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"Without deep reflection, one knows from daily life that one exists for other people."

Albert Einstein (1879 – 1955)
German physicist

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Editorial

Credat Emptor – The Sacrosanct Doctor-Patient Relationship

C Rajasoorya, [1,2,3] *FAMS, FRCP(Edin), FRCP(Lond)*

Of late, holistic patient care and rising healthcare costs have entered the public discourse, leading to a call for judiciousness in healthcare utility and for more generalist doctors. An optimal doctor-patient relationship allows patients to believe that the doctors caring for them will work for their betterment with prudent utilisation of resources. Doctors are also held in high esteem and trust because of the public's perception that there is an intricate process of professional training, certification and on their need to abide by a strong regulatory and ethical framework. When this trust is eroded, a cascading detrimental effect occurs in both the doctors' practice and patients' care. This editorial is a personal viewpoint on the problems influencing the doctor-patient relationship, and explores ways of circumventing these.

Doctors—by nature of their profession—are influential in deciding what, when and how healthcare services are delivered. It is estimated that they influence or determine at least 60% of healthcare costs,[1] with wastage in the United States accounting 20% of healthcare costs.[2] The doctor's dictum—to "do no harm"—is perhaps a timely reminder on the need to avoid causing financial harm inadvertently to patients. There have even been calls to teach doctors healthcare economics.[3] Yet, doctors may not be fully cognisant of this responsibility and power within them, preferring instead to delegate the responsibility and culpability to politicians, legal professionals, administrators, insurance companies, drug and device manufacturers, hospitals and even patients.

Doctors embark on a career that begins on a broad-based footing with the patient (rather than the disease) as the centre of focus. The lack of sufficient time spent on talking to and clinically examining patients remains a concern in current day practice, despite this playing a key role in the cost-effective care of patients. The underappreciation of bedside clinical skills and the over-reliance on costly tests that are prevalent across the spectrum of the medical profession have been highlighted.[4] We need no reminding that a clinical evaluation is not just an exercise in diagnostic data gathering but remains the bedrock of a physician's art. The clinical encounter establishes a professional doctor-patient relationship that enhances trust and confidence. Inadequate communication and a hurried assessment due to insufficient time spent during the clinical consult can further erode the trust of the patient who may feel that assessment was cursory.

Subspecialisation—with its reductionist thinking of patients as a set of multiple organs—has contributed to the deterioration of the broad-based footing acquired during the formative years. Patients can be perceived as a constellation of diseased organs that transit an "assembly line" where duplications, omissions and wastages propagate inefficiency and result in fragmented care. Institutions and hospitals have attempted to circumvent this issue by borrowing and implementing concepts from the automotive, entertainment, hospitality, mega-stores and other industries of "lean thinking" to improve efficiency and accessibility. Others have suggested a more generalist care model that thwarts this fragmentation. Changing disease patterns, population demographics, medical knowledge democratisation, technological advances, and increased complexity of health problems have heightened the need for specialist care and need not create an antipathy towards specialist practice that has its proven medical benefits.[5] Optimal healthcare is not only facilitated by a balance between specialists and generalists but by the ability of both groups to interact well in patients' best interest.

Evidence-based medicine (EBM) enhances confidence in decision-making using a heirarchy of reseach evidence. Strangely, the premise that clinical research alone is insufficient to make a clinical decision has often been glossed over; ignoring the primary tenet of EBM where the personal and clinical context of the patient as well as the values and preferences of the informed patient must contribute to a decision. Concerns have also been raised on EBM when questionable practices like relying on corrupt

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research evidence or falsified publication of data arise.[6] Individual patients differ, and to incorporate a patient into a specific protocol or pathway without due thought on his individuality or wishes is not only an aberration of good clinical practice but contributes to doctor-patient mistrust. End-of-life issues can be highly emotive and yielding to pressures of doing everything possible to increase quantitative life may occur at the expense of the wishes, quality of life and dignity of individual patients.

Doctors face a dilemma when they prescribe an intervention—even if they know it is ineffective—in order to appease the patient, to safeguard themselves from accusations of malpractice, or in the true belief that denying the patient such an option would be inappropriate.[7] The World Health Organization[8] has recommended good prescribing guidelines that include evaluation of the patient's problems, specification of the therapeutic objective, appropriate drug initiation, patient education and regular evaluation of therapy. Therapeutics is an important contributor to iatrogenic disease and the practice of deprescribing has been encouraged with mounting evidence on its efficacy.[9]

Patient care is often equated with "customer satisfaction" as an indicator of quality, with its roots in consumer marketing; hence the plethora of patient satisfaction surveys in institutions. Every patient is pleased with a doctor who understands his needs, and every doctor feels accomplished when his patient is satisfied with his care. This "satisfaction-quality" relationship, however, remains complex and has been debunked by 2 recent studies.[10,11] In part, the surprise findings has been explained by doctors' desire to satisfy patients by ordering more tests and inappropriately prescribing, yielding to patient demands (with the most demanding patients getting disproportionate care that works to their detriment). Therefore, we cannot be distracted by "customer satisfaction" as an indicator of the care we provide.

Patients benefit when inappropriate diagnostic procedures or treatments are avoided. Yielding to pressures to overtest, overdiagnose and overtreat puts doctors in a vulnerable position where they can be said to be prioritising their interests rather than the patient's. We have gradually descended into an era of intolerance for uncertainty and risk averseness (in part due to increased patient expectations and the fear of medico-legal consequences) thus enabling the practice of "defensive medicine". This has allowed our practice to over-react and for us to forget our responsibilities in protecting the safety of patients and our moral responsibility to prevent wastage of finite resources. Patients cannot in the medical professional eyes be treated like "customers" who pay, demand and get what they want. This, however, in no way, negates the doctor's need to listen to the patient's perspective. As doctors, it is good to remind ourselves that patients and their relatives are often in an extremely vulnerable position during illness and rely heavily on the managing physician, likened to entrapment in a hostage bargaining syndrome.[12] The key lies in being open minded, listening to their concerns, avoiding judgement based on our biases, educating the patient and not succumbing to threats. The Choosing Wisely campaign[13] has reinforced in us the need to stimulate conversations between doctors and patients about unnecessary tests, treatment and procedures.

A substantial proportion of lawsuits regarding malpractice arise due to poor communication and poor doctor-patient relationships[14-16] adding credence to the perception that the medical professional's best defence against being brought to court is probably not to lose the trust of his or her patient or relatives. Trust is established with good two-way communication.

An authentic and ethical doctor-patient relationship is indeed very sacrosanct allowing for a privileged licence given to the medical profession where the patient reposes trust and confidence in a practitioner to cure, protect against or palliate illness. In no other profession, can one be so advantaged to get an individual's consent to expose, look, feel, touch, move, listen and sometimes even invade their privacy. A collection of organs or systems do not entirely make a patient. The patient has feelings, wishes, desires, hope and sometimes, ambivalence or defiance. Yet evidence[17,18] suggests that doctors today often remain distant, technical, organ-focused and technology-oriented in their encounters. Healthcare organisations increasingly refer to patients as "customers", thus eroding the primary tenet of medicine that wrongfully prioritises the doctors' interest to monetary considerations and commercial interests, while dehumanising a medical issue and taking advantage of patients' vulnerabilities.

Medicine should remain a profession and not a business. As endorsed by American sociologist Everett Hughes,[19] professions should go by the motto of *credat emptor* (let the buyer believe or have trust) instead of *caveat emptor* (let the buyer beware). This has also recently been echoed by our Chief Justice who aptly highlighted that the medical profession should strive "to be worthy of the trust reposed in it by the members of the public, which have entrusted to the profession some of the most important aspects of their lives".[20] We do have a responsibility to prevent the perpetuation of mistrust, that drives our patients not to listen to us (and vice versa). In the quest for quality care and to help the healthcare conundrum, it is prudent that we, as guardians of our resources, make a concerted effort to preserve the sacrosanct doctor-patient relationship and neither abuse our patients' trust nor the public's trust in our profession.

Incorporating clinical reasoning that includes critical thinking (metacognition), clinical and communication skills,

shared decision-making, appropriate use and interpretation of diagnostic tests and understanding cognitive biases, human factors and cultural sensitivities can only enhance the trust factor in a doctor-patient relationship—a very sacrosanct relationship that cannot be allowed to be eroded.

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Original Article

Computed Tomography Urography: Comparison of Image Quality and Radiation Dose between Single- and Split-Bolus Techniques

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Abstract

Introduction: In this study, we aimed to compare the split-bolus and single-bolus computerised tomography (CT) urography and determine if this offers a reduction in radiation dose without compromising image quality. Materials and Methods: A retrospective evaluation was performed on 88 patients undergoing split-bolus CT urography and this was compared to a control group of 101 consecutive patients undergoing single-bolus CT urography. A radiation dose analysis was performed on each subject. Subjects with urinary bladder lesions, hydronephrosis, renal masses or cysts >3 cm in diameter were excluded. All images were classified according to image quality by 2 consultant radiologists. Results: Opacification of the renal parenchyma, pelvicalyceal system, proximal ureters and urinary bladder were comparable between the 2 techniques, whilst image quality of the middle and distal third of the ureters was better using the split-bolus technique. The mean dose length product (DLP) for the single-bolus technique was 1324.1 mGy·cm, whilst that of the split-bolus technique was 885.7 mGy·cm. The mean effective dose reduction was calculated to be 31.1% between the 2 groups. Conclusion: The split-bolus technique gives a reduced radiation dose without compromising image quality. The associated reduction in images is beneficial for data storage and reporting efficiency. As such, our department will adopt the split-bolus technique for young, low-risk patients.

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Key words: Intravenous pyelogram, Intravenous urogram

Introduction

Previous studies have demonstrated that computerised tomography (CT) urography is more accurate in the detection and characterisation of renal masses,[1-5] detection of urinary calculi, urinary tract abnormalities,[6-8] infective/inflammatory renal disorders[9] and for the evaluation of haematuria[10] compared with intravenous urography or ultrasound. However, it is observed that a standard triple-phase CT urography study carries an increase of approximately 1.5 times the effective radiation risk compared with conventional urography.[11-12]

A typical single-bolus, triple-phase CT examination of the urinary system will include non-contrast, nephrographic and excretory phases. In comparison, an alternate split-bolus, dual-phase technique images the urinary system in only the non-contrast and combined nephrographic-excretory phases.

Previous papers have suggested that the radiation dose reduction in a split-bolus protocol is not substantial.[3] It was also reported that limited contrast volume boluses given in a split-bolus technique may result in reduced distension of the distal ureters.[7]

The aim of our study was to determine if a split-bolus technique can produce an equivalent imaging quality to the single-bolus technique. Our secondary aim was to confirm that the split-bolus technique will reduce patient radiation dose.

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Materials and Methods

The study was approved by the hospital's Centralised Institutional Review Board. (CIRB).

Study Population/Patient Selection

Patients who had a split-bolus CT urography between September 2012 and February 2013 were selected. The decision to submit patients for a split-bolus study was made independently by the hospital urology team, who selected patients who were young and at low risk of having an urothelial malignancy. There were a total of 88 patients in this group. The control group comprised 101 consecutive subjects who had undergone a single-bolus triple-phase examination in the same period. A statistician was consulted to confirm adequacy of sample size.

Subjects with a malignant renal mass, renal cyst larger than 3 cm, urinary bladder lesions or hydronephrosis were excluded as these may confound the degree of urinary tract opacification. One subject in the control group had right renal agenesis but remained in the study although only the normal left urinary tract was evaluated.

Evaluation

All images obtained from both groups were analysed independently by 2 consultant radiologists.

The quality of opacification of the renal parenchyma, pelvicalyceal system and opacification/distention of the proximal ureters, middle ureters, lower ureters and urinary bladder were assessed using a 3-tiered scale: 1) Tier 1: Poor or streaking opacification/distention, suboptimal for diagnosis; 2) Tier 2: Incomplete opacification/distention, sufficient for diagnosis; and 3) Tier 3: Complete opacification/distention, optimal for diagnosis.

Figure 1 is an example of the degree of renal parenchymal enhancement expected in Tier 2 and Tier 3 groups. Figure 2 demonstrates a 3D coronal reconstruction of ureters taken from subjects allocated to Tier 1, Tier 2 and Tier 3 groups.

Scanning Protocols

In both groups, subjects were given 500 ml of water orally, 20 to 30 minutes prior to commencing the examination. There was no diuretic, saline infusion or abdominal examination administered during examination. The patients were mobilised outside the scan room prior to acquisition of the excretory phase. Coverage of both protocols is from just above the kidneys to the pubic symphysis.

The imaging studies were performed on 2 different CT scanners, a 64-slice CT scanner (Aquilion, Toshiba Medical Systems) and a 320-slice CT scanner (Aquilion One 320, Toshiba Medical Systems). In the control group, the 64-multi-detector computed tomography (MDCT) contributed 35 scans and the 320-MDCT contributed 55 scans, while 12 patients were imaged using the 64-MDCT and 73 using the 320-MDCT in the split-bolus group (Table 1).

Standard scan parameters for the 64-MDCT included: voltage of 120 kilovolts (kV), automatic current modulation, thickness of 1.0 x 32 (detectors), HP (Helical pitch) 27.0 and rotation time of 0.5 seconds. Standard scan parameters used on the 320-MDCT included: voltage of 120 kV, automatic current modulation, slice thickness of 0.5 x 80, HP 65.0 and rotation time of 0.5 seconds.

The single-bolus technique entailed imaging of the urinary tract in 3 phases (non-contrast, nephrographic and excretory). A single bolus of intravenous contrast (Omnipaque 350 [Iohexol], GE Healthcare) was administered after the non-contrast phase. The dose of contrast was given at 1 ml/kg, generally falling within a volume of 65 ml to 90 ml. Following contrast injection, an injection of 30 ml of normal saline is administered via an automated power injector at a rate of 1.5 ml/s. The nephrographic phase was obtained at 90 to 100 seconds in supine position and the

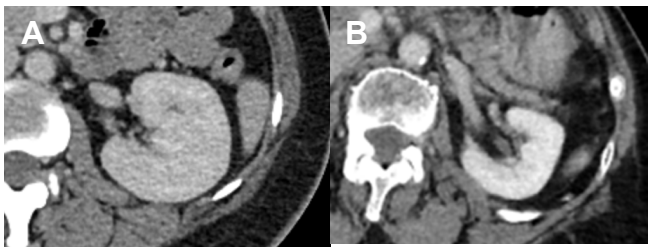

Fig. 1. An example of the difference in renal parenchymal enhancement between Tier 2 (A) and Tier 3 (B) groups on axial CT images obtained prior to contrast excretion into the pelvicalyceal system.

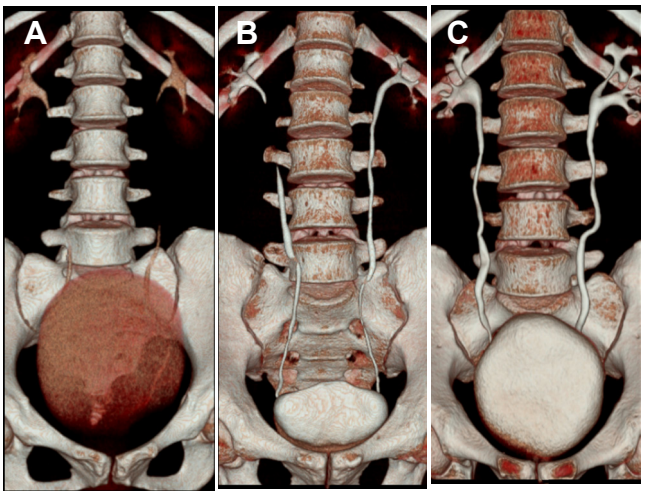

Fig. 2. An example of the differing degrees of ureteric enhancement on 3D reconstructed coronal images of the ureters, as allocated to Tier 1 (A), Tier 2 (B) and Tier 3 (C).

Table 1. The Planes Required by Each Phase for Single- and Split-Bolus CT Urography

Single-Bolus CTU Planes Acquired	Split-Bolus CTU Planes Acquired
Unenhanced phase: axial plane (3 mm thickness/3 mm reconstruction interval)	Unenhanced phase: axial and coronal planes (3 mm thickness/3 mm reconstruction interval)
Nephrographic phase: axial and coronal planes (3 mm thickness/3 mm reconstruction interval)	Combined nephrographic and excretory phase: axial and coronal planes (3 mm thickness/3 mm reconstruction interval)
Excretory phase: axial and coronal planes (3 mm thickness/3 mm reconstruction interval)	

CTU: Computed tomography urography

excretory phase was obtained at 10 minutes with the subject lying prone in order to optimise opacification of the mid and distal ureters.[13-14]

The split-bolus technique was performed using a biphasic acquisition with an unenhanced supine sequence and a single contrast-enhanced prone sequence that combined the nephrographic and excretory phases. This combined phase was achieved using 2 discrete intravenous boluses of contrast, with 45% of total dose given in the first bolus and the remaining 55% in the next bolus. The dose of contrast for this protocol was 1.5 ml/kg, with a volume ranging between 90 ml to 135 ml. For example, for a 70 kg man, the first bolus composed of 50 ml of contrast, followed by 20 ml of saline injected at a rate of 1.5 ml/s. The second bolus was administered 12 minutes later, consisting of 65 ml of contrast and 30 ml of saline at a rate of 1.5 ml/s. The result was a set of images that incorporated the nephrographic and excretory phases (Fig. 3).

Image Analysis

Images from both groups were evaluated independently by 2 experienced consultant radiologists on picture archiving and communication system (PACS) workstations.

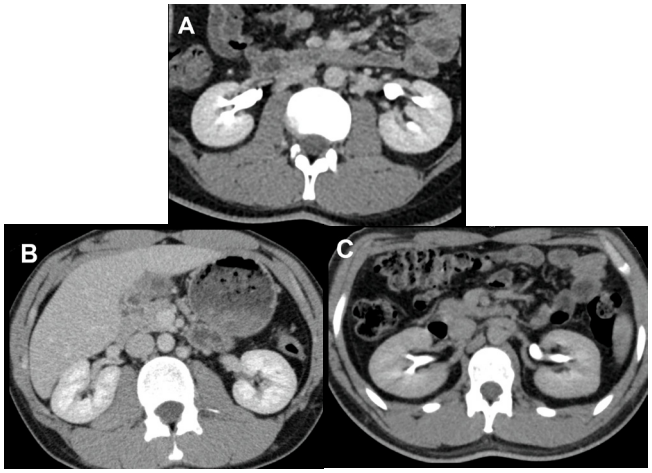

Fig. 3. How a split-bolus technique for CT urography can be utilised to produce an image (A) that incorporates the positive aspects of both the standard single-bolus nephrographic phase (B) and excretory phase (C).

For analysis, the urinary system was divided into renal parenchyma, pelvicalyceal system (calyces, infundibulum and renal pelvis), proximal ureter (from pelvi-ureteric junction to upper extent of sacroiliac joint), middle ureter (length of sacroiliac joint), distal ureter (from lower extent of sacroiliac joint to vesico-ureteric junction) and urinary bladder.

Radiation Dose Analysis

Radiation dose measurements and number of images generated for each patient were obtained from data embedded in the PACS system. Effective radiation dose (E) for all phases was calculated using E = k x dose length product (DLP), where k is a conversion unit (mSv/mGy x cm-1) and for the abdomen, it was taken as k = 0.015.

Statistical Analysis

The association between the 2 techniques and degree of opacification was assessed using Chi-squared or Fisher's exact tests, where applicable. Radiation dose was analysed using a 2 sample t-test.

Observers' agreement was measured by the weighted kappa statistic. A kappa value of 0-0.20 indicated poor agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 good agreement; and 0.81-1.00 very good agreement.

All calculations were performed using Statistical Package for the Social Sciences (SPSS) software, version 19.0 (IBM Corp. Armonk, NY).

Results

After exclusion, there remained 90 cases within the single-bolus group (72 males, 18 females and mean age of 32.6 years, range 18 to 64 years) and 85 cases in the split-bolus group (59 males, 26 females and mean age of 32.6 years, range 17 to 41 years).

Inter-observer reliability was evaluated. The range of kappa value was found to be between 0.88 and 0.97 (Table 2), denoting very good agreement.

Opacification of the Urinary System and Evaluation of Image Quality

Enhancement of the renal parenchyma was excellent in 51% (86 of 170) of the split-bolus group and 41% (73 of 180) in the single-bolus group. No subjects from the split-bolus group were found to have poor renal parenchymal enhancement, whereas 2% (4 of 180) were considered poor in the single-bolus group (Table 3).

Table 2. The Mean Opacification Score for Each Structure Using the Single-Bolus and Split-Bolus Techniques for CT Urography, Based on the Read by Both Radiologists and the Weighted Kappa Value (a Measure of Agreement between the 2 Radiologists)

Structure	Mean Opacification Score	Mean Opacification Score	Weighted Kappa Point Estimate (95%)	Mean Score from Both Readers
Single-Bolus	**Reader 1**	**Reader 2**		
Renal parenchyma	2.4	2.4	0.865	2.4
Pelvicalyceal system	2.9	2.9	0.826	2.9
Proximal ureter	2.6	2.6	0.904	2.6
Middle ureter	2.1	2.1	0.829	2.1
Distal ureter	2.0	2.0	0.879	2.0
Urinary bladder	2.5	2.6	0.793	2.6
Split-Bolus	**Reader 1**	**Reader 2**		
Renal parenchyma	2.5	2.5	0.879	2.5
Pelvicalyceal system	2.8	2.8	0.851	2.8
Proximal ureter	2.8	2.7	0.911	2.8
Middle ureter	2.6	2.6	0.831	2.6
Distal ureter	2.5	2.4	0.807	2.5
Urinary bladder	2.6	2.7	0.816	2.7

Table 3. Individual Reader Score Comparison for Both Groups

	Reader 1 Score			Reader 2 Score		
Structure	**1**	**2**	**3**	**1**	**2**	**3**
Single-bolus						
Renal parenchyma	2 (2%)	54 (60%)	34 (38%)	2 (2%)	49 (54%)	39 (44%)
Pelvicalyceal system	0 (0%)	10 (11%)	80 (89%)	0 (0%)	9 (10%)	81 (90%)
Proximal ureter	10 (11%)	16 (18%)	64 (71%)	8 (9%)	18 (20%)	64 (71%)
Mid ureter	22 (24%)	36 (40%)	32 (36%)	19 (21%)	41 (46%)	30 (33%)
Distal ureter	31 (35%)	30 (33%)	29 (32%)	26 (29%)	35 (39%)	29 (32%)
Urinary bladder	1 (1%)	40 (44%)	49 (55%)	1 (1%)	36 (40%)	53 (59%)
Split-bolus						
Renal parenchyma	0 (0%)	45 (53%)	40 (47%)	0 (0%)	39 (46%)	46 (54%)
Pelvicalyceal system	0 (0%)	13 (15%)	72 (84%)	0 (0%)	15 (18%)	70 (82%)
Proximal ureter	3 (3%)	15 (18%)	67 (79%)	3 (3%)	16 (19%)	66 (78%)
Mid ureter	4 (5%)	29 (34%)	52 (61%)	3 (3%)	29 (34%)	53 (63%)
Distal ureter	2 (2%)	38 (45%)	45 (53%)	4 (5%)	40 (47%)	41 (48%)
Urinary bladder	0 (0%)	45 (53%)	40 (47%)	0 (0%)	29 (34%)	56 (66%)

The pelvicalyceal system was completely opacified in 84% (142 of 170) of the split-bolus group and in 89% (161 of 180) of the single-bolus group. There were no incompletely opacified portions of the pelvicalyceal system in either groups.

The proximal ureters were fully opacified/distended in 78% (133 of 170) of the split-bolus group and in 71% (128 of 180) of the single-bolus group. Incompletely opacified segments were detected in 3% (6 of 170) of the split-bolus group and in 10% (18 of 180) of the single-bolus group.

The middle ureters were entirely opacified/distended in 62% (105 of 170) of the split-bolus group but only in 34% (62 of 180) in the single-bolus group. Incompletely opacified sections were demonstrated in 4% (7 of 170) of the split-bolus group compared with 23% (41 of 180) in the single-bolus group.

The distal ureter was completely opacified/distended in 51% (86 of 170) of the split-bolus group and 32% (58 of 180)

in the single-bolus group. Incompletely opacified portions were demonstrated in 4% (6 of 170) of the split-bolus group and in 32% (57 of 180) of the single-bolus group.

The urinary bladder was fully opacified/distended in 56% (90 of 170) of the split-bolus group and in 57% (102 of 180) of the single-bolus group.

There was no significant difference in opacification of the renal parenchyma and pelvicalyceal system, and opacification/distention of the proximal ureters and urinary bladder between both groups. The study showed generally higher opacification/distention scores for the middle and distal ureters in the split-bolus group, which is significant for reader 1 (Table 4).

Radiation Dose

When compared between 64-MDCT and 320-MDCT, the mean DLP was 1458.3 milli-grey per centimetre (mGy·cm) for 64-MDCT and 1229 mGy·cm for 320-MDCT in the single-bolus group. For the split-bolus group, the mean DLP was 1362.4 mGy·cm for 64-MDCT and 749.9 mGy·cm for 320-MDCT. Overall, the mean DLP was 1324.1 mGy·cm (standard deviation [SD] 687.9, range 594.0 to 3987.9 mGy·cm) for the single-bolus group, whereas the DLP for the split-bolus group was 885.7 mGy·cm (SD 595.1, range 163.2 to 2930.6 mGy·cm). The mean effective radiation dose (E) for the single-bolus group was 22.5 mSv (SD 11.7, range 10.0 to 67.8 mSV) while in the spilt-bolus group, it was 15.5 mSV (SD 10.1, range 2.8 to 49.8 mSV). The overall reduction in mean effective radiation dose between the single-bolus group and split-bolus group was 31.1%.

Number of Images

The split-bolus group produced a mean of 371 images (SD 43, range 298 to 493) whilst the single-bolus technique produced a mean of 528 images (SD 37, range 459 to 615). This equates to an average of approximately 30% fewer images for the split-bolus group compared with the single-bolus group.

Discussion

The unenhanced phase of a CT urography study is for detection of urinary calculi and provides a baseline to determine the presence of lesion enhancement in the urinary tract. The unenhanced phase is therefore considered mandatory. The nephrographic phase is when both the renal cortex and medulla are expected to be optimally enhanced while the excretory phase images allow the evaluation of the pelvicalyceal system, ureters and urinary bladder. The premise behind a split-bolus protocol is that opacification of the kidneys, pelvicalyceal system, ureters and bladders can be optimised simultaneously in 1 acquisition.

The absence of a universally standardised protocol for CT urography has given us some leeway when designing the single-bolus and split-bolus imaging protocols.[15-18]

Our CT urography protocols adhered closely to a generally accepted format. Deviations included omission of loading with intravenous fluid, abdominal compression and administration of intravenous diuretics. We did so because of the need for rapid study turnover, manpower issues and mixed opinions in the literature regarding the true benefits of these factors.[6,19] We continued to perform the excretory/combined phase in the prone position.[20-21]

Table 4. Comparison of the Proportion of Cases Achieving Full Opacification (Tier 3) in Each Group According to the Anatomical Area Under Evaluation

Structure under Evaluation	Number of Subjects with Full Opacification Ratings in the Single-Bolus Group (Total 90 [%])	Number of Subjects with Full Opacification Ratings in the Split-Bolus Group (Total 85 [%])	Significance of the Differences in the Number of Subjects Showing Full Opacification between the Groups (Expressed as *P* Values)
Reader 1			
Renal parenchyma	33 (37%)	40 (47%)	0.163
Pelvicalyceal system	80 (89%)	72 (85%)	0.413
Proximal ureter	64 (71%)	67 (79%)	0.240
Mid ureter	31 (34%)	52 (61%)	<0.001
Distal ureter	29 (32%)	48 (57%)	<0.001
Urinary bladder	49 (54%)	50 (59%)	0.559
Reader 2			
Renal parenchyma	84 (93%)	84 (99%)	0.064
Pelvicalyceal system	87 (97%)	78 (92%)	0.202
Proximal ureter	56 (62%)	56 (66%)	0.614
Mid ureter	27 (30%)	41 (68%)	0.013
Distal ureter	31 (34%)	35 (41%)	0.358
Urinary bladder	58 (57%)	57 (67%)	0.716

The patients were also mobilised before acquisition of this phase to aid mixing of opacified and non-opacified urine within the bladder. We felt this was necessary as layering of contrast would degrade the image quality and the ability to detect bladder wall lesions.[22]

Earlier papers on spilt-bolus protocols have raised concerns regarding streak artefacts from dense pelvicalyceal systems in the combined nephrographic-excretory phase, obscuring or impairing the ability to evaluate adjacent renal parenchymal lesions[4, 23] or that ureteric distension would diminish using the split-bolus technique.[7,24-25] While streak artefacts were evident in some cases in the split-bolus group, both readers concurred that none were severe enough to compromise evaluation (Fig. 4) and could be overcome through appropriate image windowing.

For our spilt-bolus protocol, a difference in timing of the excretory phase and higher amount of contrast administered were possible factors contributing to the significantly improved opacification of the middle and distal ureters in this group. We made this adjustment as earlier studies had suggest larger boluses could improve image quality.[7] The higher volume of contrast given for the second bolus may have contributed to improved distention of the ureters.

Evaluation of the radiation dose between the 2 groups showed a reduction in estimated patient dose with overall decrease in effective radiation dose of 31.1%. While differences in radiation dose reduction is affected by whether the 64-MDCT or 320-MDCT was used, both scanners demonstrated lower doses for the spilt-bolus protocol which has 1 less sequence.[26]

As anticipated, the split-bolus group boasted a 30% reduction in the mean number of images compared with the single-bolus group. The reduced image quantity offers benefits of reduced data storage requirements and a theoretical faster reporting speed.

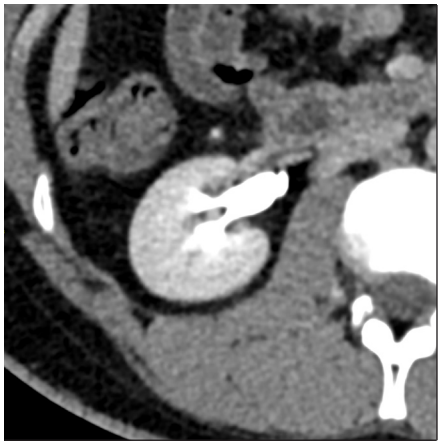

Fig. 4. An example of the degree of pelvicalyceal streak artefact detected when using the split-bolus technique.

Limitations

A double blinded format for the study was unfeasible since the image difference between both techniques would be obvious. This means that observer bias cannot be excluded.

The subjects were consecutively selected from data sets. As such, there was no subject matching between the groups. Possible confounding factors such as age, body mass index, renal function and cardiac output may alter either radiation dose, image quantity and contrast enhancement. It was hoped that the use of consecutive patients and the sample size could reduce any resultant bias.

While our study supports the opinion that image quality from a split-bolus technique is comparable to those obtained from a single-bolus technique, the diagnostic sensitivity for a lesion detected in urinary system is not directly compared. This was, however, not the aim of our study.

The 64-MDCT and 320-MDCT was used in both groups, although more patients in the split-bolus group were scanned with the 320-MDCT. This was unfortunately beyond our control given the retrospective nature of the study. Other than lower radiation dosage, the 320-MDCT confers improved temporal resolution and faster image acquisition, which is particularly advantageous for cardiac imaging.[27] However, CT urography will not require rapid scanning techniques and as such, we feel that the improvement to image quality will be minimal.

Lastly, while we feel that the image quality of the spilt-bolus technique is comparable to the single-bolus technique, appreciation of subtle enhancing lesions in the collecting system and ureters may sometimes be challenging for the split-bolus technique, given the lumens are already opacified in the postcontrast sequences. However, other signs such as mural thickening, focal calibre narrowing and upstream dilatation are usually helpful adjunct findings. Nonetheless, we continue to use a single-bolus triphasic technique for older or higher risk patients until further evidence can suggest otherwise.

Conclusion

Our split-bolus CT urography technique gives a reduced radiation dose without compromising image quality. The associated reduction in images is beneficial for data storage and reporting efficiency. As such, our department will adopt the split-bolus technique for young, low-risk patients.

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Original Article

Performance of the Paediatric Index of Mortality 3 and Paediatric Logistic Organ Dysfunction 2 Scores in Critically Ill Children

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Abstract

Introduction: The Paediatric Index of Mortality 3 (PIM 3) and Paediatric Logistic Organ Dysfunction 2 (PELOD 2) scores were recently revised. We aimed to assess the performance of these scores in a contemporary cohort of critically ill children. Materials and Methods: This is a single-centre prospective study conducted in a multidisciplinary paediatric intensive care unit (PICU). Consecutive PICU admissions over 1 year were included and admission PIM 3 and PELOD 2 scores were calculated. The performance of each of the scores was evaluated by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) and the Hosmer-Lemeshow goodness-of-fit test for the outcome of PICU mortality. Results: A total of 570 patient admissions were eligible for this study. The median age of patients was 3.1 (interquartile range [IQR]: 0.4, 8.9 years). Overall median PIM 3 and PELOD 2 scores were 1.2 (IQR: 0.4, 3.2) % and 4 (IQR: 2, 7), respectively. The overall mortality rate was 35/570 (6.1%). The PIM 3 and PELOD 2 scores had good discrimination for mortality (AUCs 0.88 [95% confidence interval (CI) 0.85, 0.91] and 0.86 [95% CI 0.83, 0.89], respectively). Goodness-of-fit was satisfactory for both scores. Higher PIM 3 and PELOD 2 scores were also associated with decreasing ventilator and PICU-free days. Conclusion: PIM 3 and PELOD 2 scores are robust severity of illness scores that are generalisable to a contemporary cohort of critically ill children in Singapore.

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Key words: Multiple organ dysfunction syndrome, Paediatric intensive care unit, Patient outcome assessment, Severity of illness index

Introduction

Initially designed to provide an indication of the risk of death in certain subsets of critically ill patients, the use of severity of illness scores in critically ill patients has evolved and these scores are now more often used to internally and externally benchmark quality of intensive care, and as markers of severity of illness for analysis in clinical studies.[1,2] Severity scores allow for more meaningful comparisons of mortality rates reported by different centres because they can be used to account for more severe presentation at centres with higher reported mortality. These scores are derived from large datasets of critically ill patients whereby clinical or demographic variables are investigated for their strength of association with the outcome of interest (e.g. mortality).[3]

The Paediatric Index of Mortality (PIM) score was designed to predict paediatric intensive care unit (PICU) mortality using variables which were present on admission to the PICU as a benchmark of the quality of care provided by the respective PICU.[4] Because of improvements in mortality rates in most PICUs, organ dysfunction is increasingly used as a surrogate outcome to mortality.[2,5] Hence, over the

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years, investigators started to examine organ dysfunction as an outcome in critically ill children.[6] The Paediatric Logistic Organ Dysfunction (PELOD) score was designed as a descriptive outcome score.[5] Both the PIM and PELOD scores had subsequently undergone extensive validation in other cohorts of patients across the globe.[6-10]

The performance of severity scores changes with time due to the changing case-mix of patients and improvements in the provision of critical care.[2,3,11] As such, intermittent revisions are required to ensure that they remain robust for clinical practice. These revisions require external validation to ensure generalisability. Hence, this study aimed to assess the performance of the recently updated PIM 3 and PELOD 2 scores in a contemporary cohort of critically ill children in Singapore. We postulated that both the PIM 3 and PELOD 2 scores had good discriminatory power in this cohort.

Materials and Methods

We conducted a single-centre prospective cohort study of all patients admitted to a multidisciplinary 16-bedded PICU of a university-affiliated, tertiary referral hospital. In addition to medical and general surgical patients, our PICU cares for children who require neurosurgery, open heart and vascular surgery, as well extracorporeal membrane oxygenation support. Consecutive children <18 years admitted to the PICU from 1 April 2015 to 31 March 2016 were included. This study was approved by the SingHealth Centralised Institutional Review Board (reference number: 2015/2231) and waiver of consent was granted as all data collected were performed as part of routine clinical care. This cohort study was conducted and reported in close accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[12]

PIM 3 and PELOD 2 Scores

PIM 3 scores were calculated from data extracted within the first hour of PICU admission.[2] The PELOD 2 score on admission was calculated from data extracted within the first 24 hours of PICU admission.[11] For the PELOD 2 scores, the most abnormal value within the day was recorded. This was done according to published equations and directions.

Data Extraction

All clinical data were collected prospectively on a standardised case report form. In addition to the parameters required for calculation of the PIM 3 and PELOD 2 scores, we also extracted data on patient demographics (e.g. age, gender, presence of comorbidities), category of admission (cardiac surgical, cardiac non-surgical, trauma, respiratory, neurological non-surgical, surgical non-cardiac and other medical diagnosis), type of admission (elective or non-elective), intubation/extubation dates, and admission/discharge dates.[2,11] Patients were monitored daily until discharge from PICU or death. Bedside data was extracted by study team members who underwent standardised training and were blinded. The completed database was counter-checked for inconsistencies or potential errors by an independent party not involved in clinical care of these patients (CPH). Inconsistent data were verified based on the patient's case notes.

Outcomes

The primary outcome was PICU mortality. The secondary outcomes were 28-days ventilator-free days (VFD) and 28-days intensive care unit-free days (IFD). VFD was defined as days alive and free from invasive mechanical ventilation for up to 28 days. IFD was defined as days alive and discharged from the PICU for up to 28 days. Patients who died were considered to have a VFD and IFD of 0. This is to eliminate mortality as a competing interest in evaluating ventilator and PICU duration. Patients were followed-up until PICU discharge or for a minimum of 28 days.

Statistical Analysis

Categorical variables were presented as frequency (proportion). Continuous variables were presented as median interquartile range (IQR). Differences between the distributions of categorical variables were compared using the chi-squared or Fisher's exact test, as deemed appropriate. We compared differences between continuous variables with the Wilcoxon rank sum or Kruskal Wallis test, where appropriate. We evaluated the predictive performance of each of the 2 scores (PIM 3, PELOD 2) to correctly predict death prior to PICU discharge. The performance of each of the scores was first evaluated using receiver operating characteristic (ROC) analysis with calculation of the area under the ROC curve (AUC) and 95% binomial confidence interval (CI). Next, we computed the number of expected deaths in each decile of increasing predicted probability of death for both the PIM 3 and PELOD 2 scores. Decile cutoffs were chosen based on distribution of each of the scores in our cohort. The sum of predicted probabilities within each decile was used to calculate the number of expected deaths. Calibration was assessed by the Hosmer-Lemeshow goodness-of-fit test for deciles of probabilities. We report observed and expected mortalities in each decile of predicted probability. We performed all statistical analyses using STATA 14.0 (StataCorp, College Station, TX) and considered a P value <0.05 statistically significant.

Results

Over the 1-year study period, there were 572 PICU admissions. All were assessed for eligibility and followed-up until PICU discharge. Two patients were eventually excluded due to missing outcome data because they were

transferred to another facility during critical illness. Hence, 570 patients were included in our final analysis (Table 1). The overall median age was 3.1 (0.4, 8.9) years including 3 patients who were >18 years of age. The majority of admissions (342/570 [60%]) were emergency admissions. The most common category of admission was surgical non-cardiac 137/570 (24%). The overall median PIM 3 and PELOD 2 scores on admission were 1.2 (0.4, 3.2) % and 4 (2, 7), respectively. The overall mortality rate was 35/570 (6.1%). The median time of death was 4 (1, 12) days after PICU admission. The observed mortality of each category of admission were 5/107 (4.7%) in cardiac surgical, 6/42 (14.2%) in cardiac non-surgical, 3/27 (11.1%) in trauma, 8/89 (9.0%) in respiratory, 4/72 (5.6%) in neurological, 2/137 (1.5%) in surgical non-cardiac and 7/96 (7.3%) in other medical diagnosis. The median IQR duration of mechanical ventilation and PICU stay was 1 (0, 3) and 2 (2, 4) days, respectively. The median IQR VFD and IFD was 27.0 (25.0, 28.0) and 26.0 (24.0, 26.0), respectively.

Performance of PIM 3 Score

The PIM 3 score AUC of the ROC curve for the entire cohort for PIM 3 score was 0.88 (95% CI 0.85, 0.91). This indicates good discriminating ability and it accurately predicted mortality in 95.4% of patients (Fig. 1). Calibration described by the Hosmer-Lemeshow test through stratification for deciles of probabilities was not significant (P = 0.297) (Table 2). The total number of expected deaths was 23/570 is equal to the sum of individual predicted probabilities by PIM 3 score. The number of observed deaths was higher (35/570 [6.1%]). The resulting standardised mortality ratio (SMR) was 1.54 (95% CI 1.24, 2.03) but goodness-of-fit test suggested adequate model fit. The VFD and IFD also showed a decrease from the first to fourth PIM 3 quartiles (P <0.001) (Table 3).

Performance of PELOD 2 Score

The PELOD 2 score AUC for PELOD 2 score was 0.86 (95% CI 0.83, 0.89) and it accurately predicted mortality in

Table 1. Characteristics of Patients Admitted to the Paediatric Intensive Care Unit (n = 570)

Characteristics	Total (n = 570), n (%)	Survivors (n = 535), n (%)	Non-Survivors (n = 35), n (%)	*P* Value
Age				0.841
0 to <1 month	61 (10.7)	59 (11.0)	2 (5.7)	
1 to 11 months	125 (21.9)	116 (21.7)	9 (25.7)	
12 to 23 months	63 (11.1)	60 (11.2)	3 (8.6)	
24 to 59 months	86 (15.1)	79 (14.8)	7 (20.0)	
60 to 143 months	134 (23.5)	127 (23.7)	7 (20.0)	
≥144 months	101 (17.7)	94 (17.7)	7 (20.0)	
Male gender	348 (61.1)	324 (60.6)	24 (68.6)	0.377
Category of admission				0.019
Cardiac surgical	107 (18.8)	102 (19.1)	5 (14.3)	
Cardiac non-surgical	42 (7.4)	36 (6.7)	6 (17.1)	
Trauma	27 (4.7)	24 (4.5)	3 (8.6)	
Respiratory	89 (15.6)	81 (15.1)	8 (22.9)	
Neurological non-surgical	72 (12.6)	68 (12.7)	4 (11.4)	
Surgical non-cardiac	137 (24.0)	135 (25.2)	2 (5.7)	
Other medical diagnoses	96 (16.8)	89 (16.6)	7 (20.0)	
Comorbidities*	333 (58.4)	310 (57.9)	23 (65.7)	0.479
Elective admission	228 (40.0)	223 (41.7)	5 (14.3)	0.001
Mechanical ventilation	302 (53.0)	270 (50.5)	32 (91.4)	<0.001
Duration of mechanical ventilation (days), median (IQR)	1 (0, 3)	0 (0, 2)	4 (2, 11)	<0.001
Duration of PICU stay (days), median (IQR)	2 (2, 4)	2 (2, 4)	5 (2, 13)	0.003

IQR: Interquartile range; PICU: Paediatric intensive care unit

*Examples of comorbidities include significant congenital heart disease, chronic lung disease, chronic renal failure, chronic liver failure, malignancies and genetics syndromes.

Categorical variables are presented in counts (percentages). Continuous variables are presented in median (interquartile range).

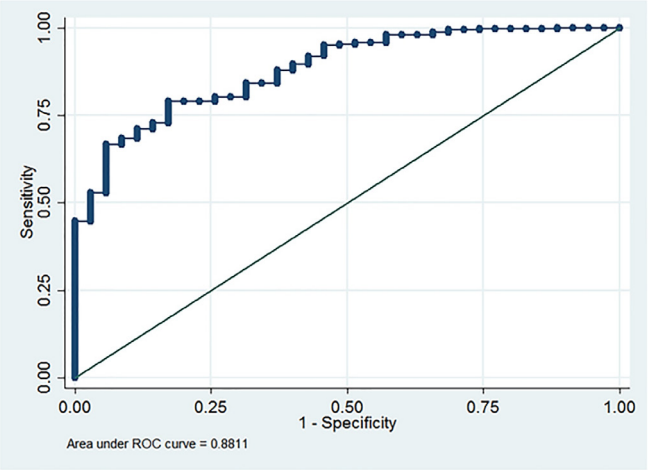

Fig. 1. Receiver operating curve for PIM 3 (Paediatric Index of Mortality 3) score for all patients.

94.9% of patients (Fig. 2). The expected number of deaths was 32/570 and this was equal to the sum of individual predicted probabilities by PELOD 2 score. The resulting SMR was 1.08 (95% CI 0.89, 1.36). In the calibration described by the Hosmer-Lemeshow test (only 7 distinct quantiles due to presence of ties), through stratification of probabilities was also not significant ($P = 0.243$), indicating acceptable goodness-of-fit (Table 2). The VFD and IFD also showed a decrease from the first to fourth PELOD 2 quartiles ($P < 0.001$) (Table 3).

Discussion

Our study evaluated the updated PIM 3 and PELOD 2 scores and demonstrated that they were robust in assessing the severity of illness in a contemporary cohort of PICU patients. Both the PIM 3 and PELOD 2 scores had good discrimination for mortality (AUCs of 0.88 [95% CI 0.85, 0.91] and AUC 0.86 [95% CI 0.83, 0.89]), respectively. Higher PIM 3 and PELOD 2 scores were robust not only

Table 2. Hosmer-Lemeshow Test for Deciles of Probabilities for PIM 3 and PELOD 2 Scores

PIM 3				PELOD 2*			
Mean Probability of Death	Number of Patients	Observed Deaths	Expected Deaths	Mean Probability of Death	Number of Patients	Observed Deaths	Expected Deaths
0.0016	58	0	0.0931	0.0013	63	1	0.0847
0.0026	57	0	0.1495	0.0032	119	1	0.3849
0.0042	57	0	0.2382				
0.0066	57	0	0.3774	0.0078	119	0	0.9335
0.0099	57	2	0.5627				
0.0129	58	0	0.7505	0.2015	105	4	2.1158
0.0167	56	4	0.9361				
0.0309	57	5	1.7588	0.0448	68	6	3.0455
0.0469	57	5	2.6715	0.0997	53	3	5.2865
0.2676	56	19	14.9867	0.4783	43	20	20.5655
$P = 0.297$				$P = 0.243$			

PELOD 2 score: Paediatric Logistic Organ Dysfunction 2 score; PIM 3 score: Paediatric Index of Mortality 3 score
*Only 7 distinct quantiles due to presence of ties.

Table 3. Ventilator-Free Days and Paediatric Intensive Care Unit-Free Days Associated with PIM 3 and PELOD Scores in Quartiles of Predicted Probabilities

	PIM 3			PELOD 2		
Quartiles	Number of Patients	VFD	IFD	Number of Patients	VFD	IFD
First quartile	143	28 (28, 28)	26 (26, 26)	184	28 (28, 28)	26 (25, 26)
Second quartile	143	26 (26, 27)	25 (24, 26)	119	28 (26, 28)	26 (25, 26)
Third quartile	143	28 (26, 28)	26 (24, 26)	139	26 (24, 27)	25 (21, 26)
Fourth quartile	143	22 (2, 26)	20 (0, 24)	130	23 (4, 26)	21 (2, 25)

IFD: Intensive care unit-free days; PELOD 2 score: Paediatric Logistic Organ Dysfunction 2 score; PIM 3 score: Paediatric Index of Mortality 3 score; VFD: Ventilator-free days
Continuous variables are presented in median (interquartile range).

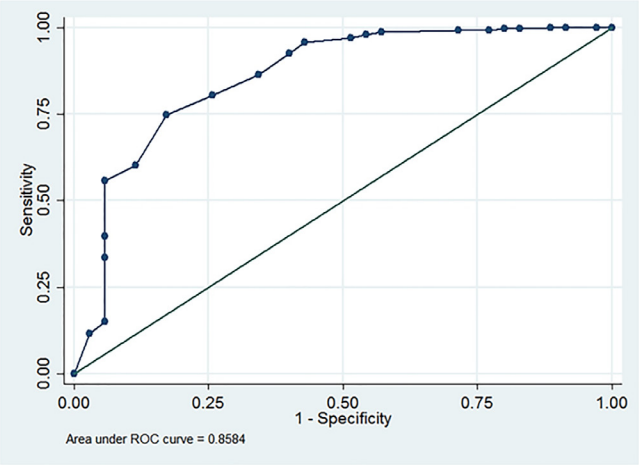

Fig. 2. Receiver operating curve for PELOD 2 (Paediatric Logistic Organ Dysfunction 2) score for all patients.

in predicting mortality but were also associated with decreasing VFD and IFDs.

Recently, both the PIM and PELOD scores were updated (PIM 3 and PELOD 2, respectively).[2,11] Compared to the PIM 2 model, the new PIM 3 model was developed based on a larger dataset across 4 countries to increase its generalisability.[2] In this recently updated version, necrotising enterocolitis was added to the list as a very high-risk diagnosis, whereas human immunodeficiency virus was removed from the list of high-risk conditions and admission following elective liver transplant was not included in the definition of liver failure (a high-risk code). This is the first prospective study to evaluate the performance of the PIM 3 score. Two previous retrospective validation studies of PIM 3 were conducted in Italy and Korea.[13,14] The former study (n = 11,109) showed that PIM3 scores had good discrimination with AUC that were fairly similar to our current study (AUC 0.88 [95% CI 0.86, 0.89]). However, the latter study (n =1710) showed only acceptable discrimination (AUC 0.76 [95% CI 0.72, 0.80]). In the Korean study, the reason for poorer discrimination was attributed to the high proportion of cardiac, haemato-oncological, and respiratory groups which carried a mortality rate higher than that estimated by severity scores.[14] In our study, we were not able to analyse subgroups of different admission categories because of insufficient patients. The total number of expected deaths was 23 as predicted by the overall PIM 3 score of 4.0%. However, the number of observed deaths was higher (35/570 [6.1%]) resulting in a SMR of 1.52. Our centre is 1 of 2 tertiary referral centres in Singapore and sees the largest number of PICU admissions nationwide. All mortalities are discussed at a monthly quality forum to identify preventable factors. It is also possible that the higher SMR may be due to the small sample size and relatively small number of deaths. Differences in SMRs across studies are most likely due to differences in resources, skills and health access in different PICUs.

The PELOD 2 score was examined in several studies after its introduction in 2013. A single-centre prospective study conducted in Portugal (n = 556) showed AUC 0.94 (95% CI 0.90, 0.98). However, there was poor calibration with the goodness-of-fit test (P = 0.022).[15] A posthoc analysis of a multicentre point-prevalence study examined the performance of PELOD 2 score in a subpopulation of children who received plasma transfusions (n = 443).[16] In this subpopulation, PELOD 2 score demonstrated acceptable discrimination (AUC 0.76 [95 % CI 0.71, 0.81]) and calibration (P = 0.76).[16] The odds ratio for death was 1.30 (95 % CI 1.22, 1.39) for each increase in PELOD 2 point.[16] The largest multicentre prospective study involving 9 PICUs in France and Belgium (n = 3669) confirmed that PELOD 2 scores offered the best discrimination on the first day of admission (AUC 0.89 [95% CI 0.86, 0.91]) with good calibration (P = 0.47).[17] The latter 2 studies evaluated the change in serial PELOD 2 scores from day 1 and demonstrated a significant association with death, for each of the observation days. Our study, with a modest sample size of Asian patients, concurs with the previous few studies showing good discrimination and calibration and thus demonstrates the generalisability of the PELOD 2 score. Overall, the PELOD 2 score performed better than the PIM 3 score in this cohort as the 95% CI of SMR crossed 1. As opposed to previous studies which evaluated the PELOD 2 score over a series of time points, we evaluated PELOD 2 score only on day 1 of PICU admission for several reasons. The day 1 PELOD 2 score has superior performance compared to other time points.[17] Because PIM 3 scores are scored within the first hour of admission, we focused on Day 1 PELOD 2 score, so as to allow us to compare these 2 scores within the early period of PICU admission.

In addition to being the first prospective study to evaluate the performance of the PIM 3 score, our study also evaluated the association between higher PIM3 and PELOD 2 scores with VFD and IFD. Investigating alternative clinically important outcomes is necessary because of the improvement in mortality rates in most PICUs. Assuming that factors leading to increase in VFD and IFD also improves mortality, the use of these alternative end points allows for smaller sample sizes.[18] Though not originally designed to predict VFD or IFD, our study demonstrated that patients with a higher quartile of PIM 3 and PELOD 2 scores had progressively decreased VFD and IFD (Table 3). This data further corroborates the 2 scores as robust predictive tools.

Limitations of this study include the small sample size (n = 570) resulting in an underpowered Hosmer-Lemeshow

test. Even though our centre is the larger of 2 national PICUs, this is nevertheless a single-centre study, and hence results are not generalisable throughout Singapore. Other limitations related to the challenges involved in determining some of the variables in the severity scores. For example, some patients did not have arterial cannulas and partial pressure of arterial oxygen could not be measured; some patients were also sedated and Glasgow Coma Scale score could not accurately be ascertained. Normal variables were keyed into the algorithm if data was missing as per the original model.[2,11] To attempt to overcome the practical challenges faced in calculating these scores, we anticipate that in the next revision of these scores, alternative variables that require less invasive monitoring such as the oxygen saturation: fraction of inspired oxygen (SpO_2/FiO_2) ratio may be included instead of the partial pressure of arterial oxygen: fraction of inspired oxygen (PaO_2/FiO_2) ratio. Lastly, we did not perform any tests to determine the inter-rater agreement of the scores. This may have introduced bias, although evaluators underwent standardised training and were blinded.

Conclusion

In a contemporary cohort of critically ill children in Singapore, PIM 3 and PELOD 2 scores performed better in those in the highest quartile of severity of illness. In addition to predicting mortality, we demonstrated that these scores are also associated with VFDs and IFDs.

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Review Article

Long-Term Morbidities in Children with Critical Illness: Gaps and Opportunities

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Abstract

Introduction: Improved mortality rates in paediatric critical care may come with the cost of increased morbidity. Goals of modern paediatric intensive care unit (PICU) management should focus on restoring long-term function of paediatric critical illness survivors. This review outlines our current knowledge on trajectories and risk factors of long-term morbidities in PICU survivors. Specifically, we aimed to identify current limitations and gaps in this area so as to identify opportunities for future investigations to reduce the burden of morbidities in these children. Materials and Methods: A review of primary studies published in PubMed, EMBASE, and Cochrane databases in the last decade (2008-2017) describing long-term morbidities in PICU survivors was conducted. Results: Children surviving critical illness continue to experience morbidities after discharge. A set of risk factors modify their long-term trajectories of recovery, with some children achieving their premorbid level of function, while some others deteriorate or die. Limitations in current methodologies of morbidity research impair our understanding on the causes of these morbidities. Opportunities for future endeavours to reduce the burden of these morbidities include identifying patients who are more likely to develop morbidities, evaluating the efficacy of early rehabilitation, identifying patients who might benefit from tight glycaemic control, characterising the optimal nutritional intervention, and improving management of increased intracranial pressure. Conclusion: Survivors of paediatric critical illness experience differing trajectories of recovery from morbidities. Future research is needed to expand our repertoire on management strategies to improve long-term function in these children.

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Key words: Intensive Care, Outcomes assessment (healthcare), Paediatrics

Introduction

Paediatric critical care has evolved in the last 3 decades, largely attributable to advances in medical care and technology. Paediatric intensive care unit (PICU) mortality rates decreased from 15% in 1982 to 2%-5% in the last decade,[1-5] and critical care is now offered to more children who require more complex care.[1,6,7]

Decreased mortality rates come at the cost of increased morbidity rates.[5] A 3-decade analysis reported that the number of PICU survivors with moderate to severe long-term disability had doubled in 2005-2006 compared to 1982.[1] In 1995, 85% of PICU survivors reported good quality of life (QOL) on follow-up, but this number decreased to 66% in 2006.[1] Children surviving critical illnesses are at risk of developing long-term physical, neurocognitive, and psychological morbidities, much like the adult post-intensive care syndrome.[8]

With decreased mortality, the goal of paediatric critical care management has shifted to restore the function of survivors to their preadmission state. This review aimed to summarise the current available literature over the last decade on the long-term morbidities of PICU survivors.

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We first describe the temporal pattern (trajectories) and risk factors of morbidities. We then focus on the gaps in our knowledge about the causes of and strategies to manage long-term morbidities in PICU survivors, to highlight opportunities for further study in this area.

Materials and Methods

In this review, we defined morbidity as any impairment in the patient's functional status, health-related quality of life (HRQOL), health status (e.g., symptoms of uncontrolled asthma), or neurodevelopmental outcomes (including cognition and behaviour). We conducted a literature search of PubMed, EMBASE, and Cochrane databases using a combination of keywords and MESH terms such as "long-term outcome", "functional outcome", and "critical illness" or "paediatric intensive care unit". Primary studies published in 2008-2017 that described long-term morbidities were included. Because of the heterogeneity of outcome measures, follow-up time, and population characteristics, no statistical analysis was performed, and a narrative approach was used to summarise the current evidence.

Results and Discussion

Long-Term Trajectory of Morbidity in PICU Survivors

PICU survivors have persistently poorer health compared to healthy children (*Online Supplementary Table 1).[3,9-11] This includes lower HRQOL, worse visual-motor integration, motor coordination, poorer memory and intelligence quotient (IQ) scores. These children are at greater risk of functional decline with hospital and PICU readmissions.[2,12] There appears to be several recovery trajectories: some PICU survivors deteriorate or die, some return to their baseline status, and some even improve beyond their baseline function. In a longitudinal cohort study of 70 PICU patients, approximately 41% of PICU survivors had worsening of function or death at 3 years, 49% returned to their baseline state, while the remainder 10% showed improvements from baseline.[2] Reported rates of recovery in other studies range from 59%-81%.[1-3] These varying trajectories in PICU survivors suggest that there are certain factors associated with morbidity and recovery. Identifying these factors would be the first step to support long-term recovery of these children.

Risk Factors for Long-Term Morbidities in PICU Survivors

The major groups of risk factors for long-term morbidities in PICU survivors are outlined in this subsection (Table 1).

Admission Diagnoses

Among all admission diagnoses, children with neurological diagnoses had the highest rate of acquired morbidity at hospital discharge and long-term follow-up.[1,5] At 1 year, 48% of children admitted with neurological diagnoses either died or had moderate or severe disability, compared to only 29% of children with other diagnoses.[1] Within the neurological diagnoses group, different aetiologies were associated with different long-term prognoses. After 6 months, survivors of severe traumatic brain injury (TBI) had higher rates of favourable outcomes (Glasgow Outcome Scale [GOS] = 4) compared to children with refractory febrile status epilepticus (90% vs 27%, respectively).[13,14]

Illness Severity

For any group of patients, higher severity of illness on PICU admission was associated with long-term morbidities. Children requiring longer duration of cardiopulmonary resuscitation (CPR) were found to have worse long-term outcomes.[15,16] Specifically, if duration of CPR was more than 30 minutes, outcomes were limited to only death, disabled, or vegetative state.[16]

PICU survivors requiring use of extracorporeal membrane oxygenation (ECMO) had been shown to have poorer quality of life at 1 month with increased time on ECMO.[15] Indeed, the neurological impairments and other morbidities in ECMO survivors are discussed in other excellent reviews.[17-19]

In acute neurological disorders, the occurrence of status epilepticus is a marker of secondary brain injury and was associated with lower functional status, QOL, higher rates of epilepsy, and worse long-term adaptive behaviour.[20,21] In children with moderate to severe TBI, a lower Glasgow Coma Score (GCS), anisocoria, arterial oxygen saturation <90%, and hypothermia were associated with poorer long-term neurological function.[22,23]

Several variables mentioned above (e.g., impaired pupillary reflexes, low GCS, hypothermia) are part of existing illness severity scoring systems in critically ill children (e.g., Paediatric Risk of Mortality [PRISM] or Paediatric Index of Mortality [PIM]).[24,25] It is therefore not surprising that these scores corresponded well with the magnitude of morbidity. Higher PRISM scores correlated with greater deterioration in Paediatric Overall Performance Category (POPC) and Paediatric Cerebral Performance Category (PCPC) scores from baseline to discharge, while higher PIM2 scores was associated with lower QOL 6 months after discharge.[3,26]

Pre-Existing Morbidities

Pre-existing morbidities affect long-term recovery in PICU survivors. Children with worse baseline function were found to have worse adaptive behaviour, functional outcome, and HRQOL at 1 month post-PICU care, higher hospital readmission rates, and persistent acquired morbidities at 6 months and 3 years.[1,2,15,27] Children with pre-existing chronic health conditions (especially neurodevelopmental disability) were at greater risk of persistent functional

*Available online at http://www.annals.edu.sg/pdf/47VolNo8Aug2018/V47N8p291.pdf (pp. 307-37)

Table 1. Studies Identifying Risk Factors for Long-Term Morbidities of PICU Patients

Study Reference	Population Characteristics	Outcome Measures Used	Risk Factors for Long-Term Morbidity
General PICU Patients			
Polic et al, 2013[*]	n = 189 General PICU, with or without pre-existing chronic health condition (CHC) Median (range) age: Without CHC: 15.5 (10,18) years With CHC: 15.3 (10,17.6) years	RAHC MOF	• Pre-existing neurodevelopmental disability • Chronic health conditions • Higher PIM2 scores
Pinto et al, 2017[†]	n = 77 General PICU Median (IQR) age: 8.60 (2.10 – 11.90) years	FSS	• Longer PICU length of stay • Higher number of ventilation days

ABAS-II: Adaptive Behaviour Assessment System-II; CPP: Cerebral perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HRQoL: Health-related quality of life; ICP: Intracranial pressure; IQR: Inter quartile range; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PICU: Paediatric Intensive Care Unit; PIQ: Performance IQ; POPC: Paediatric Overall Performance Category; RAHC MOF: Royal Alexandra Hospital for Children Measure Of Function; RE: Rehabilitation efficiency; TBI: Traumatic brain injury; THAPCA-OHCA: Therapeutic hypothermia after paediatric cardiac arrest-out of hospital cardiac arrest; VABS-II: Vineland Adaptive Behaviour Scale-II

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[‡]van Zellem L, Utens EM, Legerstee JS, Cransberg K, Hulst JM, Tibboel D, et al. Cardiac arrest in children: long-term health status and health-related quality of life. Pediatr Crit Care Med 2015;16:693-702.

[§]Moler FW, Hutchison JS, Nadkarni VM, Silverstein FS, Meert KL, Holubkov R, et al. Targeted temperature management after pediatric cardiac arrest due to drowning: outcomes and complications. Pediatr Crit Care Med 2016;17:712-20.

[‖]Slomine BS, Nadkarni VM, Christensen JR, Silverstein FS, Telford R, Topjian A, et al. Pediatric cardiac arrest due to drowning and other respiratory etiologies: Neurobehavioral outcomes in initially comatose children. Resuscitation 2017;115:178-84.

[¶]Wagenman KL, Blake TP, Sanchez SM, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and long-term outcome in critically ill children. Neurology 2014;82:396-404.

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[††]Tepas JJ 3rd, Leaphart CL, Pieper P, Beaulieu CL, Spierre LR, Tuten JD, et al. The effect of delay in rehabilitation on outcome of severe traumatic brain injury. J Pediatr Surg 2009;44:368-72.

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Table 1. Studies Identifying Risk Factors for Long-Term Morbidities of PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Risk Factors for Long-Term Morbidity
Cardiac Arrest Patients			
Van Zellem et al, 2015[‡]	n = 57 PICU population who have sustained cardiac arrest Median (range) age at follow-up: 8.7 (2.4 – 18.3) years	PCPC	• Pre-existing health condition related to the cause of cardiac arrest
Moler et al, 2016[§]	n = 68 Out of hospital cardiac arrest (OHCA) patients, and who were admitted to a PICU and remained comatose within 6 hours of return of circulation (ROC), with premorbid VABS-II scores ≥70, mean (SD) age in years: drowning group: 4.6 (4.16); other aetiologies: 5.1 (5.41)	VABS-II	• Duration of CPR >30 minutes
Slomine et al, 2017[‖]	n = 59 Out of hospital cardiac arrest (OHCA) patients who were admitted to a PICU and remained comatose within 6 hours of return of circulation (ROC), with premorbid VABS-II scores ≥70 Mean (SD) age: Drowning group: 4.6 (4.16) years Other aetiologies: 5.1 (5.41) years	VABS-II	• Older age • Higher doses of epinephrine • Aetiologies other than drowning

ABAS-II: Adaptive Behaviour Assessment System-II; CPP: Cerebral perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HRQoL: Health-related quality of life; ICP: Intracranial pressure; IQR: Inter quartile range; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PICU: Paediatric Intensive Care Unit; PIQ: Performance IQ; POPC: Paediatric Overall Performance Category; RAHC MOF: Royal Alexandra Hospital for Children Measure Of Function; RE: Rehabilitation efficiency; TBI: Traumatic brain injury; THAPCA-OHCA: Therapeutic hypothermia after paediatric cardiac arrest-out of hospital cardiac arrest; VABS-II: Vineland Adaptive Behaviour Scale-II

[*]Polic B, Mestrovic J, Markic J, Mestrovic M, Capkun V, Utrobicic I, et al. Long-term quality of life of patients treated in paediatric intensive care unit. Eur J Pediatr 2013;172:85-90.

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[‡‡]Kapapa T, König K, Pfister U, Sasse M, Woischneck D, Heissler H, et al. Head trauma in children, part 2: course and discharge with outcome. J Child Neurol 2010;25:274-83.

[§§]Thomale UW, Graetz D, Vajkoczy P, Sarrafzadeh AS. Severe traumatic brain injury in children–a single center experience regarding therapy and long-term outcome. Childs Nerv Syst 2010;26:1563-73.

[‖‖]Fulkerson DH, White IK, Rees JM, Baumanis MM, Smith JL, Ackerman LL, et al. Analysis of long-term (median 10.5 years) outcomes in children presenting with traumatic brain injury and an initial Glasgow Coma Scale score of 3 or 4. J Neurosurg Pediatr 2015;16:410-9.

[¶¶]Ebrahim S, Singh S, Hutchison JS, Kulkarni AV, Sananes R, Bowman KW, et al. Adaptive behavior, functional outcomes, and quality of life outcomes of children requiring urgent ICU admission. Pediatr Crit Care Med 2013;14:10-8.

Table 1. Studies Identifying Risk Factors for Long-Term Morbidities of PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Risk Factors for Long-Term Morbidity
Neurological Diagnoses Patients – Non-Traumatic Brain Injury			
Wagenman et al, 2014¶	n = 60 Previously neurodevelopmentally normal children with an acute neurologic condition and altered mental status who underwent cEEG Median (IQR) age: 3.9 (1.1, 12.7) years	GOS-E, PedsQL	• Electrographic status epilepticus
Abend et al, 2015#	n = 60 Previously neurodevelopmentally normal children with an acute neurologic condition and altered mental status who underwent cEEG Median age (IQR): 4.1 (2.0, 9.8) years	ABAS-II	• Electrographic seizures • Electrographic status epilepticus

ABAS-II: Adaptive Behaviour Assessment System-II; CPP: Cerebral perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HRQoL: Health-related quality of life; ICP: Intracranial pressure; IQR: Inter quartile range; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PICU: Paediatric Intensive Care Unit; PIQ: Performance IQ; POPC: Paediatric Overall Performance Category; RAHC MOF: Royal Alexandra Hospital for Children Measure Of Function; RE: Rehabilitation efficiency; TBI: Traumatic brain injury; THAPCA-OHCA: Therapeutic hypothermia after paediatric cardiac arrest-out of hospital cardiac arrest; VABS-II: Vineland Adaptive Behaviour Scale-II

*Polic B, Mestrovic J, Markic J, Mestrovic M, Capkun V, Utrobicic I, et al. Long-term quality of life of patients treated in paediatric intensive care unit. Eur J Pediatr 2013;172:85-90.

†Pinto NP, Rhinesmith EW, Kim TY, Ladner PH, Pollack MM. Long-term function after pediatric critical illness: results from the Survivor Outcomes Study. Pediatr Crit Care Med 2017;18:e122-30.

‡van Zellem L, Utens EM, Legerstee JS, Cransberg K, Hulst JM, Tibboel D, et al. Cardiac arrest in children: long-term health status and health-related quality of life. Pediatr Crit Care Med 2015;16:693-702.

§Moler FW, Hutchison JS, Nadkarni VM, Silverstein FS, Meert KL, Holubkov R, et al. Targeted temperature management after pediatric cardiac arrest due to drowning: outcomes and complications. Pediatr Crit Care Med 2016;17:712-20.

‖Slomine BS, Nadkarni VM, Christensen JR, Silverstein FS, Telford R, Topjian A, et al. Pediatric cardiac arrest due to drowning and other respiratory etiologies: Neurobehavioral outcomes in initially comatose children. Resuscitation 2017;115:178-84.

¶Wagenman KL, Blake TP, Sanchez SM, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and long-term outcome in critically ill children. Neurology 2014;82:396-404.

#Abend NS, Wagenman KL, Blake TP, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and neurobehavioral outcomes in critically ill children. Epilepsy Behav 2015;49:238-44.

**Salorio CF, Slomine BS, Guerguerian AM, Christensen JR, White JR, Natale JE, et al. Intensive care unit variables and outcome after pediatric traumatic brain injury: a retrospective study of survivors. Pediatr Crit Care Med 2008;9:47-53.

††Tepas JJ 3rd, Leaphart CL, Pieper P, Beaulieu CL, Spierre LR, Tuten JD, et al. The effect of delay in rehabilitation on outcome of severe traumatic brain injury. J Pediatr Surg 2009;44:368-72.

‡‡Kapapa T, König K, Pfister U, Sasse M, Woischneck D, Heissler H, et al. Head trauma in children, part 2: course and discharge with outcome. J Child Neurol 2010;25:274-83.

§§Thomale UW, Graetz D, Vajkoczy P, Sarrafzadeh AS. Severe traumatic brain injury in children–a single center experience regarding therapy and long-term outcome. Childs Nerv Syst 2010;26:1563-73.

‖‖Fulkerson DH, White IK, Rees JM, Baumanis MM, Smith JL, Ackerman LL, et al. Analysis of long-term (median 10.5 years) outcomes in children presenting with traumatic brain injury and an initial Glasgow Coma Scale score of 3 or 4. J Neurosurg Pediatr 2015;16:410-9.

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Table 1. Studies Identifying Risk Factors for Long-Term Morbidities of PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Risk Factors for Long-Term Morbidity
Neurological Diagnoses Patients – Traumatic Brain Injury			
Salorio et al, 2008[**]	n = 57 Survivors of paediatric moderate and severe TBI (GCS 3 – 12) admitted for rehabilitation Mean age: 10.8 +/- 3.2 years	PIQ: Wechsler Intelligence Scale for Children, DRS	Worse PIQ: • Lower initial GCS score • Hypotension Worse DRS: • Hypertension within the first 24 hours
Tepas et al, 2009[††]	n = 60 Patients with severe blunt TBI (initial GCS score ≤8) that required resuscitation, critical care, and inpatient rehabilitation Mean age: male 11.2 years, females, 10.6 years	FIM, RE: ratio of FIM improvement to length of inpatient rehabilitation	• Delayed inpatient rehab associated with reduced rehabilitation efficiency and reduced improvements in FIM scores
Kapapa et al, 2010[‡‡]	n = 48 Children who sustained head trauma requiring intensive care, receiving cerebral perfusion pressure (CPP)-orientated management Mean age: 5.9 years (range 19 days – 14.5 years)	GOS	• Elevated blood glutamic-oxaloacetic-transaminase • Elevated blood urea and glucose on the first 2 days • ≥1 occurrence of CPP value below recommended standard • Mean arterial pressure below lower limit • Central venous pressure below lower limit
Thomale et al, 2010[§§]	n = 53 Neurosurgically treated patients with diagnosis of severe TBI (GCS <9) undergoing additional decompressive craniectomy or conservative intracranial pressure (ICP) management without craniectomy Median age: craniectomy: 12 years, conservative: 7 years	GOS	• Anisocoria on admission • Arterial oxygen saturation <90% on admission

ABAS-II: Adaptive Behaviour Assessment System-II; CPP: Cerebral perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HRQoL: Health-related quality of life; ICP: Intracranial pressure; IQR: Inter quartile range; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PICU: Paediatric Intensive Care Unit; PIQ: Performance IQ; POPC: Paediatric Overall Performance Category; RAHC MOF: Royal Alexandra Hospital for Children Measure Of Function; RE: Rehabilitation efficiency; TBI: Traumatic brain injury; THAPCA-OHCA: Therapeutic hypothermia after paediatric cardiac arrest-out of hospital cardiac arrest; VABS-II: Vineland Adaptive Behaviour Scale-II

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[§]Moler FW, Hutchison JS, Nadkarni VM, Silverstein FS, Meert KL, Holubkov R, et al. Targeted temperature management after pediatric cardiac arrest due to drowning: outcomes and complications. Pediatr Crit Care Med 2016;17:712-20.

[‖]Slomine BS, Nadkarni VM, Christensen JR, Silverstein FS, Telford R, Topjian A, et al. Pediatric cardiac arrest due to drowning and other respiratory etiologies: Neurobehavioral outcomes in initially comatose children. Resuscitation 2017;115:178-84.

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Table 1. Studies Identifying Risk Factors for Long-Term Morbidities of PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Risk Factors for Long-Term Morbidity
Neurological Diagnoses Patients – Traumatic Brain Injury			
Fulkerson et al, 2015[ll]	n = 67 Paediatric head injury patients presented to neurosurgical service at a single centre with: GCS 3 (age 49.8 +/- 51.8 months) or GCS 4 (age 66.9 +/- 58.0 months)	mGOS, mortality	• Impaired pupillary response • Hypothermia • Mechanism of injury (abuse)
Other Specific Populations			
Ebrahim et al, 2013[¶¶]	n = 91; 65 completed 1-month assessment Urgently admitted (<12 hours notice) patients from inpatient ward, or had an ICU cardiac arrest and/or received ECMO treatment irrespective of the urgency of their ICU admission Mean age: 76.4 ± 69.3 months, range 1 month to 18 years	Adaptive behaviour: VABS-II, HRQoL: Peds QL, functional outcome: PCPC, POPC	Worse adaptive behaviour: • Circulatory diagnoses • Worse initial PCPC scores • Worse transcutaneous O_2 saturation • Longer cardiac compression Worse HRQoL: • Worse initial PCPC • Longer ICU stay • Longer duration of ECMO Worse functional outcome: • Same factors as HRQoL • Neurological diagnoses

ABAS-II: Adaptive Behaviour Assessment System-II; CPP: Cerebral perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HRQoL: Health-related quality of life; ICP: Intracranial pressure; IQR: Inter quartile range; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PICU: Paediatric Intensive Care Unit; PIQ: Performance IQ; POPC: Paediatric Overall Performance Category; RAHC MOF: Royal Alexandra Hospital for Children Measure Of Function; RE: Rehabilitation efficiency; TBI: Traumatic brain injury; THAPCA-OHCA: Therapeutic hypothermia after paediatric cardiac arrest-out of hospital cardiac arrest; VABS-II: Vineland Adaptive Behaviour Scale-II

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impairment (decrease in Royal Alexandra Hospital for Children Measure of Function [RAHC MOF] scores from premorbid) compared to children without chronic conditions.[3] Among cardiac arrest survivors, those with pre-existing conditions reported worse general health perception years later.[10]

PICU Length of Stay

Longer length of PICU stay was also identified as a risk factor for long-term acquired morbidities.[2] In a long-stay cohort, among children who had no or mild disability on admission, 20% was found to have long-term moderate to severe disability.[28] In comparison, in the general PICU cohort, only 4% of children ended up with long-term moderate to severe disability.[1] In our own experience of 241 long-stay (>14 days) admissions, we found that long-stayers had high rates of pre-existing comorbidities (55%) and chronic care devices (non-invasive ventilation, tracheostomy, or long-term parenteral nutrition) (49%), consistent with the literature.[4,29,30] Moreover, on PICU discharge, more children were found to require chronic care devices compared to admission.[4]

Initiation of Rehabilitation

Delay in starting rehabilitation influenced the success of subsequent recovery. A study in children with severe blunt TBI found that the duration of delay between PICU discharge and the start of inpatient rehabilitation was inversely correlated with rehabilitation efficiency and improvement in functional independence measurement scores.[31]

Gaps in Knowledge and Opportunities for Future Research

Heterogeneity in Morbidity Measurement Tools and Timing

The number of clinical studies describing long-term morbidities and associated risk factors are increasing. However, our understanding of the causes of morbidities remains inadequate due to several limitations in morbidity research.

Firstly, there is the heterogeneity of outcome measures used to quantify morbidities. This partially stems from a lack of consensus on definitions of outcome measures. For instance, some researchers consider HRQOL as part as functional status, while others consider them as separate entities.[15,32,33] Functional status has been measured using a range of global functional outcome scoring tools (e.g., PCPC), adaptive behaviour functioning scales (e.g., Vineland Adaptive Behaviour Scale-2 [VABS-2]), and QOL rating scales (e.g., RAHC MOF).[3,26,32,34] In addition, some have used unstructured questionnaires to capture long-term sequelae or impairment in functioning (e.g., poorly defined "learning difficulties", "mental impairment", or "behaviour problem").[10,35]

The lack of consensus is a barrier to synthesising and interpreting data across studies.[2,9,32,33,36] Ideally, studies should use a standardised, well defined outcome measure for each type of morbidity and use validated measurement tools to quantify outcomes. This may evolve over time as studies examining morbidities after paediatric critical illness are just recently emerging. Furthermore, we do not fully understand the scope and types of morbidities affecting PICU survivors. The adult population has a well described construct known as the post-intensive care syndrome (PICS)—categorising the acquired morbidities in ICU survivors to 3 domains: physical, neurocognitive, and psychological.[34] It has been suggested that the same construct could be applied to children so as to standardise the description of the landscape of morbidity in PICU survivors.[8]

Secondly, comparison between studies are challenging because of the lack of standardisation in design and quality of the studies, most particularly in terms of long-term follow-up. Duration of follow-up varied greatly across studies, from 1 month[14,15] to greater than 10 years.[12,37] Most long-term follow-up will assess the child's status compared to baseline, however, the time point to establish "baseline" also differed between studies—some defined "baseline" as the pre-acute illness functioning while others considered "baseline" as the 24-hours window after PICU admission.[2,3,5,15] Some studies only reported absolute morbidity, with no comparison with the child's baseline status or appropriately matched controls in the analysis. Not all studies accounted for the children lost to follow-up by ensuring they were comparable to the children remaining in the studies. The quality assessment of the included studies in our review is detailed in [*]Online Supplementary Table 2.

To achieve our goal of restoring PICU survivors to their premorbid function, it is imperative for future studies to standardise the follow-up interval and duration to allow for comparison of data across different centres. Currently, the best timing for follow-up is unknown. The available evidence suggests that recovery from morbidity may reach a plateau between 6 months and 3 years after hospital discharge. In PICU survivors, children who recover at the end of 3 years still had decreased mean Functional Status Scale (FSS) scores at 6 months compared to baseline.[2] In children with severe TBI, the optimum follow-up time may be 1 year. Median GOS improved from 4 to 5 between hospital discharge and 12 months, while scores at 5 and 11 years were the same as those at 1 year.[23,37] Additionally, studies should include baseline measurements of the child's premorbid function, or to include matched controls to serve as a benchmark. It is also important to select appropriate measures to best capture age-specific needs and to evaluate response to intervention over time.

[*]Available online at http://www.annals.edu.sg/pdf/47VolNo8Aug2018/V47N8p291.pdf (pp. 307-37)

Early Identification of Children At Risk of Developing Long-Term Morbidities

An important step in reducing long-term morbidities would be to identify patients who are at greater risk of acquired morbidities so that early interventions to reduce morbidities can be instituted.

Currently, disease severity scoring systems (e.g., PIM, PRISM, and Paediatric Logistic Organ Dysfunction [PELOD]) are used to predict risk of PICU mortality.[38,39] As disease severity is associated with morbidities, recent literature suggests that these tools could also predict acquired morbidities. In a large multicentre cohort study, Pollack et al showed that PRISM III scores could be used to simultaneously predict mortality and acquired morbidity (defined as an increase in FSS = 3 compared to baseline) at hospital discharge.[40] In this prediction model, morbidity risk initially increased with higher PRISM III scores, but then decreased with the highest PRISM III scores, as potential morbidities resulted in mortalities. The final prediction model had a strong predictive ability with volume under the surface of 0.50.

While predicting acquired morbidities at hospital discharge would enable us to intervene early during hospital stay, it could potentially miss patients who develop morbidities after hospital discharge. Indeed, a study involving 77 children demonstrated that the rates of acquired morbidity continued to increase after hospital discharge (4%), reaching 6% and 10% at 6 months and 3 years, respectively.[2]

A tool to predict development of long-term morbidities would identify both groups who develop morbidities by hospital discharge as well as those who do so after hospital discharge. It may also enable us to prevent further deterioration in these children by allocating appropriate resources posthospital discharge, including follow-up sessions for early detection of postdischarge acquired morbidities, or structured rehabilitation programmes to aid functional recovery.[41] This proposed tool could build on existing mortality prediction systems, with incorporation of additional variables associated with morbidities, including pre-existing chronic health condition or baseline functional status.

Some mortality prediction systems, such as PIM3, assign different risks into different admission diagnoses.[25] These would need to be modified, since a low-risk diagnosis for mortality might be associated with a high risk for morbidity. For instance, while PIM3 classifies seizure disorders as low-risk, a patient admitted for any neurological diagnosis should be assigned an increased risk for morbidity compared to other admitting diagnoses, and an even higher risk should be assigned for refractory febrile status epilepticus.[25] Conversely, a high risk for mortality may not apply to morbidity. For instance, a cardiac arrest preceding ICU admission would be assigned as a very high-risk for mortality in PIM3 or PRISM4.[24,25] However, up to 82% of cardiac arrest survivors attain favourable long-term outcomes, as long as the duration of CPR was less than 30 minutes.[16,42] An improvement for a morbidity prediction system would be the incorporation of risk factors for morbidities related to a particular admission diagnosis. For instance, for a patient admitted after a cardiac arrest, a high risk for long-term morbidity should be assigned if CPR exceeds 30 minutes, while in TBI patients, higher risk should be assigned if the mechanism of injury is abuse.[16,37]

The existing mortality prediction systems are based on patient parameters within the first 24 hours of PICU admission.[24,25] However, long-term morbidities could be influenced by events occurring any time during the PICU stay. In patients with altered mental status, occurrences of status epilepticus throughout PICU stay were associated with long-term morbidities.[20,21] In TBI patients, at least 1 occurrence of low cerebral perfusion pressure was associated with worse functional outcomes.[35] While prediction of long-term morbidities might be improved by continuously monitoring physiological parameters, it might be impractical to do so. An alternative might be to reassign a long-term morbidity prediction score at PICU discharge, to include additional high-risk events occurring during PICU stay.

Interventions to Reduce Morbidity Within the PICU

To reduce long-term morbidities, interventions need to target modifiable risk factors. This section will discuss some randomised controlled trials (RCTs) (Table 2) from the past decade as well as current gaps in our knowledge pertaining to this issue.

Early Mobilisation to Improve Long-Term Functional Outcomes

Despite the importance of early mobilisation for long-term recovery of function, it is not commonly practised in the PICU.[31] Only half of children received rehabilitation in the PICU, and of these, up to 70% of the rehabilitation received was non-mobile in nature (e.g., chest physiotherapy), while only less than 10% of children received early mobilisation.[43] Leading reasons for delaying mobility treatments include the lack of practice guidelines and conflicting perceptions regarding clinical thresholds and safety of early mobilisation.[44]

There is a need to evaluate the safety, clinical threshold to initiate, and efficacy of early mobilisation. Two pilot studies have reported the safety and feasibility of acute rehabilitation interventions in the PICU, using in-bed cycling and virtual reality (VR) boxing to promote early mobilisation.[45,46] The in-bed cycling pilot trial achieved its

Table 2. Randomised Controlled Trials (RCTs) Evaluating Interventions to Reduce Long-Term Morbidity in PICU Survivors

Study Reference	Study Design	Population Characteristics	Intervention	Outcome Measures Used	Follow-up Time(s)	Long-Term Outcome
Early Rehabilitation						
Abdulsatar et al, 2013*	Pilot RCT	n = 8 Children 3 – 18 years old with anticipated PICU stay >48 hours, baseline normal to moderate cognitive and functional disability Median (IQR) age: 11 (3, 16) years	Nintendo Wii™ boxing for a minimum of 10 minutes twice a day for 2 days	Safety and feasibility	NA	• No adverse events attributable to the intervention • Upper limb activity during intervention was significantly greater than average daily activity • Grip strength did not change significantly from baseline
Choong et al, 2017†	Pilot RCT	n = 30 Children 3 – 17 years old limited to bed rest with expected PICU stay of ≥48 hours Median (IQR) age: Usual care group 9 (6, 11) years Cycling group 8 (5, 14) years	Early mobilisation using in-bed cycling in addition to physiotherapy alone vs usual care (physiotherapy alone)	Safety and feasibility	NA	• No adverse events occurred in either arm • Early mobilisation was feasible • Main threat to feasibility was the availability of personnel

CBCL: Child Behaviour Checklist; CPP: Cerebral perfusion pressure; EN: Enteral nutrition; GCS: Glasgow Coma Score; HUI: Health Utilities Index; ICP: Intracranial pressure; IQR: Inter quartile range; KOSCHI: The Kings Outcome Scale for Childhood Head Injury; LOS: Length of stay; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PELOD: Paediatric logistic organ dysfunction; PICU: Paediatric intensive care unit; PN: Parenteral nutrition; RCTP: Randomised controlled trial; RRT: Renal replacement therapy; TBI: Traumatic brain injury; TGC: Tight glycaemic control

*Abdulsatar F, Walker RG, Timmons BW, Choong K. "Wii-Hab" in critically ill children: a pilot trial. J Pediatr Rehabil Med 2013;6:193-204.

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#Kumar R, Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med 2014;42:1775-87.

Table 2. Randomised Controlled Trials (RCTs) Evaluating Interventions to Reduce Long-Term Morbidity in PICU Survivors (Cont'd)

Study Reference	Study Design	Population Characteristics	Intervention	Outcome Measures Used	Follow-up Time(s)	Long-Term Outcome
Management of Hyperglycaemia						
Vlasselaers et al, 2009‡	RCT	n = 700 (317 infants, 383 aged ≥1 year) General PICU from single centre Median (IQR) age: Conventional group: 1.3 (0.3, 4.6) years Intensive group: 1.4 (0.3, 5.5) years	Intensive group: insulin infusion to target normoglycaemia of 2.8 – 4.4 mmol/L in infants and 3.9 – 5.6 mmol/L in children vs conventional group: insulin infusion only to prevent blood glucose from exceeding 11.9 mmol/L	Mortality, PICU LOS, inflammatory response (c-reactive protein)	PICU discharge	• Hypoglycaemia occurred in more in patients in the intensive group (25%) vs conventional group (1%) • Duration of PICU stay was shorter in the intensively treated group • Inflammatory response was attenuated at day 5 in the intensive group • No mortality difference between 2 arms
Mesotten et al, 2012§	Follow-up from survivors of RCT	n = 569 All PICU patients aged 0 – 16 years Median (IQR) age at follow-up: TGC: 5.3 (4.2 – 9.2) years CM: 5.1 (4.2 – 8.2) years	TGC vs conventional glucose management (CM)	Intelligence quotient (Wechsler IQ scales), neurodevelopmental testing (Beery-Buktenica Developmental Test of Visual-Motor Integration), attention, motor coordination, and executive functions (Amsterdam Neuropsychological Tasks), memory (Children's Memory Scale), behaviour (Child Behaviour Checklist)	Median (IQR) of 3.9 (3.8 – 4.1) years after randomisation	• TGC did not affect IQ scores • TCG did not increase incidence of death or severe disability precluding neurocognitive testing • Tight glucose control improved motor coordination and cognitive flexibility
Macrae et al, 2014‖	RCT	n = 1369 Non-diabetic PICU patients Age 0 – 16 years	TGC vs conventional glucose management (CM)	Short-term: Mortality, duration of ventilation, length of PICU/hospital stay, readmission rates, renal replacement therapy, infection, transfusions, seizures, PELOD score, hypoglycaemia Long-term: Mortality, attention and behaviour in TBI patients (KOSCHI, HUI, CBCL), total duration of PICU and hospital stay		

CBCL: Child Behaviour Checklist; CPP: Cerebral perfusion pressure; EN: Enteral nutrition; GCS: Glasgow Coma Score; HUI: Health Utilities Index; ICP: Intracranial pressure; IQR: Inter quartile range; KOSCHI: The Kings Outcome Scale for Childhood Head Injury; LOS: Length of stay; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PELOD: Paediatric logistic organ dysfunction; PICU: Paediatric intensive care unit; PN: Parenteral nutrition; RCTP: Randomised controlled trial; RRT: Renal replacement therapy; TBI: Traumatic brain injury; TGC: Tight glycaemic control

*Abdulsatar F, Walker RG, Timmons BW, Choong K. "Wii-Hab" in critically ill children: a pilot trial. J Pediatr Rehabil Med 2013;6:193-204.

†Choong K, Awladthani S, Khawaji A, Clark H, Borhan A, Cheng J, et al. Early exercise in critically ill youth and children, a preliminary evaluation: the wEECYCLE pilot trial. Pediatr Crit Care Med 2017;18:e546-54.

‡Vlasselaers D, Milants I, Desmet L, Wouters P, Vanhorebeek I, Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.

§Mesotten D, Gielen M, Sterken C, Claessens K, Hermans G, Vlasselaers D, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: A randomized controlled trial. JAMA 2012;308:1641-50.

‖Macrae D, Grieve R, Allen E, Sadique Z, Betts H, Morris K, et al. A clinical and economic evaluation of control of hyperglycaemia in paediatric intensive care (CHiP): a randomised controlled trial. Health Technol Assess 2014;18:1-209.

¶Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111-22.

#Kumar R, Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med 2014;42:1775-87.

Table 2. Randomised Controlled Trials (RCTs) Evaluating Interventions to Reduce Long-Term Morbidity in PICU Survivors (Cont'd)

Study Reference	Study Design	Population Characteristics	Intervention	Outcome Measures Used	Follow-up Time(s)	Long-Term Outcome
Timing of Supplemental Parenteral Nutrition						
Fivez et al, 2016[¶]	RCT	n = 1440 General PICU from 3 centres Median (IQR) age: Early PN 1.4 (0.3 – 6.1) Late PN 1.5 (0.2 – 7.2)	Early PN: PN to supplement caloric intake from EN, initiated within 24 hours after ICU admission Late PN: supplemental PN delayed until day 8 of PICU	PICU mortality, new infection rates, PICU and hospital LOS, duration of mechanical ventilation, proportion of patients receiving renal replacement therapy (RRT), plasma levels of inflammatory markers	First 7 days in PICU, PICU discharge, 90 days after PICU admission	• No mortality difference between 2 arms • Late PN associated with lower infection rate (10.7% vs 18.5%), shorter ICU (6.5 ± 0.4 vs 9.2 ± 0.8 days) and hospital LOS, shorter duration of mechanical ventilation, lower proportion of RRT, and lower plasma inflammatory markers
Management of Increased Intracranial Pressure						
Kumar et al, 2014[#]	RCT	n = 110 PICU patients with acute CNS infection with modified Glasgow Coma Scale score (m-GCS) ≤8, and evidence of raised ICP Mean age in months: 69.2 ± 37 (ICP); 62.6 ± 36.8 (CPP)	CPP vs ICP – targeted approach	Mortality, neuromorbidity (m-GOS), functional neuro-disability (PCPC), presence of hearing deficit	PICU discharge, 90 days after PICU discharge	• Cumulative mortality was significantly higher in the ICP group • Neuro-disability and hearing deficit were lower in CPP group

CBCL: Child Behaviour Checklist; CPP: Cerebral perfusion pressure; EN: Enteral nutrition; GCS: Glasgow Coma Score; HUI: Health Utilities Index; ICP: Intracranial pressure; IQR: Inter quartile range; KOSCHI: The Kings Outcome Scale for Childhood Head Injury; LOS: Length of stay; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PELOD: Paediatric logistic organ dysfunction; PICU: Paediatric intensive care unit; PN: Parenteral nutrition; RCTP: Randomised controlled trial; RRT: Renal replacement therapy; TBI: Traumatic brain injury; TGC: Tight glycaemic control

[*]Abdulsatar F, Walker RG, Timmons BW, Choong K. "Wii-Hab" in critically ill children: a pilot trial. J Pediatr Rehabil Med 2013;6:193-204.

[†]Choong K, Awladthani S, Khawaji A, Clark H, Borhan A, Cheng J, et al. Early exercise in critically ill youth and children, a preliminary evaluation: the wEECYCLE pilot trial. Pediatr Crit Care Med 2017;18:e546-54.

[‡]Vlasselaers D, Milants I, Desmet L, Wouters P, Vanhorebeek I, Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.

[§]Mesotten D, Gielen M, Sterken C, Claessens K, Hermans G, Vlasselaers D, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: A randomized controlled trial. JAMA 2012;308:1641-50.

[‖]Macrae D, Grieve R, Allen E, Sadique Z, Betts H, Morris K, et al. A clinical and economic evaluation of control of hyperglycaemia in paediatric intensive care (CHiP): a randomised controlled trial. Health Technol Assess 2014;18:1-209.

[¶]Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111-22.

[#]Kumar R, Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med 2014;42:1775-87.

goals of enrolment and 1 month follow-up rates exceeding 75%, and documented no adverse effects.[45] Similarly, the VR pilot trial did not find any adverse effects of early mobilisation and reported significantly improved upper limb activity compared to average daily activity.[46] Despite promising early results, the long-term efficacy of early mobilisation remains to be evaluated.

Management of Raised Intracranial Pressure in Children Admitted for Critical Neurological Diagnoses

Raised intracranial pressure (ICP) contributes to secondary brain injury.[47] Optimal management of increased ICP is essential to prevent mortality and morbidities.[48,49] There remains clinical equipoise on the optimal strategy to manage ICP in the PICU.[47,50] One strategy focuses on reduction of ICP ("ICP-targeted therapy"), using controlled hyperventilation, administration of hyperosmotic solutions and barbiturates.[51] Another strategy focuses on optimising cerebral perfusion pressure ("CPP-targeted therapy"), involving pharmacologically-induced increase in CPP to improve cerebral blood flow.[52]

In children with acute central nervous system (CNS) infection, a recent RCT reported the superiority of CPP- to ICP-targeted therapy for management of increased ICP.[53] The trial randomised 110 children with GCS = 8 to CPP-targeted (maintaining CPP = 60mm Hg, using normal saline bolus and vasoactive therapy) or ICP-targeted (maintaining ICP <20mm Hg using osmotherapy while ensuring normal blood pressure). The CPP-targeted group had lower mortality, as well as lower prevalence of hearing deficit and neuro-disability at 90 days after discharge. Because the study only involved patients with CNS infections, its finding may not be generalisable to other groups of patients with impaired cerebral autoregulation, such as TBI.[49]

Till date, there are no RCTs assessing the superiority of either strategy in paediatric TBI. However, available literature reported that survival with good neurological outcomes could be achieved using either strategy, ranging from 54%-60% to 70%-90% at hospital discharge and long-term, respectively.[13,23,35] Considering the high rates of morbidities of TBI survivors, a RCT comparing the 2 strategies would add valuable evidence on the superior strategy in reducing morbidities in these children.

Decompressive craniotomy (DC) is widely utilised as a treatment option for increased ICP, mainly for children with refractory high ICP or low CPP that are unresponsive to maximal medical management.[13,23,35,54] Children treated with DC were reported to have comparable long-term outcomes with children with conservative management, although initially, they have worse clinical profiles.[13,23] In a group of 48 patients with severe TBI (GCS = 8), children needing DC had worse peak ICP and lower CPP compared to those responsive to ICP-targeted medical management; however, they showed comparable neurological functional outcomes as measured by GOS scores at hospital discharge and 6 months follow-up.[13] In a similar study involving 53 children, patients needing DC had no difference in neurological functioning at 12 months compared to the children treated conservatively, who had twofold better GCS scores on presentation.[23]

Current guidelines consider DC as a controversial procedure due to insufficient data.[54,55] Two adult RCTs have reported discouraging results, with DC increasing survival but increasing long-term morbidities.[56,57] However, head injuries in children are known to be different than that in adults due to more compressible skull and brain, vulnerability to brain swelling, and different pathophysiology of intracranial hypertension.[23] Given the widespread use of this strategy, there is an urgent need for a RCT to assess the efficacy of DC in the paediatric population.

Tight Glycaemic Control

Hyperglycaemia in PICU patients is associated with adverse short-term outcomes such as organ failure and mortality.[58,59] RCTs evaluating the benefit of intensive insulin therapy for management of hyperglycaemia in PICU patients have yielded mixed results.

A Belgian RCT involving 700 children (majority were cardiac surgical patients) showed that tight glucose control (TGC) to age-adjusted normoglycaemia reduced PICU mortality, length of stay (LOS) and improved long-term motor coordination and cognitive flexibility compared to standard care.[11,60] On the other hand, a United Kingdom (UK) trial involving 1369 children showed no overall mortality or LOS benefit.[61]

TGC carries significant risk of hypoglycaemia.[60-62] In children undergoing cardiac surgery, patients with hypoglycaemic episodes had almost 5 times the mortality of patients without hypoglycaemia.[61] While a long-term follow-up study on the survivors from the Belgian RCT reported that TGC did not affect IQ scores at 4 years, symptomatic hypoglycaemia in young children has previously been reported to be associated with various patterns of brain injury and as well as neurodevelopmental impairments at 18 months.[11,63]

These data suggest that while TGC for hyperglycaemia might benefit some PICU patients, it must be carefully weighed against the risks of hypoglycaemia. Further research is needed to identify the subset of patients for whom the benefits of TGC exceed the risks of hypoglycaemia. The long-term analysis of the UK trial reported that in non-cardiac surgery patients, TGC was associated with shorter hospital stay and reduced healthcare costs at 12 months, highlighting a potential group to be investigated.[61]

Nutritional Intervention in the PICU

Nutrition delivery in PICU is generally inadequate, which may adversely impact clinical outcomes.[64-66] The Paediatric Early versus Late Parenteral Nutrition In Critical Illness (PEPaNIC) RCT explored whether early achievement of nutrition goals using parenteral nutrition (PN) would be associated with better outcomes. A total of 1440 critically ill children were randomised to receive early (within the first day) or late (after day 7 of PICU stay) supplemental PN when enteral nutrition (EN) failed to reach the prescribed caloric targets. Late PN was associated with lower rate of new infections, shorter duration of mechanical ventilation, and shorter PICU and hospital LOS.[67] Of note, the long-term developmental and neurocognitive outcomes of these patients are yet to be published.

Although some aspects of this trial have been controversial, this study highlights the gaps in our knowledge regarding nutrition provision in the PICU.[68,69] The impact of different aspects of nutrition provision (e.g., nutrition route, composition and targets) on functional outcomes of critically ill children deserves further study.

Interventions to Enhance Recovery Posthospital Discharge

The post-ICU phase is regarded as an important time period for rehabilitation.[70] However, there is paucity of research evaluating interventions posthospital discharge that might improve long-term outcomes in survivors of paediatric critical illness.

In adult ICU survivors, enrolling patients in structured programmes that provided physical and nutritional rehabilitation posthospital discharge were shown to improve long-term cognitive, psychological, physical, and functional outcomes.[41,71,72] Unfortunately, there is little reported experience on the role of structured rehabilitation programmes, particularly those combining nutrition and physical interventions, in PICU survivors posthospital discharge.

In PICU survivors, removing environmental barriers to increase child's participation at home and modifying family environment improve recovery.[27,73,74] A significant proportion of parents of PICU survivors reported that environmental factors (e.g., physical layout of the home and services available in the home) hindered the child's participation at home (e.g., school preparation, personal care and household chores).[27] This hindrance was more prevalent in children with underlying functional limitation (33%) compared to previously normal children (20%). While intervention to modify home environment is commonly practised to enhance functional independence in adults with acquired morbidities, there is paucity of research on this topic in the paediatric population.[75,76]

Family environment plays a role in long-term psychosocial outcomes of preschool children sustaining TBI. Better family functioning and parent mental health was associated with better behavioural adjustment and social functioning.[73,74] Some parenting styles were also shown to be more conducive for recovery, as authoritative (as opposed to permissive) parenting style predicted better social competence at 18 months post-TBI.[73] Future research should identify effective ways to equip not only the children, but also their caregivers, in order to create favourable family environment for recovery.

Conclusion

With improved PICU mortality rates, an emerging issue is the increasing prevalence of acquired morbidities in the survivors. In this review, we summarised the literature on trajectories and risk factors for long-term morbidity, described the current limitations of morbidity research, and discussed recent advances in improving long-term outcomes of PICU survivors. Most of the known morbidity risk factors are non-modifiable in nature, and hence improvements in our current methodologies of morbidity research are needed to elucidate modifiable risk factors of morbidity. Future research is needed for early identification of patients who are likely to develop long-term morbidities and development of effective strategies to reduce long-term morbidities of PICU survivors.

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Online Supplementary Table 1. Observational Studies in PICU Patients

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Fiser et al, 2000*	n = 11,106 All consecutive admissions to 16 general PICUs Mean age range = 53.8 – 86.9 months	POPC, PCPC, compared to baseline (premorbid) scores	PICU discharge	PCPC/POPC Normal: 58.4%/27.4% Mild disability: 17.2%/34.9% Moderate disability: 11.6%/19.9% Severe disability: 7.2%/12.2% Coma/vegetative: 1%/1% Brain death: 4.6%/4.6%	• Baseline, discharge, and delta POPC and PCPC outcome scores were associated with length of stay in the PICU and with predicted risk of mortality (PRISM score)

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Knoester et al, 2008[†]	n = 81 Previously healthy general PICU admission Age, median (range): 5.8 (1 – 14.9) years	Based on age (years): 1 – 5: TAPQOL-PF 6 – 11: TACQOL-PF 8 – 11: TACQOL-CF for children 12 – 15: TACQOL-CF for adolescents	3 months and 9 months postdischarge	Based on age groups, compared to normative population 1 – 6 years: more lung problems (3 and 9 months), worse problem behaviour (3 months) and worse liveliness (9 months) 6 – 12 years: worse motor functioning (3 months) 12 – 15 years: worse motor functioning (3 months)	NA

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Namachivayam et al, 2010‡	General PICU over 3 decades§§§§ Year: n; median age 1982: n = 700; 34 months 1995: n = 882; 31 months 2005 – 2006: n = 1733, 36 months	MGOS compared to preadmission scores, quality of life: HSUV	Median (range) in years: 1982: 2.7 (2.5 – 3.0) 1995: 3.5 (2.5 – 6.0) '05-'06: 1.1 (0.5 – 2.9)	Mortality: 1982: 14.3% 1995: 12.0% – 14.5% '05-'06: 5.4% – 13.1% Moderate-severe disability (preadmission, follow-up): 1982: 12%, 8.4% 1995: 13.9%, 9.3% '05-'06: 14.6%, 17.9% Good quality of life (HSUV 1.00 – 0.70) 1995: 84% '05-'06: 66%	NA

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
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Polic et al, 2013[§]	n = 189 General PICU, with or without pre-existing chronic health condition (CHC) Median (range) age Without CHC: 15.5 (10,18) years With CHC: 15.3 (10,17.6) years	RAHC MOF compared with baseline (preadmission) scores	6 months and 24 months after PICU discharge	RAHC MOF decreased compared to preadmission scores in 26% of PICU survivors at 6 months, 19% in 24 months	• Higher PIM2 score correlated with worsening of RAHC MOF at 6 months, but not 24 months. • Pre-existing neurodevelopmental disability, chronic health conditions correlated with worse RAHC MOF scores

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Pollack et al, 2014[l]	n = 5017 Randomly selected prospective cohort from 8 medical and cardiac PICUs Median (IQR) age 3.7 (0.8, 10.9) years	Mortality FSS: 6 – 7: good, 8 – 9: mildly abnormal, 10 – 15: moderately abnormal, 16 – 21: severely abnormal, >21: very severely abnormal Acquired morbidity: defined as increase of ≥3 in FSS compared with baseline (preadmission) scores	Baseline (preadmission), PICU discharge, hospital discharge	Of the 5017 patients, there were 242 new morbidities (4.8%), 99 PICU deaths (2.0%) and 120 (cumulative) hospital deaths (2.4%) The worst functional status profile was on PICU discharge and improved on hospital discharge	• Admission diagnoses: Highest new morbidity rates were in the neurological diagnoses (7.3%), acquired cardiovascular disease (5.9%), cancer (5.3%) and congenital cardiovascular disease (4.9%) • Operative category: Highest new morbidity in non-operative patients (5.7%) and general surgery patients (5.7%) followed by cardiac surgery (4.5%) • Age: younger age had increased rates of acquired morbidity

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Pollack et al, 2015¶	n = 10,078 General and cardiac/ cardiovascular PICUs from 7 sites Median (IQR) age 3.7 (0.8 –10.8) years	Mortality, FSS, acquired morbidity: FSS increase of ≥3 compared to baseline (premorbid)	Hospital discharge	Acquired morbidity: 4.6%; mortality: 2.7%	• Dichotomous model: increasing PRISM III scores were associated with increasing acquired morbidity and mortality risks • Trichotomous model: acquired morbidity risk initially increased with higher PRISM III scores, but further decreased among children with the highest risks of mortality
Pinto et al, 2017#	n = 77 (6 months follow-up) n =70 (3 years follow-up) General PICU Median (IQR) age 8.60 (2.10 – 11.90) years	Mortality, acquired morbidity: FSS increase of ≥3 compared to baseline (premorbid)	Baseline (preadmission), hospital discharge, 6 months, 3 years after hospital discharge	6 months: Mortality 7.8% Acquired morbidity 6.5% 3 years: Mortality 10.4% Acquired morbidity 10.4%	• Longer PICU length of stay and number of ventilation days correlated with worsening of FSS over time. All the above and vasoactive medications correlated with acquired morbidity or death

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PICU Long Stayers					
Namachivayam et al, 2012[**]	n = 233 PICU long-stayers (>28 days) Median age 4.2 (IQR 0.38 – 41.5) months	Mortality, functional status: MGOS, quality of Life: HUI1	Median of 4 years (IQR 1.4 – 7.6) after discharge from PICU	Functional outcome of survivors: 13.3% normal 15.4% mild disability 8.4% moderate disability 13.3% severe disability 49.6% death QoL of survivors aged >2 years: 21% good 8% moderate 6% poor 68% very poor	NA

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
PICU Long Stayers					
Kirk et al, 2017[††]	n = 241 PICU long stayers (≥14 days) Median (IQR) age 1.37 (0.27 – 6.35) years	Mortality	PICU discharge, hospital discharge	General PICU: Overall PICU deaths: 3.9% Long stayers: PICU mortality: 20% Cumulative hospital mortality: 22%	NA

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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Cardiac Arrest Patients					
Del Castillo et al, 2014‡‡	n = 250 Multicentre study of in-PICU cardiac arrest (CA) Age 47.9 ± 61.9 months (range: 1 month – 18 years)	Neurological outcome: PCPC, compared with prearrest scores: stratified into: (good: PCPC 1 – 2; poor: PCPC 3 – 6)	Hospital discharge, 1 year	Neurological outcome of survivors: 81.5% good 18.5% poor	NA

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Cardiac Arrest Patients					
van Zellem et al, 2015[§§]	n = 57 PICU population who sustained cardiac arrest Median (range) age at follow-up: 8.7 (2.4 – 18.3) years	Health status: medical interview, physical examination, and HUI3, HUI2; health-related quality of life: (0 – 3 years: CHQ-IT97; 4 –17 years: CHQ-PF50; 12 – 17 years: CHQ-CF87)	Median 5.6 years (range 1.8 – 11.9 years)	Long-term mortality of survivors: 9% Health status: 13% neurologic impairment 19% had 1 symptom suggestive of CKD 30% need rehabilitation 34% reported chronic symptoms (fatigue, headache, abdominal pain) 21% needed professional assistance for behaviour problem HUI2, HUI3 lower than normative data HR-QoL: Parent reported: lower on role functioning, general health perceptions, parental impact, and overall physical summary compared to normative data Self-reported: no difference from normative data	• On the CHQ-PF50, cardiac arrest-related pre-existing condition was associated with worse patients' general health perception

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Cardiac Arrest Patients					
Slomine et al, 2017[ll]	n = 59 Out of hospital cardiac arrest (OHCA) patients, and who were admitted to a PICU and remained comatose within 6 hours of return of circulation (ROC), with premorbid VABS-II scores ≥70, original RCT arms (69) : hypothermia (target temperature - 33°C) vs normothermia (target temperature - 36.8°C) Mean (SD) age: Drowning group: 4.6 (4.16) years Other aetiologies: 5.1 (5.41) years	Neurobehavioural outcomes: VABS-II; cognitive performance measures (Mullen Scales of Early Learning or Wechsler Abbreviated Scale of Intelligence); comparison made between drowning and other aetiologies of cardiac arrest	1 year	VABS-II composite and domain scores declined significantly from premorbid scores in drowning and non-drowning groups, although declines were less pronounced for the drowning group. Decline in composite scores, communication domain and motor functioning is less pronounced in drowning group. 72% of children had well below average cognitive functioning at 1-year	• Younger age, fewer doses of epinephrine, and drowning aetiology were associated with better VABS-II composite scores at 1 year follow-up

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Cardiac Surgery Patients					
Moga et al, 2011[¶]	n = 772 Patients undergoing cardiac surgery with cardiopulmonary bypass in a paediatric cardiac critical unit Median (range) age: No hyperglycaemia: 0.69 (0.02 – 14.5) Hyperglycaemia: 0.69 (0.02 – 14.5)	Composite morbidity-mortality outcome: hospital death, cardiac arrest, renal/ hepatic failure, lactic acidosis, ECMO use, or infection	PCCU discharge	31% reached composite morbidity-mortality endpoint	• There was a dose-response relationship between hyperglycaemia and odds of reaching composite morbidity-mortality endpoint. Neonates (<1 month of age) tolerated longer periods of hyperglycaemia before showing increased odds of reaching the composite morbidity-mortality endpoint. In the setting of important residual cardiac lesions, mild or moderate hyperglycaemia was not as strongly associated with adverse outcomes

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Neurological Diagnosis Patients – Non-Traumatic Brain Injury					
Wagenman et al, 2014[##]	n = 60 Previously neurodevelopmentally normal children with an acute neurologic condition and altered mental status who underwent cEEG Median (IQR) age: 3.9 (1.1, 12.7) years Subjects assessed in 3 groups: no seizure, electrographic seizure (ES), electrographic status epilepticus (ESE)	GOS-E; PedsQL proxy report and epilepsy questionnaire; GOS-E scores categorised as favourable (upper good recovery to lower moderate disability) or unfavourable (upper severe disability to vegetative state)	Median 2.7 (IQR 1.5, 3.2) years	Overall GOS-E scores: 64% favourable, 36% unfavourable Subjects with: favourable GOS-E: 64% no seizure, 23% ES, 13% ESE unfavourable GOS-E: 43% no seizure, 14% ES, 43% ESE ES: 23% favourable PedsQL, median (IQR) scores: without seizures: 86 (64, 95) ES: 94 (60, 97) ESE: 62 (48, 71)	• ESE but not ES was associated with unfavourable GOS-E, lower PedsQL scores, and higher rates of subsequently diagnosed epilepsy at follow-up

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Neurological Diagnosis Patients – Non-Traumatic Brain Injury					
Lin et al, 2017[†††]	n = 35 Febrile refractory status epilepticus patients admitted to PICU, with no history of underlying neurological disorders and prior seizures Comparison of therapeutic burst-suppression coma vs continuous administration of intravenous antiepileptic drugs Mean age 9.58 ± 4.05 years	GOS: ≥4: good outcome ≤3: bad outcome Seizure outcomes: 1) intractable epilepsy 2) favourable outcome 3) successful withdrawal from antiepileptic drug treatment	Baseline, 1 month, 6 months	6 months: Cumulative mortality: 40% Neurological functional outcomes good in 27.3% survivors, 2 returned to clinical baseline	

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Neurological Diagnosis – Traumatic Brain Injury					
Grinkevièiûtë et al, 2008[‡‡‡]	n = 48 PICU patients with severe head injury (postresuscitation GCS ≤8) and treated according to intracranial pressure (ICP)-targeted protocol of severe head trauma management Mean age 10.6 ± 5.2 years	GOS 4 – 5: Favourable outcome 1 – 3: Unfavourable outcome	Hospital discharge, 6 months	Hospital discharge GOS: 19/48 unfavourable 29/48 favourable 6 months: Mortality 2.1% GOS: 5/48 unfavourable 43/48 favourable	• The difference in outcomes between patients with and without decompressive craniectomy was not significant, although the former had higher ICP and lower CPP

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Neurological Diagnosis – Traumatic Brain Injury					
Salorio et al, 2008[§§§]	n = 57 Survivors of paediatric moderate and severe TBI (GCS 3 – 12) admitted for rehabilitation Mean age 10.8 +/- 3.2 years	Cognitive outcome: performance IQ (PIQ, Wechsler Intelligence Scale for Children). Overall functional outcome: DRS	1 year postinjury	NA	• Higher initial GCS score was associated with higher PIQ 1 year postinjury. Episodes of hypotension during the first day after injury were associated with worse cognitive outcome at 1 year. Hypertension within the first 24 hours was associated with worse DRS at 1 year

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Neurological Diagnosis – Traumatic Brain Injury					
Tepas et al, 2009[lll]	n = 60 Patients with severe blunt TBI (initial GCS score ≤8) that required resuscitation, critical care, and inpatient rehabilitation Mean age: male 11.2 years, females, 10.6 years	Functional independence measurement (FIM) score Rehabilitation efficiency (RE): ratio of FIM improvement to length of stay for inpatient rehabilitation	Not specified	NA	• Delayed inpatient rehab was associated with reduced rehabilitation efficiency and reduced improvements in FIM scores • Children with higher GCS score (6 – 8) exhibited a stronger negative correlation between RE and delay than children with GCS 3 – 5

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Neurological Diagnosis – Traumatic Brain Injury					
Kapapa et al, 2010¶¶¶	n = 48 Children who sustained head trauma requiring intensive care, who received cerebral perfusion pressure (CPP)-oriented management Mean age 5.9 years (range 19 days – 14.5 years)	Functional outcome: GOS; quality of life: Short Form 36 Health-related Quality of Life survey; health status: Visual Analogue Scale; others (unstructured questionnaire): physical sequelae, impairments in daily life, neuropsychological abilities, psychosocial characteristics, performance in school	Average 2.1 years	PICU discharge: 20.8% died, 8.3% GOS 2, 16.7% GOS 3, 10.4% GOS 4, 43.8% GOS 5 Long-term: 17 patients who were admitted in poor condition, 6 had persistent paresis or plegia, 5 had paresis of the cranial nerves, 2 were incontinent, 4 had sensory disorders, 7 had coordination disorders, and 5 had speech disorders. In 7 children who were admitted in good condition, 3 had hyperesthesia and 1 had a speech disorder Health status improved during the interval between 1 year after the trauma and the time of completing the questionnaire	• Elevated blood levels of glutamic-oxaloacetic-transaminase on the day of admission, elevated blood urea and glucose on the first 2 days, at least single occurrences of cerebral perfusion pressure values below the recommended standard, or mean arterial pressure and central venous pressure below the lower limits correlated with worse functional outcomes

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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Neurological Diagnosis – Traumatic Brain Injury					
Thomale et al, 2010[###]	n = 53 Neurosurgically-treated patients with diagnosis of severe TBI (GCS <9), who had either additional decompressive craniectomy or conservative Intracranial pressure (ICP) management without craniectomy Median age: Craniectomy: 12 years Conservative: 7 years	GOS: (GOS 4 – 5: favourable outcome, GOS 1 – 3: unfavourable outcome)	Hospital discharge, 1 year, long-term (mean 5.2 ± 2.4 years)	Hospital mortality: 11% 1 year: 86% favourable outcome in survivors; no difference in the craniectomy vs conservative group Long-term: 73% favourable outcome 7% GOS 3 20% died due to uncontrollable ICP	• Anisocoria on admission, aSO2 <90% on admission correlated with unfavourable GOS outcomes • Though initial GCS was worse in paediatric TBI patients who underwent decompressive craniectomy compared to the conservatively treated patients, long-term outcome was comparable

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Neurological Diagnosis – Traumatic Brain Injury					
Fulkerson et al, 2015[****]	n = 67 Paediatric head injury patients presented to neurosurgical service at a single centre with: GCS 3 (age 49.8 +/- 51.8 months) or GCS 4 (age 66.9 +/- 58.0 months	Mortality, mGOS: (5, good recovery with minor cognitive or neurological problems, 4, disabled neurologically or cognitively 3, severely disabled, possibly requiring institutional care 2, vegetative survival 1, death)	Hospital discharge, 1 year, long-term (mean 11.04 ± 6.1 years)	1 year mGOS: 11.9% normal 3.0% GOS 5 6% GOS 4 10.4% GOS 3 4.5% GOS 2 56.7% GOS1 Long-term: 95.5% had the same GOS score as 1 year	• Impaired pupillary response, hypothermia, and mechanism of injury (abuse) correlated with death or disability

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Other Specific Populations					
Ebrahim et al, 2013††††	n = 91; 65 completed 1 month assessment Urgently admitted (<12 hours notice) patients from inpatient ward, or had an ICU cardiac arrest and/or received extracorporeal membrane oxygenation (ECMO) treatment irrespective of the urgency of their ICU admission Mean age: 76.4 ± 69.3 months, range 1 month to 18 years	Adaptive behaviour: VABS-II; functional outcomes: PCPC and POPC; quality of life: PedsQL and VAS	1 month postadmission 24 hours (baseline), 1 month postadmission 24 hours (baseline), 1 week, 1 month postadmission	VABS-II (1 month), mean (SD) 83.2 (± 24.8) compared to a population mean (SD) of 100 (±15); mean PedsQL (1 month) was 52.8 ± 27.9; from baseline to 1 month, PCPC did not significantly change, while POPC significantly improved VAS significantly worsened from baseline to 1 week, and significantly improved from 1 week to 1 month	• Worse adaptive behaviour was correlated with circulatory diagnosis, worse initial PCPC score, worse transcutaneous oxygen saturation, and longer cardiac compression • Worse HRQoL correlated with worse initial PCPC, longer ICU stay, and longer duration of ECMO • Worse functional outcome correlated with the same factors as HRQoL, plus neurological diagnosis

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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‡‡‡‡Abu-Kishk I, Polakow-Farkash S, Elizur A. Long-term outcome after pediatric intensive care unit asthma admissions. Allergy Asthma Proc 2016;37:169-75.

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

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Other Specific Populations					
Abu-Kishk et al, 2016‡‡‡‡	n = 47 PICU patients admitted due to acute asthma exacerbation Median (IQR) age 6 (4 –11) years	Questionnaire on subsequent hospitalisations and current asthma treatment and control (GINA guidelines), pulmonary function studies, allergy skin tests	Mean 10 years after PICU admission	Compared with controls admitted to paediatric ward: PICU survivors had more hospitalisation and ICU admissions after their index admission, more recent asthma exacerbations, weekly wheezing, and bronchodilator use. Lung function tests were comparable between the 2 groups	NA

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Online Supplementary Table 2. Quality Assessment of the Included Studies

Author	Population Clearly Defined	Outcome Clearly Defined	Baseline Function Measured or Control Group Included (for Long-Term Outcome)*	Selection Bias Excluded†	Selective Loss to Follow-up Excluded‡
Fiser et al, 2000§	Yes	Yes	Yes	Yes	NA
Grinkevièiûtë et al, 2008ǀ	Yes	Yes	No	Yes	Yes
Knoester et al, 2008¶	Yes	Yes	Yes	No	No
Salorio et al, 2008#	Yes	Yes	No	No	NA

NA: Not applicable

*Study measured baseline status/scores of the children. Alternatively, study included controls in the form of normative population or matched children from non-PICU sources (eg. outpatient clinic).

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Tepas et al, 2009[**]	Yes	Yes	No	Yes	Yes
Vlasselaers et al, 2009[††]	Yes	Yes	NA	Yes	NA
Namachivayam et al, 2010[‡‡]	Yes	Yes	Yes	Yes	Yes
Kapapa et al, 2010[§§]	Yes	No	No	Yes	No

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Thomale et al, 2010‖	Yes	Yes	No	Yes	No
Moga et al, 2011¶	Yes	Yes	NA	Yes	NA
Mesotten et al, 2012##	Yes	Yes	Yes	Yes	Yes
Namachivayam et al, 2012***	Yes	Yes	No	Yes	No

NA: Not applicable

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Abdulsatar et al, 2013†††	Yes	Yes	NA	No	NA
Ebrahim et al, 2013‡‡‡	Yes	Yes	No	No	Yes
Polic et al, 2013§§§	Yes	Yes	Yes	Yes	No
Del Castillo et al 2014‖‖	Yes	Yes	No	No	No

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Kumar et al, 2014###	Yes	Yes	No	Yes	No
Pollack et al, 2014****	Yes	Yes	Yes	Yes	NA
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Author	Population Clearly Defined	Outcome Clearly Defined	Baseline Function Measured or Control Group Included (for Long-Term Outcome)*	Selection Bias Excluded†	Selective Loss to Follow-up Excluded‡
Abend et al, 2015‡‡‡‡	Yes	Yes	No	Yes	Yes
Fulkerson et al, 2015§§§§	Yes	Yes	No	Yes	No
Pollack et al, 2015¶¶¶¶	Yes	Yes	Yes	Yes	NA
van Zellem et al, 2015¶¶¶¶	Yes	Yes	Yes	No	NA

NA: Not applicable

*Study measured baseline status/scores of the children. Alternatively, study included controls in the form of normative population or matched children from non-PICU sources (eg. outpatient clinic).

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Fivez et al, 2016[*****]	Yes	Yes	NA	n/a	NA
Moler et al, 2016[†††††]	Yes	Yes	No	Yes	No
Choong et al, 2017[‡‡‡‡‡]	Yes	Yes	NA	Yes	NA

NA: Not applicable

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Kirk et al, 2017ǁǁǁǁ	Yes	Yes	NA	Yes	NA
Pinto et al, 2017¶¶¶¶¶	Yes	Yes	Yes	No	No
Slomine et al, 2017#####	Yes	Yes	Yes	Yes	No

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Commentary

Health Technology Disinvestment in Singapore

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Abstract

Healthcare decision-makers are constantly challenged by growing healthcare needs in tandem with rising healthcare costs. Disinvesting in technologies and practices that are "low in value" is one strategy to re-allocate limited resources to the most effective, safe and cost-effective technologies. We put forward a health technology reassessment framework and examined the opportunities and challenges on technology disinvestment in Singapore and deliberated on possible solutions. We coordinated and supported a disinvestment programme in 2 hospitals, 1 specialist centre and 9 primary care institutions in the public healthcare sector. The key processes were identifying, prioritising and assessing low-value health technologies and practices, disseminating and implementing disinvestment recommendations, and post-implementation evaluation. Through case studies, we explored the barriers and enablers to the success of the programme. One of the barriers to disinvestment included difficulty in demonstrating a lack of benefit of in-use technologies from published studies. Differing viewpoint and priority might preclude a healthcare leader's support in such initiatives and that posed an unsurmountable hurdle. On the other hand, engaging the stakeholder throughout the evidence review process and striking a balance between rigour and timeliness of review were likely to assure success. Lastly, monitoring the impact on resources and patient outcomes can be diverse and methods need to be developed. Understanding barriers and enablers in health technology disinvestment can translate into improved opportunities for eliminating and minimising resource wastage.

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Key words: Cost containment, Healthcare budget, Low-value, Value-based care

Introduction

Globally, there is increasing demand and spending on healthcare. The diffusion of an ever-growing number of drugs, diagnostic tests, medical devices, and procedural interventions poses strain on today's healthcare environment.[1] Health technology assessment (HTA)—the systematic assessment of health technologies regarding effectiveness and safety—has been widely employed to inform decision and to optimise the value of every healthcare dollar.[2] HTA focuses primarily on managing the entry of health technologies. Yet after a technology has entered the system, there seems no standardised process to keep track of its use or to manage its exit.[3] As a result, most in-use technologies may not have been re-evaluated since their entry into the healthcare system.[4] Under such circumstances, many technologies that are no longer effective or have become obsolete remain in the system rather than being replaced by more effective, safe and cost-

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effective alternatives.[5] Managing technologies throughout their lifespan means ensuring that they continue to achieve optimal value for money.

Health technology reassessment (HTR) is a structured, evidence-based assessment of a technology currently used in the healthcare system, to inform optimal use of that technology in comparison to its alternatives.[6] It serves to inform decisions regarding technologies and practices that are of little or no value to the patient and consequently should not be provided routinely. Disinvestment relates to the processes of (partially or completely) withdrawing health resources from any existing healthcare practices, procedures, technologies or pharmaceuticals that are deemed to deliver little or no health gain for their cost.[3] Reducing spending on low-value health technologies and practices channels resources to more effective and cost-effective care. This can achieve larger improvements in outcome while containing the increasing pressure on healthcare budgets. There are ongoing development and spread of disinvestment initiatives over the past decade.[7] The United Kingdom National Institute for Health and Care Excellence (NICE), started their programme in 2005 and is widely recognised for their "do-not-do" list.[8] In the United State, the Choosing Wisely campaign initiated in 2012[9] has since spread to Canada[10] and Australia.[11] Other recent efforts include the Spanish guidance on disinvestment[12] and the Dutch list of low-value technologies and practices.[13]

The success of any health policy requires an understanding of the possible barriers and devising strategies to overcome them. That said, the current discussion on disinvestment centred on its conceptual framework but we need more insights on the actualisation and success factors to integrate disinvestment into our healthcare systems.[14,15] The experience with disinvestment actualisation is currently contained within 11 healthcare systems of which 10 are in Western nations.[16] Founded on the principle of an individual's responsibility and affordability, Singapore has a unique healthcare model where financing is highly dependent on individuals while spending on healthcare has been consistently maintained at 4% of its gross domestic product (GDP).[17,18] The larger out-of-pocket share in healthcare financing distinguishes itself from the other healthcare financing systems i.e. tax-based universal healthcare system (for example, in the United Kingdom) and insurance-based system (for example, in the United States). Yet common to all, the rising cost of healthcare and new technologies warrant disinvesting in low-value care and services to increase healthcare efficiency and control costs without compromising outcomes. In this paper, we detailed an inaugural disinvestment programme in Singapore and addressed the challenges and potential solutions in key disinvestment processes. Through case studies, we highlighted what worked or worked against it, so as to provide insights on delivering successful disinvestment initiatives.

Materials and Methods

The disinvestment programme involved 2 hospitals, 1 specialist centre and 9 primary care institutions which come under a regional health system common cluster in the public healthcare sector. The 4 key processes were: identifying disinvestment opportunities, establishing prioritisation processes, assessing evidence on low-value health technologies and practices followed by implementing and evaluating disinvestment (Fig. 1). This was undertaken by the health technology assessment team nested in the public healthcare cluster. The objectives of the disinvestment programme were: a) to create awareness of opportunities to disinvest health technology that deliver no or low health gain for its cost; b) to optimise patient care by ensuring effective, safe and cost-effective use of health technology; and c) to contribute towards a sustainable healthcare through the efficient use of resources.

An integral part of pioneer disinvestment programmes is usually a list of low-value technologies and practices. Leveraging the databases by international HTA agencies,[8-10,13] we systematically reviewed the lists of low-value technologies and practices and identified 500 of them for consideration. After excluding those which were irrelevant to our local context, 314 candidate technologies and practices were listed for stakeholder engagement.

Given that the potential gains from disinvestment could vary widely across technologies and resources to support these initiatives were limited, prioritisation of low-value technologies and practices for assessment was warranted. The prioritisation panel—comprising key opinion leaders and senior clinicians—was charged with prioritising topics for HTR. The prioritisation panel worked with key stakeholders, such as members of the Medical Board in each institution, to deliberate based on the following criteria: a) clinical impact: we considered opinions about the potential to influence clinical practice and the perceived issue with effectiveness, safety, and cost-effectiveness of alternatives; b) clinical use: we considered if there was variation in its application among clinicians and outcomes among patients; c) financial impact: we considered the usage volume and potential benefits in terms of eliminating wastage; and d) timeliness of evidence review: we considered the decision-makers' requests on the time factor.

Besides the identified candidates, we also gathered inputs from stakeholders on potential technologies and practices which required reassessment. Disinvestment decisions should be driven by evidence on the effectiveness, safety and cost-effectiveness. Once the technologies and practices

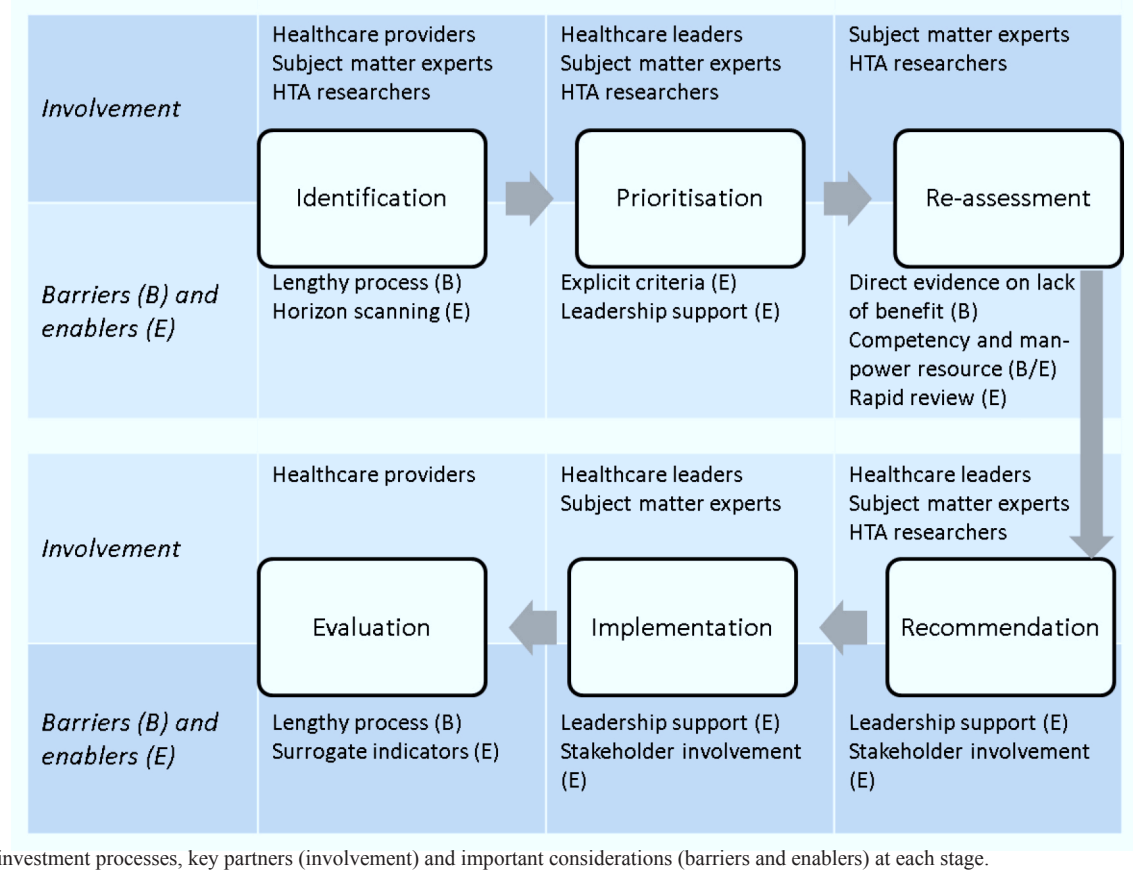

Fig. 1. Disinvestment processes, key partners (involvement) and important considerations (barriers and enablers) at each stage.

for reassessment had been identified and prioritised, we appraised the evidence to inform decisions and formulated recommendations to guide their appropriate use. This was supported by 2 full-time equivalent HTA researchers. However, reassessment needed to balance depth and rigour with timeliness. Broadly, our approach was to perform a literature search for practice guidelines and HTA reports from HTA resources, international health technology agencies and major international professional association. This was followed by a focused internet search to identify literature beyond the targeted HTA and professional bodies. We searched for published systematic reviews and subsequently carried out an update search to identify clinical studies published during the period that had elapsed since the search date on the most comprehensive review identified. In other instances, we carried out the systematic reviews, meta-analyses and cost-effectiveness analyses to support decision-making. Subject matter experts and clinicians were involved in the early stage to shape the research question and the scope of the evidence review. Subsequently, we worked collaboratively on the results of the review and formulated evidence-based disinvestment recommendations. We presented the recommendations to the institution's Medical Board for deliberation and endorsement. Thereafter, the relevant stakeholders proceeded to disseminate and implement the changes. The pre- and post-implementation evaluations varied but we generally took into consideration outcomes and savings.

Results

From the 314 candidate technologies and practices listed for stakeholder engagement, 9 underwent HTR. Here, we present 3 of them as case studies and share insights on the barriers and enablers of disinvestment (Table 1).

Case Studies

Routine Monitoring of Statin Therapy

The routine monitoring of liver function test (LFT) and creatine kinase (CK) levels is a common practice during treatment with statins. However, liver and skeletal muscle adverse events are rare at standard doses and routine LFT and CK monitoring are not recommended in asymptomatic patients.[19,20] Through evidence review, we advocated to replace such practices with measurement of alanine transaminase (ALT) or aminotransferase (AST) at initiation and within 3 to 6 months of starting treatment and at 12 months.[21-23] Besides disseminating the new recommendations to clinicians, a change in the laboratory order panel for statin monitoring was implemented in the

Table 1. Examples of Health Technology Reassessment and the Key Learning Points

Health Technology Reassessment	Disinvestment Process	Key Learning Points
Routine monitoring of statin therapy	Omit routine creatine kinase test as part of statin monitoring in asymptomatic patients	Leadership support and stakeholder engagement enhances acceptance
	Monitor aspartate/alanine aminotransferase instead of liver function test	Rapid review of existing guidelines ensures timeliness
		Electronic ordering system reinforces implementation
		Monitoring resource savings demonstrates impact
Routine sodium valproate level monitoring in bipolar disorder	Omit routine sodium valproate level monitoring when used as a mood stabiliser	Leadership support and stakeholder engagement enhances acceptance
		Rapid review of existing guidelines overcomes manpower constraint
		Electronic ordering system reinforces implementation
		Direct evidence to support disinvestment may be lacking
Routine neuroimaging in first-episode psychosis	Selective use of neuroimaging in the evaluation of first-episode psychosis	Direct evidence to support disinvestment may be lacking
		Inference of published findings and alternative sources is warranted

9 primary care institutions. The ALT, AST and CK levels were removed from the order template for lipid monitoring and this allowed the clinicians to order the test(s) only when necessary. Collectively, there were 101,700 patients receiving statin therapy in these institutions. We monitored the ordering of these tests before and after implementation. By the end of the monitoring period (i.e. 10 months post-implementation), the tests ordered were reduced by more than 50%. We calculated the cost of performing each tests and this translated into savings of S$120,000 per month. Given that this was the first successfully implemented project, it was showcased to others to gain greater conviction on disinvestment. The key success factors in this initiative included strong leadership support and detailed pre- and post-implementation monitoring to drive future disinvestment efforts.

Routine Sodium Valproate Level Monitoring in Bipolar Disorder

Unlike in the treatment of epilepsy, the utility of serum valproate level in bipolar disorder is of limited benefit given that there is no clear dose-response relationship.[24] Despite a review of the evidence on routine serum valproate measurement in the treatment of bipolar disorder, clinical studies did not directly demonstrate ineffectiveness of serum valproate level monitoring when used as a mood stabiliser. In theory, this meant subjecting patients to monitoring and comparing the desired outcome. However, it might still not be possible to distil the effectiveness of monitoring valproate levels against the efficacy of the continuum of therapy employed. Nevertheless, we established recommendations for monitoring of valproate level in patients with bipolar disorder. Serum valproate level may be useful during initiation and titration phase or when clinically indicated (e.g. assessment of compliance, effectiveness and toxicity). Here, we combined education with information technology to change the clinician's practice. The electronic drug ordering system previously incorporated a reminder for annual valproate level monitoring. Since routine valproate level monitoring was no longer a recommended practice, this reminder was removed from the drug order. Following that, there was a sharp decline from an average of 205 to 103 tests per month (50% reduction). That translated into S$2300 saved from unnecessary tests every month, from the laboratory's perspective. Making use of information technology, especially the electronic drug ordering system, was a powerful way to spread disinvestment initiatives and attain desired results.

Routine Neuroimaging in First-Episode Psychosis

In the largest local mental health institution, we worked closely with the psychiatrists and members of the Medical Board to inform clinicians on the appropriateness to perform structural neuroimaging in first-episode psychosis routinely. We conducted a systematic review with an aim to guide the appropriate use of neuroimaging in first-episode psychosis. This posed the biggest challenge given that the lack of benefit of not performing such investigation could not be quantified and was not apparent in the findings of published studies. Nevertheless, from studies which reported on the diagnostic yield and existing clinical practice guidelines,[25,26] we recommended the selective use of structural neuroimaging in first-episode psychosis. The decision to order such investigations needs to be

individualised with due consideration of medical history, clinical presentation and examination. To substantiate this, we came up with a recommended list of patient profile which warrants its use based on evidence and consensus agreement. After endorsement by the Medical Board, senior clinicians presented the evidence and disseminated the recommendations to other clinicians. Though there may be apprehension and concerns about missing a diagnosis of an organic cause of psychosis, early stakeholder involvement and leadership support were instrumental in its implementation. In the initial months, there were only slight changes in the number of magnetic resonance imaging (MRI) or computerised tomography (CT) scans ordered for patients presenting with first-episode psychosis at the emergency department. After reinforcing the recommendation at various platforms, the numbers of MRI and CT scans performed slowly declined, with a resultant savings of S$10,000 per month. This is an example where clinical studies may not directly demonstrate ineffectiveness and may present a hurdle to change in clinician's practice.

Barriers and Enablers

Barriers and enablers to the success of disinvestment were identified throughout our programme. We adopted a transparent prioritisation process which was well received by the stakeholders. We devised prioritisation criteria and improved the subjectivity of the decisions through the application of weights to the criteria. At the same time, the prioritisation structure made provision for local needs within boundary, for instance, openness to alternative views and other more pressing needs perceived by the stakeholders.

Another challenge is the mechanism for candidate technology identification.[4,27] At inauguration, the resource for this programme was limited; we worked around this issue by identifying low-value health technologies and practices via surveying existing lists. However, this may not fully capture or reflect local practices though it has served well in this inaugural programme. There should be a systematic and coordinated process to identify obsolete technologies and practices. This may include ongoing discussions with subject matter experts to identify candidate technologies and practices. A viable platform to initiate such discussions will be to coincide disinvestment discussions with the adoption of a new technology in the same class. A constant review of the hospital or institution formulary highlighting the existence of multiple technologies for the same indication can also create disinvestment opportunities (though limited to pharmaceuticals).

Unlike HTA, HTR needs to generate evidence on the lack of benefits of established technologies. In the course of our work, we came across areas with substantial difficulty in demonstrating acceptable proof of inferiority. Conceptually, it is not difficult if the objective is to discourage use. However, in reality it is often restricted by data availability and interpretation. This may not be realised in published randomised controlled trials or even with clinical studies. For instance, we were unable to locate studies which prove that routine versus selective neuroimaging test during first-episode psychosis translates into differential yield in identifying organic causes. At times, there may be inconsistent findings on efficacy which can make it difficult to justify or discredit the continual use of certain technologies. The principles of HTA remain valid but adaptation is needed to better support the evidence review and harness findings relevant for decision-making. In addition, to ensure timelines of decision-making, we adopted evidence review methods that strike an appropriate balance between rigour and speed. These include non-traditional search strategy such as searching for existing guidelines which are up-to-date.

Once perceived as the biggest barrier to disinvestment—clinician inertia and entrenchment in long-standing practices[20]—can be overcome by evidence-based recommendations. Stakeholder engagement is crucial. They were involved in every stage from identification and prioritisation of potential technologies and practices to assessment and implementation of the changes. By collaborating closely with subject matter experts and clinicians throughout the evidence review process, we addressed the issue concisely and harnessed information to better inform decision-makers. Subsequent in the process, they can influence and enhance the acceptance of decisions to de-adopt or eliminate low-value technologies and practices. However, this has to happen in tandem with support from institution leaders.[28] Supported by evidence and endorsement from institution leaders (e.g. the Medical Board), disinvestment recommendations were more readily adopted by healthcare providers. We customised the dissemination and implementation strategy to the target group (i.e. healthcare providers impacted by the resulting decision) and enhanced it through information technology. With a coordinated and evidence-based approach, healthcare leaders, stakeholders and HTA researchers can effect a change in long-standing practices among clinicians.

Discussion

Disinvestment aims to ensure that healthcare expenditure is linked to patient outcomes. This can contribute towards a sustainable healthcare by ensuring efficient allocation of resources. Though progress has been made, there is a seemingly lack of actual application of the established framework and active participation in Asian healthcare systems. A systematic review of disinvestment captured 26 unique initiatives implemented in 11 countries.[16] By

and large, the Choosing Wisely campaign has been most successful and has since spread to 6 countries. Other healthcare systems heavily involved include Australia (7 initiatives), the United Kingdom (6 initiatives), and New Zealand (3 initiatives). Although this is not a national effort, we explored on how to leverage on the existing experiences drawn from established models and adapted them to drive disinvestment locally. With that, it has provided proof that new initiatives need not start from scratch but can be fast-tracked by using existing lists of low-value technologies, for instance.

The healthcare expenditure in Singapore was 4.9% of GDP in 2014, though considered low among developed countries,[17] is on a rising trend signifying pressure on healthcare funding. Healthcare and healthcare infrastructure spending is expected to continue growing with an ageing population and increasing burden of chronic health conditions. The Ministry of Health, Singapore set up the Agency for Care Effectiveness in 2015 which focuses on new technologies for reimbursement purpose. Currently, there is a limited system in place to support the disinvestment of low-value or inappropriately applied healthcare practices.[29,30] In the absence of a formal setup, HTR can be integrated into other programmes such as clinical practice guidelines, care pathways and quality improvement initiatives. That said, disinvestment should be recognised as an emerging priority and made a national programme.

Our experience may not be sufficient to draw firm conclusions on the success factors of a disinvestment initiative. Our experience did surface to us what was most important in a novel initiative. Looking back at some notable healthcare reforms like computerised prescribing system[31] and academic medical centres,[32] the advances we can make in untested initiatives like this hinged on supportive leaders. The programme would not have proceeded or be successfully implemented without the mandate from institution leaders. We postulated that the underlying reasons for lack of support by institution leaders might stem from a low priority viewpoint and perception of negligible incentives. Hopefully, learning the success in other cases can abate these preconceived ideas.

Lastly, capturing patient outcome and satisfaction from disengaging in low-value care and services remains a key area for development. A structured approach for monitoring of healthcare resources and evaluating patient outcome resultant from disinvestment is most gratifying to healthcare providers and leaders. It can also instill credibility to the programme and encourage uptake and spread. Besides measuring the yield of disinvesting in low-value technologies and practices, which may come in the form of savings from unnecessary tests, we should also evaluate patient outcomes and satisfaction. Monitoring outcomes may sometimes prove difficult where there is a diversity of possible events or seemingly lack of events. Therefore, there ought to be concerted efforts stemming from administrators and healthcare providers in the monitoring process. We should convey to the healthcare providers involved that there is a need to actively seek out any unintended consequences.

Conclusion

What has been achieved to date demonstrated the yield and feasibility of disinvestment in the local healthcare climate and culture. Although the concept of disinvestment has yet to receive attention on a broader scale, it can be developed to effect change in medical practice and to set the stage for healthcare reform in Singapore. The dual-financing system in Singapore is unique and well suited for a disinvestment climate. Moving forward, we should also educate and empower patients to make certain decisions given that their out-of-pocket healthcare expenditure is substantial.

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Pancreatic Haemangioma: An Unusual Case of Massive Upper Gastrointestinal Bleeding with Clinical and Radiological Correlation of the Literature and Recommendations

Dear Editor,

Pancreatic haemangiomas in adults are exceedingly rare. Most cases reported have been diagnosed on postoperative histology, underlining the difficulty in preoperative diagnosis. We report the first adult patient with undiagnosed pancreatic haemangioma, presenting with massive upper gastrointestinal (GI) tract bleeding, necessitating an emergency Whipple's procedure to arrest the bleeding.

Case Report

A 62-year-old lady had presented to the Singapore General Hospital emergency department with haematemesis, haematochezia and sudden onset abdominal pain. She had previous history of malignant thymoma in remission, myasthenia gravis and connective tissue disease on oral steroids and immunosuppressants (mycophenolate mofetil).

On arrival in the emergency department, she was in hypovolaemic shock, with hypotension and tachycardia. Aggressive resuscitation with fluids and blood products was initiated. Examination found mild epigastric tenderness but no palpable mass. She was brought to the operating theatre for an emergency oesophagogastroduodenoscopy to attempt endoscopic haemostasis. Initial resuscitative efforts included a total of 9 units of packed red blood cells via a rapid transfuser.

The bleeding was localised to the third segment of the duodenum. However, the torrential bleeding made endoscopic haemostasis impossible. A laparotomy was thus performed for haemostasis. A 3 cm x 3 cm firm head of pancreas mass was found, with erosion into the third segment of the duodenum (Fig. 1). Active spurting from the erosion was seen after duodenotomy was performed. The bleeding point was controlled with a Prolene 2/0 stitch, and the decision was made to resect the mass as it was mobile, and free of adjacent structures, including the superior mesenteric artery and vein.

The final histology reports a pancreatic haemangioma, 4.5 cm x 5.5 cm, with focal erosion into overlying duodenum. Immunohistochemistry revealed CD31, CD34 and ERG-positive, supporting the diagnosis of a haemangioma.

She is currently 1-year postoperation and has recovered well.

Discussion

Vascular tumours of the pancreas (including haemangiomas, lymphangiomas, haemolymphangiomas, haemangioendothelioma, haemangiopericytoma, haemangioblastoma and angiosarcomas) are rare, and account for only 0.1% of pancreatic tumours.[1] Pancreatic haemangiomas as a subset are thus exceedingly rare. Pancreatic haemangiomas are more common in the paediatric age group, but these do not persist into adulthood (instead undergo involution and regress over several years).[2]

A total of 22 case reports describe pancreatic haemangioma in adults; the earliest by Ranstrom in 1939 (Table 1).[3-10] The most common presenting symptom of these reported cases was abdominal pain (accounting for more than half of these cases). This is the first reported case of pancreatic haemangioma presenting with massive bleeding, and requiring an emergency Whipple's procedure.

Although Ringoir et al described a case in 1961 who presented with bleeding,[4] the blood loss was not torrential as in our case. Their case had presented with 2 episodes of coffee grounds vomiting and melaena, and was haemodynamically stable on arrival. They reported a 15 cm pancreatic haemangioma, which we expect to have

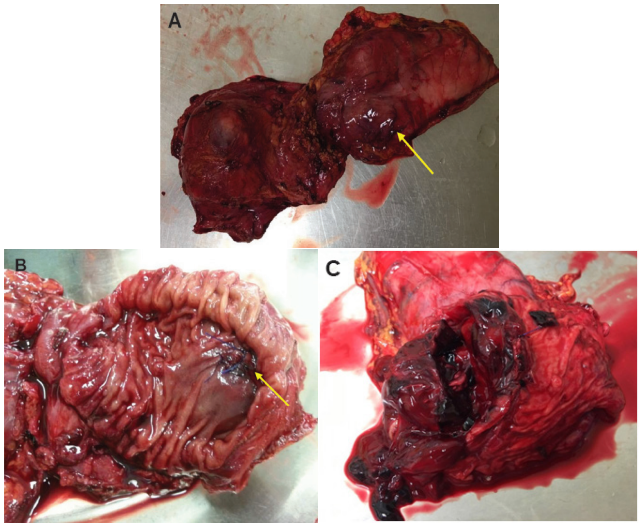

Fig. 1. A) Whipple's specimen showing mass at head of pancreas. B) Stitch haemostasis via duodenotomy, over area of erosion. C) Pancreatic lesion cut open, revealing clots and blood within.

Table 1. Summary of Previously Described Cases* of Pancreatic Haemangioma

No.	Author	Country	Year	Age/Gender	Site	Size (cm)	Presentation	Treatment
1	Ranstrom	-	1939	61/F	Head	7	Autopsy	NA
2	Derom	France	1960	-		-	Unknown	Surgery
3	Ringoir	France	1961	71/F	Head	15	Haemetemesis/ melaena	Gastroenterostomy and vagotomy
4	Colardyn	France	1972	42/F	Body		Abdominal pain	Fat-free diet and anticholinergics
5	Mangin	France	1985	62/F	Head to tail	20	Malaise, nausea, thrombocytopaenia	Laparotomy and observation
6	Kobayashi	Japan	1991	30/M	Head	20	Abdominal distension	Pancreatico-duodenectomy
7	Dageforde	Germany	1991	79/F	Body to tail	6	Abdominal pain	Observation
8	Chang	Taiwan	2003	70/F	Body to tail	4	Abdominal pain	Subtotal pancreatectomy
9	Plank	Austria	2006	36/M	Head	3	Abdominal pain	Laparotomy and observation
10	Xu	China	2008				3 cases	
11	Mundinger	United States	2009	45/F	Head	5.5	Abdominal pain	Pylorus preserving pancreatico-duodenectomy
12	Jarboui	Tunisia	2010	60/F	Body	2	Abdominal pain	Distal pancreatectomy
13	Weidenfeld	Israel	2011	73/F	Head	5	Abdominal pain	Pancreatico-duodenectomy
14	Lee	Malaysia	2011	49/F	Neck	5	Incidental US finding, non-specific dizziness	Central partial pancreatectomy and gastrostomy
15	Kersting	Germany	2012	53/M	Head	8	Asymptomatic	Extirpation of tumour
16	Zhi-hua	China	2013	23/F	Head	5.4	Incidental US finding	Subtotal pancreatectomy
17	Malik	United Kingdom	2013	70/F	Head	8	Abdominal pain	Pylorus preserving pancreatico-duodenectomy
18	Williamson	United Kingdom	2014	78/F	Head	4	Abdominal pain	Observation
19	Naito	Japan	2014	40/F	Body to tail	10	Abdominal pain	Pancreatectomy
20	Mondal	United States	2015	18/F	Head	6	Abdominal pain	Pylorus preserving pancreatico-duodenectomy
21	Liu	China	2015	28/F	Body to tail	8.8	Abdominal pain	Distal pancreatectomy
22	Kim	South Korea	2016	68/F	Tail	0.5	Incidental CT finding	Distal pancreatectomy

CT: Computed tomography; F: Female; M: Male; NA: Not applicable; US: Ultrasound

*Derom F, Ringoir S, Marlier R. [Two cases of intraabdominal hemangioma: liver and pancreas]. Acta Chir Belg 1960;59:172-82; Ringoir S, Derom F, Colle R, Mortier G. Hemangioma of the pancreas. Report of a case. Gastroenterology 1961;41:43-5; Kobayashi H, Itoh T, Murata R, Tanabe M. Pancreatic cavernous hemangioma: CT, MRI, US and angiography characteristics. Gastrointest Radiol 1991;16:307-10; Plank C, Niederle B, Ba-Ssalamah A, Schima W. Pancreatic hemangioma: imaging features with contrast-enhanced CT and with gadolinium- and mangafodipir-enhanced MRI. Eur J Radiol 2006;57:59-62; Williamson JM, Finch-Jones M, Pope I. Endoscopic ultrasonography allowing expectant management of pancreatic haemangioma. Ann R Coll Surg Engl 2014;96:e1-2; Mondal U, Henkes N, Henkes D, Rosenkranz L. Cavernous hemangioma of adult pancreas: a case report and literature review. World J Gastroenterol 2015;21:9793-802; Lu T, Yang C. Rare case of adult pancreatic hemangioma and review of the literature. World J Gastroenterol 2015;21:9228-32; Kim SH, Kim JY, Choi JY, Choi YD, Kim KS. Incidental detection of pancreatic hemangioma mimicking a metastatic tumor of renal cell carcinoma. Korean J Hepatobiliary Pancreat Surg 2016;20:93-6.

massive bleeding, if ruptured. This leads us to speculate whether the bleeding in Ringoir's case arose from erosions in a narrowed duodenum, which led to incidental discovery of an asymptomatic mass.

The risk of rupture and consequent morbidity and mortality of pancreatic haemangiomas are difficult to delineate, as they are exceedingly rare. As such, references to hepatic haemangiomas have frequently been made. Rates of spontaneous hepatic haemangioma ruptures stand at 1%-4%, mainly in giant haemangiomas larger than 6 cm.[11] The average size in cases presenting with rupture was about 11 cm, with a very high mortality rate of 35%.[12]

The use of steroids has also been shown to increase the size of haemangiomas.[12] We postulate that the steroid

treatment for our patient's connective tissue disease could have caused an enlarging haemangioma. Correlating with the data from hepatic haemangiomas, she therefore faced an increased risk of rupture with potential mortality.

Also, since the lesion is located in the head of the pancreas and abutting the duodenum, endoluminal foreign body injury and erosions into the haemangioma could have also resulted in the rupture.

Our patient was at risk of death from exsanguination from a ruptured pancreatic haemangioma. This prompted us to perform a retrospective review of our patient's computed tomography (CT) scans that had been previously done for follow-up of her malignant thymoma.

In view of the clinical diagnostic difficulty faced in characterising this pancreatic haemangioma, we retrospectively reviewed the patient's earlier scans to determine if the pancreatic haemangioma could have been definitively diagnosed earlier. On review, the pancreatic lesion was already present in 2011, then measuring almost 35 mm (Fig. 2A). The lesion was isodense in relation to the pancreas on subsequent follow-up scans, making it difficult to perceive. A tri-phasic CT scan that was performed in 2013 demonstrated draping of vessels around the isodense mass (Fig. 2B). A later CT scan performed in 2016 showed a mild increase in size to 44 mm (Fig. 2C). We postulate that it may be the slight difference in timing of the single-phase portal venous study in 2011 that rendered the mass slightly more conspicuous compared to subsequent single-phase studies.

The difficulty in diagnosis of pancreatic haemangiomas is not unique to our case. A variety of imaging modalities have been previously applied. Trans-abdominal ultrasound seems effective for larger lesions, having clinched the diagnosis in 9 of the cases, albeit all larger than 5 cm in size. One case described the use of intraoperative ultrasound for diagnosis of a smaller 4 cm haemangioma.[6] The use of endoscopic ultrasound was later used in 3 cases, but only one correctly diagnosed pancreas haemangioma.[7] Contrast-enhanced CT was performed in 12 of the cases, with 6 showing poor arterial enhancement, and the other 6 showing hyper-enhancement. Four of the reported cases underwent magnetic resonance imaging (MRI), but only 1 case by Kobayashi[5] showed classical hypo-intensity in T1-weighted images and moderate hyper-intensity signal in T2-weighted images with marked enhancement post-gadolinium. Overall, there seems to be no superior modality in the diagnosis of pancreatic haemangiomas.

In our case, on CT alone, it was difficult to definitively diagnose pancreatic haemangioma. Had the lesion been seen, perhaps further evaluation with MRI may have aided its diagnosis.

While the general consensus for management of haemangiomas is conservative in view of its benign nature, we now present this rare case with a life-threatening massive bleeding from a pancreatic haemangioma. This might open doors to consideration of surgical resection for cases deemed to be at increased risk of rupture.

Conclusion

Haemangiomas are rare lesions of the pancreas. Diagnosis with imaging remains a challenge, and a high index

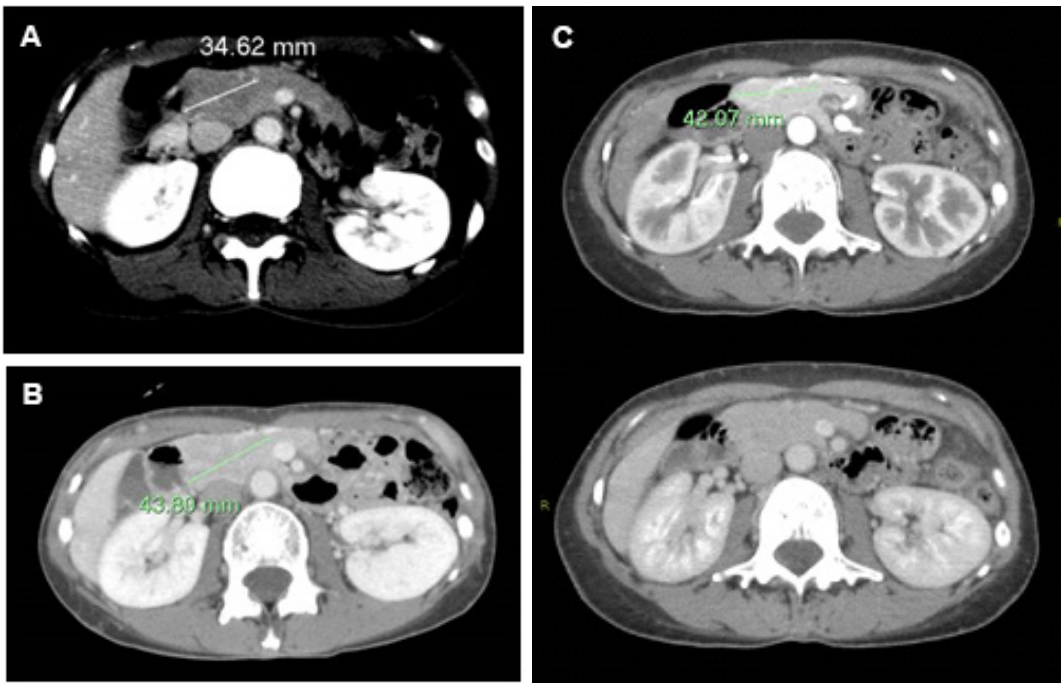

Fig. 2. Computed tomography (CT) scans of our patient. A) Scan in 2011 showing lesion in head of pancreas about 35 mm in size. B) Arterial and delayed phase scan in 2013, showing draping of vessels around isodense lesion in head of pancreas. C) Latest scan in 2016, again showing isodense lesion about 44 mm in size.

of suspicion is needed. We described the first ruptured pancreatic haemangioma presenting with massive bleeding into the GI tract, for which an emergency Whipple's procedure was performed. We urge the consideration of surgical management of pancreatic haemangiomas, if deemed at high risk of rupture.

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Oculopharyngeal Muscular Dystrophy in Singapore: Not So Rare

Dear Editor,

Oculopharyngeal muscular dystrophy (OPMD) is a late onset, inherited muscle disease, characterised by ptosis, dysphagia, variable proximal limb weakness and slow progression.[1-3] The highest reported prevalence is amongst Bukhara Jews (Israel; 1:600) and French Canadians (1:1000). Amongst East Asians, OPMD is thought to be rare.[4,5] The risk of misdiagnosis remains high, particularly when family history is not available, or symptoms are mild or isolated. Typically, diagnosis may be delayed for 3 to 20 years, with most patients undergoing extensive investigations and treatment for other suspected neurological conditions.[6,7]

There have been a few reports from China, Taiwan, Hong Kong and Japan, with a small number of genetically confirmed OPMD cases from Southeast Asia (Thailand, Malaysia).[8-14] A previous case report from Singapore (1993) described a single patient, in whom OPMD was diagnosed clinically, with no genetic confirmation.[15] Under-recognition of OPMD may be one of the causes of the assumed rarity of OPMD in East Asia. Here, we describe 4 unrelated patients from Singapore diagnosed with OPMD over the past 4 years.

Case 1: A 67-year-old Chinese gentleman presented with progressive ptosis since his 30s (Fig. 1), as well as progressive dysphagia and dysphonia for 5 years. Investigations are summarised in Table 1. Family history, which was not apparent prior to diagnosis, was notable for similar symptoms in approximately 20 family members living overseas, including his father and paternal grandfather. Mitochondrial cytopathy was initially considered, and muscle biopsy was performed (left biceps brachii muscle); needle electromyography of the contralateral biceps brachii muscle showed subpopulations of myopathic motor units. Subtle mitochondrial abnormalities were evident, with no rimmed vacuoles observed (Fig. 2). Genetic screening for OPMD showed heterozygous expansion of (GCN) in *PABPN1* (13 repeats).

Case 2: A 52-year-old Chinese gentleman presented with progressive, bilateral, asymmetrical ptosis for at least 10 years, and progressive dysphagia and dysphonia for 5 years. Ocular movements were slightly impaired bilaterally. The initial diagnosis was myasthenia gravis (MG), based on positive single fibre electromyography (SFEMG) study. He did not improve with treatment for MG. Family history was notable for diagnosis of MG (based on SFEMG alone) in his late father, who presented at age 75, with progressive ptosis and bulbar symptoms for a few years. Genetic screening for *PABPN1* gene was performed for the index patient, which showed 13 repeats.

Case 3: A 68-year-old Malay lady presented with bilateral, progressive ptosis since her 50s and mild dysphagia for 10 years. Investigations are summarised in Table 1. A similar history of ptosis and dysphagia was reported in the patient's mother and 4 siblings, with onset of symptoms in the sixth decade. No ptosis or dysphagia was reported in her children (aged 25-43 years). Genetic screening for OPMD was positive with 13 repeats.

Case 4: A 58-year-old Chinese gentleman presented with history of choking for 3 to 4 years. Mild facial and limb-girdle weakness (Medical Council Research grade 4 to 4+) was noted on examination. Initial diagnosis included MG and facioscapulohumeral muscular dystrophy. Serum creatine kinase (CK) was mildly elevated, and mild muscle membrane irritability was noted on electromyography (EMG). A detailed review was notable for mild, symmetrical ptosis (not reported by patient), and similar complaint in

Fig. 1. Top panel: Case 1- Serial photographs over 50 years showing progressive, bilateral, and symmetric ptosis. Bottom panel: Cases 2 and 3, at index presentation.

Table 1. Clinical Features, Investigations and Clinical Course of Described Cases

Variable	Case 1	Case 2	Case 3	Case 4
Age at onset of symptoms	30s	40s	68	55
Gender	Male	Male	Female	Male
Ethnicity	Chinese	Chinese	Malay	Chinese
First symptom	Ptosis	Ptosis	Ptosis	Dysphagia*
Onset to final diagnosis	≥30 years	≥10 years	≥15 years	3 – 4 years
Ptosis	Yes	Yes	Yes	Yes
Dysphagia	Yes	Yes	Yes	Yes
Limb weakness	No	No	No	Yes
Predominant symptom	Ptosis	Dysphagia and ptosis	Ptosis	Dysphagia
Suspected neurological conditions (prior to diagnosis of OPMD)	MG, Mitochondrial cytopathy	MG	MG, Mitochondrial cytopathy	FSHD, MG
Treatment for myasthenia	No	Yes	No	No
Family history of similar symptoms	Yes	Yes	Yes	Yes
Investigations				
Serum CK (IU/L; 50 – 250)	155	99	147	402
Serum lactate (fasting)	Normal	Normal	Normal	Normal
Serum anti-acetylcholine receptor antibody	Negative	Negative	Negative	Negative
Electrophysiology				
Nerve conduction study	Normal	Normal	Normal	Normal
EMG	Myopathic units in biceps	Normal	Myopathic units in frontalis	Increased insertional activity in deltoid
RNS/SFEMG	ND/ND	Negative/ positive	Negative/ND	Negative/ND
Muscle biopsy	Subtle mitochondrial abnormalities ; no rimmed vacuoles	ND	ND	ND
Genetic test *(PABPN1)*	13 repeats	13 repeats	13 repeats	ND
Other investigations prior to diagnosis	Barium swallow; CT thorax; MRI brain	video fluoroscopy, MRI orbits	MRI brain	Anti MUSK antibody, Barium swallow, video fluoroscopy
Clinical Course				
Follow-up duration	4 years	4 years	3 months	2 years
Mobility	Independent	Independent	Independent	Independent
Nasogastric tube placement	No (Modified diet)	No (Modified diet)	No	No (Modified diet)
Ocular surgery	No	No	No	No

CK: Creatine kinase; CT: Computed tomography; EMG: Electromyography; FSHD: Facioscapulohumeral dystrophy; MG: Myasthenia gravis; MRI : Magnetic resonance imaging; MUSK: Muscle-specific kinase; ND: Not done; OPMD: Oculopharyngeal muscular dystrophy; RNS: Repetitive nerve stimulation; SFEMG: Single fibre electromyography

*Ptosis not noted by patient.

patient's 2 sisters and mother. Patient declined genetic testing; however, based on the clinical evidence, final diagnosis was that of OPMD.

Discussion

We have reported 4 patients of OPMD, from 4 different families in Singapore, diagnosed over a period of 4 years. Considering that each patient reported symptomatic relatives residing in Singapore, the total number of affected individuals in Singapore is significantly higher.

OPMD is caused by an abnormal GCN expansion within the *PABPN1* gene on chromosome 14 (14q11.2-q13), with the mutated gene containing 11-17 repeats.[2,3] Mean age at diagnosis and severity of clinical symptoms correlates to the number of GCN repeats.[16] No anticipation is noted, as the expansion tends to be stable. Most cases have an autosomal dominant (AD) inheritance, and cumulative penetrance is 99% at age >69 years.[17] Autosomal recessive OPMD is rare, and tends to be later in onset (>60 years), with fewer GCN repeats (11 repeats, as compared to 12-17 repeats in AD OPMD).[18]

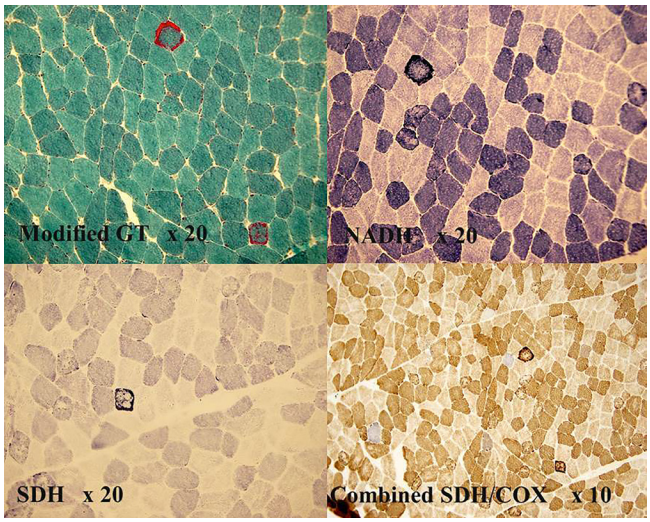

Fig. 2. Muscle biopsy (case 1); subtle mitochondrial abnormalities are noted, including (i) few ragged red fibres seen on modified GT stain, (ii) two fibres with increased subsarcolemmal densities seen on the NADH-TR and SDH stains, and (iii) few COX negative fibres. COX: Cytochrome oxidase; GT: Gomori trichrome; NADH: Nicotinamide adenine dinucleotide hydrogenase; SDH: Succinic dehydrogenase

Dysphagia precedes or is simultaneous with ptosis.[1,6,14] Proximal limb weakness tends to occur later in the course of disease, and may correlate with the size of the mutation (number of repeats). Recently, early involvement of pelvic girdle and proximal leg muscles—specifically the hip adductors and hamstrings—has been reported in a cohort of 14 Dutch patients with OPMD.[19] Extraocular muscle weakness may be noted, but complete external ophthalmoplaegia is rare. Occasional atypical or monosymptomatic presentations have been reported, especially in heterozygotes.[16,20] In this study, ptosis was the initial symptom in 3 of 4 patients, with dysphagia occuring 5 to more than 20 years thereafter. However, ptosis may initially go unnoticed by patients, as noted in Case 4. Thus, actual duration of ptosis may be much longer. Examination of serial facial photographs may be useful in such cases.

Serum CK may be elevated in patients with higher number of repeats, in homozygotes and patients with severe disease.[6,14,16] EMG examination may be normal in the early stages and in patients with only ocular and pharyngeal symptoms. In patients with limb weakness, myopathic changes and abnormal spontaneous activity may be seen. Notably, 1 of our patients had abnormal SFEMG. Increased jitter is not specific for MG, and caution must be exercised in interpretation.[21]

Common clinical misdiagnoses in OPMD include MG, mitochondrial myopathy, amyotrophic lateral sclerosis, and myotonic dystrophy. In the muscle biopsy, non-specific mitochondrial abnormalities, including large mitochondria , abnormal cristae, paracrystalline mitochondrial inclusions, on electron microscopy, are noted. Detection of filamentous intranuclear inclusions in skeletal muscle fibres (mutated *PABPN1*) by electron microscopy or immunostaining is helpful in confirming the diagnosis on biopsy.[22] Molecular genetic testing of *PABPN1* is confirmatory.

There is currently no cure for OPMD. The disease does not appear to affect life span; however, it significantly affects quality of life. Symptomatic management may include surgical procedures on the eyelids and pharyngeal muscles. Genetic counselling is a core part of management, and carrier testing may be offered to asymptomatic at-risk young adults, especially for purpose of family planning.

This study aimed to highlight that OPMD is not rare in Southeast Asia, though we acknowledge a possible tertiary centre bias. OPMD should be considered in any patient who presents with late onset, progressive ptosis, with or without dysphagia, as well as in patients who do not respond to MG treatment (Case 2); a detailed family history for similar symptoms is a useful pointer. Molecular genetic testing of *PABPN1* is recommended for suspected cases of OPMD. As shown in this study, some OPMD patients can have positive SFEMG or mitochondrial abnormalities on muscle biopsy, thus leading to wrong diagnoses. An increase in awareness of OPMD may help prevent unnecessary investigations, ineffective or potentially harmful treatment in affected individuals.

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Danger in Shopping Centres – A Study on Escalator-Related Injuries in Children in Singapore

Dear Editor,

The first escalator was patented in 1892 and installed in New York, serving as an amusement ride.[1] Today, it has evolved into a common means of transport, taking passengers from 1 level to the next.

In the United States, there are more than 10,000 escalator -related injuries annually.[2] In 2016, a young mother in China had barely managed to save her son before falling to her death as the escalator's floor plate gave way.[3] In Singapore, there were several newspaper reports of escalator-related injuries involving children in 2016.[4,5,6] These included a 5-year-old boy whose big toe was avulsed and a 6-year-old boy whose trapped foot had to be released with hydraulic tools.

Singapore is a highly urbanised country. Within a mere 719.1 km^2 land area, there are now more than 6000 registered escalators in Singapore. This number is expected to rise with the construction of new complexes.[7] This study aimed to describe the nature of escalator-related injuries involving children in Singapore.

Material and Methods

This is a retrospective study using data from the injury surveillance database at KK Women's and Children's Hospital, Singapore. The emergency department (ED) sees about 175,000 patients annually, of which an estimated 25,000 have trauma-related complaints. The injury surveillance database consists of prospectively collected data on the circumstances of injuries documented according to the International Classification of External Causes of Injury (ICECI) classification.[8] Information on circumstances surrounding the injury is obtained from the physician during the consultation. Important data fields have electronic validation checks in place to ensure completeness of data. The trauma coordinator performs quality checks at regular intervals to ensure that the data entered is accurate.

All patients below the age of 18 years who presented to the ED between January 2012 and December 2016 with an escalator-related injury were included. We ran a search for the diagnosis using both diagnostic codes and free-text inputs. Keywords such as "escalator" and "escalator-related" were used to perform the free-text search. Other keywords such as "shopping centres" and "shoes" were also included and filtered.

In this study, we subdivided the age of our patients based on their development. Infants refer to children aged 1 year and below; toddlers, between 1 and 3 years of age; preschool children between 3 and 6 years of age; primary school-going children, between 6 and 12 years of age; and secondary school-going children, above 12 years of age.

The sites of injury were grouped into broad anatomical categories of the head, neck and face region; thoracic region; abdominal region; upper extremities; and lower extremities. In cases where there was more than 1 anatomical site involved, we chose to document the site that sustained the injury of greater severity.

The types of injuries were grouped into superficial injuries (e.g. abrasions); contusions; open wounds (e.g. lacerations, punctures); fractures; dislocations; and head injuries.

Categorical data was presented using frequencies and percentages, while continuous data was presented using means (standard deviation, [SD]) or median (interquartile range [IQR]), depending on normality.

The study was given ethics approval by the local institutional review board.

Results

From January 2012 to December 2016, there were a total of 300 injuries related to the use of escalators. We see a rising trend in the number of incidents annually (Table 1). This is despite the number of annual ED attendances remaining almost the same.

The youngest patient was 1 month old and the oldest was 17 years old. The mean age was 5.9 years old (SD 3.6) (Table 2).

The most common mechanism of injury in our study was a fall (Table 2). Amongst infants, falls were the sole mechanism of injury.

Of the 111 entrapment injuries sustained, 8 (7.2%) required surgery. A majority 28/59 (47.5%) of the entrapment injuries occurred at the escalator skirting, followed by 13 (22%) between the steps, and 13 (22%) between the walls and the railing. Two incidents occurred at the comb plate of the escalator while 3 occurred at the handrails.

Shoes were the commonest objects (54/97 or 55.6%) involved. Of these, 31/54 (57.4%) were specified to be rubber clogs. Strollers (38/97 or 39.2%) were the next

Table 1. Incidence and Rates

	Escalator-Related Injuries	Trauma Attendances to the ED	Annual ED Attendance	Rates of Escalator-Related Injury Per 10,000 Trauma Cases
2012	35	23,007	175,632	15.2%
2013	45	25,753	175,996	17.5%
2014	65	27,137	172,909	23.9%
2015	70	28,295	174,429	24.7%
2016	85	26,719	184,722	31.8%

ED: Emergency department

group of objects that were associated with escalator-related injuries; 22/38 (57.9%) of those who sustained an injury associated with stroller use required inpatient admission. A majority of accidents occurred in shopping centres (Table 2).

Of the 10 patients attended to at the resuscitation bay, 5 sustained entrapment injuries, while 2 had severe falls. An 11- and a 9-year-old boy were attended to at the resuscitation bay for facial suffusion and cervical spine injury, respectively, as a result of head entrapment between a wall and the escalator railings.

The majority of injuries involved the lower extremities (178/300 or 59.3%), followed by the head, neck and facial region (79/300 or 26.3%) and the upper extremities (43/300 or 14.3%). Head injuries were the commonest amongst the infants, making up 40% (22/55) of all head injuries; 230/300 (76.7%) patients required procedures in the ED (Table 3).

A total of 49/300 (16.3%) children were hospitalised. Ten underwent surgical procedures under general anaesthesia, while the rest were admitted for inpatient observation. The surgical procedures included wound debridement and open reduction and internal fixation of fractures. The mean number of days of hospitalisation was 2.3 days (range 2.0-9.0). There were no deaths.

Discussion

While there has been an earlier publication on foot injuries associated with escalator use,[9] this study is the first to describe escalator-related injuries among children presenting to a tertiary institution. There is an increased rate of escalator-related injuries among children presenting to our institution, from 15.2% per 10,000 trauma cases seen in 2012 to 31.8% per 10,000 trauma cases seen in 2016 (Table 1).

From 2012 to 2016, Singapore's population increased from 5.3 million to 5.6 million. With population growth, more high-rise buildings will be constructed and the number of escalators in Singapore will increase. There is a need to evaluate if the current strategies put in place to prevent escalator-related injuries are sufficient, and whether more should be done to reduce the incidence of such injuries.

Table 2. Demographics and Circumstances of Injury (n = 300)

	Variables	Frequency	Percentage
Gender	Female	106	35.3%
	Male	194	64.7%
Race	Chinese	177	59.0%
	Malay	31	10.3%
	Indian	38	12.7%
	Others	54	18%
Mechanism of injury	Fall	174	58.0%
	Entrapment	111	37.0%
	Mechanical failure	2	0.7%
	Others (e.g. shaving injury)	13	4.3%
Objects involved	Not specified	203	67.7%
	Stroller	38	12.7%
	Crocs rubber clogs	31	10.3%
	Other shoes	23	7.7%
	Others (e.g. dropped toy)	5	1.7%
Location	Not specified	80	26.7%
	Shopping centres	153	51.0%
	MRT stations	30	10.0%
	Residential areas	1	0.3%
	Others (e.g.hospital compounds, airports, tourist attractions)	36	12.0%
Types of injuries	Open wounds	144	48.0%
	Contusions/sprains	57	19.0%
	Superficial injuries	54	18.0%
	Fractures	43	14.3%
	Others	2	0.7%
Body part involved	Head, neck, face	79	26.3%
	Upper extremities	43	14.3%
	Lower extremities	178	59.3%
	Foot	68	22.6%
	Toes	7	2.3%
	Knee	5	1.6%
	Leg	12	4.0%
	Shin	86	28.6%
Mode of transport to the ED	Walk-in	261	87.0%
	Ambulance	39	13.0%

ED: Emergency department; MRT: Mass rapid transit

In November 2016, the Building and Construction Authority of Singapore (BCA) put in place regulations to ensure that all escalators undergo regular maintenance checks. Escalators require a valid permit from the BCA to be operational. All incidents pertaining to escalators must be reported to the BCA.[10] Despite this, a well maintained

Table 3. Disposition and Outcomes

Investigations required (n = 300)	
X-rays	179 (59.4%)
CT scans	1 (0.3%)
Interventions required (n = 230)	
Toileting and suturing	134 (58.2%)
Wound cleaning	51 (22.2%)
Casting and immobilisation	38 (16.6%)
Nail bed repairs	4 (1.7%)
Manipulation and reduction	3 (1.3%)
Disposition (n = 300)	
Hospitalised for observation	38 (12.7%)
Hospitalised for surgery	10 (3.3%)
Discharged from ED	252 (84.0%)

CT: Computed tomography; ED: Emergency department

escalator will not completely reduce injuries caused by the improper use of escalators. In our study, only 2 children sustained injuries related to machinery fault.

From our study, 12.7% of escalator-related injuries involved prams and strollers, reinforcing results from another study[11] that more should be done to reduce the incidence of stroller-related injuries sustained on escalators.

Falls are the commonest mechanism of injury in our study, which is consistent with other studies.[11-13] While this leads to hospitalisation, entrapment injuries required longer hospital stays and complex surgical intervention. Wearing certain types of shoes, such as rubber clogs, could contribute to the increased risk of entrapment injuries as supported by a study published in 2010.[9] In our study, a large proportion of the cases had no specified objects involved. This group comprises cases that truly did not have an object involved as well as those that did not have objects specified due to incomplete documentation. This may lead to an underestimation of the number of injuries with objects involved.

We recognise the limitations to our study. This is a single-centre study and milder injuries may not present to the hospital leading lead to an underestimation of the incidence. Being a retrospective study, incomplete documentation may lead to missing data. Cases of machinery fault were likely to be underestimated because these were determined by chart review.

Conclusion and Recommendations

Efforts have been made to increase the awareness of safe escalator usage. Signs are placed at the entrance of most escalators in Singapore as a safety reminder. The effectiveness, however, is limited by the fact that these are frequently not read nor complied with. Moreover, education interventions require behavioural change amongst users in order to be effective.

We recommend making structural modifications to all escalators. Constructing a metal pole in the middle of the escalator entrance will deter parents from pushing strollers onto escalators. Reducing the gap between the steps and side-walls and fitting escalators with brush borders may reduce the incidence of entrapment injuries.

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