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"The path of sound credence is through the thick forest of skepticism."

George Jean Nathan (1882 – 1958)
American editor

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Editorial

Active Ageing to Gerotranscendence

Gabriel HZ Wong, [1], James Alvin YH Low, [1]*MBBS, FRCP*, Philip LK Yap, [1]*MBBS, MRCP*

Introduction

Ageing, old age and death have piqued the interest of philosophers and writers since antiquity. Confucius related ageing to maturity and wisdom,[1] while Shakespeare described it as a "second childhood".[2] Cicero, perhaps with premonitions of his own demise, viewed death with fondness in a metaphor, likening it to a ship approaching a harbour.[3]

Confronted by ageing demographics, Singapore has embraced "active ageing" like many developed countries. The World Health Organization (WHO) defines active ageing as "the process of optimising opportunities for health, participation and security in order to enhance quality of life".[4] This entails harnessing the elderly's instrumental value, while mitigating healthcare utilisation from chronic illnesses.

Limitations of Active Ageing

Cole and Johnson et al attributed current negative stereotypes about the elderly to the Victorian outlook that viewed midlife as the phase that determined an individual's salvation. This resulted in old age becoming evaluated on the standards of youth. Such a paradigm foreshadowed modern gerontology, which appraised the elderly on the midlife standards of autonomy, wealth and good health.[5,6]

Some aspects of active ageing may indirectly reinforce such mindsets by promoting traits associated with physical vitality, where an elderly person's worth is measured mainly by his or her physical capabilities. In reality, the human is complex and made up of highly interactive and connected "other" dimensions[7] as illustrated in the biopsychosocial model of ageing in Figure 1. This misrepresented view of ageing is further reinforced by celebrities who have been known to undergo plastic surgery or aesthetic treatments to maintain a youthful appearance necessary for their continued appeal.[8] Herein lies the slippery slope that could lead us from seeking active ageing to being anti-ageing. The latter connotes efforts to stop or reverse ageing as if it were a bane.

Inevitably, many elderly face age-related degenerative conditions that hamper their ability to partake in active ageing. Although individuals tend to link self-worth to gainful occupation and career success,[9] the truth remains that few can work until late life. Even for those who enjoy the good fortune of active ageing and employment, can it last forever?

Active Ageing to Embracing Ageing

For ageing to be all embracing, it needs to be destigmatised to allow society to better focus on elders' intrinsic worth beyond the utilitarian and instrumental. This must begin with acknowledgement and acceptance of their vulnerabilities. Acceptance helps lower ageing's "negative affect" by reducing the older person's anxiety, sadness or frustration over the loss of youthfulness.[10] The value of the elderly is intrinsic as exemplified by William Thomas' refrain, "elders are the glue that bind us together".[11]

Embracing ageing and ultimately death may help resolve Erickson's final stage of personality development in ego

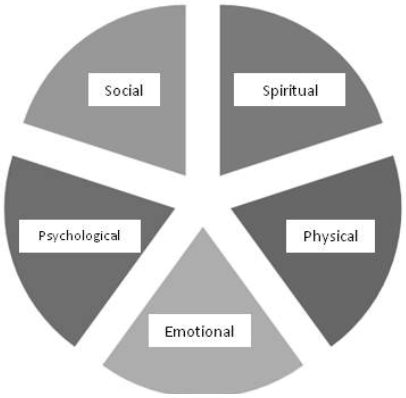

Fig. 1. The biopsychosocial model of ageing.

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integrity versus despair. Individuals who deem themselves to have lived successfully gain integrity, while those who fall short of expectation suffer from depression. Finding one's role in society and seeking answers to spirituality can engender the virtue of wisdom in the face of decline.[12]

Hence, instead of fostering youthful paradigms of active ageing in economic, physical or social terms, embracing ageing needs to focus on spiritual and philosophical dimensions.

Spirituality in Ageing

Old age may be characterised by increased spirituality (Fig. 2) as the elderly seek to make sense of the past, present and future. Spirituality, which provides meaning to existential issues, is a multidimensional construct rooted in relationships and involves bonding with the transcendent, self, others and environment.[13] Connectedness with others, fundamental to personhood, forms the essence of spirituality which in turn fosters contentment, peace and meaning.

Interestingly, a study by Hill et al showed the medical benefits of religiosity and spirituality in improving cognitive function,[14] perhaps because spirituality results in more active participation in communal activities. By offering answers to existential questions, spirituality may also reduce stress and even improve immunological function.[15] Importantly, spirituality, which focuses on well-being, guides medical care to preserve intactness and integrity of the human person.[16]

Unlike active ageing, whose pursuits may be out-of-reach for the frail, spirituality embraces the whole person and is relevant to all, even the chronically ill or disabled. Singapore's eldercare-related services can consider adding a spiritual dimension to their services, by establishing pastoral care services, chaplaincies or trained counsellors to provide comfort, counselling and spiritual care for those under their charge.

Gerotranscendence as an Eventuality

Gerotranscendence occurs as part of human growth when an individual living into old age views life from a different perspective—"from a materialistic and rational view of the world to a more cosmic and transcendent one, normally accompanied by an increase in life satisfaction."[17] As part of this transition, the elderly disengage from social roles and become more reflective. They acknowledge their inadequacies and accept the loss of independence.[18] Elderly who are gerotranscendent are less preoccupied with self. They are less concerned with the material and become more genuine as persons.[19] Liberated from societal expectations, the gerotranscendent elderly can rise above an active ageing mindset as they acquire a "cosmic" outlook on life and define reality according to their own terms.[20]

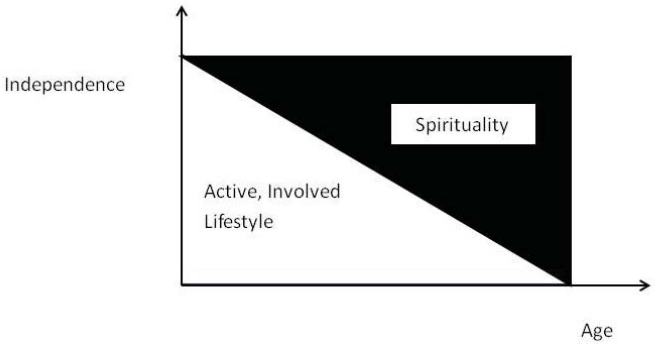

Fig. 2. Transition from active lifestyle towards spirituality.

Gerotranscendence can eventually lead to spiritual reminisce,[18] where the elderly undergo a critical evaluation of their lives to gain new insights from their past to help cope with the present and find meaning in the future. Hence, beyond the physical and material, gerotranscendence can help rechannel hope towards spiritual aspirations of inner fulfilment and anticipation of a good death. Such hope is essential to encourage the elderly to persevere through ageing's tribulations.

A concrete way to incorporate the spiritual dimension to ageing well can lie in initiating life-story reminiscence groups among seniors that gather regularly for programmes and activities, be they in day care centres, community clubs or religious settings. Spiritual reminiscence, infused in life-story work, helps the elderly find new meaning and hope in life by reframing life experiences, coming to a new understanding, acceptance and transcendence. A recent study of a 6-week spiritual reminiscence intervention evidenced positive outcomes in hope, life satisfaction, and well-being of elderly people even though they suffered from dementia.[21] Such efforts are already underway in Singapore[22] and can be implemented on a more systemic level with support from the government working through health and social care agencies.

Conclusion

Active ageing has its limits in the inevitable decline of an individual's physical and mental faculties, and the economic and social capital it exacts. Even the active elderly must transition towards acceptance and embracing of their eventual deterioration in health and ultimate mortality, and discover new hope and a reason to live.

The worth of a person is not to be judged by societal yardsticks, finding meaning in ageing, decline and loss is a personal choice. Unconstrained by external expectations, such choices express true autonomy.

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Original Article

Efficacy, Immunogenicity and Safety of a Human Rotavirus Vaccine RIX4414 in Singaporean Infants

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Abstract

Introduction: This was the first study conducted to evaluate the efficacy of 2 oral doses of the human rotavirus vaccine, RIX4414 in Singaporean infants during the first 3 years of life. Materials and Methods: Healthy infants, 11 to 17 weeks of age were enrolled in this randomised (1:1), double-blinded, placebo-controlled study to receive 2 oral doses of RIX4414 vaccine/placebo following a 0-, 1-month schedule. Vaccine efficacy against severe rotavirus (RV) gastroenteritis (Vesikari score ≥11) caused by wild-type RV strains from a period starting from 2 weeks post-Dose 2 until 2 and 3 years of age was calculated with 95% confidence interval (CI). Immunogenicity and safety of the vaccine were also assessed. Results: Of 6542 infants enrolled, 6466 were included in the efficacy analysis and a subset of 100 infants was included in the immunogenicity analysis. Fewer severe RV gastroenteritis episodes were reported in the RIX4414 group when compared to placebo at both 2 and 3 year follow-up periods. Vaccine efficacy against severe RV gastroenteritis at the respective time points were 93.8% (95% CI, 59.9 to 99.9) and 95.2% (95% CI, 70.5 to 99.9). One to 2 months post-Dose 2 of RIX4414, 97.5% (95% CI, 86.8 to 99.9) of infants seroconverted for anti-RV IgA antibodies. The number of serious adverse events recorded from Dose 1 until 3 years of age was similar in both groups. Conclusion: Two oral doses of RIX4414 vaccine was immunogenic and provided high level of protection against severe RV gastroenteritis in Singaporean children, during the first 3 years of life when the disease burden is highest.

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Key words: Diarrhoea, G and P types, Gastroenteritis, Intussusception

Introduction

Worldwide, rotavirus (RV) is the most common cause of severe dehydrating gastroenteritis (GE) among infants and young children aged 6 to 24 months.[1] RV disease causes significant morbidity and mortality;[2] in 2008, an estimated 453,000 children younger than 5 years of age died from RV diarrhoea, accounting for 37% of the 1.24 million diarrhoeal child deaths in this age group.[3] Further, 25% to 50% of diarrhoeal hospitalisations in both developed and developing nations and 23 million clinic visits in young children annually are due to RV diarrhoea.[4]

The consequences of infection due to RV vary depending on the healthcare facilities accessible to the population and the socioeconomic factors, which is apparent in Asian countries having diverse population and economies. According to the Asian Rotavirus Surveillance Network conducted across 9 Asian countries, RV was detected in 28% to 59% of hospitalised GE cases in children less than 5 years of age.[5] The high rate of hospitalisation due to RVGE has an enormous influence on healthcare costs and places a considerable burden on medical care services.[6]

Global surveillance studies have shown repeatedly that

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RV infects nearly all young children in both developed and developing countries.[7] Similar incidence rate of RV disease in diverse sanitary settings, despite the improvements in hygiene and water quality, further highlights the fact that vaccination is likely to be the most effective strategy that will aid in the reduction of RV disease burden worldwide.[5,8]

In an effort to reduce the global RV disease burden, an oral live attenuated human RV vaccine RIX4414 (Rotarix™, GlaxoSmithKline Vaccines, Belgium) was developed from the 89-12 candidate (cloned passage 43) containing the G1[P8] RV strain.[9-11] The lyophilised formulation of RIX4414 vaccine is currently licensed in over 100 countries. Phase III trials conducted across Europe and Latin America have demonstrated this vaccine to be well tolerated and efficacious in the first 2 years of life.[12,13]

This Phase III, multicentre study was conducted in high income countries of Asia, namely Singapore, Hong Kong and Taiwan to evaluate the efficacy, immunogenicity and safety of RIX4414 vaccine until 3 years of age. This paper presents the results of the Singapore cohort, while the overall study results of the Year 2 and 3 efficacy data are presented elsewhere.[14,15]

Materials and Methods

Study Design and Subjects

This multicentre, randomised, double-blind, placebo-controlled study was conducted in Singapore (NCT00329745). The study was conducted in accordance with Good Clinical Practice and adhered to all applicable local regulatory requirements including the Declaration of Helsinki. The study protocol and the consent forms were reviewed and approved by the ethics committee of the respective study centres and written informed consent was obtained from parents/guardians of all infants before any study procedures were initiated.

Healthy infants aged 11 to 17 weeks (at the time of Dose 1) were enrolled and randomised (1:1) into 2 treatment groups and subsequently received 2 oral doses of the RIX4414 vaccine or placebo following a 0-, 1-month schedule in Singapore. According to the current immunisation schedule in Singapore, 2 oral doses of RIX4414 are administered to children between 6 to 24 weeks of age with a minimum interval of 4 weeks between doses.[16] The routine vaccinations i.e. combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b (DTPa-IPV-Hib) vaccine was administered concomitantly with each RIX4414 vaccine/placebo dose. Administration of hepatitis B vaccine (HBV) and Bacille Calmette-Guérin (BCG) vaccine followed the national immunisation schedule of Singapore. Infants were excluded from the study if they had received any investigational drug/vaccine other than the study vaccine 30 days before Dose 1, had a history of allergy to any of the vaccine components or had immunosuppressive conditions. They were also excluded if they had a history of any clinically significant chronic gastrointestinal disease.

Study Vaccine

The RV vaccine, RIX4414 (Rotarix™), placebo and calcium carbonate buffer were manufactured by GlaxoSmithKline Vaccines, Rixensart, Belgium. One dose of RIX4414 vaccine contained not less than 106.0 median cell culture infective dose (CCID50) of live attenuated RIX4414 human RV strain. The composition of placebo was similar to that of the RIX4414 vaccine but without the vaccine strain. The lyophilised vaccine and placebo were reconstituted with the liquid calcium carbonate buffer prior to oral administration.

Assessment of Efficacy

The surveillance of GE episodes requiring overnight hospitalisation and/or rehydration therapy (equivalent to the World Health Organisation (WHO) Plan B or C) in a medical facility was carried out during the entire study period from Dose 1 until 3 years of age. Parents/guardians used diary cards to record GE episodes up to 2 days after the diarrhoea and vomiting had settled. If there were more than 5 symptom-free days between 2 occurrences of GE, parents/guardians were advised to consider these as 2 different episodes.

A GE episode was defined as occurrence of diarrhoea with or without vomiting. The severity of GE episodes was assessed using a 20-point Vesikari scale, where a score of ≥11 points was considered severe.[17] GE stool samples were collected preferably within 7 days of onset, during each GE episode. Collected stool samples were tested for the presence of RV using enzyme-linked immunosorbent assay (ELISA; Rotaclone™, Meridian Bioscience, USA) at GlaxoSmithKline Biologicals laboratories in Rixensart, Belgium. Furthermore, all RV-positive stool samples were tested by reverse transcriptase polymerase chain reaction (RT-PCR) followed by reverse hybridisation, to determine the G and P types at Delft Diagnostic Laboratory (DDL, The Netherlands).[18]

Assessment of Immunogenicity

The eligible infants were invited to participate in the immunogenicity subset and the first 100 infants (50 each in RIX4414 and placebo groups) with parental consent were part of the subset for immunogenicity. Blood was drawn at prevaccination and 1 to 2 months post-Dose 2, and tested

for anti-RV IgA antibody concentrations using an in-house ELISA test adapted from the assay developed by Prof RL Ward.[19] The assay cutoff was 20 units/millilitre (U/mL). A seropositive infant was defined as an infant whose IgA antibody concentration was ≥20 U/mL.

Assessment of Safety

Safety of the study vaccine was assessed in terms of serious adverse events (SAEs) including intussusception (IS), Kawasaki disease and fatal events starting from Dose 1 until 2 years of age. While safety was not an endpoint during the follow-up period between Year 2 and Year 3, investigators were asked to report any SAEs that were considered to be unusual or vaccine-related during this period.

Statistical Analyses

For the efficacy analysis (according-to-protocol [ATP] efficacy cohort), only wild-type RV (i.e. other than the vaccine strain) that were identified in an episode of GE requiring hospitalisation and/or rehydration therapy (equivalent to WHO Plan B or C) in a medical facility was considered. The ATP efficacy cohort included infants who had received 2 doses of RIX4414 vaccine/placebo, who had entered the efficacy follow-up periods and who had no RV other than the vaccine strain in their GE stool samples. The percentage reduction in the frequency of RVGE episodes in vaccinated infants when compared to the infants who received placebo was defined as vaccine efficacy (VE). VE was calculated using the formula (1 minus incidence of RVGE in the vaccine group/incidence of RVGE in the placebo group) with 95% confidence interval (CI). Efficacy analysis was performed from 2 weeks post-Dose 2 of RIX4414/placebo until 2 years of age (combined 2 year follow-up) and also from 2 weeks post-Dose 2 until 3 years of age (combined 3 year follow-up). VE against severe RVGE caused by circulating wild-type RV strains was calculated for the combined 2- and 3-year efficacy follow-up period.

For the immunogenicity analysis, the ATP immunogenicity cohort was considered. The ATP immunogenicity cohort comprised of infants who had complied with the protocol and for whom immunogenicity data were available at both prevaccination and 1 to 2 months post-Dose 2. One to 2 months post-Dose 2 of RIX4414 vaccine/placebo, the anti-RV IgA antibody seroconversion rate (anti-RV IgA antibody concentration ≥20 U/mL in infants previously seronegative) and geometric mean concentrations (GMCs) were tabulated with exact 95% CI.

Safety analysis was performed on total vaccinated cohort (TVC) which included all infants who had received at least 1 dose of RIX4414 vaccine/placebo. All statistical analyses were performed using SAS version 8.2 and 95% CI was calculated using Proc StatXact-5.

Results

Demographic Characteristics

A total of 6542 infants were enrolled between December 2003 and August 2005 to receive 2 doses of either the RIX4414 vaccine (n = 3274) or the placebo (n = 3268). The ATP cohort for efficacy included 6466 infants (3237 infants in the RIX4414 and 3229 infants in the placebo group) at 2 and 3 years of age (Fig. 1). Of these, a subset of 100 infants was included in the immunogenicity analysis.

The mean age of vaccinated infants at the time of Dose

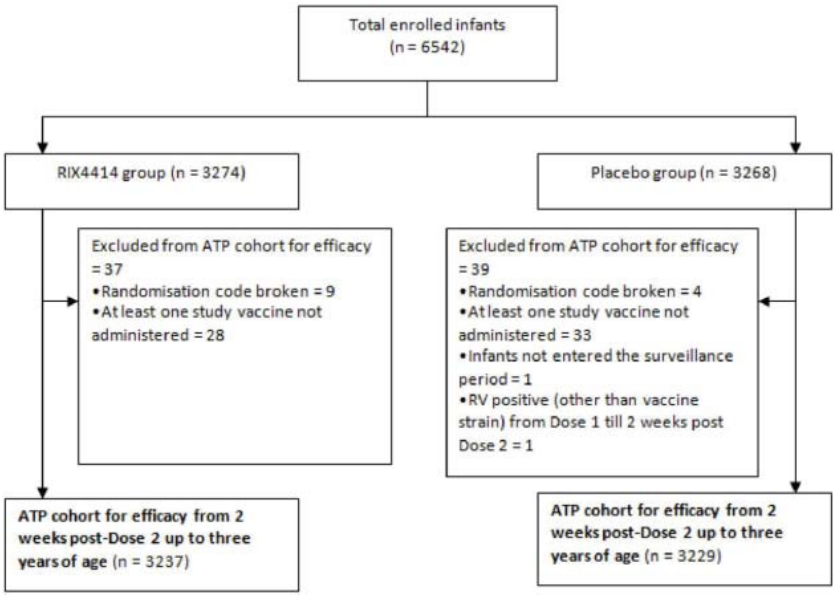

Fig. 1. Consort flowchart.
ATP: According-to-protocol; RV: Rotavirus.

1 of vaccine/placebo was 13.3 ± 0.86 weeks and 18.3 ± 1.29 weeks at Dose 2 of RIX4414 vaccine/placebo (TVC). The main race categories were Chinese (62.5%), Malay (27.9%) and Indian (7.6%). The ratio of females (50.3%) and males (49.7%) was similar in both groups. For the majority (>99%) of infants, DTPa-IPV-Hib vaccine was co-administered with both the doses of RIX4414 vaccine/placebo (Table 1).

Table 1. Co-administered Vaccines

Co-administered Vaccination at Dose 1 of RIX4414 Vaccine/Placebo			
Categories	**RIX4414 n* = 3274 n (%)†**	**Placebo n* = 3268 n (%)†**	**Total n* = 6542 n (%)†**
Any	3270 (99.9)	3261 (99.8)	6531 (99.8)
BCG	0 (0.0)	1 (0.0)	1 (0.0)
DTPa + HBV + HIB + IPV	1 (0.0)	1 (0.0)	2 (0.0)
DTPa + IPV + HIB	3268 (99.8)	3259 (99.7)	6527 (99.8)
HBV	13 (0.4)	10 (0.3)	23 (0.4)
Co-administered Vaccination at Dose 2 of RIX4414 Vaccine/Placebo			
Categories	**RIX4414 n = 3246* n (%)†**	**Placebo n = 3235* n (%)†**	**Total n = 6481* n (%)†**
Any	3246 (100)	3229 (99.8)	6475 (99.9)
DTPa + HBV	1 (0.0)	0 (0.0)	1 (0.0)
DTPa + HBV + HIB + IPV	1 (0.0)	0 (0.0)	1 (0.0)
DTPa + IPV + HIB	3244 (99.9)	3229 (99.8)	6473 (99.9)
HBV	1 (0.0)	1 (0.0)	2 (0.0)

*Total number of infants having received the considered dose of RIX4414 vaccine/placebo.

†Number/percentage of infants who received the specified vaccination on the same day as the considered dose of RIX4414 vaccine/placebo.

Vaccine Efficacy

From 2 weeks post-Dose 2 until 2 years of age, VE against severe RVGE was 93.8% (95% CI, 59.9 to 99.9) in the RIX4414 group (Table 2). Similarly, during the follow-up period from 2 weeks post-Dose 2 until 3 years of age, VE against severe RVGE was 95.2% (95% CI, 70.5 to 99.9) in the RIX4414 group (Table 2).

The RV types isolated from severe RVGE episodes during the period from 2 weeks post-Dose 2 until 3 years of age were G1P[8], G2P[4], G3P[8] and G9P[8] in the placebo group vs G9P[8] in the RIX4414 group. There was no presence of vaccine virus and wild-type G1P[8] isolated from the severe RVGE stool samples in the RIX4414 group (Table 3).

Immunogenicity

All initially seropositive infants and infants with unknown seropositivity status at prevaccination were eliminated from both groups for the purpose of ATP immunogenicity analysis. Therefore, all infants included in the ATP immunogenicity cohort were seronegative for RV at prevaccination in the RIX4414 and placebo groups. The percentage of infants with anti-RV IgA antibody concentration ≥20 U/mL 1 to 2 months post-Dose 2 was 97.5% (95% CI, 86.8 to 99.9) in the RIX4414 (n = 40) and 2.2% (95% CI, 0.1 to 11.5) in the placebo groups (n = 46). The observed GMCs in all infants 1 to 2 months post-Dose 2 were 368.5 U/mL (95% CI, 231.0 to 588.0) and <20 U/mL in the RIX4414 (n = 40) and placebo groups (n = 46), respectively. The serum anti-RV IgA GMCs calculated on seropositive infants were 404.3 U/mL in the RIX4414 group (n = 39) and 119.0 U/mL in the placebo group (n = 1).

Safety

During the combined 2-year follow-up period, at least 1 SAE was recorded in 429 infants in the RIX4414 group and 466 infants in the placebo group. The most frequently

Table 2. Vaccine Efficacy against Severe Rotavirus Gastroenteritis Caused by Circulating Wild-type Rotavirus Strains From 2 Weeks Post-Dose 2 Up To 2 Years and 3 Years of Age (ATP Cohort for Efficacy)

Follow-up	**Group**	**n***	**n**	**%† (95% CI§)**	**Vaccine Efficacy % (95% CI§)**	***P* Value‡**
Year 2	RIX4414	3237	1	0 (0 – 0.2)	93.8 (59.9 – 99.9)	<0.001
	Placebo	3229	16	0.5 (0.3 – 0.8)	-	-
Year 3	RIX4414	3237	1	0 (0 – 0.2)	95.2 (70.5 – 99.9)	<0.001
	Placebo	3229	21	0.7 (0.4 – 1)	-	-

*Number of infants included in each group.

†Number/percentage of infants reporting at least one severe rotavirus gastroenteritis episode.

‡Two-sided Fisher's exact test (significant level of $\alpha = 0.05$).

§Exact 95% confidence interval.

Table 3. Number of Severe Rotavirus Gastroenteritis Episodes Reported during the 3-year Efficacy Follow-up by G and P Types (ATP Cohort for Efficacy)

Type	RIX4414 n = 1*		Placebo n = 21*	
	n	%†	n	%†
Any	1	100	21	100
G1WT + P8WT	0	0.00	10	47.62
G2 + P4	0	0.00	2	9.52
G3 + P8WT	0	0.00	5	23.81
G9	0	0.00	1	4.76
G9 + P8WT	1	100	3	14.29

*Number of severe rotavirus gastroenteritis episodes.
†Number/percentage of severe rotavirus gastroenteritis episodes, by type.
WT: Wild-type

recorded SAEs were bronchiolitis (96 infants in the RIX4414 group and 119 infants in the placebo group) followed by GE (37 infants in the RIX4414 group and 50 infants in the placebo group). Four vaccine-related SAEs were reported—1 SAE (GE; placebo group) reported post-Dose 1, while 3 SAEs (RVGE [placebo group], urticaria [RIX4414 group] and viral GE [RIX4414 group]) were reported post-Dose 2.

There were reports of 3 fatal SAEs (all in placebo group): aspiration and metabolic disorder (1), adenoviral pneumonia (1) and interstitial lung disease (1). None of these fatal SAEs was assessed as causally related to vaccination by the investigator.

Definite IS cases were reported after Dose 2 in 3 male infants (1 in the RIX4414 group and 2 in the placebo group) during the combined 2-year follow-up period and 1 IS case (RIX4414 group) was reported between Year 2 and Year 3. All IS cases resolved and were assessed as not related to vaccination. The IS cases were reported during the 31-day follow-up period after each vaccine/placebo dose.

Kawasaki disease was recorded in 8 infants in the RIX4414 and 4 infants in the placebo groups during the combined 2-year follow-up period; all these cases occurred after the second vaccine/placebo doses. However, no Kawasaki disease was reported during the time period between Year 2 and Year 3.

Discussion

This was the first study in Singapore where the efficacy of the RV vaccine against severe RVGE was demonstrated during the first 3 years of life of children, when the disease burden is at its highest.[1] The present study showed that in the Singaporean setting, 2 doses of the live attenuated RV vaccine (RIX4414) afforded high level of protection against severe RVGE until 2 (VE = 93.8%) and 3 years of age (VE = 95.2%). These results were comparable to VE results observed in a 2-year efficacy study conducted in Europe (VE = 90.4%) but higher than that observed in Latin America (VE = 80.5%).[12,13] These efficacy results are also in line with the overall Asian multicountry results.[14,15]

RV remains the viral agent primarily responsible for acute GE among children less than 5 years of age in Singapore. In this study, a protective efficacy of 93.8% against severe RVGE in the first 2 years of life suggested that RV vaccination programmes are important and they may have potential public health impact in reducing the RV disease burden. Although the efficacy demonstrated by RIX4414 vaccine is clearly suggestive of the high level of protection yielded by the vaccine, these results may not be generalised to the whole Asian population since Asia comprises not only of high income countries like Singapore but also several impoverished low income countries. In addition to high VE of RIX4414 vaccine, the anti-RV IgA seroconversion rate observed was also high (97.5%) 1 to 2 months post-Dose 2 which were similar to results obtained in an earlier Singaporean study.[6,20]

Safety data have revealed that there was no evidence for a clinically significant difference between the RIX4414 vaccine group and the placebo group for SAEs reported from Dose 1 until 3 years of age. There were 4 cases of IS reported during this study. Epidemiological studies in Singapore over an 8-year period has indicated an IS incidence rate of 60 per 100,000 and 32 per 100,000 in <1-year-old children and <2-year-old children, respectively.[21] Furthermore, evidence from a large safety study conducted in Latin America and Finland with 63,225 infants, indicated that the RIX4414 vaccine was not associated with an increased risk of IS.[22] Keeping the background IS rate in perspective, the RV vaccine used in this study was not associated with an increased risk of IS compared to the placebo in Singaporean infants.

Due to the potential association of RV vaccination and Kawasaki disease, the Global Advisory Committee on Vaccine Safety recommended the monitoring of Kawasaki disease in all the RV vaccine trials. Although there have been no reports of Kawasaki disease in the European Union after the administration of 12 million doses of the RIX4414 vaccine, Kawasaki disease is still monitored in all ongoing trials.[23] In this study, the incidence of Kawasaki disease reported was similar in both the RIX4414 and placebo groups, with no causal association to vaccination.

A limitation of our study was that it was only powered to observe a significant difference in the incidence of severe RVGE for the pooled countries included in the study and not for individual countries. Moreover, it is possible that a

small proportion of RV infections may have gone undetected given that the sensitivity of the assay used in this study was recently reported to have 76.8% sensitivity compared to 100% sensitivity reported by the manufacturer.[24]

While improvements in sanitary conditions and hygienic practises have indeed rendered extraordinary public health benefits in Asian countries, these steps seem to have very little effect on the incidence of RV disease. Effective immunisation early in life of infants that can offer sustained protection against severe RVGE may aid in curbing the disease burden in this region.

Conclusion

This study conducted in Singapore demonstrated that the 2 oral doses of RIX4414 vaccine was immunogenic, safe and provided high protection against severe RVGE during the first 3 years of life. Given its high efficacy, this RV vaccine can be expected to have a considerable public health impact in high income Asian countries by reducing the RV disease burden and in turn hospitalisation due to GE.

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Conflict of Interest

The authors declare the following conflict of interest: PV Suryakiran and Htay Htay Han are employees of GlaxoSmithKline (GSK) group of companies. Hans L Bock and Yee Leong Teoh were employees of GlaxoSmithKline Group of companies at the time of protocol conception, study conduct and manuscript initiation and held shares of GSK. Yee Leong Teoh was employed at the National Healthcare Group Polyclinics, and was an investigator on this study. However, at the time of the ending of the studies and during manuscript preparation, he was employed by the GlaxoSmithKline group of companies. The other authors have no conflict of interest to declare.

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Original Article

Survival Prognostication in Patients with Skeletal Metastases from Nasopharyngeal Carcinoma: An Evaluation of the Scandinavian Sarcoma Group, Katagiri and Bauer Scoring Systems

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Abstract

Introduction: Nasopharnygeal carcinoma (NPC) is characterised by early metastases with the skeleton being the most common site of metastases. The ability to prognosticate survival is crucial in the decision whether or not to offer surgery to these patients and the choice of surgery offered. We aimed to evaluate the scoring systems namely: Bauer, Katagiri and Scandinavian Sarcoma Group (SSG) in NPC patients with skeletal metastases. Materials and Methods: A total of 92 patients with skeletal metastases from NPC were studied. We retrospectively analysed the actual survival of these patients and compared with predicted survival according to the 3 scoring systems. The predicted survival according to each system was calculated and labelled as A scores. These were then re-scored by assigning NPC as a better prognostic tumour and labelled as B scores. The predicted survival of scores A and B were compared to actual survival. Univariate and multivariate Cox regression analyses were performed. The predictive values of each scoring were calculated. Results: The median overall survival for the whole cohort was 13 months (range: 1 to 120 months). In multivariate analysis, general condition and visceral metastases showed significant effect on survival. There were statistically significant differences (P <0.001) between the subgroups of the SSG B as well as Katagiri B scoring systems where NPC was classified as a better prognostic tumour. SSG B provided the highest predictive value (0.67) as compared to the other 2 scoring systems. Conclusion: The SSG and Katagiri score could be used to prognosticate NPC with a statistically significant association with actual survival.

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Key words: Bone metastases, Nasopharyngeal cancer, Survival Prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is a cancer characterised by marked geographical differences in distribution; it is endemic in Southern China and Southeast Asia. Chinese people living in areas of Southern China (including Hong Kong) have a higher incidence of NPC compared with Chinese migrants living overseas.[1] In Hong Kong, NPC is the fourth most common malignancy and in Singapore, it is the eighth most common cancer among males.[2] Despite the low incidence of NPC in Europe and the United States (US),[3,4] when high risk or intermediate risk persons migrate to lower risk countries, their incidence of NPC remains much higher than those of other races.[1] Among Chinese immigrants to the US, the incidence of NPC is as high as 9.9 per 100,000 population which is comparable to 12.8 per 100,000 population in Singapore.[5]

NPC is reported to have a high incidence of early metastases, with metastases being present in 11% of patients at diagnosis. The skeleton is the most common site of metastases in 70% to 80% of NPC patients.[6] Skeletal metastases can present with intractable pain, pathological fractures and/or paralysis in the spinal metastases.[7] The survival of patients with skeletal metastases has improved due to better oncological treatments; predisposing patients to increased risk of skeletal-related complications. Surgery is an important modality of treatment for addressing skeletal-related complications. The decision regarding choice of treatment especially surgery in patients with skeletal

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metastases is influenced by estimated patient survival.[8,9]

There have been several prognostic systems developed for the prognostication of patients with skeletal metastases; these include the scoring systems of Bauer,[10] Katagiri[11] and the Scandinavian Sarcoma Group (SSG).[12] The Bauer score and its modification have been validated in the prognostication of metastatic disease to the spine,[13] while the Katagiri score has also been validated in patients with bone metastases to the proximal femur.[14] The SSG score was developed based on a retrospective study of 1195 surgically treated patients with skeletal metastases and an analysis of prognostic factors suggested by other prognostic scores.[12] It is suggested to be a reliable and simple prognostic tool; however its use has not been validated before. We note that none of these scoring systems have been validated in NPC and that NPC is not included as a site of primary tumour in all of these systems. We hereby aim to determine reliability of the above scoring systems in predicting survival by categorising NPC as both a better or worse prognostic factor. We also aim to investigate the prognostic factors for survival in NPC patients with skeletal metastases based on the findings in our cohort.

Materials and Methods

Patients and Data Collection

We retrospectively analysed all patients, with histologically proven NPC, who were treated in our institution. A total of 814 patients with NPC were identified between January 2007 to December 2011 by searching the hospital electronic records. A total of 92 patients were diagnosed with skeletal metastases. Retrospective data collection began on 1 July 2013 which ensured all patients had been followed up till death or at least 1 year. This study was approved by an institutional ethics review board. Diagnosis of skeletal metastases was made radiologically by one or more of the following modalities: magnetic resonance imaging (MRI), computed tomography (CT) and bone scan. In operated cases, bone biopsies for histological diagnosis were also taken. Patient data were collected for the demographic characteristics, tumour histology, general and specific clinical findings in relationship to the primary tumour and skeletal metastases. These specific findings included the general condition in terms of Karnofsky's performance score (KPS) and Eastern Cooperative Oncology Group (ECOG) score, number of skeletal metastases, number of visceral metastases, presence or absence of pathological fractures, as well as type of treatment received, i.e. either chemotherapy received or not. Some or all of these factors mentioned above are included in the various scoring systems, which we planned to study. Data required for scoring patient prognosis was available for all the patients on review of electronic records or case notes and no telephone interview/call backs were needed. On the basis of these findings, we retrospectively calculated the Bauer,[10] Katagiri[11] and SSG survival score[12] of these patients. The scores were calculated by the first and second authors of the paper independently with the patients' identity and actual survival blinded. Neither of these authors has been directly involved in patient care. If the scores calculated for a patient were different, the patient was re-evaluated by the 2 authors and the consensus score was used. We also analysed the influence of age, sex, race, and the above mentioned specific findings on survival. The survival period was calculated from the date of diagnosis of the skeletal metastases until death or end of the study period.

Survival Score Calculation

Scandanavian Sarcoma Group (SSG) Score

The SSG score (Supplementary Table 1) is based on 4 prognostic factors: number of skeletal metastases, presence of organ metastases, Karnofsky score and type of primary tumour. A better prognostic score is given to the following primary tumours: breast, kidney, thyroid, lymphoma and myeloma. Therefore, NPC scored worse in this category and the overall score obtained was labelled as SSG A. We then re-scored the patients by assigning NPC as a positive prognostic factor and labelled the score obtained as SSG B. The SSG divides patients into 3 scoring subgroups, with a score of 4-3, 2-1 and 0 respectively and an estimated survival of more than 6 months, 3 to 6 months and less than 3 months respectively.

Katagiri Score

In the Katagiri scoring system (Supplementary Table 2), patients are scored according to the following prognostic factors: primary tumour, presence of visceral/cerebral metastases, ECOG performance status, previous chemotherapy and presence of multiple skeletal metastases. Primary tumours are divided based on speed of growth into slow growth, moderate growth and fast growth tumours. NPC is not directly included in this scoring system, therefore, we included it in the category of primary tumour labelled as "moderate growth (other carcinoma/sarcoma)". The overall score was labelled as Katagiri A. We then re-scored the patients by assigning NPC as a slow growth tumour (better prognostic tumour) and labelled this score Katagiri B. In the Katagiri score, patients are divided into 3 scoring subgroups: 0-2, 3-5, and 6-8. The survival rate for patients in each subgroup is 0.98, 0.71, and 0.31 respectively at 6 months, and 0.89, 0.49, and 0.11, respectively at 12 months.

Bauer Score

In the Bauer score (Supplementary Table 3), patients are

scored according to the following 5 positive prognostic factors: absence of visceral metastases, and absence of pathological fracture, solitary skeletal metastases, not primary lung cancer and the presence of the following primary tumours, breast, kidney, lymphoma and myeloma. Therefore, NPC scores lower as it does not fall in Bauer scoring system. We scored the patient's based on the original Bauer score and labelled this score Bauer A. Afterwhich, we proceeded to re-score the patients by including NPC in the primary tumour group, giving it a better prognostic score and labelling this score as Bauer B. Patients can be categorised into 3 scoring subgroups: patients with a score of 4-5 having 1-year survival rate of 0.5, patients with a score of 2-3 having a 1-year survival rate of 0.25 and patients with a score of 0-1 died within 6 months of surgery.

Statistical Analysis

Survival analysis was performed with Stata Statistical software version 12. Univariate and multivariate Cox regression analyses were performed to evaluate the prognostic values of each demographic and clinical parameter on survival. Cox regression analyses, Kaplan-Meier survival estimates and log rank tests were completed for all scoring systems (A and B). Predictive values of each scoring system were measured by building receiver operating characteristics (ROC) curves using postestimation commands after Cox regression analyses. Comparison of AUCs for each scoring systems (A and B) were made using "c" statistics. Likelihood ratio test Bayesian information criterion (BIC) was also applied to compare the scoring systems in predicting survival. *P* value of less than 0.05 was considered to be statistically significant for all analyses.

Results

Our study population included a total of 92 patients in the final analysis. Table 1 demonstrates the details of patients' demographic characteristics, and clinical parameters that have potential impact on survival. Of note is the preponderance of male and Chinese patients as well as the good general condition of the patients in terms of Karnofsky score and ECOG score. In this cohort of patients, 82 patients had multiple skeletal metastases at diagnosis.

In our study, 87 (95%) patients had spinal metastases, 71 (77%) had axial metastases (skull and pelvis) and 36 (39%) had appendicular metastases. Of these patients, 8/87 of the patients with spinal metastases required surgical treatment for either cord compression or instability and 28/87 of these patients required palliative radiotherapy for pain due to spinal metastases. Only 2 of the patients with axial metastases required acetabular reconstruction for acetabular metastases and only 1 patient required open reduction internal fixation of the femur with an intramedullary device for a pathological femur fracture.

Table 1. Demographic Characteristics and Clinical Features of the Study Patients

		Frequency	Percentage
Age	Median – 52 (range: 26-90)		
Gender	Male	73	79
	Female	19	21
Race	Chinese	77	84
	Non-Chinese (Malay & others)	15	16
General condition (KPS)	<70	28	30
	≥70	64	70
General condition (ECOG)	3-4	28	30
	0-2	64	70
No. of skeletal metastases	Single	10	11
	Multiple	82	89
Visceral metastases	Absent	32	35
	Present	60	65
Pathological fracture	No	67	73
	Yes	25	27
Chemotherapy	No	60	65
	Yes	32	35

KPS: Karnofsky performance scale; ECOG: Eastern Cooperative Oncology Group

Table 2 demonstrates the number of patients alive or dead for subgroup in each of the 3 scoring systems. As for evaluation of independent significant prognostic factors, the univariate analysis revealed that general condition (either KPS or ECOG) and the presence of visceral metastasis have a statistically significant effect on survival. There was colinearity between KPS and ECOG, and hence KPS was omitted in the multivariate model. In multivariate analysis, adjusting for variables, which were significant in univariate analysis, all the same parameters were found to be significant, independent prognostic factors. The highest hazard ratio (6.37, 95% CI , 3.32 to 12.18) was found in ECOG performance status scale category of 3-4. This shows that the patients with ECOG score of 3 or 4 were 6.37 times more likely to die in a year from diagnosis than those with more favourable score of 0-2. Regarding visceral metastases, the hazard ratio was 3.04 in the group with visceral metastases. This reveals that patients who had visceral metastases were 3.04 times more likely to die in a year from diagnosis than those without visceral metastases. The prognostic values of specific parameters according to the univariate and multivariate Cox regression analyses are presented in Table 3.

Table 2. Patients' Survival in Each Scoring System Subgroup at the End of the Study

Scoring System	No. of Patients Alive (%)	No. of Patients Dead (%)	Scoring System	No. of Patients Alive (%)	No. of Patients Dead (%)
SSG A			SSG B		
Score 3-4	1 (33%)	2 (67%)	Score 3-4	20 (63%)	12 (37%)
Score 1-2	33 (49%)	35 (51%)	Score 1-2	17 (29%)	41 (71%)
Score 0	3 (16%)	16 (84%)	Score 0	-	-
Katagiri A			Katagiri B		
Score 0-2	1 (20%)	4 (80%)	Score 0-2	21 (55%)	17 (45%)
Score 3-5	26 (50%)	26 (50%)	Score 3-5	16 (31%)	36 (69%)
Score 6-8	10 (30%)	23 (70%)	Score 6-8	-	-
Bauer A			Bauer B		
Score 4-5	5 (71%)	2 (29%)	Score 4-5	15 (48%)	16 (52%)
Score 2-3	29 (40%)	43 (60%)	Score 2-3	22 (37%)	37 (63%)
Score 0-1	3 (27%)	8 (73%)	Score 0-1	-	-

SSG: Scandinavian Sarcoma Group

Actual Survival Time and Total Scores

The median overall survival time was 13 months (range: 1 to 120 months) from diagnosis of skeletal metastases. At the time of analysis, 15 (16%) patients had survived less than 3 months, 12 (13%) patients had survived 36 months and 65 (71%) patients had survived more than 6 months. The actual and predicted survivals of 3 scoring systems are presented in Table 4.

I. Scandinavian Sarcoma Group (SSG) Score

In this scoring system (Supplementary Table 1), a higher score provides a more favourable prognosis. The median SSG A score was 1 (range: 0-4) while the median SSG score B was 2 (range: 1-4). In SSG A score, 21 (23%) patients had a score of 0, while 68 (74%) patients had a score of 1-2 and 3 (3%) patients had a score of 3-4. In SSG B score, 61

Table 3. Univariate and Multivariate Analyses of Prognostic Value of Demographic and Clinical Parameters

Prognostic Factors	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
General condition (KPS)						
<70 (reference†)	1	-	-			
≥70	0.15	0.08 – 0.29	<0.001*			
General condition (ECOG)						
0 – 2 (reference†)	1	-	-	1	-	-
3 – 4	6.31	3.36 – 11.83	<0.001*	6.37	3.32 – 12.18	<0.001*
No. of skeletal metastases						
Single (reference†)	1	-	-			
Multiple	0.84	0.36 – 1.98	0.69			
Visceral Metastases						
Absent (reference†)	1	-	-	1	-	-
Present	3.09	1.58 – 6.02	0.001*	3.04	1.54 – 5.98	0.001*
Pathological fracture	0.89	0.49 – 1.62	0.7			
Chemotherapy	1.66	0.93 – 2.97	0.08			
Age	0.99	0.97 – 1.02	0.96			
Sex	1.17	0.55 – 2.50	0.67			
Race	1.11	0.61 – 2.03	0.72			

CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky performance scale
*Significant *P* value <0.05.
†Refers to baseline to which the other respective categories are compared.

Table 4. Actual and Predicted Survival of the Patients

Scoring System	Predicted Survival*	Actual Survival*
SSG A		
>6 months	52 (56.5%)	68 (73.9%)
>12 months	32 (34.8%)	49 (53.3%)
SSG B		
>6 months	75 (81.5%)	68 (73.9%)
>12 months	50 (54.4%)	49 (53.3%)
Katagiri A		
>6 months	3 (3.3%)	68 (73.9%)
Katagiri B		
>6 months	31 (33.7%)	68 (73.9%)
Bauer A		
>12 months	21 (22.8%)	49 (53.3%)
Bauer B		
>12 months	31 (33.7%)	49 (53.3%)

SSG: Scandinavian Sarcoma Group
*Values are given as the number of patients with the percentage in parentheses.

(66%) patients had a score of 1-2 and 31 (34%) patients had a score of 3-4; there were no patients who had a score of 0 (predicted survival of less than 3 months). The estimated survival for the majority of patients using both SSG A score and SSG B score was 3 to 6 months.

II. Katagiri Score

In this scoring system (Supplementary Table 2), a lower score provides a more favourable prognosis. The median Katagiri A score was 5 (range: 0-8), 2 (2%) patients had a score of 0-2, 54 (59%) patients had a score of 3-5 and 36 (39%) patients had a score of 6-8. The median Katagiri B score was 3 (range: 0-5), 37 (40%) patients had a score of 0-2 while 55 (60%) had a score of 3-5; none of the patients had a score of 6-8. The predicted survival rate for the majority of the patients using both Katagiri A score and Katagiri B score was 0.71 at 6 months and 0.49 at 12 months.

III. Bauer Score

In this scoring system (Supplementary Table 3), a higher score provides a more favourable prognosis. The median Bauer A score was 2 (range: 0-5) while the median Bauer B score was 3 (range: 2-5). In the Bauer A score, 12 (13%) patients had a score of 0-1 points, while 75 (82%) patients had a score of 2-3 points and 5 (5%) patients had a score of 4-5 points. In the Bauer B, none of the patients had a score of 0-1 points, while 62 (67%) patients had a score of 2-3 points and 30 (33%) patients had a score of 4-5 points. Using both Bauer A score and Bauer B score, the majority of patients had one 1-year survival rate of 0.25.

Evaluation of the Scoring Systems

Cox regression analyses showed that the absolute score of SSG and Katagiri scoring systems (either A or B) was significantly associated with the actual survival in all 92 patients. The higher score in SSG scoring system was associated with longer survival. The higher score in Katagiri scoring system was associated with poor survival. Each scoring system classifies the patients into different prognostic subgroups depending on the scores. We calculated the hazard ratios for each scoring subgroup within each scoring system and demonstrated the results in Table 5. The best prognostic score was used as a reference

Table 5. Cox Regression Analysis of Three Scoring Systems

Scoring System	Hazard Ratio	95 % CI	*P* Value	Scoring System	Hazard Ratio	95 % CI	*P* Value
SSG A	0.29	0.19 – 0.47	<0.001*	SSG B	0.29	0.19 – 0.47	<0.001*
Score 3-4 (reference†)	1	-	-	Score 3-4 (reference)	1	-	-
Score 1-2	0.31	0.07 – 1.32	0.11	Score 1-2	4.03	2.02 – 8.03	<0.001*
Score 0	2.24	0.51 – 9.82	0.29	Score 0	No patients		
Katagiri A	1.51	1.19 – 1.92	0.001*	Katagiri B	1.58	1.25 – 2.01	<0.001*
Score 0-2 (reference†)	1	-	-	Score 0-2 (reference)	1	-	-
Score 3-5	0.19	0.06 – 0.58	0.003*	Score 3-5	2.56	1.39 – 4.69	0.002*
Score 6-8	0.65	0.22 – 1.89	0.43	Score 6-8	No patients		
Bauer A	0.78	0.56 – 1.08	0.13	Bauer B	0.78	0.56 – 1.08	0.1
Score 4-5 (reference†)	1	-	-	Score 4-5 (reference)	1	-	-
Score 2-3	2.97	0.72 – 12.36	0.13	Score 2-3	1.67	0.91 – 3.05	0.09
Score 0-1	2.74	0.58 – 12.96	0.20	Score 0-1	No patients		

*Significant *P* value <0.05.
†Refers to baseline to which the other respective score subgroups are compared.

value of 1. The best prognostic scoring subgroup was 3-4 in SSG, 0-2 in Katagiri and 4-5 in Bauer. Statistical analysis revealed that 1 subgroup of Katagiri A (subgroup score 3-5), all subgroups of SSG B as well as Katagiri B scoring systems were significantly associated with the actual survival. However, there were no significant association between the subgroups of SSG A, Bauer A as well as B and actual survival. Bauer A (score 2-3 and score 0-1) tended to predict worse survival compared to score 4-5, however, the considerable effect size did not reach statistically significant level.

Kaplan Meier curves and log rank tests of all the scoring systems (A and B) are demonstrated in Figures 1a-f. Log rank test revealed that there were statistically significant differences in survival between the different prognostic subgroups of SSG and Katagiri scoring systems (P <0.001). Bauer scoring system showed no correlation between predicted and actual survival.

Predictive Values of the Scoring Systems

Predictive abilities of the scoring systems (A and B) measured by ROC, are presented as area under curve (AUC) in Table 6. The predictive value of SSG B, Katagiri B and Bauer B were higher as compared to that of respective SSG A, Katagiri A and Bauer A. However, no statistically significant difference was observed between the 2 AUCs of the scoring systems A and B for all 3 scoring systems. Among all these scoring systems, SSG B provided the highest predictive value (0.67) as compared to the other 2 scoring systems. Where likelihood ratio test was concerned, the smallest BIC was observed in SSG scoring systems A and B.

Table 6. Predictive Values of Scoring Systems

Scoring System	AUC	SE	Likelihood Ratio Test BIC	*P* Value*
SSG A	0.59	0.04	391.7	0.21
SSG B	0.67	0.04	391.7	
Katagiri A	0.61	0.05	404.7	0.81
Katagiri B	0.62	0.05	400.8	
Bauer A	0.52	0.04	405.9	0.64
Bauer B	0.55	0.05	405.9	

AUC: Area under curve; BIC: Bayesian information criterion; SE: Standard error; SSG: Scandinavian Sarcoma Group
**P* value from 'c' statistics showing difference between 2 AUCs in ROC.

Discussion

NPC is a cancer that is sensitive to both radiotherapy and chemotherapy. In patients with metastatic disease, chemotherapy can achieve 50% to 80% response rates with a median time to progression of disease of 5 to 11 months and median survival of 12 to 20 months which is similar to the median survival of our cohort of 13 months.[3,4]

The ability to prognosticate survival is crucial in the decision whether or not to offer surgery to a patient and the choice of surgery offered. Numerous prognostic scoring systems have been proposed to prognosticate the survival of patients with skeletal and spinal metastases, but as yet, none have been validated in NPC.[9-12,15-17]

There are a wide variety of surgical options available for the treatment of skeletal metastases and the goals of surgery include pain relief, restoration of function, mobility and improvement of quality of life. Pathological fractures are prone to non-union or delayed union due to increased osteoclast activation by tumour cell factors produced by the primary tumour. The choice of surgery must take the palliative nature of the surgery into account and not subject a patient with a short life expectancy to a radical procedure for which recovery and rehabilitation time is longer than the patient's life expectancy; at the same time, in view of the expected poor healing, implant failure and repeated surgery must be avoided by choosing the appropriate implant and surgery in a patient with a longer life expectancy.[8,18] Patients with a life expectancy of less than 6 weeks are unlikely to benefit from elective surgery while those with a prognosis of more than 6 weeks should be considered for internal fixation and stabilisation, patients predicted to survive more than 6 months may even be considered for metastatic resection and reconstruction. Thus, it is important to find an appropriate prognostic scoring system to accurately predict patient survival to determine the appropriate choice of surgery for each patient with metastatic bone disease.

The Bauer score is the only system of the 3 studied systems, which makes use of the presence of pathological fractures as a prognostic factor. Although the presence of pathological fractures has been found to be a significant survival prognostic factor in some studies,[7,19] it was not found to be a significant prognostic factor in our study group on univariate and multivariate analysis. This could be the reason why the Bauer score was not found to be associated with actual survival in our study. It is of note that in a multivariate analysis of 7 spinal metastases survival scoring systems by Leithner et al,[13] a modified Bauer score without the inclusion of pathological fractures as a prognostic factor was found to be the most highly predictive of survival in spinal metastases.

The Katagiri score[11] is similar to the Bauer score[10] and the SSG score[12] in that it makes use of primary tumour type, presence of visceral/cerebral metastases and multiple skeletal metastases as prognostic factors. However, it makes use of the ECOG score as a measure of functional status

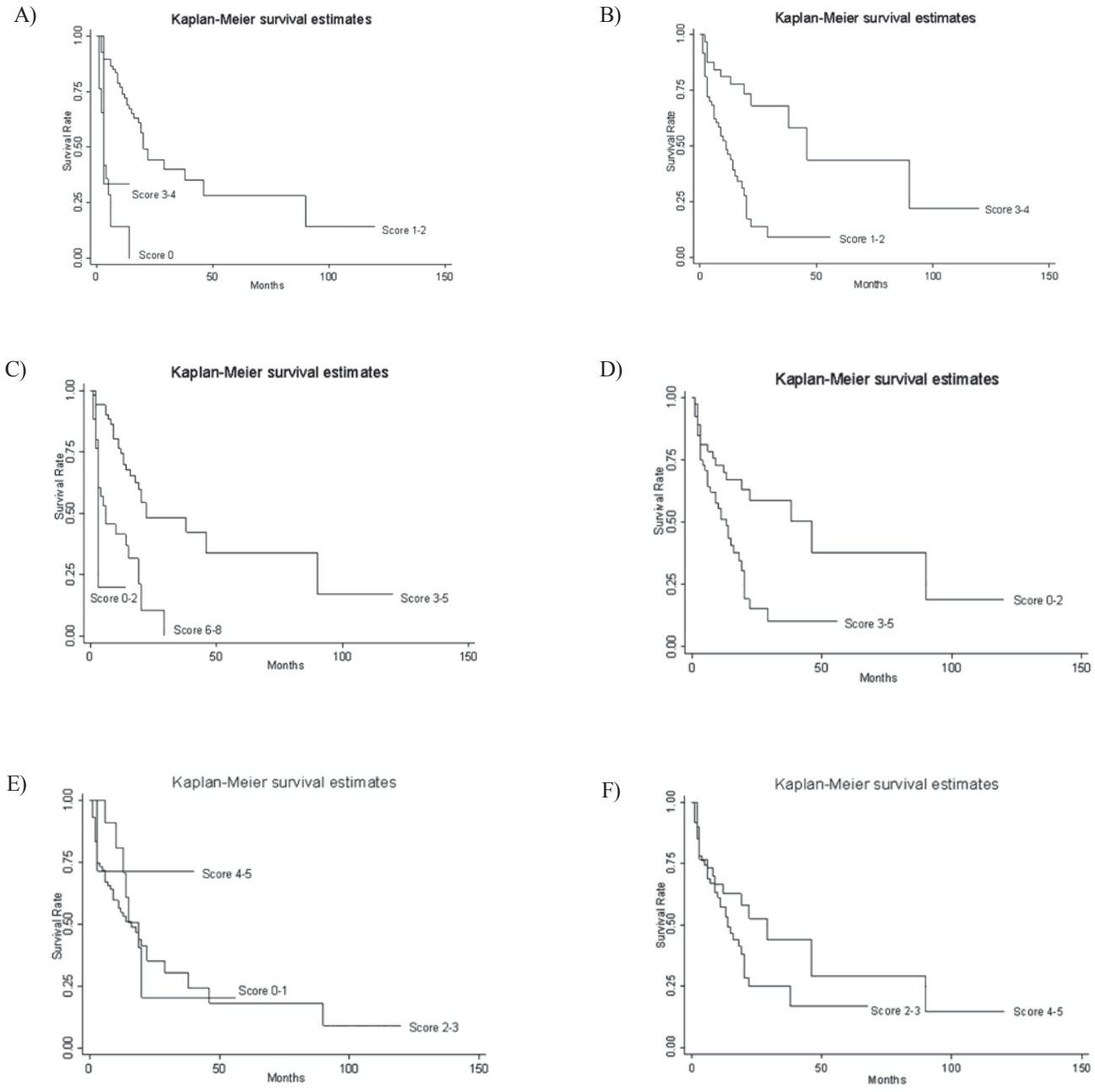

Fig. 1. Kaplan-Meier survival curves. A) for SSG A; B) for SSG B; C) for Katagiri A; D) for Katagiri B; E) for Bauer A; and F) for Bauer B.

and previous chemotherapy is considered a poor prognostic factor. A history of previous chemotherapy may indicate an advanced NPC as chemotherapy is usually prescribed only in advanced disease, and secondly patients who have already received chemotherapy prior to treatment may have fewer treatment options once skeletal metastases are diagnosed.[11] Chemotherapy was not found to be a significant prognostic factor for survival in our cohort. The ECOG score however was found to be a significant prognostic factor for survival in both univariate and multivariate analyses.

In our study, performance status (both Karnofsky and ECOG scores) and visceral metastases were found to be significant predictive factors of survival. These factors were part of each of the 3 scoring systems analysed. These findings correlate with a study by Nathan et al[9] which showed that after clinician assessment and haemoglobin

levels, number of visceral metastases, performance score, primary diagnosis and number of skeletal metastases are the most accurate predictors of survival. Of note is the finding that multiple skeletal metastases is not a predictive factor for survival in our cohort. We feel that it can be explained by the fact that 82 (89.13%) patients in our cohort had multiple bony metastases at presentation, making it a poor prognostication tool.

Through our search of PubMed index articles on NPC with skeletal metastases, we could not find any previous studies that evaluate the predictive value of the various prognostic scoring systems in this group of patients. The absolute score of SSG and the Katagiri scoring system both had statistically significant (P <0.001) association with survival on Cox regression analysis and there was statistically significant difference in survival between each subgroup of the SSG B as well as Katagiri B scoring systems where NPC was classified as a good prognostic tumour. Although the difference between the AUCs of SSG A and B, as well as Katagiri A and B, were not statistically significant, the predictive value of SSG B and Katagiri B are higher than that of SSG A and Katagiri A respectively with the highest predictive probability observed in SSG B (AUC: 0.67). By looking at the likelihood ratio test BIC, the smallest BIC (i.e. prediction is the closest to true model) was observed in SSG scoring system A and B. By also analysing the predicted and actual survival in Table 4, it was noticeable that the predicted 1-year survival by SSG B was the closest to the actual 1-year survival. Hence, the SSG B score appears to be better in predicting survival compared to Katagiri and Bauer scores.

In our study, NPC patients tended to have good general condition (69% of patients had KPS score of ≥70 and ECOG score of 0-2) despite the majority of these patients presenting with multiple skeletal metastases as well as visceral metastases. Moreover, in NPC patients, the median survival time is 13 months and 70.66% of our patients survived more than 6 months. All of the above suggests that when prognosticating NPC, it would be more appropriate to treat "NPC as a tumour with a relatively good prognosis".

Our study highlights that both the Katagiri and SSG scoring systems can be used; the SSG scoring system with our suggested modification (NPC as a tumour with better prognosis) appears to be the most accurate of these 3 systems in prognosticating the patients with metastatic skeletal disease from NPC. This is the first study to validate the above scoring systems for the prognostication of NPC patients with skeletal metastases. We recommend that one must interpret these scores with caution as the AUC is less than 0.80, which is the minimum AUC needed to consider a test to be a good one. At present, we suggest that clinical decision-making should rely on individual patient factors such as the patients' general condition and tumour load represented by presence of visceral metastases.

Strength and Limitation

Our retrospective study design is a limitation, however, given that we analysed patients with skeletal metastases from a single primary cancer namely NPC, we could minimise population heterogeneity in our study.

Conclusion

In conclusion, our study shows that NPC patients with skeletal metastases have median survival of 13 months from the diagnosis of skeletal metastases. It was observed that visceral metastases and general condition (either Karnofsky performance status or ECOG) have significant impact on survival. Katagiri and SSG scoring systems could be used to prognosticate the survival of these patients, with the SSG B scoring system appearing to be the most accurate predictor of survival. Larger studies, which assess NPC as a positive prognostic, factor in SSG scoring system should be done to validate this prognostic system for metastatic NPC.

Acknowledgement

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Supplementary Table 1. Scandinavian Sarcoma Group (SSG) Scoring Systems A and B

Prognostic Factors	Score A*	Prognostic Factors	Score B†
Number of skeletal metastases		Number of skeletal metastases	
Single	1	Single	1
Multiple	0	Multiple	0
Presence of organ metastases		Presence of organ metastases	
Absent	1	Absent	1
Present	0	Present	0
Breast cancer, kidney cancer, thyroid cancer, myeloma, lymphoma		Breast cancer, kidney cancer, thyroid cancer, myeloma, lymphoma, NPC	
Yes	1	Yes	1
No	0	No	0
Karnofsky score		Karnofsky score	
≥70	1	≥70	1
<70	0	<70	0
Estimated survival: 0 point – less than 3 months; 1-2 points – 3-6 months; 3-4 points – more than 6-12 months			

NPC: Nasopharnygeal carcinoma
*NPC was not stated in this score.
†NPC, assigned as a positive prognostic factor with a score of 1 (in view of the known good prognosis for NPC).

Supplementary Table 2. Katagiri Scoring Systems A and B

Prognostic Factors	Score A*	Prognostic Factors	Score B†
Primary lesion		Primary lesion	
Rapid growth (hepatocellular, gastric, lung carcinoma)	3	Rapid growth (hepatocellular, gastric, lung carcinoma)	3
Moderate growth (other carcinoma and sarcoma, NPC)	2	Moderate growth (other carcinoma and sarcoma)	2
Slow growth (breast, prostate, thyroid carcinoma, multiple myeloma, malignant lymphoma)	0	Slow growth (breast, prostate, thyroid carcinoma, multiple myeloma, malignant lymphoma, NPC)	0
Visceral or cerebral metastases	2	Visceral or cerebral metastases	2
Performance status (ECOG) 3 or 4	1	Performance status (ECOG)* 3 or 4	1
Previous chemotherapy	1	Previous chemotherapy	1
Multiple skeletal metastases	1	Multiple skeletal metastases	1
Estimated survival rate at 6 months: 0-2 points – 0.98; 3-5 points – 0.71; 6-8 points – 0.31 12 months: 0-2 points – 0.89; 3-5 points – 0.49; 6-8 points – 0.11 24 months: 0-2 points – 0.75; 3-5 points – 0.28; 6-8 points – 0.02			

ECOG: Eastern Cooperative Oncology Group; NPC: Nasopharnygeal carcinoma
*NPC, assigned under the moderate growth tumours with score of 2.
†NPC, assigned under the slow growth tumour with score of 0 (in view of the known good prognosis for NPC).

Supplementary Table 3. Bauer Scoring Systems A and B

Prognostic Factors	Score A*	Prognostic Factors	Score B†
No visceral metastases	1	No visceral metastases	1
No pathological fracture	1	No pathological fracture	1
Solitary skeletal metastases	1	Solitary skeletal metastases	1
Not primary lung cancer	1	Not primary lung cancer	1
Primary tumour (breast, kidney, lymphoma, multiple myeloma)	1	Primary tumour (breast, kidney, lymphoma, multiple myeloma, NPC)	1
Estimated one year survival rate: 0-1 point – died within 6 months of surgery; 2-3 points – 0.25; 4-5 points – 0.5			

NPC: Nasopharnygeal carcinoma
*NPC was not stated in this score.
†NPC, assigned as a positive prognostic factor with a score of 1 (in view of the known good prognosis for NPC).

Original Article

Health-Related Quality of Life in Children with Biliary Atresia Living with Native Livers

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Abstract

Introduction: This study aimed to quantify and investigate factors affecting the health-related quality of life (HRQoL) in children with biliary atresia (BA) living with their native livers. Materials and Methods: A cross-sectional study on the HRQoL using the PedsQL4.0 generic core scales in children with BA aged between 2 to 18 years followed up at the University Malaya Medical Centre (UMMC) in Malaysia was conducted. Two groups, consisting of healthy children and children with chronic liver disease (CLD) caused by other aetiologies, were recruited as controls. Results: Children with BA living with their native livers (n = 36; median (range) age: 7.4 (2 to 18) years; overall HRQoL score: 85.6) have a comparable HRQoL score with healthy children (n = 81; median age: 7.0 years; overall HQRoL score: 87.4; *P* = 0.504) as well as children with CLD (n = 44; median age: 4.3 years; overall score: 87.1; *P* = 0.563). The HRQoL of children with BA was not adversely affected by having 1 or more hospitalisations in the preceding 12 months, the presence of portal hypertension, older age at corrective surgery (>60 days), a lower level of serum albumin (≤34 g/L) or a higher blood international normalised ratio (INR) (≥1.2). Children who had liver transplantation for BA did not have a significantly better HRQoL as compared to those who had survived with their native livers (85.4 vs 85.7, *P* = 0.960). Conclusion: HRQoL in children with BA living with their native livers is comparable to healthy children.

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Key words: Chronic liver disease, Survivors

Introduction

Biliary atresia (BA), a progressive obliterative fibro-inflammatory cholangiopathy, usually presents with jaundice in infancy.[1] The definitive therapy for BA in the majority of infants is liver transplantation (LT).[2,3] The creation of a portoenterostomy (Kasai surgery) is now considered by many as a bridge to eventual LT.[3] Infants who have surgery before 60 days of age had a more than 80% chance of re-establishing bile flow and clearance of jaundice.[2-6] Without surgery, BA is a fatal disease for which children rarely survive beyond 3 years of age.[5] LT is indicated in those who have unsuccessful surgery.[5] In Malaysia, the overall 2-year survival rate (with native liver and after LT) of BA was 40%.[7] The outcome was adversely affected by late referral for surgery and a lack of timely LT in those who had unsuccessful surgery.[7]

Many patients with BA develop progressive liver disease with ongoing cirrhosis after surgery.[7-9] Complications include recurrent cholangitis, portal hypertension and variceal bleed, as well as bone fractures.[7,9] Therefore, lifelong follow-up is necessary to detect the complications of biliary cirrhosis. With the improvement in survival, greater attention is now being given to the assessment of quality of life (QoL) in children living with chronic illness.[10] In addition to assessing the effect on physical and mental health, QoL also assesses the impact of an underlying chronic illness on the cultural, environmental and economic well-being of the affected individual.[10]

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Health-related QoL (HRQoL) refers to the impact that health and illness may have on the well-being of an individual, and on his/her ability to function in daily life with regard to physical health as well as emotional, social and school functioning.[11] It is a multidimensional construct that assesses the physical, psychological (including emotional and cognitive) and social health dimensions, and has been used widely in the paediatric population.[12] The objective of the present study was to measure the HRQoL in children with BA who survived with their native livers and to compare them with healthy children as well as children with chronic liver disease (CLD) due to aetiologies other than BA.

Materials and Methods

This was a cross-sectional study conducted among children with BA attending our institution's paediatric gastroenterology and nutrition unit. Patients with BA who were diagnosed between January 1993 and June 2012 were identified from the hospital database. Patients were recruited and interviewed when they attended the children's liver clinic from December 2011 to March 2013. The present study was approved by the institutional ethic review committee (MEC reference: 902.15). Parental consent was obtained before the distribution of research questionnaire.

Inclusion Criteria

All children with a diagnosis of BA who attended the children's liver clinic during the study period were recruited. The diagnosis of BA was confirmed via an operative cholangiogram. Patients younger than 2 years or older than 18, or those without parental consent, were excluded.

Data Collection

Demographic, medical and laboratory data were collected. Interview and physical examination were conducted by one of the co-authors throughout the study. Medical and laboratory data were collected via chart review. No additional laboratory tests were performed for the purpose of the present study. Medical events in the preceding 12 months were collected through chart review as well as parental and patient's recall.

Definitions

Age at Kasai surgery was considered as early if the surgery was performed at or before 60 days of age. Portal hypertension was defined as presence of variceal bleed due to a documented oesophageal or gastric varices and/or splenomegaly.

Controls

A cohort of healthy children with no intercurrent or chronic illnesses was recruited as controls. They were siblings of other patients accompanying their parents to the hospital. This was a convenient sample and no attempts were made to match for age or sex with the patients with BA. Consent was obtained from their parents before the interview. A second group control consisted of children who were attending the children's liver clinic and were diagnosed with CLD caused by conditions other than BA. Similarly, this was a convenient sampling and no attempts were made to match for age or sex with patients with BA.

Survey Instrument

The HRQoL was assessed using PedsQLTM 4.0 generic core scales.[12,13] Written permission for the use of the questionnaire was obtained from the MAPI Research Institute in Lyon, France. PedsQLTM is a 23-question instrument which has been validated in healthy children aged between 2 and 18 years. It measures the core dimensions of health and includes the following domains: physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items).[13] The PedsQL 4.0 generic core scales has a parallel parent proxy-report and child self-report versions. The reported internal consistency between child self-report and parent proxy-report is excellent.[13] The items in the PedsQL 4.0 are reversely scored and linearly transformed to a scale of 0 to 100 with higher scores indicating better HRQoL. Age-appropriate questionnaires were used for different age groups (2 to 4, 5 to 7, 8 to 12 and 13 to 18 years). Both English and Malay language versions were available upon request. Parents completed the questionnaire while children aged ≥5 years were offered the child self-report version.

Demographic and Medical Factors Affecting HRQoL

Age at Kasai surgery, presence of portal hypertension, the number of hospital admissions, failure to thrive (defined as weight ≤ third centile for age and sex), serum bilirubin and albumin levels, as well as blood international normalised ratio (INR) were analysed to ascertain factors affecting the HRQoL in children with BA. We did not include the presence of visible change in skin colour (visible jaundice), as the children in the present study were from various ethnic backgrounds and had different skin colours. Thus, it was difficult to standardise the change in skin colour. Similarly, the presence of skin itchiness was not included as a factor because it was difficult to standardise the presence and the degree of itchiness in children from different sociocultural backgrounds.

Statistical Methods

Statistical Products for Social Services (SPSS; Chicago, Illinois) for Windows (version 16.0) was used. Chi-square tests were used for categorical data, while continuous data were checked for normality via Kolmogorov-Smirnov testing. To determine the agreement between child self-report and parent proxy-report, interclass correlation coefficients (ICCs) were used.[13] ICCs <0.40 were designated as poor-to-fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as good and 0.81 to 1.00 as excellent agreement.[13] One-way ANOVA was applied when comparison of more than 2 groups were made. Univariate analysis was conducted to identify demographic and clinical factors associated with impairment in the HRQoL scores in children with BA. Multivariate analysis was performed by conducting linear regression to identify significant demographic or clinical data which may influence the HRQoL. For all the statistical tests used, a *P* value of ≤0.05 was considered to be statistically significant.

Results

A total of 144 patients with a diagnosis of BA were identified (Fig. 1). Of these, the case notes of 24 patients were unavailable for review, and efforts to contact them were unsuccessful. Of the remaining 120 patients, 61 had died (55 with native liver, 6 after LT; overall survival rate 49%; Fig. 1). The overall survival rate with native liver was 46%.

Fifty-nine patients with BA (48 with native liver, 11 after LT) were identified. Of these, 44 patients (8 had LT, 18% of 44) fulfilled the inclusion criteria of the present study. Reasons for excluding the remaining 15 patients were: beyond the age limit of the study (younger than 2 years of age, n = 5; older than 18 years, n = 3), parental refusal to participate (n = 1), transferred to another hospital for care (n = 4) or defaulted on follow-up (n = 2). Eight of the 44 with BA had a successful LT and were still alive at the time of review.

Biliary Atresia

Thirty-six (median age: 7.4 years; range, 2 to 18 years) of the 44 patients with BA survived with their native livers. Of these, 25 (69%) had early Kasai surgery (≤60 days of life). Fifteen patients (42%) had portal hypertension and 3 (8%) had failure to thrive (Table 1).

Controls

Forty-four children with other aetiologies of CLD (median

Table 1. Demographic Data and Family Background of Children with Biliary Atresia, Chronic Liver Disease and Healthy Controls

Parameters	Biliary Atresia (n = 36)	Chronic Liver Diseases (n = 44)	Healthy Controls (n = 81)	All Groups (n = 161)
Age (year)				
2 – 4	14	11	26	51
5 – 7	7	5	15	27
8 – 12	7	19	19	45
13 – 18	8	9	21	38
Median ± SD	7.4 ± 4.2	9.3 ± 4.1	7.0 ± 4.4	
Gender				
Male	13	19	34	66
Female	23	25	47	95
Respondent's relationship with patient				
Father	8	17	16	41
Mother	28	27	65	120
Failure to thrive*				
Present	3 (8%)	4 (9%)‡		
Absent	33	40		
Portal hypertension†				
Present	15 (32%)	8 (18%)§		
Absent	21	36		

SD: Standard deviation
*Defined as weight ≤ third centile for age and sex.
†Defined as presence of variceal bleed due to a documented esophageal or gastric varices and/or splenomegaly.
‡*P* value = 1.0 (Fisher's exact test).
§*P* value = 0.027 (Fisher's exact test).

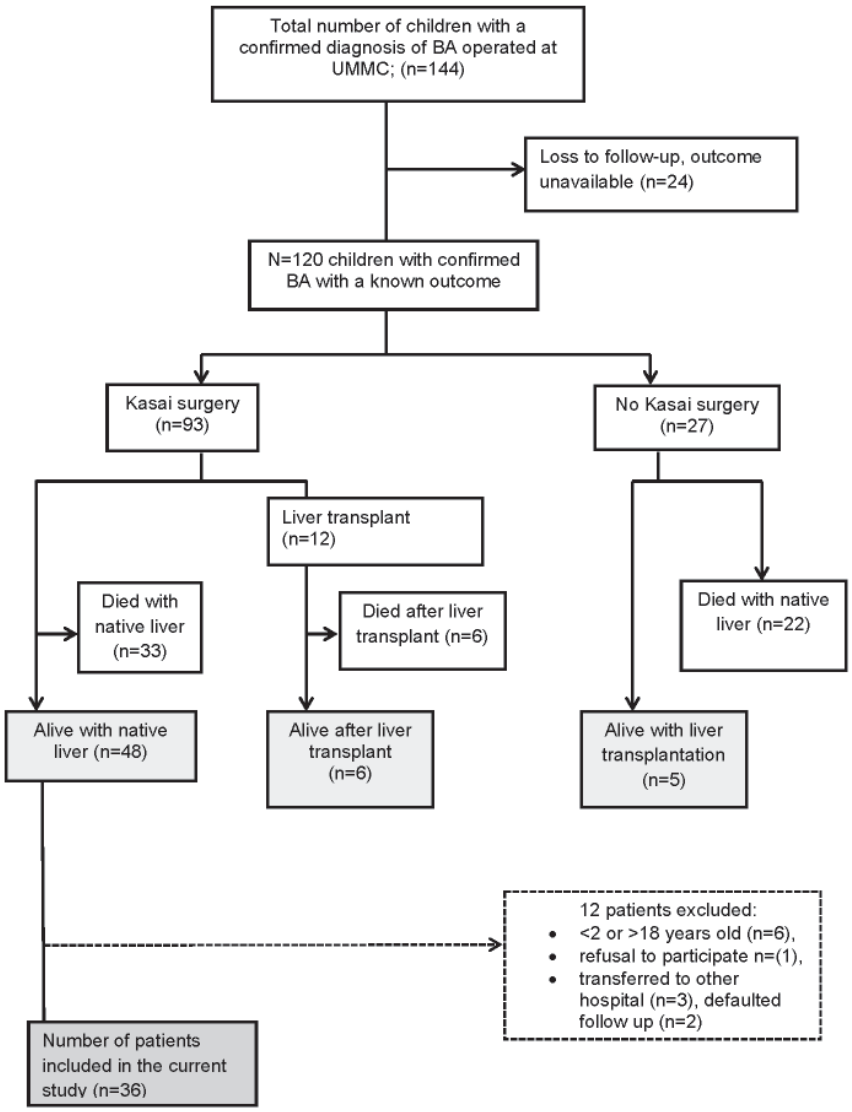

Fig. 1. Flowchart showing the recruitment process for children with a diagnosis of biliary atresia in the current study.

age ± SD = 9.3 ± 4.1 years) were recruited as controls (Table 1). The controls were recruited as a convenient sample. The diagnoses were: autoimmune hepatitis (n = 14), chronic hepatitis B (n = 14), Alagille syndrome (n = 3), idiopathic portal hypertension (n = 2), progressive familial intrahepatic cholestasis (n = 2), cystic fibrosis liver disease (n = 2), glycogen storage disease (n = 2), non-alcoholic steatohepatitis (n = 1), and idiopathic neonatal hepatitis (n = 1). Four have other medical conditions (one each for Ehler Danlos, bronchiectasis, atrial septal defect not in failure and solitary kidney). Eight of the 44 (18%) children with CLD have portal hypertension and 44 (9%) have failure to thrive. A second group of 81 healthy children (median ± SD = 7.0 ± 4.4 years) were recruited as controls.

Respondents of Questionnaire

All the parents (74% were mothers, Table 1) recruited in the 3 study groups completed the questionnaire. Child self-report version of the questionnaire was offered to the 115 children (in all 3 groups) aged 5 years and above and 106 (92% of 115) completed the questionnaire (5 to 7 years, n = 21; 8 to 12 years, n = 43; 13 to 18 years, n = 42).

Comparison of Patients with BA with CLD and Healthy Controls

For the purpose of comparing PedsQL data (Tables 2, 3 and 4), the parent proxy-report scores were used. Generally, children with BA living with their native livers were reported

Table 2. PedsQL 4.0 Generic Core Scale Scores in Children with Biliary Atresia, Chronic Liver Disease and Healthy Controls

Domains	Biliary Atresia (n = 36)		Chronic Liver Disease (n = 44)		Healthy Controls (n = 81)		All (n = 161)		*P* Value
	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)	
Physical functioning	88.7 ± 21.1	(82.3, 95.1)	89.7 ± 15.1	(85.1, 94.3)	90.8 ± 13.4	(87.8, 93.8)	90.0 ± 16.1	(87.6, 92.5)	0.776
Psychological functioning	85.2 ± 15.1	(80.6, 89.8)	87.0 ± 13.0	(83.0, 90.9)	86.0 ± 12.9	(83.2, 88.9)	86.0 ± 13.5	(84.0, 88.1)	0.829
Emotional functioning	83.4 ± 16.4	(78.4, 88.4)	86.7 ± 18.2	(81.2, 92.2)	83.9 ± 17.0	(80.1, 87.6)	84.5 ± 17.1	(81.9, 87.1)	0.600
Social functioning	90.2 ± 18.5	(84.5, 95.9)	92.5 ± 14.6	(88.1, 96.9)	91.2 ± 12.7	(88.3, 93.9)	91.2 ± 14.8	(89.0, 93.5)	0.770
School functioning	90.2 ± 18.5	(84.5, 95.9)	92.5 ± 14.6	(88.1, 96.9)	91.2 ± 12.7	(88.3, 93.9)	91.2 ± 14.8	(89.0, 93.5)	0.770
Overall score	85.6 ± 15.4	(80.91 90.3)	87.1 ± 12.6	(83.3, 91.0)	87.4 ± 11.5	(84.8, 89.9)	86.9 ± 12.8	(84.9, 88.8)	0.752

CI: Confidence interval; SD: Standard deviation

by their parents to have the lowest score in the school and emotional functioning domains and the highest score in the social functioning domain. However, healthy children and children with CLD were reported to have the highest scores in the physical and social functioning domains, and the lowest score in the school functioning domains (Table 2). As compared to healthy controls, children with BA surviving with their native livers have no significant difference in the overall PedsQL 4.0 generic core scale score (85.5 ± 15.4 vs 87.4 ± 11.5; differences in means: -1.8; $P = 0.465$; Tables 2 and 3). Analysis of the individual components of the scores yielded no significant difference as well (Table 3).

There was no significant difference in the PedsQL 4.0 generic core scale scores (both overall and subscale scores) between healthy children and children with CLD (Table 3). Similarly, no significant difference in PedsQL 4.0 generic core scale scores (both overall and subscale scores) was observed between children with BA living with their native livers and those with other forms of CLD (Table 3).

Comparison of Child Self-report and Parent Proxy-report Scores

A total of 106 child self-report and parent proxy-report pairs were available in all the 3 study groups for comparison (Table 4). There was excellent correlation between the parent proxy-report and child self-report scores in the overall score (ICC 0.844), with good correlation in the emotional, social and school functioning domains, and excellent correlation in the physical and psychosocial functioning domains. Both the parents and children reported higher scores for physical functioning as compared to the psychosocial domain.

Medical Predictors of HRQoL in Children with BA

Table 5 shows the influence of age at Kasai surgery, number of hospital admissions in the preceding 12 months, presence of portal hypertension, serum albumin and blood INR on the HRQoL scores in children with BA. Children with more hospital admissions in the preceding 12 months had significantly worse HRQoL scores.

Table 3. Comparison of PedsQL Generic Core Scale Scores in Children with Biliary Atresia, Chronic Liver Disease and Healthy Controls

Domains	BA vs Healthy Controls		BA vs CLD		CLD vs Healthy Controls	
	Mean Difference	*P* Value	Mean Difference	*P* Value	Mean Difference	*P* Value
Physical functioning	-1.2	0.702	+0.1	0.977	-1.1	0.615
Psychological functioning	-0.8	0.781	-1.8	0.463	+1.0	0.524
Emotional functioning	-1.2	0.715	-3.3	0.280	+2.8	0.346
Social functioning	+1.0	0.991	-2.3	0.483	+1.3	0.322
School functioning	+2.1	0.802	+3.0	0.744	-0.9	0.910
Overall score	-1.7	0.504	-1.5	0.563	-0.3	0.961

BA: Biliary atresia; CLD: Chronic liver disease

Table 4. Comparison of PedsQL Generic Core Scale Scores Between Parent Proxy-Report and Child Self-Report

Domains	n	Child Self-Report (Mean ± SD)	Parent Proxy-Report (Mean ± SD)	Interclass Correlation Coefficient* (*P* Value)
Physical functioning	106	87.9 ± 13.1	90.2 ± 15.7	0.776 (<0.001)
Psychosocial functioning	105	83.6 ± 12.7	86.3 ± 13.3	0.688 (<0.001)
Emotional functioning	106	82.4 ± 17.5	84.4 ± 17.4	0.613 (<0.001)
Social functioning	104	89.0 ± 12.8	91.7 ± 13.8	0.643 (<0.001)
School functioning	104	79.3 ± 17.0	81.7 ± 18.6	0.594 (<0.001)
Overall score	106	84.2 ± 14.0	87.0 ± 12.7	0.670 (<0.001)

SD: Standard deviation

*Interclass correlation coefficient <0.40 were designated as poor-to-fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as good and 0.81 to 1.00 as excellent agreement.

HRQoL Scores in Children with BA Surviving with Native Liver and After LT

There was no significant difference in the parent proxy-report HRQoL scores between the 8 children with BA surviving after LT as compared to the HRQoL scores of the 36 children with BA surviving with their native livers groups (Table 6), although the number of children who had LT in the present study was small (n = 8).

Discussion

Advances in the management of children with gastrointestinal and hepatic diseases have led to an increased survival in this group of children. Attention is now given to the QoL in children living with chronic gastrointestinal and liver disorders.[10] Cholangitis, portal hypertension, bleeding and bone fractures are important complications in children with BA surviving long-term with their native livers.[8,9] Lee et al observed that 24% of children with BA who had a successful surgery have major morbidities.[7] In those who survived for more than 20 years with their native livers, up to 61% have complications.[8]

There have been several studies on the HRQoL in children with BA, both living with their native livers and after LT.[14-17]

Table 5. Medical Variables Affecting the Overall Parent Proxy-Report PEDSQL Generic Core Scale Scores in Children with Biliary Atresia Living with their Livers

Factors	n	Overall Parent Proxy-Report Score (Mean ± SD)	Mean Difference	*P* Value
Age at surgery				
≤60 days	25	82.8 ± 16.6	-10.2	0.076
>60 days	11	93.0 ± 9.5		
Hospitalisations*				
No hospitalisation	28	86.6 ± 14.8	5.3	0.37
At least 1 hospital admission	8	81.4 ± 13.4		
Portal hypertension				
Present	15	80.9 ± 20.1	-8.2	0.166
Absent	21	89.1 ± 10.5		
Serum bilirubin level (μmol/L)				
>85 μmol/L	6	80.6 ± 14.5	-6.5	0.37
≤85 μmol/L	33	87.0 ± 16.3		
Serum albumin level (g/L)				
≤34 g/L	13	82.8 ± 15.8	-4.4	0.458
>34 g/L	19	87.2 ± 16.4		
International normalised ratio				
≤1.2	18	87.9 ± 16.6	17.4	0.094
>1.2	3	70.5 ± 5.1		

SD: Standard deviation

*In the preceding 12 months.

Table 6. Comparison of Parent Proxy-Report PEDSQL Scores in Children with Biliary Atresia Surviving with Native Liver After Liver Transplantation

	Liver Transplant	n	Mean ± SD	Mean Difference	*P* Value
Physical functioning	Yes	8	84.7 ± 24.6	5.0	0.553
	No	36	89.6 ± 20.5		
Psychosocial functioning	Yes	8	85.0 ± 15.9	0.3	0.964
	No	36	85.3 ± 15.2		
Emotional functioning	Yes	8	86.9 ± 12.8	-4.3	0.513
	No	36	82.6 ± 17.2		
Social functioning	Yes	7	85.7 ± 27.0	5.4	0.487
	No	36	91.1 ± 16.8		
School functioning	Yes	6	87.5 ± 14.1	-4.8	0.565
	No	25	82.7 ± 18.7		
Overall score	Yes	8	85.4 ± 15.7	0.3	0.960
	No	36	85.7 ± 15.6		

SD: Standard deviation

Sundaram et al observed that HRQoL in children with BA living with their native livers was significantly poorer as compared to healthy children but was similar to children who had LT,[17] although children with BA living with native livers were generally healthy with up to 62% having a state of optimal health. The most significant difference observed was in school functioning.[17] Another study comparing 30 Japanese and 25 English adolescents with BA living with their native livers showed significant impairment in general, physical, social and emotional health in patients with BA as compared with healthy children.[18]

In the present study, we observed that the overall HRQoL scores in children with BA living with their native livers were not significantly different from that of healthy children. In addition, there was no significant difference in all the measured domains of the HRQoL scores.

LT for children with end-stage liver disease or those with unacceptable QoL in Malaysia is limited.[7] The cohort of children with BA living with their native livers in the present study has significant morbidity with one-third having portal hypertension and 7% having had failure to thrive. It is therefore somewhat unexpected that based on parental proxy-report, the HRQoL in these children were found to be similar to those reported by healthy children.

However, a recent study on adults with BA living with their native livers from the Netherlands also showed a comparable health status and QoL with their healthy peers.[19] However, the number of patients enrolled was small (25 patients), and the instrument of study used was different.[19]

We observed that the overall HRQoL score in children with BA was 85.6, while the score noted in the study by Sundaram et al was 76.9.[17] The scores for healthy controls in both studies were comparable (87.4 in the present study; 84.7 in the study by Sundaram et al).[17] Possible explanation for the difference in the HRQoL scores between the 2 studies included differences in the age of the patients studied. The median age of children with BA in the present study was younger than that reported by Sundaram et al (7.4 years vs 9.75 years).[17] We postulated that HRQoL in children with BA deteriorated with age. However, neither of the studies compared the HRQoL in different age groups.

We found good-to-excellent correlation between the parent proxy-report and child self-report in the HRQoL scores across all domains in all the 3 study groups. Other authors have also observed good-to-excellent correlation between parent and child report.[20,21] Children as young as 5 years have been found to be reliable in reporting the HRQoL scores.[21] In addition to comparing between children with BA and healthy children, we were also unable to observe any differences in the HRQoL between children with BA living with their native livers and those with CLD caused by conditions other than BA.

Sundaram et al reported no difference in the HRQoL in children with BA living with native livers and after LT.[17] We did not observe any significant difference in the HRQoL in children with BA living with their native livers or after LT, although the number of children with BA after LT in the present study was small.

There are several limitations in the present study. Firstly, the number of patients with BA and CLD recruited for the present study was small. Only 36 patients with BA living with their native livers were recruited for the present study. We were unable to match the healthy controls selected for the present study with children with BA. In addition, we were unable to include a significant number of children with a diagnosis of BA.

We have previously reported that the overall survival rate among patients with BA with their native liver was 40% at 2 years after surgery.[7] Reasons for this unfavourable outcome was a delay in referral for timely diagnosis and surgery in infants with neonatal cholestasis. For those with unsuccessful surgery, a lack of timely liver transplant surgery also contributed to a poor overall survival rate.[7]

We did not find the presence of any medical factors significantly affecting the HRQoL scores in children with BA living with their native livers. Having a serum bilirubin level above 85 μmol/L or hospitalisation in the preceding 12 months did not adversely affecting the HRQoL of children with BA.

Conclusion

With good medical care, children with BA surviving with their native livers can enjoy a good QoL that is comparable with their healthy peers. Nevertheless, careful long-term follow-up, with particular attention on the various issues affecting the QoL in these children, is necessary. Strategies to prevent recurrent cholangitis leading to frequent hospital admissions is needed to further improve the QoL in children with BA living with their native livers. Children with BA surviving after LT do not necessarily have a better QoL than their peers living with their native livers.

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Generalised Anhidrosis Secondary to Intracranial Haemorrhage

Dear Editor,

A man in his 20s presented with a 3-year history of anhidrosis. There were no autonomic symptoms and he was not on any long-term medications. Five months prior to onset of symptoms, he suffered a ruptured intracranial arteriovenous malformation. On examination, there was spastic right hemiparesis. Sensory and postural blood pressure examinations were normal. Dermatological examination, including hair, nails and teeth, were normal.

Thermoregulatory sweat testing was performed in an enclosed room at 32˚C and 68% humidity. An admixture of starch and iodine powders was sprayed over his whole body and almost-complete generalised anhidrosis, including the palms, was observed (Fig. 1). Serum thyroid hormones were normal.

In vivo high-definition optical coherence tomography (HD-OCT)(Skintell®) was performed on multiple sites. Sweat ducts were present and no obstruction of the acrosyringium was visualised (Fig. 2). A cholinomimetic, carbachol (0.1 mL Miostat® 0.01%), was injected intradermally, which stimulated sweat production locally (Fig. 3). Review of brain magnetic resonance imaging (MRI) images revealed haemorrhage in the basal ganglia extending into the third ventricle (Fig. 4). The patient was managed conservatively with advice to avoid strenuous activities and medications that can exacerbate hypohidrosis.

Exogenous, drug and dermatological causes of hypohidrosis were excluded through clinical assessment. HD-OCT demonstrated intact sweat ducts and absence of acrosyringium obstruction, thereby excluding ectodermal dysplasia and miliaria respectively. Normal local sweat production upon intradermal injection of a cholinomimetic indicated that the pathology of anhidrosis was neurological rather than dermatological (such as in acquired idiopathic generalised anhidrosis,[1] a relatively common cause of generalised anhidrosis).

Neurological causes of anhidrosis can result from lesions at the hypothalamus, brainstem, spinal cord or sympathetic chain.[2] In our patient, the pathology was most likely at the hypothalamus as lesions at the other anatomical locations need to be bilateral (with resultant extensive neurological deficits) in order to cause generalised anhidrosis.

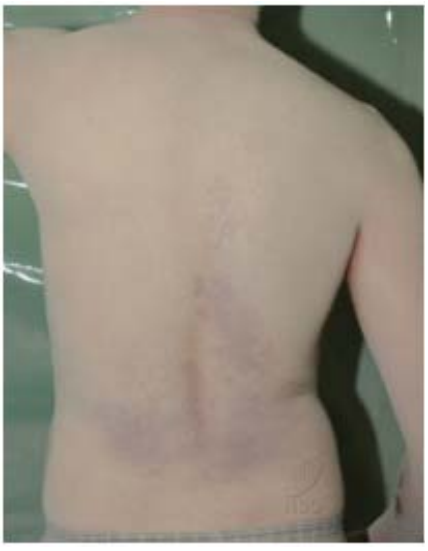

Fig. 1. Patient's back coated with an admixture of starch and iodine powders. Only light purplish patches were observed, indicating marked hypohidrosis. In controls, the powder mix turned dark purple over the whole trunk.

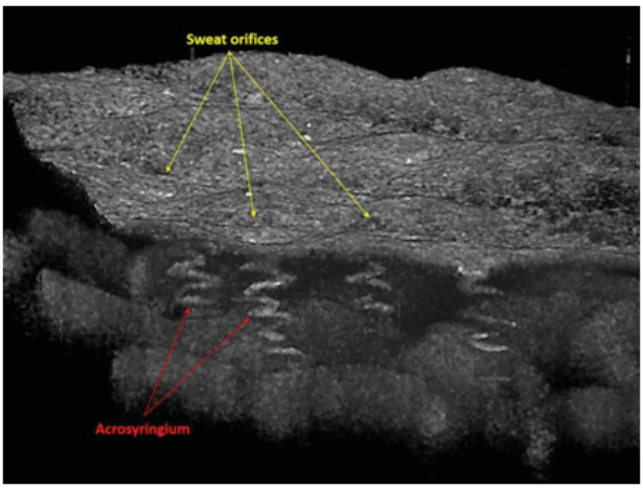

Fig. 2. Three-dimensional reconstruction of high-definition optical coherence tomography (HD-OCT) images of the palm demonstrating normal spiralling acrosyringium (intra-epidermal portion of sweat ducts) in the stratum corneum.

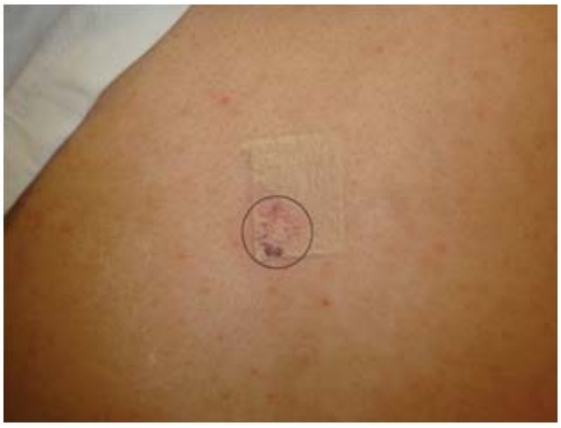

Fig. 3. Intradermal injection of carbachol stimulated sweat production, turning the admixture of starch and iodine powders purple at the sweat orifices (circled).

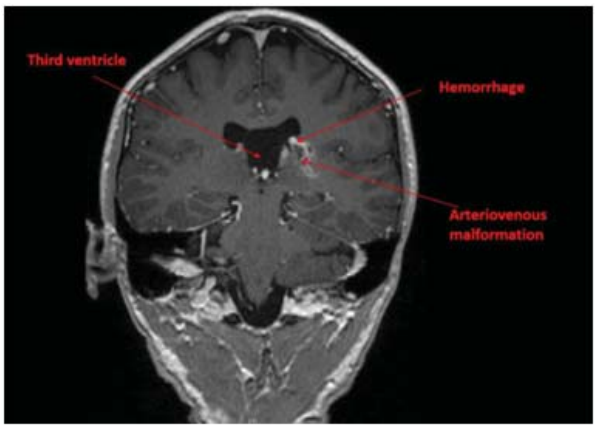

Fig. 4. Magnetic resonance image of the brain showing intracranial haemorrhage in the left basal ganglia with intraventricular extension. Small arteriovenous malformation arising in the thalamus is also visualised.

Only a few cases of anhidrosis involving hypothalamic lesions have been reported, occurring in association with neuromyelitis optica (NMO),[3] lymphocytic infundibuloneurohypophysitis[4] and multiple sclerosis.[5] Similar to the case of NMO, MRI of our patient revealed that the third ventricle, which adjoins the hypothalamus, was affected. Although our patient developed anhidrosis only 5 months after the stroke, it is known that 20% to 40% of patients with subarachnoid haemorrhage can present with delayed ischaemic neurological deficits,[6] an observation thought to be related to cerebral vasospasm from the presence of subarachnoid blood. Another possible reason for the delayed presentation is that the patient's initial poor mobility limited his exposure to heat stress, with symptoms manifesting only months later after rehabilitation and improvement in his neurological function.

We report the first case of intracranial haemorrhage causing generalised anhidrosis. Recognising and differentiating this central neurological cause from exogenous, dermatological and peripheral neurological causes is important in the management of the condition.

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Detection of Residual Lentigo Maligna Using the In Vivo Reflectance Confocal Microscopy

Dear Editor,

Lentigo maligna (LM) is a form of melanoma in situ that occurs on sun exposed skin, particularly the head and neck areas, of elderly patients.[1] A clinical diagnosis of LM at an early stage is often difficult, even for experienced dermatologists as benign lesions such as solar lentigo and seborrheic keratosis may have similar clinical features. Dermoscopy has been shown to be a valuable additional diagnostic tool with higher diagnostic accuracy, especially in the diagnosis of pigmented skin lesions, in the past 2 decades, but still leaves the clinician with diagnostic challenges.[2]

Recently, the introduction of reflectance confocal microscopy (RCM) which allows real-time non-invasive imaging of the epidermis and papillary dermis providing a cellular resolution comparable with histology has found applications in several skin diseases including LM.[3,4] In a recent study by Alarcon I et al,[5] RCM was found to be a useful complementary tool for the evaluation of LM and it has clinical benefits for the patients in terms of presurgical assessment and monitoring response of treatment and detection of subclinical recurrences.

A 50-year-old Caucasian gentleman was referred by his general practitioner for a routine mole check. A suspicious pigmented lesion was noted on his left cheek (Fig. 1a). After dermoscopy examination (Fig. 1b), a possible diagnosis of LM was made. He underwent a shave biopsy of the lesion and subsequently a CO_2 laser ablation of the lesion in another institution. The histology revealed LM. On review, the lesion appeared clinically cleared with superficial depressed scarred tissue on the left cheek (Fig. 2a). Dermoscopy examination did not show any residual features of LM. To ensure complete treatment, RCM imaging was used on the scarred area (Fig. 2a) to identify any residual presence of LM. RCM showed disarranged honeycomb pattern with perifollicular distribution of dendritic and round pagetoid cells (LM score 3) (Fig. 2b) which is consistent with the presence of LM according to the "LM score" a new simplified algorithm described by Guitera et al.[4] According to this algorithm, the score of greater than or equal to 2 has a sensitivity of 85% and a specificity of 76% (OR: 18.6; 95% CI, 9.3 to 37.1).[4] The patient underwent wide local excision with the guidance of RCM imaging and a complete clearance was confirmed by histology (Figs. 2c and 2d).

This case shows that RCM imaging is useful to detect residual LM even on a scarred area postlaser treatment. This is the first of such case in the region and this further reinforces the role of RCM as a complementary tool for the detection of subclinical recurrences of LM.

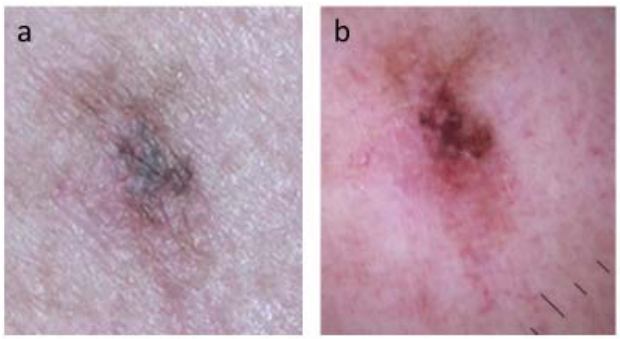

Fig. 1. In a), irregular brown pigmented macule on the left cheek is seen. In b), dermoscopy of the left cheek pigmented macule shows asymmetrical pigmented follicular openings.

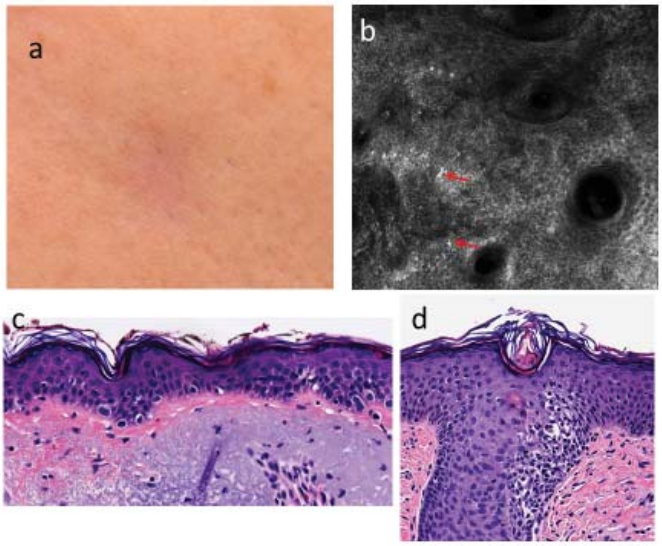

Fig. 2. In a), superficial depressed scarred tissue on the left cheek post-CO_2 laser ablation is seen. In b), RCM showed disarranged honeycomb pattern with perifollicular distribution of dendritic and round pagetoid cells. In c), histopathology shows large atypical melanocytes at the basal layer with solar elastosis in the papillary dermis (Hematoxylin-eosin stain; original magnification: x40). In d), histopathology shows atypical melanocytes at basal layer, including follicular epithelium (Hematoxylin-eosin stain; original magnification: x10).

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Progress in Singapore Family Medicine: Reflections over the Decades from 1931*

Chin Hin Chew, [1,2]*FAMS, FRCP(Ed,Glas,Lon), MACP*

Minister of State for Health, Dr Lam Pin Min, the President of the College of Family Physicians, Dr Lee Kheng Hock, Members of Council, and friends.

Allow me first to thank the President and Council for asking me to deliver the Sreenivasan Oration and to be an honorary brethren of the College. This is an incredible double honour; I, however, accepted not without hesitation and with much trepidation as President Lee knows of my ageing and failing voice box!

Prologue

Dr BR Sreenivasan was a remarkable physician, scholar, clinical teacher and administrator; even more so a thorough and compassionate gentleman (Fig. 1). I knew him from my childhood days, growing up in the grounds of the then Sepoy Lines General Hospital. The Sreenivasan family were once our neighbours at the doctors' quarters along Outram Road and have been long-standing family friends. Dr Sreenivasan and my father, Dr Benjamin Chew, were fellow colleagues with Dr Gordon Ransome, serving under Dr V Landor and Sir Brunel Hawes, the Professor of Medicine at General Hospital (SGH) and sometimes at Tan Tock Seng Hospital (TTSH), the main teaching centre for Clinical Medicine and Surgery before the Japanese invasion (Figs. 2 and 3).

Disease pattern then was very different. There was the predominance of infectious diseases and malnutrition, for example, tuberculosis (TB), typhoid, dysentery, poliomyelitis, malaria, beriberi and other dreadful diseases. Many have now been eradicated, though some still remain. Besides being fellow colleagues, Sreeni and Ben Chew shared many common interests. Both were well read in the classics and literature. They were fellow students at the King Edward VII College of Medicine, graduating with a Licentiate in Medicine and Surgery (LMS) in 1931 and 1929, respectively, with a special interest in general medicine.

With the internment of their colonial chiefs following the surrender of British Lieutenant-General Arthur Percival to General Tomoyuki Yamashita in Feb 1942, they served as Heads of Medicine—Ben Chew at TTSH and Sreenivasan at Kandang Kerbau Maternity Hospital (KKH) which also served as a general hospital, with SGH having been taken over by the Japanese for their own military. With their dedicated local staff, doctors, nurses and others, they ministered to the thousands of patients with compassion while battling the horrendous diseases during the 3 1/2 years of the Japanese Occupation.

Fig. 1. Dr BR Sreenivasan, the first Singaporean Vice Chancellor of University of Singapore from 1962 to 1964.

Fig. 2. Norris Block (Lower Block), Sepoy Lines General Hospital.

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*Delivered on 28 November 2015 at Mountbatten Room, Singapore Swimming Club. The Oration was first published in Vol. 41 No. 4 (December 2015) of the College Mirror.

Fig. 3. Straits Settlements' Students Hostel, King Edward VII College of Medicine at Tan Tock Seng Hospital, now known as the headquarters of the Lee Kong Chian School of Medicine.

Battle Against Tuberculosis

TB was a main concern with the huge numbers of well over 2500 in a population of just over a million. With hardly any effective drugs and postwar problems, the government could hardly cope. Furthermore, with discriminating colonial policies, many local doctors, including Sreenivasan and Benjamin Chew, left the service despite the promise of better conditions and scholarships for specialist training in the United Kingdom (UK). However, both continued the battle against TB in private practice; Sreeni in Little India and Ben Chew in North Bridge Road. They were supported by like-minded prominent philanthropists and former grateful prisoners-of-war (POWs) whom they had helped during their internment. The Rotary Club also funded and built the Rotary Tuberculosis Clinic at TTSH in 1948 at their behest. They, with 13 others, then founded the Singapore Anti-Tuberculosis Association (SATA) (Fig. 4).

The only effective drug was streptomycin which was discovered in 1944 but was only made available here in 1946. Treatment of TB then was the regime of bed rest and often isolation in hospitals, a nutritious diet, fresh air, and sunshine. The paltry rich, on the other hand, went to the Swiss Alps! Collapse therapy was another important measure. Thus, TTSH became the TB and Chest Centre for over 15 years after WWII (Fig. 5). An important and blessed outcome of the generosity of the Rotarians was not only the thousands of TB patients who were seen and treated, but the Rotary Clinic also became the centre of TB research trials and studies (Fig. 6). The results paved the way for the present form of treatment of a 6-month short course chemotherapy the world over, from the original regime of 2 years, and sometimes more!

Dr Sreenivasan's contributions to the control of and battle against TB as an early pioneer, have not been appreciated enough. I am sure he would be happy looking "from above" at these achievements.

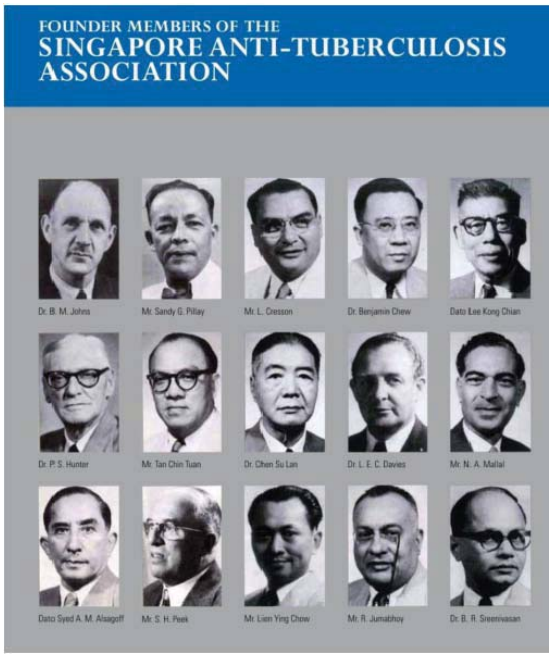
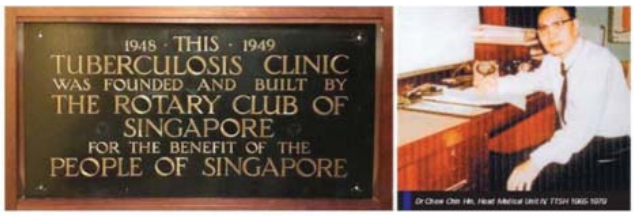


Fig. 4. Founders of Singapore Anti-Tuberculosis Association (SATA).

Thirty years ago, the space adjacent to TTSH main block was not vacant. **Prof Chew Chin Hin, Emeritus Consultant**, still vividly recalls the hustle and bustle of the first designated centre for TB treatment: Rotary Clinic.

The clinic is named after Rotary Club, which funded the construction of the building.

Fig. 5. The legacy of the Rotary Clinic lives on at Tan Tock Seng Hospital.



Through a joint effort with Prof Wallace Fox from British Research Medical Research Council, this committee introduced the revolutionary breakthrough of TB treatment such as reducing the therapeutic regime from a maximum period 24 months to just 6 months. This team also discovered the "short course regimens under full supervision" programme, which is presently known as DOT (Directly Observed Treatment).

Fig. 6. The Rotary Clinic became the centre of TB research trials and studies.

Advances in Medicine and Medical Education

With developments and technological advances in medicine seen over the decades, so too there has been a tremendous evolution in medical education and training, including in general practice and family medicine.

The diploma of LMS that Dr Sreenivasan had, which was his license to practice medicine in 1931, was a much respected qualification (Fig. 7). LMS was well recognised by the General Medical Council (GMC) of United Kingdom (UK) and was regarded as equal to any throughout the Empire! In Singapore and British Malaya, the professors were all "generalists". They taught their students how to be holistic and ethical doctors with an emphasis on good clinical skills by the bedside, through listening, taking and recording meticulous history of patients. They were all well rounded doctors at graduation. There was no mandatory housemanship. A number commenced forthwith their mostly "solo" private practice with much success.

Those who wished to further their training were selected to remain in the hospitals—SGH, TTSH or KKH, with Middleton Hospital for infectious disease or the mental hospital at Yio Chu Kang for psychiatry. Some joined the Public Health Service. Thus, the teaching of medicine with an emphasis on good bedside skills and sound ethical values was well suited for general practice. This was the situation until 1952 when a year of compulsory internship was introduced by the General Medical Council (GMC) for the UK and British colonies!

Fig. 7. King Edward VII College of Medicine, Singapore.

It was a personal privilege to watch Dr Sreenivasan in the same way as he taught students by the bedside when he was an honorary teacher in Prof Ransome's Medical Unit I in the 1950s. Here, in this image (Fig. 8), we see amongst his clinical teacher friends the late Drs Danaraj, Evelyn Hanam and Seah Cheng Siang.

Postgraduate Education and Training

Formal postgraduate education and training in Singapore became organised only in the 1950s. Following the British pattern and institutions, this began with the founding of the Academy of Medicine, Singapore (AMS) in 1957, largely

1959

Visit of Sir Stanley Davidson, President of the Royal College of Physicians of Edinburgh to the Department of Medicine, General Hospital, Singapore in 1959.

Seated from left to right:
Dr M Kelleher, Sir Gordon Ransome, Sir Stanley Davidson, Dr Evelyn Hanam, Dr T J Danaraj.

Standing from left to right:
Dr Chew Chin Hin, Dr Lim Kee Jin, Dr R Wells, Dr K S Lau, Dr Seah Cheng Siang.

Sir Stanley was an Honorary Member of the Academy of Medicine.

Fig. 8. Medical Unit I at Norris Block at SGH in 1959.

through the foresight of Sir Gordon Ransome, the first Master. In 1961, the Committee of Postgraduate Medical Studies was formed, which was the predecessor of the Postgraduate School, now known as the Division of Graduate Medical Studies (DGMS) in the National University of Singapore (NUS). This was also the period when Singapore became more politically independent (Fig. 9).

More formal traineeship began in the hospitals for potential specialists, but most still had to go abroad until we had our own professional qualifications. This was when our Master of Medicine degree was introduced in 1970, but not without difficulties! Yes, this was a breakthrough as our trainees do not have to spend time and money going to faraway places to take the various examinations.

Another significant milestone was the founding of the College of General Practitioners, Singapore (CGPS) in 1971 here, following the visit in the late 60s of the President of the British Royal College of General Practitioners, Lord Hunt. This was also the foresight of some well respected "private practitioners" including Drs Sreenivasan, Wong Heck Sing, Gordon Horne, Liok Yew Hee, Koh Eng Kheng, Wong Kum Hoong, Victor Fernandez and Evelyn Hanam, some names I dimly but happily recall. They were the giants of family medicine. I also remember whether the proposed body should be formed as a chapter within the AMS or follow the British pattern of a separate college. As many thought general practice then was not a specialist discipline, the latter prevailed; thus the CGPS in 1971! More important however, must be the promotion of the highest standards of family medicine.

A few of the founding members like Drs Gordon Horne and Evelyn Hanam, having been consultant physicians, were early fellows of the AMS. Dr Horne's family practice here was a forerunner of group practices as were those of the Ministry of Health Outpatient Service, now termed "polyclinics" as opposed to the many "solo" clinics. This is an advantage as more discussion and consultation is readily at hand for the more difficult cases. I believe the practice named Horne, Chin and Partners still remains well! I also had the immense pleasure of admitting Dr Wong Heck Sing a fellow of AMS under a special provision.

I was very glad when I was asked to officiate and open the 1st Annual Scientific Conference in 1988 at the College of Medicine Building, home of the College. In my address I said, "General practice must be seen as a rewarding discipline and the myth of general practitioners (GPs) treating only minor ailments...should be quickly put to rest", and concluded that "...while we as doctors strive to find new approaches to diseases, the hallmark of a well rounded physician is his ability to provide preventive medical education and care to his patients to keep them healthy. The family physician is best placed to ensure this...".

Progress in Family Medicine

There was a "changing of the guards" at the School of Postgraduate Medical Studies in 1988 when I succeeded Professor Seah Cheng Siang as Deputy Director (Fig. 10). It was personally gratifying to proffer full support of the School to the proposals to establish formalised training, and bringing family medicine into our medical school at

	Historical Milestones in Singapore and Postgraduate Institutions in 50s to 70s
1957	Academy of Medicine
1961	Committee of Postgraduate Medical Studies
1970	School of Postgraduate Medical Studies, MMed qualifications
1971	College of General Practitioners
Pre-1959	Singapore, a Crown Colony
1959	Singapore, self-governing State
1963	Singapore in independent Malaysia
1965	Singapore an independent Republic

Fig.9. Historical milestones in Singapore and postgraduate institutions in the 1950s and 1970s.

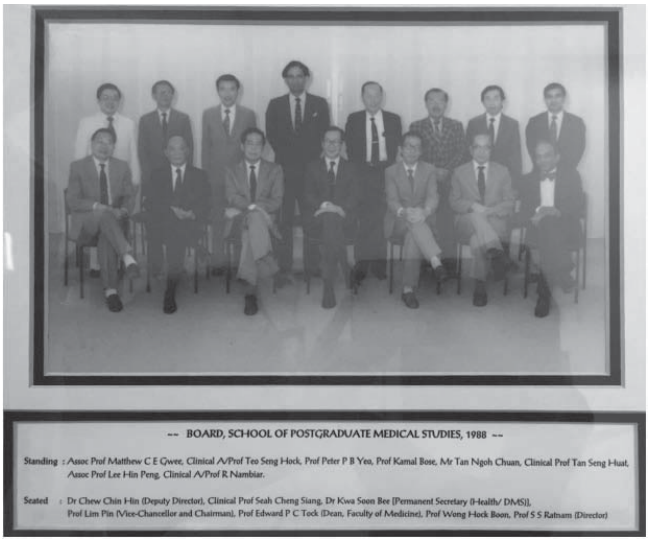


Fig. 10. "Changing of the guards" at the Postgraduate School in 1988.

the Department of Community and Occupational Medicine, and the award of the Degree of Master of Medicine (Family Medicine). The first examination was in 1993, succeeding the Membership of the College of General Practitioners (MCGP). MCGP was already of high standard since the 1970s, comparable to those of the UK Colleges and Australasia, and was also recognised by our Singapore Medical Council (SMC) as a registrable qualification. The Master of Medicine (MMed) enhanced even further the high standing of family medicine. I had the pleasure of observing the first 2 clinical examinations at SGH and was happy to view the commendable reports of the 2 external examiners from UK and Australasia (Fig. 11).

Towards the end of the 1990s, the Postgraduate School introduced several graduate diplomas for family doctors with the support of the College. The first awards of the Graduate Diplomas in Family Medicine were conceived in the auspicious year of 2000. This was an incentive for many younger doctors to further advance their training in family medicine.

Finally only last year, I had the pleasure of personally endorsing the establishment of the Chapter of Family Medicine Physicians within AMS through discussions with President KH Lee of the College and Master SH Lim of the Academy and senior Fellows (Fig. 12). However, the fraternal relationship that exists between the College and Academy must remain strong, strengthening even further with time. This indeed has been a full circle when I admitted Dr Wong Heck Sing to the fellowship of the Academy in 1973 under a special provision. Here is a photo that included us when our dear President Sheares visited our premises at the old Alumni Medical Centre (Fig. 13).

Fig. 11. The first batch of MMed (Family Medicine) graduates in 1993.

"Some Things Must Not Change"

With immense scientific and technological advances in medicine and the accompanying excitement, let us pause, reflect, and not forget that our primary duty must always be to our patients and fellowmen. I remember seeing a title of a paper in the Annals of Internal Medicine of the American College of Physicians: "Some things have not changed". I would like to add that "some things must not change".

Fig. 12. With FAMSs (Family Medicine) in March 2015.

Visit of the Patron, Dr Benjamin Henry Sheares, late President, Republic of Singapore and Mrs Sheares to the Academy on 19 January 1975. Dr Sheares was the first Patron of the Academy.

Standing (left to right):
Dr Feng Pao Hsii, Censor; Dr Wong Poi Kwong, Chairman, Chapter of Physicians; Dr Chew Chin Hin, Master; Dr Wong Heck Sing, President, College of General Practitioners; Dr Seah Cheng Siang, Censor; Dr V K Pillay, Bedel; Dr Choo Jim Eng, Bursar; Mr R Singh, ADC to the President

Sitting (left to right):
Dr Mrs Wong Heck Sing; Mrs B H Sheares; President Sheares, Patron; Dr Mrs Chew Chin Hin; Dr Beatrice T M Chen, Scribe.

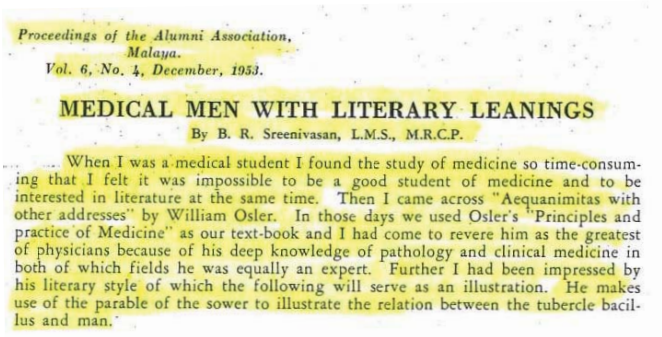
Fig. 13. Visit of President BH Sheares to Academy of Medicine, Singapore (AMS) and College of General Practitioners, Singapore (CGPS) in 1975 at 4A College Road.

These include the pillars of our medical ethics: beneficence, non-malificence, justice and autonomy, holding fast to our values of care and compassion, and never abandoning our patient-centric fundamentals. We need courage for this as the art and calling of medicine stand constantly in danger of contamination!

Epilogue

I would like to conclude by drawing your attention to a masterly paper by Dr BR Sreenivasan in the Proceedings of the Alumni Association in 1953 (Fig. 14). I had earlier mentioned that Dr Sreenivasan, together with his contemporaries and peers like Dr Benjamin Chew, was widely read. He was a man of letters and literature. When the Japanese occupied Singapore, doctors and nurses at Sepoy Lines General Hospital, with all their patients, were directed to leave almost immediately en masse. It was not possible to take much away. Let me quote Dr Sreenivasan, "I took away with me only 3 books—the Bible, Shakespeare and Osler—because I felt that Osler could help me earn a living and the other 2 would give life a meaning".

In the paper, he dealt at some length with St Luke, "the beloved physician", who was the author of the longest of the 4 Gospels and well known for his attribute of compassion. Allow me to show you a 1887 painting entitled "the Doctor" by the famous painter, Sir Luke Fildes (coincidentally named Luke!) (Fig. 15). It shows the doctor on a house visit who simply looked at the sick child and the distraught parents,



Proceedings of the Alumni Association, Malaya.
Vol. 6, No. 4, December, 1953.

MEDICAL MEN WITH LITERARY LEANINGS

By B. R. Sreenivasan, L.M.S., M.R.C.P.

When I was a medical student I found the study of medicine so time-consuming that I felt it was impossible to be a good student of medicine and to be interested in literature at the same time. Then I came across "Aequanimitas with other addresses" by William Osler. In those days we used Osler's "Principles and practice of Medicine" as our text-book and I had come to revere him as the greatest of physicians because of his deep knowledge of pathology and clinical medicine in both of which fields he was equally an expert. Further I had been impressed by his literary style of which the following will serve as an illustration. He makes use of the parable of the sower to illustrate the relation between the tubercle bacillus and man.

Fig. 14. An excerpt from Prof Sreenivasan's paper published in Proceedings of the Alumni Association, Malaya in 1953.

Fig. 15. The Doctor – An 1887 painting by Sir Luke Fildes which is displayed at the Tate Gallery in London.

and shared their anxiety with compassion. Here is another painting, an Italian classic, vividly portraying the power of compassion—the compassion of the "Good Samaritan", treating tenderly and soothing the wounds of a Jew in the rescue process, despite Samaritans being despised by all Jewry. By Dr Luke's account of this parable, the man had been robbed, badly beaten and stripped naked, and shamelessly ignored by 2 pious fellow Jews who had passed him by (Fig. 16). I show these 2 paintings to emphasise that compassion must be a fundamental attribute of us all.

Let me end with Dr Sreenivasan's words: "Men must endure their going, hence, even as their coming hither", and when I go hence, I can think of nothing I would like better for an epitaph than "Here lies a beloved physician".

President, fellows and friends allow me to wish you all well, and may the College long flourish!

Fig. 16. Portrait of Compassion – An 18th century Italian depiction of the Parable of the Good Samaritan.

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