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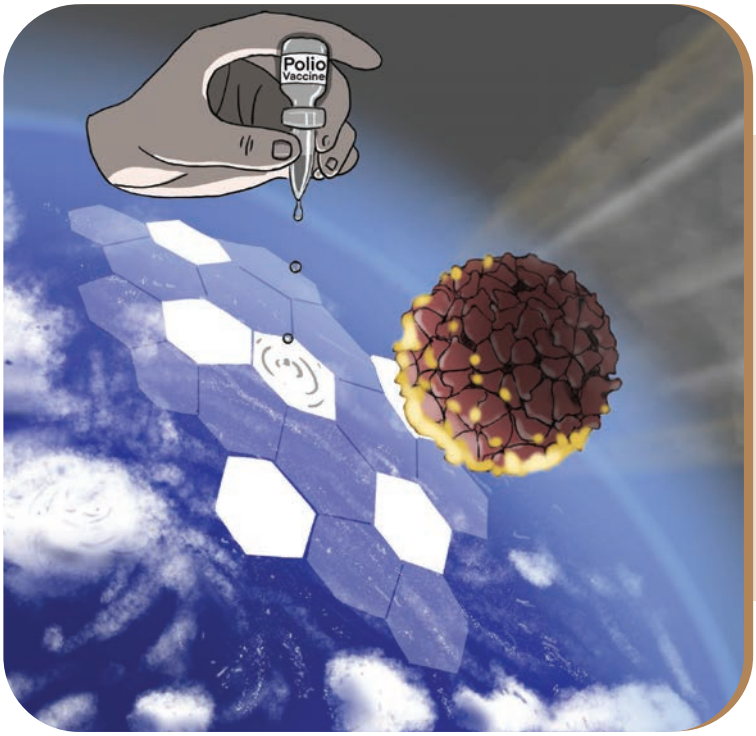

A recent resurgence of paralytic poliomyelitis (polio) cases, from vaccine-derived poliovirus (VDPV) in non-endemic countries, highlights an increased risk of re-infection from the importation and transmission of wild poliovirus and VDPV.

This review provides an update on the clinical manifestations of polio and highlights key public health interventions aimed at reducing the risk of poliovirus transmission globally.

Illustration by Xinyu Li

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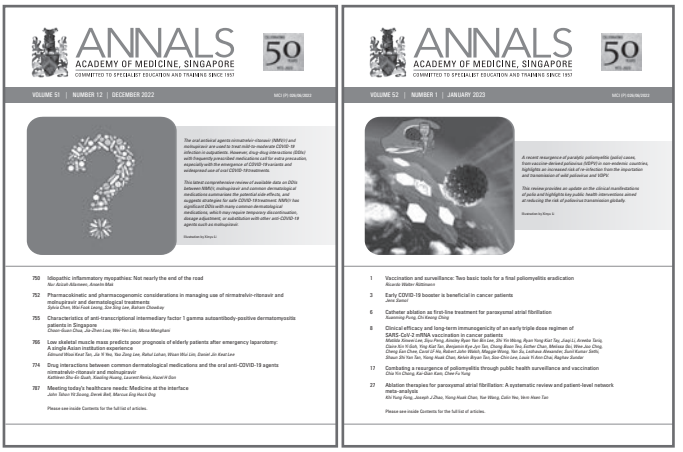

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EDITORIALS

ORIGINAL ARTICLE

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EDITORIAL

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Vaccination and surveillance: Two basic tools for a final poliomyelitis eradication

Ricardo Walter Rüttimann [1]*MD*

Over the past 3 decades, the Global Polio Eradication Initiative (GPEI) has strived to achieve a poliomyelitis (polio)-free world. Wild poliovirus (WPV) types 2 and 3 were eradicated in 2015 and 2019, respectively. The World Health Organization (WHO) South-East Asia Region was declared free of poliovirus in 2014, and the WHO African Region was certified free of WPV in August 2020. However, new barriers have risen, hampering the final steps to eradication.[1]

As the world—and health systems—adjusted to the latest global health threat posed by COVID-19, GPEI launched the Polio Eradication Strategy 2022–2025, which integrates the approaches needed to deliver on the promise of eradication.

Five mutually reinforcing objectives were set to achieve 2 elemental goals, namely, to permanently interrupt all poliovirus transmission in the remaining WPV-endemic countries of Afghanistan and Pakistan; and stop circulating vaccine-derived poliovirus (cVDPV) transmission and prevent outbreaks in non-endemic countries. The 5 strategic objectives are (1) to generate greater political will by re-envisioning GPEI's relationship with governments and systematising political advocacy; (2) to generate vaccine acceptance through community engagement that reduces refusals to vaccination and increases childhood vaccine coverage; (3) to expand integration efforts with a broader range of partners in immunisation, essential health care and community services; (4) to improve frontline success through changes to campaign and outbreak response operations, including the recognition and empowerment of the frontline workforce; and (5) to enhance detection and response through sensitive surveillance that provides the programme with critical information for action.[1]

In alignment with the WHO's Immunization Agenda 2030 (IA2030) and the Global Alliance for Vaccines and Immunization's 5-year strategy for 2021–2025 (GAVI 5.0), this new strategy by GPEI offers a more holistic approach to immunisation and shares the IA2030 principles of being people-centred, country-owned, partnership-based and data-guided.

In this issue of the *Annals*, Chong et al.[2] describe the polio vaccination and epidemiologic surveillance strategies carried out in Singapore and stress the importance of the GPEI objectives mentioned above. Singapore was declared polio-free by WHO in 2000, and the country reported its last imported polio case in 2006. The use of combined vaccines in the national immunisation programme and sustained coverage rates of >95% were crucial in achieving this goal. Although the fall in vaccination uptake peaked at about 10% at the beginning of the COVID-19 pandemic in 2020, major efforts were undertaken to recover high pre-pandemic levels. This accomplishment must be underscored since many countries and regions worldwide suffered dramatic declines in immunisation rates, as vaccine hesitance and antivaccine groups advanced to discredit immunisation programmes.[3] Finally, the authors highlight a new vaccination tool, the novel oral poliovirus vaccine type 2 (nOPV2), approved by WHO under its Emergency Use Listing for use in countries affected by cVDPVs.

Why the need for a new oral vaccine to prevent polio? We know the live-attenuated Sabin oral poliovirus vaccine (OPV) virus can revert to the virulent phenotype following replication in the human intestine. In environments with poor sanitation and low immunisation coverage, these cVDPVs can lead to paralysis outbreaks. From 2016 to 2020, the number of cVDPVs increased dramatically, particularly in Africa. In response, a scientific consortium was set up, funded by the Bill & Melinda Gates Foundation. The mission was to explore the development of more genetically stable nOPVs, which would maintain the advantages of Sabin OPV (with ease of delivery and mucosal immunogenicity) but decrease the risk of VDPV. The initial focus of this consortium was type 2 poliovirus, as WPV type 2 was no longer circulating, and the imminent global withdrawal of Sabin type 2 from trivalent OPV increased the risk of outbreaks of cVDPV type 2 (cVDPV2). Subsequently,

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it was found that cVDPV2 was the predominant strain causing paralytic polio outbreaks; from 2020 to 2022 this vaccine strain was responsible for 97–99% of all polio cases globally.

Results of phases 1 and 2 studies on nOPV2 showed that the candidate vaccine was safe, immunogenic and genetically stable in all age groups tested from the age of 18 weeks to 50 years. These results allowed the WHO Prequalification Team to authorise this candidate vaccine through their Emergency Use Listing procedure in November 2020.[4] Since March 2021, approximately 450 million doses of nOPV2 have been distributed for deployment in field settings to combat cVDPV2 outbreaks in 21 countries. More than 80% of countries where the vaccine was used did not show evidence of breakthrough cVDPV2 cases to date, confirming the safety and stability of the new vaccine.[5] After this success, nOPV types 1 and 3 are currently under development.

Chong et al. also emphasise the importance of epidemiologic surveillance. While clinical surveillance—through the reporting, follow-up and microbiological study on all cases of acute flaccid paralysis—is critical, environmental surveillance of polioviruses in sewage systems and molecular epidemiology involving genetic sequencing of detected polioviruses are also crucial. This approach has been used by the Global Polio Laboratory Network in support of GPEI, to determine the relationship between polioviruses in various chains of VDPV transmissions.[6]

Two incidents in 2022 impressed the importance of environmental surveillance. The first was the report on the presence of VDPV2 in multiple sewage samples taken from London, UK. The second was the confirmation of a case of paralytic polio due to VDPV2 in an unvaccinated young adult from an under-vaccinated community in New York, US. Although both countries exhibit high overall inactivated polio vaccine coverage, the absence of OPV use in the UK and US since 2004 and 2000, respectively, yields limited intestinal mucosal immunity. Indeed, the risk of further spread and persistent transmission of poliovirus is not trivial, particularly among immunocompromised populations.[6]

The use of novel oral vaccines and accessibility to vaccines, together with new epidemiological surveillance tools, are crucial in the final steps to eradicate polio—a disease that has afflicted humanity for centuries.

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EDITORIAL

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Early COVID-19 booster is beneficial in cancer patients

Jens Samol [1,2,3,4,5] *MD*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its corresponding coronavirus disease (COVID-19) was first reported as a cluster of pneumonia cases in Wuhan, China, on 31 December 2019[1] and led to an unprecedented pandemic in modern times. It quickly overwhelmed healthcare systems around the world, and rendered immunocompromised patients, such as those with cancer, particularly vulnerable to severe infections.

Also unprecedented was the rapid development of several highly effective vaccines, thanks to concerted global efforts. Once COVID-19 vaccinations were available, the Ministry of Health (MOH) in Singapore implemented a nationwide SARS-CoV-2 vaccination programme for healthcare staff in early January 2021, started a pilot for vaccinations for senior citizens in late January 2021, and progressively made the COVID-19 vaccine freely available for all Singaporeans and permanent residents. In line with emerging data thereafter, MOH offered a booster to immunocompromised patients as early as 2 months after the second dose. Currently, as of 7 November 2022, MOH encourages all eligible residents aged 18 years and above[2] to undergo a second COVID-19 booster or a fourth vaccination dose.

Other regulatory healthcare institutions recommended administering a COVID-19 booster within 3–6 months of the completion of the initial mRNA vaccination course and the Committee for Medicinal Products for Human Use approved an extra dose of the COVID-19 mRNA vaccines at least 28 days after the second dose.[3]

Against this background, the study by Lee et al. is timely. In their large, prospective observational study, the authors[4] presented real-world efficacy data in haematological (40/273) and solid cancer (233/273) patients in Singapore who received 2 doses of an mRNA vaccine, either BNT162b2 or mRNA1273, followed by a 3rd dose of BNT162b2 against SARS-CoV-2 during the COVID-19 pandemic. In total, 273 patients were recruited between July 2021 and March 2022 and about 3 quarters were treated with a real-world representative spread of available anti-cancer therapies in a wide range of cancer types. All patients were tested using the GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit. Patients were seronegative at baseline and underwent blood tests after each vaccination, demonstrating seroconversion rates of 35.2%, 79.4% and 92.4%, respectively. The authors stated that after 3 doses, patients treated for haematological malignancies had lower antibodies (57.3%±46.2) compared to solid cancer patients on immunotherapy (94.1%±9.56, $P<0.05$) and chemotherapy (92.8%±18.1, $P<0.05$) confirming a lower antibody response in haematological malignancies. The solid cancer patient population comprised gastrointestinal cancers at 40.3%, followed by breast cancer (19%), lung cancers (9.5%) and others. Lee et al. considered patients not receiving anti-cancer therapy, or patients receiving radiotherapy or endocrine therapy only, as the control group. Patients with severe infections, defined as infections resulting in hospitalisation, intensive care unit (ICU) care, oxygen therapy or death, had significantly lower mean antibody levels than non-infected (28.3% versus 77.0%, $P<0.05$) and mildly infected (28.3% vs 65.8%, $P<0.05$) patients. Eighteen out of 77 patients with SARS-CoV-2 infection had severe COVID-19. Of these, 9 patients were haematology patients, and 5 were solid cancer patients, with both groups receiving respective active anti-cancer therapy. Patients on active anti-cancer therapy who received a third COVID-19 vaccine dose within 90 days of their second vaccination (early booster dosing), did not suffer severe COVID-19, underlining the effectiveness of early booster administration.

A systematic review of 30 published studies that reviewed data on the administration of a third COVID-19 vaccination[5] found that in cancer or immunocompromised patients, the mean seroconversion was 39.4% before and 66.6% after the third COVID-19

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Table 1. Risks of reduced antibody responses post-COVID-19 vaccination while on anti-cancer therapy

Relevant reduction of antibody likely (>50%)	Relevant reduction of antibody possible (<50%)	Relevant reduction of antibody uncommon	Cellular therapy
• B cell depletion with monoclonal antibodies, BTK and/or BCL inhibitors • BCMA-targeted therapies • CD38-targeted therapies • JAK inhibitors	• Chemotherapy • Steroids • CDK4/6 inhibitors • Poly(ADP-ribose) polymerase inhibition	• Endocrine therapy • Tyrosine kinase inhibitors • Immune checkpoint inhibitors • Immunomodulatory drugs • Proteasome inhibitors	• Chimeric antigen receptor T cell therapy • Uncomplicated stem cell transplantation with stable engraftment

ADP: adenosine diphosphate; BTK: Bruton's tyrosine kinase; BCL: B cell lymphoma; BCMA: B cell maturation antigen; JAK: Janus kinase; CDK4/6: cyclin-dependent kinases 4 and 6

Adapted from Fendler A, de Vries EGE, GuertsvanKessel CH, et al. COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety. Nat Rev Clin Oncol 2022;19:385-401.

vaccination. In October 2022, Youssra et al.[6] published a systematic review of a third COVID-19 vaccination in haematological and solid cancers. The authors described that the response after a third dose was reduced in haematological cancers as compared to solid cancers. They also reported that systemic anti-cancer therapy led to a poorer seroconversion in haematological cancers, likely driven by B cell depletion. The authors described that the interval between the second and the third vaccination ranged from 27 to 214 days, without a median range provided. Another difference to the study by Lee et al. was that some patients received a mix of mRNA and non-mRNA vaccinations, that is, heterologous vaccinations.

In terms of systemic anti-cancer therapy, a large retrospective cohort study in 29,152 vaccinated cancer patients suggested a clinical effectiveness of 57% (95% confidence interval [CI] 23–90) for patients on chemotherapy versus 76% (95% CI 50–91) for those on endocrine therapy and 85% (95% CI 29–100) without systemic therapy.[7] Fendler et al.[8] reviewed COVID-19 vaccines in cancer patients and categorised the risk of reduced antibody response after COVID-19 vaccinations into 4 groups. These groups were divided by their likelihood of relevant reduction of antibody being likely (>50%, B cell depletion), possible (<50%, chemotherapy), uncommon (hormone therapy), or treated with cell therapy (chimeric antigen receptor [CAR]-T cells) (Table 1). The data presented by Lee et al. concur well with this risk stratification, and the prospective observational design highlighted the differences in the risk of reduced antibody responses between haematological and solid cancers, although no patients treated with CAR-T cells and uncomplicated stem cell transplantation were enrolled.

The overall low risk of total COVID-19 infection in Lee et al.'s study population—77 out of 273—challenges the narrative that immunocompromised patients do not mount a sufficient response to vaccinations, potentially negating the need to provide passive immunity and indicating that oral antiviral therapies should be prioritised instead. However, this overall low COVID-19 infection in the study population could also be due to the fact that, in September 2021, 76.6% of the Singapore population had completed 2 doses of vaccination.[4] At the same time, MOH announced that a third vaccination dose was offered to immunocompromised patients.[4] Additionally, risk mitigation measures were in place with mandatory mask-wearing, and this would also have contributed to a lower risk of COVID-19 infection in cancer patients, as well as in the Singapore population as a whole.

Lee et al. acknowledged the limitations of using antibody production to evaluate the immunogenicity of vaccinations, and that the duration is unknown for cancer patients to maintain levels necessary for an immune response. In line with many studies demonstrating waning immunity, the initial positive results of an early COVID-19 booster are likely to reduce over time. This waning immunity has led some countries, including Singapore, to offer a second COVID-19 booster.[2] Lee et al. further highlighted that cellular immunity against SARS-CoV-2 is of particular importance in patients who are unable to mount an adequate humoral response. They suggested that future studies, investigating the role of cellular immunity in conferring protection against SARS-CoV-2, will help to answer this question. With regards to different types of cancers, gastrointestinal cancer patients were predominant in Lee et al.'s study but compared to Shroff et al.,[9] the spread of cancer types did represent a real-world situation more closely.

Lee et al. added to the body of evidence that a third vaccination or first booster against SARS-CoV-2 clearly reduced the number of cancer patients with severe COVID-19. This study also added evidence that the

third booster ought to be given within 90 days from the second. During the study duration, the primary COVID-19 vaccination rate within the Singapore population rose from 51% to 89%[10], indicating a successful Singapore-wide effort to fully vaccinate the population, protecting vulnerable patients, and reducing the healthcare burden in Singapore significantly. Lee et al. have shown that the administration of an early COVID-19 booster reduced severe COVID-19 infections in cancer patients further.

With this study, Lee et al. provided real-world evidence that an early third vaccination of an mRNA vaccine given while receiving anti-cancer therapy with targeted therapy and immunotherapy did not impair an immune response. In fact, the vaccine was effective, and an early SARS-CoV-2 booster reduced severe COVID-19 infections in all patients receiving chemotherapy. These findings showed that COVID-19-vaccinated cancer patients benefitted from an early booster in Singapore, and are likely too on a global level.

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EDITORIAL

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Catheter ablation as first-line treatment for paroxysmal atrial fibrillation

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Pharmacotherapy has been the mainstay of atrial fibrillation (AF) treatment. As AF progresses from paroxysmal to persistent, electrical and structural remodelling of the atria may become irreversible, rendering future rhythm-control therapies less effective. Results of earlier trials on rhythm control were disappointing and failed to establish the superiority of a rhythm-control strategy on cardiovascular outcomes, including mortality. This was attributed to populations in trials having longer established, persistent AF with potentially more advanced atrial fibrosis; and suboptimal results in sinus rhythm maintenance with the use of antiarrhythmic drugs alone. A sub-analysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial showed that achieving and maintaining sinus rhythm was associated with better outcomes than AF rhythm, but this clinical benefit appeared to be offset by the adverse effects of antiarrhythmic drugs.[1]

In recent years, substantial technical and technological advancements in AF therapies have led to the development of various AF ablation modalities. AF catheter ablation now plays a key expanding role in rhythm-control strategy through the isolation of pulmonary veins using various energy sources. The latest multisocietal guidelines recommend a trial of antiarrhythmic drugs prior to consideration for catheter ablation for patients with paroxysmal AF. However, the time from AF diagnosis to ablation has been identified as a modifiable and independent factor that is associated with AF ablation outcomes. There is an increasing body of literature supporting catheter ablation as a first-line therapy. Mechanistic studies have shown that catheter ablation led to substantial reversal of the adverse structural remodelling, which may potentially alter the natural history of AF in disease progression.[2] Early rhythm control with catheter ablation was also associated with an increased likelihood of AF-free survival, fewer repeated procedures, fewer recurrent hospitalisations, and a reduction in the progression to persistent AF.[3-5] Compared to older studies, the Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST-AFNET 4) trial reported an increasing contemporary trend of AF catheter ablation seen in the rhythm-control arm. Cather ablation was performed in 8% of the study population at enrolment, and up to 19.4% by 2 years.[6]

The recently published multicentre PROGRESSIVE-AF trial, which was conducted at 18 centres in Canada, built on these observations and demonstrated improvement in clinical outcomes. There is primarily a 75% reduction in progression to persistent AF after first-line ablation in relatively young patients with a median age of 58 years, with few comorbidities—other than hypertension, sleep apnoea and obesity—and presenting with symptomatic episodes of AF.[7] The median duration of AF was 1 year from the onset of diagnosis, again targeting a selected group of patients with early-onset AF.

In this issue of the *Annals*, Fong et al. sought to evaluate the effectiveness of various ablation therapies or medical therapy largely in patients with paroxysmal AF.[8] Relevant studies involving patients with paroxysmal AF were selected in the analyses. First-line catheter ablation as a whole was associated with reductions in AF recurrence and hospitalisations and had a similar safety profile as antiarrhythmic drugs.[9]

In this review, a total of 24 reliable and high-quality studies comprising 18 randomised controlled trials (RCTs) and 6 propensity score matched studies (PSMs) were included to generate individual patient data (IPD) network meta-analysis (NMA), in which the raw individual-level data for each study were obtained and used for synthesis. The authors reported consistent findings that all ablation modalities were superior to antiarrhythmic drugs in achieving freedom from AF or atrial tachyarrhythmia as the primary outcome. An important challenge in interpreting the results from the analyses is knowing the variability in study design and methodologic differences among the included clinical studies. The use of IPD holds several statistical advantages and serves as a rigorous statistical method known to be particularly advantageous for time-to-event analyses.[10]

In addition to eliminating or reducing atrial tachyarrhythmia recurrences, it is also necessary to

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understand whether first-line ablation is effective in improving important clinical endpoints such as quality of life, heart failure, stroke and mortality. Due to the small study size and low event rates in the majority of RCTs and PSMs included in the review article, the analyses were underpowered to detect any hard clinical endpoints such as stroke, all-cause mortality, and periprocedural complications.

Nonetheless, freedom of AF or atrial tachyarrhythmia remains a key clinical parameter used in predicting clinical response with AF ablation. This was particularly observed in the EAST-AFNET 4 trial as the effectiveness of this trial in improving cardiovascular outcomes at 5 years was mediated by the maintenance of sinus rhythm at the end of the follow-up period,[6] again highlighting the important need in the prevention of AF and atrial tachyarrhythmia recurrence. It is well recognised that the use of patient-reported symptoms alone is inadequate to detect the recurrence of AF or atrial tachyarrhythmia, given that many patients may develop asymptomatic episodes after ablation. However, significant heterogeneity in AF monitoring has also been noted. Options for monitoring of underlying cardiac rhythm include Holter monitors; longer-term monitoring such as 30-day event monitors; intermittent rhythm recording with devices such as the Apple Watch or KardiaMobile; and implantable loop recorders.

The main strength of the review article by Fong et al. lies in its comparison of multiple individual AF ablation modalities relative to antiarrhythmic drugs. Network meta-analyses from this review ranked the individual AF ablation modalities in a quantitative manner based on their respective P-score. The results favour combined cryoballoon-plus-radiofrequency ablation in the long term, and laser-balloon ablation in the short term. The authors commented that cryoballoon and radiofrequency ablation were complementary and more efficacious due to significantly fewer pulmonary vein reconnections. However, this advantage in procedural efficacy was offset by a longer procedural time compared to all other ablation modalities based on NMA of procedure time. However, there are insufficient clinical data to justify the use of one ablation modality over another. Moreover, it is still important to bear in mind that such results from meta-analyses may not lead to further advancement in knowledge relating to the topic of interest when the main findings are driven by the results of one trial. This is particularly the case when the technique of combined cryoballoon plus radiofrequency ablation was only performed in a single study.

In conclusion, the authors ensured the reliability and stability of results through layers of data analysis, including tests for publication bias and sensitivity analysis of the results. The review article provided greater evidence to support first-line ablation as a more effective and safe method for early rhythm control strategy in selected patients with paroxysmal AF. Extended and large-scale clinical trials and cost-benefit analyses are therefore required to further determine the optimal approach and timing to first-line AF ablation.

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ORIGINAL ARTICLE

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Clinical efficacy and long-term immunogenicity of an early triple dose regimen of SARS-CoV-2 mRNA vaccination in cancer patients

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ABSTRACT

Introduction: Three doses of SARS-CoV-2 mRNA vaccines have been recommended for cancer patients to reduce the risk of severe disease. Anti-neoplastic treatment, such as chemotherapy, may affect long-term vaccine immunogenicity.

Method: Patients with solid or haematological cancer were recruited from 2 hospitals between July 2021 and March 2022. Humoral response was evaluated using GenScript cPASS surrogate virus neutralisation assays. Clinical outcomes were obtained from medical records and national mandatory-reporting databases.

Results: A total of 273 patients were recruited, with 40 having haematological malignancies and the rest solid tumours. Among the participants, 204 (74.7%) were receiving active cancer therapy, including 98 (35.9%) undergoing systemic chemotherapy and the rest targeted therapy or immunotherapy. All patients were seronegative at baseline. Seroconversion rates after receiving 1, 2 and 3 doses of SARS-CoV-2 mRNA vaccination were 35.2%, 79.4% and 92.4%, respectively. After 3 doses, patients on active treatment for haematological malignancies had lower antibodies (57.3%±46.2) when compared to patients on immunotherapy (94.1%±9.56, $P<0.05$) and chemotherapy (92.8%±18.1, $P<0.05$). SARS-CoV-2 infection was reported in 77 (28.2%) patients, of which 18 were severe. No patient receiving a third dose within 90 days of the second dose experienced severe infection.

Conclusion: This study demonstrates the benefit of early administration of the third dose among cancer patients.

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Keywords: Cancer, oncology, SARS-CoV-2, third dose, vaccination

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CLINICAL IMPACT

What is New

- This study is the first in Singapore to evaluate the real-world efficacy of a third SARS-CoV-2 vaccine in cancer patients.
- This study is among the first in the world to assess the effect of tumour-type and anti-neoplastic treatment in determining vaccine response.

Clinical Implications

- An early triple dose regimen of SARS-CoV-2 vaccination is effective in cancer patients.
- Targeted therapy and immunotherapy do not impair SARS-CoV-2 antibody production.
- More SARS-CoV-2 vaccine doses strongly correlate with reduced infection severity.

INTRODUCTION

The spread of the SARS-CoV-2 virus has led to the ongoing worldwide COVID-19 pandemic. Initial studies have reported an increased vulnerability of patients with solid and haematological malignancies to SARS-CoV-2 infections.[1,2] Global efforts to combat SARS-CoV-2 led to the unprecedented rapid development of multiple vaccines, with reported efficacies of 94–98% at preventing severe disease.[3-6] However, early trials evaluating immunogenicity were limited in immunosuppressed individuals, largely excluding cancer patients on active chemotherapy, transplant patients, and patients with immunodeficiencies. Subsequent studies demonstrated that while most patients with solid organ malignancies develop adequate anti-viral immunity, patients with haematological malignancies had significantly lower seroconversion rates.[7-9] In particular, patients who had received highly immunosuppressive therapies such as anti-CD20 monoclonal antibodies and stem cell transplantation were at the highest risk of reduced seroconversion.[8,10,11]

The increased vulnerability to SARS-CoV-2 infections in cancer patients, coupled with the blunted immune response to vaccination, has prompted a third, fourth and even fifth dose to be administered to immunosuppressed individuals. Furthermore, previous publications have reported waning immunity 6 months following the second dose of mRNA vaccine BNT162b2 in healthy subjects.[12] A similar decrease in humoral response was also reported in patients with solid tumours on active cancer treatment 3 months after the second dose,[13] supporting the recommendation for administering a third dose in immunocompromised patients. Small-scale studies have demonstrated encouraging results, with increased virus-neutralising antibody titres immediately post-third dose for cancer patients.[10,13,14]

However, existing studies primarily reported immunogenicity responses to SARS-CoV-2 vaccinations, focusing on seroconversion rates and neutralising antibody levels. Few studies have demonstrated the real-world efficacy of vaccination in association with the severity of SARS-CoV-2 infections. This is a significant gap to be addressed, especially given recent evidence suggesting that the blunted immune response by SARS-CoV-2 vaccines in oncology patients makes them more susceptible to breakthrough infections,[15] coupled with the rapid emergence of antibody-evading SARS-CoV-2 variants (Delta and Omicron).[16,17]

In September 2021, 76.6% of the Singaporean population had completed 2 doses of vaccination, compared to 63.1% in the UK, 59.5% in Israel and 54.4% in the US.[18] At the time, the Ministry of Health (MOH), Singapore announced a third dose of SARS-CoV-2 vaccination to be offered to immunosuppressed patients, as early as 2 months after the second dose.[19] By 31 March 2022, 91% of Singapore's population had received at least 2 doses of vaccine, and 72% received a booster or 3 doses. In addition, the country has a comprehensive and robust national database that accurately tracks the incidence and severity of SARS-CoV-2 infections.[20] By 6 May 2022, Singapore had a total of 1,212,337 COVID-19 cases (20.4%) out of its 5.9 million population.[21] From 1 May 2021 to 14 Apr 2022, 0.67% of fully vaccinated (without booster) and 0.24% of fully vaccinated (with booster) populations infected with SARS-CoV-2 ever required oxygen supplementation in the general ward, in intensive care unit (ICU) or died.[20] SARS-CoV-2 viral genome sequencing data showed that the Delta variant predominated in Singapore between May and December 2021, before being overtaken by the Omicron variant since January 2022.[22] The overarching national framework provides us with the opportunity to evaluate the real-world efficacy of SARS-CoV-2 vaccinations and correlating it with clinical severity of SARS-CoV-2 infections in our patients.

This study is among the first to assess the effect of tumour type and anti-neoplastic treatment in determining vaccine response to the third dose of vaccine in cancer patients, and provide real-world efficacy data on SARS-CoV-2 infections with

correlation to the neutralising antibody levels and humoral response. While there have been emerging data on the real-world efficacy of the third dose on cancer patients, the evidence is still sparse and confined to certain geographical regions.[23] This large prospective study adds to the literature on real-world efficacy of a third SARS-CoV-2 vaccine dose in patients with solid and haematological malignancies.

METHOD

Patients and sample collection

This is a prospective study using blood samples from patients with a personal history of malignancy, recruited from the 2 hospitals of the National University Cancer Institute, Singapore: the National University Hospital (NUH) and Ng Teng Fong General Hospital, Singapore, between July 2021 and March 2022. Included patients must be ≥21 years old and must have been deemed by their primary physician to be suitable to receive SARS-CoV-2 vaccination. Clinicopathological data (including age at diagnosis, sex, type of cancer, and anti-neoplastic treatment at enrolment) were collected, and de-identified. Haematological malignancies included leukaemias, myeloma and lymphomas. Types of anti-neoplastic treatments included targeted therapy, immunotherapy and chemotherapy (online Supplementary Table S1). Patients with cancer on surveillance, hormonal therapy or radiotherapy were also included and defined as the "control" group. All patients received mRNA vaccination with either the Pfizer BNT162b2 vaccine, or the Moderna mRNA1273 vaccine.

Subjects were matched with administrative data on SARS-CoV-2 vaccinations and infections reported to the Ministry of Health for the purposes of monitoring disease transmission and vaccination uptake under the Infectious Disease Act. Administrative data on vaccinations included the date and brand of vaccinations, while data on SARS-CoV-2 infections include notification date of infection, and whether cases required treatment in hospital, supplementary oxygen, ICU care and/or resulted in death.

Serology testing

Serology was tested using GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kits (GenScript Biotech Pte Ltd, Singapore), which performs rapid detection of total neutralising antibodies against SARS-CoV-2 viral spike protein receptor binding domain, with seroconversion defined as a detected output of 30% or more.[24] This form of immunoassay has been shown to perform similarly well as other commercially available immunoassays.[25]

Serology was performed by trained laboratory personnel at NUH. Blood draws were collected immediately before the first vaccine dose (T1), 3–8 weeks after the first vaccine dose or immediately before the second vaccine dose (T2), 3 months after the first vaccine dose or immediately before the third vaccine dose (T3), and 3 months after the third vaccine dose (T4) (Fig. 1).

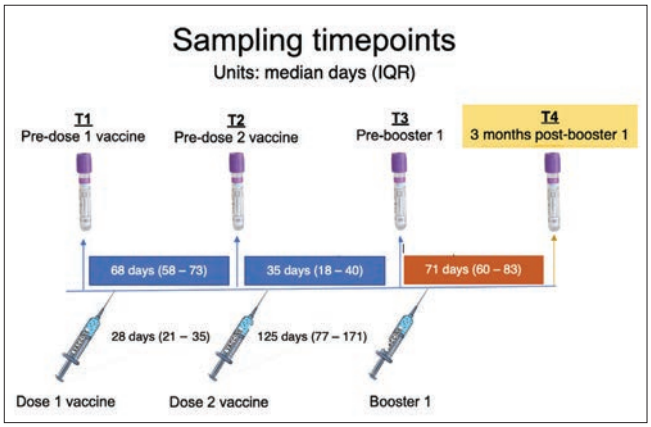

Fig. 1. Schematic of blood collection (draws) after vaccination.
IQR: interquartile range

Statistical analysis

Statistical analyses were performed using R version 4.0.1 (R Foundation, Vienna, Austria). Contingency tables and chi-square or Fisher's Exact tests (for categorical variables), t-test for comparison of means (2 means), one-way analysis of variance for comparison of means (more than 2 means) and Mann-Whitney U test for comparison of medians (for continuous variables) were used to investigate associations of serology results with clinicopathological characteristics and outcomes. A P value <0.05 was considered to indicate statistical significance unless otherwise stated.

Ethical approval

The National Healthcare Group Domain-Specific Review Board provided ethical approval for the use of patient materials in this study (reference number 2021/00523). All individuals enrolled in this study provided written informed consent as part of protocols approved by the Domain Specific Review Board of ethics and in compliance with the October 2013 Declaration of Helsinki principles. Enrolled individuals did not receive compensation for their participation in

the study. No patients nor members of the public were involved in the design of this study.

RESULTS

Patient baseline characteristics

In this prospective observational study, a total of 273 participants were recruited (Table 1). The median age of the patients was 63 years with 50.5% (138/273) female. Forty (14.7%) patients were diagnosed with haematological malignancies, 110 (40.3%) with gastrointestinal (GI) and hepatobiliary (HPB) cancers, and 123 (45.0%) with other malignancies (Table 1).

Of the participants, 204 (74.7%) were receiving active cancer therapy, including 49 (17.9%) on targeted therapies only, 23 (8.4%) on immunotherapy, 98 (35.9%) receiving systemic chemotherapy (with or without immunotherapy), and 34 (12.5%) on active treatment for haematological malignancy. Sixty-nine (25.3%) patients were not on active treatment or only receiving radiotherapy or hormone therapy. These patients were considered the "control" group in our analysis. (Table 1).

A total of 265 had completed the full 2-dose regimen with either BNT162b2 or mRNA1273 vaccine, and 216 received 3 doses of vaccination. The median duration

Table 1. Baseline characteristics of patients recruited, including types of cancer diagnosis and cancer treatment received

	Total patients recruited	Serology data for patients receiving 1 dose	Serology data for patients receiving 2 doses	Serology data for patients receiving 3 doses
	N=273	n=267	n=265	n=216
Median age (IQR), years	63 (15.3)	63 (15.5)	63 (15.0)	63 (14.0)
Median duration from previous dose (IQR), days	-	-	28 (14)	125.5 (94)
Sex, n (%)				
Male	135 (49.5)	131 (49.1)	131 (49.4)	115 (53.2)
Female	138 (50.5)	136 (50.9)	134 (50.6)	101 (46.8)
Cancer type, n (%)				
Haematological cancer (including lymphoma)	40 (14.7)	38 (14.2)	38 (14.3)	29 (13.4)
Gastrointestinal and hepato-pancreatobiliarycancers	110 (40.3)	108 (40.4)	108 (40.8)	93 (43.1)
Lung cancer	26 (9.5)	25 (9.4)	25 (9.4)	17 (7.9)
Breast	52 (19.0)	51 (19.1)	50 (18.9)	38 (17.6)
Gynaecological	17 (6.2)	17 (6.4)	16 (6.0)	14 (6.5)
Prostate	9 (3.3)	9 (3.4)	9 (3.4)	8 (3.7)
Renal	7 (2.6)	7 (2.6)	7 (2.6)	7 (3.2)
Others	12 (4.4)	12 (4.5)	12 (4.5)	11 (5.1)
Treatment received, n (%)				
Control No active treatment, radiotherapy or hormonal therapy only	69 (25.3)	68 (25.5)	68 (25.7)	56 (25.9)
Targeted therapy	49 (17.9)	48 (18.0)	47 (17.7)	36 (16.7)
Immunotherapy	23 (8.4)	23 (8.6)	23 (8.7)	19 (8.8)
Systemic chemotherapy	98 (35.9)	96 (36.0)	95 (35.8)	82 (38.0)
Active treatment for haematological cancer	34 (12.5)	32 (12.0)	32 (12.1)	23 (10.6)

IQR: interquartile range

between second and third dose of vaccine was 125 days for the entire cohort. Excluding those not on active treatment, the median duration was 113 days. Of those patients who received the third dose, 77 (35.6%) had the vaccine administered between 60 and 90 days post-second dose.

Higher antibody titres are associated with reduced severity of SARS-CoV-2 infection

We evaluated the real-world clinical efficacy of vaccination in our patient cohort. SARS-CoV-2 infection was reported in 77 of the 273 patients (28%); 36 (47%) were of the Delta variant, and 41 (53%) were of the Omicron variant, corresponding to the SARS-CoV-2 lineage prevalence in Singapore in 2021–2022.[22] Fifty-nine of the 77 patients developed mild infection, which we defined as either asymptomatic infection, or symptomatic without requiring hospital admission, such as home recovery or virtual ward care. Virtual ward care involved remote care by hospital doctors and nurses during patient isolation. Eighteen of the 77 patients suffered from severe SARS-CoV-2 infections, defined as infection resulting in hospitalisation, ICU care, oxygen therapy or death. We elected to use this distinction of infection severity to reflect the different levels of healthcare requirements and hospital facilities. Of note, only 1 patient required ICU care, and 1 death was reported in our cohort.

Last measured antibody levels prior to infection were correlated with infection severity (Fig. 2). Patients with severe infections had significantly lower mean antibody levels than non-infected (28.3% vs 77.0%, $P<0.05$) and mild infection groups (28.3% versus 65.8%, $P<0.05$). However, the mean differences between the non-infected and mild infection groups were not significant (77.0% vs 65.8%, $P=0.116$). This suggests that higher antibody titres may protect patients from severe disease, but not against mild infection.

Further analysis of patients of different infection severities (no infection, mild infection and severe infection) was performed based on the treatment modalities received**.** Patients on chemotherapy and on active treatment for haematological malignancies accounted for a greater proportion of severe infections. Of the 18 patients with severe SARS-CoV-2 infections, 9 were on active treatment for haematological malignancies and 5 were on active chemotherapy. Of the 77 patients who received their third dose of vaccine within 90 days of the second dose, none had severe infection.

Seroconversion and antibody responses to mRNA vaccination

Two doses of the SARS-CoV-2 mRNA vaccines (BNT162b2 or mRNA1273) were required to produce a significant antibody response. Seroconversion was 35.2% after the first dose, with median antibody output of 0% (0.0–60.5), compared to 79.4% seroconversion rate and median output of 85.0% (47.9–97.4) after the second dose. A third dose was able to increase antibody titres further, reaching a 92.4% seroconversion with a median output of 99.0% (91.5–99.4) (Fig. 3). Mean antibody output increased after the administration of the second dose (28.1±36.9 vs 69.5±34.9, $P<0.05$) and after the administration of a third dose (69.5±34.9 vs 87.3±26.5, $P<0.05$). Seroconversion stratified by key characteristics—including treatment type, cancer type and sex—is reported in the online Supplementary Tables S2–5.

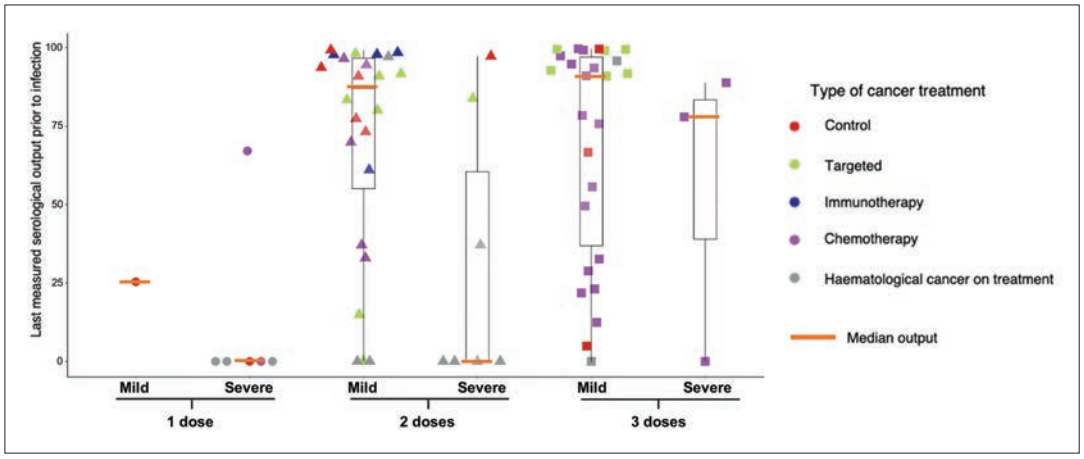

Fig. 2. Most recent antibody output level and severity of SARS-CoV-2 infection. Colours reflect the anti-neoplastic treatment modality received by patients. Shapes reflect the number of vaccine doses received (1, 2 or 3) doses when patients reported infections.

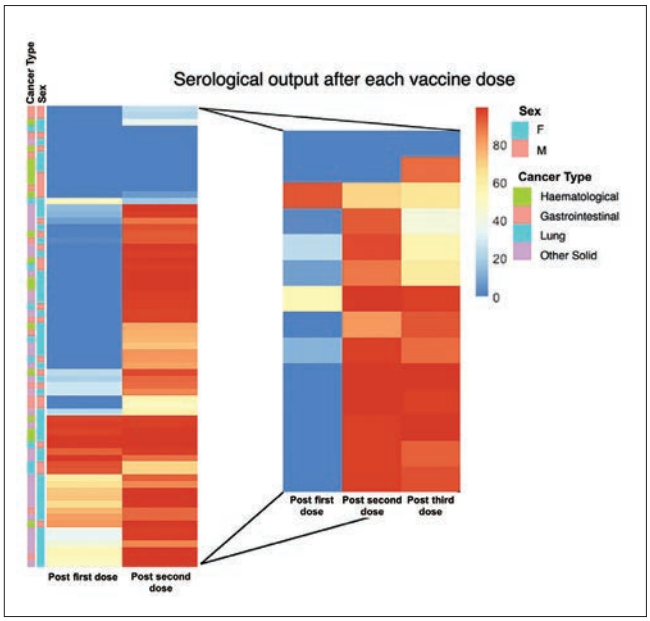

Fig. 3. Antibody responses of cancer patients to mRNA vaccination. Left: Heatmap of serological output after each dose in patients who received 2 doses of a SARS-CoV-2 vaccine. Right: Serological output of the subgroup of these patients who received 3 doses of a SARS-CoV-2 vaccine.

Association with anti-neoplastic treatment

Patients receiving different modalities of anti-neoplastic treatments demonstrated varying degrees of humoral responses and seroconversion (Fig. 4).

Serology output in patients in control group, receiving chemotherapy, targeted therapy, immunotherapy or treatment for haematological malignancy, after 1 dose, 2 doses and 3 doses of SARS-CoV-2 vaccination.

After 2 doses of SARS-CoV-2 vaccination, patients on active treatment for haematological malignancies had significantly lower mean antibody titres (46.8%) compared to patients on other forms of treatment: patients in the control group (75.4%, $P<0.05$), patients on targeted therapy (78.0%, $P<0.05$), immunotherapy (75.8%, $P<0.05$) or chemotherapy (68.1%, $P<0.05$).

After 3 doses of vaccination, patients on active treatment for haematological malignancy (57.3%) still showed significantly lower mean antibody titres compared to patients on immunotherapy (94.1%, $P<0.05$) and chemotherapy (92.8%, $P<0.05$).

Proportionally, patients on active treatment for haematological malignancy also showed lower seroconversion rates compared to other treatment groups (online Supplementary Table S2). After 2 doses of vaccination, seroconversion rates were higher in patients in the control group (83.0%), on targeted therapy (87.5%), on immunotherapy (94.1%), and on chemotherapy (79.5%), compared to 51.9% in patients with haematological malignancies on active treatment. After 3 doses of vaccination, seroconversion rates were higher in patients in the control group (92.3%), on targeted therapy (86.7%), on immunotherapy (100%), and on chemotherapy (96.9%), compared to 66.7% in patients with haematological malignancies on active treatment.

Association with tumour type

We compared the humoral response to 2 and 3 doses of the SARS-CoV-2 vaccine in patients with different tumour types. After 2 doses of vaccination, the mean antibody titres of patients with haematological malignancies (54.1%) were significantly lower than that of patients with other solid cancers (77.0%, $P<0.05$). However, other mean differences between the patients with other types of cancer (GI: 66.8%, lung: 78.1%) were not significant.

Proportionally, patients with solid organ tumours had higher seroconversion rates than patients with

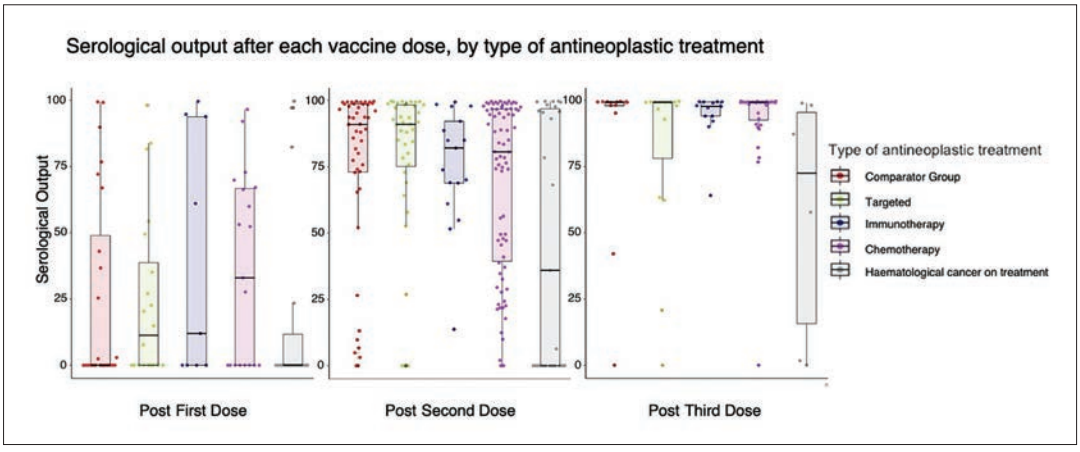

Fig. 4. Association of anti-SARS-CoV-2 antibodies with anti-cancer therapy received.

haematological malignancies (online Supplementary Tables S1–3). After 2 doses of vaccination, seroconversion rates were higher in patients with GI (78.3%), lung (89.5%) and other solid (86.7%) cancers, compared to 59.4% in patients with haematological malignancies. After 3 doses, seroconversion rates were still higher in patients with GI (93.9%), lung (100%) and other solid (96.3%) cancers, compared to 71.4% in patients with haematological malignancies. While limited by sample size, lymphoma patients appeared to perform worse than leukaemia and myeloma patients (online Supplementary Table S4).

Immunogenicity of third dose in previously seronegative patients

Forty-four (19.0%) of patients did not seroconvert after receiving a complete course of 2 doses of the vaccine. Of this group, 17 patients received the third dose, and seroconversion was successfully achieved in 13/17 (76.5%) of previously seronegative patients after the third dose. There were no significant differences in seroconversion rates or antibody levels in patients who received 3 doses of BNT162b2 (n=198), when compared to patients who received 2 doses of mRNA1273 followed by a third dose of BNT162b2 (n=6).

DISCUSSION

The SARS-CoV-2 pandemic had overwhelmed healthcare systems around the world, with immunosuppressed patients being particularly vulnerable to severe infections.[1,2] Despite the unprecedented speed of development of efficacious vaccines, oncological patients were at risk of blunted immune response to vaccinations, particularly if they are receiving immunosuppressive chemotherapy or anti-B-cell therapies.[26-29]

In accordance with other published studies,[8,14,27,28,30,31] patients on treatment for haematological malignancies demonstrated lower antibody titres and the greatest risk of non-seroconversion after 2 and 3 doses of vaccine, compared to patients receiving targeted therapy, immunotherapy or not on anti-neoplastic treatment. This is likely because patients with haematological cancer are on B -cell-depleting therapies, and it has been established that patients on therapies such as anti-CD19 and anti-CD20 therapy demonstrate a poor response to SARS-CoV-2 vaccines.[32,33] In addition, patients with B cell/plasma cell malignancies are known to have severe deficiencies in humoral immunity due to reduction in normal B/plasma cells, further contributing to reduced antibody response to vaccination.[34] Nevertheless, recent studies have demonstrated that a third mRNA-1273 vaccine is able to produce antibody concentrations comparable to healthy individuals after the standard 2-dose regimen,[35] particularly if the third dose is delayed to allow the immune system to "recuperate" after the second dose.[35]

There had been earlier concerns raised of immune checkpoint inhibitors impairing T cell function and hence possibly suppressing antibody response to SARS-CoV-2 vaccination.[36] However, our study demonstrated that patients on targeted therapy and immunotherapy seroconverted as effectively as control patients after 2 doses of SARS-CoV-2 vaccine. This provides real-world data that targeted therapy and immunotherapy did not blunt the immune system's ability to mount an effective antibody response to SARS-CoV-2 vaccination.

Singapore rolled out a rapid and comprehensive vaccination programme, with 76.6% of the population completing the full 2-dose regime by September 2021. This led to the majority of our immunosuppressed patients completing the 2-dose regimen when the Delta and Omicron variants hit the population on a background of a highly immunised general population. In our cohort, only 18 of 77 SARS-CoV-2-infected cancer patients (23%) suffered from serious infections requiring hospitalisation, with only 1 patient needing ICU-level care and another resulting in SARS-CoV-2-related mortality (1.3%). We demonstrate that low rates of severe infection can be achieved even in this highly vulnerable group of immunosuppressed patients. This is via (1) early and high rates of vaccination in cancer patients; (2) a background of a highly vaccinated general population; and (3) effective public health measures including meticulous and swift contact tracing, individual-level quarantine, as well as standard health advice such as wearing of face masks, hand-washing and social distancing. Vaccination against SARS-CoV-2 has been shown to result in milder and shorter illnesses in the general population,[37,38] and would likely confer similar protection in oncological patients who adequately seroconvert.

Most published studies to date focused on immunogenicity as a marker of vaccine efficacy, with few correlating antibody levels with the clinical severity of infection. Our study reported 77 out of 273 patients infected with SARS-CoV-2, of which 36 were presumed Delta variant, and 41 presumed Omicron variant, according to the SARS-CoV-2 lineage prevalence in Singapore from 2021–2022, comparable to the general population.[22] Singapore has a robust mandatory-reporting national database tracking each patient's infection status and progression. This permitted

accurate tracking of the clinical disease severity and correlation to the real-world efficacy of SARS-CoV-2 vaccinations in our patients.

Some countries, including Singapore, have proposed an additional fourth dose for susceptible patients to further boost the antibody response, citing waning immunity as a rationale.[12,39,40] The US Food and Drug Administration licensed the use of a fourth dose for immunocompromised individuals, and in March 2022, the UK had announced a fourth dose for all vulnerable adults. Israel was one of the first countries to administer a fourth dose of the BNT162b2 and mRNA1273 vaccines, with promising results and initial reports of an 8- and 10-fold increase in neutralising antibody titres against the Omicron variant (B.1.1.529) at 1 and 2 weeks after the additional booster dose, respectively, compared to 5 months after the third vaccine.[39]

There are limitations in our study that must be acknowledged. We assessed antibody production to evaluate the immunogenicity of vaccination. Longer follow-up is required to establish if, and for how long, cancer patients can maintain these levels of immune responses. We also assessed seroconversion using the GenScript cPASS surrogate virus neutralisation assay, which is an indirect measurement of antibody titres. Furthermore, not all neutralisation antibodies measured are necessarily receptor binding-domain (RBD) antibodies.[41] However, studies have shown that RBD-targeting neutralisation antibodies are immunodominant.[42] Despite the limitations of the assay, GenScript cPass has high specificity and sensitivity and is widely adopted.[24] Further studies may also seek to investigate the role of cellular immunity in conferring protection against SARS-CoV-2, particularly in patients who are unable to mount an adequate humoral response. Additionally, prevalence data were used to assume if patients had been infected by the Delta or Omicron variants. Future studies may want to rely on whole genomic sequencing to characterise the variants patients are infected with to better understand the relationship between levels of antibodies and sero-protection against vaccine escaping variants.

CONCLUSION

In our study, we demonstrated that each additional dose of vaccine further augmented the humoral response by increasing the seroconversion rates and antibody titres among cancer patients. This humoral response also differed depending on the tumour types and anti-neoplastic treatment. Patients on active treatment for haematological malignancies had the lowest antibody titres, followed by patients on chemotherapy. Patients receiving targeted therapy and immunotherapy had comparable differences in antibody response compared to those on radiotherapy, hormonal therapy, or no active treatment. Antibody titres were also shown to correlate with infection severity. Overall, the study shows that the early administration of third dose among cancer patients achieved high rates of seroconversion and prevented severe infection.

Data availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient confidentiality.

Disclosures

RS—honoraria (MSD, Eli Lilly, BMS, Roche, Taiho, AstraZeneca and DKSH), consulting or advisory role (Bristol Myers Squibb, Merck, Eisai, Bayer, Taiho, Novartis, MSD and GSK), travel (Roche, AstraZeneca, Taiho, Eisai, DKSH), and research funding (Paxman Coolers and MSD). SCL—grant support/research collaborations (Pfizer, Eisai, Taiho, ACT Genomics, Bayer, MSD and Adagene); Advisory Board/speaking engagement (Pfizer, Novartis, AstraZeneca, ACT Genomics, Eli Lilly, MSD and Roche); and conference support (Amgen, Pfizer and Roche).

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REVIEW ARTICLE

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Combating a resurgence of poliomyelitis through public health surveillance and vaccination

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ABSTRACT

Poliomyelitis, or polio, is a highly infectious disease and can result in permanent flaccid paralysis of the limbs. Singapore was certified polio-free by the World Health Organization (WHO) on 29 October 2000, together with 36 other countries in the Western Pacific Region. The last imported case of polio in Singapore was in 2006. Fortunately, polio is vaccine-preventable—the world saw the global eradication of wild poliovirus types 2 and 3 achieved in 2015 and 2019, respectively. However, in late 2022, a resurgence of paralytic polio cases from vaccine-derived poliovirus (VDPV) was detected in countries like Israel and the US (specifically, New York); VDPV was also detected during routine sewage water surveillance with no paralysis cases in London, UK. Without global eradication, there is a risk of re-infection from importation and spread of wild poliovirus or VDPV, or new emergence and circulation of VDPV. During the COVID-19 pandemic, worldwide routine childhood vaccination coverage fell by 5% to 81% in 2020–2021. Fortunately, Singapore has maintained a constantly high vaccination coverage of 96% among 1-year-old children as recorded in 2021. All countries must ensure high poliovirus vaccination coverage in their population to eradicate poliovirus globally, and appropriate interventions must be taken to rectify this if the coverage falters. In 2020, WHO approved the emergency use listing of a novel oral polio vaccine type 2 for countries experiencing circulating VDPV type 2 outbreaks. Environmental and wastewater surveillance should be implemented to allow early detection of "silent" poliovirus transmission in the population, instead of relying on clinical surveillance of acute flaccid paralysis based on case definition alone.

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Keywords: Acute flaccid paralysis, infectious diseases, polio vaccine, poliovirus, surveillance

INTRODUCTION

Singapore was certified poliomyelitis (polio)-free by the World Health Organization (WHO) on 29 October 2000, together with 36 other countries in the Western Pacific Region.[1] Prior to certification, there were multiple outbreaks in 1958, 1960 and 1963 with 415, 196 and 74 paralytic polio cases, respectively.[2-4] The nationwide immunisation programme in Singapore using the oral poliovirus vaccines (OPV) led to a marked decrease in outbreaks of polio. No case of indigenous polio was reported from 1978 onwards.[1] The last imported case of polio in Singapore was in 2006 when a 2-year-old Nigerian girl presented with left lower limb paralysis and her stool was positive for wild poliovirus (WPV) type 1.[5]

In this review, we seek to provide an update on the clinical manifestations of polio, other infections that can mimic polio, and the history of poliovirus vaccination. We also describe the status of global eradication efforts since the COVID-19 pandemic and highlight key public health interventions necessary to mitigate the risk of poliovirus outbreaks globally.

Characteristics of poliovirus

"Poliomyelitis" originates from the Greek words ''polio'' and ''myelon'', which mean "grey" and "marrow", respectively, due to its effect on the spinal cord. It is a highly infectious disease caused by one of the three poliovirus serotypes (poliovirus types 1, 2 or 3), belonging

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CLINICAL IMPACT

What is New

- Recently, in late 2022, a resurgence of paralytic poliomyelitis (polio) cases from vaccine-derived poliovirus (VDPV) was detected in countries such as Israel and the US, which have been polio-free since 1989 and 1979, respectively.
- VDPV was also detected during routine sewage water surveillance in the UK.
- During the COVID-19 pandemic, global routine childhood vaccination coverage fell by 5% to 81% in 2020–2021.

Clinical Implications

- Poliovirus vaccination programme is critical, and the novel oral poliovirus vaccine 2 may boost global eradication efforts.
- Environmental and wastewater surveillance may facilitate early detection of "silent" poliovirus transmission.

to the *Enterovirus* genus and *Picornaviridae* family.[6] Poliovirus can survive in the environment (soil and water) for months at 4°C, but viral infectivity can be reduced by heating. Poliovirus is resistant to common detergents and lipid solvents, but can be inactivated by formaldehyde, heat or chlorine.[6,7]

Humans are the only reservoir for poliovirus, and it can be transmitted from a symptomatic or asymptomatic carrier via the faecal-oral or oral-oral route. Transmission can also occur through close contact via oral exposure to cough or sneeze droplets. The faecal-oral route is more common in areas with poor sanitation, especially among the non-immune population. Poliovirus is most contagious from 7–10 days before and after the onset of symptoms.[8] Immunocompetent infected persons can shed poliovirus in the pharynx and stools for around 2 and 4 weeks, respectively.[8] In contrast, immune-compromised persons can shed the virus for a longer period of time, with a median length of excretion of 1.3 years.[9] The development of mucosal immune responses in the form of immunoglobulin A is associated with a decrease in viral replication, shedding and risk of transmission.[10,11] Hence, persons with deficiencies in mucosal immune responses are at higher risk of prolonged poliovirus shedding and viral transmission.[10,11]

Clinical presentation of poliomyelitis

The poliovirus enters through the oral route and multiplies in the oropharynx, tonsils, cervical lymph nodes and gastrointestinal tract. In the gastrointestinal tract, the virus can invade lymphoid tissue; it may enter the bloodstream to infect the central nervous system, causing the destruction of motor neurons.

Poliovirus can lead to one of the following disease manifestations: (1) asymptomatic infection; (2) abortive polio or minor illness; (3) non-paralytic polio or aseptic meningitis; or (4) paralytic polio, which is the most severe presentation. Table 1 summarises the characteristics of each disease manifestation.[6,7,12-19] Paralytic polio is extremely rare and seen in <1% of poliovirus infections. Therefore, the detection of a single case of polio will suggest wider unknown transmission in the population. Patients can present with severe back, neck and muscle pain associated with involvement of the spinal, mixed spinal-bulbar or bulbar paralysis. Bulbar polio has the highest mortality due to the involvement of the brainstem neurons. Involvement of the respiratory muscles can also lead to death. Polioencephalitis can also occur where patients present with confusion and seizures with upper motor neuron signs, which are indistinguishable from other viral encephalitis.[17] Sensory involvement never occurs in polio.

In children and rarely in adults, paralytic spinal polio can present classically with a biphasic course. This course is an initial period of minor illness followed by a brief symptom-free period of up to 10 days and subsequent rapid onset of acute flaccid paralysis (AFP) with asymmetrical paralysis, loss of deep tendon reflexes, fever, headache, neck stiffness and cerebrospinal fluid (CSF) pleocytosis.[13,14] Recovery may occur in some patients. In around 50% of the survivors of paralytic polio, a non-infectious post-polio syndrome (PPS) can occur 8–71 years later.[7] A new gradual onset of muscle weakness, pain and fatigue can occur in the same muscles that were affected during the course of paralytic spinal polio. Previously unaffected limb muscle groups can also be involved in PPS.

Other infectious aetiologies of AFP

AFP is a clinical syndrome characterised by an acute onset of flaccid limb weakness of <4 weeks, which can also involve the respiratory and/or swallowing muscles. Progression to maximum severity can occur within days to weeks. Other infectious aetiologies of AFP that have been described include non-polio enterovirus D68 and A71, flavivirus and human herpesvirus. Table 2 summarises the characteristics of other infections

Table 1. Summary of clinical manifestations of poliovirus infection[6,7,12-19]

Clinical manifestation	Frequency	Presenting symptoms/signs	Diagnosis	Prognosis
Asymptomatic infection	75–95% of infection	Asymptomatic or minor malaise.	Detected through isolation or polymerase chain reaction (PCR) of poliovirus from faeces or oropharynx, or through serology testing during poliovirus epidemic or outbreaks, as symptoms/presentation are not specific to poliovirus infection.	Complete recovery without complications
Abortive polio/ minor illness	4–24% of infection	Transient illness with nonspecific symptoms including fever, malaise, drowsiness, nausea, anorexia, vomiting, constipation, headache and sore throat; normal neurological examination.	Detected through isolation or PCR of poliovirus from faeces or oropharynx. CSF biochemical markers are similar to those found in viral meningitis. CSF can have increased leucocytes with a high ratio of polymorphonuclear cells to lymphocytes during early disease. CSF total protein can also be elevated at an average of 40–50mg/dL. CSF glucose level is usually normal. Unlike other viral causes of aseptic meningitis, poliovirus is rarely isolated from CSF.	High mortality for bulbar polio or spinal-bulbar polio involving the medulla, leading to cardio-respiratory compromise and death; high mortality for polioencephalitis. Permanent weakness in two-thirds of patients. Complete recovery is less likely if presenting symptoms of paralysis are severe.
Nonparalytic polio/ aseptic meningitis	1–4% of infection	Symptoms are similar to abortive polio but with the addition of meningeal irritation, neck stiffness, severe headache and pain over the limbs, back and neck that develop 1–2 days later. The illness lasts for up to 2 weeks.		
Paralytic polio	<1% of infection	Spinal paralytic polio Initial period of minor illness followed by a brief symptom-free period of up to 10 days and subsequent rapid onset of acute flaccid paralysis (AFP), loss of deep tendon reflexes, paraesthesia, fever, headache, neck stiffness and cerebrospinal fluid (CSF) pleocytosis. Lower motor neuron signs appear with classical asymmetrical distribution of flaccid paralysis. Lower limbs are more commonly affected than upper limbs. Sensory involvement is very rare. Bulbar paralytic polio Paralysis of cranial nerves especially the ninth and tenth cranial nerves innervating the soft palate and pharynx, without limb weakness. Patients can present with dysphagia, dyspnoea and pooling of saliva. Polioencephalitis Agitation, confusion, disturbances of consciousness, seizures, autonomic dysfunction and upper motor neuron signs.		
Post-polio syndrome (PPS)	Around 50% of survivors of paralytic polio	A non-infectious syndrome can occur in survivors of paralytic polio from 8–71 years later. New gradual onset of muscle weakness, pain and fatigue can occur in the same muscles that were affected during the course of paralytic polio, or previously unaffected limb muscle groups can also be involved in PPS.	No specific test for diagnosis. Most experts have validated the diagnostic criteria by Halstead et al.[19] PPS is a diagnosis of exclusion and all potential medical or surgical causes must be excluded before diagnosis of PPS is made.	Varied prognosis. In some cases, affected persons are not severely handicapped and symptoms stabilised over time. In severe cases, PPS can lead to skeletal deformities, affecting a person's ability to perform simple tasks of daily living.

Superscript numbers: Refer to REFERENCES

that can lead to AFP.[20-26] As poliovirus is only one of the causes of AFP, and there are other infections and immune-mediated syndromes that can mimic polio, WHO uses a screening case definition for surveillance of AFP to evaluate polio outbreaks.[12] This definition includes any case of AFP in children aged <15 years old, or a person of any age where polio is suspected. Clinical vigilance in notifying health authorities early about patients who fulfil the AFP case definition is important, as part of efforts to eradicate polio.

Diagnosis of poliomyelitis

Poliovirus can be detected by isolating the virus in cell culture from isolates of stool, throat swabs, blood, CSF or by polymerase chain reaction (PCR).[8,12] Viral culture or PCR from stool isolate is the most sensitive diagnostic method given the prolonged stool viral shedding. Isolation of the virus is also more common in pharyngeal specimens than blood or CSF. Viral isolates can subsequently undergo genome sequencing to aid in the identification of the poliovirus serotype, and differentiate between wild-type and vaccine (Sabin)-derived infection. Two samples of stool collected at least 24 hours apart within 2 weeks of symptom onset can further increase the sensitivity of the tests.[27] In the absence of isolates, paired acute and convalescent blood serum (with a 4-fold increase in titre during the convalescent phase) for neutralising antibodies against the three poliovirus serotypes can diagnose polio in the presence of clinical symptoms and/or epidemiolo-gical risk factors for polio. However, serologic tests cannot differentiate between wild-type and vaccine-derived polio.

Management of poliomyelitis

Currently, there is no antiviral medication for the treatment of polio. A capsid inhibitor, pocapavir, had completed a phase 1 trial and was shown to be safe and effective in improving viral clearance in immunocompromised persons.[28] However, there was a concern about emerging viral resistance in a group of study patients in the isolation facility.[28] The study was not able to accurately conclude if pocapavir had led to viral resistance directly. More studies are required to evaluate if pocapavir can indeed lead to drug resistance in immunocompromised persons and if proven so, other drug combinations may be required to overcome the resistance.

For persons who suffer from paralytic polio, various supportive management strategies including mechanical ventilation, pain management with analgaesia, neurorehabilitation and use of orthotic devices have been deployed to maximise recovery and improve outcomes.

History of poliovirus vaccinations

Historically, the first available polio vaccine was the inactivated poliovirus vaccine (IPV), which was created in the 1950s and licensed in 1955. IPV was available as the trivalent form containing the three poliovirus (PV) serotypes PV1, PV2 and PV3. OPV was initially available as a monovalent form in 1961, followed by the trivalent form (tOPV) in 1963.[12] Both IPV and OPV provide substantial immunity and protection against polio, but only OPV provides intestinal immunity, while IPV provides some nasopharyngeal immunity.[29] OPV contains live Sabin poliovirus strains, which are derived from WPV strains attenuated by multiple passages in non-human cell culture, hence reducing neurovirulence and transmissibility.[30] While the attenuated PV did not cause disease, it replicated sufficiently to induce protective immunity. However, vaccine-derived poliovirus (VDPV) can undergo genetic changes during replication, such as in reversing the mutations in the viral genome that conferred the attenuation phenotype, and/or acquiring new mutations with enhanced neurovirulence.[31,32] Since the VDPV in OPV can shed for several weeks in the oropharyngeal secretions and stools post-vaccination, the transmission of these viruses from a vaccinated person can lead to vaccine-derived paralytic polio (VDPP). VDPP is clinically identical to the paralysis caused by wild poliovirus but is a rare adverse event of OPV on its recipients and particularly, unvaccinated contacts.

The national immunisation schedule in Singapore had an all-OPV schedule comprising 6 doses of tOPV until June 2013. This was replaced with a sequential IPV-OPV schedule comprising the recommendation for 4 IPV doses given at ages 3, 4 and 5 months, with a booster dose at 18 months. A fifth dose of tOPV at 10–11 years old (primary school level 5) was recommended. The tOPV dose at 6–7 years old (primary school level 1) was discontinued at the end of 2013.

WPV type 2 virus has not been detected since 1999 and was declared to be eradicated in September 2015.[12] Consequently, WHO removed serotype 2 from tOPV in a global synchronised switch and replaced it with the bivalent OPV (bOPV) containing types 1 and 3 Sabin viruses. This became the only globally available OPV from May 2016. Monovalent OPV containing serotype 2 is only stockpiled for emergency or outbreak use.

Global eradication of WPV type 3 was declared on 24 October 2019.[12] Since 2020 when bOPV was no longer available, the national immunisation schedule in Singapore changed to an all-IPV schedule using the

Table 2. Summary of other infectious aetiologies that can lead to polio-like illness[20-26]

Organism	Route of transmission	Reservoir	Incubation	Clinical symptoms and conditions
Non-polio enterovirus • D68 • A71	Faecal-oral, respiratory droplet	Humans	2 to 10 days	Enterovirus D68 Wide range of presentations from asymptomatic to mild or severe respiratory tract symptoms such as fever, cough, runny nose, sore throat, breathlessness and wheezing. Conditions related to enterovirus D68 infections include pharyngitis, severe pneumonia and respiratory failure. Acute flaccid paralysis (AFP) can occur with sudden onset of limb weakness in one or more limbs, or involvement of respiratory or bulbar muscles. Enterovirus A71 Causes a wide range of conditions such as hand, foot and mouth disease (fever, ulcers in posterior pharynx and rashes over hands and feet), aseptic meningitis and/or encephalitis (fever, headache, neck stiffness, drowsiness and confusion), myocarditis (fever, chest pain, vomiting, loss of cardiac output and arrhythmia) and AFP.
Human parechovirus	Respiratory droplet, faecal-oral, contact	Humans	Unknown but thought to be 2 to 14 days	Asymptomatic or mild to severe disease. Symptoms include cough, runny nose, sore throat, fever and rash. Severe conditions include sepsis-like presentation, meningoencephalitis and AFP. Respiratory failure, loss of tendon reflexes and cranial nerve involvement have been reported.
Flavivirus • Japanese encephalitis virus • West Nile Virus (WNV) • Tick-borne encephalitis virus (TBE)	Japanese encephalitis virus Bites from infected *Culex* mosquitoes in rural areas in Southeast Asia, Pacific islands and the Far East WNV Bites from infected *Culex* mosquitoes in Europe, sub-Saharan and North Africa, and the Middle East; blood transfusions, organ transplants, vertical transmission through placenta and breastmilk transmission TBE Saliva of infected tick, intake of unpasteurised milk products from viraemic livestock, blood transfusion, breastfeeding	Japanese encephalitis virus Pigs, wild birds, *Culex* mosquitoes WNV Birds and *Culex* mosquitoes TBE Ticks and less frequently through viraemic animals	Japanese encephalitis 4 to 15 days WNV 2 to 14 days TBE 4 to 28 days	Japanese encephalitis virus Asymptomatic to symptoms of fever, nausea, vomiting, diarrhoea and myalgia lasting several days. Less than 0.1% develop encephalitis with altered mental status, agitation, confusion, seizure and psychosis. Cases of AFP with extrapyramidal symptoms of dystonic, choreoathetoid movements have been reported. WNV More than 50% present with headache, generalised weakness, morbilliform rash (at the time of defervescence), fever and myalgia. Less than 1% have meningism, altered mental state, AFP with marked progression over 48 hours without sensory abnormalities, extrapyramidal symptoms, and features of parkinsonism. TBE Biphasic disease occurs in 72–87% of patients with 2–10 days of illness in the first stage and a 1–21 days symptom-free interval that progresses to the second stage. Symptoms in the first stage include fever, fatigue, malaise, headache and myalgia. During the second stage, presentation ranges from mild meningitis to severe encephalitis. Myelitis and AFP involving respiratory muscles can occur. Severe disease in children younger than 3 years is rare.

Table 2. Summary of other infectious aetiologies that can lead to polio-like illness[20-26] (Cont'd)

Organism	Route of transmission	Reservoir	Incubation	Clinical symptoms and conditions
Human herpesvirus • Herpes simplex virus (HSV) • Varicella zoster virus (VZV) • Cytomegalovirus (CMV) • Epstein-Barr virus (EBV)	HSV Mucosal, oral or genital contact VZV Direct contact, respiratory secretion, inhalation of viral aerosol from skin lesions CMV and EBV Oral secretions, direct contact with infectious body fluids	Humans	HSV 2 to 12 days VZV 10 to 21 days CMV 3 to 12 weeks EBV 4 to 6 weeks	HSV Majority are asymptomatic or have mild symptoms. Other more significant symptoms include fever, myalgia, lymphadenopathy or headache. Vesicles can erupt around the site of infection (genitals, rectum or mouth) and develop into painful ulcers. Recurrent HSV infection can occur. In HSV-associated neurological manifestations, aseptic meningitis, transverse myelitis (appearing as AFP) and encephalitis (fever, confusion and seizures) can occur. VZV Prodrome of fever and malaise occur 1–2 days before the onset of generalised pruritic rash starting from the truncal area and spreading to peripheries and face. Primary or reactivation VZV infection can also lead to a range of neurological conditions such as cerebellitis, meningoencephalitis and myelitis. AFP can be one of the presenting symptoms. CMV Some are asymptomatic or have mild symptoms (fever, sore throat, fatigue and lymphadenopathy). Other symptoms include mononucleosis or hepatitis. Neurological manifestations such as encephalitis, multifocal neuropathy and polyradiculopathy (appearing as AFP) can occur, especially in immunocompromised persons. EBV Spectrum of illness including mild to severe symptoms. Can present with infectious mononucleosis (severe fatigue, sore throat, fever, headache, myalgia, lymphadenopathy and hepatosplenomegaly). Neurological manifestations include meningoencephalitis, transverse myelitis, Guillain-Barré syndrome (appearing as AFP) and cerebellitis.
Clostridium botulinum	Ingestion of spores from food (food-borne botulism); honey ingestion or environmental exposure (e.g. soil) to spores (infant botulism); contamination of wound from spores (wound botulism); inhalation of *C. botulinum* spores	Soil, aquatic sediments, intestinal tracts of birds, animals, fish and agricultural products (e.g. honey and vegetables)	Food-borne botulism 12 to 36 hours Infant botulism 3 to 30 days Wound botulism 4 to 14 days Inhalation 12 hours to 5 days	Acute, bilateral cranial neuropathy and symmetrical descending weakness (appearing as AFP). Key features include absence of fever, symmetrical neurological involvement, normal mental status, normal heart rate or bradycardia without hypotension and absence of sensory involvement. Infants with botulism can present with constipation, drooling, feeding difficulties, weak cry and hypotonia.
Borrelia burgdorferi and *Borrelia mayonii* (Lyme disease)	Ixodid tick species in parts of North America, Europe and Asia	White foot mouse, rodents, squirrels, chipmunks and shrews	3 to 32 days	Early presentation Fever, chills, headache, myalgia, arthralgia, lymphadenopathy. Erythema migrans (red, circular or oval patch of rash that expands into a bullseye, warm to touch but rarely itchy or painful) may appear at the site of the tick bite. Late presentation Secondary annular lesion, malar rash, migratory pain in joints and bone, osteomyelitis, atrioventricular nodal block and myopericarditis. Neurological manifestations include meningitis, cranial neuritis, myelitis (appears as AFP), cerebellar ataxia and facial palsy.

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5-in-1 vaccine (DTaP-IPV-Hib: against diphtheria, tetanus, acellular pertussis, inactivated polio and *Haemophilus influenzae* type b) or the 6-in-1 vaccine (DTaP-IPV-Hib-HepB: 5-in-1 and against hepatitis B) given at age 2, 4 and 6 months (schedule revised from 3, 4 and 5 months since 1 November 2020) followed by the fourth dose of 5-in-1 vaccine at 18 months. The fifth dose of IPV at age 10–11 years is given as a combined tetanus, diphtheria, pertussis, polio and IPV vaccine, i.e. Tdap-IPV (Adacel-Polio or Boostrix-Polio), to supplement waning immunity over time. The waning immunity effect was seen in a study from Sri Lanka whereby PV3 seropositivity was reduced to 75% among 15-year-old children despite 5 doses of OPV.[33] In another study, protective antibodies against all three serotypes persisted for at least 18 years after the administration of the last dose of OPV or IPV, with a longer duration of immunity against PV3 provided by IPV as compared to OPV.[34] The last seroprevalence study in Singapore conducted from 2008–2010 showed that approximately 92.3% of children aged 1–17 years had antibodies against poliovirus.[35]

In Singapore, the infant vaccination rate (3 completed doses) for polio was 96.5% in 2018 and fairly stable (96.3–96.9%) from 2014–2018. However, the first booster dose completion in 2-year-olds decreased from 90–91% in 2014–2017 to 89.3% in 2018.[36] The lowest reported first booster uptake was 83% in 2003, after which it hovered at 87–91% in 2004–2010.[1] The first booster completion rates showed a worrying trend for uptake of dose at age 18 months. In addition, the booster dose uptake at 10–11 years old (primary school level 5) decreased from 97.4% in 2016–2017 to 95.2% in 2018.[36] Reassuringly, a local review of vaccination records extracted in November 2020–December 2021 from SingHealth polyclinics showed an improvement in vaccine uptake by 10.8% (an increase from 65.9 to 76.7%) of children at 6 months old and 2.1% (from 58.9 to 61.0%) at 12 months old after the revision from 3, 4 and 5 months to 2, 4 and 6 months.[37] Another study showed that during the COVID-19 pandemic from January–April 2020, there was a 0.4–10.3% drop in 5-in-1 vaccine uptake compared to January–April 2019.[38] After the "circuit breaker" period from 7 April–1 June 2022, routine childhood vaccinations reverted to levels from pre-COVID-19 pandemic, reflecting a temporary postponement in vaccination due to the pandemic.[39]

In 2020, WHO approved the emergency use listing of a novel OPV type 2 (nOPV2) vaccine for countries experiencing circulating VDPV type 2 (cVDPV2) outbreaks.[40] The vaccine is a modified version of type 2 monovalent OPV that showed comparable protection against poliovirus in clinical trials while being more genetically stable and did not revert to virulence.[41-43] Currently, the nOPV2 vaccine is only deployed in cVDPV2 outbreaks and not for routine use globally. Available safety data on the first 65 million doses of nOPV2 use for outbreak response showed that there were no safety concerns.[12]

Re-emergence of poliovirus and public health response

In 1988, WHO established the Global Polio Eradication Initiative with the aim of achieving polio eradication by the year 2000.[12,44] The last cases of WPV type 2 were reported in 1999 in India, and WPV type 3 in 2012 in Nigeria.[12] Despite most countries being certified polio-free, polio was declared a Public Health Emergency of International Concern by WHO in 2014 with outbreaks in certain countries.[12] In the absence of global eradication, the risk of re-infection from the importation of wild or VDPV from another country or emergence and circulation of VDPV remains.

In 2015, WPV type 2 was officially declared to be eradicated. The following year, there was a global switch from tOPV to bOPV (type 1 and type 3 only) to remove the risk associated with the ongoing use of live-attenuated type 2 vaccine. To address a potential gap in immunity to type 2, one dose of IPV was recommended to coincide with the switch. Unfortunately, the process encountered challenges leading to the emergence of type 2 immunity gaps. In addition, poorly coordinated outbreak responses using monovalent OPV type 2 vaccine inadvertently resulted in the emergence of more VDPV2, especially in areas of low coverage. These issues were further exacerbated by the emergence of SARS-CoV-2 and subsequent COVID-19 pandemic, resulting in disruptions and suspension of supplementary immunisation activity in 2020. In 2021, six WPV type 1 cases were reported in only 2 endemic countries, Afghanistan and Pakistan.[45]

Relatively recently, Jerusalem, Israel and New York, US reported one case of paralytic polio each in March and July 2022, respectively.[46,47] The case in Jerusalem was an unvaccinated child, 3 years and 9 months old, with AFP presenting in February 2022 from whom VDPV type 3 was detected in the stools.[46] The case in New York was a young unvaccinated adult who developed AFP and had VDPV type 2 in his stools.[47] Prior to his illness, wastewater surveillance in his county and a neighbouring county had detected VDPV 25 days before and 41 days after his onset of illness. He presented with 5 days of low-grade fever, neck stiffness, back and abdominal pain, constipation and 2 days of

AFP. He was unvaccinated and had attended a large gathering 8 days before his illness with no international travel. The polio vaccination uptake in his county had been low at 67.0% in July 2020, which decreased to 60.3% in August 2022, with uptake as low as 37.3% in some areas.[47] In contrast, the national IPV uptake by 24-month-old children was 92.7% among infants born in 2017–2018.[48] In London, UK, sewage and wastewater surveillance also detected VDPV2 from February 2022, with no cases of paralytic polio.[49]

As of 5 October 2022, 33 countries were reported to be affected by poliovirus (Table 3).[50,51] These countries had previously stopped local transmission of WPV but now have re-infection or re-emergence of WPV or VDPV. Not surprisingly, VDPV type 2 is the predominant type of poliovirus with WPV type 1 also detected in Malawi and Mozambique. Four countries—Malawi, Mozambique, Yemen and Israel—are affected by more than one virus type. Nigeria, Yemen and the Democratic Republic of the Congo account for the majority of clinical polio cases reported. Therefore, the recent reports of VDPV in New York and London were not unique or new. However, VDPV occurrence across the world may be an indicator of a worrying trend in the global polio eradication effort and a wake-up call for all countries.

To mitigate the risks of transmission and outbreaks, there are a number of key public health interventions all countries will need to focus on regardless of their polio-free status. First, maintaining high vaccination coverage in the population is critical. Global routine childhood vaccination coverage has fallen by 5%—from 86% to 81%—for 3-dose completion of diphtheria-tetanus-pertussis vaccination during the COVID-19 pandemic.[52] Transiting out of the COVID-19 pandemic, the ongoing political instability around the world, and the associated increase in global migration are world events that will inevitably facilitate the poliovirus' movement. Since the withdrawal of tOPV, it is essential that IPV coverage improves to ensure that children are protected against the clinical manifestation of paralytic polio. There is a need to invest in and maintain surveillance systems to enable the early detection of "silent" poliovirus transmission in the population as demonstrated by the events in Israel, the UK and the US. To augment ongoing AFP surveillance, environmental surveillance systems with genomic sequencing capabilities are essential. Such systems need to be working well to ensure cases of polio—and more importantly, "silent" transmissions—in the population are detected quickly to inform public health response. Finally, the recent development and

Table 3. Poliomyelitis in non-endemic countries by type of virus and number of cases reported in 2021/2022 (as of 5 October 2022)[50,51]

Non-endemic country affected by poliovirus	Type of virus	No. of case(s)	
		2022	2021
Algeria	VDPV2	1	0
Benin	VDPV2	6	3
Burkina Faso	VDPV2	0	2
Cameroon	VDPV2	0	3
Central African Republic	VDPV2	0	0
Chad	VDPV2	18	0
Côte d'Ivoire	VDPV2	0	0
Democratic Republic of the Congo	VDPV2	120	28
Djibouti	VDPV2	0	0
Egypt	VDPV2	0	0
Eritrea	VDPV2	1	0
Ethiopia	VDPV2	0	10
Gambia	VDPV2	0	9
Ghana	VDPV2	2	0
Guinea	VDPV2	0	6
Guinea Bissau	VDPV2	0	3
Israel	VDPV3/ VDPV2	1 (VDPV3)	0
Liberia	VDPV2	0	3
Madagascar	VDPV2	8	13
Malawi	VDPV1/ WPV1	2 (VDPV1)	1 (WPV1)
Mauritania	VDPV2	0	0
Mozambique	WPV1/ VDPV2	1 (WPV1)	2
Niger	VDPV2	10	18
Nigeria	VDPV2	33	415
Senegal	VDPV2	0	17
Sierra Leone	VDPV2	0	5
Somalia	VDPV2	3	1
Togo	VDPV2	1	0
Uganda	VDPV2	0	0
Ukraine	VDPV2	1	2
United Kingdom	VDPV2	0	0
United States of America	VDPV2	1	0
Yemen	VDPV2/ VDPV1	139	66 (n=3VDPV1)

VDPV: vaccine-derived poliovirus; WPV: wild poliovirus
Superscript numbers: Refer to REFERENCES

emergency licensing of nOPV2 vaccine is much-welcomed news. The nOPV2 vaccine is genetically more stable and hence, less likely to result in the loss of key attenuation mutations.[41,53] Population acceptance and appropriate implementation of nOPV2 will minimise the risk of future seeding events.

CONCLUSION

The potential for clinical disease with significant mortality and morbidity remains for polio in light of the absence of antiviral treatment options. The poliovirus vaccination programme has been critically important to date, and the development of nOPV2 is a much-needed boost to global eradication efforts. Polio has not disappeared as evidenced by the recent resurgence of paralytic polio cases in Israel, the US and other countries, as well as the detection of VDPV in wastewater in London relatively recently. All countries must ensure high poliovirus vaccination coverage in their population, and appropriate interventions must be taken to rectify this if coverage falters. Surveillance systems, including those for the environment and wastewater should be implemented to allow early detection of "silent" poliovirus transmission in the population, instead of relying on AFP surveillance alone.

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REVIEW ARTICLE

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Ablation therapies for paroxysmal atrial fibrillation: A systematic review and patient-level network meta-analysis

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ABSTRACT

Introduction: Despite promising trials, catheter ablation is still regarded as an adjunct to antiarrhythmic drugs (AADs) in the treatment of paroxysmal atrial fibrillation (PAF). This study aimed to compare the effectiveness of various ablation therapies and AADs.

Method: Randomised controlled trials or propensity score-matched studies comparing atrial tachyarrhythmia recurrence among any combination of ablation modalities or AAD were retrieved. Kaplan-Meier curves and risk tables for this outcome were graphically reconstructed to extract patient-level data. Frequentist network meta-analysis (NMA) using derived hazard ratios (HRs), as well as 2 restricted mean survival time (RMST) NMAs, were conducted. Treatment strategies were ranked using P-scores.

Results: Across 24 studies comparing 6 ablation therapies (5,132 patients), Frequentist NMA-derived HRs of atrial fibrillation recurrence compared to AAD were 0.35 (95% confidence interval [CI]=0.25–0.48) for cryoballoon ablation (CBA), 0.34 (95% CI=0.25–0.47) for radiofrequency ablation (RFA), 0.14 (95% CI=0.07–0.30) for combined CBA and RFA, 0.20 (95% CI=0.10–0.41) for hot-balloon ablation, 0.43 (95% CI=0.15–1.26) for laser-balloon ablation (LBA), and 0.33 (95% CI=0.18–0.62) for pulmonary vein ablation catheter. RMST-based NMAs similarly showed significant benefit of all ablation therapies over AAD. The combination of CBA + RFA showed promising long-term superiority over CBA and RFA, while LBA showed favourable short-term efficacy.

Conclusion: The advantage of ablation therapies over AAD in preventing atrial tachyarrhythmia recurrence suggests that ablation should be considered as the first-line treatment for PAF in patients fit for the procedure. The promising nature of several specific therapies warrants further trials to elicit their long-term efficacy and perform a cost-benefit analysis.

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Keywords: Atrial fibrillation, catheter ablation, network meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is a pertinent health condition that is seeing a sustained rise in global incidence and prevalence.[1] In particular, paroxysmal AF (PAF), despite its transient nature, is associated with a slow but steady progression to persistent AF[2] and increased mortality compared to patients without AF.[3] Furthermore, patients with PAF have a similar rate of ischaemic stroke as patients with persistent AF; it is thus important to address PAF to prevent future cardiovascular mortality and morbidity.[4]

Medical therapy with antiarrhythmic drugs (AADs) has long been the mainstay of PAF therapy.[5] Catheter ablation is an alternative upfront treatment with a class IIa recommendation[5] and can also be performed if AAD therapy fails; the class I recommendation only applies to patients with heart failure with reduced ejection fraction.[6] The commonly used ablation techniques in practice are radiofrequency ablation (RFA)[7] and cryoballoon ablation (CBA); others include laser balloon ablation (LBA), hot balloon ablation (HBA), and pulmonary vein ablation catheter (PVAC). Recent trials

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CLINICAL IMPACT

What is New

- In this systematic review and network meta-analysis using patient-level data from high-quality studies, catheter ablation was found to be consistently superior to antiarrhythmic drugs (AADs) for the treatment of paroxysmal atrial fibrillation (PAF) in terms of preventing atrial fibrillation recurrence.
- This finding was observed across 3 different network meta-analysis models.

Clinical Implications

- This study further cements evidence for catheter ablation as a promising alternative to AADs as the first-line treatment for PAF in patients fit for the procedure.
- Promising results of combined cryoballoon plus radiofrequency ablation in the long term, and laser-balloon ablation in the short term, highlight the need for more trials and cost-benefit analyses with long-term follow-up.

have shown significant benefit for catheter ablation as a first-line therapy for PAF, and meta-analyses have indeed advocated for ablation to replace AADs in treating PAF.[8,9] However, they were limited by low numbers of included trials, or grouping all ablation modalities as a single arm. Similarly, there are meta-analyses comparing CBA and RFA, but included studies do not usually involve an AAD arm for reference.[10,11]

Given the diversity of modalities and fragmented nature of research into the field of ablation therapies for PAF, an all-encompassing synthesis of the subject using evidence from high-quality trials is sorely needed. This can be addressed by a network meta-analysis (NMA), which is an effective method to pool effect sizes across multiple studies and modalities.[12] As randomised controlled trials (RCTs) in this field are limited in number, propensity-score matched studies (PSMs) were also the sought for pooling of individual patient data (IPD). PSMs have been shown to be empirically equivalent to RCTs in generating unbiased estimates of the efficacy of treatment, while eliminating confounding factors and biases to a large extent.[13]

Hence, the aim of this IPD-NMA was to evaluate the effectiveness of various ablation therapies or medical therapy in PAF patients from RCTs or PSMs, with atrial tachyarrhythmia recurrence as the primary outcome.

METHOD

Literature search

This systematic review and IPD-NMA were performed in line with the PRISMA Guidelines for IPD Systematic Reviews. The study design and review protocol were registered with PROSPERO (CRD42022313230).

An electronic literature search from inception to 29 October 2021 was performed on PubMed, EMBASE, Web of Science and the Cochrane Controlled Register of Trials (CENTRAL), without language restrictions. The search strategy included the concepts of PAF and various ablation modalities (Supplementary Table S1 in the online version of this article). Bibliographies of included studies were screened to ensure the inclusion of all relevant studies. The abstract and full-text review were conducted by 2 independent investigators; conflicts were resolved after discussion among all the authors in this paper.

The inclusion criteria were: RCTs or PSMs comparing any combination of ablation modalities or comparing ablation modalities against AADs in patients with paroxysmal atrial fibrillation; and provision of Kaplan-Meier curves with risk tables for atrial tachyarrhythmia recurrence (or complete study follow-up if risk tables were absent). If multiple publications of the same study were retrieved, the most recent and informative publication was included. Studies comparing ablation versus AAD without specifying the exact ablation modality were excluded, as were case reports, case series, reviews and conference abstracts.

Data extraction from included studies was conducted by 2 independent investigators using a standardised data collection template with predefined data fields including study design, patient demographics and outcomes. RCTs were assessed for risk of bias using the Cochrane Risk of Bias (RoB 2) tool for RCTs, and PSMs were assessed using the Newcastle-Ottawa Scale.

Extraction of individual patient data

Given the rapid advancements in ablation therapies in recent years, more precise methods are needed to quantify comparisons among different modalities. Hence, a graphical reconstructive algorithm[14] grounded in analysis outlined by Guyot et al.[15] was employed to attain IPD for survival from atrial tachyarrhythmia recurrence, using Kaplan-Meier curves from included studies. An IPD meta-analysis is recognised as the gold standard approach for evidence synthesis.[16,17]

Network meta-analysis

First, a Frequentist NMA was conducted to compare the treatments of CBA, RFA, CBA + RFA, PVAC, LBA, HBA and AAD. Hazard ratio (HR) estimates and their 95% confidence intervals (95% CI) for each IPD study were pooled together in a 2-stage NMA. Treatment strategies were ranked using P-scores, with higher P-scores corresponding to greater efficacy.

As Cox-based models were used to derive HRs for the aforementioned analysis, the proportional hazards assumption was verified. If the assumption was violated, restricted mean survival time (RMST) for each treatment was also analysed[18-20] using 2 measures—RMST mean difference (RMST-D) and RMST ratio (RMST-R)—which were pooled under respective Frequentist NMAs. As RMST does not utilise HRs and is applicable to nonlinear covariate relationships, it acts as a further sensitivity analysis of the first NMA. Heterogeneity was assessed via the I^2 statistic, and considered low, moderate, or considerable for I^2 values <40%, 40–75%, and >75%, respectively.[21] Cochran's Q was also used to assess for heterogeneity and inconsistency.

Due to the inclusion of non-randomised studies in the form of PSM in this study, sensitivity analysis was also performed, involving a Frequentist NMA with data from RCTs only.

A further NMA was also conducted by pooling ablation procedural times in studies that compared 2 or more ablation procedures. Outcomes were assessed as mean differences (MD), with RFA as a base comparator.

All analyses were conducted in R version 4.1.2, with $P<0.05$ regarded as indicating statistical significance. Full details of the statistical analyses are provided in the online Supplementary Methods. Ethics approval was not required as this study makes use of publicly available data.

RESULTS

Study selection

The search strategy retrieved 800 studies, of which 461 duplicates were removed; the remaining 339 studies were screened by title and abstract. Thirty-eight studies were identified for full-text review,and a final 24 studies (18 RCTs and 6 PSMs) comprising 5,132 patients were included (Fig. 1).

Study characteristics

Nine studies compared CBA with RFA,[22-31] 3 compared CBA with AAD,[32-34] 5 compared RFA with AAD,[35-39]

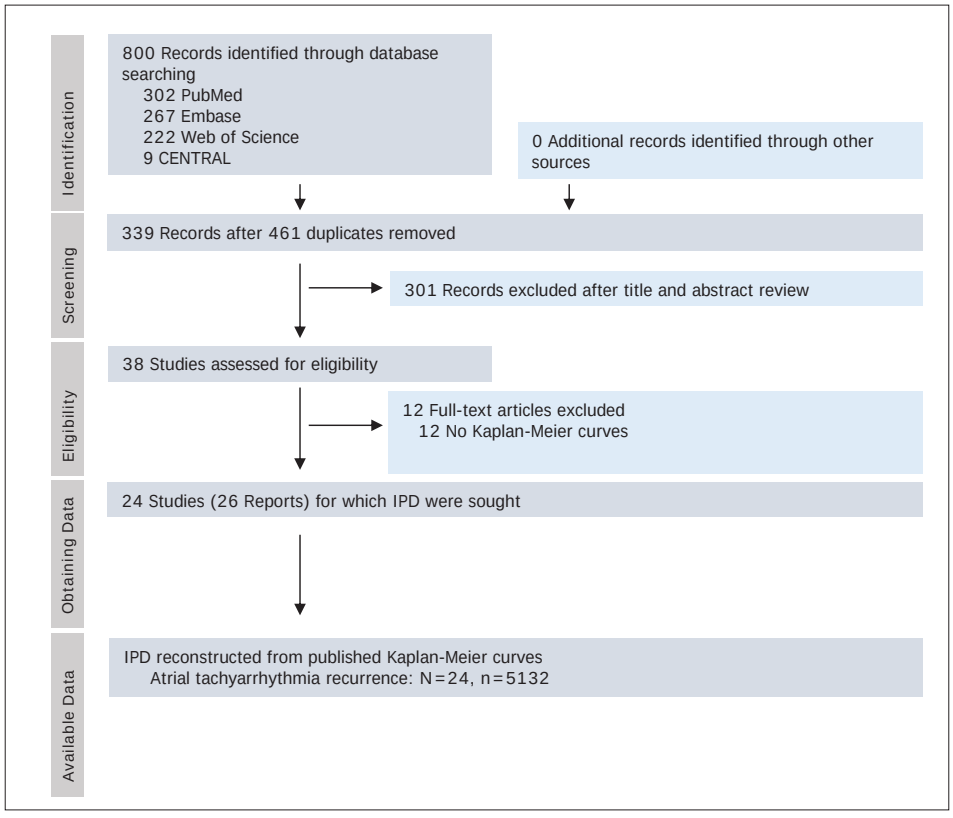

Fig. 1. PRISMA flowchart of included studies.

2 compared LBA with CBA,[40,41] 2 compared PVAC with RFA,[42,43] 1 compared HBA with CBA,[44] and 1 compared HBA with AAD.[45] The remaining study was a 3-way comparison of CBA, RFA and a combination of both (CBA + RFA)[46] (Table 1). A predominantly Caucasian, male population was involved, and the incidence of diabetes mellitus was under 25% (online Supplementary Table S2). The average duration of AF ranged from 0.4–8.6 years. Baseline beta-blocker use ranged from 5.8–67%. Only 1 study allowed AAD regimens to be newly initiated in the treatment arm.[35] In studies with an AAD arm, the most common AADs were flecainide and propafenone. Second-generation CBA was the most common subtype of CBA used in most studies, while studies with an RFA arm were mostly a mix of contact force and non-contact force subtypes. A blanking period, wherein AF recurrence after index ablation was not counted as treatment failure, was implemented in almost all studies, typically spanning 90 days. Adverse events are shown in the online Supplementary Table S3. There were no gross differences in serious adverse events between any ablation modality and AAD, or between ablation modalities, although studies were not likely powered to detect such differences. All studies were deemed to have a low risk of bias (online Supplementary Table S4).

Pairwise comparisons

Three or more studies reported direct comparisons for the following PAF treatments: CBA versus AAD, RFA versus AAD, and CBA versus RFA. IPD-derived one-stage Kaplan-Meier comparisons for the primary outcome among 3 studies showed a significant benefit of CBA over AAD (shared-frailty HR=0.44, 95% CI=0.35–0.56, P<0.001) (Fig 2A). RFA was also superior to AAD (shared-frailty HR=0.26, 95% CI=0.20–0.33, contact-force P<0.001) across 5 studies (Fig. 2B). There was no significant difference in the primary outcome between CBA and RFA (shared-frailty HR=0.91, 95% CI=0.80–1.04, P=0.174) across 10 studies (online Supplementary Fig. S1). Two-stage comparisons were concordant with one-stage comparisons (online Supplementary Figs. S2–4).

Frequentist network meta-analysis

The combined Kaplan-Meier plot of all studies is shown in Fig. 3 and the network plot of all included trials is shown in online Supplementary Fig. S5. Derived HRs of atrial tachyarrhythmia recurrence compared to AAD were 0.35 (95% CI=0.25–0.48) for CBA, 0.34 (95% CI=0.25–0.47) for RFA, 0.14 (95% CI=0.07–0.30) for CBA + RFA, 0.20 (95% CI=0.10–0.41) for HBA, 0.43 (95% CI=0.15–1.26) for LBA, and 0.33 (95% CI=0.18–0.62) for PVAC (Table 2 and online Supplementary Fig. S6). Hence, all treatments except LBA showed significant benefits compared to AAD for the primary outcome. Furthermore, CBA + RFA was significantly favoured over CBA (HR=0.41, 95% CI=0.20–0.83) and RFA (HR=0.41, 95% CI=0.21–0.83) but not against other modalities. Tests of heterogeneity (I^2=64%, Cochran's Q=52.8, P<0.001) indicated moderate between-study heterogeneity and justified the use of a random-effects model. P-scores ranked CBA + RFA as the best modality, followed by HBA (Table 3).

Restricted mean survival time network meta-analysis

When the pairwise comparison with the largest number of direct studies (CBA versus RFA) was analysed, the proportional hazards assumption was violated (online Supplementary Fig. S7). Hence, further analysis was performed using RMST-based NMAs. Separate RMST-R and RMST-D analyses both demonstrated that all ablation therapies were superior to AAD (online Supplementary Figs. S8–11, online Supplementary Tables S5 and S6), with RMST-R versus AAD ranging from 1.33–2.11 and RMST-D versus AAD ranging from 0.15–0.23 year. In the RMST-R analysis, CBA + RFA was significantly superior to all therapies except HBA. P-scores ranked CBA + RFA as the best therapy (Table 2).

Sensitivity analysis

When restricted to the 18 included RCTs only, the hazard ratio-based Frequentist NMA showed similar results to the entire cohort (online Supplementary Fig. S12, Supplementary Table S7). Moderate heterogeneity was observed (I^2=75%, Cochran's Q=51.3, P<0.001).

Network meta-analysis of procedural time

The NMA of procedural time across various therapies was found to have high heterogeneity and inconsistency between studies (I^2=92%, Cochran's Q=120, P<0.001). PVAC was ranked as the fastest procedure, followed by CBA; both had a significantly faster procedural time than RFA (online Supplementary Table S8, Supplementary Fig. S13). CBA + RFA had a significantly longer procedural time than all other ablation therapies.

DISCUSSION

Since the identification of focal origins of atrial ectopic beats and their successful ablation using radiofrequency energy,[7] subsequent modalities have aimed to achieve the same outcome via different methods of energy delivery. Alongside technical advancements such as contact force

Table 1. Characteristics of included studies

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Ang 2018 Cryo vs RF	RCT	UK	Jul 2009–Dec 2012	203	≥18	CBA vs RFA vs CBA + RFA	90	>18 years, documented PAF on at least 2 occasions and accepted for catheter ablation for AF	Severe left atrial dilatation (>50mm), severe valvular disease, previous left atrial ablation, persistent AF, potentially reversible cause of AF, any contraindication to ablation
Buist 2018	RCT	Netherlands	NR	269	12	CBA vs RFA	90	Suitable for primo PVI for drug-refractory paroxysmal or early persistent AF	Procedures in which additional ablation strategies (e.g.complex fractionated atrial electrograms, linear ablations, right atrium ablations) were applied
Kuck 2018 FIRE AND ICE	RCT	8 countries	Jan 2012–Jan 2015	750	12	CBA vs RFA	90	18–75 years, symptomatic PAF with at least 2 episodes and at least one episode documented (30 seconds length, documented by ECG within last 12 months) that was refractory to class I or class III AADs or beta blockers	Life expectancy <1 year, pregnant or breastfeeding women, active systemic infection, cryoglobulinaemia, cardiac surgery/PCI/myocardial infarction in preceding 3 months, unstable angina pectoris, contraindication to chronic anticoagulation, NYHA class III-IV heart failure, LVEF <35%, mitral prosthesis, intracardiac thrombus
Andrade 2019/ Larsen 2020 CIRCA DOSE	RCT	Canada	Sep 2014–Jul 2017	346	12	CBA vs RFA	90	>18 years, PAF refractory to at least one class I or class III AAD	Previous left atrial ablation or surgery, AF due to reversible cause, intracardiac thrombus, cardiac valve prosthesis, contraindication to anticoagulation, clinically significant mitral valve regurgitation or stenosis, NYHA class III-IV heart failure, pregnancy, stroke/TIA in preceding 6 months, LVEF <35%
Pak 2021 CRAFT	RCT	South Korea	NR	312	12	CBA vs RFA	90	Patients who underwent catheter ablation for symptomatic and drug-refractory non-valvular PAF	Persistent or permanent AF, rheumatic valvular disease, significant structural heart disease other than left ventricular hypertrophy, left atrial diameter ≥55mm, history of AF ablation or cardiac surgery
Perez-Castellano 2014 COR	RCT	Spain	Jul 2009–Mar 2011	50	12	CBA vs RFA	90	18–75 years, symptomatic recurrent PAF (42 episodes in the last 6 months) refractory to ≥1 AADs (class I or III) and an anatomical pattern consisting of 4 single pulmonary veins	Prior AF ablation, prior cardiac surgery, moderate to severe valvular heart disease, anteroposterior left atrial diameter >50mm, hyperthyroidism, intracardiac thrombus, contraindications for anticoagulant therapy, concomitant acute illness, pregnancy, unavailability for follow-up for at least 1 year

Table 1. Characteristics of included studies (Cont'd)

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Ikenouchi 2018	PSM	Japan	Jan 2012–Aug 2017	198	12	CBA vs RFA	90	Consecutive patients >75 years with PAF or persistent atrial fibrillation undergoing first PVI[a]	Left atrial thrombus, abnormal thyroid function, severe frailty, long-standing AF (>1 year), severe valvular heart disease, contraindications for the procedure
Knecht 2014 BEAT-AF	PSM	Switzerland	NR	142	12	CBA vs RFA	90	Consecutive patients with documented episodes of AF	Persistent or permanent AF, history of any previous left atrial procedure (surgical or percutaneous), use of a magnetic navigation system
Matta 2018	PSM	Italy	NR	92	12	CBA vs RFA	90	Consecutive patients suffering from paroxysmal atrial fibrillation treated with CBA or RFA	NR
Tokuda 2016	PSM	Japan	NR	246	12	CBA vs RFA	90	414 consecutive patients who had undergone an initial catheter ablation procedure for PAF	NR
Andrade 2020 EARLY AF	RCT	Canada	Jan 2017–Dec 2018	303	12	CBA vs AAD	90	>18 years with symptomatic AF and ≥1 episode of AF detected on ECG within 24 months before randomisation	History of daily use of a class I or class III AAD at therapeutic doses
Kuniss 2021 Cryo FIRST	RCT	20 sites worldwide	Apr 2014–Oct 2018	218	12	CBA vs AAD	90	18–75 years with a normal ECG, LVEF ≥50%, thickness of the inter-ventricular septum ≤12mm, left atrium diameter (short axis) <46mm, recurrent symptomatic PAF, drug naive (had not previously received a Class I or III AAD for >48 hours)	Persistent AF, previous left atrial ablation or cardiac surgery, documented typical atrial flutter, previous TIA or stroke, intracardiac thrombus, hypertrophic cardiomyopathy
Wazni 2020 STOP AF	RCT	US	Jun 2017–May 2019	203	12	CBA vs AAD	90	18–80 years with recurrent symptomatic PAF	Previous AAD treatment (class I or III) for ≥7 days, enlarged left atrial diameter (>5cm), previous left atrial ablation or left atrial surgical procedure
Kuck 2021 ATTEST	RCT	29 sites worldwide	Feb 2012–May 2018	255	36	RFA vs AAD	90	≥60 years of age with PAF for ≥2 years and with ≥2 episodes over the 6 months preceding enrolment	Reversible AF, previous diagnosis of persistent/permanent AF/AT, cardioversion >48 hours after onset of AF/AT, recent cardiovascular events

Table 1. Characteristics of included studies (Cont'd)

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Morillo 2014 RAAFT-2	RCT	16 sites worldwide	Jul 2006–Jan 2010	127	24	RFA vs AAD	90	18–75 years, symptomatic with recurrent PAF lasting > 30 seconds (≤4 episodes within the prior 6 months); experienced at least 1 episode that was documented by surface ECG, 6 months before randomisation; and had no previous AADs	Previous AAD treatment, LVEF <40%, left atrial diameter >5.5 cm; moderate-to-severe left ventricular hypertrophy (wall thickness >1.5cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months; left heart ablation procedure, complete contraindication to use of heparin, warfarin, or both
Pappone 2011 APAF	RCT	Italy	Jan 2005–May 2005	198	48	RFA vs AAD	42	18–70 years, creatinine concentration <1.5mg/dL, AF history >6 months, AF burden >2 episodes/month in the last 6 months	AF secondary to transient or correctable abnormality, intra-atrial thrombus, tumour precluding catheter insertion, LA diameter >65mm, LVEF <35%, heart failure >NYHA functional class II, prior AAD therapy with amiodarone, flecainide, and sotalol, contraindication to beta-blocking therapy
Wazni 2005	RCT	3 countries	Dec 2001–Jul 2002	70	12	RFA vs AAD	None	18–75 years, monthly symptomatic AF episodes for at least 3 months	Previous history of atrial flutter or AF ablation, previous open-heart surgery, previous treatment with AAD, contraindication to long-term anticoagulation
Wilber 2010	RCT	19 sites worldwide	Oct 2004–Oct 2007	167	9	RFA vs AAD	90	3 symptomatic AF episodes (≥1 episode verified by ECG) within the 6 months before randomisation, not responding to ≥1 AAD (class I, class III, or atrioventricular nodal blocker)	AF ≥30 days in duration, age <18 years, LVEF <40%, previous ablation for AF, documented left atrial thrombus, amiodarone therapy in the previous 6 months, NYHA class III or IV, myocardial infarction within the previous 2 months, CABG in previous 6 months, thromboembolic event in previous 12 months, severe pulmonary disease, implanted ICD, contraindication to AAD or anticoagulants
Suruga 2021	PSM	Japan	Oct 2016–Aug 2017	60	12	HBA vs CBA	90	Consecutive HBA patients and PSM CBA patients	NR

Table 1. Characteristics of included studies (Cont'd)

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Sohara 2016	RCT	Japan	NR	143	9	HBA vs AAD	84	20–75 years, refractory to ≥1 class I to IV AADs	Previous left atrial ablation or surgery for AF, refractory to selected AADs, NYHA class III–IV, myocardial infarction or unstable angina pectoris during the previous 6 months, comorbid severe ischaemic heart disease, valvular disorder, severe pulmonary hypertension, carotid occlusion, deep-vein thrombosis, history of cerebral infarction or intracerebral bleeding with apparent neurological symptoms during the previous 6 months
Chun 2021	RCT	Germany	Apr 2017–Apr 2019	200	12	LBA vs CBA	90	18–80 years, symptomatic PAF or persistent AF refractory to ≥1 AAD, including beta-blockers (class I–III)[a]	Previous PVI attempts. ineligible for treatment with oral anticoagulation, presence of an intracardiac thrombus, moderate or severe mitral valve disease
Yano 2021	PSM	Japan	Apr 2019–Jul 2020	74	3	LBA vs CBA	None	Consecutive PAF patients undergoing primary PVI with CBA or LBA	NR
Gal 2014	RCT	Netherlands	NR	460	43	PVAC vs RFA	90	Consecutive patients with symptomatic AF	NR
McCready 2014	RCT	UK	Sep 2007–Mar 2012	188	12	PVAC vs RFA	90	Patients with PAF who had failed at least one AAD who had been listed for a planned PVI procedure	Patient objection, prior AF ablation, left atrial size >60mm, mechanical prosthetic mitral valve replacement, hypertrophic cardiomyopathy, contraindications to anticoagulation, pregnancy

[a] Although persistent AF was included in the trial, only the paroxysmal AF subgroup was included in subsequent analysis.

AAD: antiarrhythmic drugs; AF: atrial fibrillation; AT: atrial tachycardia; CABG: coronary artery bypass graft; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; ECG: electrocardiogram; HBA: hot balloon ablation; ICD: implantable cardioverter-defibrillator; LA: left atrial; LBA: laser balloon ablation; LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association; PAF: paroxysmal atrial fibrillation; PSM: propensity-score matched study; PVAC: pulmonary vein ablation catheter; PVI: pulmonary vein isolation; RCT: randomised controlled trial; RFA: radiofrequency ablation; TIA: transient ischaemic attack

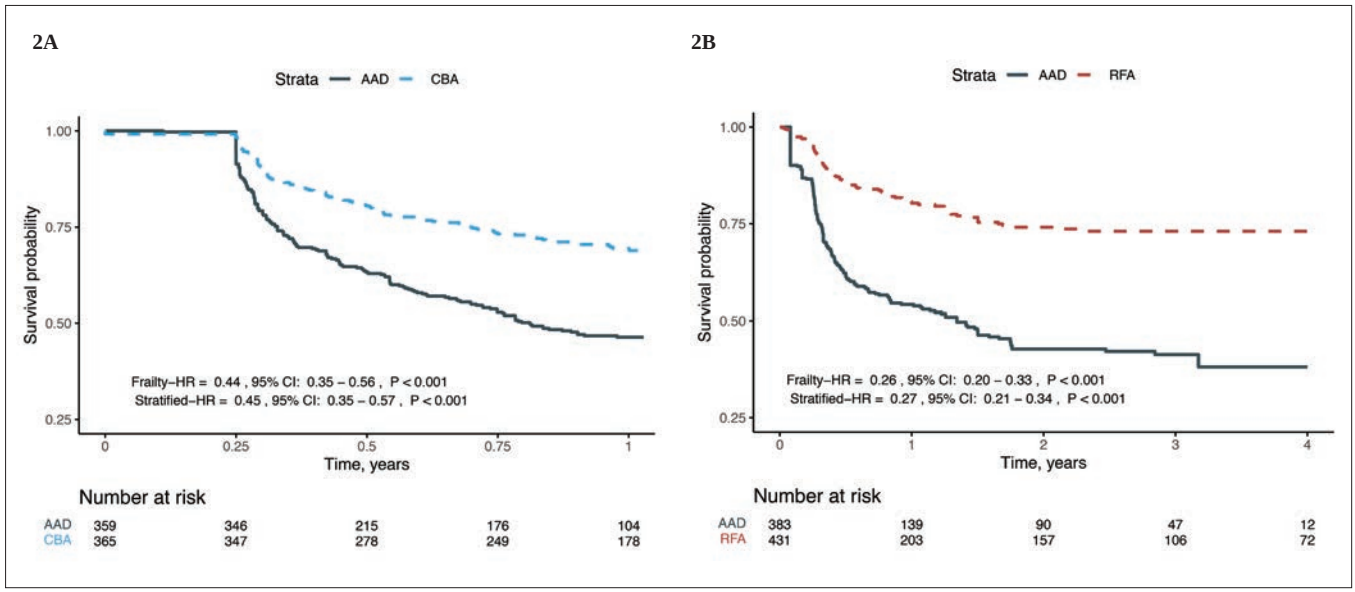

Fig 2. Individual patient data one-stage meta-analysis of freedom from atrial tachyarrhythmias for (A) CBA versus AAD, (B) RFA versus AAD.
AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CI: confidence interval; HR: hazard ratio; RFA: radiofrequency ablation

ablation, which provides real-time feedback on tissue contact, and remote magnetic navigation, which allows mapping via stereotaxis, ablation has become increasingly safer and more efficacious.[47]

Accordingly, a meta-analysis of the relative efficacies of CBA versus RFA or ablation versus AAD has been previously performed.[11] However, this can only present fragmented viewpoints of the larger picture of ablation therapies for PAF. A recent NMA by Kukendrarajah et al.[48] compared CBA, RFA, LBA and PVAC across 14 RCTs, and concluded that the efficacy of non-RFA technologies was comparable to that of RFA. However, AAD was not included as a baseline comparator. Messori et al.[49] performed an RMST-based NMA between CBA, RFA and AAD, but only 5 RCTs were included in the analysis. Hence, there remained a role to synthesise all modalities from high-quality studies using IPD, which is recognised as the gold standard approach for evidence synthesis.[16]

This IPD-NMA was congruent with previous results in showing the significance of CBA and RFA over AAD in reducing AF recurrence. Pairwise IPD comparisons, which represent more robust analyses compared to pooled study-level aggregate data, showed a large divergence in Kaplan-Meier curves for both CBA and RFA compared to AAD, suggesting a sustained long-term benefit. The certainty of their benefit is further strengthened by indirect comparisons due to the large number of trials comparing CBA to RFA. Altogether, the clinically significant benefit of commonly used ablation therapies across all 3 NMA models, along with a similar safety and adverse event profile to AAD,

Table 2. League table comparing hazard ratios of various treatments in the hazard ratio-based Frequentist network meta-analysis

CBA + RFA						
0.41 (0.20–0.83)	CBA					
0.41 (0.21–0.83)	1.01 (0.79–1.29)	RFA				
0.70 (0.25–1.94)	1.71 (0.80–3.65)	1.69 (0.79–3.63)	HBA			
0.33 (0.09–1.13)	0.80 (0.29–2.21)	0.79 (0.28–2.25)	0.47 (0.13–1.66)	LBA		
0.43 (0.18–1.02)	1.04 (0.59–1.86)	1.03 (0.61–1.74)	0.61 (0.24–1.54)	1.30 (0.40–4.20)	PVAC	
0.14 (0.07–0.30)	**0.35 (0.25–0.48)**	**0.34 (0.25–0.47)**	**0.20 (0.10–0.41)**	0.43 (0.15–1.26)	**0.33 (0.18–0.62)**	AAD

AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; LBA: laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

Bold text indicates values that crossed the threshold for significance

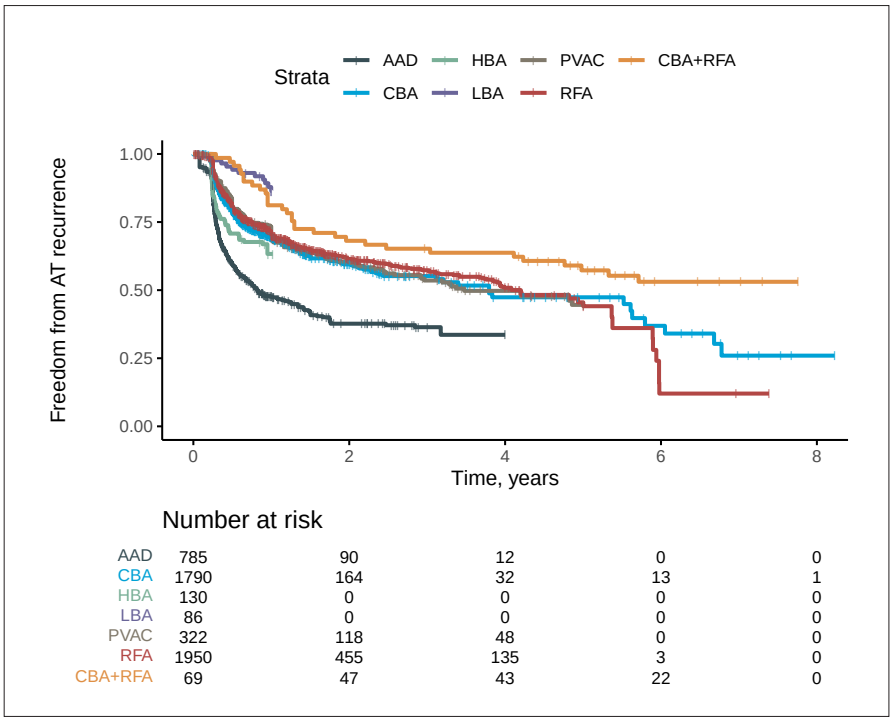

Fig. 3. Kaplan-Meier curves for atrial tachyarrhythmia recurrence, derived from reconstructed individual patient data from included studies.
AAD: antiarrhythmic drugs; AT: atrial tachyarrhythmia; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; HR: hazard ratio; LBA: laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

strengthens the case for upfront ablation therapy as a suitable alternative for patients who can tolerate the procedure. This NMA also provides Level 1A evidence for these comparisons, in support of prior observational studies that showed the benefit of ablation in reducing overall mortality and stroke,[50,51] and reinforcing current European Society of Cardiology guidelines,[5] which recommend both ablation and AAD as first-line treatment modalities for PAF depending on patient choice.

Moreover, the significance of these results can also be seen with CABANA, which is the largest RCT of upfront ablation versus AAD to date (2,204 patients in total).[52] Although only 43% of the CABANA cohort had paroxysmal AF (the rest had persistent or long-standing

Table 3. P-score rankings for various paroxysmal atrial fibrillation therapies

	Frequentist HR NMA	RMST-R NMA	RMST-D NMA
CBA + RFA	0.946	0.981	0.836
HBA	0.801	0.770	0.649
PVAC	0.492	0.419	0.482
RFA	0.460	0.429	0.482
CBA	0.444	0.434	0.492
LBA	0.348	0.465	0.552
AAD	0.011	0.002	0.007

Higher P-scores indicate greater estimated treatment efficacy. The top 3 treatments for each analysis are ranked with a colour gradient, with darker grey representing a higher P-score.

AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; HR: hazard ratio; LBA: laser balloon ablation; NMA: network meta-analysis; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation; RMST-D: restricted mean survival time difference; RMST-R: restricted mean survival time ratio

persistent AF), significant reductions in AF recurrence were seen (HR=0.52, 95% CI=0.45–0.60, $P<0.001$). No differences in mortality, death or cardiovascular hospitalisation were noted, but a lower-than-expected mortality rate in the AAD group may have contributed to the lower precision of the effect size estimate. CABANA was excluded from our analysis as the exact breakdown of RFA and CBA was not specified; however, severe adverse effect profiles were favourable with a 0.8% incidence of cardiac tamponade.

Within the modalities evaluate in this NMA, CBA and RFA showed similar outcomes in both pairwise and NMA comparisons. Previous RCTs have noted the relative ease of performing CBA compared to RFA, with CBA requiring more extensive fluoroscopic guidance.[23] This comparison is further complicated by the presence of newer technologies (contact force sensing and second-generation cryoballoon catheters), which were not well stratified within included studies to conduct a subgroup analysis. Contact force-guided catheters offer lower radiation exposure, procedural times, and cardiac perforation rates, but their association with other safety outcomes and clinical efficacy remains unclear.[53] Second-generation cryoballoons markedly decrease AF recurrence compared to the first generation.[54] A multicentre comparison of contact-force-guided RFA versus second-generation CBA found no significant difference in 18-month atrial arrhythmia freedom, with no periprocedural deaths in either group,[55] indicating that both are similarly safe and effective.

CBA + RFA was only performed in 1 included study,[46] involving RFA followed by 2 CBA freezes in a single procedure. The reported 5-year freedom from AF recurrence of 57%, and gross difference in Kaplan-Meier curves versus other techniques (Fig. 3), make it a frontrunner in this field. This was quantitatively supported by HR-based and RMST-R analyses, which found CBA + RFA significantly superior to CBA or RFA alone. CBA + RFA was associated with significantly fewer pulmonary vein reconnections (PVR) than CBA or RFA. Moreover, the different patterns of PVR observed in CBA and RFA—inferiorly for most of the former, superiorly for most of the latter[56]—are postulated to account for the synergy of combining both in a single procedure. Nonetheless, the NMA of procedural time found it significantly more time-consuming than all other ablation modalities. Accordingly, a more in-depth cost-benefit and safety-profile analysis of this technique is necessary, and more studies should be conducted in view of the current evidence for this technique being based solely on one RCT.

Studies of HBA only followed patients for up to 1 year. This lack of long-term follow-up may have led to the unexpected finding of HBA ranking second by way of *P* values within all 3 NMA methods. Plotting the results of all studies that used AAD as the control arm (online Supplementary Figs. S14 and S15), the AAD arm of Sohara et al.[45] had a much greater recurrence of atrial tachyarrhythmia than AAD arms in other studies. All patients in this study were refractory to 1 or more AADs upon enrolment, in contrast to some included studies[34,36] that excluded patients previously treated with an AAD. Combined with the slight variation in AADs used, it is possible that the relatively poor performance of the AAD arm in this study is a random error compounded by the low number of patients (n=43). Hence, the relatively inflated value of the HR for this study, which led to its high P-score ranking, may not be a true reflection of its efficacy. Nonetheless, HBA has been noted to have a more favourable learning curve compared to CBA,[57] which may render it a favourable starting point for centres without prior specialisation in ablation.

The remaining modalities, despite not being widely used, similarly showed significant benefits over AAD. PVAC is a modified form of RFA using a multielectrode, circular, bidirectional catheter; it may offer lower procedural times compared to conventional RFA but is no longer widely used due to concerns over the considerable levels of pulmonary stenosis after treatment.[58] LBA was significantly favoured over AAD in the RMST-based analyses but not the HR-based analysis, which may be attributed to the presence of only 2 LBA studies and its short follow-up. The visually guided LBA used was similar to RFA in requiring point-by-point ablations, as the aiming beam produces an arc covering only ~30^{o} of a circle. LBA was ranked as the third-best modality by way of P-scores in both RMST analyses. The questionable ranking of HBA as the second-best therapy, as mentioned previously, may point to LBA being a stronger contender for second place. From Kaplan-Meier curves alone (Fig. 3), the trajectory of LBA resembles CBA + RFA—the highest-ranked modality—more than other modalities. A recent meta-analysis of LBA versus CBA suggested a trend towards higher 12-month procedural success for LBA,[59] but no head-to-head studies of LBA versus AAD have been performed. Hence, further trials with long-term follow-up are needed to fill these gaps in evidence.

Pulsed-field ablation (PFA) has emerged in recent years as a tool for pulmonary vein isolation. Nonetheless, promising outcomes in terms of myocardial tissue

specificity and dramatically lower procedural time, combined with a unique safety profile, have been found in single-arm trials.[60] Although one of the major points in favour of CBA usage is its lower procedural time, PFA may offer a promising alternative in the future. Further RCTs are needed to compare PFA to the myriad of technologies in this review.

Despite the use of IPD reconstruction as a rigorous statistical method that accounts for follow-up and censoring status, a noteworthy limitation was the inability to account for effects exerted by patient-level prognostic covariates on arrhythmia freedom. Moreover, all NMAs are limited by the assumptions of methodological equivalence and the similarity of baseline patient characteristics. Included studies were broadly similar in methodology barring the different study designs (RCT and PSM) which have been shown to be empirically equivalent to a large extent. Conversely, baseline patient characteristics varied considerably across studies —an inevitable limitation for essentially all NMAs. Several potential studies which provided Kaplan-Meier curves without risk tables were excluded, as graphical reconstruction is considerably less accurate without risk tables.[15] Measures of safety outcomes among studies were heterogeneous, and most were not sufficiently powered to detect differences in adverse effects; hence, a NMA of safety outcomes was also not feasible, although CABANA has shown favourable safety outcomes in a more adequately powered cohort.[52] Outcomes such as stroke, all-cause mortality, and periprocedural complications remain an important avenue for clinical decision-making, and future RCTs of individual ablation modalities should aim to be adequately powered for these outcomes as well. Cost-benefit analysis is also an important consideration, with catheter ablation as a whole shown to be reasonably cost-effective compared to AAD.[61] The results of this NMA, which quantitatively ranks 6 ablation techniques, provide a basis for a comprehensive cost-benefit analysis of individual ablation strategies.

CONCLUSION

In addressing the diverse field of ablation therapies for PAF using findings derived from robust networks of high-quality studies, this NMA found a consistent advantage of ablation therapies over AADs in preventing atrial tachyarrhythmia recurrence. Coupled with the large divergence of Kaplan-Meier curves in the CBA versus AAD, and RFA versus AAD pairwise comparisons, ablation represents a suitable first-line alternative to AAD for PAF in patients who are fit for the procedure. Intriguingly, the combination of CBA + RFA showed promising long-term superiority over conventional techniques, while LBA showed favourable short-term efficacy that may warrant a long-term investigation in future trials.

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LETTER TO THE EDITOR

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Case studies of fetal mosaicisms detected by non-invasive prenatal testing

Dear Editor,

The American College of Medical Genetics and Genomics recommended that all pregnant women be offered non-invasive prenatal testing (NIPT) regardless of the patient's risk profile.[1] With increasing NIPT uptake, encounters with genetic conditions other than the 3 common fetal trisomies are becoming prevalent. We report 2 cases of fetal mosaicisms for chromosomes 13 and 22, respectively.

Case 1. The patient was 37 years old and opted for NIPT at 12 weeks (w). Cell-free DNA from maternal plasma was extracted for subsequent low-pass whole genome sequencing. Results showed high risk for trisomy 13, while Y-chromosomal sequences were detected, indicating a male fetus. Fetal fraction was 10.7%. Amniocentesis was performed at 16w, and karyotype showed mosaic 47,XY,+13[3]/46,XY[36] (Fig.1A). Trisomy 13 mosaicism was diagnosed with 7.7% abnormal cells. She was referred for genetic counselling (GC) and extensively counselled that the fetus is at increased risk of systemic structural abnormality and intellectual disability. After GC and fetal ultrasound scan, the patient decided to proceed with termination of pregnancy (TOP) at 19w.

Case 2. The patient was 40 years old and an early scan showed no obvious structural abnormality. At 12w, she opted for NIPT and the blood was processed in the same way as in Case 1. NIPT results showed high risk for trisomy 22, and no Y-chromosomal sequences were detected, indicating a female fetus. Fetal fraction was 11.3%. Amniocentesis was performed at 15w, and karyotype showed mosaic 47,XY,+22[3]/46,XX[12] (Fig. 1B). Low-level trisomy 22 mosaicism was diagnosed with 20.0% abnormal cells. She was referred for GC and counselled on the fetal risk of hemihypertrophy, cardiac defects and development issues. Patient decided to wait for anomaly scans to screen for structural defects before proceeding with TOP. Fetal ultrasonographies at 17–19w showed a growth-restricted fetus with all parameters <1%. There was no obvious structural abnormality seen at that stage. A repeat ultrasonography done at 22w confirmed a severely growth-restricted fetus. The patient underwent medical TOP at 23w.

Both patients were referred for GC when the diagnosis was made. For case 1, she was seen by a genetic counsellor at 18w. At that time she was counselled on the karyotype results and was given an option of waiting for fetal anomaly scan to screen for any structural abnormality. She was also informed that the presence of normal structures does not exclude the possibility of the issues and the couple opted for TOP.

Case 2 was seen by the geneticist at 17w. During GC, she was counselled on the severity range of mosaic trisomy 22 from normal and asymptomatic to phenotype with structural differences. She was also given the option of TOP versus waiting for fetal anomaly scan to screen for structural differences before deciding on TOP. The couple was also counselled on the postnatal evaluation and monitoring for the baby should they decide on continuing with the pregnancy. She decided to proceed with ultrasound scan monitoring before deciding. She had serial growth scans which showed that the fetus was growth restricted. An ultrasound scan at 22w showed that the fetus was severely growth restricted. Given the poor prognosis, the couple decided to proceed with TOP.

Both cases were referred for Women's Emotional Health Service upon diagnosis as well as after TOP for emotional and grief support.

In this report, we described 2 cases where low-level mosaicism of trisomy 13 and trisomy 22 were detected by NIPT. Amniocenteses were performed for both cases where low level 7.7% trisomy 13 and 20.0% trisomy 22 mosaicisms were found, respectively. Chromosome mosaicism is defined as having more than one cell population coexisting within the same tissue, i.e. one cell population has a normal karyotype and the other has an abnormal karyotype. It is generally recognised that phenotype will be affected if the proportion of abnormal cells exceeds 20%. However, the proportion of abnormal cells can be grossly over- or under-estimated as it depends on sampling, cell growth during culture, and type of cells that were harvested for karyotyping. It is therefore challenging to predict the severity of the phenotype based on the percentages of the abnormal cell population. Detailed fetal ultrasonography will be of importance to confirm the presence or absence of morphological abnormalities in order to estimate the phenotype. In these 2 cases, ultrasonography showed no obvious structural abnormality except severe growth restriction

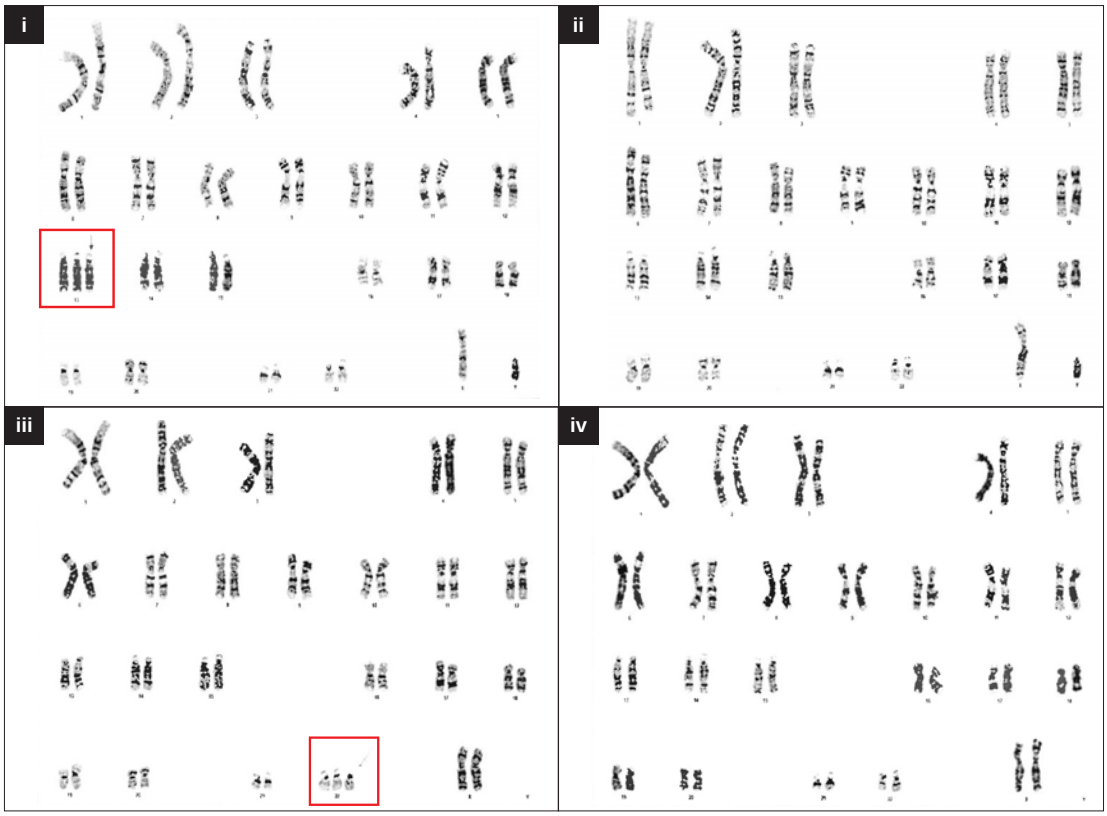

Fig. 1. The karyotypes of the amniotic fluid cultures performed for Cases 1 and 2. (A) In Case 1, cytogenetics analysis shows the presence of two cell lines with (i) trisomy 13, and (ii) normal diploid cell line. (B) In Case 2, two cell lines with (iii) trisomy 22, and (iv) normal diploid cell line were present. The karyotypes of Cases 1 and 2 are 47,XY,+13[3]/46,XY[36] and 47,XY,+22[3]/46,XX[12], respectively.

for Case 2 with trisomy 22 mosaicism as the pregnancy progresses. In trisomy 22 cases, fetuses with low-level chromosome mosaicism confined to the placenta (i.e. confined placental mosaicisms), have been reported to be compatible with life. However, mosaicism at amniocentesis and in liveborn children are rarely reported. One of these studies described low-level trisomy 22 mosaicism at amniocentesis in a pregnancy with a favourable outcome.[2] Trisomy 22 has been reported to be associated with normal live-born babies with low-level mosaicism of 5–30%.[3-5] Therefore, the affected couple decided to continue the pregnancy with close ultrasound monitoring. Unfortunately for Case 2, at 22w, severe growth restriction was observed in ultrasound and the pregnancy was terminated, given the poor prognosis.

As methodologies and algorithms improve, an increasing number of cases with low-level mosaicisms can be detected by NIPT. In pretest counselling, the patient should be informed that the detection rate of NIPT is higher than that of maternal serum screening. This includes the possibility of detecting low-level mosaicisms that will require invasive prenatal diagnosis. In addition, as NIPT analyses the cell-free fetal DNA that originates from the placenta rather than the fetus, false positives can occur in the presence of confined placental mosaicisms. To exclude false positive results, confirmatory invasive prenatal diagnostic tests using amniotic fluid and not chorionic villus sampling should be performed. As amniocentesis is performed after 15w, this will result in further delay of confirmatory diagnosis. The availability of GC is therefore of utmost importance before the healthcare provider offers NIPT. In addition, NIPT results must be interpreted in the context of the patient's clinical data and family history, so that follow-up testing or close monitoring via ultrasonography can be recommended.

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Clinical outcome of bacterial endogenous endophthalmitis in 15 patients

Dear Editor,

Endophthalmitis refers to the inflammation of the ocular cavities and their immediate adjacent structures without extension beyond the sclera, usually secondary to infection. Endogenous endophthalmitis (EE) results from haematogenous spread of microorganisms in patients with bacteraemia or fungaemia into the eye and represents 2–15% of endophthalmitis cases.[1-3] The last study conducted on the incidence of bacterial endogenous endophthalmitis (BEE) in Singapore was published in 2000 by Wong et al.[4]

The study reported *Klebsiella spp.* as the most common organism causing BEE especially among patients with hepatobiliary infections. Since then, it has become a routine practice to refer patients with *Klebsiella* bacteraemia to the ophthalmology service for endophthalmitis screening, independent of visual symptoms. However, there has been little new Singapore data evaluating the incidence and profiles of BEE, especially that of *Klebsiella* endogenous endophthalmitis in recent years.

We retrospectively reviewed the charts of all patients diagnosed with BEE in a tertiary centre in Singapore from 1 January 2014 to 31 December 2021. In this study, endophthalmitis was defined clinically by the presence of inflammation of the posterior segment with or without anterior chamber inflammation. We also collected the blood culture results positive for *Klebsiella pneumoniae* over the study period to review the incidence of EE among patients with *Klebsiella* bacteraemia.

We found 15 patients diagnosed with BEE at our tertiary centre during the study period. All patients had unilateral BEE. The patients' ages ranged from 36 to 74 years, with the median being 57 years. There was a slight male preponderance seen in our cohort (60.0%, n=9). Eleven (73.3%) patients were Chinese, 3 (20.0%) were Malay and 1 (6.7%) was Indian.

Seven patients (46.7%) initially presented to the emergency department for evaluation of their visual symptom(s), while the remaining 8 patients were diagnosed and treated for BEE as inpatients. All patients received intravenous antimicrobial therapy (Table 1). Twelve out of 15 patients (80.0%) had underlying diabetes mellitus.

Most of the patients (86.7%, n=13) presented with blurring of vision, with 3 of them reporting concomitant floaters (Table 1). One patient reported having floaters without blurring of vision. Presenting visual acuity (VA) ranged from 6/7.5 to perception of light with 7 patients (46.7%) having vision of hand movement only or worse. Eight patients (53.3%) had hypopyon. All patients had vitritis, with 5 of them (33.3%) having retina and/or choroidal abscess on presentation.

The number of intravitreal injections received by the group during their treatment period ranged from 1 to 6 injections, with both the mean and median being 3 injections. Each injection might constitute either a monotherapy or combination of either vancomycin, amikacin, and/or ceftazidime. Seven patients (46.7%) underwent vitrectomy (Table 1). Final VA ranged from 6/6 to no perception of light. One patient had an eye eviscerated, and 2 patients passed away from their systemic infection.

Liver abscess (n=4, 26.7%) and urinary tract infection (n=3, 20%) were the most frequent sources of systemic infection. The infective sources of bacteraemia in the rest of our patients are summarised in Table 1. One (6.7%) patient (Patient 10) had septicaemia without any localising foci of infection despite extensive investigations.

Nine (60.0%) patients had positive blood cultures with gram-positive bacteria being the predominant organism—4 patients with *Streptococcus agalactiae* (Group B) bacteraemia and 2 patients with methicillin-sensitive *Staphylococcus aureus* bacteraemia. Three patients (20.0%) had gram-negative bactaeremia and all 3 had *K. pneumoniae* detected in their blood cultures. Six patients (40.0%) had negative blood cultures. Of these, 4 patients (26.7%) had culture-proven sources of extra-ocular infection (Patients 3, 6, 9 and 13). The remaining 2 patients (13.3%; Patients 1 and 5) had their sources of infection established clinically and radiologically.

During the same study period, there were 2,014 patients with blood cultures positive for *K. pneumoniae* being treated in our centre. Three of these patients were diagnosed with endogenous endophthalmitis (Patients 12, 14 and 15). Patient 12 had his blood culture done in another centre and was subsequently transferred to our hospital for further treatment of his liver abscess.

Table 1. Clinical details of patients diagnosed with bacterial endogenous endophthalmitis in our cohort

Patient no.	Year	Age/ Sex	Ethnicity	Systemic conditions	Laterality	Source(s) of infection	Blood culture	Cultures from vitreous fluid	Other cultures	Visual symptoms	Signs	No. and types of intravitreal injections	Vitrectomy	Initial VA	Latest VA	Systemic antibiotics	On antibiotics prior to diagnosis of EE[a]	Mortality
1	2014	57M	Malay	DM, IHD, previous hepatic and retropharyngeal abscess, ESRF	R	Pyelonephritis	No growth	No growth	NA	Blurring of vision	Hypopyon, vitritis	1-4 : V/A	Yes (x2)	PL	6/30	Ciprofloxacin	No	No
2	2014	53M	Chinese	DM	R	UTI	MSSA	MSSA	Urine: MSSA	Blurring of vision, eye pain	Hypopyon, vitritis	1 : V/A 2 : V/C	Yes (x1)	PL	PL	Cloxacillin	No	No
3	2015	60M	Chinese	DM	R	UTI	No growth	*Klebsiella pneumoniae*	Urine: *Klebsiella pneumoniae*	Blurring of vision, eye pain	Hypopyon, vitritis	1-5 : V/C 6 : G	Yes (x1)	HM	NPL	Ciprofloxacin	No	No
4	2015	64M	Chinese	DM, HTN, IHD	R	Infective endocarditis	GBS	No growth	NA	Blurring of vision, eye pain, floaters	Vitritis, choroidal abscess	1 : V/A 2 : V	nil	CF	6/7.5	Ceftriaxone	No	No
5	2016	49M	Chinese	DM, HLD	L	Liver abscess	No growth	No growth	NA	Blurring of vision, eye pain	Hypopyon, vitritis	1: V/C 2 :C 3 : A	nil	PL	NPL	Ciprofloxacin, ceftriaxone, meropenem	Yes	No
6	2016	74M	Chinese	HTN, IHD, AF, COPD	R	Septic arthritis	No growth	Mixed bacterial growth[b]	Joint fluid: *Pseudomonas aeruginosa*	Blurring of vision, eye pain	Hypopyon, hyphema, vitritis	1 : V/C 2 : V/A	nil	PL	-	Piperacillin/ tazobactam, voriconazole, fluconazole, vancomycin, levofloxacin	Yes	Yes
7	2017	58F	Chinese	HTN, ESRF, NPC, hypothyroidism	R	Infective endocarditis	GBS	No growth	NA	Blurring of vision, eye pain	Hypopyon, vitritis	1 : A/C 2-4 : V	nil	CF	-	Ampicillin, vancomycin, ceftriaxone, meropenem, gentamicin, penicillin G	No	Yes
8	2017	57F	Chinese	DM	R	Septic arthritis	MSSA	No growth	Joint fluid: MSSA	Blurring of vision, floaters	Vitritis	1 : V	Yes (x1)	N18	6/7.5	Cefazolin	Yes	No
9	2017	36F	Malay	DM	R	Large axillary abscess	No growth	No growth	Abscess: MSSA	Floaters, eye redness	Vitritis, choroidoretinal abscess	1 : V/C	nil	6/7.5	6/6	Cloxacillin	Yes	No

Table 1. Clinical details of patients diagnosed with bacterial endogenous endophthalmitis in our cohort (Cont'd)

Patient no.	Year	Age/ Sex	Ethnicity	Systemic conditions	Laterality	Source(s) of infection	Blood culture	Cultures from vitreous fluid	Other cultures	Visual symptoms	Signs	No. and types of intravitreal injections	Vitrectomy	Initial VA	Latest VA	Systemic antibiotics	On antibiotics prior to diagnosis of EE[a]	Mortality
10	2018	68M	Chinese	Nil	R	Unknown[b]	GBS	GBS	Urine: no growth	Blurring of vision, eye pain	Hypopyon, vitritis	1-5 : V/C	Yes (x2)	HM	- (Eviscerated)	Ceftriaxone	No	No
11	2019	56F	Chinese	DM, CKD, HTN	L	Gastrointestinal tract infection	GBS	No growth	Peripheral line: *Candida albicans*	Blurring of vision	Vitritis, choroidoretinal abscess	1 : V	Yes (x2)	CF	CF	Meropenem, clindamycin, vancomycin, piperacillin/ tazobactam, levofloxacin, anidulafungin, fluconazole	Yes	No
12	2020	42M	Indian	DM	L	Liver abscess	*Klebsiella pneumoniae*	No growth	Abscess: *Klebsiella pneumonia*	Blurring of vision	Vitritis, retinal abscess	1 : V/A 2 : A 3-4 : V/C	Yes (x1)	CF	PL	Ceftriaxone, ciprofloxacin	Yes	No
13	2021	57F	Chinese	DM	R	Disseminated abscesses (lung and kidney)	No growth	No growth	Perinephric abscess: *Escherichia coli*	Blurring of vision	Hyopyon, vitritis, choroidal abscess	1-3 : V/C 4-5 : C	nil	HM	CF	Ceftriaxone	No	No
14	2021	50M	Chinese	DM, HLD	R	Liver abscess	*Klebsiella pneumoniae*	No growth	Abscess: *Klebsiella pneumonia*	Blurring of vision, floaters	Vitritis	1-4 : C	nil	N6[b]	6/6	Ceftriaxone, ciprofloxacin	Yes	No
15	2021	66F	Malay	DM	L	Liver abscess	*Klebsiella pneumoniae*	No growth	Abscess: *Klebsiella pneumonia*	Nil	Retinal infiltrates, mild vitreous haze	1 : V/C	nil	N12[c]	6/9	Meropenem, ceftriaxone, piperacillin/ tazobactam, ciprofloxacin	Yes	No

AF: atrial fibrillation; A: amikacin; C: ceftazidime; CF: counting finger; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; EE: endogenous endophthalmitis; ESRF: end-stage renal failure; F: female; GBS: *Streptococcus agalactiae* (Group B); HLD: hyperlipidaemia; HM: hand movement; HTN: hypertension; IHD: ischaemic heart disease; L: left; M: male; MSSA: methicillin-sensitive *Staphylococcus aureus*; NA: not available; NPC: nasopharyngeal carcinoma; NPL: no perception of light; PL: perception of light; R: right; UTI: urinary tract infection; V: vancomycin; VA: visual acuity

[a] Endogenous endophthalmitis was the first presentation in patients who were not on systemic antibiotics prior to diagnosis

[b] *Pseudomonas stutzeri*, Coagulase-negative *Staphylococcus, Moraxella spp., Micrococcus spp.*

[c] Bedside assessment with handheld near chart

This brought the incidence of *Klebsiella* BEE in our centre to 0.1% (2 out of 2,014) over 8 years.

Diabetes mellitus was the most common underlying systemic risk factor among our patients having BEE, with liver abscess and urinary tract infection being the most frequent sources of systemic infection in our cohort, similar to the trend observed in earlier studies on BEE.[2,4,5] The last Singapore study on BEE by Wong et al. found gram-negative bacteria, particularly *Klebsiella spp.*, to be the predominant causative organism in their cohort.[4] In comparison, despite having an all-Asian cohort, our study found that gram-positive bacteria accounted for 60.0% of positive blood cultures. Interestingly, all 3 patients with gram-negative bacteraemia in our study had *K. pneumoniae* in their blood cultures.

An overwhelming proportion of our patients were symptomatic at the point of presentation, with 14 out of 15 patients reported to have blurring of vision and/or floaters. It was not possible to obtain history in one patient as she had altered mental status from underlying septic shock upon initial review. Of note, it is a routine practice in our centre to refer all patients with *Klebsiella* bacteraemia to the ophthalmology service for endophthalmitis screening. Considering the low incidence of *Klebsiella* EE among patients with *Klebsiella* bacteraemia, it may be worthwhile to reconsider the current workflow of routine *Klebsiella* EE screening to one that is based on visual symptoms. Patients who are unable to give reliable history should still be screened for endophthalmitis by an ophthalmologist.

In summary, BEE was exceedingly rare, averaging around 2 cases per year in our centre. Hepatobiliary and urinary tract infections were the most frequent infective sources of our patients with BEE, with diabetes being the most common underlying comorbidity. As most patients with BEE are symptomatic upon presentation, routine endophthalmitis screening is of low value and should be reserved for patients with symptoms and those who cannot provide reliable history.

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LETTER TO THE EDITOR

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Surgical margins assessment reduces re-excision rates in breast-conserving surgery

Dear Editor,

Breast-conserving surgery (BCS) followed by radiation therapy for breast cancer offers improved cosmetic results and comparable long-term survival rates as mastectomy.[1] However, BCS is associated with a higher risk for local recurrence, and published literature has reported re-excision rates as high as 20–70% due to positive resection margins of the tumour. The increased re-excision rates are associated with unfavourable consequences, including increased utilisation of healthcare resources and decreased patient satisfaction.[2] An important factor in reducing local recurrence rates in BCS is to achieve a microscopically clear margin absent of tumour cells.[3,4] Intraoperative assessment with frozen section (FS) analysis has been described as a popular method to reduce re-excision rates.[4] FS also offers significant cost savings to patients while improving efficiency in the utilisation of hospital resources through reduced re-operations.[5] On the other hand, opponents of routine use of intraoperative FS cite these reasons as barriers to adoption of the technique: longer operating times; little role for FS evaluation of resection margins that are grossly free of the tumour because of the fatty nature of the margins; diversion of pathologists' resources; and higher patient fees.[6-8] This study aims to audit the effect of intraoperative FS in BCS in a Singapore regional hospital.

After approval from the ethics board, a retrospective study was conducted on consecutive breast cancer patients from Khoo Teck Puat Hospital (KTPH) in Singapore. We identified 186 patients who underwent BCS from January 2012 to February 2020. Eligible patients had either invasive or in situ carcinoma and were deemed to be candidates for BCS after clinical and radiographic evaluation. Patients who had metastases or a history of recurrent breast cancer were excluded. From 2017 onwards, our unit began to perform intraoperative FS routinely, with margins taken from the tumour cavity. Intraoperative ultrasound was also used as an adjunct to aid wide local excision in selected cases where the tumour was small and not well defined by clinical palpation.

The following clinical factors were collected: patient's age, multifocality of the tumour, primary tumour size, staging of the tumour, histological type, and grade. Additionally, information on the type of surgery performed, duration of the surgery (defined from initial skin incision to skin closure including axillary procedures if any), and data on neoadjuvant therapy were assessed. Our study compared the outcomes of BCS with and without intraoperative FS. Statistical analysis was performed using SPSS Statistics software, version 26.0 (IBM Corp, Armonk, US). All continuous data were expressed as median and compared using two-sample t-tests. All categorical variables were described as percentages and compared using chi-square analysis. Univariate and multivariate logistic regression models were used to analyse the factors associated with the final margin involvement rate. For all analyses, a P value of <0.05 was accepted to be statistically significant.

All 186 patients underwent BCS, with about 20% of them performed utilising hookwire localisation or radioguided occult lesion localisation (ROLL), while the remaining were palpable. Intraoperative FS was performed in 145 (78%). The clinicopathologic features were comparable in the 2 groups (Table 1). The use of intraoperative FS in BCS was associated with a longer median operative duration of 115 (91.5–155) minutes compared to 110 (80–125.5) minutes, P=0.016. Positive surgical margins were identified in 31 patients (21.4%) during intraoperative FS, and intraoperative re-excision was performed until negative margins were achieved. The final margin involvement rate was lower in the FS group compared to the non-FS group (13.1% versus 26.8%, P=0.035). The re-operation rates were lower in the FS group (9% vs 19.5%, P=0.060), with no increase in mastectomy rates (3.4% vs 7.3%, P=0.965). Patients with positive final margins due to involvement of posterior margins microscopically had excision of the pectoralis muscle fascia. Their tumour bed was also clipped and underwent postoperative radiotherapy with additional boosts to tumour bed; hence repeat surgery for additional margins was not performed. After adjusting for risk factors associated with re-operation, such as larger tumour size (>2cm), multifocality, ductal carcinoma in situ type (DCIS), locally advanced tumours with nodal involvement, or post-neoadjuvant chemotherapy, the use of FS was still found to be an independent predictor for reduced final margin involvement rates, odds ratio 0.37, (confidence interval 0.16–0.89), P=0.026.

Table 1. Clinicopathological features of patients and outcomes of patients undergoing breast-conserving therapy, with or without frozen section

Factors	**Without frozen section n=41**	**With frozen section n=145**	***P* value**
Age (IQR), years[a]	57 (53–64)	57 (49–63.5)	0.207
Multifocality (%)	4 (9.8)	7 (4.8)	0.238
Tumour maximal diameter (IQR), cm[a]	2.0 (1.5–3.0)	2.0 (1.3–2.5)	0.171
T stage (p-staging) (%)			0.060
T0 (pathological complete response)	0	2 (1.4)	
Tis	7 (17.1)	16 (11.0)	
T1	14 (34.1)	68 (46.9)	
T2	15 (36.6)	56 (38.6)	
T3	1 (2.4)	1 (0.7)	
T4	4 (9.8)	2 (1.4)	
N stage (p-staging) (%)			0.508
N0	35 (85.4)	111 (76.6)	
N1	3 (7.3)	27 (18.6)	
N2	2 (4.9)	5 (3.4)	
N3	1 (2.4)	2 (1.4)	
Type of surgery (%)			0.717
Wide local excision	33 (80.5)	108 (76.8)	
Hookwire localisation	4 (9.8)	20 (13.8)	
ROLL and excision	4 (9.8)	17 (11.7)	
Histology (%)			0.179
Invasive ductal carcinoma	33 (80.4)	123 (84.8)	
Invasive lobular carcinoma	1 (2.4)	6 (4.1)	
Ductal carcinoma in situ	7 (17.1)	16 (11.0)	
Grade (%)			0.994
Low	5 (12.2)	17 (11.7)	
Intermediate	14 (34.1)	49 (33.8)	
High	22 (53.7)	79 (54.5)	
Operative duration (IQR), min[a]	110.0 (80.0–125.5)	115.0 (91.5–155.0)	0.016*
Neoadjuvant therapy	1 (2.4)	11 (7.6)	0.236
Outcomes	**Without frozen section n=46**	**With frozen section n=147**	***P* value**
Positive intraoperative frozen section with re-excision till negative margins (%)	NA	31 (21.4)	NA
Final margin involved (%)	11 (26.8)	19 (13.1)	0.035*
Indeterminate margin rate	NA	10.3%	NA
Re-operation rate (%)	8 (19.5)	13 (9.0)	0.060
Re-excision (%)	5 (12.2)	8 (5.5)	0.965
Conversion to mastectomy (%)	3 (7.3)	5 (3.4)	0.965
Multivariate logistic regression analysis for factors associated with positive final margins			
Factors	**Odds ratio**	**Confidence interval**	***P* value**
Frozen section	0.37	0.16–0.89	0.026*
Multifocality	1.16	0.23–5.95	0.855
Neoadjuvant chemotherapy	1.21	0.24–6.04	0.819
Tumour >2cm	1.27	0.56–2.88	0.576
Nodal involvement	2.27	0.91–5.64	0.079
Ductal carcinoma in situ	1.45	0.41–5.11	0.563

IQR: interquartile range; NA: not applicable; ROLL: radioguided occult lesion localisation
*$P<0.05$ is statistically significant
[a]Age, tumour maximal diameter and operative duration are measured in median

Our study demonstrated a significant reduction in final margin involvement rates by more than half (13.1% vs 26.8%, *P*=0.035) in the FS group. This reduction extended to a subgroup of patients at higher risk of positive surgical margins and re-operation, including patients with large, multifocal or DCIS-type tumours, nodal involvement and neoadjuvant chemotherapy undergoing BCS.[9] A review of the cases with positive final margin involvement revealed that 26 out of 30 of the cases involved invasive carcinoma, with the remaining 4 being DCIS. Further stratification by tumour biology demonstrated these groups of breast cancer within the invasive carcinoma group: 11 luminal A, 5 luminal B, 2 human epidermal growth factor receptor 2 (HER2)-enriched and 5 triple-negative. The remaining 3 invasive carcinoma cases were not candidates for anti-HER2 therapy; hence fluorescence in situ hybridisation (FISH) was not performed to determine HER2 status. Within the DCIS group, 3 were estrogen receptor-positive, progesterone receptor-positive (ER+PR+), and the remaining 1 was ER-PR-. Furthermore, our FS false-negative rates of 13.1% compared favourably to international studies that reported up to 23% of false-negative rates,[4] thus lowering overall re-excision rates. Our practice is to use the cutting mode on diathermy, or the use of a new blade instead of the coagulation mode on diathermy, when taking margins for intraoperative FS. This is to prevent the creation of charring artefacts that could affect the analysis of margins on frozen sections, which may alter false-negative or false-positive rates.

On the other hand, the drawback to intraoperative FS is its 10.3% "indeterminate" margin rate, which required additional margins of breast tissue to be taken intraoperatively. Indeterminate margins are defined as margins taken during surgery where carcinoma could not be excluded, and which were subsequently found on paraffin assessment to be negative. Among the indeterminate patients, invasive cancer accounted for 12 out of 15 of all indeterminate cases, with the remaining 3 being DCIS. Other drawbacks to intraoperative FS include longer operative times and increased workload for pathology staff.[6] Although the operative duration in the FS group in our study was significantly longer, a median additional duration of 5 minutes (115 minutes in FS vs 110 minutes in the non-FS group) is not clinically significant in real-life practice. The processing time for FS of margins is approximately 20 minutes. However, by performing the wide local resection of the tumour first and sending the margins for FS analysis before performing any sentinel lymph node biopsy, this sequence of surgery could negate some of the additional time required for FS processing of margins. The availability of a dedicated pathology team to process the specimens in a timely fashion may deliver improved outcomes for patients undergoing BCS with intraoperative FS. Logistical challenges can be further addressed with good pre-planning and deconflict of schedule between surgeons and pathologists prior to surgery for cases that require FS of margins.

Limitations of our study include its inherent retrospective nature, lack of standardisation of the volume of margins taken, lack of data on total specimen volume excised and follow-up of any cosmetic concerns in the postoperative period. Through this audit, it improved understanding and collaboration between the Pathology Department and the Breast Service in our hospital to obtain the common goal of achieving lower re-excision rates for better patient outcomes.

With the increasing adoption of oncoplastic surgery by breast surgeons and the ability to perform wider resection margins without compromising on final cosmetic outcomes,[10] the case for intraoperative FS may be less compelling in selected cases in future. Similarly, breast surgeons from our unit are undergoing formal fellowship training in oncoplastic breast surgery, and this may change the practice of intraoperative FS in our unit in the future.

In conclusion, the use of intraoperative FS for BCS has been shown to decrease re-excision rates significantly by more than half in our unit's audit, and we believe the results of this study could be applicable to other centres with available logistical support.

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Association between self-care and chronic kidney disease in patients with type 2 diabetes mellitus

Dear Editor,

Chronic kidney disease (CKD) is one of the key complications occurring in 25–40% of patients with type 2 diabetes mellitus (T2DM).[1] Our earlier study also showed that CKD was present in 53% of patients with T2DM recruited from a secondary care diabetes centre and primary care polyclinic in Singapore.[2] T2DM management comprises not only medical care, but also "self-care", which is crucial in preventing end-organ complications.[3]

The Summary of Diabetes Self-Care Activities (SDSCA) questionnaire[4] is a reliable and valid measure of diabetes mellitus (DM) self-care adherence in observational and interventional studies. These studies have addressed issues related to psychological well-being and quality of life, but not diabetic nephropathy.[5] Current scant literature[6] suggests that self-care potentially reduces the risks of developing diabetic nephropathy. We examine the association between self-care and CKD in T2DM patients, and aim to establish if glycaemic control mediates the possible association between self-care and CKD.

This was a cross-sectional study of 631 patients with T2DM (age 57.0±11.5 years, 54.7% male, 45.2% Chinese, 33.3% Malay and 20.0% Indian) recruited from November 2017 to December 2020 from the Diabetic Kidney Disease – Onset and Progression Risk Factors (DORIS) cohort in Singapore.[7] Patients self-administered SDSCA to quantify the following self-care activities performed over 7 days: general diet, specific diet, exercise, self-monitoring of blood glucose (SMBG), and foot care. CKD, with a prevalence of 62.3% in the cohort, was defined as estimated glomerular filtration rate (eGFR) <60mL/min/1.73m^2 and/or urinary albumin-to-creatinine ratio (uACR) ≥30mg/g from blood and urine samples collected according to Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease guidelines.[8] Group differences between non-CKD and CKD were examined by Student's t-test, Wilcoxon rank sum test for continuous variables, and chi-square test for categorical variables. Logistic regression models examined the association between self-care measures and CKD in T2DM patients. Mediation analysis based on Baron and Kenny's framework[9] was performed to examine the role of haemoglobin A1c (HbA1c) as a possible mediator for the association between SDSCA score for SMBG and the presence of CKD. Results with $P<0.05$ were considered statistically significant.

The distribution of ethnicity of patients in this study was: Chinese 45.2%, Malay 33.3% and Indian 20.0%. Patients with CKD were older in age and belonged to a lower educational background ($P<0.001$). They had a longer DM duration, alongside a more deleterious metabolic profile: higher body mass index, higher systolic blood pressure, higher Hb1Ac, higher triglycerides, lower eGFR and higher uACR ($P<0.001$). They were on more medications, whether oral and insulin, insulin only, or a renin-angiotensin system antagonist ($P<0.001$).

Mean scores (±standard deviation) (higher scores more favourable) for self-care were: general diet 3.9±2.1; specific diet 4.8±1.5; exercise 2.8±2.0; SMBG 2.0±2.1; and foot care 3.7±2.8. SMBG had the lowest score. This trend was similar for both non-CKD and CKD patients, with no significant difference in scores for SMBG between both groups of patients. Higher SMBG scores, suggestive of better self-care, were inversely associated with reduced odds of CKD (odds ratio [OR] after adjusting for demographics 0.91, 95% confidence interval [CI] 0.84–0.99; $P=0.024$) and also after adjusting for demographics, metabolic profile and medications (OR 0.90, 95% CI 0.82–0.99; $P=0.035$). The other self-care measures were not significantly associated with CKD (Table 1).

SDSCA scores for SMBG were positively correlated with age and eGFR, and negatively correlated with triglycerides ($P<0.05$). In terms of DM medications, SDSCA scores for SMBG were higher in patients on insulin only (3.4±1.8) compared to those on oral medication(s) only (1.8±2.1), and combined oral medication(s) and insulin (2.3±2.1) ($P=0.002$). There was no association between SDSCA scores for SMBG and ethnicity ($P=0.064$), education level ($P=0.179$) and housing type ($P=0.821$).

Table 1. Association between Summary of Diabetes Self-Care Activities (SDSCA) scores and chronic kidney disease

	Odds ratio (95% confidence interval), *P* value		
SDSCA score	Unadjusted	Model 1	Model 2
General diet	0.98 (0.91–1.06), 0.649	0.97 (0.89–1.06), 0.515	1.05 (0.95–1.16), 0.382
Specific diet	1.09 (0.97–1.21), 0.144	0.98 (0.87–1.12), 0.808	0.98 (0.84–1.14), 0.798
Exercise	0.94 (0.87–1.02), 0.119	0.95 (0.87–1.03), 0.223	0.99 (0.89–1.10), 0.833
Blood glucose testing	0.94 (0.87–1.01), 0.089	0.91 (0.84–0.99), 0.024	0.90 (0.82–0.99), 0.035
Foot care	1.07 (1.01–1.13), 0.029	1.00 (0.94–1.07), 0.919	0.95 (0.87–1.03), 0.244

Model 1 adjusted for age, sex and ethnicity
Model 2 adjusted for age, sex, ethnicity, housing type, education, diabetes duration, systolic blood pressure, haemoglobin A1c, type of diabetes medications and use of renin-angiotensin antagonist

In the mediation analysis, a higher SDSCA score for SMBG was negatively associated with HbA1c when adjusted for age, sex and ethnicity, with a coefficient of -0.13 (P=0.006). HbA1c was positively associated with CKD, with a coefficient of 0.26 (P<0.001). Higher SDSCA score for SMBG was negatively associated with CKD, with a coefficient of -0.12 (P=0.012). The association between the SDSCA score for SMBG and CKD was attenuated upon adjusting for HbA1c with a coefficient of -0.11 (P=0.035). Putting the various pathways together, HbA1c mediated 24.9% of the overall association between SMBG and CKD (P=0.017). Therefore, more frequent SMBG could result in a reduced HbA1c, of which higher HbA1c scores are inimical to CKD.

SMBG was the only aspect of self-care independently associated with lower odds of CKD. We postulate that SMBG is a more objective measure of self-care quantified by the SDSCA scale. Patients implicitly receive actionable feedback on the effects of their lifestyle measures with SMBG, which can motivate them to keep up or improve their self-care.

Nevertheless, while SMBG was independently associated with lower odds of CKD, the SDSCA score for SMBG was the lowest among patients, similar to other studies performed.[10] The association between SMBG and CKD could be explained by the mediation analysis, where HbA1c acted as a mediator. Moreover, SDSCA scores for SMBG were positively correlated with eGFR (P<0.05). Some possible explanations for the poor performance of SMBG include the cost of test strips, pain due to finger pricking, and the low priority of SMBG compared to other self-care practices.[10]

To our knowledge, this is the first study in Singapore that evaluates the relationship between self-care and CKD in T2DM patients. However, we note that the ethnic distribution in our sample population is not entirely reflective of the Singapore population. The small CKD group size is a limitation. Other residual confounding factors may be significant, such as the nature of the person doing SMBG, in addition to SMBG itself.

In conclusion, while SMBG was independently associated with lower odds of CKD, it was the most under-performed among patients. Heightened awareness and efforts in SMBG may play a role in reducing CKD in T2DM. Moreover, other self-care aspects such as diet, exercise and foot care were not correlated with CKD progression. This suggests that lifestyle modification alone may not suffice; a holistic approach including testing, medication and compliance is essential in improving chronic disease management outcomes.

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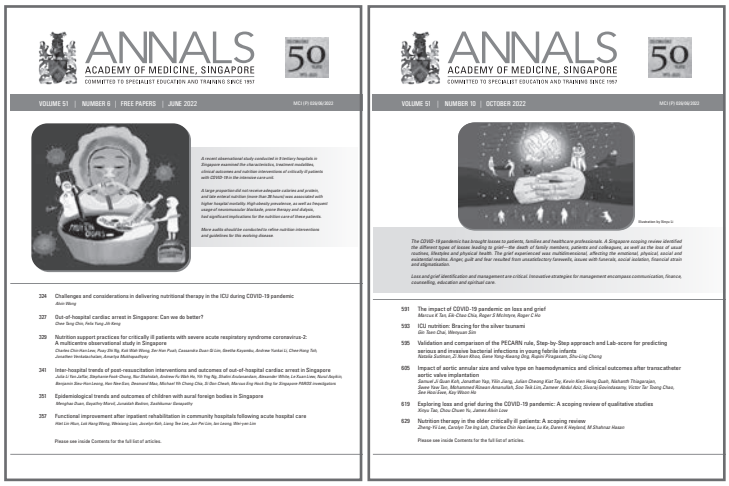

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