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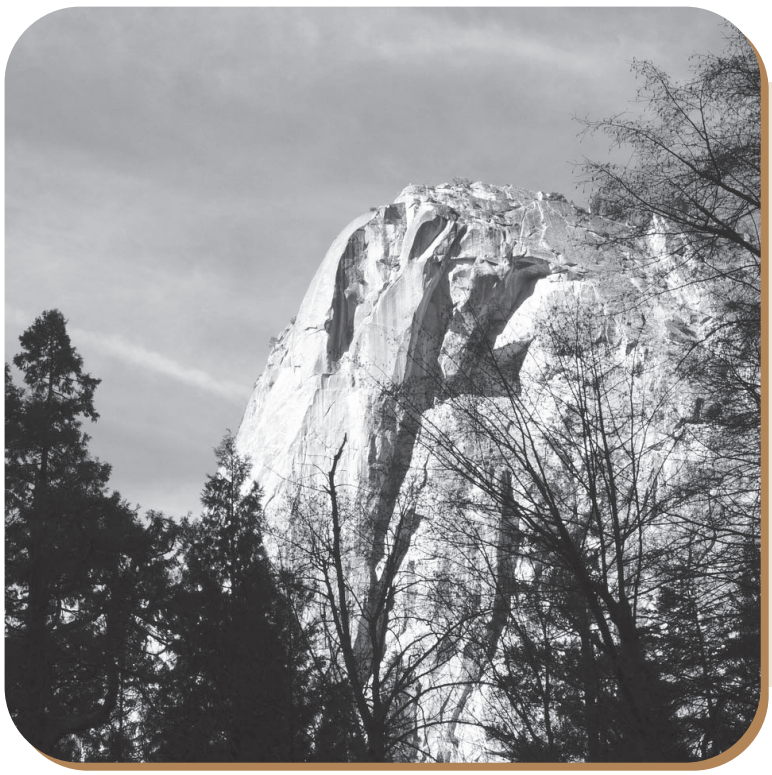

"He who lives with his senses well controlled, moderate in his food and drink, he will not be overthrown, any more than the wind throws down a rocky mountain."

Gautama Buddha (563 – 483 BC)
Leader

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Images in Medicine

Editorial

Managing Suicide Ideation: A Targeted Approach

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Introduction

Suicide, the deliberate act to end one's life, has been described as the "result of fractures with oneself".[1] It could manifest as a direct consequence of psychiatric illness—such as severe depression with an overwhelming sense of hopelessness—or a compliant act under the influence of a command hallucination in psychotic illnesses. However, suicides can also occur in the absence of any known prior psychiatric disorders, but in the presence of "profound distress and psychological pain that has become unbearable … suicide is seen as the perfect solution".[2]

In recent years, suicide has become the leading cause of death in those aged between 10 and 29. In 2018, 397 lives were lost to suicide in Singapore alone and men accounted for 71% of completed suicides. The number of suicides also rose by 10% to 8.36 individuals in 100,000 Singapore residents. More alarmingly, suicide in male youths reached a peak in 27 years. According to the non-profit suicide prevention organisation, Samaritans of Singapore, "There are 2.8 times more deaths from suicide than transport accidents in 2018. For every suicide, at least 6 suicide survivors are left behind."[3]

Suicide prevention remains a priority in public health. To raise awareness of the importance of suicide prevention, the International Association for Suicide Prevention and the World Health Organization (WHO) have designated September 10 of each year as World Suicide Prevention Day. For many healthcare professionals, the prospect of working with suicidal patients can pose a great challenge since it can engender in them feelings of anxiety and a sense of helplessness and ineffectiveness.[4]

Suicide ideation is described as thoughts of ending one's life and marks the start of a continuum that progresses to suicide planning and, eventually, suicide. This continuum could be arrested or mitigated at each stage when targeted intervention is carried out successfully.

A survey of 21 countries by WHO had found that suicide ideation (thought of self-harm) was relatively common with a 12-month prevalence of approximately 2%[5] and a lifetime prevalence of 9%.[6] It was especially prevalent in individuals who had experienced hopelessness when they were under severe distress triggered by adjustment disorder, major life event stressors, depression, major psychiatric conditions, personality disorders or chronic illnesses (with or without chronic pain).

A cross-national study of suicide risks, suicide plans and suicide attempts had shown a strong association between suicide ideation and suicide plans and attempts.[6] In individuals with a history of suicide ideation, the probability of making a suicide plan and suicide attempt was approximately 33% and 30%, respectively. For those who had a history of suicide ideation and suicide planning, the probability of an attempted suicide was approximately 55%. Among those without a suicide plan, the likelihood of attempted suicide was only 15%. About 60% of participants in the study who transitioned from suicide ideation to suicide plan and attempted suicide occurred within the first year after onset of suicide ideation. These findings underscore the urgent need for careful assessment of suicide risk and early intervention in suicide ideation, especially during the first year upon onset of the latter.[6]

A Targeted Approach to Treat Suicide Ideation

Early Recognition and Identification: Mental Health Literacy

The mental health literacy of a population has been shown to correlate with the mental wellness of a community and the efficacy of its suicide prevention efforts.[7,8] When family members and peers are able to identify and recognise individuals who have suicide ideation and suicidal plans, they can help to refer them to mental health experts based at primary care medical facilities, social service agencies and emergency units in hospitals for immediate assessment and intervention.

During assessment and intervention, a careful and empathetic assessment of the individual's overall mental and physical health, social support, history of alcohol and substance abuse and use of prescription medicines that could trigger suicidal ideas could be made.

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Safety Containment, Legislation and Psychological First Aid

When there is a high risk of an individual with limited family or social support acting out with severe suicide ideation, the need for safe containment and early treatment in a mental health facility is often necessitated after consent has been given. In the absence of any consent that can be given, the Mental Health (Care and Treatment) Act has made provision for affected individuals to be removed to such facilities for treatment.[9] These measures provide time and an opportunity for mental health practitioners to carry out timely intervention and effect treatment to mitigate the risk of suicide.

There have been several developments in the treatment of suicide ideation and efforts to increase help-seeking behaviour in at-risk individuals.[10] Current evidence points towards the use of a multi-pronged strategy that comprises medical, psychological and social interventions as an effective means to treat suicide ideation in these individuals.[11]

Psychotherapy

Many psychological disorders and symptoms are associated with high levels of emotional dysregulation and increased suicide risk. It is believed that "Deficits in the ability to regulate emotion and inability to withstand negative affect have been implicated in the development of suicidal ideation and suicidality."[1]

Recent evidence has shown that cognitive behavioural therapy[12] and dialectic behavioural therapy[13] could help suicidal patients to explore and process cognitive issues that make them feel suicidal and to learn to manage their emotions and impulses more effectively. In Singapore, both psychotherapies are offered by several private and public healthcare facilities either as stand-alone treatment or as part of a therapeutic framework.

Pharmacotherapy

Depending on the underlying psychiatric condition associated with suicide ideation, the use of antidepressants, antianxiety medications and even antipsychotic medicines could help to improve the moods of patients and mitigate their suicide ideation and impulsivity. These drugs act by mediating the harmful effects that emanate from an imbalance in the serotonin, dopamine and noradrenaline pathways. In patients with bipolar and mood disorders, it was reported that the extended use of lithium carbonate could reduce suicide ideation and risk.[14]

Recent clinical trials on the use of ketamine have demonstrated that a single dose of intravenous ketamine infusion—similar to that used in a treatment trial involving patients with major depression—can induce a rapid decline in suicide ideation. In their study on the effect of ketamine use on suicide ideation, Wilkinson et al reported that "Within a day, about 55 percent of individuals who received ketamine no longer had suicidal ideations, compared to 20 percent who received a placebo. This reduction in suicidal ideations lasted for at least seven days."[15]

The encouraging findings on ketamine use have prompted several centres dedicated to the treatment of mood disorders to conduct further trials to evaluate the long-term efficacy and safety of intravenous ketamine administration in emergency and acute suicide care management pathways.[16] A new intranasal ketamine spray is available in the United States and an application for its clinical use in Singapore is currently pending an outcome.

Neurostimulation Therapy

As a form of neurostimulation therapy, the effectiveness of electroconvulsive therapy (ECT) to treat severely depressed patients with high suicidal tendencies is well documented. However, negative public perception of ECT has meant that it is reduced to being considered only as a form of contingency treatment. Since it has been shown that "expressed suicidal intent in depressed patients was rapidly relieved with ECT", it was recommended that "evidence-based treatment algorithms for major depressive mood disorders should include dichotomization according to suicide risk, as assessed by interview; and for patients at risk, ECT should be considered earlier than at its conventional 'last resort' position."[17]

Another novel neurostimulation therapy is repetitive transcranial magnetic stimulation (rTMS) that is used to treat depressed patients. The findings on rTMS seemed to suggest that it can also help to lessen suicide ideation.[18] A randomised sham-controlled crossover study that used accelerated intermittent theta-burst stimulation delivered over the left dorsal prefrontal cortex in treatment-resistant depressed patients had shown a reduction in the suicide ideation score over time in both active and sham treatment groups.[19]

Conclusion

Suicide is a growing issue in public health. There are multiple agencies in the healthcare and social service sectors that continue to provide outreach services to individuals at risk of suicide and self-harm. Consequently, there is a need to develop an integrated and coordinated intervention strategy and therapy programme that involve social service agencies, families, the police and healthcare facilities. It should also incorporate evidence-based interventions that target the root causes of suicide ideation and attempts at self-harm.[20] Additionally, it would strengthen acute management of suicidal individuals in the first year of

presentation which include medical stabilisation, reduction in immediate risk of self-harm, facilitation of early treatment planning, management of underlying medical and psychiatric disorders and case management to monitor at-risk individuals.

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Original Article

Reliability of Graders and Comparison with an Automated Algorithm for Vertical Cup-Disc Ratio Grading in Fundus Photographs

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Abstract

Introduction: We aimed to investigate the intergrader and intragrader reliability of human graders and an automated algorithm for vertical cup-disc ratio (CDR) grading in colour fundus photographs. Materials and Methods: Two-hundred fundus photographs were selected from a database of 3000 photographs of patients screened at a tertiary ophthalmology referral centre. The graders included glaucoma specialists (n = 3), general ophthalmologists (n = 2), optometrists (n = 2), family physicians (n = 2) and a novel automated algorithm (AA). In total, 2 rounds of CDR grading were held for each grader on 2 different dates, with the photographs presented in random order. The CDR values were graded as 0.1-1.0 or ungradable. The grading results of the 2 senior glaucoma specialists were used as the reference benchmarks for comparison. Results: The intraclass correlation coefficient values ranged from 0.37-0.74 and 0.47-0.97 for intergrader and intragrader reliability, respectively. There was no significant correlation between the human graders' level of reliability and their years of experience in grading CDR (*P* = 0.91). The area under the curve (AUC) value of the AA was 0.847 (comparable to AUC value of 0.876 for the glaucoma specialist). Bland Altman plots demonstrated that the AA's performance was at least comparable to a glaucoma specialist. Conclusion: The results suggest that AA is comparable to and may have more consistent performance than human graders in CDR grading of fundus photographs. This may have potential application as a screening tool to help detect asymptomatic glaucoma-suspect patients in the community.

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Key words: Eyes, Glaucoma, Intraocular pressure

Introduction

Glaucoma is one of the world's leading causes of irreversible blindness, with certain types of glaucoma such as angle-closure glaucoma being more prevalent in East Asia.[1] The global prevalence is currently estimated to be 3.54% in those aged 40-80 years old.[2] People affected by glaucoma in 2013 was estimated to be 64.3 million.[2] This is expected to rise to 111.8 million by 2040.[2] This trend of an increasing eye disease burden is also expected to be seen in Singapore in future.[3,4] As glaucoma is asymptomatic in the early stages, it is important for early detection and diagnosis so that blindness may be prevented with early treatment.[5] Glaucoma is primarily diagnosed by ophthalmologists in tertiary eye care and commonly after incidental findings of high intraocular pressure or a raised vertical cup-disc ratio (CDR) detected on retinal photographs.

Apart from a simple colour photograph, there are other methods of glaucoma screening, such as the use of tonometry, the Van Herrick method, optical coherence tomography (OCT), OCT-angiography, macula vessel density, ganglion cell inner plexiform layer thickness and automated perimetry tests.[6-9] Studies have shown that the determination of the optic disc margin based on colour photographs does not always correlate with the Bruch's membrane opening,

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which should be the anatomically correct disc margin.[10,11] This leads to a mismatch between the clinically perceived disc margin and the true Bruch's membrane opening, which can be detected by OCT.[10] This can cause errors in the estimation of the optic disc size and therefore errors in CDR estimation. Hence, OCT had been proposed to be used in clinical assessment for better accuracy and consistency at measuring CDR.[12] Accurate measurement of CDR is important as variability in measurements may affect the risk estimation and subsequent management of patients who are glaucoma-suspects.[13] However, many of the above approaches require expensive bulky equipment and are usually not practical for screening purposes. Primary care physicians often use colour fundus photographs as the main ocular screening modality as there is a large number of diabetic patients who require regular diabetic retinopathy screening. Most fundus photographs are either optic disc or macula centred images and the optic nerve head can be analysed for features of glaucomatous optic neuropathy, especially raised vertical CDR.

The optic nerve head appearance—in particular the vertical CDR—is usually determined subjectively by a grader who can include one of the following: ophthalmologists, optometrists, primary care physicians, trained graders or research staff within a grading centre. Studies have shown that this is prone to high intra and intergrader variability which could be worse in real-world clinical setting that is typically without standardised training.[14] As such, the use of automated algorithms (AA) in the detection of vertical CDR on optic disc photos might have the potential to be used in mass screening settings.

For the current study, we aimed to determine the intergrader and intragrader reliability between different professionals namely glaucoma specialists, general ophthalmologists, family physicians and optometrists. In addition, we aimed to validate and compare human grading with a novel AA in determining vertical CDR from colour fundus photographs.

Materials and Methods

This study was approved by the Domain Specific Review Board of the National Healthcare Group in Singapore. Fundus photographs were obtained from patients who came for routine eye screening at the ophthalmology department of a tertiary referral hospital. The photographs were taken using VISUCAM$^{PRO\ NM}$ (Carl Zeiss Meditec Inc., United States of America). We selected 200 macular-centred fundus photographs for the grading process. The photographs were selected to show optic discs with different vertical CDR as well as poor quality images of optic discs. The photographs were grouped as vertical CDR 0.1-0.2, 0.3-0.4, 0.5-0.6, 0.7-0.8, 0.9-1.0 and ungradable images. The sample photographs of each group are shown in Figure 1. There were 33, 33, 33, 34, 34 and 33 photographs in each group, respectively.

In this study, graders with different levels of experience in assessing vertical CDR on colour photographs were included. They included glaucoma specialists (n = 3), general ophthalmologists (n = 2), family physicians (n = 2) and optometrists (n = 2). Of the glaucoma specialists, there were 2 fellowship-trained glaucoma senior specialists, each with more than 10 years of experience, while another was a glaucoma specialist with 5 years of experience. One general ophthalmologist had 10 years of experience and the other had 5 years of experience. Both optometrists had at least 5 years of experience working in an ophthalmology department of a tertiary hospital. Both family physicians included in this study had basic knowledge of the optic nerve head anatomy but had graded less than 10 colour fundus photographs a year.

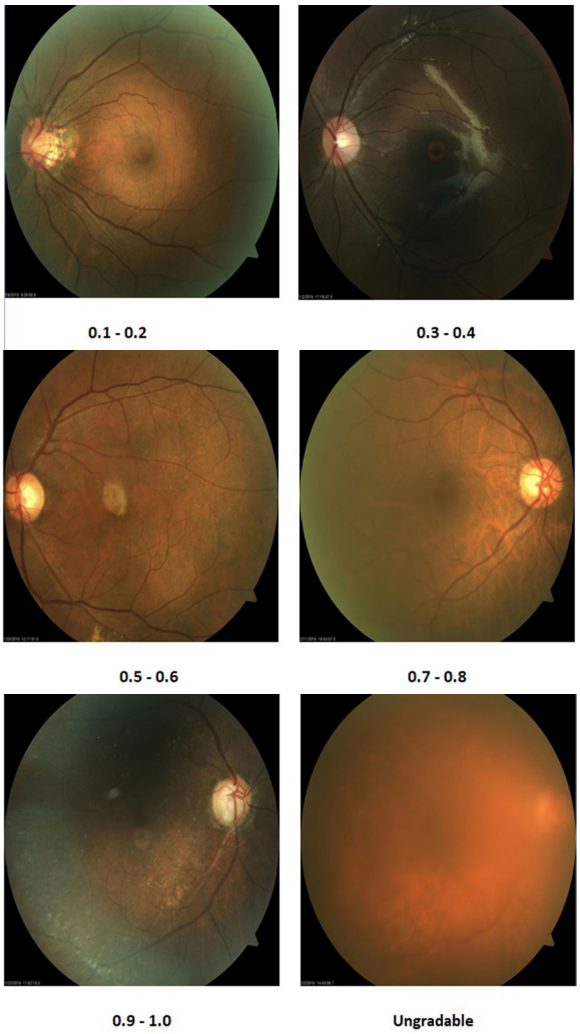


Fig. 1. Sample photographs of each vertical cup-disc ratio group.

The newly developed AA assessed in this study is currently an unvalidated system in large-scale clinical settings, particularly in Asia. It had been tested on various known datasets of mixed-ethnic groups, achieving comparable performance of what is state-of-the-art in the literature.[15] The AA is mainly based on a deep learning model named U-Net, which is a U-shaped convolutional network originally developed for biomedical image segmentation. We developed a modified U-Net model for optic disc and cup segmentation. The proposed optic disc and cup segmentation procedure involves 2 main steps. A colour fundus image is firstly preprocessed with contrast enhancement, followed by resizing to the dimension of 512 × 512 pixels. Then, our single-label modified U-Net model is applied to roughly segment the optic disc region in the image as the region of interest (ROI). In step 2, the ROI is resized to the dimension of 512 × 512 pixels. Our multilabel U-Net model is employed to segment the optic disc and cup simultaneously. The predicted optic disc and cup from step 2 are further processed via a morphological postprocessing module for the finetuning of their boundaries. Finally, vertical CDR is calculated using the vertical diameter of the optic cup versus that of the optic disc.

Graders reviewed and graded all 200 fundus photographs independently. Each photograph was graded with vertical CDR to 1 decimal place or as "ungradable". "Ungradable" was defined as a poor quality photograph including unfocused image of the optic disc and obstruction over the optic disc that precluded grading. Two rounds of grading were conducted for each human grader using the same 200 photographs on 2 different dates. During the second round of grading, the photographs were presented back to them at random, in a different order compared to the first round of grading.

Statistical analysis was carried out using SPSS Statistics (Version 25). The gradings by the 2 senior glaucoma specialists were set as "gold standards" in the study to serve as the 2 reference points for comparison to other graders. Analysis was carried out to assess intragrader and intergrader reliabilitiy. This was measured by the intraclass correlation coefficient (ICC). The ICC can be categorised into different levels of reliability. Values <0.5 indicate poor reliability, 0.5-0.75 indicate moderate reliability, 0.75-0.9 indicate good reliability and >0.90 indicate excellent reliability.[16] Statistical significance was set at P <0.05. Correlation between levels of reliability and years of experience were assessed using logistic regression. Correlation was also assessed using Bland Altman plots.

In addition, receiver operating characteristic (ROC) curves were plotted. ROC serves to assess characteristics of the AA via area under the curve (AUC). Outcomes in the ROC curve were dichotomised into binary outcomes based on the senior glaucoma specialists' gradings of "Normal CDR" and "Referable CDR" (with CDR values of <0.6 being classified as "Normal CDR"). The cut-off value of 0.6 was chosen because once CDR ≥0.6, the probability of abnormality increases dramatically.[17] Ungradable images were also classified under "Referable CDR". This division was to determine the functional capability of the AA (if adapted in future for community eye screening) to classify patients correctly into the 2 categories—healthy individuals or individuals who are potential glaucoma-suspects that need further specialist assessment.

Results

The results of intergrader reliability are shown in Table 1 with senior glaucoma specialist 1 as the reference. Table 2 shows the intergrader reliabilitiy with senior glaucoma specialist 2 as the reference. Both senior glaucoma specialists achieved moderate intergrader reliability. ICC values showed a "moderate" level of reliability for most of our graders compared to the reference grader. One grader (optometrist) exhibited a "poor" level of intergrader reliability (ICC 0.37). Interestingly, there was no significant correlation between the graders' level of intergrader reliability and their experience in CDR grading (Table 3). The family physician group—who had minimal grading experience—was able to display a similar level of reliability to that of the glaucoma specialists. On the other hand, for the optometrists—despite having similar experience—there was a large disparity in their levels of reliability.

The intragrader reliabilitiy are shown in Table 4. Once again, there was no relationship between grader experience

Table 1. Intergrader Reliability in Vertical Cup-Disc Ratio Grading (Senior Glaucoma Specialist 1 As Reference)

	Intergrader Reliability			
	Intraclass Correlation Coefficient	95% Confidence Interval	*P* Value	Level of Reliability
Senior glaucoma specialist 2	0.69	0.46 – 0.80	<0.001	Moderate
Glaucoma specialist	0.69	0.61 – 0.76	<0.001	Moderate
General ophthalmologist 1	0.70	0.62 – 0.76	<0.001	Moderate
General ophthalmologist 2	0.71	0.62 – 0.77	<0.001	Moderate
Optometrist 1	0.74	0.67 – 0.80	<0.001	Moderate
Optometrist 2	0.37	0.19 – 0.52	<0.001	Poor
Family physician 1	0.61	0.51 – 0.69	<0.001	Moderate
Family physician 2	0.67	0.58 – 0.74	<0.001	Moderate
Automated algorithm	0.52	0.39 – 0.63	<0.001	Moderate

Table 2. Intergrader Reliabilitiy in Vertical Cup-Disc Ratio Grading (Senior Glaucoma Specialist 2 As Reference)

	Intergrader Reliability			
	Intraclass Correlation Coefficient	95% Confidence Interval	*P* Value	Level of Reliability
Senior glaucoma specialist 1	0.69	0.46 – 0.80	<0.001	Moderate
Glaucoma specialist	0.71	0.60 – 0.80	<0.001	Moderate
General ophthalmologist 1	0.72	0.41 – 0.64	<0.001	Moderate
General ophthalmologist 2	0.49	0.16 – 0.69	<0.001	Poor
Optometrist 1	0.73	0.54 – 0.83	<0.001	Moderate
Optometrist 2	0.37	0.21 – 0.45	<0.001	Poor
Family physician 1	0.66	0.49 – 0.77	<0.001	Moderate
Family physician 2	0.55	0.19 – 0.74	<0.001	Moderate
Automated algorithm	0.65	0.55 – 0.72	<0.001	Moderate

Table 3. Correlation Between Grader Experience and Reliability Levels (Senior Glaucoma Specialist 1 As Reference)

	Years of Experience	Inter-grader Reliability	*P* Value	Intra-grader Reliability	*P* Value
Glaucoma specialist	5	Moderate	0.91	Moderate	0.57
General ophthalmologist 1	10	Moderate	0.91	Moderate	0.57
General ophthalmologist 2	5	Moderate	0.91	Good	0.57
Optometrist 1	5	Moderate	0.91	Moderate	0.57
Optometrist 2	5	Poor	0.91	Good	0.57
Family physician 1	0	Moderate	0.91	Poor	0.57
Family physician 2	0	Moderate	0.91	Moderate	0.57

Table 4. Intragrader Reliability in Vertical Cup-Disc Ratio Grading

	Intergrader Reliability			
	Intraclass Correlation Coefficient	95% Confidence Interval	*P* Value	Level of Reliability
Senior glaucoma specialist 1	0.70	0.61 – 0.76	<0.001	Moderate
Senior glaucoma specialist 2	0.97	0.96 – 0.98	<0.001	Excellent
Glaucoma specialist	0.71	0.63 – 0.77	<0.001	Moderate
General ophthalmologist 1	0.87	0.83 – 0.90	<0.001	Good
General ophthalmologist 2	0.64	0.55 – 0.71	<0.001	Moderate
Optometrist 1	0.87	0.83 – 0.90	<0.001	Good
Optometrist 2	0.47	0.36 – 0.57	<0.001	Poor
Family physician 1	0.52	0.41 – 0.61	<0.001	Moderate
Family physician 2	0.62	0.52 – 0.70	<0.001	Moderate

and level of intragrader reliability (Table 3). Senior glaucoma specialist 2, who served as one of the reference standards, achieved an "excellent" level of intragrader reliability. One of the optometrists and a general ophthalmologist achieved a "good" level of intragrader reliability, which was better than the glaucoma specialist.

The ROC curves were plotted for the AA and senior glaucoma specialist 1 (Fig. 2) and for senior glaucoma specialist 2 (Fig. 3). In comparison to the reference standard set by senior glaucoma specialist 1, AUC for the AA was 0.829 (comparable to the AUC value of 0.823 of the glaucoma specialist). Comparing to senior glaucoma specialist 2, the AUC for AA was 0.847, while AUC of the glaucoma specialist was 0.876. These results suggest that the AA grader had discriminative power that was comparable to that of a glaucoma specialist.[18]

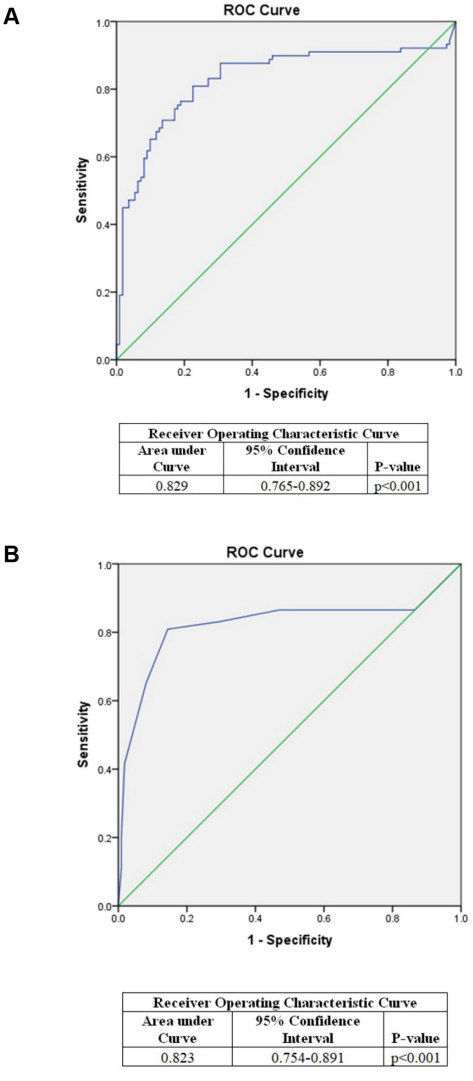
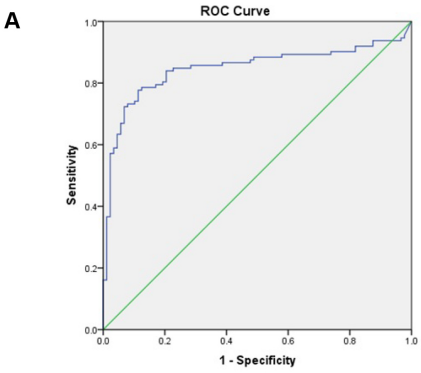
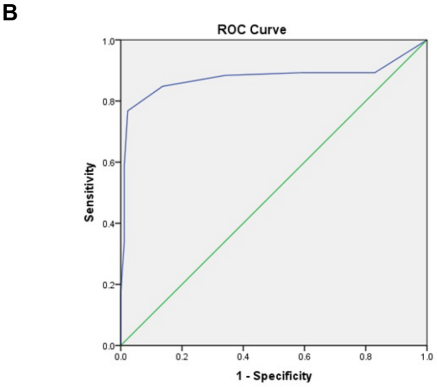


Fig. 2. Receiver operating characteristic curves. A: Automated algorithm (senior glaucoma specialist 1). B: Glaucoma specialist (senior glaucoma specialist 1).



Receiver Operating Characteristic Curve		
Area under Curve	95% Confidence Interval	P-value
0.847	0.789-0.905	p<0.001



Receiver Operating Characteristic Curve		
Area under Curve	95% Confidence Interval	P-value
0.876	0.821-0.931	p<0.001

Fig. 3. Receiver operating characteristic curves. A: Automated algorithm (senior glaucoma specialist 2). B: Glaucoma specialist (senior glaucoma specialist 2).

In addition, Bland Altman plots were performed. The plots compared the results of the AA against the 2 senior glaucoma specialists (Fig. 4). There appears to be more proportional bias in Figure 4A, which may be related to the poorer intragrader reliability of senior glaucoma specialist 1 as compared to senior glaucoma specialist 2. Hence, for subsequent plots, senior glaucoma specialist 2 was used as the reference grader in comparison to other graders (Fig. 5). Based on the plots, the AA appears to have reliability comparable to that of a glaucoma specialist.

Discussion

Fundus photography remains one of the most common and simplest methods for eye screening, especially for clinics located in the community where family medicine is practised. In such settings, sophisticated and expensive ophthalmology equipment are not practical or cost-effective. Hence, fundus photography remains a useful modality for

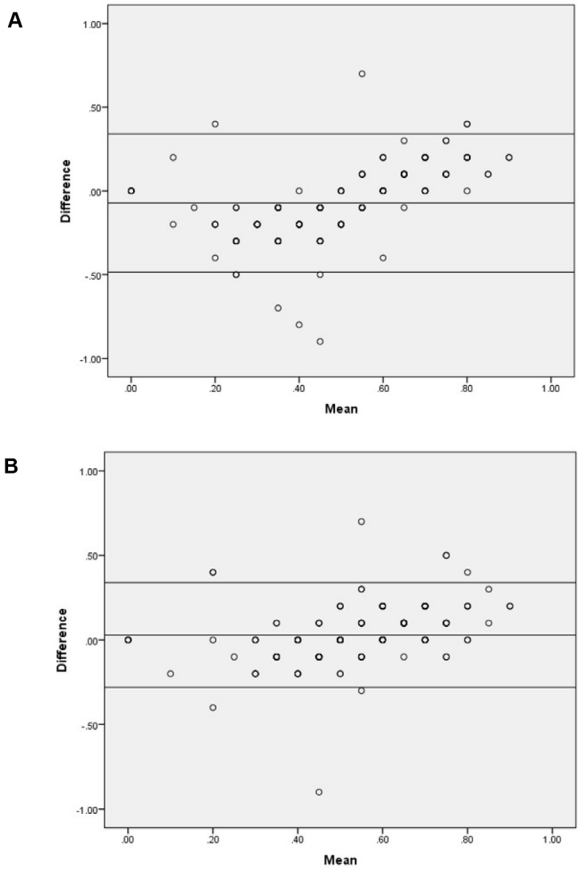


Fig. 4. Bland Altman plots of the automated algorithms. A: Against senior glaucoma specialist 1. B: Against senior glaucoma specialist 2.

the screening of ocular diseases and is the focus in the development of AAs for mass screening. Portable fundus cameras are also an option for use in tele-ophthalmology diagnosis of glaucoma which can potentially benefit patients with mobility issues and who face difficulties visiting eye clinics due to the long distance from their homes.[19,20] They may also benefit people living in more rural areas with minimal access to tertiary eye care. Use of the same imaging modality for subsequent fundus photographs will also allow monitoring of CDR and for the detection of any changes.[21]

Developing an AA system to determine CDR accurately does not come without challenges. Many methods have been previously proposed for the processes of optic disc extraction, optic cup extraction and peripapillary atrophy (PPA) localisation.[22] Different methods exhibit different levels of accuracy.[22] Various new AA systems are being developed for possible future use in glaucoma screening.[23-25] Each system employs different techniques for glaucoma detection on colour fundus photographs. Some used OCT imaging for CDR calculation while another used a combination of structural and non-structural features for glaucoma detection.[23,25] Shibata et al developed

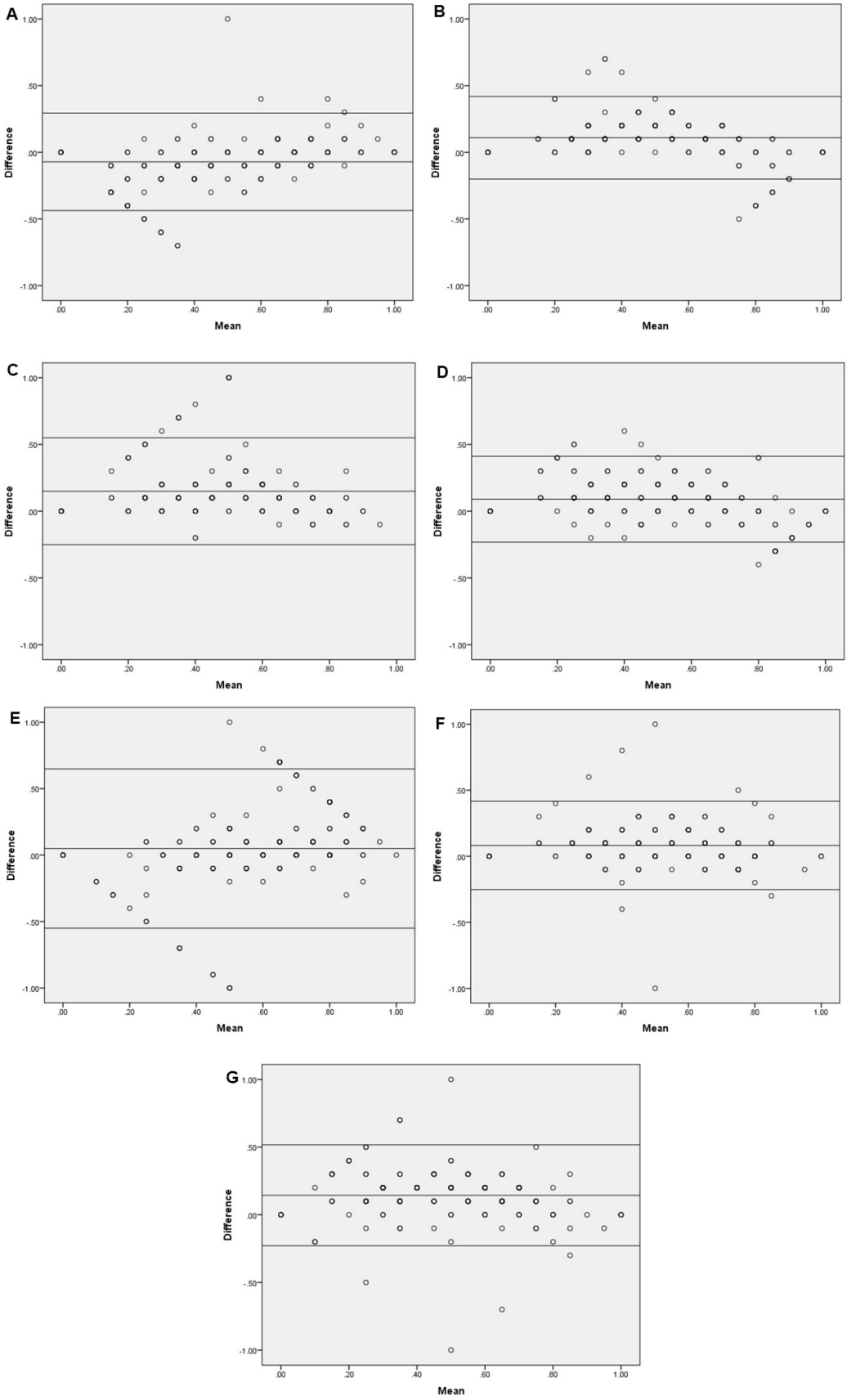


Fig. 5. Bland Altman plots. A: Glaucoma specialist against senior glaucoma specialist 2. B: General ophthalmologist 1 against senior glaucoma specialist 2. C: General ophthalmologist 2 against senior glaucoma specialist 2. D: Optometrist 1 against senior glaucoma specialist 2. E: Optometrist 2 against senior glaucoma specialist 2. F: Family physician 1 against senior glaucoma specialist 2. G: Family physician 2 against senior glaucoma specialist 2.

an AA that showed higher diagnostic performance to their ophthalmology residents.[26] Christopher et al also evaluated various deep learning architectures to assess their performance in detecting varying degrees of glaucomatous optic neuropathy in fundus photographs.[27] Their best performing model achieved an AUC of 0.91 for healthy eyes, 0.89 in eyes with mild glaucoma and 0.97 in moderate to severe glaucomatous eyes.[27] These 2 systems aimed to detect various glaucomatous changes, all at the same time based on retinal images alone and not just to calculate CDR. The changes included rim notching, laminar dot sign, disc edge haemorrhages and retinal nerve fibre layer defects.[26] In a previous study that is similar to ours, Muramatsu et al proposed a method of automated CDR determination on stereo fundus images via segmentation of the cup region using a depth map.[28] AUC achieved by the AA system in that study was 0.90 compared to an ophthalmologist's assessment.[28] In another recent study, Li et al presented a deep learning algorithm that achieved an AUC of 0.986 in detecting glaucomatous optic neuropathy on fundus photographs.[29]

Our study differs from those described as our main focus is for the AA to accurately determine only the vertical CDR from colour fundus photographs. The aim is for the AA to serve as an initial screening tool to detect glaucoma-suspects and when found, the patients would still require prompt specialist assessment for diagnosis, monitoring and treatment. It is not meant to be a substitute for a full ocular assessment by an ophthalmologist. The method of detecting raised CDR is also simple and easier to comprehend, even for non-medical personnel. If any doubts arise when it is implemented in clinical practice, a trained human grader can help to verify the CDR determined by the AA. In contrast, verifying other signs of glaucomatous change on the optic nerve—such as rim notching and laminar dot sign—may not be as easy for the untrained grader. Unlike Muranatsu et al, we did not use stereo images in our study.[28] Our aim is also for the AA to function in the community without advanced equipment such as stereo fundus photography. In our validation study, the AA's AUC is very similar to that of a glaucoma specialist, suggesting that it can detect referable CDR accurately. With additional training, the AA system might be used as a good first-line screening tool in large groups of people in the community, followed by subsequent assessment by doctors when there is suspicion of glaucoma. It is difficult to compare AAs in various studies because they were evaluated by different methods that used different public or private databases.

There is a significant amount of variability between observers in determining clinical vertical CDR.[14] Our study also showed the inherent intergrader and intragrader variations in CDR assessment among different individuals. This is expected as the method of manual grading by looking at the physical appearance of the optic nerve is highly subjective. The reasons for this may be due to differences in prior training in grading colour fundus photographs, lack of stereoscopic views, variations in optic disc morphology and lack of familiarity in CDR grading.[30,31] Even between glaucoma specialists in our study, there is considerable intergrader variability.[32] This suggests that a more standardised automated screening tool might be useful in improving consistency. First, it will minimise intergrader variations during colour fundus photograph grading of vertical CDR. Second, an AA will be faster in screening a large number of optic disc photographs.

This study has various limitations. First, the number of fundus photographs was small and comprised only Asian eyes. In future, larger numbers of fundus photographs are needed to obtain results that will be representative of screening large numbers of people. The AA has yet to be validated on large-scale clinical datasets. In addition, before it can be applied in real life, it should ideally be evaluated under clinical conditions where a large number of patients with different demographics and ocular issues (e.g., presence of cataracts) are assessed. However, it is interesting to note that the current AA is also able to identify "ungradable" optic disc images and this would be useful in a clinical setting. Second, this study was done with assessment made in reference to CDR grading by either 1 of the 2 designated "gold standard" graders who were senior glaucoma specialists. Identification of true glaucoma cases is inadequate and accurate CDR measurements are prone to grader variability. It will be better if fundus photographs are interpreted in conjunction with other ocular investigations, such as OCT scans of the retinal nerve fibre layers and visual field tests. This will enable the identification of true glaucoma patients and consistent CDR measurements, thereby creating an accurate reference for comparison to other graders.

In conclusion, we showed that there is significant inter and intragrader variability among human graders for vertical CDR in fundus photographs. The use of an AA is comparable to a glaucoma specialist and can potentially play an important role in mass screening of glaucoma-suspects.

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Original Article

Positive Fluid Balance is Associated with Poor Clinical Outcomes in Paediatric Severe Sepsis and Septic Shock

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Abstract

Introduction: Growing evidence suggests there is potential harm associated with excess fluid in critically ill children. This study aimed to evaluate the association between percentage fluid overload (%FO) and paediatric intensive care unit (PICU) mortality in children with severe sepsis and septic shock. Materials and Methods: Patients with severe sepsis and septic shock admitted to the PICU were identified through discharge codes. Data on clinical characteristics, fluid input and output were collected. %FO was calculated as: (total daily input - total daily output [L]/admission body weight [kg]) × 100. The primary outcome was PICU mortality. Secondary outcomes were 28-day ventilator-free days (VFD), intensive care unit-free days (IFD) and inotrope-free days (InoFD). Multivariate analysis adjusting for presence of comorbidities, Pediatric Index of Mortality (PIM) 2 score and multiorgan dysfunction were used to determine the association between cumulative %FO over 5 days and outcomes. Results: A total of 116 patients were identified, with a mortality rate of 28.4% (33/116). Overall median age was 105.9 (23.1-157.2) months. Cumulative %FO over 5 days was higher in non-survivors compared to survivors (median [interquartile range], 15.1 [6.3-27.1] vs 3.6 [0.7-11.1]%; *P* <0.001). Cumulative %FO was associated with increased mortality (adjusted odds ratio 1.08, 95% confidence interval 1.03-1.13; *P* = 0.001) and decreased VFD, IFD and InoFD (adjusted mean difference -0.37 [-0.53 - -0.21] days, -0.34 [-0.49 - -0.20] days, and -0.31 [-0.48 - -0.14] days, respectively). Conclusion: Cumulative %FO within the first 5 days of PICU stay was consistently and independently associated with poor clinical outcomes in children with severe sepsis and septic shock. Future studies are needed to test the impact of restrictive fluid strategies in these children.

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Key words: Multiorgan dysfunction, Percentage fluid overload, Ventilator-free days

Introduction

For many years, the clinical dogma of early goal-directed therapy (EGDT) with fluid resuscitation was one of the cornerstones of treatment in sepsis.[1,2] Surviving Sepsis Campaign guidelines recommended fluid resuscitation to restore mean circulating filling pressure guided by bedside parameters for patients with sepsis.[3] However, recent studies have challenged this approach to fluid resuscitation, demonstrating that positive fluid balance was associated with poor clinical outcomes.[4,5] In light of the Fluid Expansion As Supportive Therapy (FEAST) trial in critically ill African children, where aggressive early fluid resuscitation in children with severe febrile illness was associated with relative risk of mortality of almost 1.5, recent World Health Organization (WHO) guidelines for fluid resuscitation in children with severe sepsis and septic shock now advocate for a more conservative approach to fluid resuscitation.[4,6]

Beyond the initial fluid resuscitation period, however, there is growing evidence on the potential harm of positive fluid balance in critically ill patients.[5] Adult sepsis studies

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demonstrated that positive cumulative fluid balance and volume overload lead to increased mortality, organ dysfunction, mechanical ventilation (MV) duration and need for renal replacement therapy.[5,7] Positive fluid balance over 7 days in adults with sepsis and septic shock was associated with mortality.[8] Other studies have demonstrated a "dose-dependent" relationship of cumulative fluid balance and mortality.[9] Fluid overload in other subgroups of patients such as adults with acute lung injury was associated with longer MV duration and intensive care unit (ICU) stay.[7]

With only a limited number of studies, the impact of fluid balance on septic children after admission to the paediatric intensive care unit (PICU) remains controversial.[10-12] In critically ill children with severe sepsis and septic shock, fluid overload—whether given within the first 24 hours or within 7 days of PICU admission—was shown to be associated with increased mortality.[11,12] Interestingly, a multicentre study reported that the effect of positive fluid balance on mortality was only present in those who had a low mortality risk from septic shock; whereas in the high mortality risk group, there was no association between fluid balance and worse clinical course.[10] Fluid overload in other groups of critically ill children including those with acute lung injury and those on continuous renal replacement therapy (CRRT) provides indirect evidence of its negative effects.[13-15] A recent meta-analysis of 3200 patients studying the association between fluid balance and a general cohort of critically ill children reported a 6% increase in odds of mortality for every 1% increase in percentage fluid overload (%FO).[16]

Therefore, there is equipoise on the impact of fluid balance in children with severe sepsis and septic shock. We postulated that a greater amount of positive fluid balance is associated with poor clinical outcomes. This study aimed to: 1) identify the risk factors for mortality in paediatric severe sepsis and septic shock; and 2) evaluate the relationship between %FO and PICU mortality in this group of patients.

Materials and Methods

This is a retrospective cohort study performed in a multidisciplinary PICU of the largest tertiary, university-affiliated paediatric hospital in Singapore. Intensivists treated patients with sepsis according to current sepsis guidelines though practice was not strictly protocolised. This study was approved by the SingHealth Centralised Institutional Review Board (reference number: 2016/2171) and waiver of consent was granted.

Study Design

Patients were identified based on their discharge diagnosis from hospital-wide administrative-linked electronic databases. The study population was one with paediatric severe sepsis or septic shock as defined by the International Pediatric Sepsis Consensus Conference.[17] To ensure complete pick-up, we identified all patients discharged with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM) after 12 January 2012 equivalent for codes A02.1, A31.2, A32.7, A39.1, A39.2, A40, A41, A48.3 and A49.9 or with the key words "bacteraemia", "sepsis", "severe sepsis" and "septic shock". Case records were examined to determine if the definition for severe sepsis or septic shock was fulfilled and thus eligible for inclusion in the study. Patients admitted to the PICU between 1 January 2010 and 31 October 2017 were included. Patients were 0 to 18 years of age and from any source of admission (whether from the ward or emergency room).

Data Collection

We extracted demographic, microbiological, clinical and detailed fluid input and output data from electronic medical records. Comorbidities were considered based on the "Complex Chronic Conditions" list of diseases.[18] The Pediatric Index of Mortality (PIM) 2 and Pediatric Logistic Organ Dysfunction (PELOD) scores were taken on PICU admission.[19,20] Data on the use of diuretics and renal replacement therapy were also collected. Organ dysfunction was defined according to the International Pediatric Sepsis Consensus Conference definitions.[7] Day 1 of sepsis was defined as the first day the patient fulfilled the criteria for severe sepsis or septic shock in the PICU.

Total daily input was calculated as the sum of all intravenous and oral fluids administered to the patient. Total daily output was calculated as the sum of all output volumes including urine, gastrointestinal aspirates, drains and fluid removal by renal replacement therapies. Insensible losses were not taken into account. For standardisation, fluid calculations were done based on 6 am input/output. This was done for the first 5 days of sepsis. The magnitude of positive fluid balance was expressed as %FO and was calculated using the following formula: Daily %FO = (total daily input - total daily output [L]/admission body weight [kg]) × 100.[16] Cumulative %FO was calculated as the sum of daily % FO over the first 5 days of sepsis.

Outcomes

Our primary outcome was PICU mortality. PICU mortality was treated as a binary variable with the categories of "survivors" and "non-survivors". Secondary outcomes were ventilator-free days (VFD), intensive care unit-free days (IFD) and inotrope-free days (InoFD), of up to 28 days. This was to account for mortality as a competing outcome. VFD was defined as days-free and alive from MV up to 28

days. Hence, if a patient was on MV for 28 days or more, or died at any time during PICU admission, his/her VFD was taken as zero. InoFD was defined as days-free and alive from inotropic support up to 28 days. IFD was defined as days alive and discharged from the PICU up to 28 days. VFD, IFD and InoFD were treated as continuous data.

Statistical Analysis

All demographic, clinical and microbiological data were summarised with respect to PICU mortality status. Categorical and continuous data were summarised as counts (percentages) and median (interquartile range [IQR]), respectively. Mortality groups were compared using Mann-Whitney U and chi-squared tests for continuous and categorical variables, respectively. Univariate and multivariate logistic regression was used to adjust for a priori determined covariates on the basis of previously established associations including %FO, presence of comorbidities, PIM 2 score and multiorgan dysfunction for the binary outcome of PICU mortality.[21-23] Association from logistic regression was expressed as odds ratio (OR) with 95% confidence interval (CI). Univariate and multivariate linear regression was used to estimate association between all secondary outcomes (i.e. VFD, InoFD, IFD and covariates).

Receiver operating characteristic (ROC) curve analysis was performed to examine the ability of %FO to discriminate between survivor and non-survivor patients. Sensitivity against (1− specificity) was plotted at each level and the area under the ROC curve (AUROC)—which reflects the probability of correctly identifying survivor and non-survivor patients—was calculated. The Youden index (sensitivity+ specificity−1) was calculated to determine the best compromise between sensitivity and specificity; the closer the value to 1, the greater the diagnostic power.[24] %FO cut-offs were determined based on the best Youden Index. Univariate and multivariate models based on %FO as a continuous or categorical variable were also compared. %FO cut-offs were also used for all secondary outcomes.

All statistical tests were 2-sided and P values <0.05 were considered statistically significant. Statistical analyses were performed using SAS 9.4 statistical software (SAS Institute, North Carolina, United States of America).

Results

There were 116 patients with severe sepsis or septic shock over the study period (Fig. 1). A total of 33/116 (28.4%) patients died with a median time to death of 4 (2-10) days. The overall median age was 105.9 (23.1-157.2) months (Table 1). Majority of patients (95/116 [81.9%]) were admitted to the PICU either directly from the emergency room or within 1 day of hospital admission. First-dose antibiotics were received within an hour of presentation

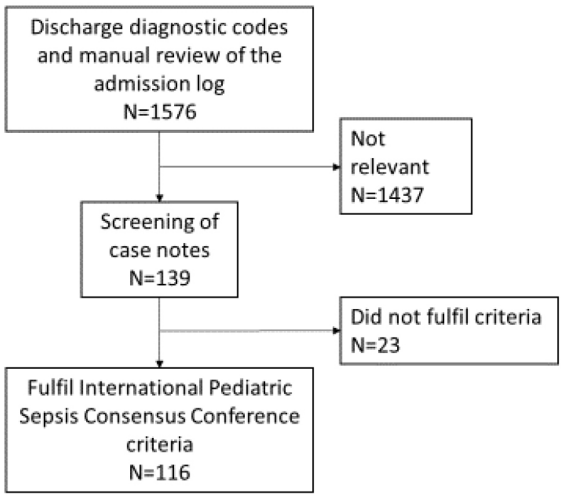

Fig. 1. Flowchart demonstrating the identification process of patients with severe sepsis and septic shock.

in 55/116 (47.4%) patients and the most common first-line antibiotic was a second-generation cephalosporin (45/55 [81.8%]). Fluid bolus and inotropes were received within an hour of presentation in 87/116 (75.0%) and 26/116 (22.4%) patients, respectively. Bacteraemia was present in 20/116 (17.2%) patients. The most common bacterial and viral aetiology of sepsis in our cohort was *Streptococcus species* (11/116 [9.5%]), influenzae (7/116 [6.0%]) and adenovirus (7/116 [6.0%]), respectively (Table 2).

Non-survivors had higher admission PIM 2 (5.0 [4.0-14.3]% vs 2.7 [1.1-6.4]%; P <0.001) and PELOD (22.0 [12.0-32.0] vs 11.0 [10.0-20.0]; P<0.001) scores compared to survivors. Non-survivors were also more likely to have underlying comorbidities (24/33 [72.7%] vs 35/83 [42.2%]; P = 0.004). Compared to survivors, there was a greater proportion of non-survivors with multiorgan dysfunction (33/33 [100%] vs 53/83 [63.9%]; P <0.001) and who required PICU support in the form of inotropes (33/33 [100%] vs 58/83 [69.9%]; P <0.001), MV (32/33 [97.0%] vs 42/83 [50.6%]; P ≤0.001) and CRRT (9/33 [27.3%] vs 4/83 [4.8%]; P = 0.002). The overall VFD, InoFD and IFD were 23 (0-28), 25 (0-28) and 21 (0-26) days, respectively.

Daily %FO on the first 5 days of sepsis was higher in non-survivors (Fig. 2). Non-survivors had persistently high daily %FO up to the 5th day of PICU admission. Cumulative %FO over 5 days was significantly higher in non-survivors compared to survivors (median [IQR], 15.1 [6.3-27.1] vs 3.6 [0.7-11.1]%; P <0.001) (Table 3).

In the multivariable logistic regression model, cumulative %FO was independently associated with mortality (adjusted OR, 1.08; 95% CI, 1.03-1.13; P = 0.001] (Table 4). Hence, for every 1% FO increase, there was an increase in mortality

Table 1. Clinical Characteristics of Patients with Severe Sepsis and Septic Shock

Characteristic	Non-Survivor (n = 33)	Survivor (n = 83)	All (n = 116)	*P* Value
Age, months	78.1 (28.4 – 1567.0)	112.8 (21.4 – 159.1)	105.9 (23.1 – 157.2)	0.951
Weight, kg	18.0 (12.0 – 30.9)	27.5 (11.0 – 45.0)	24.7 (11.4 – 40.0)	0.118
PIM 2	5.0 (4.0 – 14.3)	2.7 (1.1 – 6.4)	3.7 (1.3 – 9.6)	**<0.001**
PELOD	22.0 (1.02 – 32.0)	11.0 (10.0 – 20.0)	12.0 (10.0 – 22.0)	**<0.001**
Male gender	16 (48.5)	36 (43.4)	52 (44.8)	
Comorbidities	24 (72.7)	35 (42.2)	59 (50.9)	**0.004**
Multiorgan dysfunction	33 (100.0)	53 (63.9)	86 (74.1)	**<0.001**
Systemic corticosteroids	8 (24.2)	15 (18.1)	23 (19.8)	0.450
Mechanical ventilation	32 (97.0)	42 (50.6)	74 (63.8)	**<0.001**
Diuretics	11 (33.3)	28 (33.7)	11 (33.3)	1.000
CRRT	9 (27.3)	4 (4.8)	13 (11.2)	**0.002**
Duration of mechanical ventilation, days	3 (1 – 10)	2 (0 – 6)	2 (0 – 7.5)	**0.008**
Duration of PICU stay, days	4 (2 – 10)	4 (2 – 10)	4 (2 – 10)	0.973
Inotropes	33 (100.0)	58 (69.9)	91 (78.4)	**<0.001**
Dopamine	27 (81.8)	45 (54.2)	72 (62.1)	**0.006**
Adrenaline	31 (93.9)	20 (24.1)	51 (44.0)	**<0.001**
Noradrenaline	25 (75.8)	33 (39.8)	58 (50.0)	**<0.001**
Dobutamine	3 (9.1)	10 (12.0)	13 (11.2)	0.756
Vasopressin	12 (36.4)	3 (3.6)	15 (12.9)	**<0.001**
Milrinone	3 (9.1)	5 (6.0)	8 (6.9)	0.686
Duration of inotropes, days	2 (1 – 5)	1 (0 – 4)	2 (0 – 4)	**<0.001**
ECMO	4 (12.1)	4 (4.8)	8 (6.9)	0.221

CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; PELOD: Pediatric Logistic Organ Dysfunction; PICU: Paediatric intensive care unit; PIM 2: Pediatric Index of Mortality 2
Continuous and categorical data are presented as median (interquartile range) and counts (percentage), respectively.

Table 2. Microbiological Characteristics of Patients with Severe Sepsis and Septic Shock

Characteristic	Non-Survivor (n = 33)	Survivor (n = 83)	All (n = 116)	*P* Value
Bacterial sepsis	13 (39.4)	30 (36.1)	43 (37.1)	0.832
Viral sepsis	16 (48.5)	25 (30.1)	41 (35.3)	0.085
Fungal sepsis	4 (12.1)	2 (2.4)	6 (5.2)	0.054
No organism	7 (21.2)	33 (39.8)	40 (34.5)	0.083
Source of infection				
Lower respiratory tract	17 (51.5)	40 (48.2)	57 (49.1)	0.838
Genitourinary	2 (6.1)	3 (3.6)	5 (4.3)	0.622
Central nervous system	5 (15.2)	5 (6.0)	10 (8.6)	0.145
Soft tissue	1 (3.0)	5 (6.0)	6 (5.2)	0.673
Gastrointestinal	7 (21.2)	14 (16.9)	21 (18.1)	0.600
Others	1 (3.0)	14 (16.9)	15 (12.9)	0.064

Categorical data is presented as counts (percentage).
Values may not add up due to overlapping categories.

by 8%. The ROC curve analysis identified 2 cut-offs (2.3 and 14.6%FO) with the highest Youden index (data available from authors upon request). Patients with cumulative %FO in the range of 2.3-14.6% had 5-fold increased odds of mortality, whereas those with >14.6% had a nearly 20-fold increased odds of mortality (Table 5). Cumulative %FO was also independently associated with decreased VFD, InoFD and IFD (Table 4). Comparing the same %FO cut-offs, there was also a dose-dependent reduction in VFD, IFD and InoFD with increasing %FO.

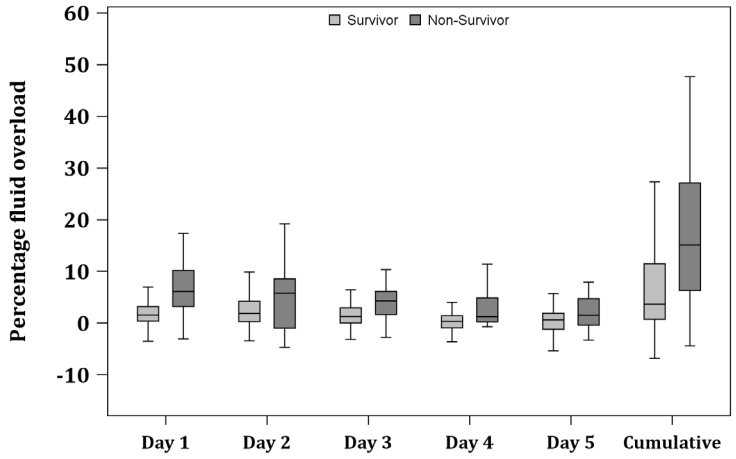

Fig. 2. Daily percentage fluid overload in survivors and non-survivors. The box spans the interquartile range. The median value is marked by the horizontal line within the box and the whiskers represent the minimum and maximum values.

Table 3. Percentage Fluid Overload in Survivors and Non-Survivors

Percentage Fluid Overload	Non-Survivor (n = 33)	Survivor (n = 83)	All (n = 116)	*P* Value
Day 1	6.1 (3.2 – 10.2)	1.5 (0.1 – 3.2)	2.3 (0.6 – 5.0)	**<0.001**
Day 2	5.8 (-1.0 – 8.5)	1.8 (0.2 – 4.1)	2.4 (0.2 – 5.8)	**0.046**
Day 3	4.3 (1.6 – 6.1)	1.0 (0.0 – 2.9)	1.6 (0.0 – 3.8)	**0.002**
Day 4	1.2 (0.2 – 4.8)	0.5 (-1.0 – 2.0)	0.7 (-0.5 – 2.2)	**0.035**
Day 5	1.5 (-0.5 – 4.7)	0.6 (-0.9 – 1.8)	0.9 (-0.7 – 2.1)	0.082
Cumulative	15.1 (6.3 – 27.1)	3.6 (0.7 – 11.1)	5.6 (1.2 – 14.3)	**<0.001**

Continuous data is presented as median (interquartile range).

Table 4. Multivariate Analysis for Primary and Secondary Outcomes

Outcome	Covariate	Unadjusted		Adjusted	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
PICU mortality*	Comorbidities (ref: no)	3.66 (1.52 – 8.83)	0.0039	2.89 (1.04 – 7.99)	**0.041**
	PIM 2	1.02 (1.000 – 1.05)	0.0507	1.01 (0.98 – 1.03)	0.555
	Multiorgan dysfunction (ref: no)	38.22 (2.16 – 676.95)	0.0130	16.21 (0.9 – 292.34)	0.059
	% fluid overload	1.11 (1.06 – 1.16)	<0.0001	1.08 (1.03 – 1.13)	**0.001**
		β (95% CI)	*P* Value	β (95% CI)	*P* Value
VFD†	Comorbidities (ref: no)	-8.82 (-14.34 – -3.31)	0.0017	-3.97 (-8.68 – 0.73)	0.098
	PIM 2	-0.11 (-0.33 – 0.11)	0.3197	0.01 (-0.16 – 0.19)	0.881
	Multiorgan dysfunction (ref: no)	-14.39 (-20.15 – -8.64)	<0.0001	-8.45 (-14.14 – -2.76)	**0.004**
	% fluid overload	-0.50 (-0.66 – -0.33)	<0.0001	-0.37 (-0.53 – -0.21)	**<0.001**
IFD†	Comorbidities (ref: no)	-7.97 (-13.15 – -2.78)	0.0026	-3.51 (-7.73 – 0.71)	0.104
	PIM 2	-0.20 (-0.40 – 0.00)	0.0523	-0.08 (-0.23 – 0.07)	0.312
	Multiorgan dysfunction (ref: no)	-14.42 (-19.66 – -9.18)	<0.0001	-8.29 (-13.4 – -3.19)	**0.002**
	% fluid overload	-0.48 (-0.62 – -0.33)	<0.0001	-0.34 (-0.49 – -0.20)	**<0.001**
InoFD†	Comorbidities (ref: no)	-9.98 (-15.30 – -4.67)	0.0002	-5.97 (-10.88 – -1.05)	**0.018**
	PIM 2	-0.08 (-0.29 – 0.14)	0.4996	0.02 (-0.16 – 0.20)	0.817
	Multiorgan dysfunction (ref: no)	-12.67 (-18.55 – -6.80)	<0.0001	-6.85 (-12.80 – -0.91)	**0.024**
	% fluid overload	-0.43 (-0.60 – -0.26)	<0.0001	-0.31 (-0.48 – -0.14)	**<0.001**

CI: Confidence interval; IFD: 28-day intensive care unit-free days; InoFD: 28-day inotrope free-days; OR: Odds ratio; PICU: Paediatric intensive care unit; PIM 2: Pediatric Index of Mortality 2; Ref: Reference group; VFD: 28-day ventilator-free days

*Logistic regression.

†Linear regression.

Table 5. Association Between Categories of Cumulative Percentage Fluid Overload (Determined by Receiver Operating Curve Analysis) and Clinical Outcomes

Cumulative % Fluid Overload (Ref <2.3%)	Adjusted β Estimate (Days)	*P* Value
28-day ventilator-free days*		
2.3 – 14.6		
>14.6	-17.25 (-22.89 – -11.6)	**<0.001**
28-day intensive care unit days*		
2.3 – 14.6	-7.71 (-12.13 – -3.29)	**<0.001**
>14.6	-15.72 (-20.79 – -10.64)	**<0.001**
28-day inotrope-free days*		
2.3 – 14.6	-6.08 (-11.51 – -0.65)	**0.028**
>14.6	-13.49 (-19.72 – -7.26)	**<0.001**
	Adjusted OR (95% CI)	***P* Value**
Mortality†		
2.3 – 14.6	5.81 (1.29 – 26.25)	**0.022**
>14.6	19.10 (3.94 – 92.56)	**<0.001**

CI: Confidence interval; OR: Odds ratio; Ref: Reference group
*Linear regression.
†Logistic regression.
Covariates: Comorbidities, Pediatric Index of Mortality 2 and multiorgan dysfunction.

Discussion

The main overall finding of this study is that cumulative positive balance over the first 5 days of paediatric severe sepsis and septic shock is consistently, independently and in a dose-dependent manner associated with poor clinical outcomes including increased mortality, decreased VFD, IFD and InoFD. Other independent risk factors for mortality include the presence of comorbidities.

In adults with severe sepsis, there are conflicting data with regard to the impact of fluid balance and clinical outcomes. Retrospective studies in adults demonstrated that higher fluid balance was associated with increased mortality/organ dysfunction.[5,25,26] This association was supported in a single-centre prospective cohort of 173 adults with sepsis: positive fluid balance over 7 days was associated with mortality in all patients (adjusted hazard ratio [aHR], 1.01; 95% CI, 1.01-1.02 per ml/kg increase; P <0.001) and within the subgroup with septic shock (aHR, 1.01; 95% CI, 1.01-1.02; P <0.001).[8] A multicentre prospective observational study (n = 1808) involving 730 ICUs globally demonstrated a stepwise increased hazard ratio of mortality with higher quartiles of cumulative fluid balance on the 3rd day of admission in septic patients with and without septic shock.[9]

Nevertheless, there was also evidence of reduced mortality with higher fluid volumes in the subgroup of patients who remained in shock for longer periods.[27] When adults in septic shock from another prospective multicentre observational study were evaluated after day 3 of shock, 95/164 patients were deemed to be still in shock. Of these, the patients who received higher fluid volumes had lower 90-day mortality rates (40% vs 62%, P = 0.03) than those receiving lower volumes in spite of comparable simplified acute physiology score II and sequential organ failure assessment scores.[27]

Similar to critically ill adults, fluid management beyond the initial period of fluid resuscitation remains a controversial topic in children with severe sepsis. In these children, the impact of fluid balance after the initial resuscitation period was studied in 2 retrospective studies.[10,11] A single-centre study of 202 children with severe sepsis showed that fluid overload in the first 24 hours (aOR, 1.20; 95% CI, 1.08-1.33; P = 0.001) and PICU-acquired daily fluid overload for 7 days (aOR, 5.47 per log increase; 95% CI, 1.15-25.96; P = 0.032) were independent risk factors for mortality.[11] A multicentre retrospective cohort study involving 317 children with septic shock stratified patients into low-, intermediate- and high-risk categories using a validated biomarker-based stratification tool (the Pediatric Sepsis Biomarker Risk [PERSEVERE] model).[10,28] Cumulative positive fluid balance up to 7 days was associated with increased mortality in the low-risk category (OR, 1.04; 95% CI, 1.00-1.07) but not in the high-risk category (aOR, 0.93; 95% CI, 0.97-1.02; P = 0.536). Results from our study are contrary to the findings in this latter study. We still found an association between fluid balance and worse clinical outcomes after adjusting for severity of illness as measured by the PIM 2 score. However, our finding must be interpreted in the context that there is a possibility that severity of sepsis measured by the PIM 2 score is less robust compared to the PRESERVE biomarker model.

Taken together, findings from other paediatric studies and ours demonstrate that progressive fluid overload is associated with poorer clinical outcomes. This clinical observation is substantiated by cellular and pathophysiological studies. Due to increased capillary leak and protein extravasation, excessive fluid administration results in tissue oedema, impaired oxygen and metabolite diffusion, distorted tissue architecture and impaired lymphatic and capillary drainage which contribute to progressive organ dysfunction.[29,30] In the lung, the consequences of pulmonary oedema are evident by reduced compliance and impaired gas exchange.[31] Myocardial oedema causes impaired contractility and diastolic dysfunction.[32] Fluid accumulation also causes cerebral, hepatic, renal interstitial and gastrointestinal oedema and is associated with poor outcomes.[30] These adverse pathophysiologic changes correlate with our study findings which show an association between cumulative fluid balance and the need for MV and inotropic support as well as length of PICU stay. This is reinforced by our finding of association with poor clinical outcomes with higher cut-offs of cumulative %FO consistent with data from adult studies.[9] These thresholds may be considered for planning future randomised controlled trials.

Our study, however, has several limitations. Patients were identified by diagnostic codes and this may be incomplete as some patients may have been coded according to their original site of infection (e.g. pneumonia, urinary tract infection, etc.). The small sample size over a long period of time may have introduced confounders in treatment strategies over the years. Moreover, the retrospective design cannot exclude confounding by indication. Greater fluid administration and hence greater cumulative fluid balance may be due to greater illness severity associated with increased vascular leakage and third spacing of fluid, rather than a direct cause of increased mortality. The type of fluids received for resuscitation and maintenance were not protocolised and not investigated in this study. However, we did show that cumulative %FO was associated with poor clinical outcomes even after adjusting for severity of illness, comorbidities and multiorgan dysfunction. The retrospective design also precludes us from accounting for other unknown and unmeasurable confounders of disease severity and patient characteristics. However, given the challenge of performing a randomised controlled trial in this group of critically ill children, our study provides preliminary data that requires validation in future prospectively designed trials.

Conclusion

This retrospective study showed that cumulative fluid balance over the first few days of sepsis was associated with mortality, VFD, IFD and InoFD—with greater harm associated with a greater magnitude of positive balance. This association requires further validation and confirmation in future larger prospective studies. Specifically, future studies examining the impact of a liberal versus conservative fluid balance strategy in children with severe sepsis and septic shock need to inform on the impact of fluid balance in these critically ill children.

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Pralatrexate Induces Long-Term Remission in Relapsed Subcutaneous Panniculitis-Like T-Cell Lymphoma

Dear Editor,

In subcutaneous panniculitis-like T-cell lymphoma (SPTL), infiltration of subcutaneous tissue by pleomorphic T-cells and benign macrophages is seen in skin nodules that mimic lobular panniculitis. SPTL affects young patients and about 20% develop haemophagocytic syndrome (HPS) which worsens survival significantly.[1,2] We describe a case of aggressive SPTL in a patient with HPS who relapsed after multiple lines of therapy, but achieved complete and durable remission after extended pralatrexate therapy.

Although the PROPEL trial had demonstrated that pralatrexate, an antifolate, induced a durable response in relapsed/refractory peripheral T-cell lymphoma (PTCL), it did not include patients with SPTL.[3] To our knowledge, treatment beyond 6 cycles of pralatrexate has not been reported. Our case illustrates, for the first time, the use of extended pralatrexate therapy in the treatment of aggressive SPTL.

Case Report

A 39-year-old man presented with fever of 2 weeks' duration and tender abdominal nodules. There was no lymphadenopathy or hepatosplenomegaly. Laboratory data revealed raised lactate dehydrogenase, raised ferritin (22,060 µg/L), pancytopenia (haemoglobin, 9.7 g/dL; absolute neutrophil count, 0.81 × 10^9/L; platelet, 91 × 10^9/L) and low fibrinogen (0.69 g/L). Positron emission tomography (PET) and computed tomography (CT) showed hypermetabolic activity in the subcutaneous fat of the abdominal wall. Abdominal nodule biopsy demonstrated atypical lymphocytes rimming adipocytes in the subcutis that are CD8+CD4- alpha/beta cells with high Ki67 expressing granzyme, CD2 and CD7, but losing CD5 (Fig. 1). Epstein-Barr virus-encoded small ribonucleic acid by in situ hybridisation was negative and lymphocytes did not stain for gamma/delta T-cell receptor. Bone marrow biopsy showed histiocytic proliferation with haemophagocytosis.

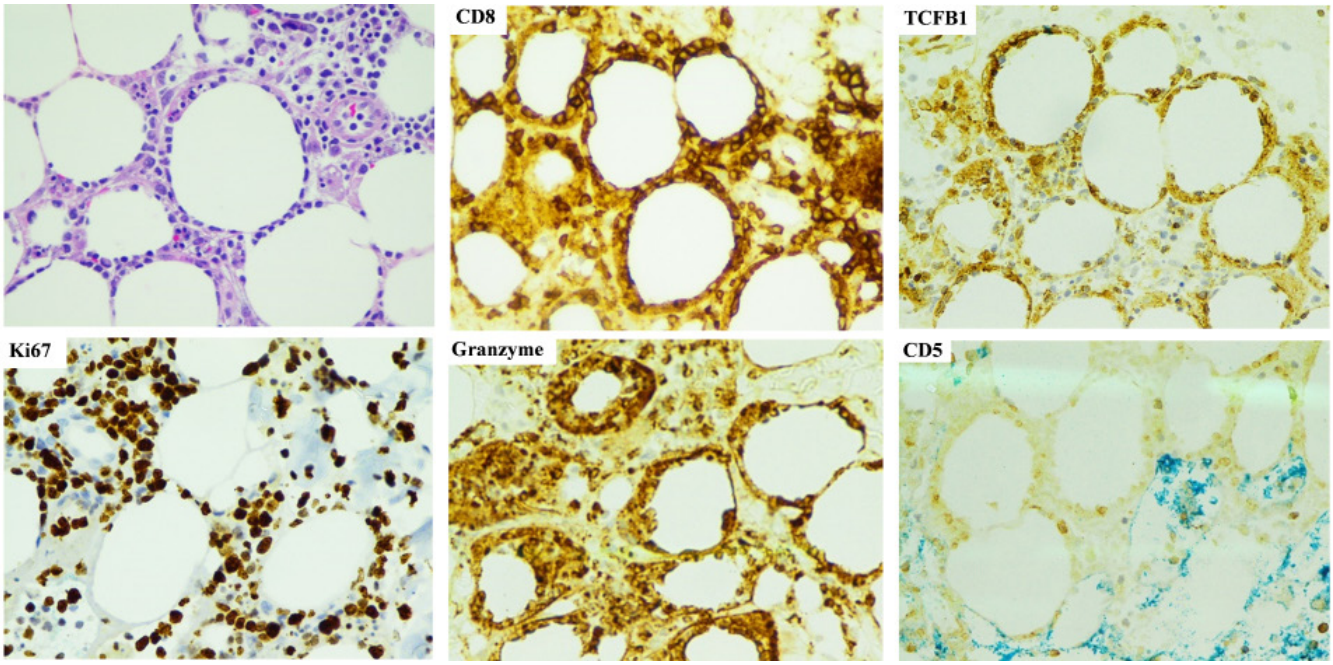

Fig. 1. Photomicrographs (× 40) showed subcutaneous infiltration by atypical lymphoid cells with rimming of adipocytes that are CD8+ alpha/beta subtype, expressing granzyme, high Ki67 (60-70%) and loss of CD5.

The patient was started on cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). However, fever returned after a brief respite and he was given romidepsin and cyclosporine in view of clinical non-response. After 5 cycles of romidepsin/cyclosporine, PET and CT scans showed progression with increased abdominal and new gluteal lesions. He was then given gemcitabine, dexamethasone and cisplatin for 6 cycles and achieved complete metabolic remission. He declined allogeneic stem cell transplantation as consolidation for long-term disease control.

Eight months later, he presented with a left axillary nodule and biopsy showed recurrence of SPTL (Fig. 2). According to the protocol for PTCL, he was started on pralatrexate at 30 mg/m^2 weekly for 6 of the 7 weeks for each cycle. To prevent mucositis, he was treated prophylactically with folinic acid and methylcobalamin. After the first cycle, treatment was administered in the outpatient clinic without mucositis or significant toxicity. He achieved metabolic remission after 6 cycles, but relapsed 3 months after cessation of pralatrexate. He was then restarted on pralatrexate for 1 year. At 18 months, he remained in complete metabolic response.

Discussion

For indolent SPTL, immunosuppressive agents such as prednisolone and cyclosporine—or systemic biologic agents such as bexarotene and methotrexate—may be used.[4] In cases of aggressive presentation with haemophagocytic syndrome, intensive chemotherapy such as CHOP or CHOP-like regimens—followed by consolidation with autologous stem cell transplantation—is commonly used.[5] However, this intervention has high failure and relapse rates.

On the other hand, novel drugs such as pralatrexate and romidepsin may achieve a durable response in a small group of patients.[6,7] This case suggests that patients who had initially benefitted from pralatrexate can be re-treated when there is disease progression. Additionally, an extended treatment regimen can maintain response.

Extended pralatrexate therapy offers a treatment regimen that is well tolerated in responding patients. It also provides

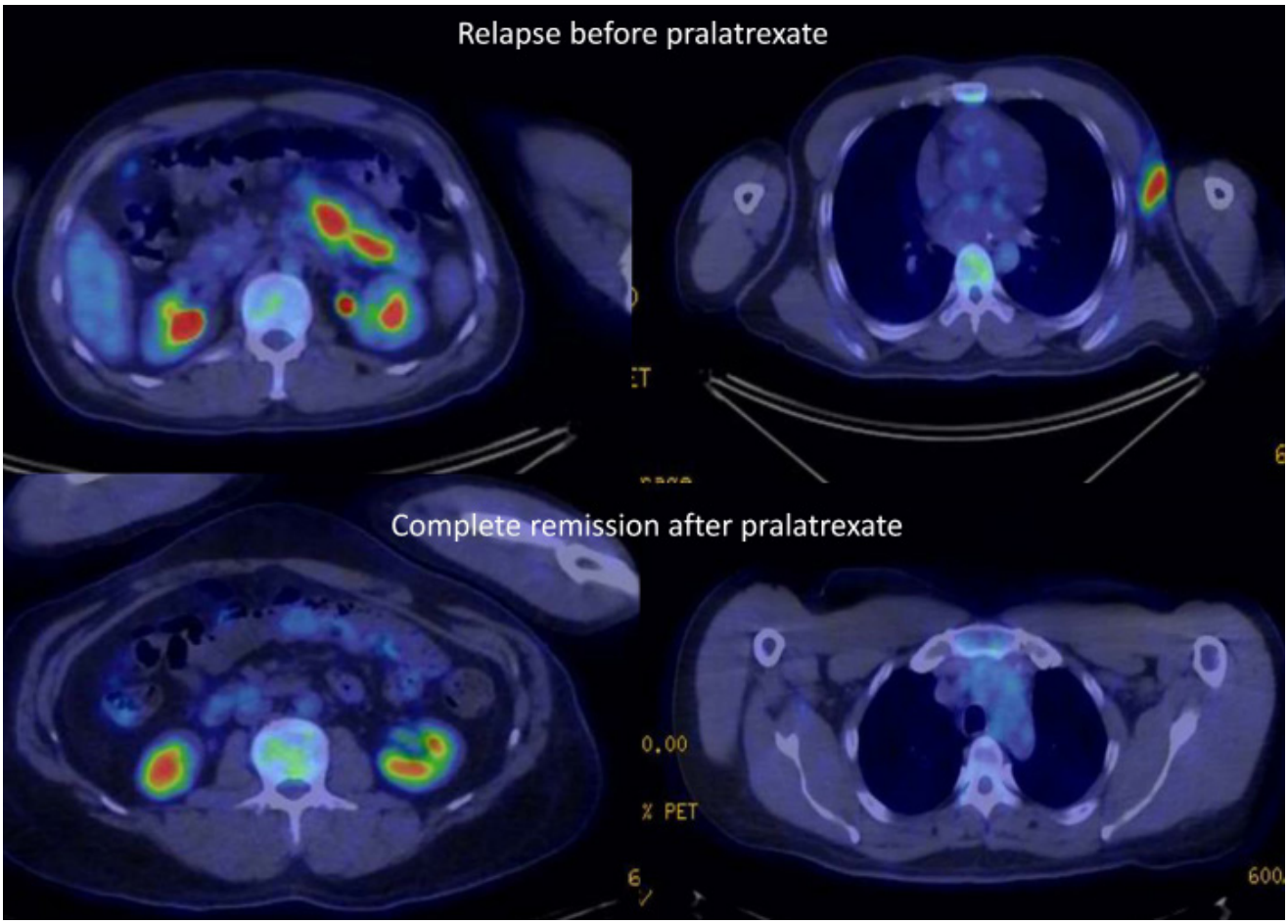

Fig. 2. Positron emission tomography at relapse (top) showed hypermetabolic soft tissue in the small bowel mesentery abutting the duodenum, jejunum and axilla and remission (bottom) post-treatment with pralatrexate.

time to organise a transplant or to maintain the quality of life in patients who are not eligible for the procedure. Additionally, it can provide a basis for studies that compare novel agents to time-limited intensive chemotherapy. Due to the selective activity of novel therapies, more research is needed to identify predictive biomarkers so that treatment strategies can be personalised for patients with this rare condition.

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Characteristics and Management of Autoimmune Bullous Disease in Psoriasis Patients

Dear Editor,

Psoriasis is a common chronic inflammatory skin disease. On the other hand, autoimmune bullous diseases (AIBD) are less prevalent. Several case reports and studies have documented AIBD in patients with psoriasis.[1,2] However, their causative factors are unclear. It has been hypothesised that certain antipsoriatic treatments such as ultraviolet irradiation, psoralen and coal tar could have triggered off the development of autoantibodies that cause AIBD.[3] Treatment of AIBD in patients with psoriasis is challenging since systemic corticosteroids may potentially cause flares of pustular psoriasis. We report our experience in the management of psoriasis patients with AIBD in the National Skin Centre, a tertiary dermatology institution, in Singapore.

This retrospective case series included 17 patients who were clinically diagnosed with "psoriasis" and either "pemphigoid" or "pemphigus" according to the International Classification of Diseases between 1 January 2003 and 31 July 2017 (Fig. 1). The diagnosis of AIBD was confirmed by histopathological examination (Fig. 2), immunofluorescence studies and/or serological tests. The clinical records of the patients were reviewed and details including demographics, disease severity, AIBD onset and treatment were extracted and analysed. This study was approved by the Institutional Review Board (Protocol 2017/00572).

The demographics and clinical findings of our patients are shown in Table 1. There were 15 Chinese and 2 Malay patients. Male (70.6%) patients vastly outnumbered female (29.4%) patients. Mean age at AIBD onset was 72 years. Psoriasis preceded AIBD in all patients (94.1%) except for 1 case. Mean duration between psoriasis and AIBD onset was 14 years. More than half of them (64.7%) had moderate psoriasis, defined as having body surface area (BSA) involvement of between 5-10%. Three (17.6%) patients had mild psoriasis (BSA <5%) and another 3 (17.6%) patients had severe psoriasis (BSA >10%).

All patients had a single type of AIBD. Bullous pemphigoid (BP) was the most prevalent form and it affected 13 (76.5%) patients. Three patients had pemphigus foliaceus and 1 had pemphigus vulgaris (PV). Our cohort did not include patients with antilaminin gamma-1 (p200) pemphigoid.

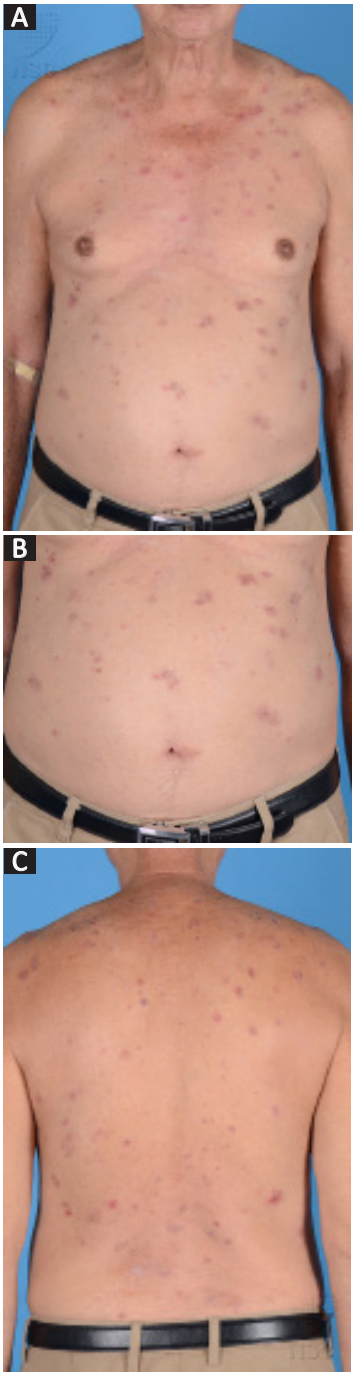

Fig. 1. Patient with pre-existing psoriatic lesions. A: Blisters and vesicles are seen on the anterior trunk. B: Vesicles overlie thin psoriasiform plaques. C: Blisters and vesicles are visible on the posterior trunk.

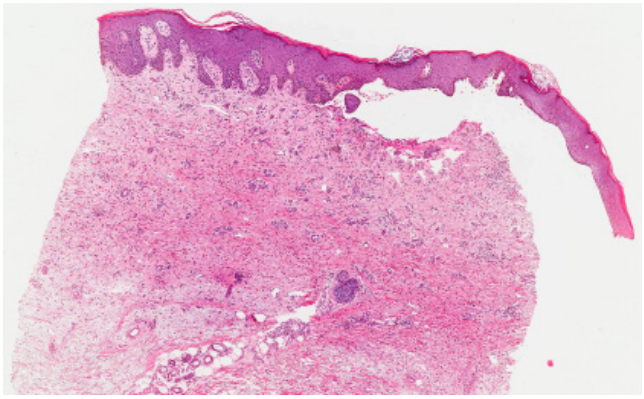

Fig. 2. Subepidermal blister with eosinophils and adjacent psoriasiform dermatitis.

Fourteen (82.4%) patients were on only topical steroids during AIBD onset. The 3 remaining patients developed AIBD while they were being treated with cyclosporine, hydroxyurea and narrow-band ultraviolet B (NBUVB) phototherapy, respectively. In the patient who was on cyclosporine, treatment ceased due to cost issues. In the other 2 patients, hydroxyurea and NBUVB ceased after methotrexate was started.

As part of their AIBD treatment, 13 (76.5%) patients received systemic corticosteroids with or without other immunomodulators such as mycophenolate mofetil. Two (11.8%) patients were treated with only methotrexate and another 2 (11.8%) were conservatively managed with highly potent topical corticosteroids (Table 2). Clinical improvement and disease control were seen in all patients. In patients who were on systemic corticosteroids, prednisolone was initiated with a mean dose of 0.47 ± 0.24 mg/kg/day and it was tapered over a mean period of 17.0 ± 11.3 months with no exacerbation of psoriatic lesions.

In a recent pooled analysis of case-control studies, a significant association between BP and psoriasis was reported.[2] However, the precise mechanisms responsible for the development of AIBD in patients with psoriasis are not known. Researchers have speculated that exogenous factors such as systemic antipsoriatic treatment and UV exposure can possibly precipitate bullous eruptions by stimulating antibody release or promoting expression of prior subclinical bullae.[3] Since most of our patients had no prior exposure to known exogenous factors, our study did not support previous findings of psoriasis as a cause or trigger for the development of AIBD.

In our study, psoriasis preceded bullous eruptions by a mean of 10 years. This suggests that the endogenous pro-inflammatory environment in psoriasis may promote a phenomenon known as "break of immune tolerance" when antigens and cytokines are released and upregulated. This may expose and induce autoimmunity against basement membrane zone components such as BP antigens that lead to autoimmune bullous lesions.[4,5] Other factors that may play an important role in epidermal splitting include downstream factors such as complement activation, mast cell degranulation, macrophage activation and neutrophilic chemotaxis.[6] These mechanisms cannot be measured by the levels of antibodies against BP antigens 180 (BP180) and 230 (BP230) and desmogleins 1 (DSG1) and 3 (DSG3).

A recent review had discussed a possible relationship between psoriasis and pemphigoid diseases that included local inflammation and upregulation of neutrophils and matrix metalloprotease.[7] The presence of neutrophil elastase in psoriasis[8] may play a role in the degradation of dermoepidermal junction and the formation of blisters. It was also reported that BP lesions have increased expression of interleukin-17,[9] a cytokine important to the development of psoriasis.

Interestingly, 1 patient who had PV (which was consistent on histology as well as direct and indirect immunofluorescence assays) also had antibodies to BP180 and BP230 in addition to DSG1 and DSG3. BP antigens and desmogleins are not known to be closely related, and the coexistence of BP and PV in a patient is rare.[10] Currently, the mechanisms responsible for the production of multiple autoantibodies in a patient are not known. As such, more research is needed on them in mixed bullous diseases.

A limitation of our study is that none of the patients were subjected to a complete diagnostic test. Additionally, immunoblot analysis was not performed in any of them. Some patients also did not undergo a complete serological and direct immunofluorescence evaluation (Table 2). However, histology and immunofluorescence features characteristic of antilaminin gamma-1 (p200) pemphigoid and epidermolysis bullosa acquisita were not seen in any of them. In their study, Ohata et al had demonstrated an association between psoriasis and antilaminin gamma-1 pemphigoid in 145 Japanese patients.[1] In comparison, our study is limited to a much smaller patient cohort. It is, however, the first study that examined an association between AIBD and psoriasis in a multiracial population that included the Chinese and Malays in Southeast Asia. It also describes, in detail, the management and outcomes in these patients that were not highlighted in other reported case series.

Management of psoriasis patients with AIBD is challenging. Initiation and withdrawal of systemic corticosteroids in patients with extensive psoriasis can expose them to the risk of developing serious sequelae of pustular or erythrodermic psoriasis. Despite the absence and discouragement of systemic corticosteroids in most psoriasis management guidelines, they remain the most common systemic treatment prescribed by dermatologists

Table 1. Demographics and Clinical Characteristics of Subjects

Variable	Aggregate (%)
Gender	
Male	12 (70.6)
Female	5 (29.4)
Race	
Chinese	15 (88.2)
Malay	2 (11.8)
Median age at AIBD onset (range, years)	72 (59 – 77)
40 – 49	3 (17.6)
50 – 59	2 (11.8)
60 – 69	1 (5.9)
70 – 79	9 (52.9)
80 – 89	1 (5.9)
≥90	1 (5.9)
Median duration from psoriasis to AIBD onset (range, years)	14 (8 – 20)
<0	1 (5.9)
0 – 9	5 (29.4)
10 – 19	6 (35.3)
20 – 29	5 (29.4)
Body surface area of psoriasis (%)	
<5	3 (17.6)
5 – 10	11 (64.7)
>10	3 (17.6)
Psoriasis type	
Plaque	16 (94.1)
Guttate	1 (5.9)
Pustular	–
AIBD type	
Bullous pemphigoid*	13 (76.5)
Pemphigus foliaceus†	3 (17.6)
Pemphigus vulgaris†	1 (5.9)
Therapy at AIBD onset	
Topical steroids only	14 (82.4)
Cyclosporine	1 (5.9)
Hydroxyurea	1 (5.9)
Narrow-band ultraviolet B phototherapy	1 (5.9)

AIBD: Autoimmune bullous diseases
*Patients with bullous pemphigoid (BP) showed subepidermal bullae with eosinophils on histology, linear immunoglobulin G (IgG) and complement 3 (C3) in basement zone membrane on direct immunofluorescence assay and had circulating autoantibodies directed against BP antigens 180 and/or 230.
†Patients with pemphigus showed intraepidermal vesicles with acantholysis on histology and intracellular IgG and C3 in epidermis on direct immunofluorescence assay. Patients with pemphigus foliaceus and pemphigus vulgaris had serum IgG autoantibodies against desmoglein 1 and 3, respectively.

Table 2. Descriptive Analysis of Subjects

AIBD Type, Severity and Patient Number	Bullae Histology	Direct IF Assay	Indirect IF Assay	Autoantibody Serology	Psoriasis Management	AIBD Management	Outcome
Bullous pemphigoid							
Mild (<5% of BSA)							
1	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	BP180/BP230 positive	Topical corticosteroids	Prednisolone 0.42 mg/kg/day	Improved
2	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/40	BP180 positive	Topical corticosteroids	Prednisolone 0.25 mg/kg/day	Improved
3	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/80	No data	Topical corticosteroids	Prednisolone 0.33 mg/kg/day	Improved
Moderate (5 – 10% of BSA)							
4	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	No data	Topical corticosteroids	Prednisolone 0.67 mg/kg/day, methotrexate 10 mg/week	Improved
5	Erosion with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/20	No data	Topical corticosteroids	Prednisolone 1.00 mg/kg/day	Improved
6	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	No data	Topical corticosteroids	Prednisolone 0.50 mg/kg/day, methotrexate 7.5 mg/week	Improved
7	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	BP180 positive	Topical corticosteroids	Prednisolone 0.50 mg/kg/day, methotrexate 10 mg/week	Improved
8	Subepidermal bullae with eosinophils	No data	Split skin substrate; roof pattern, 1/160	BP180 positive	Topical corticosteroids	Prednisolone 0.25 mg/kg/day	Improved
9	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/20	No data	Topical corticosteroids	Prednisolone 0.50 mg/kg/day	Improved
10	Subepidermal bullae with eosinophils	Linear C3 in BMZ	No data	BP180 positive	Topical corticosteroids	Prednisolone 0.33 mg/kg/day	Improved
Severe (>10% of BSA)							
11	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	No data	No data	Topical corticosteroids	Methotrexate 5 mg/week	Improved
12	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	No data	No data	Topical corticosteroids	Topical corticosteroids	No change
13	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	BP180/BP230 positive	Hydroxyurea	Methotrexate 5 mg/week	Improved
Pemphigus foliaceus							
Mild (<5% of BSA)							
14	Psoriasiform hyperplasia with eosinophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	DSG1 positive	Cyclosporine	Prednisolone 0.50 mg/kg/day, mycophenolate mofetil 500 mg	Improved
Moderate (5 – 10% of BSA)							
15	Intraepidermal vesicle with acantholysis and eosinophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	DSG1 positive	Topical corticosteroids	Prednisolone 0.50 mg/kg/day	Improved
16	Intraepidermal vesicle with acantholysis and eosinophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	DSG1 positive	NBUVB phototherapy	Prednisolone 0.67 mg/kg/day, methotrexate 12.5 mg/day	Improved
Pemphigus vulgaris							
Moderate (5 – 10% of BSA)							
17	Intraepidermal bullae with neutrophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	BP180/BP230/DSG1/DSG3 positive	Topical corticosteroids	Topical corticosteroids	No change

AIBD: Autoimmune bullous diseases; BMZ: Basement membrane zone; BP180: Bullous pemphigoid antigen 180; BP230: Bullous pemphigoid antigen 230; BSA: Body surface area; C3: Complement 3; DSG1: Desmoglein 1; DSG3: Desmoglein 3; IF: Immunofluorescence; IgG: Immunoglobulin G; NBUVB: Narrow-band ultraviolet B

for psoriasis patients.[11] The use of systemic corticosteroids in immunobullous disease is well documented in the literature and clinical practice. Although methotrexate monotherapy may be useful in psoriasis patients with AIBD, the use of systemic corticosteroids appeared to be more common in our study. This may be attributed to rapid resolution of bullous lesions with systemic corticosteroids and physician preference after considering the comorbidities of patients.

In our study, most patients achieved good disease control of both AIBD and psoriasis after they were initiated on systemic corticosteroids. None of them developed pustular flares during or after steroid taper. Additionally, no improvement was seen in their bullous lesions in the absence of systemic corticosteroids. As such, systemic corticosteroids may be a safe treatment option in these patients. More research is needed to establish the unique pathogenetic relationship between psoriasis and concomitant AIBD before a review of the therapeutic guidelines for these patients can be undertaken.

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An Unusual Cause of Stroke-Like Symptoms in an Elderly Patient

A 60-year-old man with a history of chronic kidney disease, type 2 diabetes mellitus and hearing impairment presented with short-term memory loss and slurring of speech. There was no neck stiffness, limb weakness, photophobia or sensory disturbances. He was afebrile and his vital signs were stable. No seizures were reported throughout the disease duration. On examination, he was found to have both expressive and receptive dysphasia, visual agnosia and apraxia.

Non-contrast-enhanced computed tomography (CT) of the brain (Fig. 1) revealed an ill-defined area of hypodensity in the left occipital and temporal lobes that traversed the left middle cerebral artery (MCA) and posterior cerebral artery (PCA). Magnetic resonance imaging (MRI) of the brain (Fig. 2) was performed to further characterise the lesion. Time-of-flight (TOF) magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) were also performed.

Cerebrospinal fluid (CSF) analysis revealed no evidence of pleocytosis. CSF lactate was also absent. Panel test for common causative agents of community-acquired encephalitis was negative. Serum lactate was, however, mildly elevated at 2.6 mmol/L (normal range, 0.7-2.1 mmol/L). Electroencephalography revealed waveform abnormalities in the left posterior occipital, parietal and temporal lobes.

What is the most likely diagnosis?

A. Viral encephalitis
B. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
C. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
D. Acute left PCA infarct
E. Status epilepticus

Discussion

MELAS is one of the most common mitochondrial disorders with marked phenotypic and genetic heterogeneity. It is characterised by stroke-like episodes, encephalopathy with epileptic seizures, dementia, lactic acidosis and ragged red fibres in skeletal muscle.[1] Diabetes and sensorineural hearing loss were the most common systemic manifestations seen in our patient.[1] To date, 30 pathogenic variants of mitochondrial deoxyribonucleic acid (mtDNA) that cause MELAS have been reported.[1] The pathogenic *m.3243A>G* mutation located in the $tRNA^{Leu(UUR)}$ of the mitochondrial genome accounts for >80% of MELAS cases.[1] This point mutation disrupts mitochondrial protein translation and impairs respiratory chain function, leading to impairment of neuronal oxidative energy production and neuronal death.[1]

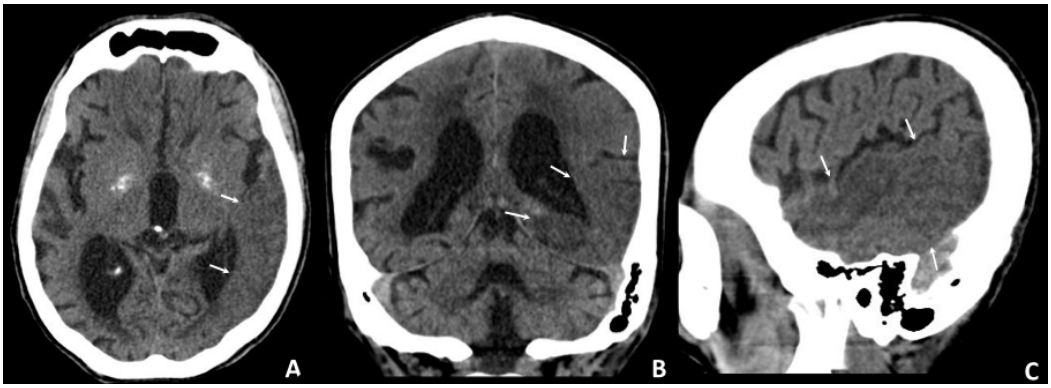

Fig. 1. Computed tomography of the brain. (A) Axial, (B) coronal and (C) sagittal images showed ill-defined hypodensities with loss of normal grey-white matter differentiation in the left occipital and temporal lobes (white arrows). This was associated with adjacent ventricular and cerebral sulcal effacement.

Answer: B

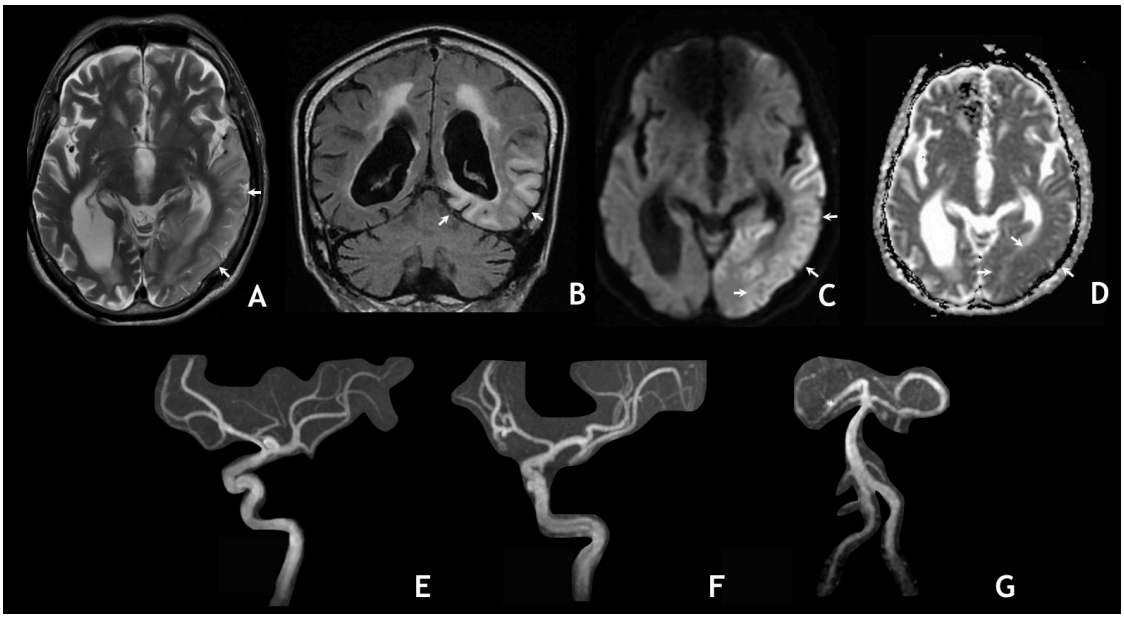

Fig. 2. Magnetic resonance images of the brain. (A and B) Axial T2-weighted and coronal fluid attenuated inversion recovery images, respectively, confirmed the presence of cortical and subcortical white matter hyperintensities (white arrows) in the left occipital and temporal lobes that encompassed the left middle cerebral artery and posterior cerebral artery. (C and D) Axial diffusion-weighted images showed gyriform pattern of increased signal (white arrows) with corresponding low signal on apparent deficient coefficient map which is in keeping with diffusion restriction. (E to G) Three-dimensional time-of-flight images of the right internal carotid artery, left internal carotid artery and vertebrobasilar artery, respectively, demonstrate normal flow signal.

On CT imaging studies, cortical areas of decreased attenuation are seen and they often involve the parieto-occipital and parieto-temporal regions. These "metabolic strokes" often transcend the vascular boundaries and could involve the left MCA and PCA which was the case in our patient. Angiographic studies will show patent vessels in the affected area which is a crucial feature that differentiates MELAS from ischaemic stroke.

On MRI, these stroke-like lesions typically show T2 hyperintense signal with predominant involvement of the cortex.[2] Subsequent imaging studies will show a reduction of these lesions. They may also show complete resolution or develop into an area of atrophy with cortical signal alteration.[3] Variable diffusion characteristics of stroke-like lesions of MELAS have been described in the literature[3] and are possibly related to the combination of cytotoxic and vasogenic oedema. Diffuse cerebellar atrophy and leukoencephalopathy are rarely seen. The detection of a lactate peak that resonates at 1.3 ppm on proton spectroscopy may aid in the diagnosis of an underlying mitochondrial disease. However, it is not useful in the acute setting since a lactate peak may also be seen in ischaemic stroke.[2]

Our case was atypical for MELAS given the late onset of this condition in our patient. Over 90% of patients present with MELAS before the age of 40.[1] A review of the literature revealed only 5 cases of adult-onset MELAS with *m.3243A>G* mutation over the age of 40.[1] The reasons for the late onset of neurological symptoms in certain patients with MELAS are unclear. Some researchers have suggested a correlation between mtDNA variant load and disease burden.[1] MELAS is characterised by a phenomenon known as heteroplasmy in which a high variability of the mitochondrial mutation load can be found in different individuals from the same family, various organs of an individual or different cells in the same organ.[1] Our patient presented with multiple vascular risk factors which made it difficult to exclude the possibility of an arterial ischaemic stroke. Lesions that cross vascular boundaries—which were seen in our patient—are not typical for an ischaemic stroke.

Viral encephalitis is an important consideration since it can present with imaging findings that are similar to those seen in MELAS. However, our patient was not clinically septic and remained afebrile throughout the disease duration. Panel test for common causative agents of community-acquired meningoencephalitis also did not yield a positive result. These findings rendered the diagnosis of viral encephalitis as highly unlikely. Herpes simplex virus encephalitis is the most common cause of fatal sporadic viral encephalitis. It is characterised by signal alteration in the cortical and subcortical regions of the bilateral fronto-temporal lobes, cingulate gyri and insula. In our patient, the absence of such involvement made herpes an unlikely diagnosis.

CADASIL should be considered in patients with stroke-like symptoms and cognitive deficits, especially in young and middle-aged adults. Subcortical lacunar infarcts and leukoencephalopathy are characteristic imaging features

of CADASIL and involve penetrating cerebral and leptomeningeal vessels. Due to the absence of these imaging features, late disease onset and absence of a positive family history, CADASIL was excluded in our patient.

Arterial ischaemic stroke is the most common aetiology for the acute onset of neurological deficits in elderly patients with cardiovascular risk factors. An acute ischaemic stroke is often seen on CT scans as a wedge-shaped, ill-defined hypodensity confined within vascular boundaries unlike the lesion seen in our patient which traversed the left MCA and PCA territories. The gyriform pattern of diffusion restriction seen in our patient was also unusual for an arterial infarct. An arterial infarct often demonstrates a wedge-shaped area of restricted diffusion on MRI. Cerebral infarcts secondary to venous thrombosis may cross arterial territories but they are often haemorrhagic, which was not the case in our patient. Additionally, TOF MRA and MRV did not show arterial occlusion or dural venous sinus thrombosis.

Status epilepticus may result in transient MRI signal changes and swelling that are found predominantly in cortical grey matter, subcortical white matter and/or hippocampus. In our patient, the absence of seizures exclude the diagnosis of seizure-related changes observed in the MRI findings.

MELAS requires multidisciplinary management that supports mitochondrial function to prevent acute neurological deterioration and progressive neurodegeneration.[1] Genetic counselling also plays a crucial role in the management of patients with MELAS.[4] The clinical course is often unpredictable and is fraught with acute episodes and gradual deterioration.[4] In Figure 3, we described the diagnostic

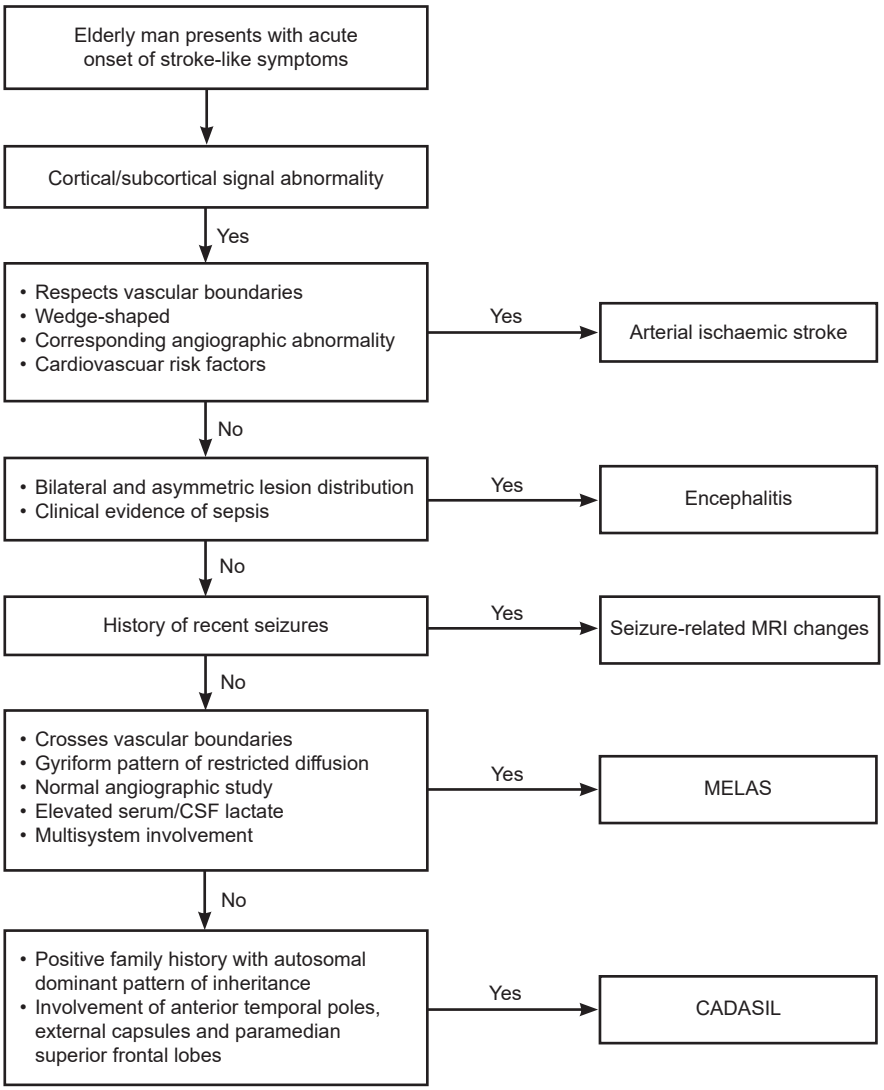

Fig. 3. Flow chart to diagnose cortical/subcortical lesion in an elderly patient presenting with stroke-like symptoms. CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF: Cerebrospinal fluid; MELAS: Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MRI: Magnetic resonance imaging

approach to identify the cortical/subcortical lesion in our patient who presented with stroke-like symptoms.

Conclusion

Though rare, MELAS should be one of the differential diagnoses for cortical/subcortical lesions in elderly patients who present with stroke-like symptoms. This is especially true when atypical imaging features such as crossing of vascular territories and gyriform pattern of restricted diffusion are present. It is not always possible to make a definitive diagnosis based only on radiograph findings. A correlation with clinical information and a thorough exploration of family history must also be attempted.

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