ANNALS
ACADEMY OF MEDICINE, SINGAPORE
COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

DIAMOND JUBILEE CELEBRATION 60 years 1957-2017

VOLUME 47 | NUMBER 2 | FREE PAPERS | FEBRUARY 2018

MCI (P) 104/07/2017

"Not knowing when the dawn will come
I open every door."

Emily Dickinson (1830 – 1886)
American poet

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Editorial

Follow-up Care and Outcome Evaluation of High-Risk Preterm Infants: A Life-Course Commitment

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Neonatology can be considered as one of the most successful medical innovations of the latter half of the twentieth century. A slow, synergistic accretion of scientific and clinical insights—combined with an evolution in the way physical spaces of hospitals were built and shaped, and the elaboration and articulation of a moral stance toward the activities being developed—eventually led to a new separate field of medicine that drastically improved infant mortality rates throughout the world. Rarely have the processes and products of scientific medicine been as heralded and harangued, as lauded and condemned, and as publicised and misunderstood as they have in the context of neonatal intensive care.[1]

Neonatal care in the last century can be divided into 3 stages. Right up to the 1950s, neonatal mortality was high and those who managed to survive had to be contented with whatever minimal care that was available, and the morbidity was relatively low. Neonatal care then entered into the second stage when heroic attempts were made to salvage high-risk infants without a good understanding of the scientific basis of neonatal disorders. The mortality rates were lowered at great costs of accompanying high incidence of severe disabilities among the survivors. For example, the indiscriminate administration of oxygen to premature babies with respiratory distress had resulted in blindness from retrolental fibroplasia. The subsequent arbitrary restriction of oxygen then resulted in mental retardation and cerebral palsy amongst the survivors. Most opponents to the development of neonatal care nowadays are still referring to the experience during this "dark age" of neonatology history. The development of neonatal intensive care in Singapore in the 1980s took place at the stage of advances in neonatology when significant progress had been made in the better understanding of the pathophysiology of many neonatal diseases such as hyaline membrane disease, periventricular-intraventricular haemorrhage (PIVH), bronchopulmonary dysplasia, necrotising enterocolitis, nutritional deficiencies, hyperbilirubinaemia, and retinopathy of prematurity. Technological innovations had enabled safer and more scientific-assisted ventilation, non-invasive monitoring, and effective nutritional care. These have resulted in better and more precise management of many neonatal disorders and a reduction of iatrogenic diseases. However, proper scientific evaluation of new treatment policies and innovations is mandatory to prevent their ever-enthusiastic implementation and adverse consequences.[2] We have also arrived at a period when we have great opportunities to critically examine the many epidemiological research data worldwide. This will lead to further refinement of prognostication, as well as to allow us to understand the cost-effectiveness of neonatal intensive care.

Advances in neonatal-perinatal care have been responsible for the improved survival of high-risk newborns. Babies who had been born too early have been the major beneficiaries. However, a major concern that newer therapies may result in an increased number of disabled survivors still persists. Neurodevelopmental follow-up is therefore a critical component of the evaluation of the neurological development and ongoing clinical needs of high-risk newborns. A substantial number of these infants will experience later neurological and developmental difficulties that are likely to seriously limit their educational, social, and other life-course opportunities. Unfortunately, it is not always possible to accurately predict—in the neonatal period—which infants will experience these problems and which will not. Furthermore, children's skills and abilities develop with age and experience, with simpler skills often forming the foundation for the learning of more complex skills. Thus, it is often not until a child fails, or is slower to develop a specific skill compared with other children of his or her age, that his or her problems become fully apparent. The developmental timing of this will also depend on the function of interest, with motor deficits tending to emerge in the first year of life, while cognitive and behavioural impairments develop more slowly from early childhood to adolescence. Therefore, high-risk infants require close

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monitoring and developmental surveillance as part of our ongoing responsibility for care and optimisation of their outcomes beyond merely survival and discharge from the neonatal unit.

Neurodevelopmental follow-up is also important for family support. The initial continuity-of-care should be provided by the neonatologist as it is important to reassure the family that the same personnel responsible for the life-saving decisions are continuing to assume responsibility for the child's adaptation into home life. Families want to know if their child is healthy and growing normally, or if problems are likely to be encountered in the future. Such information is valuable for both stress management and family decision-making. It also enables families to proactively plan and advocate for their child's needs. Families also need advice and support at key transition points in a child's life when additional challenges may be encountered by a child, such as starting childcare or enrolling into schools.

Information about high-risk children's outcomes is crucial for the improvement of existing neonatal-perinatal services. Specifically, possible positive and negative effects of different medical interventions on neurological and developmental outcomes may not be apparent in the first years of life. Therefore follow-up data can provide valuable feedback information about the efficacy and potential risks associated with different clinical care approaches beyond survival and short-term health outcomes. Finally, careful follow-up screening helps ensure that problems are detected early so that timely targeted interventions can be instituted to treat or to prevent significant health problems, which may worsen and place the child at increased risk of more complex impairments. Early intervention not only serves to minimise distress and strengthen families, but also to reduce the burden of long-term care on public health, social, and educational services over the child's life span.

Resource availability would determine how extensive and elaborate a follow-up programme would be, but the minimal requirement for the clinical monitoring of outcomes is a periodic assessment of growth and neurosensory development during the first 2 years of life. The ideal is a comprehensive programme involving all aspects of care, including well-baby care, evaluation of outcome, social and educational intervention, and therapy when needed. A home-visiting programme, especially during the early postdischarge period, and parent support groups for selected high-risk conditions (e.g. children with chronic lung disease) could also be considered. Because it is impossible to provide ongoing high-risk follow-up care for all infants treated in the neonatal intensive care unit, specific criteria have been proposed to identify children at greatest risk for sequelae. Traditionally, follow-up programmes primarily targeted children with birth weight of <1500 g (very low birth weight, VLBW) or gestational age of <32 weeks. Increasingly, most reports from developed countries would only cover infants with birth weight <1000 g (extremely low birth weight, ELBW) or gestational age <28 weeks; and even those born at the threshold of viability.

Neurodevelopmental outcome typically refers to cognitive, neurological and/or sensory outcomes. Traditionally in outcome studies, neurodevelopmental impairment has been defined as the presence of 1 or more of the following: a) cognitive delay based on scores on standardised cognitive tests that are 2 standard deviations below the mean (this would correspond to a score of 70 or below on the Mental Developmental Index of the Bayley Scales of Infant Development); b) moderate to severe cerebral palsy defined as a score of >2 on the Gross Motor Function Classification System; c) hearing deficit/loss requiring amplification; d) severe visual impairment with visual acuity of 20/200 or less in the better-seeing eye with best conventional correction (legal blindness). Increasingly, behavioural, psychological and functional outcomes are being recognised as important long-term neurodevelopmental outcomes.

Neurodevelopmental outcomes of several large cohorts of preterm infants around the world have been reported.[3,4,5,6,7,8,9] They are: the Victorian Infant Collaborative Study (VICS) Group; the EPICure 1 and 2 Studies from United Kingdom; Japan Neonatal Research Network; Eunice Kennedy Schriver NICHD Neonatal Research Network Follow-up Study Group; the Extremely Preterm Infants in Sweden Study (EXPRESS); and the Swiss National Cohort Study of Extremely Preterm Infants. What can we learn from their experiences?

Interpretation of the neurodevelopmental outcomes literature on preterm infants is challenging. Differences in defining the study population make comparison of data from different studies difficult. For example, the use of birth weight classification versus gestational age can be problematic as the more mature infants who are small for gestational age (SGA) may be included in a given birth weight category. This may have an impact on the outcome results as the SGA infants are known to have a greater risk of neonatal morbidities and poorer outcomes compared to their appropriate for gestational age (AGA) counterparts.

The assessment tools used in the studies vary. For example, several studies have shown that results from the Bayley Scales 3rd edition (BSID III, 2006) result in higher cognitive scores than the 2nd edition (BSID II, 1992).[10,11] It remains unclear whether the BSID III overestimates or is a more valid assessment of the cognitive performance compared with BSID II.

There are significant differences and changes in perinatal and neonatal clinical policies and practices over time. The

impact on outcome is difficult to accurately ascertain as the improved survival rate has outpaced any concomitant decrease in the rate of long-term neurodevelopmental sequelae. Even in developed countries, there are global and regional differences in their perinatal approach to infants at the threshold of viability, making comparison of survival and outcome data between studies very difficult.

Over the past few decades, several changes in perinatal care are known to have significant impact on the neurodevelopmental outcome of preterm infants—directly or indirectly—by reducing complications such as PIVH. Infants who received antenatal corticosteroids had a lower death rate and a reduced incidence of moderate to severe cerebral palsy. The beneficial effect was dose-dependent and maximal benefit was associated with a complete course of antenatal steroids.[12,13] On the other hand, early administration of dexamethasone (before 8 days of age) was associated with an increased risk of cerebral palsy; although sequelae remain uncertain with late administration or lower doses for shorter duration.[14,15]

The successful introduction of exogenous surfactant for the treatment of hyaline membrane disease had increased survival of extremely preterm infants. Improvements in neonatal-assisted ventilation including non-invasive methods (e.g. continuous positive airway pressure) and improved strategies of mechanical ventilation (e.g. high-frequency oscillation, volume-targeted and synchronised ventilation) have improved survival and reduced morbidities (e.g. pulmonary air leak, bronchopulmonary dysplasia and severe PIVH), with remarkable impact on neurodevelopmental outcomes. Although yet to be universally accepted, clinical trials have shown that preterm infants whose mothers receive magnesium sulphate at impending preterm deliveries have lower risk of cerebral palsy and severe motor dysfunction compared with non-exposed infants.[16,17]

There are also many other confounding factors that may subsequently affect neurodevelopmental outcome, making comparison of results from studies difficult. These are the social and family support ecosystem, ongoing health issues and the access to quality early intervention programmes and early childhood education in the community. These factors are inseparable from the level and standards of neonatal-perinatal care in determining the long-term outcomes of preterm infants. Beyond the conventional 5 to 8 years of follow-up period, they also have strong influences on the child's development of behavioural and psychological problems, functional disabilities, academic achievement and subsequent quality of life.

Despite difficulties in interpreting world literature on the outcomes of preterm infants, some observations are well supported by the current outcome data.

Individuals born preterm are at increased risk for impaired neurodevelopmental outcomes compared with those born at-term. The risk of impairment increases with decreasing gestational age. Former preterm infants are more likely than those born at-term to develop behavioural and psychological problems. These include attention deficit hyperactivity disorder, general anxiety, depression, difficulty in peer interactions, and autism spectrum disorder.[18,19,20] School-age children born preterm are at increased risk of functional disabilities that may cause them problems in managing daily activities. These are subtle problems such as motor coordination (non-cerebral palsy motor impairment), social interactive skills and executive functions (working memory, problem-solving, planning and organisation).[21,22]

There were contrasting reports on the adult outcome of preterm infants. Earlier studies reported lower rates of academic achievement, independent living, lower income and employability in preterm adult survivors compared with those born full-term.[19,20] In contrast, other studies suggest that despite their increased risk of neurodevelopmental disability, adults who were born preterm may overcome their difficulties and become functional young adults at a comparable rate to those who were born full-term in terms of high school graduation, post-secondary education opportunities, employment, independent living, marriage, and parenthood.[23,24] Differences in outcome may be due to higher socioeconomic status of the study population, and access to healthcare and educational support. We hope to have our local data when the 'Quality of Life Study' on children with chronic medical problems and disabilities (sponsored by the National Council of Social Service, Singapore) is completed in 2019. It is equally important to understand that patients and their parents have a better perception of their quality of life than healthcare professionals. Healthcare providers need to be aware of this difference so that they do not only focus narrowly on neurodevelopmental disabilities of their patients but to broaden their definition of outcome to include the ability of the adult survivors to overcome their limitations with a positive self-perception of their quality of life.[25,26]

The notion that increased survival brought an additional burden of disability into the population remains even today. There were local published reports on the survival and neurodevelopmental outcomes of preterm infants.[27,28] The paper on 'Long-term neurodevelopmental outcomes of premature infants in Singapore' published in this issue of Annals, Academy of Medicine, Singapore has given us further reassurance that the increased survival of preterm infants in Singapore has not been accompanied by an increase in adverse neurodevelopmental outcomes among the survivors. The overall neurodevelopmental outcomes over the 10-year period from Epoch I (1994-1995) to

Epoch II (2004-2005) did not worsen despite a lower mean gestational age, with an improvement in long-term visual impairment rates and intelligence quotient (IQ) scores. Notable changes in clinical practice worldwide during this period have been an increase in antenatal corticosteroids use, increased use of exogenous surfactant, saturation targeting to reduce excessive oxygen exposure, and limiting the use of postnatal corticosteroids.

One common limitation of this study and previous reports is that they are essentially data from a relatively small population being cared for in tertiary institutions. The difference in outcomes between the inborn and outborn high-risk infants is well recognised. In Singapore, about 60% of the annual births take place at private hospitals. The major shortcoming of our perinatal care delivery has been our failure in the regionalisation of neonatal-perinatal care—a system with proven cost-effectiveness in most countries. A nationwide perinatal audit and neonatal follow-up network have yet to be formally established to provide a constant feedback mechanism to the existing system, as well as to provide more accurate national data which can then be benchmarked against the well established international networks.

The low follow-up and high follow-up attrition rates introduce another bias issue. Some studies report that infants who fail to keep follow-up appointments, or are followed only with great difficulty, are more likely to have developmental impairment. Many complex socioeconomic and medical factors may be associated with increased attrition—which is of concern not only because of the potential bias introduced but also because those children and families lost to follow-up could potentially benefit most from supports and services. Nevertheless, questions related to generalisability of findings may be inherent, regardless of outstanding follow-up rates. Thus population-based or large regional-based cohorts (eg. VICS, EPICure, EXPRESS), may be considered the ideal model of prospective observational studies of high-risk infants.

Improving the survival rate without increasing the adverse outcomes of the extremely preterm (<28 weeks' gestation) and ELBW (<1000 g) infants—especially those born at the threshold of viability—would be our new frontier in management in the coming decades. They contribute disproportionately to overall hospital days and consume a large percentage of neonatal intensive care unit personnel time, effort, and costs of care. Ethical guidelines on perinatal care at the threshold of viability have been drawn out and will be regularly reviewed.[29] Care of these infants is in constant evolution, as a result of new discoveries in both basic and clinical research as well as growing clinical experience.

The definitions of 'long-term follow-up' are changing, and there is a need for 'long-term' to be even longer. There is a growing reliance on complete evaluation and reporting of neurodevelopmental outcomes in prospective studies and trials and an increasing recognition that it is crucial to fully understand outcomes beyond the initial hospitalisation and even beyond early childhood. Yet, the challenges of following a cohort for years or decades and the potential barriers to achieving reliable results are numerous. Long-term follow-up requires time, dedication, and persistence from both follow-up staff and families. However, data certainly suggests that follow-up until school years is warranted for several reasons. First, infant and early childhood developmental measures are poor to modest predictors of long-term child outcomes, particularly for cognitive scores.[30,31] Second, some developmental disorders cannot be reliably and accurately assessed at a young age, such as executive function impairments, specific learning problems (e.g. dyscalculia, dyslexia), and common mental health disorders such as attention deficit hyperactivity disorder and anxiety disorders. Third, there is an increasing body of data indicating that disability rates change between early childhood and school age.[32,33] A large population-based study of preterm infants followed for 10 years identified that although the majority of these children remained in their 2-year disability category, there were shifts. Early preterm infants showed a small shift from moderate and severe to no or mild disability. In contrast, there was a shift of moderate and late preterm infants with no or mild disability at age 2 to moderate or severe disability at age 10.[34]

The transition of high-risk infants from the neonatal intensive care unit to a comprehensive follow-up programme that involves early interventions, education, and social and family support is almost equivalent to transferring the child to another intensive care environment in the community. Certainly, it is a time- and resource-intensive undertaking. But we are unlikely to truly transform long-term care and improve the lifetime outcomes of high-risk infants without such an investment in the future. Today's neonatologists should go beyond their comfort zone of medical care and continue to be ready to take on the leadership role in ensuring the best possible outcomes of high-risk infants. This will be their life-course commitment.

REFERENCES

1. Lantos JD, Meadow WL. Neonatal Ethics: The Moral Challenges of Modern Innovation. Baltimore, Maryland: The Johns Hopkins University Press; 2006.
2. Ho LY. Neonatology: Then and Now. Paediatrics, Child and Adolescent Health 2006;46:86-8.
3. Doyle LW, Roberts G, Anderson PJ, Victorian Infant Collaborative Study Group. Outcomes at age 2 years of infants <28 weeks' gestational age born in Victoria in 2005. J Pediatr 2010;156:49-53.

4. Hintz SR, Kendrick DE, Wilson-Costello DE, Das A, Bell EF, Vohr BR, et al. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. Pediatrics 2011;127:62-70.
5. Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M, Neonatal Research Network Japan. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics 2013;132:62-71.
6. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ 2012;345:e7961.
7. Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. N Engl J Med 2015;372:1801-11.
8. Schlapbach LJ, Adams M, Proietti E, Aebischer M, Grunt S, Borradori-Tolsa C, et al. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. BMC Pediatr 2012;12:198.
9. Serenius F, Sjors G, Binnow M, et al. EXPRESS study shows significant regional differences in 1-year outcome of extremely preterm infants in Sweden. Acta Paediatr 2014;103;27-37.
10. Vohr BR, Stephens BE, Higgins RD, Bann CM, Hintz SR, Das A, et al. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. J Pediatr 2012;161:222-8.
11. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. J Pediatr 2012;160:553-8.
12. Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA 2011;306:2348-58.
13. Chawla S, Natarajan G, Shankaran, S, Pappas A, Stoll BJ, Carlo WA, et al. Association of neurodevelopmental outcomes and neonatal morbidities of extremely premature infants with differential exposure top antenatal steroids. JAMA Pediatr 2016;170:1164-72.
14. Chang YP. Evidence for the adverse effect of perinatal glucocorticoid use on the developing brain. Korean J Pediatr 2014;57:101-9.
15. Champagne DL, de Kloet ER, Joels M. Fundamental aspects of the impact of glucocorticoids on the immature brain. Semin Fetal Neonatal Med 2009;14:136-42.
16. Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med 2008;359:895-905.
17. Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Lévêque C, Hellot MF, et al. Magnesium sulfate given before very-preterm birth to protect infant brain. The randomized, controlled PREMAG trial. BJOG 2007;114:310-8.
18. Hack M, Youngstrom EA, Cartar L, Schluchter M, Taylor HG, Flannery D, et al. Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. Pediatr 2004;114:932-40.
19. Higa Diez M, Yorifuji T, Kado Y, Sanada S, Doi H. Preterm birth and behavioural outcomes at 8 years of age: a nationwide survey in Japan. Arch Dis Child 2016;101:338-43.
20. Lindstrom K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. Pediatr 2011;127:858-65.
21. Edwards J, Berube M, Erlandson K, Haug S, Johnstone H, Meagher M, et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. J Dev Behav Pediatr 2011;32:678-87.
22. Costa DS, Miranda DM, Burnett AC, Doyle LW, Cheong JLY, Anderson PJ, et al. Executive function and academic outcomes in children who were extremely preterm. Pediatr 2017;140:e20170257.
23. Cooke RW. Health lifestyle and quality of life for young adults born very preterm. Arch Dis Child 2004;89:201-6.
24. Mathiason R, Hansen BM, Nybo Anderson AM, Greisen G. Socio-economic achievements of individuals born very preterm at the age of 27 to 29 years: a nationwide cohort study. Dev Med Child Neurol 2009;51:901-8.
25. Saigal S, Stoskopf B, Streiner D, Boyle M, Pinelli J, Paneth N, et al. Transition of extremely low birth-weight infants from adolescence to young adulthood: comparison with normal birth-weight cohorts. JAMA 2006;295:667-75.
26. Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, et al. Psychological functioning and health-related quality of life in adulthood after preterm birth. Dev Med Child Neurol 2007;49:597-602.
27. Agarwal P, Lim SB. Long-term follow-up and outcomes of extremely low-birth-weight (ELBW) infants. Ann Acad Med Singapore 2003;32:346-53.
28. Poon WB, Ho SK, Yeo CL. Short- and long-term outcomes at 2.3, and 8 years old for neonates at borderline viability – an 11-year experience. Ann Acad Med Singapore 2013;42:7-17.
29. Ho LY. Perinatal care at the threshold of viability: from principles to practice. Ann Acad Med Singapore 2003;32:362-75.
30. Wong HS, Santhakumaran S, Cowan FM, Modi N, Medicines for Neonates Investigator Group. Developmental assessments in preterm children: a meta-analysis. Pediatrics 2016;138:e20160251.
31. Spittle AJ, Spencer-Smith MM, Eeles AL, Lee KJ, Lorefice LE, Anderson PJ, et al. Does the Bayley-III Motor Scale at 2 years predict motor outcome at 4 years in very preterm children?. Dev Med Child Neurol 2013;55:448-52.
32. Luu TM, Vohr BR, Allan W, Schneider KC, Ment LR. Evidence for catch-up in cognition and receptive vocabulary among adolescents born very preterm. Pediatrics 2011;128:313-22.
33. Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor G, Schluchter M, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000-2002. Pediatrics 2007;119:37-45.
34. Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, et al. The economic burden of prematurity in Canada. BMC Pediatr 2014;14:93-102.

Original Article

Triaging Primary Care Patients Referred for Chest Pain to Specialist Cardiology Centres: Efficacy of an Optimised Protocol

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Abstract

Introduction: Patients referred for chest pain from primary care have increased, along with demand for outpatient cardiology consultations. We evaluated 'Triage Protocol' that implements standardised diagnostic testing prior to patients' first cardiology consultation. Materials and Methods: Under the 'Triage Protocol', patients referred for chest pain were pretriaged using a standardised algorithm and subsequently referred for relevant functional diagnostic cardiology tests before their initial cardiology consultation. At the initial cardiology consultation scheduled by the primary care provider, test results were reviewed. A total of 522 triage patients (mean age 55 ± 13, male 53%) were frequency-matched by age, gender and risk cohort to 289 control patients (mean age: 56 ± 11, male: 52%). Pretest risk of coronary artery disease was defined according to a Modified Duke Clinical Score (MDCS) as low (<10), intermediate (10-20) and high (>20). The primary outcome was time from referral to diagnosis (days). Secondary outcomes were total visits, discharge rate at first consultation, patient cost and adverse cardiac outcomes. Results: The 'Triage Protocol' resulted in shorter times from referral to diagnosis (46 vs 131 days; *P* <0.0001) and fewer total visits (2.4 vs 3.0; *P* <0.0001). However, triage patients in low-risk groups experienced higher costs due to increased testing (S$421 vs S$357, *P* = 0.003). Adverse cardiac event rates under the 'Triage Protocol' indicated no compromise to patient safety (triage vs control: 0.57% vs 0.35%; *P* = 1.000). Conclusion: By implementing diagnostic cardiac testing prior to patients' first specialist consultation, the 'Triage Protocol' expedited diagnosis and reduced subsequent visits across all risk groups in ambulatory chest pain patients.

Ann Acad Med Singapore 2018;47:56-62

Key words: Algorithm, Cardiac pain, Triage

Introduction

Cardiovascular disease is a leading cause of death worldwide[1] and constitutes 30% of total deaths in Singapore.[2] Chest pain is a common presentation in primary care.[3-5] However, only a small proportion of primary care referrals for chest pain to tertiary cardiology centres are eventually found to have significant cardiac abnormalities.[4,5] Locally, the number of patients referred to outpatient centres for chest pain has grown by 31% in the last 5 years (unpublished data; National Heart Centre, Singapore statistics), which has strained capacity and increased wait times.[6] The challenge for cardiologists is the safe and expedient management of referrals to identify patients with underlying cardiovascular disease for further management.

Studies to improve cardiology outpatient chest pain diagnostic workflows have expedited patient diagnoses in the United Kingdom (UK) and Canada. Cardiac Ensuring Access and Speedy Evaluation (EASE) in Canada is an outpatient pretriage and prospective diagnostic testing cardiology programme that has decreased wait time and time to diagnosis while increasing capacity.[7] Similarly, rapid access chest pain clinics (RACPCs) in the UK have used

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risk-stratified cardiac testing and one-stop clinics led by cardiologists to rapidly diagnose chest pain patients.[8] We sought to evaluate the effectiveness and safety of an optimised diagnostic chest pain protocol in an Asian population.

Materials and Methods

We conducted a prospective cohort study at the largest national outpatient cardiac centre in Singapore, which sees about half of all nationwide primary care cardiology referrals. The 'Triage Protocol' was designed to pretriage and prospectively test patients with chest pain referred from primary care (Fig. 1).

Triage patients presenting from 1 April 2015 to 31 January 2016 were compared to historical control (conventional diagnostic pathway) patients presenting during the period 1 April 2014 to 31 January 2015. Control patients were frequency-matched to triage patients based on gender, age and risk score. Referrals for chest pain were obtained from SingHealth Polyclinics, a leading national primary care provider. Exclusion criteria were as follows: patients below 21 years old, patients with signs of acute coronary syndrome (i.e. elevated cardiac biomarkers, electrocardiogram [ECG] ST segment elevation, etc.) requiring medical attention within 14 days of presentation, patients whose chief complaint was not chest pain (e.g. pedal oedema, syncope, palpitations, shortness of breath, etc.), and patients who defaulted in the initial triaging process (28 patients).

Intervention: The 'Triage Protocol'

The 'Triage Protocol' enables eligible chest pain referrals to receive standard non-invasive diagnostic tests prior to their first cardiac consultation (Fig. 1). Patient referrals were received from the primary care provider and reviewed by a triage cardiologist using our standardised diagnostic testing algorithm (Fig. 1). The algorithm is based on the 2012 ACCF/AHA Guidelines for Stable Ischaemic Heart Disease[9] and states that a patient should undergo an exercise treadmill test if the following 3 criteria are met: i) <45 years of age, ii) able to exercise, and iii) has an interpretable ECG. If any of the 3 criteria are not met (i.e. age ≥45 years, ECG uninterpretable [e.g. left bundle branch block, paced rhythms, etc.] or inability to exercise) the patient undergoes stress imaging (e.g. myocardial perfusion imaging) (Fig. 1). The triage cardiologist orders the indicated diagnostic tests for patients, with allowance for minor discretionary variations to the algorithm. Patients with test results defined as high-risk by the AHA/ACC Guidelines 1999[10] are expedited for review by a cardiologist within 7 days. Otherwise, test results are made available to the cardiac specialist at the patient's first outpatient cardiology consultation, as originally scheduled by the primary care provider.

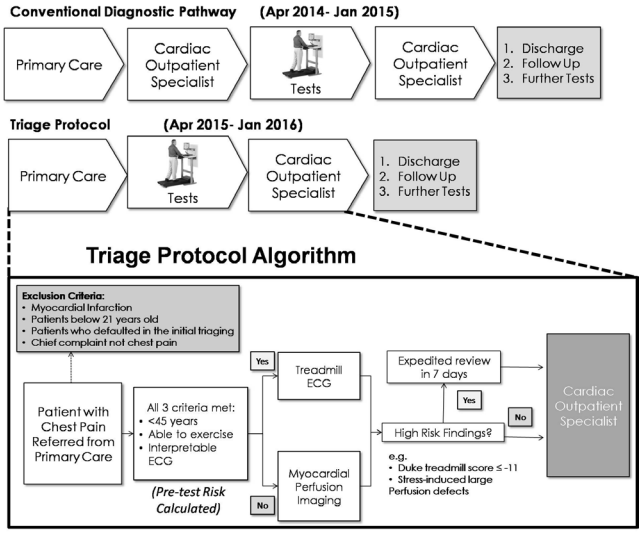

Fig. 1. Illustration of conventional versus triage pathways.

Outcome Variables

All patients were followed-up for 6 months from their first consultation. The primary outcome variable was the time from referral to clinical diagnosis—defined as the number of days from referral by the primary care physician to clinical diagnosis by the cardiologist specialist (as per current clinical practice). Secondary outcomes were patient discharge rate at first consultation, total number of consultations, diagnostic tests and visits (i.e. consultations and tests) and patient costs for tests and consultations over the first 6 months. All discharged patients were followed for an additional 6 months via the SingHealth electronic records database to capture any adverse cardiac events (myocardial infarct, percutaneous intervention, coronary artery bypass, congestive heart failure, stroke or death). The study protocol and team did not influence the clinical decision and management by the primary cardiologist.

Assessing Patients' Risk Score

A Modified Duke Clinical Score (MDCS)[11] was used to calculate pretest risk of coronary artery disease (CAD) in a South East Asian population of chest pain patients. Components of the MDCS are age, gender, type of chest pain, smoking status and comorbidities of diabetes, hypertension and hyperlipidaemia. The MDCS was validated locally in a cohort of 1589 patients. It yielded results comparable to the original Duke Clinical Score.[12,13] Patients were stratified into 3 risk cohorts according to the MCDS score: low (<10), intermediate (10-20) and high (>20); and compared between triages and controls. A sensitivity analysis was performed using the CAD Consortium Risk Score[14] (CRS)—a published European cardiovascular risk score not validated locally—

to assess robustness of triage outcomes irrespective of cardiovascular risk score (MDCS or CRS).

Statistical Analysis

Statistical analysis was performed using SAS V9.4 (SAS Cary, NC, USA). Baseline variables were compared between triage and control intervention groups using the 2-sample t-test for normal variables, the Wilcoxon rank-sum test for non-normal variables and Fisher's Exact test for categorical variables. The outcome variables—referral to diagnosis time, total number of visits, total number of tests, total cost of tests and consultations—were analysed using standard analysis of variance. Model effects were 'intervention' (triage, control), 'risk group' (low, intermediate, high), 'intervention × risk group interaction', 'smoking history (yes, no), 'hypertension' (yes, no), 'gender', 'age', 'angina type' (typical, atypical, non-specific), 'hyperlipidaemia' (yes, no) and 'diabetes mellitus' (yes, no). The first 3 model terms were relevant to answering questions addressed by the study, whereas the remaining terms were included as confounders or potential confounders. The variance-covariance matrix was blocked on 'intervention type' to accommodate unequal variances between intervention types. Inferences on the 'intervention × risk group least-squares (LS) means were of primary interest. LS means, adjusted for confounders, were compared for statistical significance between triage and controls at each 'risk group' level and 95% confidence intervals calculated on the differences. Statistical significance was set at $P \leq 0.05$.

Results

Study Population

A total of 522 triage patients (mean age 55 ±13, male 53%) and 289 age-, sex- and risk score frequency-matched controls (mean age 56 ± 13, male 52%) were included (Fig. 2). Baseline characteristics exhibited no statistically significant differences (Table 1). Default rates were lower for triage patients compared to all patients in the prior year (2014), of which the controls were a subset, for both new cases (triage vs 2014 historical: 14% vs 22%) and follow-up cases (triage vs 2014 historical: 7% vs 16%). New case defaulters were patients who failed to attend their first consultation. Follow-up case defaulters were patients who failed to attend subsequent visits (tests or consultations) and for whom a clinical diagnosis could not be reached. Seven triage patients (1.1%) required expedited review (within 7 days) by a cardiologist owing to abnormal diagnostic results with high-risk findings.

Table 1. Baseline Characteristics Compared between Control and Triage Patients

Variable	Control n = 289	Triage n = 522	*P* Value
Demographics			
Mean age ± SD (years)	56 ± 11	55 ± 13	0.2554
Male (%)	52	53	0.7691
Female (%)	48	47	0.7691
Medical history, %			
Diabetes mellitus	21	17	0.1614
Hypertension	46	47	0.8832
Hyperlipidaemia	58	53	0.1221
Current smoker	12	11	0.3641
Ex-smoker	8	6	0.3641
Risk cohort, %			
Low	64	66	0.3202
Intermediate	25	26	0.3202
High	11	8	0.3202

SD: Standard deviation

Outcomes

Referral to Diagnosis Times

The 'Triage Protocol' was associated with a mean referral to diagnosis time of 46 days which was 65% shorter than the 133 days for patients in the control group (Fig. 3, Table 2).

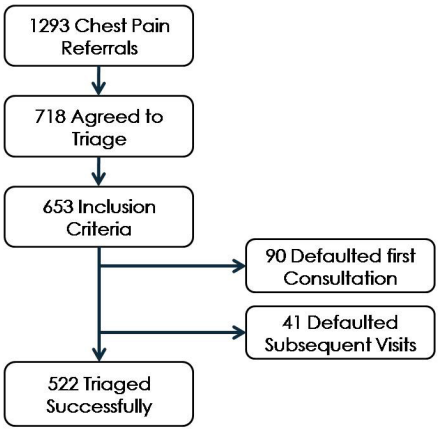

Fig. 2. Flow chat depicting patients enrolled in the 'Triage Protocol'.

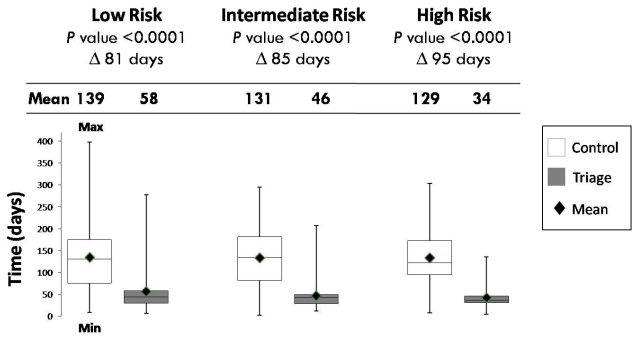

Fig. 3. Comparison of referral to diagnosis time between triage and control patients by risk group.

Table 2. Outcomes for Control versus Triage by Risk Groups

Multivariate Analysis	**Control (n = 289)**	**Triage (n = 522)**	**Difference**	**CI on Difference**	***P* Value**
Referral to diagnosis time (days)					
Overall	13	46	86	(75, 99)	<0.0001
Low-risk	139	58	80	(69, 92)	<0.0001
Intermediate-risk	131	46	85	(67, 103)	<0.0001
High-risk	129	34	95	(66, 125)	<0.0001
Total no. of visits per patient					
Overall	2.96	2.41	0.56	(0.31, 0.80)	<0.0001
Low-risk	2.64	2.39	0.24	(0.02, 0.47)	0.0329
Intermediate-risk	3.09	2.43	0.66	(0.31, 1.01)	0.0002
High-risk	3.16	2.40	0.76	(0.17, 1.36)	0.0117
Total no. of tests per patient					
Overall	1.31	1.30	0.01	(-0.17, 0.18)	0.9326
Low-risk	1.10	1.26	-0.16	(-0.32, 0.00)	0.0536
Intermediate-risk	1.38	1.29	0.09	(-0.16, 0.34)	0.4846
High-risk	1.45	1.35	0.09	(-0.33, 0.52)	0.6690
Costs, test + consultation (S$)					
Overall	357	421	-64	(-106, -22)	0.0030
Low-risk	364	459	-94	(-133, -55)	<0.0001
Intermediate-risk	365	417	-52	(-112, 8)	0.0915
High-risk	341	387	-45	(-148, 57)	0.3847
Test cost (S$)					
Overall	299	382	-83	(-123, -43)	<0.0001
Low-risk	311	419	-108	(-145, -71)	<0.0001
Intermediate-risk	305	377	-72	(-129, -14)	0.0143
High-risk	281	350	-69	(-167, 28)	0.1642
Univariate Analysis	**Control (n = 289)**	**Triage (n = 522)**	**Difference**	**CI on Difference**	***P* Value**
Discharge rate at first consultation, %					
Overall	19	69	50	(44,56)	<0.0001
Low-risk	24	72	48	(40,55)	<0.0001
Intermediate-risk	10	65	55	(43,65)	<0.0001
High-risk	9	61	52	(30,66)	<0.0001
Adverse cardiac event rate, % (pts)					
Overall	0.35 (1)	0.57 (3)	-0.23	(-1.40, 1.37)	1.000
Low-risk	0.00 (0)	0.29 (1)	-0.58	(-1.51, 3.20)	1.000
Intermediate-risk	0.74 (1)	2.78 (2)	2.04	(-1.83, 8.87)	1.000
High-risk	0.00 (0)	0.00 (0)	0.00	(-10.72, 8.57)	1.000

CI: Confidence interval

Patients in all risk groups experienced significantly shorter times from referral to diagnosis compared to controls (P <0.0001). Mean differences were comparable across risk groups and did not differ significantly (P = 0.6344) (Tables 2 and 3). On average, the 'Triage Protocol' resulted in shorter time to diagnosis for all risk cohorts (Fig. 3).

Total Visits

Total visits (including test visits) were decreased on average by 0.56 visits (triage patients vs control patients, 2.41 vs 2.96), with 75% of triage patients discharged by 2 visits compared to 33% of control patients (Fig. 4). However, it was noted that 19% of control patients were

Table 3. Multivariate Analysis of Variance Summary

Effect	Wait Time Referral to Diagnosis	Total Visits	Diagnosis Total Test Count	Diagnosis Test Consultation Cost
Intervention	<0.0001	<0.0001	0.9326	0.0030
Risk group	0.2289	0.2149	0.2712	0.4796
Intervention × risk group	0.6344	0.0671	0.1930	0.4117
Smoker history	0.0023	0.1945	0.1532	0.3517
Hypertension	0.5319	0.6813	0.6363	0.9275
Gender	0.7987	0.1339	0.3035	0.2721
Age	0.8388	0.0019	0.0011	<0.0001
Angina type	0.1820	0.0560	0.0699	0.0042
Hyperlipidaemia	0.6668	0.3689	0.1727	0.0463
Diabetes mellitus	0.2006	0.6898	0.6400	0.0820

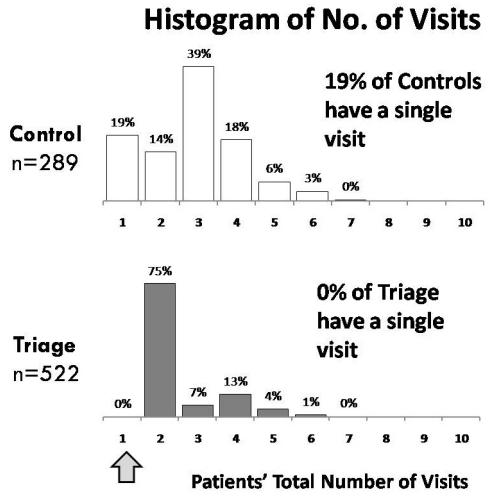

Fig. 4. Histogram comparing total visits for control and triage patients.

discharged after a single visit (1 consultation) whereas all triage patients had a minimum of 2 visits (1 test and 1 consultation), resulting in 0% of triage patients with only a single-visit (Fig. 4). The 19% of single-visit control patients consisted of a higher proportion of low-risk patients (78%) compared to non-single-visit control patients (64%) and triage patients (66%). Otherwise, baseline characteristics of single-visit control patients were comparable to non-single-visit control and triage patients.

Tests: Number and Type

The mean number of tests did not differ statistically between the triage (1.30) and control (1.31) groups (P = 0.9326). A trend was observed wherein the low-risk cohort underwent 0.16 more tests (P = 0.0536) and the intermediate- and high-risk cohorts both underwent 0.09 fewer tests (P = 0.4846 and P = 0.6690, respectively) on average under the 'Triage Protocol' compared to the controls (Table 2).

The 'Triage Protocol' was associated with a different pattern in the type of tests ordered for a patient's initial diagnostic investigation compared to controls (P <0.0001). In the triage group, first tests ordered consisted of 81% myocardial perfusion single photon emission computed tomography (SPECT) studies, 14% exercise ECG stress tests and 5% other tests. In contrast, first tests ordered in the control group consisted of 22% stress echocardiography, 21% myocardial perfusion SPECT studies, 9% exercise ECG stress tests, 8% computed tomography calcium score and 19% other tests.

In both the control and triage groups, 9% of patients had positive first test results. Among these patients with a positive first test, 54% of control patients and 39% of triage patients subsequently underwent non-invasive or invasive angiography, while 8% of control patients and 7% of triage patients underwent stress echocardiography. False-positive results were defined as a normal result on stress echocardiography or <50% stenosis found on non-invasive or invasive angiography, despite a positive first test initially. The false-positive rate was not statistically significant between both groups (triage vs control: 20% vs 29%, P = 0.383).

Discharge Rates at First Consultation

The discharge rate at first consultation was significantly higher in the triage group than control group (69% vs19%, P <0.0001) (Table 2). Intermediate- and high-risk cohorts were associated with higher discharge rates compared to controls (P <0.0001).

Patient Costs

Mean consultation cost (in SGD) per patient decreased by 32% from $59 (for controls) to $40 (for triage [$P$ <0.0001]). However, test costs were increased, resulting in an overall increase in patient costs (inclusive of tests and consultations) from $357 to $421 ($P$ = 0.0030). When stratified by risk, the low-risk group showed a significant increase in total cost (triage vs control, $459 vs $364, P <0.0001), whereas the intermediate- and high-risk groups exhibited no significant differences (triage vs control: intermediate, $417 vs $365, P = 0.0915 and high, $387 vs $341, P = 0.3847).

Adverse Cardiac Outcomes

The percentage of patients with adverse cardiac outcomes (death, heart failure, coronary artery bypass, percutaneous intervention or hospitalisation for stroke or myocardial infarction) within 6 months from discharge was not significantly different between triage (0.57%) and control (0.35%) patients (P = 1.000). The patient count with adverse cardiac events in the triage and control groups

was 3 and 1, respectively. In the triage group, 1 patient required hospitalisation for stroke and 2 patients had acute coronary syndrome requiring percutaneous intervention. In the control group, 1 patient had a myocardial infarction requiring percutaneous intervention.

Discussion

Our study demonstrated that the 'Triage Protocol' reduced referral to diagnosis times and total visits, and increased rates of discharge after the first consultation, with no perceptible increase in adverse outcomes. Costs were comparable in the intermediate- and high-risk group but higher in the low-risk group. As to effect on capacity, the 'Triage Protocol' saved an average of 626 specialist outpatient visits over 12 months or 52 visits per month at our outpatient cardiology centre.

Internationally, several institutions have implemented outpatient chest pain algorithms to streamline workflows for chest pain referrals. UK's RACPCs provide a fast-route entry system for chest pain patients to see cardiologists within 2 weeks for quick diagnosis and treatment. The algorithm of RACPCs under NICE 95 Guidelines is as follows: Very low-risk patients are reassured and discharged; low-risk patients are offered cardiac computed tomography (CT); intermediate-risk patients are offered functional imaging; and high-risk patients are offered invasive coronary angiography or functional testing.[15-17] With over160 clinics rolled out in the UK and adoption in Australia,[18,19] reviews on RACPCs have been mixed. The system uses evidence-based medicine to shorten diagnosis times[20] and provides patients with faster reassurance,[21] but in some studies, it has increased investigation costs and hence, overall costs.[16,22,23] Cardiac EASE in Canada provides prospective testing based on a physician-approved algorithm, previsit triage and a multidisciplinary clinic.[7] The Cardiac EASE algorithm bears similarities to the RACPC's, whereby low-risk CAD patients obtain a cardiologist assessment without tests, intermediate-risk CAD patients undergo functional tests if they have valvular or pericardial disease or ventricular dysfunction, and high-risk CAD patients are referred to an emergency department based on chest pain evaluation programme.[7] Cardiac EASE has reduced time to initial cardiac consultation, time to clinical diagnosis and increased referral numbers.[7]

Locally, the 'Triage Protocol' has yielded similar results. The percentage reduction in time to a clinical diagnosis under the Cardiac EASE was comparable to that of the 'Triage Protocol' (Cardiac EASE vs 'Triage Protocol': 58% vs 65%). The triage algorithm follows the 2012 ACCF/AHA guidelines on stable heart disease[9] and aids in the resource allocation of specialists to patients requiring follow-up, without a compromise in patient safety. The algorithm incorporates a locally validated MDCS, which unlike the Duke Clinical Score, does not require an ECG. In a sensitivity analysis, outcomes using the MDCS were compared to those using the European CAD Consortium Risk Score with no substantive differences. The 'Triage Protocol' was tailored to the local patient population while capitalising on available resources and cardiology services in Singapore.

Higher costs in the low-risk cohort can be attributed to a shift in number of tests ordered as a result of the triage algorithm. The algorithm resulted in an increased in number of functional tests ordered in the low-risk group, which may not have been ordered in the prior system. To improve our current algorithm, we can adopt practices from the RACPCs and Cardiac EASE. UK RACPCs which use NICE Clinical Guideline 95 found that at very low pretest likelihood of CAD (<10% on the Pryor et al CAD score),[13] patients could be reassured and did not require further testing.[17] Similarly, the Cardiac EASE algorithm exempts low-risk patients from tests, sending them straight to an EASE cardiologist for assessment.[7] Further refinements to the testing protocol for those in the low-risk groups would be needed to minimise unnecessary functional testing, exposure to radiation and costs. Work is also in progress to introduce risk stratification at the onset of the protocol and to focus mainly on intermediate- and high-risk patients, to minimise unnecessary testing in the low-risk group.

A few limitations exist in our study. First, our primary outcome of time to diagnosis might be biased by our study design, which inherently reduces time to clinical diagnosis by ensuring that tests occur prior to the first cardiology consultation. However, this is the exact benefit we wanted to accrue for our patients—allowing an earlier time to diagnosis while ensuring their safety and the protocol's efficacy. Second, the study was a single centre experience and outcomes of implementation may vary in other institutions. Fortunately, the protocol is simple and could potentially be easily applied to other centres. Third, the authors were unable to adjust for confounding effects of administrative initiatives introduced during the study periods. Finally, while our 'Triage Protocol' focuses on stress ECG and myocardial perfusion imaging as our main initial testing modalities, other testing strategies may also be viable (e.g. stress echocardiogram, CT coronary angiogram). Due to constraints in scheduling, we did not incorporate these alternative methods in this study. Non-invasive coronary CT angiography is relatively cost-effective and has a 95%-99% sensitivity in diagnosing cardiovascular disease, but involves radiation exposure and may sometimes require further testing to evaluate the functional significance of a coronary stenosis.[24,25] Stress echocardiography offers a 85% sensitivity in detecting cardiovascular disease, reduced radiation exposure, incremental information on valvular

function, a lower cost-point than myocardial perfusion imaging, but is operator-dependent.[26] These options were not included due to logistical reasons and resource availability during the initial implementation of the protocol. We chose to use primarily myocardial perfusion imaging as we had the capacity to assign and schedule patients for this test in our institution. To some extent, our findings should be broadly applicable to other tests used, though the cost estimates would differ accordingly. The feasibility of alternative testing strategies being integrated into the protocol is currently being studied.

Conclusion

In summary, the 'Triage Protocol' showed a significant decrease in referral to diagnosis time and total visits for all risk cohorts and should be considered as a useful adjunct in optimising resources in the busy outpatient setting.

REFERENCES

1. World Health Organization Cardiovascular Diseases Fact Sheet. 2016.
2. Office NRoD. Trends in acute myocardial infarction in Singapore 2007-2013. Singapore Myocardial Infarction Registry Report No 3. 2015.
3. Verdon F, Herzig L, Burnand B, Bischoff T, Pecoud A, Junod M, et al. Chest pain in daily practice: occurrence, causes and management. Swiss Med Wkly 2008;138:340-7.
4. Bösner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sönnichsen AC, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. Eur J Gen Pract 2009;15:141-6.
5. Nilsson S, Scheike M, Engblom D, Karlsson LG, Molstad S, Akerlind I, et al. Chest pain and ischaemic heart disease in primary care. Br J Gen Pract 2003;53:378-83.
6. Liew WD HS. Waiting times for new appointments at Specialist Outpatient Clinics (SOC) in Restructured Hospitals. Ministry of Health Information Paper. 2007.
7. Bungard TJ, Smigorowsky MJ, Lalonde LD, Hogan T, Doliszny KM, Gebreyesus G, et al. Cardiac EASE (Ensuring Access and Speedy Evaluation) - the impact of a single-point-of-entry multidisciplinary outpatient cardiology consultation program on wait times in Canada. Can J Cardiol 2009;25:697-702.
8. Boyle RM. Value of rapid-access chest pain clinics. Heart 2007;93:415-6.
9. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:2564-603.
10. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, et al. ACC/AHA/ACP–ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). Circulation 1999;99:2829-48.
11. Tan O, Allen J, Tay YL, Chua T, Tan SY. Comparison of Duke Clinical Score Versus a Simplified Local Risk Model in Predicting Obstructive Coronary Artery Disease in a South East Asian Population. J Am Coll Cardiol 2014;63(12_S).
12. Pryor DB, Harrell FE Jr., Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. Am J Med 1983;75:771-80.
13. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. Ann Intern Med 1993;118:81-90.
14. Almeida J, Fonseca P, Dias T, Ladeiras-Lopes R, Bettencourt N, Ribeiro J, et al. Comparison of Coronary Artery Disease Consortium 1 and 2 Scores and Duke Clinical Score to Predict Obstructive Coronary Disease by Invasive Coronary Angiography. Clin Cardiol 2016;39:223-8.
15. Athauda-Arachchi PM, Hutcheon SD. Assessing the implications of implementing the NICE guideline 95 for evaluation of stable chest pain of recent onset: a single centre experience. Scottish Medical Journal 2013;58:12-5.
16. Patterson C, Nicol E, Bryan L, Woodcock T, Collinson J, Padley S, et al. The effect of applying NICE guidelines for the investigation of stable chest pain on out-patient cardiac services in the UK. QJM 2011;104:581-8.
17. Lee AJX, Michail M, Quaderi SA, Richardson JA, Aggarwal SK, Speechly-Dick ME. Implementation of NICE Clinical Guideline 95 for assessment of stable chest pain in a rapid access chest pain clinic reduces the mean number of investigations and cost per patient. Open Heart 2015;2:e000151.
18. Elford A, Black A, Flood J. Establishment of a rapid access chest pain clinic at the Royal Hobart Hospital. Heart Lung Circ 2015;24:S147.
19. Klimis H, Thiagalingam A, Bhaskaran A, Kovoor P, Vukasovic M, Zecchin R, et al. Evaluation of cardiology rapid access clinics within a large NSW tertiary referral centre - pilot. Heart Lung Circ 2015;24:S147-8.
20. Debney MT, Fox KF. Rapid access cardiology—a nine year review. QJM 2012;105:231-4.
21. Price JR, Mayou RA, Bass CM, Hames RJ, Sprigings D, Birkhead JS. Developing a rapid access chest pain clinic: qualitative studies of patients' needs and experiences. J Psychosom Res 2005;59:237-46.
22. Rogers T, Dowd R, Yap HL, Claridge S, Al Fakih K, Byrne J. Strict application of NICE Clinical Guideline 95 'chest pain of recent onset' leads to over 90% increase in cost of investigation. Int J Cardiol 2013;166:740-2.
23. Ghosh A, Qasim A, Woollcombe K, Mechery A. Cost implications of implementing NICE guideline on chest pain in rapid access chest pain clinics: an audit and cost analysis. J Public Health (Oxf) 2012;34:397-402.
24. Genders TS, Petersen SE, Pugliese F, Dastidar AG, Fleischmann KE, Nieman K, et al. The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis. Ann Intern Med 2015;162:474-84.
25. Moss AJ, Williams MC, Newby DE, Nicol ED. The Updated NICE Guidelines: Cardiac CT as the First-Line Test for Coronary Artery Disease. Curr Cardiovasc Imaging Rep 2017;10:15.
26. Senior R, Monaghan M, Becher H, Mayet J, Nihoyannopoulos P. Stress echocardiography for the diagnosis and risk stratification of patients with suspected or known coronary artery disease: a critical appraisal. Supported by the British Society of Echocardiography. Heart 2005;91:427-36.

Original Article

Long-Term Neurodevelopmental Outcomes of Premature Infants in Singapore

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Abstract

Introduction: Neonatal care advances have resulted in improved survival but have raised concerns of increase in neurodevelopmental impairment. This study looked at long-term neurodevelopmental outcomes at ages 5 and 8 years of very low birthweight infants born in the 2000s as compared to the 1990s. Neurodevelopmental assessment at 2 years old was compared to that at 5 and 8 years to determine if assessment at 2 years was predictive of later outcomes. Materials and Methods: A retrospective cohort study of consecutive infants with birthweight less than 1250 grams admitted to a tertiary centre in Singapore between January 1994 to December 1995 (Epoch I) and January 2004 to December 2005 (Epoch II) were included. Neurodevelopmental impairment was defined as having an intelligence quotient (IQ) of less than 70, cerebral palsy, legal blindness, or hearing impairment requiring hearing aids. Results: Mean gestational age was lower for Epoch II compared to Epoch I (28.1 ± 2.5 vs 29.4 ± 2.7 weeks, *P* = 0.004). Death or neurodevelopmental impairment rates did not differ (24.3% and 17.1% at 5 years old, *P* = 0.398; 29.1% and 25.0% at 8 years old, *P* = 0.709). There was improvement in visual impairment rate at 8 years in Epoch II (10.7% vs 34.0%, *P* = 0.024). Mean IQ was better in Epoch II (109 and 107 vs 97 and 99 at 5 [*P* = 0.001] and 8 years [*P* = 0.047], respectively). All infants with no neurodevelopmental impairment at 2 years remained without impairment later on. Conclusion: Over a decade, neurodevelopmental outcomes did not worsen despite lower mean gestational age. Long-term improvement in IQ scores and a reduction in visual impairment rates were seen. Our data suggests that children without neurodevelopmental impairment at 2 years are without impairment later on; therefore, they may need only developmental monitoring with targeted assessments instead of routine formal IQ assessments.

Ann Acad Med Singapore 2018;47:63-70

Key words: Development, Very low birthweight infants

Introduction

The survival rates for very low birthweight (VLBW) infants have increased over the last 2 decades due to advances in neonatal intensive care,[1-7] changes in institutional practices at the turn of the century (including the rise in use of antenatal steroids and decrease in use of postnatal steroids), and the increase in caesarean section deliveries.[8] With improved survival of premature infants, there are concerns about the concomitant increase in neurodevelopmental impairment among survivors. Most studies on neurodevelopmental outcomes of preterm infants focused on short-term outcomes at about 2 years of corrected age.[2-4,6] Recently, there have been studies from Singapore, Japan and Germany that looked at the long-term impacts of these interventions after 5 years of age, showing a general trend in improvement of moderate to severe neurodevelopmental impairment.[9-11] However, long-term neurodevelopmental outcomes in different countries for VLBWs are affected by a wide variety of factors – from the different antenatal, perinatal and neonatal care to

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subsequent follow-up and interventions, social factors such as family setup and parenting practices, and educational factors of schooling such as early intervention programmes and special schools. Hence, it is important to look at the neurodevelopmental outcomes in a particular local setting.

According to the World Health Organization (WHO), Singapore's prematurity rate of 11.5% ranks 67th globally.[12] Low birthweight is the second leading cause of disease burden in children in Singapore, accounting for 7.7% of disability-adjusted life years (DALYs) in 0- to 14-year-old children.[13] Thus, we sought to assess the outcomes in premature infants born during the 2 periods (1994 to 1995 versus 2004 to 2005) that reflected the changes in perinatal practices.

This study aimed to compare the rates of survival, neonatal morbidity, mortality and neurodevelopmental impairment in 2 cohorts of VLBW infants born in our centre in the mid-1990s and mid-2000s, longitudinally at 2, 5 and 8 years of age.

Materials and Methods

This is a retrospective cohort study of consecutive infants with birthweight less than 1250 grams born between January 1994 to December 1995 (Epoch I) and January 2004 to December 2005 (Epoch II).

Although the study was retrospective in nature, the majority of the primary hospitalisation data were collected into the departmental VLBW database prospectively while the infants were still admitted. Surviving infants were assessed at 2 years of corrected age, and 5 and 8 years of chronological age as per the departmental follow-up protocol.

Neurological examinations were performed by a certified neonatologist and standardised assessments were performed by a trained child psychologist. At the corrected age of 2 years, patients underwent the Bayley Scale of Infant Development Edition II (BSID-II) or III (BSID-III), depending on the year it was performed (BSID-III was used for patients born in 2005). The BSID is one of the most widely and commonly used tools to measure developmental delays in high-risk and preterm infants between 1 to 42 months. With the knowledge that BSID-III tends to overestimate ability compared to BSID-II,[14-17] scores of the former were converted using a conversion factor as derived from a study performed on 185 extremely preterm infants that produced a predicted Mental Development Index (MDI) score and a Combined Bayley-III (CBI-III) score, which allowed us to compare scores from BSID-II and BSID-III more accurately.[13] At 5 years of age, patients underwent the Wechsler Preschool and Primary Scale of Intelligence Edition II (WPPSI-II) or III (WPPS-III) depending on the year it was performed. At 8 years of age, they underwent the Wechsler Intelligence Scale for Children Edition III (WISC-III) or IV (WISC-IV) depending on the year it was performed. The WISC is the most commonly used tool for measuring cognitive ability.

Outpatient case notes were retrospectively reviewed and data regarding the child's growth parameters, schooling and interventions received, presence of epilepsy, visual or hearing impairment, neurological examination and results of neurodevelopmental assessments were collected.

Neurodevelopmental impairment at 2 years of age was defined as having BSID-II MDI less than 70 or CBI-III less than 80, cerebral palsy, hearing impairment requiring hearing aids or being legally blind. Neurodevelopmental impairment at 5 and 8 years of age was defined as having full scale intelligence quotient (IQ) score (FSIQ) or performance IQ score (PIQ) (if FSIQ was not available) of less than 70, cerebral palsy, hearing impairment requiring hearing aids or being legally blind. Cases of cerebral palsy were characterised according to the pattern of neurological findings, e.g. diplegia, monoplegia, hemiplegia and quadriplegia, and not according to the severity of impairment.

Intraventricular haemorrhage (IVH) was diagnosed through serial cranial ultrasounds which were performed twice a week for the first 2 weeks of life and subsequently weekly using the Papile et al classification.[18] Necrotising enterocolitis (NEC) was defined according to modified Bell's criteria based on clinical and radiological features.[19] Retinopathy of prematurity (ROP) was diagnosed by paediatric ophthalmologists, which established the presence and staging of ROP according to the international classification of ROP for babies with gestation less than 32 weeks or birthweight less than 1250 grams.[20] Chronic lung disease (CLD) was defined as oxygen dependency at 36 weeks postmenstrual age or beyond. Sepsis (nosocomial) was defined as blood culture-positive sepsis occurring beyond 72 hours of life.

The primary outcomes that were compared for the 2 periods (Epoch I and Epoch II) were death or neurodevelopmental impairment in survivors at 2, 5 and 8 years of age. Secondary outcomes were neurodevelopmental measures at 2, 5 and 8 years of age using scores on standardised neurodevelopmental assessments, cerebral palsy, visual or hearing impairment, and whether the child needed special education. Finally, we analysed for potential factors that may affect neurodevelopmental outcomes. We also assessed whether neurodevelopmental outcomes at 2 years of age predicted the outcomes at subsequent follow-up at 5 and 8 years of age.

The data was analysed using IBM SPSS Statistics 21.0. Categorical variables were analysed using chi-square, parametric data was analysed using independent t-test and non-parametric data was analysed using the Mann-Whitney U test. Logistic regression was used to determine perinatal variables associated with neurodevelopmental impairment.

Spearman's correlation coefficient was used to determine the strength of association between the MDI or CBI score at 2 years of age and the FSIQ or PIQ score at 5 and 8 years of age.

Results

A total of 90 infants in Epoch I and 55 infants in Epoch II were evaluated. The patient disposition is shown in Figure 1.

Of the infants who survived, the baseline characteristics of those who were lost to follow-up were similar to the group who were not, except for higher rates of severe IVH (8.3% vs 1.3%, $P = 0.049$) and major malformations (14.6% vs 3.8%, $P = 0.030$) in the infants lost to follow-up (Table 1).

Table 2 summarises the perinatal characteristics. Infants born in Epoch II had significantly lower gestational age, were more likely to be delivered via caesarean section, had older mothers, were more likely to have maternal gestational diabetes and prolonged rupture of membranes. They were also more likely to have completed at least 1 course of antenatal steroids.

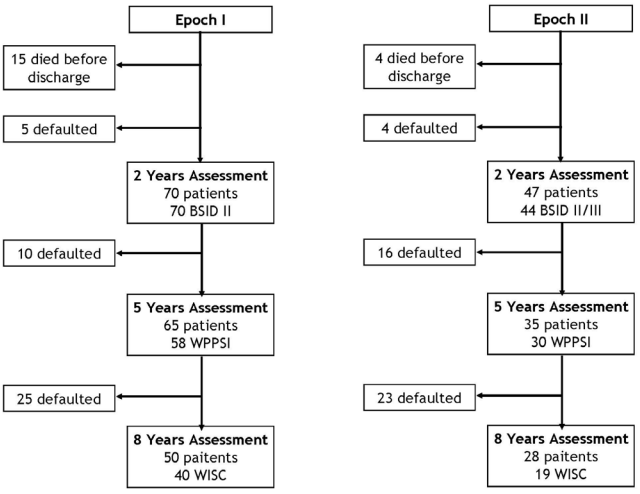

Fig. 1. Flowchart of the recruitment of patients with type 2 diabetes mellitus. BSID: Bayley Scale of Infant Development; WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Preschool and Primary Scale of Intelligence

Table 1. Background Demographics of Survey Participants

	Not Followed-up* n = 48	Followed-up* n = 78	*P* Value
PDA requiring:			
Medical therapy	17 (35.4)	35 (44.9)	0.295
Surgical ligation	1 (2.1)	7 (9.0)	0.123
Chronic lung disease	9 (18.8)	23 (29.5)	0.179
Necrotising enterocolitis	1 (2.1)	3 (3.8)	0.584
ROP	10 (20.8)	21 (26.9)	0.441
Severe ROP†	3 (6.2)	5 (6.4)	0.971
IVH	6 (12.5)	7 (9.0)	0.528
Severe IVH‡	4 (8.3)	1 (1.3)	0.049
Bilateral IVH	4 (8.3)	2 (2.6)	0.140
Shunt for hydrocephalus	1 (2.1)	0 (0.0)	0.201
Seizures requiring anti-convulsants	3 (6.2)	4 (5.1)	0.790
Blood culture-positive septicaemia	7 (14.6)	15 (19.2)	0.505
Meningitis	1 (2.1)	1 (1.3)	0.727
Major malformation	7 (14.6)	3 (3.8)	0.030

IVH: Intraventricular haemorrhage; PDA: Patent ductus arteriosus; ROP: Retinopathy of prematurity

*Numbers represent n (%).

†Severe ROP defined as grade 3 or 4 ROP or ROP requiring laser or cryotherapy.

‡Severe IVH defined as grade 3 or 4 IVH.

Table 2. Perinatal Characteristics

	Epoch I* n = 90	Epoch II* n = 55	*P* Value
Gestational age†	29.4 ± 2.7	28.1 ± 2.5	0.004
Birthweight (grams)‡	1020 (833.8 – 1160.0)	976 (795.0 – 1130.0)	0.360
Small for gestational age	30 (33.3)	16 (29.1)	0.594
Gender (male)	46 (51.1)	27 (49.1)	0.813
Race			0.574
Chinese	63 (70.0)	42 (76.5)	
Malay	18 (20.0)	7 (12.7)	
Indian	5 (5.6)	2 (3.6)	
Others	4 (4.4)	4 (7.3)	
Multiple births	22 (24.4)	14 (25.5)	0.891
Maternal age†	30.8 ± 5.6	32.8 ± 4.2	0.022
Maternal employment	48 (54.5)	36 (63.6)	0.284
Maternal pre-eclampsia	24 (26.7)	16 (29.1)	0.751
Maternal gestational diabetes	1 (1.1)	5 (9.1)	0.019
Antepartum haemorrhage	9 (10.0)	11 (20.0)	0.090
Rupture of membranes >24 hours	17 (18.9)	19 (34.5)	0.034
Antenatal steroids used	45 (50.0)	41 (74.5)	0.004
In-vitro fertilisation	8 (8.9)	7 (12.7)	0.461
Outborn	14 (15.6)	9 (16.4)	0.897
Caesarian delivery	46 (51.1)	39 (70.9)	0.019
1-minute Apgar Score‡	5 (3.0 – 6.3)	6 (5.0 – 7.0)	0.010
5-minutes Apgar Score‡	8 (7.0 – 9.0)	8 (7.0 – 9.0)	0.007

*Numbers represent n (%).

†Mean ± standard deviation.

‡Median (interquartile range).

Table 3 summarises the morbidities and mortality. In terms of the treatment given, infants in Epoch II received continuous positive airway pressure (CPAP) for a significantly longer duration and this is likely due to less proportion of babies being intubated and mechanically ventilated. Infants in Epoch II received significantly lower mean oxygen concentration in the first week of life and postnatal steroids. Rates of major morbidities—defined as IVH, CLD, NEC and ROP—were similar between Epoch I and II. Infants born in Epoch II had a longer length of stay but were discharged at around the same postmenstrual age of 38 to 39 weeks, which may be due to having a lower gestational age at birth.

The mortality rate in Epoch I was higher than Epoch II (16.7% vs 7.3%) but this was not statistically significant. Of the infants who died, 5 in Epoch I had major congenital malformations, including anencephaly, trisomy 18 with oesophageal atresia and hypoplastic left heart syndrome, pentalogy of Cantrell, major chromosomal translocation and hydrops fetalis, and 1 in Epoch II had mesocardia with right lung hypoplasia.

Table 4 summarises the neurodevelopmental outcomes at different ages. There was no statistical difference between the 2 epochs for death or neurodevelopmental impairment as well as neurodevelopmental impairment alone in survivors.

While the MDI at 2 years of age was significantly poorer in Epoch II, IQ scores were significantly better at 5 and 8 years of age. Also, a greater proportion of children in Epoch II had a normal IQ at 5 and 8 years of age, although this was not statistically significant. Using the actual cognitive scores instead of the predicted MDI scores for the patients who had done the BSID-III at 2 years old, the scores of Epoch II approached that of Epoch I (mean MDI score for Epoch I, 91.2 ± 23.0; mean MDI/cognitive score for Epoch II, 87.4 ± 14.2, P = 0.278). Similarly, using the cutoff of MDI or cognitive score of less than 70 to define neurodevelopmental impairment, there was a non-significant trend of improvement in the primary outcome of death or neurodevelopmental impairment at 2 years of age (31.8% for Epoch I vs 22.9% for Epoch II, P = 0.278).

The rate of visual impairment, including myopia and astigmatism, was significantly reduced in Epoch II (8 years of age adjusted OR: 0.13; 95% CI, 0.03 to 0.60). There was no difference in rates of cerebral palsy, hearing impairment, or special school attendance between the 2 epochs.

Logistic regression analysis was conducted to identify predictors of neurodevelopmental impairment at 2, 5 and 8 years of age using the following predictors: demographic and family characteristics including gestational age, birthweight, gender, race, maternal age and employment; neonatal practices including use of antenatal and postnatal steroids, use of surfactant, and mean fraction of inspired oxygen; and morbidities including NEC, ROP, patent ductus arteriosus, CLD and IVH. Birthweight and use of antenatal steroids were significant predictors of neurodevelopmental impairment at 2 years of age (B -0.004, P = 0.001 and B 1.227, P = 0.036 respectively). Presence of CLD was a significant predictor for neurodevelopmental impairment at 5 years of age (B 2.501, P = 0.029). No significant predictors were found for neurodevelopmental impairment at 8 years of age.

Table 3. Major Morbidities and Mortality during Primary Hospitalisation

	Epoch I* n = 90	Epoch II* n = 55	*P* Value
Died	15 (16.7)	4 (7.3)	0.104
Hyaline membrane disease	41 (45.6)	25 (45.5)	0.991
Surfactant given	24 (26.7)	12 (21.8)	0.512
Mechanical ventilation	60 (66.7)	28 (50.9)	0.059
Mechanical ventilation duration (days)§	6 (2 – 23)	7 (2 – 35)	0.880
CPAP duration (days)§	11 (3 – 33)	32 (18 – 43)	0.001
Oxygen exposure			
Duration of oxygen (days)§	7 (1 – 34)	21 (4 – 49)	0.057
Mean oxygen concentration (%)§	30 (22 – 40)	24 (21 – 30)	0.004
Postnatal systemic steroids	17 (18.9)	1 (1.8)	0.002
Chronic lung disease	19 (21.1)	15 (27.3)	0.395
Necrotising enterocolitis	3 (3.3)	3 (5.5)	0.534
ROP	16 (17.8)	15 (27.3)	0.176
Severe ROP†	4 (4.4)	4 (7.3)	0.469
IVH	7 (7.8)	7 (12.7)	0.328
Severe IVH‡	5 (5.6)	2 (3.6)	0.601
Bilateral IVH	4 (4.4)	3 (5.5)	0.783
Shunt for hydrocephalus	0 (0)	1 (1.8)	0.199
Seizures requiring anti-convulsants	6 (6.7)	3 (5.5)	0.769
Blood culture positive septicaemia	13 (14.4)	13 (23.6)	0.162
Meningitis	0 (0)	2 (3.6)	0.069
Length of stay (days)§	60 (53 – 83)	72 (56 – 88)	0.050
Postmenstrual age at discharge (weeks)§	39 (37 – 41)	38 (37 – 40)	0.429

CPAP: Continuous positive airway pressure; IVH: Intraventricular haemorrhage; ROP: Retinopathy of prematurity

*Numbers represent n (%).

†Severe ROP defined as grade 3 or 4 ROP or ROP requiring laser or cryotherapy.

‡Severe IVH defined as grade 3 or 4 IVH.

§Median (interquartile range).

Table 4. Comparison of Primary and Secondary Outcomes

	Age of Follow-up	Epoch I*	Epoch II*	*P* Value
Death or neurodevelopmental impairment	2 years	27/85 (31.8)	16/48 (33.3)	0.853
	5 years	18/74 (24.3)	6/34 (17.1)	0.398
	8 years	16/55 (29.1)	6/23 (25.0)	0.709
Neurodevelopmental impairment	2 years	12/70 (17.1)	12/44 (27.3)	0.197
	5 years	3/58 (5.1)	2/30 (6.5)	0.788
	8 years	1/40 (2.5)	2/19 (10.0)	0.209
MDI at 2 years, FSIQ or PSIQ if FSIQ was not available at 5 and 8 years of age Mean ± SD	2 years	91.2 ± 23.2	79.7 ± 16.3	0.005
	5 years	97.0 ± 12.3	109.0 ± 15.8	0.001
	8 years	99.0 ± 15.0	107.0 ± 12.2	0.047
≤70	2 years	12/70 (17.1)	11/44 (25.0)	0.010
	5 years	1/58 (1.7)	0/30 (0.0)	0.103
	8 years	1/40 (2.5)	0/19 (0.0)	0.740
71 – 84	2 years	10/70 (14.3)	15/44 (34.1)	0.010
	5 years	7/58 (12.1)	0/30 (0.0)	0.103
	8 years	3/40 (7.5)	1/19 (5.3)	0.740
≥85	2 years	48/70 (68.6)	18/44 (40.9)	0.010
	5 years	50/58 (86.2)	30/30 (100.0)	0.103
	8 years	36/40 (90.0)	18/19 (94.7)	0.740
Cerebral palsy	2 years	2/70 (2.9)	3/47 (6.4)	0.355
	5 years	2/64 (3.1)	1/35 (2.9)	0.970
	8 years	0/50 (0.0)	1/28 (3.7)	0.171
Visual impairment (any)	2 years	15/70 (21.4)	2/47 (4.3)	0.010
	5 years	17/64 (26.6)	6/35 (17.1)	0.289
	8 years	17/50 (34.0)	3/28 (10.7)	0.024
Hearing impairment (any)	2 years	2/70 (2.9)	3/47 (6.4)	0.355
	5 years	1/64 (1.5)	2/35 (5.7)	0.243
	8 years	0/50 (0.0)	2/28 (7.1)	0.056
Attending special school	2 years	4/38 (10.5)	3/47 (6.4)	0.103
	5 years	1/65 (1.5)	1/35 (2.9)	0.478
	8 years	2/50 (4.0)	1/28 (3.6)	0.753

FSIQ: Full scale intelligence quotient; MDI: Mental Development Index; PSIQ: Performance scale intelligence quotient; SD: Standard deviation
*Numbers represent n (%).

All the patients who were categorised to have no neurodevelopmental impairment at 2 years of age continued to remain unimpaired at 5 and 8 years of age. Of these children who were unimpaired at 2 years of age, 19.0% had received some form of therapy, including speech therapy, occupational therapy or physiotherapy. Of those who were categorised to have neurodevelopmental impairment at 2 years of age, only about a third of them continued to have impairment at 5 and 8 years of age (Table 5). The positive predictive value of being neurodevelopmentally

Table 5. Neurodevelopmental Impairment at 2, 5 and 8 Years of Age

		Neurodevelopmental Impairment at 5 Years of Age		Neurodevelopmental Impairment at 8 Years of Age	
		Yes	No	Yes	No
Neurodevelopmental impairment at 2 years of age	Yes	5 (33.3)	10 (66.7)	3 (30.0)	7 (70.0)
	No	0 (0.0)	74 (100.0)	0 (0.0)	48 (100.0)

impaired at 8 years of age, if the child was classified as neurodevelopmentally impaired at 2 years of age, was 0.3. The negative predictive value was 1.0. There was a significant, positive correlation between the predicted MDI at 2 years and IQ score at 5 years of age (Spearman correlation coefficient: 0.385, $P \leq 0.001$) and at 8 years of age (Spearman correlation coefficient: 0.312, $P = 0.018$).

Discussion

As expected, there were differences in the 2 epochs studied in our study in terms of perinatal characteristics and morbidities. However, mortality, neurodevelopmental impairment and outcomes were not significantly different between the 2 periods. The overall neurodevelopmental outcomes did not worsen despite a lower mean gestational age in the mid-2000s (Epoch II) compared to the mid-1990s (Epoch I), with an improvement in long-term visual impairment rates and IQ scores. Our data also suggested that children with no neurodevelopmental impairment at 2 years of age were without major impairment at 5 and 8 years of age; therefore, they may need only developmental monitoring for late effects and targeted formal psychological assessments instead of routine repeated cognitive assessments in later years.

Improving survival rates in local VLBW cohorts carry the concern of whether there is a concomitant increase in neurodevelopmental impairment. These improvements in survival and neurodevelopmental outcomes in the mid-2000s in VLBW infants have been well documented in the literature to be associated with increased antenatal corticosteroid use, saturation targeting to reduce excessive oxygen exposure, increased use of surfactant and limiting the use of postnatal systemic steroids.[21,22]

Our study cohort had less patients in Epoch II compared to Epoch I. A 24% reduction in live birth rate in Singapore from the first to the second epoch (74,666 vs 98,189 total live births) may have partially accounted for the difference in admission rates between the 2 epochs.[23] We also expect year-to-year variation in prematurity rates.

The difference between death or neurodevelopmental impairment rates at both 5 and 8 years of age were non-significant for the 2 epochs. However, we should not ignore an important trend towards improved survival rates despite significantly lower gestational age, although this did not reach statistical significance. Looking at the combined outcome of death or neurodevelopmental impairment, there was also a discernible trend towards improvement as the numbers for death or neurodevelopmental impairment were consistently lower at 5 and 8 years of age, although this again did not reach statistical significance. Both of these results could be explained by the small numbers involved.

IQ scores were significantly better in Epoch II with a 12-point increase at 5 years and an 8-point increase at 8 years of age. While we recognise that the Flynn effect (rising intelligence test performance in the general population over time and generations) may be a contributory factor, meta-analyses estimate average IQ score gain per decade to be only 2.8 to 2.93. Although this phenomenon is widely accepted, its substantive meaning and causes remain elusive, varies enigmatically across countries and intelligence domains, and estimates of its magnitude and error of measurement are controversial.[24,25]

The reason behind the observation that the mean adjusted cognitive score on the BSID-III was lower in Epoch 2 is uncertain. However, it is heartening to note that the formal assessments of intellectual ability of these children at 5 and 8 years of age were normal, with the BSID-III at 2 years of age underestimating their intellectual ability. Using the unadjusted BSID-III cognitive scores, patients in Epoch II had a trend towards decreased neurodevelopmental impairment, which was similar to that found at 5 and 8 years of age. The differences in 2 years of age scores and proportion of patients categorised as having neurodevelopmental outcomes between the adjusted and non-adjusted scores for the patients who received the BSID-III were similar to the findings published by the National Institute of Child Health and Network Human Development Neonatal Research in 2012.[17] Whether the BSID-III is an overestimate of cognitive performance or a more valid assessment of emerging cognitive skills than BSID-II is still unclear. In addition, this overestimation of cognitive performance on the BSID-III and the use of the conversion factor have not been validated in our local population.

In our study, all children classified as having no neurodevelopmental impairment at 2 years of age remained classified as having no neurodevelopmental impairment at 5 and 8 years of age (negative predictive value of 1.0). This finding was similar to a study by Hack et al in 2005 which involved 330 extremely low birthweight infants born between 1992 and 1995. This study measured their cognitive functioning at 20 months of corrected age using the BSID-II and at 8 years of age using the Kaufman Assessment Battery for Children, and the negative predictive value was 0.98. This suggested that the assessment at 2 years of age was useful in predicting later outcomes and the information could be used for better counselling of parents and resource allocation (i.e. more resources can be allocated to those who were classified as having neurodevelopmental impairment at 2 years of age). While this may be preliminary data, it suggested that formal IQ assessments may not need to be routinely repeated at later years if the child's IQ was normal earlier on. These children should, however, continue to have developmental surveillance by trained developmental

paediatricians. If the index of suspicion for conditions such as autism, attention-deficit hyperactivity disorder, or learning disorders is high, then targeted formal assessments (beyond cognitive assessments alone) for these conditions should be performed.

The key strength of the study is that the data available has enabled the comparison between the 2 different sets of practices from the 2 periods (Epoch I and II) to see whether the increase in survival of the number of preterm infants over time has correspondingly led to an increase in the neurodevelopmental outcomes in these survivors. This would have been otherwise impossible in a prospective study design since many of the practices and interventions used in the earlier epoch have now become standard of care and it would have been no longer ethically or practically possible to quantify their impact in a real-world, local setting.

Our finding of chronic lung disease being a predictor of neurodevelopmental impairment at 5 years of age is consistent with known literature.[26-28] Interestingly, despite birthweight being a significant predictor of neurodevelopmental outcome at 2 years of age, the neurodevelopmental outcome remained the same in the 2 epochs even though infants in Epoch II had a lower birthweight. This reflects that there were possibly other factors that had an impact on the neurodevelopmental outcomes, for example perinatal practices, which was not statistically significant in our analysis. Unfortunately, owing to the small sample size, we were not able to delve much into the factor(s) that may have contributed to the neurodevelopmental outcomes in these preterm infants. Future studies may explore these factors in a prospective design to understand the role of each of these factors/practices/interventions that may have an impact on the neurodevelopmental outcomes. Alternatively, it may be that, instead of a single intervention/practice, it was a particular set of practices that may have complemented each other resulting in better neurodevelopmental outcomes in these preterm infants.

The limitations of our study were the small sample size and low follow-up rates. Comparison between the group that was followed-up versus that which was not showed that both were similar in baseline characteristics, except for higher rates of severe IVH and major malformations. Given the longitudinal nature of the data analysis, especially for an uncommon disease, increasing the sample size by way of inclusion of patients from various centres may introduce more biases on account of confounding factors such as differences in neonatal care practices and disease severity. At the same time, expanding the period of data may introduce more biases on account of the changes in neonatal practices with time. Having a control group of typically developing children born in Singapore in the same 2 periods and measuring their IQ scores would have helped to confirm if the improvement in IQ score is truly significant.

Conclusion

Overall neurodevelopmental outcomes over a decade did not worsen despite a lower mean gestational age. Long-term improvement in IQ scores and a reduction in visual impairment rates were seen. The assessment of neurodevelopmental impairment at 2 years of age may serve as a good cutoff to predict 5- and 8-year outcomes, thus requiring only developmental monitoring for late effects and targeted formal assessments as needed. However, these are preliminary findings and further studies would be required to understand the reasons underlying the differences in outcomes observed in the 2 periods in order to delineate the possible factors that have contributed to the neurodevelopmental outcomes.

Acknowledgement

The authors would like to thank Dimple D Rajgor, PhD, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, for her contributions in editing and formatting the manuscript.

REFERENCES

1. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. Semin Perinatol 2003;27:281-7.
2. Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor G, Schluchter M, et al. Improved neurodevelopmental outcomes for extremely low birthweight infants in 2000-2002. Pediatrics 2007;119:37-45.
3. Jang DH, Sung IY, Jeon JY, Moon HJ, Kim KS, Kim EA, et al. Neurodevelopmental outcomes in very low-birth-weight infants in Korea: 1998-2007 vs 1989-1997. J Child Neurol 2011;26:1405-10.
4. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birthweight infants in the 1990s. Pediatrics 2005;115:997-1003.
5. Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. Arch Pediatr Adolesc Med 1998;152:425-35.
6. Emsley HC, Wardle SP, Sims DG, Chiswick ML, D'Souza SW. Increased survival and deteriorating developmental outcome in 23 to 25 week old gestation infants, 1990-4 compared with 1984-9. Arch Dis Child Fetal Neonatal Ed 1998;78:F99-104.

7. Robertson CM, Watt MJ, Dinu IA. Outcomes for the extremely premature infant: what is new? And where are we going? Pediatr Neurol 2009;40:189-96.
8. Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for extremely premature infants. Anesth Analg 2015;120:1337-51.
9. Poon WB, Ho SK, Yeo CL. Short- and long-term outcomes at 2, 5 and 8 years old for neonates at borderline viability – an 11-year experience. Ann Acad Med Singapore 2013;42:7-17.
10. Kono Y, Mishina J, Yonemoto N, Kusuda S, Fujimura M. Outcomes of very-low-birthweight infants at 3 years of age born in 2003-2004 in Japan. Pediatr Int 2011;53:1051-8.
11. Herber-Jonat S, Streiftau S, Knauss E, Voigt F, Flemmer AW, Hummler HD, et al. Long-term outcome at age 7-10 years after extreme prematurity – a prospective, two centre cohort study of children born before 25 completed weeks of gestation (1999-2003). J Matern Fetal Neonatal Med 2014;27:1620-6.
12. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013;10 Suppl 1:S2.
13. Ministry of Health, Singapore. Singapore Burden of Disease Study 2010. Available at: https://www.moh.gov.sg/content/dam/moh_web/Publications/Reports/2014/Singapore%20Burden%20of%20Disease%20Study%202010%20Report_v3.pdf. Accessed on 10 March 2017.
14. Duncan AF, Bann C, Boatman C, Hintz SR, Vaucher YE, Vohr BR, et al. Do currently recommended Bayley-III cutoffs overestimate motor impairment in infants born <27 weeks gestation? J Perinatol 2015;35:516-21.
15. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. J Pediatr 2012;160:553-8.
16. Reuner G, Fields AC, Wittke A, Löpprich M, Pietz J. Comparison of the developmental tests Bayley-III and Bayley-II in 7 month-old infants born preterm. Eur J Pediatr 2013;172:393-400.
17. Vohr BR, Stephens BE, Higgins RD, Bann CM, Hintz SR, Das A, et al. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. J Pediatr 2012;161:222-8.
18. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birthweights less than 1,500gm. J Pediatr 1978;92:529-34.
19. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. Curr Probl Pediatr 1987;17:213-88.
20. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.
21. Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for extremely premature infants. Anesth Analg 2015;120:1337-51.
22. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity — moving beyond gestational age. N Engl J Med 2008;358:1672-81.
23. Number of Births and Deaths, Singapore. Available at: http://www.singstat.gov.sg/statistics/visualising-data/charts/number-of-births-and-deaths. Accessed on 22 November 2017.
24. Pietschnig J, Voracek M. One century of global IQ gains: a formal meta-analysis of the Flynn effect (1909-2013). Perspect Psychol Sci 2015;10:282-306.
25. Trahan LH, Stuebing KK, Fletcher JM, Hiscock M. The Flynn effect: a meta-analysis. Psychol Bull 2014;140:1332-60.
26. O'Shea TM, Goldstein DJ, deRegnier RA, Sheaffer CI, Roberts DD, Dillard RG. Outcome at 4 to 5 years of age in children recovered from neonatal chronic lung disease. Dev Med Child Neurol 1996;38:830-9.
27. Robertson CM, Etches PC, Goldson E, Kyle JM. Eight-year school performance, neurodevelopmental, and growth outcome of neonates with bronchopulmonary dysplasia: a comparative study. Pediatrics 1992;89:365-72.
28. Hughes CA, O'Gorman LA, Shyr Y, Schork MA, Bozynski ME, McCormick MC. Cognitive performance at school age of very low birthweight infants with bronchopulmonary dysplasia. J Dev Behav Pediatr 1999;20:1-8.

Commentary

Mandated Consent – Not a Viable Solution for Organ Transplant in Singapore

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The last decade has seen an alarming increase in the prevalence of end-stage renal failure in Singapore, attributed to factors such as dietary and environmental triggers, improved healthcare accessibility and a rapidly ageing population. This, in turn, has contributed to a relentless increase in demand for renal transplant. As in many first world countries, this demand is not matched by kidneys available, leading to long waiting time for renal transplant.

Singapore stands out among many Asian countries as one which has since 1987 legislated an "opt-out" presumed consent model in its national organ donation scheme. Under the Human Organ Transplant Act (HOTA), a citizen or permanent resident is presumed to have given his or her consent to the removal of specified organs for purpose of transplantation upon death, unless an objection form (HOTA opt-out form) has been actively filled to indicate an objection to the removal of some or all of the specified organs. Observers have noted that despite the amendment of HOTA in 2004, 2008 and 2009 to widen the deceased donor pool, the incident of deceased or cadaveric renal transplant rate has remained relatively static.[1] The statistics reflect that despite a high percentage of potential donors among the population as a result of the default donor system adopted by HOTA, the number of actual organ transplants has not risen correspondingly.[2]

Presumed consent is intended to be ethically equivalent to a valid informed consent, with the qualifying criteria of an informed consent all assumed to be present. Individuals who do not actively register an objection will automatically be presumed to have received and understood the information provided, and made the decision without being coerced. The absence of an objection is presumed to be a positive expression of agreement to donate the organs for transplantation in the event of brain death. Critics of presumed consent contend that it is more accurately a "presumed lack of objection", and one cannot dispel the possibility that the failure to formally register a refusal represents either ignorance or a failure on the part of the deceased donor to overcome the inertia to confront the decision, rather than an active expression of his genuine willingness to opt-in as a future organ donor.[3] In many of the organ donation systems based on presumed consent, there is also no requirement to ascertain that a donor's family is unaware of any objection (on the part of the deceased patient) to donating as a criteria for validating the presumed consent. This frequently becomes the flash point for family members to object strongly to organ donation, arguing vehemently that the deceased either did not receive or had never comprehended the relevant and critical information needed to make the decision. Some have even insisted that the deceased had consistently been against organ donation, but just did not get down to executing his refusal in accordance to the prescribed legal procedures. The conflict between the family of the deceased and hospital staff—perceived in these conflicts as agents executing the "unjust" system of presumed consent—can be highly emotional and antagonistic, and may potentially lead to a failure to actualise the organ donation.[4]

This dissatisfaction with presumed consent has led to the call for an alternative system of "mandated consent",[5] a plea similarly echoed by some in Singapore.[2,6] In mandated consent, a competent adult is required by law to explicitly indicate a choice regarding his wishes to donate his organs after his death through various registration mechanisms.[5] This choice generally includes whether or not to donate and which organs to donate. It is mandatory as individuals must register a decision; failure to make a choice is not legally permitted. One commonly employed approach is to make it compulsory for an individual to declare his (or her) preferences regarding organ donation when performing a state-regulated task, such as obtaining or renewing his driver's license, or filling a tax return.

Mandated consent is perceived by its proponents as a more ethical and enforceable form of consent as it represents an enhancement of a person's autonomy—expressed as a clear and explicit decision towards organ donation—rather than a permission that has been presumed via an overt absence of objection. The clear indication provides a strong and unambiguous directive from the donor to supersede any future objection from family members, thereby having the potential to increase the number of organ transplant actualised in hospitals, particularly those which tend to

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submit to pressures from the deceased's family. Critics of presumed consent argue further that a system of mandated choice helps to distinguish the "true donors" from those who are in the donor registry simply because of procrastination in their act of formally filing a refusal. Acknowledging organ donation as an act of social good and which saves lives—a "modified mandated consent"—where processes and communication materials are deliberately directed towards and biased in favour of organ donation help to balance the ethical imperatives of beneficence and autonomy.[7]

Mandated consent, however, is not without its detractors. One of the most frequently cited ethical flaw is the potential coercion associated with its execution. As its name suggests, mandated consent inevitably involves giving individuals—including those who do not wish to think about death and organ donation—no choice but to deliberate and decide on such issues against their own free will. It remains questionable whether it should be framed as a form of statutory living will, as forcing a decision to donate one's organs well in advance of death is arguably very different from making end-of-life choices nearer or at the time of death.

The tying of the execution of a mandated choice policy to a state-regulated task like registering or renewing of driver's license gives rise intrinsically to several issues. Firstly, it is conceivable that the quality and quantity of communication related to organ donation would be compromised in order to sustain the usual efficiency of the task it is paired with. The misgiving for the quality, and hence validity, of the mandated consent inevitably raises ethical questions similar to those hurled at a presumed consent policy. Secondly, the desire to complete the state-regulated task without delays—usually of greater contemporaneous social relevance to the applicant—for instance registering or renewing one's driving license, can constitute an inducement that would result in a hurried decision that lacks both altruism and careful consideration. Again, this casts a shadow of doubt on the validity of mandated consent. Thirdly, there are very few state-regulated tasks that have been tested and shown to involve a convincing proportion of the eligible population. In fact, many were left out due to lack of relevance of the twinned task, and consequently their choices remained unregistered.

Given that attempts at adopting mandated consent in several Western countries have seen varying outcomes—and the policy has even been abandoned with a reversal back to an "opt-in" consent model in Australia and in Texas—one cannot help but ask if it will be relevant and effective in Singapore. A reasonable question that should be answered before deciding on implementation would therefore be whether a mandated choice system will succeed in making a significant impact in enhancing the rate of organ transplant in Singapore, given the small country's unique political, social and cultural environment.[6]

Some of the pros and cons of a mandated consent policy discussed above are applicable to varying extents in Singapore. On one hand, one can argue that the much-admired efficiency of Singapore's state-run agencies puts the country in a good position to execute this twinning of task adeptly and reliably. However, this can cut both ways, possibly inviting accusations of bullying and coercing the public into making a choice to donate their organs even when they are not willing or ready.

But perhaps an even more pertinent question is whether the number of organ transplants will increase significantly with a switch from presumed to mandated consent. For organs to be suitable for cadaveric transplant, organ donors need to deteriorate to brain death. Typically, these are patients who have suffered catastrophic intracranial injuries. Furthermore, organ donors who decline to the point of brain death need to have their cardiopulmonary functions artificially supported to keep the organs viable for transplant. Invariably, this can only take place in intensive care units of acute hospitals. Taken in combination, these requirements will inevitably limit the number of potential donors in Singapore. This was indirectly affirmed in a study looking at patients admitted to Singapore's largest neuro-intensive care unit from 2004 to 2011, which found only 365 cases of severe traumatic brain injury (TBI) over a period of 7 years. Of these, 180 (49.3%) died in hospital, giving an annual figure of approximately 26 in-hospital deaths from severe TBI.[8] Of note, a majority (76.7%) of these fatalities were cases above 60 years old,[8] and many of these older patients tend to have pre-existing chronic multisystem pathologies that render their organs unsuitable for transplant. Therefore, contrary to the views of some advocates of mandated consent,[2,6] the rates of organ donation converted into actual organ transplant is unlikely to increase in any impactful way via a policy switch from presumed to mandated consent.

Another challenge to Singapore lies in selecting the appropriate state-regulated task for twinning with the registration of the mandated choice. This task should cover a sizable proportion of eligible donors. Otherwise, the mandated consent system will have a serious inclusion issue, and will expectedly lead to a large number of citizens and residents who never had an opportunity, thus leaving their choices unregistered. For example, in Singapore, not everyone has a driver's license, and an even smaller number pay taxes. Overall, this will cause a reduction in number of potential donors.

Take registration and renewal of driving license as an example of a state-regulated task twinned to mandated consent. In 2016, there were only 1,967,619 persons holding

valid driving licenses in Singapore. The actual number would probably be lower if those below the statutory age for pledging organs for donation (of 21 years) are excluded. Using the population above the age of 21 years as a denominator, this makes up only about 55% to 56% of the population eligible for organ donation.[9,10,11] Tax filing suffers from the same issue. In 2016, there were only 1,728,499 tax residents,[12] though the real number covered statutorily under the provisions of HOTA is smaller due to the exclusion of foreign tax residents. This constitutes lower than 50% of the population above the age 21 years. These statistics reflect the restricted reach in Singapore of these 2 commonly employed mechanisms in mandated choice systems.

In addition, a hypothetical choice experiment seems to suggest that a mandated choice policy which fails to cover many individuals, thereby leaving their choices unregistered, may independently make it more challenging for hospitals to obtain permission from their next-of-kin for organ donation.[13] This will further reduce the number of organ donors.

Lessons from early pilots and movers elsewhere have indicated that an effective mandated consent system must include the presence of several elements. Registrations must be made legally binding, and enforcement must therefore be consistent. A third option of designating the decision to a family member is considered by many to be helpful.[14,15] The task chosen should be inclusive in order to reach a maximum number of potential donors. The process must fulfill the requirements of informed consent, where individuals must be able to register their choice in an environment conducive to communication and contemplation. It should also include a user-friendly method to change one's choice. There needs to be adequate design-thinking applied to the operating model as negative experience resulting from cumbersome and difficult methods of registration have been shown to result in lower rates of organ donation.[14] The failure to address even one of these elements will prevent mandated consent from being the magic bullet for meeting organ transplant needs.

While there is no denying the ethical value of a properly administered mandated consent policy, the practical solution for Singapore's low rate of cadaveric organ transplant in the immediate and near future is unlikely to be found in such a system. What is critical to sustaining organ transplantation as a collective societal institution is to step up the efforts to change mindsets through sharing of knowledge and promotion of altruism and social compact between citizens. Ultimately, we need to negotiate an appropriate and sustainable balance between an individual's right of autonomy and his obligation towards communal interests.

REFERENCES

1. Chan-on C and Sarwal MM. A comprehensive analysis of the current status and unmet needs in kidney transplantation in Southeast Asia. Front Med (Lausanne) 2017;4:84.
2. Low D. Organ donation: consider mandated consent. The Straits Times. 2016 May 25.
3. Crigger BJ. The AMA Code of Medical Ethics' Opinions Relevant to Organ Transplantation and Procurement. AMA Journal of Ethics 2016;18:22-125.
4. Kwek TK, Lew TWK, Tan HL, Kong S. The transplantable organ shortage in Singapore – has implementation of presumed consent to organ donation made a difference? Ann Acad Med Singapore 2009;38:346-53.
5. Institute of Medicine. Organ donation: opportunities for action. Childress JF, Liverman CT, editors. Washington, DC: The National Academies Press; 2006.
6. Goh DPS. Increasing Singapore's organ transplant rate. Parliamentary debates, Singapore: Official Report 2016;94:24.
7. Chouhan P, Draper H. Modified mandated choice for organ procurement. J Med Ethics 2003;29:157-62.
8. Wee JZ, Yang YRJ, Lee QYR, Cao K, Chong CT. Demographic profile and extent of healthcare resource utilisation of patients with severe traumatic brain injury: still a major public health problem. Singapore Med J 2016;57:491-6.
9. Ministry of Home Affairs - Singapore Police Force. Driving license information - qualified driving licence holders. Available at: https://data.gov.sg/dataset/driving-licence-information-qualified-driving-licence-holders. Accessed on 27 September 2017.
10. Singapore Department of Statistics. Age pyramid of resident population 2016. Available at: http://www.singstat.gov.sg/statistics/visualising-data/charts/age-pyramid-of-resident-population. Accessed on 27 September 2017.
11. National Population and Talent Division, Singapore Department of Statistics, Ministry of Home Affairs and Immigration and Checkpoints Authority. Population in brief 2016. Available at: https://www.nptd.gov.sg/PORTALS/0/HOMEPAGE/HIGHLIGHTS/population-in-brief-2016.pdf. Accessed on 27 September 2017.
12. Inland Revenue Authority of Singapore. Tax statistics. Available at: https://www.iras.gov.sg/IRASHome/Publications/Statistics-and-Papers/Tax-Statistics/#NewBookmark. Accessed on 27 September 2017.
13. Kessler JB, Roth AE. Getting more organs for transplantation. Am Econ Rev 2014;104:425-30.
14. Cotter H. Increasing consent for organ donation: mandated choice, individual autonomy, and informed consent. Health Matrix Clevel 2011;21:599-626.
15. Sanders J. Bodies, organs and saving lives: the alternatives. Clin Med 2010;10:26-9.

Letter to the Editor

A Comparison of Mandated, Presumed, and Explicit Consent Systems for Deceased Organ Donation among University Students in Singapore

Dear Editor,

Since the first transplant surgery was performed in Singapore, Parliament has passed 2 acts to facilitate organ transplants. First, in 1972, the Medical (Therapy, Education and Research) Act was enacted allowing individuals to opt-in for organ donation through an "explicit consent" scheme.[1] Later, to boost deceased organ donations, the government implemented the Human Organ Transplant Act (HOTA) in 1987.[2]

HOTA is a "presumed consent" scheme allowing doctors to remove the kidney, liver, heart, and corneas from deceased Singaporeans and permanent residents who have not opted out.[2] Although this system produces a larger pool of donors than explicit consent,[3] implementation has come with problems. For example, individuals may be opposed to organ donation without being aware of HOTA. Procurement of organs would then breach their autonomy. Similarly, families may perceive presumed consent as being invalid. If so, proceeding with organ transplant could grief the family and erode the patient-doctor relationship. Because of these concerns, doctors have, at times, refrained from using the presumed consent. Instead, they have resorted to a "soft" opt-out, allowing the family's wishes to be considered by offering alternatives such as terminal extubation before brain death is established.[4] These practices have led to missed opportunities in the face of a mounting organ shortage.

As a substitute to presumed consent, there have been growing calls for the government to use a "mandated consent" approach to organ donation.[5] Under this scheme, it would be compulsory for all residents to register their preference for organ donation after death (with no default indicated). Previous studies found that: i) mandated consent led to higher consent rates than explicit consent, and that ii) these rates did not differ from those of presumed consent.[3,6] Accordingly, mandated consent has been mooted in Parliament as a solution to Singapore's shortage of transplantable organs.[7]

To inform this debate, we conducted a survey exploring the willingness of Singaporeans and permanent residents to donate their organs as a function of the explicit, presumed, and mandated consent systems. To our knowledge, this is the first Asian dataset addressing this question.

Materials and Methods

The survey was conducted in November 2016 at the National University of Singapore. Research assistants approached students who met the eligibility criteria for the HOTA (Singapore citizens or permanent residents aged ≥21 years old). Respondents completed a self-administered survey in English, in accordance with a protocol approved by the university's Institutional Review Board.

Three types of survey forms were prepared, with each form presenting one of the organ donation systems. In the presumed consent version, respondents were told that by default, everyone was a donor but they could choose not to donate. They were then asked whether they would like to keep the default option (to donate) or if they would like to opt-out (and not donate). In the explicit consent scenario, respondents were told the reverse: by default, nobody was an organ donor but they could choose to donate. Again, they were asked whether they would like to keep the default (not donate), or if they would like to opt-in (and donate). Finally, in the mandated choice scenario, respondents were simply told that they had to register their decision regarding organ donation; they were then asked whether they would like to become an organ donor or not. Participants were randomly allocated to receive one of the survey forms based on a computer-generated randomisation list.

In all 3 forms, an additional question asked participants to rate how confident they were that they had made a right decision. Responses were made using a 10 cm visual analogue scale (VAS) anchored on one end with "0%, not at all confident that I have made the right decision" and on the other with "100%, extremely confident that I have made the right decision".

As the primary analysis, a chi-squared test of independence was used to examine whether agreement to donate one's organs (yes or no) depended upon policy type (presumed, explicit, and mandated consent). Follow-up chi-squared tests were run to compare agreement rates under mandated choice versus presumed consent; mandated choice versus explicit consent; and explicit consent versus presumed consent. The type 1 decision-wise error rate was controlled at $\alpha = 0.05$, with power calculations showing that there was statistical power at the recommended 0.80 level to detect a proportion difference of ~0.25 in agreement rates.

All analyses were conducted using Statistical Package for the Social Sciences (SPSS) and R.

Results

Baseline Characteristics

A total of 157 respondents were enrolled in the study. As shown in Table 1, participants allocated to the 3 groups were comparable in: age, gender, country of birth, nationality, ethnicity, religion, marital status, highest qualification, house type, and household size.

Willingness to Donate One's Organs

There was a significant relation between willingness to donate and policy type, (χ^2 = 10.5, [2, n = 157], P = 0.005) (Fig. 1). Namely, a larger proportion of participants agreed to be organ donors in the presumed consent group (95% CI: 85.4% to 99.3%) than in either the mandated (95% CI: 68.6% to 91.1%; χ^2 = 4.99, [1, n = 102], P = 0.025) or explicit consent groups (95% CI: 58.8% to 83.5%; χ^2 = 10.72, [1, n = 106], P = 0.001). Although there was a higher proportion of organ donors in the mandated consent

Table 1. Baseline Characteristics of Study Participants

Variable	Presumed Consent (n = 51)	Explicit Consent (n = 55)	Mandated Consent (n = 51)
Age (year) mean and SD	21.9 ± 1.81	22.1 ± 1.22	22.1 ± 1.1
Gender, n (%)			
Male	34 (66.7)	39 (70.9%)	34 (66.7%)
Female	17 (33.3)	16 (29.1%)	17 (33.3%)
Country of birth, n (%)			
Singapore	50 (98)	55 (100%)	50 (98%)
Others	1 (2)	0 (0%)	1 (2%)
Nationality, n (%)			
Singapore/PR	51(100)	55 (100)	51 (100)
Others	0 (0)	0 (0)	0 (0)
Ethnicity, n (%)			
Chinese	43(84.3)	53 (96.4)	47 (92.2)
Malay	2 (3.9)	2 (3.6)	3 (5.9)
Indian	3 (5.9)	0 (0)	1 (2)
Eurasian	3 (5.9)	0 (0)	0 (0)
Others	0 (0)	0 (0)	0 (0)
Religion, n (%)			
Buddhism	6 (11.8)	3 (5.5)	6 (11.8)
Taoism/Chinese belief	2 (3.9)	2 (3.6)	2 (3.9)
Islam	3 (5.9)	0 (0)	0 (0)
Hinduism	0 (0)	1 (1.8)	1 (2)
Sikhism	0 (0)	0 (0)	0 (0)
Roman Catholicism	3 (5.9)	5 (9.1)	5 (9.8)
Christian	14 (27.5)	24 (43.6)	15 (29.4)
No religion	19 (37.3)	19 (34.5)	22 (43.1)
Others	4 (7.8)	1 (1.8)	0 (0)
Marital status, n (%)			
Single	41 (80.4)	44 (77.2)	38 (74.5)
Dating	10 (19.6)	11 (19.3)	13 (25.5)
Married	0 (0)	0 (0)	0 (0)
Widowed	0 (0)	0 (0)	0 (0)
Separated	0 (0)	0 (0)	0 (0)
Divorced	0 (0)	0 (0)	0 (0)

HDB: Housing and Development Board; ITE: Institute of Technical Education; PR: Permanent resident; SD: Standard deviation

Table 1. Baseline Characteristics of Study Participants (Cont'd)

Variable	Presumed Consent (n = 51)	Explicit Consent (n = 55)	Mandated Consent (n = 51)
Highest qualification, n (%)			
No formal education	0 (0)	0 (0)	0 (0)
Primary school	0 (0)	0 (0)	0 (0)
'N' level	0 (0)	0 (0)	0 (0)
'O' level	0 (0)	0 (0)	0 (0)
'A' level	38 (74.5)	43 (78.2)	38 (74.5)
ITE	0 (0)	0 (0)	0 (0)
Diploma	3 (5.9)	4 (7.3)	3 (5.9)
Degree	8 (15.7)	8 (14.5)	9 (17.6)
Postgraduate	0 (0)	0 (0)	0 (0)
Others	2 (3.9)	0 (0)	1 (2)
House type, n (%)			
HDB 1- to 2-room	0 (0)	0 (0)	1 (2)
HDB 3-room	1 (2)	3 (5.5)	2 (3.9)
HDB 4-room	9 (17.6)	11 (20)	12 (23.5)
HDB 5-room/executive flat	20 (39.2)	18 (32.7)	19 (37.3)
Condominium/private apartment	9 (17.6)	10 (18.2)	7 (13.7)
Landed property	10 (19.6)	13 (23.6)	7 (13.7)
Others	2 (3.9)	0 (0)	3 (5.9)
Household size, mean and SD	4.72 ± 1.33	4.49 ± 1.12	4.16 ± 1.07

HDB: Housing and Development Board; ITE: Institute of Technical Education; PR: Permanent resident; SD: Standard deviation

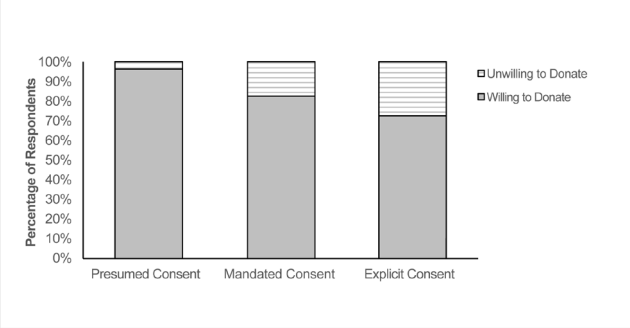

Fig. 1. Graph showing willingness to donate organs as a function of which policy participants encountered. Bars represent the percentage of participants who chose either to donate or not to donate their organs.

than in the explicit consent group, this difference was not significant ($\chi^2 = 1.4$, [1, n = 106], $P = 0.237$).

To explore whether participant demographics moderated the effects of policy type, we conducted a logistic regression analysis of policy condition, age, gender, country of birth, nationality, ethnicity, religion, marital status, highest qualification, house type, and household size on willingness to donate one's organs. Overall, prediction success was 85.7% (95.5% for donors and 35.3% for non-donors), with the Wald criterion indicating that only the policy type significantly predicted whether participants would donate or not ($P = 0.006$). This finding highlights the magnitude of the policy framing effect, over and above standard demographic variables.[3]

Confidence in Decision

As a secondary outcome, we ran a 1-way analysis of variance (ANOVA) to explore how confident participants were as a function of the policy they read. Surety in decision-making did not depend on policy type, F (2,154) = 0.54, $P = 0.58$ (mean for the presumed consent group: 76.5% ± 15.2%, mandated consent: 76.2% ± 23.4%, explicit consent: 73.1% ± 17.2%).

Discussion

This is the first demonstration of how presumed, mandated, and explicit consent systems may affect organ donation rates in Singapore. We found that presumed consent was the most effective scheme, increasing donation rates relative to both mandated and explicit consent. Additionally, we found no evidence that mandated consent was more effective than explicit consent.

Together, our findings provide important data for the ongoing discussion on organ donation laws.[5,7,8] As we noted in the introduction, previous studies had suggested that the size of donor pools would be equivalent under both mandated consent and presumed consent.[3,6] If this

were the case, mandated consent should be favoured over presumed consent since actualisation rates do not merely depend on the donor pool.[4]

Unlike previous studies, however, we found that mandated consent was inferior to presumed consent in the Singaporean context. This suggests that if HOTA was amended to a mandated consent system, this would come at the cost of a smaller donor pool. What remains unknown is whether the decrease in the donor pool can be compensated by a decrease in the number of soft "opt-outs", resulting in a net increase in donor actualisation rates. Accordingly, we urge policymakers to undertake further research before making changes to the current presumed consent laws.

Our study had some limitations. First, we used a sample size of 157. Although this matched Johnson et al's seminal study comparing donation rates under the 3 policy types,[3] our study was inadequately powered to detect small-effect sizes. This could account for the lack of a significant effect between the mandated and explicit consent policies. Second, our study involved university students who were primarily from middle- to upper-class families. Although this sample is not representative of the larger Singapore population, our report nonetheless cautions against implementing mandated consent without further local data.

Conclusion

In conclusion, our research suggests that replacing presumed consent with mandated consent will likely decrease Singapore's donor pool. This highlights how studies conducted in Western countries may not apply to Singapore, and shows the need for further research to understand the complex factors affecting actualisation rates.

Acknowledgements

This research was funded by a grant awarded to CWL, ST, HVK, JCJL from National University of Singapore Humanities and Social Sciences research fund (grant number: HSS-1502-P02). The authors gratefully acknowledge Chow Kit Ying, Sean Olivia Nicholas, Hans Toby Limanto and Lim Jia Ying for assistance in data collection.

REFERENCES

1. Medical (Therapy, Education And Research) Act (Chapter 175), 1987.
2. Human Organ Transplant Act, 2012.
3. Johnson EJ, Goldstein D. Do defaults save lives? Science 2003;302:1338-9.
4. Kwek TK, Lew TW, Tan HL, Kong S. The transplantable organ shortage in Singapore: has implementation of presumed consent to organ donation made a difference? Ann Acad Med Singapore 2009;38:346-8.
5. Low D. Organ donation: consider mandated consent. The Straits Times. 2016 May 25.
6. van Dalen HP, Henkens K. Comparing the effects of defaults in organ donation systems. Soc Sci Med 2014;106:137-42.
7. Goh DPS. Increasing Singapore's organ transplant rate. Speech made in the Singapore Parliament, 2016.
8. Niu R. Make organ donation a mandated choice. The Straits Times. 2016 Dec 7.

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Letter to the Editor

Clinical Prevalence and Associated Factors of Erectile Dysfunction in Patients Undergoing Haemodialysis

Dear Editor,

Several studies among men with end-stage renal disease have estimated the prevalence of erectile dysfunction (ED) to range from 41.5% to 82%.[1-3] The aetiology of ED in men with chronic kidney disease (CKD) is multifactorial. As such, ED represents the sequel of the complex neuroendocrine and metabolic changes typical of uraemic syndrome.[3,4] In addition, pharmacological therapy for uraemia and the attendant physical and psychological stress may also play an important role in the genesis of this problem.[5]

This study aimed to assess the prevalence of sexual dysfunction, to identify the correlates of social, psychological, behavioural and metabolic factors, and to assess the extent of risk of comorbid cardiovascular and metabolic factors associated with the occurrence of ED in these male uraemic patients.

Materials and Methods

This is a cross-sectional study based on data collected over a 3-year period—November 2011 to November 2014. A total of 1711 male renal patients were screened. Of this, 200 who had met the eligibility criteria of: i) age 21-65 years, and ii) undergoing haemodialysis therapy and clinical management at the National University Hospital, Singapore were recruited. All participants in this study were in stable relationships. Participants with cognitive deficiency and inability to communicate were excluded. Patients with chronic ambulatory peritoneal dialysis (CAPD) were also excluded to avoid other confounding factors for reporting of ED such as practical/physical constraints of CAPD and different baseline characteristics of CAPD patients.

Ethics approval for this questionnaire-based study was obtained from the National Healthcare Group Domain Specific Review Board (DSRB-ID-2011-00112) and all participants gave written informed consent. All participants completed 3 sets of questionnaires including a questionnaire concerning sociodemographic information, marital status, education, sexual intimacy, medical history, stress and lifestyle behaviour; the International Index of Erectile Function (IIEF) questionnaire; and the Patient Health Questionnaire (PHQ-9) which measures the severity of depression.

Coexisting medical conditions and duration on haemodialysis were ascertained from patients' medical records. To enable meaningful analysis of relationship of ED with haemodialysis, the cutoff for aetiology of end-stage renal failure was ≥90 days in the present study. Of the original 200 subjects who were initially recruited for the study, 39 were excluded for the following reasons: i) duration of haemodialysis <90 days (n = 36), and ii) incomplete answers on the questionnaire (n = 3). Ultimately, 161 patients were included in the final analyses of this study.

Statistical analysis was performed using SPSS 21.0PL for Windows. Multivariate logistic regression model was used to estimate odds ratio (OR), confidence interval (CI) of 95% for the relationship of ED with age, depression score, exercise, smoking, alcohol consumption and medical conditions in uraemia patients. *P* values <0.05 were considered statistically significant.

Results

Sociodemographic Characteristics

The study sample was made up of 200 male patients, of whom 117 (58.5%) were Chinese, 55 (27.5%) were Malays and 21 (10.5%) were Indians. The age of participants ranged from 22 to 65 and mean ± SD age was 53.9 ± 8.8. The majority of participants (45%) were between 51 and 60 years old. At the time of the survey, 189 participants (84.5%) were married and 102 (51%) had secondary school education.

Prevalence of ED

The prevalence for each of the 5 categories of ED is shown in Table 1. With IIEF cutoff score of 25 to define ED, the prevalence of ED of any degree was 93.3% (153/164) in this cohort. About 63% of uraemic subjects reported severe ED.

The comorbid cardiovascular and metabolic risk factors such as the prevalence of hypertension, diabetes mellitus

Table 1. Prevalence by Severity of Erectile Dysfunction

Severity of ED	Severe (0 to 6)	Moderate (7 to 12)	Mild to Moderate (13 to18)	Mild (19 to 24)	No ED (25 to 30)	Total
Frequency	104	14	17	18	11	164
Prevalence*	63.4	8.5	10.4	11.0	6.7	100

ED: Erectile dysfunction

*In percentage (%).

and hyperlipidaemia among the ethnic groups in Singapore are presented in Table 2. There was no significant association observed between the comorbid conditions and ethnic groups.

Correlation of Severe ED Status with Other Factors

As the proportion of 'severe ED' was quite high (63.4%), severe ED status was subsequently used as a binary variable to test for potential association with various factors including depression score, age, conditions (diseases), smoking, alcohol consumption, exercise frequency, and stress. The 2 minor ethnic groups—Indians (n = 18) and Others (n = 2)—were merged for multivariate logistic regression analysis.

As shown in Table 3, 75.8% of cohort were aged ≥50 years. In view of the small number of young subjects, binarised age was used to explore the relationship of age with severe ED. Analysis based on binarised age (<50 or ≥50) revealed a significant higher odds of having severe ED as age increased (OR: 5.81 with 95% CI: 2.27 to 14.88; *P* value <0.001). Interestingly, among the ethnic groups, Malays had significantly lower odds of having severe ED (OR: 0.31 with 95% CI: 0.13 to 0.74; *P* value <0.008).

About 54% of the subjects had diabetes which significantly increased odds of uraemic patients having severe ED (OR: 2.95 with 95% CI: 1.2 to 7.27; *P* value = 0.019). The overall prevalence of other comorbid cardiovascular problems, obesity, hyperlipidaemia and hypertension was 38.5%, 7.5%, 52.2% and 75.2% respectively. However, no significant association was observed between severe ED status and prevalence of these cardiovascular and metabolic conditions.

Severe ED status was also not associated with mean depression score (5.65 for severe ED group vs 4.95 for not severe ED group; OR: 1.02 with 95% CI: 0.95 to 1.1; *P* value = 0.600) or smoking and alcohol consumption. A significant association between exercise and severe ED status was observed when participants' responses to the question on frequency of exercise in the recent 1 month (daily/once or twice a week/once or twice a month/never) was analysed. The trend was potentially U-shaped suggesting that those who exercise moderately (i.e. exercise once or twice a week) were least likely to have severe ED.

Discussion

To the best of our knowledge, this study is the first to assess the prevalence, severity and clinical correlates of ED in male uraemia patients undergoing dialysis in Singapore. The incidence and severity of ED was notably high in the current study. Using IIEF as a tool to assess ED, 93.3% of men on haemodialysis reported ED, whereas 63.4% experienced severe ED. These values are considerably higher than those estimated from recent cohort studies (>100 subjects) in Latin American and European countries (68.2% to 83% for ED and 43.0% to 47.0% for severe ED).[6,7] The higher prevalence of ED in the current study may be accountable by the higher rate of diabetes (54%)—which is an established independent risk factor of ED—as compared to 18.4% and 25.1% in the study population undertaken by Costa et al[6] and Vecchio et al[7] respectively. Another aggravating factor could possibly be that the proportion of participants in this study aged above 50 (75.8%) was considerably higher than that of the cohort in the study by Vecchio and colleagues (63%).[7] The differences in reported prevalence rates of ED between different studies had been attributable to age, study populations, and type of study tool used to assess the presence of ED.[8]

In clinical setting, the low incidence of ED in Malays may be due to some Malays quitting smoking. Due to data size restriction in the present study, the true incidence of ED in Malay haemodialysis patients awaits further confirmation in a larger patient cohort.

Consistent with previous studies on male haemodialysis patients, our multivariate regression analysis revealed that age (>50) and diabetes are key correlates to severe ED in uraemia.[2,9] Based on our data, the incidence of ED in men with haemodiaylsis is almost twofold of that in the general population.[10] The lack of significance of important comorbid risk factors may be related to the extremely high prevalence of ED in our cohort and our analysis of cohorts with severe ED versus not severe ED—as opposed to extreme ends of the spectrum which might explain the lack of differentiation between the cohorts with regard to individual risk factors.

Table 2. Prevalence of Comorbid Cardiovascular and Metabolic Factors by Ethnicity

Medical Condition		Chinese n (%)	Malays n (%)	Indians n (%)	Others n (%)	Total n	*P* Value
Hypertension	No	17 (41.5)	17 (41.5)	5 (12.2)	2 (4.9)	41	0.222
	Yes	74 (60.2)	36 (29.3)	13 (10.6)	0 (0)	123	
Diabetes	No	45 (58.4)	24 (31.2)	7 (9.1)	1 (1.3)	77	0.864
	Yes	46 (52.9)	29 (33.3)	11 (12.6)	1 (1.1)	87	
Cardiovascular	No	58 (56.9)	35 (34.3)	7 (6.9)	2 (2.0)	102	0.756
	Yes	33 (53.2)	18 (29.0)	11 (17.7)	0 (0)	62	
High cholesterol	No	42 (53.2)	26 (32.9)	10 (12.7)	1 (1.3)	79	0.919

Table 3. Multivariate Analysis Stratified by Age, Ethnicity, Lifestyle Risk Behaviour and Medical Condition in 161 Subjects With and Without Severe Erectile Dysfunction

Type	Variable	Levels	n (%)	Severe ED n (%)	Not Severe ED n (%)	Odds Ratio (95% CI)	SE	*P* Value
Basic	Age (binary)	<50	39 (24.2)	14 (35.9)	25 (64.1)	1 (reference)		
		≥50	122 (75.8)	88 (72.1)	34 (27.9)	5.81 (2.27 to 14.88)	0.48	<0.001
	Ethnicity	1 (Chinese)	89 (55.3)	66 (74.2)	23 (25.8)	1 (reference)		0.018*
		2 (Malay)	52 (32.3)	26 (50)	26 (50)	0.31 (0.13 to 0.74)	0.44	0.008
		3 (Indian & Others)	20 (12.4)	10 (50)	10 (50)	0.38 (0.11 to 1.26)	0.61	0.114
	Depression score†		5.39†	5.65†	4.95†	1.02 (0.95 to 1.1)	0.04	0.600
	Exercise frequency	1 (daily)	35 (21.7)	22 (62.9)	13 (37.1)	1 (reference)		0.045*
		2 (once or twice a week)	33 (20.5)	13 (39.4)	20 (60.6)	0.43 (0.14 to 1.37)	0.59	0.153
		3 (once or twice a month)	18 (11.2)	11 (61.1)	7 (38.9)	1.26 (0.32 to 5.05)	0.71	0.740
		4 (never)	75 (46.6)	56 (74.7)	19 (25.3)	1.87 (0.68 to 5.16)	0.52	0.224
Lifestyle risk behaviour	Smoke	No	136 (84.5)	85 (62.5)	51 (37.5)	1 (reference)		
		Yes	25 (15.5)	17 (68)	8 (32)	1.06 (0.34 to 3.29)	0.58	0.916
	Consume alcohol	No	158 (98.1)	100 (63.3)	58 (36.7)	1 (reference)		
		Yes	3 (1.9)	2 (66.7)	1 (33.3)	0.7 (0.04 to 13.08)	1.49	0.814
Medical condition	Diabetes	No	74 (46.0)	39 (52.7)	35 (47.3)	1 (reference)		
		Yes	87 (54.0)	63 (72.4)	24 (27.6)	2.95 (1.2 to 7.27)	0.46	0.019
	Obesity	No	149 (92.5)	93 (62.4)	56 (37.6)	1 (reference)		
		Yes	12 (7.5)	9 (75)	3 (25)	2.93 (0.56 to 15.22)	0.84	0.201
	High cholesterol	No	77 (47.8)	47 (61.0)	30 (39)	1 (reference)		
		Yes	84 (52.2)	55 (65.5)	29 (34.5)	0.77 (0.3 to 1.98)	0.48	0.583
	Hypertension	No	40 (24.8)	24 (60)	16 (40)	1 (reference)		
		Yes	121 (75.2)	78 (64.5)	43 (35.5)	0.81 (0.33 to 2.01)	0.46	0.648
	Cardiovascular	No	99 (61.5)	62 (62.6)	37 (37.4)	1 (reference)		
		Yes	62 (38.5)	40 (64.5)	22 (35.5)	0.58 (0.24 to 1.38)	0.44	0.216
Total			161	102	59			

CI: Confidence interval; ED: Erectile dysfunction; SE: Standard error
*Overall *P* value of the corresponding predictor.
†Mean score.

The increased incidence of ED in haemodialysis patients may be caused by vascular diseases (endothelial dysfunction, arteriosclerosis), neuroendocrine and metabolic changes including lower testosterone levels, suppression of the pituitary testicular axis, hyperprolactinaemia, hyperthyroidism and zinc deficiency.[11,12] Chronic fatigue and anxiety (e.g. financial strain of the disease) which are prevalent in patients undergoing dialysis may lead to lack of sexual desire and decline in frequency of sexual activity. In addition, fear that sex may worsen the condition may further negatively impact on the frequency of intercourse.

It has been estimated that about 20% to 30% of dialysis patients are depressed at any one time.[12] However, the present study did not find any significant association between depression and severe ED even though the presence of depressive symptoms has been identified as an independent factor of sexual dysfunction in male haemodialysis patients.[7,9,13] Failure to detect significant association between depression and severe ED may be due to cross-sectional design or limitations in the instrument/questions used to assess depression.

A limitation of this study is that administration of medication known to be causally associated with ED such as beta blockers, thiazide diuretics, tricyclic antidepressants, and selective serotonin reuptake inhibitors have not been ruled out.[14,15] This study also did not evaluate metabolic factors such as dialysis adequacy, albumin and parathyroid hormone levels which may have played a part in the prevalence of ED in male patients undergoing haemodialysis.[7]

Conclusion

Our cross-sectional study reveals that 63.4% of uraemia patients experienced severe ED. Both diabetes and ageing

were significantly associated with severe ED. These observations reinforce the importance of prophylactic and/or management options for improvement of reproductive/sexual health-related quality of life for men with uraemia and their partners.

Acknowledgement

This work was supported by the National Kidney Foundation Singapore – Venerable Yen Pei Research Fund (NKFRC/2010/07/15).

REFERENCES

1. Palmer BF. Sexual dysfunction in uremia. J Am Soc Nephrol 1999;10:1381-8.
2. Rosas SE, Joffe M, Franklin E, Strom BL, Kotzker W, Brensinger C, et al. Prevalence and determinants of erectile dysfunction in hemodialysis patients. Kidney Int 2001;59:2259-66.
3. Nassir A. Sexual function in male patients undergoing treatment for renal failure: a prospective view. J Sex Med 2009;6:3407-14.
4. Bellinghieri G, Santoro D, Mallamace A, Savica V. Sexual dysfunction in chronic renal failure. J Nephrol 2008;21 Suppl 13:S113-7.
5. Lew-Starowicz M, Gellert R. The sexuality and quality of life of hemodialyzed patients – ASED multicenter study. J Sex Med 2009;6:1062-71.
6. Costa MR, Reis AM, Pereira BP, Ponciano VC, Oliveira EC. Associated factors and prevalence of erectile dysfunction in hemodialysis patients. Int Braz J Urol 2014;40:44-55.
7. Vecchio M, Palmer S, De Berardis G, Craig J, Johnson D, Pellegrini F, et al. Prevalence and correlates of erectile dysfunction in men on chronic haemodialysis: a multinational cross-sectional study. Nephrol Dial Transplant 2012;27:2479-88.
8. Navaneethan SD, Vecchio M, Johnson DW, Saglimbene V, Graziano G, Pellegrini F, et al. Prevalence and correlates of self-reported sexual dysfunction in CKD: a meta-analysis of observational studies. Am J Kidney Dis 2010;56:670-85.
9. Peng YS, Chiang CK, Hung KY, Chiang SS, Lu CS, Yang CS, et al. The association of higher depressive symptoms and sexual dysfunction in male haemodialysis patients. Nephrol Dial Transplant 2007;22:857-61.
10. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994;151:54-61.
11. Kaufman JM, Hatzichristou DG, Mulhall JP, Fitch WP, Goldstein I. Impotence and chronic renal failure: a study of the hemodynamic pathophysiology. J Urol 1994;151:612-8.
12. Suzuki E, Nishimatsu H, Oba S, Takahashi M, Homma Y. Chronic kidney disease and erectile dysfunction. World J Nephrol 2014;3:220-9.
13. Park HC, Yoon HB, Son MJ, Jung ES, Joo KW, Chin HJ, et al. Depression and health-related quality of life in maintenance hemodialysis patients. Clin Nephrol 2010;73:374-80.
14. Chrysant SG. Antihypertensive therapy causes erectile dysfunction. Curr Opin Cardiol 2015;30:383-90.
15. Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. J Clin Psychopharmacol 2009;29:157-64.

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Acute Trauma Coagulopathy: Prevalence and Impact on Outcomes of Trauma Patients Presenting to the Emergency Department

Dear Editor,

Trauma remains a leading cause of death and disability worldwide. Coagulopathy occurring within minutes of a major trauma is seen in 10-25%[1] of severely injured trauma patients. The pathophysiology behind this phenomenon is incompletely understood but is thought to involve tissue trauma as well as systemic hypoperfusion. This leads to activation of endothelial Protein C, followed by rapid anticoagulation and fibrinolysis.[2,3] This phenomenon, termed Acute Trauma Coagulopathy (ATC), is associated with a four-fold increase in mortality, increased transfusion requirements and organ failure.[4,5]

We aimed to determine the prevalence of ATC and its impact on outcomes in severely injured trauma patients presenting to our Emergency Department (ED). Our ED is one of the busiest in Singapore, seeing an average of about 450 patients a day.

Materials and Methods

A retrospective observational cohort study was performed, using our trauma database. The details of all patients who presented between 1 January 2013 and 31 December 2013 with a diagnosis corresponding to trauma and an Injury Severity Score (ISS) of 15 and above were extracted from this database. The following patients were then excluded: 1) Age at presentation below 16, 2) Patients who had missing or incomplete data, 3) Patients transferred in from another facility, 4) Patients whose initial blood tests were performed more than 24 hours from the time of injury, and 5) Patients who were known to be on anticoagulants such as warfarin.

Apart from epidemiological data, the following parameters were recorded: time of first blood test from time of injury, initial vital signs to calculate Revised Trauma Score (RTS), coagulation profiles such as activated Partial Thromboplastin Time (aPTT) and International Normalised Ratio (INR). ATC was defined as INR greater than 1.2 or aPTT greater than 54s (1.5 times the upper limit of our laboratory's normal range) on the initial laboratory test upon arrival in the ED, in line with the definitions used in the literature.[1–4] The two groups of patients were then compared.

Statistical analysis was performed using SPSS Statistics 19 (IBM), and results were expressed as mean standard deviation (SD) and median interquartile (IQR) range for description of variable spread. Comparisons between groups were conducted using Fisher's Exact test or chi-squared test as appropriate, and we considered $P < 0.05$ to be statistically significant. This study was approved by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) for exemption according to its policies.

Results

The characteristics of the study population are as shown in Table 1. A total of 309 patients were included, with the majority being male (71.5%) and of Chinese ethnicity (79.9%). The ethnic distribution of the patients was similar to the general population of Singapore—a majority being Chinese, followed by Malays, Indians and then a small minority of other races (3%).

Almost all of our patients had blunt injuries; the most common mechanism of injury being fall from height (67.6%), and followed by motor vehicle accidents (25.9%). A breakdown of the different mechanisms of injury is shown in Figure 1.

The median ISS of the study cohort as a whole was 21 (IQR 17-26) and the mean probability of survival (PS) was 84.7% (SD 19). Time taken was calculated from the recorded time of injury to the time stamp on the laboratory investigation. The median time taken for the first blood test from time of injury was 115 min (IQR 66-223).

Table 1. Characteristics of Study Group

Variables	Values
Study population	309
Chinese	247 (79.9%)
Indian	31 (10.0%)
Malay	22 (7.1%)
Male gender	221 (71.5%)
Blunt injury	304 (98.4%)
Median ISS	21 (IQR 17 – 26)
Mean PS	84.7% (SD 19.0)
Median time to first blood	115 min (IQR 66 – 223)
Mortality	16.5%

IQR: Interquartile range; ISS: Injury severity score; PS: Probability of survival; SD: Standard deviation

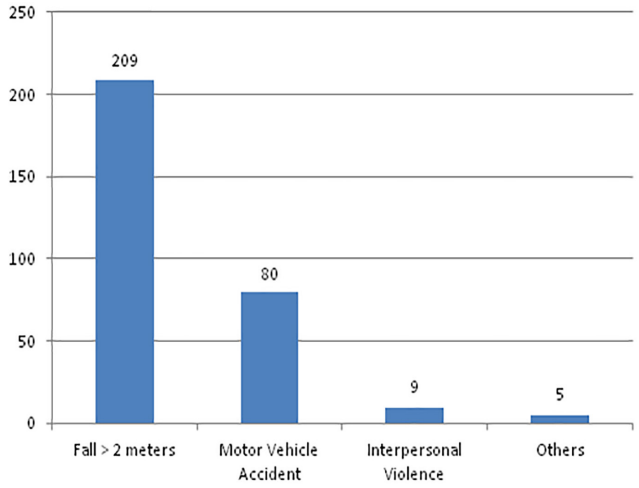

Fig. 1. Mechanisms of injury.

Table 2. Comparison between ATC and Non-ATC Groups

	Patients With ATC	Patients Without ATC	*P* Value
Median ISS	26 (IQR 19 – 30)	21 (IQR 17 – 26)	<0.01
Patients with worse RTS on arrival in ED compared to on-scene	18.9%	8.0%	<0.01
Mean PS	70.9%	87.9%	<0.01
Mortality rate	46.6%	9.6%	<0.01
Proportion of patients with base excess <-2	82.1%	61.5%	0.03
Proportion of patients with lactate >2 mmol/L	92.9%	50%	<0.01

ATC: Acute trauma coagulopathy; ED: Emergency department; ISS: Injury severity score; IQR: Interquartile range; PS: Probability of survival; RTS: Revised trauma score

A total of 58 patients were found to be coagulopathic on arrival in the ED, placing the prevalence of ATC at 18.8% (Table 2). The median time from injury to first blood test was 84 min (IQR 57-180) for the patients with ATC, and 121 min (IQR 72-235) in the patients without ATC. Patients in the ATC group had higher median ISS scores (26 vs 21) as well as worse PS (70.9% vs 87.9%). The association between probability of survival and presence of ATC was found to be statistically significant (P <0.001).

RTS was calculated for each group of patients based on their systolic blood pressure and heart rate both on-scene as well as upon arrival at the ED, and the two values were compared. A greater proportion of patients with ATC had a worse RTS score in ED compared to on-scene (P <0.001) than those in the non ATC group, likely reflecting clinical deterioration despite initial treatment by prehospital staff.

Discussion

ATC is a discrete phenomenon previously described,[1–5] and may be exacerbated by ongoing blood loss (if rapid haemostasis is not achieved), haemodilution due to intravenous fluid resuscitation, acidosis and hypothermia. One previous systematic review[6] in 2011 found that ATC leads to increased mortality, longer ICU stay, hospital stay and increased risk of organ failure.

We set out to determine the prevalence and impact of ATC in our trauma population, and our findings are similar to those published in existing literature[1,4,5,7] despite the differences in the trauma patient population in our local context. Leow et al[8] demonstrated that in our setting, almost all trauma patients had blunt injuries (97.5%) as opposed to penetrating injuries; the most common cause was road traffic accidents, whereas Western studies[9,10] reported varying rates of penetrating injuries (14-49%) and a lower proportion of road traffic accidents (22.4%).

The initial landmark studies done by Brohi and Macleod[7,11] in identifying ATC used conventional laboratory-based PT, aPTT and INR tests in their studies. These are time consuming (with a turnaround time of 30-60 minutes) and do not assess other contributory pathways in the coagulation cascade such as the fibrinolytic and platelet aggregation systems. While these tests have good correlation in the outpatient population for monitoring of patients on warfarin, their utility in the trauma population is less certain. Some authors have found laboratory-based INR measurements to be valuable[6,12] while others do not recommend their usage.[13,14] In our ED, laboratory-based tests are widely used to make decisions on the management of coagulopathy.

Newer point-of-care (POC) tests have been developed to overcome these challenges and aid decision-making during the resuscitation process itself. Two examples of these are thromboelastography (TEG) and rotational thromboelastometry (ROTEM). These tests provide global information on dynamics of clot involvement, stabilisation and dissolution (reflecting in vivo haemostasis). They assess both thrombosis and thrombolysis, and in effect measure all the different pathways along the coagulation cascade. The availability of results within 10 minutes means that these tests can be used for rapid decision-making, both in an ED as well as a critical care setting.

The limitations to POC tests include the need for multiple daily calibrations, specially trained personnel and lack of familiarity among the general physician population. In addition, there remains technical variations on how these tests are performed and there is a lack of worldwide consensus on "normal" values. Recent studies[13,15] have shown poor

correlation between POC tests and conventional laboratory-based tests, and only moderate quality observational studies are available with no randomised controlled trials as of yet. Resuscitation algorithms utilising POC tests have also not shown a convincing benefit in studies to date.

Even as more interest develops in identifying and treating ATC, there is no universally accepted definition. Different authors have used a variety of tests and cut-off values, and there is no consensus or evidence to prove one superior to another. Any conclusions drawn should thus be applied cautiously, taking into account local patient population and practice setting.

Treatment of ATC usually involves goal-directed therapy with balanced transfusion. In our practice, we use a 1:1:1 ratio of packed red blood cells, platelets and fresh frozen plasma to closely emulate the losses suffered by a severely injured patient. Tranexamic acid injections should also be considered for all trauma patients who have hypotension.

Additional limitations of this study were the small sample size and the lack of information about prehospital interventions such as intravenous fluid administration which could have a significant impact on our findings. Other limitations were incomplete data on other patient outcomes such as length of ICU stay and hospital stay that precluded their inclusion in the analysis.

Opportunities for future research in this field are significant, given the multiple areas of uncertainty. Although it would be difficult to conduct randomised controlled trials in this setting, it could potentially be informative to compare on-scene coagulation profiles using POC tests with those on arrival to ED. Evaluation of blood products required in patients with ATC could also be compared to patients without ATC to further delineate its impact on management.

Conclusion

ATC is a distinct phenomenon occurring in approximately 1 in 5 severely injured trauma patients, and has a recognisable impact on patients' clinical status and mortality rate. The prevalence and impact on morbidity in our population is similar to that published in the Western literature despite differences in the injury pattern. It is important to attempt to detect these patients early, and treat them aggressively with balanced transfusion to optimise patient outcomes.

REFERENCES

1. Mitra B, Cameron PA, Mori A, Fitzgerald M. Acute coagulopathy and early deaths post major trauma. Injury 2012;43:22-5.
2. Ganter MT, Pittet JF. New insights into acute coagulopathy in trauma patients. Best Pract Res Clin Anaesthesiol 2010;24:15-25.
3. Davenport R. Pathogenesis of acute traumatic coagulopathy. Transfusion 2013;53:23S-27S.
4. Frith D, Brohi K. The acute coagulopathy of trauma shock: clinical relevance. Surgeon 2010;8:159-63.
5. Frith D, Goslings JC, Gaarder C, Maegele M, Cohen MJ, Allard S, et al. Definition and drivers of acute traumatic coagulopathy: Clinical and experimental investigations. J Thromb Haemost 2010;8:1919-25.
6. Lier H, Böttiger BW, Hinkelbein J, Krep H, Bernhard M. Coagulation management in multiple trauma: A systematic review. Intensive Care Med 2011;37:572-82.
7. Brohi K, Singh J, Heron M, Coats T. Acute Traumatic Coagulopathy. J Trauma Inj Infect Crit Care 2003;54:1127-30.
8. Leow JJ, Lim VW, Lingam P, Go KT, Teo LT. Ethnic disparities in trauma mortality outcomes. World J Surg 2014;38:1694-8.
9. Søreide K, Krüger AJ, Vårdal AL, Ellingsen CL, Søreide E, Lossius HM. Epidemiology and contemporary patterns of trauma deaths: Changing place, similar pace, older face. World J Surg 2007;31:2092-103.
10. Plummer JM, Brown H, Jones K, Fearon-Boothe D, Meeks-Aitken N, McDonald AH. Trauma: the burden of a preventable problem. West Indian Med J 2010;59:26-8.
11. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early Coagulopathy Predicts Mortality in Trauma. J Trauma Inj Infect Crit Care 2003;55:39-44.
12. Peltan ID, Vande Vusse LK, Maier RV, Watkins TR. An International Normalized Ratio-Based Definition of Acute Traumatic Coagulopathy Is Associated With Mortality, Venous Thromboembolism, and Multiple Organ Failure After Injury. Crit Care Med 2015;43:1429-38.
13. da Luz LT, Nascimento B, Rizoli S. Thrombelastography (TEG): Practical considerations on its clinical use in trauma resuscitation. Scand J Trauma, Resusc Emerg Med 2013;21:29.
14. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK. Effect of thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Crit Care 2014;18:518.
15. Mistral T, Boué Y, Bosson J-L, Manhes P, Greze J, Brun J, et al. Performance of point-of-care international normalized ratio measurement to diagnose trauma-induced coagulopathy. Scand J Trauma Resusc Emerg Med 2017;25:59.

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A Case of a Child with Undescended Left Testis Presenting with Acute Right Scrotal Swelling

A 6-month-old male infant with a history of undescended left testis, presented to the emergency department with acute onset of right scrotal swelling associated with vomiting. There was no history of scrotal trauma and neither was there associated fever. On examination, tense right inguinoscrotal swelling was observed associated with erythema and tenderness. Bilateral testes were not palpable. The abdomen was soft and not distended. Imaging study of an ultrasound scrotum was performed to investigate his right scrotal swelling.

What do the ultrasound images in Figure 1 and intra-operative photographs in Figure 2 show? What is the diagnosis of the right inguinoscrotal swelling?

A. Testicular torsion
B. Epididymo-orchitis
C. Torsion of the testicular appendage
D. Incarcerated inguinal Littre's hernia
E. Acute hydrocele

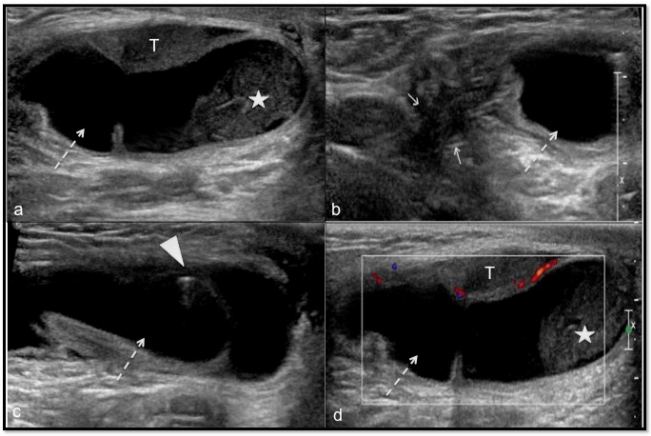

Fig. 1 (a,b,c,d). Ultrasound images of the patient's right scrotum reveal a dilated loop of bowel (dashed arrow) extending from a narrow opening (arrow) in the right inguinal canal to the right scrotum adjacent to the normal appearing right testis (T). Intraluminal gas (arrowhead) and debris (asterisk) are seen within the bowel loop. Intramural vascularity of the bowel wall is preserved. Appearance is consistent with an obstructed right inguinal hernia containing a loop of bowel.

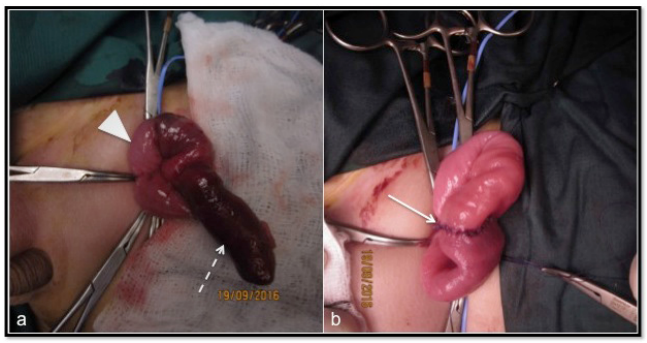

Fig. 2. (a, b). Intra-operative photographs reveal the Meckel's diverticulum (dashed arrow) attached to the adjacent small bowel (arrowhead) within the right inguinal hernia sac and small bowel anastomosis post-diverticulectomy (arrow).

Findings and Diagnosis

The ultrasound images reveal a large tubular cystic structure (dashed arrow) extending from a narrow opening (arrow) in the right inguinal canal into the right scrotum adjacent to the normal appearing right testis (T). Intraluminal gas (arrowhead) and dependent debris (asterisk) are seen within the cystic structure (Figs. 1a,b,c). The overall appearances are suggestive of an obstructed right inguinal hernia containing a loop of bowel. Intramural vascularity of the bowel wall is preserved (Fig. 1d). Serum investigations showed elevated platelet count (587 x 103/uL [150-450]) and elevated total white blood cell count (17.8 x 103/uL [6.0-17.5]) with neutrophilia (11.8 x 103/uL [1.5-8.5]). Serum C-reactive protein level, electrolytes and liver function tests were normal. Urinalysis reveal elevated white blood cells (18uL [0-10]).

An attempt was made to reduce the right inguinal hernia by the patient's bedside, which was successful. Shortly after, there was recurrence of the right inguinal hernia. The patient subsequently underwent a right inguinal herniotomy. Intraoperatively, a note was made of a Meckel's diverticulum (dashed arrow) seen within the right inguinal hernia sac which appeared congested with borderline viability (Fig. 2a). Small bowel resection and diverticulectomy was performed followed by small bowel anastomosis (arrow)

Answer: D

and right inguinal herniotomy (Fig. 2b). Postoperatively, the patient made a rapid and uneventful postoperative recovery. Histology of the specimen revealed presence of a diverticulum within sections of the resected small bowel with submucosal haemorrhage. Ganglion cells were seen suggesting the presence of a Meckel's diverticulum (MD). Overall findings confirmed the diagnosis of an incarcerated right inguinal Littre hernia (LH).

Discussion

LH is the protrusion of a MD through a potential abdominal opening.[1] LH was described 1700 by French surgeon Alexandre de Littre for the first time as an "ileal diverticula in the inguinal hernia" after autopsy findings of 2 patients. Johann Friedrich Meckel described diverticula of the distal ileum in 1809 and suggested their congenital origin.[2]

MD is a true diverticulum in that it contains all tissue layers of the bowel. Embryologically, MD is the persistent part of the omphaloenteric duct through which the midgut communicates with the umbilical vesicle until the fifth week. It arises from the antimesenteric border of the ileum, usually located 30 cm to 90 cm from the ileocaecal valve. It usually measures 3 cm to 6 cm in length and 2 cm in diameter.[1]

MD occurs in about 2% of the population and may present at any age, but most commonly before the age of [2,3,4] Its incidence is found to be equal in male and females, but complications occur more frequently in males.[5] It is the most common congenital anomaly of the gastrointestinal tract that is generally asymptomatic and only manifests in a specific way when complications occur. Only about 1% to 4% of patients with MD develop complications of haemorrhage, inflammation, obstruction or perforation.[6] Several factors associated with a higher risk of complications include: male sex, age below forty, a diverticulum of more than 2 cm in length or with a narrow neck, the presence of heterotopic mucosa or the existence of a diverticular band.

Heterotopic tissue of gastric, duodenal, pancreatic or colonic morphology in MD has been reported to occur in 6% to 17%; gastric mucosa being the most common type.[5,7] This heterotopic mucosa is the main underlying pathological reason behind complications such as haemorrhage and perforation.[5]

Sometimes, MD may be accompanied by the ileal loop to which it is attached; rarely, it may undergo incarceration or strangulation, necrosis, and perforation.[1] Hernial strangulation of MD (Littre hernia) is a rare anatomoclinical form representing 10% of all complications of MD.[7] The most usual locations of LH are: inguinal (50%), umbilical (20%) and femoral (20%).[1] In the adult age, about half of LH occurs in the inguinal region.[2] In children, it is mostly found in umbilical hernias, and the diverticulum is more prone to adhere to the sac.[1] Due to the low incidence of LH, it is generally unsuspected. Clinically, a distinction between the involvement of a small bowel loop versus a MD in an inguinal hernia cannot be made, hence the diagnosis of LH is often made in the perioperative period.[8] In addition, the signs and symptoms of an incarcerated MD on presentation are thought to progress slower than a hernia involving small bowel, hence making preoperative diagnosis of LH difficult.[8,9] Despite difficulty of making a preoperative diagnosis of LH, findings such as incomplete manual reduction of an incarcerated hernia, hernial faecal fistula and previous history of rectal bleeding should alert the clinician about LH.[2]

Surgery is the mainstay of treatment for LH. The techniques for surgical resection of MD include a simple diverticulectomy using a linear gastrointestinal (GI) stapler or segmental resection of the involved small bowel and primary anastomosis. In situations of perforation, bowel ischaemia or where presence of ectopic tissue is definitive, resection and small bowel anastomosis are recommended.[8] This is followed by closure of the hernial sac.

In our case of an infant presenting with acute painful right inguinoscrotal swelling, the likely differential diagnosis considering patient's age, clinical presentation and examination findings included that of testicular torsion, epididymo-orchitis or torsion of the testicular appendage, which commonly occurs in the paediatric age group.[10] However, given the normal appearances of the right testis and right epididymis on ultrasound, the above differential diagnoses were unlikely. Another possible differential diagnosis that was considered was an acute hydrocele, which demonstrates a similar appearance to an inguinoscrotal hernia on ultrasound. However, it is avascular on Doppler evaluation and is often painless. In view of the examination and ultrasound findings, an incarcerated inguinoscrotal hernia was considered the most likely primary preoperative diagnosis. Finally, the diagnosis of incarcerated inguinal LH was confirmed intraoperatively and on histology.

Conclusion

The clinical presentation of LH is not significantly different from any hernia, whether complicated or not. However, while evaluating a child beyond the newborn period with an incarcerated hernia, an incomplete or failed manual reduction should raise the possibility of a LH, as in our patient's case. In addition, querying the history of rectal bleeding or repetitive abdominal pain in these cases should increase the suspicion of LH. Furthermore, LH, although rare, should be considered at the time of repair for any abdominal hernia involving small bowel as resection of the MD is critical in avoiding recurrent complications.[2]

REFERENCES

1. Skandalakis PN, Zoras OM, Skandalakis JE, Mirilas P. Littre hernia: surgical anatomy, embryology and techique of repair. Am Surg 2006;72:238-43.
2. Pampal A, Aksakal ED. Littre hernia in childhood: a case report with a brief review of the literature. Afr J Paediatr Surg 2011;8:221-4.
3. Moore TC. Omphalomesenteric duct malformations. Semin Pediatr Surg 1996;5:116-23.
4. St-Vil D, Brandt ML, Panic S, Bensoussan AL, Blanchard H. Meckel's diverticulum in children: A 20- year review. J Pediatr Surg 1991;26:1289-92.
5. Rattan KN, Singh J, Dalal P, Rattan A. Meckel's diverticulum in children: our 12-year experience. Afr J Paediatr Surg 2016;13:170-4.
6. Akin M, Kurukahvecioglu O, Tezcaner T, Anadol AZ, Onur K. Acute hemiscrotum due to inguinoscrotal Littre hernia: a case report. Am J Emerg Med 2008;26:973.
7. Mirza MS. Incarcerated Littre's femoral hernia: case report and review of the literature. J Ayub Med Coll 2007;19:60-1.
8. Horkoff MJ, Smyth NGC, Hunter JM. A large incarcerated Meckel's diverticulum in an inguinal hernia. Int J Surg Case Rep 2014;5:899-901.
9. Biel A, Vilallonga R, López-de-Cenarruzabeitia I, Rodríguez N, Armengol M. Littré s hernia: unusual find in inguino-scrotal hernial repair. Rev Esp Enferm Dig 2010;102:506-7.
10. Vasdev N, Chadwick D, Thomas D. The acute pediatric scrotum: presentation, differential diagnosis and management. Curr Urol 2012;6:57-61.

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