, in particular, Southeast Asia.

Given the strong association between anti-TIF1-γ Ab and cancer, close surveillance for cancer in this subgroup of dermatomyositis patients to allow early detection and treatment is advocated. The International Myositis Assessment and Clinical Studies Group has established a special interest group that aims to develop evidence-based cancer screening guidelines for newly diagnosed IIM patients.[33] In addition, small studies have shown potential biomarker value in anti-TIF1-γ Ab titre serial measurements to monitor dermatomyositis activity for detecting cancer recurrence.[34]

The objective of this study was to determine the clinical profile and outcomes of patients with anti-TIF1-γ Ab-positive dermatomyositis at a single tertiary centre in Singapore and to propose a cancer screening programme for Singapore dermatomyositis patients.

METHOD

We analysed dermatomyositis patients seen at the Department of Rheumatology, Allergy and Immunology in Tan Tock Seng Hospital, Singapore from 1 January 2015 to 30 June 2021. Inclusion criteria included age of onset ≥18 years and the diagnosis of either definite or probable IIM according to the Bohan and Peter criteria. The International Myositis Classification Criteria score was also calculated for each case and only those with a score of at least 55% ("probable IIM") and cutaneous manifestations consistent with dermatomyositis were included.

Clinical information on disease manifestations, laboratory data, imaging data, presence of malignancy, treatment and outcome was obtained from medical chart review. The following parameters were assessed: age of onset, sex, clinical features, laboratory data at the time of dermatomyositis diagnosis, history of malignancy (including type, timing of diagnosis in relation to

dermatomyositis, staging and pathological classification), treatment for both dermatomyositis and malignancy, mortality rate, and cause of mortality. All patients were tested for the presence of MSA/myositis-associated autoantibodies (MAAs). Whole-blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) tubes to enable separation of plasma by centrifugation, permitting autoantibody testing for determination of the presence of MSAs and MAAs using the Euroline Autoimmune Inflammatory Myopathies 16 Antigen Profile panel. All patients were followed up until mortality, loss to follow-up or 30 June 2021.

Ethics approval was granted. As strict local Personal Data Protection Act guidelines were observed and data collected would facilitate improvement in future patient care, waiver of patient consent was granted by the ethics committee.

Statistical analysis

Between-group comparisons of normally distributed measurement data were conducted using Student's t-test or the Mann-Whitney U test. The chi-square test was used to analyse differences between baseline characteristics data. To identify independent risk factors, the odds ratio (OR) and 95% confidence interval (CI) were analysed using multivariate Cox proportional hazards regression analysis. Variables with $P<0.05$ in univariate analysis were analysed using the Kaplan-Meier curve and the log-rank test. All statistical analyses were carried out using Stata version 14.0 (StataCorp, College Station, US). The results were reported as the median (interquartile range [IQR]). $P<0.05$ was considered to indicate a statistically significant difference.

RESULTS

Demographic data

Of the 96 patients with dermatomyositis, 63 (65.6%) were women and 33 (34.4%) were men. The median age of the patients at the time of dermatomyositis onset was 57 years (IQR 44.75–64.00 years) and the median follow-up duration was 48 months (16.75–78.97 months). Patients were divided into 2 groups: 36 patients with anti-TIF1-γ Ab, and 60 without anti-TIF1-γ Ab. The most common MSA/MAAs detected in the anti-TIF1-γ Ab group were anti-Ro52 (37/60, 61.7%), anti-MDA5 (22/60, 36.7%) and anti-PL7 (13/60, 21.7%). Anti-NXP2 was found in 3 out of 96 dermatomyositis patients (3.1%), of which 1 co-existed in a patient with positive anti-TIF1-γ Ab. The proportion of patients with malignancy in the anti-TIF1-γ Ab-positive group was significantly higher than in those without anti-TIF1-γ Ab. Demographic characteristics of the 2 groups are presented in Table 1.

Clinical data of patients with positive anti-TIF1-γ Ab

Of the 36 anti-TIF1-γ Ab-positive dermatomyositis patients, 10 (27.8%) were men and 26 (72.2%) were women. Six (16.7%) of this group were smokers and the median age of dermatomyositis diagnosis was 61.5 years (IQR 29–96). Twenty-three (63.9%) patients were diagnosed with malignancies; NPC and breast cancer were the most common with 6 (26.1%) patients each. Other malignancies included 2 gastrointestinal (13.0%), 2 lung (8.7%), 2 non-Hodgkin lymphoma (8.7%), and 1 (4.3%) each for cervical, fallopian tube, thyroid and kidney. Breast cancer (6/17, 35.3%), NPC (3/17, 17.6%) and gastrointestinal (2/17, 11.8%) were the most common types of malignancy in female CAM patients. NPC (3/6, 50%), followed by lung, gastrointestinal and non-Hodgkin lymphoma (1/6 for each, 16.7%) were most common in male CAM patients. Of those anti-TIF1-γ Ab-positive NPC, 66.6% presented with advanced stage (Stage III or more) and all had undifferentiated histology.

Cancer characteristics of those with and without anti-TIF1-γ Ab are presented in Table 2. Malignancy was detected at the time of dermatomyositis diagnosis in 7/23 (30.4%) patients, following dermatomyositis diagnosis in 7/23 (30.4%) patients, and prior to dermatomyositis diagnosis in 9/23 (39.2%) patients. Malignancy was detected within 1 year before or after dermatomyositis diagnosis in 17 patients (73.9%). Of the 23 cancer patients, 21 were diagnosed with both dermatomyositis and cancer at age 39 years and above. The remaining 2 were females diagnosed with dermatomyositis at age 29 and 32 years, respectively. Both had breast cancers diagnosed 13 months before and 20 months after dermatomyositis diagnosis, respectively. The former had a strong family history of cancer (breast and cervical) but the latter had none. Table 3 summarises the clinical information of the anti-TIF1-γ Ab-positive dermatomyositis patients with cancers.

Baseline and follow-up cancer screening

Our dermatomyositis patients underwent various combinations of cancer screening investigations. Investigations performed were based on patients' symptoms and signs, family cancer history, contraindications and patients' preferences. A total of 32 of the 96 dermatomyositis patients (33.3%) underwent a complete

Table 1. Demographic and clinical characteristics of patients with anti-TIF1-γ Ab-positive and anti-TIF1-γ Ab-negative dermatomyositis

N=96	**Anti-TIF1-γ Ab-positive** (n=36, 37.5%)	**Anti-TIF1-γ Ab-negative** (n=60, 62.5%)	***P* value**
Demographics			
Age, median (range), years	61.5 (29–96)	54 (20–76)	0.005
Time from symptoms onset to diagnosis, median (range), months	2.5 (1–24)	3 (1–120)	0.137
Female, n (%)	26 (72.2)	37 (61.7)	0.292
Smoker, n (%)	6 (16.7)	9 (15.3)	0.855
Ethnicity, n (%)			0.352
Chinese	31 (86.1)	42 (70)	
Malay	5 (13.9)	12 (20)	
Indian	0	4 (6.7)	
Cutaneous manifestations			
Heliotrope rash	26 (72.2)	18 (30)	<0.001
Shawl sign	18 (50.0)	4 (6.7)	<0.001
Periungual erythema	25 (69.4)	20 (33.3)	0.001
Holster sign	8 (22.2)	2 (3.3)	0.005
Gottron's papules	26 (72.2)	27 (45.0)	0.009
Cutaneous ulcers	2 (5.6)	18 (30)	0.004
Mechanic's hands	4 (11.1)	20 (33.3)	0.015
Palmar papules	0	8 (13.3)	0.023
Violaceous rash	7 (19.4)	20 (33.3)	0.143
Inverse Gottron's	2 (5.6)	6 (10.0)	0.706
Musculoskeletal			
Proximal muscle weakness, n (%)	29 (80.6)	38 (63.3)	0.075
Amyopathy, n (%)	7 (19.4)	22 (36.7)	0.075
- Raised creatinine kinase >250 U/L, n (%)	1 (14.3)	11 (50.0)	-
- Abnormal electromyogram, n (%)	5 (71.4)	8 (36.3)	-
- Raised creatine kinase and abnormal electromyogram, n (%)	1 (14.3)	3 (13.6)	-
Truncal weakness, n (%)	10 (27.8)	6 (10.0)	0.024
Dysphagia, n (%)	15 (41.7)	9 (15.0)	0.003
Polyarthritis, n (%)	0	20 (33.3)	<0.001
Highest creatine kinase, median (range), U/L	473 (58–9512)	499.5 (35–36776)	0.54
Pulmonary			
Interstitial lung disease, n (%)	2 (5.6)	34 (56.7)	<0.001
Cancer and mortality			
Cancer, n (%)	23 (63.9)[a]	5 (8.5)	<0.001
Mortality, n (%)	13 (36.1)	10 (16.7)	0.031
Time from diagnosis to death (among those who died), median (range), months	12 (2–34)	4.5 (0–168)	0.419

[a] Cancer data for one anti-TIF1-γ Ab-positive patient were not available

Table 2. Characteristics of anti-TIF1-γ Ab-positive and anti-TIF1-γ Ab-negative dermatomyositis patients with cancer

N=28	**Anti-TIF1-γ Ab-positive** (n=23)		**Anti-TIF1-γ Ab-negative** (n=5)	
Demographics				
Age on dermatomyositis onset, median (range), years	64 (29–96)		52 (41–76)	
Time from dermatomyositis diagnosis to cancer diagnosis, median (range), months	0 (-288–22)		2 (0–72)	
Interquartile range for time from dermatomyositis diagnosis to cancer diagnosis in months	0–2		-8.5–2	
Female, n (%)	17 (73.9)		1 (20)	
Smoker, n (%)	4 (17.4)		1 (20)	
Ethnicity, n (%)				
Chinese	21		4	
Malay	2		1	
Indian	-		-	
Mortality, n (%)	10 (43.5)		2 (40)	
Time from dermatomyositis diagnosis to death (among those who died), median (range), months	14 (5–34)		45 (16–73)	
Cancer characteristics				
	Male	Female	Male	Female
Site				
Nasopharyngeal	3	3	1	-
Breast	-	6	-	1
Bowel	1	2	-	-
Lung	1	1	-	-
Thyroid	-	1	-	-
Cervical	-	1		
Fallopian tube	-	1	-	-
Non-Hodgkin lymphoma	1	1	-	-
Kidney	-	1	-	-
Prostate	-	-	2	-
Tonsil	-	-	1	-
Advanced stage	13		3	

baseline cancer screening comprising: (1) a neck and posterior nasal space (PNS) assessment with computed tomography (CT) scan of neck, magnetic resonance imaging (MRI) of the neck and PNS (MRI neck/PNS), and/or otolaryngology (ENT) review; (2) CT scan of the thorax/abdomen-pelvis (CT thorax/abdomen-pelvis); (3) oesophago-gastro-duodenoscopy (OGD); and (4) colonoscopy (or CT colonography). A higher proportion of anti-TIF1-γ Ab-positive patients (16/36, 44.4%) underwent a complete baseline cancer screen compared to the Ab-negative group (16/60, 26.7%). Seventy-five (78.1%) patients underwent at least a CT thorax/abdomen-pelvis scan as baseline cancer screen at dermatomyositis diagnosis. Of 63 female dermatomyositis patients, 34 (54%) underwent a baseline mammogram (MMG) and 7 (11.1%) received a Papanicolaou (Pap) smear. A higher proportion of anti-TIF1-γ Ab-positive female patients underwent MMG and Pap smear (MMG: 17/26, 65.4%; Pap smear: 6/26, 23.1%) compared to Ab negative group (MMG: 17/37, 45.9%; Pap smear: 1/37, 2.7%).

Clinical features associated with anti-TIF1-γ Ab-positive dermatomyositis

Clinical features found more commonly in anti-TIF1-γ Ab-positive compared to Ab-negative dermatomyositis patients were heliotrope rash (72.2% vs 30.0%, $P<0.001$), shawl sign (50.0% vs 6.7%, $P<0.001$), periungual erythema (69.4% vs 33.3%, $P=0.001$), holster sign (22.2% vs 3.3%, $P=0.005$), Gottron's papules (72.2% vs 45.0%, $P=0.009$), dysphagia (41.7% vs 15.0%, $P=0.003$), truncal weakness (27.8% vs 10.0%, $P=0.024$) and proximal myopathy (80.6% vs 63.3%, $P=0.075$). Patients with raised creatine kinase >250 U/L in both groups were similar: 24/36 (66.7%) in the anti-TIF1-γ Ab-positive group and 38/60 (63.3%) in Ab-negative patients. Presence of interstitial lung disease (5.6% vs 56.7%, $P<0.001$), polyarthritis (0% vs 33.3%, $P<0.001$), cutaneous ulcers (5.6% vs 30.0%, $P=0.004$), palmar papules (0% vs 13.3%, $P=0.023$) and mechanic's hands (11.1% vs 33.3%, $P=0.015$) were less common in the Ab-positive group (Table 1).

Immunosuppressive treatment of anti-TIF1-γ Ab-positive CAM patients

The majority (18/23, 78.3%) of our anti-TIF1-γ Ab-positive CAM patients displayed significant signs and symptoms that required initial high-dose corticosteroid treatment in the forms of intravenous hydrocortisone and/or pulsed methylprednisolone.

Table 3. Summary of anti-TIF1-γ Ab-positive dermatomyositis patients with cancer

Case	Age at diagnosis of dermatomyositis (years)	Sex	Ethnicity	Cancer and treatment			Time from dermatomyositis diagnosis to cancer diagnosis (months)	Dermatomyositis treatment	Outcome of dermatomyositis/ outcome of cancer/cause of death (if applicable)
				Site/Type	Stage	Treatment			
1	29	Female	Malay	Breast/metastatic carcinoma (ER+/PR-/ HER2+)	IIIA	Surgery, chemotherapy, radiotherapy, hormonal therapy	-13	MP, hydrocort, pred, HCQ, AZA, MTX, MMF, IVIg	Relapse/ remission/ -
2	32	Female	Chinese	Breast/invasive ductal (ER/PR/HER2 not available)	IIA	Surgery, chemotherapy	20	MP, hydrocort, pred, AZA, MTX, CsA, IVIg	Improved and stable/ remission/ -
3	47	Female	Chinese	Nasopharyngeal/ undifferentiated	III	Chemotherapy, radiotherapy	1	MP, hydrocort, pred, HCQ, AZA, MTX, CsA, IVIg	Improved and stable/ remission/ -
4	49	Female	Chinese	Nasopharyngeal/ undifferentiated	II	Radiotherapy	0	Pred, AZA, MTX	Improved and stable/ remission/ -
5	52	Female	Chinese	Bowel/adenocarcinoma	IIIB	Surgery, chemotherapy	0	Pred, HCQ, AZA	Improved and stable/ remission / -
6	55	Female	Chinese	Breast/invasive ductal (ER-/PR-/HER2+)	IIIA	Surgery, chemotherapy, hormonal therapy	4	Hydrocort, pred, HCQ, IVIg	Improved and stable/ remission/ -
7	57	Female	Chinese	Breast/invasive ductal (ER-/PR-/HER2 equivocal)	IIA	Surgery, chemotherapy	0	Pred, HCQ	Improved and stable/ remission/ -
8	63	Female	Chinese	Breast/invasive ductal (ER-/PR-/HER2 equivocal)	IIA	Chemotherapy	3	Pred, HCQ	Improved and stable/ remission/ -
9	65	Female	Chinese	Thyroid/follicular carcinoma	I	Surgery, radioactive iodine	4	MP, hydrocort, pred, HCQ, MTX, CsA, IVIg	Improved and stable/ remission/ -
10[a]	73	Female	Chinese	Renal/transitional cell carcinoma	IV	No available information	-12	MP, hydrocort, pred	Improved and stable/ - / -
11	76	Female	Chinese	Breast/papillary cell carcinoma (ER+/PR+/ HER2 equivocal)	IIA	Surgery	3	Hydrocort, pred, HCQ, AZA, IVIg	Improved and stable/ remission/ -
12	63	Male	Chinese	Nasopharyngeal/ undifferentiated	III	Chemotherapy, radiotherapy	0	MP, hydrocort, pred, HCQ, IVIg	Improved and stable/ remission/ -
13	64	Male	Chinese	Nasopharyngeal/ undifferentiated	I	Radiotherapy	0	Pred, MTX	Improved and stable/ remission/ -
14	64	Female	Chinese	Fallopian tube/poorly differentiated	IIIA	Surgery, chemotherapy	-4	Hydrocort, pred, IVIg	Improved and stable/ metastatic/died, no available information

Table 3. Summary of anti-TIF1-γ Ab-positive dermatomyositis patients with cancer (Cont'd)

Case	Age at diagnosis of dermatomyositis (years)	Sex	Ethnicity	Cancer and treatment			Time from dermatomyositis diagnosis to cancer diagnosis (months)	Dermatomyositis treatment	Outcome of dermatomyositis/ outcome of cancer/cause of death (if applicable)
				Site/Type	Stage	Treatment			
15	67	Female	Chinese	Nasopharyngeal/ undifferentiated	IVB	Chemotherapy	22	MP, hydrocort, pred, AZA, MTX, IVIg	Persistently active/ metastatic/died, nasopharyngeal carcinoma
16	68	Female	Chinese	Bowel/adenocarcinoma	IIIC	Chemotherapy, radiotherapy	-7	MP, hydrocort, IVIg	Active/metastatic/died, pneumonia
17	77	Female	Chinese	Non-Hodgkin lymphoma/diffuse large B-cell lymphoma	IVA	Chemotherapy	-48	Hydrocort	Active/care transferred, no available information/ died, no available information
18	80	Female	Malay	Lung/adenocarcinoma (EGFR exon21 L858R)	IV	Chemotherapy, tyroxine kinase inhibitor	0	Hydrocort, pred, HCQ, AZA	Persistently active/ metastatic/died, no available information
19	96	Female	Chinese	Cervical	II	Radiotherapy	-6	Hydrocort, pred, HCQ	Improved and stable/ metastatic/died, myocardial infarction and infection
20	42	Male	Chinese	Nasopharyngeal/ undifferentiated	IVB	Surgery, chemotherapy, radiotherapy	0	MP, hydrocort, pred, HCQ, AZA, CsA, IVIg	Persistently active/ metastatic/died, nasopharyngeal carcinoma
21	74	Male	Chinese	Non-Hodgkin lymphoma/zone lymphoma, MALT	I	Surgery	-45	MP, hydrocort, pred, HCQ, AZA, MMF, IVIg	Improved and stable/remission/ died, intracerebral haemorrhage
22	77	Male	Chinese	Lung/non-small cell lung carcinoma	IIIA	Chemotherapy	-10	Hydrocort, pred	Persistently active/ metastatic/died, pneumonia
23[b]	89	Male	Chinese	Bowel	IV	Surgery	-288	MP, hydrocort, pred, IVIg	Active/relapse/died, colorectal cancer

AZA: azathioprine; CsA: ciclosporin; EGFR: epidermal growth factor receptor; HCQ: hydroxychloroquine; hydrocort: hydrocortisone; IVIg: intravenous immunoglobulin; MALT: mucosa-associated lymphoid tissue; MMF: mycophenolate mofetil; MP: methylprednisolone; MTX, methotrexate; pred: prednisolone

[a] Patient returned to the neighbouring home country after initial management at our centre.

[b] Patient was first diagnosed with ascending colon carcinoma 288 months prior to dermatomyositis diagnosis and underwent hemicolectomy with adjuvant chemotherapy. Interval surveillance did not reveal cancer recurrence. Presumptive recurrence of metastatic cancer at diagnosis of dermatomyositis with mass at the gastroesophageal junction and metastatic lesions to liver and lung; patient declined scopes and biopsy.

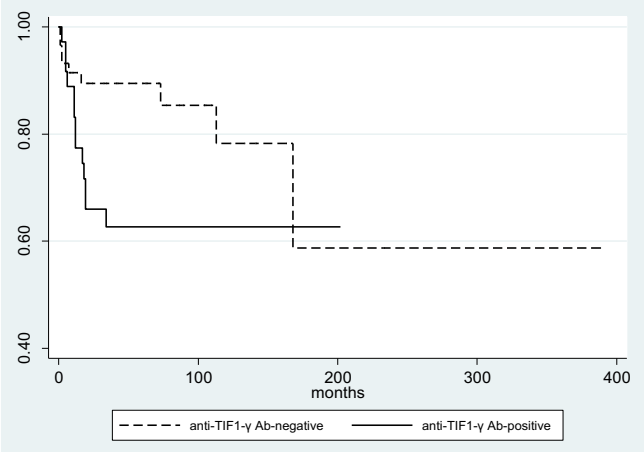

Fig. 1. Kaplan-Meier survival estimates for patients with anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1-γ Ab)-positive and anti-TIF1-γ Ab-negative dermatomyositis.

Thirteen patients (56.5%) received intravenous immunoglobulins (IVIg) as a corticosteroid-sparing agent for treating dermatomyositis while receiving concurrent cancer-treatment therapies. Among these 13 patients, 6 improved and remained stable, 1 improved but sustained a relapse of dermatomyositis, and 6 died. Of the latter 6, 5 had advanced cancers of at least stage III or worse. Other immunomodulators used in our patients were hydroxychloroquine (13), azathioprine (10), methotrexate (7), ciclosporin (4), and mycophenolate mofetil (2). More CAM survivors (8/13, 61.5%) received immunomodulators compared to those who died (4/10, 40.0%).

Survival analysis

A total of 23 mortalities occurred among the 96 dermatomyositis patients (24.0%) during the follow-up period. The mortality rate was significantly higher in anti-TIF1-γ Ab-positive (n=13, 36.1%) compared to the Ab-negative group (n=10, 16.7%, P=0.031). Within the anti-TIF1-γ Ab-positive group, mortality was higher in those patients with malignancy (n=10, 76.9%) than those without (n=3, 23.1%). Among the CAM mortalities, 8/10 (80.0%) had advanced cancers of at least stage III or worse. Kaplan-Meier survival curves (Fig. 1) revealed a significant difference in survival times between both groups, with 24-month survival in the anti-TIF1-γ Ab-positive group at 66%, and 89% in the anti-TIF1-γ Ab-negative group (log-rank test P=0.0153).

DISCUSSION

To our knowledge, this is the first study that describes the clinical profile and outcomes of patients with anti-TIF1-γ Ab-positive dermatomyositis in a multiethnic Southeast Asian cohort. Our results revealed a significantly higher prevalence of malignancy among anti-TIF1-γ Ab-positive dermatomyositis patients compared to Ab-negative ones (63.9 vs 8.3%) with a diagnostic odds ratio (DOR) of 19.1 (95% CI 6.1–59.8; P<0.001). This is consistent with the reported overall DOR of 9.37 (95% CI 5.37–16.34) among anti-TIF1-γ Ab-positive IIM patients in a meta-analysis performed by Best et al.[30] The sensitivity and specificity of anti-TIF1-γ Ab for CAM diagnosis in our study were 82.14% and 80.88%, respectively, indicating its value in predicting CAM. The median time interval between cancer and dermatomyositis diagnosis in the Ab-positive patients was 0 month, with interquartile range of 8.5 months before and 2 months after dermatomyositis diagnosis. Eighteen CAM patients (78.3%) had cancer in the period of 13 months before and 4 months after dermatomyositis diagnosis. Our study, therefore, agrees with the observation that cancers were more likely to be diagnosed during the year before and after myositis onset, with a progressive decrease thereafter that has been reported in other studies.[1]

In terms of clinical features, the presence of cutaneous manifestations like heliotrope rash, shawl sign, periungual erythema, holster sign, and Gottron's papules, as well as dysphagia were significantly more common in our anti-TIF1-γ Ab-positive group compared with the Ab-negative group. On the other hand, the findings of interstitial lung disease and polyarthritis were significantly uncommon. These clinical features are congruent with other reports and would be useful in describing the anti-TIF1-γ Ab-positive dermatomyositis phenotype in places where testing of MSA/MAAs is not readily accessible.[1]

Contrary to the observations made by Oldroyd et al. and Fujimoto et al., where no patients with anti-TIF1-γ Ab-positive CAM developed cancer below age 39 years, 2 of our patients developed cancer below this age. Our findings indicate the need to exercise high vigilance in cancer screening among anti-TIF1-γ Ab-positive dermatomyositis patients regardless of age, particularly those with a family history of cancer.[14,31]

In terms of cancer types, almost all CAM patients suffered from solid organ cancers (26/28, 92.9%) vs haematological malignancy (2/28, 7.1%). These findings were consistent with the observations made by Best et al. in a meta-analysis of 18 studies on adult dermatomyositis patients, which found a higher prevalence of solid organ cancers (19.9%) compared with haematological malignancies (1.4%).[30] Among all anti-TIF1-γ Ab-positive dermatomyositis patients, NPC and breast cancer were the most prevalent malignancies (each 6/23, 26.1%); NPC was the most common cancer among males (3/6, 50%) and second-most common cancer

among the females (3/17, 17.6%). A similar observation on the high prevalence of NPC among Asian CAM patients was made in various studies before TIF1-γ was discovered and/or MSAs/MAAs were widely tested.[4-9]

Breast cancer was the most common cancer among anti-TIF1-γ Ab-positive dermatomyositis female patients (6/17, 35.3%) in our study, which was similar to a large UK-based adult dermatomyositis cohort study by Oldroyd et al.[14] However, unlike the UK cohort, none of our patients had ovarian cancer.[14] In a separate Scandinavian cohort study, ovarian cancer was the most common cancer followed by breast cancer in female dermatomyositis patients.[2] Breast cancer was not found to be the most common cancer among a Korean cohort, but ovarian cancers were reported among the same group of CAM patients.[32] Overall, these findings indicate significant variability in the types of cancers found in CAM patients dependent on geographical location, and therefore cancer screening programmes need to take local disease patterns into account.

Given the strong association between dermatomyositis and malignancy, especially NPC, our centre has developed a specific cancer screening programme for newly diagnosed dermatomyositis patients. On diagnosis, patients undergo an MRI neck/PNS, CT thorax/abdomen-pelvis, an ENT review, OGD and colonoscopy. Females also undergo an MMG and Pap smear. In the higher cancer-risk anti-TIF1-γ Ab-positive group, more stringent cancer screening in the immediate 3 years after dermatomyositis diagnosis is offered. This programme includes a 4-monthly ENT review and yearly CT neck/thorax/abdomen-pelvis. Annual MMG and Pap smears are offered to females. The ENT review for NPC surveillance comprises (1) oral cavity examination, (2) endoscopy of the aero-digestive tract (nasal cavity, nasopharynx, oropharynx and hypopharynx), (3) examination for cervical lymph nodes, and (4) ear examination to look for middle ear effusion. For anti-TIF1-γ Ab-negative dermatomyositis patients, a 6-monthly otolaryngology review is offered, and the remaining imaging and Pap smear are repeated based on conventional age/sex-specific screening recommendations and initial surveillance results. The frequency of repeated endoscopy depends on findings from the initial assessments for all patients. Tumour markers are not mandated or used in isolation for cancer screening due to their low sensitivity in the early stages of malignancy.[1,35]

IVIg with high-dose glucocorticoids was used at onset in most of our CAM patients. Commonly used immunosuppressants to induce remission in severe IIM patients, such as cyclophosphamide and mycophenolate mofetil, were generally not used initially, avoided or delayed, as patients were often commenced on chemotherapy agents at the time of diagnosis. The evidence on the efficacy of IVIg for CAM remains sparse and is limited by the poor long-term patient outcome from concomitant malignancy, with very few case reports and small retrospective studies performed to date.[36-40] Despite this, we feel that a reasonable approach is to treat CAM patients with prednisolone (1mg/kg/day) and/or IVIg. We note that Selva-O'Callaghan et al. recommend treating CAM patients with prednisolone, IVIg (2g/kg/month) and/or ciclosporin (3–5mg/kg/day), in view of the overall immunomodulatory vs immunosuppressive roles of these agents.[1] In addition, we work closely with oncologists and surgeons to coordinate therapeutic plans in order to optimise patients for surgery if required and avoid potential drug interactions between chemotherapy and immunosuppressive therapeutics.

Limitations included the retrospective nature of this study, which may lead to inaccuracies in the identification of the exact onset of dermatomyositis, resulting in under- or over-estimation of the temporal relationship between the onset of dermatomyositis and cancer occurrence. Further, our centre neither repeats MSA/MAA test following dermatomyositis/cancer treatment nor measures anti-TIF1-γ Ab titres routinely, and hence no conclusions can be drawn on using anti-TIF1-γ Ab tires as biomarkers.[14,34]

CONCLUSION

This study confirms the strong association between anti-TIF1-γ Ab positivity and malignancy in dermatomyositis patients and the long-term temporal relationship between the onset of dermatomyositis and cancer in these patients. Most Ab-positive CAM patients developed cancers in the interval of 1 year before and 1 year after dermatomyositis-onset and are ≥39 years of age at the onset of dermatomyositis. There was a higher prevalence of solid cancers, and NPC and breast cancer were the most common malignancy in our study population. When managing dermatomyositis patients, we recommend additional attention on cancer screening be paid towards those who are anti-TIF1-γ Ab-positive, at the time of dermatomyositis diagnosis, and for at least the subsequent 3 years. Although older patients are at higher risk of developing cancers, younger anti-TIF1-γ Ab-positive patients are not spared the risk of malignancy and should also undergo routine screening. In terms of screening strategy, a customised approach based on local cancer trends should be taken.

Ethics

This study complies with the Declaration of Helsinki. Ethics approval was granted. Waiver of patient consent was also granted by the ethics committee as strict Singapore Personal Data Protection Act guidelines were observed and data collected would facilitate improvement in future patient care.

Data availability statement

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

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ORIGINAL ARTICLE

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Low skeletal mass predicts poor prognosis of elderly patients after emergency laparotomy: A single Asian institution experience

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ABSTRACT

Introduction: Sarcopenia, defined as low skeletal muscle mass and poor muscle function, has been associated with worse postoperative recovery. This study aims to evaluate the significance of low muscle mass in the elderly who require emergency surgeries and the postoperative outcomes.

Method: Data from the emergency laparotomy database were retrieved from Khoo Teck Puat Hospital, Singapore, between 2016 and 2019. A retrospective analysis was performed on patients aged 65 years and above. Data collected included skeletal muscle index (SMI) on computed tomography scan, length of stay, complications and mortality. Low muscle mass was determined based on 25th percentile values and correlation with previous population studies.

Results: A total of 289 patients were included for analysis. Low muscle mass was defined as L3 SMI of <22.09cm^2/m^2 for females and <33.4cm^2/m^2 for males, respectively. Seventeen percent of our patients were considered to have significantly low muscle mass. In this group, the length of stay (20.8 versus 16.2 P=0.041), rate of Clavien-Dindo IV complications (18.4% vs 7.5% P=0.035) and 1-year mortality (28.6% vs 14.6%, P=0.03) were higher. Further multivariate analysis showed that patients with low muscle mass had increased mortality within a year (odds ratio 2.16, 95% confidence interval 1.02–4.55, P=0.04). Kaplan-Meier analysis also shows that the 1-year overall survival was significantly lower in patients with low muscle mass.

Conclusion: Patients with low muscle mass have significantly higher post-surgical complication rates and increased mortality.

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Keywords: Emergency laparotomy, geriatrics, mortality, postoperative outcome, sarcopenia

INTRODUCTION

Emergency laparotomy (ELAP) for elderly patients is associated with higher mortality and increased postoperative complications compared with those undergoing elective surgery.[1-3] Elderly patients, who are more likely to have comorbidities, have lower functional reserves to cope with the increased physiological demand due to their acute illness and eventual surgical stress. Studies have shown that elderly patients tend to fare poorer postoperatively—including higher mortality rate,[3] functional decline and loss of independence, with an increased likelihood of discharge to nursing homes and step-down units.[4] Due to the global trend of an ageing population, we are increasingly performing ELAP for elderly patients. This will inherently lead to poorer surgical outcomes and the increased utilisation of more resources.[5,6] Surgeons must now gain a better understanding of the fundamental pathophysiology of the elderly that distinctly affects their perioperative care.

There has been growing interest in frailty and sarcopenia, and their relationship with surgical outcomes.[7,8] Frailty is described as a geriatric syndrome primarily determined by physical function and overlaps with sarcopenia, the loss of muscle mass.[9,10] Sarcopenia is widely regarded as a marker of poor health and suggestive of chronic illness, which makes patients more vulnerable to poor outcomes.[11,12] The definition and diagnosis of sarcopenia are still evolving as new findings challenge current understanding.[13]

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CLINICAL IMPACT

What is New

- Elderly patients with low muscle mass have an increased risk of complications and mortality following emergency surgeries.
- Low muscle mass can be determined using available computed tomography (CT) images often available in the emergency setting to calculate CT-derived L3 skeletal mass index values. This provides a quick and simple way to identify at-risk populations and guides clinical decision-making without additional procedures or costs.

Clinical Implications

- The study highlights the importance of identifying elderly with low muscle mass and poor surgical outcomes.
- CT-derived L3 skeletal muscle index could facilitate accurate postoperative prognostication and clinical decision-making.

Recently, the Asian Working Group on Sarcopenia (AWGS) and the International Working Group on Sarcopenia have defined sarcopenia as low muscle mass and poor muscle function in older people.[10,13] A growing body of literature has focused on this definition of sarcopenia and its effect on postoperative outcomes. Studies have shown its association with higher mortality and morbidity in emergency[14-16] and elective operations for gastric cancer,[17] pancreatic cancer,[18] liver tumours[19] and colorectal cancer.[20]

Based on recent consensus, low skeletal muscle mass remains crucial in establishing sarcopenia diagnosis.[21,22] Furthermore, AWGS 2019 recommends screening for sarcopenia by measuring calf circumference as it has moderate-to-high sensitivity and specificity in predicting sarcopenia or low skeletal muscle mass.[21] In addition, existing strength and performance assessments, which involve specialised clinical tests such as measurement of gait speed and hand grip strength assessment, can be time-consuming and labour-intensive, requiring specially trained professionals to assess.[23] However, the precarious conditions of critically ill patients and the relatively limited time before surgery make these examinations impractical in the emergency setting.

On the other hand, computed tomography (CT) scans, which are almost always performed preoperatively in emergencies for diagnostic reasons, are readily available. They can be used to quantify muscle mass and aid in screening sarcopenia owing to their ability to separate fat from other soft tissues. CT is also considered to be the gold standard for non-invasive assessment of muscle quantity/mass.[22] Recent studies have shown that CT-derived low muscle mass measurements may indicate sarcopenia.[24] The cross-section skeletal muscle index (SMI) at the L3 level can predict overall skeletal muscle mass.[25,26] Therefore, it provides the opportunity to quantify muscle mass promptly with no additional cost.

In this study, we looked at SMI values measured via muscle area at the L3 level on CT scans to assess if lower muscle mass was a predictor of poor outcomes for elderly patients who underwent ELAP. Although many studies have looked at sarcopenia and postoperative outcome, there is no consensus on a cut-off value for SMI that correlates to the reported outcomes, as it varies with different population groups. Given the difference in body size, lifestyle, and background of the Asian population compared to Caucasians,[13] the cut-off in the Asian population is likely to differ. Our study is also pioneering in Singapore to correlate CT-derived SMI scores with postoperative outcomes.

METHOD

Study population

Patients were selected from the Emergency Laparotomy Pathway Database of Khoo Teck Puat Hospital, Singapore. The database was developed with criteria modelled after the National Emergency Laparotomy Audit in the UK.[27] All general surgery patients undergoing laparotomies had their details, surgical procedure and the outcome recorded in our database. Patients over 65 years of age were reviewed by a geriatric specialist postoperatively. Procedures involving subspecialists such as hepatopancreatobiliary, vascular and gynaecological surgeries were excluded. For this study, a retrospective analysis was done on patients aged 65 years and above between 2016 and 2019. Clinical variables for our study included age, sex, race/ethnicity, American Society of Anesthesiology (ASA) score, Charlson Comorbidity Index, type of operative procedures and the indications for surgery. This study was approved by the National Health Group Domain Specific Review Board.

Outcomes assessments

Our primary outcomes were that of 30-day and 1-year mortality. Secondary outcomes include the length of stay in the acute hospital, Clavien-Dindo grade III and above complications, and discharge destination.

Image analysis: Screening for sarcopenia

A retrospective analysis of CT images was done for the patients identified. The skeletal and psoas muscle area was analysed using our hospital's radiology system (Centricity version 6.0, GE Healthcare, Chicago, US). The cross-sectional area of skeletal muscle was measured manually, outlining the skeletal muscles using a freehand region of interest (ROI) tool. Measurements were done by a medical student and a junior radiologist, both trained by a senior radiologist following a predefined method of ROI measurement. A consultant radiologist then rechecks the dataset and key images to confirm the measurements. The readers and consultant radiologists were blinded to the clinical outcomes. Skeletal muscle area (SMA) in cm^2 was derived by radiodensity measurement in Hounsfield units (HU) and defined by a HU range of −29 to +150. Measurements were obtained for all the skeletal and psoas muscles in a single 3mm slice at the mid-L3 level (Fig. 1). These muscle area values were then normalised by the patient's height to calculate the skeletal muscle index (SMI = total SMA divided by height squared) for each patient.

We initially used the cut-off for SMI based on the study population's lowest quartile, or the 25th percentile. This methodology is commonly described in various papers reporting the link between low skeletal mass and postoperative outcome.[28-30] These values were determined to be 33.4 and 26.3cm^2/m^2 in males and females, respectively. However, based on a local epidemiological population study by the Yishun Study group,[31] they have determined that the SMI cut-off for the female group was lower at <22.09cm^2/m^2. Our study data did not exhibit a normal distribution, so the 25th percentile data may not have accurately defined low muscle mass. Hence, we use the SMI values of <22.09cm^2/m^2 for females as a radiographic threshold to better represent low muscle mass. Cut-off for males remains at <33.4cm^2/m^2.

Statistical analysis

Data were summarised with descriptive statistics using SPSS Statistics software version 28.0 (IBM Corp, Armonk, US). Differences between the 2 groups (low muscle against normal muscle mass) were assessed using Student's t-test for continuous data and Pearson's chi-square test or Fisher's Exact test for categorical data where appropriate. Fisher's Exact test calculated *P* values for small sample sizes (when more than 20% of cells have expected cell counts >5). Mann-Whitney U test was used to compare the median length of stay across both groups.

Multivariate analysis was used to examine the association between low muscle mass and mortality by estimating the odds ratio (OR) of association and their 95% confidence interval (CI). The test accounted for confounding by adjusting for the patient's age, Charlson Comorbidity Index and malignant disease. These factors were chosen as they are biomarkers related to the geriatric population and have a known influence on survival. Kaplan-Meier survival curves were used to illustrate the relationship between the 2 groups and survival. Follow-up was censored one year after surgery, and a patient was deemed a censored case when they were alive at the end of 1 year post-surgery. *P* values for the survival curves were determined using the log-rank test from the Kaplan-Meier survival curves. Results with $P<0.05$ are considered statistically significant.

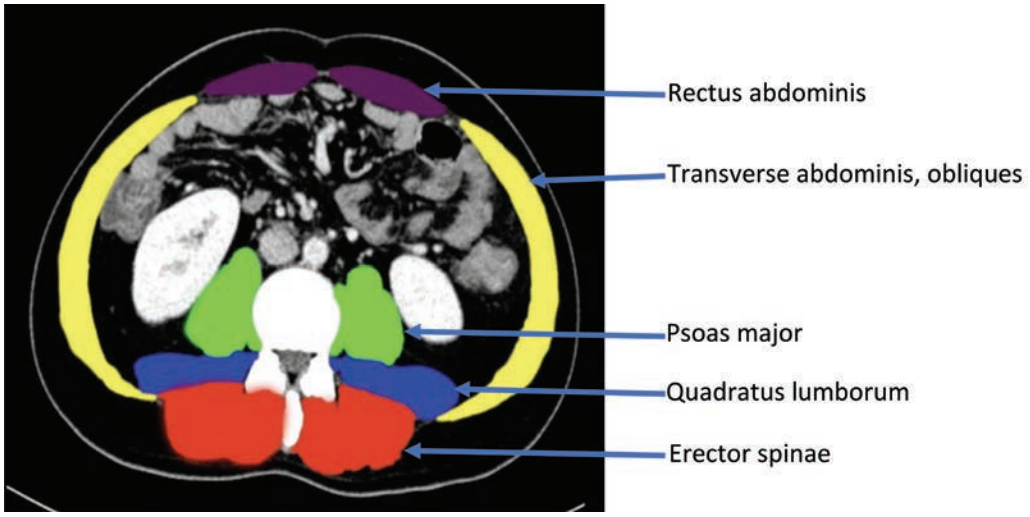

Fig. 1. Sample image of L3 skeletal muscle index measurement on computed tomography imaging.

RESULTS

Between 2016 and 2019, there were 302 emergency laparotomies performed in Khoo Teck Puat Hospital on patients aged 65 years old and above. Thirteen cases were excluded as they did not have preoperative CT scans. A total of 289 cases were analysed and had their L3 SMI calculated. The most common pathology resulting in surgery was due to bowel obstruction (63%), followed by perforation (24%), bowel ischaemia (9%) and others (4%), which include haemorrhage, severe abdominal infection and anastomotic leakage. Thirty percent of these operative cases were malignant in nature.

Based on our SMI cut-off (female SMI <22.09, male <33.4), 17% of our patients were considered to have low muscle mass at presentation. As shown in Table 1, both groups were comparable for most demographic variables except that patients with low muscle mass are older (mean age 78 years vs 75 years), and there were more male patients (75.5%). No statistical difference was observed in the incidence of malignant cases between both groups (34.7% in the low muscle group and 28.3% in the normal muscle mass group, *P*=0.47).

When examining the clinical outcomes for both groups (Table 2), patients with low muscle mass had a higher rate of Clavien-Dindo IV complications (18.4% vs 7.5%, *P*=0.035), a longer overall length of stay (20.8 vs 16.2 days, *P*=0.041) and a lower rate of discharge to own home (46.9% vs 63.3%, *P*=0.048). In terms of mortality, patients with low muscle mass had a higher 30-day and 1-year mortality rate, but only differences seen at 1-year mortality were deemed statistically significant (28.6% vs 14.6%, *P*=0.03). Further multivariate analysis (Table 3) showed that patients with low muscle mass were twice as likely to die within 1 year of surgery (OR=2.16, 95% CI 1.023–4.550, *P*=0.043). Cancer patients also had a greater likelihood of 1-year mortality among those that underwent emergency laparotomy (OR 2.756, 95% CI 1.441–5.270, *P*=0.002). The Kaplan-Meier analysis (Fig. 2) shows that the 1-year overall survival differs significantly between the low and normal muscle mass groups (*P*=0.014). The low muscle mass group had a steeper decline rate, particularly within the first half of the year.

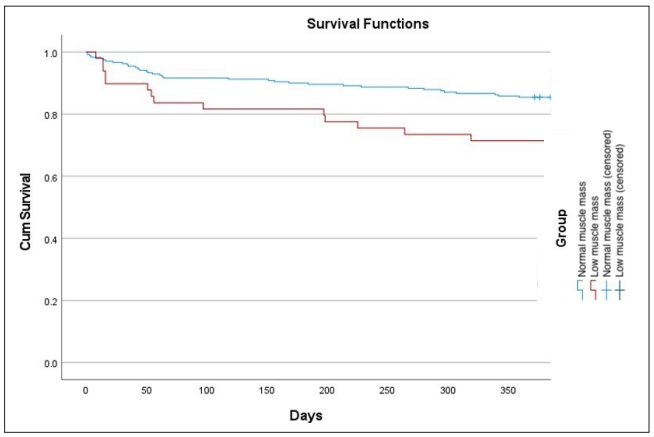

Fig. 2. Kaplan-Meier analysis of 1-year overall survival between low and normal muscle mass groups.

DISCUSSION

The rapid ageing of populations around the world presents an unprecedented set of challenges, with shifting disease burdens and increased health expenditure.[32] The world now sees a paradigm shift in geriatric surgical care, with increasing attention focused on the quality of life and survival outcomes postoperatively.[33] Host-related factors, including premorbidities and body muscle composition, often have a significant association with survival postoperatively. In many studies, reduced skeletal muscle mass, or sarcopenia, has led to worse overall outcomes.[15,16] Therefore, preoperative diagnosis of sarcopenia may be imperative in clinical decisions for considering an alternative approach to divert an acute surgical emergency to a semi-emergent one. This would buy time for these patients, to be optimised medically in the emergency setting prior to a major surgery.

During an emergency, the additional evaluation of preoperative CT-derived L3 SMI value, based on a pre-existing readily available CT, can add to the current armamentarium of risk stratification tools to predict higher morbidity and mortality in patients whose values fall below the cut-off. Thus, L3 SMI values can be used to predict outcomes, aid in preoperative counselling, and manage patient and family expectations. In addition, using CT-derived L3 SMI values in surgical risk prediction in an emergency set-up is attractive for several reasons. Many studies have consistently demonstrated the ease of using routine staging CT scans to measure body composition.[21,22,24,26,30] The issue of radiation exposure is irrelevant, as most patients already have the required imaging for diagnostic or preoperative planning purposes. Secondly, while sarcopenia has also been associated with poor grip strength, muscle mass analysis, and gait speed, these assessment tools are often impractical to execute in the emergency setting. It may also be challenging for acutely ill and frail elderly patients to comply with such assessment tests. On the contrary, cross-sectional views of trunk musculature on CT scans can provide a quick, practical and objective method for estimating lean muscle mass in an emergency setting.

Table 1. Demographic and baseline characteristics of the study population

	Low muscle mass (female: SMI <22.09, male: SMI <33.4)	**Normal muscle mass**	***P***
Total cases, N	49	240	-
Age, mean ± SD, years	78 ± 6	75 ± 7	**0.000**
Sex			
Male	37 (75.5)	130 (54.2)	**0.009**
Female	12 (24.5)	110 (45.8)	
Ethnicity, n (%)			
Chinese	37 (75.5)	179 (74.6)	0.892
Malay	9 (18.4)	43 (17.9)	0.940
Indian	2 (4.1)	14 (5.8)	1.000
Others	1 (2.0)	4 (1.7)	1.000
Charlson Comorbidity Index, mean ± SD	4.9 ± 2.3	4.5 ± 1.9	0.187
Charlson Comorbidity Index, median (range)	4 (2–13)	4 (1–11)	-
American Society of Anesthesiologists (ASA) score, n (%)			
1	3 (6.1)	6 (2.5)	0.182
2	12 (24.5)	81 (33.8)	0.273
3	26 (53.1)	119 (49.6)	0.774
4	8 (16.3)	32 (13.3)	0.744
5	0	2 (0.8)	-
3–5	34 (69.4)	153 (63.7)	0.556
Pathology, n (%)			
Benign	32 (65.3)	172 (71.7)	0.472
Malignant	17 (34.7)	68 (28.3)	-
Indication for surgery, n (%)			
Intestinal obstruction	22 (44.9)	117 (48.8)	0.738
Gastric/bowel perforation	15 (30.6)	56 (23.3)	0.370
Bowel ischaemia	4 (8.2)	23 (9.6)	1.000
Adhesiolysis	8 (16.3)	36 (15.0)	0.986
Others*	0	8 (3.3)	0.359

SMI: skeletal muscle index; SD: standard deviation
* Include anastomotic leak, haemorrhage and abdominal infection

The assessment of sarcopenia has been performed in various contexts and populations using different tools. One component of assessment is to quantify skeletal muscle mass through a reduced CT-derived SMI. Unfortunately, the current literature for defining sarcopenia using CT-derived L3 SMI is heterogenous, with various statistical methods and cut-off values utilised in different populations and contexts. Not surprisingly, the varying cut-off values in other population groups can be attributed to diverse demographics or even to differing physiques between Asians and their Western counterparts.[13]

While lower L3 SMI values are unequivocally associated with poorer survival,[34] the challenge remains

Table 2. Comparison of clinical outcomes between low and normal muscle mass groups

Clinical outcomes	Low muscle mass (n=49)	Normal muscle mass (n=240)	*P*
Postoperative complications, n (%)			
Clavien-Dindo III	1 (2.0)	13 (5.4)	0.477
Clavien-Dindo IV	9 (18.4)	18 (7.5)	**0.035**
Clavien-Dindo V	4 (8.2)	9 (3.8)	0.245
Clavien-Dindo III–V	14 (28.6)	40 (16.7)	0.081
Hospital length of stay			
Overall length of stay, mean ± SD, days	20.8 ± 14.8	16.2 ± 14.0	**0.041**
Overall length of stay, median (IQR), days	16.0 (9.5–27.5)	12.0 (8.0–18.0)	**0.016**
Critical care days, mean ± SD	7.2 ± 6.8 (n=31)	6.4 ± 7.6 (n=125)	0.608
Critical care days, median (IQR)	2.0 (0–6.0)	1.0 (0–4.0)	0.110
Discharge facility			
Home	23 (46.9)	152 (63.3)	**0.048**
Other acute hospitals	0	1 (0.4)	-
Community hospitals	19 (38.8)	74 (30.8)	0.359
Nursing homes	2 (4.1)	4 (1.7)	0.270
Overall mortality			
30-day mortality	5 (10.2)	9 (3.8)	0.068
90-day mortality	8 (16.3)	20 (8.3)	0.145
1-year mortality	14 (28.6)	35 (14.6)	**0.030**

IQR: interquartile range; SD: standard deviation

Table 3. Multivariate analysis of factors associated with 1-year mortality

	Odds ratio	95% confidence interval		*P* value
		Lower	Upper	
Age ≥75 years	1.710	0.873	3.347	0.118
Charlson Comorbidity Index ≥5	1.713	0.888	3.304	0.108
Malignancy	2.756	1.441	5.270	**0.002**
Low muscle mass	2.158	1.023	4.550	**0.043**

to establish an appropriate cut-off value that best predicts negative outcomes. In our study, by establishing the 25th percentile of L3 SMI values for our Singapore population undergoing emergency laparotomy, we identified the values for low muscle mass as <33.4cm^2/m^2 and <26.3cm^2/m^2 in males and females, respectively, to prognosticate poorer outcomes. Previous studies have used the 25th percentile of the study population as an indicator of sarcopenia with a normal distribution of enrolled cases.[28-30] However, since the SMI data in this study did not show a normal distribution, using the 25th percentile was not robust enough to measure a significant difference in outcomes. As such, to better refine our Singapore diagnostic criteria for low muscle mass, we correlated our data with a similar population-based study conducted by Pang et al.[31] The latter seeks

to describe the prevalence of elderly with low skeletal muscle mass among community-dwelling adults according to the Asian Working Group for Sarcopenia criteria, 2019 (AWGS2019),[21] and European Working Group on Sarcopenia in Older People criteria, 2018 (EWGSOP2) guidelines.[22] Pang et al. identified the appendicular lean mass (ALM) sarcopenia cut-off measured using dual-energy X-ray absorptiometry for this population. This was determined to be 5.28kg/m^2 and 3.69kg/m^2 in males and females, respectively.[31] Using a linear regression model previously formulated to determine the relationship between ALM and SMI, the SMI cut-off for sarcopenia in this local population was extrapolated to be <37.4cm^2/m^2 and <22.09cm^2/m^2 for males and females, respectively.[31] We selected the lower threshold for SMI values of <33.4cm^2/m^2 and <22.09cm^2/m^2 for both males and females, respectively, and subsequently showed that they could predict statistically significant negative outcomes. Significantly, we were able to establish the CT-derived L3 SMI values that could predict negative effects in our Asian population in Singapore.

Nevertheless, the retrospective nature of our study in a single institution limits the generalisability of our results. In addition, muscle strength and physical performance evaluations often described within the definition of sarcopenia were not measured in this study, as such examinations may not be feasible in acutely ill patients and there is limited time before surgery. There is also a lack of consensus surrounding sarcopenic thresholds; for example, the most frequently used cut-off points come from Martin et al.[35] and Prado et al.[36] Both studies used optimal stratification to define their cut-off points in a Canadian population of obese and mixed body mass index cohort of gastrointestinal and respiratory tract tumours.[35,36] Optimal stratification is one known and validated statistical tool used by other groups to identify cohort-specific cut-offs.[35] However, when applying Martin's or Prado's cut-offs, the prevalence of sarcopenia in published cohorts ranges from 41–47% and 15–60%, respectively.[35-37] In our Singapore data of patients above 65 years old who required emergency laparotomy, using these published cut-offs did not find any statistically significant adverse outcomes as such. Applying population-specific cut-off points by optimal stratification may be helpful only if they have not been previously defined in a similar population. There is not a universally accepted or easily generalisable cut-off value for low muscle mass, as we can naturally expect Asian cohorts to have a lower cut-off than their Caucasian counterparts.[13,21] The pitfall in using a reference cut-off value lies in its generalisability due to inherent differences in population demographics. Using a cut-off value will be appropriate and meaningful only when validated within the native population.

CONCLUSION

In conclusion, the literature on sarcopenia and adverse outcomes rapidly evolves and continues to gain traction. Our data suggest that patients with low muscle mass requiring emergency surgeries have a higher risk of postoperative complications, an increase in the overall length of hospital stay, and a greater risk of 1-year mortality than those with higher muscle mass. The availability of CT-derived SMI scores preoperatively in the emergency setting may help with preoperative decision-making and predict postoperative outcomes. Emergency surgery in geriatric surgical patients remains an exciting field, and using CT-derived SMI value may revolutionise perioperative care and patient selection, as well as guide decisions for surgery.

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REVIEW ARTICLE

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Drug interactions between common dermatological medications and the oral anti-COVID-19 agents nirmatrelvir-ritonavir and molnupiravir

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ABSTRACT

Introduction: The oral antiviral agents nirmatrelvir-ritonavir (NMV/r) and molnupiravir are used to treat mild-to-moderate COVID-19 infection in outpatients. However, the use of NMV/r is complicated by significant drug-drug interactions (DDIs) with frequently prescribed medications. Healthcare professionals should be aware of the possible risk of DDIs, given the emergence of COVID-19 variants and the widespread use of oral COVID-19 treatments. We reviewed available data on DDIs between NMV/r, molnupiravir and common dermatological medications; summarised the potential side effects; and suggest strategies for safe COVID-19 treatment.

Method: A systematic review using PubMed was conducted on data published from inception to 18 July 2022 to find clinical outcomes of DDIs between NMV/r, molnupiravir and dermatological medications. We also searched the Lexicomp, Micromedex, Liverpool COVID-19 Drug Interactions database and the National Institutes of Health COVID-19 Treatment Guidelines for interactions between NMV/r and molnupiravir, and commonly used dermatological medications.

Results: NMV/r containing the cytochrome P-450 (CYP) 3A4 inhibitor ritonavir has DDIs with other medications similarly dependent on CYP3A4 metabolism. Dermatological medications that have DDIs with NMV/r include rifampicin, clofazimine, clarithromycin, erythromycin, clindamycin, itraconazole, ketoconazole, fluconazole, bilastine, rupatadine, dutasteride, ciclosporin, cyclophosphamide, tofacitinib, upadacitinib, colchicine and systemic glucocorticoids. With no potential DDI identified yet in in vitro studies, molnupiravir may be an alternative COVID-19 therapy in patients taking medications that have complicated interactions with NMV/r, which cannot be stopped or dose adjusted.

Conclusion: NMV/r has significant DDIs with many common dermatological medications, which may require temporary discontinuation, dosage adjustment or substitution with other anti-COVID-19 agents such as molnupiravir.

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Keywords: COVID-19, dermatology, drug interactions, molnupiravir, nirmatrelvir-ritonavir, pharmacology

INTRODUCTION

In December 2021, an Emergency Use Authorisation was issued by the U.S. Food and Drug Administration (FDA) for the use of the orally active antiviral medications nirmatrelvir-ritonavir (NMV/r, PAXLOVID) and molnupiravir (LAGEVRIO) in the treatment of patients with mild COVID-19, who are at risk of developing severe disease resulting in hospital admission or mortality.[1,2]

Unfortunately, the use of oral COVID-19 therapies is complicated by their significant drug-drug interactions (DDIs) with many medications. With the emergence of highly transmissible dominant variants such as the Omicron strain and its new subvariants BA.2.12.1, BA.4 and BA.5, coupled with the increasing use of oral COVID-19 therapies and the widespread use of dermatological medications by patients, it is crucial for physicians to recognise DDIs involving the most widely

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CLINICAL IMPACT

What is New

- To our knowledge, this is currently the most comprehensive and in-depth review on drug-drug interactions (DDIs) between the 2 current oral anti-COVID-19 agents—nirmatrelvir-ritonavir (NMV/r) and molnupiravir—and dermatological medications.

Clinical Implications

- Physicians should be aware of and cautious about possible DDIs when prescribing NMV/r in patients taking concomitant medications, including dermatological drugs.
- Molnupiravir may be a suitable substitute anti-COVID-19 agent for NMV/r, particularly when potential complicated DDIs have been identified between NMV/r and medications.

used COVID-19 oral agent, NMV/r, and dermatological medications. This can help to support safe decision-making and initiation of COVID-19 treatment as soon as possible after diagnosis, preferably within 5 days of symptom onset.

We aimed to consolidate and review available data on DDIs between NMV/r, molnupiravir and dermatological medications. We also aimed to provide a summary of potential adverse events, details of the expected duration of the *CYP3A4* gene-related inhibitory effect of ritonavir; and to suggest an appropriate management of co-medications that can potentially interact with NMV/r and molnupiravir.

METHOD

A systematic review (protocol registered with PROSPERO, CRD 42022346065) was conducted to identify the clinical outcomes of DDIs between NMV/r, molnupiravir and dermatological medications, using PubMed from inception to 18 July 2022. The search terms used were: dermatology* AND (nirmatrelvir OR ritonavir OR molnupiravir OR Paxlovid OR Lagevrio). Clinical studies reporting DDI between dermatological drugs and NMV/r or molnupiravir were included in the review. Articles without mention of DDI in the title or abstract were excluded. Conference articles, clinical images/photographic quizzes, as well as pharmacokinetic investigations without clinical outcomes were also excluded. Two authors independently reviewed the titles and abstracts, and the relevant papers were then selected for full-text review. Any disagreement was resolved by discussion with a third author.

The Lexicomp, Micromedex, Liverpool COVID-19 Drug Interactions database, and the National Institutes of Health COVID-19 Treatment Guidelines were also searched for DDIs between NMV/r and molnupiravir with commonly used dermatological medications from the time of inception to 18 July 2022. Lexicomp and Micromedex were selected as the drug interaction resources because of their completeness, accuracy and ease of use.[3,4] The Liverpool COVID-19 Drug Interactions[5] checker is a user-friendly and leading database for DDI with anti-COVID-19 drugs. Apart from their extensive DDI databases, these sources also conduct regular surveillance of ongoing pharmacovigilance and pharmaceutical publications, as well as announcements on new drug developments. In view of the inconsistency among drug interaction resources, we used more than one drug interaction resource.[6]

To predict potential drug interactions with NMV/r or molnupiravir concerning drugs without information in all 4 drug interaction resources, we referred to the pertinent drug monograph to determine whether the drug is an inhibitor, inducer, or substrate of the drug-metabolising enzymes (expressed by the following genes: *CYP3A4*, *CYP2D6*, *CYP2B6*, *CYP2C19*, *CYP2C9* and *CYP1A2*) and the P-glycoprotein. P-glycoprotein—also known as multidrug resistance protein 1, adenosine triphosphate (ATP)-binding cassette subfamily B member 1, and cluster of differentiation 243—is an important ATP-dependent efflux pump with broad substrate specificity, which transports many foreign substances out of the cells.

For drugs identified independently by 2 authors to have clinically significant interactions with NMV/r or molnupiravir, the individual drug prescribing information was reviewed for recommended actions, including the need for withdrawal, dosage reduction or continued use with close monitoring. Any disagreement was resolved by discussion, and further issues were escalated to a third author.

RESULTS

A total of 54 studies were screened, but none of the studies was relevant to be included in the systematic review. The published drug interaction resources, however, generated sufficient data to support our analysis, based on the drug monographs associated with NMV/r and molnupiravir, and on inferences from studies on ritonavir and other CYP450 3A4 enzyme inhibitors.

DISCUSSION

Nirmatrelvir-ritonavir (NMV/r)

Nirmatrelvir is an orally effective SARS-CoV-2 3-chymotrypsin-like protease inhibitor involved in the prevention of viral replication in COVID-19 and other coronavirus infections. It is co-administered with ritonavir, a pharmaco-enhancer and strong CYP450 3A4 enzyme inhibitor, to inhibit the metabolism of nirmatrelvir, a CYP3A4 substrate, to maintain the plasma drug concentration at therapeutic levels.[7]

NMV/r is currently the most effective oral antiviral therapy for COVID-19.[8] However, NMV/r might not be suitable for all patients due to its potential for significant DDIs with co-administered medications.

Drug-drug interactions

The main target molecules of DDIs of NMV/r include other CYP3A4 substrates, with ritonavir-mediated CYP3A4 inhibition, maximal within 48 hours from the first dose of NMV/r, producing an increase in drug plasma concentration, and in the risk of concentration-dependent toxicity.[9] The concomitant administration of NMV/r with CYP3A4 inhibitors raises the risk of adverse effects from NMV/r. In contrast, CYP3A4 inducers cause a significant reduction of antiviral therapeutic effect, with a potential for the development of viral resistance.

As ritonavir is an irreversible CYP3A4 inhibitor, these DDIs persist even after its discontinuation because time is required for the reduction in CYP3A4 inhibition through synthesis of new CYP3A4 enzyme in the microsomes of liver cells. A significant 80% resolution of CYP3A4 inhibition occurs by 48 hours and 72 hours after the last dose of NMV/r, in adults aged 20–50 years and >60 years, respectively.[10] Hence, in most individuals, a 3-day rule can effectively guide the management of DDI with NMV/r, since medications that interact with NMV/r may be safely restarted, or alternatively restored to their original dose, 3 days after the last dose of NMV/r.[10]

As the duration of NMV/r treatment for COVID-19 is only 5 days, many long-term dermatological medications with known drug interactions may be withdrawn or dose adjusted, where clinically appropriate, for a short 8 days to allow for safe treatment with NMV/r. Since NMV/r is currently the only highly effective oral antiviral therapy against COVID-19, DDI should be managed where feasible to allow its use.[8]

Systemic glucocorticoids

Short courses of oral glucocorticoids are used to treat severe acute exacerbations of atopic dermatitis. Many commonly used glucocorticoids, such as prednisolone and prednisone, are dependent on CYP3A4-mediated metabolism. Thus, co-administration with NMV/r can increase systemic glucocorticoid exposure and the risk of adverse effects, such as hyperglycaemia, adrenal suppression and Cushing's syndrome.[11] Recommendations include careful monitoring for the adverse effects.

Systemic immunomodulators

Ciclosporin is a calcineurin inhibitor used to prevent organ rejection. It is also used to treat severe resistant atopic dermatitis and psoriasis. As ciclosporin is primarily metabolised by hepatic and intestinal CYP3A4 enzymes, ritonavir-mediated CYP3A4 inhibition during concomitant administration will greatly elevate its plasma concentrations, with a significantly increased risk of ciclosporin toxicity, including nephrotoxicity, systemic hypertension and hepatotoxicity.[12] Vogel et al. demonstrated the interaction between ritonavir-boosted antiretroviral therapy and ciclosporin in liver transplant human immunodeficiency virus-infected patients.[13] They were observed to have flattening of absorption/elimination curves with little changes in plasma levels of ciclosporin over 12 hours and an increase of terminal half-life from 4–6 hours up to 38 hours.[13] Even though ciclosporin doses in liver-transplant patients are much higher than those for dermatology patients, elevated ciclosporin levels due to slower clearance is expected with dermatological use of ciclosporin. In view of a significantly increased risk of ciclosporin toxicity during concomitant administration with NMV/r, it is recommended to discontinue ciclosporin during NMV/r treatment, and resume it 3 days after the last dose of NMV/r.

Cyclophosphamide, an alkylating agent, is used in cytotoxic chemotherapy for cutaneous T-cell lymphomas and in the treatment of severe, refractory autoimmune skin conditions.[14] It is administered as a prodrug requiring activation by hepatic CYP450 enzymes, including CYP2B6 and to a lesser extent, CYP3A4. As ritonavir is a CYP2B6 inducer, the concomitant use of cyclophosphamide with NMV/r results in increased risk for toxic effects such as oral mucositis and neutropaenia, for which patients must be monitored carefully.[15] Patients with genetic variants associated with reduced CYP2B6 function may be less affected than those with increased CYP2B6 function.[16]

Janus kinase (JAK) inhibitors are a relatively new treatment for autoimmune diseases such as psoriatic arthritis, for which tofacitinib and upadacitinib have both been approved for use—the latter recently approved by FDA for atopic dermatitis as well.[17,18]

The metabolism of both tofacitinib and upadacitinib is mediated primarily by hepatic CYP3A4, hence elevated plasma concentrations of the active drugs occur in co-administration with NMV/r via ritonavir-mediated CYP3A4 inhibition. For tofacitinib, a maximum of 5mg once-daily dosing of the immediate-release formulation is recommended.[17] For upadacitinib, a maximum daily dose of 15mg is recommended.[18] Dose reductions should be carried out throughout the NMV/r treatment and for another 3 days from completion of the last NMV/r dose.

Abrocitinib, another JAK inhibitor recently approved for use in atopic dermatitis, is less dependent on CYP3A4 metabolism. Although elevated plasma concentrations are expected in co-administration of abrocitinib with NMV/r, their interaction has not been identified as clinically significant and there are no recommendations for dose adjustments or additional monitoring.[19]

Acitretin, apremilast, azathioprine, dimethyl fumarate, methotrexate, mycophenolate mofetil and sulfasalazine may be safely co-administered with NMV/r without expected clinically significant interaction. However, the risk of immunosuppressants such as azathioprine, methotrexate and mycophenolate mofetil exacerbating the COVID-19 infection should be weighed against the risk of a flare-up of the dermatological condition, before deciding whether to continue immunosuppressants during the COVID-19 infection.[20]

Table 1. Preferred systemic dermatologic medications during nirmatrelvir-ritonavir use[a]

Immunomodulators	**Anti-acne agents**
Acitretin	Isotretinoin
Apremilast	Spironolactone
Azathioprine	
Baricitinib	**Hair agents**
Dimethyl fumarate	Finasteride
Methotrexate	Minoxidil
Mycophenolate mofetil	
Sulfasalazine	**Antibiotics**
	Azithromycin
Biologicals	Cephalosporins
Adalimumab	Dapsone
Anakinra	Isoniazid
Certolizumab	Metronidazole
Dupilumab	Penicillins
Etanercept	Pyrazinamide
Guselkumab	Sulfonamides
Infliximab	Tetracyclines
Ixekizumab	Tinidazole
Omalizumab	
Risankizumab	**Antifungals**
Rituximab	Griseofulvin
Secukinumab	Nystatin
Spesolimab	Terbinafine
Tildrakizumab	
Ustekinumab	**Antivirals**
	Aciclovir
Antihistamines	Valaciclovir
Buclizine	
Chlorpheniramine	**Antiscabetic agent**
Desloratadine	Ivermectin
Diphenhydramine	
Loratadine	**Miscellaneous: Statins**
	Fluvastatin
	Pravastatin

[a] Consult the Liverpool COVID-19 Drug Interactions website[5] for updated drugs

Superscript number: refer to REFERENCES

Biologicals

Treatment with biologicals (Table 1) may be safely continued during treatment with NMV/r, without dose adjustment or additional clinical monitoring, if the patient is clinically indicated to continue biologicals during the COVID-19 infection.

Antibacterial drugs

Macrolides such as clarithromycin and erythromycin are indicated for use in acne, rosacea, and staphylococcal skin infections. When co-administered with NMV/r, the CYP3A4-mediated metabolism of clarithromycin and erythromycin is inhibited by ritonavir, and the raised plasma concentration of these macrolides increases the risk of side effects (e.g. hepatotoxicity and QT-interval prolongation).[21,22] For erythromycin, it is recommended to stop use and replace it with other antibacterial drugs with less interaction with NMV/r. Examples include replacing erythromycin with tetracycline-class drugs for acne and rosacea, and penicillins or cephalosporins for staphylococcal skin infections, barring any drug hypersensitivity. For clarithromycin, which is less dependent on CYP3A4 metabolism than erythromycin, careful monitoring for adverse effects is suggested, with dose reduction required only in patients with renal impairment (Kidney Disease Improving Global Outcomes stage ≥3, with creatinine clearance [CrCl] ≤60mL/min). Clarithromycin prescribing information suggests dose reduction by 50% and 75% in patients with CrCl 30–60mL/min and <30mL/min, respectively.[22]

However, on use of clarithromycin in non-tuberculous mycobacterial infections, replacement by another antibiotic is recommended. Although co-administration of clarithromycin and ritonavir in NMV/r increases the plasma concentration of clarithromycin, there is a reduction in plasma concentration of the active metabolite 14-OH-clarithromycin. The efficacy of clarithromycin treatment might thus be compromised, and the physician should consider replacement with other antibiotics as appropriate.[22]

Clindamycin and clofazimine are 2 other antibacterials that depend on CYP3A4 metabolism, and therefore require careful monitoring for adverse effects.

Rifampicin, an anti-tuberculosis agent, is also used in patients with hidradenitis suppurativa, as well as in staphylococcal and non-tuberculous mycobacterial infections.[23] As a potent CYP3A4 inducer, the co-administration of rifampicin with NMV/r would produce decreased plasma concentrations of ritonavir, a CYP3A4 substrate. This can significantly decrease the therapeutic effect of NMV/r, leading to poor treatment outcomes and promoting the development of viral resistance to NMV/r.[24] Also, as the induction of CYP3A4 by rifampicin persists for a long time after discontinuation, it is not sufficient to stop rifampicin use before starting NMV/r therapy.[7] Therefore, it is recommended to consider an alternative COVID-19 treatment, such as molnupiravir, for patients on rifampicin.

Table 1 shows antibacterial drugs often used in skin disorders. The drugs lack an expected interaction with NMV/r, and may be safely continued during NMV/r treatment without dose adjustments or additional monitoring.

Antifungal agents

Systemic azoles, including fluconazole, itraconazole and ketoconazole, are commonly prescribed as oral treatment in extensive or resistant dermatophyte infections, pityriasis versicolor, and other cutaneous fungal infections. All the 3 azoles have significant DDIs with NMV/r as they inhibit CYP3A4 and would produce both raised plasma concentrations of NMV/r, and an increased risk of NMV/r adverse effects. Moreover, itraconazole and ketoconazole are also substrates of CYP3A4, and ritonavir-mediated CYP3A4 inhibition increases the bioavailability and plasma concentrations of these 2 azoles. This raises the risk of side effects, including gastrointestinal symptoms, transaminitis and QT-interval prolongation due to ketoconazole.

The recommendations for fluconazole include careful electrocardiogram (ECG) monitoring, as both fluconazole and ritonavir are known to prolong the QT interval; their concomitant use therefore increases the risk of an additive effect.[25] For itraconazole and ketoconazole, dose reduction to a maximum of 200mg daily is suggested, on top of monitoring for side effects.[26,27]

Antiparasitic agents

The antihelminthic agent albendazole, when co-administered with ritonavir, decreases the plasma albendazole concentration.[28] Thus, monitoring for a reduced clinical response to albendazole therapy is proposed in co-administration with NMV/r.

Antihistamines

Antihistamines are one of the most commonly prescribed drugs in dermatology, ranging from use in pruritic skin dermatoses to cutaneous hypersensitivity reactions, such as urticaria and angioedema.

Hydroxyzine is dependent on hepatic CYP3A4 metabolism; co-administration with the CYP3A4-inhibitor ritonavir will result in elevated hydroxyzine plasma concentrations, increasing the risk of adverse effects, such as QT-interval prolongation.[29] Recommendations include close ECG monitoring for a prolonged QT interval.

Bilastine and rupatadine are second-generation antihistamines with significant drug interactions with NMV/r, as they are dependent on P-glycoprotein-mediated efflux and CYP3A4 metabolism, respectively—both processes which are inhibited by ritonavir. The resultant increase in plasma concentrations of these antihistamines increases the risk of side effects like QT-interval prolongation. The Lexicomp Drug Interactions resource lists both bilastine and rupatadine as contraindicated for concomitant use during ritonavir administration.[30,31] Discontinuation of these antihistamines during the NMV/r treatment course and for an additional 3 days after the last dose of NMV/r is recommended.

Other second-generation antihistamines, such as cetirizine, fexofenadine and loratadine are also dependent on P-glycoprotein-mediated efflux and CYP3A4 metabolism. Drug interaction with ritonavir may result in increased central antihistaminic effects, including drowsiness and prolonged reaction times, but with a minimal risk of severe adverse effects such as QT-interval prolongation. As such, no dosage adjustment or additional monitoring is suggested.

The preferred choices of antihistamines during NMV/r treatment include desloratadine, chlorpheniramine, diphenhydramine and buclizine, for which no clinically significant interactions are expected.

Anti-acne agents

Oral contraceptives with anti-androgenic properties are widely used in treating acne and hirsutism, and in polycystic ovarian syndrome with underlying hyperandrogenism and adult female acne. The synthetic oestrogen ethinyloestradiol is contained in combined oral contraceptive pills (COCPs) with various progestogens (progestins). In co-administration with

ritonavir, the bioavailability and plasma concentration of ethinyloestradiol decrease, probably via ritonavir-mediated induction of CYP2C9 and CYP1A2. On the other hand, progestogen is primarily metabolised by CYP3A4, and elevated plasma progestogen results from the drug interaction with ritonavir, thus raising the risk of side effects, including irregular menstrual bleeding and venous thrombosis. Other side effects with certain progestogens include the risk of hyperkalaemia with drospirenone, as well as hepatotoxicity and hot flashes with cyproterone acetate. Recommendations for co-administration of progestogen-only pills or COCPs with NMV/r include careful monitoring for adverse effects. Patients taking COCPs should be advised to consider additional non-hormonal (i.e. barrier) contraceptives for the prevention of pregnancy during and up to 1 menstrual cycle after completing the course of NMV/r,[7] although a clinically significant reduction in contraceptive efficacy is unlikely to result from a decreased plasma concentration of ethinyloestradiol during the standard short course of NMV/r.

Hair agents

Dutasteride and finasteride have been shown to be effective in the treatment of male androgenetic alopecia via the inhibition of dihydrotestosterone production. Of these 2 medications, dutasteride depends on CYP3A4 metabolism; drug interaction with the CYP3A4 inhibitor ritonavir elevates the plasma dutasteride concentration, and increases the risk of side effects, including erectile dysfunction and libido reduction. Close monitoring for the adverse effects is suggested for dutasteride, if used concomitantly with NMV/r.[32] For finasteride, no additional monitoring is needed.

Topical and oral minoxidil are also used in the treatment of androgenetic alopecia. Minoxidil is not expected to have DDI with NMV/r, and systemic treatment may be safely continued without dosage adjustment or additional monitoring.

Other drugs commonly prescribed for dermatology patients

Colchicine is an anti-gout agent, and also used in treating skin disorders (e.g. leukocytoclastic and urticarial vasculitis, and neutrophilic dermatoses, including Sweet's syndrome). Colchicine is primarily dependent on hepatic CYP3A4 metabolism; co-administration with the potent CYP3A4 inhibitor ritonavir greatly increases plasma colchicine concentrations, thereby risking potentially life-threatening acute colchicine toxicity, which encompasses severe gastrointestinal symptoms, seizures, bone marrow suppression and multiorgan failure.[33] The use of colchicine during NMV/r treatment is therefore contraindicated. If colchicine therapy is required in a patient who is taking or has taken NMV/r within the last 14 days, and there are no appropriate alternatives, dose reduction of colchicine is recommended (Table 2).[34]

Dyslipidaemia is common in the general population. In dermatology, abnormal plasma lipoproteins occur particularly in patients with psoriasis and hidradenitis suppurativa, which are conditions linked to the metabolic syndrome; and in patients receiving medications such as retinoids (e.g. isotretinoin and acitretin) and ciclosporin, which predispose to dyslipidaemia.[35] As the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors lovastatin, simvastatin and to a lesser degree, atorvastatin, primarily depend on CYP3A4 metabolism, their co-administration with the CYP3A4-inhibitor ritonavir can increase risks of statin-related myopathy and rhabdomyolysis. Lovastatin and simvastatin intake should cease at least 12 hours before the first dose of NMV/r, during NMV/r treatment, and for another 3 days after the last NMV/r dose.[36] For atorvastatin, brief cessation, or dose reduction to 10mg daily with resumption of its usual dose 3 days after completing NMV/r treatment, is recommended. Rosuvastatin is known to have an elevated plasma concentration when co-administered with ritonavir.[36] Thus, recommendations for rosuvastatin are similarly to stop temporarily or reduce dose to 10mg daily until 3 days after completing NMV/r treatment. Neither pravastatin nor fluvastatin are expected to have clinically significant interactions with NMV/r.

Molnupiravir

As of December 2022, the use of molnupiravir is still under Emergency Use Authorisation by FDA.[37] Molnupiravir has yet to be authorised for use in the European Union.[38] In Singapore, molnupiravir (LAGEVRIO) has been granted interim authorisation for the treatment of mild to moderate COVID-19 in patients aged ≥18 years, and are at risk of progression to severe COVID-19 and/or hospitalisation, as well as in cases when alternative COVID-19 treatment cannot be used.[39]

Molnupiravir is administered as a prodrug, subsequently converted to the active metabolite β-D-N^4-hydroxycytidine (NHC), phosphorylated, and incorporated by viral ribonucleic acid (RNA) polymerase into viral RNA, thereby inhibiting viral replication.[40] Further studies are needed to explore any potential long-term mutagenic effects of molnupiravir to the host.[41]

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications[a]

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
Systemic corticosteroids				
Dexamethasone	Vitiligo	↑ Dexamethasone (Dependent on CYP3A4 metabolism)	Systemic glucocorticoid effects (hyperglycaemia, Cushing's syndrome, adrenal suppression)	Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Hydrocortisone	Angioedema Anaphylaxis	↑ Hydrocortisone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C) Micromedex Drug Reference indicates no drug interactions.
Methylprednisolone	Pemphigus	↑ Methylprednisolone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Prednisolone	Allergic contact dermatitis Atopic dermatitis Bullous pemphigoid Pemphigus Urticaria Vitiligo	↑ Prednisolone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C) Micromedex Drug Reference indicates no drug interactions.
Prednisone	Allergic contact dermatitis Angioedema Urticaria	↑ Prednisone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Immunomodulators				
Abrocitinib	Atopic dermatitis	↑ Abrocitinib (Dependent on CYP3A4 metabolism)		No dose adjustment or additional monitoring necessary.
Ciclosporin	Atopic dermatitis Psoriasis	↑ Ciclosporin (Dependent on CYP3A4 metabolism)	Renal impairment Hypertension	Stop use of ciclosporin during treatment and resume 3 days after last dose of NMV/r. If unable to stop ciclosporin, consider alternative COVID-19 treatment. (Liverpool Drug Interactions checker) (Lexicomp Risk Rating D, Micromedex Severity: Major)
Cyclophosphamide	Autoimmune diseases Dermatomyositis Mycosis fungoides	↑ Cyclophosphamide (Dependent on CYP3A4 and CYP2B6 metabolism)	Oral mucositis Neutropaenia Infection	Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Tofacitinib	Psoriatic arthritis	↑ Tofacitinib (Dependent on CYP3A4 metabolism)	Transaminitis Neutropaenia Infection	Dose reduction to 5mg once daily. Avoid tofacitinib XR and replace with immediate-release tofacitinib.[17] (Lexicomp Risk Rating D, Micromedex Severity: Moderate)

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications[a] (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
Upadacitinib	Atopic dermatitis Psoriatic arthritis	↑ Upadacitinib (Dependent on CYP3A4 metabolism)	Infection Thrombosis	Careful monitoring for adverse effects at upadacitinib 15mg/day dosing.[18] Avoid higher doses of upadacitinib during NMV/r treatment and 3 days after completion of NMV/r treatment. (Lexicomp Risk Rating D)
Antibiotics				
Clarithromycin	Acne Rosacea Staphylococcal skin infections Nontuberculous mycobacterium infections	↑ Clarithromycin but ↓ clarithromycin active metabolites (Dependent on CYP3A4 metabolism)	Hepatotoxicity QT-interval prolongation	Consider alternative antibiotics for mycobacterial infections as efficacy may be compromised. (Micromedex, Lexicomp) Careful monitoring for adverse effects especially in patients with renal impairment. No dose adjustment necessary in patients with normal renal function. Avoid clarithromycin doses greater than 1,000mg/day. Dosage should be reduced by 50% and 75% in patients with CrCl 30–60mL/min and <30mL/min, respectively.[22] (Lexicomp Risk Rating D, Micromedex Severity: Major)
Clindamycin	Hidradenitis suppurativa Staphylococcal skin infections	↑ Clindamycin (Dependent on CYP3A4 metabolism)	Gastrointestinal symptoms Nephrotoxicity	Careful monitoring for adverse effects. (Lexicomp Risk Rating C; however, Micromedex states no drug interactions)
Clofazimine	Leprosy	↑ Clofazimine (Dependent on CYP3A4 metabolism)	QT-interval prolongation	Careful monitoring for adverse effects, including ECG monitoring. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Erythromycin	Acne Rosacea Staphylococcal skin infections	↑ Erythromycin (Dependent on CYP3A4 metabolism)	Gastrointestinal symptoms Hepatotoxicity QT-interval prolongation	Stop and replace with another antibiotic that has less interaction with NMV/r. Alternatively, carefully monitor for adverse effects and consider dose reduction. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Rifampicin	Hidradenitis suppurativa Staphylococcal skin infections Nontuberculous mycobacterium infections	↓ NMV/r (rifampicin is a CYP3A4 inducer)	Reduced therapeutic effects of NMV/r Risk of loss of virological response	Concomitant use of rifampicin is contraindicated. Consider alternative COVID-19 treatment or antimycobacterial therapy (e.g. rifabutin) or alternative treatment for hidradenitis suppurativa. (Lexicomp Risk Rating X, Micromedex Severity: Contraindicated)
Antifungals				
Fluconazole	Dermatophyte infections Pityriasis versicolor Candidiasis	↑ NMV/r (fluconazole is a CYP3A4 inhibitor)	Gastrointestinal symptoms Transaminitis QT-interval prolongation	Careful monitoring for adverse effects, including ECG monitoring. (Lexicomp Risk Rating C, Micromedex Severity: Contraindicated)

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications[a] (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
Itraconazole	Dermatophyte infections Onychomycosis Pityriasis versicolor	↑ Itraconazole (Dependent on CYP3A4 metabolism) ↑ NMV/r (itraconazole is an CYP3A4 inhibitor)	Gastrointestinal symptoms Transaminitis QT-interval prolongation	Avoid high doses (>200mg/day) of itraconazole and carefully monitor for adverse effects.[26] (Lexicomp Risk Rating D, Micromedex Severity: Moderate)
Ketoconazole	Dermatophyte infections Pityriasis versicolor	↑ Ketoconazole (Dependent on CYP3A4 metabolism) ↑ NMV/r (ketoconazole is an CYP3A4 inhibitor)	Gastrointestinal symptoms Transaminitis QT-interval prolongation	Avoid high doses (>200mg/day) of ketoconazole and carefully monitor for adverse effects.[27] (Lexicomp Risk Rating D, Micromedex Severity: Major)
Antiparasitics				
Albendazole	Parasitic worm infections	↓ Albendazole (ritonavir is an inducer of hepatic metabolism of albendazole)		Monitor for reduced clinical response to albendazole therapy. (Lexicomp Risk Rating C)
Antihistamines				
Bilastine	Angioedema and other allergic dermatological reactions Atopic dermatitis Urticaria Pruritus	↑ Bilastine (Dependent on P-glycoprotein efflux)	QT-interval prolongation	Stop use of bilastine during NMV/r treatment, especially in patients with moderate-severe renal impairment, and resume 3 days after last dose of NMV/r. (Lexicomp Risk Rating X)
Hydroxyzine		↑ Hydroxyzine (Dependent on CYP3A4 metabolism)	QT-interval prolongation Torsades de pointes	Consider close ECG monitoring for QT-interval prolongation. (Micromedex Severity: Major)
Rupatadine fumarate		↑ Rupatadine fumarate (Dependent on CYP3A4 metabolism)	QT-interval prolongation Torsades de pointes	Concomitant use of rupatadine with NMV/r is contraindicated.[31] Stop use during treatment and resume 3 days after last dose of NMV/r. (Lexicomp Risk Rating X)
Cetirizine Fexofenadine Levocetirizine		↑ Cetirizine ↑ Fexofenadine ↑ Levocetirizine (Dependent on P-glycoprotein efflux and CYP3A4 metabolism)	Greater central antihistamine effects (reduced alertness, longer reaction times) (Lexicomp)	No dose adjustment or additional monitoring necessary. (Lexicomp Risk Rating B)

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications[a] (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
Acne agents				
Oral contraceptives Oestradiol Ethinyloestradiol	Acne Prevention of pregnancy	↓ Ethinyloestradiol (Probable CYP2C9 and CYP1A2 metabolism)	Irregular bleeding Venous thrombosis Dyslipidaemia Hyperkalaemia (drospirenone) Hepatotoxicity (cyproterone) Hot flashes (cyproterone)	Careful monitoring for adverse effects. Reduction in contraceptive efficacy is unlikely to be clinically significant given the short course of NMV/r. However, patients on oestrogen-containing hormonal contraception are advised to consider additional non-hormonal method of contraception during and up to 1 menstrual cycle after completing the course of NMV/r.[7]
Progestogen (progestin) Chlormadinone acetate Dienogest Levonorgestrel Norethindrone Norgestimate Norgestrel Drospirenone Cyproterone acetate		↑ Chlormadinone acetate ↑ Dienogest ↑ Levonorgestrel ↑ Norethindrone ↑ Norgestimate ↑ Norgestrel ↑ Drospirenone ↑ Cyproterone acetate (Dependent on CYP3A4 metabolism)		
Hair agents				
Dutasteride	Androgenetic alopecia	↑ Dutasteride (Dependent on CYP3A4 metabolism)	Erectile dysfunction Decreased libido	Careful monitoring for adverse effects. (Lexicomp Risk Rating C)
Other commonly encountered drugs in dermatology patients				
Colchicine	Leukocytoclastic vasculitis Neutrophilic dermatoses Sweet's syndrome Urticarial vasculitis	↑ Colchicine (Dependent on CYP3A4 metabolism) Risk of serious toxicity	Acute colchicine toxicity (gastrointestinal symptoms, seizures, bone marrow suppression, multiorgan failure)	Concomitant use of colchicine with NMV/r is contraindicated.[7] Stop use during NMV/r treatment if possible. A colchicine dose adjustment is required in patients who are taking or have taken NMV/r within the past 14 days. Recommendations on dose adjustment for dermatologic indications are not available but can be inferred from dose adjustment for other indications. For the treatment of a gout flare-up with concomitant use of NMV/r, the adjusted dose of colchicine is 0.6mg once, then 0.3mg 1 hour later (repeated no earlier than every 3 days). For the prophylaxis of gout flare, if the original dose is 0.6mg 2 times daily, the adjusted dose is 0.3mg once daily. If the original dose is 0.6mg once daily, the adjusted dose is 0.3mg every other day. In patients with familial Mediterranean fever with concomitant use of NMV/r, the maximum daily dose of colchicine is 0.6mg (may be given as 0.3mg twice daily).[34]

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications[a] (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
HMG-CoA reductase inhibitors Atorvastatin Rosuvastatin	Dyslipidaemia E.g. in acne patients taking isotretinoin or psoriasis patients taking acitretin	↑ Atorvastatin ↑ Rosuvastatin (Less dependent on CYP3A4 metabolism than simvastatin or lovastatin)	Myopathy Rhabdomyolysis	Consider stopping use during treatment and resuming 3 days after last dose of NMV/r. If concomitant intake of atorvastatin and NMV/r is required, atorvastatin dose should be reduced to 10mg daily and resume the usual dose 3 days after completion of NMV/r. (Liverpool Drug Interactions checker) If concomitant intake of rosuvastatin and NMV/r is required, maximum rosuvastatin dose should be 10mg daily and resume the usual dose 3 days after completion of NMV/r. (Liverpool Drug Interactions checker) Monitor carefully for adverse effects. (Micromedex Severity: Major; Lexicomp Risk Rating D and C for atorvastatin and rosuvastatin, respectively)
Simvastatin Lovastatin		↑ Simvastatin ↑ Lovastatin (Dependent on CYP3A4 metabolism)		Concomitant use of simvastatin or lovastatin with NMV/r is contraindicated.[7] Stop use at least 12 hours before first dose of NMV/r and resume 3 days after last NMV/r dose. (Lexicomp Risk Rating X, Micromedex Severity: Contraindicated)

CYP: cytochrome; ECG: electrocardiogram; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; ↑: increased plasma drug concentration; ↓: decreased plasma drug concentration
[a]Consult the Liverpool COVID-19 Drug Interactions[5] checker for updated drugs. If a drug is not listed here, co-administration cannot be automatically assumed to be safe.
Superscript numbers: refer to REFERENCES

Currently, no DDIs involving molnupiravir have been identified. In vitro studies show that molnupiravir and its metabolite NHC are not substrates, inhibitors or inducers of major drug metabolising CYP450 enzymes. Also, they are not substrates of P-glycoprotein or breast cancer resistance protein efflux transporters, which are important mediators of intestinal absorption and subsequent excretion of drugs.[37] Therefore, molnupiravir can be an option for alternative COVID-19 therapy in patients who are clinically indicated for oral COVID-19 antiviral therapy, but are contraindicated for NMV/r. Molnupiravir is contraindicated during pregnancy, and men and women of childbearing potential should practise contraception for 3 months after the last dose.

Limitations

This present review has 4 main limitations. First, the list of drugs reviewed within this article is not exhaustive, and might not include newer drugs still pending approval by the European Medicines Agency and FDA. To the best of our knowledge, this is the most comprehensive and in-depth review of drug interactions between dermatological medications and the 2 current oral COVID-19 medications. Second, some of the drugs were not listed on the Liverpool COVID-19 Drug Interactions checker at the time of our literature search, and cannot be assumed to be safe to co-administer with NMV/r, although we attempted to corroborate with the individual product monographs. Third, given that NMV/r interacts with many medications, the focus on dermatological medications may be too specialised for generalists and other specialists. However, as patients in the community often present with comorbidities including dermatological conditions, information on DDIs between NMV/r and dermatological agents can be useful for physicians. Moreover, some of the medications discussed here are frequently prescribed by generalists and/or specialists (e.g. systemic glucocorticosteroids, antibiotics, statins, immunomodulators and biologicals). Lastly, information contained within our review is based on our literature search ending on 18 July 2022—recommendations and practices may vary between regions and with time.

CONCLUSION

Clinically significant DDIs exist between NMV/r and numerous dermatological medications, mostly due to CYP3A4 inhibition caused by ritonavir. Genetic variations in the *CYP450* genes encoding the drug metabolising enzymes may also influence the extent of drug interaction between NMV/r and concomitant

medication. Long-term dermatological medications linked to potential drug interactions should be withdrawn or dose-adjusted as appropriate, for 8 days to enable safe and timely access to treatment with NMV/r. Molnupiravir may be considered as an alternative COVID-19 therapy for patients who take medications that have complicated drug interactions with NMV/r, and are not suitable for temporary cessation or dose reduction.

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HH Oon is a speaker, advisory board member and researcher for Galderma, Janssen and Novartis. She has also been a clinical investigator for Pfizer, as well as a speaker and advisory board member for AbbVie and Eli Lilly.

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COMMENTARY

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Meeting today's healthcare needs: Medicine at the interface

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ABSTRACT

The demographic of Singapore has undergone dramatic change. Historically, younger patients with communicable diseases predominated, whereas patients are now older with chronic multimorbidity and functional impairment. This shift challenges existing health and social care systems in Singapore, which must pivot to meet the changing need. The consequences of mismatched health and social care to patient needs are the fragmentation of care, dysfunctional acute care utilisation and increasing care costs. In Singapore and internationally, there is an inexorable rise in acute care utilisation, with patients facing the greatest point of vulnerability at transitions between acute and chronic care. Recently, innovative care models have developed to work across the boundaries of traditional care interfaces. These "Interface Medicine" models aim to provide a comprehensive and integrated approach to meet the healthcare needs of today and optimise value with our finite resources. These models include Acute Medical Units, Ambulatory Emergency Care, Extensivist-Comprehensivist Care, Virtual Wards, Hospital-at-Home and Acute Frailty Units. We describe these models of care across the acute care chain and explore how they may apply to the Singapore setting. We discuss how these models have evolved, appraise the evidence for clinical effectiveness, point out gaps in knowledge for further study and make recommendations for future progress.

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The demographic of Singapore has undergone dramatic changes. Historically, younger patients with communicable diseases predominated; however, patients are now older with chronic multimorbidity and functional impairment. This demographic shift challenges existing health and social care systems in Singapore, which must pivot to meet the changing need. The consequences of mismatched health and social care to patient needs include fragmentation of care among different specialties,[1] and between the acute hospitals and the community, as well as dysfunctional acute care utilisation[2] with increasing care costs.[3] A recent Singapore study found at least 36% of patients experience care fragmentation.[1] A large cross-sectional study of regional health in east Singapore found heterogeneous chronic comorbidity patterns across population segments, associated with high acute care utilisation and cost.[2] Despite having one of the most cost-efficient healthcare systems in the world (4.9% of the national gross domestic product in 2018), healthcare inflation in Singapore is one of the highest in Asia (average 2.2% per annum).[3]

In Singapore and across the world, there is an inexorable rise in acute care utilisation. The rate of increase in emergency department (ED) attendance in Singapore far outstrips population growth (5.6% versus 1.3% in 2016),[4] exacerbated further by the recent COVID-19 pandemic. Additionally, the point of greatest vulnerability appears to be at the interfaces of care, particularly the transition of acute and chronic care as ongoing care needs extend beyond the acute care episode.[5] Because of these challenges, there are calls for a paradigm shift in how healthcare systems deliver acute and chronic care to be fit for purpose.

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Recently, innovative care models have developed to work across the boundaries of traditional care interfaces between the acute hospital and primary care. These include, not exhaustively, Acute Medical Units (AMUs), Ambulatory Emergency Care (AEC), Extensivist-Comprehensivist Care, Virtual Wards, Hospital-at-Home (HAH) and Acute Frailty Units (AFU). These "Interface Medicine" models aim to provide an integrated approach to meet the healthcare needs of today, with some commonalities across the models. Firstly, the practising physician is advantageously a generalist who can effectively manage acute presentations while optimising chronic disease, and necessarily comfortable with managing clinical uncertainty while working over different environments and settings. Secondly, there is a focus on appropriate gatekeeping of health resources, relational continuity with patients and carers, effective multidisciplinary team-working, and functional knowledge of manoeuvring resources to meet patient needs. Thirdly, the adoption of evolving technology—such as electronic health records, point-of-care testing, teleconferencing and remote monitoring—has enabled effective care across care settings. We describe these models of care (Tables 1 and 2) across the acute care chain (Figs. 1A and 1B) and explore how they may apply to the Singapore setting.

Acute Medical Unit (AMU)

The Royal College of Physicians Acute Medicine Taskforce report in 2007 outlined key aspects of quality for acute medical care,[6] forming the basis of core functions for AMUs. AMUs are dedicated receiving wards for the assessment, investigation, and stabilisation of those with acute medical conditions, and provide continuing care for up to 72 hours. Key enabling structures include sufficient bed-base to be able to discharge at least 50% of admissions without the need for further downstream ward movement, appropriate staffing and competence (e.g. 12-hour, 7-day consultant presence) for levels of patient acuity and throughput, geographic co-location to ED and timely access to diagnostics, specialist opinion and therapy services.

AMUs have spread to Europe, Australia and Asia. Acute Medicine has evolved into a medical specialty in the UK. The authors are aware of at least 5 AMUs in Singapore public hospitals.[7,8] Systematic reviews[9] and observational studies[10] suggest AMUs are associated with reductions in length of hospital stay (mean 0.3 to 2.62 days), improved patient experience, and possibly overall mortality reduction (+0.1% to −8.8% mortality rate) compared with non-AMU wards.

Ambulatory Emergency Care (AEC)

Also termed Same Day Emergency Care (SDEC), AEC involves the redesign of patient pathways to allow assessment and treatment of emergency conditions within the same day as an alternative to hospital admission. They involve observation units paired with rapid access to clinic facilities, diagnostics, and medical procedures. They have evolved to also reduce the length of stay for those with ongoing diagnostic or care requirements, who no longer require hospitalisation.

AEC models may target specific conditions for pathway creation. Alternatively, validated tools such as the Amb score are used for patient selection. Co-location with ED or AMU has been found to increase throughput, and adopters find that up to 30% of acute medical admissions can be managed via AEC. The evidence for the effectiveness of AEC arises mainly from observational studies[11] and are condition-specific (e.g. venous thromboembolism and pneumonia), but demonstrate high patient satisfaction and lower costs. An implementation of AEC at a Singapore public hospital was associated with reduction in 30-day readmission (0.5%) and cost to the patient (45% reduction), as well as acute bed days saved (mean 1.2 days) compared to pre-implementation.[12]

Extensivist-Comprehensivist

The hospitalist movement expanded rapidly in the 1990s within the US, with a focus on improving patient outcomes and reducing acute care costs. This involved having inpatient care managed and coordinated by a generalist physician specialised in the care of hospitalised patients rather than primary care physicians, which was normal practice at the time. The subsequent break in care continuity between primary and secondary care may adversely affect some patients, manifested as frequent ED attendance and acute hospitalisation.[13]

The Extensivist-Comprehensivist model, which is resource intensive, seeks to empanel patients with previous high acute care utilisation and complex care needs to intensive outpatient management by a multidisciplinary team. A secondary care generalist physician leads the team in patient care, rather than hand over the patient to a primary care physician after hospitalisation. To further improve longitudinal care continuity and strengthen the physician-patient relationship, the inpatient and outpatient episodes are ideally managed by the same physician or team. Implementation of this model by the US CareMore Medical Group resulted in a 20% reduction in hospitalisation, 23% reduction in acute bed days and

Table 1. Interface Medicine models and characteristics

Model	Value proposition	Purpose	Population target	Competence	Temporality	Location
Acute Medical Unit (AMU)	"Right Physician, Right Place, Right Time, First Time for the patient with acute medical illness"	• Patient safety • Optimised patient flow through hospital • Decreased length of hospital stay	Majority of undifferentiated acute medical hospital admissions	Acute Medicine Curricula (UK); specialty or internal medicine	• 24/7 • Extended consultant coverage (e.g. 0800–2000 hours)	• Co-located with ED and diagnostics • Some include semi-critical care setting
Ambulatory Emergency Care (AEC)	"Treating emergency medical conditions without bed & breakfast"	• Admission avoidance • Decreased length of hospital stay	Acute emergencies in patients who can be managed in ambulatory fashion	Specialty or internal medicine	• Mostly 0900–1700 hours • Few extended hours and weekends	• Co-located with ED and diagnostics • Some housed within AMU
Extensivist-Comprehensivist Care	"Empanelment of patients to care-coordination and intensive out-patient care to prevent hospitalisation"	• Admission avoidance • Decreased cost of care • Continuity of care	History or persistent high acute care utilisation	Internal medicine; care coordination; complex case management	• Inpatient care as usual • Intensive outpatients	• Same physician manages inpatient and outpatient episodes
Virtual Ward	"Patients followed up in their homes by medical team using ward level processes"	• Patient safety • Decreased length of hospital stay • Admission avoidance • Continuity of care	Patients who do not fulfil criteria for continuing inpatient hospital stay but require frequent review of condition	Specialty, internal medicine or family practice	• Once a day "ward" round • Can be simple (e.g. telephone) or tech-enabled interaction (e.g. remote monitoring of vitals)	• Patient in own home but reviewed as part of team ward round
Hospital-at-Home	"Hospital level treatment and monitoring in the patients' own home"	• Patient safety (nosocomial morbidity) • Decreased length of hospital stay • Admission avoidance • No need to build hospitals!	Fulfil criteria for inpatient care (monitoring, skilled nursing, therapy e.g. O_2) to be provided in patients own home	Specialty, internal medicine or family practice	• Mostly 0900–1700 hours • Few out-of-hours service	• Patient in own home
Acute Frailty Unit	"Early review of frail older persons by skilled older persons team to facilitate early discharge"	• Patient safety for vulnerable elderly • Decreased length of hospital stay • Prevent decline	Older person with frailty or complex social needs	Frailty and comprehensive geriatric assessment; knowledge of and access to community resources	• Mostly 0900–1700 hours	• Co-location with ED

AMU: Acute Medical Unit; AEC: Ambulatory Emergency Care; ED: emergency department

Table 2. Main benefits and challenges of each Interface Medicine models

Model	Benefits	Challenges
Acute Medical Unit	• Early diagnosis and treatment	• Break in continuity of care
Ambulatory Emergency Care	• Manage acute/ emergency conditions without the need for hospital admission • Potential reduction in nosocomial harm (e.g. infection)	• Only benefits "mobile" patients (e.g. contactable by phone, able to return to hospital, degree of self-care and activation implicit)
Extensivist-Comprehensivist	• Longitudinal care across acute and chronic setting by generalist physician • Care-coordination	• Resource intensive—costly if patient selection not appropriate
Hospital at Home	• Provision of acute care in patients own home • Potential reduction in nosocomial harm (e.g. infection)	• Resource intensive—costly if patient selection not appropriate • Ideally requires out-of-hours support
Virtual Ward	• Hospital ward level processes and monitoring to patient in their own home	• Resource intensive—costly if patient selection not appropriate
Acute Frailty Unit	• Comprehensive geriatric assessment and management early in acute care journey	• Acute care environment not conducive for frailty assessment and longitudinal management

4% decrease in average length of hospital stay compared to Medicare average.[14]

Virtual Ward

Virtual wards were first introduced in Croydon, UK in 2006 as having 2 components: a predictive model to identify populations at risk of future acute hospitalisation (e.g. PARR-30), paired to a period of intense multidisciplinary care with the patient residing at home using the systems, staffing and daily processes of a hospital ward.[15] This model has been adopted internationally and applied in diverse populations, such as for chronic respiratory disease and frailty. A recent systematic review finds a reduction in mortality and acute hospitalisations in those with heart failure, but not undifferentiated chronic disease.[16]

In Singapore, the model has been applied to post-discharge patients assessed to have a high risk of rehospitalisation, with evidence of reduced ED attendances (incidence rate ratio [IRR] 0.67, 95% confidence interval [CI] 0.52–0.86, P=0.001) and acute hospitalisation (IRR 0.60, 95% CI 0.46–0.79, P<0.001) compared to usual care, sustained up to 6 months.[17] More recently, in response to pressures for hospital beds, virtual wards have been used to reduce acute hospitalisation rates for higher-risk COVID-19-positive patients who were ineligible for the Home Recovery Programme.

Hospital-at-Home (HAH)

The HAH model started in mid-1990s in the US, UK and Australia in response to rising demand for hospital beds and concerns of nosocomial injury to a vulnerable aged subgroup (e.g. functional decline, delirium and infection). The model aims to provide hospital-level monitoring and treatment for a subgroup of patients in their own home. Studies evaluating HAH take the form of small single-centre trials. A systematic review of HAH for the purposes of hospital admission avoidance reports reduced institutionalisation rates (risk ratio [RR] 0.35, 95% CI 0.22–0.57, P<0.0001) with no significant difference in acute hospital readmission rates compared to usual care.[18] A systematic review of HAH for the purpose of early hospital discharge finds moderate evidence of reduction of length of stay (7 days, 95% CI 10.19–3.17 days), particularly for elective surgery, but increased risk of hospital readmission for medical patients (RR 1.25, 95% CI 0.98–1.58) compared to usual care. Both reviews report improved patient satisfaction and no increase in mortality, but no clear evidence of cost reduction.[19] The authors know of at least 3 HAH services at Singapore public hospitals.

Acute Frailty Unit (AFU)

Also termed Acute Care for Elders (ACE) unit, AFUs started in the mid-1990s with the aim of reducing functional impairment in older adults with acute hospitalisation. The 4 principles include a specially designed environment, patient-centred care, comprehensive discharge planning and comprehensive medical review to minimise polypharmacy or unwarranted procedures. Systematic reviews find AFUs are associated with fewer falls (RR 0.51, 95% CI 0.29–0.88), delirium (RR 0.73, 95% CI 0.61–0.88), functional decline (RR 0.87, 95% CI 0.78–0.97) and institutionalisation (RR 0.82, 95% CI 0.68–0.99) compared to usual hospital admission.[20] An implementation of an AFU within the ED of a Singapore public hospital was associated with reduction in conversion to hospital admission from ED attendance (81.4%), with no increase in ED reattendance or hospital readmission at 6 months compared to usual care.[21]

1A

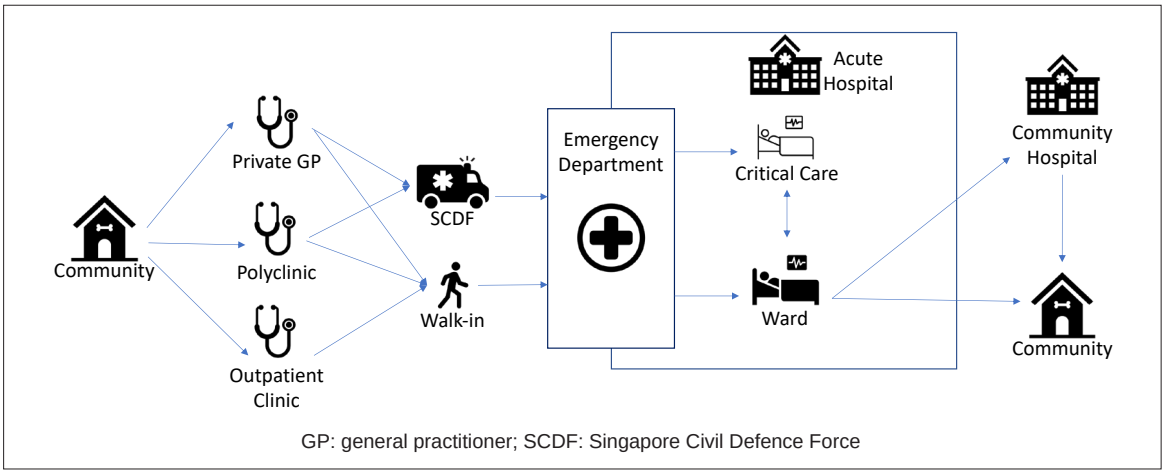

Fig. 1A. The Acute Care Chain in Singapore. The flow of patients into the hospital is via the emergency department (ED) from walk-ins, polyclinics, private general practitioners and specialist clinics, with ambulant patients approaching ED directly or patients being conveyed by ambulance. Patients move from the ED into hospital wards (including critical care), and from hospital wards to home or a community facility.

1B

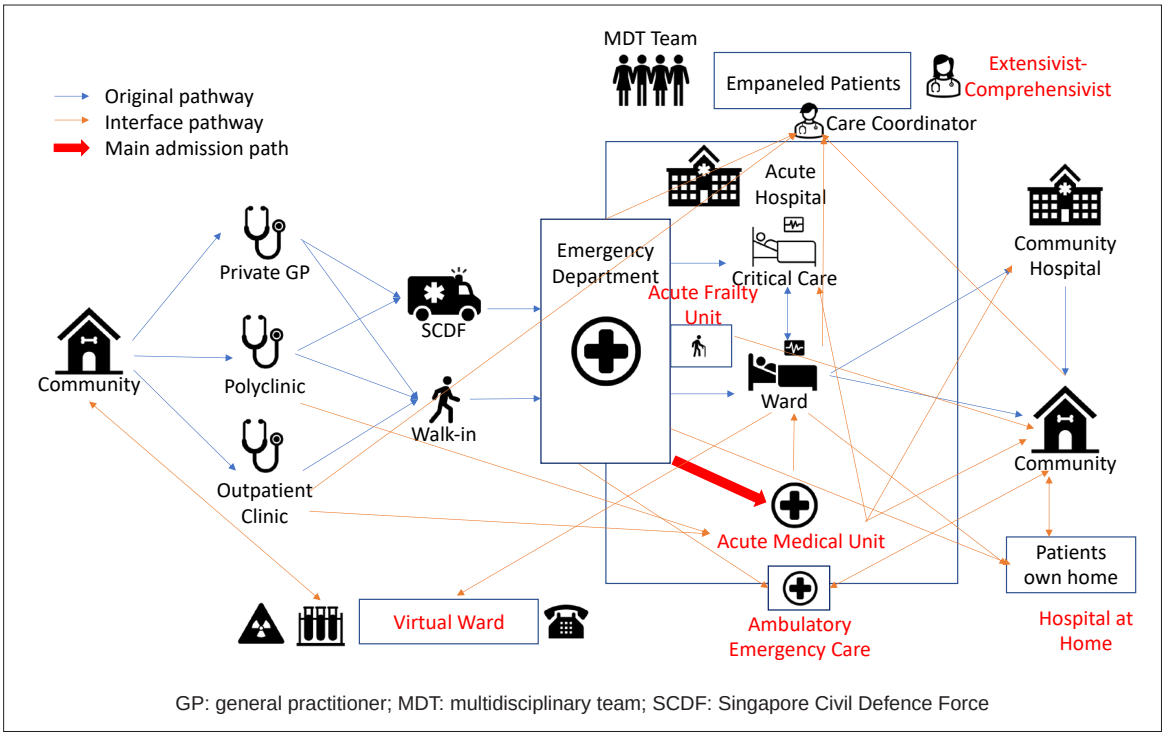

Fig. 1B. Interface Models in relation to acute care chain in Singapore.

Acute Medical Unit (AMU): The majority of medical admissions to the hospital flow through AMU, with some patients from polyclinic or specialist clinic being admitted directly bypassing ED. Patients are discharged directly from AMU (72 hours) to home or community facility or flow to an appropriate specialist hospital ward for ongoing care.

Ambulatory Emergency Care (AEC): Selected patients from ED are discharged on the same day with ongoing investigations, treatment and review via rapid access follow-up clinic.

Extensivist-Comprehensivist: Frequent acute hospital attenders are managed intensively in outpatient settings supported by a multidisciplinary team and patient navigator.

Virtual Ward: Multidisciplinary care with the patient residing at home using the systems, staffing and daily processes of a hospital ward.

Hospital-at-Home (HAH): Hospital-level monitoring and treatment for a subgroup of patients in their own home.

Acute Frailty Unit (AFU): Early review of frail older persons by a skilled older person team to facilitate early return to the community from acute hospital.

As health systems organise to meet the needs of the patients they serve, functional interfaces of care delivery naturally arise. For some, where demographic change increases vulnerability, these care interfaces can be dysfunctional and lead to care fragmentation, increased risk of adverse outcomes, poor experience, and excess cost. These models of care aim to bridge these gaps, to improve patient safety and health system effectiveness.

There are common challenges and opportunities. Firstly, as these care models span the divide across interfaces of care, they are often challenged by fragmented governance and financial structures. Integrating these structures into a cohesive, cost-effective configuration is a crucial step for scale-up and spread. Secondly, these care models are not mutually exclusive and overlap in population target and value proposition. This importantly allows for synergistic relationships between models without the need for extra resources, especially in terms of workforce. For example, many AMUs house AEC units maximising existing resources, while increasing throughput. Understanding how these models may work together to meet patient needs with optimal effectiveness and efficiency is a research priority. Lastly, the models have been heterogeneously implemented, with evidence of their effectiveness based on single-centre trials or observational studies. Health service interventions are often complex and occur in the "open-range" of a working health system. Given finite resources, implementing new models of care risks destabilising existing systems. Rigorous evaluation of real-world effectiveness is a priority. A deeper understanding of contextual factors is required for optimal implementation, otherwise we risk creating new health system dysfunction, which paradoxically these models seek to eradicate.

Over time, evolving understanding of the natural sciences has allowed the development of efficacious therapeutics. The practice of medicine has also continued to evolve to be more effective in meeting patient needs. The blurring of healthcare across the community, primary and secondary settings is a growing international phenomenon. These models of care continue to evolve and may be the future of mainstream practices. The challenges and opportunities described are a roadmap for future development and study.

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Multidisciplinary lung cancer clinic: An emerging model of care

Dear Editor,

Lung cancer management is progressively complex and multidisciplinary input is often needed. The recent publication of CheckMate 816 heralds a paradigm shift in the treatment of resectable non-small cell lung cancer (NSCLC),[1] with many other perioperative trials soon to follow.[2] Oligometastasis and oligoprogression in stage IV NSCLC are now recognised as distinct entities. Oligometastasis refers to a limited number of metastases at the initial diagnosis of lung cancer, whereas oligoprogression is defined as a limited number of lesions with progression while on systemic therapy.[3] Radical intent treatment can be considered in some patients under both circumstances, resulting in improved outcomes.[4] As such, multimodality treatment is increasingly utilised across the various stages of NSCLC and input from multiple disciplines is often needed.

While multidisciplinary tumour boards are commonplace, patients are usually not involved and still require multiple clinic visits to various specialties, which can be challenging to navigate and prolong time to treatment initiation.[5] Recognising the need to improve patient care, particularly amid the global coronavirus pandemic,[6] we started a weekly multidisciplinary clinic (MDC) in August 2020 comprising medical oncology, radiation oncology and cardiothoracic surgery. We describe our experience running this service in National Cancer Centre Singapore, an Asian tertiary cancer centre.

MDC was a physician-led referral service that served as a "one-stop" session for any lung cancer patient who required multidisciplinary input as deemed by their primary physician, such that counselling and treatment options could be provided in one setting. Any physician from Medical Oncology, Radiation Oncology, Cardiothoracic Surgery or Respiratory Medicine could refer patients to this service. MDC was run once a week in the specialist outpatient centre and attended by a medical oncologist, radiation oncologist, cardiothoracic surgeon and patient navigator. Each patient was allotted a 30–45-minute clinic time slot, and appointments were arranged within 2 weeks of the referral date. Patients were charged as per standard clinic consultation charges, which were adjusted according to the number of specialists being consulted.

Between August 2020 and May 2022, 46 patients were seen in MDC. Teleconsultation was arranged for one patient residing overseas. The median age was 63.5 years (range 42–81); 58.7% (27/46) male and 60.9% (28/46) were never smokers. Distribution by stage was 15% (7/46) Stage I, 26% (12/46) Stage III and 59% (27/46) Stage IV. Among the 40 patients with adenocarcinoma, 32 (80%) had an oncogenic driver mutation of which epidermal growth factor receptor (EGFR) was the most common at 25 (63%), followed by human epidermal growth factor receptor 2 (HER2) at 8% (3/40) and anaplastic lymphoma kinase (ALK) at 5% (2/40).

The reasons for referral to MDC (Fig. 1A) show the most common being oligoprogression at 35% (16/46), followed by consolidation therapy for metastatic disease at 17% (8/46), and stage 3 NSCLC for multimodality treatment at 13% (6/46). The median number of oligoprogressive sites was 1.5 (range 1–5).

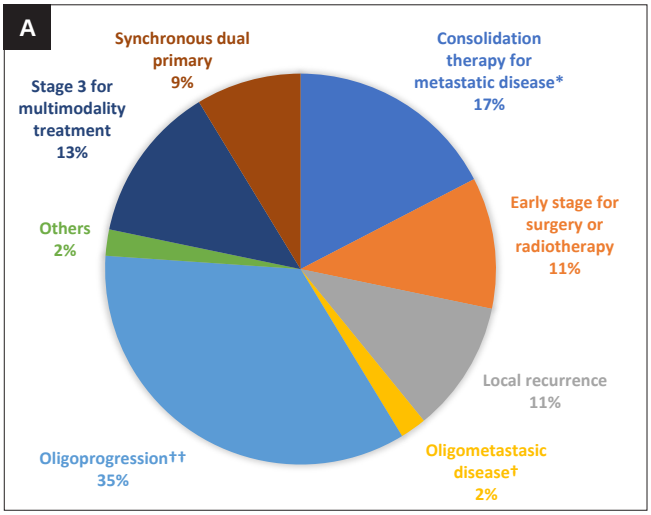

Fig. 1A. Reasons for referral to multidisciplinary clinic.

* Local therapy to remaining sites of disease after response to systemic therapy
† Limited number of metastases at initial diagnosis of lung cancer
†† Limited number of lesions with progression while on systemic therapy

MDC treatment recommendations are summarised in Fig. 1B, demonstrating changes in management for many patients. Among 27 patients with stage IV disease, 12 (44%) were recommended radical treatment (6 surgery, 5 radiation and 1 chemoradiation). Of the 16 patients with oligoprogression, 10 (63%) were recommended radical local therapy (5 radiotherapy and 5 surgery) without change in systemic therapy. All 6 patients with stage III disease were recommended radical treatment

(2 surgery, 2 radiation and 2 chemoradiation), and one patient was enrolled in a clinical trial 33 days after the MDC visit. Molecular profiling was performed in 16 patients, of which an actionable mutation was found in 7 (44%), including EGFR T790M (n=2) and EGFR C797S (n=1) (Fig. 1C).

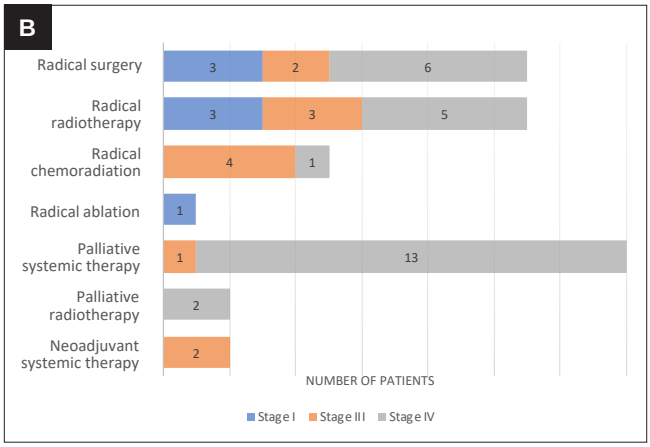

Fig. 1B. Treatment recommendations following multidisciplinary clinic.

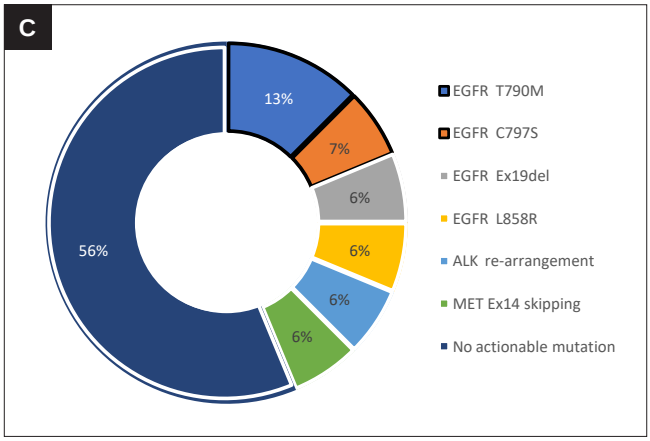

Fig. 1C. Molecular profiling results.
ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor

Radical treatment was recommended for 28 patients, of which 25 underwent recommended treatment successfully. Two patients declined radical radiotherapy and surgery was held off for 1 patient due to disease progression. There was no change in systemic therapy for 96.0% (24/25) of patients when radical intent treatment was recommended. The median time from MDC visit to treatment initiation was 28 days (range 4–111), with reduced hospital dwell time during COVID-19. No treatment-related mortalities were observed at 30 days. At the time of data analysis in July 2022, 9 patients who had undergone radical intent treatment had developed disease progression, with a median time to treatment failure of 189 days (range 37–449).

Feedback was collated prospectively by patient navigators, with 93.5% (29/31) of patients reporting that the service was helpful. The main reasons cited included the opportunity to hear opinions from multiple specialists in one visit, more treatment options presented, and shortened waiting time to start treatment. Similarly, physicians felt that MDC helped in the decision-making process by facilitating simultaneous discussions with other specialties together with the patient.

Our centre's positive MDC experience affirms the feasibility and value of this model of care. Advantages such as decreased time from diagnosis to treatment, increased patient satisfaction, and closer collaboration between healthcare providers have been similarly reported by other multidisciplinary cancer clinics, although the impact on patient survival is less established.[7] Beyond expediting treatment initiation and reduced hospital dwell time, which was of particular importance to reduce COVID-19 exposure risk during the global pandemic,[6] we also demonstrated that MDC provided more treatment options and reduced the need to switch systemic therapy among patients with oligoprogression. Local therapy in oligoprogressive and oligometastatic oncogene-addicted NSCLC has been shown to improve disease control and allow continuation of targeted therapy,[8,9] consistent with our experience and especially relevant since most patients referred to MDC had an oncogenic driver mutation.

Patient involvement in complex treatment discussions is paramount as the lung cancer treatment landscape swiftly evolves, necessitating in-depth dialogues and shared decision-making between patients and physicians.[10] An increased uptake of multimodality treatment is anticipated in the perioperative and oligometastatic/oligoprogression setting, underscoring the importance of close interdisciplinary collaboration and adequate resourcing such as facilitating teleconsultations and access to patient navigators.

Our study had several limitations. A single-centre study performed in a tertiary Asian cancer centre could limit the generalisability of the data. Furthermore, as this was an observational study without a formal control arm, we were unable to quantify the improvement in survival by implementing MDC. Nonetheless, our experience supports the feasibility of running a multidisciplinary lung cancer clinic and such a service should be provided where possible.

In conclusion, MDC is feasible and achieves encouraging clinical outcomes, on top of improved patient and physician satisfaction. Close interdisciplinary collaboration and adequate resourcing are essential for the success of this service and MDCs will likely see an expanded role.

Disclosures

Dr Saw reports personal fees from Pfizer, Bayer, AstraZeneca and MSD, non-financial support from Guardant Health, outside the submitted work. Dr Chua reports personal fees from AstraZeneca, outside the submitted work. Dr Ong reports personal fees from AstraZeneca, non-financial support from Johnson & Johnson, personal fees from Medtronic, personal fees and non-financial support from Stryker, personal fees from MSD, outside the submitted work. Dr Lai reports personal fees from Amgen and grants from Merck, AstraZeneca, Pfizer, Amgen, Bristol Myers Squibb, and Roche outside the submitted work. Dr DSW Tan reports grants from Amgen, Novartis, GlaxoSmithKline, AstraZeneca and Pfizer, consulting fees from Novartis, Bayer, Boehringer Ingelheim, AstraZeneca, Eli-Lilly, MSD, GlaxoSmithKline and LOXO and personal fees from Takeda, Novartis, Roche, Pfizer, Merck and Boehringer Ingelheim.

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Tozinameran (Pfizer-BioNTech COVID-19 vaccine)-induced AGEP-DRESS syndrome

Dear Editor,

A 40-year-old woman with scalp psoriasis was maintained on topical mometasone furoate therapy from 2019 with no major psoriatic flares until she presented with one week of an acute generalised pustular eruption and fever in June 2021. Physical examination revealed numerous discrete and confluent pustules studded on her scalp, trunk and limbs, on a background of suberythroderma (Fig. 1). Laboratory investigations were significant for eosinophilia (1.21 x 10^3/µL, reference 0.03–0.77 x 10^3/µL) and transaminitis (AST 65 IU/L, reference 2–32 IU/L, ALT 66 IU/L, reference 2–32 IU/L). She had received 2 doses of tozinameran (Pfizer-BioNTech COVID-19 vaccine), given 11 and 7 weeks prior, and had not used other medications in the preceding 3 months. She had no family or personal history of a drug hypersensitivity reaction. Polymerase chain reactions for human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) were negative.

A biopsy of the right forearm pustule showed subcorneal pustules containing neutrophils, spongiosis and a superficial perivascular infiltrate of numerous eosinophils with dermal oedema (Fig. 2). She was treated with prednisolone 30mg daily tapered over 4 weeks and intensive topical 0.05% clobetasol propionate

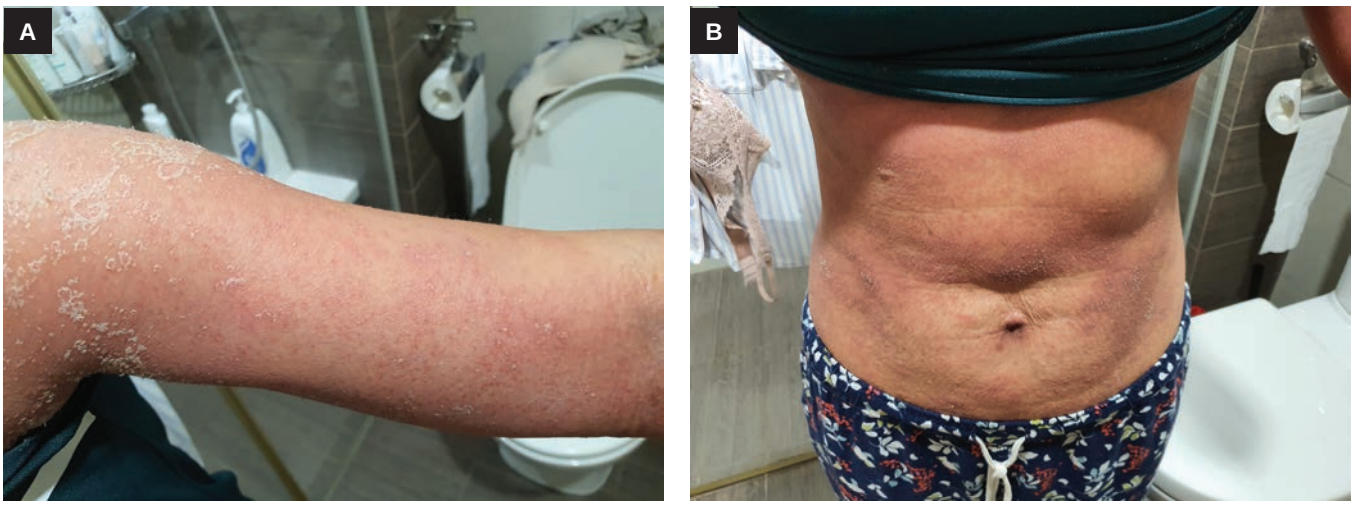

Fig. 1. (A) Clinical photograph showing both discrete and confluent pustules in the left arm, and (B) extensive exanthem in trunk with both discrete and confluent pustules.

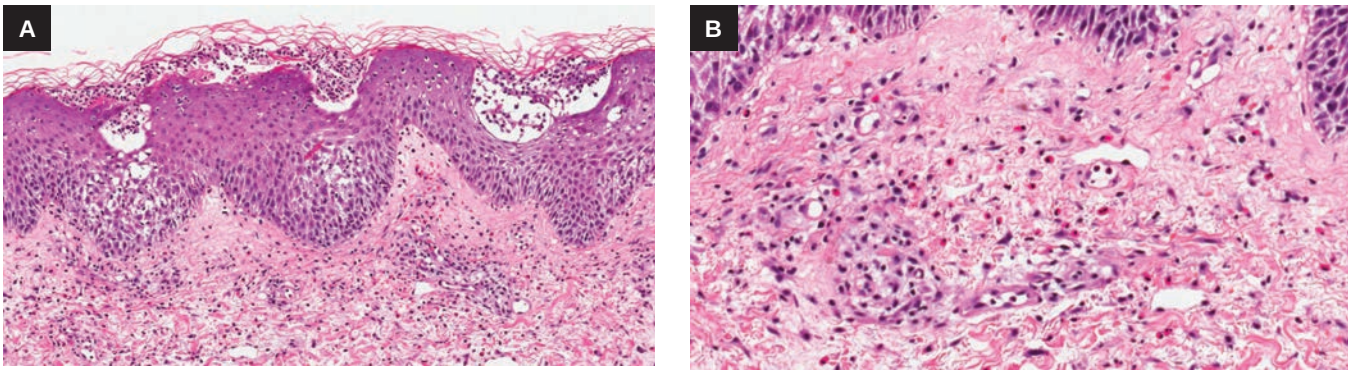

Fig. 2. Skin biopsy from the right forearm showing a basketweave stratum corneum with subcorneal pustules containing neutrophils. (A) The epidermis shows spongiosis, and the dermis a superficial perivascular infiltrate of lymphocytes with many eosinophils (haematoxylin and eosin stain: 100x magnification). (B) There are increased numbers of eosinophils within the dermis (haemotoxylin and eosin stain: 200x magnification).

cream twice daily. There was a near resolution of symptoms and normalisation of eosinophilia and transaminitis after 2 months.

The initial provisional diagnosis was an acute generalised pustular psoriasis (GPP) flare. However, as the disease progressed, features not in keeping with GPP such as serum eosinophilia and histological perivascular infiltrates of eosinophils were seen. Instead, the long latency, protracted course of the disease, fever and systemic involvement supported the diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Though pustules are reported in DRESS, the consistent histopathological findings with the presence of discrete and confluent pustules were more typical of acute generalised exanthematous pustulosis (AGEP). The RegiSCAR score for DRESS in this patient was 4 (probable, scored as such: no fever >38.5°C = -1, presence of eosinophilia = 1, skin rash = 2, organ involvement = 1, exclusion of other causes = 1) and EuroSCAR score for AGEP was 5 (probable, scored as such: typical pustules = 2, typical erythema = 2, typical distribution = 2, post-pustular desquamation = 1, no acute onset = -2, no resolution <15 days = -4, fever = 1, histology of spongiform subcorneal pustules with papillary oedema = 3).[1,2] As the patient had some features consistent with both, we favoured the diagnosis of acute generalised exanthematous pustulosis (AGEP)-drug reaction with eosinophilia and systemic symptoms (DRESS) overlap syndrome secondary to tozinameran. AGEP-DRESS overlap syndrome is not a new entity, and it has been reported in association with another COVID-19 vaccine, Janssen Ad26.COV2.S, a recombinant-vector vaccine.[3]

We opine that in our patient, tozinameran instigated an overly robust host response, leading to a cytokine imbalance syndrome, and precipitated an AGEP-DRESS overlap syndrome. This delayed cutaneous manifestation may be related to the host immune cytokine response rather than true allergies, an observation similar to Juay et al. in their 3 cases of vesiculobullous cutaneous reactions to tozinameran.[4] Other vaccines, such the MMR vaccine, have also been previously demonstrated to exacerbate atopic dermatitis via elevated IL-4 levels, disrupting the Th1 and Th2 lymphocytic balance.[5] COVID-19 vaccinations have been reported in association with many cutaneous side effects in many local institution-based studies.[6,7] However, AGEP-DRESS overlap syndrome has thus far neither been observed in association with primary SARS-CoV-2 viral infection, nor after tozinameran vaccination. Further patho-immunological studies should follow to better establish the causal association of tozinameran and DRESS syndrome.

In conclusion, it is important for dermatologists to consider mRNA COVID-19 vaccine as a potential culprit agent in patients presenting with AGEP and/or DRESS syndrome, as illustrated by this case. The safety of future mRNA COVID-19 vaccinations for such patients will need to be reviewed as well.

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LETTER TO THE EDITOR

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Rapid exome sequencing to aid diagnostics in genetic disorders: Implementation and challenges in the Singapore context

Dear Editor,

There is a high burden of genetic disorders in patients admitted to the intensive care unit (ICU), ranging from 45–56%,[1,2] and delayed definitive diagnoses with a long diagnostic odyssey often contribute to increased healthcare costs.[3] The application of clinical exome sequencing in ICU has been gaining traction, where short turnaround time (usually within 2 weeks), coupled with relatively high diagnostic yield (30–40%), allows for significant changes in the medical management of patients with rare diseases,[3,4] and provides answers to patients and their families.

As a follow-up to the Singapore Undiagnosed Disease research programme,[5,6] we worked on translating the research into a rapid exome sequencing (RapidSeq) in April 2018. This exercise focused on known Mendelian genes, for critically ill patients admitted to the neonatal ICU (NICU) or children's ICU (CICU) with suspected genetic disorders. Since then, we have extended this to include other families requiring urgent genetic testing outside the ICU setting.

This study is a prospective, observational study on the use of rapid genomics-based diagnostics for patients at KK Women's and Children's Hospital, Singapore where a genetic disease was suspected. The aim was to provide a genetic diagnosis within 10 days for these patients and/or families. In this study, we present our framework as well as initial results in implementing RapidSeq and highlight the lessons learnt and challenges faced, some of which are unique in the Singapore context.

Ethics approval was obtained from the SingHealth Central Institutional Review Board. Using existing hospital services, our team comprised a clinical research coordinator, laboratory scientists, bioinformaticians, genetic counsellors, a genetics specialty nurse, and a team of clinical geneticists to oversee the logistics and implementation. The overall process from enrolment to results analysis and disclosure is described in the online Supplementary Materials and Fig. S1.

Patients were eligible if admitted to the NICU/CICU, or needed an urgent result, e.g. for prenatal care, and deemed suitable for testing by the clinical genetics team. Patients were ineligible if (1) a secure clinical diagnosis (such as Down syndrome) was made or previously known, (2) an underlying genetic aetiology was considered unlikely, or (3) parents were unavailable or declined to participate.

Clinical features were characterised by the attending geneticist, with provisional clinical diagnoses established. When indicated, chromosomal abnormalities were ruled out using karyotyping and/or chromosomal microarray analysis. Individuals who fulfilled the inclusion and exclusion criteria were then recruited, and pre-test counselling and consenting were performed by genetic counsellors.

Targeted sequencing of exonic regions of 4,813 genes associated with human diseases (i.e. clinical exome) was performed on extracted DNA, followed by bioinformatic analysis. Variants were classified according to the published guidelines[7] with a clinical report being generated within a target turnaround time of 10 days.

From April 2018 to January 2019, 10 cases were enrolled into RapidSeq, with ages ranging from 3 days to 4.5 months old. Seven were from NICU, 2 were from CICU, and 1 was a stored fetal DNA sample where the mother was 12 weeks pregnant with a second pregnancy (online Supplementary Table S1).

In 5 of the 10 cases (50%), a genetic diagnosis was achieved (Table 1), although 1 case was only diagnosed on re-analysis of data 2 years later. For 3 of the 5 cases, the diagnosis led to changes being implemented in the patient's management plan. The median turnaround time for results was 9.5 working days (range 5–19 days) (online Supplementary Table S2).

For cases 2, 6 and 10, the discovery of an underlying unifying diagnosis provided more clarity to the patient's care team, allowing for targeted management and surveillance. For example, case 6 had a pathogenic mutation in *SAMD9*, consistent with an ultra-rare diagnosis of MIRAGE (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes and Enteropathy) syndrome. Prior to diagnosis, the child was being managed by multiple specialists in an organ-centric manner. Identification of her diagnosis allowed for a more holistic and targeted management, and furthermore facilitated surveillance for other complications, including haematological malignancy and immunodeficiency.

Several challenges were faced during implementation. These included (1) facilitating care in a multidisciplinary team, which required effective coordination between the clinical and laboratory teams; (2) prolonged turnaround

Table 1. Patients with positive genetic results

	Gene	Variant	Zygosity	Variant classification	Inheritance	Clinical features*	Clinical impact	
							Change in management	**Genetic counselling for family planning**
Case 2	*KIF1A*	c.757G>A (p.Glu253Lys)	Heterozygous	Pathogenic	De novo	**Developmental delay**, intellectual disability, peripheral neuropathy, microcephaly, distal arthrogryposis	☒ Allowed holistic management of the child with surveillance for complications such as eye review for optic atrophy and visual impairment.	☒
Case 5	*IFT122*	c.1980C>A (p.Tyr660Ter) c.694G>A (p.Gly232Ser)	Heterozygous Heterozygous	Pathogenic Likely pathogenic	Paternal Maternal	Cranioectodermal dysplasia: **skeletal dysplasia**, ectodermal defects, joint laxity	□ Not applicable	☒
Case 6	*SAMD9*	c.3406G>C (p.Glu1136Gln)	Heterozygous	Likely pathogenic	De novo	MIRAGE (Myelodysplasia, infection, restriction of growth, drenal hypoplasia, genital phenotypes and enteropathy) syndrome: **developmental delay, adrenal insufficiency**, genital underdevelopment, **thrombocytopaenia and/or anaemia**, **severe invasive infections** and **immunologic abnormalities**.	☒ Allowed holistic and targeted management, with surveillance for other complications, including haematological malignancy and immunodeficiency.	☒
Case 8	*FGFR3*	c.1620C>A (p.Asn540Lys)	Heterozygous	Pathogenic	De novo	Hypochondroplasia: **short stature**, **lumbar lordosis**, short and broad bones, caudad narrowing of the interpediculate distance of the lumbar spine.	☒ Surveillance for skeletal complications of hypochondroplasia.	☒
Case 10	*SHOC2*	c.4A>G (p.Ser2Gly)	Heterozygous	Pathogenic	De novo	Noonan-like syndrome with loose anagen hair: **short stature**, **cognitive deficits**, **cardiac defects**, ectodermal abnormalities.	☒ Allowed holistic and targeted management, with surveillance for other complications such as short stature and need for regular growth monitoring.	☒

* Clinical features in bold are those seen in our patients
☒ present □ absent

time due to (a) difficulties with pre-test counselling as parents were overwhelmed by the medical issues, and concerns about insurance discrimination; and (b) sample limitations such as blood transfusions, often necessitating alternative sample collection methods such as skin biopsy for skin fibroblast culture and DNA extraction (case 6 in online Supplementary Table S3); (3) cost of testing is prohibitive, with RapidSeq calculated to cost SGD6,000 at present; and (4) difficulty with coordination of bioinformatics processing due to limited internet access of the computers in the Singapore public healthcare sector. Genomics data have to be transferred via a physical hard disk, which requires coordination between the laboratory and the bioinformatics team.

There are limitations to RapidSeq testing, including only the clinical exome being targeted, the bioinformatics filtering process and variants of uncertain significance (case 7, online Supplementary Table S3). Lack of local reference genomic databases often results in patients of Asian ancestry being more likely to receive ambiguous genetic test results or variants of uncertain significance.[8] We used trio-based sequencing as a way to improve our variant filtering process, balancing it against the increased cost associated with sequencing, as illustrated by the reduced number of candidate variants (online Supplementary Table S4). Correlation with clinical phenotype may also be difficult, especially in the neonatal setting, whereby clinical features may develop with age and be less recognisable when young,[9] (case 8, online Supplementary Table S3). This emphasises the importance of re-analysing data from unsolved cases at a later time point, which could uncover the presence of variants in newly discovered genes or new phenotype-genotype associations.[10]

Our results emphasise the potential clinical utility of RapidSeq in critically ill patients. RapidSeq is an effective method for diagnosing patients with rare diseases, which aids in shortening the diagnostic odyssey, while allowing clinicians to appropriately tailor management for the underlying disorder. However, many challenges still remain, and continued efforts to optimise RapidSeq for future use are needed.

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Diagnostic accuracy of multiparametric MRI in endometrial cancer and its adjunctive value in identifying high-risk women requiring surgical staging

Dear Editor,

Endometrial cancer is the most common gynaecological cancer in developed countries, with a five-year survival rate of 81%.[1,2] Prognostic factors include the International Federation of Gynecology and Obstetrics (FIGO) stage, depth of myometrial invasion (MI), lymph node involvement, cervical stromal involvement, and histological grade. Total hysterectomy with bilateral salpingo-oophorectomy (THBSO), pelvic and para-aortic lymph node dissection is the standard staging procedure for endometrial cancer.[3] Decision on adjuvant therapy for endometrial carcinomas is based upon clinicopathologic factors such as FIGO stage and tumour grade.[4] Multiparametric magnetic resonance imaging (mpMRI) has been reported to have high sensitivity and specificity in the detection of deep MI.[5-7]

We sought to evaluate the diagnostic accuracy of pelvic mpMRI in determining MI and the adjunctive value that it may add to high-grade carcinoma detected on endometrial biopsy ("high-grade endometrial biopsy") in identifying high-risk patients (deep MI or ≥ Stage 1B disease).

We reviewed consecutive cases of all primary endometrial cancers on the database at the National Cancer Centre Singapore over a 5-year period from 1 January 2010 to 31 December 2014. The inclusion criteria were: patients with newly diagnosed non-metastatic primary endometrial carcinomas, preoperative pelvic mpMRI, THBSO performed with curative intent, pathological review, and management plan discussed at the Gynaecologic Oncology tumour board. Cases with synchronous tumours or insufficient data were excluded.

Our MRI protocol included anatomical T1-weighted and T2-weighted sequences, combined with functional diffusion-weighted imaging and dynamic contrast-enhanced (DCE) imaging. The depth of MI was measured on MRI and then dichotomised as <50% or ≥50%.

All pathological specimens were reviewed by 2 gynaecologic pathologists. The microscopic depth of MI in millimetres (mm) in relation to the total thickness of the myometrium was classified as <50% or ≥50% without reference to MRI findings.

A total of 171 cases were analysed. There were 72 (42.1%) cases classified as FIGO Stage ≥1B. The majority (152/171, 88.9%) were of the endometrioid adenocarcinoma subtype. Lymph node dissection was performed in 149/171 (87.1%) of cases, of which 17/149 (11.4%) were positive for lymph node involvement.

Of the 171 cases, 64 (37.4) were found to have radiologic evidence of deep MI while 59 (34.5%) showed histopathologic evidence of deep MI. The overall sensitivity was 81.4% (95% confidence interval [CI] 69.1–90.3) and the specificity was 85.7% (95% CI 77.8–91.6). The positive predictive value (PPV) was 75.0% (95% CI 65.2–82.8) and the negative predictive value (NPV) was 89.7% (95% CI 83.6–93.7). The positive likelihood ratio (LR+) was 5.69 (95% CI 3.56–9.11) and the negative likelihood ratio (LR-) was 0.22 (95% CI 0.13–0.37).

The overall sensitivity of preoperative pelvic mpMRI in the detection of ≥ Stage 1B disease was 66.7% (95% CI 54.6–77.3) and specificity was 83.8% (95% CI 75.1–90.5). The PPV was 75.0% (95% CI 65.1–82.9) and the NPV was 77.6% (95% CI 71.2–82.9). The LR+ was 4.12 (95% CI 2.56–6.65) and the LR- was 0.40 (95% CI 0.28–0.56) (Table 1).

In this analysis, 130 (76%) cases with pre-hysterectomy endometrial biopsy performed were included. In the detection of deep MI (≥50%), sensitivity increased from 37.2% (high-grade endometrial biopsy alone) to 90.7% with the addition of preoperative pelvic mpMRI. PPV increased from 50.0% to 60.0% and NPV increased from 72.5% to 93.9%. LR+ increased from 2.02 to 3.03.

In the detection of ≥ Stage 1B disease, sensitivity increased from 34.6% (high-grade endometrial biopsy alone) to 76.9% with the addition of preoperative pelvic mpMRI. PPV increased from 56.3% to 61.5% and NPV increased from 65.3% to 81.5%. LR+ increased from 1.93 to 2.40.

Depth of MI is the most important prognostic factor in endometrial cancer with a strong correlation to tumour grade, cervical extension, and lymph node involvement.[8-10] DCE imaging shows higher sensitivity in detecting deep MI compared to single-phase contrast-enhanced imaging.[7]

Our study showed that mpMRI yielded a sensitivity of 81.4% and specificity of 85.7% in the detection of deep MI (within the range reported in several meta-analyses in the literature[5-7]). Improved sensitivity (85.1%) and specificity (86.7%) were obtained when cases of non-endometrioid histology subtypes were excluded.

Table 1. Diagnostic accuracy of mpMRI

	For the identification of ≥50% depth of MI on final histology		For the identification of ≥ Stage 1B disease (high-risk) on final histology	
	All cases (n=171)	**Cases with endometrioid histology only (n=152)**	**All cases (n=171)**	**Cases with endometrioid histology only (n=152)**
Sensitivity, %	81.4 (69.1–90.3)	85.1 (71.7–93.8)	66.7 (54.6–77.3)	66.1 (52.6–77.9)
Specificity, %	85.7 (77.8–91.6)	86.7 (78.6–92.5)	83.8 (75.1–90.5)	83.9 (74.8–90.7)
PPV, %	75.0 (65.2–82.8)	74.1 (63.4–82.5)	75.0 (65.1–82.9)	72.2 (61.2–81.1)
NPV, %	89.7 (83.6–93.7)	92.9 (86.7–96.3)	77.6 (71.2–82.9)	79.6 (73.0–84.9)
LR+	5.69 (3.56–9.11)	6.38 (3.86–0.55)	4.12 (2.56–6.65)	4.10 (2.49–6.74)
LR-	0.22 (0.13–0.37)	0.17 (0.09–0.34)	0.40 (0.28–0.56)	0.40 (0.28–0.58)

LR+ : positive likelihood ratio; LR- : negative likelihood ratio; MI: myometrial invasion; mpMRI: multiparametric MRI, MRI: magnetic resonance imaging; NPV: negative predictive value; PPV: positive predictive value
Values inside parentheses represent associated 95% confidence intervals

In the identification of patients with ≥ Stage 1B disease, preoperative pelvic mpMRI has moderate sensitivity of 66.7% but maintains a high specificity of 83.8%. The low false positive rate improves the selection of patients who are likely to have higher risk features other than MI alone, such as cervical involvement, parametrial extension and lymph node involvement, thereby reducing the likelihood of low-risk patients having to undergo more extensive surgery unnecessarily.

The tumour grade of endometrial biopsy is a significant prognostic factor in endometrial cancer and a grade 3 lesion is associated with deep MI. Our results showed high specificity (81.6%) for preoperative high-grade endometrial biopsy in predicting MI ≥50%. However, its sensitivity is unacceptably low (37.2%), indicating a significant proportion of patients with grade 1 or 2 preoperative endometrial biopsy also have deep MI. The addition of pelvic mpMRI to endometrial biopsy grading improved sensitivity while maintaining moderate specificity. This highlights the adjunctive value of mpMRI to preoperative endometrial biopsy as it considers not only inherent disease biology based on grading but also the extent of tumour progression in terms of MI at the time of diagnosis when treatment decisions need to be made.

In the detection of deep MI or high-risk (≥ Stage 1B) disease, mpMRI alone provided moderate to high sensitivity and specificity. When utilised together with preoperative endometrial biopsy grading, there was a further increase in sensitivity with a slight reduction in specificity. This is important as it helps to exclude lower-risk patients from having to undergo full surgical staging, including pelvic lymphadenectomy.

We reviewed discordant cases to understand the intrinsic limitations in the accuracy of mpMRI in predicting the depth of MI. The presence of fibroids was the most common contributing factor. Other factors include difficulty in obtaining an accurate measurement in cases where the native myometrium was very thin, the presence of myometrial adenomyosis, and the nature of the tumour invasion pattern.

Based on our findings, preoperative mpMRI provides moderate sensitivity and specificity in detecting deep MI in endometrial cancer and provides an adjunctive value in improving the sensitivity of detecting high-risk women requiring full surgical staging compared to endometrial biopsy alone.

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Lichen planus pemphigoides after pembrolizumab immunotherapy in an older man

An 84-year-old Chinese man with stage IV non-small cell lung cancer was initiated on pembrolizumab, an anti-programmed cell death (PD)-1 monoclonal antibody, 4 times per week. Seven weeks later, on the day of his third cycle, he developed a rash on his chest and right axilla, which subsequently resolved with 1% hydrocortisone cream, and there was no interruption to his immunotherapy. Eleven weeks after the initiation of pembrolizumab, the patient reported new pruritic, purpuric papules on his buttocks, forearms and legs. There were associated blisters seen on his feet. The rash progressively worsened despite topical steroids (Fig. 1).

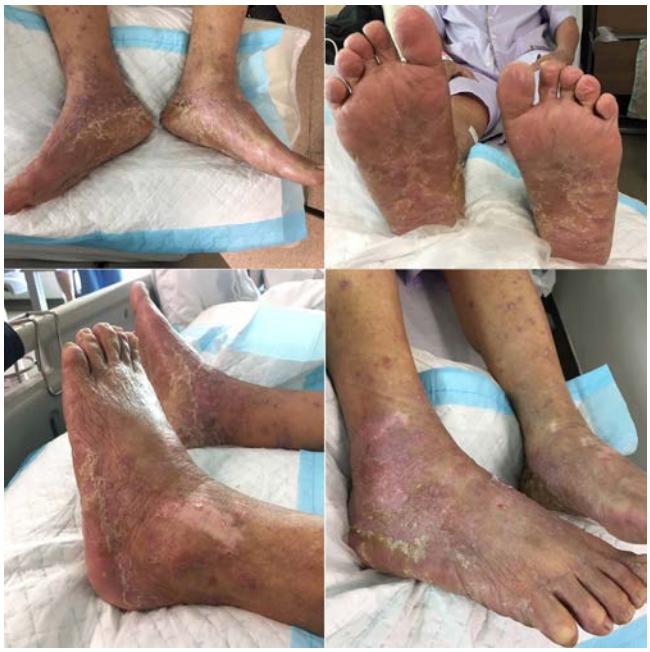

Fig 1. Violaceous plaques and flat-topped papules on both legs.

What is your diagnosis?

A. Bullous pemphigoid
B. Bullous lichen planus
C. Disseminated superficial actinic porokeratosis
D. Lichen planus pemphigoides
E. Lichenoid graft versus host disease

A skin biopsy was performed on his right shin. Histologically, basal vacuolar alteration with a few apoptotic keratinocytes and subepidermal clefting (Max-Joseph spaces) were observed, accompanied by a lichenoid infiltrate of lymphocytes, histiocytes and eosinophils. Melanin incontinence and melanophages were also present within the upper dermis (Fig. 2). Direct immunofluorescence (DIF) demonstrated bright linear deposits of immunoglobulin G and complement 3 along the basement membrane zone (Fig. 3). Overall, the findings were consistent with lichen planus pemphigoides (LPP).

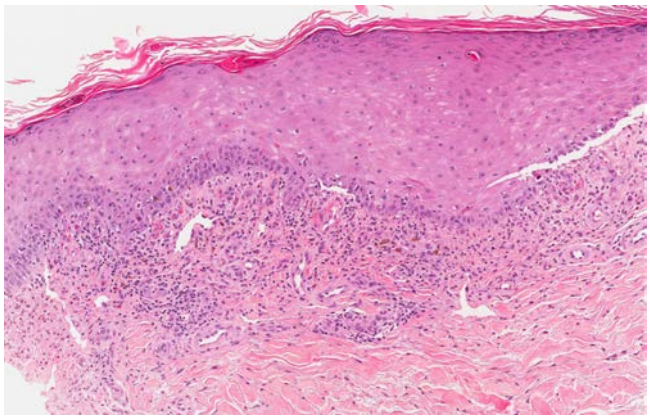

Fig. 2. Haematoxylin and eosin staining (100x magnification). Basal vacuolar alteration with a few apoptotic keratinocytes, accompanied by a lichenoid infiltrate of lymphocytes, histiocytes and eosinophils.

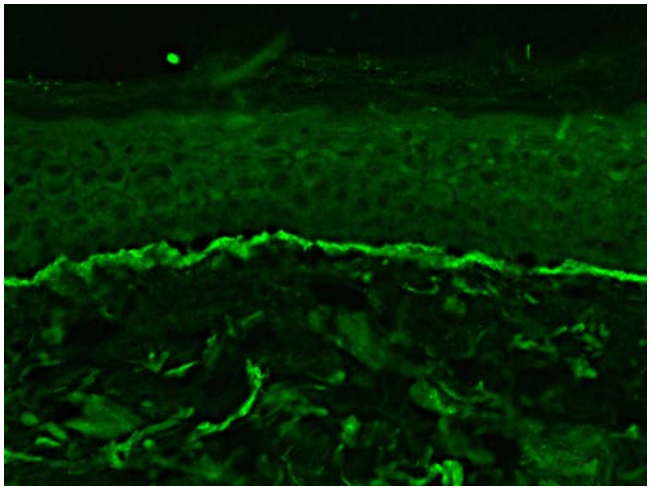

Fig. 3. Direct immunofluorescence showing bright linear deposits of immunoglobulin G and complement 3 along the basement membrane zone.

Answer: D

The patient was treated with topical clobetasol ointment, and the rash went into remission 6 weeks later, leaving post-inflammatory hyperpigmentation. Despite his cutaneous eruption, there was no interruption to his immunotherapy. He continued to receive infusions of pembrolizumab 4 times per week and has remained quiescent for 4 months.

Close differential diagnoses are bullous pemphigoid and bullous lichen planus (LP). Bullous pemphigoid is an autoimmune blistering disease that is characterised by the presence of urticated plaques and tense blisters. It may also be precipitated by PD-1 inhibitors. However, our patient does not have urticated plaques. His rash consisted of violaceous flat-topped papules and plaques.

Bullous LP is a variant of LP where bullae develop at sites of pre-existing LP lesions. This is due to severe basal vacuolar degeneration at the dermo-epidermal junction (DEJ). DIF findings of bullous LP are the deposition of immunoglobulins in cytoid bodies at the DEJ. In our patient, blisters developed on his skin, unaffected by LP lesions.

Disseminated superficial actinic porokeratosis (DSAP) is an inherited keratinisation disorder that causes red-brown scaly, annular papules and plaques mainly over the limbs. DSAP may also arise in patients who are immunocompromised. Although our patient also had a rash distributed over the limbs, the morphology of the rash is inconsistent with DSAP.

Lichenoid graft versus host disease (GVHD) is a variant of GVHD that can occur following bone marrow transplantation. A skin rash that resembles LP can occur on many sites, including nails and mucosal surfaces. This is not the diagnosis for our patient as he did not undergo bone marrow transplantation and did not exhibit extracutaneous manifestations of GVHD.

Cutaneous side effects have been reported in approximately 20–40% of patients treated with PD-1 inhibitors.[1] Common cutaneous adverse events include eczematous dermatitis and pruritus, though a wide range of cutaneous manifestations such as vitiligo, lichenoid dermatitis, psoriasiform eruptions and bullous pemphigoid have also been observed.[2]

The treatment of lichenoid reactions from anti-PD1 agents similarly includes topical and systemic corticosteroids, based on a case series by Tetzlaff et al.[3] Most patients had improvements in their skin lesions after using topical corticosteroids and stopping their anti-PD-1 therapy.

Among the 7 U.S. Food and Drug Administration-approved checkpoint inhibitors, LPP has been reported in treatment involving the use of nivolumab (3 cases), pembrolizumab (2 cases) and atezolizumab (1 case) thus far. Drug latency ranged from 12–24 weeks, with 2 cases developing LPP after drug cessation. In Sato et al.'s report, the patient had also been on vildagliptin, and this was deemed to be the more culpable drug.[4] Okada et al. reported the onset of bulla 12 weeks after pembrolizumab cessation, although the patient had already developed prior lesions consistent with LP 12 weeks into pembrolizumab treatment.[5] Lindner et al. reported an attempt to continue nivolumab, which led to further cutaneous worsening 12 weeks later and eventual cessation of the drug.[6] In all other 3 cases, anti-PD1 agents were discontinued contemporaneously, with improvement or resolution of skin lesions occurring after 0.5 to 6 months. Of note, Schmidgen et al. highlighted the potentially recalcitrant nature of this dermatosis, whereby the skin lesions could not be controlled over a 12-month period despite potent immunosuppression including prednisolone, rituximab or sirolimus; remission was eventually achieved with a 6-month course of dapsone 50mg twice daily.[7]

Indeed, our patient's drug latency corresponds to that in the literature, but to our knowledge, we also demonstrate the first successful resumption of immunotherapy without a worsening of LPP lesions. Immune-related adverse events (irAEs) to checkpoint inhibitors—of which LPP is one—may arise from the following mechanisms. First, pharmacologic blockade of the PD-1 pathway promotes T cell responses towards both malignancy and self. The latter results in proliferation of self-reactive T cells, which drive autoimmunity and thus, irAEs.[8] Second, cross-reactivity between tumour antigens and self-antigens, including skin epitopes,[9] has been described. Such molecular mimicry may account for cutaneous irAEs as bystander sequelae, a result of T cell-mediated anti-tumour responses. Indeed, evidence of irAEs being associated with superior oncologic outcomes[10] lends weight to the above mechanistic hypotheses in the second point. Extrapolating from the second hypothesis, it is the authors' view that successful treatment with anti-PD-1 therapy leading to a reduction in tumour burden also concomitantly reduces tumour antigen load and thus, risk of cross-reactivity. This may potentially explain the lack of LPP recurrence despite continuation of anti-PD-1 therapy, as experienced by our patient.

With the increasing use of PD-1 antibodies in the treatment of various malignancies, recognising rare cutaneous toxicities would become increasingly important. Our case demonstrated typical features of LP pemphigoides both clinically and immunohistologically,

and highlights the need to characterise and biopsy patients presenting with immunotherapy-induced rashes to improve understanding of this phenomenon. The case also demonstrates that a lichenoid reaction with pembrolizumab may not preclude the continuation of immunotherapy.

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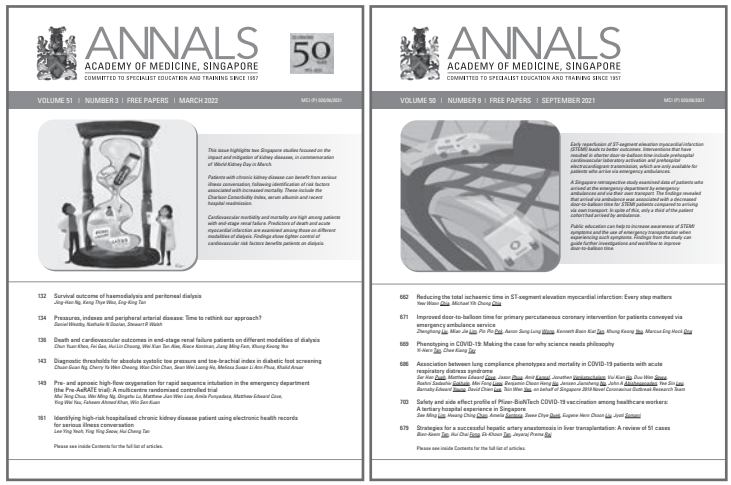

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