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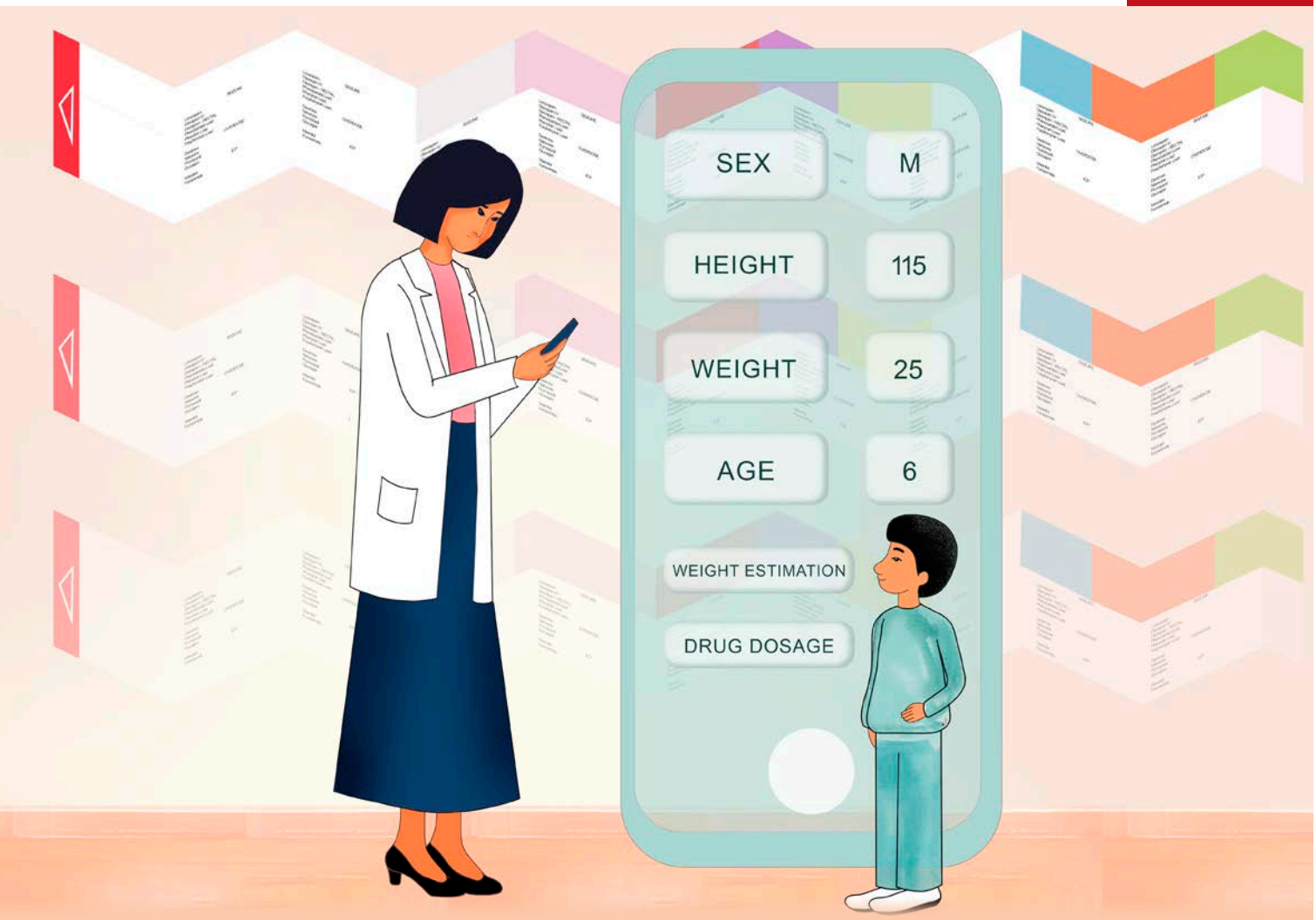

An augmented reality mobile application for weight estimation in paediatric patients: A prospective single-blinded cross-sectional study

A study team developed an augmented reality smartphone application for length-based weight estimation called the Paediatric Augmented Reality Scale, and evaluated its performance. (See full article on p.660)

Illustration by Nata Blackthorn

Also in this issue

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EDITORIAL

Vascular surgeons and best medical therapy: Missed opportunities?

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Multiple guidelines recommend the use of best medical therapy (BMT) as secondary prevention for patients with peripheral arterial disease (PAD) but prescription and adherence are generally sub-optimal.[1] The issue is not specific to vascular surgeons. Patients referred with suspected peripheral arterial disease are only started on antiplatelet agents and statins by their primary care physician in about half of cases.[2] Following coronary artery bypass grafting, 1 in 5 patients are discharged without a statin prescription.[3] Using a series of structured interviews through an implementation science lens, Xu et al. have identified a number of potential obstacles to improve BMT prescription patterns.[4]

Two particular issues stand out. The healthcare workers interviewed (10 of 11 were doctors) were all aware of the significance of PAD in terms of potential morbidity and mortality. They were also aware of the importance of secondary prevention. There was less clarity regarding the existence of guidelines or which guidelines to follow. One vascular surgeon commented that "there are so many guidelines". Another interviewee noted that "there is the European Society of Vascular Surgery, the Society for Vascular Surgery, there is the American Heart Association, and I'm sure there are more." A quick search does reveal a plethora of other guidelines. In such a crowded space, it becomes difficult for individual practitioners to stay current with all the guidance, let alone make a determination as to which set is most applicable to their patient cohort. Regional variations in reimbursement and drug availability may also influence guideline adherence.

The other issue highlighted is the challenge created by the shared care required by patients with PAD. Many of them are also receiving care from endocrinologist, cardiologist and nephrologist. With multiple overlapping specialties, some feel it is best "not to rock the boat in other ways" by initiating or amending BMT, especially if PAD was not the primary reason for admission for these patients. With only 11 interviewees, meaningful analysis of responses by speciality is not possible but one wonders whether vascular surgeons may be more likely to avoid "rocking the boat" than colleagues with training in general internal medicine?

Vascular surgical training focuses on the acquisition and optimal application of advanced technical skills. The prescription of best medical therapy at best tends to be regarded as a footnote issue. A recent national training needs assessment in vascular surgery considered only training in technical procedures with no consideration of training options around BMT provision.[5] While vascular surgery training remains focussed on procedural skills, the potential role of BMT is evolving, with emerging evidence suggesting it may become the cornerstone of management of at least some vascular surgery presentations of systemic atherosclerosis.[6]

The interviewees presented a range of potential measures that might improve prescribing patterns. Internal teaching, smartphone apps and educational posters were all suggested but are unlikely to address the core underlying issues—too many guidelines and too little vascular surgical confidence. Development of a multidisciplinary global task force to harmonise BMT guidelines between the major societies would be helpful. More importantly, vascular surgeons should take the lead in managing patients whose initial atherosclerotic presentation is in vascular beds that are outside the heart or brain. It is incumbent on vascular surgery as a speciality to be as comfortable with BMT prescription as our medical colleagues. Training in BMT requires increased emphasis in vascular surgery training programmes and collaboration with medical colleagues if we are to improve our patients' outcomes.

Declaration

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Keywords: barriers, evidence-based medical therapy, facilitators, guideline implementation, peripheral artery disease, qualitative study

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EDITORIAL

Optimising polycystic ovary syndrome diagnosis accuracy

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, experienced by 1 in 10 women of childbearing age. Its aetiology is multifactorial and complex and its clinical presentation is heterogeneous with menstrual irregularities, high levels of androgens and the presence of multiple follicles or cysts in the ovaries giving its name to the condition. In addition, PCOS has been linked to reproductive, cardiometabolic, dermatologic and psychological complications making it a significant public health concern.[1] Diagnosing PCOS has always been a challenge with some women remaining undiagnosed hence potentially experiencing delays in their care.[2] Therefore, optimising PCOS diagnosis accuracy is of crucial importance.

In this issue of the *Annals*, Yong et al. have elegantly attempted to achieve that goal by proposing a simplified set of 3 criteria to define PCOS for an East Asian phenotype.[3] In that study, the authors have focused on PCOS diagnosis and provided a detailed summary of the diagnosis evolution, from Stein and Leventhal's first description in 1935 to now. Over time, several groups and societies have attempted to refine PCOS diagnosis according to women's life stage, physical characteristics or ethnic differences. Overall, they all agree that PCOS diagnosis is established if 2 out of the following 3 criteria are met: (1) menstrual irregularities, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic ovaries, provided that other mimicking disorders have been excluded. However, the complexity of the diagnosis lies in the lack of standardisation in the definition of these 3 main features.

Yong et al. explain the individual criteria and their limitations with an explanation of their proposed simplified option. They commence with menstrual irregularities as it is the main consultation reason for PCOS. For this first criterion, they decided to limit menstrual irregularities to oligo-menorrhea or amenorrhea, defined as cycles longer than 35 days. While this is one of the manifestations of oligo or anovulation, it has its limitations because this definition only covers 85–90% of menstrual disorders experienced by PCOS women.[4] In this context, 10–15 % of adult PCOS patients with normal or shorter menstrual cycles will be missed. Conversely, some adolescents within the first 3 years after menarche, with longer menstrual cycles due to an immature hypothalamus pituitary ovarian axis, might be unnecessarily screened and/or wrongly diagnosed. This is the reason why the 2018 international evidence-based guidelines for assessment and management of PCOS have included in their definition of oligo or anovulation an exhaustive list of menstrual irregularity types that should be considered and assessed for PCOS.[5] So, while narrowing the first criterion to women with longer cycles could help identify a majority of PCOS patients, a more detailed list of eligible menstrual cycle types should be considered in order to screen all possible PCOS patients.

With regard to the other two criteria, Yong et al. adopted a compelling model: they performed a prospective cross-sectional study with 200 healthy East Asian adult women to identify predictive factors of menstrual cycle variability.[6] The 5 factors strongly associated with menstrual cycle variability were: ovarian volume, AFC (antral follicle count), AMH (anti-Mullerian hormone), serum testosterone and LH (luteinising hormone). Interestingly, these parameters coincide with the factors playing a role in PCOS physiopathology. Among these 5 components, 2 parameters are required: one that would be reflective of androgen excess and the second as a marker of polycystic ovaries. With that in mind, Yong et al. analysed these factors further to select the 2 that would effectively complement oligomenorrhea for PCOS diagnosis.

To define androgen excess, most PCOS guidelines use clinical and or biochemical measures. Clinically, the modified Ferriman and Gallwey (mFG) score is the tool used to quantify the degree of hirsutism. However, its usefulness is debatable because it is operator-dependant and requires an ethnicity-based interpretation. This is particularly valid in East Asian populations. Chinese patients, for example, tend to have a naturally undetectable mFG score, making mFG score a futile non-discriminant parameter for them. For this reason, Yong et al. chose to exclude the use of the mFG

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score for their patients. On the other hand, serum testosterone is fairly stable across the menstrual cycle and was flagged as a predictive factor of cycles variability. Hence, the authors decided to solely rely on serum testosterone as a marker of hyperandrogenism. While this is practical and legitimate, the type of marker they have selected is arguable. In fact, serum-free testosterone or free androgen index measures would be more coherent as they are reflective of the bio-active form of serum testosterone. Indeed, around 70% of circulating testosterone is bound to serum sex hormone binding globulin (SHBG) and when testosterone is bound, it is inactive. The serum total testosterone is a combination of free testosterone and testosterone bound to SHBG. Obesity and/or insulin resistance, often associated to PCOS, can cause the serum SHBG level to drop and therefore increase the level of bio-available testosterone, which will not be reflected by the serum total testosterone alone.[7] The total serum testosterone might then underestimate the biochemical hyperandrogenism.

Finally, the last criterion is about polycystic ovaries or polycystic ovary morphology (PCOM), which is a sign of increased number of follicles in the ovary. The assessment of the follicles number can be done directly, via a transvaginal pelvic ultrasound (AFC) or indirectly via a biochemical marker (serum AMH). AMH is secreted by the granulosa cells of the preantral and small antral ovarian follicles and is strongly correlated with AFC; AMH and AFC can therefore be used interchangeably.[8] Serum AMH is significantly higher in women with PCOS and as mentioned earlier, AFC and AMH were identified by Yong et al. as factors significantly correlated with menstrual variability. Because pelvis ultrasound often poses challenges, Yong et al. recommend to replace AFC with AMH as a marker of polycystic ovaries. The threshold suggested for AMH is 37pmol/L, based on a prospective cross-sectional study performed in Singapore.[6] This new criterion will be useful and cost-effective for patient assessed for PCOS even tough further studies will be required to ensure that population and assay specific cut-offs are used. Furthermore, it is meaningful to mention that a few months ago, the International Evidence-based guidelines for assessment and management of PCOS have released their 2023 recommendations where AMH has also been added as an acceptable marker of PCOM as an alternative to AFC[9].

To summarise, Yong et al. present the use of the following 3 criteria for the diagnosis of PCOS in an East Asian population: (1) menstrual cycles longer than 35 days, (2) raised serum total testosterone, and (3) AMH ≥37pmol/L. These criteria are mainly applicable for adult patients. Studies with a larger sample size would be required to confirm the AMH cut-off, and serum free testosterone should be considered instead of total testosterone. However, despite these 3 limitations, the authors provide clinicians with a simplified and cost-effective set of PCOS diagnostic criteria for identifying a large proportion of East Asian adult PCOS women.

Declaration

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Keywords: *AMH, endocrinology, obstetrics and gynaecology, polycystic ovary syndrome, simplified diagnostic criteria*

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EDITORIAL

Fluid management in renal transplantation: Is it time to move towards goal-directed directed therapy?

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Achieving optimal fluid balance for a patient undergoing major surgery, especially transplant surgery, has always been the lofty goal of peri-operative care,[1] which often proves to be an elusive target. While keeping the patient well hydrated improves organ perfusion, being too generous with fluids can result in morbidity, such as venous congestion and tissue oedema. On the flip side, keeping the patient less than well hydrated may potentially reduce blood loss, but water deprivation exposes organs to the risk of injury. The complex process of achieving optimal fluid management is further amplified in renal transplantation, where the interplay of different factors such as tissue oedema leading to vascular anastomotic failure against acute tubular necrosis from intraoperative hypotension and dehydration, creates a convoluted puzzle waiting to unfold. One can no longer rely on the traditional goal of achieving an adequate urine output but rather, depend on other markers to gauge the patient's fluid status.

Over the years, a longstanding and widely accepted goal for fluid management for renal transplant was to maintain the central venous pressure (CVP)[2] at a range of 8–12 mmHg, and this was thought to be a marker of adequate fluid management in order to provide adequate perfusion to renal graft. It is believed that more fluid is required for transplant surgery than for non-transplant surgery. This subsequently contributed to the practice where a large volume of fluids administered is considered beneficial for renal transplantation.[3] However, in the past few decades, most physicians have shown and widely accepted that CVP has poor association with fluid responsiveness.[4] Neither is it an accurate and reliable estimate of the preload to the heart, which one hopes will predict perfusion to the kidney graft. Static reading of the CVP is no longer considered a good predictor of fluid responsiveness.[5]

Several physiologic parameters measured by cardiac output monitors have shown promising data in predicting fluid responsiveness in non-transplant surgeries as well as in intensive care units. The non-invasive cardiac output measurement technologies include pulse contour analysis, pulse wave transit time, thoracic electrical bioimpedance/bioreactance and transoesophageal doppler.[6] Among these newer technologies, pulse contour analysis has gained traction as a simple, non-invasive cardiac output monitor for frequent clinical use. The pulse contour analysis system measures the area under the curve from the systolic phase of the arterial waveform to derive the stroke volume. Dynamic variations of the systolic pressure, stroke volume and pulse pressure in mechanically ventilated patients give an index that predicts the probability of fluid responsiveness reliably. Based on these promising data, several studies have been performed to explore the use of these physiologic monitoring technologies for renal transplantation.

In this issue of the Annals, a meta-analysis by Choo et al. on the effect of goal-directed fluid therapy on postoperative outcomes in renal transplantation was published.[7] It aims to explore if goal-directed therapy (GDT) improves outcomes in terms of graft function and requirements for dialysis. The authors of this meta-analysis have done a comprehensive search on the available evidence of GDT for renal transplant, but the main limitation of this analysis is the insufficient quality of studies included. The studies consist of small randomised controlled trials and are also heterogenous to each other in terms of the type of renal transplantation, patient characteristics and goal-directed and control protocols. However, the studies that can significantly affect the outcome of fluids used have yet to be analysed or performed. Hence, finding no significant difference in the primary outcome is not unexpected.

However, it is interesting to note that the likelihood of postoperative tissue oedema and respiratory complications was significantly lower in the GDT group, which may suggest the beneficial effect of GDT. A lower likelihood of tissue oedema could be beneficial in ensuring graft function. One study demonstrated an association between the fluid volume administered and endothelial

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glycocalyx degradation.[8] Fluid overload may induce endothelial injury.

Other factors can affect delayed graft functions, which are predictors of subsequent clinical courses.[9] These factors include immunological processes, haemodynamic parameters, prolonged ischaemic time and manner of graft preservation, which will influence the development of acute tubular necrosis—the most common cause of delayed graft function.[10] With a myriad of factors that can influence the outcome of graft function, it will be challenging to have a universal algorithm that will fit every individual in the study design. However, this should not deter further extensive studies from being performed.

The Consensus Statement of the Committee on Transplant Anaesthesia of the American Society of Anesthesiologists[11] states there is low-quality evidence for a more significant volume of fluid administration targeting a higher CVP during renal transplantation. They also concluded that using CVP as a guide to fluid administration is only weakly supported. Using stroke volume variation, oesophageal Doppler and Pleth Variability Index (PViR) to guide administration is promising but limited in evidence.

Fluid management for renal transplants is akin to walking on a tightrope. Too much of it will result in tissue oedema, and too little will result in tissue ischaemia; both situations will affect graft function. While there is limited evidence to support the GDT, this meta-analysis suggests that postoperative renal function is better with GDT as demonstrated by a lower creatinine and reduced incidence of dialysis for mainly cadaveric graft patients. The signal favouring the use of GDT being stronger with cadaveric renal transplants may be due to a longer ischaemic time and this is associated with increased risk of delayed graft function. GDT may have a beneficial effect in this group of patients. Fluid management, in addition to blood pressure, should be individualised to the specific patient, and guidance from physiologic goals may help achieve that.

Keywords: *fluid management, goal-directed therapy, nephrology, renal failure, renal transplantation*

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ORIGINAL ARTICLE

Understanding the use of evidence-based medical therapy in patients with peripheral artery disease: A qualitative study using the Tailored Implementation for Chronic Diseases Framework

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ABSTRACT

Introduction: The global burden of peripheral artery disease (PAD) has been increasing. Guidelines for PAD recommend evidence-based medical therapy (EBMT) to reduce the risks of cardiovascular events and death but the implementation of this is highly variable. This study aimed to understand the current practices regarding EBMT prescription in PAD patients and the key barriers and facilitators for implementing PAD guidelines.

Method: A qualitative study was conducted in the largest tertiary hospital in Singapore from December 2021 to March 2023. The participants included healthcare professionals and in-patient pharmacists involved in the care of PAD patients, as well as patients with PAD who had undergone a lower limb angioplasty revascularisation procedure. Data were collected through in-depth, individual semi-structured interviews conducted face-to-face or remotely by a trained research assistant. Interviews were audio-recorded, transcribed and systematically coded using data management software NVivo 12.0. The Tailored Implementation for Chronic Diseases (TICD) framework was used to guide the interviews and analysis.

Results: Twelve healthcare professionals (4 junior consultants, 7 senior consultants, and 1 senior in-patient pharmacist) and 4 patients were recruited. Nine themes in 7 domains emerged. Only a small proportion of doctors were aware of the relevant guidelines, and the generalisability of guidelines to patients with complicated conditions was the doctors' main concern. Other barriers included cost, frequent referrals, lack of interprofessional collaboration, not being the patients' long-term care providers, short consultation time and patients' limited medication knowledge.

Conclusions: Findings from this study may inform strategies for improving healthcare professionals' adherence to guidelines and patients' medication adherence.

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Keywords: barriers, evidence-based medical therapy, facilitators, guideline implementation, peripheral artery disease, qualitative study

CLINICAL IMPACT

What is New

- Using the Tailored Implementation for Chronic Diseases (TICD) framework, this qualitative study examines healthcare workers' and patients' perceptions of the implementation of evidence-based medical therapy (EBMT) in the treatment of peripheral artery disease (PAD).

Clinical Implications

- This qualitative study highlights existing barriers to the use of EBMT in PAD patients, including lack of guideline awareness, frequent referrals, the limited generalisability of the guidelines to all patients, and cost.
- Future interventions, such as collaborative care and focused training, are needed to enhance EBMT utilisation in PAD management.

INTRODUCTION

The global burden of peripheral artery disease (PAD) has been increasing, with 237 million adults living with PAD worldwide in 2015,[1] rising from 202 million in 2010.[2] A population-based study in Singapore found the overall prevalence in Chinese, Malays and Indians to be 3.5%, 5.2% and 5.6%,

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respectively.[3] Given the increasing prevalence of diabetes in Singapore,[4] it is unsurprising that there is an increasing number of PAD cases in the country. Apart from the risk of major amputation, PAD is strongly associated with increased cardiovascular morbidity and all-cause mortality.[5] Despite its rising prevalence and adverse impact on quality of life, this condition remains underdiagnosed and undertreated.[6,7] As part of the evidence-based PAD risk management, pharmacotherapy recommended by various internal guidelines includes antiplatelet therapy and statin agents in all PAD patients as well as antihypertensive and anti-diabetic medications as secondary preventative therapies.[8-10]

Despite clear guideline recommendations, EBMT implementation for PAD management is inadequate. A local drug utilisation study of EBMT in chronic limb-threatening ischaemia (CLTI) patients revealed that the use of statins and antiplatelets at admission for angioplasty was only 66% and 47%, respectively.[11] Similarly, data from Danish nationwide administrative registries also showed that relative to coronary artery disease alone, patients with PAD and without history of coronary artery disease were less likely to use any antiplatelet or statins at 18 months after diagnosis.[12] However, EBMT use at discharge was strongly associated with 6-month post-procedural use for recommended medications.[13] A retrospective analysis of EBMT use in patients undergoing lower limb angioplasty in our institution also found suboptimal EBMT use, especially statins, at discharge, indicating a potential opportunity for improvement.[11]

There have been studies examining the factors of non-adherence to cardiovascular disease guidelines,[14,15] but there are few focusing on PAD guidelines. Moreover, most studies focused on patient factors alone,[16,17] rather than taking a more systemic approach to investigate other factors that could potentially affect EBMT adherence. Using a comprehensive checklist, the Tailored Implementation for Chronic Diseases (TICD) checklist,[18] allows us to study various determinants of the implementation of clinical practice guidelines systematically. The TICD checklist includes 57 potential determinants in 7 domains, namely, individual health professional factors, professional interactions, guideline factors, patient factors, incentives and resources, capacity for organisational change, and social, political and legal factors.

With the guidance of the TICD framework, we conducted a qualitative study in patients with PAD and healthcare workers (HCWs) interacting with PAD patients to understand the current practices regarding their EBMT prescription and investigate the key barriers and facilitators for implementing PAD guidelines.

METHOD

Study design and setting

A qualitative study was conducted in Singapore General Hospital, the largest tertiary hospital in Singapore, from December 2021 to March 2023. In-depth, semi-structured interviews were conducted individually in person or remotely. This study was approved by the SingHealth Centralised Institutional Review Board (CIRB) [Ref No.: 2021/2746]. The Consolidated Criteria for Reporting Qualitative Studies guideline was used to guide the reporting of qualitative research.[19]

Participants

Study participants were recruited using purposive (i.e. non-random) sampling. We invited doctors from departments of endocrinology, vascular surgery, vascular intervention, internal medicine, renal medicine, vascular and interventional radiology, as well as inpatient pharmacists who interacted with PAD patients to participate in the study via email. PAD patients who had undergone a lower limb angioplasty and returned for their first follow-up appointment were also invited to participate. Eligible patients were identified by doctors and approached by research coordinators. Those who were not able to converse in either English or Mandarin were excluded.

Study procedures

We developed 2 structured interview guides based on the TICD framework, for healthcare professionals and patients, respectively. Before the interview commenced, written informed consent was taken by the research coordinators. Interviews were conducted face-to-face or via Zoom. All interviews were conducted by one of the authors, a trained research assistant who had no pre-existing relationships with the participants. All the face-to-face interviews were carried out in a private and conducive environment in the hospital using the interview guide. For interviews conducted remotely, written informed consent was taken prior to the day of the interview in person where possible. Each interview lasted 30–45 minutes and was audio recorded. Each participant was reimbursed for their time. Recruitment was continued until data saturation, which was determined by discussion among team members.

Data analysis

Data management was performed by NVivo 12 (QRS International, Burlington, Massachusetts). All English or Mandarin interviews were transcribed from audio file format to text using Otter.ai (Otter.ai, Inc, CA) or Sonix.ai (Sonix Inc, CA), respectively. The transcriptions were then manually checked and edited. Transcripts for interviews conducted in Mandarin were translated into English. Two investigators familiarised themselves with the transcripts to get a better understanding of the interviews and generate codes individually. The codes were then compared for their similarities and differences. Similar codes were clustered to create categories and themes. All disagreements were resolved through discussions among the authors. Data analysis was performed simultaneously with data collection, which continued until data saturation was reached, where no new codes were identified.

RESULTS

A total of 12 healthcare professionals (4 junior consultants, 7 senior consultants, and 1 senior in-patient pharmacist) and 4 patients completed the interviews. The majority of the HCWs interviewed were doctors (10/11), including nephrologists, vascular surgeons and consultants. Participants' demographics are shown in Table 1. From the analysis, 9 themes in 7 TICD domains emerged (Table 2).

Table 1. Participant demographics.

Variable	n = 16
Healthcare professionals (n=12)	
Gender, n (%)	
Female	5 (41.7)
Male	7 (58.3)
Department, n (%)	
Renal medicine	4 (33.3)
Internal medicine	4 (33.3)
Vascular intervention	2 (16.7)
Vascular surgery	1 (8.3)
In-patient pharmacy	1 (8.3)
Seniority, n (%)	
Consultant	3 (25.0)
Senior consultant	4 (33.3)
Associate consultant	4 (33.3)
Senior principal pharmacist	1 (8.3)
Patients (n=4)	
Age, mean ± SD	70 ± 3.6
Sex, %	
Female	75
Male	25
Ethnicity, %	
Chinese	100

Domain 1: Individual health professional factors

Theme 1: Limited awareness of the relevant guidelines

The HCWs were familiar with the risks that PAD patients faced, in particular limb ischemia and limb amputation. They also cited that PAD patients had higher rates of cardiovascular outcomes and death and were more susceptible to infections. The participants were also familiar with PAD-related symptoms and the treatment. All the doctors interviewed reported that treatment consisted of statin and antiplatelets, as well as diabetic or blood pressure medications to treat the underlying cause.

Some participants, especially vascular surgeons, were aware of the relevant guidelines. One surgeon noted, "There is the European Society of vascular surgery, the Society for Vascular Surgery, there is the American Heart Association, and I'm sure there are more" (SGH-HCW-013, vascular surgeon). However, other participants acknowledged that they were not aware of any guidelines, nor had they kept themselves updated on the latest guidelines due to certain reasons. First, due to the frequent referrals they made, they did not find a need to read the guidelines. As a nephrologist said, "I do, however, know the basic principles of treating and when to refer the patients" (SGH-HCW-005, nephrologist). The second reason was that a major part of PAD management was to control cardiovascular risk factors. According to a nephrologist, "I didn't really go to search the guidelines. But as long as I know [sic], we usually give to control [sic] the cardiovascular risk factors, such as giving the antiplatelets and statins to control cholesterol, optimise blood pressure and diabetes control", according to a nephrologist (SGH-HCW-001).

Not being aware of the latest guideline was cited as one of the barriers to implementing EBMT. A radiologist said, "[Consultants are] still only familiar with the evidence that when you were training [sic], and if your department isn't doing regular updates or like continuing medical

Table 2. Tailored Implementation for Chronic Diseases (TICD) Framework analysis with inductively developed belief statements.

Domain	Theme	Sample illustrative quote
Domain 1: Individual health professional factors	Limited awareness of the relevant guidelines	"I think I have a general understanding. It can lead to limb ischemia, and then loss of limb and then the milder complications would be the usual loss of sensation, insensate, and then chronic pain." (SGH-HCW-004, internal medicine doctor) "If you are talking specifically about PAD risks, of course then they face risk of amputation, the loss of limb ischemia, and with that you lose ambulation status, you become more dependent on other people because PAD patients generally mean patients have other comorbidities and other issues. So, they also have higher rates of cardiovascular death, mortality and other cardiovascular related outcome that is not so good for them." (SGH-HCW-005, nephrologist) "[Guidelines] Not that I'm aware of." (SGH-HCW-001, nephrologist) (SGH-HCW-003, radiologist) "I'm not sure about under vascular but I mean, under cardiology, there would be [guidelines], a couple years back where they did recommend aspirins or statins. Okay, yes, that's all I know." (SGH-HCW-002, internal medicine doctor)
Domain 2: Professional interactions	Shared responsibilities in the PAD management across different departments	"And then for the disease management, depending on their risk factors, then I think it may involve like a lot of people such as the cardiologists, endocrinologists, obesity managers, etc." (SGH-HCW-003, radiologist) "Actually, if you're talking about PAD specifically if we do notice that they have PAD signs and symptoms, we will be referring them usually to the vascular surgeons for further review, and if it's for basic things like screening tests, skin care of the foot is actually the podiatrist. So, these are the two main sources of referral that we will make for patients with evidence of PAD." (SGH-HCW-005, nephrologist) "We do work closely with other departments due to the fact that our patients generally have a lot of comorbid conditions, and some of them are managed by specialists. We also work closely with other allied health care professionals as well." (SGH-HCW-006, internal medicine doctor) "If they have symptoms, or they have a wound, we actually refer to the vascular surgeon. On our side, we will just mainly do primary care, advise them on foot care, and then advise them on wearing proper shoes, and then check their pulses. And then if they have a wound, we'll try to refer them to the vascular team early for assessment." (SGH-HCW-012, nephrologist) "If, for example, somebody starts the patient on a new medication for peripheral artery disease, then that will actually make me want to know more why the patient has settled on this new medication that I'm not aware of. And I will do more research for that" (SGH-HCW-001, nephrologist)
	Doctors' concerns about implementing EBMT due to polypharmacy and comorbidities	"Maybe it has been started 10 years ago, but the GP and they had some side effect and they stopped it or something like that …… do prefer not to rock the boat in other ways and just keep them in the care of their respective specialists. So that's probably one of the main reasons why I don't start certain medicines, don't drastically change medications for inpatients." (SGH-HCW-006, internal medicine doctor)

Table 2. Tailored Implementation for Chronic Diseases (TICD) Framework analysis with inductively developed belief statements. (Cont'd)

Domain	Theme	Sample illustrative quote
Domain 3: Guideline factors	Doctors' mixed opinions on following the guidelines	"So, a lot of times, just following the recommended management for one single condition cannot apply that way because my patients have multiple medical issues at the same time, and sometimes the recommendations do contradict one another." (SGH-HCW-006, internal medicine doctor) "If they are at high risk, with a high risk of bleeding, for example. And then, in terms of lipid therapy, in the renal literature, we do know that in a patient who is started on dialysis, the lipid lowering doesn't improve the chance of MI heart attacks. So, it's mainly protective, only if before that they already have pre-existing. So, we do not really give it primarily for PAD, but we give it mainly for coronary artery disease prevention" (SGH-HCW-012, nephrologist)
Domain 4: Patient factors	Lack of patient understanding of PAD and associated medications	"Maybe it's because my 'thing' is blocked. This will make my blood a little 'thinner'. [The doctor] said that my blood is 'thick'." (SGH-PT-001, patient) "Too many medications. Additionally, I don't feel any different after taking my medications. I feel the same." (SGH-PT-003, patient) "When I wake up in the morning, I will arrange my medications nicely. I'll take this pack (points to the medication) in the morning, and I'll put it in my pocket." (SGH-PT-004, patient)
Domain 5: Incentives and resources	Cost and lack of time as the main barriers to implementing EBMT	"Mainly because of cost. I have to say, I'm very mindful of cost because my particular population of patients are, tend to be of lower income." (SGH-HCW-007, nephrologist) "Most of the time, yes, except in terms of the dual pathway inhibition because of cost. And we don't see them in follow up, we may not prescribe it as often." (SGH-HCW-013, vascular surgeon) "Probably a potential barrier may be communication to the patient about the importance of adherence because there may not be enough time to discuss the importance of adherence to therapy and the complications that can arise if the patient is not adherent." (SGH-HCW-004, internal medicine doctor) "But in the clinic, I really have no time to just go to the NEHR and adjust that and change it and stuff like that." (SGH-HCW-006, internal medicine doctor)
	Collaborative care to improve interprofessional communication and patient education	"I think what you can do is firstly, speak to the pharmacists, the pharmacists are very educated. And they also advise the doctors to make sure that we don't make too big of an error. So, I think the pharmacists have to buy in first, and make sure that they also believe because they are super good at looking at pharmacokinetics and drug safety. So that's what they're really good at. So, I think we should make use of all this allied help, help them to familiarise the drugs first." (SGH-HCW-005, nephrologist) "……having a support for the patient that the patients can call on the advanced practice nurse for contact. That will be helpful to facilitate the patient's understanding of the disease and taking the prescribed medication." (SGH-HCW-004, internal medicine doctor) "I personally think that, that basically having healthcare professionals like advanced nurse practitioners, who can actually spend time with patients, to counsel them as to why they need to take certain things." (SGH-HCW-008, radiologist)

Table 2. Tailored Implementation for Chronic Diseases (TICD) Framework analysis with inductively developed belief statements. (Cont'd)

Domain	Theme	Sample illustrative quote
Domain 6: Capacity for organisational change	Internal sharing to improve the prescription rate of EBMT on the departmental level	"I feel if there is a guideline and the guideline is…. really differs a lot from what we are practicing for now, it is very important to incorporate this into medical teaching. Yeah, if it is such guidelines, or even the department can do a roadshow, incorporate into department teaching, that will be very useful." (SGH-HCW-001, nephrologist) "I think a continuous engagement is probably a way to start. I think having regular topic updates on like PAD management with like, a very broad perspective on the inputs from multidisciplinary perspectives." (SGH-HCW-003, radiologist) "If there's a guideline available on the infopedia, then that will be helpful." (SGH-HCW-004, internal medicine doctor)
Domain 7: Social, political and legal factors	To raise patients' awareness of healthy behaviours in the community	"There are some practices that are happening. But I think on the ground, it's, I don't see it. So, I think education, level of education or information done at source points, you know, coffee shops, in the community, can be done better. To make people aware of things. I think a lot of people are not aware." (SGH-HCW-008, radiologist)

education events or people don't share their knowledge, then that could be a potential challenge that I can see" (SGH-HCW-003, radiologist).

Domain 2: Professional interactions

Theme 2: Shared responsibilities in the PAD management across different departments

As patients with PAD generally have various comorbid conditions, disease management is often multidisciplinary, involving different specialists such as cardiologists, endocrinologists, obesity managers and allied health professionals (such as podiatrists).

On the departmental level, all participants denied the existence of a department protocol in the PAD department. Instead, doctors were allowed to make the judgment based on their own clinical acumen and online resources. Their practice patterns would also be influenced by their colleagues.

Theme 3: Doctors' concerns about implementing EBMT due to polypharmacy and comorbidities

For safety reasons, inpatient doctors had concerns about starting patients on new chronic medication because they were not the patients' long-term care providers. One participant, an internal medicine doctor, stated that "sometimes PAD is not the primary condition that the patient gets admitted. I do prefer not to rock the boat in other ways and just keep them in the care of their respective specialists" (SGH-HCW-006, internal medicine doctor). In addition, due to limited consultation time and a heavy workload, doctors were unable to educate the patients about the medication and ensure adherence. "[Specialists] will be able to explain to them why [they] need to continue it and make sure that they adhere to it. That's the main reason why there's poor compliance with the guidelines," said a radiologist (SGH-HCW-008).

Domain 3: Guideline factors

Theme 4: Doctors' mixed opinions on following the guidelines

The majority of the participants agreed on the recommended therapy and believed that the guidelines were, as a nephrologist noted, "useful in summarising the evidence and giving you a starting point" (SGH-HCW-007, nephrologist), and they would usually follow the guidelines "unless there's some other reason for this patient not to be on them" (SGH-HCW-002, internal medicine doctor).

However, doctors also had concerns about following the guidelines. The major reason was that the guidelines may not apply to all their patients or the local context. According to a nephrologist, "Individuals themselves change over time. So, you have to adapt to their current status, which fluctuates hugely, especially [for] the elderly." Another reason was that sometimes doctors had to weigh risks against benefits before making decisions. For example, for a patient with PAD who recently had a heart attack, while the doctor was clear that beta-blockers should be administered with extreme caution, he still had

to initiate beta-blocker, because "you need it for its antianginal [properties], to reduce myocardial oxygen demand" (SGH-HCW-006, internal medicine doctor). The doctor explained that "Sometimes I might choose and decide that the heart is more important than the leg and start the beta blocker anyway" (SGH-HCW-006).

Domain 4: Patient factors

Theme 5: Lack of patients' understanding of PAD and associated medications

Having had PAD for 2 to 10 years, all patients claimed that they were able to take their medications daily without any difficulties or reminders because it had become their routine. Said one patient (SGH-PT-002), "I consume them every day and I won't forget to take them." However, they denied that the purpose of taking medications was well explained as such knowledge was beyond their understanding. A patient noted, "The thing is very complicated. I will just take whatever medications that [doctors] prescribe to me" (SGH-PT-004).

Regarding patients' adherence levels, HCWs' estimations varied, ranging from ≤40% to >95%, which was judged based on each patient's blood test results. Estimation of antiplatelet adherence was more difficult. On why patients had difficulty adhering to their medications, doctors listed multiple factors—including cost, polypharmacy, side effects, inconvenience of insulin injection, no effects, difficulties in behavior change, poor understanding and poor social support.

Domain 5: Incentives and resources

Theme 6: Cost and lack of time as main barriers to implementing EBMT

Cost was considered one of the barriers to adhering to the guidelines. Regardless of guidelines-recommended medications, doctors would prioritise the prescription of affordable medications, given the fact that "the most effective medicine is the one that the patient can actually afford, [that] he actually takes," noted a nephrologist (SGH-HCW-007). Besides cost, a lack of time to check potential interactions was another barrier. "It takes ages to login into the Electronic Health Record system and we don't have time for that. So, we just kind of prescribed [sic] whatever we think is the safest, most basic, and then we move on (SGH-HCW-007)."

Theme 7: Collaborative care to improve interprofessional communication and patient education

A group of facilitators frequently mentioned by the doctors were allied HCWs, such as pharmacists and advanced practice nurses in PAD management. They not only boost doctors' confidence in prescribing certain medications but also provide counselling and education to patients. In addition, pharmacists' role in educating patients on why and how to take medications could contribute to a higher adherence rate in patients. Similarly, nurses can also play an important role in improving patients' medication adherence by "counselling and highlighting the complications of the disease and the importance of medication adherence," noted an internal medicine doctor (SCH-HCW-004)".

Domain 6: Capacity for organisational change

Theme 8: Internal sharing to improve the prescription rate of EBMT on the departmental level

Some participants pointed out that the existence of various guidelines made it difficult for different HCWs to reach an agreement. "There are so many guidelines and depends on which one you follow. So, it'd be difficult to get everybody to agree on one," noted a vascular surgeon (HCW-SGH-013). To increase the prescription rate, doctors suggested having internal teaching or publishing guidelines that "really differ a lot from what we are practising now" on the organisation's intranet (HCW-SGH-001, nephrologist). They also suggested holding webinars to share vascular surgeons' opinions on PAD management, and through knowledge sharing, to engage multidisciplinary teams in PAD management. Another suggestion they raised was to have quick access to the references, such as "little posters or reference cards or a QR code that we can have it on our phones or save somewhere that we can refer to," as suggested by a radiologist (HCW-SGH-003).

Domain 7: Social, political and legal factors

Theme 9: Raise patients' awareness of healthy behaviours in the community

One of the doctors pointed out that, despite several ongoing government campaigns, patients' health awareness did not improve. To overcome this, more information, including healthy diets, should be broadcast in the community, and at source points such as coffee shops "to make people aware of things that they don't know," noted a radiologist (SGH-HCW-008).

DISCUSSION

In this study, we applied the TICD framework to examine the current practices of EBMT use and factors for adherence and non-adherence to EBMT use in patients with PAD. We found that although most doctors were not familiar with updated PAD treatment guidelines, their practice was aligned with the recommended pharmacotherapy. We identified multiple barriers to implementing EBMT, and facilitators and strategies to improve EBMT adherence were also discussed.

At the healthcare provider level, a surprising finding was that most doctors were either not aware of any PAD guidelines or never searched for relevant guidelines. This result was similar to other studies that found inadequate awareness of clinical practice guidelines among practitioners in other disease areas.[15,20] Several reasons led to the lack of awareness of guidelines. First, as PAD is one of the existing conditions, doctors' usual practice is to continue patients' existing medications without making changes. Second, due to the low referral threshold, doctors who did the initial assessment and referrals were not responsible for prescribing EBMT. Third, doctors believed that they were able to provide the treatment without guidelines, based on their expertise. Fourth, there was no regular internal education or sharing to make guidelines available to all the HCWs. The large gap in PAD guidelines awareness or familiarity highlights the need for effective internal education about the latest treatment guidelines and the need of developing easy-accessible reference tools.

At the patient level, the most significant barrier to adhering to EBMT was inadequate knowledge of their medications. It has been widely accepted that medication knowledge plays a substantial role in medication adherence in patients with chronic diseases.[21] Limited health literacy is a possible explanation for why many patients were not on antiplatelet therapy even though they had gone through several surgical interventions, a disappointing fact shared by a vascular surgeon who was interviewed. To tackle this problem, the doctors highlighted an urgent need to involve HCWs to educate them on the importance of taking medications.

At the system level, measures need to be taken to improve interprofessional collaboration. In the inpatient setting, patients with PAD and multiple comorbid conditions were admitted to the hospital for various reasons, while specialists tended to focus on one specific condition and failed to provide holistic care. Ironically, with too many doctors involved, no one was in charge of making decisions. One doctor pointed out that the lack of interprofessional communication led to the inadequate use of EBMT. A radiologist (SGH-HCW-003) said, "So sometimes, some patients don't have like [sic] a regular doctor who knows them very well that it can get lost if there are too many doctors involved, none of them are communicating with each other." Not knowing a patient's history also resulted in doctors' relying more on their expertise rather than the guidelines, which further limited EBMT use.[20] This highlights the need to improve interprofessional communication by engaging a care manager to share regular updates of a patient and develop a comprehensive coordinated care plan.

This study had several limitations. First, our findings may have been affected by selection bias due to the low response rate of the HCWs, especially vascular surgeons, endocrinologists and cardiologists. However, our inclusion criteria made it possible that HCWs from departments that commonly interacted with PAD patients were included. Second, our findings may have been limited by the small sample size. However, this study fulfilled the requirement of having a sample size of at least 12 to reach data saturation.[22,23] Third, the majority of the participants were not aware of PAD guidelines, resulting in limited insights into the barriers and facilitators to implementing the guidelines provided by them. However, our study was qualitative in nature, and we successfully explored patients' perspectives on potential difficulties in taking medications through in-depth interviews.

The findings of this study will help build needed evidence for future interventions for improving guideline adherence in PAD management. The inefficiency in implementing EBMT in the current practice calls for actions to facilitate interprofessional communication and patient education. Future EBMT implementation may benefit from engaging specialists, primary care providers, and allied HCWs, and using a collaborative care approach plus focused training.

CONCLUSION

EBMT in PAD management remained underutilised and we identified several factors contributing to this. The key ones were HCWs' lack of guideline awareness, frequent referrals, the limited generalisability of the guidelines to all patients, patients' complicated conditions, patients' limited understanding of their medications, cost, and short consultation time. Future interventions are needed to enhance EBMT utilisation in PAD management.

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Conflict of interest

The authors declared no conflicts of interest.

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ORIGINAL ARTICLE

An augmented reality mobile application for weight estimation in paediatric patients: A prospective single-blinded cross-sectional study

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ABSTRACT

Introduction: Determining the exact weight of children is a challenging task during emergency situations. Current guidelines recommend the use of length-based weight-estimating tapes. However, healthcare providers must either always carry the tapes or take time to locate them. Moreover, they may not know how to use them. To address these issues, we developed an augmented reality smartphone application for length-based weight estimation called the Paediatric Augmented Reality Scale (PARS). We evaluated its performance and compared it to that of the Broselow tape (BT) and Paediatric Advanced Weight Prediction in the Emergency Room extra-long and extra-large (PAWPER-XL) tape methods.

Method: A prospective, single-blinded cross-sectional study was conducted with children aged 1 month to 12 years who visited the emergency department of the tertiary university hospital in Bucheon, South Korea between July 2021 and February 2022. This study aimed to evaluate the measurement agreement and performance of 3 methods: BT, PAWPER-XL and PARS.

Results: In all, 1090 participants were enrolled, and 639 (58.6%) were male. The mean age of the participants was 4.1 ± 2.8 years, with a mean height of 102.7 ± 21.7 cm and mean weight of 18.8 ± 9.5 kg. Compared to BT and PAWPER-XL, PARS exhibited lower mean absolute percentage error (9.60%) and root mean square percentage error (3.02%). PARS achieved a higher proportion of weights estimated within 10% of the actual weight (63.21%), outperforming BT (57.25%) and PAWPER-XL (62.47%). The intraclass correlation coefficients for the actual and estimated weights of BT, PAWPER-XL and PARS were 0.952, 0.969 and 0.973, respectively (P<0.001).

Conclusion: PARS exhibited a modestly better performance than BT and PAWPER-XL in estimating body weight. PARS-estimated body weights correlated fairly accurately with the actual body weights. PARS holds potential utility in paediatric emergencies.

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Keywords: augmented reality, body weight, Broselow tape, mobile application, paediatrics

CLINICAL IMPACT

What is New

- We developed the Paediatric Augmented Reality Scale (PARS), a mobile application that combines the strengths of the body habitus-adjusted, length-based weight estimation method with the accessibility and convenience of smartphone augmented reality.

Clinical Implications

- The performance of PARS was modestly better than that of the Broselow tape and Paediatric Advanced Weight Prediction in the Emergency Room extra-long and extra-large (PAWPER-XL) tape.
- A mobile application PARS may be useful for paediatric weight estimation.

INTRODUCTION

Drug and defibrillation energy doses for children rely on accurate weight measurement, making it essential during emergencies.[1,2] However, quickly weighing children in distress is often a challenging task.[3,4] Conventionally, age-dependent formulas and length-based tapes like the Broselow tape (BT) and Paediatric Advanced Weight Prediction in the Emergency Room extra-long and extra-large (PAWPER-XL) tape, have been utilised.[5-8] While the age-dependent method does not require any equipment, it performs less effectively compared to length-based methods.[2] BT, a widely used length-based method, is employed worldwide to determine optimal drug doses and the necessary dimensions of endotracheal tubes and laryngoscopes.[5] However, BT has a limited range of applicability, covering lengths from 46 to 146.5 cm, making it less suitable for populations that fall outside this length range, particularly those who are overweight or underweight.[3,9,10] The

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PAWPER-XL tape takes into account the 7 types of body habitus, making it more suitable for overweight and underweight patients.[8] However, healthcare providers are required to either carry a tape at all times or locate one when needed. Additionally, there may be instances where providers are unfamiliar with its usage, leading to potential delays in drug administration and increased risk of dosing errors.[11,12] A survey conducted among paramedics indicated that these disadvantages were significant in emergency situations, highlighting the need for other measurement methods.[12,13]

Augmented reality (AR) combines digital information with the real environment and enables accurate measurement of object dimensions.[14] AR is widely utilised in various medical fields, including surgical planning and telemedicine, due to its high level of convenience and accessibility.[15,16] We developed a mobile application called Paediatric Augmented Reality Scale (PARS), which combines the advantages of the body habitus-adjusted, length-based weight estimation method with the accessibility and convenience of smartphone-based AR. In this study, our objective was to assess the accuracy of PARS and compare its performance with that of BT and PAWPER-XL.

METHOD

Study design and setting

This prospective, single-blinded cross-sectional study was conducted with paediatric patients aged 1 month to 12 years who visited the emergency department (ED) of a tertiary university hospital in South Korea between July 2021 and February 2022. The exclusion criteria included the following: height outside of the range of BT (<45.9 or >146.5 cm), a need for emergency intervention, underlying genetic or neuromuscular diseases or congenital malformations affecting height or weight, refusal to participate, and/or an uncooperative child.[9] The study was approved by the Institutional Review Board (Approval no. 2021-07-005) of the Soonchunhyang University Bucheon Hospital. The study procedure was explained to the participants or their legal guardians, and informed consent was obtained.

PARS

PARS was developed by Bory Inc (Ansan-si, Gyeonggi-do, Republic of Korea) using Google ARCore and Unity 3D. Google ARCore enables an Android smartphone camera to recognise its surroundings by tracking feature points. In ARCore, visual information from the camera is processed through simultaneous localisation and mapping, while movement and rotation information collected from accelerometers and gyroscopes is processed through the inertial measurement unit. For accurate measurements, it is ideal for the distance between the camera and the child to be similar to the child's height. However, as long as the camera is not too close or too far from the patient, minor variations in distance are not a significant issue. Also, if the camera is positioned between the child's head and toes, the angle at which it is positioned does not matter. Through this process, PARS determines the height from head to heel in a supine position. It is important to note that regional differences may exist in length-based weight estimation methods, as they are based on the World Health Organization (WHO) growth charts.[17] In our study, we utilised the 2017 growth chart from the Korea Center for Disease Control and Prevention (KCDC) for all age groups of our study participants.

PARS utilises a 3-step process for weight estimation. The first step involves obtaining a baseline weight estimation derived from the supine length measured by PARS, similar to other length-based weight estimation methods. This estimated weight corresponds to the 50th percentile of the KCDC weight-for-length growth charts. In the second step, the baseline weight is revised based on the child's body habitus score (HS). A 7-point body habitus scoring system is used to assign a body HS to the child, including HS1 (5th percentile) for underweight, HS2 (25th percentile) for thin, HS3 (50th percentile) for normal weight, HS4 (75th percentile) for overweight, HS5 (95th percentile) for fat, HS6 (97th percentile) for obese, and HS7 (99th percentile) for severely obese.[6,8] Depending on the child's HS, the baseline weight can be adjusted downwards, upwards or remain unchanged. In the third step, the sex of the child is entered. PARS utilises the length, sex and HS of the child to estimate the weight. Additionally, PARS provides information on emergency drug doses, required equipment dimensions and defibrillation energy. Supplementary Fig. S1 provides detailed instructions on the usage of PARS.

Data collection, measurements and sample size

Weights and heights were measured by a nurse, who was blinded to the aim of the study, when patients visited the ED. The measurements were performed with a precision of 0.1 kg for weight and 0.1 cm for height. Patients usually stood on an electronic scale (HM-201; Fanics, Busan, Republic of Korea) for measurement. In cases where standing was not possible, measurements were taken with the patients in the supine position using a measuring device (BF-100A; Fanics, Busan, Republic of Korea). The collected data, along

with age and sex information, were stored in electronic medical records. A total of 7 ED medical technicians were responsible for measuring the patients' heights using BT (2017), PAWPER-XL and PARS. Prior to the measurements, each technician received 30 minutes of training on the use of these modalities and body habitus scoring. They remained blinded to the actual weights and heights of the patients until all measurements were completed. To estimate weight, the participants were placed in the supine position, and the distance between the top of the head and the tip of the heel was measured. This measurement was used to calculate weight using the respective methods. The sample size for the study was determined based on the assumption that the PARS method would have a PW10 (proportion of weights estimated within 10% of the actual weight) that is 10% better than BT (PW10: 60%), with a power of 80% and a 2-sided risk alpha of 0.05.[18] Consequently, a minimum of 1016 patients were required for the study.

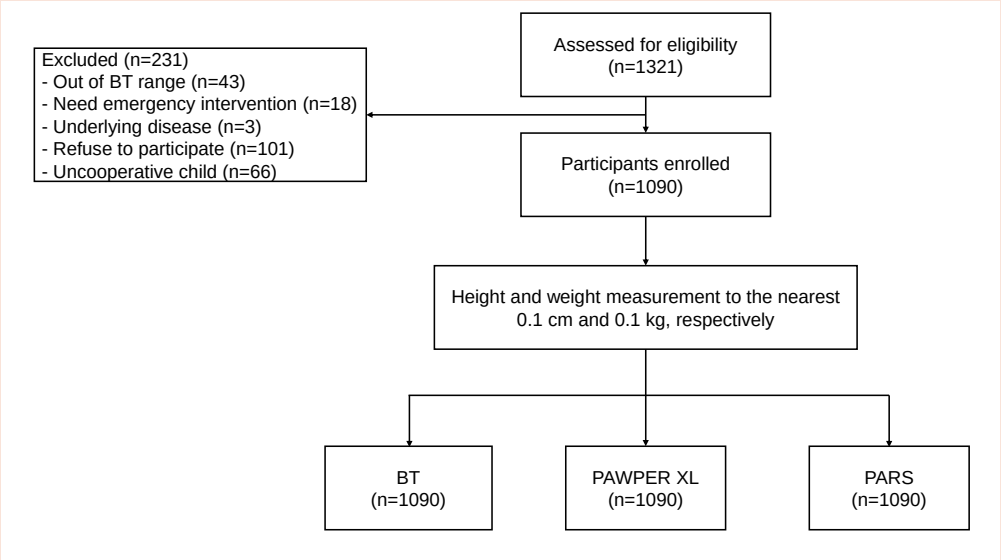
Statistical analysis

We conducted the statistical analyses using IBM SPSS Statistics version 26.0 (IBM Corp, Armonk, NY, US) and R version 3.5.3 (R Development Core Team, Vienna, Austria) software. Categorical variables are presented as absolute numbers with percentages, while continuous variables are reported as means ± standard deviations. The participants were divided into 3 age subgroups: 1–12 months, 2–5 years and 6–12 years, for the purpose of analysis.[19] The performance of BT, PAWPER-XL and PARS was evaluated based on the median percentage error (MPE), median absolute percentage error (MAPE) and root mean square percentage error (RMSPE). MPE assesses predictive bias, while MAPE and RMSPE evaluate predictive accuracy. Additionally, the percentages of weight estimations within 10% and 20% of the actual weights (PW10 and PW20, respectively) were calculated. McNemar test was used to compare differences between PARS and other weight estimation methods (BT and PAWPER-XL). The sensitivity, specificity, positive predictive value and negative predictive value between PARS and the 2 other methods were also calculated. Intraclass correlation coefficients (ICCs) were calculated to assess the agreement between the predicted weight (Wp) and actual weight (Wa). The ICC values were classified as inadequate (<0.7), good (0.7–0.89) or excellent (≥0.9).[20] Furthermore, Bland–Altman plots were constructed to visualise the agreement between Wp and Wa, as well as between the predicted height (Hp) and actual height (Ha). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

We included a total of 1321 Korean paediatric patients who visited our ED during the designated study period. From this initial pool, we excluded 43 (3.3%) patients whose height fell outside the range of BT, 18 (1.4%) patients who required emergency interventions, 3 (0.2%) patients with underlying diseases, 101 (7.6%) patients who declined to participate, and 66 (5%) patients who displayed uncooperative behaviour. The final data comprised 1090 participants (Fig. 1).

Fig 1. Flow chart of patient enrolment.



BT: Broselow tape; PARS: Paediatric Augmented Reality Scale; PAWPER-XL: Paediatric Advanced Weight Prediction in the Emergency Room XL

General characteristics of the participants

Of the 1090 participants, 639 (58.6%) were male. Among them, 108 were aged 1–12 months, 651 were aged 2–5 years, and 331 were aged 6–12 years. The mean age of the participants was 4.1 ± 2.8 years, with a mean height of 102.7 ± 21.7 cm, mean weight of 18.8 ± 9.5 kg, and mean body mass index of 16.9 ± 3.0 kg/m². The distribution of body HS was as follows: HS1, 0 (0%); HS2, 106 (9.7%); HS3, 752 (69.0%); HS4, 184 (16.9%); HS5, 38 (3.5%); HS6, 10 (0.9%); and HS7, 0 (0%) (Table 1).

Performance of BT, PAWPER-XL and PARS

For BT, MPE was -0.45%, MAPE was 11.08% and RMSPE was 3.77%. For PAWPER-XL, MPE was -1.19%, MAPE was 12.52% and RMSPE was 3.78%. Regarding PARS, MPE was 2.59%, MAPE was 9.60% and RMSPE was 3.02%. The limits of agreement for BT, PAWPER-XL and PARS were -6.95 to 7.76 kg, -6.66 to 7.94 kg, and -4.95 to 6.49 kg, respectively. The PW10 was 57.25% for BT, 62.47% for PAWPER-XL and 63.21% for PARS. PARS showed lower RMSPE in the 1–12 months age group (1.05%) and 6–12 years age group (4.63%) compared to BT and PAWPER-XL. Additionally, PARS exhibited higher PW10 values in all age subgroups compared to BT and PAWPER-XL (Table 2). Moreover, the comparisons of performance and diagnostic accuracy between PARS and the 2 other methods (BT and PAWPER-XL) are shown in Tables S1 and S2, respectively.

Correlations between predicted and actual values

The overall ICCs for BT, PAWPER-XL and PARS were 0.952, 0.969 and 0.973, respectively. Specifically, the ICC for PARS in the 1–12 months age group was 0.940, compared to 0.918 and 0.916 for BT and PAWPER-XL in the equivalent age groups, respectively. In the 2–5 years age group, the ICC was 0.927 for PARS, 0.921 for PAWPER-XL, and 0.908 for BT. For the 6–12 years age group, the ICC was 0.915 for PARS, 0.911 for PAWPER-XL, and 0.816 for BT (Table 3). The Bland–Altman plot demonstrated a narrower limit of agreement and smaller overall mean difference for PARS compared to BT and PAWPER-XL (Fig. 2). The ICC between the Ha and Hp was 0.9986 (95% confidence interval [CI] 0.9984–0.9987) for PARS. The corresponding Bland–Altman plot is presented in Fig. S2.

Table 1. General characteristics of the study participants.

	Total (n=1090)	Aged 1–12 months (n=108)	Aged 2–5 years (n=651)	Aged 6–12 years (n=331)
Age, years	4.1 ± 2.8	0.6 ± 0.3	2.8 ± 1.2	7.8 ± 1.5
Sex, no. (%)				
Male	639 (58.6)	55 (50.9)	378 (58.1)	206 (62.2)
Female	451 (41.4)	53 (49.1)	273 (41.9)	125 (37.8)
Height, cm	102.7 ± 21.7	67.6 ± 8.1	95.8 ± 12.1	127.9 ± 10.2
Weight, kg	18.8 ± 9.5	8.2 ± 2.1	15.0 ± 4.0	29.7 ± 8.8
BMI, kg/m²	16.9 ± 3.0	17.8 ± 2.6	16.2 ± 2.6	17.9 ± 3.6
HS, no. (%)				
HS1	0 (0)	0 (0)	0 (0)	0 (0)
HS2	106 (9.7)	3 (2.8)	61 (9.4)	42 (12.7)
HS3	752 (69.0)	67 (62.0)	489 (75.1)	196 (59.2)
HS4	184 (16.9)	32 (29.6)	92 (14.1)	60 (18.1)
HS5	38 (3.5)	6 (5.6)	8 (1.2)	24 (7.3)
HS6	10 (0.9)	0 (0)	1 (0.2)	9 (2.7)
HS7	0 (0)	0 (0)	0 (0)	0 (0)

Values are presented as mean ± standard deviation or no. (%).
BMI: body mass index; HS: habitus score

Table 2. Performances of BT, PAWPER-XL and PARS.

	BT	PAWPER-XL	PARS
All patients (n=1090)			
MPE, %	-0.45	-1.19	2.59
MAPE, %	11.08	12.52	9.60
RMSPE, %	3.77	3.78	3.02
LOA, kg	-6.95 to 7.76	-6.66 to 7.94	-4.95 to 6.49
PW10, %	57.25	62.47	63.21
PW20, %	84.31	87.98	88.72
1–12 months (n=108)			
MPE, %	6.47	1.54	3.53
MAPE, %	12.48	11.13	9.59
RMSPE, %	1.30	1.22	1.05
LOA, kg	-1.79 to 2.87	-2.19 to 2.55	-1.60 to 2.30
PW10, %	47.22	55.56	59.26
PW20, %	77.78	80.56	89.81
2–5 years (n=651)			
MPE, %	-3.06	0.03	2.17
MAPE, %	9.85	9.10	9.18
RMSPE, %	2.22	2.03	2.52
LOA, kg	-4.59 to 4.05	-3.76 to 4.16	-4.34 to 5.34
PW10, %	63.13	66.51	67.13
PW20, %	89.56	91.71	92.01
6–12 years (n=331)			
MPE, %	2.40	4.65	2.90
MAPE, %	13.02	10.79	11.06
RMSPE, %	6.05	4.82	4.63
LOA, kg	-9.70 to 13.1	-6.45 to 10.61	-7.15 to 10.10
PW10, %	48.94	56.50	56.80
PW20, %	76.13	84.29	82.45

BT: Broselow tape; LOA: limits of agreement (95% confidence intervals); MAPE: mean absolute percentage error; MPE: mean percentage error; PARS: Paediatric Augmented Reality Scale; PAWPER: Paediatric Advanced Weight Prediction in the Emergency Room; RMSPE: root mean square percentage error; PW10: percentage of weight estimations within 10% of the actual weight; PW20: percentage of weight estimations within 20% of the actual weight.

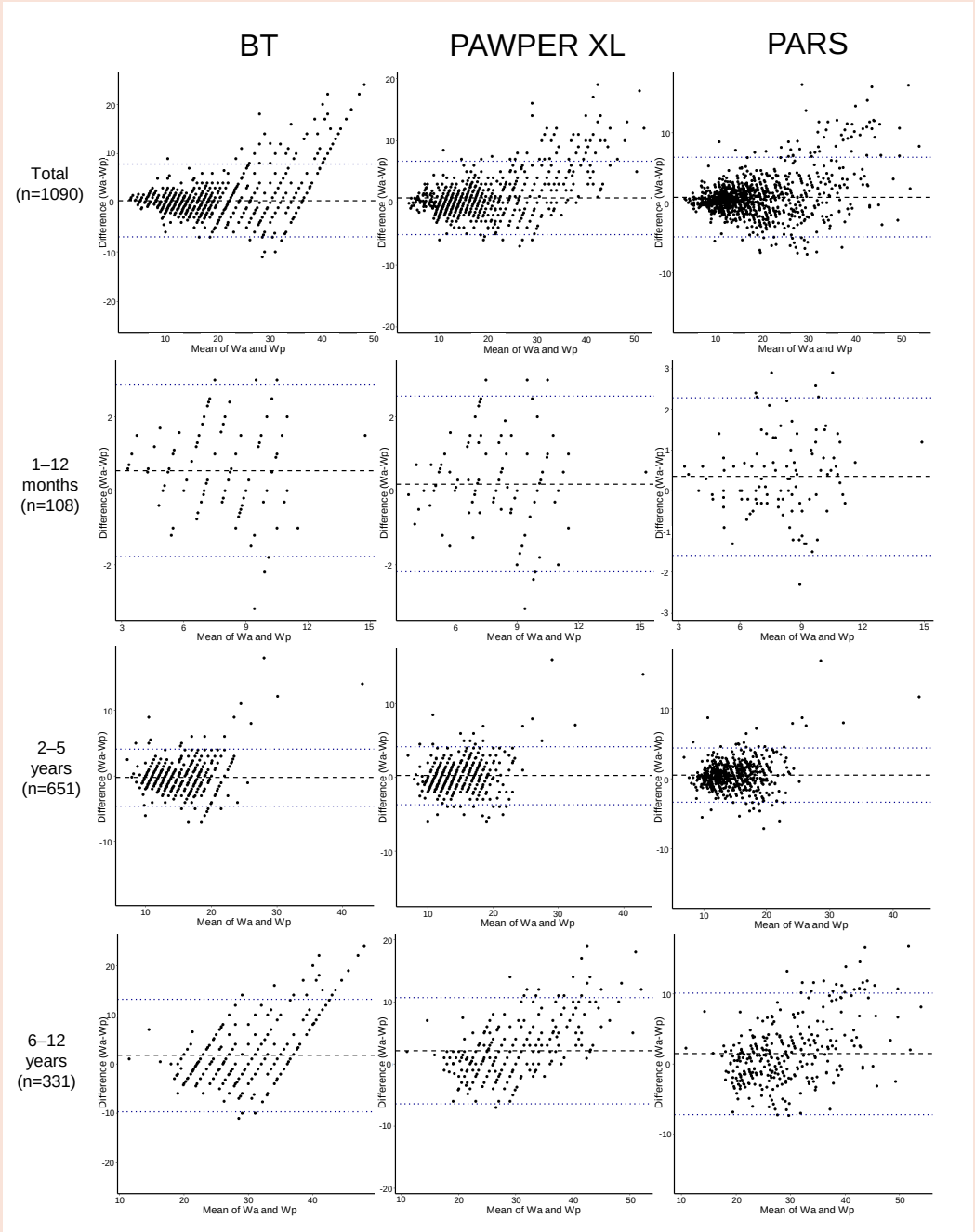
Measures of bias, precision and accuracy are shown by age group.

Table 3. Correlations between estimated and actual weights in various age subgroups.

	BT			PAWPER-XL			PARS		
	ICC	95% CI	*P* value	ICC	95% CI	*P* value	ICC	95% CI	*P* value
All patients (n=1090)	0.952	0.946–0.957	<0.001	0.969	0.966–0.973	<0.001	0.973	0.969–0.976	<0.001
1–12 months (n=108)	0.918	0.88–0.944	<0.001	0.916	0.878–0.943	<0.001	0.940	0.911–0.959	<0.001
2–5 years (n=651)	0.908	0.892–0.921	<0.001	0.921	0.907–0.932	<0.001	0.927	0.914–0.937	<0.001
6–12 years (n=331)	0.816	0.772–0.852	<0.001	0.911	0.889–0.928	<0.001	0.915	0.895–0.932	<0.001

BT: Broselow tape; CI: confidence interval; ICC: intraclass correlation coefficient; PARS: Paediatric Augmented Reality Scale; PAWPER: Paediatric Advanced Weight Prediction in the Emergency Room. *P*<0.05 was taken to indicate statistical significance.

Fig. 2. Bland–Altman plots for all weight estimation methods with 95% limits of agreement.



Wa: actual weight; Wp: predicted weight

DISCUSSION

We evaluated the weight-estimating AR application PARS and obtained the following key findings. The weight estimates provided by PARS exhibited favourable agreement with the actual weights, and PARS demonstrated modestly higher accuracy compared to BT and PAWPER-XL tapes. Moreover, the estimated body weights obtained through PARS displayed significant correlations with the actual body weights. It is worth noting that previous smartphone applications have also demonstrated high PW10 values.[18,21,22] However, a previous application developed by Wetzel et al. had the limitation of requiring a 20×20 cm square to be positioned adjacent to the patient.[21] Another application developed by Park et al. exhibited a superior PW10 value compared to PARS, but it had the drawback of necessitating a significant amount of space and the positioning of 4 red markers (150×38.5 cm) at regular intervals.[18] A recent study using ARKit found that the proportion of height estimations within a 20% range of the accurate values was 99.6%. However, it should be noted that the study did not include overweight and underweight patients.[22] PARS offers convenience, as it eliminates the need for additional reference objects, enabling accurate body weight estimations for both underweight and overweight patients by adjusting the HS.

PARS demonstrated superior accuracy, precision and bias compared to BT across all age groups, likely due to its adjustment of length-based weight estimations based on the HS, similar to PAWPER-XL.[18,23] The PAWPER-XL tape utilises WHO growth charts derived from surveys conducted in various countries, including the US, Oman, India, Norway, Ghana and Brazil, which may limit its suitability for other nations. Previous research has indicated that utilising local growth charts is more advantageous than relying solely on WHO charts. In fact, a study assessing a Korean paediatric population recommended the use of a Korean growth chart for children aged over 24 months, despite utilising a WHO growth chart for evaluation purposes.[17,24] Therefore, we employed the KCDC growth chart, which could account for the modestly superior performance of PARS compared with PAWPER-XL.

For accurate weight estimation, it is crucial for PARS to fulfil the PW10 (60–70%) and PW20 (90–95%) criteria.[8,25] The PW10 and PW20 values of PARS for all patients were 63.21% and 88.72%, respectively, which were comparable to the reference values. These values outperformed those of PAWPER-XL. It is worth noting that the KCDC 2017 and WHO Growth Chart indicate that males and females with the same height and body HS exhibit variations in weight.[24,26] Thus, PARS, which takes into consideration sex differences, may perform better than PAWPER-XL, which does not consider sex differences.[24,26] However, the PW10 and PW20 values of PARS for the 6–12 years age group were inferior to those of the other age subgroups, likely due to the AR application not handling longer surfaces effectively.[27] PAWPER-XL and PARS demonstrated lower PW10 and PW20 values for the 6–12 years age group compared to the 2–5 years age group. These findings are consistent with recent studies utilising PAWPER-XL that have reported similar results.[28,29] The decrease in accuracy is likely attributed to the inaccurate evaluation of body HS in obese school-aged children.[30,31]

The ICC reflects the variability between variables and the measurement error. The overall ICC for Wp and Wa using PARS was 0.976 (≥0.9), indicating excellent agreement.[20] However, the ICC for Wp and Wa using BT was significantly lower for school-aged children (6–12 years). A previous study found that the rate of obesity increased with age in schoolchildren but not in preschool children.[32] The ICC values for Wp and Wa in the 6–12 years age group were higher for PAWPER-XL and PARS than for BT. This is likely because the former values were adjusted based on body HS. However, careful interpretation of ICC value is required that a low ICC implies poor agreement/accuracy, whereas a high ICC does not guarantee good agreement/accuracy.

PARS is a length-based weight estimation method, similar to BT and PAWPER-XL, but it has distinct strengths. First, PARS is highly accessible. Smartphone medical applications are widely used by healthcare providers worldwide.[33] PARS will assist healthcare providers in emergency situations inside and outside of hospitals. Second, PARS is highly portable, as it does not require additional reference objects like existing smartphone applications.[18,21] Last, PARS is accurate, as it considers underweight and overweight statuses.

Limitations

This study had several limitations. First, it was conducted at a single centre in South Korea, which may limit the generalisability of the findings to other countries or populations. The use of PARS in different countries may be restricted due to its reliance on the KCDC growth chart. Thus, the growth parameters obtained may not be accurate for other populations. Second, our study only included relatively stable patients who did not require emergency treatment. This limits the applicability of PARS in situations where patients have uneven surfaces due to the presence of other medical instruments, such as spinal boards or

splints. One potential alternative approach could be marking 2 points parallel to the direction of the child's head and feet using PARS and measuring the distance between these points. Further investigation is needed to assess the utility and accuracy of PARS in patients who are severely injured or ill. Third, a factor that adjusts for the potential inaccuracies in assessing body HS is needed for PARS, similar to how PAWPER-XL-MAC considers mid-arm circumference.[31] Fourth, we did not analyse the required time for weight estimation when using PARS compared to BT and PAWPER-XL. Fifth, there are limitations regarding the absence of participants corresponding to HS1 and HS7, and the unequal distribution of lighter and heavier children across each age subgroup. Further research is needed to address these limitations.

CONCLUSION

PARS exhibited a modestly better performance than BT and PAWPER-XL in estimating body weight. The PARS-estimated body weights correlated fairly accurately with the actual body weights. PARS holds potential utility in paediatric emergencies.

Funding

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REVIEW ARTICLE

Polycystic ovary syndrome v.2023: Simplified diagnostic criteria for an East Asian phenotype

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ABSTRACT

Introduction: Two decades after the Rotterdam 2003 consensus workshop, there have been considerable advances in elucidating the pathophysiology and epidemiology of polycystic ovary syndrome (PCOS). This has prompted the re-examination of the features that characterise this common condition. Current definitions have led to great heterogeneity in the prevalence of PCOS and have contributed to inconsistent treatment protocols and assessment of therapeutic outcomes. Diagnosis is further complicated by the lack of universal agreement on threshold cut-offs for ovarian dysfunction and ethnic differences in hirsutism; both of which are key features in the definitions that are commonly used currently. These challenges often result in dissatisfaction with medical care among PCOS patients and their physicians.

Method: Our factor analysis mathematically identified anti-Mullerian hormone (AMH), associated polycystic ovarian morphology (PCOM) and serum testosterone as the only significant cluster associated with menstrual cycle length variability.

Results and Conclusion: As such, we propose a simplified criteria wherein the presence of at least 2 of the 3 features below would be sufficient to define PCOS: (1) chronic oligo-ovulation or anovulation as indicated by oligomenorrhea (cycle lengths >35 days) or amenorrhea; (2) PCOM: raised AMH ≥37.0 pmol/L instead of transvaginal ultrasound assessment of ovaries; and (3) Androgen excess, or raised serum androgens above the laboratory reference for women. Further studies are required to examine whether the proposed criteria would reduce diagnostic confusion and improve care and outcomes, especially among patients of East Asian ethnicities.

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Keywords: AMH, anti-Mullerian hormone, endocrinology, obstetrics and gynaecology, polycystic ovary syndrome, simplified PCOS diagnostic criteria

CLINICAL IMPACT

What is New

- Simplified criteria for PCOS diagnosis in East Asian women developed based on Singapore data
- Requires at least 2 out of the 3 features of oligomenorrhea/amenorrhea, anti-Mullerian hormone >37.0 pmol/L and elevated serum androgens

Clinical Implication

- Consistent diagnosis of PCOS using time-efficient diagnostic tools will ensure timely and appropriate treatment for our patients.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine condition affecting 6–19% of women of reproductive age, depending on the reference population and definition used.[1,2] The incidence of PCOS is increasing and the syndrome can be considered the single most common endocrine abnormality among women of reproductive age.[3] Although its pathophysiology is still being debated, the cardinal features of PCOS are considered to be chronic anovulation or oligo-ovulation, hyperandrogenism (HA) and the presence of multiple small cysts in the ovary.[4] PCOS is associated with increased difficulty in conceiving; abnormal menstrual bleeding patterns; higher pregnancy complication rates; and raised cardiometabolic, oncological and psychiatric risks.[5] This results in substantial economic burden, conservatively estimated to exceed an annual total cost of US$8 billion in the US alone, which include healthcare costs related to diagnosis, reproductive, metabolic,

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vascular, pregnancy-related and long-term morbidities of PCOS.[6]

Current diagnostic criteria for PCOS

There is consensus that PCOS should be considered a syndrome, meaning a constellation of clinical features where no single feature is diagnostic. However, the syndrome is still enigmatic, and establishing agreement on diagnostic features has proven problematic.[7] Varying definitions of PCOS have been proposed, including that from the Japan Society of Obstetrics and Gynecology.[8,9] Nevertheless, 3 definitions of PCOS are commonly used globally, since the seminal series of 7 cases comprising amenorrhea associated with bilateral polycystic ovaries was first described by Drs Irving Stein and Michael Leventhal.[10]

The US National Institutes of Health (NIH) convened a meeting in 1990 that defined PCOS to be primarily a condition of HA and chronic anovulation, with both features necessary for diagnosis.[11] The Rotterdam 2003 definition, arising from a European consensus meeting, broadened the NIH 1990 definition by adding a third criteria: polycystic ovarian morphology (PCOM). The existence of PCOM, detected by transvaginal ultrasound, was indicated by ovarian antral follicle counts (AFC) of ≥12 (each follicle measuring 2–9 mm) and/or ovarian volume >10 mls.[13] The advent of transvaginal ultrasound probes with a higher resolution of >8 mHz increased the ovarian AFC threshold for PCOM to 19–26 antral follicles.[14] The 2 other criteria were clinical and/or biochemical HA and chronic anovulation. Two out of the 3 items are sufficient to define PCOS.[13] This definition remains the most widely used criteria among publications in the 2 decades following its introduction.[15,16,17] The concept of PCOS as an androgen excess disorder was re-emphasised by the Androgen Excess and PCOS Society definition wherein both HA (clinical and/or biochemical) and ovarian dysfunction (oligo-ovulation and anovulation and/or polycystic ovaries) are needed for diagnosis.[18]

Current international evidence-based guideline for PCOS diagnosis

In 2018, a comprehensive international guideline was published to provide practitioners the best available evidence on PCOS diagnosis with the following recommendations being made based on evidence[19]: (1) biochemical HA should be established using free testosterone, free androgen index or calculated bioavailable testosterone using high-quality assays; (2) there is more evidence that AMH assays will be more accurate in picking up PCOM, but AMH levels have not been used as an alternative for PCOM or diagnostic of PCOS on its own; and (3) emphasis on screening for obesity, insulin resistance, cardiovascular disease, sleep, mental health issues and other comorbid conditions associated with PCOS.

Unfortunately, the 2018 guideline did not address the practical difficulties in obtaining accurate AFC through transvaginal ultrasound, which requires expert sonographic skills, is time-consuming and cannot be done in many patients due to discomfort from this intrusive procedure.

Table 1. Current polycystic ovary syndrome diagnostic criteria.

Features of PCOS	Chronic anovulation	Ovarian variables	HA	Diagnostic criteria
NIH 1990[11]	Present	Nil	Biochemical hyperandrogenaemia and/or clinical hirsutism	Both features needed
Rotterdam 2003[13]	Present	PCOM	Biochemical hyperandrogenaemia and/or clinical hirsutism	2 of 3 features
AE-PCOS Society 2009[18]	Present	PCOM	Biochemical hyperandrogenaemia and/or clinical hirsutism	HA (clinical and/or biochemical) and ovarian dysfunction (chronic anovulation and/or PCOM)
JSOG 2013[8]	Present	PCOM	Hyperandrogenaemia or high level of serum LH with normal range of FSH	All 3 features are required
Proposed PCOS (v.2023)[17]	Present	AMH	Biochemical hyperandrogenaemia	2 of 3 features

AE-PCOS: Androgen Excess & Polycystic Ovary Syndrome Society; AMH: anti-Mullerian hormone; FSH: follicle-stimulating hormone; HA: hyperandrogenism; JSOG: Japan Society of Obstetrics and Gynecology; LH: luteinising hormone; NIH: National Institutes of Health; PCOM: polycystic ovarian morphology

The guideline emphasises the role of obesity and insulin resistance and the metabolic syndrome in the assessment and management of PCOS. While relevant to the Caucasian population, this may be less so for the Singapore and other East Asian populations where obesity is less prominent.[20]

It is increasingly recognised that the 2018 guideline is work in progress.[21] Clinical reproductive and diagnostic features may be poorly correlated and may not represent true phenotypes. In a landmark study, a recent unsupervised phenotypic clustering analysis predicts different reproductive and metabolic PCOS subtypes in different populations.[22] There remains room for diagnostic criteria targeted towards specific population subtypes.[23]

Recent surveys also indicate that inconsistencies exist in current recommendations on PCOS diagnosis in adolescents, optimal lifestyle interventions, hirsutism and acne treatments, interventions to reduce the risk of ovarian hyperstimulation syndrome, the frequency and screening criteria for metabolic and cardiovascular disease, and optimal screening tools for mental health illness in women with PCOS.[24]

Confusion for patients, clinicians and researchers

These varying definitions result in heterogenous manifestations of PCOS phenotype, complicating diagnoses and assessments of therapeutic outcomes.[25] The diagnosis of PCOS can be made variously by general practitioners, gynaecologists, reproductive endocrinologists and general internists.[26,27] Diagnosis of PCOS is further complicated by a lack of universal agreement on the exact AFC,[14,28,29] need for transvaginal ultrasound assessment[30] and modified Ferriman–Gallwey (mFG) scoring of hirsutism in non-Caucasian populations.[31] Furthermore, an unsupervised phenotypic clustering analysis identified different PCOS subtypes with varying levels of sex hormone-binding globulin (SHBG), body mass index (BMI), glucose, insulin and luteinising hormone (LH).[22] This raises the question on whether an existing diagnostic criterion can sufficiently identify patients with PCOS, given the biochemical heterogeneity of the condition.

These challenges often result in delayed diagnosis and dissatisfaction with care among physicians[32] and patients.[33] In Singapore, a survey of 160 gynaecologists, endocrinologists, family physicians and general practitioners found that a large percentage (60.5%) of these physicians were unable to identify the correct PCOS clinical features.[16] Only 8.8% of respondents correctly used clinical and biochemical HA, menstrual disturbances and pelvic ultrasound to diagnose PCOS, without performing unnecessary and incorrect investigations. Many physicians (37.3%) seek standardisation of PCOS diagnosis and management guidelines. Moreover, 19.4% of physicians would specifically like to have resources for diagnosing PCOS in primary care. The study highlighted the need for greater harmonisation of diagnostic processes and holistic evidence-based management of PCOS patients, through standardised workplace protocols and patient education resources. With widespread confusion among medical practitioners, it is not surprising that the advice given to and treatment of patients with suspected PCOS are unclear and unsatisfactory.[25,26] There is a need for greater diagnostic clarity to reduce inappropriate labelling and the potential psychological harm that may accompany misdiagnosis.[32,33]

This narrative review aims to explore various concepts that may improve clarity on the features necessary to diagnose PCOS.

METHOD

Unbiased factor group analyses to determine an objective PCOS phenotype

To identify features that define PCOS in an unbiased manner, we performed factor analyses using variables known to affect menstrual cycle length variability and/or related to PCOS.[36] Since the factor analysis algorithm does not require any preconception about what defines PCOS, we hypothesise that the clustering of features mathematically would provide an unprejudiced PCOS phenotype.

We used infrequent menstruation or oligomenorrhea as the underlying variable for factor analysis, as chronic anovulation and subfertility are the main concerns of patients with PCOS.[36] We did not utilise mid-luteal serum progesterone, as this variable is not routinely measured to detect the absence of ovulation given difficulty in predicting the mid-luteal phase in irregular menstrual cycles.[37] There is increasing appreciation that PCOS is not a binary all-or-none condition but represents a continuum of those with none, 1, 2 or more of the phenotypic features associated with PCOS, such as HA, oligo/amenorrhoea and PCOM.[38] We enrolled subjects attending an annual health screening at a tertiary hospital in Singapore. Known cases of PCOS were excluded since we wanted to have an unbiased identification of features that may cluster together.

RESULTS

We examined 23 lifestyle, physical, metabolic, pituitary, ovarian, estrogenic and androgenic

variables to identify key predictors of menstrual cycle length variability in healthy women.[36] Unsupervised factor analyses segregated the 23 potential predictors of menstrual cycle length into 7 factor groups with eigenvalues >1. Only 1 factor group was significantly associated with menstrual cycle length variability (P<0.001). This factor group (contributing 17.8% of total variance in the dataset) included 5 variables: 3 relating to the ovaries (i.e. ovarian volume, AFC, AMH), testosterone and LH as described in Table 2. Transvaginal ultrasound measurements were made using a Voluson E8 machine with 6–12 MHz transducer. Ovarian volume was derived via the formula for prolate ellipsoid volume (0.523 x length x height x width). The ultrasound was performed by the same operator to decrease the interoperator variability. Each follicle <10 mm from 2 to 10 mm was documented, and their size was measured in 3 dimensions. The 3D ovarian images were also stored for cross-checking.[17] The second factor group (contributing 13.3% of the variance) included the metabolic variables BMI, waist-to-hip ratio, insulin, glucose and triglycerides. Interestingly in this Singapore cohort, hirsutism defined by mFG scores was clustered with acne in the sixth factor group, contributing <8% of the total variance.

Our factor analyses identified ovarian variables (AMH, AFC, ovarian volume), serum testosterone and LH as the only significant cluster of variables affecting menstrual cycle length variability.[36] These findings are reminiscent of another principal component analysis wherein ovarian, androgenic parameters and LH segregate into a distinct principal component of control and PCOS patients.[39]

The abnormal secretion of LH has long been recognised as one being prevalent in PCOS. LH and LH/follicle-stimulating hormone ratio are currently used in the PCOS diagnostic criteria of the Japan Society of Obstetrics and Gynecology.[9] However, the measurement of LH is problematic because of the pulsatile nature of its secretion. It would therefore be prudent to have the ovarian variables, serum testosterone and menstrual cycle length as the key elements of a simplified PCOS diagnostic criterion, relevant to the Singapore and possibly other East Asian populations.

Ovarian variable measurement: The case for anti-Mullerian hormone (AMH)

Since factor analyses identified ovarian variables as a constituent of the "syndrome", a simplification of PCOM measurement should be a top consideration. Currently, the determination of PCOM requires transvaginal ultrasound examination which necessitates expert sonographic skills. This is time-consuming, may not be readily available in primary care setting, and cannot be performed in many patients due to discomfort from this intrusive process.[36] The advent of transvaginal ultrasound probes with higher resolution of >8 mHz increased the ovarian AFC threshold for PCOM to 19–26 antral follicles.[14,17] The above contribute to the complexity for the diagnosis of PCOM.

AMH is an important regulator of ovarian folliculogenesis and is intimately involved in the pathophysiology of PCOS.[42] AMH levels are closely associated with ovarian AFC.[43] AMH is 4-fold higher in women with AFC ≥25 compared to those with AFC <12 (Fig. 1). As such, there have been proposals to replace ovarian AFC by serum AMH levels to diagnose PCOM.[28-30] On the basis of the area under curve (AUC)-calculated cut-offs, the diagnostic cut-off values of AMH for PCOM have been proposed to be 20–30 pmol/L (AUC: 0.67–0.92) in adults and 50 pmol/L (AUC: 0.87) in adolescents.[45] AMH thresholds above 35 pmol/L (4.9 ng/mL), as a surrogate for PCOM, have also been proposed for other populations.[43]

Our studies in Singaporean women suggest that an AMH level ≥37.0 pmol/L best predicted PCOM.[17] A cut-off value of ≥37.0 pmol/L for AMH has a receiver operating curve (ROC) of 80.9% (95% confidence interval [CI] 73.0–88.7), sensitivity of 79.2% and specificity of 82.6% to predict PCOM, defined by AFC ≥22 and/or ovarian volume of ≥8.4 mL in either ovary. Cases defined by AMH >37 would result in 94% of PCOS cases overlapping with those defined with the transvaginal ultrasound measurement of PCOM with the current Rotterdam 2003 diagnostic criteria.[17,46] The adoption of AMH would result in most of the current PCOS cases to still have the diagnosis of PCOS, without the discomfort and the cost of transvaginal ultrasound. The universal standardisation of AMH assays would improve its utilisation in the diagnosis of PCOS and making AMH part of the diagnostic criteria in the future.[47]

Hirsutism assessment: the problem of ethnic differences

Androgen excess is determined clinically by mFG score, in the NIH 1990, Rotterdam 2003 and AE-PCOS 2009 criteria. Nine body areas, namely, the upper lip, chin, chest, upper back, lower back, upper and lower abdomen, upper arm and thigh, are assigned a score of 0–4 based on the density of terminal hairs.[48] A score of 0 represents the absence of terminal hairs, a score of 1 minimally evident terminal hair growth and a score of 4

Table 2. Factor group analysis of 23 variables from subjects (n=200) participating in an annual health screen offered to all employees of a large university hospital.[32]

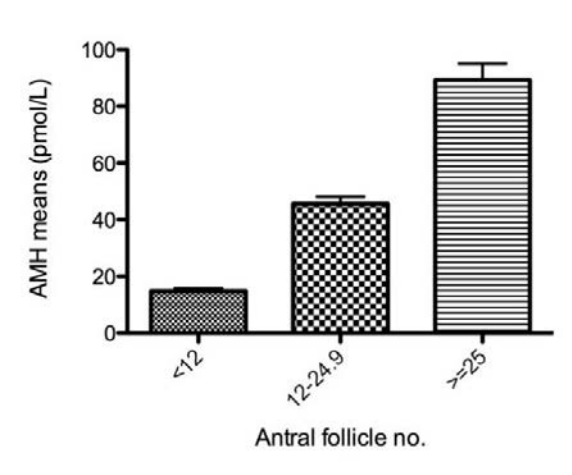
	MENSTRUAL CYCLE IRREGULARITY						
	Factor groups						
	1b	2	3	4	5	6	7
Ovarian Variables:							
Ovarian Volume	0.751						
AFC	0.882						
AMH	0.836						
Metabolic Variables:							
BMI		0.736					
WHR		0.673					
Insulin		0.749					
Glucose		0.561					
Cholesterol				0.958			
Triglycerides		0.401					0.594
HDL					0.588		
LDL				0.909			
Androgen Variables:							
DHEAS			0.682				
Androstenedione				0.522			
Testosterone	0.596						
DHT			0.869				
SHBG			-0.41		0.44		
mFG						0.412	
Acne score						0.584	
Estrogen Variables:							
Estrone			0.829				
Estradiol					0.805		
Pituitary Variables:							
PRL						0.612	
LH	0.716						0.448
FSH							0.654

[a] Factor groups with eigenvalues >1 were listed. Only variables with factor loadings >0.4 were included.
[b] Only factor group 1 was associated with menstrual cycle length variability (P<0.001).
AFC: antral follicle count; AMH: anti-Mullerian hormone; BMI: body mass index; DHEAS: dehydroepiandrosterone-sulfate; DHT: dihydrotestosterone; FSH: follicle-stimulating hormone; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LH: luteinising hormone; mFG: modified Ferriman-Gallwey score; SHBG: sex hormone binding globulin; WHR: waist-to-hip ratio

terminal hair growth equivalent to a hairy man. Hair growth on the forearms and legs are relatively less responsive to androgens and hence not part of mFG scoring. Hirsutism in women is defined conventionally as mFG scores ≥8, present in <5% of Caucasian populations.[48]

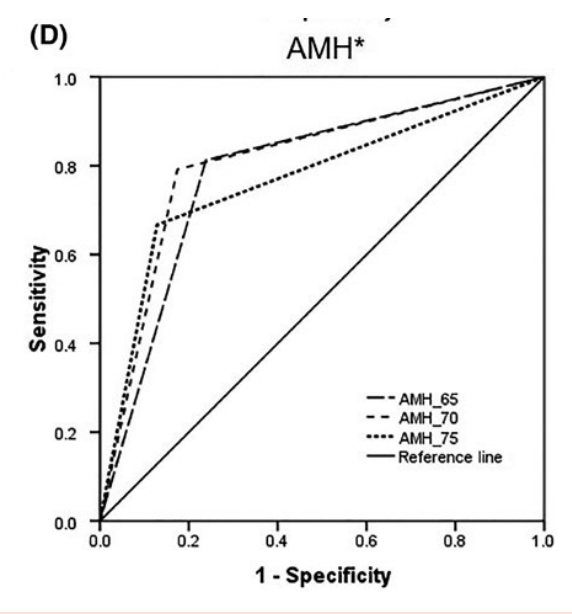
Presence of body hair is second only to skin colour as a feature of racial differences, and the prevalence of hirsutism varies widely according to ethnicity in normal populations.[48-50] Hirsutism is lowest in Han Chinese (0%) and highest in Mediterranean countries and South Asians (32–36%) populations (Fig. 3). Taking the >95th percentile of the mFG score as the threshold, mFG cut-offs for hirsutism would vary between ≥2–3 for Chinese and Thai populations, to ≥10–11 for Middle Eastern and Hispanic populations (Table 3).[51] In Singapore, the 95% percentile for healthy women in an annual health screen (excluding women with PCOS) was 4.4 (Fig. 4). Hence, hirsutism is determined to be mFG score ≥5 among Singaporean women, similar to that of

Fig. 1. Relationship between serum anti-Mullerian hormone levels and ovarian antral follicle counts.[36]



Data are mean ± standard error of means.
AMH: anti-Mullerian hormone

Fig. 2. Receiver operating characteristic curves for anti-Mullerian hormone (AMH) to predict PCOM (antral follicle count ≥21.5 and/or ovarian volume ≥8.44 ml in either ovary).[17]



AMH: anti-Mullerian hormone

a Southern Chinese population.[52]

The different cut-offs make the determination of hirsutism very confusing for practitioners. Assessing hirsutism by mFG scoring is intrusive and invades the privacy of patients, although this can be ameliorated by limiting the examination to facial and abdominal regions.[31] Coupled with the fact that the mFG score is not a significant variable with respect to menstrual irregularity in cluster analysis (Table 2), it justifies the removal of hirsutism as a criterion for the definition of PCOS in the Singapore population. In this scenario, hirsutism would be an associated clinical feature of PCOS, like obesity and insulin resistance. Therefore, androgen excess would only be defined by raised serum levels of androgens, which has already been adopted in the Japanese definition of PCOS.[8]

Simplified PCOS diagnostic criteria (version 2023)

We therefore propose simplified criteria to diagnose PCOS.[17] The criteria would need to be straightforward so that practitioners, patients and researchers can easily recall the definition. The criteria should include clinical and biochemical features with objectively defined thresholds that are evidence-based with minimal variability in normal, healthy and ethnic-specific populations. Ideally, the revised definition needs to be consistent with historical usage and encompass almost all patients identified with PCOS currently for the continuity of care and consistency in research findings, including women with known PCOS.

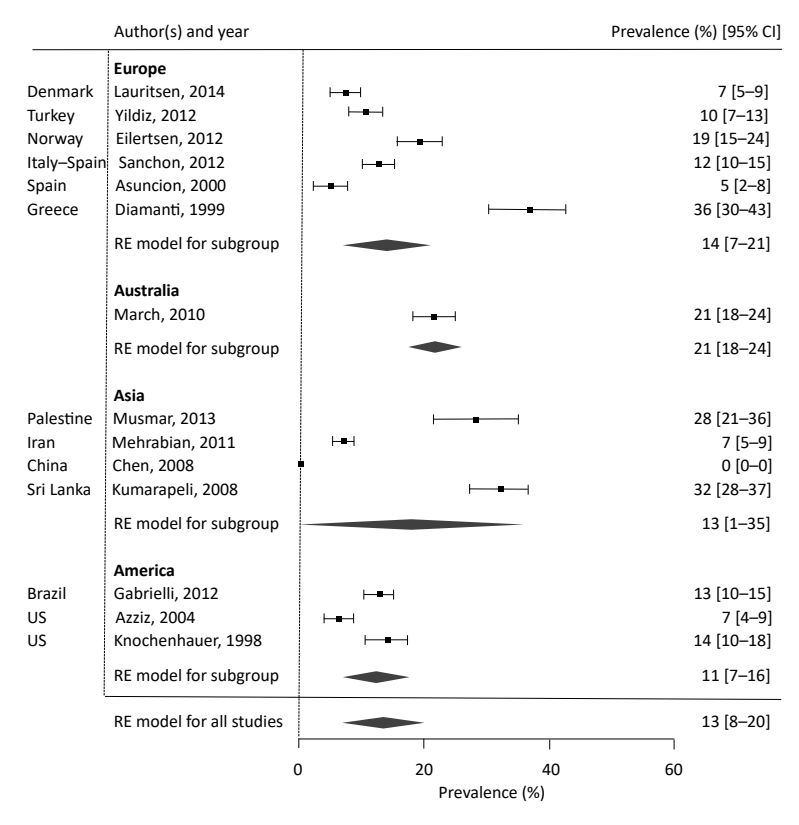
We propose the following simplified criteria. In our proposed simplified criteria, the presence of at least 2 of the 3 features below would be sufficient to define PCOS[17]: (1) Length of menstrual cycle: Chronic oligo-ovulation or anovulation as indicated by oligomenorrhea (cycle lengths >35 days) or amenorrhea; (2) PCOM with raised AMH ≥37.0 pmol/L; and (3) Androgen excess, or raised serum androgens (i.e. testosterone) above the laboratory reference for women.

Limitations of the simplified PCOS diagnostic criteria (version 2023)

This proposal for revised criteria needs to be interpreted in context, as our proposed criteria are based on studies done in Singapore. Although the cases were recruited from the 2 major tertiary referral hospitals on our island nation, our findings may not be directly applicable to other populations.

There should be standardisation in the measurement of AMH, as different test kits are currently used. The 95th percentile of controls without PCOM was 4.2 ng/mL (30 pmol/L) with automatic assays and 5.6 ng/mL (40 pmol/L) with manual assays.[53] The performance of the different AMH assays for PCOS diagnosis was comparable, and different threshold values may need to be used for manual and automatic assays.[53] Newer automated assay systems, such as the VIDAS and Elecsys-AMH, appear comparable in terms of technical performance for clinical use.[53] The upper threshold of serum AMH levels needs to be validated worldwide in populations of various

Fig. 3. Prevalence of hirsutism vary widely among unselected women in different populations.



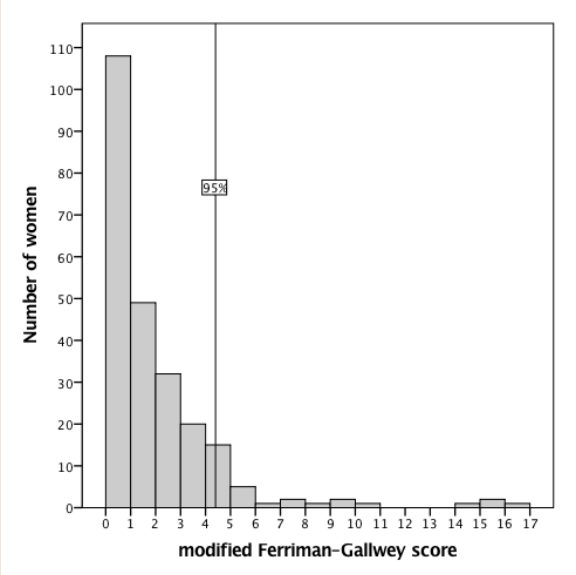
Note: Modified from Bozdag et al. (2016)[50]
RE: random-effects (models for indicated subgroups)

Table 3. Suggested cut-offs for the mFG hirsutism score according to the 95th percentile in different unselected populations of premenopausal women.

Author, year	Year	Country	Race	Ethnicity	Sample size	Suggested mFG cut-offa
Tellez and Frenkel (1995)	1995	Chile	White	Hispanic	236	≥6
Asuncion et al. (2000)	2000	Spain	White	Mediterranean	154	≥8
Sagsoz et al. (2004)	2004	Turkey	White	Middle Eastern	204	≥9
Cheewadhanaraks et al. (2004)	2004	Thailand	Asian	Thai and Chinese	531	≥3
DeUgarte et al. (2006)	2006	USA	White	Caucasian and Hispanic	283	≥8
			Black	African-American	350	≥8
Zhao et al. (2007)	2007	China	Asian	Chinese Han	623	≥2
Api et al. (2009)	2009	Turkey	White	Middle Eastern	121	≥11
Moran et al. (2010)	2010	Mexico	White	Hispanic	150	≥10
Noorbala and Kefaie (2010)	2010	Iran	White	Middle Eastern	900	≥10
Kim et al. (2011)	2011	Korea	Asian	Chinese	1010	≥6
Gambineri (2011, personal communication)	2011	Italy	White	Mediterranean	200	≥9
Escobar-Morreale (2011, personal communication)	2011	Spain	White	Mediterranean	291	≥10

Note: Modified from Escobar-Morreale HF et al. (2012)[50]
[a]As defined by the 95th percentile of an unselected population of premenopausal women.
mFG: modified Ferriman–Gallwey score

Fig. 4. Distribution of modified Ferriman–Gallwey score in women without PCOS (n=153) in the National University Hospital annual health screen for staff.



Vertical line represents 95% percentile cut-off with mFG score of 4.4

ethnicities. AMH can vary according to age, and BMI and relevant adjustments have to be made.[54-56] It is relevant to note that these limitations apply to AFC and serum testosterone as well.

The prevalence of hirsutism in the Singapore population is relatively low, and studies need to be replicated in other populations where the prevalence of hirsutism is higher to see whether the clustering of features defining PCOS is consistent with our proposed revised criteria.

CONCLUSION

There have been considerable advances in our knowledge of the pathophysiology, epidemiology and diagnostic tools of PCOS since currently used diagnostic criteria were first proposed over 2 decades ago. Despite an extensive 2018 review,[19] there remain many challenges to understanding the diagnosis and treatment of PCOS. Evidence suggests that clinicians and consumers are not satisfied with the timeliness of diagnosis and treatment options. Although some women benefit considerably from a diagnosis of PCOS, including the metabolic and mental health consequences through increased awareness and reassurance, many women with minimal symptoms may experience more harm than benefit, including long-lasting anxiety and altered life plans.[57] Special attention to diagnosis at the ends of the reproductive spectrum are still needed, and the remaining areas of controversy need to be resolved.[58] There is a need to re-evaluate the clinical features of PCOS and establish an integrated and comprehensive evidence-based guideline for the diagnosis of PCOS. Unbiased factor analyses had identified PCOM and serum testosterone as significant features associated with menstrual cycle length variability.[17] We propose simplified criteria to diagnose PCOS.

Further studies are required to examine whether the adoption of the proposed criteria would enhance the diagnosis and management of women with PCOS as well as ameliorate mislabelling of women and allow medical practitioners to better care for them.

Disclosure

This paper was first presented on 9 October 2022 as part of the 100th anniversary celebration of the NUS Department of Obstetrics and Gynaecology at Raffles Convention Centre, Singapore.

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REVIEW ARTICLE

A systematic review and meta-analysis on the effect of goal-directed fluid therapy on postoperative outcomes in renal transplantation surgeries

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ABSTRACT

Introduction: This systematic review and meta-analysis investigated the impact of intraoperative goal-directed therapy (GDT) compared with conventional fluid therapy on postoperative outcomes in renal transplantation recipients, addressing this gap in current literature.

Method: A systematic search of patients aged ≥18 years who have undergone single-organ primary renal transplantations up to June 2022 in PubMed, Embase, Scopus and CINAHL Plus was performed. Primary outcome examined was postoperative renal function. Secondary outcomes assessed were mean arterial pressure at graft reperfusion, intraoperative fluid volume and other postoperative complications. Heterogeneity was tested using I^2 test. The study protocol was registered on PROSPERO.

Results: A total of 2459 studies were identified. Seven eligible studies on 607 patients were included. Subgroup assessments revealed potential renal protective benefits of GDT, with patients receiving cadaveric grafts showing lower serum creatinine on postoperative days 1 and 3, and patients monitored with arterial waveform analysis devices experiencing lower incidences of postoperative haemodialysis. Overall analysis found GDT resulted in lower incidence of tissue oedema (risk ratio [RR] 0.34, 95% CI 0.15–0.78, *P*=0.01) and respiratory complications (RR 0.39, 95% CI 0.17–0.90, *P*=0.03). However, quality of data was deemed low given inclusion of non-randomised studies, presence of heterogeneities and inconsistencies in defining outcomes measures.

Conclusion: While no definitive conclusions can be ascertained given current limitations, this review highlights potential benefits of using GDT in renal transplantation recipients. It prompts the need for further standardised studies to address limitations discussed in this review.

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Keywords: end-stage renal failure, goal-directed therapy, postoperative outcomes, renal transplantation, systematic review

CLINICAL IMPACT

What is New

- Goal-directed therapy (GDT) in renal transplantation surgeries may offer benefits in postoperative outcomes, including reduced incidence of tissue oedema and respiratory complications.
- GDT showed potential renal protective benefits, with lower early postoperative serum creatinine levels in cadaveric transplantations, and lowered postoperative haemodialysis incidences in patients monitored with arterial waveform analysis devices.

Clinical Implications

- This underscores the importance of considering fluid management strategies in renal transplantation surgeries.
- GDT's impact varies across patient groups and modalities, emphasising the necessity for tailored approaches.

INTRODUCTION

Renal transplantation is the superior treatment for chronic kidney disease patients, providing better survival outcomes and quality of life compared with other renal replacement therapies.[1] The recipient's intraoperative fluid management is crucial due to its impact on postoperative graft function, morbidity and mortality.[2-6] However, fluid management in such patients is challenging due to their impaired ability to maintain fluid balance, which increases the risk of complications such as fluid overload or depleted intravascular volume, leading to graft dysfunction post-transplantation.

The main intraoperative objective for renal transplantation recipients is to ensure sufficient

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graft perfusion. Traditionally, this is achieved through aggressive intraoperative volume expansion. Conventional methods involve maintaining targets for heart rate, blood pressure, central venous pressure (CVP) or urine output.[7,8] However, studies have demonstrated that these conventional fluid therapy protocols inaccurately assess fluid responsiveness and can lead to complications related to excessive fluid administration.[9-13]

Goal-directed therapy (GDT) is a protocol that optimises flow-related parameters like cardiac index, stroke volume index, stroke volume variation, stroke volume and pulse pressure variation. GDT dynamically monitors a patient's fluid responsiveness per the Frank-Starling curve. It individualises the amount and timing of fluid administration to avoid under- or over- resuscitation. GDT includes a spectrum of techniques like (1) transoesophageal echocardiogram, (2) pulmonary artery catheterisation, (3) arterial waveform analysis-based techniques (e.g. FloTrac and ClearSight, Edwards Lifesciences, Irvine, CA, US), (4) oesophageal Doppler monitoring and (5) bio-impedance-based technologies.[14]

Several studies have acknowledged potential benefits of GDT, including improved renal perfusion and mortality benefits.[15,16] However, benefits vary based on surgical settings.[17] Therefore, there is interest in studying the use of GDT in renal transplantation recipients due to the complexity of fluid management. It is crucial for practitioners to ensure adequate preload for end-organ tissue perfusion while avoiding complications related to aggressive fluid administration.[18,19]

However, current limited literature comparing GDT and conventional therapy in the context of renal transplantation has yielded mixed results, and ideal clinical goals for GDT remain uncertain.[20] This prompted our team to conduct a systematic review and meta-analysis to ascertain postoperative benefits of GDT protocols compared with conventional fluid therapy protocols.

METHOD

This review was prospectively registered and conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. The study protocol was registered in the international prospective register of systematic reviews.[21] Institutional review board approval was not required for this secondary analysis of previously published data.

The search strategy was formulated using the Population, Intervention, Control, Outcome and Study model, a recommended approach for systematic reviews designed to study clinical interventions. The primary selection criteria of our review are shown in Supplementary Table S1. Articles were regarded as potentially eligible if they met all criteria.

Population

Only adult end-stage renal failure patients aged ≥18 years, who have undergone their first single-organ renal transplantation were included. Paediatric patients and patients who have undergone multiple organ transplantation operations or secondary renal transplantation were excluded.

Intervention

The intervention group had to utilise goal-directed therapy, defined as intraoperative use of cardiac output monitoring and the manipulation of dynamic flow-related parameters using fluids alone or in combination with inotropes or vasopressors.

Control

The control group had to receive conventional fluid therapy, defined as the routine administration of fluids and/or inotropic drugs based on either a standard institutional-based fluid protocol or targeting non-flow-related haemodynamic parameters using fluids alone or in combination with inotropes or vasopressors.

Outcomes

The primary outcome examined in the eligible studies was postoperative renal function, encompassing all markers of renal function. Secondary outcomes assessed included mean arterial pressure at reperfusion, volume of intraoperative intravenous fluids administered, and the incidence of any non-renal postoperative complications. No limitations were imposed on the type of postoperative complications considered.

Study design

Only interventional studies were included with no restrictions imposed on setting, publication date or ethnic group. Only articles published in English were considered.

A systematic search for relevant articles was performed in PubMed, EMBASE, Scopus and CINAHL Plus from inception until June 2022. A logical construction of search strings, comprising both medical subject headings terms and free-text search terms, was created specific to each database as shown in Supplementary Table S2. Reference sections of all eligible studies were also searched for possible inclusion of additional studies.

Two independent reviewers screened the full-text articles that were retrieved. In case of disagreements in the choice of articles, a third and fourth

reviewer were consulted to reach a final consensus. The shortlisted full-text articles were approved by all the authors prior to the data extraction process. A data extraction table was used to include relevant preoperative information of the renal transplantation recipients, types of donor kidney, modality of fluid status optimisation and postoperative outcomes measured.

The risk of bias was assessed using the Cochrane Collaboration risk of bias tool, which considers selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. All outcomes were also assessed for publication bias with Egger's regression test, and a funnel plot was constructed and inspected for asymmetry.

Data analysis was performed using Review Manager (RevMan) [Computer Program], Version 5.4, The Cochrane Collaboration, 2020. Continuous data were presented as mean difference (MD) and its 95% confidence interval (CI). Dichotomous data were presented as risk ratio (RR) and 95% CI. The individual effect sizes were weighted per the reciprocal of their variance. If the standard deviation was not available for continuous outcomes, it was calculated as per the Cochrane Collaboration guidelines. Heterogeneity was examined using the I^2 test.

In determining the choice of statistical methods, the random effects model was chosen as the default model due to the intrinsic heterogeneity of the research question with expected sources from differences in immunotherapy regimens and recipient as well as donor graft characteristics. However, for outcomes with a minimal possibility of heterogeneity (i.e. I^2 test equating to zero), the fixed-effects model was employed. This decision was made to counteract the potential result inflation that could arise in random effects models when dealing with small studies.[22]

The meta-analysis results were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for certainty. The initial quality of evidence was considered moderate when a mix of randomised and non-randomised studies was included, and low when all studies were non-randomised. Further downgrading occurred if the I^2 value exceeded 40% or its *P* value was <0.1, indicating significant heterogeneity. Downgrading also took place in case of inconsistencies among studies (e.g. contradictory results or outcome definition variations) or when there was notable imprecision. No downgrading was necessary due to publication biases.[23]

Subgroup analyses were conducted based on the type of donor kidney received (living versus cadaveric), the modality of GDT (arterial waveform analysis technique versus oesophageal monitoring technique), and the methods of fluid optimisation (fluids alone versus fluids combined with inotropes and/or vasopressors) due to their influence on postoperative graft function. Chi-squared tests for heterogeneity were utilised to identify the distinctions between subgroups.

RESULTS

The study selection process is shown in Supplementary Fig. S1. There were 2459 unique publications identified from the databases; 2446 were excluded after screening through titles and abstracts. Full texts of the remaining 13 articles with titles and abstracts that met the inclusion criteria were retrieved. Thereafter, 6 articles were excluded as they either did not measure any postoperative renal outcomes, were non-interventional studies, included paediatric patients, or involved secondary renal transplantation or multi-organ transplantation surgery. The reference list of retrieved studies was screened through, but did not identify any additional articles. Seven articles were eventually included in the study.[24-30]

Table 1 presents the characteristics of the included studies, which were published between 2015 and 2022. The sample sizes ranged from 39 to 214 participants. Various fluid monitoring techniques were employed in both the GDT and conventional therapy groups. One study (Cassai et al.)[24] compared arterial waveform analysis technique to free fluid administration. Four studies (Cavaleri et al., Goyal et al., Kannan et al. and Zhang et al.) [25,27,28,30] compared arterial waveform analysis technique to maintaining CVP targets, either alone or in combination with systolic blood pressure and mean arterial pressure (MAP) targets. Two studies (Corbella et al. and Srivastava et al.) [26,29] compared oesophageal Doppler monitoring to maintaining CVP targets with or without a combination of systolic blood pressure and MAP targets. The type of donor kidney varied among the studies. Two studies (Goyal et al. and Srivastava et al.) received grafts from living donors. Two studies (Cassai et al. and Corbella et al.) received cadaveric grafts. Three studies (Cavaleri et al., Kannan et al. and Zhang et al.) did not specify the type of graft or included both living and cadaveric grafts in their patient selection. Furthermore, 3 studies (Cassai et al., Goyal et al. and Srivastava et al.) optimised targets using fluid therapy alone, while 4 studies (Cavaleri et al., Corbella et al., Kannan et al. and Zhang et al.) utilised a combination of fluid therapy and inotropes and/or vasopressors.

Table 1. Summary of characteristics and main outcomes of included studies.

Author (year)	RCT	Country	Type of donor kidney	GDT (n)	Control (n)	GDT protocol	Control protocol	Therapy method	Measure of postoperative renal function	Postoperative renal outcome	Intraoperative intravenous fluid	MAP at reperfusion	Other postoperative outcomes	Conclusion
Cassai et al. (2020)[24]	Yes	Italy	Cadaveric	19	20	Arterial waveform analysis: PPV <12%	Baseline 10 mL kg^{-1} h^{-1} infusion with one for one replacement for bleeding	Fluids	Dialysis within 1 week of transplant, serum biomarkers (urea, creatinine), urine output	GDT significantly reduced serum urea and creatinine levels. No statistical difference was found in urine output and incidence of dialysis.	GDT group used significantly less fluids.	Both groups were comparable.	No difference in incidences of patients with clinical and radiological signs of fluid overload requiring oxygen therapy, cumulative furosemide dose or total length of stay.	GDT is as adequate a strategy as liberal fluid management and may reduce incidences of fluid overload.
Cavaleri et al. (2019)[25]	No	Italy	Unknown	33	33	Arterial waveform analysis: SVI <10% of optimal SV	CVP 8–12 mmHg MAP ≥80 mmHg	Fluids and vasoactive agents	Dialysis within 1 week of transplant; serum biomarkers (creatinine, blood urea nitrogen, potassium); urine output	GDT significantly reduced serum creatinine level and incidence of dialysis. No statistical difference in serum biomarkers or urine output.	GDT group used less fluids but not statistically significant.	Both groups were comparable.	GDT group had statistically fewer acute coronary syndromes in first postoperative week, lower rate of ileus in first 72h post-transplant. No difference in respiratory distress syndrome, pneumonia, acute pulmonary oedema, congestive cardiac failure or 30-day morbidity.	GDT may be renal protective and may reduce postoperative morbidity.

Table 1. Summary of characteristics and main outcomes of included studies. (Cont'd)

Author (year)	RCT	Country	Type of donor kidney	GDT (n)	Control (n)	GDT protocol	Control protocol	Therapy method	Measure of postoperative renal function	Postoperative renal outcome	Intraoperative intravenous fluid	MAP at reperfusion	Other postoperative outcomes	Conclusion
Corbella et al. (2018)[26]	Yes	Canada	Cadaveric	26	24	Oesophageal Doppler monitoring: SV >75% baseline	CVP 12–15 mmHg Systolic blood pressure >100 mmHg	Fluids and inotropes	Dialysis within 1 week of transplant; serum biomarkers (creatinine)	No difference between groups in all measures.	GDT group used more fluids but not statistically significant.	Not mentioned.	GDT group had statistically more incidences of cardiac events that included new onset arrhythmia, myocardial infarction, pulmonary embolism, cardiogenic pulmonary oedema and cardiac arrest. No difference in length of stay and other complications (respiratory, infectious, neurological).	Further trials are required to determine the benefits of GDT.
Goyal et al. (2022)[27]	Yes	India	Living	35	40	Arterial waveform analysis: PPV <10–13%	CVP >15 mmHg	Fluids	Dialysis within 1 week of transplant; serum biomarkers (creatinine); urine output	No difference between groups in all measures.	GDT group used less fluids but not statistically significant.	Both groups were comparable.	GDT group had statistically less incidences of tissue oedema (swelling on eyelid, face and feet). No difference in incidences of mechanical ventilation, postoperative nausea and vomiting, pulmonary oedema and postoperative serum lactate levels.	GDT may be renal protective and may reduce postoperative morbidity.

Table 1. Summary of characteristics and main outcomes of included studies. (Cont'd)

Author (year)	RCT	Country	Type of donor kidney	GDT (n)	Control (n)	GDT protocol	Control protocol	Therapy method	Measure of postoperative renal function	Postoperative renal outcome	Intraoperative intravenous fluid	MAP at reperfusion	Other postoperative outcomes	Conclusion
Kannan et al. (2022)[28]	Yes	India	Mixed	35	35	Arterial waveform analysis: PPV <9%	CVP 5 mmHg until the clamping of donor renal vessels; CVP 12–15 mmHg at reperfusion	Fluids and vasoactive agents	Dialysis within 1 week of transplant; serum biomarkers (urea, creatinine, rate of creatinine reduction); urine output	No difference between groups in all measures.	GDT group used significantly less fluids.	Both groups were comparable.	No difference in serum lactate levels; and no difference in tissue oedema or need for mechanical ventilation between the groups.	GDT reduces total intraoperative fluids used but further studies are required to determine benefits of postoperative morbidity.
Srivastava et al. (2015)[29]	No	India	Living	110	104	Oesophageal Doppler monitoring: flow time corrected >350 ms	CVP >15 mmHg	Fluids	Dialysis within 1 week of transplant; serum biomarkers (creatinine); urine output	No difference between groups in all measures.	GDT group used significantly less fluids.	Both groups were comparable.	GDT group had statistically less need for postoperative supplemental oxygen, and incidence of postoperative visual oedema. No difference in postoperative mechanical ventilation.	GDT may be beneficial in reducing fluid overload complications.
Zhang et al. (2021)[30]	No	China	Unknown	49	48	Arterial waveform analysis: SVV <10%	CVP 6–9 mmHg MAP ±20% of basal value and >90 mmHg	Fluids and vasoactive agents	Dialysis within 1 week of transplant; serum biomarkers (creatinine, blood urea nitrogen, creatinine clearance rate); urine output	GDT group had significantly lower serum creatinine level and incidence of dialysis but no statistical difference in serum biomarkers or urine output.	GDT group used significantly less fluids.	Both groups were comparable.	No difference in pulmonary oedema, respiratory failure or heart failure.	GDT can reduce intraoperative fluid infusion, and has benefits in postoperative renal outcomes.

CVP: central venous pressure; GDT: goal-directed therapy; MAP: mean arterial pressure; PPV: pulse pressure variation; RCT: randomised controlled trial; SV: stroke volume; SVI: stroke volume index; SVV: stroke volume variation
Superscript numbers: refer to REFERENCES

Included studies had at least 1 potential source of bias (Supplementary Table S3). Three of 7 studies (Cassai et al., Corbella et al. and Kannan et al.) had appropriate methods of randomisation with concealed allocation. However, blinding of the outcome assessors was unclear in all studies. Lack of standardisation of primary outcomes and measures of outcomes across all studies led to risk of detection bias and confounding. Risk of detection bias was further increased with the use of subjective measures such as visual assessment of tissue oedema. No significant intercepts were found in the Egger's regressions, and there were no outlier studies identified upon visual inspection of the funnel plots, indicating no publication bias.

The results of the meta-analyses and the GRADE ratings are shown in Table 2. Forest plots of incidences of postoperative haemodialysis, tissue oedema and respiratory complications are shown in Fig. 1.

Table 2. Effect of intraoperative fluid protocols on postoperative outcomes in adult renal transplantation recipients. Summary of the meta-analyses with GRADE rating of evidence.

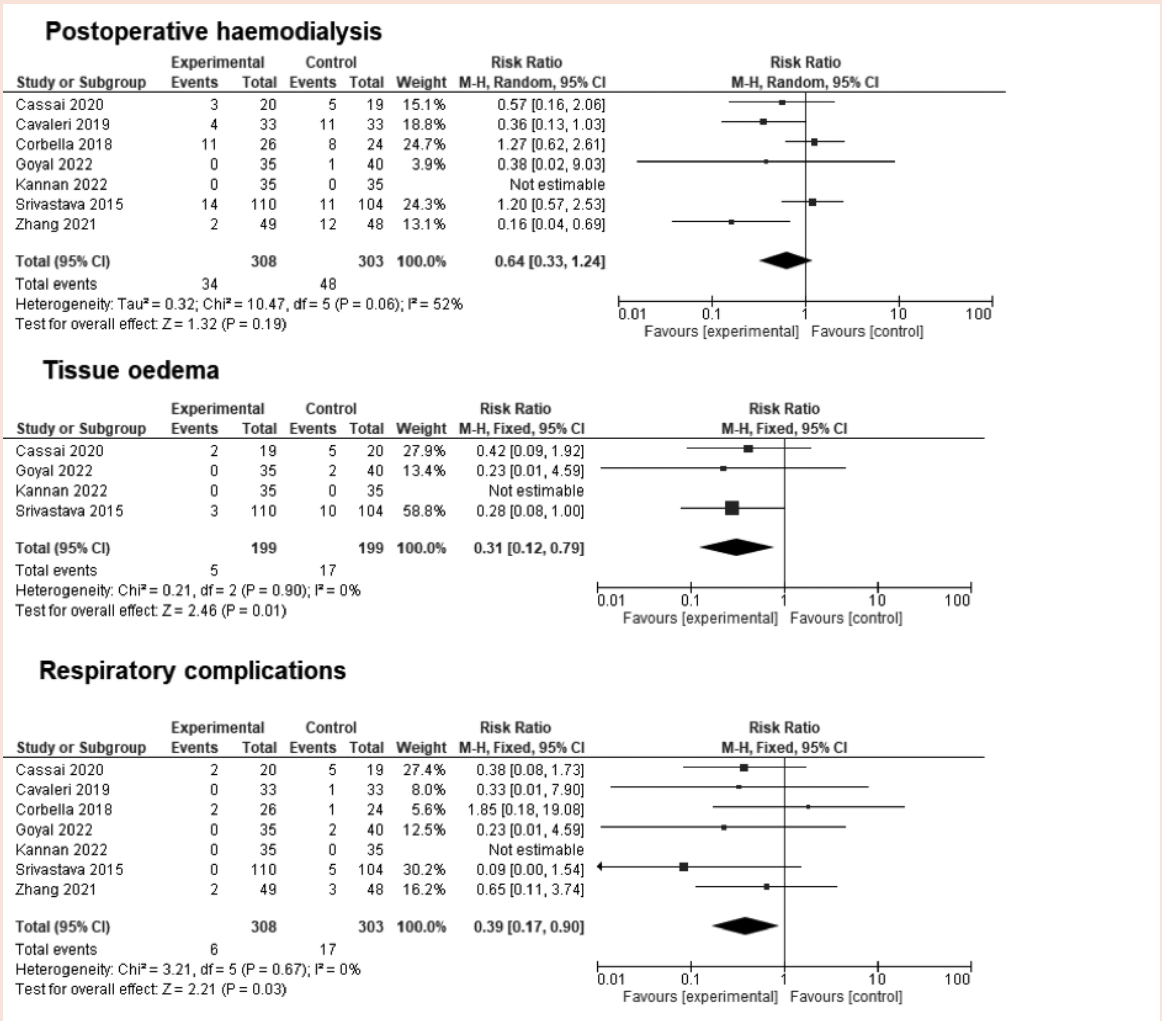
Outcome variable	No. of studies	No. of subjects		MD or RR (95% CI)	*P* value	I^2 [b] (*P* value)	Random or fixed effects	Quality of evidence (GRADE)
		GDT	Control[a]					
Postoperative haemodialysis	7	308	303	RR = 0.64 (0.33 to 1.24)	0.19	52% (*P* = 0.06)	Random	Low
POD 0 urine output, L	3	194	187	MD = -0.05 (-0.30 to 0.19)	0.66	0% (*P* = 0.93)	Fixed	Moderate
POD 1 urine output, L	5	247	240	MD = 0.03 (-0.32 to 0.37)	0.88	36% (*P* = 0.18)	Random	Moderate
POD 3 urine output, L	3	192	185	MD = 0.15 (-0.28 to 0.58)	0.50	78% (*P* = 0.01)	Random	Very Low
POD 7 urine output, L	2	143	137	MD = 0.39 (-0.18 to 0.96)	0.18	69% (*P* = 0.08)	Random	Very Low
POD 0 serum creatinine, mg.dL^{-1}	6	275	271	MD = -0.29 (-0.67 to 0.09)	0.13	0% (*P* = 0.85)	Fixed	Moderate
POD 1 serum creatinine, mg.dL^{-1}	7	308	304	MD = -0.27 (-0.91 to 0.38)	0.42	72% (*P* = 0.002)	Random	Low
POD 3 serum creatinine, mg.dL^{-1}	6	273	269	MD = -0.28 (-0.88 to 0.32)	0.37	58% (*P* = 0.04)	Random	Low
POD 7 serum creatinine, mg.dL^{-1}	6	273	269	MD = -0.38 (-0.85 to 0.09)	0.11	49% (*P* = 0.08)	Random	Low
POD 0 serum urea, mmol.L^{-1}	2	84	83	MD = -1.29 (-3.83 to 1.26)	0.32	0% (*P* = 0.39)	Fixed	Moderate
POD 1 serum urea, mmol.L^{-1}	4	137	136	MD = -1.01 (-3.26 to 1.23)	0.38	0% (*P* = 0.61)	Fixed	Moderate
POD 3 serum urea, mmol.L^{-1}	3	102	101	MD = -1.95 (-6.12 to 2.21)	0.36	44% (*P* = 0.17)	Random	Low
POD 7 serum urea, mmol.L^{-1}	2	53	53	MD = -2.55 (-12.43 to 7.34)	0.61	68% (*P* = 0.08)	Random	Low
Tissue oedema[c]	4	199	199	RR = 0.31 (0.12 to 0.79)	0.01	0% (*P* = 0.90)	Fixed	Low
Respiratory complications[d]	7	308	303	RR = 0.39 (0.17 to 0.90)	0.03	0% (*P* = 0.67)	Fixed	Low
Cardiovascular complications[e]	2	59	57	RR = 1.03 (0.02 to 49.30)	0.99	86% (*P* = 0.007)	Random	Very Low
Serum lactate, mmol.L^{-1}	2	70	75	MD = 4.90 (-5.30 to 15.10)	0.35	100% (*P* <0.00001)	Random	Low
Length of stay, days	3	94	92	MD = -0.14 (-0.34 to 0.06)	0.17	0% (*P* = 0.99)	Fixed	Low

Table 2. Effect of intraoperative fluid protocols on postoperative outcomes in adult renal transplantation recipients. Summary of the meta-analyses with GRADE rating of evidence. (Cont'd)

Outcome variable	No. of studies	No. of subjects		MD or RR (95% CI)	*P* value	$I^{2\,b}$ (*P* value)	Random or fixed effects	Quality of evidence (GRADE)
		GDT	Control[a]					
Intraoperative MAP at reperfusion, mmHg	6	248	242	MD = -0.33 (-1.8 to 1.17)	0.67	32% (P = 0.20)	Random	Low

CI: confidence interval; GDT: goal-directed therapy; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MAP: mean arterial pressure; MD: mean difference; POD: postoperative day; RR: risk ratio
[a] Routine administration of fluids and/or inotropic drugs based on either a standard institutional-based fluid protocol or targeting non-flow-related haemodynamic parameters.
[b] Heterogeneity coefficient >40% was considered significant.
[c] Clinical and/or radiological signs of excessive fluid accumulation.
[d] Need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure.
[e] New-onset arrhythmia, myocardial infarction, pulmonary embolism, cardiogenic pulmonary oedema or cardiac arrest.
Population: adult (age ≥18 years) end-stage renal failure patients undergoing first single-organ renal transplantation surgery.
Intervention: GDT protocols.
Control: conventional fluid therapy protocols.
Values in bold are statistically significant.

Fig. 1. Forest plots of meta-analyses performed for incidences of postoperative haemodialysis, tissue oedema and respiratory complications. No statistical difference in overall incidences of postoperative haemodialysis (risk ratio [RR] 0.64, 95% confidence interval [CI] 0.33–1.24, *P*=0.19). However, lower incidences of postoperative tissue oedema and respiratory complications were found in the GDT group (RR 0.31, 95% CI 0.12–0.79, *P*=0.01 and RR 0.39, 95% CI 0.17–0.90, *P*=0.03, respectively).



M-H: Mantel-Haenszel test

The overall data analysis indicated no statistically significant difference in the primary outcome of postoperative renal indices. Incidence of postoperative haemodialysis within the first week of transplantation was reported in all 7 studies. There was no statistical difference between GDT versus conventional protocols (*P*=0.19). Other postoperative renal markers, such as urine output, serum creatinine and serum urea, also showed no significant difference in the first 7 postoperative days (all *P*>0.05).

Four studies (Cassai et al., Goyal et al., Kannan et al. and Srivastava et al.) measured incidences of postoperative tissue oedema, defined as clinical and/or radiological signs of excessive fluid accumulation. The likelihood of postoperative tissue oedema was significantly lower in the GDT group compared with the conventional group (RR 0.31, 95% CI 0.12–0.79, *P*=0.01). All 7 studies reported respiratory complications, which included the need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure. Patients in the GDT group were less likely to have respiratory complications than their counterparts in the conventional group (RR 0.39, 95% CI 0.1–0.90, *P*=0.03).

In all 7 studies, the total amount of intraoperative fluids used was reported, and no statistically significant difference was found between GDT and conventional protocols (*P*=0.25). Six studies reported intraoperative MAP at reperfusion.[24,25,27,28-30] There was no statistical difference between GDT versus conventional protocols (*P*=0.67).

Other secondary outcomes that were described in the original studies also yielded insignificant results. Two studies (Cavaleri et al. and Corbella et al.) analysed incidences of cardiovascular complications, which included new onset arrhythmia, myocardial infarction, pulmonary embolism, cardiogenic pulmonary oedema, or cardiac arrest. Pooled estimates of these found no difference in such cardiovascular complications (*P*=0.99). Two studies (Kannan et al. and Goyal et al.) analysed postoperative serum lactate and found no statistical difference between groups (*P*=0.35). Three studies (Cassai et al., Corbella et al. and Zhang et al.) compared length of stay between intervention and control groups, and found no statistical difference as well (*P*=0.17).

Subgroup analyses were conducted to compare outcomes between patients who received kidney grafts from cadaveric donors and those from living donors. Results are presented in Table 3. Subgroup results revealed that among patients with cadaveric donor kidneys, the use of GDT protocols was linked to lower serum creatinine levels on postoperative days 1 and 3 (MD -1.59 $mg.dL^{-1}$, 95% CI -2.82 to -0.37, *P*= 0.01 and MD -1.57 $mg.dL^{-1}$, 95% CI -3.08 to -0.07, *P*=0.04, respectively; X^2=5.62, *P*=0.02 and X^2=4.17, *P*=0.04, respectively). However, no such association was found among patients who received kidneys from living donors on postoperative day 0 (X^2=1.14, *P*=0.29) and day 7 (X^2=2.83, *P*=0.09). This subgroup analysis did not find any differences in other studied outcomes, including the postoperative incidence of haemodialysis, tissue oedema, respiratory complications and urine output on postoperative day 1.

Subgroup analyses were also conducted to compare outcomes between patients who were treated with fluid therapy alone versus a combination of fluids and vasoactive and/or inotropic agents. These results are presented in Table 4. There was no statistical difference in the outcomes studied, which included incidence of postoperative haemodialysis, volume of intraoperative fluids used, and MAP at reperfusion.

The results of the subgroup analysis comparing oesophageal Doppler monitoring with arterial waveform analysis are presented in Table 5. Arterial waveform analysis was associated with a lower likelihood of postoperative haemodialysis compared with conventional monitoring (RR 0.35, 95% CI 0.17–0.69, *P*=0.002. X^2=8.43, *P*=0.004). No such difference in postoperative haemodialysis was observed in the oesophageal Doppler monitoring group compared to the conventional monitoring group (*P*=0.42). Oesophageal Doppler monitoring led to significantly higher urine output on postoperative day 3 compared with conventional fluid therapy (MD 0.49 L, 95% CI 0.26–0.72, *P*<0.0001). However, there was no significant difference in urine output between arterial waveform analysis and conventional therapy (*P*=0.82). Patients monitored by arterial waveform analysis received less intraoperative fluids than the control group (MD -324.44 mL, 95% CI -567.61 to -81.28, *P*<0.009). However, the overall subgroup difference was not significant (X^2=0.36, *P*=0.55). No statistical subgroup differences were found in other analysed outcomes, including postoperative incidence of tissue oedema, respiratory complications and serum creatinine levels.

DISCUSSION

Limited published literature exists on the use of GDT in renal transplantation surgeries. Previous studies in non-renal surgeries have demonstrated positive postoperative outcomes with GDT, but they varied in patient populations, protocols, monitoring devices and outcome measures.[31-40]

Table 3. Results of subgroup analysis between living and cadaveric donors.

	Living donor					Cadaveric donor					
Outcomes[a]	**No. of studies**	**GDT (no. of subjects)**	**Control (no. of subjects)**	**MD or RR (95% CI)**	***P* value**	**No. of studies**	**GDT (no. of subjects)**	**Control (no. of subjects)**	**MD or RR (95% CI)**	***P* value**	**Subgroup analysis**
Postoperative haemodialysis	2	145	144	RR 1.13 (0.55 to 2.34)	0.73	2	46	43	RR 1.02 (0.50 to 2.06)	0.96	$X^2 = 0.04$ $P = 0.84$
Tissue oedema[b]	2	145	144	RR 0.27 (0.09 to 0.88)	**0.03**	1	19	20	RR 0.42 (0.09 to 1.92)	0.26	$X^2 = 0.19$ $P = 0.66$
Respiratory complications[c]	2	145	144	RR 0.14 (0.02 to 1.10)	0.06	1	26	24	RR 1.85 (0.18 to 19.08)	0.61	$X^2 = 2.65$ $P = 0.10$
POD serum creatinine, mg.dL^{-1}	2	145	144	MD -0.09 (-0.60 to 0.42)	0.73	2	45	44	MD -0.85 (-2.13 to 0.44)	0.20	$X^2 = 1.14$ $P = 0.29$
POD 1 serum creatinine, mg.dL^{-1}	2	145	144	MD -0.05 (-0.40 to 0.30)	0.78	2	45	44	MD -1.59 (-2.82 to -0.37)	**0.01**	$X^2 = 5.63$ $P = \mathbf{0.02}$
POD 3 serum creatinine, mg.dL^{-1}	2	145	144	MD 0.02 (-0.22 to 0.25)	0.88	2	45	44	MD -1.57 (-3.08 to -0.07)	**0.04**	$X^2 = 4.17$ $P = \mathbf{0.04}$
POD 7 serum creatinine, mg.dL^{-1}	2	145	144	MD 0.02 (-0.24 to 0.27)	0.90	2	45	44	MD -1.21 (-2.61 to 0.19)	0.09	$X^2 = 2.82$ $P = 0.09$
POD 1 urine output, L	1	110	104	MD 0.25 (-0.18 to 0.68)	0.26	1	19	20	MD 0.57 (-0.62 to 1.76)	0.35	$X^2 = 0.25$ $P = 0.62$

CI: confidence interval; MD: mean difference; POD: postoperative day; RR: risk ratio

[a] Random-effect for all analyses.

[b] Clinical and/or radiological signs of excessive fluid accumulation.

[c] Need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure.

Values in bold are statistically significant.

Table 4. Results of subgroup analysis between optimisation of cardiac output using fluids alone versus fluid and inotropes.[a]

	Fluid alone					Fluid and inotropes					
Outcomes[b]	**No. of studies**	**GDT (no. of subjects)**	**Control (no. of subjects)**	**MD or RR (95% CI)**	***P* value**	**No. of studies**	**GDT (no. of subjects)**	**Control (no. of subjects)**	**MD or RR (95% CI)**	***P* value**	**Subgroup analysis**
Postoperative haemodialysis	2	55	59	RR 0.47 (0.11 to 1.95)	0.30	4	143	140	RR 0.45 (0.13 to 1.54)	0.20	$X^2 = 0.00$ $P = 0.98$
Intraoperative fluids, mL	3	164	164	MD -1286.72 (-3515.43 to 941.98)	0.26	4	143	140	MD -183.97 (-553.68 to 185.73)	0.33	$X^2 = 0.92$ $P = 0.34$
Intraoperative MAP reperfusion, mmHg	3	164	159	MD -1.47 (-3.75 to 0.82)	0.21	2	84	83	MD -1.57 (-4.09 to 0.94)	0.22	$X^2 = 0.00$ $P = 0.95$

CI: confidence interval; MAP: mean arterial pressure; MD: mean difference; RR: risk ratio
[a] No statistical differences were found in outcomes.
[b] Random-effect for all analyses.

Table 5. Results of subgroup analysis between monitoring using oesophageal Doppler monitoring versus arterial waveform analysis.[a]

	Arterial waveform analysis					Oesophageal Doppler monitoring					
Outcomes[b]	**No. of studies**	**GDT (no. of subjects)**	**Control (no. of subjects)**	**MD or RR (95% CI)**	***P* value**	**No. of studies**	**GDT (no. of subjects)**	**Control (no. of subjects)**	**MD or RR (95% CI)**	***P* value**	**Subgroup analysis**
Postoperative haemodialysis	5	172	175	RR 0.35 (0.17 to 0.69)	0.002	2	136	128	RR 1.24 (0.74 to 2.08)	0.42	$X^2 = 8.43$ $P = 0.004$
Tissue oedema[c]	3	87	93	RR 0.31 (0.08 to 1.26)	0.10	1	110	104	RR 0.26 (0.07 to 0.99)	0.05	$X^2 = 0.03$ $P = 0.86$
Respiratory complications[d]	3	117	121	RR 0.45 (0.11 to 1.84)	0.26	2	136	128	RR 0.43 (0.02 to 10.41)	0.61	$X^2 = 0.00$ $P = 0.99$
POD 0 serum creatinine, mg.dL^{-1}	4	138	143	MD -0.41 (-0.88 to 0.06)	0.08	2	136	128	MD -0.06 (-0.71 to 0.59)	0.86	$X^2 = 0.74$ $P = 0.39$
POD 1 serum creatinine, mg.dL^{-1}	5	171	176	MD -0.24 (-1.16 to 0.68)	0.61	2	136	128	MD -0.33 (-1.32 to 0.65)	0.51	$X^2 = 0.02$ $P = 0.89$
POD 3 serum creatinine, mg.dL^{-1}	4	136	141	MD -0.42 (-1.50 to 0.65)	0.44	2	136	128	MD -0.17 (-0.86 to 0.53)	0.64	$X^2 = 0.15$ $P = 0.70$
POD 7 serum creatinine, mg.dL^{-1}	4	136	141	MD -0.64 (-1.40 to 0.11)	0.09	2	136	128	MD -0.06 (-0.65 to 0.53)	0.85	$X^2 = 1.44$ $P = 0.23$
POD 3 urine output, L	2	82	81	MD -0.03 (-0.28 to 0.22)	0.82	1	110	104	MD 0.49 (0.26 to 0.72)	<0.0001	$X^2 = 8.8$ $P = 0.003$
Intraoperative fluids, mL	5	175	179	MD -324.44 (-567.61 to -81.28)	<0.009[e]	2	136	128	MD -1377.68 (-4786.31 to 2030.96)	0.43	$X^2 = 0.36$ $P = 0.55$
Intraoperative MAP at reperfusion, mmHg	3	142	141	MD -1.28 (-3.46 to 0.89)	0.25	1	110	104	MD -1.83 (-4.49 to 0.83)	0.18	$X^2 = 0.10$ $P = 0.76$

CI: confidence interval; MAP: mean arterial pressure; MD: mean difference; POD: postoperative day; RR: risk ratio

[a] Postoperative haemodialysis was less likely compared with conventional therapy when arterial waveform analysis methods were used (P=0.002). There was significantly higher urine output on POD 3 in the oesophageal Doppler monitoring group compared with conventional fluid therapy (P<0.0001).

[b] Random-effect for all analyses.

[c] Clinical and/or radiological signs of excessive fluid accumulation.

[d] Need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure.

[e] Overall analysis and subgroup analysis not significant.

Values in bold are statistically significant.

This systematic review and meta-analysis aimed to comprehensively assess the effect of GDT on postoperative outcomes specifically in renal transplantation recipients.

While overall analysis showed that GDT did not result in significant differences in postoperative markers of renal function, subgroup analyses revealed potential renal protective benefits. This aligns with previous meta-analyses by Brienza et al. (2009) and Giglio et al. (2019), which reported that GDT improved postoperative renal outcomes in patients undergoing non-renal transplantation surgery.[41,42] Such renal advantages have been attributed to GDT's principle of individualising fluid management based on flow-related parameters to maintain tissue perfusion while minimising over-hydration. This is particularly relevant in the context of renal transplantation, where ischaemia-induced graft endothelial glycocalyx degradation occurs, especially in cadaveric renal transplantation with prolonged cold ischaemic insults. This degradation leads to heightened vascular permeability and interstitial oedema, making newly transplanted grafts more susceptible to tissue oedema and venous congestion caused by over-hydration. These complications have been associated with graft dysfunction.[43-47]

Renal benefits may be implied from our subgroup analysis, which found that cadaveric renal transplantations using GDT protocols had lower serum creatinine levels in the early post-operative periods. A review of 100,000 renal transplantations by First et al. (2003) established a correlation between 6- and 12-month serum creatinine levels and annual rates of graft loss.[48] While correlation between immediate postoperative serum creatinine levels and long-term graft outcomes are not yet well-established,[48] serum creatinine levels in the immediate postoperative period may still offer insights into intraoperative graft perfusion. This assessment allows us to observe graft function before the influence of postoperative factors becomes evident.[49]

Another finding suggesting potential renal benefits of GDT emerged from our subgroup analysis comparing different GDT modalities. Patients monitored with arterial waveform analysis methods had lower incidences of postoperative haemodialysis compared to those receiving conventional therapy. This outcome has been recognised as a significant prognostic consideration for long-term graft function.[50] However, oesophageal Doppler monitoring did not yield similar findings, suggesting that not all GDT modalities are equally effective. This discrepancy may be attributed to the disadvantages of oesophageal Doppler monitoring, such as its operator-dependence and labour-intensiveness in comparison with arterial waveform analysis.[51]

The subgroup analysis also demonstrated that patients using oesophageal Doppler monitoring had higher urine output on postoperative day 3 compared to conventional therapy, while no significant difference was found in the arterial waveform analysis group. The result is difficult to interpret, as postoperative urine output is also confounded by postoperative fluid management, and has weak correlation to long-term renal function.[52]

Our overall analysis found a significant association (P=0.01) between the implementation of GDT protocols and reduced incidences of postoperative tissue oedema in renal transplantation recipients. This further supports the notion that GDT protocols can be tailored to effectively provide appropriate fluid administration for patients in need, while preventing excessive fluid intake in others. In a study by Prasad et al. (2021) focusing on non-renal transplantation surgery, GDT was also found to decrease the incidence of tissue oedema.[53] This finding has clinical relevance, as our review also found lower occurrences of respiratory complications when GDT protocols were employed (P=0.003).

The MAP at reperfusion was similar between the GDT and conventional therapy protocols, indicating that GDT effectively maintains adequate tissue perfusion. In terms of total intraoperative fluids used, our review did not reveal statistically significant differences between the protocols. However, the absolute volume of fluid used does not fully account for other factors, such as the patient's weight, preoperative fasting protocols, underlying comorbidities and duration of surgery.

A meta-analysis of adult patients undergoing major surgery by Giglio et al. (2019) attributed the lower incidence of postoperative acute kidney injury in GDT protocols to the synergistic utilisation of fluid therapy and inotropes.[42] However, our subgroup analysis that examined the administration of fluid alone versus a combination of fluids and/or inotropes revealed no significant differences in outcomes analysed. Such observed benefits may be context-dependent. Fluid protocols vary greatly based on the patient's characteristics, such as in a renal transplantation recipient. Our findings suggest that unexamined factors, such as differences in GDT protocol guidelines, may influence the observed benefits. Moreover, limitations in the subgroup analysis, including small study populations and heterogeneity in dose and

timing of fluids and vasopressors/inotropic agents, should be considered.

There are several limitations to this systematic review and meta-analysis. The primary challenge lies in the heterogeneity of included studies, with variations in baseline patient characteristics (e.g. duration of preoperative renal replacement therapy and type of immunosuppressant therapy), donor kidney type, haemodynamic monitoring methods and fluid optimisation protocols. While subgroup analyses were performed to address these variables, they were not able to adjust for all confounding factors. Furthermore, definition of outcome measures varied among included studies. This could have weakened statistical associations and was considered during the assessment of the quality of evidence of our results. Future studies could identify target- and study-specific patient-centred postoperative outcomes instead.

Another limitation is the small number of available studies on GDT in renal transplantation surgeries, resulting in potential publication bias despite efforts to include all relevant published reports. The current literature in this area remains limited, and the inclusion of studies with small sample sizes and non-randomised designs may introduce biases. For example, the non-randomised controlled study by Srivastava et al. (2015) significantly influenced the analysis of postoperative tissue oedema and respiratory complications, raising concerns about potential blinding bias.[29] Other sources of bias to be addressed should be in the blinding of clinicians not directly involved in the intervention, including those measuring postoperative outcomes.

Further investigation into graft quality is warranted as it presents another confounding factor. While our subgroup analysis does account for differences between living versus cadaveric grafts, this comparison may be more complex. Grafts from living donors and standard criteria cadaveric donors are expected to have lower rates of delayed graft function, while grafts from extended criteria cadaveric donors and renal donation after cardiac death often suffer from higher rates of delayed graft function. GDT protocols may be particularly advantageous in such groups of renal transplantation recipients and can be further explored.

Moreover, continuous cardiac output monitoring may be advantageous in complex fluid management during renal transplantation surgeries. Renal transplantation recipients undergo a triphasic approach to fluid management, transitioning from preoperative fluid restriction to intraoperative directed fluid therapy for euvolaemia, followed by relative over-hydration in the immediate postoperative period. Continuously striking this balance in real-time can potentially optimise graft survival, and reduce tissue oedema and respiratory complications.

However, present experimental studies are not standardised to achieve specific consensus on what is the ideal protocol to direct fluid therapy and what modality of monitoring is best suited to achieve it. With more renal transplantations in the past decade being done without placement of invasive lines, along with increased use of minimally invasive strategies to measure cardiac output, the convention of what contributes to the goal of directed fluid therapy needs reappraisal. Future initiatives for GDT can commence in the preoperative period and continue meticulously from the intraoperative period to the postoperative phase, where the operating surgical team, anaesthesiologists and renal physicians work collaboratively to achieve a smooth transition in care of renal transplantation recipients.

CONCLUSION

Few studies have explored the benefits of GDT in renal transplantation surgeries. This review highlights that renal transplantation recipients may benefit from judicious fluid management using GDT. Within the limitations of existing data, the review showed that intraoperative GDT protocols may offer benefits in postoperative outcomes, with potential renal protective benefits, lower incidences of tissue oedema and respiratory complications in renal transplantation recipients. However, care must be taken before definite conclusions can be made as renal protective benefits were only seen in subgroup analysis while no such findings were found in the overall analysis. Future randomised controlled studies need to address several important limitations. These include the need for standardised reporting of outcome measures to improve consistency and comparability across studies. In addition, the impact of specific aspects of GDT, such as the method of monitoring cardiac output, strategies for optimising cardiac output, and variations in therapeutic goals should be explored. It is also crucial to account for confounding factors and potential sources of bias to obtain more accurate and reliable results. These areas of focus will contribute to enhancing the quality and reliability of research in this field.

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COMMENTARY

Artificial intelligence in medicine: Ethical, social and legal perspectives

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"Our future is a race between the growing power of our technology and the wisdom with which we use it. Let's make sure that wisdom wins."

—Stephen Hawking

ABSTRACT

Artificial intelligence (AI) has permeated into every aspect of medicine and promises to provide accurate diagnosis, better management decision and improved outcome for patients and healthcare system. However, ethical, social and legal issues need to be resolved for successful implementation of AI tools in clinical practice. In order to gain trust and acceptance, AI algorithms should offer maximum explainability and inclusiveness. Robust evidence of benefit to patients and healthcare services has to be provided to gain justification of using these tools. Doctor–patient relationship needs to be maintained in order to gain trust and acceptance of users. Autonomy of decisions and dignity of patients need to be preserved while using machine in healthcare. Responsibility and accountability in the use of AI in medicine should be deliberated and defined before mishaps and damage occur. A new role of healthcare providers will emerge with the advancement of technology and changes are inevitable.

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Keywords: artificial intelligence, autonomy, ethics, healthcare, medical-legal

The tsunami of artificial intelligence (AI) has arrived in medicine, penetrating every clinical specialty. Deep learning algorithms enable highly sensitive and specific diagnosis of diabetic retinopathy. Breast cancer screening using mammography can be performed by machine-learning devices, saving much time and effort for radiologists. Automated classification of skin conditions using convoluted neural network (CNN) programme in smart phones enables dermatologists to make vital diagnosis from a distance. Neural network algorithms can detect and characterise colorectal polyps during colonoscopy, reducing the chance of missing such potentially malignant lesions and deciding on whether polypectomy is needed. AI may also facilitate patient education, checking medication compliance and enhancing self-management, such as diet and exercise in chronic diseases. Increasingly, machine learning (ML) devices will replace repetitive, time-consuming, labour-intensive and mundane tasks of clinicians. If that is so simple, why is the implementation of AI in medicine still going relatively slow?

While there are numerous reports on innovations of AI in medicine, we can summarise its potential into three categories: (1) at the level of individual clinician-led consultation, AI can improve the speed and accuracy of diagnosis (especially with image-interpretation assisting diagnosis), recommend and direct best choice of therapy and prognosticate outcome; (2) at the healthcare system level, AI can improve efficiency and accessibility of healthcare service; and (3) at the population level, AI can help individuals in the public to modify their lifestyle and behaviour, hence promoting health of the population. The power of AI in medicine is summarised in Fig. 1.

However, in order to be able to achieve these capabilities, AI tools require three things: (1) collection of huge volume of genomic, environmental and lifestyle data of high quality and representative of the respective populations; (2) immense analytic capability to build models and algorithms for the study of diseases based on strong and weak signals in the individual's genome and environment; and (3) good governance system of data collection, analysis and utilisation of such tools developed.

Technology alone cannot solve all problems instantaneously. We cannot simply impose technology into healthcare systems and medical practices without considering trust, acceptance and compliance of stakeholders, including healthcare providers and receivers. Before AI can be extensively used in clinical practice and widely trusted by doctors and patients, there are a series of ethical, social and legal issues that need to be resolved.

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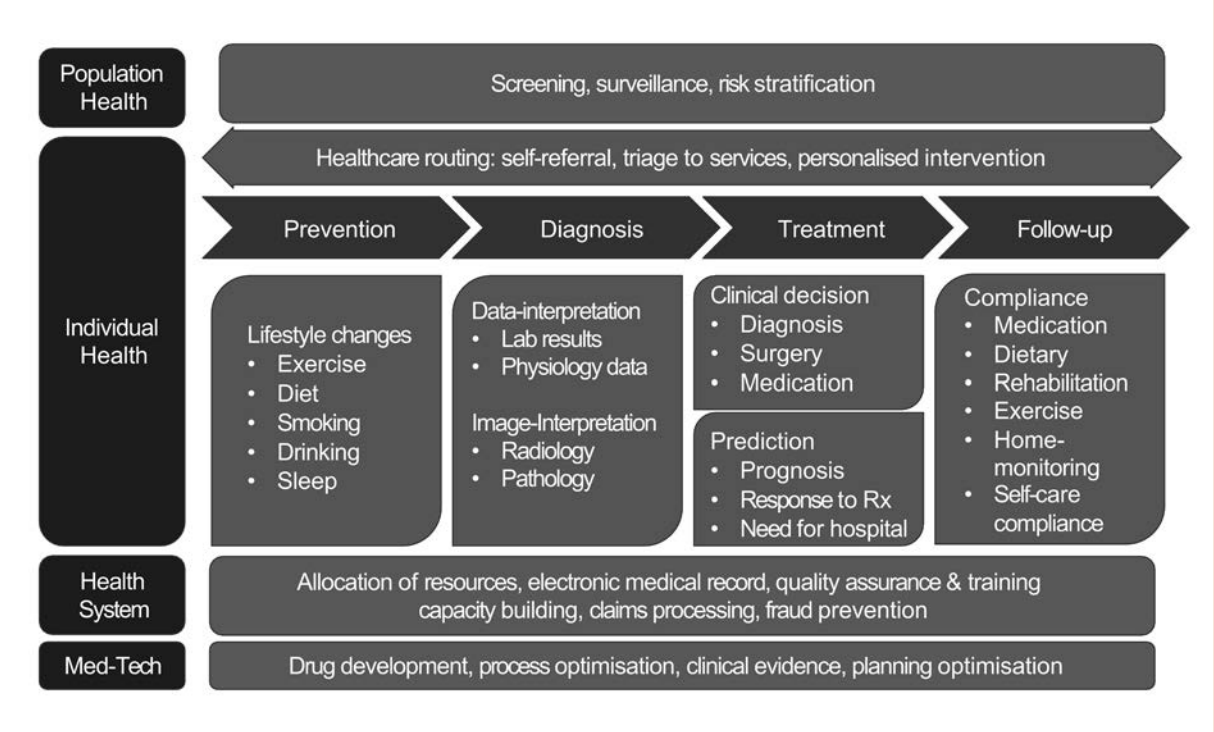
Fig. 1. Potential capabilities of AI in healthcare, from individual level to healthcare system and population health.



Successful Implementation of AI. First, in order to gain trust and acceptance of stakeholders, AI algorithms should have maximum "explainability" and "interpretability", explaining why such diagnoses are made, what basis are recommendations formulated and what are the mechanisms and rationale behind them. Modern AI algorithms based on complex ML methods are often not annotated and unsupervised. Because of their complexity, such tools provide answers beyond biological rationalisation and human comprehension, and these algorithms are widely treated as "black boxes". When specific features of differentiation in the ML process cannot be explained fully, it becomes difficult for doctors to explain their recommendation to patients, and patients may hesitate to accept recommendations from a machine that even their doctors do not understand.

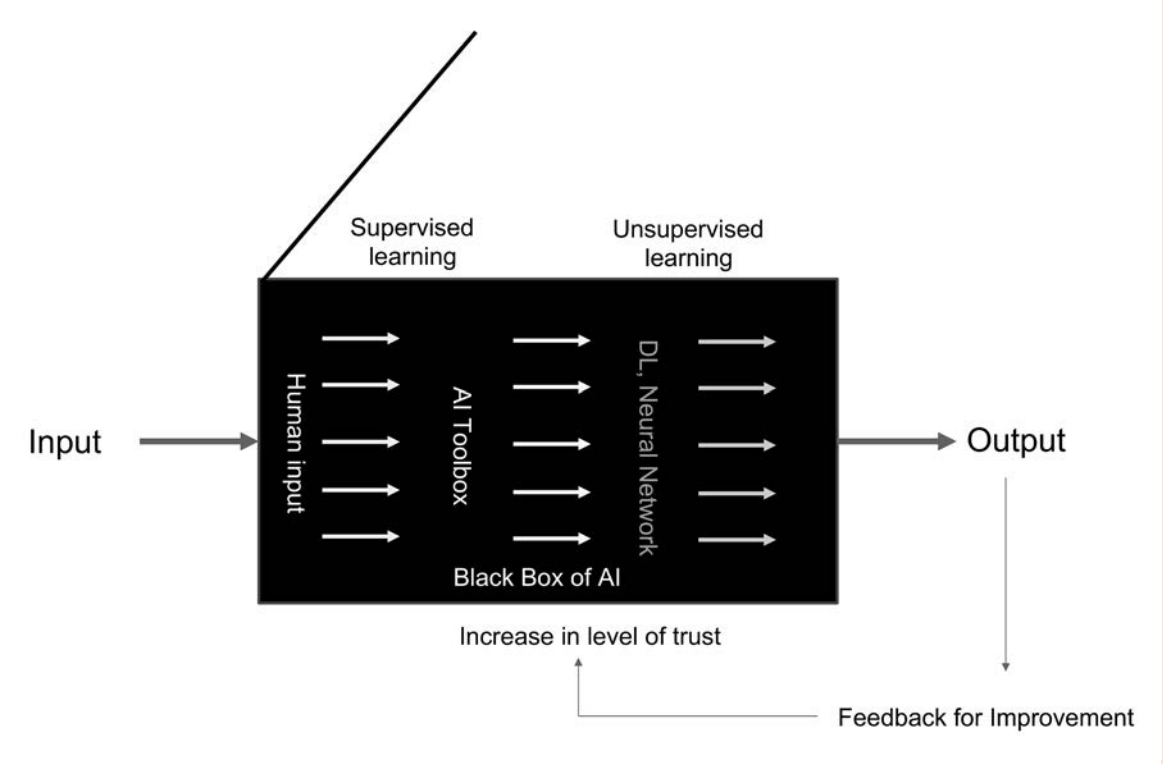
Some AI believers argue that many time-honoured effective drugs, such as aspirin, metformin and acetaminophen, have been used for decades with undisputed efficacy; yet their mechanism of action is still unclear. They point out that healthcare strategies should not insist on demanding full interpretability as it may stifle development of new treatment modalities.[1] Most clinicians and the public, however, believe that AI developers and scientists should continue to maximise the explainability and interpretability of algorithms in these tools. As development of AI tools strive to achieve maximum explainability and interpretability, the process should continue to evolve and improve while being used.

Explainability of AI tools can be uncovered in a stepwise approach. The output of algorithm, which can be a clinical diagnosis, choice of treatment and prognostication of outcome, can be tested in validation cohorts and clinical studies.[2] When clinical experience accumulates, iteration and feedback of clinical experience should offer the opportunity to continue improving the algorithms. The cycle of revision and reinvention should continue to expand the applications of such algorithms.

Since we may not understand fully the rationale behind these algorithms, AI tools should be validated with solid clinical evidence for healthcare benefit. To date, robust evidence of benefit in using AI tools for clinical management is lacking in many applications. Improved outcomes, such as shortened hospital stay, obviation of invasive procedures and surgery, lower treatment cost, improved quality of life and lengthening survival are strong evidence to support use of AI.

The number of AI-related articles in medical literature has increased dramatically in the past decade, but only a minority of them are prospective randomised controlled trials (RCT) and even fewer

Fig. 2. Stepwise approach to opening the "black box" of AI in medicine, by increasing the "explainability" of algorithms, with continuous improvement through feedback.



produce clinically relevant outcomes. Systematic reviews published recently showed that among over 12,000 publications from 13 medical specialties using AI in healthcare, there are only a handful of RCTs compared to numerous AI-assisted tools in standard-of-care management.[3,4] Furthermore, not all published studies utilised the clinically relevant endpoints mentioned above. Carefully designed clinical trials are urgently needed to justify the use of AI tools in medicine.

As we are striving for evidence to prove that AI works well in management of diseases, AI should be used to support but not undermine the doctor–patient relationship. In the past decades, developed countries such as the US, UK and Europe reported that the modern healthcare system was spending more money, expending more manpower, and allocating more time for patient management, but in return, resulting in lower patient satisfaction. Patients often feel that their doctors spend too much time during consultations on the computer in front of them and spare no time to talk or even listen to them for their complains and suffering.

Despite the advancements in science and technology, the doctor-patient relationship remains the cornerstone of healthcare. When AI is introduced into health services, it is meant to assist, not to replace, healthcare providers' role in the caring process. This underpins the importance of integrating doctors and machines working together as a "team". Patients value the doctor–patient relationship and this should not be jeopardised because of the use of machines in the care process.[5] Social and emotional support from the healthcare providers to patients suffering from chronic conditions are crucial, on top of professional services. With AI assisting in retrieving and interpreting data for the clinical decisions, providers should have more time to listen, understand the need of the patients, and explain to them the options and expected outcome of treatment. Doctors are not, and should not be, technicians to carry out orders of machines or AI tools. With AI technology integrated into healthcare, doctor–patient relationships should be enhanced and not undermined.

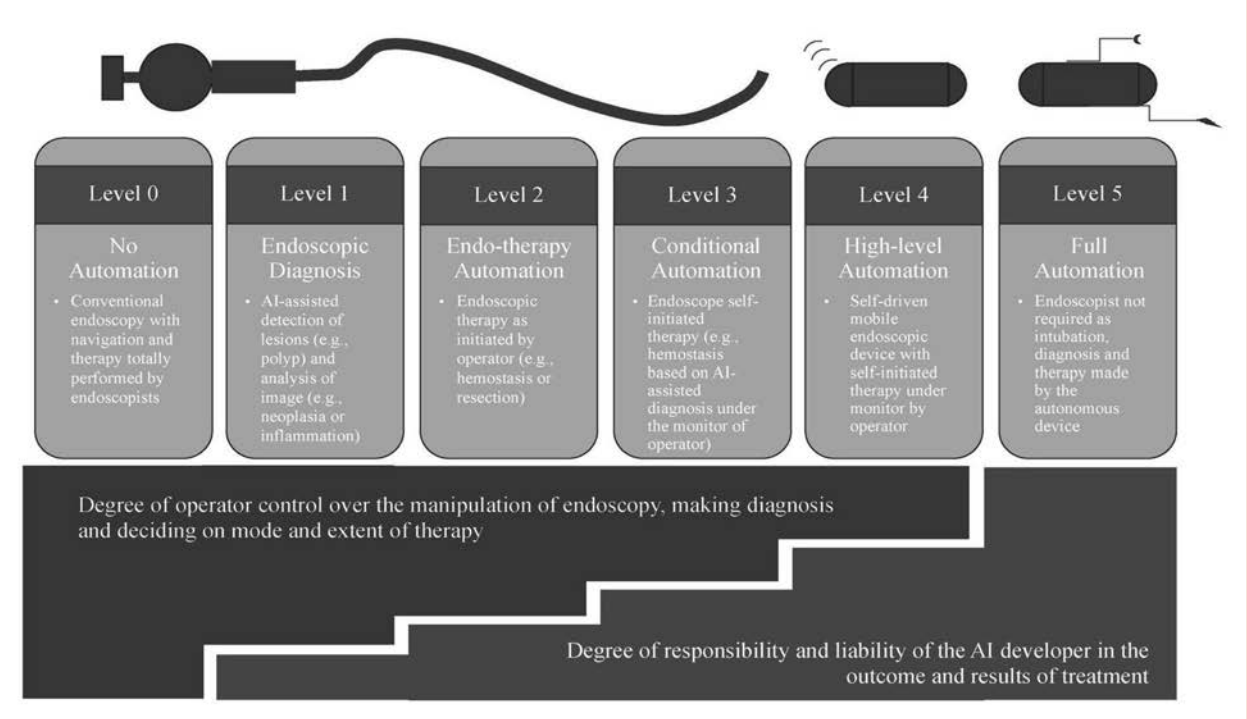
In order to enhance integration of healthcare providers and machine to work as a team, the importance of early access to education and training to work with machines cannot be overstated. Training should start from school days, and the medical curriculum needs to be extensively revised and overhauled. AI tools should also be developed with an aim to eliminate, or at least minimise, existing biases arising from differences in race, culture, age and gender. AI devices must not

only serve the wealthy and technology savvy population. Instead, it should be used to provide services to the under-privileged community and the technology-deprived populations, such as the elderly and the disabled. The government needs to eliminate the pre-existing "digital divide" to the use of technologies so that the benefit can be inclusive.

Ethical and Legal Considerations. Furthermore, the use of AI must not undermine human autonomy.[6] Autonomy is about respecting one's values: to treat or not to treat, quality of life versus length of survival, dignity versus efficacy of treatment, etc. In the context of healthcare, this means that humans should remain in control of medical decisions and the choice of therapy. Ideally, patients' values and their preferred choices of treatment could be incorporated into the algorithm. This is especially important in patients suffering from multiple comorbidities and chronic illnesses where options are many and choices can be made. Respect for a person's dignity is an important principle in care services, and this moral attitude should be kept in the centre stage in decision-making by individuals, groups and institutions.[7] When offering AI-assisted treatment to patients, healthcare professionals need to allow patients to apply their own values to consent and participation.[8] If employed wisely, AI has the potential to empower patients and communities to assume control of their own healthcare better. But if we do not implement it carefully, AI could lead to situations where life-and-death decisions, that should be made by providers and their patients, are transferred to machines, leading to loss of autonomy.[6]

Last, but not least, responsibility and accountability in the use of AI in medicine should be deliberated and better defined. Despite strong efforts on national, regional and international levels to develop frameworks ensuring quality control of AI tools and patient safety, there is still uncertainty regarding the exact requirements to be enacted by regulatory agencies.[9] In the case of misdiagnosis or mistreatment of a patient involving the use of AI, liability should be shared among various parties from manufacturer, health administrator to care provider depending on issues such as the scope of duty of care, causation and remoteness of damage and finding of vicarious liability. In legal proceedings, responsibility is often a function of "control" over consequences. Depending on the specific facts and circumstances of each case, the degree of "control" exercised by each party over the AI system and the decision-making process can be

Fig. 3. Stepwise approach of degree of responsibility and liability depending on the degree of operator control over consequences in medical care.



an important factor in allocation of responsibility.[10] Liability should be apportioned to the producer, users and healthcare system according to their respective share of "control" in the decision-making process (Fig. 3).

AI is coming to redefine the role of doctors and allied health workers. For successful implementation of this powerful tool into daily clinical practice, robust clinical studies need to be conducted, explainability of the AI algorithms need to be maximised, autonomy of patients and healthcare providers need to be preserved, doctor–patient relationships cannot be undermined, and legal and liability issues need to be deliberated.

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LETTER TO THE EDITOR

Outcomes of COVID-19 infection in patients on dialysis and kidney transplant recipients: A single-centre audit

Dear Editor,

Patients with end-stage kidney disease (ESKD) are at increased risk of adverse outcomes following COVID-19 infection. Their vulnerability stems from multiple factors including kidney failure, comorbid illnesses, close contact in the haemodialysis centre, and transplant immunosuppression. European registry data in the pre-vaccination era report a COVID-19 mortality rate of 20% among patients on dialysis and 19.9% in kidney transplant recipients, with transplant recipients having 1.28 times the mortality risk of matched dialysis patients.[1] More recent studies have reported mortality rates of 7–20% among vaccinated patients on dialysis or transplant recipients.[2–4]

During the COVID-19 pandemic, the Department of Renal Medicine at the Singapore General Hospital performed an Institutional Review Board-approved audit (Singhealth CIRB 2021/2823) to monitor COVID-19 caseload and treatment outcomes. This letter presents this important data to prepare for the next pandemic.

All patients on dialysis or transplant recipients treated for SARS-CoV-2 infection at the Singapore General Hospital from 1 September 2021 to 30 April 2022, and who had a positive SARS-CoV-2 polymerase chain reaction with cycle threshold <25, were included. Patients aged <18 years, who required only temporary dialysis, or who initiated dialysis or underwent transplantation during the same admission were excluded. Cases were classified as occurring during the delta or omicron wave based on the cut-off date of 1 December 2021 on which the Omicron variant was first reported in Singapore.[5] The primary endpoint was inpatient mortality. Secondary endpoints include mechanical ventilation and allograft dysfunction in transplant recipients.

Deidentified patient information was collected from medical records. SPSS Statistics version 28 (IBM Corp, Armonk, NY, US) was used for data analysis. Differences in baseline characteristics and outcomes were compared between patients on dialysis and kidney transplant recipients using chi-square, Fisher's Exact test and t-test as appropriate. The association between baseline characteristics and mortality was explored using binary logistic regression. Multivariate logistic regression was used to investigate the association between patient characteristics, clinical factors, and admission investigations with mortality. *P* values <0.05 were considered significant.

The audit included 491 patients: 259 patients on dialysis (247 haemodialysis, 12 peritoneal dialysis) and 232 transplant recipients. Transplant recipients were younger than patients on dialysis (age, mean [standard deviation], 65.6 [12.4] versus 57.6 [10.9], *P*<0.001), and had lower Charlson comorbidity indices (7.21 [2.43] vs 3.71 [1.51], *P*<0.001). Overall, 441 patients (89.8%) were fully vaccinated with ≥2 doses of a COVID-19 vaccine, of which 286 patients (58.2% of total) had also received a booster dose. Transplant recipients were more likely than patients on dialysis to be fully vaccinated (94.8% vs 85.3%, *P*<0.001) or have had a booster dose (78.0% vs 40.5%, *P*<0.001), yet were more likely to have inadequate immunoglobulin G (IgG) antibodies (<500 BAU/mL) against the receptor-binding domain of the SARS-CoV-2 virus (56.3% vs 32.7%, *P*<0.001) at the time of infection.

Cohort mortality was 2.9%. Transplant recipients had lower mortality (0.4%) than patients on dialysis (5.0%) odds ratio [OR] 0.082, 95% confidence interval [CI] 0.011–0.631, *P*=0.002). Mortality was higher during the delta (5.1%) than the omicron wave (2.1%), but this did not reach statistical significance (OR 2.48, 95% CI 0.840–7.30, *P*=0.11). Mechanical ventilation was required in 3.1% of all patients, less often in transplant recipients (1.3%) than in patients on dialysis (4.6%) (OR 0.271, 95% CI 0.075–0.972, *P*=0.037). Thirty-two transplant recipients (13.8%) had allograft dysfunction, with 1 graft loss (0.4%).

On univariate analysis, baseline characteristics associated with mortality include: patient on dialysis, age (per year increase, OR 1.12, 95% CI 1.06–1.19, *P*<0.001), and higher Charlson comorbidity index (per point increase, OR 1.30, 95% CI 1.09–1.55, *P*=0.003). Admitting investigations associated with mortality include consolidation on chest X-ray (OR 4.26, 95% CI 1.39–13.0, *P*=0.011), higher white cell count (per $1x10^9$/L increase, OR 1.39, 95% CI 1.23–1.56, *P*<0.001), higher C-reactive protein (per 1mg/L increase, OR 1.48, 95% CI 1.28–1.73, *P*<0.001), and lower albumin (per 1g/L decrease, OR 1.15, 95% CI 1.06–1.24, *P*<0.001). The 4C score predicted mortality in this cohort (per 1 point increase, OR 1.90, 95% CI 1.41–2.56, *P*<0.001). Vaccination status or SARS-CoV-2 antibody levels were not significantly associated with mortality.

On multivariate analysis, independent predictors of mortality were age (per year increase, OR 1.14,

Table 1. Characteristics and outcomes of COVID-19 infection.

		Dialysis (n=259)	Transplant (n=232)	*P* value
Baseline characteristics				
Age	mean ± SD	65.6 ± 12.4	57.6 ± 10.9	<0.001[a]
Male sex	n (%)	157 (60.6)	125 (53.9)	0.144
Aetiology of kidney failure				
- Diabetes	n (%)	141 (55.3)	28 (12.1)	
- Glomerulonephritis	n (%)	53 (20.8)	166 (71.6)	
- Hypertension	n (%)	39 (15.3)	54 (23.3)	
- Polycystic kidney disease	n (%)	7 (2.7)	9 (3.9)	
- Others	n (%)	15 (5.9)	14 (6.0)	
Duration on dialysis or transplant, years	mean ± SD	4.52 ± 4.77	12.4 ± 9.37	<0.001[a]
Charlson Comorbidity Index	mean ± SD	7.21 ± 2.43	3.75 ± 1.51	<0.001[a]
Fully vaccinated (≥2 doses)	n (%)	221 (85.3)	39 (94.8)	<0.001[a]
Fully vaccinated with booster	n (%)	105 (40.5)	181 (78.0)	<0.001[a]
SARS-CoV-2 IgG antibody level <500 BAU/mL	n (%)	65 (32.7)	125 (53.9)	<0.001[a]
At presentation				
Symptomatic infection	n (%)	202 (78.0)	226 (97.4)	<0.001[a]
Haemoglobin (g/dL)	mean ± SD	10.6 ± 1.70	13.5 ± 15.4	0.005[a]
White cell count (x10^9/L)	mean ± SD	6.96 ± 3.03	6.63 ± 2.23	0.167
Platelet count (x10^9/L)	mean ± SD	194 ± 4.56	210 ± 67.1	0.008[a]
C-reactive protein (mg/L)	mean ± SD	39.8 ± 3.02	21.0 ± 32.2	<0.001[a]
Albumin (g/L)	mean ± SD	34.3 ± 4.92	37.8 ± 6.28	<0.001[a]
Consolidation on X-ray	n (%)	56 (24.5)	25 (10.8)	<0.001[a]
Treatment				
Monoclonal antibody	n (%)	34 (13.1)	118 (50.9)	<0.001[a]
Remdesivir	n (%)	157 (60.6)	109 (47.0)	0.003[a]
Dexamethasone	n (%)	45 (17.4)	11 (4.7)	<0.001[a]
Tocilizumab	n (%)	1 (0.4)	2 (0.9)	0.605
Outcomes				**OR (95% CI), *P* value**
Mortality - all	n (%)	13/259 (5.0)	1/232 (0.4)	0.082 (0.011–0.631), 0.002[a]
- delta (n=117)	n (%)	6/91 (6.6)	0/26 (0)	0.248 (0.014–4.55), 0.034
- omicron (n=374)	n (%)	7/168 (4.2)	1/206 (0.5)	0.112 (0.014–0.921), 0.025[a]
Ventilation - all	n (%)	12/259 (4.6)	3/232 (1.3)	0.271 (0.075–0.972), 0.037[a]
- delta (n=117)	n (%)	4/91 (4.4)	2/26 (7.7)	1.813 (0.313–10.5), 0.613
- omicron (n=374)	n (%)	8/168 (4.8)	1/206 (0.5)	0.098 (0.012–0.788), 0.013[a]
Oxygen requirement	n (%)	56 (21.6)	11 (4.7)	5.54 (2.83–10.9), <0.001[a]
4C score	mean ± SD	9.56 ± 2.60	4.95 ± 3.01	*P*<0.001[a]

CI: confidence interval; OR: odds ratio; SD: standard deviation
[a] Statistically significant variables.

95% CI 1.05–1.24, *P*=0.003), higher white cell count (per 1mg/dL increase, OR 1.51, 95% CI 1.24–1.83, *P*<0.001), higher C-reactive protein (per 1g/L increase, OR 1.01, 95% CI 1.002–1.023, *P*=0.020), and lower serum albumin (per 1g/L decrease, OR 1.15, 95% CI 1.02–1.30, *P*=0.024). The type of renal replacement therapy was not significant on multivariate analysis.

COVID-19 therapeutics employed in this cohort included remdesivir (54.2% of all patients), monoclonal antibodies (31.0%), dexamethasone (11.4%), and tocilizumab (0.6%). Transplant recipients were more likely than dialysis patients to receive monoclonal antibodies (50.9% vs 13.1%, *P*<0.001), but less likely to receive remdesivir (47.0% vs 60.6%, *P*=0.003). Mortality was higher in patients receiving remdesivir (OR 11.5, 95% CI 1.49–88.7, *P*=0.002) or dexamethasone (OR 35.2, 95% CI 9.47–131, *P*<0.001). There was no association between receipt of monoclonal antibodies and mortality.

Our audit identified a mortality of 2.9% and a mechanical ventilation rate of 3.1% among COVID-19 patients on renal replacement therapy, which compares favourably with international case fatality rates in ESKD cohorts, but is significantly higher than the overall case fatality rate in Singapore of 0.07%.[6] Older age, leukocytosis, elevated C-reactive protein, or hypoalbuminaemia on admission should alert clinicians to an elevated risk of COVID-19 mortality. While COVID-19 vaccination and SARS-CoV-2 antibody levels were protective in prior literature,[7,8] these were not associated with reduced mortality in our audit, which may be due to inadequate statistical power. Contrary to popular belief, transplant recipients had lower mortality than patients on dialysis (although non-significant on multivariate analysis), despite immunosuppression. This may be due to a selection of fitter patients (as reflected in a lower Charlson comorbidity index) for transplantation, higher uptake of COVID-19 vaccination in transplant patients, and better ability to self-isolate. Hence, a potential consideration in planning for future pandemics may be modifying dialysis centre infrastructure to enable isolation of patients from each other, and empowering dialysis centres to vaccinate patients on-site.

Significant differences in treatment strategy between transplant recipients and dialysis patients were noted. Transplant recipients may have been more likely to be offered oral monoclonal antibodies in accordance with a previously published hospital-at-home model for COVID-19 infected transplant recipients.[9,10] The higher mortality observed in patients receiving remdesivir or dexamethasone may reflect a selection of patients with severe disease. From retrospective audit data, it is difficult to distinguish whether varying treatment strategies contributed to differences in outcomes, or if treatment choices reflected differing disease severity, and this is an important limitation of our study.

Finally, our audit is limited by the inclusion of only patients managed in tertiary care, and may not reflect outcomes among COVID-19 patients managed in primary care or at outpatient dialysis centres. Transplant recipients generally have tight links to their transplant coordinators and may be more likely to present to tertiary care.

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LETTER TO THE EDITOR

Four cases of HIV infection in men taking pre-exposure prophylaxis in Singapore

Dear Editor,

Pre-exposure prophylaxis (PrEP) with co-formulated tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) is an effective prevention strategy against sexual transmission of human immunodeficiency virus (HIV) in at-risk populations.[1] It can be taken daily, or on-demand for cisgender men who have sex with men (MSM) and transwomen who have sex with men.[2] In spite of this, breakthrough infections have still been reported.[3,4] Additionally, despite PrEP being available in Singapore for several years, accurate Singapore data on its utilisation is lacking.[5] A Singapore study in February 2018 found that only 15% of MSM on a geosocial networking application (Grindr) had used PrEP.[6] However, to our knowledge, there are no published Singapore cases on PrEP failures. We present 4 such cases (Table 1).

Chart review of cases of PrEP failures in a tertiary hospital infectious disease clinic was conducted. These cases of PrEP failures were identified when newly diagnosed persons with HIV were screened for recent or current PrEP use. Assessment of a patient's adherence to PrEP and understanding of PrEP dosing regime was qualitatively determined by the attending physician after each clinical encounter.

Case 1. In March 2020, an MSM in his 30s was started on daily TDF/FTC PrEP by a sexual health clinic after a negative 4th generation point-of-care (POCT) HIV test. He purchased the generic TDF/FTC formulation online. In June 2020, he underwent his last non-reactive HIV test. In September 2020, he switched to event-driven PrEP, around when he experienced an extended period of fever and sore throat but did not seek medical attention. He was then diagnosed to have HIV seroconverted during POCT routine testing in November 2020. His adherence to event-driven PrEP dosing was confirmed again, and he reported no condomless anal sex without PrEP.

Case 2. An MSM in his 50s self-initiated daily PrEP without consultation with a healthcare provider for several years. In March 2021, he switched to event-driven PrEP on his own. He reported good understanding of PrEP dosing regimen and demonstrated adherence. He regularly performed self-testing for HIV using unvalidated POCT kits purchased online, with his last negative test in March 2021. However, in July 2021, during syphilis testing at a sexual health clinic, he was found to have HIV seroconverted on POCT testing.

Case 3. An MSM in his 40s was initiated on daily PrEP in 2018 by a private medical provider. However, he discontinued follow-up after a few months and obtained medications online. In May 2021, he self-switched to event-driven PrEP, taking 2 tablets before sex, followed by 2 tablets 24 hours later, only occasionally taking an additional single tablet 48 hours after sex. His last negative POCT HIV test was in March 2021. He subsequently only underwent POCT HIV testing inconsistently when offered by anonymous community testing sites. He continued using PrEP until he tested HIV-positive on POCT in August 2021. At the time of diagnosis, he exhibited a limited understanding of event-driven PrEP dosing.

Case 4. An MSM in his 30s was first seen in 2018 for treatment of syphilis and was found to be eligible to start PrEP but did not return for follow-

Table 1. Characteristics of PrEP failure cases at time of HIV seroconversion.

Case no.	Age and gender	PrEP regime at seroconversion	At point of diagnosis			
			Good understanding of dosing and adherence	Follow-up with PrEP provider	Resistance-associated mutations	Coinfection
1	30s M	TDF/FTC (event-driven)	Yes	Yes	M184V, V106I	Syphilis Hepatitis C
2	50s M	TDF/FTC ("do-it-yourself" event-driven)	Yes	No	M184V	Syphilis
3	40s M		No	No	M184V	Syphilis Hepatitis B (natural immunity)
4	30s M		No	No	M184V	Syphilis

M: male; PrEP: pre-exposure prophylaxis; TDF/FTC: co-formulated tenofovir disoproxil fumarate and emtricitabine

up. Instead, he obtained TDF/FTC online without prescription. In August 2022, he self-initiated event-driven PrEP using incorrect dosing schedules—taking only 1 tablet prior and 1 tablet after sex; or taking a single tablet after sex only. His last non-reactive POCT HIV test was in 2021. He presented again in November 2022 complaining of a rash where investigations confirmed secondary syphilis and HIV seroconversion.

"Do-it-yourself" PrEP and PrEP adherence. Only 1 of the 4 cases was regularly monitored by a PrEP provider, while none obtained TDF/FTC from local pharmacies, opting for online generic versions without prescriptions. This highlights the impact of barriers, e.g. high costs and stigma on PrEP utilisation, which discourage potential users to seek PrEP from established local providers.[6]

All 4 cases utilised event-driven PrEP at the time of HIV seroconversion. Although event-driven PrEP has been proven effective in MSM,[7,8] the dosing regimen's complexity necessitates regular reinforcement during counselling sessions to ensure correct dosing: taking 2 tablets 2 to 24 hours before sexual encounter, then taking a single tablet each 24 and 48 hours after. Out of the 3 cases who were continuing event-driven PrEP without guidance of a medical professional, 2 (cases 3 and 4) showed poor understanding of PrEP dosing, which likely contributed to its failure.

TDF/FTC resistance. The M184V mutation, associated with emtricitabine resistance, was detected in all 4 cases upon HIV diagnosis on baseline genotype testing. Two mechanisms explain the development of drug-resistant mutations in PrEP failure. Transmitted resistance is the transmission of virus that already carries resistance-associated mutations, which may render TDF/FTC ineffective as PrEP. Acquired resistance occurs when an individual, infected with a wild-type virus due to suboptimal adherence or poor understanding of dosing, continues PrEP without a third antiretroviral agent (which is insufficient treatment for an established HIV infection). This causes selective drug pressure by TDF/FTC in the presence of unsuppressed viral load, and the initially fully-sensitive virus develops mutations associated with resistance to TDF and/or FTC.

Assuming cases 1 and 2 were fully adherent to TDF/FTC, they may have been infected with a resistant strain (transmitted resistance), while cases 3 and 4 likely acquired resistance by continuing PrEP despite being HIV-positive. Since all cases were on event-driven PrEP at the point of seroconversion, analysing tenofovir plasma levels at diagnosis did not give any reflection about their PrEP adherence.

Medication authenticity. In Singapore, Truvada (Gilead Sciences, Foster City, CA, US), the branded co-formulated TDF/FTC, can cost up to SGD 900 (about USD 680) for a 30-tablet supply, leading patients to seek cheaper, less regulated sources locally or from overseas. Counterfeit HIV medication is prevalent globally.[9] It is hence crucial to investigate the authenticity of such medications and their contribution to PrEP failures.

Sexually transmitted infection (STI) coinfection. Contracting an STI can be a result of sexual practices associated with increased risk of HIV transmission. Active STIs are known to augment HIV transmission in seronegative individuals.[10] However, this association is less clear in PrEP failure cases. All 4 cases had coinfection with syphilis and 1 with hepatitis C. It remains uncertain if STI coinfection increased risk of PrEP failure or if it stemmed from increased sexual exposures.

Barriers to accessing PrEP. It should be recognised that external factors may influence individuals' behaviour and decisions regarding PrEP. These include limited access to reliable PrEP information, high costs of laboratory tests and PrEP, as well as stigma related to both sex and HIV among healthcare providers. All these can contribute to barriers to accessing PrEP from official sources.

A limitation of this case series is its reliance on self-reported information from patients about their sexual behaviour and medication adherence, introducing recall and social desirability biases, particularly given the stigma around discussing sex and HIV. To mitigate these biases, enhancements like using a self-reporting form instead of interviewer-administered surveys or introducing a PrEP navigator from the community to provide care coordination could be considered. Another limitation was the inability to definitively exclude that the initial negative HIV test occurred within the test's window period, because patients either initiated PrEP on their own or had it done by a private medical provider.

In conclusion, while PrEP is highly effective, it does not eliminate the risk of HIV transmission, which should be communicated to users. Follow-up with a PrEP provider is crucial for counselling, verifying understanding of dosing, and regular HIV testing to prevent acquired resistance in case of PrEP failure. Two of the cases here could have possibly been prevented with proper provider follow-up. Better outreach and engagement with populations at risk of HIV are needed to address potential gaps in PrEP services access, and to ultimately reduce "do-it-yourself" PrEP approaches.

Disclosure

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Keywords: *HIV, pre-exposure prophylaxis, PrEP, treatment failure*

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LETTER TO THE EDITOR

Knowledge, attitudes and practices of doctors on constipation management in Singapore

Dear Editor,

Constipation is a common gastrointestinal disorder, affecting about 15% of the global population and severely impacting patients' quality of life.[1] The global constipation treatment market is estimated to worth USD22.93 billion in 2025. Patients with functional constipation had the highest treatment dissatisfaction at 63.4%. Poor satisfaction was reported due to ineffective treatment, adverse side effects of medication, concerns with long-term safety of medication and lack of treatment options.[2]

Doctors' awareness of standardised guidelines, diagnostic criteria and treatment options can affect their confidence in the diagnosis and management of constipation. However, there is often a lack of adherence to standardised guidelines in primary care, which could impact treatment outcomes and satisfaction.[3] As constipation is commonly treated in different settings, it is important to examine potential gaps and variations in constipation management between specialties that could contribute to poor treatment satisfaction. Therefore, the current study aims to investigate the knowledge, attitudes and practices of doctors across specialties regarding constipation management in Singapore.

A cross-sectional survey on doctors' knowledge, attitudes and practices regarding constipation management was conducted using a 49-item online questionnaire that was distributed via snowball sampling to doctors across Singapore over 6 months (July 2021 to December 2021). The questionnaire was designed with input from gastroenterologists and generalists to ensure clinical relevance and appropriateness of survey items for the study's objectives. Responses to knowledge and attitude items were examined using chi-square tests to compare between 4 groups: gastroenterology (GE), family medicine (FM), general medicine (GM) and other specialties. A composite knowledge score was created to assess doctors' overall knowledge about constipation management. Three questionnaire items were used to obtain attitude scores: (1) "Chronic constipation can be easily identified"; (2) "Chronic constipation is very difficult to treat"; and (3) "I know how to diagnose functional constipation confidently." Further analyses were conducted with knowledge and attitude scores using a 1-way analysis of variance (ANOVA) for comparison among GE, GM, FM and other specialties. Significant group effects were analysed post hoc using Tukey's Honestly Significant Difference (HSD) test. Simple linear regression analysis was performed to investigate the effects of overall knowledge on attitudes, specifically on the identification, treatment and diagnosis of constipation.

Table 1. Demographic data of participants.

Demographic characteristics	Total (n=153)	
	n	%
Specialty		
Gastroenterology	21	13.7
Family Medicine	50	32.7
General Medicine	43	28.1
Other specialties	39	25.5
No. of years in medical practice		
Less than 2 years	16	10.5
3–5 years	66	43.1
6–10 years	34	22.2
More than 10 years	37	24.2
Sex		
Female	83	54.2
Male	70	45.8
Adequacy of training in management of constipation		
Very adequate	17	11.1
Somewhat adequate	106	69.3
Not adequate	18	18.3
It was not taught	2	1.3

We found that only 11.1% reported having very adequate training in management of constipation. This was reflected in the limited knowledge exhibited: only 34% were familiar with Rome IV criteria of functional constipation. While 81.0% of gastroenterologists indicated that it is safe to consume osmotic laxatives in the long term, a proportion of doctors from GM (55.8**%**), FM (48.0%) and other specialties (71.8**%**) indicated long-term consumption to be unsafe. Furthermore, a substantial percentage of doctors (GM, 51.2%; FM, 40.0%; GE, 14.3%; other specialties, 30.8%) incorrectly identified lactulose to have better efficacy for the elderly than polyethylene glycol (PEG). Almost all doctors were agreeable that

constipation is a common health problem. It was found that knowledge score significantly predicted attitude score for confidence in diagnosing functional constipation (β=-.203, *P*<0.001). For the diagnosis of functional constipation, doctors from GE were significantly more confident than doctors from all other groups (*P*<0.001). In addition, 61.4% of doctors felt that digital technology can aid chronic constipation management.

The limited knowledge of our doctors, especially FM and GM doctors, is worrying as majority of patients with functional constipation are encountered in generalist settings.[4] Although osmotic laxatives are commonly used by generalists, it is alarming that almost half of them do not know the long-term safety of osmotic laxatives and that PEG has a better efficacy. A recent Cochrane review reported that PEG was better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional product use.[5]

More than half of the FM and GM doctors were unable to identify the Rome IV criteria, possibly due to a lack of usage of Rome IV diagnostic criteria in non-specialist practice.[6] Limited knowledge could be due to our doctors' unfamiliarity with constipation guidelines. A study in Canada showed that despite 69% of respondents being aware of the guideline, only half found the guideline helpful and most wanted a more applicable local treatment algorithm.[7] Recently, we have also seen regional or national guidelines on chronic constipation, including an Asian-based constipation guideline for primary care physicians developed by the Asian Neurogastroenterology Motility Association.[4] It is critical for doctors to stay updated with novel guidelines relevant to various cultural contexts, in order for patients to receive appropriate treatment.

Many studies have reported that patients with constipation are dissatisfied with their treatment and the gap between doctors' knowledge and practice could be a contributing factor.[2,8] Only 28.1% of doctors were confident in diagnosing functional constipation, and 66.7% reported that constipation was very difficult to treat. One of the keys to improving patient satisfaction lies in accurate diagnosis, as we may be underdiagnosing defecation disorder (DD) in which laxative is ineffective. The prevalence of DD among patients with chronic constipation (CC) ranges from 27% to 59% in the West, and about 40% in Asia.[9] Given the high prevalence and ineffectiveness of laxatives for DD, it is important to diagnose patients with DD.

In the past decade, the US Food and Drug Administration (FDA) approved several new treatment options that are more effective than lifestyle changes and over-the-counter drugs.[10] With the use of digital technology that was positively received by most doctors, they can access updated guidelines on new FDA approved drugs, including safety profiles and usage recommendations.

One limitation of our study is self-reporting bias. Conducting a clinical audit could be explored to assess the actual practice. We also acknowledge that a lower response rate than the expected sample size of 374 limits the generalisability of our results.

Our study showed that most doctors can appreciate the prevalence and burden of constipation. However, it is surprising to reveal issues facing constipation management from limited familiarity with guidelines to significant knowledge deficit in the management of constipation. Future research should investigate how interdisciplinary collaboration through digital technology may assist CC education and management.

Keywords: *family medicine, gastroenterology, internal medicine, medical education, epidemiology*

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