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

DIAMOND JUBILEE CELEBRATION 1957-2017 60 years

VOLUME 47 | NUMBER 9 | FREE PAPERS | SEPTEMBER 2018

MCI (P) 104/07/2017

"Cogito, ergo sum."

René Descartes (1596 – 1650)
French philosopher

Reproduced with permission from:
Anonymous

Please see inside Contents for the full list of articles.

Acknowledgements

The Editorial Board of the Annals, Academy of Medicine, Singapore gratefully acknowledges the generous support of:

The Lee Foundation

*****

Forthcoming Issues

Vol 47 No. 10, October 2018 – Free Papers
Vol 47 No. 11, November 2018 – Free Papers
Vol 47 No. 12, December 2018 – Free Papers
Vol 48 No. 1, January 2019 – Free Papers
Vol 48 No. 2, February 2019 – Free Papers

* * * * *

General Information

* * * * *

For all enquiries, please contact the Annals Editorial Office at: Annals, Academy of Medicine, Singapore, 81 Kim Keat Road, #11-00 & 12-00, NKF Centre, Singapore 328836. Email: annals@ams.edu.sg; Homepage: http://www.annals.edu.sg

Online submission: http://www.annals.edu.sg/OnlineManuscript/

Free Papers

Editorial

Predicting Suicide and its Prevention

John CM Wong, [1,2]*MBBS (S'pore), MMed (Psych), FAMS (Psych)*

Suicide, "the act of taking one's own life", is a behaviour that has existed over many centuries and across different cultures of human civilisation. This complex issue often reflects the distress, pain and hopelessness of an individual, in a critically negative emotional and social state. Over the course of their practice, health professionals will usually be exposed to suicidal individuals at some point.

A loved one's suicide often deals a great blow to relatives and friends, even more so when it comes as unexpected news. This is especially the case when the victim is young or physically healthy. The pain it brings and the shock it causes often traumatises and leaves their loved ones feeling anguished. Having access to lethal means to kill oneself is indeed a major risk factor.

Prevalence and National Statistics

Understanding suicide as the consequence of a diverse and multifaceted process, and playing a role in preventing it, is a complex but important core competency that health practitioners should possess.

In research on suicide, challenges presented by social stigma, taboo and lack of organised suicide registry data often leads to under-reporting and misclassification of suicide into other causes of death. This renders poor data quality for suicide research. Researchers have turned to studying postmortem records of suicide cases, as well as investigating suicidal thoughts and risk factors in groups of attempted suicide and deliberate self-harm individuals, who survived their episodes of attempt.

Attempted suicide or non-fatal suicidal behaviour, where one acts with the desire to end one's life that does not result in death but self-injury, could yield important insight into the risk factors of suicide and possible preventive measures.[1] Examining cases of non-suicidal deliberate self-harm may also provide insight into the stress diathesis of these troubled individuals.

According to the Suicide Statistic report[2] by the Samaritans of Singapore (SOS), there were 361 reported suicides in Singapore in 2017. This accounts statistically for almost 1 death from suicide a day. The largest group are those aged 10-29, with males accounting for more than two-thirds of all suicides.[3]

From 2012 to 2016, the average suicide rate was 9.14 deaths per 100,000 residents. In 2017, this dropped to an all-time low of 7.74 suicide deaths per 100,000 residents.[2]

According to the SOS, while "the total suicide deaths is at its lowest in recent years, the number of the elderly aged 60 and above who took their own lives in 2017 has risen to 129". While the elderly population has grown in numbers in recent years,[4] it was noted that "the high prevalence of suicide mortality among the elderly is a worrying trend in Singapore, with the number of elderly suicide in 2017 rising to an alarming 123 per cent of that in 2011".[2] Elderly callers to the SOS hotline often share "their struggles with loneliness, social disconnection, fear of being a burden to their families and friends, impairments to daily functioning due to physical challenges and deteriorating mental health".[2] Studies have shown that elderly who are depressed and feeling a sense of hopelessness have a higher risk for suicidal ideas,[5] and could turn to suicide as a means to end their pain and struggles.

In another suicide research study funded by the Ministry of Social and Family Development (MSF),[6] Singaporean adolescents who attempted suicide, with the intent of ending their lives, reported significantly higher stressors in the domains of social, family, academic and financial matters compared to matched-controls. In particular, younger adolescents with a history of suicide attempt have more stressors compared to older adolescents especially in the domains of academic and financial matters.

In the study, adolescents with a history of suicide attempt are found to have tendency to exhibit withdrawn behaviours towards new persons, objects, situations or events. They tend to be less adaptable to changes in routine and the environment, to have a general negative outlook and less jovial behaviour, and to have an irregular daily sleep-wake

[1]Department of Psychological Medicine, National University Health System, Singapore
[2]Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Address for Correspondence: A/Prof John Wong Chee Meng, Department of Psychological Medicine, National University Health System, NUHS Tower Block, Level 9, 1E Kent Ridge Road, Singapore 119228.
Email: pcmwcmj@nus.edu.sg

cycle. Male adolescents who have attempted suicide tend to be more restless, fidgety and have a higher motor activity level compared to male adolescents from the control group.

Reflecting on their parent's parenting style, adolescents who have attempted suicide reported lower parental warmth, higher parental hostility, higher maternal neglect and higher maternal rejection compared to matched-controls. Parenting practices among fathers and mothers differed significantly from each other.

Adolescents who have attempted suicide are more at risk of experiencing psychiatric symptoms across domains in mood disorders, anxiety disorders, eating disorders and schizophrenic disorders. The most prevalent personality disorder traits among adolescents who have attempted suicide were borderline personality traits, avoidant personality traits, and paranoid personality traits.

In another Singapore study on deliberate self-harm (DSH) behaviour,[7] the prevalence of DSH in a sample of youth attending the state psychiatric hospital clinic in Singapore was 58.8% in 12 months. Cutting/carving (25.4%) and hitting (20.4%) were the most common forms of DSH. It was found that DSH acts were performed primarily for emotion regulation purposes. And "the risk factors identified for DSH in this study were younger age group, female gender, abuse history and higher depression scores. Gender and age group were the factors that were differentially associated with cutting and hitting oneself".

Neurobiology of Suicide

A review by Heeringen et al[8] on the stress-diathesis model suggests that "suicide is the result of an interaction between state-dependent (environmental) stressors and a trait-like susceptibility to suicidal behaviour, independent of psychiatric disorders". Postmortem studies of the brain and genomic, in vivo neuroimaging studies indicate "a biological basis with early-life adversity and epigenetic mechanisms explain some of the link between suicide risk and brain circuitry with neurochemistry abnormalities".

Recent evidence showed "impairments of the serotonin neurotransmitter system and the hypothalamic-pituitary-adrenal axis stress-response system in the diathesis for suicidal behaviour, manifesting as impaired cognitive control of mood, pessimism, reactive aggressive traits, impaired problem-solving, over-reactivity to negative social signs, excessive emotional pain, and suicidal ideation, leading to suicidal behaviour".[9]

Serotonergic hypofunction, in turn, could lead to a predisposition to impulsive and aggressive behaviour, probably due to a breakdown in the inhibitory function of the ventral prefrontal cortex as a result of less serotonin input in suicide and serious suicide cases.[10] Medical therapy in depressed and suicidal patients are clearly indicated.

Prevention of Suicide

Assessing and predicting the risk of suicide, identification of treatment and prevention targets beyond major psychiatric illnesses are the main goals of suicide prevention.

National policies and programmes providing a safety net targeting at socioeconomic factors, e.g. unemployment, financial distress, real and perceived social isolation and neglect are important preventive measures against suicide.

Early detection and effective treatment intervention of mental disorders and substance abuse have proven to be keys to mitigate the inherent risk of suicide in this population.

The World Suicide Prevention Day[11] (WSPD) is an awareness day observed annually on 10 September since 2003, organised by the International Association for Suicide Prevention (IASP) and co-sponsored by the World Health Organization (WHO). It aims to showcase a worldwide commitment towards implementing effective intervention to prevent suicides. It raises a collective awareness and mobilises national resources to better understand suicidal behaviours and effectively prevent them collectively from a social-health-political vantage.

In Singapore, there has been a concerted national effort to involve multiple agencies across ministries, educational, social and health entities with a workgroup formed to study adolescent suicide in 2015 when 27 youths committed suicide—a significant increase from 17 the year before. The workgroup reviewed health, social and educational data, studied best practices in suicide prevention programmes and policies overseas, and formulated an action plan in suicide prevention. In 2017, the number of youth who died from suicide was reduced to 12, less than half that in 2015. This was an assuring relief and early affirmation of a national effort in suicide prevention. In recent years, many youth social work agencies, educators, youth peers and parents were acknowledged for their effort in raising awareness of suicide prevention, actively looking out for at-risk youth and providing them timely access to social and medical support systems.

Now, the rising needs of an elderly population and the rising numbers of elderly suicide signal an urgent call for national agencies to better understand and mitigate the adversities our elderly are facing from financial strain, social isolation, loneliness, depression, chronic pain and frailties from chronic medical illnesses.

In the battle against elderly suicide, while social agencies have a challenging task meeting the rising number of elderly, the medical fraternities and medical social work agencies provide important touch points helping to identify at-risk elderly, in order to better prevent and manage chronic pain, disabilities and provide early treatment of depression. This would tie in with a holistic patient-centred care model of

population health, extending across primary care to specialist care services.

Furthermore, with increased level of outreach effort, financial support, political commitment and greater awareness across health services, the at-risk elderly would be helped to overcome moments of distress and receive hope.

Tools for Suicide Risk Assessment

Medical services and facilities are commonplace where individuals with frailties and chronic medical conditions present. Those with comorbid depressed mood and suicidal ideation could be screened and identified for early intervention.

Screening instruments could help health professionals identify any patients at risk of depression and suicide. Besides the depression inventory, a multitier comprehensive suicide risk assessment (Tool for Assessment of Suicide Risk [TASR])[10] could help health professionals administer a structured assessment in clinic. It collates an individual's risks, symptoms, suicide beliefs and plans, and buffer profiles to generate an overall risk of suicide for the patient. Alternatively, the Suicidal Affect-Behaviour-Cognition Scale[12] (SABCS) is a 6-item self-reporting tool together with a risk barometer, providing a quick risk estimate of suicide, making it a useful short instrument for use in a busy clinical facility like the emergency department.

Conclusion

The medical fraternity can play a big part providing support and resources for people at risk of suicide, and contribute towards the larger national effort of building emotional resilience and good physical health in the population. Providing timely and effective pain management, evaluating a patient's hopefulness or evidence of hopelessness, directing them to social support agencies, early mobilisation of psych-social support and providing supportive care to address underlying triggers and existential crisis, can effectively help reduce the risk of suicidal ideation progressing into action. Giving hope to the hopeless and depressed is always a privilege given to the medical profession.

REFERENCES

1. Klonsky ED, May AM, Saffer BY. Suicide, suicide attempts, and suicidal ideation. Annu Rev Clin Psychol 2016;12:307-30.
2. Samaritans of Singapore. Report on suicide statistics. Singapore; 2017.
3. Samaritans of Singapore. Report on suicide statistics. Singapore; 2016.
4. Singapore Department of Statistics, Singapore Youth, Adult and Elderly Profile 2017. Available at: https://www.singstat.gov.sg/find-data/search-by-theme/population/elderly-youth-and-gender-profile/latest-data. Accessed on 18 September 2018.
5. Uncapher H, Gallagher-Thompson D, Osgood NJ, Bongar B. Hopelessness and suicidal ideation in older adults. Gerontologist 1998;38:62-70.
6. Wong CMJ, Tan CH, Loh SWA, Feng L, Nyein N, Pooi KC, et al. Case control study of Asian adolescents who attempted suicide: their temperament, parenting experienced, mental disorders, life stressors and help-seeking behaviour. Ministry of Social & Family Development Family Research Grant Technical Report 2014. Available at: https://www.msf.gov.sg/research-and-data/ResearchGrants/Documents/. Accessed on 18 September 2018.
7. Shahwan S, Abdin E, Zhang Y, Sambasivam R, Fauziana R, Mahesh M, et al. Deliberate self-harm in psychiatric patients aged 14-35 years in Singapore. Ann Acad Med Singapore 2017;47:360-72.
8. Kutcher SP, Chehil S. Suicide risk management: a manual for health professionals. Oxford, UK: Blackwell Pub;2007.
9. Heeringen K van, Mann JJ. The neurobiology of suicide. Lancet Psychiatry 2014;1:63-72.
10. Kamali M, Oquendo MA, Mann JJ. Understanding the neurobiology of suicidal behavior. Depress Anxiety 2001;14:164-76.
11. International Association for Suicide Prevention. World Suicide Prevention Day. Washington DC, USA; 2018. Available at: https://iasp.info/wspd2018/. Accessed on 18 September 2018.
12. Harris KM, Syu JJ, Lello OD, Chew YLE, Willcox CH, Ho RH. The ABC's of suicide risk assessment: applying a tripartite approach to individual evaluations. PLoS One 2015;10:e0127442.

Original Article

Deliberate Self-Harm in Psychiatric Outpatients Aged 14-35 Years in Singapore

Shazana Shahwan, [1]*MClinPsych*, Edimansyah Abdin, [1]*PhD*, Yunjue Zhang, [1]*BPsych*, Rajeswari Sambasivam, [1]*BSc*, Restria Fauziana, [1]*BA*, Mithila Mahesh, [1]*MSc*, Say How Ong, [2]*MBBS, MMed (Psych), FAMS*, Siow Ann Chong, [1]*MMed (Psych), MD, FAMS*, Mythily Subramaniam, [1]*PhD, MBBS, MHSM*

Abstract

Introduction: The main aim of the study was to identify the prevalence of deliberate self-harm (DSH) in a sample of youth outpatients attending the state psychiatric hospital in Singapore and to identify the sociodemographic and psychological/clinical risk factors associated with DSH. The secondary aim of the study was to examine if different forms of DSH had distinguishing risk factors. Materials and Methods: A total of 400 outpatients at the Institute of Mental Health completed a self-report survey comprising sociodemographic questions, the Functional Assessment of Self-Mutilation, Childhood Trauma Questionnaire, Parental Bonding Instrument and the Patient Health Questionnaire Depression Scale. Logistic regression models were used to test the associations. Results: The overall prevalence of DSH in our clinical population was 58.8%. Cutting/carving (25.4%) and hitting (20.4%) were the most common forms of DSH in the past 12 months. DSH acts were performed primarily for emotion regulation purposes. The risk factors for DSH in general were younger age group, female gender, abuse history and higher depression scores. Gender and age group were the factors that were differentially associated with cutting and hitting one's self. Conclusion: There was a high prevalence of DSH in the psychiatric outpatient population. The risk factors identified in this study are consistent with those of international studies which point to their stability across cultures.

Ann Acad Med Singapore 2018;47:360-72

Key words: Abuse, Asian, Cutting, Depression, Prevalence, Risk factors, Youth

Introduction

The purposeful act of harming oneself physically—usually without suicidal intent such as by cutting, hitting or burning—is referred to in clinical literature by varied nomenclature including non-suicidal self-injury, deliberate self-harm, self-mutilation and parasuicide.[1] Historically regarded as a symptom of borderline personality disorder (BPD),[2] it has gathered renewed interest in the last 2 decades as a distinct syndrome due to its occurrence and significant impairment in the absence of other key BPD features.[3] In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), non-suicidal self-injury is included as a new condition for further study following argument by proponents in the hope for better understanding, management and treatment of the condition.[4] The term 'non-suicidal self-injury' explicitly excludes behaviours engaged with any level of suicidal intention. By contrast, the term 'deliberate self-harm' (DSH) is frequently employed as a more encompassing term for self-injurious behaviours both with and without suicidal intent that have non-fatal outcomes.[5] This term will be used in the rest of the paper in line with our investigation on deliberate self-injurious behaviours, both with and without the intention of death.

DSH behaviour peaks sharply during the adolescent years. Systematic reviews have pointed to parenting and childhood adverse events (e.g. childhood physical, emotional, sexual

[1]Research Division, Institute of Mental Health, Singapore
[2]Department of Developmental Psychiatry, Institute of Mental Health, Singapore
Address for Correspondence: Ms Shazana Shahwan, Research Division, Institute of Mental Health, Buangkok Green Medical Park, 10 Buangkok View, Singapore 793747.
Email: shazana_mohamed_shahwan@imh.com.sg

abuse and emotional neglect) as salient predisposing factors.[6,7] Glassman et al revealed that emotional abuse during a child's formative years could result in a tendency to internalise critical thinking toward the self.[8] In the face of stressful events, adolescents who have developed such a cognitive style may be more likely to engage in DSH for self-punishment. Dissociation has also been shown to link the experience of childhood abuse with subsequent self-harming behaviour.[9] When individuals, especially children, are overwhelmed by an external stressor, they resort to disengagement (i.e. dissociation) as a way of coping. In van der Kolk et al's study, it was found that dissociation was specifically related to cutting oneself.[10] Patton et al, on the other hand, attributed the rise in DSH during adolescence to developmental and life-stage changes such as intensifying peer dynamics, the emergence of greater life stressors and psychological shifts in response to stress such as ruminative and self-blaming coping styles.[11]

DSH, though distinct from suicidal behaviour, is an important risk factor for suicide.[12,13] Stanley et al estimated that 55% to 85% of self-injuring individuals have a history of at least 1 suicide attempt.[14] A local study on 207 Singaporeans aged between 15 to 24 years found that resolution of a suicide precipitant was an important factor to differentiate DSH and suicide attempts with low and high perceived lethality.[15] Joiner hypothesised that the ability to end one's life is acquired by overcoming the fear and pain associated with it.[16] By repetitively engaging in non-suicidal self-injury, individuals become desensitised to the pain and fear related to attempting suicide.

Singapore is a city-state country located on the southern tip of the Malay Peninsula which has a small land area of 719 km^2 and a population of 5.5 million. While local voluntary welfare organisations such as the Singapore Children's Society and the Samaritans of Singapore have observed a spike in youth self-harming (from 2005 to 2013 as reported in the popular press),[17] few systematic studies on DSH have been done in Singapore. The main aim of the study was to identify the prevalence and characteristics of DSH in a relatively large sample of youth outpatients attending a tertiary psychiatric hospital as well as the sociodemographic and psychological/clinical risk factors of DSH. Since many of the studies have focused on cutting behaviours, we also examined if self-hitting was associated with distinct factors.

Materials and Methods

Participants

Participants were 400 outpatients from the Institute of Mental Health (IMH) aged 14-35 years. IMH is Singapore's only state psychiatric hospital and the largest provider of mental health services in the country. The age range considered for our sample was based on 2 local definitions of youth: 1) the Children and Young Persons Act (1993), which defines a young person as 14-16 years, and 2) the National Youth Council's which defines youths as those aged 15-35 years.[18] There was almost an equal number of male and female (males = 51%) participants. The ethnic distribution of the sample, like the general Singapore population,[19] was mainly Chinese (71%), followed by Malays (18%), Indians (9%) and other ethnicities (3%). The majority of participants were diagnosed with mood disorders (34%), followed by psychotic disorders (23%), adjustment disorders (19%), anxiety disorders (13%), disorders usually diagnosed in childhood (6%) and other diagnoses (6%).

Procedure

Participants were recruited at the child and adult outpatient clinics in IMH between October 2015 and June 2016. Ethics approval was attained and clinicians were informed of the study. Participants either volunteered by responding to posters in the outpatient clinics or they were referred by clinicians who were study team members. Patients were screened for intellectual disability as the researchers felt that the requirements of the study required considerable insight, Primary 6 reading level and the ability to retrospect. An intellectual disability diagnosis was a quick way to identify and exclude those who would most likely not be able to do so. The clinical team ensured that only patients who met these criteria were referred to the research team. The research team also confirmed the patient's history by accessing the medical records after receiving written informed consent to ensure that all inclusion and exclusion criteria were met. Although a waiver of parental consent was obtained, the study was explained to parents of adolescents less than 21 years of age who came accompanied. Nevertheless, the research officers ensured that the self-administered questionnaires were completed independently by the participants.

Measures

Sociodemographic data used in this analysis were age, gender, ethnicity, religion, marital status, highest level of education, and type of housing which is regarded as an indicator for socioeconomic status.

The Functional Assessment of Self Mutilation (FASM) assessed the methods, frequency and functions of self-reported DSH.[20] It consisted of a checklist of DSH behaviours; respondents were asked whether they purposefully engaged in each of 11 different DSH behaviours within the past 12 months and, if so, the frequency of occurrence. The scale also asked the age at which DSH first began (onset); and whether any of those behaviours was a suicide attempt. Motivations for DSH was presented as 22 statements in checklist format and rated on a 4-point

Likert scale, ranging from 'never' to 'often'. The FASM has strong psychometric properties, including good reliability and validity with youth samples[21] and has been used in an adolescent psychiatric outpatient sample locally.[22]

The Childhood Trauma Questionnaire (CTQ) is a 28-item inventory that measures the severity of 5 types of childhood adverse events—Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect and Physical Neglect.[23] Each subscale is measured by 5 items rated on a 5-point scale from 1 (never true) to 5 (very often true). It provides a brief, reliable and valid screening for histories of abuse and neglect.[24] The internal consistency for all scales was good (r = 0.85-0.94) except for the Physical Neglect scale (r = 0.56), as has also been found in previous samples.[25] The CTQ has been used locally with psychiatric patients.[26]

The Parental Bonding Index (PBI) is a 25-item instrument that assesses recall of the parental rearing styles in the first 16 years of life.[27] Each of the 25 items is rated on a 4-point scale from 0 (very like my parent) to 3 (very unlike my parent). The items are grouped into 2 scales: 'care' and 'overprotection', and the measure is completed twice, once for each parent. Unhealthy parent-child bonding is indicated by lower 'care' scores and higher 'overprotection' scores. The PBI has been used in Singapore.[28-29] The PBI has good psychometric properties[30] with good internal consistency of r = 0.83-0.92 for this sample.

The Patient Health Questionnaire-8 (PHQ-8) depression scale assesses how often in the past 2 weeks participants experienced 8 depressive symptoms: which are rated on a 4-point scale ranging from 0 (not at all) to 3 (nearly every day).[31] The items are summed to yield a total score. The PHQ-8 has been widely used in Singapore[32-33] and has a good internal consistency of r = 0.92.

Statistical Analyses

Descriptive statistics were first conducted to examine the characteristics of DSH in an outpatient sample. Then, we conducted a simple logistic regression analysis to examine relationships between sociodemographic and clinical/psychological variables and DSH in order to make decisions about predictors to enter into the multiple logistic regression models to maximise model-fit. We then compared the forward selection and backward elimination methods in multiple logistic regression analyses to estimate the influence of sociodemographic and psychological/clinical factors on 1) any type of DSH, 2) cutting and, 3) hitting. Age, gender, ethnicity, religion, marital status, highest level of education, and type of housing as well as types of childhood adverse events, parental rearing styles and depressive symptoms were included as predictors. In these analyses, several model-fit indices were considered to determine the best fitted regression model. The overall model-fit was examined using Hosmer-Lemeshow goodness-of-fit (GOF) tests and area under the receiver operating characteristics (ROC) curve while multicollinearity between predictors was examined using variance inflation factor values. Statistical significance was evaluated at the 0.05 level using 2-sided tests.

Table 1. Sociodemographic Profile of Sample

	Overall Sample		14 – 21 Years		22 – 35 Years		
	n	%	n	%	n	%	*P* Value
Gender							
Female	195	48.75	97	50.79	98	46.89	0.436
Male	205	51.25	94	49.21	111	53.11	
Ethnicity							
Chinese	284	71.00	143	74.87	141	67.46	0.267
Malay	71	17.75	30	15.71	41	19.62	
Indian	34	8.50	12	6.28	22	10.53	
Others	11	2.75	6	3.14	5	2.39	
Religion							
Christianity	111	27.75	49	25.65	62	29.67	0.215
Buddhism	89	22.25	47	24.61	42	20.10	
Hinduism	16	4.00	6	3.14	10	4.78	
Islam	74	18.50	30	15.71	44	21.05	
Taoism	13	3.25	4	2.09	9	4.31	
Free thinker	79	19.75	10	5.24	8	3.83	
Others	18	4.50	45	23.56	34	16.27	

HDB: Housing and Development Board; NITEC: National Institute of Technical Education Certificate; PSLE: Primary School Leaving Examination
*Due to zero cell counts in certain groups, chi-squared tests were conducted after regrouping the categories (e.g. married, separated and divorced were merged as ever married while degree holders were merged with Other diploma and professional qualification).

Table 1. Sociodemographic Profile of Sample (Cont'd)

			14 – 21 Years		22 – 35 Years		
	n	%	n	%	n	%	*P* Value
Marital Status							
Single	356	89.00	189	98.95	167	79.90	<0.0001*
Married	35	8.75	0	0.00	35	16.75	
Separated	4	1.00	1	0.52	3	1.44	
Divorced	5	1.25	1	0.52	4	1.91	
Education level							
PSLE and lower	29	7.25	25	13.09	4	1.91	<0.0001*
Secondary	40	10.00	30	15.71	10	4.78	
'O'/'N' level	113	28.25	72	37.70	41	19.62	
'A' level	23	5.75	14	7.33	9	4.31	
NITEC/higher NITEC	45	11.25	16	8.38	29	13.88	
Polytechnic diploma	83	20.75	24	12.57	59	28.23	
Other professional qualification	29	7.25	10	5.24	19	9.09	
Degree and higher	38	9.50	0	0.00	38	18.18	
Type of housing							
Semi-D/terrace	15	3.75	8	4.19	7	3.35	0.076
Private flat/condo	36	9.00	25	13.09	11	5.26	
4/5 room HDB	230	57.50	106	55.50	124	59.33	
2/3 room HDB	89	22.25	42	21.99	47	22.49	
1 room HDB	17	4.25	5	2.62	12	5.74	
Others	13	3.25	5	2.62	8	3.83	
Primary diagnosis							
Adjustment disorders	65	16.29	39	20.53	26	12.44	<0.0001
Anxiety disorders	61	15.29	29	15.26	32	15.31	
Childhood disorders	21	5.26	16	8.42	5	2.39	
Mood disorders	137	34.34	72	37.89	65	31.10	
Schizophrenia spectrum	91	22.81	18	9.47	73	34.93	
Others	24	6.02	16	8.42	8	3.83	

HDB: Housing and Development Board; NITEC: National Institute of Technical Education Certificate; PSLE: Primary School Leaving Examination
*Due to zero cell counts in certain groups, chi-squared tests were conducted after regrouping the categories (e.g. married, separated and divorced were merged as ever married while degree holders were merged with Other diploma and professional qualification).

Results

The sociodemographic profile of the sample is shown in Table 1. The mean age of the sample was 23.3 years (SD = 6.04).

Prevalence/Frequencies and Descriptive Characteristics

The mean age of onset of DSH was 16.5 years (range: 6-34 years) amongst the patients included in the study. A total of 58.8% had committed at least 1 of the self-injurious behaviours in the FASM checklist in the past 12 months. The prevalence of committing any of the DSH behaviours was significantly higher in the 14-21 years age group (72.8%) compared to the 22-35 years age group (45.9%).

As shown in Table 2, the most common forms of DSH were hitting self on purpose, cutting/carving self, biting self and picking on a wound. Table 2 also shows the number of times the acts were committed. Most of those who had harmed themselves had done so 2-5 times in the past 12 months. Notably, a large proportion of self-harmers had done the acts over 11 times in the past 12 months (20.5%-36% for the most common forms of DSH). The 5 most highly endorsed motivations of DSH reported were 'to stop bad feelings (66.2%)', 'to relieve feeling numb/empty (64.3%)', and 'to punish self (59.1%)', 'to feel something even if it was pain (53.7%)' and 'to feel relaxed (47.2%)'. Out of those who had ever self-harmed, 32% reported that they ever tried to kill themselves.

Table 2. Frequency and Percentages of DSH in the Past 12 Months

	Ever DSH in Past 12 Months		No. of Times in the Past 12 Months							
			Once		2 – 5 Times		6 – 10 Times		>11 Times	
Type of DSH	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hit self on purpose	157	39.3	13	8.3	67	42.7	33	21	42	26.8
Cut/carved on skin	122	30.5	16	13.1	61	50	19	15.6	25	20.5
Bit self	89	22.3	10	11.2	32	36	15	16.9	32	36
Picked at a wound	83	20.8	8	9.6	44	53	13	15.7	17	20.5
Pulled hair out	60	15	8	13.3	25	41.7	7	11.7	20	33.3
Scraped skin	51	12.8	5	9.8	29	56.9	3	5.9	14	27.5
Picked areas of body to the point of drawing blood	43	10.8	3	7	17	39.5	9	20.9	14	32.6
Burned skin	29	7.3	4	13.8	18	62.1	4	13.8	3	10.3
Gave self a tattoo	24	6	7	29.2	11	45.8	2	8.3	2	8.3
Inserted objects under nails or skin	13	3.3	1	7.7	7	53.8	1	7.7	4	30.8
"Erased" skin	11	2.8	1	9.1	5	45.5	2	18.2	3	27.3
Any of the above	235	58.8								

DSH: Deliberate self-harm

Sociodemographic and Psychological/Clinical Correlates of DSH

Simple and multiple logistic regression analyses examining the association between sociodemographic and psychological/clinical variables and 1) any DSH, 2) self-cutting, and 3) self-hitting are presented in Tables 3, 4 and 5, respectively. The forward selection and backwards elimination (data available on request) models yielded identical findings for 'any DSH behaviour' and 'hitting'.

Those who endorsed any of the 11 types of DSH assessed tended to belong to the younger age group, female gender, had a mood disorder (vs anxiety or schizophrenia spectrum disorder), higher sexual abuse score and higher PHQ depression score (Table 3). We observed some discrepancy between the forwards selection and backwards elimination model when predicting cutting. While both models identified younger age group, female and higher PHQ score as risk factors, the backwards model did not identify mood disorder (vs anxiety disorder) as a predictor. Additionally the forwards selection model (Table 4) found emotional abuse to be a significant predictor whereas the backwards elimininationmodel found physical abuse to be a significant predictor. No multicollinearity was observed between predictors. Since logistic regression results derived from forwards selection model (Pseudo R^2 = 27.42%, GOF tests = 365.58, *P* value = 0.5112, ROC = 0.841) provided slightly better fit indices than backwards elimination model (Pseudo R^2 = 26.14%, GOF tests = 318.71, *P* value = 0.3397, ROC = 0.836), the forward selection model was used.

Lastly, those who endorsed hitting themselves had higher emotional abuse and higher PHQ depression scores (Table 5).

Discussion

The overall prevalence of DSH in our sample of psychiatric outpatients was 58.8%, and 72.8% and 45.9% for those aged 14-21 and those aged 22-35, respectively—which mirrored the elevated rates typically observed in adolescent/young adult psychiatric samples (40% to 80%).[34] Our finding is far higher than that of an earlier local study by Loh et al which reported a rate of 23.6% in a similar psychiatric outpatient sample of adolescents aged 12-19 years.[35] A likely reason for this wide margin of difference could be that DSH data in Loh's study was extracted through medical records whereas the current study utilised the multi-item FASM. DSH is a notoriously furtive behaviour and disclosure through an anonymous survey may be less threatening than a face-to-face consultation, particularly where a parent might be present. In addition, multi-item instruments have been found to produce significantly higher prevalence rates.[5] Prevalence estimates for DSH rates using behavioural-checklist measures assessment have been shown to be nearly 3 times higher than single-item assessments.[5] However, while it is difficult to determine if single-item assessments are underestimating the prevalence or if the behavioural assessments are inflating rates, an assessment bias clearly exists.

Our study also pointed to the use of DSH primarily for emotion-regulating functions (rather than to regulate one's social environment) and the repetitiveness of the behaviour. DSH has been construed as having addictive qualities due to its tension-releasing properties.[36-37] This relatively fast and easily accessible means of serving the proposed functions can be performed quickly in virtually any context

Table 3. Sociodemographic and Psychological/Clinical Correlates of Any Form of Self-Harm

	Simple Logistic Regression				Multiple Logistic Regression			
	Odds Ratio	***P* Value**	**95% CI**		**Odds Ratio**	***P* Value**	**95% CI**	
Sociodemographic variables								
Age group								
14 – 21 years	3.15	0.000	2.07	4.78	2.85	0.000	1.62	5.02
22 – 35 years	(ref)							
Gender								
Male	(ref)							
Female	2.58	0.000	1.71	3.89	2.93	0.000	1.67	5.14
Ethnicity								
Chinese	(ref)							
Malay	1.11	0.707	1.71	3.89				
Indian	2.12	0.064	0.96	4.71				
Others	1.34	0.649	0.38	4.67				
Religion								
Christianity	(ref)							
Buddhism	0.7	0.209	0.40	1.22				
Hinduism	1.5	0.479	0.49	4.61				
Islam	0.89	0.715	0.49	1.62				
Taoism	1.09	0.885	0.34	3.55				
Freethinker	0.68	0.452	0.25	1.85				
Others	1.47	0.211	0.80	2.70				
Marital status								
Single	(ref)							
Married	1.07	0.857	0.53	2.17				
Divorced/separated	1.42	0.622	0.35	5.78				
Education level								
PSLE and lower	(ref)							
Secondary	0.66	0.451	0.22	1.94				
O'/'N' level	0.56	0.221	0.22	1.42				
A' level	0.49	0.248	0.15	1.63				
NITEC/higher NITEC	0.52	0.224	0.18	1.49				
Polytechnic diploma	0.33	0.021	0.13	0.85				
Other professional qualification	0.39	0.102	0.13	1.20				
Degree	0.19	0.002	0.06	0.54				
Type of housing								
Semi-D/terrace	1.09	0.869	0.38	3.18				
Private condo	2.19	0.055	0.98	4.86				
4/5 room	(ref)							
2/3 room	0.94	0.790	0.57	1.53				
1 room	1.75	0.308	0.60	5.13				
Others	0.32	0.067	0.10	1.08				

CI: Confidence interval; GOF: Goodness-of-fit; NITEC: National Institute of Technical Education Certificate; PHQ-8: Patient Health Questionnaire-8; PSLE: Primary School Leaving Examination; ROC: Receiver operating characteristics

Table 3. Sociodemographic and Psychological/Clinical Correlates of Any Form of Self-Harm (Cont'd)

	Simple Logistic Regression				Multiple Logistic Regression			
	Odds Ratio	***P* Value**	**95% CI**		**Odds Ratio**	***P* Value**	**95% CI**	
Clinical/psychological variables (diagnosis)								
Mood disorders	(ref)							
Adjustment disorders	0.93	0.838	0.47	1.83	1.19	0.681	0.51	2.78
Anxiety disorders	0.25	0.000	0.13	0.46	0.28	0.002	0.12	0.62
Childhood disorders	0.25	0.004	0.10	0.64	0.49	0.244	0.15	1.62
Schizophrenia	0.2	0.000	0.11	0.35	0.45	0.040	0.21	0.96
Others	0.55	0.199	0.22	1.37	1.23	0.717	0.41	3.72
Parental bonding								
Mother care	0.96	0.003	0.94	0.99				
Mother overprotection	1.02	0.178	0.99	1.05				
Father care	0.98	0.125	0.96	1.01				
Father overprotection	1.03	0.072	1.00	1.06				
Childhood trauma								
Emotional abuse	1.13	0.000	1.09	1.18				
Physical abuse	1.07	0.001	1.03	1.12				
Sexual abuse	1.1	0.001	1.04	1.16	1.08	0.050	1.00	1.17
Emotional neglect	1.06	0.003	1.02	1.10				
Physical neglect	1	0.968	0.92	1.09				
Depression PHQ-8 score	1.16	0.000	1.12	1.20	1.11	<0.0001	1.07	1.17
Fit indices								
Pseudo-R^2						25.55%		
Hosmer-Lemeshow GOF tests						307.91 (*P* value = 0.4266)		
ROC						0.824		

CI: Confidence interval; GOF: Goodness-of-fit; NITEC: National Institute of Technical Education Certificate; PHQ-8: Patient Health Questionnaire-8; PSLE: Primary School Leaving Examination; ROC: Receiver operating characteristics

and does not require the time and paraphernalia involved in other behaviours that may serve a similar function (e.g. exercise, alcohol) making it an attractive behaviour for adolescents and young adults who have difficulty regulating their emotions and behaviour and who may not have ready access to alcohol or drugs.

The risk factors identified for committing any form of DSH for our sample were younger age group, female, diagnosis of mood disorder, elevated depression score and sexual abuse which are consistent with extant literature. The risk factors identified from our analysis predicting 'cutting' were almost identical to that of the general model (i.e. any form of DSH), with the only difference being emotional abuse (rather than sexual abuse) being identified as a risk factor, which suggests that the phenomenon of DSH in general or at least the types of DSH listed in the FASM (e.g. picking a wound, scraping the skin, picking skin to the point of drawing blood) are similar. In our preliminary work consisting of a subset of this sample, Peh and colleagues found that a history of childhood maltreatment in general was associated with current depression and difficulties in emotion regulation.[38] Peh and colleagues, through mediation analysis demonstrated emotional dysregulation to be the mechanism linking childhood maltreatment and DSH. While childhood maltreatment was a distal factor, the need to avoid or escape unwanted emotions which were the most highly endorsed motivations in our survey could be proximal factors. Literature on the development of DSH suggests that poor modelling of emotion regulation by abusive caregivers[39] and internalisation of abuse (e.g. self-criticism)[8] to be some of the pathways leading to DSH.

Our secondary aim was to compare 'cutting' and 'hitting'. While both behaviours were associated with emotional abuse and elevated depression scores, female gender and younger age group were associated with cutting but not hitting. The socialisation hypothesis has been proposed for the preference for cutting among females. In particular, You et al asserted that women are socialised to internalise negative emotions and cutting can be viewed as acting in behaviour that tends to leave less extensive bodily damage than acting out displays of violent behaviours like punching

Table 4. Sociodemographic and Psychological/Clinical Correlates of Cutting

	Simple Logistic Regression				Multiple Logistic Regression			
	Odds Ratio	***P* Value**	**95% CI**		**Odds Ratio**	***P* Value**	**95% CI**	
Sociodemographic variables								
Age group								
14 – 21 years	3.35	0.000	2.13	5.26	2.78	0.001	1.49	5.21
22 – 35 years	(ref)							
Gender								
Male	(ref)							
Female	4.38	0.000	2.74	6.98	4.86	<0.0001	2.56	9.21
Ethnicity								
Chinese	(ref)							
Malay	1.13	0.682	0.64	1.98				
Indian	1.98	0.065	0.96	4.08				
Others	1.43	0.575	0.41	5.02				
Religion								
Christianity	(ref)							
Buddhism	0.82	0.543	0.44	1.54				
Hinduism	0.79	0.698	0.24	2.62				
Islam	1.13	0.697	0.6	2.14				
Taoism	0.71	0.618	0.18	2.74				
Freethinker	1.18	0.758	0.41	3.42				
Others	1.37	0.313	0.74	2.53				
Marital status								
Single	(ref)							
Married	0.66	0.325	0.29	1.51				
Divorced/separated	1.79	0.393	0.47	6.79				
Education level								
PSLE and lower	(ref)							
Secondary	0.50	0.164	0.19	1.33				
O'/'N' level	0.31	0.007	0.13	0.72				
A' level	0.17	0.005	0.05	0.59				
NITEC/higher NITEC	0.20	0.002	0.07	0.54				
Polytechnic diploma	0.18	0.000	0.07	0.45				
Other professional qualification	0.23	0.010	0.08	0.7				
Degree	0.09	0.000	0.03	0.31				
Type of housing								
Semi-D/terrace	1.35	0.593	0.45	4.12				
Private condo	1.94	0.074	0.94	3.99				
4/5 room	(ref)							
2/3 room	1.31	0.319	0.77	2.23				
1 room	3.05	0.028	1.13	8.25				
Others	0.49	0.366	0.11	2.29				

CI: Confidence interval; NITEC: National Institute of Technical Education Certificate; PHQ-8: Patient Health Questionnaire-8; PSLE: Primary School Leaving Examination

Table 4. Sociodemographic and Psychological/Clinical Correlates of Cutting (Cont'd)

	Simple Logistic Regression				Multiple Logistic Regression			
	Odds Ratio	*P* Value	95% CI		Odds Ratio	*P* Value	95% CI	
Clinical/psychological variables (diagnosis)								
Mood disorders	(ref)							
Adjustment disorders	0.89	0.689	0.49	1.61	1.75	0.183	0.77	3.98
Anxiety disorders	0.24	0.000	0.11	0.52	0.35	0.034	0.13	0.92
Childhood disorders	0.13	0.008	0.03	0.59	0.44	0.355	0.08	2.52
Schizophrenia	0.25	0.000	0.13	0.47	0.73	0.506	0.29	1.83
Others	0.51	0.165	0.2	1.32	1.58	0.452	0.48	5.16
Parental bonding								
Mother care	0.94	0.000	0.92	0.97				
Mother overprotection	1.04	0.014	1.01	1.073				
Father care	0.98	0.107	0.95	1.005				
Father overprotection	1.04	0.012	1.01	1.074				
Childhood trauma								
Emotional abuse	1.16	0.000	1.11	1.21	1.11	0.001	1.04	1.17
Physical abuse	1.10	0.000	1.06	1.149				
Sexual abuse	1.10	0.000	1.05	1.154				
Emotional neglect	1.08	0.000	1.04	1.126				
Physical neglect	1.05	0.296	0.96	1.147				
Depression score								
PHQ-8	1.13	0.000	1.09	1.166	1.1	0.000	1.05	1.16
Fit indices								
Pseudo-R^2						27.42%		

CI: Confidence interval; NITEC: National Institute of Technical Education Certificate; PHQ-8: Patient Health Questionnaire-8; PSLE: Primary School Leaving Examination

walls.[40] Self-hitting has been found to be more associated with males in several studies but our study—like the results of Bresin's meta-analysis on gender differences in non-suicidal self-injury—did not find this gender bias.[41] We argue that the association between younger age and cutting (but not hitting) is related to age-defined social expectations. Miskeg and McGee[42] highlighted how popular psychology has attributed cutting oneself to "teenage angst" or emotionality associated with simply being an adolescent. Thus, it follows that cutting is seen as a behaviour that one should eventually outgrow. Thus, judgements against cutting in adulthood may be intensified as the individual is perceived as both emotionally unstable and teen-like. DSH by cutting often leaves very telling scars. Hitting by contrast causes bruising or in more severe cases, fractures but usually do not result in permanent disfigurement. Thus, we postulate that the visibility and resulting shame of wounds from cutting results in higher social costs to adults compared to hitting, though further studies are required to corroborate these postulations.

In contrast to earlier studies that established an association between DSH and low education level as well as low socioeconomic status,[6] we did not observe these associations in the final regression models. We observed some evidence that DSH was less likely to occur among those with higher education level, though the pattern of finding for living arrangement was inconsistent. We also did not find any association between DSH and the PBI in the final models though univariate analyses were significant. We observed high intercorrelations between the CTQ and PBI scales. Thus, it is likely that PBI variables did not contribute uniquely after the CTQ variables were added in the logistic regression models.

We noted that 32% of those who had DSH had attempted suicide. Although this percentage is lower than Stanley et al's prediction,[14] it nevertheless constitutes a substantial proportion of individuals who commit DSH. According to the addiction model of DSH,[43] frequency and severity of DSH increases over time for individuals to achieve the same effect, which may lead one along the path of fatality whether intentional or unintentional. DSH can be reduced using selective serotonin reuptake inhibitor (e.g. fluoxetine) by improving impulse control. Due to the addictive nature of DSH, opioid antagonist, naltrexone was found to be

Table 5. Sociodemographic and Psychological/Clinical Correlates of Hitting

	Simple Logistic Regression				Multiple Logistic Regression			
	Odds Ratio	***P* Value**	**95% CI**		**Odds Ratio**	***P* Value**	**95% CI**	
Sociodemographic variables								
Age group								
14 – 21 years	1.66	0.014	1.11	2.49				
22 – 35 years	(ref)							
Gender								
Male	(ref)							
Female	1.84	0.003	1.23	2.77				
Ethnicity								
Chinese	(ref)							
Malay	1.29	0.352	0.76	2.18				
Indian	1.98	0.062	0.97	4.04				
Others	2.11	0.227	0.63	7.08				
Religion								
Christianity	(ref)							
Buddhism	0.92	0.784	0.52	1.64				
Hinduism	2.11	0.167	0.73	6.09				
Islam	1.12	0.712	0.61	2.05				
Taoism	1.03	0.965	0.32	3.35				
Freethinker	0.47	0.207	0.14	1.52				
Others	1.31	0.371	0.73	2.35				
Marital status								
Single	(ref)							
Married	1.73	0.122	0.86	3.48				
Divorced/separated	1.31	0.691	0.35	4.96				
Education level								
PSLE and lower	(ref)							
Secondary	1.11	0.826	0.43	2.91				
O'/'N' level	0.98	0.955	0.43	2.22				
A' level	0.79	0.680	0.26	2.41				
NITEC/higher NITEC	0.82	0.681	0.32	2.11				
Polytechnic diploma	0.56	0.192	0.24	1.34				
Other professional qualification	1	1.000	0.36	2.82				
Degree	0.38	0.071	0.13	1.09				
Type of housing								
Semi-D/terrace	1.06	0.920	0.36	3.07				
Private condo	1.27	0.512	0.62	2.58				
4/5 room	(ref)							
2/3 room	0.98	0.935	0.59	1.62				
1 room	1.41	0.497	0.52	3.78				
Others	0.7	0.569	0.21	2.35				

CI: Confidence interval; GOF: Goodness-of-fit; NITEC: National Institute of Technical Education Certificate; PHQ-8: Patient Health Questionnaire-8; PSLE: Primary School Leaving Examination; ROC: Receiver operating characteristics

Table 5. Sociodemographic and Psychological/Clinical Correlates of Hitting (Cont'd)

	Simple Logistic Regression				Multiple Logistic Regression			
	Odds Ratio	***P* Value**	**95% CI**		**Odds Ratio**	***P* Value**	**95% CI**	
Clinical/psychological variables (diagnosis)								
Mood disorders	(ref)							
Adjustment disorders	0.68	0.209	0.38	1.24				
Anxiety disorders	0.47	0.019	0.25	0.89				
Childhood disorders	0.45	0.107	0.17	1.19				
Schizophrenia	0.29	0.000	0.16	0.52				
Others	0.37	0.039	0.14	0.95				
Parental bonding								
Mother care	0.95	0.000	0.92	0.97				
Mother overprotection	1.03	0.024	1.00	1.07				
Father care	0.97	0.015	0.95	0.99				
Father overprotection	1.03	0.074	1.00	1.06				
Childhood trauma								
Emotional abuse	1.15	0.000	1.10	1.20				
Physical abuse	1.09	0.000	1.04	1.13				
Sexual abuse	1.1	0.000	1.05	1.16				
Emotional neglect	1.08	0.000	1.04	1.12	1.11	<0.0001	1.05	1.17
Physical neglect	1	0.939	0.92	1.09				
Depression score								
PHQ-8	1.17	0.000	1.13	1.21	1.15	<0.0001	1.10	1.20
Fit indices								
Pseudo-R^2							19.77%	
Hosmer-Lemeshow GOF tests							264.274, *P* value = 0.2736	
ROC							0.788	

CI: Confidence interval; GOF: Goodness-of-fit; NITEC: National Institute of Technical Education Certificate; PHQ-8: Patient Health Questionnaire-8; PSLE: Primary School Leaving Examination; ROC: Receiver operating characteristics

effective in severe cases of DSH.[44] Other researchers have also hypothesised that DSH and suicide attempt are on the same spectrum of self-destructive acts, wherein a suicide attempt might ensue with an accumulation of risk factors, greater loading of psychopathology and environmental difficulties.[1] Furthermore, DSH without intention to attempt suicide does not involve a life or death debate. In contrast, suicide attempts often involve high wish to die and low wish to live.[45] A previous local study on adults found that more men than women made suicide attempts with higher perceived lethality[46] but whether gender plays such a role in DSH among adolescent and young adults remains unknown. Future studies are required to identify specific factors that increase the risk of suicide attempts among individual with DSH so that appropriate interventions can be initiated.

Limitations and Strengths

Our study had several limitations. Firstly, it was based on cross-sectional data. Therefore, causality cannot be inferred. Secondly, the study relied on retrospective report and was thus prone to recall error as well as the biases associated with self-report. Thirdly, the sample comprised a help-seeking group. Given that youths who self-harm rarely present to clinical services, the results might not be generalisable to the same in the community. Additionally, we were not able to establish the non-participation rate, thus those who participated could have been very different from outpatients who did not participate. Fourthly, this study did not include drug overdose as one of the methods of DSH. In Singapore, more than 50% of women who had drug overdose perceive their attempts as non-lethal and the patient might perceive drug overdose, especially with small quantities of drugs as DSH.[47] Lastly, this study did not capture symptoms of psychotic illness, borderline personality disorder, psychosomatic complaints (e.g. headaches), reports of adverse life events such as unemployment, relationship problems and quarrels, experience of negative feelings, and usage of alcohol which were associated with risk of

repeated suicide attempts[48] but the effect of these factors on DSH in adolescents and young adults remain unknown.

One of the strengths of this study is that it is one of the few local studies to use a standardised psychometric tool to assess DSH. The mode of self-completion was likely to facilitate honest reporting. Next, we had a relatively large sample size that provided sufficient power to conduct the above analysis. Our findings contribute considerably to the general dearth of empirical research pertaining to DSH as much of coverage in the local press has been based on anecdotal evidence. Our findings also support the use of evidence-based therapies used to treat DSH in Western countries given that the risk factors of DSH are very similar.

Clinical Implication and Conclusion

A previous local study in older Singaporeans urged psychiatrists to aggressively treat major psychiatric disorders, engage social services to resolve social problems in patients with a history of suicidal behaviour, and reduce access to alcohol.[49] Similar strategies can be adopted to reduce DSH among Singaporean adolescents and young adults. Clinicians working in medical or surgical departments should routinely screen for suicidal plans in patients presenting with DSH. As prior studies have found that young adults prefer internet-based psychological interventions and the efficacy for these interventions are comparable to face-to-face interventions, future research should explore the use of this mode of delivery to reduce DSH among Singaporean adolescents and young adults.[50,51]

Acknowledgements

This research is supported by the Singapore Ministry of Health's National Medical Research Council under the Centre Grant Programme (Grant No.: NMRC/CG/004/2014).

REFERENCES

1. Butler AM, Malone K. Attempted suicide v. non-suicidal self-injury: behaviour, syndrome or diagnosis? Br J Psychiatry 2013;202:324-5.
2. Linehan M. Cognitive-behavioral treatment of borderline personality disorder. New York: The Guilford Press; 1993.
3. Muehlenkamp JJ. Self-injurious behavior as a separate clinical syndrome. Am J Orthopsychiatry 2005;75:324.
4. In-Albon T, Ruf C, Schmid M. Proposed diagnostic criteria for the DSM-5 of nonsuicidal self-injury in female adolescents: diagnostic and clinical correlates. Psychiatry J 2013;2013:159208.
5. Muehlenkamp JJ, Claes L, Havertape L, Plener PL. International prevalence of adolescent non-suicidal self-injury and deliberate self-harm. Child Adolesc Psychiatry Ment Health 2012;6:10.
6. Fliege H, Lee JR, Grimm A, Klapp BF. Risk factors and correlates of deliberate self-harm behavior: a systematic review. J Psychosom Res 2009;66:477-93.
7. Gratz KL. Risk factors for and functions of deliberate self-harm: an empirical and conceptual review. Clinical Psychology Science and Practice 2003;10:192-205.
8. Glassman LH, Weierich MR, Hooley JM, Deliberto TL, Nock MK. Child maltreatment, non-suicidal self-injury, and the mediating role of self-criticism. Behav Res Ther 2007;45:2483-90.
9. Low G, Jones D, MacLeod A, Power M, Duggan C. Childhood trauma, dissociation and self-harming behaviour: A pilot study. Br J Med Psychol 2000;73:269-78.
10. van der Kolk BA, Perry JC, Herman JL. Childhood origins of self-destructive behavior. Am J Psychiatry1991;148:1665.
11. Patton GC, Hemphill SA, Beyers JM, Bond L, Toumbourou JW, McMorris BJ, et al. Pubertal stage and deliberate self-harm in adolescents. J Am Acad Child Adolesc Psychiatry 2007;46:508-14.
12. Hawton K, Zahl D, Weatherall R. Suicide following deliberate self-harm: long-term follow-up of patients who presented to a general hospital. Br J Psychiatry 2003;182:537-42.
13. Wilkinson P, Kelvin R, Roberts C, Dubicka B, Goodyer I. Clinical and psychosocial predictors of suicide attempts and nonsuicidal self-injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). Am J Psychiatry 2011;168:495-501.
14. Stanley B, Gameroff MJ, Michalsen V, Mann JJ. Are suicide attempters who self-mutilate a unique population? Am J Psychiatry 2001;158:427-32.
15. Choo CC, Harris KM, Chew PK, Ho RC. What predicts medical lethality of suicide attempts in Asian youths? Asian J Psychiatr 2017;29:136-41.
16. Joiner T. Why people die by suicide. Cambridge, Massachusetts & London, England: Harvard University Press;2005.
17. Teng A. Rising trend of self-harm among the young. The Straits Times. 28 December 2015. Available at: http://www.straitstimes.com/singapore/rising-trend-of-self-harm-among-the-young. Accessed on 3 April 2018.
18. Youthpolicy.org. Definition of youth. Available at: http://www.youthpolicy.org/factsheets/country/singapore/. Accessed on 3 April 2018.
19. Department of Singapore Statisics. Population Trends, 2016. Available at: https://www.singstat.gov.sg. Accessed on 3 April 2018.
20. Lloyd EE. Self-mutilation in a community sample of adolescents. Available at: https://digitalcommons.lsu.edu/cgi/viewcontent.cgi?article=7545&context=gradschool_disstheses. Accessed on 19 September 2018.
21. Lloyd-Richardson EE, Perrine N, Dierker L, Kelley ML. Characteristics and functions of non-suicidal self-injury in a community sample of adolescents. Psychol Med 2007;37:1183-92.
22. Tan AC, Rehfuss MC, Suarez EC, Parks-Savage A. Nonsuicidal self-injury in an adolescent population in Singapore. Clin Child Psychol Psychiatry 2014;19:58-76.
23. Bernstein DP, Fink L. Childhood Trauma Questionnaire: A Retrospective Self-Report Manual. Psychological Corporation;1998.
24. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry 1997;36:340-8.
25. Kim D, Bae H, Han C, Oh HY, MacDonald K. Psychometric properties of the Childhood Trauma Questionnaire-Short Form (CTQ-SF) in Korean patients with schizophrenia. Schizophr Res 2013;144:93-8.
26. Tay SA, Chen YH, Poon LY, Abidin E, Verma S. Childhood Trauma Exposure and Severity of Psychotic Symptoms in a First Episode Psychosis Group on Singapore. In: Early Intervention in Psychiatry. Volume 10. NJ, USA: Wiley-Blackwell; 2016. p.66
27. Parker G, Tupling H, Brown LB. A parental bonding instrument. Psychology and Psychotherapy: Theory, Research and Practice 1979;52:1-10.
28. Kok LP, Tian CS. Susceptibility of Singapore Chinese schoolgirls to

anorexia nervosa – part II (family factors). Singapore Med J 1994;35:609-12.

29. Rapisarda A, Nah GQ, Renjan V, Lam M, Lee J. Poster# S228: The association between reported childhood trauma, perceived parenting and psychopathological risk. In: Abstracts of the 4th Biennial Schizophrenia International Research Conference. Schiz Res 2014;153:S172.
30. Parker G. The Parental Bonding Instrument: psychometric properties reviewed. Psychiatr Dev 1989;7:317-35.
31. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. Psychiatric Annals 2002;32:509-15.
32. Vaingankar JA, Subramaniam M, Abdin E, Picco L, Phua A, Chua BY, et al. Socio-demographic correlates of positive mental health and differences by depression and anxiety in an Asian community sample. Ann Acad Med Singapore 2013;42:514-23.
33. Jeyagurunathan A, Vaingankar JA, Abdin E, Sambasivam R, Seow E, Pang S, et al. Gender differences in positive mental health among individuals with schizophrenia. Compr Psychiatry 2017;74:88-95.
34. Kerr PL, Muehlenkamp JJ, Turner JM. Nonsuicidal self-injury: a review of current research for family medicine and primary care physicians. J Am Board Fam Med 2010;23:240-59.
35. Loh C, Teo YW, Lim L. Deliberate self-harm in adolescent psychiatric outpatients in Singapore: prevalence and associated risk factors. Singapore Med J 2013;54:491-5.
36. Favazza AR, Rosenthal RJ. Diagnostic issues in self-mutilation. Hosp Community Psychiatry 1993;44:134-40.
37. Faye P. Addictive characteristics of the behavior of self-mutilation. J Psychosoc Nurs Ment Health Serv 1995;13:36-9.
38. Peh CX, Shahwan S, Fauziana R, Mahesh MV, Sambasivam R, Zhang Y, et al. Emotion dysregulation as a mechanism linking child maltreatment exposure and self-harm behaviors in adolescents. Child Abuse Negl 2017;67:383-90.
39. Lang CM, Sharma-Patel K. The relation between childhood maltreatment and self-injury: a review of the literature on conceptualization and intervention. Trauma Violence Abuse 2011;12:23-37.
40. You J, Leung F, Fu K, Lai CM. The prevalence of nonsuicidal self-injury and different subgroups of self-injurers in Chinese adolescents. Arch Suicide Res 2011;15:75-86.
41. Bresin K, Schoenleber M. Gender differences in the prevalence of nonsuicidal self-injury: a meta-analysis. Clin Psychol Rev 2015;38:55-64.
42. Miskec J, McGee C. My scars tell a story: self-mutilation in young adult literature. Children's Literature Association Quarterly 2007;32:163-78.
43. Nixon MK, Cloutier PF, Aggarwal S. Affect regulation and addictive aspects of repetitive self-injury in hospitalized adolescents. J Am Acad Child Adolesc Psychiatry 2002;41:1333-41.
44. Puri BK, Ho R, Hall A. Revision notes in psychiatry. CRC Press; 2013. p. 627.
45. Harris KM, Syu JJ, Lello OD, Chew YE, Willcox CH, Ho RH. The ABC's of suicide risk assessment: applying a tripartite approach to individual evaluations. PLoS One 2015;10:e0127442.
46. Choo CC, Harris KM, Ho RC. Prediction of lethality in suicide attempts: gender matters. Omega (Westport) 2017;30222817725182.
47. Ho CS, Ong YL, Tan GH, Yeo SN, Ho RC. Profile differences between overdose and non-overdose suicide attempts in a multi-ethnic Asian society. BMC Psychiatry 2016;16:379.
48. Choo C, Diederich J, Song I, Ho R. Cluster analysis reveals risk factors for repeated suicide attempts in a multi-ethnic Asian population. Asian J Psychiatr 2014;8:38-42.
49. Ho RC, Ho EC, Tai BC, Ng WY, Chia BH. Elderly suicide with and without a history of suicidal behavior: implications for suicide prevention and management. Arch Suicide Res 2014;18:363-75.
50. Batterham PJ, Calear AL. Preferences for internet-based mental health interventions in an adult online sample: findings from an online community survey. JMIR Ment Health 2017;4:e26.
51. Barak A, Hen L, Boniel-Nissim M, Shapira NA. A comprehensive review and a meta-analysis of the effectiveness of internet-based psychotherapeutic interventions. Journal of Technology in Human services 2008;26:109-60.

Original Article

Does Low Birth Weight Vary Geospatially in Singapore?

Stella Rizalina Sasha, [1]*MBBS*, Seyed Ehsan Saffari, [2]*PhD*, John Carson Allen, [2]*PhD*, George SH Yeo, [3]*FRCOG*, Kok Hian Tan, [3]*FRCOG*

Abstract

Introduction: Low birth weight (LBW, <2500 g) is an important risk factor for perinatal mortality and morbidity. We performed the first geospatial study of LBW in Singapore, with focus on the public sector and analysis of the national planning areas. Materials and Methods: A dataset of 24,615 singleton deliveries from 2012 to 2014 was obtained from the largest maternity hospital in Singapore. Maternal residences were identified with 28 planning areas according to postal code. Multiple logistic regression was used to examine associations between LBW rates and planning areas. Moran's I statistic was used to test for geospatial clustering of LBW rates among planning areas. Results: The LBW rate across planning areas ranged from 5.3 to 11.5 per 100 live births (median, 8.4). High LBW rates were associated with: 1) a lower individual socioeconomic status, 2) non-compliance to antenatal visits, and 3) biological factors such as maternal hypertension, low body mass index and Indian race. Moran's statistic indicated no geospatial clustering of LBW rates among the 28 planning areas ($P = 0.12$). LBW rates were moderately correlated with the Socioeconomic Disadvantage Index (r = 0.58) but uncorrelated with distance travelled to hospital (r = -0.08). Conclusion: There was no evidence of clustering of LBW rates among planning areas in Singapore that would indicate inequitable distribution of health resources among planning areas. The 2 areas showing the highest rates of LBW infants were Outram and Bukit Merah. We recommend targeted health interventions and outreach programmes to encourage antenatal visits in these areas.

Ann Acad Med Singapore 2018;47:373-80

Key words: Moran's statistic, Planning areas, Socioeconomic Disadvantage Index

Introduction

Low birth weight (LBW) is defined as birth weight <2500 g and is associated with perinatal mortality, morbidity, chronic disease in later life (e.g. cardiovascular disease, diabetes), and learning and behavioural problems.[1-5] The causes for LBW are complex and likely an interaction between the biological determinants of mother and the fetus, parent's socioeconomic status and effectiveness of medical care during the perinatal period.[6] There has been growing interest in measuring spatial variations of birth outcomes. This is because the living environment has been shown to influence birth outcomes through environmental pollution,[7] hospital accessibility,[8-9] socioeconomic status, psychosocial stress and maternal health behaviour.[10] Outreach programmes and case management for high-risk communities have led to improvements in birth outcomes internationally.[11-12]

In Singapore, geospatial analytics has been increasingly utilised to provide geographical insights and solutions to public health problems. For example, the study of spatial variation in out-of-hospital cardiac arrests led to the optimisation of ambulance response time.[13-14] Residents in public rental housing were found to have higher readmission

[1]Division of Obstetrics and Gynaecology, KK Women's and Children's Hospital, Singapore
[2]Centre for Quantitative Medicine, Office of Clinical Sciences, Duke-NUS Medical School, Singapore
[3]Department of Maternal Fetal Medicine, KK Women's and Children's Hospital, Singapore
Address for Correspondence: Dr Stella Rizalina Sasha, Division of Obstetrics and Gynaecology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: stella.sasha@mohh.com.sg

risk and can be targeted to reduce unnecessary utilisation of hospital services.[15] An index of area-level socioeconomic status has been derived by Earnest et al specifically for health service research,[16] and has been shown to be associated with visual impairment in Singapore.[17]

This is the first study to assess variations in the rates of LBW rates in the public sector across planning areas in Singapore, as well as to identify individual and regional risk factors associated with LBW rates.

Materials and Methods

Obstetric data on all deliveries (n = 34,711) in KK Women's and Children's Hospital (KKH) for the years 2012 to 2014 was obtained from the Obstetric Information System (OIS). From this data, we excluded: 1) deliveries of multiple births (n = 1294), 2) deliveries for which there were missing data (n = 8535), and 3) deliveries in planning areas with less than 100 births counted over the 3-year study period (n = 267) in order to reduce sampling variability in LBW prevalence. The study cohort comprised 24,615 singleton births.

Maternal residences were geo-referenced to national planning areas based on postal codes. There are a total of 55 planning areas in Singapore, as demarcated in the Urban Redevelopment Authority's Master Plan 2008 (URA MP08).[18] Each planning area has a population of about 150,000 and is served by a town centre and several neighbourhood commercial and recreational facilities. The data extracted on deliveries at KKH represented maternal postal codes spanning 28 planning areas.

The 'OG Labour, Delivery and Infant Record' is an electronic, structured record that is completed by a midwife or doctor for each delivery in KKH. From these records, we obtained individual variables previously shown to influence adverse birth outcomes.[19] Child variables were gestational age, gender, birth order (1, 2-4, >5) and congenital malformations; maternal variables were race (Chinese, Indian, Malay, Others), age (<20, 20-35, >35), marital status (single, married, divorced), resident status (citizen, permanent residents, non-residents, foreign residents), hospital bed class (A1, B1, B2+, B2, C), number of antenatal visits (<7 non-compliant, ≥7 compliant), body mass index (BMI) (<18.5, ≥18.5) and medical risk factors (hypertension, diabetes mellitus, anaemia and antepartum haemorrhage).

Both child congenital malformations and maternal medical risk factors were derived using International Classification of Diseases (ICD)-9 and ICD-10 codes. The discharge bed classes A1 and B1 correspond to private-paying patients while B2+, B2 and C correspond to subsidised-paying patients; hence, bed class was used as a surrogate marker of the individual's socioeconomic status. According to United Kingdom guidelines, a minimum of 7 antenatal visits is considered adequate for a parous woman with an uncomplicated pregnancy.[20] Based on this standard, women (both nulliparous and multiparous) who undergo at least 7 antenatal visits are classified as antenatal-care compliant.

The study looked at 3 regional characteristics of LBW rates: 1) Socioeconomic Disadvantage Index (SEDI), 2) travel distance between the planning area and KKH and, 3) Moran's I spatial autocorrelation among planning areas.

SEDI, derived by Ernest et al, is a single composite index that measures the socioeconomic status of planning areas in Singapore.[16] It incorporates areal factors (e.g. household and personal income, housing, education and occupation) from the Singapore Census of Population 2010 indicative of socioeconomic status. A high SEDI score indicates relatively poor socioeconomic status.

The travel distance between each planning area and KKH was calculated as an average of 3 driving distances (produced by the web mapping and route planning service, Google Maps) and the information was requested at different times of day—namely 0800 hr, 1200 hr and 1600 hr. This took into consideration that Google Maps suggests different routes based on the shortest travelling time at the particular time of day that the information is requested.

Statistical analysis was performed using SAS version 9.4 for Windows (SAS, Inc., Cary, NC, USA). Observed LBW rates were calculated for each planning area—using number of LBW births as the numerator and number of live births as the denominator. The association between individual potential risk factors and LBW was tested using univariate logistic regression model. Multivariable logistic regression analysis was performed using the stepwise variable selection approach with statistical significance set at $P \leq 0.05$. Ten variables—child gestational age, gender, birth order and congenital abnormalities; maternal age, race, hospital bed class, number of antenatal visits, BMI and hypertension—were included in the final regression model. The Pearson correlation coefficient was used to assess association between adjusted LBW rates and regional factors, i.e., SEDI and travel distance to KKH.

Moran's I statistic, a spatial autocorrelation statistic, takes into account the longitude and latitude of each planning area and measures the degree of dependency among observed LBW rates across planning areas. The null hypothesis is a random distribution of LBW rates among planning areas. The Moran statistic is used to evaluate whether a pattern expressed is clustered, dispersed or random. For example, on a checkerboard, the red and black squares are perfectly dispersed, so Moran's I would be -1. If all red squares were on one side of the board and all black squares on the other, Moran's I would be close to +1.[21]

This study received ethics approval from the SingHealth Centralised Institutional Review Board (CIRB) (Ref: 2016/2344) on 12 May 2016.

Results

Mean birth weight and gestational age were 3081 g (range: 420-5410 g) and 37.9 weeks (range: 23-42 weeks), respectively, in this singleton cohort study (n = 24,615). The median number of births in each planning area was 767 (range: 144-2138). Planning areas with the highest number of births were Woodlands (2138), followed by Sengkang (2125) and Yishun (1784).

Association of LBW with Individual Characteristics

The overall LBW rate was 8.3 per 100 live births. LBW rates differed markedly by child and maternal characteristics (Table 1). As expected, LBW rates were higher among premature babies (56.9 per 100 live births), female babies (9.19 per 100 live births), first-order babies (9.41 per 100 live births) and babies with congenital abnormalities (12.0 per 100 live births).

At both ends of the age spectrum, teenage mothers (13.8 per 100 live births) and mothers with advanced maternal age (9.49 per 100 live births) tended to have higher LBW rates. The Indian race had higher LBW rates (9.87 per 100 live births), compared to the Malays (9.55 per 100 live births) and Chinese (7.64 per 100 live births). Mothers in the subsidised-paying class (12.5 per 100 live births) had higher LBW rates compared to mothers in private-paying class (5.56 per 100 live births). Mothers who attended <7 antenatal visits (15.8 per 100 live births) had higher LBW rates compared to those who attended ≥7 antenatal visits (6.44 per 100 live births). Mothers who were underweight (i.e. BMI less than 18.5) had a higher LBW rate (12.4 per 100 live births). Mothers with hypertension in pregnancy (41.3 per 100 live births) were at risk of having babies with LBW.

Resident status, marital status and maternal medical conditions such as diabetes mellitus, antepartum haemorrhage and anaemia were not significantly associated with LBW after adjusting for potential confounders in this study (Table 2).

Regional Variation in Observed and Adjusted LBW Rates

Observed LBW rate across planning areas ranged from 5.3 to 11.5 per 100 live births (median, 8.4; interquartile range, 7.3-9.0). After controlling for the identified risk factors, adjusted LBW rates across planning areas ranged from 5.7 to 10.4 per 100 live births (median 8.2; interquartile range: 7.8-8.9) (Table 3). Outram and Bukit Merah exhibited the highest LBW rates, while Queenstown and Serangoon exhibited the lowest LBW rates.

Table 1. Demographics and Patient Characteristics of Singleton Birth Cohort (n = 24,615) and Observed LBW Rates

Characteristic	Cohort %	LBW Rate
Newborn Characteristics		
Gestational age		
Preterm (<37 weeks)	7.89	56.9
Term (37 – 40 weeks)	91.35	4.19
Postdates (>40 weeks)	0.77	1.06
Gender		
Female	48.3	9.19
Male	51.7	7.50
Birth order		
≤1	46.05	9.41
2 – 4	51.95	7.28
≥5	2.00	10.4
Congenital malformations	16.43	12.0
Maternal Characteristics		
Race		
Chinese	43.8	7.64
Malays	26.5	9.55
Indians	13.0	9.87
Others	16.8	6.98
Age		
<20 years	19.3	13.8
20 – 34 years	77.9	7.84
≥35 years	19.3	9.49
Residency status		
Resident	87.8	8.49
Non-resident	12.2	7.17
Marital status		
Married	92.1	8.05
Single	2.66	15.9
Divorced	0.51	9.52
Others	4.73	9.27
Hospital bed class		
Private (class A, B1)	59.9	5.56
Subsidised (class B2, C)	40.1	12.5
No. of antenatal visits		
Compliant (≥7 visits)	79.8	6.44
Non-compliant (<7 visits)	20.2	15.8
BMI less than 18.5	8.56	12.4
Hypertension	1.78	41.3
Diabetes mellitus	7.78	7.99
Antepartum haemorrhage	3.15	20.9
Anaemia	5.87	11.1
Overall		8.32

BMI: Body mass index; LBW: Low birth weight

Table 2. Logistic Regression Analysis Summary on Association of LBW rates with Newborn and Maternal Characteristics

Variable	Unadjusted OR (95% CI)	*P* Value	Omnibus *P* Value	Adjusted OR* (95% CI)	*P* Value	Omnibus *P* Value
Newborn Characteristics						
Gestational age						
Term	Reference		<0.0001	Reference		<0.0001
Preterm	30.21 (27.03, 33.76)	<0.0001		25.4 (22.5, 28.7)	<0.0001	
Postdate	0.30 (0.09, 1.07)	<0.0001		0.28 (0.08, 0.97)	0.0442	
Gender						
Male	Reference			Reference		
Female	1.25 (1.14, 1.37)	<0.0001		1.56 (1.4, 1.74)	<0.0001	
Birth order						
2 – 4	Reference		<0.0001	Reference		<0.0001
1	1.32 (1.21, 1.45)	0.3162		1.53 (1.37, 1.72)	<0.0001	
≥5	1.49 (1.10, 2.00)	0.0869		1.01 (0.7, 1.45)	0.9745	
Congenital malformations	1.66 (1.49, 1.85)	<0.0001		1.27 (1.11, 1.45)	0.0005	
Maternal Characteristics						
Race						
Chinese	Reference		<0.0001	Reference		<0.0001
Indian	1.33 (1.16, 1.52)	0.0004		1.46 (1.24, 1.72)	<0.0001	
Malay	1.28 (1.15, 1.42)	0.0005		1.06 (0.92, 1.21)	0.4455	
Others	0.91 (0.79, 1.04)	<0.0001		0.87 (0.73, 1.02)	0.0855	
Age						
20 – 34 years	Reference		<0.0001	Reference		0.0053
<20 years	1.89 (1.51, 2.37)	<0.0001		0.98 (0.74, 1.3)	0.8953	
≥35 years	1.23 (1.10, 1.38)	0.1534		1.26 (1.1, 1.45)	0.0012	
Residency status						
Resident	Reference			Reference		
Non-resident	0.83 (0.72, 0.97)	0.0154		1.08 (0.89 – 1.31)	0.4249	
Marital status						
Married	Reference		<0.0001	Reference		0.4874
Single	2.17 (1.75, 2.69)	<0.0001		1.21 (0.91 – 1.62)	0.1941	
Divorced	1.25 (0.69, 2.24)	0.7659		1.27 (0.66 – 2.45)	0.4684	
Others	1.17 (0.96, 1.44)	0.2374		1.08 (0.84 – 1.38)	0.5538	
Hospital bed class						
Private	Reference			Reference		
Subsidised	2.42 (2.21, 2.65)	<0.0001		1.8 (1.6, 2.02)	<0.0001	
No. of antenatal visits						
Compliant (≥7 visits)	Reference			Reference		
Non-compliant (<7 visits)	2.73 (2.48, 3.00)	<0.0001		1.39 (1.23, 1.58)	<0.0001	
BMI						
>18.5	Reference			Reference		
≤18.5	1.63 (1.42, 1.88)	<0.0001		2.06 (1.75, 2.44)	<0.0001	
Hypertension	8.42 (6.92, 10.24)	<0.0001		2.93 (2.23, 3.85)	<0.0001	
Diabetes mellitus	0.95 (0.80, 1.13)	0.5973		1.00 (0.81 – 1.22)	0.9663	
Antepartum haemorrhage	3.08 (2.58, 3.69)	<0.0001		1.26 (0.99 – 1.60)	0.0587	
Anaemia	1.41 (1.19, 1.67)	<0.0001		0.92 (0.75 – 1.14)	0.4658	

CI: Confidence interval; OR: Odds ratio; LBW: Low birth weight

*Adjusted for gestational age, child gender, birth order, congenital malformations, maternal race, age, hospital bed class, compliance to antenatal visits, BMI, and hypertension, using stepwise selection approach.

Table 3. Regional Characteristics of the Singleton Birth Cohort (n = 24,615)

Planning Area	n	Observed LBW Rate	Adjusted LBW Rate*	Socioeconomic Disadvantage Index (SEDI)†	Distance Travelled (km)
Ang Mo Kio	1055	10.24	8.87 (7.78, 10.10)	107.9	8.4
Bedok	1562	8.13	8.27 (7.20, 9.45)	102	12.6
Bishan	285	10.88	8.96 (7.93, 10.10)	92.8	7.3
Bukit Batok	633	6.48	6.88 (5.95, 7.95)	100.6	11.9
Bukit Merah	762	11.29	10.37 (9.15, 11.71)	110.1	6.2
Bukit Panjang	959	6.57	7.49 (6.53, 8.60)	100.9	13.1
Bukit Timah	144	6.94	5.67 (4.85, 6.63)	79.8	9.5
Choa Chu Kang	943	8.80	7.87 (6.84, 9.02)	97.6	16.8
Clementi	310	6.77	7.91 (6.88, 9.08)	100.3	12.3
Geylang	771	9.99	9.11 (8.00, 10.35)	109.3	7.6
Hougang	1184	8.61	8.74 (7.67, 9.94)	102.8	8.9
Jurong East	341	7.62	8.10 (7.08, 9.26)	99.9	15.2
Jurong West	1510	7.28	8.30 (7.28, 9.46)	101.6	19.9
Kallang	715	8.11	8.68 (7.61, 9.87)	110.1	3.7
Marine Parade	223	8.97	9.36 (8.11, 10.77)	94.5	7.7
Novena	261	9.58	7.86 (6.81, 9.07)	96.3	3.1
Outram	156	11.54	10.08 (8.83, 11.48)	120.1	5
Pasir Ris	791	7.21	7.81 (6.83, 8.91)	90.7	18.7
Punggol	1676	8.11	7.64 (6.71, 8.69)	-‡	17.6
Queenstown	433	5.31	7.87 (6.82, 9.06)	106.9	10.3
Rochor	144	9.03	7.18 (6.18, 8.33)	111	1.7
Sembawang	561	8.56	8.91 (7.82, 10.12)	100.8	23
Sengkang	2125	8.38	8.07 (7.08, 9.17)	100.2	15.3
Serangoon	435	6.44	6.83 (5.89, 7.92)	94.2	7.9
Tampines	1733	8.83	8.86 (7.81, 10.02)	99.8	17.1
Toa Payoh	981	7.95	8.26 (7.23, 9.42)	107.2	6.3
Woodlands	2138	8.79	8.89 (7.80, 10.13)	102.7	19.4
Yishun	1784	7.90	8.18 (7.14, 9.37)	105.6	17.3

LBW: Low birth weight

*Adjusted for gestational age, child gender, birth order, congenital malformations, maternal race, age, hospital bed class, compliance to antenatal visits, body mass index and hypertension using stepwise selection approach.

†SEDI was derived from Earnest et al's study. Higher SEDI scores indicate areas with higher socioeconomic disadvantage.

‡Punggol was not included in the abovementioned study, hence no SEDI index score was available.

Association of Adjusted LBW Rates and Regional Characteristics

The *P* value for Moran's I statistic was *P* = 0.12, inferring randomly distributed LBW rates across planning areas. The mean SEDI was 101.7 (range: 79.8-120.1). Planning areas with the highest SEDI values were Outram (120.1), Rochor (111.0) and Bukit Merah (110.1) (Table 3). SEDI was moderately positively correlated with adjusted LBW rates, r = 0.58 (*P* value = 0.001). The mean travelling distance from planning area to KKH was 11.6 km (range 1.7-23.0 km). Regions located the furthest distance from KKH are Sembawang (23.0 km), followed by Jurong West (19.9 km) and Woodlands (19.4 km) (Table 3). There was no linear correlation between travelling distance to hospital with adjusted LBW rates, r = -0.08 (*P* value = 0.70).

Discussion

This study found that LBW rates varied twofold across planning areas in Singapore. The distribution of LBW rates is reflective of multiple identified risk factors that are either inherent in mother or child (firstborn, preterm gestational age, female gender child, congenital abnormalities, Indian race, age), associated with socioeconomic status (bed class, SEDI) or clinical risk factors (antenatal visit compliance,

low BMI, hypertension) (Fig. 1). After adjustment for these risk factors, marked variation in LBW rates persisted, demonstrating that a significant extent of LBW risk remains unexplained and is linked to place of maternal residence and perinatal health care delivery.

Although individual risk factors play a significant role in LBW rates, the role of maternal race or individual socioeconomic status in LBW rates across planning areas may be mitigated by the public housing system in Singapore. Known as the Housing and Development Board (HDB), this system began in the 1960s and at presently, houses 82% of residents across all planning areas.[22] HDB prevents racial enclaves by introducing ethnic quotas for HDB blocks based on the ethnic makeup of Singapore. It similarly prevented the grouping of income segments by offering different flat types (i.e. 2- to 5-room flats, executive flats) to cater to different household size and budget within a precinct. The relative spatial homogenisation of different ethnic groups and income brackets across planning areas contributes to reducing variation in LBW rates across planning areas in Singapore.

The SEDI is a characterisation of the socioeconomic status in each planning area. This index is the only regional factor to have a moderate correlation with adjusted LBW (r =0.58). Living in a disadvantaged neighbourhood influences birth outcomes through: 1) psychosocial and, 2) materialist pathway.[10] Psychosocial stress can result in adverse pregnancy outcomes directly through neuroendocrine and immunological processes; or indirectly through maternal health behavioural changes, such as increased smoking, reduced prenatal care and poor dietary intake. The materialist pathway looks at the provision of public services and infrastructure that facilitate women's access to medical care and their ability to make healthy lifestyle choices. Planning areas in Singapore are relatively self-sufficient; residents have accessibility to neighbourhood resources (e.g. recreation facilities, food stores, medical clinics and schools) and social support (e.g. community centres and places of worship).[22] However, there are still measurable differences in SEDIs across planning areas that influence LBW rates.

We further investigated the correlation of travel distance (from home) to LBW rates. One hypothesis might be that longer travel distance may become a physical barrier or disincentive to women to attend their routine antenatal visits, which we have already shown to be a significant risk factor. Although KKH is located centrally, a large proportion of women delivering at KKH come from planning areas outside

Planning Area	n	Observed LBW Rates	Gestational Age Preterm	Child Gender Female	Birth Order 1	Congenital Malformations	Race		Maternal Age More than 35	Hospital Bed Class Class B2/ C	Antenatal Visits Non-Compliant	BMI <18.5	Hypertension	SEDI
							Indian	Malay						
Ang Mo Kio	1055	10.24	8.25	46.54	48.53	15.36	13.46	16.4	23.41	43.32	18.58	9.76	2.37	107.9
Bedok	1562	8.13	7.36	46.8	47.31	15.69	13.76	27.91	19.91	41.42	21.45	9.99	1.66	102
Bishan	285	10.88	9.82	48.59	51.23	15.79	14.04	10.88	25.26	25.96	22.46	8.42	1.75	92.8
Bukit Batok	633	6.48	5.21	46.29	49.92	15.48	12.48	27.96	19.75	39.97	17.38	6.95	2.05	100.6
Bukit Merah	762	11.29	11.15	47.77	46.06	17.45	13.65	21.52	25.98	42.65	26.77	9.19	1.05	110.1
Bukit Panjang	959	6.57	6.67	47.76	45.88	18.25	9.49	33.79	17.52	39.1	18.77	8.13	1.88	100.9
Bukit Timah	144	6.94	4.17	52.08	49.31	14.58	4.17	2.08	28.47	9.72	20.83	18.06	1.39	79.8
Choa Chu Kang	943	8.80	7.53	47.93	45.6	14.74	10.71	32.56	19.19	40.62	21.1	8.27	1.7	97.6
Clementi	310	6.77	6.77	51.29	51.29	14.19	12.9	19.68	24.19	30.97	24.19	13.87	0.65	100.3
Geylang	771	9.99	8.17	51.75	48.38	17.25	14.4	22.7	19.2	49.03	23.09	8.17	2.2	109.3
Hougang	1184	8.61	8.19	49.49	47.13	16.22	15.96	18.58	19.93	40.2	19.76	10.73	2.03	102.8
Jurong East	341	7.62	7.92	43.99	42.23	13.49	13.78	28.74	20.82	43.11	24.05	7.33	0.29	99.9
Jurong West	1510	7.28	8.01	47.55	41.59	15.96	9.8	28.15	19.93	41.66	20.79	7.02	2.32	101.6
Kallang	715	8.11	8.11	48.39	45.31	16.5	24.06	13.29	21.54	36.78	20.56	8.95	2.24	110.1
Marine Parade	223	8.97	9.87	47.98	41.7	17.04	9.87	24.66	29.15	38.57	27.8	8.07	1.35	94.5
Novena	261	9.58	7.28	47.89	41	18.01	21.84	16.86	26.05	34.1	24.14	8.05	1.92	96.3
Outram	156	11.54	10.26	48.72	46.79	16.67	7.05	26.92	17.95	52.56	26.92	10.26	1.28	120.1
Pasir Ris	791	7.21	7.71	50.44	43.49	13.91	11.5	34.01	22.38	32.49	19.85	7.08	0.76	90.7
Punggol	1676	8.11	6.98	48.81	49.94	15.75	12.29	27.68	14.86	31.5	14.92	9.84	1.61	.
Queenstown	433	5.31	6.93	50.58	51.5	17.55	12.24	19.4	16.17	37.88	22.86	9.47	0.69	106.9
Rochor	144	9.03	6.25	52.78	43.75	15.97	30.56	6.94	18.75	28.47	14.58	5.56	2.08	111
Sembawang	561	8.56	9.63	45.99	42.07	15.86	11.94	24.42	23.17	39.22	17.83	6.77	2.67	100.8
Sengkang	2125	8.38	7.81	49.86	46.64	16.52	15.72	25.79	16.47	33.41	14.82	8.38	1.84	100.2
Serangoon	435	6.44	5.29	47.36	49.89	17.47	15.4	8.74	25.06	30.11	16.78	8.74	2.07	94.2
Tampines	1733	8.83	9.29	45.76	46.22	17.31	12.93	34.68	18.7	37.28	20.72	6.75	1.62	99.8
Toa Payoh	981	7.95	7.65	45.16	44.75	18.04	10.4	12.84	18.14	50.87	21.3	8.26	1.22	107.2
Woodlands	2138	8.79	8.51	50.19	41.81	16.79	11.09	38.26	17.4	48.32	23.01	7.95	2.25	102.7
Yishun	1784	7.90	7.29	48.93	46.3	17.71	10.65	32.79	16.03	48.04	20.91	8.52	1.68	105.6

Legend:
High Risk — Low Risk

Fig.1. The number of deliveries and observed LBW rates in each planning area are shown. Risk factors (represented in percentage) are shaded red if they contribute to the planning areas having a higher LBW rate or they are shaded blue if they contribute to the planning areas having a lower LBW rates. BMI: Body mass index; LBW: Low birth weight; SEDI: Socioeconomic Disadvantage Index.

the central area, for example, Sengkang, Woodlands and Yishun (Fig. 2), which correspond to the areas with newer public housing developments that are home to many young families and couples. Despite having to travel a longer distance to KKH, these women do not have higher rates of LBW (r = -0.08). In Singapore, the car ownership rate is about 11%, and most people commute by public transport. The public transport system consists of the Mass Rapid Transit (MRT) and Light Rail Transit (LRT) rail systems (9 lines), a system of bus routes throughout the island, as well as taxis and private hire cars such as Uber and Grab. The impact of variation in travelling distance to hospitals is largely mitigated by the efficient public transport system.

Outram and Bukit Merah were identified as planning areas with the highest LBW rates; associated risk factors were lower socioeconomic status and non-compliance to antenatal visits. For these areas, we recommend a targeted social and health interventions, as well as outreach programmes and case management for pregnant women to encourage antenatal visits. We investigated the hypothesis that planning areas with high LBW rates were clustered together geographically, as such clustering may indicate preferential, inadequate or inequitable access or distribution of health services resources among planning areas. However, we found no statistical evidence of clustering (Moran's I statistic, *P* value = 0.12).

Strength and Limitations

The strength of this study is that it included a large and representative sample of deliveries from the public sector hospitals to which government healthcare resources are directed towards. Based on the annual Registration of Births and Deaths report 2014, 60% of women delivered in private sector hospital. Of the 40% of women who delivered in public sector hospitals, two-thirds of the deliveries were in KKH.[23]

Currently, there is no data on the geographical distribution of patients who delivered in other hospitals. Hence, for each planning area, the proportion of patients who delivered in KKH is unknown. Women from residences in core central areas like Newton, Tanglin and River Valley were relatively less represented in the data from KKH. The abovementioned planning areas correspond to the higher socioeconomically advantaged regions in Ernest et al's study,[16] and pregnant women in these planning areas likely booked in private hospitals. These deliveries may not be relevant to our study that focused on deliveries in the public sector.

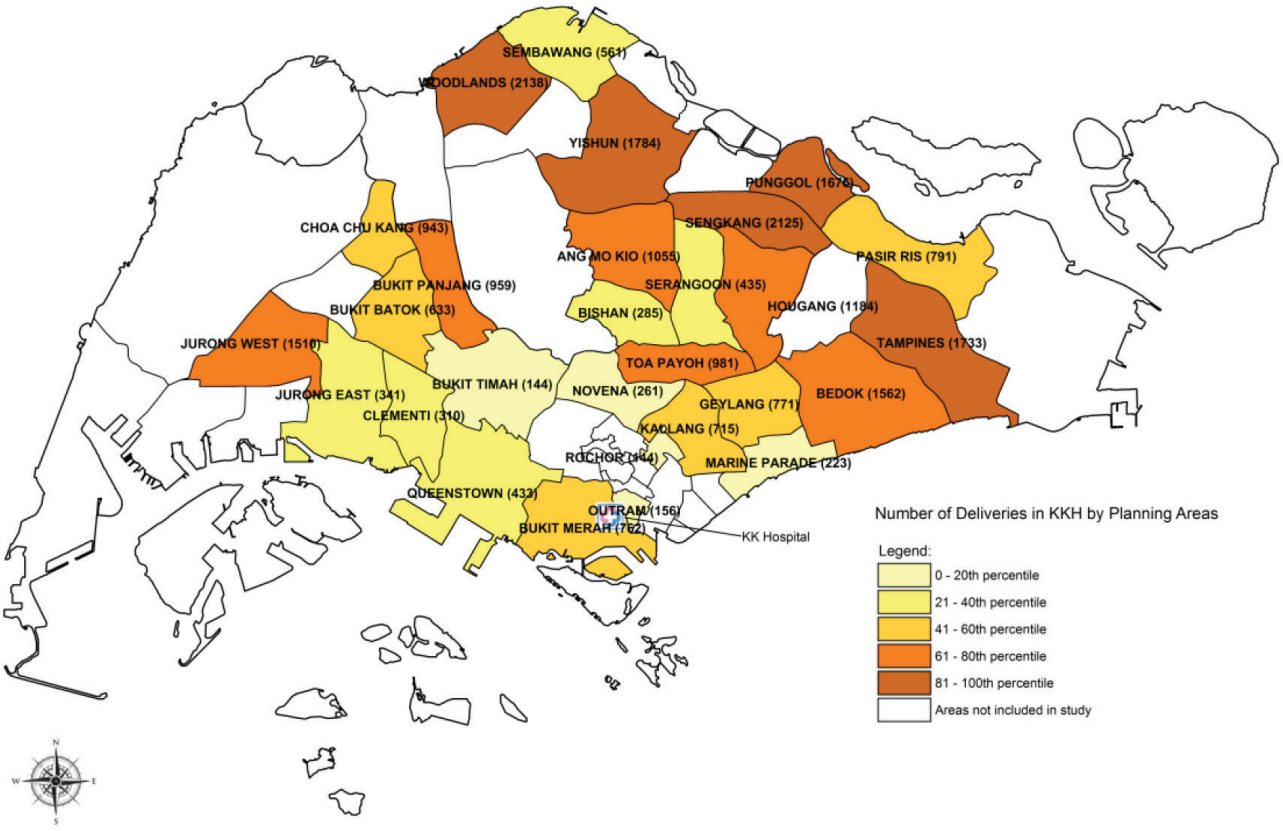

Fig. 2. Map showing the distribution of deliveries in KKH by planning areas.

A total of 8535 out of 34,711 cases were excluded due to missing data on maternal BMI and marital status—characteristics that were not reliably recorded on the OIS in KKH. Our investigation showed that these missing cases were more or less uniformly distributed across planning areas, so any impact on the study would be uniform across all planning areas and we have no reason to believe that these exclusions would have materially influenced the outcome of the study.

Lastly, our analysis of LBW rates neglected the heterogeneity within each planning area, which has an average area of 12.0 km^2. It would have been ideal to analyse LBW rates at a finer postal code level, so as to pinpoint the "highest risk" targets for intervention. Unfortunately, such data is not made available to researchers in Singapore.

Conclusion

LBW rates varied twofold across planning areas in Singapore. The distribution of LBW rates is reflective of the multiple identified risk factors in our study, like socioeconomic status and non-compliance to antenatal visits, as well as unknown risk factors that require further analyses. The 2 areas with the highest rates of LBW infants were Outram and Bukit Merah. For these areas, we recommend targeted social and health interventions, outreach programmes and case management encouraging antenatal visits. There was no statistical evidence indicating clustering relative to high or low LBW rates among planning areas that would indicate inadequate or inequitable access or distribution of health services resources among planning areas.

Acknowledgement

This study was supported by the National Medical Research Council (NMRC) Integrated Platform for Research in Advancing Metabolic Health Outcomes of Women and Children (IPRAMHO) Study Group (NMRC CGAug16C008).

REFERENCES

1. Barder DJ. Adult consequences of fetal growth restriction. Clin Obstet Gynecol 2006;49:270-83.
2. Stein RE, Siegel MJ, Bauman LI. Are children of moderately low birth weight at increased risk for poor health? A new look at an old question. Pediatrics 2006;118:217-23.
3. Coutinho PR, Cecatti JG, Surita FG, Costa ML, Morais SS. Perinatal outcomes associated with low birth weight in a historical cohort. Reprod Health 2011;8:18.
4. Teo CM, Poon WB, Ho SK. Long-term neurodevelopmental outcomes of premature infants in Singapore. Ann Acad Med Singapore 2018;47:63-70.
5. Poon WB, Fook-Chong SM, Ler GY, Loh ZW, Yeo CL. Creation and validation of the Singapore birth nomograms for birth weight, length and head circumference based on a 12-year birth cohort. Ann Acad Med Singapore 2014;43:296-304.
6. Thompson LA, Goodman DC, Chang CH, Stukel TA. Regional variation in rates of low birth weight. Pediatrics 2005;116:1114-21.
7. Shi X, Ayotted JD, Onda A, Miller S, Rees J, Gilbert-Diamond D, et al. Geospatial association between adverse birth outcomes and arsenic in groundwater in New Hampshire, USA. Environ Geochem Health 2015;37:333-52.
8. Ravelli AC, Jager KJ, de Groot MH, Erwich JJ, Rijninks-van Driel GC, Tromp M, et al. Travel time from home to hospital and adverse perinatal outcomes in women at term in the Netherlands. BJOG 2011;118:457-65.
9. Parker L, Dickinson HO, Morton-Jones T. Proximity to maternity services and stillbirth risk. Arch Dis Child Fetal Neonatal Ed 2000;82:F167-8.
10. Meng G, Thompson ME, Hall GB. Pathways of neighbourhood-level socio-economic determinants of adverse birth outcomes. Int J Health Georgr 2013;12:32.
11. Chong S, Nelson M, Byun R, Harris L, Eastwood J, Jalaludin B. Geospatial analyses to identify clusters of adverse antenatal factors for targeted interventions. Int J Health Georgr 2013;12:46.
12. Perloff JD, Jaffee KD. Late entry into prenatal care: the neighbourhood context. Soc Work 1999;44:116-28.
13. Ong ME, Earnest A, Shahidah N, Ng WM, Foo C, Nott DJ. Spatial variation and geographic-demographic determinants of out-of-hospital cardiac arrests in the city-state of Singapore. Ann Emerg Med 2011;58:343-51.
14. Ong ME, Chiam TF, Ng FS, Sultana P, Lim SH, Leong BS, et al. Reducing ambulance response times using geospatial-time analysis of ambulance deployment. Acad Emerg Med 2010;17:951-7.
15. Low LL, Wah W, Ng MJ, Tan SY, Liu N, Lee KH. Housing as a social determinant of health in Singapore and its association with readmission risk and increased utilization of hospital services. Front Public Health 2016;4:109.
16. Earnest A, Ong ME, Shahidah N, Chan A, Wah W, Thumboo J. Derivation of indices of socioeconomic status for health services research in Asia. Prev Med Rep 2015;2:326-32.
17. Wah W, Earnest A, Sabanayagam C, Cheng CY, Ong ME, Wong TW, et al. Composite measures of individual and area-level socio-economic status are associated with visual impairment in Singapore. PLoS One 2015;10:e0142302.
18. Government of Singapore. The Planning Act. Master Plan Written Statement 2008. Singapore: Urban Redevelopment Authority; 2008. Available at: https://www.ura.gov.sg/uol/~/media/User%20Defined/URA%20Online/master-plan/master-plan-2008/written-statementMP2008.ashx. Accessed on 1 April 2018.
19. Viegas OA, Singh K, Cheng EL, Ratnam SS. Risk factors for low birth weight in Singapore: strategies for prevention. Int J Gynaecol Obstet 1988;26:379-87.
20. National Institute for Health and Care Excellence (NICE). Antenatal care for uncomplicated pregnancies; Clinical guidelines [CG 62]. United Kingdom: NICE; 2008. Available at: https://www.nice.org.uk/guidance/cg62/resources/antenatal-care-for-uncomplicated-pregnancies-pdf-975564597445. Accessed on 6 March 2017.
21. Moran PA. Notes on continuous stochastic phenomena. Biometrika 1950;37:17-23.
22. Cheong SM. Public housing in Singapore: well-being of communities, family and the elderly: HDB sample household survey 2008. Singapore: Research and Planning Department, Housing and Development Board; 2010.
23. Registry of Births and Deaths. Report on registration of births and deaths 2014. Immigration and Checkpoints Authority, Singapore; 2015. Available at: https://www.ica.gov.sg/stats. Accessed on 1 April 2018.

Review Article

Cancer Immunotherapy – The Target is Precisely on The Cancer and Also Not

Si Lin Koo,[*] [1]*MBBS (Singapore), MRCP (UK)*, Who Whong Wang,[*] [1]*BSC (Singapore), PhD (Manchester)*, Han Chong Toh, [1,2]*MBBCHIR (Camb), FRCP (Edin), FAMS*

Abstract

In recent years, the impressive number of cancer immunotherapy drugs approved has been unprecedented—building on over a century of understanding on how the immune system combats cancer, and how cancer evades it. Leading the charge are the immune checkpoint inhibitor monoclonal antibodies, and adoptive cell therapy with chimeric-antigen-receptor (CAR)-T cell therapy. These breakthrough therapies have led to improved survival in patients with many advanced cancers. Some of the clinical outcomes have been striking, and may even be potentially curative in some terminal cancer patients. While immune checkpoint inhibitors work by blocking regulatory immune checkpoint signals between cancer and the immune cells to awaken an effective anticancer immunity, CAR-T cell therapy targets specific molecules on cancer cells. Tumour antigens as cancer targets take many forms and may not necessarily be proteins related to known functional cellular mechanisms. The convergence of cutting edge omics, bioinformatics, protein synthesis, immunobiology and immunotherapy have led to novel, potentially highly effective cancer targeting against neoantigens, hence reviving the quest for anticancer vaccines. Early clinical trials of neoantigen vaccines have provided proof-of-principle efficacy, especially in melanoma patients. Combinations of immunotherapies through rational design are underway aiming to further improve clinical outcomes. Moving forward, cancer immunotherapy will gain even more momentum from the discovery of more cancer targets—both on the cancer itself and in the tumour microenvironment as well as the identification of biomarkers of treatment resistance and efficacy.

Ann Acad Med Singapore 2018;47:381-7

Key words: Checkpoint inhibitor, Microenvironment, Neoantigens, Vaccine

Introduction

The immune system is intricately designed with unerring sophistication to identify—and if necessary—destroy invading pathogens, classically by distinguishing "self" from "non-self" proteins. The immune system can also attack "self" proteins such as when immune dysregulation results in autoimmune disease and/or when a danger signal triggers an immune response to "self" proteins. A role for the immune system in cancer surveillance and control has long been suggested, supported by evidence such as the observation of higher incidence of malignancies in immunocompromised patients (e.g. organ transplant patients on immunosuppressive drugs and acquired immunodeficiency).

Cancer immunotherapy harnesses the immune system to target cancer—either directly or indirectly. Although cancer cells originate from the patient's own cells, they may be potentially recognised as foreign and be targeted by the immune system due to aberrant expression of tumour-associated antigens (TAA) that are not normally expressed or at significantly lower expression levels by normal cells. These antigens could be viral antigens in virus-associated cancers, such as Epstein-Barr virus (EBV) antigens in nasopharyngeal carcinoma (NPC) and post-transplant lymphoproliferative disease or human papillomavirus (HPV) in HPV+ oropharyngeal cancer and cervical cancer; or "self" antigens such as the cancer/

[*]These two authors contributed equally to the writing of this manuscript.
[1]Division of Medical Oncology, National Cancer Centre Singapore, Singapore
[2]Duke-NUS Medical School, Singapore
Address for Correspondence: Dr Toh Han Chong, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: toh.han.chong@singhealth.com.sg

testis antigens, whose expressions are found in germ cell cancers like testicular cancer, colorectal cancer, non-small cell lung cancer (NSCLC) and melanoma. Targets on cancer cells for immunotherapy need not have known mechanistic functions in the cancer cell machinery. Conversely, they could be critical receptors of oncogenic signalling such as cerb-B2 (HER2/neu) in breast cancer.

Immune recognition of TAAs is commonly impaired in cancer patients largely due to immune tolerance and an inhibitory immune suppressive tumour microenvironment.[1,2] The immune suppressive components include regulatory T lymphocytes (Tregs), tolerogenic dendritic cells (DCs), myeloid-derived suppressor cells and angiogenic factors, all of which contribute to counteract specific cancer immunotherapy.[3] Immune evasion is now recognised as one of the major hallmarks that contributes to cancer emergence.[4] Immunotherapy strategies for cancer are therefore designed to directly target cancer proteins or restore and activate effective immunity against the cancer cells.[5,6] In the last few years, monoclonal antibodies specifically targeting immune checkpoints between cancer and immune cells such as the fusion protein cytotoxic T-lymphocyte-associated antigen 4-IgG1 (CTLA4Ig), programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, and adoptive T cell therapy with CAR-T cells targeting the CD19 protein on B cell malignancies have shown convincing and often striking clinical benefit[7]. Monoclonal antibodies that target other tumour stromal and immune components, such as anti-vascular endothelial growth factor (VEGF) and anti-CD25 antibodies that target the vasculature and regulatory T cells, respectively, are also being actively explored (the former already established in clinical practice across tumour types).[8,9] These immunotherapies have led to cancer immunotherapy being hailed as "Breakthrough of The Year" by one of the leading scientific journals, 'Science', in 2013.[7]

In 2017, the Food and Drug Administration (FDA) approved CAR-T cell therapy tisagenlecleucel (Kymriah) targeting the protein CD19 for the treatment of relapsed acute B cell leukaemia in children and young adults, and similarly, CAR-T cell therapy axicabtagene ciloleucel (Yescarta) for the treatment of advanced B cell lymphoma. Kymriah achieves complete remission in 80% to over 90% of relapsed cases (mostly heavily pretreated acute B cell leukaemias). Yescarta renders 50% of pretreated advanced B cell lymphoma into remission. The basis of CAR-T cell technology is single-chain variable fragment (scFv) portion of an anti-CD19 immunoglobulin transduced by a lentivirus into T cells; and this receptor has an integrated signalling domain that unleashes a potent costimulatory signal to in vivo activate and expand CAR-T cells in patients with B cell leukaemia and lymphoma[10]. T cell therapy differs from classical antineoplastic drugs such as cytotoxic chemotherapy, antibodies and small molecules. There are regarded as "living therapy", can expand exponentially in vivo, and potentially persist in the body for months and years. Immune checkpoint inhibitors generally have a half-life of a few weeks.

Immune checkpoint inhibitor antibodies are the other major paradigm shift in the war on cancer—that immunological targets against cancer do not come from targets on the cancer itself. Instead, these antibodies target the axis of immune checkpoints that regulate specific T cell-mediated immune responses against cancer. Landmark clinical trials of CTLA4Ig, PD1 and PDL1 Inhibitors proving improved survival in cancer patients have led to a quick succession of FDA regulatory approvals in the last few years for cancers including malignant melanoma, Hodgkin's lymphoma, bladder cancer, head and neck cancer, NSCLC, gastric cancer, Merkel cell carcinoma, renal cell cancer, hepatocellular carcinoma, microsatellite instable (MSI^{high}) colorectal cancer and any cancer with a high mutational burden.[11]

The Early Years and Fears

The earliest observation that the immune system may be stimulated to attack cancer (demonstrated in pioneering clinical experiments) can be dated back to the 1860s (Fig. 1). Dr Rudolf Virchow, an eminent 19th century German physician, observed and described infiltration of leukocytes in cancer tissues and was the first to hypothesise a connection between the immune system and cancer.[12,13] Also around the same time, 2 other German physicians, Drs William Busch and Friedrich Fehleisen, noticed in some cancer patients that their tumours regressed following accidental infection by erysipelas caused by *Streptococcus*. Soon after, in 1868, Dr Busch became the first physician to treat cancer by deliberately infecting patients with bacteria. He infected a patient with an inoperable soft tissue sarcoma of the neck with erysipelas and reported noticeable shrinkage of the tumour.[14] In the 1890s, American orthopaedic surgeon, Dr William Coley, treated terminal bone and soft-tissue sarcoma patients with "Coley's toxins"—a vaccine comprising attenuated *Streptococcus pyogenes* and *Serratia marcescens*. The vaccine which aimed at non-specifically stimulating the immune system against the patients' cancers[15] had been provided to him by German bacteriologist, Dr Robert Koch. A significant number of his patients achieved tumour regression—fever and chills as side effects notwithstanding—and there were even reported cures![16] At that time, Russian physician and renowned writer Anton Chekhov, was also convinced that bacterial infection like erysipelas could activate an immune response against cancer.[17] The field waned, and active research in

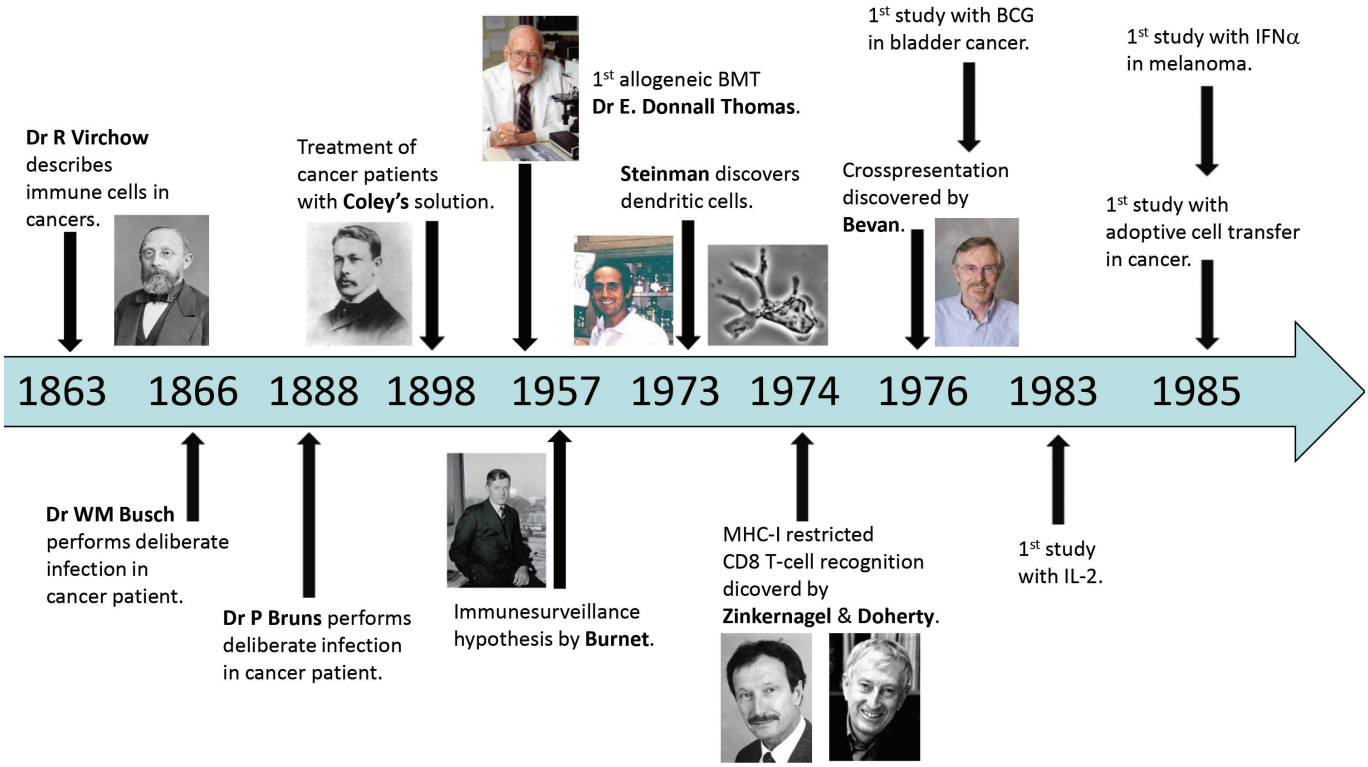

Fig. 1. Chart showing the key milestones in cancer immunotherapy development. (Reproduced with permission from Dr Jens Samol, Johns Hopkins Singapore International Medical Centre).

cancer immunotherapy only rekindled in the mid-twentieth century. Such earlier efforts successfully led to the regulatory approval of intravesicular Bacillus Calmette Guerin (BCG) vaccine for superficial bladder cancer in 1990.[18]

Cancer Vaccines – Waning or Winning

Cancer vaccine development gained momentum in the 1990s. The rationale for this targeted cancer immunotherapy strategy is to boost anti-TAA immune response to activate and expand TAA-specific cytotoxic T lymphocytes (CTLs) to kill tumour cells expressing the tumour antigens. Therapeutic cancer vaccination can be achieved by TAA-pulsed antigen-presenting cells, such as DC derived from peripheral blood monocytes or designing peptides of the said TAA or encoding the TAA in a vector such as a replication-deficient virus to be delivered to the patient or given as a peptide vaccine by itself. There are many ways cancer antigens can be delivered on a cancer vaccine vehicle. Overall, therapeutic cancer vaccines have been proven safe with minimal adverse events.

Over the decades, numerous cancer vaccines have been developed and tested in clinical trials—with the most promising results seen in lymphoma and hormone-refractory prostate cancer patients.[19,20] However, the clinical efficacy of especially the earlier generation of therapeutic cancer vaccines have in general been disappointing.[21,22] In a meta-analysis of all major cancer vaccine studies in colorectal cancer, an overall objective response rate of only 3.3% was observed in cancer vaccine treatments of over a thousand cancer patients with advanced disease.[22] The lack of efficacy is likely due to poor immunogenicity of the tumour, local and systemic immune suppression mediated by the growing tumour and its local environment, and tumour evasion of the immune system such as downregulation of the major histocompatibility antigen (MHC; or termed 'human leukocyte antigen', HLA, in humans).[3,23] An ideal cancer vaccine needs to target a uniquely expressed TAA, and also overcome immune tolerance. Examples of self TAA candidates include WT1, MUC-1 and the family of cancer/testis antigens such as NY-ESO-1, MAGE and SSX.[24] Strategies to further augment the specific anti-TAA immunity include adding immunoadjuvants and immune potentiating molecules into the cancer vaccine constructs.

A widely adopted cancer vaccine vehicle to optimise tumour antigen presentation is the DC vaccine. While the tumour-associated inhibitory mechanisms hamper the functions of endogenous DCs, ex vivo generated DCs are free from such inhibition during their development. DCs

are the most powerful professional antigen presenting cells (APC) capable of presenting relevant antigens to the adaptive immune system. We conducted a single-arm phase II MAGE-antigen (classic self TAA) lysate pulsed autologous DC vaccine study in advanced colorectal cancer patients who had received prior chemotherapy—many having been treated with multiple drugs. Twenty patients, biopsy-proven to express at least 1 of 6 MAGE antigen expression (identified as part of the tumour lysate), received up to 10 biweekly intradermal vaccinations of MAGE antigen-pulsed (an allogenic lysate) autologous DCs. The DC vaccine clinical benefit rate was 40% (1 partial response, 7 stable disease), with two stage 4 colon cancer patients surviving more than 6 years, 1 with multiple lung metastases remains alive after over 10 years.[25] These long-term survivors with advanced cancers are a small, select group characteristic of immunotherapy treatments including immune checkpoint inhibitors, and have been termed "supersurvivors".

We also completed a phase II clinical trial of an autologous DC vaccine transduced with an adenoviral vector to express the NPC-associated Epstein-Barr virus antigens LMP-1 and LMP-2 (classic non-self viral proteins) in 16 heavily pretreated advanced NPC patients. Two patients (12.5%) achieved disease stabilisation for over 18 weeks and 1 patient achieved partial response, leading to an overall clinical benefit of 19%.[26]

With innumerable clinical vaccine trials published since the 1990s, there is still only 1 FDA-approved therapeutic cancer vaccine—Sipuleucel-T (Provenge)—based on a landmark phase III study of in vivo infusion of activated monocytes (a DC-like approach) in 512 advanced hormone-refractory prostate cancer patients. Sipuleucel-T comprises autologous peripheral blood cells pulsed ex vivo with a fusion protein of prostatic acid phosphatase (PAP) antigen as target plus granulocyte-macrophage colony-stimulating factor (GM-CSF), included to activate endogenous DCs (PAP-GM-CSF). This cell-based vaccine's proven improved overall survival benefit in patients with advanced hormone-refractory prostate cancer led to it becoming the historic first-approved cellular therapy product in any cancer.[27]

New generation therapeutic cancer vaccination strategies include incorporating immune-modulating elements into the vaccine construct. In a first-in-human phase I clinical trial that we recently completed, 18 epithelial cancer patients with advanced disease were subcutaneously administered an adenoviral vector that encodes a fusion protein of the MUC-1 antigen and the extracellular domain of CD40L (Ad-sig-hMUC-1/ecdCD40L).[28] This vaccine via CD40L aims at activating the endogenous DCs that would potentially further improve MUC-1-specific immunity. MUC-1 is a polymorphic, type I transmembrane protein expressed at low levels on the apical surface of normal epithelial cells, which functions to stabilise the protective layer of mucous. It is highly expressed on neoplastic cells in 90% of epithelial cancers of the breast, ovary, colon, prostate, and lung.[29-31] In these epithelial cancers, MUC-1 overexpression disrupts E-cadherin function, leading to anchorage-independent tumour cell growth and metastases.[30,31] MUC-1 is hypoglycosylated in cancer cells, making it a prime TAA vaccine candidate. Several MUC-1-based cancer vaccine clinical trials had been conducted, including a recombinant MUC-1+IL-2 encoding vaccinia virus vector vaccine for advanced prostate cancer patients, as well as a viral vector-based vaccine clinical study in NSCLC patients.[32,33] CD40L is a strong adjuvant for induction of antigen presenting cell activation. It binds to DCs and induces cytokine production, leading to tumouricidal activity and proliferation of activated T cells.[34] In the preclinical murine model study, this Ad-sig-hMUC-1/ecdCD40L vaccine activated DCs and induced a potent CD8+ tumour suppressive immune response against hMUC-1 antigen, breaking tolerance in old mice where anergy exists to these antigens.[35,36] This vaccine, on an adenoviral backbone, was shown to be safe at all dose levels (tested with increasing viral titres and with no grade 3 or more toxicity). Clinical efficacy is observed and full evaluation is ongoing (unpublished).

One of the key reasons for the underperformance of therapeutic cancer vaccines is that it is normally given to heavily pretreated patients with large, aggressively growing tumour, an immunosuppressive network, and an anergic, exhausted ineffective immune system. To avoid this disadvantage, the landmark MAGRIT Trial aimed to evaluate the benefit of a MAGE-A3 peptide vaccine with an immunostimulant in surgically resected NSCLC patients. This randomised clinical trial recruited 2312 NSCLC patients—the largest therapeutic cancer vaccine trial ever conducted—to evaluate if the peptide-based cancer vaccine could significantly reduce cancer relapse (disease-free survival) in these cancer-free patients. It failed to meet its objective.[37] This negative phase III clinical trial dealt a big blow to the field of cancer vaccines.

A New Dawn with Neoantigens

In the decades that have been characterised with more disappointments than successes in identifying ideal tumour targets to optimise clinically impactful cancer vaccine strategies, a new window has opened. Genome instability that underlies the hallmarks of cancer allows tumour to acquire mutations that help it gain survival advantage.[4] These mutations, both driver (implicated in oncogenesis) and passenger (that do not confer a growth advantage), may generate proteins that are not part of the individual's proteome and are exclusively expressed by the tumour

cells.[38-40] When classically processed by the body's antigen-presenting machinery into short peptides, these antigens (referred to as tumour-specific neoantigens [TSAs]), are then presented by major histocompatibility complex (MHC) on the cell surface to the immune system. The recognition of these neoantigens as foreign thereby initiates an antitumour immune response. These ever-evolving neoantigens have not been subject to time-dependent immune tolerance. Therapeutic strategies that aim to identify the individual's TSAs, and utilise the ability of the immune system to recognise self and non-self, are hence the epitome of this new era of personalised and precision medicine that go beyond targeting oncogene addiction.

One of the earliest preclinical studies that demonstrated the ability of the immune system to recognise neoantigens was led by Boon et al.[41,42] In vitro mutagen-induced mouse tumour cell lines that expressed aberrant peptides failed to form tumours when injected into syngeneic mice, as opposed to the original tumour cell lines. Through a gene transfection method, they were able to identify the specific mutations that generated neoantigens. These neoantigens could be recognised by cytolytic T cells. In more recent years, clinical studies demonstrated the presence of T cells in melanoma patients that were able to recognise and generate antitumour response against TSAs.[43-45] Collectively, these studies helped to pave the way in developing better immunotherapy as the next cornerstone in cancer treatment. And so the field of cancer vaccines has been revived from its near-death journey. By the same principle, immune checkpoint inhibitors unleash T cells that can recognise neoantigens, as evidenced by its unique efficacy in cancers with a high mutational burden (such as MSI^{high} colorectal cancer).[11]

Technological advancements in recent years have enabled identification of TSAs employing different strategies. A common in silico approach guided by exome sequencing of the individual's tumour and matched normal tissue, first identifies somatic mutations found within the tumour.[39,46-48] The mutated deoxyribonucleic acid (DNA) sequences are translated to their corresponding amino acid sequences and non-synonymous mutations are selected for. Using various filtering steps which may include transcriptomic data to identify expressed genes, proteosomal processing, peptide transportation and MHC-binding prediction algorithms, these candidate neoantigens are then identified and prioritised. The TSA landscape has not surprisingly been noted to be highly variable both within and across tumour types.[49]

Both preclinical and clinical studies have shown that only a small fraction of the predicted neoantigens is capable of eliciting T cell reactivity.[50,51] Using next generation sequencing data and the NETMHC-3.4 prediction algorithm, Yadav et al identified 170 and 6 predicted neoepitopes in MC-38 and TRAMP-C1 murine tumour models, respectively. Simultaneously, mass spectrometry analysis was performed on the tumours to identify MHC Class I presented epitopes and only 7 predicted neoantigens in MC-38 were identified. Of these, 3 neoantigens were validated to be immunogenic through in vivo immunisation of murine models. Through mining exome data of melanoma tumours derived from 3 patients and using NetMHC prediction algorithm, Robbins et al identified neoepitope candidates that were predicted to bind with their respective HLA with high affinity. Only 3% to 6% of these tumour-specific neoantigens were found to be recognised by corresponding tumour-infiltrating lymphocytes. With the understanding that the various in silico prediction algorithms have differing focus, strengths and weaknesses, a large consortium from more than 35 research groups united to help refine, validate and identify the best algorithms.[52]

As clinical proof-of-principle of this new translational technology, the Rosenberg group successfully treated a patient with metastatic cholangiocarcinoma and another with metastatic colon cancer using an adoptive T cell approach.[53,54] Through whole-exome sequencing of the tumours, TSAs were identified and evaluated for reactivity with the corresponding tumour-infiltrating lymphocytes. These neoantigen reactive T cells were then expanded ex vivo and infused back into the patients, resulting in remarkable objective tumour regression. Another therapeutic approach using highly personalised TSA vaccines has been reported in 3 recent phase 1 studies in melanoma.[55-57] With each study utilising a different vaccine delivery approach (i.e. DC vaccine, peptide vaccine and ribonucleic acid [RNA]-based poly-neo-epitope vaccine), early readouts to detect T cell responses against TSAs were seen across the studies. Several important observations are noteworthy from these studies. Such neoepitope vaccines may be used as powerful adjuvant treatment in cancer patients at high risk of relapse (as illustrated in the melanoma studies where the vaccines were delivered to already cancer-free melanoma patients at high risk of relapse). Compellingly, these high-risk patients did not relapse after several years postvaccination. Also, when the neoepitope vaccine is combined with an immune checkpoint inhibitor, the clinical efficacy appears even more potent, capable of inducing complete tumour remissions.[56,57] While early results are promising, larger studies are required to address the relevant therapeutic endpoints, optimal vaccine delivery methods and the potential synergism in combining vaccine with other treatments. A limitation is that the time from neoantigen discovery to vaccine delivery is still in months than days but this will improve with further advancements in technology, bioinformatics and production.

The route to personalised, precision cancer immunotherapy comes closer to reaching its destination. New biomarkers, and an even greater understanding into the tumour-immune interaction will be crucial in contributing to this eventual success.

Conclusion

Historically, cancer therapy has followed the path of the proverbial William Tell[58]—with his bow and arrow aiming directly at the apple (cancer target) above his nervous son's head (normal cells). In those ancient days, the arrows were blunt tools that did not always fly straight. Today, arrows are much sharper, stronger and more precise. Also, another revolutionary paradigm has emerged—that cancer immunotherapy can also activate surrounding, previously inactive immune cells to hit the cancer target. This is like William Tell calling on nearby sleepy birds to swoop down and eat the apple. Combining 2 "arrows" is likely going to be even more effective in some cancers than using 1 "arrow", as long as the cumulative toxicities are manageable.

As Winston Churchill once said, "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning". So, too, with cancer immunotherapy.

REFERENCES

1. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480-9.
2. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009;9:162-74.
3. Itoh K, Yamada A, Mine T, Noguchi M. Recent advances in cancer vaccines: an overview. Jpn J Clin Oncol 2009;39:73-80.
4. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
5. Romero P, Banchereau J, Bhardwaj N, Cockett M, Disis ML, Dranoff G, et al. The Human Vaccines Project: A roadmap for cancer vaccine development. Sci Transl Med 2016;8:334ps9.
6. Sukari A, Nagasaka M, Al-Hadidi A, Lum LG. Cancer Immunology and Immunotherapy. Anticancer Res 2016;36:5593-606.
7. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science 2013;342:1432-3.
8. Sitohy B, Nagy JA, Dvorak HF. Anti-VEGF/VEGFR therapy for cancer: reassessing the target. Cancer Res 2012;72:1909-14.
9. Okita R, Yamaguchi Y, Ohara M, Hironaka K, Okawaki M, Nagamine I, et al. Targeting of CD4+CD25high cells while preserving CD4+CD25low cells with low-dose chimeric anti-CD25 antibody in adoptive immunotherapy of cancer. Int J Oncol 2009;34:563-72.
10. Jain MD, Davila ML. Concise Review: Emerging Principles from the Clinical Application of Chimeric Antigen Receptor T Cell Therapies for B Cell Malignancies. Stem Cells 2018;36:36-44.
11. Pento JT. Monoclonal cntibodies for the treatment of cancer. Anticancer Res 2017;37:5935-9.
12. Hajdu SI. A note from history: Rudolph Virchow, pathologist, armed revolutionist, politician, and anthropologist. Ann Clin Lab Sci 2005:203-5.
13. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539-45.
14. Busch W. Aus der Sitzung der medicinischen Section vom 13 November 1867. Berlin Klin Wochenschr 1868;5:137. [German]
15. Parish CR. Cancer immunotherapy: the past, the present and the future. Immunol Cell Biol 2003;81:106-113.
16. Starnes CO. Coley's toxins in perspective. Nature 1992;357:11-2.
17. Gresser I. A. Chekhov, M.D., and Coley's toxins. N Engl J Med 1987;317:457.
18. Lum BL, Torti FM. Adjuvant intravesicular pharmacotherapy for superficial bladder cancer. J Natl Cancer Inst 1991;83:682-94.
19. Timmerman JM, Levy R. Cancer vaccines: pessimism in check. Nat Med 2004;10:1279;author reply 1279-80.
20. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med 2004;10:909-15.
21. Engell-Noerregaard L, Hansen TH, Andersen MH, Thor Straten P, Svane IM. Review of clinical studies on dendritic cell-based vaccination of patients with malignant melanoma: assessment of correlation between clinical response and vaccine parameters. Cancer Immunol Immunother 2009;58:1-14.
22. Nagorsen D, Thiel E. Clinical and immunologic responses to active specific cancer vaccines in human colorectal cancer. Clin Cancer Res 2006;12:3064-9.
23. Lowy DR, Schiller JT. Preventive cancer vaccines. In: Vincent T, DeVita J, Hellman S, Rosenberg SA, editors. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 548-55.
24. Scanlan MJ, Gure AO, Jungbluth AA, Old LJ, Chen YT. Cancer/testis antigens: an expanding family of targets for cancer immunotherapy. Immunol Rev 2002;188:22-32.
25. Toh HC, Wang WW, Chia WK, Kvistborg P, Sun L, Teo K, et al. Clinical benefit of allogeneic melanoma cell lysate-pulsed autologous dendritic cell vaccine in MAGE-positive colorectal cancer patients. Clin Cancer Res 2009;15:7726-36.
26. Chia WK, Wang WW, Teo M, Tai WM, Lim WT, Tan EH, et al. A phase II study evaluating the safety and efficacy of an adenovirus-DeltaLMP1-LMP2 transduced dendritic cell vaccine in patients with advanced metastatic nasopharyngeal carcinoma. Ann Oncol 2012;23:997-1005.
27. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.
28. Zhang L, Tang Y, Akbulut H, Zelterman D, Linton PJ, Deisseroth AB. An adenoviral vector cancer vaccine that delivers a tumor-associated antigen/CD40-ligand fusion protein to dendritic cells. Proc Natl Acad Sci U S A 2003;100:15101-6.
29. Taylor-Papadimitriou J, Burchell J, Miles DW, Dalziel M. MUC1 and cancer. Biochim Biophys Acta 1999;1455:301-13.
30. Koido S, Kashiwaba M, Chen D, Gendler S, Kufe D, Gong J. Induction of antitumor immunity by vaccination of dendritic cells transfected with MUC1 RNA. J Immunol 2000;165:5713-9.
31. Ren J, Agata N, Chen D, Li Y, Yu WH, Huang L, et al. Human MUC1 carcinoma-associated protein confers resistance to genotoxic anticancer agents. Cancer Cell 2004;5:163-75.

32. Pantuck AJ, van Ophoven A, Gitlitz BJ, Tso CL, Acres B, Squiban P, et al. Phase I trial of antigen-specific gene therapy using a recombinant vaccinia virus encoding MUC-1 and IL-2 in MUC-1-positive patients with advanced prostate cancer. J Immunother 2004;27:240-53.
33. Tosch C, Bastien B, Barraud L, Grellier B, Nourtier V, Gantzer M, et al. Viral based vaccine TG4010 induces broadening of specific immune response and improves outcome in advanced NSCLC. J Immunother Cancer 2017;5:70.
34. Banchereau J, Bazan F, Blanchard D, Brière F, Galizzi JP, van Kooten C, et al. The CD40 antigen and its ligand. Annu Rev Immunol 1994;12:881-922.
35. Tang Y, Zhang L, Yuan J, Akbulut H, Maynard J, Linton PJ, et al. Multistep process through which adenoviral vector vaccine overcomes anergy to tumor-associated antigens. Blood 2004;104:2704-13.
36. Tang Y, Akbulut H, Maynard J, Petersen L, Fang X, Zhang WW, et al. Vector prime/protein boost vaccine that overcomes defects acquired during aging and cancer. J Immunol 2006;177:5697-707.
37. Vansteenkiste JF, Cho BC, Vanakesa T, De Pas T, Zielinski M, Kim MS, et al. Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small-cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016;17:822-35.
38. Heemskerk B, Kvistborg P, Schumacher TN. The cancer antigenome. EMBO J 2013;32:194-203.
39. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015;348:69-74.
40. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature 2009;458:719-24.
41. De Plaen E, Lurquin C, Van Pel A, Mariamé B, Szikora JP, Wölfel T, et al. Immunogenic (tum-) variants of mouse tumor P815: cloning of the gene of tum- antigen P91A and identification of the tum- mutation. Proc Natl Acad Sci U S A 1988;85:2274-8.
42. Van Pel A, Warnier G, Van den Eynde B, Lethe B, Lurquin C, Boon T. Tum- antigens, TSTA, and T cell immune surveillance. Ann N Y Acad Sci 1991;636:43-51.
43. van Rooij N, van Buuren MM, Philips D, Velds A, Toebes M, Heemskerk B, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol 2013;31:e439-42.
44. 44. Lu YC, Yao X, Crystal JS, Li YF, El-Gamil M, Gross C, et al. Efficient identification of mutated cancer antigens recognized by T cells associated with durable tumor regressions. Clin Cancer Res 2014;20:3401-10.
45. Lennerz V, Fatho M, Gentilini C, Frye RA, Lifke A, Ferel D, et al. The response of autologous T cells to a human melanoma is dominated by mutated neoantigens. Proc Natl Acad Sci U S A 2005;102:16013-8.
46. Castle JC, Kreiter S, Diekmann J, Löwer M, van de Roemer N, de Graaf J, et al. Exploiting the mutanome for tumor vaccination. Cancer Res 2012;72:1081-91.
47. Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature 2012;482:400-4.
48. Gubin MM, Artyomov MN, Mardis ER, Schreiber RD. Tumor neoantigens: building a framework for personalized cancer immunotherapy. J Clin Invest 2015;125:3413-21.
49. Charoentong P, Finotello F, Angelova M, Mayer C, Efremova M, Rieder D, et al. Pan-cancer Immunogenomic analyses reveal genotype-immunophenotype relationships and predictors of response to checkpoint blockade. Cell Rep 2017;18:248-62.
50. Yadav M, Jhunjhunwala S, Phung QT, Lupardus P, Tanguay J, Bumbaca S, et al. Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing. Nature 2014;515:572-6.
51. Robbins PF, Lu YC, El-Gamil M, Li YF, Gross C, Gartner J, et al. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. Nat Med 2013;19:747-52.
52. Parker Institute for Cancer Immunotherapy. Available at: https://www.parkerici.org/. Accessed on 24 January 2018.
53. Tran E, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Science 2014;344:641-5.
54. Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med 2016;375:2255-62.
55. Carreno BM, Magrini V, Becker-Hapak M, Kaabinejadian S, Hundal J, Petti AA, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science 2015;348:803-8.
56. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 2017;547:217-21.
57. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017;547:222-6.
58. Stein S. Them Apples. Available at: https://www.theparisreview.org/blog/2014/11/18/them-apples/. Accessed on 27 January 2018.

Kawasaki Disease: A Condition of Many Guises

Dear Editor,

Kawasaki disease (KD) is a systemic vasculitis that primarily affects children younger than 5 years of age. Its incidence rate varies from 3.4 per 100,000 children <5 years of age in Thailand[1] to 218.6 per 100,000 children <5 years of age in Japan.[2] Though there are well defined criteria for the diagnosis of KD,[3,4] its presentation can be varied[5] and the diagnosis of KD remains a challenge in febrile children who do not fulfill the diagnostic criteria but have several findings compatible with those of KD.

Case Report

The patient is a 5 months old male infant who presented with a 3-day history of fever (highest temperature reached was 38.4°C) associated with mild running nose, red and cracked lips, bilateral non-suppurative conjunctivitis and generalised rash with involvement of the trunk and peripheral limbs predominantly. Physical examination of the patient on admission revealed a playful afebrile infant with mild bilateral non-suppurative injected conjunctiva. There were bilateral small palpable cervical lymph nodes measuring less than 0.5 cm in greatest diameter. There were, however, no features of red lips or strawberry tongue, rash, erythema (in contrast to what had been highlighted in the history), oedema of the hands and feet or erythema/induration at Bacillus Calmette-Guerin (BCG) inoculation site, to suggest the presence of KD. Cardiovascular and abdominal examinations in the infant were unremarkable.

Investigations performed included a full blood count (FBC) which showed total white cell count of 16.11 x 10^9/L, with absolute neutrophil count of 6.27 x 10^9/L and absolute lymphocyte count of 7.13 x 10^9/L, with occasional reactive lymphocytes seen. Haemoglobin level was 10.2 g/dL, and platelet count was 484 x 10^9/L. C-reactive protein (CRP) level was 26 mg/L. Liver function test performed did not reveal any elevated transaminases or hypoalbuminaemia (serum albumin 38 g/L) and urine formed elements did not reveal any pyuria. Respiratory virus immunofluorescence, including adenovirus, was negative.

The infant was initially treated symptomatically with oral paracetamol with good effect. The infant remained afebrile for the subsequent 28 hours during the hospital stay before developing a temperature of 37.7°C (day 5 of illness). The patient was also noted to develop red and cracked lips and a macular rash over the right cheek subsequently on day 6 of illness. A decision was hence made to repeat FBC which revealed a total white cell count of 20.29 x 10^9/L, with absolute neutrophil count of 8.74 x 10^9/L and absolute lymphocyte count of 8.51 x 10^9/L. Haemoglobin level was 10.4 g/dL and platelet count was 621 x 10^9/L (platelet clumps were seen suggesting that the true platelet count was higher). Repeat CRP was also mildly increased to 34 mg/L. A 2-dimensional echocardiography was thus performed for the patient in light of these new findings, evaluating for possible incomplete KD. The scan showed a mildly ectatic right coronary artery (RCA) with a measurement of 2.2 mm (Z-score + 2.7). A diagnosis of incomplete KD was hence established in view of presence of fever of more than 5 days, rash and red lips, and further supported by CRP of 34 mg/L and echocardiographic finding of ectatic RCA with Z-score of + 2.7.[6]

The patient was thus given intravenous immunoglobulin (IVIG) of 2g/kg and commenced on high-dose oral aspirin of 100 mg/kg/day. The infant became afebrile whilst on IVIG infusion and remained so for more than 48 hours after completion of IVIG. His lips were no longer red and there was resolution of rash. Repeat FBC 48 hours post-IVIG showed a decrease in total white cell count and CRP to 10.91 x 10^9/L and 7 mg/L, respectively.

The above case report illustrates the treachery involved in the diagnosis of incomplete KD and the unusual progression of clinical signs and symptoms, including a playful, not irritable infant, good response of fever to paracetamol and patient becoming afebrile for more than 24 hours before the redevelopment of fever and other symptoms associated with KD.

Incomplete KD is more common in young infants[7] and may be made in cases with fewer classical diagnostic criteria but with several fitting clinical, laboratory or echocardiographic findings after exclusion of other causes of febrile illness. The diagnosis of incomplete KD should be entertained in children—especially young infants—with unexplained fever of ≥5 days associated with 3 or less of the clinical criteria but with compatible laboratory and/or echocardiographic features.[6] Infants ≤6 months old with fever ≥5 days and evidence of systemic inflammation

ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Tel: +65 6593 7800 | Fax: +65 6593 7867 | E-mail: annals@ams.edu.sg | Homepage: http://www.annals.edu.sg

with no obvious explanation may also benefit from echocardiography which will contribute to clinching the diagnosis of KD.

REFERENCES

1. Durongpisitkul K, Sandtawesin C, Khongphatthanayopthin A, Panamonta M, Sopontammarak S, Sittiwangkul R, et al. Epidemiologic study of Kawasaki disease and cases resistant to IVIG therapy in Thailand. Asian Pac J Allergy Immunol 2006;24:27-32.
2. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Chihara I, Aoyama Y, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2007-2008 nationwide survey. J Epidemiol 2010;20:302-7.
3. Council on Cardiovascular Disease in the Young; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; American Heart Association. Diagnostic guidelines for Kawasaki disease. Circulation 2001;103:335-6.
4. JCS Joint Working Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008) – digest version. Circ J 2010;9:1989-2020.
5. Lim TC, Yeo WS, Loke KY, Quek SC. Bilateral facial nerve palsy in Kawasaki disease. Ann Acad Med Singapore 2009;38:737-8.
6. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004;114:1708-33.
7. Sonobe T, Kiyosawa N, Tsuchiya K, Aso S, Imada Y, Imai Y, et al. Prevalence of coronary artery abnormality in incomplete Kawasaki disease. Pediatr Int 2007;49:421-6.

Wee Song Yeo, [1,2]*MMed, FRCPE, FRCPCH*

[1]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore

Address for Correspondence: Dr Yeo Wee Song, Department of Paediatrics, Yong Loo Lin School of Medicine, National University Health System, 1E Lower Kent Ridge Road, NUHS Tower Block, Level 12, Singapore 119228. Email: paeyws@nus.edu.sg

Trends in Cataract Surgery Technique and Anaesthesia Preferences in Singapore: A 2016 Survey

Dear Editor,

Cataract surgery is one of the most commonly performed operations in Singapore.[1] Anaesthesia techniques for cataract surgery have evolved over the past decades,[2] with variations in preferences and practices worldwide.[3-10] Current options include general anaesthesia, topical anaesthesia, as well as various regional anaesthesia techniques (peribulbar, retrobulbar and sub-Tenon's anaesthesia). We have repeated a similar survey from 2004[11] to describe any changes in cataract surgery technique and anaesthesia preferences.

Materials and Methods

In October 2016, an electronic survey by Google Doc was distributed to Singapore ophthalmologists via the College of Ophthalmologists, Academy of Medicine, Singapore using its electronic membership mailing list. Ethics approval was obtained from the Domain Specific Review Board. The questions included in the survey and the results are summarised in Table 1. A reminder email was sent in December 2016. There were no financial incentives for completing the survey and no identifiable data were collected. The results were tabulated and analysed in Microsoft Excel.

Results

There were 143 eligible members (Fellows) in the College of Ophthalmologists, Academy of Medicine, Singapore. A total of 84 responses were received (response rate = 59%). Of these, 62 (74%) and 22 (26%) were members from public institutions and private practice, respectively. Just under half of all respondents (48%) had completed ophthalmology training 10 or more years ago, and 47% performed more than 20 cataract operations on average per month over the last year.

Most respondents (n = 83, 99%) preferred phacoemulsification for routine cataract extraction, with only 1 surgeon (1%) preferring femtosecond laser-assisted cataract surgery (FLACS). Topical anaesthesia with or without intracameral anaesthesia was the technique of choice (n = 54, 64%), followed by peribulbar anaesthesia (n = 23, 28%), combined retrobulbar and facial block (n = 3, 3.6%), sub-Tenon's anaesthesia (n = 2, 2.4%), modified lateral peribulbar block (n = 1, 1.2%) and retrobulbar block (n = 1, 1.2%).

For mature cataracts, both phacoemulsification (n = 39, 46%) and extra-capsular cataract extraction (ECCE) (n = 39, 46%) were equally preferred, with the remaining 6 respondents (8%) opting for FLACS. ECCE was the operation of choice for surgeons who had completed their

Table 1. Survey Questions

What Type of Institution Are You Currently Practising in (Majority of the Time)? (n = 84) (%)		
Public	62 (74%)	
Private	22 (26%)	
How Long Ago Did You Complete Your Ophthalmology Training?		
0 – 4 years	27 (32%)	
5 – 9 years	17 (20%)	
10 – 14 years	12 (14%)	
15 – 19 years	12 (14%)	
20 – 24 years	8 (10%)	
25 – 29 years	3 (4%)	
30 – 34 years	3 (4%)	
35 – 39 years	2 (2%)	
How Many Cataract Surgeries Did You Perform Per Month (Average for the Last 1 Year)?		
0 – 4	10 (12%)	
5 – 9	9 (11%)	
10 – 14	16 (19%)	
15 – 19	9 (11%)	
20 – 24	21 (25%)	
25 – 29	1 (1%)	
30 – 34	8 (9%)	
>35	10 (12%)	
What is Your Preferred Surgical Technique for:	**Routine Cataract Surgery**	**Mature Cataract Surgery**
Phacoemulsification	83 (99%)	39 (46%)
ECCE	0	39 (46%)
FLACS	1 (1%)	6 (8%)

ECCE: Extracapsular cataract extraction; FLACS: Femtosecond laser-assisted cataract surgery; MLPA: Modified lateral peribulbar anaesthesia; PA: Peribulbar anaesthesia; RA: Retrobulbar anaesthesia; SA: Sub-tenon's anaesthesia; TA: Topical anaesthesia

*Percentages do not add up to 100% as respondents were allowed to give more than one reason.

†Mild sedation is defined as the level of sedation in which the patient is able to respond purposefully to verbal commands and be easily roused.

Table 1. Survey Questions (Cont'd)

Which is Your Preferred Anaesthesia Technique for:					
	Routine Cataract Surgery		**Mature Cataract Surgery**		
	Phacoemulsification	**FLACS**	**Phacoemulsification**	**ECCE**	**FLACS**
RA	1 (1%)	0	3 (8%)	0	0
RA + facial block	3 (4%)	0	1 (3%)	5 (13%)	0
PA	23 (28%)	0	24 (61%)	31 (79%)	0
SA	2 (2%)	0	4 (10%)	2 (5%)	0
TA alone	37 (45%)	1 (100%)	6 (15%)	1 (3%)	5 (83%)
TA + intracameral anaesthesia	16 (19%)	0	1 (3%)	0	0
MLPA	1 (1%)	0	0	0	1 (17%)
Why Do You Prefer a Particular Anaesthesia Technique for:*					
	Routine Cataract Surgery		**Mature Cataract Surgery**		
Patient comfort	54 (64%)		59 (70%)		
Patient's choice	3 (4%)		3 (4%)		
Surgeon comfort	25 (30%)		62 (74%)		
Surgeon's choice	48 (57%)		58 (69%)		
Speed/efficiency	37 (44%)		7 (8%)		
Safer technique	19 (23%)		10 (12%)		
Who Administers the Anaesthesia for Your Cataract Surgery?					
Nurse			4 (5%)		
Anaesthetist			2 (2%)		
Trainee surgeon			3 (4%)		
Myself			75 (89%)		
Do You Routinely Give Mild Sedation for Your Cataract Operations?†					
Yes			59 (70%)		
No			25 (30%)		
What Kind of Anaesthesia Support Do You Have When You Operate?					
Monitoring by surgeon			1 (1%)		
Monitored anaesthesia care (MAC) by anaesthetist			80 (95%)		
Mixture of the above			3 (4%)		

ECCE: Extracapsular cataract extraction; FLACS: Femtosecond laser-assisted cataract surgery; MLPA: Modified lateral peribulbar anaesthesia; PA: Peribulbar anaesthesia; RA: Retrobulbar anaesthesia; SA: Sub-tenon's anaesthesia; TA: Topical anaesthesia

*Percentages do not add up to 100% as respondents were allowed to give more than one reason.

†Mild sedation is defined as the level of sedation in which the patient is able to respond purposefully to verbal commands and be easily roused.

ophthalmology training more than 15 years ago (n = 19/28, 67%). Surgeons who completed their ophthalmology training less than 15 years ago preferred phacoemulsification (n = 33/56, 59%) over ECCE (n = 20/56, 36%). The uptake of newer technology FLACS appeared independent of graduation year. The 6 surgeons who used FLACS in mature cataracts completed their training ranging from 5 to 24 years.

Peribulbar anaesthesia was preferred in mature cataracts for both phacoemulsification (n = 21, 62%) and ECCE (n = 31, 79%) while topical anaesthesia was the preferred option for surgeons performing FLACS (n = 5, 83%). The anaesthesia choice for mature cataract operations was distributed in a similar proportion in the different surgeon graduation year groups.

The reasons behind surgeons' preference for anaesthesia techniques are shown in Table 1. For routine cataract extraction, patient comfort (n = 54, 64%) was the most prominent factor, followed by surgeon choice (n = 48, 57%) and efficiency of turnaround (n = 37, 44%). On the other hand, surgeon comfort (n = 62, 74%) was prioritised in mature cataract extraction, followed by patient comfort (n = 59, 70%) and surgeon choice (n = 58, 69%).

All respondents except 1 (n = 83, 99%) operated under monitored anaesthesia care (MAC) provided by anaesthetists. Seventy percent (n = 59) of the respondents complemented MAC with mild sedation—defined as the level of sedation in which the patient is able to respond purposefully to verbal commands and be easily roused. Thirty-four respondents provided the type of sedation used during cataract surgery, of which, most preferred the use of propofol (n = 19, 56%) followed by midazolam (n = 12, 35%) and fentanyl (n = 8, 24%). Eleven respondents used these drugs in different combinations.

Discussion

This survey provides a summary of the current cataract practice in Singapore and shows some variations in preferences between surgeons, both in surgical and anaesthesia techniques. This survey is also the first amongst the others performed internationally[3-10] to stratify results into 2 groups based on the maturity of cataract.

All respondents in Singapore now use phacoemulsification (with or without femtosecond laser) for routine cataract surgery compared to 92% in 2004[11] (when 8% preferred ECCE). In 2004, 28% of surgeons performed phacoemulsification for all types of cataract (compared to 54% in 2016). This shift may reflect the comfort levels of surgeons with phacoemulsification due to training and improved technology. ECCE is still commonly used in mature cataracts (46%), however, surgeons who completed ophthalmology training for 15 or more years were much more likely to use ECCE technique than those who completed ophthalmology training less than 15 years earlier (67% vs 36%, respectively). One surgeon chose FLACS as the preferred routine technique. A recent Cochrane review comparing FLACS and standard phacoemulsification found a lack of evidence to suggest superiority of 1 technique over the other.[12] As technology evolves, there may be a shift in the standard of care in the future.

We compared our findings with longitudinal data available from studies in some countries, notably United States of America (USA), Canada, New Zealand, United Kingdom (UK), Korea and Japan (Table 2). Anaesthesia preferences for routine cataract surgery vary significantly across the world. While sub-Tenon's anaesthesia was the most popular technique in Japan (42%),[9] New Zealand (78.3%)[6] and UK (46.9%),[7] it is infrequently used in Singapore (2%). Topical anaesthesia—with or without intracameral anaesthesia—was the technique of choice in Singapore (64%), which is similar to findings in the USA (51%),[3] Korea (69%)[8] and Canada (95.5%).[5] The main difference was that Canadian surgeons were twice more likely to supplement topical

Table 2. International Comparison of Anaesthesia Preferences in Cataract Surgery (%)

Anaesthesia Technique	Singapore (Current Study) (n = 84)	Singapore* (2004; 2007)** (n = 88)	USA† (2003; 2004)** (n = 985)	Canada‡ (2016; 2017)** (n = 114)	New Zealand§ (2007; 2008)** (n = 83)	UK‖ (2001– 2006; 2006)** (n = 55, 567)	Korea¶ (2012; 2015)** (n = 62)	Japan# (1999; 2001)** (n = 457)
TA alone	45.2	36	17	29.1	8.4	22.3	69	26
TA + IC	19	6	44	66.4	15.7	4.7	69	4
PA	27.4	43	17	0.9	12	19.5	4	4
RA alone	1.2	6	11	0.9	1.2	0.5	10	10
RA + FB	3.6	7	9	0	2.4	0	10	11
SA	2.4	1	2	0.9	78.3	46.9	17	42
Others‡‡	1.2	1	0	0	1.2	6.1	0	0

FB: Facial block; IC: Intracameral anaesthesia; PA: Peribulbar anaesthesia; RA: Retrobulbar anaesthesia; SA: Sub-tenon's anaesthesia; TA: Topical anaesthesia; UK: United Kingdom; USA: United States of America

*Zhao LQ, Zhu H, Zhao PQ, Wu QR, Hu YQ. Topical anesthesia versus regional anesthesia for cataract surgery: a meta-analysis of randomized controlled trials. Ophthalmology 2012;119:659-67.

†Leaming DV. Practice styles and preferences of ASCRS members – 2003 survey. J Cataract Refract Surg 2004;30:892-900.

‡Ong-Tone L. Practice patterns of Canadian ophthalmological society members in cataract surgery-2016 survey. Can J Ophthalmol 2017;52:2.

§Pick ZS, Leaming DV, Elder MJ. The fourth New Zealand cataract and refractive surgery survey: 2007. Clin Exp Ophthalmol 2008;36:604-19.

‖Oshika T, Amano S, Araie M, Majima Y, Leaming DV. Current trends in cataract and refractive surgery in Japan: 1999 survey. Jpn J Ophthalmol 2001;45:383-7.

¶Eichel R, Goldberg I. Anaesthesia techniques for cataract surgery: a survey of delegates to the Congress of the International Council of Ophthalmology, 2002. Clin Exp Ophthalmol 2005 Oct;33:469-72.

#Wagle AA, Wagle AM, Bacsal K, Tan CS, Chee SP, Au Eong KG. Practice preferences of ophthalmic anaesthesia for cataract surgery in Singapore. Singapore Med J 2007;48:287-90.

**The first year quoted refers to the year in which the study was conducted, while the second year refers to the year in which the study was published.

††Combined results as the study did not provide separate results for each individual anaesthesia technique.

‡‡Other techniques, e.g. modified lateral peribulbar block, subconjunctival anaesthesia, general anaesthesia.

anaesthesia with intracameral lignocaine compared to their Singapore counterparts. A common trend was the move away from sharp needle techniques, such as retrobulbar and peribulbar blocks, observed in Singapore (32% in 2016, from 58% in 2004), New Zealand (13.1% in 2007, from 65.7% in 1997) and UK (19.5% in 2006, from 34% in 2003). This may be explained by the higher risk of injection-related complications,[13] leading to increasing popularity of topical anaesthesia.

The respondents in our survey were asked to indicate their rationale anaesthesia preference. The reasons were broadly grouped into the following: patient comfort, patient's choice, surgeon comfort, surgeon's choice, speed or efficiency and safety of the technique. Patient comfort and surgeon's choice was more commonly indicated to be a consideration for mature cataracts (74%) compared to routine cases (64%). This reflects on the complexity of mature cataracts and need for greater control of eye movement and pain.

A quick turnaround time of surgery was prioritised by nearly half of the respondents (44%) in routine cataract surgery, compared to just 8% in mature cataract extraction, indicating a demand for high-volume surgery for routine cases, but surgeons are willing to sacrifice turnaround time in complex cases, especially since most surgeons prefer to administer the regional anaesthesia themselves (89%).

All but 1 of the respondents (99%) operated under MAC with an anaesthetist. This is comparable with international practice in countries such as UK (74%), New Zealand (82%) and Australia (97%).[10] The majority of respondents (70%) supplemented anaesthesia with mild sedation, a practice that is notably more prevalent in Singapore, with only USA (86%) reporting a higher figure.[10] Propofol is the most preferred drug, likely due to its rapid recovery and antiemetic properties.[14] This survey is limited by the relatively small sample size, compared to larger national databases set up in countries such as UK.[7] While the survey may be considered a valid representation of practice patterns in Singapore, it was unable to take into account the practice preferences of the surgeons who did not respond (n = 59/143, 41%), as well as that of ophthalmology trainees who have yet to qualify as Fellows of the College of Ophthalmologists, Academy of Medicine, Singapore.

Conclusion

Phacoemulsification under topical anaesthesia with sedation and MAC is the technique of choice for routine cataract surgery in Singapore. For mature cataracts, either phacoemulsification or ECCE is equally preferred, under peribulbar anaesthesia with sedation and MAC. Overall, there has been a shift towards phacoemulsification and FLACS (away from ECCE), and towards topical anaesthesia (away from regional anaesthesia) since the last survey in 2004.

REFERENCES

1. Lee SY, Tan D. Changing trends in cataract surgery in Singapore. Singapore Med J 1999;40:256-9.
2. Athanasiov P, Henderson T. Ocular anaesthesia and the never-ending story. Br J Ophthalmol 2010;94:1.
3. Leaming DV. Practice styles and preferences of ASCRS members – 2003 survey. J Cataract Refract Surg 2004;30:892-900.
4. Bellan L, Dunn E, Black C. Practices associated with cataract surgery in Canada: results of a national survey. Can J Ophthalmol 1997;32:315-23.
5. Ong-Tone L. Practice patterns of Canadian ophthalmological society members in cataract surgery-2016 survey. Can J Ophthalmol 2017;52:2.
6. Pick ZS, Leaming DV, Elder MJ. The fourth New Zealand cataract and refractive surgery survey: 2007. Clin Exp Ophthalmol 2008;36:604-19.
7. El-Hindy N, Johnston RL, Jaycock P, Eke T, Braga AJ, Tole DM, et al. The cataract national dataset electronic multi-centre audit of 55,567 operations: anaesthetic techniques and complications. Eye (Lond) 2009;23:50-5.
8. Wi JM, Moon HS, Kim KH, Shyn KH. 2012 survey of KSCRS and KOS member: current trends in cataract surgery in Korea. J Korean Ophthalmol Soc 2015;56:1181-7.
9. Oshika T, Amano S, Araie M, Majima Y, Leaming DV. Current trends in cataract and refractive surgery in Japan: 1999 survey. Jpn J Ophthalmol 2001;45:383-7.
10. Eichel R, Goldberg I. Anaesthesia techniques for cataract surgery: a survey of delegates to the Congress of the International Council of Ophthalmology, 2002. Clin Exp Ophthalmol 2005 Oct;33:469-72.
11. Wagle AA, Wagle AM, Bacsal K, Tan CS, Chee SP, Au Eong KG. Practice preferences of ophthalmic anaesthesia for cataract surgery in Singapore. Singapore Med J 2007;48:287-90.
12. Day AC, Gore DM, Bunce C, Evans JR. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. Cochrane Database Syst Rev 2016;7:CD010735.
13. Zhao LQ, Zhu H, Zhao PQ, Wu QR, Hu YQ. Topical anesthesia versus regional anesthesia for cataract surgery: a meta-analysis of randomized controlled trials. Ophthalmology 2012;119:659-67.
14. Vann MA, Ogunnaike BO, Joshi GP. Sedation and anesthesia care for ophthalmologic surgery during local/regional anesthesia. Anesthesiology 2007;107:502-8.

Yong Seng Tam, [1], Chandra M Kumar, [2,3] *MBBS, FFARCS, FRCA*, Kah Guan Au Eong, [4-6] *MMed (Ophth), FRCS, FAMS (Ophth)*, Chee Chew Yip, [4,7] *MBBS FRCOphth*, Jason Cheng, [4,7] *MBBS FRCOphth*

[1]Medical School, The University of Sheffield, United Kingdom
[2]Department of Anaesthesia, Khoo Teck Puat Hospital, Singapore
[3]Medical School, Newcastle University, Johor, Malaysia
[4]Department of Ophthalmology & Visual Sciences, Khoo Teck Puat Hospital, Singapore
[5]Singapore International Eye Cataract Retina Centre, Mount Elizabeth Medical Centre, Singapore
[6]International Eye Cataract Retina Centre, Farrer Park Medical Centre, Singapore
[7]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for Correspondence: Dr Jason Cheng, Department of Ophthalmology & Visual Sciences, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828.
Email: chengophthalmology@gmail.com

Letter to the Editor

Diagnosis of Diffuse Parenchymal Lung Disease Using Transbronchial Cryobiopsy in an Ambulatory Setting

Dear Editor,

Diffuse parenchymal lung disease (DPLD) is encountered not only in pulmonary medicine as idiopathic interstitial pneumonias or interstitial lung disease (ILD), but also in transplant medicine, infectious disease, connective tissue diseases and drug-induced ILDs.[1] The incidence of DPLD in Singapore is currently unknown but its prevalence appears to be increasing worldwide. For example, the incidence of idiopathic pulmonary fibrosis in North America and Europe is 3 to 9 cases per 100,000 person-years and in South America and East Asia, it is reported as <4 cases per 100,000 person-years.[2] Treatment of DPLD is different ranging from steroids to antimicrobials to withdrawal of an implicated drug. Therefore, it is imperative to establish an accurate diagnosis.

Data show that samples from transbronchial biopsy via flexible bronchoscopy may only provide a confirmed diagnosis in 20% to 30% of patients with ILD, even when combined with clinical and high resolution computed tomography (CT) input.[3] Biopsy samples are limited in size[3] and subject to crush artefact[4] from both the closure of forceps, as well as withdrawal through the narrow working channel of the scope. Surgical lung biopsies have a diagnostic yield of 93% to 98% but mortality ranges from 1.7% to 2.7%.[4-6] In addition, mortality is significantly higher in non-elective biopsies (16%) and risks are related to age and co-morbidities.[5] These factors have driven research in obtaining high quality lung biopsy specimens in a safer manner.

Bronchoscopic cryobiopsies can obtain larger specimens[7] and meta-analyses data suggest that the diagnostic yield for DPLD is 83.7%.[6] The Joule-Thomson effect of a rapidly expanding gas (carbon dioxide) is utilised to reduce the temperature of the cryoprobe tip to -79°C. This causes cryo-adherence to tissue which then allows large biopsies to be taken. Because the scope and the cryoprobe are removed together in order to recover the sample without passing through the working channel of the bronchoscope, there is the added advantage of avoiding crush artifact.[8] Cryobiopsies have a procedure-related mortality of 0.3% and median hospitalisation is 2.6 days.[4] There is also evidence to show that bronchoscopic cryobiopsies are able to increase the diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis.[9]

However, there is limited data of performing transbronchial cryobiopsies in an ambulatory setting under moderate sedation, without the need for endotracheal intubation, general anaesthesia or endobronchial blockers. It is envisaged that the number of specimens that can be obtained may be smaller and the diagnostic yield of such a compromise is also unknown. The attraction of this ambulatory approach goes beyond reduced costs. It may make cryobiopsies widely available because minimal additional equipment and personnel will be needed compared to routine flexible bronchoscopy. The aim of this pilot study is to evaluate the safety and diagnostic yield of transbronchial cryobiopsy for DPLD in an ambulatory setting in Singapore.

Materials and Methods

Prospectively collected data from a bronchoscopy database included all patients from Singapore General Hospital who underwent transbronchial cryobiopsy for DPLD. Data from July 2015 to November 2017 were analysed in this study. Inclusion criteria were age 18 to 80, and presence of diffuse lung disease on CT that was consistent with DPLD. Exclusion criteria included contraindication to bronchoscopy such as haemodynamic instability, respiratory failure, uncorrected coagulopathy, as well as suspected pregnancy or focal lung disease on chest radiology. Patients who had CT findings that met all criteria for a radiological diagnosis of usual interstitial pneumonia were excluded as well and managed accordingly.[10] Institutional review board approval (no.: 2011/350/C) was obtained and ClinicalTrials.gov identifier is NCT01374542.

A positive diagnostic result was defined as either a confirmed histopathological or microbiological diagnosis that was both compatible with the clinical picture and did not require further diagnostic testing. Patients with non-diagnostic biopsies were treated empirically based on the clinical diagnosis or followed up with radiological surveillance for at least 6 months. None of the patients were subject to alternative biopsy procedures. Bronchoscopic complications such as pneumothorax, bleeding, hypoxia, and hypotension were recorded down whenever they were present and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[11]

Cryobiopsies were performed with a flexible cryoprobe (Erbecryo, Erbe Elektromedizin GmbH, Tubingen, Germany). This probe has an outer diameter of 1.9 mm and a length of 900 mm. All procedures were performed under moderate sedation using a combination of fentanyl and midazolam. Bronchoscopic intubation was done orally instead of nasally. This allowed for extubation once the specimen was obtained and subsequent re-intubation. No endotracheal tube or rigid bronchoscope was used. Bronchoalveolar lavage was first performed in the targeted subsegment of the lung before cryobiopsy was performed. The cryobiopsy freeze cycle was set at 4 seconds and after obtaining the biopsy, the tip of the cryoprobe was placed in a container of normal saline to facilitate rapid thawing. The specimen was then recovered from the container of saline and placed in formaldehyde before being sent to the histopathology laboratory. Fluoroscopy was utilised for all cryobiopsies and the probe was activated <10 mm from the pleural margin.

Results

Transbronchial cryobiopsy was performed in 22 consecutive patients presenting with DPLD. Demographic and procedure details are shown in Table 1. Cryobiopsy sample size was 5.1 ± 1.7 mm in diameter and alveolar tissue was identified in all samples. The mean alveolar surface area per sample was 8.5 ± 5.6 mm^2. Large airways were present in 15/22 (68%), small airways in 100% and large vessels in 19/22 (86%). It was possible to do histopathological stains on all specimens and the cryobiopsy technique does not appear to impede or distort histological investigations.

A positive diagnostic result from the bronchoscopy was obtained in 16/22 (73%) patients (Table 2). Cryobiopsy histology was diagnostic in 10/22 (45%) and microbiology was positive from bronchoalveolar lavage in 6/22 (27%). Examples of definitive cryobiopsy results are shown in Figure 1. The remaining 6 patients without a diagnosis were discussed at multidisciplinary meetings before a diagnosis was assigned. In our follow-up, 1 patient with post-inflammatory scar and 3 patients with bacterial pneumonia were considered to be true negatives.

Complications were documented in 7/22 cases (32%). Six patients experienced moderate endobronchial bleeding immediately postbiopsy and were managed by local therapy such as ice cold saline and tamponade of the endobronchial segment with the flexible bronchoscope. One patient required 500 cc of intravenous normal saline for transient hypotension. None of the patients required endobronchial blocker placement. One other patient developed hypoxaemia that needed face mask and bagging for <1 min. This was attributed to the sedation given. No ventilator support was required postprocedure. All patients had screening fluoroscopy at the end of the bronchoscopy and then a check chest radiograph. No pneumothorax was detected. None of the patients required escalation of care and no one was readmitted following the bronchoscopy.

Table 1. Demographics and Procedure Details

	n (%)
Total number of patients	22
Female gender	11 (50)
Median age in years (range)	58.5 (26 – 77)
Chinese ethnicity	12 (55)
Never smokers	12 (55)
ASA scoring	
ASA 1	5 (23)
ASA 2	10 (45)
ASA 3	7 (32)
CT findings*	
Ground glass opacification	8 (36)
Nodular opacities	7 (32)
Consolidative infiltrates	10 (45)
Mean duration of bronchoscopy in minutes	20.7 ± 4.7
Sedation	
Median midazolam dose in mg (range)	4 (2 – 5)
Median fentanyl in mcg (range)	100 (50 – 100)
Median number of cryobiopsy samples per patient (range)	2 (1 – 4)
Mean diameter of biopsy sample in mm	5.1 ± 1.7
Biopsy site	
One bronchopulmonary segment	15 (68)
Two bronchopulmonary segments	7 (32)
Complications†	
Pneumothorax	0
Bleeding grade 2	6 (27)
Hypoxaemia grade 3	1 (5)

ASA: American Society of Anesthesiologists; CT: Computed tomography
*With overlaps to account for multiple findings.
†Descriptions found at: National Cancer Institute NIoH, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. 2009. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed on 6 September 2017.

Discussion

Data from our pilot study showed that transbronchial cryobiopsy can be performed safely in patients presenting with DPLD in an ambulatory setting, under moderate sedation and without the deployment of an endobronchial blocker. No rigid bronchoscope or endotracheal tube was necessary. The only other previous report in the literature to describe this technique necessitated 2 bronchoscopes, 2

Table 2. Clinical-Radiological-Pathological Correlation and Final Diagnosis of All Patients

Patient Age/Gender/Ethnicity	CT Findings			Cryobiopsy Histology	Bronchoalveolar Lavage Microbiology	Diagnosis on Clinical and Radiological Follow-up
	GGO	Nodules	Consolidation			
41/F/I	×	✓	×	Hypersensitivity pneumonitis	Non-diagnostic	Hypersensitivity Pneumonitis
73/F/C	✓	×	×	Drug-induced ILD	Non-diagnostic	Drug-induced ILD
70/M/E	✓	×	×	Drug-induced ILD	Non-diagnostic	Drug-induced ILD
41/F/I	✓	×	×	Drug-induced ILD	Non-diagnostic	Drug-induced ILD
57/M/C	✓	×	✓	Drug-induced ILD	Non-diagnostic	Drug-induced ILD
67/M/C	✓	×	×	Organising pneumonia	Non-diagnostic	Cryptogenic organising pneumonia
69/F/C	×	×	✓	Organising pneumonia	Non-diagnostic	Cryptogenic organising pneumonia
72/F/C	×	×	✓	Organising pneumonia	Non-diagnostic	Cryptogenic organising pneumonia
60/F/C	✓	✓	×	Chronic interstitial pneumonia (lymphocytic interstitial pneumonia like)	Non-diagnostic	Lymphocytic interstitial pneumonia
52/M/C	×	✓	×	Foreign body reaction	Non-diagnostic	Foreign body reaction
53/F/C	×	×	✓	Non-diagnostic	*Klebsiella pneumonia*	*Klebsiella pneumonia*
54/M/O	×	×	✓	Non-diagnostic	Influenza A	Influenza A pneumonia
77/M/M	×	×	✓	Non-diagnostic	*Klebsiella pneumonia*	*Klebsiella pneumonia*
26/F/O	×	✓	×	Non-diagnostic	Tuberculosis	Tuberculosis
75/M/C	×	✓	×	Non-diagnostic	Tuberculosis	Tuberculosis
74/F/O	×	×	✓	Non-diagnostic	Non-tuberculous mycobacteria	Non-tuberculous mycobacteria
51/M/O	✓	×	×	Non-diagnostic	Non-diagnostic	Desquamative interstitial pneumonia
54/F/C	✓	×	✓	Non-diagnostic	Non-diagnostic	Postinflammatory scar
62/M/C	×	×	✓	Non-diagnostic	Non-diagnostic	Bacterial pneumonia
34/M/I	×	×	✓	Non-diagnostic	Non-diagnostic	Bacterial pneumonia
67/F/C	×	✓	×	Non-diagnostic	Non-diagnostic	Bacterial pneumonia
52/M/I	×	✓	×	Non-diagnostic	Non-diagnostic	Non-diagnostic

C: Chinese; E: Eurasian; F: Female; GGO: Ground glass opacity; I: Indian; ILD: Interstitial lung disease; M: Male; M: Malay; O: Others

processors and 2 interventional pulmonologists.[12] Not only have we shown that this additional logistics is not necessary, but it is also possible to make a confirmed diagnosis in 73% of patients when microbiological evaluation from bronchoalveolar lavage was added to the histological analysis of cryobiopsy.

Conventional wisdom suggests that the larger samples from cryobiopsies result in substantial postbiopsy bleeding[13] and necessitate the use of rigid bronchoscopy and pre-emptive endobronchial blocker deployment.[14,15] Two meta-analyses showed that the risk of moderate bleeding was 12% (95% CI, 2.0% to 25%) and 4.9% (95% CI, 2.2% to 10.7%), respectively.[4,6] Furthermore, it is thought to be easier to control bleeding when the patient is under deep sedation or general anaesthesia compared to moderate sedation, especially when the patient starts coughing. Our data has challenged all these assertions.

The bleeding risk was mitigated in our study by limiting cryofreeze duration to 4 seconds in our protocol as opposed to 5 seconds or longer in other studies.[4] In addition, fewer biopsies were obtained in our study with an average of 2 samples per patient. Moreover, in 68% of patients, only a single bronchopulmonary segment was sampled despite the presence of diffuse radiological infiltrates. Regardless of these limitations, the mean biopsy diameter met the 5 mm target that has been recommended for acceptable cryobiopsies.[8] Other criteria require at least 1 fragment of alveolated lung parenchyma to classify the biopsy as adequate.[15] All our samples met this adequacy criteria as well.

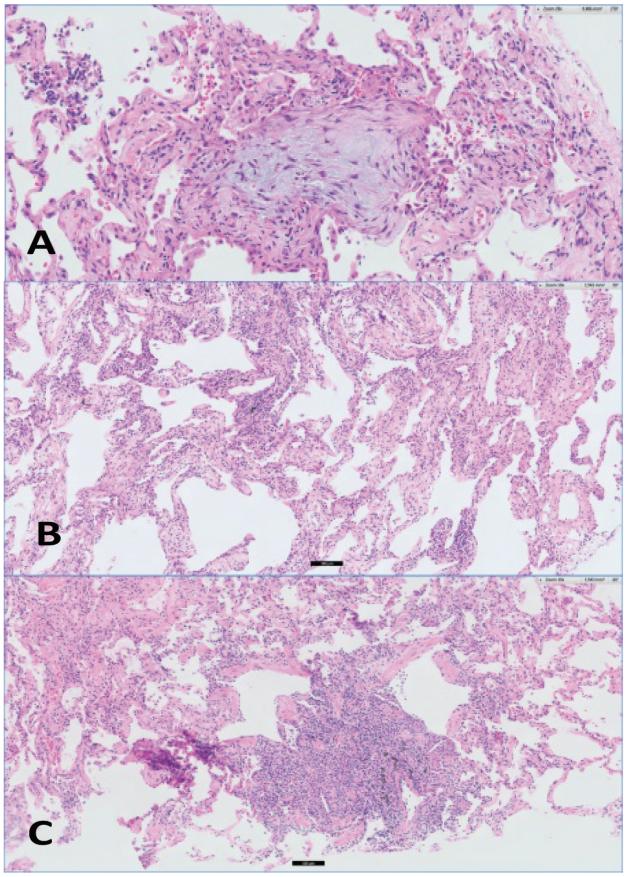

Fig. 1. Representative cryobiopsies providing definitive diagnoses after clinical radiological correlation: A) Organising pneumonia x20; B) Lymphocytic interstitial pneumonia x10; and C) Hypersensitivity pneumonitis x10.

There is the possible criticism that cryobiopsy alone contributed to a diagnostic yield of only 45% (10/22) in our study. However, on further analysis of the remaining 12/22 patients, 1 patient with desquamative interstitial pneumonia, 3 patients with mycobacterial disease and 1 further patient with no confirmed final diagnosis were truly non-diagnostic. In the remaining 6 cases of slowly resolving pneumonia and 1 case of postinflammatory scar, there were no pathognomonic histological features and hence non-specific inflammatory changes were correctly identified (7/22). Hence, among cases in which a diagnosis was actually possible on histology, the cryobiopsy samples were successful in 10/15 (67%). This is concordant with analysis of current data on diagnostic yield that ranges from 50% to >90%.[4] Given the confidence gained from performing transbronchial cryobiopsies in this study, future attempts with this procedure should sample multiple bronchopulmonary segments because of data showing increased yield if samples are obtained from 2 segments within the same lobe rather than the same segment.[13]

The risk of pneumothorax from transbronchial cryobiopsy is 6% (95% CI, 2% to 11%) and 9.5% (95% CI, 5.9% to 14.9%) according to 2 recent meta-analyses.[4,6] The limited number and size of biopsies are likely to have contributed to the lower risk in our pilot study. The limitations of this study is the small sample size and the fact that all procedures were carried out by only 1 endoscopist (DA) or read by just 1 histopathologist (AT). However, this can also be a strength because of standardisation of procedures. In addition, there were limited numbers of patients with fibrotic lung disease such as usual interstitial pneumonia or non-specific interstitial pneumonia. This may be reflective of a general respiratory practice with a predominance of pulmonary infections and drug-induced pneumonitis.[16]

Conclusion

Transbronchial cryobiopsies have become established in the evaluation of DPLD. As bronchoscopists, our commitment to patients is to perform the procedure such that diagnostic yield is maximised and complications are minimised while making the technology as widely available as possible. This pilot study has showed that transbronchial crybiopsies can be carried out safely in an ambulatory setting under moderate sedation. With a shorter freeze time and fewer samples, a reasonable diagnostic rate is still possible. There is drive towards standardisation of the transbronchial cryobiopsy procedure internationally. However, before any guidelines are determined, the true range of options available should be evaluated and this includes performing transbronchial cryobiopsy under moderate sedation without endotracheal intubation, general anaesthesia or endobronchial blockers.

REFERENCES

1. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165:277-304.
2. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J 2015;46:795-806.
3. Sheth JS, Belperio JA, Fishbein MC, Kazerooni EA, Lagstein A, Murray S, et al. Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. Chest 2017;151:389-99.
4. Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, et al. Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. Respiration 2016;91:215-27.

5. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. Am J Respir Crit Care Med 2016;193:1161-7.
6. Iftikhar IH, Alghothani L, Sardi A, Berkowitz D, Musani AI. Transbronchial lung cryobiopsy and video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse parenchymal lung disease. A meta-analysis of diagnostic test accuracy. Ann Am Thorac Soc 2017;14:1197-211.
7. Griff S, Ammenwerth W, Schonfeld N, Bauer TT, Mairinger T, Blum TG, et al. Morphometrical analysis of transbronchial cryobiopsies. Diagn Pathol 2011;6:53.
8. Colby TV, Tomassetti S, Cavazza A, Dubini A, Poletti V. Transbronchial cryobiopsy in diffuse lung disease: update for the pathologist. Arch Pathol Lab Med 2017;141:891-900.
9. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, et al. Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2016;193:745-52.
10. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.
11. National Cancer Institute NIoH, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. 2009. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed on 6 September 2017.
12. Bango-Alvarez A, Ariza-Prota M, Torres-Rivas H, Fernandez-Fernandez L, Prieto A, Sanchez I, et al. Transbronchial cryobiopsy in interstitial lung disease: experience in 106 cases – how to do it. ERJ Open Res 2017;3: pii 00148-2016.
13. Ravaglia C, Wells AU, Tomassetti S, Dubini A, Cavazza A, Piciucchi S, et al. Transbronchial lung cryobiopsy in diffuse parenchymal lung disease: comparison between biopsy from 1 segment and biopsy from 2 segments – diagnostic yield and complications. Respiration 2017;93:285-92.
14. Yarmus L, Akulian J, Gilbert C, Illei P, Shah P, Merlo C, et al. Cryoprobe transbronchial lung biopsy in patients after lung transplantation: a pilot safety study. Chest 2013;143:621-6.
15. Casoni GL, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, et al. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. PLoS One 2014;9:e86716.
16. Low SY, Koh MS, Ong TH, Phua GC, Anantham D. Use of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of granulomatous mediastinal lymphadenopathy. Ann Acad Med Singapore 2014;43:250-4.

Jane JX Lim, [1]*MBBS*, Angela Takano, [2]*MBBS, AMBD*, Devanand Anantham, [3]*MBBS, MRCP (UK), FAMS*

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2]Department of Pathology, Singapore General Hospital, Singapore
[3]Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore

Address for Correspondence: Asst/Prof Devanand Anantham, Department of Respiratory and Critical Care Medicine, Academia, Level 3, Singapore General Hospital, 20 College Road, Singapore 169856.
Email: anantham.devanand@singhealth.com.sg

Non-Pruritic Acral Rash in a Middle-Aged Male

A 56-year-old man presented with progressive rash on the face, hands and feet for over 6 months. He was treated with topical steroids cream and oral antihistamine pills, but no obvious improvement was achieved. His clinical history also included progressive hoarseness, stridor and a 10kg weight loss for 1 year. A diagnosis of primary squamous cell carcinoma (SCC) of the larynx was made a month before.

On physical examination, the patient had symmetrical desquamative, intensive violaceous erythema on the nose and cheek (Fig. 1) and in the helix and lobule of the ears (Fig. 2). His fingers were swollen and thickened with fine scales. The central palmarplantar skin was relatively spared. Prominent nail dystrophy, onycholysis, hyperkeratotic subungal debris and loss of cuticles were observed on all finger nails (Fig. 3). There was a 6 cm lump representing the cervical lymphadenopathy on the right neck. Skin biopsy from the right hand revealed non-specific findings including hyperkeratosis, acanthosis and slight dermal infiltration of lymphocytes. Laboratory tests including blood counts, liver function, chemistry panel and ANA (anti-nuclear antibody, antibodies against SS-A/Ro and SS-B/La) panel were unremarkable.

What is the likely diagnosis?

A. Acrokeratosis paraneoplastica
B. Dermatomyositis
C. Cutaneous lupus erythematosus
D. Hyperkeratotic eczema
E. Palmoplantar psoriasis

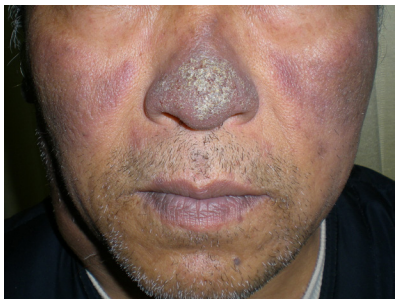

Fig. 1. Intensive violaceous erythema with scales and crust seen on the nose and cheek.

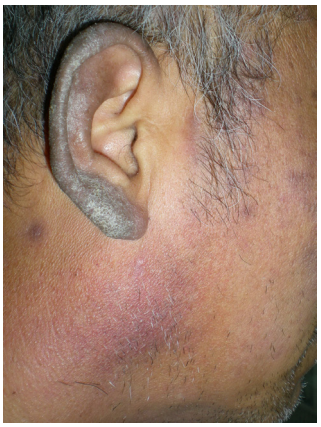

Fig. 2. Induration and violaceous erythematous swelling with scales on the right ear helix and lobule.

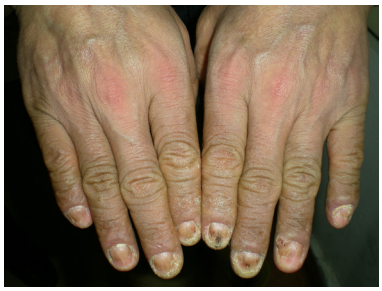

Fig. 3. Prominent nail dystrophy comprising yellow discolouration, vertical ridging and splitting, onycholysis, hyperkeratotic subungal debris and loss of cuticles.

Discussion

In the context of the patient's known malignancy, the typical clinical features and pathological finding were consistent with acrokeratosis paraneoplastica of Bazex.

Acrokeratosis paraneoplastica belongs to paraneoplastic skin diseases, and is most frequently associated with SCC—usually of the upper aerodigestive tract, and metastatic cervical lymphadenopathy.[1] Skin lesions tend to precede the tumour diagnosis by 1 year.[2] Symptomatic improvement can be achieved by effective treatment of the underlying tumour, and the relapse of skin lesions is associated with the recurrence of the tumour.[3] Our patient received systemic chemotherapy and palliative radiation therapy but died 6 months later.

Answer: A

Options B, C, D and E are possible differential diagnoses for the initial clinical presentation. The commonest skin signs of dermatomyositis are Gottron's papules/sign, heliotrope rash and nail fold telangiectasia. Histology usually demonstrates interface dermatitis.[4] These clinical and histological features were not identified in our patient. Moreover, he showed no muscle weakness and negative laboratory findings. Thus, dermatomyositis was excluded. Systemic lupus erythematosus (SLE) was ruled out because the patient had no symptoms of fever, oral ulcer, photosensitivity, joint pain and negative laboratory findings. Discoid lupus erythematosus (DLE) is another differential diagnosis. However, the lesions of DLE typically demonstrate atrophy, scarring, and areas of both hyperpigmentation and depigmentation. Besides, histological examination of DLE usually shows hydropic degeneration of the basal layer of the epidermis and patchy perivascular and periadnexal lymphoid inflammatory infiltrate. Clinically, the skin lesions of our patient were non-pruritic, progressively thickening (without improvement to topical steroids therapy) and atypically distributed on the ears and nasal tip which are not consistent with that of eczema or psoriasis. In contrast, prominent nail changes and unusual distribution of violaceous erythematous swelling with scales on the ear and nasal tip are the hallmark of acrokeratosis paraneoplastica.

Acrokeratosis paraneoplastica is rare and only a limited number of cases have been reported so far in the literature. A case is presented here to highlight that prompt recognition of acrokeratosis paraneoplastica may lead to the earlier detection and potential treatment of an underlying malignancy.

REFERENCES

1. Fleming JD, Stefanato CM, Attard NR. Bazex syndrome (acrokeratosis paraneoplastica). Clin Exp Dermatol 2014;39;955-6.
2. Rassler F, Goetze S, Elsner P. Acrokeratosis paraneoplastica (Bazex syndrome) – a systematic review on risk factors, diagnosis, prognosis and management. J Eur Acad Dermatol Venereol 2017;31;1119-36.
3. Humphrey SR, Hussain AS, Chandran R, Wilson B, George B. Acute onset of acrokeratosis paraneoplastica (Bazex syndrome). JAMA Dermatol 2015;151;677-8.
4. Liu WC, Ho M, Koh WP, Tan AW, Ng PP, Chua SH, et al. An 11-year review of dermatomyositis in Asian patients. Ann Acad Med Singapore 2010;39;843-7.

Zhouwei Wu,[1] *MD, PhD*

[1]Department of Dermatology, Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai, People's Republic of China

Address for Correspondence: Dr Wu Zhouwei, Department of Dermatology, Shanghai First People's Hospital, Shanghai Jiaotong University, No. 100 Road Haining, Shanghai 200080, People's Republic of China.
Email: 418950049@qq.com

ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Tel: +65 6593 7800 | Fax: +65 6593 7867 | E-mail: annals@ams.edu.sg | Homepage: http://www.annals.edu.sg