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*"No bubble is so iridescent or floats longer than
that blown by the successful teacher."*

William Osler (1849 – 1919)
Canadian scientist & professor of medicine

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Population-based Healthcare: The Experience of a Regional Health System

Eugene Shum, ¹*MPH, FAMS*, Chien Earn Lee, ²*M Med (PH), FAMS*

Introduction

Asian populations are experiencing a much faster rate of ageing compared to western countries.¹ Western countries such as France and the United States took 115 years and 69 years respectively for the percentage of population aged 65 years and over to rise from 7% to 14%. In contrast, it is projected that countries such as South Korea, Singapore, Thailand and China would experience this increase within a much shorter time frame of 18 to 26 years. In Singapore, the percentage of population aged 65 years and over is projected to increase from 8.4% in 2005 to 18.7% in 2030.² Accordingly, the period that Singapore has to respond to the demands of a rapidly ageing population in terms of socio-cultural changes and healthcare system is much shorter.

Singapore has a healthcare system that is ranked highly internationally in terms of performance and efficiency. It was ranked sixth for health system performance in the World Health Report 2000³ and first in the Bloomberg second annual ranking of countries with the most efficient healthcare.⁴ A key contributing factor is Singapore's continued investment and development of the healthcare system. In response to the increasing demand for healthcare, the government health expenditure has increased by 46% from \$4.1 billion in 2011 to \$6 billion in 2013.⁵

With a rapidly ageing population, there will be more frail older persons with chronic diseases living in the community. There will be a need to support these older persons in terms of healthcare services and social support to live independently in the community. Similarly, there will be a need to engage them in advance care planning and support them in end-of-life care. It is imperative to shift from an acute hospital centric model of care to a population-based approach where the healthcare services that a person needs across different settings are well-planned and coordinated.

Development of Regional Health Systems

In 2000, the public healthcare institutions in Singapore were organised into 2 healthcare clusters—SingHealth and National Healthcare Group. The aim was to allow better integration of public health institutions such as polyclinics, acute hospitals and national specialty centres. This allowed

the competition to shift from being between individual institutions to integrated networks. However, the limitation of the 2 cluster systems was that it included only public sector institutions which might not have necessarily corresponded to the way patients accessed healthcare services. It was also constrained in addressing healthcare at the population level as some key stakeholders (e.g. general practitioners (GPs) and voluntary welfare organisations) were not included.

The Singapore healthcare system further evolved with the formation of 6 regional health systems (RHS). Each RHS was responsible for the population in a region. The aim was to move from episodic to patient level care; from providing healthcare services to also keeping individuals in good health; and from interventions at individual level to also include systems level interventions focussing on population health. This necessitated close partnerships and collaboration beyond the public health institutions to also include voluntary welfare organisations and private healthcare providers in particular primary care providers.

Eastern Health Alliance and Changi General Hospital

The Eastern Health Alliance, the RHS for the population in eastern Singapore, was officially launched on 18 November 2011. Amongst the 6 RHS, the Eastern Health Alliance is unique in its formal partnership with a range of healthcare organisations each with a specific focus along the healthcare continuum. These foundation partners are Changi General Hospital (CGH), Health Promotion Board, St Andrew's Community Hospital, SingHealth Polyclinics and the Salvation Army Peacehaven Nursing Home. Each of these organisations is independent as only Changi General Hospital is owned by the Eastern Health Alliance. They have joined together with the shared purpose of providing seamless integrated care in the east. This in turn provided for the close partnership between the management and operations teams of the various organisations.

The Eastern Health Alliance takes a population health approach in the development and delivery of health services in the eastern region of Singapore which has a population of more than one million residents. At the RHS HQ level, the Eastern Health Alliance has a convenor and coordinating

¹Corporate Development, Eastern Health Alliance, Singapore

²Executive Office, Changi General Hospital, Singapore

Address for Correspondence: Dr Eugene Shum, Eastern Health Alliance, 5 Tampines Central 1, Tampines Plaza #08-01/05, Singapore 529541.

Email: eugene.shum@easternhealth.sg

role. This is analogous to being the conductor of an orchestra. It analyses and understands the profile and healthcare needs of specific populations and local communities; it identifies partners, resources and assets in the community; and it coordinates programme delivery, link partners and where necessary develop new services. This allows residents in the east to have access to a comprehensive range of services across the healthcare continuum that is coordinated by the RHS HQ in collaboration with its partners.

Community-led initiatives such as the Naturally Occurring Retirement Communities⁶ and the Village model⁷ have an important role in facilitating ageing-in-place. Learning from these initiatives, the Neighbours for Active Living programme was set up by the Eastern Health Alliance in partnership with the South East Community Development Council (SE CDC) in July 2013. This programme supports patients with high medical and social needs who are living in the east. It has a team of social work professionals and para-professionals who assess and ensure that clients receive the support services that they require. The programme is unique in several aspects. Firstly, the community care team is embedded in the community. Each team is sited full time in a local community where they support clients living in the area and work closely with the organisations sited there. An added advantage of this is that they also serve as “sensors” in the community to detect and help those who may not step forward to seek assistance. Secondly, there is close participation by the community. The SE CDC organises the Friend-a-Senior programme to engage and train residents in the community to be volunteer befrienders. With the strong support from the community, clients can continue to be monitored and follow-up longitudinally by the RHS for as long as they require it. Thirdly, the programme bridges both the health and social needs of the client. Since the launch of the programme, more than 1000 clients have been enrolled in the programme.

Within this ecosystem, the hospital is a very important component. It is an expensive resource but it can be a cost-effective resource if used appropriately. CGH has defined its role in the healthcare ecosystem to focus on 4 key thrusts. Firstly, it is to save lives through timely intervention. The hospital still remains the most appropriate place to manage patients with acute conditions such as myocardial infarct, stroke and serious trauma that require complex investigations and interventions. Secondly, the hospital plays a critical role in restoring functionality by mitigating the deconditioning effects of hospitalisation and illness. The aim is to present patients in as good a condition as possible within as short a time as possible to our partners in the community to continue the recovery process. For example, operating to fix fragile hip fractures within 48 hours accompanied by active rehabilitation has been shown

to improve functional status of patients (and also reduce use of resources and saving costs).⁸ Thirdly, with the increasing capability of primary care providers, outpatient care at the hospital should focus on patients with complex medical conditions requiring multidisciplinary, multispecialty care. Fourthly, CGH also serves as a resource for the Eastern Health Alliance and its partners. For example as part of the GPFirst programme, there is a 24/7 hotline for GPs on the programme to discuss cases with the emergency department consultant if necessary.

It is critical for the hospital and RHS to work in tandem and collaboratively to meet the needs of the population—complementing and leveraging on each other’s strengths to ensure that individual and systems/population perspectives are addressed.

Conclusion

The setting up of the RHS has allowed for a population-based approach to healthcare. It has led to a healthcare system that is more responsive to the needs of our population. It takes into account the life cycle stages and needs of the patient and their caregiver as an important factor. For example, the needs of a single young adult may be different from a married person with young children even if they have the same medical condition. Finally, it has allowed us more options in considering the patient experience and to address what matters to the patient even as we manage issues such as compliance with treatment.

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Clinician Scientists in Public Sector Hospitals—Why and How?

E Shyong Tai, ¹MB ChB, PhD, FAMS

Introduction

The Singapore Biomedical Sciences (BMS) initiative was launched in June 2000 to develop the Biomedical Sciences cluster as one of the key pillars of Singapore economy. Beginning in the late 2000's, the initiative evolved with an increasing focus on establishing a critical mass of high quality clinician scientists in the belief that this will facilitate the successful implementation of the research initiatives. In this editorial, I hope to share my thoughts in relation to 2 questions. Firstly, in an environment where we are short of clinicians to deliver essential services in our public hospitals, and a workforce that increasingly seeks work-life balance, why should we encourage clinicians in public hospitals to participate in activities that do not directly contribute to patient care? Secondly, if we do want clinician scientists in our public health institutions, how do we find them and retain them?

My Personal Experience

I was trained as a physician in the United Kingdom and returned to Singapore in 1991 where I received training, first in internal medicine, then in endocrinology. I secured my first grant from the National Medical Research Council (NMRC) in 1997, as a registrar, and eventually, became one of the 7 physicians to embark on the “clinician scientist scheme” in the Singapore General Hospital. I committed 8 years to working on a number of research projects, earning a PhD in the process. I like to think that I became a pretty credible clinician scientist. In 2010, I accepted an appointment as head of the Division of Endocrinology in the National University Hospital. All of a sudden, I was confronted with the very real issues of filling up rosters for clinical duties, scheduling clinicians to teach and examine under- and post-graduate students, shortening waiting times for new appointments in the specialist outpatient clinics, discharging patients early to ease the bed crunch, all of which were far more urgent and pressing than the need for research. Why should I encourage or even allow the clinicians in my division to do research? Here are my thoughts after 4 years as the head of endocrinology.

Challenges for Healthcare Providers in The Future

Over the next several decades, our population will age rapidly. This will result in a great increase in the demand for healthcare as the prevalence of chronic diseases increases. At the same time, we will see a decline in the number of individuals in the workforce, who are required to provide the care that we will all need. The healthcare issues of the future cannot be solved by simply increasing the number of healthcare providers. They will simply not be available. Nor is the solution to make healthcare providers “just work harder”. Recognising this, the Ministry of Health, along with our public health institutions, has begun a process that will transform the landscape of healthcare in Singapore. I believe that this process of transformation will pose challenges for the healthcare providers of the future. While I cannot purport to know what precise changes will take place, I think we can make some predictions about some of the characteristics of the healthcare environment of the future, which may help us identify some of these challenges.

Firstly, change is inevitable, and given the way things move in Singapore, it will occur rapidly. There will also be a great deal of uncertainty. All countries, including the most developed ones, are struggling with many of the same issues and it is not evident that the solution has been found. As such, healthcare providers of the future will need to possess the same kind of creativity and innovation that allowed Jeff Bezos, through Amazon, to transform the business of selling books. They will also need to be prepared to carefully measure the outcomes resulting from any changes they implement, which will allow them to change track using data to guide the next strategy.

Secondly, it is likely to involve the development and use of new technologies, and it will be an incredibly data rich environment. In addition to the great gains made in the biomedical sciences, the advent of the internet and mobile technologies has changed the way we communicate and interact in our daily lives. These technologies have the power to enable the healthcare transformation that is required.¹ To begin with, the widespread adoption of electronic medical records will lead to the accumulation of mountains of data

¹Division of Endocrinology, Department of Medicine, National University Health System, Singapore

Address for Correspondence: Dr Tai E Shyong, Division of Endocrinology, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, 10 Medical Drive, Singapore 117597.

Email: e_shyong_tai@nuhs.edu.sg

about our patients over time which can now be mined to predict and prevent adverse outcomes in our patients. This will allow us to transform our healthcare system from one that is primarily reactive (i.e. treating the patient when he or she comes to us with a symptom) to a proactive one, where we predict an adverse outcome and put in place measures to prevent it. These data will also facilitate clinical decision support, which will reduce unjustified variation in the healthcare provided and reduce errors. Finally, mobile technology can be used to enhance our interactions with patients, moving away from the “office consult” as the primary channel of communication, not just between patient and healthcare provider, but even between different healthcare providers. They also serve as a novel channel of communication through which we can engage our patients so that they can better participate in their own care. Our National Electronic Health Record is a great example of the technology that is being built to support our healthcare system.² However, technology is only an enabler. To take advantage of these opportunities, clinicians will need to decide what technologies are required, when they should be deployed, and how to interpret the data that is collected using these technologies. As such, they need to become familiar with the technologies and their capabilities, and be familiar with handling and interpreting large volumes of data that will be collected.

Finally, integration and coordination of care for individual patients needs to take place across institutions and throughout a patient’s lifetime as his or her health and social circumstances change. This requires the healthcare leaders of the future to be able to influence other healthcare providers and build collaborations that do not rely on the traditional levers of appraisals and salaries, and often take place (given the new technologies available) without opportunities for a handshake, or a face-to-face conversation.

What Does This Have To Do with Clinician Scientists?

As clinician scientists, our ability to do work that is funded and eventually gets published is dependent on the creativity of the investigator. A competitive funding environment makes innovation a key component of every successful grant application. One must constantly question the status quo and seek to do better than what is currently available. Clinician scientists are taught to withhold judgment until they have collected data in a rigorous manner, and interpreted the said data with scientific discipline. Clinician scientists are also used to being wrong. My research career is strewn with hypotheses have proven to be false, often through studies that I have conducted myself. But good clinician scientists always learn from these mistakes, and use that data to refine their next hypothesis. They are also used to failure. With a 15% to 20% success rate for grant funding in Singapore, I have written more grants that have not been

funded, than grants that have been funded. Failure to accept acknowledged guidelines, indecisiveness in the face of insufficient data, being wrong, frequent failure; these are not attributes that we commonly associate with physicians, who often have to make decisions on the spot, when faced with life threatening situations, sometimes in the absence of adequate data because the randomised clinical trial simply has not been conducted yet. Nonetheless, I believe that these attributes will serve them well during the next several decades as we transform the healthcare system.

Clinician scientists are also used to taking technologies that they have never used before, and seeing if they can use it to answer the questions that they are interested in asking. Or they develop new technologies to solve problems that they have in the clinic.^{3,4} Finally, the current research environment has required clinician scientists to develop the leadership skills to manage the complex healthcare system of the future. When I started out studying the genetics of human disease, we were carrying out what we thought were large studies involving a few hundred patients.⁵ Over time, we realised that these studies were largely underpowered, and could lead to misleading conclusions. Today, it is appreciated that large datasets (often in the tens to hundreds of thousands of samples) are required to make discoveries that we are confident in. The result is papers and publications that involve hundreds of authors.⁶ These investigators came together because they realised that together, they could achieve something that each could not achieve on their own. They were prepared to share the “glory” of authorship with others for a common purpose, of learning more about the biological processes that underlie human disease. In this context, not only do clinician scientists learn to handle large volumes of data, they are forced to acquire the ability to build collaborations based on a common purpose, to negotiate agreements and concessions between parties, to communicate across the world often without an opportunity to get to know each other face to face. These same skills will be required to unite the diverse components of Singapore’s healthcare system, which includes public health institutions, private sector providers, voluntary welfare and non-profit organisations, multiple government agencies, patients and their families, together in a common purpose: providing for the health of a population.

I encourage clinicians in the Division of Endocrinology to undertake research not just because they may find a cure for the key diseases that plague mankind. I believe that having research as part of the division helps me create an environment where creativity and innovation can thrive, where clinicians can challenge current beliefs, and be wrong, in the “safe” environment of the well-controlled clinical trial or research protocol. Where they can learn to embrace, or develop, new technologies; handle large

volumes of data; and acquire the skills they will need to lead future generations through the transformation that is coming. Failure to provide this environment not only fails to develop innovation and creativity in our existing clinicians, it actually propels the most innovative and creative of our profession out of the public sector. A close friend and a mentor in the private sector told me once, “E Shyong, you need to realise that the skills required for a successful career in research and the skills required for a really successful career in the private sector are the same. They are just applied to achieve different ends.” If we fail to provide an environment where creativity and innovation thrive, then the most innovative clinicians will find other environments in which to exercise their creativity, in building their businesses in the private sector; and they will be extremely successful.

Recruiting and Retaining Clinician Scientists

Having created the right environment, how then, do we recruit and retain clinician scientists in public sector healthcare? The provision of funding for salaries and research funding for clinician scientists at all different levels (through the National Medical Research Councils Talent Development Scheme⁷) is necessary but insufficient. One thing I have learnt is that clinician scientists are highly motivated individuals. It is this motivation that allows them to continue even when their experiments fail, or their grants do not get funded, or their papers get rejected. This motivation comes from a sense of higher purpose and I have become convinced that our ability to recruit and retain clinician scientists in our public health system is highly dependent on our ability to give them this sense of purpose. How do we do that? I believe that many clinician scientists are physicians first and scientists second. For this reason, clinician scientists often aspire to excellence in their field of clinical service, and not just their research. We don't like being the odd balls in the hospital, traipsing in and out of the lab, blissfully unaware of what it takes to treat a real patient. As such, we need to give them opportunities to shape clinical care and become leaders in their field. To this end, I have believed for a long time that the very existence of the term clinician scientist is detrimental to our ability to attract and retain these highly creative and motivated people in our healthcare system.

Convergence

This brings me to my final point, which relates to convergence. I believe that dividing the practice of medicine into 3 missions: research, education and clinical service, and telling clinician scientists that their role is only to work in one of these areas, is not only artificial, it makes it less attractive for clinician scientists to stay in the system.

There is only one mission: to provide state-of-the-art care for our patients of today and to reshape the healthcare system in a way that will provide for the health of our future generations. To achieve this, we need to give our patients the best care available (clinical service), develop new treatments and more effective ways to deliver and fund healthcare (research), and prepare our medical students and junior doctors for this role (education). We all need to do this together, with each of us contributing to each of these roles in different proportions at different times, depending on our interests, skills and aspirations. Convergence is also important for maintaining work-life balance. I often tell young clinician scientists that the best way to meet their aspirations, of being excellent clinicians, educators and researchers, is to seek convergence in what they do. Their research should be as close to what they do in the clinic as possible. They should approach their clinical work with the same scientific discipline as they might a laboratory experiment, and where they have a novel idea, they should formulate an experiment and carefully measure and evaluate the outcomes of any changes that they make. Then they should write about it and teach it to future generations of clinicians. In this way, one piece of work can satisfy our need to do research, provide clinical service and educate future generations. It's time to bring research, clinical service and education in medicine together.

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Oncologic Outcomes of Neoadjuvant Chemoradiation for Locally Advanced Rectal Cancer: A Single-institution Experience

Yiat Horng Leong,^{1,2}MBBS, Cheng Nang Leong,^{1,2}MBBS, FRANZCR, Guan Sze Tay,³MBBS, FRCS (Edin), Richard Sim,³MBBS, FRCS (Edin and Glasg), FAMS, Gilberto Lopes,⁴MD, Wilson Low,⁵BSc, MSc (Epidemiology), Bok Ai Choo,^{1,2}MBChB, MRCP, FRCR, Jeremy Tey,^{1,2}MBBS, FRANZCR

Abstract

Introduction: This study reports the outcomes of patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation followed by surgery in a local population of Singapore. **Materials and Methods:** The records of 85 patients who underwent neoadjuvant chemoradiation for locally advanced rectal cancer followed by surgery at the Tan Tock Seng Hospital (TTSH) between November 2002 and January 2012 were reviewed. The treatment protocol comprised radiotherapy to a total dose of 50.4 Gy concurrent with 5-fluorouracil-based chemotherapy. Patients underwent total mesorectal excision surgery following the completion of neoadjuvant chemoradiation. Local control, disease-free survival and overall survival were analysed using Kaplan-Meier methods. **Results:** Median age of the patients was 61 years. All of them completed radiotherapy. One patient did not complete neoadjuvant chemotherapy. The median time to surgery was 52 days. Fifty-five percent (47 of 85) of patients achieved pathological downstaging and 13% (11 of 85) of patients had a pathologic complete response to preoperative treatment. The neoadjuvant chemoradiation was well tolerated. Four percent of patients had grade 3 diarrhoea and 4% of them had grade 3 dermatitis. There were no grade 4 toxicities. With a median follow-up of 41 months, the 5-year actuarial local recurrence, disease-free survival and overall survival rates were 7%, 71.9%, and 83.2% respectively. Univariate analysis showed that patients with positive surgical margins had significantly worse disease-free survival and overall survival ($P = 0.012$ and $P < 0.001$ respectively) and a trend towards a higher rate of local recurrence ($P = 0.08$). **Conclusion:** Our study provides evidence that neoadjuvant chemoradiation is an effective treatment for locally advanced rectal cancer. Our outcomes are comparable with internationally published data and demonstrate the reproducibility of the neoadjuvant approach in an Asian population.

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Key words: Chemoradiotherapy, Preoperative, Rectal carcinoma

¹Department of Radiation Oncology, National University Hospital, National University Cancer Institute, Singapore

²Department of Radiation Oncology, Tan Tock Seng Hospital, National University Cancer Institute, Singapore

³Department of Surgery, Tan Tock Seng Hospital, Singapore

⁴Johns Hopkins Singapore International Medical Centre, Singapore

⁵Clinical Research Unit, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Yiat Horng Leong, Department of Radiation Oncology, National University Hospital, National University Cancer Institute, Singapore, NUHS Tower Block Level 7, 1E Kent Ridge Road, Singapore 119228.

Email: yiat_horng_leong@nuhs.edu.sg

Oncologic Outcomes of Neoadjuvant Chemoradiation for Locally Advanced Rectal Cancer: A Single-institution Experience

Yiat Horng Leong,^{1,2}MBBS, Cheng Nang Leong,^{1,2}MBBS, FRANZCR, Guan Sze Tay,³MBBS, FRCS (Edin), Richard Sim,³MBBS, FRCS (Edin and Glasg), FAMS, Gilberto Lopes,⁴MD, Wilson Low,⁵BSc, MSc (Epidemiology), Bok Ai Choo,^{1,2}MBChB, MRCP, FRCP, Jeremy Tey,^{1,2}MBBS, FRANZCR

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Introduction

In Singapore, colorectal cancer is the most common cancer in males and second most common cancer in females, with rectal cancers accounting for 30% to 40% of all colorectal cancers.¹ Local recurrence after treatment of rectal cancer results in significant morbidity and mortality and poses significant management challenges.^{2,3} Advances in surgical techniques with the adoption of total mesorectal excision (TME) surgery and improvement in chemoradiation strategies have led to better outcomes but local recurrence remains difficult to manage.⁴ The optimal management

of locally advanced rectal cancer consists of a combined modality approach with surgery as the cornerstone of cure. Randomised trials in the 1990s have shown that for patients with locally advanced cancer, postoperative chemoradiotherapy improves local control and overall survival.^{5,6} Further efforts to improve local control and preserve the function of the anal sphincter have led to the consideration of neoadjuvant approaches.^{7,8} The results of a large randomised trial comparing neoadjuvant versus adjuvant chemoradiation clearly demonstrated that toxicity

¹Department of Radiation Oncology, National University Hospital, National University Cancer Institute, Singapore

²Department of Radiation Oncology, Tan Tock Seng Hospital, National University Cancer Institute, Singapore

³Department of Surgery, Tan Tock Seng Hospital, Singapore

⁴Johns Hopkins Singapore International Medical Centre, Singapore

⁵Clinical Research Unit, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Yiat Horng Leong, Department of Radiation Oncology, National University Hospital, National University Cancer Institute, Singapore, NUHS Tower Block Level 7, 1E Kent Ridge Road, Singapore 119228.

Email: yiat_horng_leong@nuhs.edu.sg

is reduced and local control is improved with a neoadjuvant approach, thus representing the prevailing paradigm for treatment at this time.⁹

Since 2002, our institution has adopted neoadjuvant chemoradiation for patients with locally advanced rectal cancer. The purpose of this study is to report the outcomes of patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation followed by surgery in our institution.

Materials and Methods

Patients

The medical records of 102 patients with locally advanced rectal cancer who were planned for neoadjuvant chemoradiation at the Tan Tock Seng Hospital (TTSH) in Singapore from January 2002 to January 2012 were reviewed. The patients were first identified from the radiation oncology department electronic database and further clinical information was obtained from hospital-wide medical records. Patients must have had biopsy-confirmed rectal adenocarcinoma. The tumours must have been locally advanced, defined as T3 or T4 and/or node positive disease and within 15 cm from the anal verge, with (only oligometastasis) or without distant metastases.¹⁰ Low, mid and high rectal tumours were defined as tumours that were ≤ 5 cm, 5.1 cm to 10 cm and 10.1 cm to 15 cm from the anal verge respectively.¹¹ Patients who did not undergo surgery, who received previous radiotherapy or those who were treated with palliative intent were excluded. Seventeen patients were excluded from analysis (1 declined radiotherapy, 10 declined surgery, 2 had surgery upfront, 3 had progression of disease after radiation, 1 died of unrelated pneumonia before surgery). Eighty-five patients were eligible for analysis.

Pre-treatment Evaluation

Local tumour and nodal stages were established using magnetic resonance imaging (MRI) or computed tomography (CT) of the pelvis or transrectal ultrasound (TRUS). Distant stage was established with CT of the thorax and abdomen. The 7th edition of the American Joint Committee on Cancer (AJCC) TNM (tumour, node, metastases) staging criteria was used.¹⁰

Radiotherapy

Three-dimensional conformal radiotherapy was delivered using high energy 6 or 10 MV photons from a linear accelerator. A 3- or 4-beam arrangement was used. The field borders were defined as follows: the superior border was the L5-S1 intervertebral space, the inferior border

was the inferior obturator foramen or 2 cm below the inferior edge of the tumour, the lateral border was 1 to 1.5 cm lateral to the pelvic brim, the anterior border was the posterior edge of the pubic symphysis and the posterior border was 1 cm posterior to the sacrum. Boost clinical target volumes (CTV) extended to the entire mesorectum and presacral regions at involved levels, including 2 cm cephalad and caudad in the mesorectum and 2 cm on the gross tumour within the anorectum. Planning target volumes (PTV) included the clinical target volume (CTV) with a 0.5 to 1 cm expansion. All patients received a total pelvic dose of 45 Gy in 25 fractions in 1.8 Gy daily fractions over a period of 5 weeks plus a PTV boost of 5.4 Gy in 3 fractions in 1.8 Gy daily fractions to a total dose of 50.4 Gy. Attempts were made to exclude small bowel from the fields using multileaf collimators and bladder distension. The following dose constraints were applied: whole small bowel <45 Gy, whole bladder <65 Gy, femoral heads V45 Gy (volume that receives 45 Gy) <50%.

Chemotherapy

Seventeen patients received intravenous 5-fluorouracil (5-FU) at a dose of 225 mg/m²/day as a continuous infusion for 6 weeks. Sixty-seven patients received oral capecitabine at a dose of 825 mg/m² twice a day for 5 days a week during the course of radiation. One patient declined neoadjuvant chemotherapy. Seventy-eight (92%) patients received adjuvant chemotherapy in the form of 5-FU or capecitabine for a further 4 to 8 cycles. The reasons for not giving adjuvant chemotherapy were as follows: 2 patients declined, 1 had renal failure, 4 unknown.

Toxicity

Toxicities were recorded using version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE).¹²

Surgery

Surgery was planned to take place 4 to 8 weeks after completion of chemoradiation. Preoperative imaging was obtained where possible. Total mesorectal excision (TME) was performed for low and mid rectal tumours and wide mesorectal excision (WME) with preservation of the distal rectum for high rectal tumours. Surgery included low anterior resection, ultra low anterior resection and abdominoperineal resection. Postoperative complications were recorded. Pathologic response to neoadjuvant treatment was assessed and recorded. The circumferential resection margin was deemed involved if on histopathological examination, there was tumour at a distance of 1 mm or less from the margin.¹³

Follow-up

Patients were followed-up with 3-monthly history and physical examination for 2 years, then 6-monthly up to 5 years and annually thereafter. Full blood count, renal panel, liver function and carcinoembryonic antigen (CEA) tests were performed every 3 to 6 months for the first 2 years and 6-monthly CEA obtained till at least 5 years. CT of the thorax, abdomen and pelvis were performed yearly for at least the first 2 years from treatment. Colonoscopy was performed within a year from surgery for patients who had anterior resection. Local recurrence was determined either via colonoscopy plus biopsy or radiologically. Distant recurrence was determined radiologically.

Statistics

Recurrence and survival were analysed according to the Kaplan-Meier method. Univariate analysis was carried out on factors that potentially might influence the outcomes. The Cox regression model was used to compare survival estimates and to calculate *P* values and hazard ratios, with a *P* value of <0.05 considered statistically significant. The IBM SPSS version 19.0 software (SPSS Inc., Illinois, USA) was used for generating the statistical values and curves.

Results

Patients

Between 2002 and 2012, 85 patients with locally advanced rectal cancer received neoadjuvant chemoradiation followed by surgery. Median follow-up was 41 months (range, 4 to 120 months). The patient characteristics are summarised in Table 1.

Surgery

The median time from completion of chemoradiation to surgery was 52 days (range, 19 to 179 days). The upper limit of this range was 179 days due to 1 patient's delay in surgery because of concurrent coronary artery disease. Sixty-three percent of patients had preoperative imaging in the form of CT, while 16% of them had MRI, 1% had TRUS and 20% did not have any. The median time to performing preoperative imaging was 30 days (range, 13 to 120 days) from the completion of radiation. One patient had preoperative imaging done 13 days prior to completion of radiotherapy as part of the inpatient investigations for grade 3 diarrhoea. Twenty-six patients had abdominoperineal resection, 51 had low anterior resection, 6 had Hartmann's procedure, 1 had total proctectomy and 1 had exenteration. Sphincter preservation rate was 60%. TME was performed in 81 patients with low to mid rectal tumours and WME on 4 patients with high rectal tumours. Clear resection margins were achieved in 85% of patients. There was no perioperative

mortality. The median time from surgery to hospital discharge was 6 days (range, 2 to 27 days). One patient had anastomotic leak, 2 had wound infection, 2 had postoperative sepsis, 3 had postoperative ileus that were conservatively managed and 1 had high stoma output.

Pathologic Response and Downstaging

Table 2 shows the downstaging effects of chemoradiation on the tumour and lymph nodes. Histopathological examination was performed on all the surgical specimens. Eleven patients (13%) achieved pathological complete response (pCR), of which 8 had a preoperative TNM stage of III and 3 had a preoperative stage of II. For T stage, 34% of cT2, 28% of cT3 and 55% of cT4 tumours were downstaged by chemoradiation. For N stage, 62% of cN1 tumours and 83% of cN2 tumours were downstaged. Overall, taking into account both T and N stages, 55% of patients were downstaged.

Table 1. Patient Characteristics

Characteristics	n = 85 (%)	
Sex	M	66 (78)
	F	19 (82)
Age (years)	Median	61
	Range	29 – 82
Race	Chinese	72 (84)
	Malay	7 (8)
	Indian	3 (4)
	Others	3 (4)
ECOG performance score	0 – 1	83 (98)
	2	2 (2)
Pre-chemoradiation staging modality	MRI	39 (46)
	CT	40 (47)
	TRUS	6 (7)
Pre-chemoradiation TNM stage	II	19 (22)
	III	62 (73)
	IVA	4 (5)
Rectal tumour location	Low	48 (56)
	Mid	33 (39)
	High	4 (5)
Chemotherapy regimen	Capecitabine	Capecitabine
	5FU	5FU
	None	None
Type of resection	Abdominoperineal	26 (31)
	Low anterior	51 (60)
	Hartmann	6 (7)
	Others	2 (2)

5FU: 5-Fluorouracil; CT: Computed tomography; ECOG: Eastern Cooperative Oncology Group; MRI: Magnetic resonance imaging; TNM: Tumour, node, metastasis; TRUS: Transrectal ultrasonography

Table 2. Preoperative TNM Staging and Tumour Downstaging After Neoadjuvant Chemoradiation

Preoperative Stage (Clinical and/or Radiological)	n = 85 (% of Study Population)	Postoperative Stage (Pathological)	n (% of Preoperative Stage)
T2	6 (7%)	T0	1 (17%)
		T1	1 (17%)
		T2	2 (33%)
		T3	2 (33%)
T3	69 (81%)	T0	8 (12%)
		T1	3 (4%)
		T2	8 (12%)
		T3	49 (71%)
		T4	1 (1%)
T4	9 (11%)	T0	1 (11%)
		T1	0 (0%)
		T2	2 (22%)
		T3	2 (22%)
		T4	4 (45%)
Tx	1 (1%)	T3	1 (100%)
N0	19	N0	14 (74%)
		N1	5 (26%)
N1	48	N0	30 (62%)
		N1	10 (21%)
		N2	8 (17%)
N2	18	N0	8 (44%)
		N1	7 (39%)
		N2	3 (17%)
M0	81	-	-
M1 (oligometastases)	4	-	-

TNM: Tumour, node, metastases

Local Recurrence and Survival

Only one patient was lost to follow-up. Five patients developed local recurrence. The actuarial 5-year local recurrence rate was 7% (Fig. 1). Twenty patients developed distant metastasis. The main sites of metastases were lung, liver and bone. At the end of the follow-up period, 10 patients have died. The 5-year actuarial disease-free survival and overall survival rates were 71.9 % and 83.2% respectively (Figs. 2 and 3).

Univariate Analysis

Cox regression analysis was performed on factors that might potentially have an impact on local recurrence and survival. Factors analysed were age, gender, pre-chemoradiation carcinoembryonic antigen (CEA) level, chemotherapy regimen, pathologic node positivity, surgical margins and presence of tumour downstaging (Table 3). Age and gender were found to have no influence on local recurrence and survival (data not shown). A raised CEA

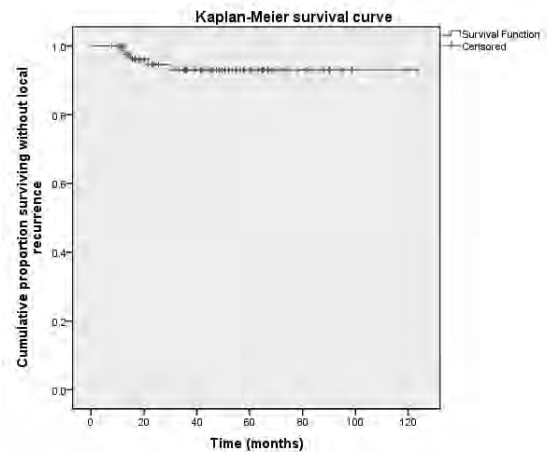


Fig. 1. Local recurrence-free survival in 85 patients who received neoadjuvant chemoradiation.

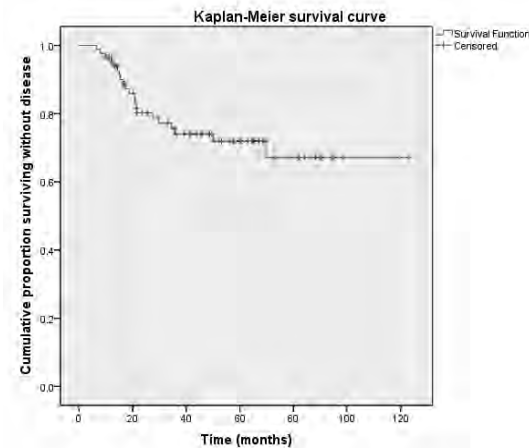


Fig. 2. Disease-free survival in 85 patients who received neoadjuvant chemoradiation.

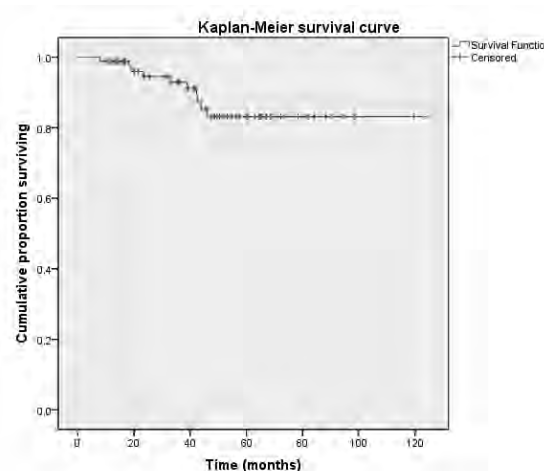


Fig. 3. Overall survival in 85 patients who received neoadjuvant chemoradiation.

level prior to chemoradiation did not have an impact on local recurrence and survival. For chemotherapy regimen, patients who were treated in the earlier years (from 2002 to 2007) received intravenous 5-FU while patients who were treated from 2007 to 2012 received oral capecitabine. Our analysis did not demonstrate any statistical difference in local recurrence and survival between patients who received the 2 regimens. Patients with positive circumferential margins had significantly worse disease-free survival and overall survival, with a trend towards higher rate of local recurrence. For T-stage, downstaging by neoadjuvant chemoradiation resulted in statistically significant improved overall survival and a trend towards improved local control and disease-free survival. Pathologic node positivity did not have an influence on local recurrence and survival. Pathologic complete remission, which was achieved in 11 patients, was not associated with improved local control and survival.

Toxicity

All patients completed the prescribed course of radiotherapy. One patient declined neoadjuvant chemotherapy. Table 4 shows the acute toxicities of the patients. The neoadjuvant regimen was well tolerated with no grade 4 acute toxicities recorded. Three (4%) patients had grade 3 diarrhoea. Three (4%) patients had grade 3 dermatitis. Four (5%) patients had grade 3 haematological toxicities. Overall, grade 3 acute toxicities were found in 8 patients (9%). For late toxicities, 4 (5%) patients had grade 3 toxicities (2 anastomotic strictures, 1 urethrorectal fistula, 1 small bowel adhesions). No patients had grade 4 late toxicities.

Discussion

This is the first paper to date to report the oncologic results of neoadjuvant chemoradiation for rectal cancer in a local

Table 3. Factors Affecting Local Recurrence and Survival by Univariate Analysis

Variable	Local Recurrence		Disease-free Survival		Overall Survival	
	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)
Raised CEA	0.628	1.72 (0.19 – 15.42)	0.978	0.99 (0.37 – 2.60)	0.647	0.74 (0.21 – 2.65)
Chemotherapy regimen	0.214	NA*	0.128	2.87 (0.74 – 11.14)	0.050	NA*
Margin positivity	0.080	4.76 (0.79 – 28.61)	0.012	3.36 (1.30 – 8.72)	<0.001	12.80 (3.54 – 46.32)
T-downstaging	0.076	NA*	0.054	0.34 (0.11 – 1.02)	0.012	NA*
Node positivity	0.302	2.56 (0.42 – 15.35)	0.476	1.37 (0.58 – 3.26)	0.710	1.27 (0.36 – 4.52)
Pathological complete response	0.369	NA*	0.564	0.65 (0.15 – 2.80)	0.219	NA*

CEA: Carcinoembryonic antigen; CI: Confidence interval; HR: hazard ratio; NA: Not applicable

*Hazard ratio is not applicable as there was no event in one category of the analysed variable.

Table 4. Acute Toxicities Associated with Neoadjuvant Chemoradiation*

	Grade n (%)				
	0	1	2	3	4
Nausea/vomiting	84 (99)	1 (1)	0 (0)	0 (0)	0 (0)
Diarrhoea	23 (27)	45 (53)	14 (16)	3 (4)	0 (0)
Cystitis	40 (47)	39 (46)	6 (7)	0 (0)	0 (0)
Dermatitis	20 (23)	38 (45)	24 (28)	3 (4)	0 (0)
Haematological	45 (53)	22 (26)	14 (16)	4 (5)	0 (0)

*Multiple toxicities in the same patient scored as separate events

population in Singapore. Following the conclusive results of the landmark German Rectal Cancer Trial, neoadjuvant chemoradiation for locally advanced rectal cancer has become increasingly accepted in our institution and today, it is the standard of care. This trend has been paralleled by a decrease in the number of patients who received upfront surgery and adjuvant chemoradiation.

The results from our study are consistent with internationally published data. The German Rectal Cancer Trial reported a 5-year local relapse rate of 6% in the preoperative arm and the 5-year overall survival rate was 76%. In that same arm, grade 3 or 4 toxicities occurred in 27% of patients. We treated patients with similar a regimen consisting of 50.4 Gy of radiation delivered in fractions of 1.8 Gy per day with concurrent 5-FU based chemotherapy. The median time from completion of chemoradiation to surgery in our study was 52 days, which was similar to the duration of 6 weeks in the German Rectal Cancer Trial. All patients underwent TME or WME surgery. Median follow-up was also similar. We report a comparable local recurrence rate of 7% and 5-year overall survival rate (83.2%) and lower rates of acute and long term grade 3 toxicities (9% and 5% respectively). The preoperative regimen was well tolerated and the compliance rate in our study was 99%.

The number of patients that had MRI staging was 47%. Before 2008, the majority of patients had staging with CT or EUS. The ability of MRI in staging rectal cancer is now well established.¹⁴ The use of MRI for staging is now the standard of care in our institution.

The favourable influence of tumour downstaging has been demonstrated in various studies.^{15,16} In our subgroup analysis, we found a statistically significant improvement in survival rates with T-downstaging. Nodal positivity on surgical specimens has been shown to be a significant predictor of long-term oncologic outcomes.¹⁷ However, we were not able to demonstrate this. This could be due to the small number of patients in our subgroup analysis to demonstrate an effect. We demonstrated that patients with positive margins had significantly worse disease-free survival and overall survival, with a trend towards higher rate of local recurrence. This is in line with results from various large studies which have shown the influence of circumferential resection margins as an independent determinant of local recurrence and survival.^{18,19} Although preoperative radiotherapy has been shown to reduce local recurrence, the benefit of radiotherapy has not been proven to be significantly greater in patients with positive circumferential margins.²⁰ This implies that radiotherapy does not make up for the poorer outcomes associated with having positive resection margins.

The pCR rate in our study was 13%. This was consistent with the results from Sauer et al.⁹ Although we did not

demonstrate better local control and survival in patients with pCR likely because of a small sample size, other studies have raised the prospect of cure from just chemoradiation alone and whether patients with pCR can be spared the surgical procedure.^{20,21} However, there is currently no conclusive evidence for eliminating surgery from the management of patients with pCR. The determination of complete clinical responders from clinical assessment is a complex issue and studies are needed to look at standardisation of clinical assessment of response. Future research will need to explore radiological or molecular markers to predict which group of patients is likely to be complete responders to neoadjuvant treatment.

Another area of research potential is on dose escalation in preoperative radiation to locally advanced rectal cancers. Some studies have demonstrated encouraging results in using a higher dose by employing intensity-modulated radiotherapy (IMRT) methods.^{22,23} There are ongoing trials addressing the issue of dose escalation and the results are awaited. Favourable results from these dose escalation trials will further improve local control of rectal cancers, the recurrence of which remains a difficult management issue for both physicians and patients.

The chemotherapy regimen used by the German Rectal Cancer Group was infusional 5-FU. Capecitabine has been shown to be equivalent to intravenous 5-FU in terms of local recurrence rates and was non-inferior to 5-FU for 5-year overall survival rates.²⁴ There was also less leucopenia with capecitabine. As capecitabine gained popularity on the background of evidence for its efficacy and safety profile, coupled with the relative ease of its administration, its use in our patients increased. In our study, 17 patients (20%) had intravenous 5-FU while 67 (79%) patients had oral capecitabine. Our subgroup analysis did not demonstrate any difference in outcomes between intravenous 5-FU and capecitabine use.

The German Rectal Cancer Trial highlighted the lack of effect on survival with neoadjuvant chemoradiation, highlighting the need for better systemic therapy. Five-FU based regimens given concurrent with radiotherapy is the current standard of care. The addition of oxaliplatin during radiotherapy did not show any benefit, nor did the addition of irinotecan.^{25,26} There are no phase III randomised studies demonstrating the efficacy of targeted agents. In the adjuvant setting, 5-FU-based regimens are widely used based on recommendations by the National Cancer Comprehensive Network (NCCN) guidelines, although the optimal adjuvant regimen is still yet to be determined.²⁷ With excellent local control rates using neoadjuvant chemoradiation, the search for better systemic therapy to address the issue of micrometastases and distant failure has become important and future research will have to focus on this.

Conclusion

In conclusion, our study confirmed that neoadjuvant chemoradiation with single agent chemotherapy with 5-FU or capecitabine is an effective treatment for locally advanced rectal cancer. A high rate of local control was shown with low rates of toxicities. The outcomes of our study are comparable to internationally published data. This study also shows the reproducibility of the results in a local population of Singapore, thus lending credence for its widespread adoption worldwide. For these reasons, we advocate and have adopted the neoadjuvant approach for the management of locally advanced rectal cancer.

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Association of Socioeconomic Status (SES) and Social Support with Depressive Symptoms among the Elderly in Singapore

Charis WL Ng, ¹MPH, Woan Shin Tan, ¹MSocSc (Economics), Pradeep PG Gunapal, ¹MSc (Epidemiology), Lai Yin Wong, ¹MTCM, Bee Hoon Heng, ¹MBBS, MSc (Public Health), FAMS

Abstract

Introduction: Depression in the elderly is a major public health issue. Socioeconomic status (SES) and social support are strong risk factors for depression. This study aimed to investigate the influence of SES and social support in elderly depression, and the modifying effect of social support on the relationship between SES and depression. **Materials and Methods:** A community-based survey was conducted on residents ≥ 60 years old. Depressive symptoms were determined with scores ≥ 5 using the 15-item Geriatric Depression Scale (GDS). Multivariable logistic regression was performed to determine the odds ratio (OR) of depressive symptoms with respect to SES and social support, and interaction terms between the two variables. **Results:** Of 2447 responses analysed, 188 (7.8%) respondents had depressive symptoms. Living in 2-room housing, living alone/with a domestic helper, infrequent leisure time with children/grandchildren or being childless, and feeling socially isolated were independently associated with depressive symptoms. Relative to residents living with spouse and children in 4-/5-room housing, the highest ORs for depressive symptoms were those living with spouse and children in 2-room (OR: 3.06, $P < 0.05$), followed by living with children only in 3-room (OR: 2.98, $P < 0.05$), and living alone/with a domestic helper in 4-/5-room (OR: 2.73, $P < 0.05$). Living with spouse only appears to buffer against depressive symptoms across socioeconomic classes, although the effect was not statistically significant. **Conclusion:** Low social support and low SES significantly increased the odds of depressive symptoms. The moderating effect of social support on depression was however not consistent across SES groups. Specific interventions need to target different SES groups to better help older adults at risk of developing depression.

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Key words: Asia, Depression, Older adults, Social factors

¹Health Services & Outcomes Research, National Healthcare Group, Singapore

Address for Correspondence: Charis Wei Ling Ng, Health Services & Outcomes Research, National Healthcare Group, 3 Fusionopolis Link, #03-08 Nexus@one-north (South Lobby), Singapore 138543.

Email: charis_wl_ng@nhg.com.sg

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Introduction

Depression in the elderly is a major public health issue. Associated morbidities such as higher risk of impairment in physical, mental and social functioning can be substantial,¹ with the most serious complication being suicide. In the elderly, depression can often be undiagnosed and untreated because it may be related to various factors commonly associated with aging, such as comorbid diseases, loss of independence and function, and bereavement.² In Singapore, population-based surveys have found that about 6% of community-dwelling older adults have depression, while 13% of them have depressive symptoms.^{3,4} Depression is also the second leading cause of disability.⁵

Depression in the elderly is often a function of many contributing factors, which include biological, psychosocial,

or environmental characteristics.^{6,7} Reflecting the impact of social structures on an individual's mental health, socioeconomic status (SES) has consistently been found to be associated with depression in elderly populations.⁶⁻⁹ The theoretical framework of Gallo and Matthews explains that low SES reduces individuals' capacity to manage stress, and thereby increase one's vulnerability to negative emotions and cognitions.¹⁰ Furthermore, as individuals age, the accumulated exposure to social stressors may result in a higher prevalence of depressive symptoms among those in the lower social strata.¹¹

Low social support is a strong risk factor for depression in older adults. Social support can be defined as "support accessible to an individual through social ties to other

¹Health Services & Outcomes Research, National Healthcare Group, Singapore

Address for Correspondence: Charis Wei Ling Ng, Health Services & Outcomes Research, National Healthcare Group, 3 Fusionopolis Link, #03-08 Nexus@one-north (South Lobby), Singapore 138543.

Email: charis_wl_ng@nhg.com.sg

individuals, groups, and the larger community”.¹² Some forms of social support related to depression in the elderly include living arrangements, contact time with relatives, and perceived social isolation. Research has often found that elderly living alone were more likely to be depressed than those living with family or others.¹³⁻¹⁵ Older adults who perceive themselves to be socially isolated also tend to rate their mental health poorly.¹⁶ Additionally, having infrequent contacts with relatives increased the risk for depressive symptomatology in older adults.¹⁷

The unequal distribution of social support across socioeconomic classes has been reported in many studies.¹⁸⁻²⁰ Individuals from the lower socioeconomic groups were found to have smaller social networks, and less organisational involvement.²¹ Therefore, the lack of social support reinforces the negative impact on mental health for individuals from lower socioeconomic groups. Social support may also moderate the impact of SES on health.^{22,23} The mediating effect of social support on the relationship between SES and depression has been examined in literature. A prospective longitudinal study of Finnish adolescents found low level of social support to have a greater impact on depression among lower SES individuals.²⁴ However, this relationship varied depending on the domain of social support, life stage and gender. Other studies reported minimal impact of social support on psychological health across socioeconomic groups.²⁵

Several studies in Singapore have examined the association of drug use, biological factors, and chronic diseases with depressive symptoms.^{3,26-30} Studies that focused on psychosocial risk factors examined the association of loneliness, living arrangements and social networks with depressive symptoms in elderly persons.^{13,31} In this study, we investigated SES differences in elderly depression and the influence of social support. As local evidence regarding the association between social relations and health across SES groups is unclear, we also studied the modifying effect of social support on the relationship between SES and depression.

Materials and Methods

Study Setting

Singapore has a multiethnic resident population of 3.8 million, of which 74% are Chinese, 13% Malay, 9% Indian, and 3% others. Presently, 14% of the population is aged 60 years and older.³² A majority of the elderly population (81%) reside in high-rise public housing units, with 86% living with their spouse or children.³³

Marine Parade Elderly Needs Survey 2011

The Marine Parade Elderly Needs Survey was conducted

in 2011 by the Marine Parade Grassroots Organisation, in collaboration with the Ministry of Community Development, Youth and Sports (MCYS), the Ministry of Health (MOH), the Ministry of National Development (MND), the Health Promotion Board (HPB), Agency for Integrated Care (AIC), and the Centre for Enabled Living (CEL). The objective of the survey was to facilitate a better understanding of the needs of community-dwelling elderly persons. Survey domains included in the questionnaire were developed using the major determinants of the Active Ageing policy framework documented by the World Health Organisation (WHO).³⁴ The questions in the survey were subjected to cognitive testing, and were translated and back-translated from English to Mandarin and Malay.

The population of community-dwelling adults aged 60 years and older living in 2- to 5-room public housing in the Marine Parade estate was stratified by 4 age groups (60 to 64, 65 to 74, 75 to 84, and 85+ years). The sample size was then computed based on the following criteria: (a) 0.5%, 1.0%, 3.0% and 4.5% margin of error for the 4 age groups respectively; (b) 2.0%, 5.0%, 10.0% and 25.0% impairment in at least one Activity of Daily Living (ADL) for the 4 age groups respectively.³⁵ Assuming a 60% response rate, a random sample of 4200 adults was drawn from the national database of dwellings from the Housing Development Board (HDB). Adults aged 60 to 64 and 85+ years were oversampled.

Residents were invited to participate in the study through mail. A team of trained interviewers administered the survey from April to May 2011 through face-to-face interviews with residents in their homes. Residents who refused to participate, and who were not contactable after 3 household visits were considered non-respondents. Proxy interviews were conducted with family members or caregivers for residents who were cognitively challenged or uncommunicative. These were excluded from the subsequent analysis as depressive symptoms, perception of the quality of familial relationships, and sense of social isolation, which required self-reporting, were not assessed through the proxy.

Outcome Variable: Depressive Symptoms

The presence of depressive symptoms was determined using the 15-item Geriatric Depression Scale (GDS-15). A widely used and reliable index, the GDS-15 has been validated locally^{36,37} and is the recommended tool to screen for depression among the elderly according to Singapore's clinical practice guidelines.³⁸ Each item in the scale allows for a dichotomous response (“yes/no”), and is scored depending on how the respondent felt over the past week. The scores range from 0 to 15, and scores ≥ 5 were suggestive of depression.³⁸

Measurement of Socioeconomic Status (SES)

We have measured SES by the respondent's education level (primary and lower, secondary and higher), and housing type (2-room, 3-room, 4-/5-room) (Appendix 1). In Singapore, housing type is positively correlated with household income and is often used as a surrogate of income status. The median monthly household income by type of dwelling was S\$1492 (US\$1147) for 2-room; S\$4169 (US\$3205) for 3-room; and S\$6133 to S\$8788 (US\$4715 to US\$6756) for 4-/5-room.³⁹ Self-reported monthly income was collected but excluded from the current analysis because data was missing for 20% of the sample.

Measurement of Social Support

Social support was measured using living arrangement, frequency of contact with family members, and the perception of being socially isolated (Appendix 1). Respondents were grouped into 5 mutually exclusive living arrangement categories: (a) living with spouse and children/grandchildren; (b) living with spouse only; (c) living with children/grandchildren only; (d) living alone (or with domestic helper), and (e) living with others (person other than spouse or child, e.g. relatives, friends, tenant, etc.). The frequency of spending leisure time with children/grandchildren was grouped according to: (a) at least once a month; (b) less than once a month; and (c) no children and grandchildren (childless). Respondents were also asked, "How often do you feel left out or isolated from others?" with their responses grouped as: (a) never or rarely, and (b) occasionally or often.

Confounding Variables: Chronic Diseases, Functional Status, Pain and Cognition

Besides age, gender and ethnicity, the analysis was adjusted for chronic diseases, functional status, pain and cognition. Chronic diseases included diabetes, high blood pressure, heart attack or failure, stroke, weak or failing kidneys. Functional status was determined as requiring assistance in 6 basic ADL (feeding, dressing and undressing, getting in and out of bed/chair, taking a shower, using the toilet, and mobility) and 7 instrumental ADL (using the telephone, getting to places that were not within walking distance, shopping for groceries/clothes, preparing meals, doing housework, taking medications, and handling money). Other functional disabilities included urinary incontinence, vision impairment, and hearing loss.

Pain was determined using the pain/discomfort dimension (moderate or extreme pain or discomfort) of the EQ-5D, which is a standardised measure of health status developed by the EuroQol Group.⁴⁰ Cognitive impairment was measured using the Abbreviated Mental Test (AMT), a 10-

item cognitive screening instrument that assesses memory, concentration and orientation.⁴¹ The Singapore version of the AMT⁴² was validated in an earlier study, and a score of ≤ 7 was found to optimally identify cognitive impairment.⁴³

Statistical Analysis

General descriptive analyses were performed to compare respondents with and without depressive symptoms. For all variables, 2-way tabulations calculating a Pearson chi-square statistic, corrected for complex survey design or stratified sample, were used. The adjusted odds ratio (OR) of having depressive symptoms with respect to SES and social support was determined using a multivariable logistic regression, adjusting for confounding variables. The modifying effect of social support on the relationship between SES and depression was studied by including interaction terms between SES and social support variables.

Sampling weights based on the total population of Marine Parade by age were used in all analyses to provide accurate estimates that could be generalised to the broader population in Marine Parade. The sampling weights accounted for the unequal probabilities of selection as a result of the planned oversampling of certain age groups.⁴⁴ The reported percentages of respondents given in the results section incorporated these sampling weights and thus reflect overall population estimates. However, the numbers given are the actual number of respondents to the survey, and are not the product of the percentages and the total population. All statistical analyses were performed using the Stata Statistical Software, version 12.0 (Stata Corp., College Station, Texas).

Approval for this study was obtained from the Institutional Review Board of the National Healthcare Group, Singapore.

Results

Sample Description

From the random sample of 4200 elderly residents from 58 blocks of dwellings in Marine Parade, a total of 3752 residents were eligible for inclusion in the study (210 moved out, 136 institutionalised, 58 died, 30 not contactable as houses were vacant, 14 non-Singapore citizens or permanent residents). Among these, 791 (21.1%) refused participation, 387 (10.3%) were not contactable after 3 household visits, and 16 (0.4%) were unable to participate due to various reasons such as language barriers. A total of 2558 residents were interviewed, giving an overall response rate of 68.2%. Of these, only 2447 respondents were included in the analysis after excluding proxies.

Sociodemographic Characteristics

A total of 188 respondents (7.8%) reported depressive symptoms (GDS scores ≥ 5). Table 1 summarises the characteristics of respondents. Compared to respondents without depressive symptoms, a greater proportion of those with depressive symptoms were respondents with primary and lower education (63.3%), living in 2-room housing (33.0%), living alone (22.9%), who spent less than once a month leisure time with their children/grandchildren (22.3%) or who were childless (23.4%), and who occasionally or often felt socially isolated (29.8%). Additionally, a higher proportion of those with depressive symptoms were aged 85 and above (9.6%), of Malay (17.0%) and Indian ethnicity (6.4%), have diabetes (36.7%), high blood pressure (63.3%), heart attack or failure (12.8%), stroke (12.2%), weak or failing kidneys (7.4%), required assistance in 3 or more basic (12.2%) and instrumental ADL (27.7%), have urinary incontinence (23.4%), vision impairment (18.6%), hearing loss (22.3%), pain or discomfort (49.5%), and cognitive impairment (22.3%).

Effects of SES and Social Support on Depressive Symptoms

Table 2 shows the multivariable logistic regression analysis of the effects of SES and social support on depressive symptoms in the elderly. The odds of depression for residents living in lower income housing (2-room) was 3-times that of those living in 4-/5-room housing. Strong social support as indicated by frequent leisure time spent with children/grandchildren (Adj OR: 0.74, 95% CI, 0.31 to 1.77) were found to have a protective effect against depression, although the results did not reach statistical significance (Table 2). In terms of living arrangements, residents who lived alone or with a domestic helper had 1.7 times higher odds of reporting depressive symptoms than those who lived with their spouses and children/grandchildren (Adj OR: 2.73, 95% CI, 1.31 to 5.69, $P = 0.007$). Furthermore, the elderly who occasionally or often felt socially isolated were 7 times as likely to have depressive symptoms as those who never or rarely felt so (Adj OR: 7.12, 95% CI, 4.87 to 10.40, $P < 0.001$).

Modifying Effect of Social Support on Relationship between SES and Depression

Table 3 presents the adjusted OR of the interaction between social support measured by living arrangement and SES measured by housing type. Reflecting the highest extent of social support and SES, residents living with their spouse and children/grandchildren in 4-/5-room housing defined the reference group. In comparison, elderly residents living in 2-room housing with the same extended family structure had the highest odds of depression (Adj OR: 3.06, 95% CI,

1.52 to 6.16, $P < 0.05$). Individuals living with their children only in 3-room housing (Adj OR: 2.98, 95% CI, 1.10 to 8.11, $P < 0.05$), and those living alone or with a domestic helper in 4-/5-room housing (Adj OR: 2.73, 95% CI, 1.31 to 5.69, $P < 0.05$) also exhibited higher odds of depression.

Conversely, elderly residents living with others (relatives, friends and tenant) in 2-room housing were 70% less likely to have depressive symptoms than those living in 4-/5-room housing with spouse and children/grandchildren (Adj OR: 0.29, 95% CI, 0.09 to 0.93, $P < 0.05$). Living with spouse only appears to buffer against depressive symptoms across socioeconomic classes, although the effect was not statistically significant.

Discussion

The overall prevalence of depressive symptoms in our study sample of elderly aged 60 years and older was 7.8%, which was consistent with previous population-based surveys in Singapore that found 5.5% to 13.3% of community-dwelling older adults to have depression and depressive symptoms.^{3,4}

This study examined the association of SES and social support with depressive symptoms, and the modifying effect of social support on SES and depression among the elderly in Singapore. The results suggested that elderly residents who were of lower SES were more likely to have depressive symptoms. A similar finding was seen among residents who received lesser social support. Additional results indicated that the effect of SES on depressive symptoms varied by living arrangements within the household.

SES and Depression

Using education and housing type as measures of SES, we found that education was not strongly associated with depressive symptoms as other studies have found.^{8,17,45} Housing type was found to be a stronger factor in this study, which is unique to Singapore as housing type is often used as a surrogate of income status and is positively correlated with household income. The elderly living in smaller housing (lower income) were more likely to report depressive symptoms. This finding corroborates with studies that revealed positive associations between poor economic conditions or financial strain with depression among elderly persons in Hong Kong⁴⁶ and Taiwan.⁴⁷ Further, it has been suggested that lower income may be related to poor access to health and mental health services, which can influence the diagnosis and treatment of depression, as patients are unlikely to have their health care needs attended to on a regular basis, and are even more unlikely to be screened for depressive disorders.⁶ Although Singapore has a health service system that provides patients with easy

Table 1. Characteristics of Respondents with and without Depressive Symptoms

	GDS-15				
	n (2447)	With Depressive Symptoms (n = 188)		Without Depressive Symptoms (n = 2259)	
		No.	%	No.	%
Socioeconomic Status					
Highest education level					
Secondary and higher	1295	69	36.7%	1226	54.3%
Primary and lower	1152	119	63.3%	1033	45.7%
Housing type					
4-/5-room	1226	65	34.6%	1161	51.4%
3-room	829	61	32.4%	768	34.0%
2-room	392	62	33.0%	330	14.6%
Social Support					
Living arrangement					
Spouse with child(ren)/grandchild(ren)	847	38	20.2%	809	35.8%
Spouse only	683	46	24.5%	637	28.2%
Child(ren)/grandchild(ren) only	396	40	21.3%	356	15.8%
Alone or with domestic helper	304	43	22.9%	261	11.6%
Others (relatives, friends, tenant)	217	21	11.1%	196	8.6%
Frequency of leisure time spent					
At least once a month	1744	102	54.3%	1642	72.7%
Less than once a month	333	42	22.3%	291	12.9%
Childless	370	44	23.4%	326	14.4%
Social isolation					
Never or rarely	2317	132	70.2%	2185	96.7%
Occasionally or often	130	56	29.8%	74	3.3%
Covariates					
Age					
85+	113	18	9.6%	95	4.2%
75 – 84	341	18	9.6%	323	14.3%
65 – 74	1184	92	48.9%	1092	48.3%
60 – 64	809	60	31.9%	749	33.2%
Gender					
Female	1399	112	59.6%	1287	57.0%
Male	1048	76	40.4%	972	43.0%
Ethnic group					
Chinese	1934	135	71.8%	1799	79.6%
Indian	114	12	6.4%	102	4.5%
Malay	300	32	17.0%	268	11.9%
Others	99	9	4.8%	90	4.0%
Diabetes					
No	1887	119	63.3%	1768	78.3%
Yes	560	69	36.7%	491	21.7%
High blood pressure					
No	1048	69	36.7%	979	43.3%
Yes	1399	119	63.3%	1280	56.7%
Heart attack/failure					
No	2285	164	87.2%	2121	93.9%
Yes	162	24	12.8%	138	6.1%

GDS-15: 15-item Geriatric Depression Scale; BADL: Basic activities of daily living; IADL: Instrumental activities of daily living

Table 1. Characteristics of Respondents with and without Depressive Symptoms (Con't)

	GDS-15				
	n (2447)	With Depressive Symptoms (n = 188)		Without Depressive Symptoms (n = 2259)	
		No.	%	No.	%
Stroke					
No	2365	165	87.8%	2200	97.4%
Yes	82	23	12.2%	59	2.6%
Weak/failing kidneys					
No	2386	174	92.6%	2212	97.9%
Yes	61	14	7.4%	47	2.1%
Assistance in no. of BADL					
≤ 2	2409	165	87.8%	2244	99.3%
3+	38	23	12.2%	15	0.7%
Assistance in no. of IADL					
≤ 2	2291	136	72.3%	2155	95.4%
3+	156	52	27.7%	104	4.6%
Urinary incontinence					
No	2139	144	76.6%	1995	88.3%
Yes	308	44	23.4%	264	11.7%
Vision impairment					
No	2271	153	81.4%	2118	93.8%
Yes	176	35	18.6%	141	6.2%
Hearing loss					
No	2135	146	77.7%	1989	88.0%
Yes	312	42	22.3%	270	12.0%
Pain/discomfort					
None	1941	95	50.5%	1846	81.7%
Moderate & extreme	506	93	49.5%	413	18.3%
Cognitive impairment					
Ok	2261	146	77.7%	2115	93.6%
Suggestive	186	42	22.3%	144	6.4%

GDS-15: 15-item Geriatric Depression Scale; BADL: Basic activities of daily living; IADL: Instrumental activities of daily living

Table 2. Multivariable Analysis of the Effects of Socioeconomic Status and Social Support on Depressive Symptoms in the Elderly

	Adjusted Odds Ratio†	95% CI	P Value
Socioeconomic Status			
Highest education level			
Secondary and higher*	1.00		
Primary and lower	1.29	0.94 – 1.77	0.112
Housing type			
4-/5-room*	1.00		
3-room	1.10	0.61 – 1.98	0.755
2-room	3.06	1.52 – 6.16	0.002
Social Support			
Living arrangement			
Spouse with child(ren)/grandchild(ren)*	1.00		
Spouse only	1.05	0.57 – 1.93	0.879
Child(ren)/grandchild(ren) only	0.74	0.31 – 1.77	0.494
Alone or with domestic helper	2.73	1.31 – 5.69	0.007
Others (relatives, friends, tenant)	1.82	0.78 – 4.24	0.166
Frequency of leisure time spent			
At least once a month*	1.00		
Less than once a month	1.51	1.04 – 2.19	0.028
Childless	1.73	1.14 – 2.60	0.009
Social isolation			
Never or rarely*	1.00		
Occasionally or often	7.12	4.87 – 10.40	<0.001

*Reference group

†Adjusted for age, gender, ethnic group, diabetes, high blood pressure, heart attack/failure, stroke, weak/failing kidneys, assistance in no. of basic activities of daily living (BADL), assistance in no. of instrumental activities of daily living (IADL), urinary incontinence, vision impairment, hearing loss, pain/discomfort, and cognitive impairment

Table 3. Adjusted Odds Ratio† (95% CI) of Interactions between Social Support and Socioeconomic Status

		Social Support				
Socioeconomic status		Alone or with Domestic Helper	Others (Relatives, Friends and Tenant)	Child(ren)/Grandchild(ren) Only	Spouse Only	Spouse and Child(ren)/Grandchild(ren)
	2-room	0.47 (0.18 – 1.25)	0.29* (0.09 – 0.93)	0.93 (0.28 – 3.16)	1.06 (0.42 – 2.68)	3.06* (1.52 – 6.16)
	3-room	0.54 (0.21 – 1.37)	0.39 (0.11 – 1.34)	2.98* (1.10 – 8.11)	1.00 (0.42 – 2.39)	1.10 (0.61 – 1.98)
	4-/5-room	2.73* (1.31 – 5.69)	1.82 (0.78 – 4.24)	0.74 (0.31 – 1.77)	1.05 (0.57 – 1.93)	1.00 (ref)

*P < 0.05

†Adjusted for age, gender, ethnic group, diabetes, high blood pressure, heart attack/failure, stroke, weak/failing kidneys, assistance in no. of basic activities of daily living (BADL), assistance in no. of instrumental activities of daily living (IADL), urinary incontinence, vision impairment, hearing loss, pain/discomfort, and cognitive impairment

access to affordable primary care or subsidised specialist care for mental health services, it was found that elderly Singaporeans who reported financial resource limitations for medical care were less likely to use mental health service.⁴⁸

Social Support and Depression

Poor social support (living alone or with domestic helper, infrequent leisure time with children/grandchildren or being childless, and feeling socially isolated occasionally and often) was another factor that was found to be associated with depressive symptoms.

Living arrangements affect the amount of social support that elderly residents receive from their family, and living alone is often an indication of low access to social support.^{13,14,31} Like other Asian societies, Singapore values family unity where co-residence of older parents and children are highly encouraged. Currently, about 67.0% of elderly individuals live with their children.³³ As such, living alone could have a negative effect on the psychological well-being of the elderly, as supported by evidence that older adults living alone had significantly higher depressive symptoms.^{13,31}

A study on the relationship between social support and depressive symptoms among Chinese elderly in Hong Kong also found that social support from family members was more important than support from friends.⁴⁹ The frequency of quality time spent with children/grandchildren is a reflection of the relationship and the amount of social and emotional support that elderly residents have with and receive from their family members. Given the high proportion of elderly in Singapore living with their children/grandchildren, frequency of quality time spent is expected to be high due to the daily contact. However, even for those who were not living with their children/grandchildren, intergenerational ties remained strong with 90.8% of older residents receiving visits or visiting their married children at least once a month to have meals, exchange suggestions and advice about personal problems, and going on outings.⁵⁰ It was therefore not surprising that older adults who spent infrequent leisure time (less than once a month) with their children/grandchildren were more likely to have depressive symptoms, and that this effect was even more pronounced in childless older adults. Adult children are important sources of social and financial support to parents. In Singapore, 62.8% of elderly residents depend on their children's allowances as their main source of financial support.³³ For older adults without children, work is often the first source of income, which suggests that childless older persons have to continue work in old age.⁵¹ Hence, childlessness can be a predisposing factor for elderly depression.⁹

Perceived social isolation is the subjective experience of

the absence of social support in an individual's life.⁵² For older adults who are more likely to need social support in their later years due to bereavement and increasing health problems, social isolation can be particularly detrimental.⁵³ In a study that investigated the extent of social isolation among Chinese Singaporeans aged 65 years and older, 63.0% of the respondents were forced to live alone because they outlived their family networks, never had children, or were estranged from their children.⁵⁴ In a society that champions family ties and filial eldercare, this physical isolation makes elderly living alone more susceptible to social isolation. The isolation is also further exacerbated by Singapore's swift modernisation, leaving many older adults feeling disconnected from their social milieu. The elderly in Singapore tend to use colloquial terms for certain places unknown to majority of Singaporeans, which can make communicating with people on the street an awkward and embarrassing experience. The lack of education further alienates the elderly from middle-aged and younger generations, and with little ability or finances for contemporary lifestyles, the elderly can become increasingly isolated.⁵⁴ Older adults who experience social isolation have been found to be at greater risk of depression.^{31,55}

Social Support Moderates Relationship between SES and Depression

While our study examined the main effect of SES on depressive symptoms, further results suggested that the association was modified by living arrangements within the household. We observed that among elderly residents living in 4-/5-room housing (high SES), those who were living alone or with a domestic helper (low social support) had higher (OR) for depressive symptoms compared to those who were living with their spouse and children/grandchildren. However, the results were reversed for persons living in 2-room housing. Stronger social support indicated by larger family size was associated with higher odds of depression. Our results point out that social support had a non-linear moderating effect on the relationship between SES and depression.

This phenomenon may reflect the differential impact of income and social support on mental health across SES groups. Diener and Biswas-Diener suggested that the impact of increased income in improving subjective well-being is limited only to the point where basic material needs are satisfied.⁵⁶ After which, income becomes less important to mental health. Additionally, for low-income families who may be facing financial strain, literature has found that family social support may do little to moderate the impact on depression.⁵⁷

Limitations

This study is not without limitations. Firstly, the findings were derived from cross-sectional data, and therefore unable to determine causality. Secondly, the use of GDS scores ≥ 5 only identified respondents who were indicative of depression, which did not equate to a clinical diagnosis of depression. Thirdly, the measures of SES were restricted to using educational level and housing type as a proxy for income, as a substantial proportion of self-reported monthly income was missing. Social support was also derived from non-standardised questions on living arrangements, frequency of time spent with children/grandchildren, and perceived social isolation, which may not adequately reflect the actual and perceived family support that respondents received. Lastly, the study lacked information on the marital status and lifestyle habits (alcohol consumption and smoking) of respondents, which may influence the magnitude and direction of the observed associations. However, the study also has strengths in that the sample size was large, and the response rate of 68.2% was considerably higher than the usual response rate for surveys conducted among older adults.

Conclusion

Our results showed that low social support and low SES significantly increased the odds of depressive symptoms. The moderating effect of social support as measured by living arrangements, on depression was however not consistent across the SES groups. Depression interventions for the elderly in Singapore should take a holistic approach to attend to the financial and social needs of older adults.^{6,17} In addition, specific interventions need to target different SES groups to better help older adults who may be at risk of developing depression. In the design of preventive programmes, it is important to pay special focus on social support resources for individuals in higher SES groups since living alone or with domestic helper was a significant risk factor. However, for low SES groups, the availability of social support in the form of an extended family was not a protective factor. Strategies to improve the financial situation of these households may need to be considered.

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Appendix 1

Questions on Socioeconomic Status (SES) and Social Support

Q1. Highest Education Level Attained		
a) No formal qualifications		1 ☐
b) Primary (PSLE)		2 ☐
c) Secondary ('O'/'N' levels)		3 ☐
d) Junior college ('A' levels)		4 ☐
e) Diploma/other professional qualification		5 ☐
f) Degree and higher		6 ☐
Q2. Housing Type	Current residence	Other property (if any)
a) 1-/2-room flat	1 ☐	1 ☐
b) 3-room flat	2 ☐	2 ☐
c) 4-room flat	3 ☐	3 ☐
d) 5-room flat	4 ☐	4 ☐
e) Others: _____	5 ☐	5 ☐
Q3. Do you live alone?		
a) Yes		1 ☐
b) No		2 ☐
Q4. Currently staying with:		
a) Spouse		1 ☐
b) Children/grandchildren		2 ☐
c) Relatives		3 ☐
d) Friends		4 ☐
e) Tenant		5 ☐
f) Maid		6 ☐
g) Others: _____		7 ☐

Q5. Please think of the grandchild(ren)/child(ren) you see most often, regardless of whether they are staying with you, and tell us how often do you interact (talking, having meals, doing recreational activities) with them?	Have meals together	Spend leisure time together (eg. chat, outings, recreational activities, others)
a) Everyday b) 4 to 6 times a week c) 2 to 3 times a week d) Once a week e) 2 to 3 times a month f) Once a month g) <Once a month h) NA (no child(ren) <u>AND</u> grandchild(ren))	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 99 ☐	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 99 ☐
Q6. How often do you feel left out/isolated from others?		
a) Never b) Rarely c) Occasionally d) Often		1 ☐ 2 ☐ 3 ☐ 4 ☐

Overcoming Barriers to Mammography Screening: A Quasi-randomised Pragmatic Trial in a Community-based Primary Care Setting

Theresa Seetoh, ¹BSocSci (Hons), MSc, Wei Fong Siew, ²MBBS, MMed FM, DIP (Family Practice Dermatology), Alvin Koh, ³MBBS, MPH, Wei Fong Liau, ²RN, BN, MN, Gerald CH Koh, ¹MBBS, MMed FM, PhD, Jeannette JM Lee, ¹MBBS, MD, Mee Lian Wong, ¹MBBS, MPH, MD, Adeline Seow, ¹

MBBS, MMed (Public Health), MD

Abstract

Introduction: Breast cancer is the leading cancer among women in Singapore. Five years after a population-wide breast cancer screening programme was introduced, screening rates remained relatively low at 41%. Studies have shown decreased screening propensity among medically underserved women typically of minority or socioeconomically disadvantaged status. We conducted a quasi-randomised pragmatic trial aimed at encouraging mammography screening among underscreened or unscreened women in a publicly funded primary care facility in Singapore. **Materials and Methods:** The study was conducted from May to August 2010. Components of intervention included (1) tailored education, (2) doctor's reminder, and (3) cost reduction. Researchers administered a structured questionnaire to eligible female polyclinic attendees and patient companions aged 40 to 69 years. Individual knowledge, attitudes, beliefs, and barriers towards mammography screening were identified and educational messages tailored. Doctor's reminder and cost reduction were implemented additively. **Results:** Overall, out of 448 participants, 87 (19.4%, 95% confidence interval (CI), 15.8% to 23.1%) completed mammography screening across 3 arms of study. Participants who received a cost reduction were more likely to attend screening compared to participants in other intervention arms (adjusted odds ratio (OR) 2.4, 95% CI, 1.2 to 4.5, $P = 0.009$). Cost of screening, ethnicity, prior screening history, and attitudes towards mammography screening were identified as significant factors predicting mammogram attendance. **Conclusion:** Including a cost reduction component was the most effective intervention that increased mammography screening rates. Women's underlying beliefs, attitudes, and other predisposing factors should also be considered for integration into existing breast cancer screening programmes.

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Key words: Asia, Breast cancer, Community health services, Patient navigation, Singapore

¹Saw Swee Hock School of Public Health, National University of Singapore, Singapore

²National Healthcare Group Polyclinics, Singapore

³Primary Care Development Division, Agency for Integrated Care, Singapore

Address for Correspondence: A/Prof Adeline Seow, Saw Swee Hock School of Public Health, National University of Singapore, MD3, 16 Medical Drive Singapore 117597.

Email: adeline_seow@nus.edu.sg

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Introduction

Breast cancer is the leading cancer among women in Singapore, accounting for 29% of all cancers occurring in women between 2006 and 2010.¹ Evidence shows that breast cancer screening with mammography is effective at reducing breast cancer mortality, particularly where the uptake of screening is high, at a recommended 70%,^{2,3} with good quality control.⁴

The first large-scale study of the use of mammography in Asian women was the Singapore Breast Screening Project,⁵ conducted in 1994. The study demonstrated the usefulness of a population-level screening programme in the

detection and treatment of early-stage breast cancer. This was followed by the launch of a nationwide, population-based breast cancer screening programme, BreastScreen Singapore, in 2002. The programme offered mammography screening at a government-subsidised rate, and was open to Singapore female residents and permanent residents, aged 40 to 69 years. Through a series of public awareness campaigns, mammography screening was widely promoted as an accepted modality for early detection of breast cancer.

Five years after the programme was introduced, the estimated rate of women who participate in mammography screening at recommended intervals remained relatively

¹Saw Swee Hock School of Public Health, National University of Singapore, Singapore

²National Healthcare Group Polyclinics, Singapore

³Primary Care Development Division, Agency for Integrated Care, Singapore

Address for Correspondence: A/Prof Adeline Seow, Saw Swee Hock School of Public Health, National University of Singapore, MD3, 16 Medical Drive Singapore 117597.

Email: adeline_seow@nus.edu.sg

low at 41%.⁶ Five-year mortality for breast cancer in Singapore is also relatively poor, at an observed survival rate of 64%.⁷ In countries such as the United States, patient navigation has been shown to improve the accessibility of breast cancer screening programmes, particularly for underserved populations, by helping women identify barriers to timely diagnosis as well as guide them through the completion of a healthcare service.^{8–13} Other measures such as health education,¹⁴ reminders,^{15,16} responding in a culturally-sensitive manner¹⁷ and setting up collaboration between academic and medical centres,¹¹ have also reported improved screening uptake.

Our goal was to test if a practical and sustainable intervention could be introduced and integrated at the primary care level to overcome barriers and improve screening rates in Singapore. The suite of interventions included (1) tailored education delivered by a patient navigator, (2) doctor's reminder, and (3) cost reduction.

Materials and Methods

The pilot study was designed as a quasi-randomised pragmatic trial conducted in a public service primary care facility (Clementi Polyclinic) in Singapore from May to August 2010. Enrolment was by successive presentation at the polyclinic. A formal protocol was established with structured training provided to interviewers fluent in English, Mandarin, and Malay, who simulated the role of a patient navigator. A circular was also disseminated to inform doctors of the pilot study. This provided a structure within which communication by patient navigators and doctors could be adapted to individual patient's needs. Ethical approval was obtained prior to the commencement of the study.

The study was conducted over 2 consecutive weeks, comprising 3 intervention phases: a baseline of tailored education over a period of 2 days, a doctor's reminder, and cost reduction added progressively over 2 periods of 4 days each. A structured questionnaire was administered to female attendees between the ages of 40 to 69 years and their companions to identify individual knowledge, attitudes, beliefs, and barriers towards mammography screening (Table 1). Respondents due and eligible for mammography screening under BreastScreen Singapore were recruited as study participants and written informed consent was obtained. In the first intervention of the study, patient navigators delivered tailored education messages based on individually-expressed concerns and misconceptions on mammography screening, gleaned from study participants' responses on the questionnaire and communicated in a language they can comfortably understand. During the second intervention of the study, doctors reinforced the rationale and importance of early detection through mammography screening, in addition

Table 1. Components of the Scales Used to Measure Knowledge, Attitudes, Beliefs and Barriers among Study Population in a Primary Care Facility in Singapore (May to August 2010)

Factor	Question or Statement Posed*
Knowledge	- Do you know that you can have a mammogram done at Clementi Polyclinic? (Yes/No) - I know at what age I should start going for a mammogram. - I know how regularly I should go for a mammogram.
Attitudes	- I am fearful of the potential pain involved in mammogram screening. - I would rather not know if I have breast cancer.
Beliefs	- Mammograms are safe for the early detection of breast cancer. - Mammograms are effective for early detection of breast cancer. - I am at risk of getting breast cancer as my age increases. - I do not need a mammogram if I do not display any breast symptoms (such as lumps, nipple discharge, and/or pain). - A mammogram is not necessary for a woman with no family history of breast cancer.
Barriers	- A mammogram is too costly for me. - I can find time for a mammogram if I wish to go for one.

*Except for the first question, all responses were on the 5-point Likert scale (strongly agree, agree, unsure, disagree, strongly disagree)

to participants receiving the tailored education message. A supplemental cost reduction measure in the form of a discount voucher was introduced as the third intervention.

Upon presentation of the discount voucher valid only at the mammogram facility sited on the premises of the same primary care clinic, participants were eligible for a mammography screening discount of S\$25. This was equivalent to a 50% reduction of the cost of a mammogram for Singapore citizens and a 33% reduction for permanent residents. To prevent unauthorised duplication or transfer of the voucher, each voucher bore an individualised serial number and was linked to the identification number of the participant carrying the voucher. The outcome measured was the number of participants who completed mammograms in the 12 weeks following the study. Mammography screening records belonging to the mammography facility were checked to identify participants who had successfully completed a mammogram by referencing their identification number, and this was verified via an anonymised matching link with BreastScreen Singapore.

Sample Size Calculations

Based on results of a pre-pilot study (unpublished data), we estimated that the baseline uptake of mammography would

be 8% in the study population. To detect a 2-fold increase in attendance to 16% in each of the other 2 intervention phases, a sample size of about 147 would be required in each intervention arm to achieve 80% power at a 5% level of significance (2-sided).

Data Analysis

Analysis was done on an intention-to-treat basis to evaluate the effectiveness of the suite of interventions under practical experience. The data was analysed using SPSS (version 17, IBM Corporation) software. The main exposure of interest was the intervention rendered, and the primary outcome was completion of a mammography screening within 12 weeks of intervention. Demographic and other predictors of screening were also analysed in relation to primary outcome.

To ensure comparability between intervention arms, the distribution of baseline characteristics were compared and differences were tested using Pearson chi-square test. Components of the health belief model used to measure knowledge, attitudes, beliefs and barriers were scored using the 5-point Likert scale, with 0 score for “unsure”, and positive and negative scoring on either side of the scale depending on the question asked. For instance, for the question, “A mammogram is too costly for me”, a respondent who answered “strongly agree” was accorded negative 2 score, “agree” was accorded negative 1 score, “unsure” was accorded 0 score, while “disagree” and “strongly disagree” were respectively accorded 1 and 2 score. The decision to categorise each component into high/low subgroups was made using the mean score within each factor as cut-off point.

Mantel-Haenszel crude odds ratio (OR) was obtained for each binary variable against outcome, while logistic regression was performed for ordinal variables against outcome to give stratum-specific crude OR. Potential confounders were explored by cross-tabulating other exposure variables against the main exposure of interest as well as cross-tabulating against outcome. Variables resulting in a considerable change of 10% of the adjusted OR compared to the crude OR were considered confounders and were included in the final model. Multivariable analysis was performed using logistic regression to obtain an adjusted measure of effect, with results at $P < 0.05$ taken as significant. Effect of intervention on screening uptake was stratified by sociodemographic characteristics to test for effect modification.

Results

The team approached a total of 788 women over the study period. Two-thirds (523 or 66.4%) were due for screening

while a third (257 or 32.6%) had been screened within the last 2 years. Of those due for screening, 448 (85.7%) consented to the study and were recruited as participants. The remaining declined study participation. Overall, 87 (19.4%, 95% CI, 15.8% to 23.1%) out of 448 participants completed mammography screening across 3 arms of the study. Attendance varied significantly with intervention received.

Majority (180 or 40.2%) of the 448 women recruited were in the 50 to 59 age group, while 125 (27.9%) and 143 (31.9%) women were in the 40 to 49 and 60 to 69 age groups respectively (Table 2). The Chinese (301 or 67.2%) was the majority ethnic group, followed by the Malays (105 or 23.4%) and the Indians/Others (42 or 9.4%). Most women (221 or 49.3%) stayed in public housing with 4 to 5 rooms, consistent with the residential distribution served by the polyclinic. More than half (259 or 57.8%) received at least a secondary education or above and 181 (40.5%) were in employment. The remaining were either unemployed (216 or 48.3%) or retired (50 or 11.2%). The group which received the tailored education-doctor’s reminder-cost reduction intervention had a higher proportion of Chinese ($P = 0.005$) and women who were more well educated ($P = 0.021$) and lived in private residence ($P = 0.026$). Other baseline characteristics did not differ across intervention groups.

Mammogram attendance across 3 intervention arms at completion of study was 15.1% (95% CI, 8.3% to 21.9%) from the tailored education arm, 9.9% (95% CI, 6.0% to 15.3%) from the tailored education-doctor’s reminder arm, and 32.9% (95% CI, 25.7% to 40.2%) from the tailored education-doctor’s reminder-cost reduction arm (Fig. 1). Adjusted analysis of the association between the type of intervention received and screening uptake showed that study participants from the tailored education-doctor’s reminder-cost reduction arm were 2.4 (95% CI, 1.2 to 4.5, $P = 0.009$) times more likely to complete a mammography screening compared to participants from the tailored education arm, whereas those from the tailored education-doctor’s reminder arm were not more likely to complete a screening compared to those from the tailored education arm (Table 3).

Adjusted analysis also showed that Chinese participants were 2.0 (95% CI, 1.0 to 4.1, $P = 0.063$) times more likely to attend screening compared to Malay participants (Table 3). Women who had ever been screened were 2.1 (95% CI, 1.1 to 3.9, $P = 0.021$) times more likely to complete screening compared to women who had never been screened. Stratification of the effect of intervention on screening uptake by sociodemographic characteristics showed women in the tailored education-doctor’s reminder-cost reduction arm who lived in public housing of 1 to 3 rooms were 3.0

Table 2. Demographic Characteristics of Study Participants at a Primary Care Facility in Singapore (May to August 2010), by Intervention Group

Variable		Tailored Education	Tailored Education with Doctor's Reminder	Tailored Education, Doctor's Reminder and Cost Reduction	All Participants
		n = 106 (%)	n = 181 (%)	n = 161 (%)	n = 448 (%)
Age group	40 – 49 years	31 (29.2)	44 (24.4)	50 (31.1)	125 (27.9)
	50 – 59 years	40 (37.7)	79 (43.6)	61 (37.9)	180 (40.2)
	60 – 69 years	35 (33.1)	58 (32.0)	50 (31.0)	143 (31.9)
Ethnicity	Chinese	52 (58.5)	116 (64.1)	123 (76.4)	301 (67.2)
	Malay	31 (29.2)	48 (26.5)	26 (16.1)	105 (23.4)
	Indian/others	13 (12.3)	17 (9.4)	12 (7.5)	42 (9.4)
Dwelling type	Public housing 1-/3-room flat	49 (46.2)	73 (40.3)	54 (33.5)	176 (39.3)
	Public housing 4-/5-room flat	50 (47.2)	90 (49.7)	81 (50.3)	221 (49.3)
	Private apartment or house	7 (6.6)	18 (10.0)	26 (16.2)	51 (11.4)
Education*	No formal	12 (11.3)	19 (10.5)	7 (4.3)	38 (8.5)
	Primary	36 (34.0)	62 (34.3)	53 (32.9)	151 (33.7)
	Secondary	45 (42.4)	72 (39.7)	64 (39.8)	181 (40.4)
	Tertiary	13 (12.3)	28 (15.5)	37 (23.0)	78 (17.4)
Employment status	Employed	45 (42.5)	67 (37.2)	69 (42.9)	181 (40.5)
	Not employed	51 (48.1)	94 (52.2)	71 (44.1)	216 (48.3)
	Retired	10 (9.4)	19 (10.6)	21 (13.0)	50 (11.2)
Screening history	Never been screened	35 (33.0)	72 (39.8)	46 (28.6)	153 (34.2)
	Ever been screened	71 (67.0)	109 (60.2)	115 (71.4)	295 (65.8)
Knowledge score	Low	43 (40.7)	75 (41.4)	68 (42.2)	186 (41.6)
	High	63 (59.3)	106 (58.6)	93 (57.8)	262 (58.4)
Attitude score	Low	69 (64.8)	99 (54.7)	84 (52.2)	252 (56.2)
	High	37 (35.2)	82 (45.3)	77 (47.8)	196 (43.8)
Belief score	Low	25 (24.1)	72 (39.8)	54 (33.5)	151 (33.8)
	High	81 (75.9)	109 (60.2)	107 (66.5)	297 (66.2)
Barriers score	Low	47 (44.4)	86 (48.0)	92 (57.1)	225 (50.4)
	High	59 (55.6)	93 (52.0)	69 (42.9)	221 (49.6)

*Highest education attained. Primary consists 6 years of education, secondary consists 10 to 11 years of education, and tertiary consists 12 or more years of education

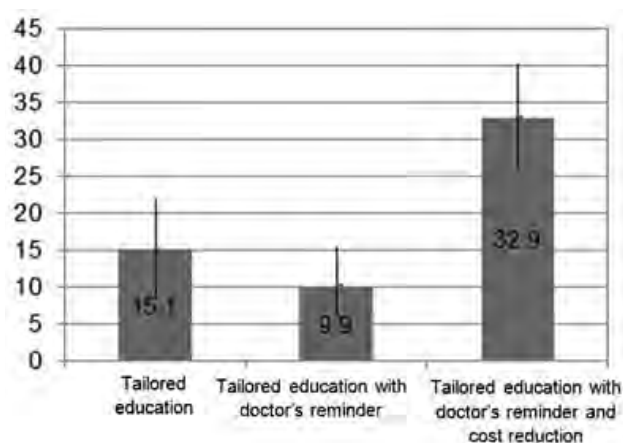


Fig 1. Mammogram attendance (%) at an urban primary care facility in Singapore (May to August 2010) across 3 intervention arms at completion of study (vertical bars indicate 95% confidence intervals).

Table 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Mammogram Attendance in a Primary Care Facility in Singapore (May to August 2010) In Relation to Demographic and Other Predictors of Screening

		Crude OR (95% CI)	Adjusted* OR (95% CI)	P Value
Age	Per year increase	0.99 (0.96 – 1.03)	0.98 (0.95 – 1.02)	0.261
Ethnicity	Malay	1.0 (ref)	1.0 (ref)	-
	Chinese	2.7 (1.4 – 5.4)	2.0 (1.0 – 4.1)	0.063
	Indian/others	1.5 (0.5 – 4.3)	1.2 (0.4 – 3.6)	0.759
Dwelling type	Public housing 1-/3-room flat	1.0	1.0	-
	Public housing 4-/5-room flat	1.2 (0.7 – 1.9)	1.0 (0.6 – 1.8)	0.954
	Private apartment/house	1.7 (0.8 – 3.6)	1.0 (0.5 – 2.3)	0.956
Education†	No formal	1.0		
	Primary	1.1 (0.4 – 2.9)		
	Secondary	1.4 (0.6 – 3.7)		
	Tertiary	1.5 (0.5 – 4.2)		
Screening history	Never been screened	1.0	1.0	-
	Ever been screened	2.5 (1.4 – 4.4)	2.1 (1.1 – 3.9)	0.021
Knowledge score	Low	1.0		
	High	1.3 (0.8 – 2.1)		
Attitude score	Low	1.0	1.0	-
	High	1.7 (1.1 – 2.8)	1.6 (1.0 – 2.7)	0.053
Beliefs score	Low	1.0		
	High	1.0 (0.6 – 1.7)		
Barrier score	Low	1.0		
	High	0.9 (0.6 – 1.5)		
Intervention group	Tailored education	1.0	1.0	-
	Tailored education with doctor's reminder	0.6 (0.3 – 1.3)	0.6 (0.3 – 1.3)	0.212
	Tailored education with doctor's reminder and cost reduction	2.8 (1.5 – 5.3)	2.4 (1.2 – 4.5)	0.009

*Adjusted for age, ethnicity, dwelling type, prior screening and attitude towards screening. Further adjustment for education level did not affect the estimates. Knowledge, beliefs, and barrier score were not entered into model because $P > 0.05$.

†Highest education attained. Primary consists 6 years of education, secondary consists 10 to 11 years of education, and tertiary consists 12 or more years of education.

(95% CI, 1.1 to 8.4) times more likely to attend screening compared to women in the tailored education arm who shared a similar dwelling type (Table 4). The effect of tailored education-doctor's reminder-cost reduction was only significant amongst women with at least a secondary education (adjusted OR 3.2, 95% CI, 1.3 to 7.5) and not among those with few years of education (adjusted OR 1.7, 95% CI, 0.6 to 4.7).

Discussion

Cost reduction, as part of an intervention package, increased mammographic screening rates in this study population. This appeared to have a greater effect among

women from a lower socioeconomic background,^{18,19} but notably also varied with education level. Consistent with other findings, while cost may be an important factor deterring screening,^{17,20} educational measures are also needed to address non-financial factors that may influence health-seeking behaviour.²¹

Chinese women were more likely than Indian and Malay women to attend screening. Given the observed discrepancy in uptake rates, culturally-relevant interventions are needed to bridge the persistent ethnic gap.^{22,23} Women who have had a previous screening were more likely to return. Prior experience was likely to have helped develop trust and acceptability, thus encouraging further utilisation of

Table 4. Effect of Intervention on Screening Uptake in a Primary Care Facility in Singapore (May to August 2010), By Sociodemographic Characteristics

Adjusted Odds Ratio (95% CI)		
Dwelling type	Public housing 1-/3-room flat (n = 176)	Public housing 4-/5-room flat and private property (n = 272)
Tailored education	1.0	1.0
Tailored education with doctor's reminder	0.5 (0.1 – 1.7)	0.8 (0.3 – 2.0)
Tailored education, doctor's reminder and cost reduction	3.0 (1.1 – 8.4)	2.3 (1.0 – 5.3)
Education	Below secondary (n = 189)	Secondary and above (n = 259)
Tailored education	1.0	1.0
Tailored education with doctor's reminder	0.5 (0.1 – 1.5)	0.9 (0.3 – 2.3)
Tailored education, doctor's reminder and cost reduction	1.7 (0.6 – 4.7)	3.2 (1.3 – 7.5)

services.²⁴ These women could also have been comparatively more proactive and aware of the tools of cancer prevention and early detection, and were therefore more responsive.

Non-attendees might be inhibited by a range of reasons. The lack of time, and “not having thought about it” were reasons previously cited.^{25,26} The rationality of these responses may however obscure the underlying fatalistic attitude or fear of pain associated with the reluctance to screen, and the lack of acceptability of mammography as a screening modality.²¹ The use of a personalised approach in this study aimed to address this specific challenge, particularly among women with low attitude and belief scores.

This study was designed as a quasi-randomised pragmatic trial. Experimental blinding was thus not implemented. Analysis was done on an intention-to-treat basis, and the risk of treatment effect dilution was small despite 2 instances of cross-over.

Doctors' reminders were not consistently delivered because participants did not always present their cues upon consultation. Whilst cost reduction appeared to result in a pronounced effect and could reasonably be hypothesised as singularly achieving an effect in the absence of a doctor's reminder, possible reasons for the blunted effectiveness of the doctor's reminder intervention, as compared to other studies,^{27,28} may be the lack of time, or lack of standardisation, as reminders were not scripted. Future studies could address these factors, as observational studies suggest that the role of the doctor in promoting screening could be a positive one. The current study did not attempt to assess the effect of all possible predictors of screening, but focused on those most relevant to the intervention.

Participants screened beyond the study period were not captured. Although a standardised protocol was followed, patient navigators could have unconsciously varied

their behaviour towards different individuals, leading to experimenter bias. Misclassification and recall bias could not be excluded as self-reported information was not verified. Interventions were designed as a package and isolated effects were not analysed. Nonetheless, the study, which was designed to model care under routine settings, benefits from a higher external validity.

Conclusion

The demonstrated effectiveness of the overall intervention strengthens the proposition for a longer-term, community-based cancer prevention and outreach initiative that includes patient navigation and cost reduction components. There is a need for larger, more generalisable studies to validate these results across multiple study sites. This would require building on collaborations with the network of polyclinics and diagnostics services, integrating patient navigation into existing workflow and record-keeping. Interface with the national screening programme, BreastScreen Singapore, would assist in the detection of under- and un-screened cases and the generation of cues for staff and clinicians at the primary care facility. Financing subsidy for mammograms for low income and medically underserved women would also be needed, as well as coordination with clinicians and the training of patient navigators.

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Physiologically-guided Balanced Resuscitation: An Evidence-based Approach for Acute Fluid Management in Paediatric Major Trauma

Jade PH Kua, ¹*MBBS, MRCS (A&E) Edin, FAMS*, Gene YK Ong, ¹*MBBS, MRCPCH (UK)*, Kee Chong Ng, ¹*MBBS, MMed (Paeds)*

Abstract

Trauma is a major cause of death, and haemorrhage represents an important target for improving outcomes after severe injury. Volume replacement with crystalloids in resuscitation might become harmful in large amounts because of coagulopathy. A fine balance must be achieved between haemodynamic and haemostatic resuscitation. Permissive hypotension refers to permitting some degree of hypotension in such adult patients in an attempt to attain this fine balance. For patients who require a significant volume of blood product resuscitation, the term ‘massive transfusion protocol’ (MTP) is used. There is very little data on transfusion protocols for paediatric trauma patients, and children respond to hypovolemic shock in a different physiological manner compared to adults. Hence, concepts such as permissive hypotension may not be appropriate when treating children involved in major trauma. We recently embarked on a plan to streamline the management of blood transfusion in massive bleeding during paediatric trauma, to reduce the logistical problems associated with the transport of blood products from the blood bank to the patient. From this, we evolved a MTP for paediatric major trauma. Nonetheless, further studies will be needed to see if there is indeed improved outcome after MTP in paediatric major trauma as current evidence is extrapolated from adult studies.

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Key words: Compensated versus decompensated shock, Damage control resuscitation, Massive transfusion protocol, Permissive tachycardia

¹Department of Emergency Medicine, KK Women's & Children's Hospital, Singapore

Address for Correspondence: Dr Phek Hui Jade Kua, Department of Emergency Medicine, KK Women and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: jade.kua.ph@kkh.com.sg

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Jade PH Kua,¹ MBBS, MRCS (A&E) Edin, FAMS, Gene YK Ong,¹ MBBS, MRCPCH (UK), Kee Chong Ng,¹ MBBS, MMed (Paeds)

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Trauma is a major cause of death, and haemorrhage represents an important target for improving outcomes after severe injury. Volume replacement with crystalloids in resuscitation might become harmful in large amounts because of coagulopathy. A fine balance must be achieved between haemodynamic and haemostatic resuscitation. Permissive hypotension refers to permitting some degree of hypotension in such adult patients in an attempt to attain this fine balance. For patients who require a significant volume of blood product resuscitation, the term ‘massive transfusion protocol’ (MTP) is used. There is very little data on transfusion protocols for paediatric trauma patients, and children respond to hypovolemic shock in a different physiological manner compared to adults. Hence, concepts such as permissive hypotension may not be appropriate when treating children involved in major trauma. We recently embarked on a plan to streamline the management of blood transfusion in massive bleeding during paediatric trauma, to reduce the logistical problems associated with the transport of blood products from the blood bank to the patient. From this, we evolved a MTP for paediatric major trauma. Nonetheless, further studies will be needed to see if there is indeed improved outcome after MTP in paediatric major trauma as current evidence is extrapolated from adult studies.

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Introduction

The Burden of Major Trauma and Recent Advances

Trauma is a major cause of death and disability worldwide.^{1,2,3} Since haemorrhage is responsible for more than 40% of all trauma deaths, it is an important target for improving outcomes after severe injury.⁴ With paucity of research in paediatric major trauma, one would be tempted to simply cut and paste existing adult protocols for use in paediatric trauma. However, the management of traumatic haemorrhagic shock in adults and children cannot be the same.

In adults, it is widely recognised that volume replacement in haemorrhagic shock resuscitation might become harmful if a large volume of crystalloids is used in exsanguinating major trauma patients with continuing blood loss. While the volume may be “adequate”, the tonicity and components of the volume infused will be important as large crystalloid

volumes will result in dilutional effects and a whole series of unintended sequelae, including coagulopathy. Therefore, in major trauma, a fine balance must be achieved between haemodynamic/volume and adequate haemostatic resuscitation. When a certain threshold of blood loss is reached, fluid resuscitation consisting of crystalloid administration must be supplemented with the transfusion of blood products, sometimes in large amounts and in preset ratios (massive transfusion).⁵

Massive transfusion has its origins in adult major trauma management⁶ where blood component therapy (packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets and cryoprecipitates of clotting factors) is common.

Our paediatric emergency department (ED) at KK Women’s and Children’s Hospital (KKH) sees about 178,000 patients a year. According to the KKH Trauma Registry, from 2011 to 2012, we saw a total of 51,001 trauma patients,

¹Department of Emergency Medicine, KK Women’s & Children’s Hospital, Singapore

Address for Correspondence: Dr Phek Hui Jade Kua, Department of Emergency Medicine, KK Women and Children’s Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: jade.kua.ph@kkh.com.sg

of whom 28 were Tier 1 (Injury Severity Score (ISS) equal to or more than 16), 101 were Tier 2 (ISS between 9 and 15, inclusive) and the rest were Tier 3.

In major paediatric trauma, coagulopathy is prevalent. In fact, in paediatric trauma patients who are ill enough to require transfusion, there is a strong association with mortality.⁷ Massive transfusion protocol (MTP) is recommended to improve outcomes in such ill patients.⁸ Further studies need to be conducted to ascertain if paediatric patients have good outcomes after MTP. Currently the benefits of MTP are largely extrapolated from adult studies.

Key Concept in Adult Major Trauma: The Problem of Coagulopathy

Much has been written about the lethal triad⁹ in trauma: coagulopathy, acidosis and hypothermia. It is estimated that 10% of severe trauma cases are hypocoagulable with the most severely injured being more coagulopathic.⁹ This coagulopathy presents very early after injury.¹⁰ Therefore, coagulopathy is not merely due to excessive crystalloid infusion where at a cellular level, Ringer's lactate and normal saline increase reperfusion injury and leukocyte adhesion.^{11,12}

Coagulopathy in trauma is multifactorial.¹³ Firstly, in haemorrhage where there is volume/haemodynamic resuscitation, dilution and hypothermia cause dilutional coagulopathy and further haemorrhage. In addition, haemorrhage itself causes a stream of effects including shock, acidosis and hypothermia that worsen coagulopathy. To compound the problem, trauma and shock cause acute coagulopathy of trauma-shock which is associated with factor consumption and fibrinolysis. Finally, coagulopathy has also been found to be associated with trauma-induced inflammation.¹³

Finding the Balance: Haemostatic Resuscitation in Adults

During shock resuscitation, clots are potentially unstable if the pressure is elevated to a level that is considered normal. A high blood pressure, while allowing better perfusion to the tissues, might contribute to further bleeds and hypocoagulopathy. Therefore, a certain degree of hypotension might be helpful during haemorrhagic shock resuscitation—what is termed “permissive hypotension”—to allow clots to stabilise and prevent clot dislodgement and coagulopathy. A “balanced resuscitation” approach is taken—which incorporates the important concept of haemostatic resuscitation as opposed to the conventional absolute volume and haemodynamic pressor resuscitation alone.

Exceptions to the use of “permissive hypotension” in major adult trauma are when patients have severe head

injuries or are in spinal shock. In such cases, allowing low blood pressure will highly predispose the patient to insufficient cerebral perfusion pressure and hypoxia, and secondary brain injury/damage. Hence, permissive hypotension is not advocated for major adult trauma where there is severe head injury or spinal shock.

It has been shown in various adult studies where patients with severe head injuries are excluded, that a systolic blood pressure (SBP) greater than 80 to 90 or mean arterial pressure (MAP) greater than 60 is associated with a higher risk of rebleeding, with 76% rebleed at pressures greater than 80 mmHg. One centre that has endorsed permissive hypotension in adult polytrauma is the National Institute for Health and Clinical Excellence which advises against fluid administration in patients without head injury if a radial pulse is palpable.¹⁴ However, in the management of polytrauma patients with significant head injuries, as the importance of maintaining cerebral perfusion pressure is well recognised, permissive hypotension is contraindicated.¹⁵

MTP and Damage Control Resuscitation in Adults

Adult MTP originated in the military and has been extrapolated to civilian clinical studies. These data along with recommendations of an international consensus conference on early massive transfusion for trauma,¹¹ make it possible to rapidly identify and treat patients at high risk for coagulopathy on arrival to the resuscitation room. Damage control resuscitation (DCR) is a structured intervention that begins in the ED where targets include normalising the coagulopathy, acidosis and hypothermia, until damage control surgery achieves haemostasis, and is described by Holcomb in this way: Resuscitation is limited to keep systolic blood pressure at 90 mmHg, which prevents rebleeding from recently clotted vessels.^{11,12} Intravascular volume restoration is accomplished with thawed plasma in at least a 1:1 ratio with PRBCs.^{16,17} For casualties who are anticipated to require continued resuscitation, the blood bank is notified to activate the MTP which results in the delivery of 6 units of plasma, 6 units of PRBCs, 6 packs of platelets and 10 units of cryoprecipitate stored in individual coolers.¹⁷ Of note, in the adult military population, for the most severely injured, fresh warm whole blood is used as a primary resuscitative fluid.^{18,19} Crystalloids are only used to keep lines open between blood products.²⁰

The outcome of DCR in adults is positive based on the 10-year institutional experience with DCR described by Frischknecht et al. Patients were categorised as early survivors or early deaths. During the study period, 319 patients underwent DCR. Overall, 52 patients (16.3%) died (early deaths) and 267 patients (83.7%) survived the first 72 hours (early survivors). In the latter group, survival in severely injured trauma patients managed with

DCR exceeded 90%.⁸ Further randomised control trials are required to prove significant survival advantage.

Coagulation in Paediatric Patients

Coagulopathy in paediatric patients is a significant problem, just as it is in adults. Holmes et al reviewed the medical records of all patients younger than 15 years old who were hospitalised at a level 1 trauma centre for either blunt head or torso trauma over a 4-year period. A total of 1082 patients' records were reviewed, and the 830 (77%) patients with coagulation studies obtained composed of the study population. Elevated coagulation studies were detected in 232 (28%) patients, and 49 (6%) of these were found to be markedly elevated. In the multivariate analysis, a Glasgow Coma Scale (GCS) ≤ 13 (odds ratio [OR]: 8.7, 95% confidence interval [CI], 4.3, 17.7), low systolic blood pressure (OR: 4.0, 95% CI, 1.6, 9.9), open/multiple bony fractures (OR: 2.9, 95% CI, 1.4, 6.2), and major tissue wounds (OR: 2.8, 95% CI, 1.4, 5.6) were independently associated with markedly elevated coagulation studies. Their conclusion was that hospitalised paediatric blunt trauma patients frequently have minor elevations in ED coagulation studies. Marked elevations are independently associated with a GCS ≤ 13 , low systolic blood pressure, open/multiple bony fractures, and major tissue wounds.²¹

Hendrickson et al looked at paediatric trauma patients requiring blood transfusion within 24 hours of arrival. Coagulation values on ED arrival, clinical details and outcome were analysed. A total of 102 children (mean age, 6 years; mean injury severity score 22, mean Glasgow Coma Scale 7, 80% blunt trauma victims) were studied over a 4-year period. An abnormal prothrombin time was found in 72% of the children, partial thromboplastin time in 38%, fibrinogen in 52%, haemoglobin in 58%, and platelet count in 23%. An abnormal prothrombin time, partial thromboplastin time, and platelet count were strongly associated with mortality ($P = 0.005$, 0.001 , and <0.0001 , respectively) and remained significantly associated in multivariate analysis after adjusting for injury severity score. The team concluded that coagulopathy was prevalent in paediatric trauma patients ill enough to require a transfusion and is strongly associated with mortality.⁷

These 2 studies have shown that children with major trauma do experience significant coagulopathy, as do adults.

Physiologically-guided Resuscitation: Adults versus Children

Based on these studies and evolving established principles for the adult polytrauma, can these principles be adopted in the acute management of paediatric polytrauma patients? The key issue is whether children respond to shock, hypoxia

and hypovolaemia in the same way that adults do.

In adults, the first sign of shock is a narrow pulse pressure because of decreased venous return, decreased cardiac output and increased peripheral resistance from neural and hormonal response. Shock usually results in concomitant rise in heart rate and drop in blood pressure.

When monitoring a child's cardiovascular system, we closely monitor the age-adjusted heart rate of the child and the estimated/expected systolic blood pressure which is calculated as $70 + 2 \times (\text{age in years})$, as well as the general clinical condition of the child, rather than just the pulse pressure. In children during compensated shock there is a period of tachycardia without a concomitant drop in blood pressure. With sustained shock, blood pressure eventually drops precipitously as illustrated in Figure 1. In early "compensated" shock, vital organ function is maintained by intrinsic compensatory mechanisms, such as vasoconstriction and peripheral vasoconstriction. Blood pressure is usually maintained, heart rate is increased, pulse pressure is narrowed and signs of peripheral vasoconstriction (cold extremities and prolonged capillary filling time) are present. In decompensated shock, despite intense arteriolar constriction and tachycardia, blood pressure and cardiac output decline. Patients may demonstrate an impairment of major organ perfusion which may manifest as altered mentation, oliguria and myocardial ischaemia. Prolonged shock is characterised by progressive reduction in blood pressure and cardiac output leading to prolonged hypoperfusion of the brain, heart and kidneys which leads to ischaemic cell death. Clinically, this manifests as progressive worsening of coma, renal failure, pulmonary oedema and multi-organ failure.

Therefore, trying to "permit" hypotension in paediatric polytrauma is illogical. By the time the child has documented age-adjusted hypotension, the child is already at death's door. In major paediatric trauma, in the absence of severe

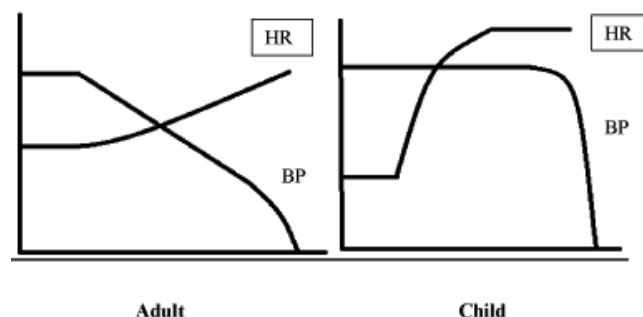


Fig. 1. Adult's versus child's physiological response to shock.*

*Adapted from The Advanced Resuscitation for Children course by the Singapore Paediatric Society

head injury and spinal shock, we can promote a more physiological state by allowing the heart rate to be raised (permissive tachycardia) while the blood pressure is maintained in the normal range (isotension). The optimal range of increased heart rate needs to be determined by prospective randomised controlled study of the treatment outcomes.

The Need For A Paediatric-centred MTP

In adult literature, 3 definitions of MTP are commonly used:²² Transfusion of 10 or more units of red blood cells (RBC) within 24 hours, transfusion of 4 or more units of RBC within 1 hour with anticipation of continued need, and replacement by transfusion of 50% total blood volume (TBV) in 3 hours.

There are several reasons why we cannot apply these definitions for adult MTP indiscriminately to paediatric MTP. Firstly, the TBV, along with volume loss and volume replacement, in neonates and children vary considerably according to age.²³ Hence, any definition of MTP in paediatric patients must be relative to the TBV of each individual patient, or at least likely weight groups. Diab YA et al²⁴ suggested that paediatric MTP may be defined as transfusion of >50% TBV in 3 hours, transfusion of >100% TBV in 24 hours, or transfusion to replace ongoing blood loss of >10% TBV per minute.

Studies in adult trauma have consistently shown that trauma-associated coagulopathy is common and associated with adverse outcomes.^{10,25-27} Likewise, coagulopathy in paediatric trauma patients is prevalent and strongly associated with mortality. These associations have been observed in paediatric trauma patients suffering from blunt or penetrating injuries, with or without head involvement. When it comes to predicting mortality in paediatric trauma patients, the BIG score which incorporates coagulation data (BIG score: base deficit + [2.5 x international normalised ratio] + [15 – Glasgow Coma Scale score]) may be a more accurate scoring system.^{7,21,28-31}

Despite an increasing realisation of the prevalence of paediatric trauma and the importance of coagulopathy, the implementation of MTP for paediatric patients has lagged behind that of adults.^{32,33} This may be due to the different mechanisms of injuries in children compared to adults (with less penetrating trauma and exsanguination) as well as difficulties in adapting a universal protocol for children of all ages and weights.

Finally and more importantly, the child responds in a very different manner to hypovolaemia as compared to the adult. While hypotension is a relatively late sign in adults compared to the narrow pulse pressure and tachycardia, children have such resilient cardiovascular reserves that frank hypotension

indicates a point of physiological derangement when severe morbidity is likely despite resuscitation. Therefore, in paediatric MTP, as more extensively explained above, one should consider permissive tachycardia rather than the adult MTP concept of permissive hypotension.

International Experience with Paediatric MTP

There have been 2 significant single-centre studies that describe their experience with MTP in paediatric patients. Hendrickson et al conducted a retrospective study on 53 children after implementing paediatric MTP that utilised FFP and red blood cells in a 1:1 ratio of FFP:RBC and alternating weight-adjusted amounts of aphaeresis platelets or cryoprecipitate units. These data were then compared with data from historical controls. Although there was no improvement in outcome with MTP, there were 2 important conclusions that arose: (1) majority of patients had coagulopathy at presentation; and (2) implementation of paediatric MTP with increased FFP:RBC ratios and early plasma transfusion to coagulopathic children is feasible.³²

Chidester et al conducted a prospective cohort study of 55 children, of whom 22 received transfusions according to their MTP and 33 received transfusions at physician's discretion. Although there was no improvement in mortality with MTP, there was 1 interesting finding: thromboembolic events were observed exclusively in the non-MTP group, possibly related to under-transfusion in these patients.³⁴

In both studies, there was a delay in transfusing plasma due to additional time required for thawing, so neither study was able to reach the protocol's goal for 1:1 ratio for FFP/RBC transfusions.

Local Experience: Setting up MTP in KKH

Members of our paediatric trauma committee as well as other important stakeholders undertook an extensive literature review and used an evidence-based approach to develop our own in-house paediatric MTP protocol (see Appendices 1 and 2).

Massive transfusion is defined in our hospital as transfusion of >40 mL/kg (blood volume in children over the age of 1 month is approximately 80 mL/kg). Indications for the use of MTP include: (1) primary cause of shock is haemorrhagic shock from uncontrolled bleeding; or (2) the child who has been given more than 40 mL/kg of non-blood products or more than 20 mL/kg of blood products. This is given for haemodynamic stabilisation and the aim is to limit crystalloid resuscitation with use of blood products for haemodynamic resuscitation. The rate of blood products to be given will be determined acutely by the haemodynamic status of the paediatric patient. Having MTP protocols would allow blood products in the appropriate 1PCT:1FFP:1platelet ratio to

be continuously made available as required during trauma resuscitation and limit waiting time usually required for ad hoc requests for such blood products. The MTP activation process is summarised in Appendix 1.

Concurrently, the lethal triad of hypothermia, coagulopathy and acidosis must be avoided and corrected with close monitoring upon activation of MTP.

Other Interventions for Coagulopathy in Trauma

Early Intervention with Tranexamic Acid

As time is of the essence in managing haemorrhagic shock, early intervention is key. One such intervention that could potentially be started in the prehospital setting is tranexamic acid (TXA). TXA minimises blood loss by inhibiting lysine binding sites on plasminogen, thereby preventing the conversion of plasminogen to plasmin. This inhibits fibrinolysis and reduces clot breakdown, resulting in a reduction in bleeding,³⁵ and has been used to minimise blood loss associated with surgery.

The CRASH-2 randomised controlled trial was the first extensive multicentre trial to evaluate the use of TXA in civilian trauma care.^{36,37} CRASH-2 studied the early administration of TXA in adult trauma patients in 274 hospitals in 40 countries. Patients ($n = 20,211$) were enrolled if the treating physician judged them to have or be at risk for significant haemorrhage and were randomised to either TXA or placebo. Within 8 hours of injury, participants received a 1 g intravenous (IV) loading dose of either TXA or placebo over 10 minutes; a 1 g infusion over 8 hours followed. Patients and study staff were blinded to the treatment groups. The primary outcome was overall mortality in the 4 weeks after injury. Secondary outcomes included vascular occlusive events, major surgical intervention, quantity of blood transfusion (if any), and cause of death (bleeding, vascular occlusion, multi-organ failure, head injury, or other cause).

TXA reduced all-cause mortality in the first month after trauma (relative risk [RR] = 0.91; 95% confidence interval [CI], 0.85 to 0.97; $P = .0035$; number needed to treat [NNT] = 68). There were 3076 deaths from all causes in both groups, 35% of which were the result of bleeding. Among patients who received TXA, the overall risk of death due to bleeding was 4.9%, vs 5.4% in the placebo group (RR = 0.85; 95% CI, 0.76 to 0.96; $P = 0.0077$; NNT = 119). For those treated with TXA within the first hour of injury, the risk of death due to bleeding was 5.3%, vs 7.7% for the placebo group (RR = 0.68; 95% CI, 0.57 to 0.82; $P < 0.0001$; NNT = 41). Giving TXA between one and 3 hours of injury also reduced the risk of death due to bleeding, to 4.8%, vs 6.1% for the placebo group (RR = 0.79; 95% CI, 0.64 to

0.97; $P = 0.03$; NNT = 77).

However, TXA administered more than 3 hours after injury, appeared to increase the risk of death due to bleeding, to 4.4% compared with 3.1% for the placebo group (RR = 1.44; 95% CI, 1.12 to 1.84; $P = 0.004$; number needed to harm = 77). Therefore, the earlier it is given after injury, the better the outcome.

TXA is easy to store and does not require refrigeration or reconstitution prior to administration. TXA has been included in both the United States and British army trauma protocols. In addition, TXA is used by National Health Service ambulances in the United Kingdom, and given to all adults and teenagers who incur major traumatic injury.³⁸ Given the short time window for its benefit, TXA may be most appropriate in the prehospital setting.

At present, there is no published data on TXA in paediatric major trauma. Prior use of TXA in paediatrics include the field of scoliosis³⁹ and cardiac surgery.^{40,41} The Royal College of Paediatrics and Child Health working group recommendations recognise that the adverse effects of TXA are rare and there are no thromboembolic effects noted from other uses.

Use of Recombinant Factor VIIa in Severe Bleeding in Major Trauma and MTP

Traditionally, recombinant activated factor VII has been successfully used in the management of bleeding paediatric patients with haemophilia and high anticoagulation factor antibodies titres. However, there were increasing off-label reports of its use for bleeding post major surgeries and in major trauma. Recent high quality systematic reviews of the use of recombinant factor VIIa for the treatment of bleeding in adult patients without haemophilia had not shown to offer any significant therapeutic advantage.^{42,43} Observational studies for its routine use during MTP protocols had also not shown any significant long-term survival benefits.⁴⁴⁻⁴⁶

Specifically for the paediatric population, a review of its use in the management of bleeding in the paediatric population without haemophilia showed that the lowest rates of complete response were seen in younger patients and patients with trauma. Reported decreased in the requirement of blood product transfusion after the use of factor VIIa (recombinant) versus standard therapies or placebo was commonly observed but was not statistically significant in many cases.⁴⁷

Given the lack of well-designed controlled studies and cost-effectiveness of its use, the current evidence is inconclusive regarding the safety and efficacy of factor VIIa (recombinant) for unlabeled indications in paediatric patients with severe trauma and during MTP.

Thromboelastometry and Goal-Directed Therapy in Haemostatic Resuscitation

Thromboelastometry® (TEM®, previously named rotational thromb-elasto-metry/-graphy) is an established viscoelastic method for haemostatic testing in whole blood. TEM® essentially analyses the viscoelastic properties of clot formation and the established point-of-care (POC) equipment currently in the market are ROTEM® and Thromboelastography® (TEG®).⁴⁸⁻⁵⁵

TEM® investigates the interaction of coagulation factors, their inhibitors, anticoagulant drugs, blood cells, specifically platelets, during clotting and subsequent fibrinolysis. The rheological conditions mimic the sluggish flow of blood in veins. TEM® can be performed with the ROTEM® or TEG® whole blood analysers and is an enhancement of thrombelastography, originally described by Hartert in 1948.⁵⁶

Rapid POC is to manage coagulopathy in major trauma and calibrate correction of coagulopathy in major trauma, and it is a much faster way to anticipate coagulopathy not just in polytrauma, but in ECMO and major surgery as well. TEM® also can sensitively identify patients with postinjury hypercoagulability. However, the use of TEM® to compare the degree of hypercoagulability and fibrinolysis after different types of trauma has not been described.⁵⁷

As in the standard prothrombin time/activated partial thromboplastin time (PT/APTT) standards, adjustments and calibrations must be made for the paediatric community. Oswald et al⁵⁸ from Austria analysed 407 children (American Society of Anaesthesiology Classification, ASA I and II) undergoing elective surgery in a prospective, 2-centre, observational study. Subjects were grouped into 0 to 3, 4 to 12, 13 to 24 months, 2 to 5, 6 to 10, and 11 to 16 years. Study objectives were to establish age-dependent reference ranges for ROTEM® assays, analyse age dependence of parameters, and compare ROTEM® data with standard coagulation tests.

Data from 359 subjects remained for final analysis. Except for extrinsically activated clot strength and lysis, parameters for ROTEM® assays were significantly different among all age groups. The most striking finding was that subjects aged 0 to 3 months exhibited accelerated initiation and propagation of coagulation.

We should therefore move towards adopting TEM® for acute use in managing coagulopathy in paediatric polytrauma so that in addition to MTP for paediatrics, we can institute a more goal-directed management plan in correcting and managing coagulopathy.

Conclusion

In conclusion, the management of haemorrhagic shock in major trauma for children needs to be refined. In major trauma, there must be a focus not just on volume/haemodynamic resuscitation but also haemostatic resuscitation to address coagulopathies rather than volume alone.

For volume replacement, blood should be used when the threshold is reached. While there is a role of permissive hypotension in adult polytrauma sans severe head injury/spinal shock—there is no role for this for paediatric major trauma. One should instead consider permissive tachycardia with a normal blood pressure measurement in such cases without severe head injury/spinal shock as children do not respond in the same physiological manner as in adults during shock.

One should also move towards more defined and refined goal-directed approaches to correcting the coagulopathies in polytrauma through use of POC tests like ROTEM® or TEM®. Finally, robust studies in the paediatric population need to be done to ascertain the use and timing of prohemostatic agents like recombinant factor VIIa.

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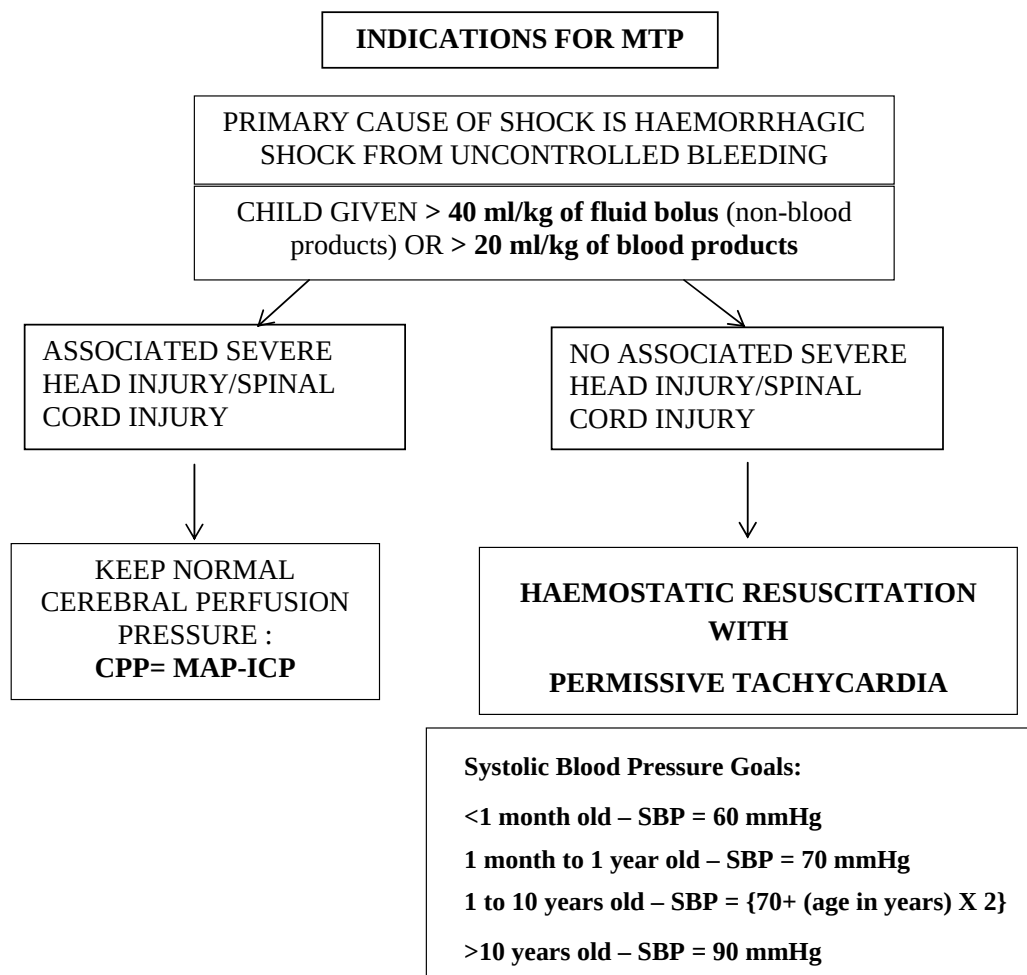
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Appendix 1

KK Women's and Children's Hospital's MTP for Paediatrics

Massive transfusion is defined* in adults as replacement of >1 blood volume in 24 hours or >50% of blood volume in 4 hours (adult blood volume is approximately 70 mL/kg). In children, it is defined as transfusion of >40 mL/kg (blood volume in children over 1 month old is approximately 80 mL/kg).

*As defined by the Australian Red Cross Blood Service

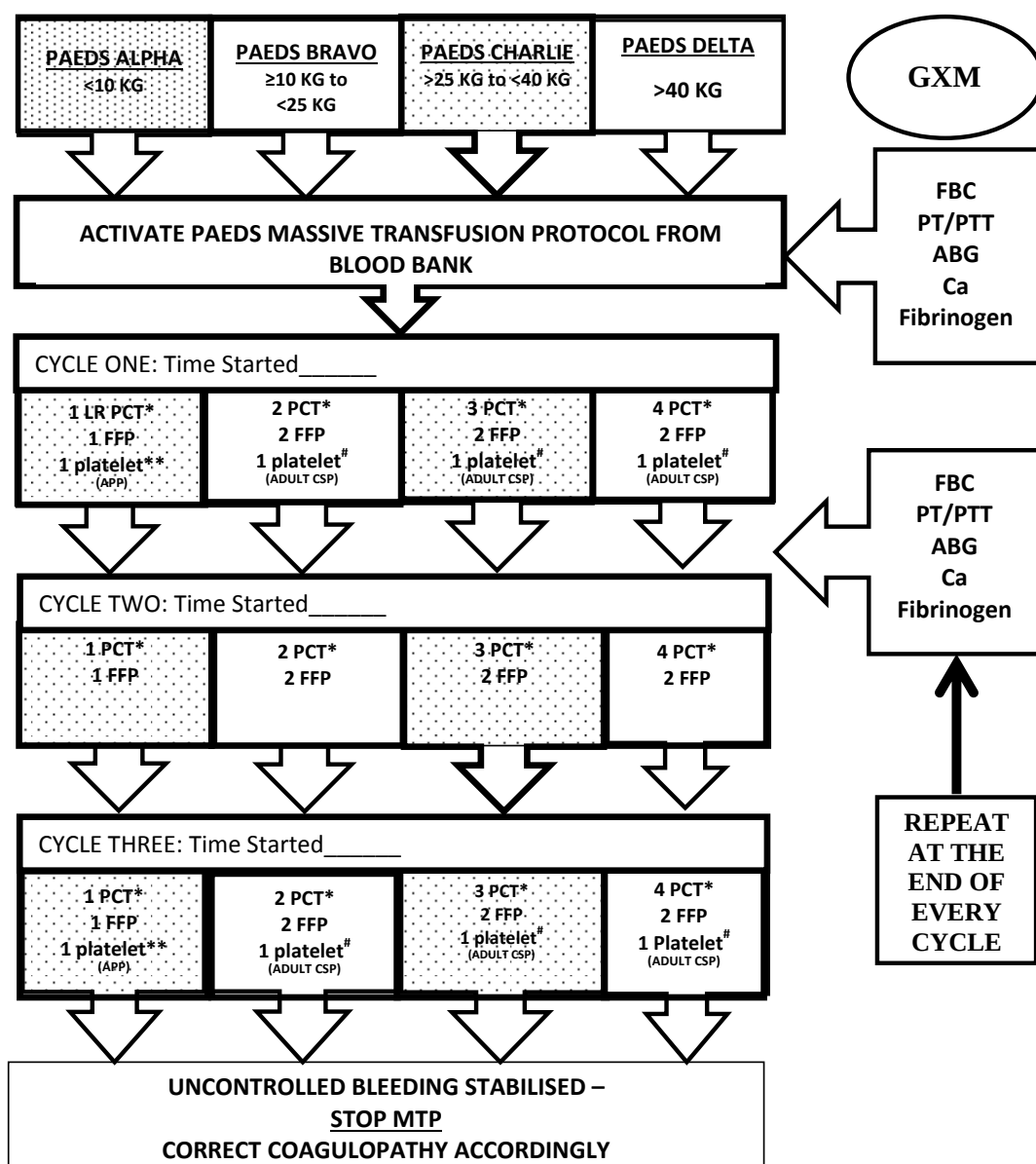


MONITOR FOR:

- Temperature >35°C and treat hyperthermia aggressively
- Treat hypotension aggressively in patients with head or spinal cord injury
- Full blood count
 - Platelets $\geq 50 \times 10^9/L$ if no significant head injury
 - Platelets $\geq 100 \times 10^9/L$ if significant head injury present
- Blood gases
 - pH >7.2
 - Base excess < -6
 - Ca^{2+} >1.1 mmol/L
 - K^+ : monitor for hyper K^+
- Coagulation profile
 - PT/APTT <1.5 × normal
 - INR ≤ 1.5
- Fibrinogen (if done) >1.0 g/L
- Lactate (if done) <3 mmol/L

Appendix 2

MTP for Paediatric Trauma in KK Women's and Children's Hospital

**Notes**

PCT*: Packed cells are O+ for MTP (should the patient be known to be O-, further follow-up and counselling will be undertaken following subsequent patient stabilisation)

LR PCT: Leukocyte-reduced packed cells

Platelets** (for less than 10 kg): APP (Apheresed platelets)

Platelets# (For >10 kg): Adult platelets (CSP or pooled platelets)

If ionised calcium <1 mmol/L, give 0.1 ml/kg 10% calcium gluconate

Fibrinogen levels are not processed in-house

Haemostatic resuscitation

If ongoing haemorrhage after 1st Box 3 - if PT/PTT prolonged, consider additional 20 ml/kg of FFP

If fibrinogen <1 g/L, consider additional 5 ml/kg cryoppt and IV tranexamic acid 10 mg/kg (max 1 g) over 10 minutes and 8 H/prn (NB: cryoppt will not be available stat)

Keep platelets >50, KIV consider additional 10 ml/kg platelets if lower

Probing the Brain White Matter in Psychotic Disorders Using Neuroimaging

Kang Sim,^{1,2} MBBS, MMed (Psychiatry), MSchPE, FAMS

Psychotic disorders are severe psychiatric conditions which are characterised by losses, namely the loss of touch with reality during which the patient may often experience auditory hallucinations, persecutory delusions, and which are often accompanied by a crippling loss of awareness about the need for treatment and ensuing social disability.¹ The paradigmatic example of a psychotic disorder is schizophrenia which occurs in 1% of the population and the patient often suffers from a loss of ability to plan, work and not infrequently, a loss of interpersonal relationships in the longer term.² According to the World Health Organisation (WHO), schizophrenia lists amongst the top 10 leading causes of years lost to disability worldwide,³ and is one of the medical conditions with the highest disability weights.⁴ Due to the huge burden of illness for both patients and carers, there is a pressing need to better understand its underlying neurobiology so as to inform and hopefully reform treatment of these incapacitating conditions.

In the study of the pathophysiology of any complex neurobehavioural disorder including psychotic disorders, one seeks to look for unifying hypotheses which take into account 3 cardinal aspects, namely the context of continuing evidence, core neurobiology based on current investigations, as well as clinical relevance to the patient's experience.⁵ In this regard, one such hypothesis posits that white matter brain changes underlie psychotic disorders and its clinical manifestations, and which can be studied with current neuroimaging modalities including structural magnetic resonance imaging (MRI) and diffusion tensor imaging.⁶ In terms of the continuity of evidence, there is mounting evidence to suggest that brain white matter anomalies underlie psychotic conditions from neuropathological, genetic and neuroimaging studies. Earlier neuropathological studies found reductions in the quantity as well as altered spatial distributions of cortical oligodendrocytes in patients with schizophrenia when compared with controls.^{7,8} One of the earliest genetic studies found differential expression of myelination-related genes suggesting a disruption of oligodendrocyte function germane to white matter brain

changes.⁹ This was further supported by subsequent studies highlighting dysregulation of white matter genes in psychotic patients versus healthy controls.^{10,11} Later in vivo neuroimaging studies of schizophrenia have reported reductions of specific white matter brain volumes involving the frontal, temporal and parietal cortical regions.¹²

In terms of core neurobiology, there are several patterns that have been noted. In early onset schizophrenia, disruptions of white matter integrity were found in the cortical, subcortical brain regions and white matter associative and commissural tracts, suggesting that changes of cortical-subcortical white matter integrity were found at an early stage of the disorder.¹³ In more chronic schizophrenia, differences in the area and volume of the commissural white matter tract, corpus callosum, were greatest in patients whose condition was longstanding relative to patients with a first episode and controls.¹⁴ These findings emphasise the need to understand the wider brain network as well as progressive white matter changes over the illness course. Another area of interest regarding core neurobiology relates to sustained efforts to examine relationships between genetic biomarkers and intermediate phenotypes such as brain white matter changes. The proliferation of recent genome-wide association studies (GWAS) for the last few years encapsulates the vigour in trying to map out heritable biomarkers which may allow better detection of illness and delineation of disease mechanisms.¹⁵ Past GWAS have pointed to genetic signals related to neuronal communication, signaling, and neuroplasticity underlying schizophrenia.¹⁶ A recent landmark study involving 150,000 subjects, 300 collaborators and spanning 30 countries uncovered more than 80 novel genetic loci which have not been previously identified and which are related to body systems including the immune system and gut brain axis.¹⁷ This and other collaborative strategies in medicine would augur well for the future as resources are pooled together by different international groups to generate more generalisable findings in the united quest to advance our understanding of disease mechanisms which can later point

¹Department of General Psychiatry, Woodbridge Hospital/Institute of Mental Health, Singapore

²Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for Correspondence: Dr Kang Sim, Woodbridge Hospital/Institute of Mental Health, 10, Buangkok View, Singapore 539747.

Email: kang_sim@imh.com.sg

towards potential treatment targets. Based on such genetic signals from GWAS, we have studied their genotype-intermediate phenotype relationships related to brain white changes in schizophrenia. We found that genome-wide supported susceptibility genes such as *ZNF804A*, *NRGN* and *CACNA1C* affect cortico-limbic white matter network,¹⁸ thalamocortical morphology,¹⁹ as well as extensive cortical white matter integrity,²⁰ respectively, in our local patients with schizophrenia.

Regarding daily clinical relevance, there are ongoing efforts to elucidate brain white matter changes underlying psychotic phenomenology. Hubl et al²¹ found specific greater fractional anisotropy (FA) in the temporoparietal section of the arcuate fasciculus and anterior corpus callosum which are related to auditory hallucinations, suggesting ongoing neurodevelopmental or neuroplastic changes involving white matter tracts. We found that the distressing control-override passivity phenomena was associated with white matter integrity changes involving the frontal cortex, cingulate gyrus and subcortical structures such as thalamus and striatum.²² For positive psychotic symptoms, the white matter integrity of fornix in proximity with the medial temporal lobe correlated negatively with the severity of these clinical manifestations as measured using the Positive and Negative Syndrome Scale (PANSS).²³ Furthermore, greater left FA lateralisation in the temporal segment of the arcuate fasciculus was associated with more severe positive psychotic symptoms supporting the notion of aberrant fronto-temporal connectivity underlying schizophrenia psychopathology.²⁴ It is hoped that a better understanding of these white matter changes may further support the development of new promyelinating therapies including biological interventions such as brain-derived neurotrophic factor mimetic peptides, growth factor release promoters, glutamatergic antagonists^{25,26} and even psychosocial interventions with the prospect of influencing white matter neuroplasticity.²⁷ Peering ahead, there is even greater need to better integrate the multiple research platforms including neuroimaging, genomics, systems biology models, and clinical correlations in order to test different unifying hypotheses to get us closer to clarification of pathogenetic mechanisms underlying psychotic disorders.

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